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(54) INDOLE DERIVATIVES

(71) We, AYERST, McKENNA & HARRISON LIMITED, of 1025 Laurentien Boulevard, St. Laurent, Province of Quebec, Canada, a corporation organized and existing under the laws of Canada, (assignee of CHRISTOPHER ALEXANDER DEMERSON, LESLIE GEORGE HUMBER, ANDRE ALFRED ASSELIN, IVO LADISLAV JIRKOVSKY, THOMAS ALBERT DOBSON and KAREL PELZ), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

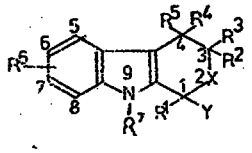
The present invention relates to pyranoindole and thiopyranoindole derivatives, to processes for their preparation and to intermediates used in these processes.

More specifically, the present invention relates to pyranoindole and thiopyranoindole derivatives possessing valuable pharmacologic properties. For example, these derivatives exhibit useful antidepressant properties at dosages which do not elicit undesirable side effects. Furthermore the present derivatives exhibit properties useful for the treatment and prevention of ulcers. The combination of these pharmacologic properties together with a low order of toxicity render the pyranoindoles and thiopyranoindoles of the invention therapeutically useful.

Only a rather limited number of reports dealing with pyrano[3,4-b]indole derivatives are available. In the few that do exist, pyranoindoles are treated more in the manner of chemical curiosities. For the most part these reports discuss the preparation of pyranoindoles in which the pyran portion thereof exists as a lactone. For example, see H. Plieninger, Chem. Ber., *83*, 271 (1950) and S. Sakurai and T. Ito, Nippon Kagaku Zasshi, *78*, 1665 (1957); [Chem Abstr., *54*, 1488f (1960)].

The thiopyranoindoles of the prior art, for example, 5-(3-aminopropyl)-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole, M. E. Freed, *et al.*, J. Med. Chem., *7*, 628 (1964) are distinguished from the present compounds of this invention by having a different ring structure and by lacking substituents on the thiopyran ring.

The pyranoindole and thiopyranoindole derivatives of this invention are characterized by having an amino(lower)alkyl radical attached to a pyrano[3,4-b]indole or thiopyrano[3,4-b]indole nucleus. The preferred derivatives of this invention are represented by formula I,



I.

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in which R^1 is lower alkyl or lower cycloalkyl; R^2, R^3, R^4 and R^5 are the same or different selected from the group consisting of hydrogen and lower alkyl; R^6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, nitro or halo; R^7 is hydrogen, lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl or an amino(lower)alkyl radical of formula —Alk—NR^8R^9 wherein Alk is an alkylene selected from

$$CR^{10}R^{11}CR^{12}R^{13}, \quad CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15} \quad \text{and}$$
$$CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}CR^{16}R^{17}$$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are hydrogen or lower alkyl and R^8 and R^9 are either the same or different selected from the group consisting of hydrogen and lower alkyl, or R^8 and R^9 together with the nitrogen atom to which they are joined form a heterocyclic amine radical selected from 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, piperazinyl, 4-(lower alkyl)-1-piperazinyl and 4-[hydroxy(lower)-alkyl]-1-piperazinyl; X is oxy or thio; and Y is lower alkyl, phenyl(lower)alkyl or an amino(lower)alkyl radical of formula —Alk—NR^8R^9 wherein Alk is an alkylene selected from

$$CH^{10}R^{11}, \quad CR^{10}R^{11}CR^{12}R^{13}, \quad CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15} \quad \text{and}$$
$$CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}CR^{16}R^{17}$$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are hydrogen or lower alkyl and R^8 and R^9 are as defined herein; with the proviso that at least one of R^7 and Y is —Alk—NR^8R^9.

In the above definitions it is understood that Alk, R^8 and R^9 in each case are entitled to the full range of their definitions as listed above, so that Alk, R^8 and R^9 of Alk—NR^8R^9 linked to position 9 need not necessarily be the same as Alk, R^8 and R^9 of Alk—NR^8R^9 linked to position 1.

Various processes for the preparation of the compounds of formula I are disclosed.

The terms "piperidino", "morpholino" and "piperazino" as used herein designate that these heterocyclic systems carry a substituent at positions 1, 4 and 1 of the respective ring systems.

The term "lower alkyl" as used herein contemplates both straight and branched chain alkyl radicals containing from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, 2-methylpentyl and the like.

The term "lower alkenyl" as used herein contemplates both straight and branched chain alkenyl radicals containing from two to six carbon atoms and includes vinyl, allyl, 1-propenyl, methallyl, 2-ethyl-3-butenyl and the like.

The term "phenyl(lower)alkyl" as used herein contemplates a phenylalkyl radical in which the alkyl portion thereof contains from one to four carbon atoms and includes benzyl, phenethyl, α-methylphenethyl and the like.

The term "lower cycloalkyl" as used herein contemplates saturated cyclic hydrocarbon radicals containing from three to six carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl and the like.

The term "lower alkoxy" as used herein contemplates both straight and branched chain alkoxy radicals containing from one to four carbon atoms and includes methoxy, ethoxy, isopropoxy and the like.

The term "lower alkanoyloxy" as used herein contemplates both straight and branched chain alkanoyloxy radicals containing from two to six carbon atoms and includes acetoxy, propionyloxy, hexanoyloxy and the like.

The term "halo" as used herein contemplates halogens and includes fluorine, chlorine, bromine and iodine.

The compounds of formula I are capable of forming acid addition salts with pharmaceutically acceptable acids. Such acid addition salts are included within the scope of this invention.

The acid addition salts are prepared by reacting the base form of the appropriate compound of formula I with either one to four equivalents, depending on the number of basic nitrogens in the compound, or preferably with an excess of the appropriate acid in an organic solvent, for example, ether or an ethanol-ether mixture. These salts, when administered to mammals, possess the same pharmacologic activities as the corresponding bases. For many purposes it is preferable to administer the salts rather than the base compounds. Among the acid addition salts suitable for this purpose are salts such as the sulfate, phosphate, lactate, tartrate, maleate, citrate, hydro-

bromide and hydrochloride. Both the base compounds and the salts have the distinct advantage of possessing a relatively low order of toxicity.

Also included in this invention are the stereochemical isomers of the compounds of formula I which result from asymmetric centers, contained therein. These isomeric forms are prepared by different methods and are purified readily by crystallization or chromatography.

Individual optical isomers, which might be separated by fractional crystallization of the diastereoisomeric salts formed thereof, for instance, with d- or l- tartaric acid or D-(+)-α-bromocamphor sulfonic acid, are also included.

The useful antidepressant activity of the compounds of formula I and their acid addition salts with pharceutically acceptable acids are demonstrated in standard pharmacologic tests, such as, for example, the tests described by F. Hafliger and V. Burckhart in "Psychopharmacological Agents", M. Gordon, Ed., Academic Press, New York and London, 1964, pp. 75—83.

More specifically, as noted in the latter reference the antidepressant properties of a compound may be demonstrated by its capacity to antagonize the depressant effects of reserpine. Furthermore, it is well documented that reserpine in animals produces a model depression which can be used for detecting antidepressant properties. Accordingly, the compounds of the present invention antagonize reserpine effects in mice at doses ranging from about 1 to 100 mg/kg. Several of the preferred compounds, for instance,

1-[(2-dimethylamino)ethyl]-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole oxalate (Example 309),

1-methyl-[3-(methylamino)propyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole oxalate (Example 310),

1-[3-(dimethylamino)propyl]-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole oxalate (Example 312),

1-[2-(dimethylamino)ethyl]-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole maleate (Example 330),

1-[2-(dimethylaminoethyl]-1-methyl-9-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole maleate (Example 683), and

1-[2-(dimethylamino)ethyl]-9-ethyl-1-methyl-1,3,4,9-tetrahydrothiopyrano[4,3-b]-indole hydrochloride (Example 911),

antagonize the effects of reserpine in mice at dose ranges from about 1 to 15 mg/kg.

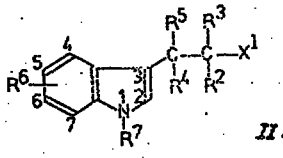
When the compounds of this invention are used as antidepressants in warm-blooded mammals, e.g. rats and mice, they may be used alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay or so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of the present therapeutic agents will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a level that is in a range of from about 0.1 mg to about 50 mg per kilo per day, although as aforementioned variations will occur. However, a dosage level that is in the range of from about 0.5 mg to about 25 mg per kilo per day is most desirably employed in order to achieve effective results.

The compounds of formula I of this invention possess another useful pharmacologic property; that is, they are useful antiulcer agents. More particularly, the said compounds of this invention exhibit antiulcer activity in standard pharmacologic tests, for example, the test described by D. A. Brodie and L. S. Valitski, Proc. Soc. Exptl. Biol. Med., *113*, 998 (1963), based on the prevention of stress-induced ulcers.

When the compounds of formula I are employed as antiulcer agents, they may be formulated and administered in the same manner as described above for their use as antidepressant agents.

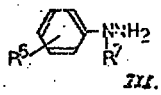
For the preparation of the pranoindole and thiopyranoindole derivatives of this invention we prefer to use as starting materials the compounds of general formula II,



II.

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in the first instance and X^1 is hydroxy, mercapto, —S—SO_3—Na or —S—SO_3K.

The starting materials of formula II in which X^1 is hydroxy are either known, for example, tryptophol, described by H. R. Snyder and F. J. Pilgrim, J. Am. Chem. Soc. *70*, 3770 (1948), or they are obtained by the following process:



III.

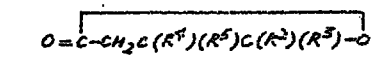
$$+ \underset{\text{IV.}}{HCCH_2C(R^4)(R^5)C(R^2)(R^3)OH} \longrightarrow$$

$$II(X^1 = OH)$$

With reference to this process phenylhydrazines of formula III and the hydroxyaldehyde of formula IV are reacted together according to the conditions of the "Fischer Indole Synthesis", for example, see P. L. Julian, E. N. Myer and H. C. Printy, "Heterocylic Compounds", R. C. Elderfield, Ed., Vol. 3, John Wiley and Sons, Inc., New York, 1952, pp. 8—11, to form the desired starting material (II, $X^1 = OH$).

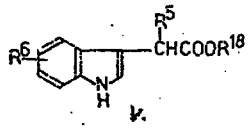
The phenylhydrazines of formula III are either known or are prepared according to known methods. A convenient method involves the diazotization of the appropriately substituted aniline to give the corresponding diazo derivative. The latter compound is then reduced with stannous chloride or sodium sulfite to give the corresponding phenylhydrazine, see L. F. Fieser and M. Fieser, "Advanced Organic Chemistry", Reinhold Publishing Corporation, New York, 1961, p. 734.

The hydroxyaldehydes of formula IV are either known, see for example, "Rodd's Chemistry of Carbon Compounds", S. Coffey, Ed., Vol. I d, 2nd ed., Elsevier Publishing Co., Amsterdam, 1965, pp. 44—49, or they are prepared according to known methods. A convenient method involves reduction of an appropriate lactone of formula



with bis-(3-methyl-2-butyl)borane, H. G. Brown and D. B. Bigley, J. Am. Chem. Soc., *83*, 486 (1961), diisobutyl aluminum hydride, L. I. Zakharkkin and I. M. Khorlina, Tetrahedron Letters, 619 (1962) or sodium aluminum hydride, L. I. Zakharkin *et al.*, Tetrahedron Letters, 2087 (1963). The appropriate lactones utilized in this condensation are either commercially available, for example, δ-valerolactone, α-methyl-butyrolactone, or they are described with a variety of methods for their preparation in organic chemistry textbooks: such as the textbooks, Methoden der Organischen Chemie", Houben-Weyl, E. Muller, Ed., Vol. VI/2, Georg Thieme Verlag, Stuttgart, 1963, pp. 561—852 or L. F. Fieser and M. Fieser, "Advanced Organic Chemistry", cited above.

Alternatively, the starting materials of formula II in which R^2, R^3, R^4 and R^7 are hydrogen and X^1 is hydroxy are prepared by lithium aluminum hydride reduction (N. G. Gaylord, "Reduction with Complex Metal Hydrides", Interscience Publishers, Inc., New York, 1956, pp. 322—370) of compounds of formula V described by T. Y. Shen, U.S. Patent No. 3,161,654, Dec. 15, 1964:



wherein R^{18} is lower alkyl and R^5 and R^6 are as defined in the first instance.

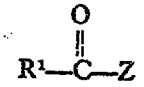
In addition, convenient processes are available for the specific synthesis of certain starting materials of formula II. For example, starting materials of formula II in which R^2, R^3, R^4, R^5 and R^7 are hydrogen and X^1 is hydroxy are obtained by reduction of the appropriate ethyl 3-indoleglyoxylate with lithium aluminum hydride, British Patent 778,823 and T. Nogrady and T. W. Doyle, Can. J. Chem., *42*, 485 (1964). Starting materials of formula II in which R^2 and R^4 are hydrogen, R^3, R^5 and R^7 are hydrogen or lower alkyl and X^1 is hydroxy are obtained by reacting indole or an appropriately substituted indole with ethylene oxide or lower alkyl substituted ethylene oxide according to the process of M. Julia *et al.*, Bull. Soc. Chim., Fr., 2291 (1966).

The starting materials of formula II in which X^1 is mercapto, —S—SO_3Na or —S—SO_3K, and R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in the first instance are obtained by the following process: The appropriate compound of formula II ($X^1 = OH$) described above, is treated with phosphorus tribromide in an inert solvent, for example, ether or carbon tetrachloride, to afford the corresponding 3-(2-bromoethyl)-indole derivative. The latter compound is then converted to the desired starting material of formula II ($X^1 = SH$) by a procedure similar to that described by N. N. Suvorov and V. N. Buyanov, Khim.-Farm. Zh., *1*, (1967), [Chem. Abstr. *67*, 73474a (1967)], for converting 3-(2-bromoethyl)indole to indole-3-ethanethiol (II; R^2, R^3, R^4, R^5 and $R^6 = H$ and $X^1 = SH$). Accordingly, the appropriate 3-(2-bromoethyl)-indole derivative is treated with sodium or potassium thiosulfate to afford the corresponding sodium or potassium β-(3-indolyl)ethyl thiosulfate derivative, respectively; namely the desired starting materials of formula II (X = —S—SO_3Na or —S—SO_3K). Treatment of the latter product with strong alkali, for example, sodium or potassium hydroxide, yields the corresponding bis[ω-(3-indolyl)ethyl]disulfide derivative. Reduction of the latter compound with lithium aluminum hydride gives the desired compounds of formula II ($X^1 = SH$).

Alternatively, the preceding thiosulfate derivative is treated with acid, for example, dilute aqueous solutions of hydrochloric acid, sulfuric acid or phosphoric acid, to give directly the latter compound of formula II.

It should be noted that the preceding processes may not be entirely practical for the preparation of the compounds of formula II in which X^1 is mercapto, —S—SO_3Na or —S—SO_3K, and R^5 is hydroxy or lower alkanoyloxy. For this reason, the preferred starting materials of formula II for the ultimate preparation of the compounds of formula I in which R^6 is hydroxy or lower alkanoyloxy and X is thio are the corresponding compounds of formula II in which R^6 is benzyloxy, i.e., a hydroxyl with a protecting benzyl group or other suitable protecting group, see J. F. McOmie, "Advances in Organic Chemistry", Vol. 3, R. A. Raphael, *et al.* Ed., Interscience Publishers, New York, 1963, pp. 191—294. When the latter compounds are used as starting materials in this manner, they are first subjected to the process (II + VI ⟶ VII), described below. Subsequently, the benzyloxy group is removed by hydrogenation, in the presence of a catalyst, for example, 10% palladium on carbon, just prior to affording the desired corresponding compound of formula I in which R^6 is hydroxy. The latter are converted, if desired, to the corresponding compound of formula I in which R^6 is lower alkanoyloxy by conventional means, for example, by treatment with the appropriate lower alkanoic anhydride preferably in the presence of pyridine. Likewise, it should be noted that similar use of the starting materials of formula II in which X^1 is hydroxy and R^6 is lower alkanoyloxy by conventional means, for example, by treatment with the appropriate lower alkanoic anhydride preferably in the presence of pyridine. Likewise, it should be noted that similar use of the starting materials of formula II in which X^1 is hydroxy and R^6 is benzyloxy to obtain the corresponding compound of formula I in which R^6 is hydroxy or lower alkanoyloxy is also preferred.

The above described starting materials of formula II in which R^2, R^3, R^4, R^5, R^6, R^7 and X^1 are as defined in the first instance are now subjected to a key reaction comprising the treatment of said starting materials with a compound of formula



(VI)

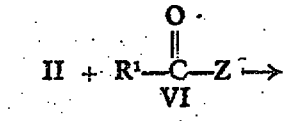
in which R^1 is as defined in the first instance and Z is selected from
(a) $COOR^{19}$ and $Alk^1—COOR^{19}$ in which R^{19} is hydrogen or lower alkyl and Alk^1 is an alkylene selected from

$$CR^{10}R^{11},\ CR^{10}R^{11}CR^{12}R^{13} \text{ and } CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}$$

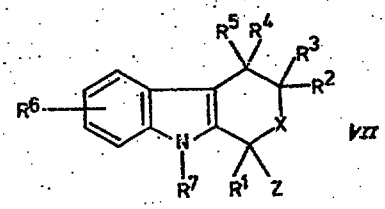
wherein R^{19}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are hydrogen or lower alkyl,
(b) $CONR^8R^9$ and $Alk^1—CONR^8R^9$ in which Alk^1, R^8 and R^9 are as defined above.
(c) CH_2OCOR^{20} and $Alk^1—CH_2OCOR^{20}$ in which R^{20} is hydrogen or lower alkyl and Alk^1 is as defined above,
(d) $Alk^2—L$ in which Alk^2 is an alkylene selected from

$$CR^{10}R^{11}CHR^{12},\ CR^{10}R^{11}CR^{12}R^{13}CHR^{14} \text{ and } CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}CHR^{16}$$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are as defined above and L is halo,
(e) Alk NR^8COR^{21} in which Alk and R^8 are as defined in the first instance and R^{21} is hydrogen or lower alkyl containing from one to five carbon atoms,
(f) $Alk—NO_2$ in which Alk is as defined in the first instance,
(g) Lower alkyl and phenyl(lower)alkyl, and
(h) $Alk—NR^8R^9$ in which Alk, R^8 and R^9 are as defined in the first instance, in the presence of an acid catalyst to yield the compounds of formula VII in which R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Z are as defined above.



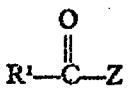
VI



VII

Thereafter the appropriate compound of formula VII is converted to the desired pyranoindole of formula I according to the processes described hereinafter or is actually the desired compound of formula I in the case where Z is $Alk—NR^8R^9$, as described above.

In practising the condensation (II + VI ⟶ VII) a solvent is used generally as a reaction medium. Any solvent inert to the reaction conditions may be used. Suitable solvents include aromatic hydrocarbon, for example benzene, or toluene, ethers and cyclic ethers, for example diethyl ether, dioxan, or tetrahydrofuran, halogenated hydrocarbons, for example methylene dichloride, or carbon tetrachloride and the like. Benzene and tetrahydrofuran are especially convenient and practical for this use. A variety of suitable acid catalysts may be used for this condensation, for example, the type of catalyst used in a Friedel-Crafts reaction, i.e. *p*-toluenesulfonic acid, aluminum chloride, phosphorus pentoxide, boron trifluoride, zinc chloride, hydrochloric acid, perchloric acid, trifluoroacetic acid, sulfuric acid and the like. *p*-Toluenesulfonic acid, aluminum chloride, boron trifluoride and phosphorus pentoxide are included among the preferred acid catalysts. The amount of acid catalyst used is not especially critical and may range from 0.01 molar equivalents to 100 molar equivalents; however, a range of from 0.1 to 10 molar equivalents is generally preferred; however, note that the amount of acid catalyst should be in excess with respect to the basic nitrogens that may be present in R^7 of the starting material of compound II or the compound of formula

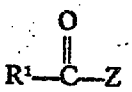


when Z is Alk—NR^8R^9. The time of the reaction may range from 10 minutes to 60 hours, with the preferred range being from one-half to 24 hours. The temperature of the reaction may range from 20°C. to the boiling point of the reaction mixture. Preferred temperature ranges include 20° to 120°C.

A more detailed description of the preparation of the above intermediate compounds of formula VII and a description of their subsequent conversion to pyranoindole and thiopyranoindole derivatives of formula I are disclosed below. For convenience these descriptions are catagorized into sections according to the group selected for Z for the intermediate.

(a) Preparation and Conversion of Intermediates of Formula VII (Z=$COOR^{19}$ and Alk^1—$COOR^{19}$)

Intermediates of formula VII (Z=$COOR^{19}$ and Alk^1—$COOR^{19}$ in which R^{19} is hydrogen or lower alkyl and Alk^1 is as defined in the first instance, R^7 is hydrogen and R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in in the first instance) are readily obtained by the condensation (II + VI $\longrightarrow$ VII) by using ketoacids or ketoesters of formula



in which R^1 is as defined in the first instance and Z is $COOR^{19}$ or Alk^1—$COOR^{19}$ as defined above together with the starting material of formula II (R^7=H).

Generally comparable yields of product are obtained in this process when either the ketoacid or the corresponding ketoester is used. However, in the case where it is desired to prepare an acid compound of formula VII (R^7=H) in which Z is Alk^1—$COOR^{19}$ wherein Alk^1 is $CR^{10}R^{11}$ and R^{10} is hydrogen (i.e., an acid intermediate of formula VII), it is preferable to first condense the appropriate β-ketoester of formula VI rather than the corresponding β-ketoacid and then hydrolyze the resulting ester product to give the desired acid compound.

Moreover, in the general practice of this invention it is often more convenient to prepare the acid compounds of formula VII (R^7=H) by using the ketoester instead of the ketoacid in this process and then hydrolyze the resulting ester product to the desired acid, the reason being simply that the ketoesters are generally more readily available either commercially or by synthesis.

The hydrolysis of compounds of formula VII (R^7=H) in which Z is $COOR^{19}$ or Alk^1COOR^{19} wherein Alk^1 is as defined in the first instance and R^{19} is lower alkyl, i.e. ester intermediates of formula VII (R^7=H), to their corresponding acids of formula VII (R^7=H) is readily effected by treatment with a suitable alkali, for example, potassium hydroxide or sodium carbonate, in aqueous methanol or aqueous ethanol or by treatment with lithium iodide in a suitable organic solvent, for example, collidine, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, 1967, pp. 615—617.

The α-, β-, γ- and δ- ketoacids and -ketoesters of formula VI are either known, for example, ethyl pyruvate, levulinic acid, ethyl α,α-dimethylacetoacetate, and β,β-dimethyllevulic acid, or they are prepared by known methods described in general organic chemistry textbooks. For example, a comprehensive review on the properties and preparation of such α-, β-, γ- and δ-ketoacids and -ketoesters may be found in "Rodd's Chemistry of the Carbon Compounds", cited above, Vol. Id, pp. 226—274.

Thereafter these intermediate acids and esters of formula VII (R^7=H) are converted to compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined in the first instance, and Y is —Alk—NR^8R^9 in which Alk is CH_2 or Alk^1—CH_2 wherein Alk^1 is as defined in the first instance and R^8 and R^9 are as defined in the first instance. This conversion is accomplished by amidation, reduction and if desired N-alkylation of the indolic nitrogen. The order of these steps is not critical. However, we have found the following sequence of these steps to be both convenient and practical.

First, when it is desired to prepare the derivatives of the latter group of compounds of formula I in which R^7 is H, i.e., N-alkylation of the indolic nitrogen is not desired, either the above acid intermediate or ester intermediate may be employed.

In the case where the acid intermediate of formula VII (R^7=H) is employed, said acid is subjected to amidation by treatment with a lower alkyl chloroformate, preferably ethyl chloroformate, in the presence of triethylamine affording the corresponding mixed

anhydride, which is converted by treatment with the appropriate amine of formula HNR^8R^9 in which R^8 and R^9 are as defined in the first instance, for example, ammonia, methylamine or dimethylamine, to yield the corresponding amide of formula VII in which Z is $CONR^8R^9$ or $Alk^1CONR^8R^9$ in which Alk^1, R^8 and R^9 are as described in the first instance.

Alternatively, the latter amides are also obtained by treating the ester intermediates of formula VII ($R^7=H$) with the appropriate amine according to known amidation methods, for example, see A. L. F. Beckwith in "The Chemistry of Amides", J. Zalicky, Ed., Interscience Publishers, New York, 1970, pp. 96—105.

Secondly, the amides so obtained are reduced with a suitable complex metal hydride to yield the desired pyranoindoles and thiopyranoindoles. Examples of suitable complex metal hydrides are lithium aluminum hydride, lithium aluminum hydride-aluminum chloride, aluminum hydride-aluminum chloride, diborane and sodium borohydride-aluminum chloride. Lithium aluminum hydride is preferred.

On the other hand when it is desired to prepare the compounds of formula I of the above group in which R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in the first instance, R^7 is lower alkyl, or lower alkenyl, propargyl, phenyl(lower)alkyl or amino(lower)alkyl and Y is —Alk—NR^8R^9 in which Alk is CH_2 or Alk^1CH_2 wherein Alk^1 is as defined in the first instance and R^8 and R^9 are as defined in the first instance, the acid or ester intermediate of formula VII ($R^7=H$) is first subjected to N-alkylation by treatment with a molar excess of the appropriate organic halide, namely a lower alkyl halide, lower alkenyl halide, propargyl halide, phenyl(lower)alkyl halide or amino(lower)alkyl halide, respectively, in an inert solvent in the presence of a proton acceptor. Suitable inert solvents include tetrahydrofuran, benzene, toluene and dimethylformamide. Suitable proton acceptors include sodium hydride, alkali metal carbonate and triethylamine. Preferred conditions for effecting this N-alkylation include the use of sodium hydride as a proton acceptor and tetrahydrofuran as an inert solvent. Although the optimum temperature and reaction time will vary depending on the reactants employed, the reaction is generally performed at the boiling point of the reaction mixture for a period of 30 minutes to 48 hours.

The lower alkyl halides, lower alkenyl halides, propargyl halide, phenyl(lower)-alkyl halides and aminoalkyl(lower)halides employed herein are either known, for exampe, ethyl bromide, allyl bromide and dimethylaminoethyl chloride, or they are prepared by known methods, usually by the treatment of the corresponding alcohols with a halogenating agent, for instance, thionyl chloride, see D. J. Collins and J. J. Hobbs, Aust. J. Chem., *20*, 1413 (1967) and R. B. Moffett, J. Org. Chem., *14*, 862 (1949).

In this manner, the corresponding N-alkylated derivatives of the above acid and ester derivatives of formula VII are obtained. Thereafter these derivatives are subjected to the amidation and reduction steps according to the conditions described hereinabove in this section, to afford the desired compounds of formula I in which R^7 is lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl, or amino(lower)alkyl.

Although the above sequence of steps for the conversion of the acid and ester intermediates of formula VII ($R^7=H$) to the above desired pyranoindoles is convenient and efficacious, a change in the order of the steps whereby the amides of formula VII ($R^7=H$) are treated with the appropriate organic halide according to the N-alkylation conditions described above, followed by reduction with a complex metal hydride, as described above, also affords the above desired compounds of formula I, in which R^7 is lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl or amino(lower)-alkyl described above, of the resulting corresponding amide derivative in which the indolic nitrogen is alkylated, also affords the above desired compounds of formula I, in which R^7 is lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl or amino-(lower)alkyl.

Furthermore, another change in the order of the steps for preparing the latter compounds of formula I is realized by N-alkylation, as described above, of the corresponding compounds of formula I in which R^7 is hydrogen, described above. In this case when the starting material employed is a pyranoindole or thiopyranoindole of formula I in which Y is —Alk—NR^8R^9 in which Alk is CH_2 or Alk^1CH_2 wherein Alk^1 is as defined in the first instance and R^8 is hydrogen and R^9 is hydrogen or lower alkyl, i.e., a primary or secondary amine function is present in the molecule in addition to the indolic nitrogen, it is expedient to use only one molar equivalent of the appropriate organic halide to avoid alkylation of the primary or secondary amine if so desired.

Another aspect of the present intermediates of formula VII relates to their conver-

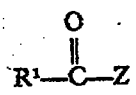
sion to compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as described in the first instance and Y is —Alk—NR^8R^9 in which Alk is CH_2 or Alk^1CH_2 wherein Alk^1 is as defined in the first instance and R^8 is hydrogen and R^9 is lower alkyl, i.e. secondary amines. When it is desired to prepare the latter compounds a modification involving the protection of the secondary amine with a benzyl group or other suitable protecting group, see J. F. McOmie, cited below, is especially convenient. For example, the aforementioned acid or ester intermediate of formula VII is reacted with an amine of formula HNR^8R^9 in which R^8 is benzyl and R^9 is lower alkyl according to the amidation step described above. The resulting amide is N-alkylated on the indolic nitrogen, if desired, and then reduced with a complex metal hydride according to the above procedures. Thereafter the benzyl group is removed by hydrogenolysis in the presence of a catalyst, preferably 10% palladium on carbon, to afford the desired secondary amine compounds of formula I.

Still another modification relates to a more general reduction of the above amides of formula VII in which Z is $CONR^8R^9$ or Alk^1—$CONR^8R^9$ wherein Alk^1, R^8 and R^9 are as defined in the first instance. In other words this modification is applicable to the reduction of tertiary, secondary and primary amides, described herein, and is a preferred modification for the reduction of the latter two. In practising this modification, the aforementioned amide of formula VII is treated with triethyloxonium fluoroborate or dimethyl sulfate, see H. Bredereck, *et al.*, Chem. Ber., *98*, 2754 (1965), in an inert solvent, for example, methylene dichloride, whereby the corresponding iminoether fluoroborate or methyl sulfate salt is obtained, respectively. Subsequent reduction of the salt thus obtained with a complex metal hydride, similar to the reduction described previously for the amides, yields the corresponding compounds of formula I. Alternatively, the above fluoroborate or methyl sulfate salt derived from a secondary or primary amide is decomposed by base treatment, for example, with 10% sodium hydroxide or triethylamine, to give the corresponding iminoether which is then reduced in a like manner to the desired compound of formula I.

When applying the aforementioned steps in the preparation of compounds of formula I in which R^6 is hydroxy or lower alkanoyloxy, it is preferable to use corresponding intermediates in which R^6 is benzyloxy followed by the appropriate transformations as noted previously to yield the desired compounds of formula I.

(b) Preparation and Conversion of Intermediates of Formula VII (Z=$CONR^8R^9$ and Alk^1—$CONR^8R^9$).

The intermediates of formula VII in which R^7 is hydrogen and Z is $CONR^8R^9$ and Alk^1—$CONR^8R^9$ wherein R^8, R^9 and Alk^1 are as defined in the first instance, described in the previous section, are also obtained directly by utilizing the appropriate starting materials of Formula II and α-, β-, γ- or δ-ketoamides of formula



in which R^1 is as defined above and Z is $CONR^8R^9$ or Alk^1—$CONR^8R^9$ in which Alk^1, R^8 and R^9 are as defined above. The ketoamides required for this condensation are either known, for example pyruvamide or α,α-dimethylacetoacetamide, or they are prepared by known methods, for instance, see "Rodd's Chemistry of the Carbon Compounds", cited above, Vol. 1d, pp. 226—274.

Thereafter these amides are converted by the reduction process, described above, to the compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in the first instance, R^7 is hydrogen and Y is —Alk—NR^8R^9 in which Alk is CH_2 or Alk^1—CH_2 wherein Alk^1 is as defined in the first instance and R^8 and R^9 are as defined in the first instance.

(c) Preparation and Conversion of Intermediates of Formula VII (Z=CH_2OCOR^{20} and Alk^1—CH_2OCOR^{20})

Intermediates of formula VII in which R^7 is hydrogen and Z is CH_2OCOR^{20} and Alk^1—CH_2OCOR^{20} in which Alk^1 and R^{20} is as defined in the first instance, are obtained when a starting material of formula II (R^7=H) is condensed with a ketoalcohol lower alkanoic acid ester of formula $R^1COCH_2OCOR^{20}$ or

R^1CO—Alk^1—CH_2OCOR^{20}

in which R^1, Alk^1 and R^{20} are as defined in the first instance in the presence of a suitable acid catalyst according to the conditions described above for the condensation (II + VI ⟶ VII). The ketoalcohol lower alkyl esters are either known, for example, acetonyl acetate or 5-acetoxy-pentan-2-one, or are prepared by known methods, for

instance, see "Rodd's Chemistry of the Carbon Compounds", cited above, Vol. 1d, pp. 49—54.

These intermediates of formula VII may then be utilized for the preparation of compounds of formula I of this invention in the following manner. The intermediate is hydrolyzed with an aqueous alcoholic solution of a suitable alkali, for example, sodium hydroxide in aqueous methanol to afford the corresponding primary alcohol. The primary alcohol is then oxidized to the corresponding aldehyde. Although a variety of methods are known for the oxidation of a primary alcohol to its corresponding aldehyde, see for example, "Rodd's Chemistry of the Carbon Compounds", cited above, Vol. 1c, pp. 4—10, we have found that the method of K. E. Pfitzner and J. G. Moffat, J. Am. Chem. Soc., *87*, 5670 (1965), using N,N-dicyclohexylcarbodiimide and dimethyl sulfoxide in the presence of a suitable acid, for example, trifluoroacetic acid, is both efficacious and convenient. Thereafter the aldehyde is reacted with an amine of formula HNR^8R^9 in which R^8 and R^9 are as defined in the first instance according to the method of K. N. Campbell, *et al.*, J. Amer. Chem. Soc., *70*, 3868 (1948) in the case when the amine used is ammonia or a primary amine or according to the method of N. J. Leonard and J. V. Paukstelis, J. Org. Chem., *28*, 1397 (1963) when the amine is a secondary amine to give the corresponding Schiff base or immonium salt, respectively. The product so obtained is reduced with sodium borohydride, see E. Schenker, Angew. Chem., *73*, 81 (1961), to yield compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in the first instance, R^7 is hydrogen and Y is

$$—Alk—NR^8R^9$$

in which Alk is CH_2 or $Alk^1—CH_2$ and R^8 and R^9 are as defined in the first instance.

Alternatively, the latter compounds of formula I are obtained by converting the above corresponding alcohol to a reactive intermediate such as the corresponding halide, mesylate or tosylate, which are then reacted with a two molar excess of an amine of formula HNR^8R^9 in which R^8 and R^9 are as defined in the first instance. Preferably this reaction is performed in a suitable inert solvent, for example, tetrahydrofuran, at the boiling point of the reaction mixture for a period of eight to 24 hours. In connection with alkylations of amines of formula HNR^8R^9 in which R^8 is hydrogen and R^9 is lower alkyl as disclosed herein, it is generally preferable to perform the alkylation with the corresponding N-benzyl derivative of said amine, i.e., an amine of formula HNR^8R^9 in which R^8 is benzyl and R^9 is lower alkyl. Thereafter, when all appropriate transformation have been performed, the N-benzyl group is removed by hydrogenolysis with a catalyst, preferably 10% palladium on carbon, to give the desired compounds of formula I.

Thereafter, and if desired, these latter compounds of formula I are converted to their corresponding derivatives in which R^7 lower alkyl, lower alkenyl, propargyl, phenyl(lower)allyl or amino(lower)alkyl by N-alkylation with one molar equivalent of the appropriate organic halide in the manner described for the N-alkylation in section (a).

Alternatively, the above aldehyde is oxidized with a suitable oxidizing agent to yield the corresponding acid intermediates of formula VII ($R^7 = H$) described in section (a). Although a variety of suitable oxidizing agents may be used for this purpose, for example, silver oxide, alkaline permanganate, hydrogen peroxide, we prefer to use silver oxide according to the method of M. Delepine and P. Bonnet, Compt. rend., *149*, 39 (1909).

Again alternatively, the above aldehyde is converted to its oxime which on reduction with a complex metal hydride yields the corresponding primary amine of formula I in which R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in the first instance, R^7 is hydrogen and Y is —Alk—NR^8R^9 in which Alk is CH_2 or $Alk^1—CH_2$ wherein Alk^1 is as defined in the first instance and R^8 and R^9 are hydrogen.

If desired these latter primary amine compounds of formula I may be N-alkylated on the indolic nitrogen in the manner described above with a molar equivalent of the appropriate organic halide to give the corresponding compounds of formula I in which R^7 is lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl or Alk—NR^8R^9 wherein Alk, R^8 and R^9 are as defined in the first instance.

In turn these latter compounds of formula I may be further N-alkylated on the nitrogen of the primary amine with the appropriate lower alkyl halide to the corresponding compounds of formula I in which Y is —Alk—NR^8R^9 wherein Alk is CH_2 or $Alk^1—CH_2$ wherein Alk^1 is as defined in the first instance and R^8 is hydrogen or lower alkyl and R^9 is lower alkyl (i.e. secondary or tertiary amines with respect to Y). In

this case depending on the particular derivative desired the N-alkylation is effected with one or two moles of the alkyl halide to give respectively the secondary (R^8 = H and R^9 = lower alkyl with respect to Y) or tertiary amine ($R^8 = R^9$ = lower alkyl with respect to Y). On the other hand the N-alkylation may be effected in two steps introducing a different alkyl group each time to afford the corresponding tertiary amine in which R^8 and R^9 are different lower alkyls with respect to Y.

When it is desired to prepare the above tertiary amine compounds in which R^8 or R^9 are either or both methyl, an alternative alkylation method comprises reacting the appropriate corresponding primary or secondary amine with an aqueous mixture of a substantial excess of formaldehyde and formic acid according to the conditions of the Eschweiler-Clarke reaction, see M. L. Moore, Organic Reactions, 5, 301 (1949), whereby N-methylation is effected.

Another N-alkylation method which is applied to the above primary and secondary amines involves acylation with a lower alkanoic anhydride or acid halide and subsequent reduction of the resulting amide.

Furthermore, the above primary amines are used to prepare compounds of formula I in which Y is —Alk—NR^8R^9 wherein Alk is CH_2 or Alk¹—CH_2 and R^8 and R^9 together with the nitrogen atom to which they are joined from a heterocyclic amine radical as defined in the first instance. When used in this manner the primary amines are subjected to known N-alkylation methods, for example, see method J in Moffett, cited above, with the appropriate α,ω-dibromides, for example, tetramethylene dibromide, pentamethylene dibromide, bis(2-chloroethyl)ether, bis(2-chloroethyl)-benzylamine followed by hydrogenation in the presence of 10% palladium on carbon to remove the protecting benzyl group, a bis(2-chloroethyl)lower alkylamine or a bis(2-chloroethyl)-N-[hydroxy(lower)alkyl]amine, to give the corresponding, desired compound of formula I wherein Y is an amino(lower)alkyl in which the amino portion thereof is pyrrolidino, piperidino, morpholino, piperazino, 4-(lower)alkyl-1-piperazinyl or 4-[hydroxy(lower)alkyl]-1-piperazinyl, respectively.

If during the above N-alkylations it is desired to protect primary or secondary amine functions that are present in the R^7 portion of compounds of formula I, such protection may be afforded by the use of appropriate protecting groups, for example, a benzyl group; see also, J. F. W. McOmie in "Advances in Organic Chemistry", Vol. 3, R. A. Raphael, *et al.*, Ed., Interscience Publishers, New York, 1963, pp. 191—294.

(d) Preparation and Conversion of Intermediates of Formula VII (Z = Alk²—L).

Intermediates of formula VII in which R^7 is hydrogen and Z is Alk²—L wherein Alk² and L are as defined in the first instance, are obtained when a starting material of formula II (R^7 = H) is condensed with a β,γ- or δ-haloketone of formula R^1CO—Alk²—L in which R^1, Alk² and L are as defined in the first instance in the presence of a suitable acid catalyst according to the conditions described above for the condensation (II + VI → VII). The haloketones are either known, for example, 4-chlorobutan-2-one, or they are prepared by known methods, for instance, see "Rodd's Chemistry of Carbon Compounds", cited above, Vol. 1 c, pp. 70—71 and "Methoden der Organischen Chemie", Houben-Weyl, E. Müller, Ed., Vol. V/3, Georg Thieme Verlag, Stuttgart, 1962, pp. 511—1076.

Thereafter these intermediates of formula VII are treated with a two molar excess of an amine of formula HNR^8R^9 in which R^8 and R^9 are as defined in the first instance to yield the compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6 and X are as described in the first instance, R^7 is hydrogen and Y is —Alk—NR^8R^9 in which Alk is Alk² as defined in the first instance and R^8 and R^9 are as defined in the first instance. Preferred conditions for this reaction include the use of a suitable inert solvent, for example, tetrahydrofuran, temperatures ranging from 40—100°C. or at the boiling point of the reaction mixture and a reaction time of from eight to 24 hours.

If desired the latter pyranoindoles and thiopyranoindoles may be N-alkylated on the indolic nitrogen with an appropriate lower alkyl halide or aminoalkyl halide according to the method described for the N-alkylation of the pyranoindoles and thiopyranoindoles in section (a).

(e) Preparation and Conversion of Intermediates of Formula VII (Z = AlkNR^8COR^{21})

Intermediates of formula VII in which R^7 is hydrogen and Z is AlkNR^8COR^{21} wherein Alk, R^8 and R^{21} are as defined in the first instance are readily obtained by the condensation (II + VI → VII) by using ketoamides of formula

$$R^1—\overset{\overset{O}{\|}}{C}—Alk—NR^8COR^{21}$$

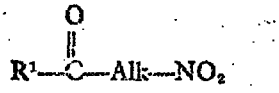
in which R^1, Alk, R^8 and R^{21} are as defined in the first instance together with the appropriate starting material of formula II (R^7=H).

The ketoamides used herein are either known, for example, formamidoacetone [A. Treibs and W. Sutter, Chem. Ber., *84*, 96 (1951)] and see [R. H. Wiley and O. H. Borum, J. Amer. Chem. Soc., *70*, 2005 (1948)] or they are prepared by known procedures, for example, see "Methoden der Organischen Chemie", cited above, Vol. XI/1, 1957, especially pp. 58—62, 285—289 and 508—509, and F. F. Blicke, Organic Reactions, *1*, 303 (1942).

Thereafter, reduction with a complex metal hydride and if desired N-alkylation of the indolic nitrogen as described in section (a) converts the instant intermediates of formula VII to pyranoindoles of formula I in which R^1, R^2, R^3, R^4, R^5, R^6, R^7, X are as defined in the first instance and Y is $AlkNR^8R^9$ in which Alk and R^8 are as defined in the first instance and R^9 is lower alkyl.

(f) Preparation and Conversion of Intermediates of Formula VII (Z=Alk—NO_2)

Intermediates of formula VII in which R^7 is hydrogen and Z is Alk—NO_2 wherein Alk is as defined in the first instance, are obtained by the condensation (II + VI → VII) when the starting materials of formula II (R^7=H) and appropriate α-, β-, γ-, and δ-nitroketones of formula



in which R^1 and Alk are as defined in the first instance are employed therein in the presence of a suitable acid catalyst. In this case trifluoroacetic acid is the preferred acid catalyst.

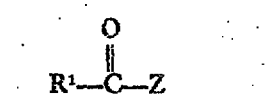
The nitroketones used herein are either known, for example, 1-nitro-2-propanone, N. Levy and C. W. Scaife, J. Chem. Soc., 1100, (1946) and 5-nitro-2-hexanone, H. Shechter, *et al.*, J. Amer. Chem. Soc., *74*, 3664 (1952) or they are prepared by known methods, for example, see Levy, and Scaife, cited above, Shechter, *et al.*, cited above, "Rodd's Chemistry of Carbon Compounds", cited above, Vol. 1c, pp. 71—72 and "Methoden der Organischen Chemie", cited above, Vol. X/1, 1971, p. 203.

Thereafter, these intermediates of formula VII are reduced with a complex metal hydride, preferably lithium aluminum hydride, to afford the pyranoindoles of formula I in which R^1, R^2, R^3, R^4, R^5, R^6 and X are so defined in the first instance, Y is hydrogen and Z is —Alk—NR^8R^9 in which Alk is defined in the first instance and R^8 and R^9 are hydrogen.

If desired the latter compounds may be N-alkylated according to the methods described in section (c) to give the compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined in the first instance and Y is Alk—NR^8R^9 in which Alk, R^8 and R^9 are as defined in the first instance.

(g) Preparation and Conversion of Intermediates of Formula VII (Z=lower alkyl or phenyl(lower)alkyl)

Intermediates of formula VII (Z=lower alkyl or phenyl(lower)alkyl, R^7 is hydrogen and R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in the first instance) are readily obtained by the condensation (II + VI → VII) by using the starting materials of formula II and the ketones of formula



in which R^1 is as defined in the first instance and Z is lower alkyl or phenyl(lower)-alkyl.

The ketones used herein are either available commercially, for example, acetone or phenylacetone, or they are prepared by conventional methods, for example, see P. Karrer, "Organic Chemistry", 2nd. ed., Elsevier Publishing Co., Inc., New York, 1946, pp. 149—169 and V. Migrdichian, "Organic Synthesis", Vol. 1, Reinhold Publishing Corp., New York, 1957, pp. 100—129.

These intermediates of formula VII are converted to the compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in the first instance, R^7 is —(Alk)—NR^8R^9 in which Alk, R^8 and R^9 are as defined in the first instance and Y is is lower alkyl or phenyl(lower)alkyl by N-alkylation of the indolic nitrogen with the

appropriate amino(lower)alkyl halide according to the method of N-alkylation described in section (a).

(h) Preparation of Compounds of Formula VII ($Z = Alk—NR^8R^9$) ≡ Compounds of Formula I ($Y = Alk—NR^8R^9$)

The above described starting materials of formula II in which R^2, R^3, R^4, R^5, R^6, R^7 and X^1 are as defined in the first instance are condensed in the presence of an acid catalyst with an aminoketone of formula $R^1CO—Alk—NR^8R^9$ in which R^1, Alk, R^8 and R^9 are as defined in the first instance to give directly the pyrano- and thiopyrano-indole derivatives of formula I of this invention.

The requisite aminoketones for this reaction are either known, for example, 1-dimethylamino-3-butanone, 1-methylamino-3-pentanone, see F. F. Blicke, cited above, or they may be prepared by known procedures, for example, see "Methoden der Organischen Chemie", cited above, Vol. XI/I, 1957, pp. 58—62, 285—289 and 508—509.

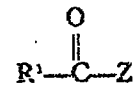
In practising this present condensation it is generally advantageous to utilize substantially equimolar amounts of the starting material of formula II and the aminoketone in the presence of an acid catalyst. In this particular condensation the amount of the aforementioned acid catalyst to employ ranges generally from about 1.01 to 100 molar equivalents with respect to the amount of aminoketone reactant, a range of from 1.05 to 10 molar equivalents being preferred. If more than one basic nitrogen is present in the reactants, for example, when R^8 and R^9 together with the nitrogen atom to which they are attached represent a piperazino radical, then additional acid catalyst is added to compensate for such basic nitrogens. Optionally, one may employ the acid addition salts of the aforementioned aminoketones and starting materials of formula II if R^7 is an amino(lower)alkyl radical, for example the hydrochloride or the sulfate salt. In this case the amount of acid catalyst may range from 0.01 to 100 molar equivalents, preferably 0.1 to 10 molar equivalents. Boron trifluoride is a preferred acid catalyst for the present condensation. The reaction may be performed conveniently and advantageously without a solvent, although a high boiling solvent, for example, toluene, o-xylene or isobutyl ether, may be used. When the solvent is omitted, it is desirable to heat the reactants to a melt and stir the melt in an inert atmosphere, for example, nitrogen or helium. Reaction time and temperature depends on the particular reactants employed and may be varied. The most convenient reaction time is from one-half to 48 hours, preferably one-half to four hours, and reaction temperatures from 20 to 200°C, preferably 60 to 140°C. The reaction in each individual case is performed preferably at the lowest temperature at which the reaction proceeds smoothly and expeditiously with a minimum of decomposition.

In the case where the starting material is one of formula II in which Y is —S—SO_3Na or —SO_3K, it is preferable to have at least one equivalent of water present in the reaction mixture. This water may be added directly to the reaction or it may be included as part of the acid catalyst. Examples of the latter instance would be when *p*-toluenesulfonic acid containing water of crystallization or concentrated hydrochloric acid are employed as the acid catalyst.

Finally, it is the intention to cover all changes and modifications of the embodiment of the invention herein chosen for the purpose of disclosure which are within the scope of the appended claims. Such changes and modifications include those variations which depend on well known interconversions of amines, amides, acids and esters or alternation of the order of the steps in the processes disclosed herein.

For example, the act of subjecting the corresponding derivative of the starting material of formula II in which the indolic nitrogen is alkylated with a lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl or amino(lower)alkyl, to condensation with an appropriate compound of formula VI according to the conditions of the key reaction taught in the present disclosure to yield the corresponding intermediate compound of formula VII in which the indolic nitrogen is so alkylated would not depart from the scope or spirit of this invention.

More specifically, exemplified, the compounds of formula I in which R^7 is lower alkyl are prepared conveniently and generally in good yields by using the starting material of formula II in which R^7 is lower alkyl and subjecting the starting material to treatment with the appropriate compound of formula



and subsequent conversions, if necessary, according to the teachings of the present disclosure.

The following examples illustrate further this invention. Examples 1 to 308, 488 to 673, 776—777, 779 and 783 to 837 are directed to intermediates for the compounds of formula I. Examples 309 to 487, 674—775, 778, 780—782 and 838—915 are directed to compounds of formula I.

EXAMPLE 1.

1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-ACETIC ACID (VII; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7 = H$, $X = O$ AND $Z = CH_2COOH$)

Ethyl acetoacetate (23.4 g., 0.18 moles) is added to a solution of the starting material of formula II, tryptophol (10.0 g., 0.06 moles), in 200 ml. of benzene. After standing for 10 minutes, *p*-toluenesulfonic acid (1.3 g.) and about 5 g. of hydrated alkali-aluminum silicate (Molecular Sieves No. 4) are added. The mixture is subjected to reflux for thirty minutes, 600 mg. more of *p*-toluenesulfonic acid is added and refluxing continued for 2½ hours. The molecular sieves are collected and the benzene solution washed successively with 5% sodium bicarbonate and water, dried over sodium sulfate, and evaporated under reduced pressure to dryness affording an oil. The oil is subjected to chromatography on silica gel. Elution with 5% ether in benzene yields the ester, 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid ethyl ester, as an oil, $\nu_{max}^{CHCl_3}$ 1715 cm^{-1}.

Hydrolysis of this ester to the title compound is effected as follows: The ester is dissolved in 230 ml. of methanol. To this is added 10 g. of KOH in 30 ml. of H_2O and the solution is allowed to stand at room temperature overnight. The methanol is evaporated, water added and the solution washed with benzene. The aqueous phase is acidified with 6N HCl, and extracted with benzene. This organic phase is washed with water, dried over sodium sulfate and evaporated to dryness to give an oil, which is crystallized from benzene containing a trace of petroleum ether to afford the title compound, m.p. 150—152°C., $\nu_{max}^{CHCl_3}$ 3325 and 1705 cm^{-1}.

An equivalent amount of methyl acetoacetate may replace ethyl acetoacetate in the procedure of this Example. In this case, 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-acetic acid methyl ester, m.p. 87—90°C. after recrystallization from benzene-hexane, is obtained as the ester.

An equivalent amount of propyl acetoacetate may replace ethyl acetoacetate in the procedure of this Example. In this case, 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetic acid propyl ester is obtained as the ester.

EXAMPLE 2.

1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-PROPIONIC ACID (VII; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7 = H$, $X = O$ AND $Z = CH_2CH_2COOH$)

A mixture of the starting material of formula II, tryptophol (500 mg.), levulinic acid (580 mg.), 75 ml. of benzene, 1.7 g. of phosphorus pentoxide and about 0.5 g. of diatomaceous earth (Celite; "Celite" is a registered Trade Mark) is stirred magnetically at room temperature for 15 minutes and then at 70°C. for 1½ hrs. The reaction mixture is filtered. The filtrate is washed three times with 5N NaOH; the combined aqueous phase is washed twice with ether and then rendered acidic with cold 50% HCl. The aqueous phase is extracted with chloroform. The chloroform extract is dried (Na_2SO_4) and evaporated to dryness. The residue is crystallized from ethyl acetate-petroleum ether to afford the title compound, m.p. 104—110°C., nmr ($CDCl_3$) δ 1.47 (3H), 21.8 (4H), 2.74 (2H), 3.96 (2H), 7.18 (4H), 7.85 (1H), 9.60 (1.H).

The above title compound is also obtained by following the procedure of Example 1 but replacing ethyl acetoacetate with an equivalent amount of ethyl levulinate. In this case 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-propionic acid ethyl ester, m.p. 116—118°C., $\nu_{max}^{CHCl_3}$ 1716 cm^{-1}, after crystallization from benzene-petroleum ether, is obtained as the ester prior to hydrolysis.

EXAMPLE 3.

1-METHYL-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]INDOLE-1-ACETIC ACID (VII; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7 = H$, $X = S$ AND $Z = CH_2COOH$)

Indole-3-ethanethiol (1.5 g.) and methyl acetoacetate are mixed with 50 ml. of benzene and the solution heated for 30 min. (bath temperature 70—80°C.). *p*-Toluenesulfonic acid (0.15 g.) is added and the reaction mixture is subjected to reflux and stirring for 12 hours. Water formed in the reaction mixture during this period is collected by a water separator. After cooling the benzene solution is washed with 10% solution of sodium bicarbonate, water, saturated brine and dried over sodium sulfate. Evaporation of the benzene solution yields the ester, 1-methyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole-1-acetic acid methyl ester as a semi-solid, $\nu_{max}^{CHCl_3}$ 1715 cm^{-1}.

This ester is then treated with aqueous alcoholic KOH in the manner described for the esters in Example 1 and 2 to afford the title compound, m.p. 147—149°C., nmr ($CDCl_3$) δ 1.86 (S, 3H), 306 and 812 (6H), 7.35 (multiplet, 4H), 8.71 (1H), 10.31 (1H), after recrystallization from benzene-hexane.

The procedures of Examples 1, or 3 are followed to prepare other compounds of formula VII in which R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in the first instance, R^7 is hydrogen and Z is $COOR^{19}$ or $Alk^1—COOR^{19}$ wherein R^{19} and Alk^1 are as defined in the first instance. Examples of such compounds of formula VII are listed in Tables I and II. In each of these examples an equivalent amount of the starting material of formula II listed therein is used instead of the starting material of formula II described in the procedures of Examples 1 and 3. Note that in each of these examples the ester obtained prior to hydrolysis is a corresponding ester compound of formula VII.

Similarly, the procedure of Example 2 is used to prepare the products listed in Tables I and II. In this case an equivalent amount of the starting material of formula II, listed therein, is used instead of the starting material of formula II described in Example 2 and an equivalent amount of the corresponding ketoacid of formula VI is used instead of the ketoester of formula VI listed therein.

TABLE I

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $R^1—C(=O)—Alk^1—COOR^{10}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	$Alk^1—CO$	R^{10}	PREFIX//SUFFIX
4	H	H	H	H	H	O	CH_3	CO	C_2H_5	1-methyl//carboxylic acid
5	CH_3	H	H	H	H	O	C_2H_5	CO	C_2H_5	1-ethyl-3-methyl//carboxylic acid
6	n-C_3H_7	H	H	H	5-CH_3	O	n-C_3H_7	CO	CH_3	1,3-diisopropyl-6-methyl//carboxylic acid
7	CH_3	CH_3	H	H	5-OH	O	CH_3	CO	CH_3	1,3,3-trimethyl-6-hydroxy//carboxylic acid
8	H	H	H	H	7-C_2H_5	O	n-C_3H_7	CO	CH_3	8-ethyl-1-propyl//carboxylic acid
9	H	H	i-C_3H_7	H	H	O		CO	CH_3	1-cyclopropyl-4-isopropyl//carboxylic acid
10	CH_3	CH_3	C_2H_5	C_2H_5	H	O		CO	CH_3	1-cyclopentyl-4,4-diethyl-3,3-dimethyl//carboxylic acid
11	H	H	CH_3	H	H	O	CH_3	CH_2CO	C_2H_5	1,4-dimethyl//acetic acid
12	H	H	H	H	H	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl//acetic acid, m.p. 137—140°C.
13	H	H	H	H	H	O	n-C_3H_7	CH_2CO	C_2H_5	1-propyl//acetic acid, m.p. 148—151°C.
14	H	H	H	H	H	O	i-C_3H_7	CH_2CO	C_2H_5	1-isopropyl//acetic acid, m.p. 150—152°C.
15	CH_3	H	H	H	H	O	n-C_3H_7	CH_2CO	C_2H_5	3-methyl-1-propyl//acetic acid; m.p. 75—80°C. (Isomer A), m.p. 146—148°C. (Isomer B).
16	CH_3	H	C_2H_5	CH_3	H	O	C_2H_5	CH_2CO	C_2H_5	1,4-diethyl-3-methyl//acetic acid

TABLE I—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $R^1—C(=O)—Alk^1—COOR^{1'}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	$Alk^1—CO$	$R^{1'}$	PREFIX//SUFFIX
17	H	H	H	H	H	O	CH_3	$CH(CH_3)CO$	C_2H_5	α,1-dimethyl//acetic acid; m.p. 154—156°C. (Isomer A), m.p. 163—165°C. (Isomer B).
18	H	H	H	H	H	O		$C(CH_3)_2CO$	C_2H_5	1-cyclohexyl-α,α-dimethyl// acetic acid
19	H	H	H	H	H	O	t-C_4H_9	CH_2CO	C_2H_5	1-t-butyl//acetic acid, m.p. 210—212°C.
20	H	H	H	H	H	O	n-C_4H_9	CH_2CO	C_2H_5	1-butyl//acetic acid, m.p. 124—127°C.
21	H	H	H	H	7-CH_3	O	n-C_3H_7	CH_2CO	C_2H_5	8-methyl-1-propyl//acetic acid, m.p. 127—128°C.
22	H	H	H	H	5-Br	O	C_2H_5	CH_2CO	C_2H_5	6-bromo-1-ethyl//acetic acid, m.p. 182—184°C.
23	H	H	H	H	5-OCH_3	O	CH_3	CH_2CO	CH_3	6-methoxy-1-methyl//acetic acid, m.p. 142—143°C.
24	H	H	H	H	5-$OCOCH_3$	O	CH_3	CH_2CO	C_2H_5	6-acetoxy-1-methyl//acetic acid, m.p. 142—143°C.
25	H	H	H	H	5-benzyoloxy	O	CH_3	CH_2CO	C_2H_5	6-benzyloxy-1-methyl//acetic acid, m.p. 163.5°C.
26	H	H	H	H	4-CH_3	O	n-C_3H_7	CH_2CO	C_2H_5	5-methyl-1-propyl//acetic acid, m.p. 177—178°C.
27	H	H	H	H	6-CH_3	O	n-C_3H_7	CH_2CO	C_2H_5	7-methyl-1-propyl//acetic acid, m.p. 157—158°C.
28	H	H	H	H	5-NO_2	O	n-C_3H_7	CH_2CO	C_2H_5	6-nitro-1-propyl//acetic acid, m.p. 119—120°C.

TABLE I—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $R^1—C(=O)—Alk^3—COOR^{10}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	$Alk^3—CO$	R^{10}	PREFIX//SUFFIX
29	H	H	CH_3	CH_3	H	O	n-C_3H_7	CH_2CO	C_2H_5	4,4-dimethyl-1-propyl//acetic acid, m.p. 184—185°C.
30	CH_3	CH_3	H	H	5-OC_2H_5	O		$CH(C_2H_5)CO$	C_2H_5	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy//acetic acid
31	CH_3	CH_3	C_2H_5	C_2H_5	6-C_2H_5	O		$C(CH_3)_2CO$	C_2H_5	1-cyclohexyl-α,α,3,3-tetramethyl-4,4,7-triethyl//acetic acid
32	CH_3	H	n-C_3H_7	n-C_3H_7	4-n-C_3H_7	O	C_2H_5	$CH(CH_3)CO$	C_2H_5	α,3-dimethyl-1-ethyl-4,4,5-tripropyl//acetic acid
33	H	H	H	H	H	O	n-C_3H_7	$C(CH_3)_2CO$	C_2H_5	α,α-dimethyl-1-propyl//acetic acid
34	C_2H_5	C_2H_5	C_2H_5	C_2H_5	4-C_2H_5	O	t-C_4H_9	$C(i\text{-}C_3H_7)_2CO$	C_2H_5	1-t-butyl-α,α-diisopropyl-3,3,4,4,5-pentaethyl//acetic acid
35	H	H	H	H	4-I	O	i-C_3H_7	CH_2CH_2CO	C_2H_5	5-iodo-1-isopropyl//propionic acid
36	CH_3	CH_3	CH_3	CH_3	7-$OCCH_3$ (O)	O	C_2H_5	$CH_2CH(CH_3)CO$	C_2H_5	8-acetoxy-1-ethyl-α,3,3,4,4-pentamethyl//propionic acid
37	H	H	H	H	6-OH	O	n-C_3H_7	$CH_2C(C_2H_5)_2CO$	C_2H_5	β,β-diethyl-7-hydroxy-1-propyl//propionic acid
38	CH_3	H	H	H	7-NO_2	O		$CH(n\text{-}C_3H_7)CH_2CO$	C_2H_5	1-cyclobutyl-3-methyl-8-nitro-α-propyl//propionic acid
39	H	H	CH_3	H	5-CH_3	O		$C(CH_3)_2C(CH_3)_2CO$	C_2H_5	1-cyclopropyl-$\alpha,\alpha,\beta,\beta$,4,6-hexamethyl//propionic acid
40	H	H	H	H	H	O	CH_3	$CH_2C(n\text{-}C_3H_7)_2CO$	C_2H_5	1,3-dimethyl-α,α-dipropyl//propionic acid

TABLE I—continued.

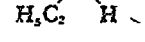
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $R^1—C(=O)—Alk^1—COOR^{10}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	$Alk^1—CO$	R^{10}	PREFIX//SUFFIX
41	CH_3	H	C_2H_5	C_2H_5	H	O	C_2H_5	$CH(CH_3)C(CH_3)_2CO$	CH_3	$\alpha,\alpha,\beta,3$-tetramethyl-1,4,4-triethyl//propionic acid
42	H	H	CH_3	CH_3	H	O	C_2H_5	$C(CH_3)_2CH_2CO$	CH_3	1-ethyl-$\beta,\beta,4,4$-tetramethyl//propionic acid
43	H	H	n-C_3H_7	H	4-OCC_2H_5 (=O)	O		$C(C_2H_5)_2C(C_2H_5)CO$	CH_3	1-cyclopentyl-5-propionoxy-4-propyl-α,β,β-triethyl//propionic acid
44	n-C_3H_7	H	H	H	4-OCH_3	O	n-C_3H_7	$CH_2CH(CH_3)CO$	C_2H_5	1,3-dipropyl-5-methoxy-α-methyl//propionic acid
45	C_2H_5	H	H	H	5-NO_2	O	CH_3	$C(C_2H_5)_2C(C_2H_5)_2CO$	C_2H_5	1-methyl-6-nitro-$\alpha,\alpha,\beta,\beta,3$-pentaethyl//propionic acid
46	C_2H_5	C_2H_5	H	H	4-C_2H_5	O	n-C_3H_7	$CH(n\text{-}C_3H_7)CH_2CO$	CH_3	β,1-dipropyl-3,3,5-triethyl//propionic acid
47	H	H	H	H	6-OC_2H_5	O		$CH(C_2H_5)CH(C_2H_5)CO$	C_2H_5	1-cyclopropyl-α,β-diethyl-7-ethoxy//propionic acid
48	H	H	H	H	H	O	CH_3	$CH_2CH_2CH_2CO$	C_2H_5	1-methyl//butyric acid, m.p. 132—135°C.
49	CH_3	H	H	H	H	O	C_2H_5	$CH(CH_3)CH_2CH_2CO$	C_2H_5	γ,3-dimethyl-1-ethyl//butyric acid
50	CH_3	CH_3	H	H	H	O	n-C_3H_7	$C(C_2H_5)_2CH_2CH_2CO$	C_2H_5	γ,γ-diethyl-3,3-dimethyl-1-propyl//butyric acid
51	CH_3	CH_3	n-C_3H_7	H	H	O		$C(n\text{-}C_3H_7)_2CH(n\text{-}C_3H_7)CH_2CO$	C_2H_5	1-cyclobutyl-3,3-dimethyl-$\beta,\gamma,\gamma,4$-tetrapropyl//butyric acid
52	H	H	C_2H_5	C_2H_5	6-Cl	O	CH_3	$[C(C_2H_5)_2]_2—CCO$ 	C_2H_5	7-chloro-$\alpha,\beta,\beta,\gamma,\gamma,4,4$-heptaethyl-1-methyl//butyric acid

TABLE I—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Alk^1—CO	R^{10}	PREFIX//SUFFIX
53	H	H	CH_3	H	4-CH_3	O	C_2H_5	$[C(CH_3)_2]_3CO$	C_2H_5	1-ethyl-$\alpha,\alpha,\beta,\beta,\gamma,\gamma,4,4,5$-octamethyl//butyric acid
54	C_2H_5	C_2H_5	C_2H_5	H	5-$OCCH_3$ (O)	O	n-C_3H_7	$CH(C_2H_5)[C(C_2H_5)]_2CO$	C_2H_5	6-acetoxy-$\alpha,\alpha,\beta,\beta,\gamma,3,3,4$-octaethyl-1-propyl//butyric acid
55	H	H	CH_3	CH_3	7-OCH_3	O	□	$CH_2[C(CH_3)_2]_2CO$	C_2H_5	1-cyclobutyl-$\alpha,\alpha,\beta,\beta,4,4$-hexamethyl-8-methoxy//butyric acid
56	H	H	H	H	4-Br	O	⬠	$CH_2CH(CH_3)C(CH_3)_2CO$	C_2H_5	5-bromo-1-cyclopentyl-α,α,β-trimethyl//butyric acid
57	CH_3	CH_3	H	H	4-n-C_3H_7	O	△	$CH_2CH_2C(C_2H_5)_2CO$	C_2H_5	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-5-propyl//butyric acid
58	H	H	H	H	7-C_2H_5	O	C_2H_5	$CH_2CH_2CH(CH_3)CO$	C_2H_5	1,8-diethyl-α-methyl//butyric acid
59	CH_3	CH_3	CH_3	H	5-F	O	n-C_4H_9	$[CH(CH_3)]_3CO$	C_2H_5	1-butyl-6-fluoro-$\alpha,\beta,\gamma,3,3,4$-hexamethyl//butyric acid
60	CH_3	CH_3	H	H	4-CH_3	O	n-C_3H_7	$CH(C_2H_5)CH_2CH(C_2H_5)CO$	C_2H_5	α,γ-diethyl-1-propyl-3,3,5-trimethyl//butyric acid
61	C_2H_5	H	H	H	6-NO_2	O	n-C_4H_9	$[C(CH_3)_2]_3CO$	C_2H_5	1-butyl-3-ethyl-7-nitro-α,β,γ-trimethyl//butyric acid
62	CH_3	CH_3	H	H	4-n-C_3H_7	O	n-C_3H_7	$CH_2[CH(C_2H_5)]_2CO$	C_2H_5	α,β-diethyl-3,3-dimethyl-1,5-dipropyl//butyric acid
63	H	H	H	H	7-OH	O	C_2H_5	$C(CH_3)_2CH_2C(CH_3)_2CO$	C_2H_5	1-ethyl-8-hydroxy-$\alpha,\alpha,\gamma,\gamma$-tetramethyl//butyric acid
64	CH_3	H	CH_3	H	4-OC_2H_5	O	C_2H_5	$[C(CH_3)_2]_2CO$	C_2H_5	5-ethoxy-1-ethyl-$\alpha,\alpha,\beta,\beta,\gamma,\gamma,3,4$-octomethyl//butyric acid

TABLE I—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $R^1—C(=O)—Alk^1—COOR^{1a}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	$Alk^1—CO$	R^{1a}	PREFIX//SUFFIX
64a	H	H	H	H	4-CH_3	O	CH_3	CH_2CO	C_2H_5	1,5-dimethyl//acetic acid, m.p. 150—152°C.
64b	H	H	H	H	4-Cl	O	CH_3	CH_2CO	CH_3	5-chloro-1-methyl//acetic acid, m.p. 183—184°C.

TABLE II

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI O ‖ R^1—C--Alk^2—$COOR^{19}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIO-PYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Alk^2—CO	R^{19}	PREFIX//SUFFIX
65	H	H	H	H	H	S	CH_3	CO	C_2H_5	1-methyl//carboxylic acid
66	CH_3	H	H	H	H	S	C_2H_5	CO	C_2H_5	1-ethyl-3-methyl//carboxylic acid
67	i-C_3H_7	H	H	H	5-CH_3	S	i-C_3H_7	CO	CH_3	1,3-diisopropyl-6-methyl//carboxylic acid
68	CH_3	CH_3	H	H	5-OH	S	CH_3	CO	CH_3	1,3,3-trimethyl-6-hydroxy-1-(1-propyl)//carboxylic acid
69	H	H	H	H	7-C_2H_5	S	n-C_3H_7	CO	CH_3	8-ethyl-1-propyl//carboxylic acid
70	H	H	i-C_3H_7	H	H	S		CO	CH_3	1-cyclopropyl-4-isopropyl//carboxylic acid
71	CH_3	CH_3	C_2H_5	C_2H_5	H	S		CO	CH_3	1-cyclopentyl-4,4,-diethyl-3,3-dimethyl//carboxylic acid
72	H	H	CH_3	H	H	S	CH_3	CH_2CO	C_2H_5	1,4-dimethyl//acetic acid
73	H	H	H	H	H	S	C_2H_5	CH_2CO	C_2H_5	1-ethyl//acetic acid, m.p. 138°C.
74	H	H	H	H	H	S	n-C_3H_7	CH_2CO	C_2H_5	1-propyl//acetic acid, m.p. 127—129°C.
75	H	H	H	H	H	S	i-C_3H_7	CH_2CO	C_2H_5	1-isopropyl//acetic acid
76	CH_3	H	H	H	H	S	n-C_3H_7	CH_2CO	C_2H_5	3-methyl-1-propyl//acetic acid
77	CH_3	H	C_2H_5	CH_3	H	S	C_2H_5	CH_2CO	C_2H_5	1,4-diethyl-3-methyl//acetic acid
78	H	H	H	H	H	S	CH_3	$CH(CH_3)CO$	C_2H_5	α,1-dimethyl//acetic acid
79	H	H	H	H	H	S		$C(CH_3)_2CO$	C_2H_5	1-cyclohexyl-α,α-dimethyl//acetic acid
80	H	H	H	H	H	S	t-C_4H_9	CH_2CO	C_2H_5	1-t-butyl//acetic acid

TABLE II—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI 			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIO-PYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^3	R^5	R^6	R^7	R^8	X	R^1	Alk^1—CO	R^{10}	PREFIX//SUFFIX
81	H	H	H	H	H	S	n-C_4H_9	CH_2CO	C_2H_5	1-butyl//acetic acid
82	H	H	H	H	7-CH_3	S	n-C_3H_7	CH_2CO	C_2H_5	8-methyl-1-propyl//acetic acid
83	H	H	H	H	5-Br	S	n-C_3H_7	CH_2CO	C_2H_5	6-bromo-1-propyl//acetic acid
84	H	H	H	H	5-OCH_3	S	CH_3	CH_2CO	CH_3	6-methoxy-1-methyl//acetic acid
85	H	H	H	H	5-$OCOCH_3$	S	CH_3	CH_2CO	C_2H_5	6-acetoxy-1-methyl//acetic acid
86	H	H	H	H	5-benzyloxy	S	CH_3	CH_2CO	C_2H_5	6-benzyloxy-1-methyl//acetic acid
87	H	H	H	H	4-CH_3	S	n-C_3H_7	CH_2CO	C_2H_5	5-methyl-1-propyl//acetic acid
88	H	H	H	H	6-CH_3	S	n-C_3H_7	CH_2CO	C_2H_5	7-methyl-1-propyl//acetic acid
89	H	H	H	H	7-F	S	CH_3	$C(C_2H_5)_2CO$	C_2H_5	α,α-diethyl-8-fluoro-1-methyl//acetic acid
90	CH_3	CH_3	H	H	5-Cl	S	n-C_3H_7	$CH(i\text{-}C_3H_7)CO$	C_2H_5	6-chloro-3,3-dimethyl-α-isopropyl-1-propyl//acetic acid
91	CH_3	CH_3	H	H	5-OC_2H_5	S		$CH(C_2H_5)CO$	C_2H_5	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy//acetic acid
92	CH_3	CH_3	C_2H_5	C_2H_5	6-C_2H_5	S		$C(CH_3)_2CO$	C_2H_5	1-cyclohexyl-α,α,3,3-tetramethyl-4,4,7-triethyl//acetic acid
93	CH_3	H	n-C_3H_7	n-C_3H_7	4-n-C_3H_7	S	C_2H_5	$CH(CH_3)CO$	C_2H_5	α,3-dimethyl-1-ethyl-4,4,5-tripropyl//acetic acid
94	H	H	H	H	H	S	n-C_3H_7	$C(CH_3)_2CO$	C_2H_5	α,α-dimethyl-1-propyl//acetic acid
95	C_2H_5	C_2H_5	C_2H_5	C_2H_5	4-C_2H_5	S	t-C_4H_9	$C(i\text{-}C_3H_7)_2CO$	C_2H_5	1-t-butyl-α,α-diisopropyl-3,3,4,4,5-pentaethyl//acetic acid
96	H	H	H	H	H	S	CH_3	CH_2CH_2CO	C_2H_5	1-methyl//propionic acid

TABLE II—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $R^1—C(=O)—Alk^1—COOR^{10}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIO-PYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	$Alk^1—CO$	R^{10}	PREFIX//SUFFIX
97	CH_3	CH_3	CH_3	CH_3	7-$OCCH_3$ (=O)	S	C_2H_5	$CH_2CH(CH_3)CO$	C_2H_5	8-acetoxy-1-ethyl-α,3,3,4,4-pentamethyl//propionic acid
98	H	H	H	H	6-OH	S	n-C_3H_7	$CH_2C(C_2H_5)_2CO$	C_2H_5	β,β-diethyl-7-hydroxy-1-propyl//propionic acid
99	CH_3	H	H	H	7-NO_2	S	□	$CH(n\text{-}C_3H_7)CH_2CO$	C_2H_5	1-cyclobutyl-3-methyl-8-nitro-α-propyl//propionic acid
100	H	H	CH_3	H	5-CH_3	S	△	$C(CH_3)_2C(CH_3)_2CO$	C_2H_5	1-cyclopropyl-α,γ,β,β,4,6-hexamethyl//propionic acid
101	CH_3	H	H	H	H	S	CH_3	$CH_2C(n\text{-}C_3H_7)_2CO$	C_2H_5	1,3-dimethyl-α,α-dipropyl//propionic acid
102	CH_3	H	C_2H_5	C_2H_5	H	S	C_2H_5	$CH(CH_3)C(CH_3)_2CO$	CH_3	1,4,4-triethyl-α,α,β,3-tetramethyl//propionic acid
103	H	H	CH_3	CH_3	H	S	C_2H_5	$C(CH_3)_2CH_2CO$	CH_3	1-ethyl-β,β,4,4-tetramethyl//propionic acid
104	H	H	n-C_3H_7	H	4-OCC_2H_5 (=O)	S	⬠	$C(C_2H_5)_2C(C_2H_5)CO$	CH_3	1-cyclopentyl-5-propionoxy-4-propyl-α,β,β-triethyl//propionic acid
105	n-C_3H_7	H	H	H	4-OCH_3	S	n-C_3H_7	$CH_2CH(CH_3)CO$	C_2H_5	1,3-dipropyl-5-methoxy-α-methyl//propionic acid
106	C_2H_5	H	H	H	5-NO_2	S	CH_3	$C(C_2H_5)_2C(C_2H_5)_2CO$	C_2H_5	1-methyl-6-nitro-α,α,β,β,3-pentaethyl//propionic acid
107	C_2H_5	C_2H_5	H	H	4-C_2H_5	S	n-C_3H_7	$CH(n\text{-}C_3H_7)CH_2CO$	CH_3	β,1-dipropyl-3,3,5-triethyl//propionic acid

TABLE II—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $R^1—C(=O)—Alk^1—COOR^{19}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIO-PYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	$Alk^1—CO$	R^{19}	PREFIX//SUFFIX
108	H	H	H	H	6-OC_2H_5	S		$CH(C_2H_5)CH(C_2H_5)CO$	C_2H_5	1-cyclopropyl-α,β-diethyl-7-ethoxy//propionic acid
109	H	H	H	H	H	S	CH_3	$CH_2CH_2CH_2CO$	C_2H_5	1-methyl//butyric acid
110	CH_3	H	H	H	H	S	C_2H_5	$CH(CH_3)CH_2CH_2CO$	C_2H_5	γ,3-dimethyl-1-ethyl//butyric acid
111	CH_3	CH_3	H	H	H	S	n-C_3H_7	$C(C_2H_5)_2CH_2CH_2CO$	C_2H_5	γ,γ-diethyl-3,3-dimethyl-1-propyl//butyric acid
112	CH_3	CH_3	n-C_3H_7	H	H	S		$C(n\text{-}C_3H_7)_2CH(n\text{-}C_3H_7)CH_2CO$	C_2H_5	1-cyclobutyl-3,3-dimethyl-$\beta,\gamma,\gamma,4$-tetrapropyl//butyric acid
113	H	H	C_2H_5	C_2H_5	6-Cl	S	CH_3	$[C(C_2H_5)_2]_2CH(C_2H_5)CO$	C_2H_5	7-chloro-$\alpha,\beta,\beta,\gamma,\gamma,\gamma,4,4$-heptaethyl-1-methyl//butyric acid
114	H	H	CH_3	H	4-CH_2-O-C(=O)-CH_3	S	C_2H_5	$[C(CH_3)_2]_3CO$	C_2H_5	1-ethyl-$\alpha,\alpha,\beta,\beta,\gamma,\gamma,\gamma,4,5$-octamethyl//butyric acid
115	C_2H_5	C_2H_5	C_2H_5	H	5-O-C(=O)-CH_3	S	n-C_3H_7	$CH(C_2H_5)[C(C_2H_5)_2]_2CO$	C_2H_5	6-acetoxy-$\alpha,\alpha,\beta,\beta,\gamma,\gamma,3,3,4$-octaethyl-1-propyl//butyric acid
116	H	H	CH_3	CH_3	7-OCH_3	S		$CH_2[C(CH_3)_2]_2CO$	C_2H_5	1-cyclobutyl-$\alpha,\alpha,\beta,\beta,4,4$-hexamethyl-8-methoxy//butyric acid
117	H	H	H	H	4-Br	S		$CH_2CH(CH_3)C(CH_3)_2CO$	C_2H_5	5-bromo-1-cyclopentyl-α,α,β-trimethyl//butyric acid
118	CH_3	CH_3	H	H	4-n-C_3H_7	S		$CH_2CH_2C(C_2H_5)_2CO$	C_2H_5	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-5-propyl//butyric acid
119	H	H	H	H	7-C_2H_5	S	C_2H_5	$CH_2CH_2CH(CH_3)CO$	C_2H_5	1,8-diethyl-α-methyl//butyric acid
120	CH_3	CH_3	CH_3	H	5-F	S	n-C_4H_9	$[CH(CH_3)]_3CO$	C_2H_5	1-butyl-6-fluoro-$\alpha,\beta,\gamma,3,3,4$-hexamethyl//butyric acid

TABLE II—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $R^1-\overset{O}{\overset{\|}{C}}-Alk^1-COOR^{1'}$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Alk^1—CO	$R^{1'}$	PREFIX//SUFFIX
121	CH_3	CH_3	H	H	4-CH_3	S	n-C_3H_7	$CH(C_2H_5)CH_2CH(C_2H_5)CO$	C_2H_5	α,γ-diethyl-1-propyl-3,3,5-trimethyl//butyric acid
122	C_2H_5	H	H	H	6-NO_2	S	n-C_4H_9	$[C(CH_3)_2]_2CO$	C_2H_5	1-butyl-3-ethyl-7-nitro-α,β,γ-trimethyl//butyric acid
123	CH_3	CH_3	H	H	4-n-C_3H_7	S	n-C_3H_7	$CH_2[CH(C_2H_5)]_2CO$	C_2H_5	α,β-diethyl-3,3-dimethyl-1,5-dipropyl//butyric acid
124	H	H	H	H	7-OH	S	C_2H_5	$C(CH_3)_2CH_2C(CH_3)_2CO$	C_2H_5	1-ethyl-δ-hydroxy-α,α,γ,γ-tetramethyl//butyric acid
125	CH_3	H	CH_3	H	4-OC_2H_5	S	C_2H_5	$[C(CH_3)_2]_3CO$	C_2H_5	5-ethoxy-1-ethyl-α,α,β,β,γ,γ,3,4-octomethyl//butyric acid

EXAMPLE 126.

N,N,1-TRIMETHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-ACETAMIDE [VII; $R^1=CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7=H$, $X=O$ AND $Z=CH_2CON(CH_3)_2$]

To a stirred solution of 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid (15 g, 0.061 mole), prepared as described in Example 1, in dry tetrahydrofuran (300 ml), cooled to −5°C., is added triethylamine (18.5 g, 0.183 mole) followed by ethyl chloroformate (16.6 g, 0.153 mole). The mixture is stirred at −5°C. for 2 hrs. This mixture, which now contains the mixed anhydride of the above starting material, is added dropwise to a cooled 40% aqueous solution of the amine, dimethylamine (225 ml). The resulting mixture is stirred at room temperature for one-half hour. Most of the tetrahydrofuran is evaporated, and the residue partitioned between chloroform and water. The organic phase is washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The residue is subjected to chromatography on silica gel. Elution with 20% ethyl acetate in benzene, followed by

crystallization of the eluate from ethyl acetate affords the title compound, m.p. 149—151°C., $\nu_{max}^{CHCl_3}$ 3375, 1634 cm^{-1}.

In the same manner but replacing the 40% aqueous solution of dimethylamine with an equivalent amount of ammonium hydroxide (concentrated), methylamine (30% aqueous solution), n-hexylamine (20% aqueous solution), diethylamine (30% aqueous solution), isopropylamine (40% aqueous solution), ethylamine (70% aqueous solution), pyrrolidine (50% aqueous solution), piperidine, morpholine, N-methylpiperazine,

1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide, m.p. 158—160°C.,

N,1-dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide, m.p. 138—140°C.,

N-hexyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide,

N,N-diethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide, m.p. 99°C., $\nu_{max}^{CHCl_3}$ 3350, 1620 cm^{-1},

N-isopropyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide, m.p. 151—153°C.,

N-ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide, m.p. 152—153°C.,

1-[(1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl]pyrrolidine, m.p. 119—120°C.,

1-[(1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl]piperidine, m.p. 148—149°C.,

1-[(1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl]morpholine, m.p. 141—142°C., and

1-methyl-4-[(1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-yl)acetyl]piperazine, are obtained respectively.

By following the procedure of Example 126 but using as starting material an equivalent amount of one of the acid compounds of formula VII, described in Examples 2 to 125, instead of 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid, and using an equivalent amount of an appropriate amine such as ammonia or a primary or secondary amine described in Example 126, then the corresponding amide compound of formula VII is obtained. Examples of such amides are listed as products in Tables III, IV, V and VI together with the appropriate starting material and amine used for the preparation of the amide. In each case the starting material is noted by the example in which it is prepared.

TABLE III

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
127	2	CH_3NH_2	N,1-dimethyl//propionamide, m.p. 149—150°C.
128	2	NH_3	1-methyl//propionamide
129	2	$(CH_3)_2NH$	N,N,1-trimethyl//propionamide
130	2	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//propionamide
131	2	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//propionamide
132	4	CH_3NH_2	N,1-dimethyl//carboxamide
133	4	NH_3	1-methyl//carboxamide, m.p. 188—189°C.
134	4	$(CH_3)_2NH$	N,N,1-trimethyl//carboxamide
135	4	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//carboxamide
136	4	$C_2H_5NH_2$	N-ethyl-1-methyl//carboxamide
137	5	CH_3NH_2	N,3-dimethyl-1-ethyl//carboxamide
138	9	$(CH_3)_2NH$	1-cyclopropyl-N,N-dimethyl-4-isopropyl//carboxamide
139	11	$(CH_3)_2NH$	N,N,1,4-tetramethyl//acetamide
140	12	CH_3NH_2	1-ethyl-N-methyl//acetamide
141	12	NH_3	1-ethyl//acetamide
142	12	$(CH_3)_2NH$	N,N-dimethyl-1-ethyl//acetamide
143	12	$n\text{-}C_{16}H_{13}NH_2$	1-ethyl-N-hexyl//acetamide
144	12	$(C_2H_5)_2NH$	N,N,1-triethyl//acetamide

TABLE III—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
145	13	CH_3NH_2	N-methyl-1-propyl//acetamide
146	13	NH_3	1-propyl//acetamide
147	13	$(CH_3)_2NH$	N,N-dimethyl-1-propyl//acetamide, m.p. 159—162°C.
148	13	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-propyl//acetamide
149	13	$(C_2H_5)_2NH$	N,N-diethyl-1-propyl//acetamide
150	14	CH_3NH_2	1-isopropyl-N-methyl//acetamide
151	14	NH_3	1-isopropyl//acetamide
152	14	$(C_2H_5)_2NH$	N,N-diethyl-1-isopropyl//acetamide
153	15	CH_3NH_2	N,3-dimethyl-1-propyl//acetamide
154	15	$(CH_3)_2NH$	1-propyl-N,N,3-trimethyl//acetamide
155	15	$n\text{-}C_6H_{13}NH_2$	n-hexyl-3-methyl-1-propyl//acetamide
156	15	$(C_2H_5)_2NH$	N,N-diethyl-3-methyl-1-propyl//acetamide
157	17	CH_3NH_2	N,α,1-trimethyl//acetamide
158	17	NH_3	α,1-dimethyl//acetamide
159	17	$(CH_3)_2NH$	N,N,α,1-tetramethyl//acetamide
160	17	$n\text{-}C_6H_{13}NH_2$	α,1-dimethyl-N-hexyl//acetamide
161	17	$(C_2H_5)_2NH$	N,N-diethyl-α,1-dimethyl//acetamide
162	18	CH_3NH_2	1-cyclohexyl-N,α,α-trimethyl//acetamide

TABLE III—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
163	21	CH_3NH_2	N,8-dimethyl-1-propyl//acetamide
164	25	NH_3	6-benzyloxy-1-methyl//acetamide
165	26	$(CH_3)_2NH$	1-propyl-N,N,5-trimethyl//acetamide
166	30	n-$C_6H_{13}NH_2$	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy-N-hexyl//acetamide
167	35	CH_3NH_2	5-iodo-1-isopropyl-N-methyl//propionamide
168	38	NH_3	1-cyclobutyl-3-methyl-8-nitro-α-propyl//propionamide
169	41	$(CH_3)_2NH$	N,N,α,α,β,3-hexamethyl-1,4,4-triethyl//propionamide
170	44	$(C_2H_5)_2NH$	N,N-diethyl-1,3-dipropyl-5-methoxy-α-methyl//propionamide
171	46	CH_3NH_2	N-methyl-β,1-dipropyl-3,3,5-triethyl//propionamide
172	48	$(CH_3)_2NH$	N,N,1-trimethyl//butyramide
173	48	CH_3NH_2	N,1-dimethyl//butyramide
174	48	NH_3	1-methyl//butyramide
175	48	n-$C_6H_{13}NH_2$	N-hexyl-1-methyl//butyramide
176	51	CH_3NH_2	1-cyclobutyl-β,γ,γ,4-tetrapropyl-N,3,3-trimethyl//butyramide
177	53	$(CH_3)_2NH$	N,N,$\alpha,\alpha,\beta,\beta,\gamma,\gamma$,4,5-decamethyl-1-ethyl//butyramide

TABLE III—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)]
			PREFIX//SUFFIX
178	56	NH_3	5-bromo-1-cyclopentyl-α,α,β-trimethyl//butyramide
179	58	CH_3NH_2	1,8-diethyl-N,α-dimethyl//butyramide
180	62	$(C_2H_5)_2NH$	1-propyl-N,N,α,γ-tetraethyl-3,3,5-trimethyl//butyramide
181	62	$n\text{-}C_6H_{13}NH_2$	α,β-diethyl-3,3-dimethyl-1,5-dipropyl-N-hexyl//butyramide

TABLE IV

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
182	2	pyrrolidine	1-[(1-methyl//propionyl]pyrrolidine
183	2	piperidine	1-[(1-methyl//propionyl]piperidine
184	2	morpholine	4-[(1-methyl//propionyl]morpholine
185	2	piperazine	1-[(1-methyl//propionyl]piperazine
186	2	N-methyl-piperazine	1-methyl-4-[1-methyl//propionyl]piperazine
187	2	N-piperazine-ethanol	1-(2-hydroxyethyl)-4-[(1-methyl//propionyl]-piperazine
188	4	pyrrolidine	1-[(1-methyl//carbonyl]pyrrolidine
189	4	morpholine	4-[(1-methyl//carbonyl]morpholine
190	5	N-ethyl-piperazine	1-ethyl-4-[(1-ethyl-3-methyl//carbonyl]piperazine
191	11	piperidine	1-[(1,4-dimethyl//acetyl]piperidine
192	12	morpholine	4-[(1-ethyl//acetyl]morpholine
193	12	N-piperazine-propanol	1-(3-hydroxypropyl)-4-[(1-ethyl//acetyl]-piperazine
194	13	pyrrolidine	1-[(1-propyl//acetyl]pyrrolidine
195	13	morpholine	4-[(1-propyl//acetyl]morpholine
196	14	piperidine	1-[(1-isopropyl//acetyl]piperidine
197	15	piperazine	1-[(3-methyl-1-propyl//acetyl]piperazine
198	17	N-ethyl-piperazine	1-ethyl-4-[(α,1-dimethyl//acetyl]piperazine
199	25	pyrrolidine	1-[(6-benzyloxyl-1-methyl//acetyl]pyrrolidine

TABLE IV—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
200	26	piperidine	1-[(5-methyl-1-propyl//acetyl]piperidine
201	30	morpholine	4-[(1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy//acetyl]morpholine
202	36	piperazine	1-[8-acetoxy-1-ethyl-α,3,3,4,4-pentamethyl//propionyl]piperazine
203	39	N-piperazine-ethanol	1-(2-hydroxyethyl)-4-[(1-cyclopropyl-$\alpha,\alpha,\beta,\beta$,4,6-hexamethyl//propionyl]piperazine
204	40	pyrrolidine	1-[(1,3-dimethyl-α,α-dipropyl//propionyl]-pyrrolidine
205	42	morpholine	4-[(1-ethyl-β,β,4,4-tetramethyl//propionyl]-morpholine
206	47	N-propyl-piperazine	1-propyl-4-[(1-cyclopropyl-α,β-diethyl-6-ethoxy//propionyl]piperazine
207	48	pyrrolidine	1-[(1-methyl//butyryl]pyrrolidine
207a	48	N-piperazine-methanol	1-(hydroxymethyl)-4-[(1-methyl//butyryl]-piperazine
208	50	piperidine	1-[γ,γ-dimethyl-3,3-dimethyl-1-propyl//butyryl]-piperidine
209	52	morpholine	4-[(7-chloro-$\alpha,\beta,\beta,\gamma,\gamma$,4,4-heptaethyl-1-methyl//butyryl]morpholine
210	59	piperazine	1-[(1-butyl-6-fluoro-α,β,γ,3,3,4-hexamethyl//butyryl]piperazine

TABLE V

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
211	3	CH_3NH_2	N,1-dimethyl//acetamide
212	3	NH_3	1-methyl//acetamide
213	3	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//acetamide
214	3	$(CH_3)_2NH$	N,N,1-trimethyl//acetamide, m.p. 182°C.
215	3	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//acetamide
216	96	CH_3NH_2	N,1-dimethyl//propionamide
217	96	NH_3	1-methyl//propionamide
218	96	$(CH_3)_2NH$	N,N,1-trimethyl//propionamide
219	96	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//propionamide
220	96	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//propionamide
221	65	CH_3NH_2	N,1-dimethyl//carboxamide
222	65	NH_3	1-methyl//carboxamide
223	65	$(CH_3)_2NH$	N,N,1-trimethyl//carboxamide
224	65	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//carboxamide
225	65	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//carboxamide
226	66	CH_3NH_2	N,3-dimethyl-1-ethyl//carboxamide
227	69	NH_3	8-ethyl-1-propyl//carboxamide
228	70	$(CH_3)_2NH$	1-cyclopropyl-N,N-dimethyl-4-isopropyl//carboxamide

TABLE V—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
229	72	$(CH_3)_2NH$	N,N,1,4-tetramethyl//acetamide
230	73	CH_3NH_2	1-ethyl-N-methyl//acetamide
231	73	NH_3	1-ethyl//acetamide
232	73	$(CH_3)_2NH$	N,N-dimethyl-1-ethyl//acetamide
233	73	$n\text{-}C_6H_{13}NH_2$	1-ethyl-N-hexyl//acetamide
234	73	$(C_2H_5)_2NH$	N,N,1-triethyl//acetamide
235	74	CH_3NH_2	N-methyl-1-propyl//acetamide
236	74	NH_3	1-propyl//acetamide
237	74	$(CH_3)_2NH$	N,N-dimethyl-1-propyl//acetamide
238	74	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-propyl//acetamide
239	74	$(C_2H_5)_2NH$	N,N-diethyl-1-propyl//acetamide
240	75	CH_3NH_2	1-isopropyl-N-methyl//acetamide
241	75	NH_3	1-isopropyl//acetamide
242	75	$(C_2H_5)_2NH$	N,N-diethyl-1-isopropyl//acetamide
243	76	CH_3NH_2	N,3-dimethyl-1-propyl//acetamide
244	76	NH_3	3-methyl-1-propyl//acetamide
245	76	$(CH_3)_2NH$	1-propyl,N,N,3-trimethyl//acetamide
246	76	$n\text{-}C_6H_{13}NH_2$	N-hexyl-3-methyl-1-propyl//acetamide
247	76	$(C_2H_5)_2NH$	N,N-diethyl-3-methyl-1-propyl//acetamide

TABLE V—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)]
			PREFIX//SUFFIX
248	78	CH_3NH_2	N,α,1-trimethyl//acetamide
249	78	NH_3	α,1-dimethyl//acetamide
250	78	$(CH_3)_2NH$	N,N,α,1-tetramethyl//acetamide
251	78	n-$C_6H_{13}NH_2$	α,1-dimethyl-N-hexyl//acetamide
252	78	$(C_2H_5)_2NH$	N,N-diethyl-α,1-dimethyl//acetamide
253	79	CH_3NH_2	1-cyclohexyl-N,α,α-trimethyl//acetamide
254	82	CH_3NH_2	N,8-dimethyl-1-propyl//acetamide
255	83	NH_3	6-bromo-1-propyl//acetamide
256	89	$(CH_3)_2NH$	α,α-diethyl-8-fluoro-N,N,1-trimethyl//acetamide
257	91	n-$C_6H_{13}NH_2$	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy-N-hexyl//acetamide
258	99	NH_3	1-cyclobutyl-3-methyl-8-nitro-α-propyl//propionamide
259	102	$(CH_3)_2NH$	N,N,α,α,β,3-hexamethyl-1,4,4-triethyl//propionamide
260	105	$(C_2H_5)_2NH$	N,N-diethyl-1,3-dipropyl-5-methoxy-α-methyl//propionamide
261	107	CH_3NH_2	β,1-dipropyl-N-methyl-3,3,5-triethyl//propionamide
262	108	CH_3NH_2	1-cyclopropyl-α,β-diethyl-6-ethoxy-N-methyl//propionamide
263	109	$(CH_3)_2NH$	N,N,1-trimethyl//butyramide

TABLE V—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)]
			PREFIX//SUFFIX
264	109	CH_3NH_2	N,1-dimethyl//butyramide
265	109	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//butyramide
266	112	CH_3NH_2	1-cyclobutyl-$\beta,\gamma,\gamma,4$-tetrapropyl-N,3,3-trimethyl//butyramide
267	113	$(CH_3)_2NH$	7-chloro-$\alpha,\beta,\beta,\gamma,\gamma,4,4$-heptaethyl-N,N,1-trimethyl//butyramide
268	117	NH_3	5-bromo-1-cyclopentyl-α,α,β-trimethyl//butyramide
269	119	CH_3NH_2	δ-diethyl-N,α-dimethyl//butyramide
270	121	$(C_2H_5)_2NH$	1-propyl-N,N,α,γ-tetraethyl-3,3,5-trimethyl//butyramide
271	123	$n\text{-}C_6H_{13}NH_2$	α,β-diethyl-3,3-dimethyl-1,5-dipropyl-N-hexyl//butyramide

TABLE VI

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
272	3	pyrrolidine	1-[(1-methyl//acetyl]pyrrolidine
273	3	piperidine	1-[(1-methyl//acetyl]piperidine
274	3	morpholine	4-[(1-methyl//acetyl]morpholine
275	3	piperazine	1-[(-methyl//acetyl]piperazine
276	3	N-methyl-piperazine	1-methyl-4-[1-methyl//acetyl]piperazine
277	3	N-piperazine-ethanol	1-(2-hydroxyethyl)-4-[(1-methyl//acetyl]-piperazine
278	96	pyrrolidine	1-[(1-methyl//propionyl]pyrrolidine
279	96	piperidine	1-[(1-methyl//propionyl]piperidine
280	96	morpholine	4-[(1-methyl//propionyl]morpholine
281	96	piperazine	1-[(1-methyl//propionyl]piperazine
282	96	N-methyl-piperazine	1-methyl-4-[1-methyl//propionyl]piperazine
283	96	N-piperazine-ethanol	1-(2-hydroxyethyl)-4-[(1-methyl//propionyl]-piperazine
284	65	pyrrolidine	1-[(1-methyl//carbonyl]pyrrolidine
285	65	morpholine	4-[(1-methyl//carbonyl]morpholine
286	66	N-ethyl-piperazine	1-ethyl-4-[(1-ethyl-3-methyl//carbonyl]piperazine
287	72	piperidine	1-[(1,4-dimethyl//acetyl]piperidine
288	73	morpholine	4-[(1-ethyl//acetyl]morpholine

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TABLE VI—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
289	73	N-piperazine-propanol	1-(3-hydroxypropyl)-4-[(1-ethyl//acetyl]-piperazine
290	74	pyrrolidine	1-[(1-propyl//acetyl]pyrrolidine
291	74	morpholine	4-[(1-propyl//acetyl]morpholine
292	75	piperidine	1-[(1-isopropyl//acetyl]piperidine
293	76	piperazine	1-[(3-methyl-1-propyl//acetyl]piperazine
294	78	N-ethyl-piperazine	1-ethyl-4-[(α,1-dimethyl//acetyl]piperazine
295	86	pyrrolidine	1-[(6-benzyloxy-1-methyl//acetyl]pyrrolidine
296	87	piperidine	1-[(5-methyl-1-propyl//acetyl]piperidine
298	91	morpholine	4-[(1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy//acetyl]morpholine
299	97	piperazine	1-[(8-acetoxy-1-ethyl-α,3,3,4,4-pentamethyl//propionyl]piperazine
300	100	N-piperazine-ethanol	1-(2-hydroxyethyl)-4-[(1-cyclopropyl-$\alpha,\alpha,\beta,\beta$,4,6-hexamethyl//propionyl[]piperazine
301	101	pyrrolidine	1-[(1,3-dimethyl-α,α-dipropyl//propionyl]-pyrrolidine
302	103	morpholine	4-[(1-ethyl-β,β,4,4-tetramethyl//propionyl]-morpholine
303	108	N-propyl-piperazine	1-propyl-4-[(1-cyclopropyl-α,β-diethyl-6-ethoxy//propionyl]piperazine
304	109	pyrrolidine	1-[(1-methyl//butyryl]pyrrolidine

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TABLE VI—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
305	109	N-piperazine-methanol	1-(hydroxymethyl)-4-[(1-methyl//butyryl]-piperazine
306	111	piperidine	1-[(γ,γ-diethyl-3,3-dimethyl-1-propyl//butyryl]piperidine
307	113	morpholine	4-[(7-chloro-α,β,β,γ,γ,4,4-heptaethyl-1-methyl//butyryl]morpholine
308	120	piperazine	1-[(1-butyl-6-fluoro-α,β,γ,3,3,4-hexamethyl//butyryl]piperazine

EXAMPLE 309.

1-[2-(DIMETHYLAMINO)ETHYL]-1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE [I; $R^1=CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R'=H$, $X=O$ AND $Y=CH_2CH_2N(CH_3)_2$]

A solution of N,N,1-trimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide (5.0 g, 0.018 mole), prepared as described in Example 126, is added dropwise to a cooled, well-stirred mixture of lithium aluminum hydride (1.4 g, 0.036 mole) in 200 ml of ether. Stirring is continued for one hour at room temperature, then the mixture is heated under reflux for 2 hrs.

After cooling in an ice-water bath, 6.2 ml of water is added dropwise to destroy the excess hydride. Then 100 ml more of water is added and the ether phase decanted. The aqueous phase is extracted once with benzene. The combined organic phases are washed with water, dried over sodium sulfate, and evaporated to dryness to afford 5 g of oil which crystallized on standing. The crystallized product is recrystallized from ether to afford the pure title compound, m.p. 133—135°C., nmr ($CDCl_3$) δ 1.53 (s, 3H), 2.07 (2H), 9.74 (1H), 10.55 (6H).

The corresponding oxalic acid addition salt (oxalate), 1-[(2-dimethylamino)-ethyl]-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole oxalate, has m.p. 181—183°C. after crystallization from methanol-ether.

In the same manner but replacing lithium aluminum hydride with an equivalent amount of lithium aluminum hydride-aluminum chloride, aluminum hydride-aluminum chloride, diborane and sodium borohydride-aluminum chloride, the title compound is also obtained.

In the same manner but replacing N,N,1-trimethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetamide with an equivalent amount of the following amides described in Example 126,

1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide,
N,1-dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide,
N-hexyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide,
N,N-diethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide,
N-isopropyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide,
N-ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide,
1-[(1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl]pyrrolidine,
1-[(1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl]piperidine,
1-[(1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl]morpholine, and
1-methyl-4-[(1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl]piperazine,

then there are obtained,

1-(2-aminoethyl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole, m.p. 80—84°C., $\nu_{max}^{CHCl_3}$ 3455, 3280 cm^{-1},

1-methyl-1-[2-(methylamino)ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole, m.p. 160—163°C., (m.p. of corresponding oxalic acid addition salt, 140—144°C.),

1-[2-(hexylamino)ethyl]-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole,

1-[2-(diethylamino)ethyl]-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole, m.p. 74—76°C, m.p. of corresponding maleic acid addition salt, 98—100°C.,

1-[2-(isopropylamino)ethyl]-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole,

1-[2-(ethylamino)ethyl]-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole,

1-methyl-1-[2-(1-pyrrolidinyl)ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole, nmr ($CDCl_3$) δ 1.62 (3H), 2.00 (m, 4H), 4.05 (m, 2H), m.p. of corresponding maleic acid addition salt (maleate), 192, 192°C.,

1-methyl-1-(2-piperidinoethyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole, m.p. 146—148°C., m.p. of corresponding maleic acid addition salt, 147—149°C.,

1-methyl-1-(2-morpholinoethyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole, nmr (DMSO-d_6) δ 1.50 (3H), 6.07 (2H), 6.87—7.65 (m, 4H), 10.86 (1H), m.p. of corresponding maleic acid addition salt, 192—193°C., and

1-methyl-1-[2-(4-methyl-1-piperazinyl)ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole, nmr ($CDCl_3$) δ 1.47 (3H), 2.58 (3H), 3.87 (t, 2H), [m.p. of corresponding maleic acid addition salt (i.e. dimaleate), 208—210°C.], respectively.

By following the procedure of Example 309 but using as starting material an equivalent amount of one of the amide compounds of formula VII, described in Examples 127 to 308 instead of N,N,1-trimethyl-1,3,4,9-tetrahydropyrano[3,4-b]-inole-1-acetamide, then the corresponding compounds of formula I in which R' is hydrogen are obtained. Examples of such compounds of formula I are listed as products in Tables VII and VIII together with the appropriate starting material, amides of formula VII. In each case the starting material is noted by the example in which it is prepared.

TABLE VII

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4,-b]-INDOLE
310	127	1-methyl-1-[3-(methylamino)propyl], nmr ($CDCl_3$) δ 1.48 (3H), 1.87 (4H), 2.47 (3H), corresponding oxalic acid addition salt has m.p. 110°C.
311	128	1-(3-aminopropyl)-1-methyl
312	129	1-methyl-1-[3-(dimethylamino)propyl], m.p. 114—116°C., corresponding oxalic acid addition salt has m.p. 168—172°C.
313	130	1-[3-(hexylamino)propyl]-1-methyl
314	131	1-[3-(diethylamino)propyl]-1-methyl
315	132	1-methyl-1-[(methylamino)methyl]
316	133	1-(aminomethyl)-1-methyl, $\gamma_{max}^{CHCl_3}$ 3465, 3400, 3180, 2930, corresponding hydrochloric acid addition salt (hydrochloride) has m.p. 251—252°C.
317	134	1-[(dimethylamino)methyl]-1-methyl
318	135	1-[(hexylamino)methyl]-1-methyl
319	136	1-[(ethylamino)methyl]-1-methyl, nmr (DMSO-d_6) δ 1.18 (3H), 1.62 (3H), 2.80 (2H); corresponding hydrochloric acid addition salt has m.p. 242—243°C.
320	137	1-ethyl-3-methyl-1-[(methylamino)methyl]
321	138	1-cyclopropyl-1-[(dimethylamino)methyl)-4-isopropyl
322	139	1,4-dimethyl-1-[2-(dimethylamino)ethyl]
323	140	1-ethyl-1-[2-(methylamino)ethyl]
324	141	1-(2-aminoethyl)-1-ethyl
325	142	1-[2-(dimethylamino)ethyl]-1-ethyl
326	143	1-ethyl-1-[2-(hexylamino)ethyl]
327	144	1-[2-(diethylamino)ethyl]-1-ethyl
328	145	1-[2-(methylamino)ethyl]-1-propyl
329	146	1-(aminoethyl)-1-propyl
330	147	1-[2-(dimethylamino)ethyl]-1-propyl, nmr ($CDCl_3$) 0.84 (t, 3H), 1.21 (3, 6H), 2.79 (t, 5 = 5.5 cps, 2H) corresponding maleic acid addition salt has m.p. 152—154°C.

TABLE VII—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: *(PREFIX LISTED BELOW)*-1,3,4,9-TETRAHYDROPYRANO[3,4,-b]-INDOLE
331	148	1-[2-(hexylamino)ethyl]-1-propyl
332	149	1-[2-(diethylamino)ethyl]-1-propyl
333	150	1-isopropyl-1-[2-(methylamino)ethyl]
334	151	1-(2-aminoethyl)-1-isopropyl
335	152	1-[2-(diethylamino)ethyl-1-isopropyl
336	153	3-methyl-1-[2-(methylamino)ethyl]-1-propyl
337	154	1-[2-(dimethylamino)ethyl]-3-methyl-1-propyl
338	155	1-[2-(hexylamino(ethyl]-3-methyl-1-propyl
339	156	1-[2-(diethylamino)ethyl]-3-methyl-1-propyl
340	157	1-[1-methyl-2-(methylamino)ethyl]-1-methyl
341	158	1-(2-amino-1-methyl-ethyl)-1-methyl
342	159	1-[2-(dimethylamino)-1-methyl-ethyl]-1-methyl
343	160	1-[2-(hexylamino)-1-methyl-ethyl)-1-methyl
344	161	1-[2-(diethylamino)-1-methyl-ethyl]-1-methyl
345	162	1-cyclohexyl-1-[1,1-dimethyl-2-(methyl-amino)ethyl]
346	163	8-methyl-1-[2-(methylamino)ethyl]-1-propyl
347	164	1-(2-aminoethyl)-6-benzyloxy-1-methyl
348	165	1-[2-(dimethylamino)ethyl]-5-methyl-1-propyl
349	166	1-cyclopropyl-1-[1,1-diethyl-2-(hexylamino)-ethyl]-3,3-dimethyl-6-ethoxy
350	167	5-iodo-1-isopropyl-1-[3-(methylamino)propyl]
351	168	1-[3-amino-2-propyl-propyl)-1-cyclobutyl-3-methyl-8-nitro
352	169	1-[3-(dimethylamino)-1,2,2-trimethyl-propyl]-1,4,4-triethyl
353	170	1-[3-(diethylamino)-2-methyl-propyl]-1,3-dipropyl-5-methoxy
354	171	1-[1-propyl-3-(methylamino)-propyl]-1-propyl-3,3,5-trimethyl
355	172	1-[4-(dimethylamino)butyl]-1-methyl

TABLE VII—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4,-b]-INDOLE
356	173	1-[4-(methylamino)butyl]-1-methyl
357	174	1-(4-aminobutyl)-1-methyl
358	175	1-[4-(hexylamino)butyl]-1-methyl
359	176	1-cyclobutyl-3,3-dimethyl-1-[4-(methylamino)-1,1,2-tripropyl-butyl]-4-propyl
360	177	4,5-dimethyl-1-ethyl-1-[4-dimethylamino)-1,1,2,2,3,3-hexamethylbutyl]
361	178	1-(4-amino-2,3,3-trimethyl-butyl)-5-bromo-1-cyclopentyl
362	179	1,8-diethyl-1-[3-methyl-4-(methylamino)butyl]
363	180	1-[1,3-diethyl-4-(diethylamino)butyl]-1-propyl-3,3,5-trimethyl
364	181	1-[2,3-diethyl-4-(hexylamino)butyl]-3,3-dimethyl-1,5-dipropyl
365	182	1-methyl-1-[3-(1-pyrrolidinyl)propyl], m.p. 124—127°C.
366	183	1-methyl-1-(3-piperidinopropyl)
367	184	1-methyl-1-(3-morpholinopropyl)
368	185	1-methyl-1-(3-piperazinopropyl)
369	186	1-methyl-1-[3-(4-methyl-1-piperazinyl)propyl]
370	187	1-{3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl}-1-methyl
371	188	1-methyl-1-[(1-pyrrolidinyl)methyl]
372	189	1-methyl-1-(morpholinomethyl)
373	190	1-ethyl-3-methyl-1-[(4-methyl-1-piperazinyl)-methyl]
374	191	1,4-dimethyl-1-(2-piperidinoethyl)
375	192	1-ethyl-1-(2-morpholinoethyl)
376	193	1-ethyl-1-{2-[4-(3-hydroxypropyl)-1-piperazinyl]-ethyl}
377	194	1-propyl-1-[2-(1-pyrrolidinyl)ethyl]
378	195	1-propyl-1-(2-morpholinoethyl)
379	196	1-isopropyl-1-(2-piperidinoethyl)

TABLE VII—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4,-b]-INDOLE
380	197	3-methyl-1-(2-piperazinoethyl)-1-propyl
381	198	1-ethyl-1-[1-methyl-2-(4-methyl-1-piperazinyl)-ethyl]
382	199	6-benzyloxy-1-methyl-1-[2-(1-pyrrolidinyl)ethyl]
383	200	5-methyl-1-(2-piperidinoethyl)-1-propyl
384	201	1-cyclopropyl-1-(1,1-diethyl-2-morpholinoethyl)-3,3-dimethyl-6-ethoxy
385	202	8-acetoxy-1-ethyl-3,3,4,4-tetramethyl-1-(2-methyl-3-piperazinopropyl)
386	203	1-cyclopropyl-4,6-dimethyl-1-{3-[4-(2-hydroxyethyl)-1-piperazinyl]-1,1,2,2-tetramethylpropyl}
387	204	1,3-dimethyl-1-[2,2-dipropyl-3-(1-pyrrolidinyl) propyl]
388	205	4,4-dimethyl-1-ethyl-1-(1,1-dimethyl-3-morpholinopropyl)
389	206	1-cyclopropyl-1-[1,2-diethyl-3-(4-propyl-1-piperazinyl)propyl]-6-ethoxy
390	207	1-methyl-1-[4-(1-pyrrolidinyl)butyl]
391	207a	1-{4-[4-(hydroxymethyl)-1-piperazinyl]butyl}-1-methyl
392	208	1-[(1,1-diethyl-4-piperidino)butyl]-3,3-dimethyl-1-propyl
393	209	7-chloro-4,4-diethyl-1-methyl-1-(4-morpholino-1,1,2,2,3-pentaethylbutyl)
394	210	1-butyl-6-fluoro-1-(4-piperazino-1,2,3-trimethylbutyl)-3,3,4-trimethyl

TABLE VIII

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
395	211	1-methyl-1-[2-(methylamino)ethyl]
396	212	1-(2-aminoethyl)-1-methyl
397	213	1-[(2-hexylamino)ethyl]-1-methyl
398	214	1-[2-(dimethylamino)ethyl]-1-methyl, m.p. 119—121°C.
399	215	1-[2-(diethylamino)ethyl]-1-methyl
400	216	1-methyl-1-[3-(methylamino)propyl]
401	217	1-(3-aminopropyl)-1-methyl
402	218	1-[3-(dimethylamino)propyl]-1-methyl
403	219	1-[3-(hexylamino)propyl]-1-methyl
404	220	1-[3-(diethylamino)propyl]-1-methyl
405	221	1-methyl-1-[(methylamino)methyl]
406	222	1-(aminomethyl)-1-methyl
407	223	1-[(dimethylamino)methyl]-1-methyl
408	224	1-[(hexylamino)methyl]-1-methyl
409	225	1-[(diethylamino)methyl]-1-methyl
410	226	1-ethyl-3-methyl-1-[(methylamino)methyl]
411	228	1-cyclopropyl-1-[(dimethylamino)methyl)-4-isopropyl
412	229	1,4-dimethyl-1-[2-(dimethylamino)ethyl]
413	230	1-ethyl-1-[2-(methylamino)ethyl)
414	231	1-(2-aminoethyl)-1-ethyl
415	232	1-[2-(dimethylamino)ethyl]-1-ethyl
416	233	1-ethyl-1-[2-(hexylamino)ethyl]
417	234	1-[2-(diethylamino)ethyl]-1-ethyl
418	235	1-[2-(methylamino)ethyl]-1-propyl
419	236	1-(aminoethyl)-1-propyl
420	237	1-[2-(dimethylamino)ethyl]-1-propyl
421	238	1-[2-(hexylamino)ethyl]-1-propyl
422	239	1-[2-(diethylamino)ethyl]-1-propyl

TABLE VIII—continued

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
423	240	1-isopropyl-1-[2-(methylamino)ethyl]
424	241	1-(2-aminoethyl)-1-isopropyl
425	242	1-[2-(diethylamino)ethyl)-1-isopropyl
426	243	3-methyl-1-[2-(methylamino)ethyl]-1-propyl
427	245	1-[2-dimethylamino)ethyl]-3-methyl-1-propyl
428	246	1-[2-(hexylamino)ethyl]-3-methyl-1-propyl
429	247	1-[2-(diethylamino)ethyl]-3-methyl-1-propyl
430	248	1-[1-methyl-2-(methylamino)ethyl]-1-methyl
431	249	1-(2-amino-1-methylethyl)-1-methyl
432	250	1-[2-(dimethylamino)-1-methyl-ethyl]-1-methyl
433	251	1-[2-(hexylamino)-1-methyl-ethyl]-1-methyl
434	252	1-[2-(diethylamino)-1-methyl-ethyl]-1-methyl
435	253	1-cyclohexyl-1-[1,1-dimethyl-2-(methylamino)-ethyl]
436	254	8-methyl-1-[2-(methylamino)ethyl]-1-propyl
437	255	1-(2-aminoethyl)-6-bromo-1-propyl
438	257	1-cyclopropyl-1-[1,1-diethyl-2-(hexylamino)-ethyl]-3,3-dimethyl-6-ethoxy
439	258	1-(3-amino-2-propyl-propyl)-1-cyclobutyl-3-methyl-8-nitro
440	259	1-[3-(dimethylamino)-1,2,2-trimethyl-propyl]-1,4,4-triethyl
441	260	1-[3-(diethylamino)-2-methylpropyl]-1,3-dipropyl-5-methoxy
442	261	1-[1-propyl-3-(methylamino)-propyl]-1-propyl-3,3,5-trimethyl
443	263	1-[4-(dimethylamino)butyl]-1-methyl
444	264	1-[4-(methylamino)butyl]-1-methyl
445	265	1-[4-(hexylamino)butyl]-1-methyl
446	266	1-cyclobutyl-3,3-dimethyl-1-[4-(methylamino)-1,1,2-tripropyl-butyl]-4-propyl
447	267	7-chloro-4,4-diethyl-1-[4-dimethylamino-1,1,2,2,3-pentaethylbutyl]-1-methyl

TABLE VIII—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
448	268	1-(4-amino-2,3,3-trimethyl-butyl)-5-bromo-1-cyclopentyl
449	269	1,8-diethyl-1-[3-methyl-4-(methylamino)butyl]
450	270	1-[1,3-diethyl-4-(diethylamino)butyl]-1-propyl-3,3,5-trimethyl
451	271	1-[2,3-diethyl-4-(hexylamino)butyl]-3,3-dimethyl-1,5-dipropyl
452	272	1-methyl-1-[2-(1-pyrrolidinyl)ethyl]
453	273	1-methyl-1-(2-piperidinoethyl)
454	274	1-methyl-1-(2-morpholinoethyl)
455	275	1-methyl-1-(2-piperazinoethyl)
456	276	1-methyl-1-[2-(4-methyl-1-piperazinyl)ethyl]
457	277	1-{2-[4-(2-hydroxyethyl)-1-piperazinyl]ethyl}-1-methyl
458	278	1-methyl-1-[3-(1-pyrrolidinyl)propyl]
459	279	1-methyl-1-(3-piperidinopropyl)
460	280	1-methyl-1-(3-morpholinopropyl)
461	281	1-methyl-1-(3-piperazinopropyl)
462	282	1-methyl-1-[3-(4-methyl-1-piperazinyl)propyl]
463	283	1-{3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl}-1-methyl
464	284	1-methyl-1-[(1-pyrrolidinyl)-methyl
465	285	1-methyl-1-(morpholinomethyl)
466	286	1-ethyl-3-methyl-1-[(4-ethyl-1-piperazinyl)methyl]
467	287	1,4-dimethyl-1-(2-piperidinoethyl)
468	288	1-ethyl-1-(2-morpholinoethyl)
469	289	1-ethyl-1-{2-[4-(3-hydroxy-propyl)-1-piperazinyl]ethyl}
470	290	1-propyl-1-[2-(1-pyrrolidinyl)ethyl]
471	291	1-(2-morpholinoethyl)-1-propyl
472	292	1-isopropyl-1-(2-piperidinoethyl)
473	293	3-methyl-1-(2-piperazinoethyl)-1-propyl

TABLE VIII—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
474	295	1-methyl-1-[1-methyl-2-(4-methyl-1-piperazinyl)-ethyl]
475	296	6-benzyloxy-1-methyl-1-[2-(1-pyrrolidinyl)ethyl]
476	297	5-methyl-1-(2-piperidinoethyl)-1-propyl
477	298	1-cyclopropyl-1-(1,1-diethyl-2-morpholinethyl)-3,3-dimethyl-6-ethoxy
478	299	8-acetoxy-1-ethyl-3,3,4,4-tetramethyl-1-(2-methyl-3-piperazinopropyl)
479	300	1-cyclopropyl-4,6-dimethyl-1-{3-[4-(2-hydroxy-ethyl)-1-piperazinyl]-1,1,2,2-tetramethylpropyl}
480	301	1,3-dimethyl-1-[2,2-dipropyl-3-(1-pyrrolidinyl)-propyl]
481	302	4,4-dimethyl-1-ethyl-1-(1,1-dimethyl-3-morpholinopropyl)
482	303	1-cyclopropyl-6-ethoxy-1-[1,2-diethyl-3-(4-propyl-1-piperazinyl)propyl
483	304	1-methyl-1-[4-(1-pyrrolidinyl)-butyl]
484	305	1-{4-[4-(hydroxymethyl)-piperazinyl]butyl}-1-methyl
485	306	1-[(1,1-diethyl-4-piperidino)butyl]-3,3-dimethyl-1-propyl
486	307	7-chloro-4,4-diethyl-1-methyl-1-(4-morpholino-1,1,2,2,3-pentaethylbutyl)
487	308	1-butyl-6-fluoro-1-(4-piperazino-1,2,3-trimethyl-butyl)-3,3,4-trimethyl

EXAMPLE 488.

1,9-DIMETHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-ACETIC ACID (VII; R^1 AND $R^7 = CH_3$, R^2, R^3, R^4, R^5 AND $R^6 = H$, $X = O$ AND $Z = CH_2COOH$

1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid (10 g., 0.04 mole), prepared as described in Example 1, in 150 ml. of tetrahydrofuran is added dropwise to a stirred suspension of sodium hydride (4.4 g. of 55% dispersion) in 200 ml. of tetrahydrofuran. This mixture is heated at 50°C. with stirring for 2 hrs. Methyl iodide (14.2 g. 0.1 mole) is added dropwise and heating and stirring is continued for a further 2 hrs.

After cooling, water is added until the solution is clear. The tetrahydrofuran is evaporated off under reduced pressure, the residue is partitioned between water and benzene. The aqueous phase is washed once with benzene, made acidic with HCl, and extracted with benzene (3 ×). The organic phase is washed with water, dried over sodium sulfate and treated with charcoal. The organic layer is evaporated. The residue

is crystallized from benzene and then ether-petroleum ether to afford the title compound, m.p. 105—108°C., nmr ($CDCl_3$) δ 1.73 (S, 3H), 2.83 (t, J=5.5, 2H), 3.0 (2H), 3.68 (3H), 4.08 (t, J=5.5, 2H), 7.34 (4H), 9.47 (1H).

In the same manner but replacing methyl iodide with an equivalent amount of ethyl iodide, or propyl iodide, the N-ethyl analog of the title compound, 9-ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid, m.p. 134—136°C., and the N-propyl analog of the title compound, 1-methyl-9-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid, m.p. 120—122°C., are obtained, respectively.

By following the procedure of Example 488 but using as starting material an equivalent amount of the acid compounds of formula VII, in which R^7 is hydrogen, described in Examples 1 to 125, inclusive, instead of 1-methyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid, and using an equivalent amount of an appropriate organic halide, then the corresponding N-alkylated acid compounds of formula I are obtained. Examples of these latter compounds are listed as products in Tables IX and X together with the appropriate starting material of formula VII and organic halide used for their preparation. In each case the starting material is noted by the Example in which it is prepared.

TABLE IX

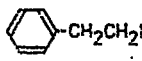
EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
489	1	$CH_2=CHCH_2Br$	9-allyl-1-methyl//acetic acid, m.p. 103—105°C.
490	1	$CH_2=CHBr$	1-methyl-9-vinyl//acetic acid
491	1	$CH\equiv CCH_2Br$	1-methyl-9-propargyl//acetic acid
492	2	$n\text{-}C_3H_7I$	1-methyl-9-propyl//propionic acid
493	2	CH_3I	1,9-dimethyl//propionic acid
494	2		1-methyl-9-phenethyl//propionic acid
495	2	1-(3-chloropropyl)piperazine	1-methyl-9-(3-piperidinopropyl)//propionic acid
496	4	1-(2-chloroethyl)-pyrrolidine	1-methyl-9-[2-(1-pyrrolidinyl)ethyl]// carboxylic acid
497	6	$CH\equiv CCH_2Br$	1,3-diisopropyl-6-methyl-9-propargyl// carboxylic acid
498	7	CH_3I	6-hydroxy-1,3,3,9-tetramethyl//carboxylic acid
499	8	$CH_3CH=CHBr$	8-ethyl-9-(1-propenyl)-1-propyl//carboxylic acid
500	10	C_2H_5Br	1-cyclopentyl-4,4,9-triethyl-3,3-dimethyl// carboxylic acid
501	12	CH_3I	1-ethyl-9-methyl//acetic acid
502	12	C_2H_5Cl	1,9-diethyl//acetic acid
503	12	$CH_2=CHCH_2Br$	9-allyl-1-ethyl//acetic acid
504	12	2-(dimethylamino)-ethyl chloride	9-[2-(dimethylamino) 1-ethyl//acetic acid

TABLE IX—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
505	13	CH_3I	9-methyl-1-propyl//acetic acid
506	13	n-C_3H_7Cl	1,9-dipropyl//acetic acid
507	13	$CH_2=CHCH_2Br$	9-allyl-1-propyl//acetic acid
508	13	$CH_2=C(CH_3)CH_2Br$	9-methallyl-1-propyl//acetic acid
509	14		9-benzyl-1-isopropyl//acetic acid
510	14	$CH_2=CHBr$	1-isopropyl-9-vinyl//acetic acid
511	15	n-C_3H_7Cl	1,9-dipropyl-3-methyl//acetic acid
512	16	$CH_2=CHCH_2Br$	9-allyl-1,4-diethyl-3-methyl//acetic acid
513	17	CH_3I	α,1,9-trimethyl//acetic acid
514	18	n-C_3H_7Cl	1-cyclohexyl-α,α-dimethyl-9-propyl//acetic acid
515	19	$CH_2=CHCH_2Br$	9-allyl-1-t-butyl//acetic acid
516	20	$CH_2=CHCH_2I$	9-allyl-1-butyl//acetic acid
517	23	CH_3Cl	1,9-dimethyl-6-methoxy//acetic acid, m.p. 129—132°C.
518	28	$CH_2=CHBr$	6-nitro-1-propyl-9-vinyl//acetic acid
519	32	$CH\equiv CHCH_2Br$	α,3-dimethyl-1-ethyl-9-propargyl-4,4,5-tripropyl//acetic acid
520	34	CH_2CHCH_2Br	9-allyl-1-t-butyl-α,α-diisopropyl-3,3,4,4,5-pentaethyl//acetic acid

TABLE IX—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
521	37	C_2H_5I	7-hydroxy-1-(propyl)-β,β,9-triethyl//propionic acid
522	38	CH_3I	1-cyclobutyl-3,9-dimethyl-8-nitro-α-propyl//propionic acid
523	41	$CH_2=C(CH_3)CH_2Cl$	1,4,4-triethyl-9-methallyl-α,α,β-3-tetramethyl//propionic acid
524	45		1-methyl-6-nitro-$\alpha,\alpha,\beta,\beta$,3-pentaethyl-9-phenethyl//propionic acid
525	47	1-(3-chloropropyl)piperazine	1-cyclopropyl-α,β-diethyl-7-ethoxy-9-(3-piperazinopropyl)//propionic acid
526	48	CH_3I	1,9-dimethyl//butyric acid
527	48		9-benzyl-1-methyl//butyric acid
528	49	C_2H_5Cl	1,9-diethyl-γ,3-dimethyl//butyric acid
529	51	$CH_2=CHBr$	1-cyclobutyl-3,3-dimethyl-β,γ,γ,4-tetrapropyl-9-vinyl//butyric acid
530	52	$CH_2=CHBr$	7-chloro-$\alpha,\beta,\beta,\gamma,\gamma$,4-heptaethyl-1-methyl-9-vinyl//butyric acid
531	58	C_2H_5I	α-methyl-1,8,9-triethyl//butyric acid
532	62	CH_3I	α,β-diethyl-1,5-dipropyl-3,3,9-trimethyl//butyric acid
532a	64a	CH_3I	1,5,9-trimethyl//acetic acid, m.p. 132—134°C.

TABLE IX—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-(*SUFFIX LISTED BELOW*)]
			PREFIX//SUFFIX
532b	25	C_2H_5Br	6-benzyloxy-9-ethyl-1-methyl//acetic acid, nmr ($CDCl_3$) δ 1.73 (s, 3H), 5.12 (s, 2H)
532c	64b	CH_3I	5-chloro-1,9-dimethyl//acetic acid, m.p. 105—110°C.
532d	784	CH_3I	6-benzyloxy-1,9-dimethyl//acetic acid, m.p. 167—168°C.

TABLE X

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
533	3	$CH_2=CHCH_2Br$	9-allyl-1-methyl//acetic acid
534	3	CH_3I	1,9-dimethyl//acetic acid
535	3	4-(2-chloroethyl)morpholine	1-methyl-9-(2-morpholinoethyl)//acetic acid
536	96	$n\text{-}C_3H_7I$	1-methyl-9-propyl//propionic acid
537	96	CH_3I	1,9-dimethyl//propionic acid
538	96	$CH{\equiv}CCH_2Br$	1-methyl-9-propargyl//propionic acid
539	96	$CH_2=CHCH_2Cl$	9-allyl-1-methyl//propionic acid
540	65	CH_3I	1,9-dimethyl//carboxylic acid
541	65	1-(3-chloropropyl)piperidine	1-methyl-9-(3-piperidinopropyl)//carboxylic acid
542	68	CH_3I	6-hydroxy-1-(1-propyl)-3,3,9-trimethyl//carboxylic acid
543	70	$CH_3CH=CHBr$	1-cyclopropyl-4-isopropyl-9-(1-propenyl)//carboxylic acid
544	73	CH_3I	1-ethyl-9-methyl//acetic acid
545	73	C_2H_5Cl	1,9-diethyl//acetic acid
546	73	4-(2-chloroethyl)morpholine	1-ethyl-9-(2-morpholinoethyl)//acetic acid
547	73	$CH{\equiv}CCH_2Br$	1-ethyl-9-propargyl//acetic acid
548	74	CH_3I	9-methyl-1-propyl//acetic acid
549	74	$n\text{-}C_3H_7Cl$	1,9-dipropyl//acetic acid
550	74	$CH_2=CHCH_2Br$	9-allyl-1-propyl//acetic acid

TABLE X—continued.

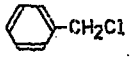
EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
551	74	$CH_2=C(CH_3)CH_2Br$	9-methallyl-1-propyl//acetic acid
552	75	CH_3I	9-methyl-1-isopropyl//acetic acid
553	75	$CH_2=CHBr$	1-isopropyl-9-vinyl//acetic acid
554	76	n-C_3H_7Cl	1,9-dipropyl-3-methyl//acetic acid
555	76		9-benzyl-3-methyl-1-propyl//acetic acid
556	78	CH_3I	α,1,9-trimethyl//acetic acid
557	79	n-C_3H_7Cl	1-cyclohexyl-α,α-dimethyl-9-propyl//acetic acid
558	84	CH_3Cl	1,9-dimethyl-6-methoxy//acetic acid
559	89	$CH_2=CHBr$	α,α-diethyl-1-methyl-9-vinyl-8-fluoro//acetic acid
560	93	C_2H_5Cl	α,3-dimethyl-1,9-diethyl-1-phenyl-4,4,5-tripropyl//acetic acid
561	95	$CH_2=CHCH_2Br$	9-allyl-1-t-butyl-α,α-diisopropyl-3,3,4,4,5-pentaethyl//acetic acid
562	98	C_2H_5I	7-hydroxy-1-propyl-β,β,9-triethyl//propionic acid
563	99	CH_3I	1-cyclobutyl-3,9-dimethyl-8-nitro-α-propyl//propionic acid
564	106	$CH_2=CHCl$	1-methyl-6-nitro-$\alpha,\alpha,\beta,\beta$,3-pentaethyl-9-vinyl//propionic acid
565	108	C_2H_5Cl	1-cyclopropyl-6-ethoxy-α,β,9-triethyl//propionic acid
566	109	CH_3I	1,9-dimethyl//butyric acid

TABLE X—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
567	109	$CH_2=CHCH_2Cl$	9-allyl-1-methyl//butyric acid
568	110	C_2H_5Cl	1,9-diethyl-γ,3-dimethyl//butyric acid
569	112	$CH_2=CHBr$	1-cyclobutyl-3,3-dimethyl-β,γ,γ,4-tetrapropyl-9-vinyl//butyric acid
570	119	C_2H_5I	α-methyl-1,8,9-triethyl//butyric acid

EXAMPLE 571.

By following the procedure of Example 488 but using as the starting material an equivalent amount of the ester compounds of formula I in which R′ is hydrogen, obtained prior to hydrolysis in Example 1 and 3 to 125, inclusive, instead of 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid, and using an equivalent amount of the appropriate organic halide, then the corresponding N-alkylated ester compound of formula I in which R′ is lower alkyl, lower alkenyl, propargyl or phenyl(lower)alkyl is obtained.

For example, when following the procedure of Example 488, the replacement of 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid by an equivalent amount of its corresponding ethyl ester, described in Example 1, and then use of the same alkyl halide, methyl iodide, affords 1,9-dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid ethyl ester.

Similarly, the replacement of 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid by an equivalent amount of 1-methyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]-indole-1-acetic acid methyl ester, described in Example 3, affords 1,9-dimethyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole-1-acetic acid methyl ester.

By following the procedure of Example 126 but using as starting material an equivalent amount of one of the N-alkylated acid compounds of formula I, described in Examples 488 to 570, inclusive, instead of 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetic acid, and using an equivalent amount of an appropriate amine such as ammonia or a primary or secondary amine, described in Example 126, then the corresponding amide compound of formula I in which R′ is lower alkyl, lower alkenyl, propargyl phenyl(lower)alkyl and amino(lower)alkyl is obtained. Examples of such amides are listed as products in Tables XI, XII, XIII, and XIV together with the appropriate starting material, noted by the example in which it is prepared, and the amine used for the preparation of the amide.

TABLE XI

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
572	488 (title compound)	$(CH_3)_2NH$	N,N,1,9-tetramethyl//acetamide
573	488 (title compound)	CH_3NH_2	N,1,9-trimethyl//acetamide, m.p. 136—138°C.
574	488 (title compound)	NH_3	1,9-dimethyl//acetamide, m.p. 105—106°C.
575	488 (title compound)	$n\text{-}C_6H_{13}NH_2$	1,9-dimethyl-N-hexyl//acetamide
576	488 (title compound)	$(C_2H_5)_2NH$	N,N-diethyl-1,9-dimethyl//acetamide
577	488 (N-ethyl analog)	$(CH_3)_2NH$	9-ethyl-N,N,1-trimethyl//acetamide
578	488 (N-ethyl analog)	CH_3NH_2	N,1-dimethyl-9-ethyl//acetamide, m.p. 108—109°C.
579	488 (N-ethyl analog)	NH_3	9-ethyl-1-methyl//acetamide, m.p. 130—133°C.
580	488 (N-propyl analog)	$(CH_3)_2NH$	9-propyl-N,N,1-trimethyl//acetamide, m.p. 84—87°C.
581	488 (N-propyl analog)	CH_3NH_2	N,1-dimethyl-9-propyl//acetamide
582	489	CH_3NH_2	9-allyl-N,1-dimethylacetamide
583	491	$(CH_3)_2NH$	9-propargyl-N,N,1-trimethyl//acetamide
584	493	$(CH_3)_2NH$	N,N,1,9-tetramethyl//propionamide
585	493	CH_3NH_2	N,1,9-trimethyl//propionamide, m.p. 148—150°C
586	493	$(C_2H_5)_2NH$	1,9-dimethyl-N,N-diethyl//propionamide
587	495	NH_3	1-methyl-9-(3-piperidinopropyl)//propionamide
588	495	$(CH_3)_2NH$	9-(3-piperidinopropyl-N,N,1-trimethyl//propionamide

TABLE XI—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
589	497	CH_3NH_2	1,3-diisopropyl-N,6-dimethyl-9-propargyl//carboxamide
590	498	$(C_2H_5)_2NH$	N,N-diethyl-6-hydroxy-1,3,3,9-tetramethyl//carboxamide
591	501	CH_3NH_2	N,9-dimethyl-1-ethyl//acetamide
592	503	$(C_2H_5)_2NH$	9-allyl-N,N,1-triethyl//acetamide
593	504	$(CH_3)_2NH$	N,N-dimethyl-9-[2-(dimethylamino)ethyl]-1-ethyl//acetamide
594	505	CH_3NH_2	N,9-dimethyl-1-propyl//acetamide
595	507	$(C_2H_5)_2NH$	9-allyl-N,N-diethyl-1-propyl//acetamide
596	514	CH_3NH_2	1-cyclohexyl-9-propyl-N,α,α-trimethyl//acetamide
597	516	$n\text{-}C_6H_{13}NH_2$	9-allyl-1-butyl-N-hexyl//acetamide
598	517	$(CH_3)_2NH$	6-methoxy-N,N,1,9-tetramethyl//acetamide, m.p. 118—120°C.
599	519	CH_3NH_2	1-ethyl-9-propargyl-4,4,5-tripropyl-N,α,3-trimethyl//acetamide
600	524	$(C_2H_5)_2NH$	N,N,α,α,β,β,3-heptaethyl-1-methyl-6-nitro-9-phenethyl//propionamide
601	525	$(C_2H_5)_2NH$	1-cyclopropyl-7-methoxy-N,N,α,β-tetraethyl-9-(3-piperidinopropyl)//propionamide
602	526	CH_3NH_2	N,1,9-trimethyl//butyramide
603	527	$(CH_3)_2NH$	9-benzyl-N,N,1-trimethyl//butyramide

TABLE XI—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
604	528	NH_3	1,9-diethyl-γ,3-dimethyl//butyramide
605	532	CH_3NH_2	α,β-diethyl-1,5-dipropyl-N,3,3,9-tetramethyl//butyramide
605a	532a	$(CH_3)_2NH$	N,N,1,5,9-pentamethyl//acetamide, nmr ($CDCl_3$) δ 1.75 (s, 3H), 2.66 (s, 3H), 2.96 (s, 3H), 3.08 (s, 3H), 3.78 (s, 3H)
605b	532b	$(CH_3)_2NH$	6-benzyloxy-9-ethyl-N,N,1-trimethyl//acetamide, $\nu_{max}^{CHCl_3}$ 1650 cm^{-1}
605c	532c	$(CH_3)_2NH$	5-chloro-N,N,1,9-tetramethyl//acetamide, nmr ($CDCl_3$) δ 1.72 (s, 3H), 2.93 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H)
605d	532d	$(CH_3)_2NH$	6-benzyloxy-N,N,1,9-tetramethyl//acetamide, nmr ($CDCl_3$) δ 1.73 (s, 3H), 2.95 (s, 3H), 3.05 (s, 3H), 3.75 (s, 3H), 5.12 (s, 2H)

TABLE XII

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-YL)-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
606	488 (title compound)	pyrrolidine	1-[(1,9-dimethyl//acetyl]pyrrolidine, nmr ($CDCl_3$) δ 1.77 (3H), 2.82 (2H), 3.78 (3H).
607	488 (title compound)	piperidine	1-[(1,9-dimethyl//acetyl]piperidine
608	488 (title compound)	morpholine	1-[(1,9-dimethyl//acetyl]morpholine, nmr ($CDCl_3$) δ 1.73 (3H), 3.03 (2H), 3.70 (3H)
609	488 (title compound)	N-methyl-piperazine	1-methyl-4-[1,9-dimethyl//acetyl]piperazine, $\nu_{max}^{CHCl_3}$ 1640 cm^{-1}
610	488 (N-ethyl analog)	pyrrolidine	1-[(9-ethyl-1-methyl//acetyl]-pyrrolidine
611	488 (N-ethyl analog)	piperidine	1-[(9-ethyl-1-methyl//acetyl]piperidine
612	488 (N-propyl analog)	morpholine	1-[(1-methyl-9-propyl//acetyl]morpholine
613	488 (title compound)	N-piperazine-ethanol	1-(2-hydroxyethyl)-4-[1,9-dimethyl//acetyl]-piperazine, ν_{max}^{film} 1625 cm^{-1}.
614	492	pyrrolidine	1-[(1-methyl-9-propyl//propionyl]pyrrolidine
615	493	piperidine	1-[(1,9-dimethyl//propionyl]piperidine
616	494	morpholine	1-[(1-methyl-9-phenethyl//propionyl]morpholine
617	495	piperazine	1-[1-methyl-9-(3-piperidinopropyl)//propionyl]piperazine
618	496	pyrrolidine	1-{1-methyl-9-[2-(1-pyrrolidinyl)-ethyl]//carbonyl}pyrrolidine
619	501	morpholine	1-[(1-ethyl-9-methyl//acetyl]morpholine

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TABLE XII—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-YL)-(*SUFFIX LISTED BELOW*)]
			PREFIX//SUFFIX
620	502	N-piperazine-propanol	1-(3-hydroxypropyl)-4-[1,9-diethyl//acetyl]-piperazine
621	505	pyrrolidine	1-[(9-methyl-1-propyl//acetyl]pyrrolidine
622	507	morpholine	1-[(9-allyl-1-propyl//acetyl]morpholine
623	509	piperidine	1-[(9-benzyl-1-isopropyl//acetyl]piperidine
624	511	piperazine	1-[(1,9-dipropyl-3-methyl//acetyl]piperazine
625	513	N-ethyl-piperazine	1-ethyl-4-[(α,1,9-trimethyl-α//acetyl]piperazine
626	525	N-propyl-piperazine	1-propyl-4-[(1-cyclopropyl-α,β-diethyl-6-ethoxy-9-(3-piperidino-propyl//propionyl]piperazine
627	566	pyrrolidine	1-[(1,9-dimethyl//butyryl]pyrrolidine
628	527	N-piperazine-methanol	9-benzyl-1-(hydroxymethyl)-4-[(1-methyl//butyryl]piperazine
629	530	morpholine	1-[(7-chloro-α,β,β,γ,γ,4,4-heptaethyl-1-methyl-9-vinyl//butyryl]morpholine

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TABLE XIII

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
630	534	$(CH_3)_2NH$	N,N,1,9-tetramethyl//acetamide
631	534	CH_3NH_2	N,1,9-trimethyl//acetamide
632	534	NH_3	1,9-dimethyl//acetamide
633	534	$n\text{-}C_6H_{13}NH_2$	1,9-dimethyl-N-hexyl//acetamide
634	534	$(C_2H_5)_2NH$	N,N-diethyl-1,9-dimethyl//acetamide
635	533	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//acetamide
636	537	CH_3NH_2	N,1,9-trimethyl//propionamide
637	537	$(C_2H_5)_2NH$	1,9-dimethyl-N,N-diethyl//propionamide
638	539	NH_3	9-allyl-1-methyl//propionamide
639	539	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//propionamide
640	541	CH_3NH_2	N,1-dimethyl-9-(3-piperidinopropyl)//carboxamide
641	542	$(C_2H_5)_2NH$	N,N-diethyl-6-hydroxy-1-propyl-3,3,9-trimethyl//carboxamide
642	544	CH_3NH_2	N,9-dimethyl-1-ethyl//acetamide
643	546	$(C_2H_5)_2NH$	9-(2-morpholinoethyl)-N,N,1-triethyl//acetamide
644	547	$(CH_3)_2NH$	N,N-dimethyl-1-ethyl-9-propargyl//acetamide
645	548	CH_3NH_2	N,9-dimethyl-1-propyl//acetamide
646	550	$(C_2H_5)_2NH$	9-allyl-N,N-diethyl-1-propyl//acetamide
647	557	CH_3NH_2	1-cyclohexyl-9-propyl-N,α,α-trimethyl//acetamide

TABLE XIII—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)]
			PREFIX//SUFFIX
648	558	$(CH_3)_2NH$	6-methoxy-N,N,1,9-tetramethyl//acetamide
649	564	$(C_2H_5)_2$	N,N,α,α,β,β,3-heptaethyl-1-methyl-6-nitro-9-vinyl//propionamide
650	565	$(C_2H_5)_2NH$	1-cyclopropyl-6-ethoxy-N,N,α,β,9-pentaethyl//propionamide
651	566	CH_3NH_2	N,1,9-trimethyl//butyramide
652	567	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//butyramide
653	568	NH_3	1,9-diethyl-γ,3-dimethyl//butyramide

TABLE XIV

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-YL)-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
654	533	pyrrolidine	1-[(9-allyl-1-methyl//acetyl]pyrrolidine
655	534	piperidine	1-[(1,9-dimethyl//acetyl]piperidine
656	535	morpholine	1-[(1-methyl-9-(2-morpholinoethyl)//acetyl]-morpholine
657	536	pyrrolidine	1-[(1-methyl-9-propyl//propionyl]pyrrolidine
658	537	piperidine	1-[(1,9-dimethyl//propionyl]piperidine
659	538	morpholine	1-[(1-methyl-9-propargyl//propionyl]morpholine
660	539	piperazine	1-[9-allyl-1-methyl//propionyl]piperazine
661	539	N-methyl-piperazine	1-methyl-4-[9-allyl-1-methyl//propionyl]-piperazine
662	540	pyrrolidine	1-[(1,9-dimethyl//carbonyl]pyrrolidine
663	541	morpholine	1-{(1-methyl-9-(3-piperidinopropyl)//carbonyl}morpholine
664	544	morpholine	1[(1-ethyl-9-methyl//acetyl]morpholine
665	547	N-piperazine-propanol	1-(3-hydroxypropyl)-4-[(1-ethyl-9-propargyl//acetyl]piperazine
666	548	pyrrolidine	1-[(9-methyl-1-propyl//acetyl]pyrrolidine
667	549	morpholine	1-[(1,9-dipropyl//acetyl]morpholine
668	552	piperidine	1-[(1-isopropyl-9-methyl//acetyl]piperidine
669	555	piperazine	1-[9-benzyl-3-methyl-1-propyl//acetyl]piperazine
670	556	N-ethyl-piperazine	1-ethyl-4-[α,1,9-trimethyl//acetyl]piperazine

TABLE XIV—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-YL)-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
671	565	N-propyl-pyrazine	1-propyl-4-[(1-cyclopropyl-6-ethoxy-α,β,9-triethyl//propionyl]piperazine
672	566	pyrrolidine	1-[(1,9-dimethyl//butyryl]pyrrolidine
673	567	N-piperazine-methanol	1-(hydroxymethyl)-4-[(9-allyl-1-methyl//butyryl]piperazine

EXAMPLE 674.

1,9-DIMETHYL-1-[2-(DIMETHYLAMINO)ETHYL]-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE [I; $R^1 = CH_3$, R^2, R^3, R^4, R^5, AND $R^6 = H$, $R^7 = CH_3$, $X = O$ AND $Y = CH_2CH_2N(CH_3)_2$]

A solution of N,N,1,9-tetramethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide (12.0 g), described in Example 572, in dry tetrahydrofuran (100 ml.) is added dropwise to a mechanically stirred mixture of lithium aluminium hydride (5 g) in dry tetrahydrofuran (THF) (100 ml.). The mixture is heated at reflux for twenty hours under nitrogen. Water-THF (1:1, 50 ml.) is added to destroy the excess hydride. The mixture is filtered through celite, diluted with water (300 ml.) and extracted three times with ether. The organic phase is dried over sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield the title compound, nmr ($CDCl_3$) δ 1.66 (3H), 2.70 (6H), 3.83 (3H).

The corresponding hydrochloric acid addition salt, 1,9-dimethyl-1-[2-(dimethylamino)ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole hydrochloride, has m.p. 229—230°C. after crystallization from methylene dichloride-benzene.

The title compound is resolved by the use of d- and l- di-*p*-toluoyl-tartaric acid into the optical isomer, (−)-1,9-dimethyl-1-[2-(dimethylamino)ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole, $[\alpha]_D^{CHCl_3} = -41.5°$ and its corresponding (+) antipode having $[\alpha]_D^{CHCl_3}$ 34.6°.

By following the procedure of Example 674 but using as starting material an equivalent amount of one of the N-alkylated amide compounds of formula VII, described in Examples 573 to 673 instead of N,N,1,9-tetramethyl-1,3,4,9-tetrahydro-[3,4-b]indole-1-acetamide then the corresponding N-alkylated amine compound of formula I is obtained. Examples of such compounds are listed as products in Tables XV and XVI together with the appropriate starting material. In each case the starting material is noted by the example in which it is prepared.

TABLE XV

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE
675	573	1,9-dimethyl-1-[2-(methylamino)ethyl] nmr ($CDCl_3$) δ 1.10 (1H), 1.66 (S, 3H), 2.33 (S, 3H), corresponding hydrobromic acid addition salt has m.p. 223—225°C.
676	574	1-(2-aminoethyl)-1,9-dimethyl, $\nu_{max}^{CHCl_3}$ 3369, 1570 cm^{-1}.
677	575	1,9-dimethyl-1-[2-(hexylamino)ethyl]
678	576	1-[2-(diethylamino)ethyl]-1,9-dimethyl, nmr ($CDCl_3$) δ 0.94 (t, 6H), 1.06 (S, 3H), 2.50 (m, 10H).
679	577	1-[2-(dimethylamino)ethyl]-9-ethyl-1-methyl, nmr ($CDCl_3$) δ 1.39 (3H), 1.70 (3H), 2.73 (m, 12H), corresponding hydrochloric acid addition salt has m.p. 202—205°C.
680	578	9-ethyl-1-methyl-1-[2-(methylamino)ethyl]
681	579	1-(2-aminoethyl)-9-ethyl-1-methyl
682	580	1-[2-(dimethylamino)ethyl]-1-methyl-9-propyl, nmr ($CDCl_3$), δ 1.00 (t, 3H), 1.65 (S, 3H), corresponding maleic acid addition salt has m.p. 125—126°C.
683	581	1-methyl-1-[2-(methylamino)ethyl]-9-propyl
684	582	9-allyl-1-methyl-1-[2-(methylamino)ethyl]
685	583	1-[2-(dimethylamino)ethyl]-1-methyl-9-propargyl
686	584	1,9-dimethyl-1-[3-(dimethylamino)propyl], nmr ($CDCl_3$) δ 1.60 (3H), 2.68 (6H), corresponding maleic acid addition salt has m.p. 115—118°C.
687	585	1,9-dimethyl-1-[3-(methylamino)propyl], nmr ($CDCl_3$) δ 1.6 (3H), 2.9 (3H), 3.6 (3H), corresponding hydrochloric acid addition salt has m.p. 194—196°C.
688	586	1-[3-(diethylamino)propyl]-1,9-dimethyl
689	587	1-(3-aminopropyl)-1-methyl-9-(3-piperidinopropyl)
690	588	1-[3-(dimethylamino)propyl-1-methyl-9-(3-piperidinopropyl)
691	589	1,3-diisopropyl-1-methyl-1-(methylamino)methyl-9-propargyl
692	590	1-(diethylamino)methyl-6-hydroxy-1,3,3,9-tetramethyl

TABLE XV—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE
693	591	1-ethyl-9-methyl-1-[2-(methylamino)ethyl]
694	592	9-allyl-1-[2-(diethylamino)ethyl]-1-ethyl
695	593	1,9-bis-[2-(dimethylamino)ethyl]-1-ethyl
696	594	9-methyl-1-[2-(methylamino)ethyl-1-propyl
697	595	9-allyl-1-[2-(diethylamino)ethyl]-1-propyl
698	596	1-cyclohexyl-1-[1,1-dimethyl-2-(methylamino)-ethyl]-9-propyl
699	597	9-allyl-1-butyl-1-[2-(hexylamino)ethyl]
700	598	1,9-dimethyl-1-[2-(dimethylamino)ethyl]-6-methoxy, nmr ($CDCl_3$) δ 2.60 (S, 3H), 3.85 (S, 3H), corresponding maleic acid addition salt has m.p. 109—111°C.
701	599	1-ethyl-3-methyl-1-[1-methyl-2-(methylamino)-ethyl]-9-propargyl-4,4,5-tripropyl
702	600	1-[3-diethylamino)-1,1,2,2-tetraethylpropyl]-3-ethyl-1-methyl-6-nitro-9-phenethyl
703	601	1-cyclopropyl-1-[1,2-diethyl-3-(diethylamino)-propyl]-7-ethoxy-9-(3-piperidinopropyl)
704	602	1,9-dimethyl-1-[4-(methylamino)butyl]
705	603	9-benzyl-1-[4-(dimethylamino)butyl]-1-methyl
706	604	1,9-diethyl-1-(4-amino-1-methylbutyl)
707	605	1-[2,3-diethyl-4-(methylamino)butyl]-1,5-dipropyl-3,3,9-trimethyl
708	606	1,9-dimethyl-1-[2-(1-pyrrolidinyl)ethyl], nmr ($CDCl_3$) δ 1.62 (s, 3H), 3.74 (s, 3H), m.p. of corresponding hydrochloric acid addition salt, 230—231°C.
709	607	1,9-dimethyl-1-(2-piperidinoethyl), nmr ($CDCl_3$) δ 1.61 (s, 3H), 2.32 (m, 6H), 9.81 (m, 2H), m.p. of corresponding hydrochloric acid addition salt, 233—235°C.
710	608	1,9-dimethyl-1-(2-morpholinoethyl) nmr ($CDCl_3$) δ 1.62 (3H), 2.77 (2H), 3.72 (3H), hydrochloric acid addition salt has m.p. 230—231°C.
711	609	1,9-dimethyl-1-[2-(4-methyl-1-piperazinyl)ethyl], nmr ($CDCl_3$), δ 1.56 (s, 3H), 2.22 (s, 3H), 2.3 (m, 8H), dimaleate addition salt has m.p. 194—195°C.

TABLE XV—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE
712	610	9-ethyl-1-methyl-1-[2-(1-pyrrolidinyl)ethyl]
713	611	9-ethyl-1-methyl-1-(2-piperidinoethyl)
714	612	1-methyl-1-(2-morpholinoethyl)-9-propyl
715	613	1,9-dimethyl-1-{2-[4-(2-hydroxyethyl)-1-piperazinyl]ethyl}, nmr ($CDCl_3$) δ 1.60 (s, 3H), 3.70 (s, 3H), m.p. of corresponding dihydrochloride salt, m.p. 219—220°C.
716	614	1-methyl-9-propyl-1-[3-(1-pyrrolidinyl)propyl]
717	615	1,9-dimethyl-1-(3-piperidinopropyl)
718	616	1-methyl-1-(3-morpholinopropyl)-9-phenethyl
719	617	1,9-bis-(3-piperazinopropyl)-1-methyl
720	618	1-methyl-1-[(1-piperazinyl)methyl]-9-[2-(1-pyrrolidinyl)ethyl]
721	619	1-ethyl-9-methyl-1-(2-morpholinoethyl)
722	620	1,9-diethyl-1-{2-[4-(3-hydroxypropyl)-1-piperazinyl]ethyl}
723	621	9-methyl-1-propyl-1-[2-(1-pyrrolidinyl)ethyl]
724	622	9-allyl-1-(2-morpholinoethyl)-1-propyl
725	623	9-benzyl-1-isopropyl-1-(2-piperidinoethyl)
726	624	1,9-dipropyl-3-methyl-1-(2-piperazinoethyl)
727	625	1,9-dimethyl-1-[1-methyl-2-(4-methyl-1-piperazinyl)ethyl]
728	626	1-cyclopropyl-1-{1,2-diethyl-3-(4-propyl-1-piperazinyl)propyl}-6-ethoxy-9-(3-piperidino-propyl)
729	627	1,9-dimethyl-1-[4-(1-pyrrolidinyl)butyl]
730	628	9-benzyl-1-{4-[4-(hydroxymethyl)-1-piperazinyl]-butyl}-1-methyl
731	629	7-chloro-4,4-diethyl-1-methyl-1-(4-morpholino-1,1,2,2,3-pentaethylbutyl)-9-vinyl
731a	605a	1-[2-dimethylamino)ethyl]-1,5,9-trimethyl, nmr ($CDCl_3$) δ 1.63 (s, 3H), 2.20 (s, 6H), 2.67 (s, 3H), 3.74 (s, 3H), malcate salt has m.p. 144—145°C.
731b	605b	6-benzyloxy-1-[2-dimethylamino)ethyl]-9-ethyl-1-methyl, nmr ($CDCl_3$) δ 1.38 (t, J = 7, 3H), 1.62 (s, 3H), 2.18 (s, 6H), hydrochloride salt has m.p. 216—217°C.

TABLE XV—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE
731c	605c	5-chloro-1-[2-(dimethylamino)ethyl]-1,9-dimethyl, nmr ($CDCl_3$) δ 1.63 (s, 3H), 2.18 (s, 6H), 3.72 (s, 3H), maleate salt has m.p. 148—151°C.
731d	605d	6-benzyloxy-1,9-dimethyl-1-[2-(dimethylamino)-ethyl], nmr ($CDCl_3$) δ 1.60 (s, 3H), 2.17 (s, 6H), 3.68 (s, 3H), 5.12 (s, 2H), hydrochloride salt has m.p. 238—239°C.

TABLE XVI

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: *(PREFIX LISTED BELOW)*-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
732	630	1,9-dimethyl-1-[2-(dimethylamino)ethyl], nmr ($CDCl_3$) δ 3.72 (s, 6H), 6.40 (s, 3H)
733	631	1,9-dimethyl-1-[2-(methylamino)ethyl]
734	632	1-(2-aminoethyl)-1,9-dimethyl
735	633	1,9-dimethyl-1-[2-(hexylamino)ethyl]
736	634	1-[2-diethylamino)ethyl]-1,9-dimethyl
737	635	9-allyl-1-[2-(dimethylamino)ethyl]-1-methyl
738	636	1,9-dimethyl-1-[3-(methylamino)propyl]
739	637	1-[3-(diethylamino)propyl]-1,9-dimethyl
740	638	9-allyl-1-(3-aminopropyl)-1-methyl
741	639	9-allyl-1-[3-(dimethylamino)propyl]-1-methyl
742	640	1-methyl-1-[(methylamino)methyl]-9-(3-piperidinopropyl)
743	641	1-[(diethylamino)methyl]-6-hydroxy-1-propyl-3,3,9-trimethyl
744	642	1-ethyl-9-methyl-1-[2-(methylamino)ethyl]
745	643	1-[2-(diethylamino)ethyl]-1-ethyl-9-(2-morpholinoethyl)
746	644	1-[2-(dimethylamino)ethyl]-1-ethyl-9-propargyl
747	645	9-methyl-1-[2-(methylamino)ethyl]-1-propyl
748	646	9-allyl-1-[2-(diethylamino)ethyl]-1-propyl
749	647	1-cyclohexyl-1-[1,1-dimethyl-2-(methylamino)-ethyl]-9-propyl
750	648	1,9-dimethyl-1-[2-(dimethylamino)ethyl]-6-methoxy
751	649	1-[3-(diethylamino)-1,1,2,2-tetramethylpropyl)-3-ethyl-6-nitro-9-vinyl
752	650	1-cyclopropyl-1-[1,2-diethyl-3-(diethylamino)-propyl]-6-ethoxy-9-ethyl
753	651	1,9-dimethyl-1-[4-(methylamino)butyl]
754	652	9-allyl-1-[4-(dimethylamino)butyl]-1-methyl
755	653	1-[4-amino-1-methylbutyl)-1,9-diethyl-3-methyl
756	654	9-allyl-1-methyl-1-[2-(1-pyrrolidinyl)ethyl]

TABLE XVI—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
757	655	1,9-dimethyl-1-(2-piperidinoethyl)
758	656	1-methyl-1,9-bis(2-morpholinoethyl)
759	657	1-methyl-9-propyl-1-[3-(1-pyrrolidinyl)propyl]
760	658	1,9-dimethyl-1-(3-piperidinopropyl)
761	659	1-methyl-1-(3-morpholinopropyl)-9-propargyl
762	660	9-allyl-1-methyl-1-(3-piperazinopropyl)
763	661	9-allyl-1-methyl-1-[3-(4-methyl-1-piperazinyl)-propyl]
764	662	1,9-dimethyl-1-[1-pyrrolidinyl)methyl]
765	663	1-methyl-1-(morpholinomethyl)-9-(3-piperidino-propyl)
766	664	1-ethyl-9-methyl-1-(2-morpholinoethyl)
767	665	1-ethyl-1-{2-[4-(3-hydroxypropyl)-1-piperazinyl]-ethyl}-9-propargyl
768	666	9-methyl-1-propyl-1-[2-(1-pyrrolidinyl)ethyl]
769	667	1,9-dipropyl-1-(2-morpholinoethyl)
770	668	1-isopropyl-9-methyl-1-(2-piperidinoethyl)
771	669	9-benzyl-3-methyl-1-(2-piperazinoethyl)-1-propyl
772	670	1,9-dimethyl-1-[1-methyl-2-(4-methyl-1-piperazinyl)ethyl]
773	671	1-cyclopropyl-6-ethoxy-9-ethyl-1-[1,2-diethyl-3-(4-propyl-1-piperazinyl)propyl
774	672	1,9-dimethyl-1-{4-(1-pyrrolidinyl)butyl]
775	673	9-allyl-1-{4-[4-(hydroxymethyl)-1-piperazinyl]-butyl}-1-methyl

EXAMPLE 776.

1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-CARBOXAMIDE (VII; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7 = H$, $X = O$, AND $Z = CONH_2$

By following the procedure of Example 1 but using boron trifluoride-ethenole as the acid catalyst and an equivalent amount of pyruvamide instead of ethyl acetoacetate, 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-carboxamide, m.p. 188—189°C. after recrystallization from benzene-hexane, identical with the product of Example 133, is obtained.

In the same manner but using an equivalent amount of the appropriate starting material of formula II together with the appropriate α-, β-, γ- or δ-ketoamide, the

products listed in Tables III and IV are obtained. For example, by using tryptophol (II; R^2, R^4, R^4, R^5, R^6 = H and X^1 = OH) and the β-ketoamide, N,N-dimethyl-acetoacetamide, in the procedure of the Example, N,N,1-trimethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetamide, identical with the product of Example 126, is obtained.

EXAMPLE 777.

1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-CARBOXALDEHYDE

A mixture of the starting material, tryptophol (32.2 g, 0.2 mole), acetonyl acetate (23.2 g, 0.2 mole) and 3.2 g of *p*-toluenesulfonic acid in 500 ml of benzene is refluxed for 1½ hrs. in the presence of a Dean-Stark water trap. The benzene solution is washed with 5% sodium bicarbonate, water, dried and evaporated to afford an oil. The oil is subjected to chromatography on a silica gel column using 10% ethyl acetate in benzene as eluent. The acetate 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-methanol acetate is obtained as an oil, nmr ($CDCl_3$) δ 1.52 (S, 3H), 2.08 (S, 3H), 4.35 (2H).

This acetate is dissolved in 250 ml of methanol and stirred at room temperature. To this solution is added dropwise 20 ml of 10N NaOH. Hydrolysis is immediate. Most of the methanol is removed under reduced pressure, and water is added. The mixture is rendered neutral and extracted with chloroform. The chloroform extract is dried and evaporated to afford the primary alcohol, 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-methanol, m.p. 145—147°C., nmr ($CDCl_3$) δ 1.43 (s, 3H), 2.68 (t, J = 5.5 cps, 2H), 3.65 (d, J = 6 cps, 2H), 3.86 (t, J = 5.5 cps, 2H), after crystallization from benzene-petroleum ether.

N,N-dicyclohexylcarbodiimide (17.36 g, 0.084 mole) is added to a cooled, stirred solution of the above primary alcohol (6.09 g, 0.028 mole) in 63 ml of dimethyl sulfoxide-benzene (2:1) containing trifluoroacetic acid (1.12 ml, 0.014 mole) and pyridine (2.24 ml, 0.028 mole). The reaction is stirred at room temperature under nitrogen for 5 hrs. The reaction mixture is now diluted with 600 ml of ether, followed by the dropwise addition of a solution of oxalic acid (7.56 g) in 21 ml of methanol. After thirty minutes, water (600 ml) is added and the insoluble material is collected. The organic phase is washed with water (2 ×), 5% aqueous sodium bicarbonate (2 ×) and water (2 ×). After drying ($MgSO_4$) the organic phase is evaporated to yield an oil. The oil is purified by chromatography on silica gel. Elution with 10% ether in benzene affords the title compound as eluate, nmr ($CDCl_3$) δ 1.59 (s, 3H), 2.84 (t, J = 5.5 cps, 2H), 4.15 (t, J = 5.5 cps, 2H).

EXAMPLE 778.

1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-carboxaldehyde, described in Example 777, is treated with an excess of dimethylamine according to the method of K. N. Campbell, *et al.*, J. Amer. Chem. Soc., *70*, 3868 (1948), to yield the corresponding Schiff base. Reduction of the latter compound with sodium borohydride according to the procedure described by E. Schenker, Angew Chem., *73*, 81 (1961), affords 1-[2-(dimethylamino)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole, identical to the product of Example 309.

By following the procedures of Examples 777 and 778 in sequence, but using as starting material in Example 777 an equivalent amount of the appropriate starting material of formula II, for example, those described in Examples 1 to 125, inclusive, and using an equivalent amount of the appropriate ketoalcohol lower alkyl ester of formula VI, described above, and in the procedure of Example 778 using an appropriate amine of formula HNR^8R^9 in which R^8 and R^9 are as defined in the first instance, then the respective compounds of formula I, for example, those described in Example 309 (other than the title compound) to 487, inclusive, are obtained.

More specifically exemplified, the use of indole-3-ethanethiol, acetonyl acetate and n-hexylamine in the manner just described for the starting material of formula II, the appropriate ketoalcohol lower alkyl ester and amine, respectively, yields 1-[2-(hexylamino)ethyl]-1-methyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole.

EXAMPLE 779.

Oxidation of 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-carboxaldehyde, described in Example 777, with silver oxide according to the method of Delépine and Bonnet, cited above, affords 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-carboxylic acid, nmr ($CDCl_3$) δ 1.79 (s, 3H), 2.83 (t, 2H), 4.17 (t, 2H), 9.20 (1H), identical to the product obtained in Example 4.

By following the procedures of Examples 777 and 779, in sequence, but using as

starting material an equivalent amount of the appropriate starting material of formula II, for example, those described in Examples 1 to 125, inclusive, instead of tryptophol, and using an equivalent amount of the appropriate ketoalcohol lower alkyl ester of formula VI, in which R^1 is as defined in the first instance and Z is CH_2OCOR^{20} or $Alk^1CH_2OCOR^{20}$ wherein R^{20} and Alk^1 are as defined in the first instance, then the acid compound of formula I in which R^7 is hydrogen and Y is COOH or Alk^1COOH wherein Alk^1 is as defined above, for example, the respective products of Examples 1 to 125, inclusive, are obtained.

More specifically exemplified, according to the procedures of Examples 777 and 779, the use of tryptophol and 6-acetoxy-2-hexanone, affords 1-methyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole-1-butyric acid, identical to the product of Example 48. Similarly, the use of tryptophol and 5-acetoxypentan-2-one affords 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-propionic acid, identical to the product of Example 2.

EXAMPLE 780.

1-(AMINOMETHYL)-1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE (I, $R^1=CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7=H$, $X=O$ AND $Y=CH_2CH_2$

A solution of 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-carboxaldehyde (547 mg), described in Example 777, aqueous hydroxylamine hydrochloride (2.5 ml of 5N) and aqueous sodium acetate (2.5 ml of 5N) and methanol (5 ml) is heated at 50—60°C. for 5 min. and then kept at 4°C. for 16 hrs. The precipitate is collected and recrystallized from ethanol water to afford 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-carboxaldehyde oxime, m.p. 176—178°C.

The latter compound (230 mg) in dry THF (10 ml) is added dropwise to a stirred mixture of lithium aluminum hydride (200 mg) in 15 ml. of THF at ice bath temperature. The mixture is stirred for 1 hr., during which time it is allowed to come to room temperature. Excess lithium aluminum hydride is destroyed by the careful addition of H_2O/THF (1:1). Insoluble material is collected on a filter and the filtrate is concentrated. The concentrate is taken up in ether. The ether solution is dried ($MgSO_4$), filtered and concentrated to afford the title compound, identical with the compound of the same name described in Example 316.

EXAMPLE 781.

1-METHYL-1-[3-(1-PYRROLIDINYL)PROPYL]-1,3,4,9-TETRAHYDRO-PYRANO[3,4-b]INDOLE [I, $R^1=CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7=H$, $X=O$

AND $Y=$ 

To a solution of tryptophol (15 g, 0.09 M) in 150 ml of benzene, 5-chloro-2-pentanone (12 g, 0.10 M) is added. The mixture is heated in the presence of 200 mg of p-toluenesulfonic acid and hydrated alkali-aluminum silicate (Molecular Sieves No. 4). After 1 hr. of refluxing, 400 mg more of acid is added. After a total of 2 hrs. the reaction is cooled, filtered and washed with 5% sodium bicarbonate, water and dried over sodium sulfate. Evaporation under reduced pressure affords an oil. This oil is purified by chromatography on silica gel. Elution with benzene and concentration of the eluent gives 1-(3-chloropropyl)-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole nmr ($CDCl_3$) δ 1.33 (3H); 1.93 (4H), 2.75 (2H).

A solution of the latter compound (250 mg, 0.9 millimoles) in 10 ml of THF and 1.5 ml of pyrrolidine is heated at reflux for 16 hrs. The mixture is concentrated under reduced pressure and the residue partitioned between 5% sodium carbonate and chloroform. The organic phase is washed with water, dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the title compound, identical with the product of Example 365.

By following the procedure of Example 781 but using as starting material an equivalent amount of the appropriate starting material of formula II, for example, those described in Examples 1 to 125, inclusive, instead of tryptophol, and using an equivalent amount of the appropriate β-, γ-, or δ-haloketone of formula VI, described above, and the appropriate amine of formula HNR^8R^9, described above, then the respective compounds of formula I, for example those described in Examples 309 to 487, inclusive, are obtained.

$$R^1\text{—}\overset{\overset{O}{\|}}{C}\text{—Alk}NO_2,$$

described above, then the respective primary amine compounds of formula I are obtained.

EXAMPLE 784.

6-HYDROXY-1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-ACETIC ACID (VII; $R^1=CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7=H$, $R^5=6$-OH, $X=O$, AND $Z=CH_2COOH$)

A mixture of 6-benzyloxy-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid (5.3 g., 0.015 mole), prepared as described in Example 25, in 250 ml. of anhydrous ethanol, and 1.1 g. of 10% palladium on carbon is stirred at room temperature under a hydrogen atmosphere until no more hydrogen is being taken up by the reaction mixture. The catalyst is removed by filtration through diatomaceous earth (Celite) and the filtrate concentrated. The residue is recrystallized from ethanol-benzene to afford the title compound, m.p. 170—171°C.

The corresponding benzylamine salt is prepared by the mixing of equimolar ethereal solutions of benzylamine and the above product. The resulting solid is recrystallized from acetonitrile to afford 6-hydroxy-1-methyl-1,3,4,9-terrahydropyrano-[3,4-b]indole-1-acetic acid benzylamine salt, m.p. 191—193°C. The corresponding acetate is prepared by allowing a mixture of the title compound and a five molar excess of acetic anhydride in pyridine solution to stand for 24 hrs. Dilution of the mixture with water extraction with ether and recrystallization of the extract residue from benzene-petroleum ether, affords 6-acetoxy-1-methyl-1,3,4,9-tetrahydro[3,4-b]indole-1-acetic acid, identical with the product of Example 24.

b] By following the procedure of this example but replacing 6-benzyloxy-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid with an equivalent amount of 6 - benzyloxy - 1 - [2 - (dimethylamino)ethyl] - 9 - ethyl - 1 - methyl - 1,3,4,9 - tetrahydropyrano[3,4-b]indole hydrochloride, described in Example 731b, then 1-[2-(dimethylamino)ethyl] - 9 - ethyl - 1 - methyl - 1,3,4,9 - tetrahydropyrano[3,4 - b]indol-6 - ol hydrochloride, m.p. 213—214°C; the corresponding free base of the latter compound has nmr ($CDCl_3$) δ 1.36 (t, J = 7, 3H), 1.6 (s, 3H), 2.18 (s, 6H). Likewise, replacement with 6-benzyloxy-1,9-dimethyl-1-[2-(dimethylamino)ethyl]-1,3,4,9-tetrahydropyrano[3,4 - b]indole hydrochloride described in Example 731d, gives 1,9 - dimethyl-1-[2-(dimethylamino)ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indol-6-ol hydrochloride, m.p. 242—244°C., corresponding free base has nmr ($CDCl_3$) δ 1.6 (s, 3H), 2.2 (s, 6H), 3.7 (s, 3H).

EXAMPLE 785.

1,1-DIMETHYL-1,3,4,9-TETRAHYDROPYRANO-3,4-b]INDOLE (VII; $R^1=CH_3$, R^2, R^3, R^4, R^5, R^6, AND $R^7=H$ AND $Z=CH_3$)

A solution of tryptophol (8 g, 0.05M), acetone (5 g) and *p*-toluenesulfonic acid (100 mg) in 100 ml of benzene containing hydrated alkali-aluminium silicate (Molecular Sieves No. 4) is heated to reflux for 1 hr. More *p*-toluenesulfonic acid (100 mg) and the ketone, acetone (3 g), is added and the reflux continued for a further 1.5 hrs.

The mixture is filtered and the filtrate is washed with 5% sodium bicarbonate and water. After drying over sodium sulfate the benzene is evaporated under reduced pressure affording a solid. Chromatography of this solid on silica gel using 30% ethyl acetate in benzene as eluant gives a white product which is recrystallized once from benzene-petroleum ether to give the title compound, m.p. 142—144°C., nmr ($CDCl_3$) δ 2.76 (t, J = 5.5 cps, 2H), 4.03 (t, J = 5.5 cps, 2H).

The procedure of Example 785 is followed to prepare other compounds of formula VII in which R^1, R^2, R^3, R^4, R^5, R^6 are as defined in the first instance, R^7 is hydrogen and Z is lower alkyl or phenyl(lower)alkyl. Examples of such compounds are listed in Tables XVII and XVIII. In each example an equivalent amount of the starting material of formula II listed therein is used instead of the starting material of formula II described in Example 785, together with the appropriate ketone.

TABLE XVII

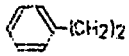
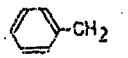
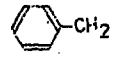
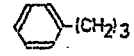
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETONE OF FORMULA O ‖ R¹—C—Z		PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE
	R^2	R^3	R^4	R^5	R^6	X	R^1	Z	
786	H	H	H	H	H	O	C_2H_5	n-C_3H_7	1-ethyl-1-propyl
787	H	H	H	H	H	O	CH_3	n-C_3H_7	1-methyl-1-propyl, m.p. 91—93°C.
788	H	H	H	H	H	O	C_2H_5		1-ethyl-1-phenethyl
789	H	H	H	H	H	O	CH_3		1-benzyl-1-methyl, m.p. 141—145°C.
790	CH_3	H	H	H	H	O	CH_3	CH_3	1,1,3-trimethyl
791	n-C_3H_7	H	H	H	H	O	CH_3	n-C_3H_7	1,3-dipropyl-1-methyl
792	CH_3	CH_3	H	H	H	O		CH_3	1-cyclopropyl-1,3,3-trimethyl
793	C_2H_5	H	C_2H_5	H	H	O		n-C_3H_7	1-cyclohexyl-3,4-diethyl-1-propyl
794	H	H	CH_3	n-C_3H_7	H	O	CH_3	n-C_3H_7	1,4-dimethyl-1,4-dipropyl
795	CH_3	CH_3	CH_3	CH_3	H	O	CH_3		1-benzyl-1,3,3,4,4-pentamethyl
796	H	H	H	H	4-CH_3	O		CH_3	1-cyclopropyl-1,5-dimethyl
797	H	H	H	H	5-C_2H_5	O			1-cyclopentyl-6-ethyl
798	C_2H_5	H	H	H	6-OCH_3	O	C_2H_5	C_2H_5	7-methoxy-1,1,3-triethyl
799	CH_3	CH_3	H	H	7-OC_2H_5	O	CH_3	CH_3	8-ethoxy-1,1,3,3-tetramethyl
800	C_2H_5	H	H	H	5-NO_2	O	C_2H_5		1,3-diethyl-6-nitro-1-(3-phenylpropyl)
801	H	H	H	H	7-NO_2	O	CH_3	CH_3	1,1-dimethyl-8-nitro

TABLE XVII—Continued.

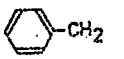
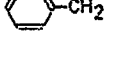
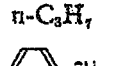
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETONE OF FORMULA O ‖ $R^1—C—Z$		PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE
	R^2	R^8	R^4	R^5	R^6	X	R^1	Z	
802	H	H	H	CH_3	6-CH_3COO	O	C_2H_5	CH_3	7-acetoxy-1,4-dimethyl-1-ethyl
803	n-C_3H_7	n-C_3H_7	H	H	5-C_2H_5COO	O			1-benzyl-1-cyclopropyl-3,3-dipropyl-6-propionyloxy
804	H	H	H	H	4-Cl	O		CH_3	5-chloro-1-cyclopropylmethyl
805	CH_3	H	H	H	6-Cl	O			1-benzyl-7-chloro-1-cyclohexyl-3-methyl
806	C_2H_5	H	H	H	5-Br	O	C_2H_5	C_2H_5	6-bromo-1,1,3-triethyl
807	H	H	n-C_3H_7	n-C_3H_7	7-Br	O	n-C_3H_7	CH_3	8-bromo-1-methyl-1,4,4-tripropyl
808	CH_3	CH_3	CH_3	CH_3	4-F	O	CH_3	CH_3	5-fluoro-1,1,3,3,4,4-hexamethyl
809	H	H	H	H	6-F	O		n-C_3H_7	1-cyclopropyl-7-fluoro-1-propyl
810	CH_3	H	CH_3	H	7-I	O	CH_3		8-iodo-1-phenethyl-1,3,4-trimethyl
811	H	H	H	H	5-I	O	CH_3	CH_3	1,1-dimethyl-6-iodo

TABLE XVIII

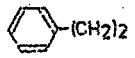
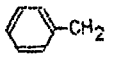
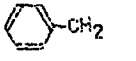
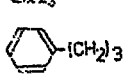
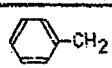
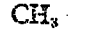
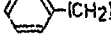
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETONE OF FORMULA O ‖ R¹—C—Z		PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO [3,4-b] INDOLE
	R^2	R^3	R^4	R^5	R^6	X	R^1	Z	
812	H	H	H	H	H	S	CH_3	CH_3	1,1-dimethyl
813	H	H	H	H	H	S	CH_3	$n\text{-}C_3H_7$	1-methyl-1-propyl
814	H	H	H	H	H	S	C_2H_5		1-ethyl-1-phenethyl
815	H	H	H	H	H	S	CH_3		1-benzyl-1-methyl
816	CH_3	H	H	H	H	S	CH_3	CH_3	1,1,3-trimethyl
817	$n\text{-}C_3H_7$	H	H	H	H	S	CH_3	$n\text{-}C_3H_7$	1,3-dipropyl-1-methyl
818	CH_3	H	H	H	H	S		CH_3	1-cyclopropyl-1,3,3-trimethyl
819	C_2H_5	H	C_2H_5	H	H	S		$n\text{-}C_3H_7$	1-cyclohexyl-3,4-diethyl-1-propyl
820	H	H	CH_3	$n\text{-}C_3H_7$	H	S	CH_3	$n\text{-}C_3H_7$	1,4-dimethyl-1,4-dipropyl
821	CH_3	CH_3	CH_3	CH_3	H	S	CH_3		1-benzyl-methyl-1,3,3,4,4-pentamethyl
822	H	H	H	H	$4\text{-}CH_3$	S		CH_3	1-cyclopropyl-1,5-dimethyl
823	H	H	H	H	$5\text{-}C_2H_5$	S			1-cyclopentyl-6-ethyl
824	C_2H_5	H	H	H	$6\text{-}OCH_3$	S	C_2H_5	C_2H_5	7-methoxy-1,1,3-triethyl
825	CH_3	CH_3	H	H	$7\text{-}OC_2H_5$	S	CH_3	CH_3	8-ethoxy-1,1,3,3-tetramethyl
826	C_2H_5	H	H	H	$5\text{-}NO_2$	S	C_2H_5		1,3-diethyl-6-nitro-1-(3-phenylpropyl)
827	H	H	H	H	$7\text{-}NO_2$	S	CH_3	CH_3	1,1-dimethyl-8-nitro
828	H	H	H	CH_3	$6\text{-}CH_3COO$	S	C_2H_5	CH_3	7-acetoxy-1,4-dimethyl-1-ethyl

TABLE XVIII—Continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETONE OF FORMULA O ‖ R¹—C—Z		PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO [3,4-b]INDOLE
	R^2	R^3	R^4	R^5	R^6	X	R^1	Z	
829	n-C_3H_7	n-C_3H_7	H	H	5-C_2H_5COO	S			1-benzyl-1-cyclopropyl-3,3-dipropyl-6-propionyloxy
830	H	H	H	H	4-Cl	S		CH_3	5-chloro-1-cyclopropyl-1-methyl
831	CH_3	H	H	H	6-Cl	S			1-benzyl-7-chloro-1-cyclohexyl-3-methyl
832	C_2H_5	H	H	H	5-Br	S	C_2H_5	C_2H_5	6-bromo-1,1,3-triethyl
833	H	H	n-C_3H_7	n-C_3H_7	7-Br	S	n-C_3H_7	CH_3	8-bromo-1-methyl-1,4,4-tripropyl
834	CH_3	CH_3	CH_3	CH_3	4-F	S	CH_3	CH_3	5-fluoro-1,1,3,3,4,4-hexamethyl
835	H	H	H	H	6-F	S		n-C_3H_7	1-cyclopropyl-7-fluoro-1-propyl
836	CH_3	H	CH_3	H	7-I	S	CH_3		8-iodo-1-phenethyl-1,3,4-trimethyl
837	H	H	H	H	5-I	S	CH_3	CH_3	1,1-dimethyl-6-iodo

EXAMPLE 838.

1,1-DIMETHYL-9-[2-(DIMETHYLAMINO)ETHYL]-1,3,4,9-TETRAHYDRO-PYRANO[3,4-b]INDOLE (I; R^1 AND $Y = CH_3$, R^2, R^3, R^4, R^5 AND $R^6 = H$, AND $R^7 = CH_2CH_2N(CH_3)_2$]

To 4.2 g. of a 50% dispersion of sodium hydride in 20 ml. of dimethylformamide is added a solution of 7 g. of 1,1-dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole, described in Example 785, in 20 ml. of dimethylformamide. The addition is made dropwise at room temperature while stirring vigorously. The mixture is heated for 1 hr. at 40°C. Then an excess of the organic halide, dimethylaminoethyl chloride (free base obtained from 15 g. of the hydrochloride) is added and stirring continued at 40°C. overnight.

The reaction mixture is poured into ice-water, acidified with 6N HCl and washed with ether. The aqueous phase is rendered alkaline with 10% NaOH and extracted with benzene. The organic phase is washed with water, dried over sodium sulfate, and evaporated under reduced pressure to yield the title compound, nmr ($CDCl_3$) δ 1.63 (6H), 2.36 (6H), 2.79 (m, 4H), 4.10 (m, 4H), 7.18 (m, 4H).

The corresponding hydrochloric acid addition salt, 1,1-dimethyl-9-[(2-dimethylamino)ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole hydrochloride, has m.p. 198—200°C., after crystallization from methanol-ether.

The procedure of Example 838 is followed to prepare other compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in the first instance, R^7 is aminoalkyl as defined above and Y is lower alkyl or phenyl(lower)alkyl. Examples of such compounds are listed in Tables XIX and XX. In each example an equivalent amount of the appropriate starting material of formula VII in which R^1, R^2, R^3, R^4, R^5, R^6 are as defined in the first instance, R^7 is hydrogen and Z is lower alkyl or phenyl(lower)alkyl, described in Examples 785 to 837, is used in place of 1,1-dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole if required. In each case the starting material of formula VII is noted by the example in which it is prepared.

TABLE XIX

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE
839	785	$(CH_3)_2N(CH_2)_3Cl$	1,1-dimethyl-9-[3-(dimethylamino)propyl], nmr ($CDCl_3$) δ 1.62 (6H), 2.00 (m, 2H), 2.25 (6H), corresponding hydrochloric acid addition salt has m.p. 201—203°C.
840	785	$CH_3NH(CH_2)_2Cl$	1,1-dimethyl-9-[2-(methylamino)ethyl]
841	785	$i\text{-}C_3H_7NH(CH_2)_2Cl$	1,1-dimethyl-9-[2-(isopropylamino)ethyl]
842	786	$NH_2CH_2C(CH_3)_2CH_2Br$	9-(3-amino-2,2-dimethylethyl)-1-ethyl-1-propyl
843	787	$(CH_3)_2N(CH_2)_2Cl$	9-[2-(dimethylamino)ethyl]-1-methyl-1-propyl, $\nu_{max}^{CHCl_3}$ 2960, 1470, 1085 cm^{-1}, maleate salt has m.p. 144—147°C.
844	788	$C_2H_5NH(CH_2)_3Cl$	1-ethyl-9-[3-(ethylamino)propyl]-1-phenethyl]
845	789	$(CH_3)_2N(CH_2)_2Cl$	1-benzyl-9-[2-(dimethylamino)ethyl]-1-methyl, nmr ($CDCl_3$) δ 1.55 (s, 3H), 2.92 (6H), 3.95 (2H), corresponding hydrochloric acid addition salt has m.p. 218—220°C.
846	789	$CH_3NH(CH_2)_2Cl$	1-benzyl-1-methyl-9-[2-(methylamino)ethyl]
847	789	$NH_2(CH_2)_3Cl$	9-(4-aminobutyl)-1-benzyl-1-methyl
848	790	$(CH_3)_2NCH_2[CH(CH_3)]_2Cl$	9-[1,2-dimethyl-3-(dimethylamino)propyl]-1,1,3-trimethyl
849	791	$(C_2H_5)_2NCH(C_2H_5)CH_2Cl$	9-[2-(diethylamino)-2-ethylethyl]-1,3-dipropyl-1-methyl]
850	792	$CH_3NH(CH_2)_3Cl$	1-cyclopropyl-9-[3-(methylamino)propyl]-1,3,3-trimethyl

TABLE XIX—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE
851	793	$(CH_3)_2N(CH_2)_2Cl$	1-cyclohexyl-3,4-diethyl-9-[2-(dimethylamino)-ethyl]-1-propyl
852	794	$(n\text{-}C_3H_7)_2N(CH_2)_3Cl$	1,4-dimethyl-1,4-dipropyl-9-[3-(dipropylamino)-propyl]
853	795	$(CH_3)_2NCH(n\text{-}C_3H_7)CH_2Cl$	1-benzyl-9-[2-(dimethylamino)-2-propylethyl]-1,3,3,4,4-pentamethyl
854	796	$(CH_3)_2N[CH(n\text{-}C_3H_7)]_3\text{-}CH_2Cl$	1-cyclopropyl-1,5-dimethyl-9-[4-(dimethylamino)-2,3,4-tripropylbutyl]
855	797	$(C_2H_5)_2N(CH_2)_2Cl$	1-cyclopentyl-9-[2-(diethylamino)ethyl]-6-ethyl
856	798	$CH_3NH(CH_2)_3Cl$	7-methoxy-9-[3-(methylamino)propyl]-1,1,3-triethyl
857	799	$n\text{-}C_3H_7NH(CH_2)_2Cl$	8-ethoxy-9-[2-(propylamino)ethyl]-1,1,3,3-tetramethyl
858	800	$i\text{-}C_3H_7NH(CH_2)_2Cl$	1,3-diethyl-9-[2-(isopropylamino)ethyl]-6-nitro-1-(3-phenylpropyl)
859	801	$(CH_3)_2N(CH_2)_2Cl$	1,1-dimethyl-9-[2-(dimethylamino)ethyl]-8-nitro
860	802	$C_2H_5NH(CH_2)_3Cl$	7-acetoxy-1,4-dimethyl-1-ethyl-9-[3-ethylamino)-propyl]
861	803	$(CH_3)_2N(CH_2)_2Cl$	1-benzyl-1-cyclopropyl-9-[2-(dimethylamino)-ethyl-3,3-dipropyl-6-propionyloxy
862	804	$n\text{-}C_3H_7NH(CH_2)_3Cl$	5-chloro-1-cyclopropyl-1-methyl-9-[3-(propyl-amino)propyl
863	805	1-(3-chloropropyl)pyrrolidine	1-benzyl-7-chloro-1-cyclohexyl-3-methyl-9-[3-(1-pyrrolidinyl)propyl]

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TABLE XIX—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: (*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE
864	806	1-(2-chloroethyl)piperidine	6-bromo-9-(2-piperidinoethyl)-1,1,3-triethyl
865	807	4-(2-chloroethyl)morpholine	8-bromo-1-methyl-9-(2-morpholinoethyl)-1,4,4-tripropyl
866	808	1-(3-chloropropyl)piperazine	5-fluoro-1,1,3,3,4,4-hexamethyl-9-(piperazinopropyl)
867	809	1-(3-chloroethyl)-4-methylpiperazine	1-cyclopropyl-7-fluoro-9-[2-(4-methyl-1-piperazinyl)ethyl]-1-propyl
868	810	1-(2-chloroethyl)-4-(hydroxyethyl)piperazine	9-{2-[4-(hydroxyethyl)-1-piperazinyl]ethyl}-8-iodo-1-phenethyl-1,3,4-trimethyl
869	811	1-(2-chloroethyl)pyrrolidine	1,1-dimethyl-6-iodo-9-[2-(1-pyrrolidinyl)ethyl]
870	785	1-(3-chloropropyl)piperidine	1,1-dimethyl-9-(3-piperidinopropyl)
871	785	4-(4-chlorobutyl)morpholine	1,1-dimethyl-9-(4-morpholinobutyl)
872	789	1-(4-chlorobutyl)-4-methylpiperazine	9-[4-(4-methyl-1-piperazinyl)butyl]
873	789	1-(2-chloroethyl)-4-(3-hydroxypropyl)piperazine	1-benzyl-9-{2-[4-(hydroxypropyl)-1-piperazinyl]-ethyl}-1-methyl

TABLE XX

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
874	812	$(CH_3)_2N(CH_2)_3Cl$	1,1-dimethyl-9-[3-(dimethylamino)propyl]
875	812	$CH_3NH(CH_2)_2Cl$	1,1-dimethyl-9-[2-(methylamino)ethyl]
876	812	$i\text{-}C_3H_7NH(CH_2)_2Cl$	1,1-dimethyl-9-[2-(isopropylamino)ethyl]
877	812	$NH_2CH_2C(CH_3)_2CH_2Br$	9-(3-amino-2,2-dimethylethyl)-1,1-dimethyl
878	813	$(CH_3)_2N(CH_2)_2Cl$	9-[2-(dimethylamino)ethyl]-1-methyl-1-propyl
879	814	$C_2H_5NH(CH_2)_3Cl$	1-ethyl-9-[3-(ethylamino)propyl]-1-phenethyl
880	815	$(CH_3)_2N(CH_2)_2Cl$	1-benzyl-9-[2-(dimethylamino)ethyl]-1-methyl
881	815	$CH_3NH(CH_2)_2Cl$	1-benzyl-1-methyl-9-[2-(methylamino)ethyl]
882	815	$NH_2(CH_2)_3Cl$	9-(4-aminobutyl)-1-benzyl-1-methyl
883	816	$(CH_3)_2NCH_2[CH(CH_3)]_2Cl$	9-[1,2-dimethyl-3-(dimethylamino)propyl]-1,1,3-trimethyl
884	817	$(C_2H_5)_2NCH(C_2H_5)CH_2Cl$	9-[2-(diethylamino)-2-ethylethyl]-1,3-dipropyl-1-methyl
885	818	$CH_3NH(CH_2)_3Cl$	1-cyclopropyl-9-[3-(methylamino)propyl]-1,3,3-trimethyl
886	819	$(CH_3)_2N(CH_2)_2Cl$	1-cyclohexyl-3,4-diethyl-9-[2-(dimethylamino)-ethyl]-1-propyl
887	820	$(n\text{-}C_3H_7)_2N(CH_2)_3Cl$	1,4-dimethyl-1,4-dipropyl-9-[3-(dipropylamino)-propyl]
888	821	$(CH_3)_2NCH(n\text{-}C_3H_7)CH_2Cl$	1-benzyl-9-[2-(dimethylamino)-2-propylethyl]-1,3,3,4,4-pentamethyl

TABLE XX—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
889	822	$(CH_3)_2N[CH(n\text{-}C_3H_7)]_3\text{-}CH_2Cl$	1-cyclopropyl-1,5-dimethyl-9-[4-(dimethylamino)-2,3,4-tripropylbutyl]
890	823	$(C_2H_5)_2N(CH_2)_2Cl$	1-cyclopentyl-9-[2-(diethylamino)ethyl]-6-ethyl
891	824	$CH_3NH(CH_2)_3Cl$	7-methoxy-9-[3-(methylamino)propyl]-1,1,3-triethyl
892	825	$n\text{-}C_3H_7NH(CH_2)_2Cl$	8-ethoxy-9-[2-(propylamino)ethyl]-1,1,3,3-tetramethyl
893	826	$i\text{-}C_3H_7NH(CH_2)_2Cl$	1,3-diethyl-9-[2-(isopropylamino)ethyl]-6-nitro-1-(3-phenylpropyl)
894	827	$(CH_3)_2N(CH_2)_2Cl$	1,1-dimethyl-9-[2-(dimethylamino)ethyl]-8-nitro
895	828	$C_2H_5NH(CH_2)_3Cl$	7-acetoxy-1,4-dimethyl-1-ethyl-9-[3-(ethylamino)-propyl]
896	829	$(CH_3)_2N(CH_2)_2Cl$	1-benzyl-1-cyclopropyl-9-[2-(dimethylamino)-ethyl]-3,3-dipropyl-6-propionyloxy
897	830	$n\text{-}C_3H_7NH(CH_2)_3Cl$	5-chloro-1-cyclopropyl-1-methyl-9-[3-(propyl-amino)propyl
898	831	1-(3-chloropropyl)pyrrolidine	1-benzyl-7-chloro-1-cyclohexyl-3-methyl-9-[3-(1-pyrrolidinyl)propyl]
899	832	1-(2-chloroethyl)piperidine	6-bromo-9-(2-piperidinoethyl)-1,1,3-triethyl
900	833	4-(2-chloroethyl)morpholine	8-bromo-1-methyl-9-(2-morpholinoethyl)-1,4,4-tripropyl
901	834	1-(3-chloropropyl)piperazine	5-fluoro-1,1,3,3,4,4-hexamethyl-9-(piperazino-propyl)

TABLE XX—Continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ORGANIC HALIDE	PRODUCT: (*PREFIX LISTED BELOW*)-(1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE
902	835	1-(3-chloroethyl)-4-methylpiperazine	1-cyclopropyl-7-fluoro-9-[2-(4-methyl-1-piperazinyl)ethyl]-1-propyl
903	836	1-(2-chloroethyl)-4-(hydroethyl)piperazine	9-{2-[4-(hydroxyethyl)-1-piperazinyl]ethyl-8-iodo-1-phenethyl-1,3,4-trimethyl
904	837	1-(2-chloroethyl)pyrrolidine	1,1-dimethyl-6-iodo-9-[2-(1-pyrrolidinyl)ethyl]
905	812	1-(3-chloropropyl)piperidine	1,1-dimethyl-9-(3-piperidinopropyl)
906	812	4-(4-chlorobutyl)morpholine	1,1-dimethyl-9-(4-morpholinobutyl)
907	815	1-(4-chlorobutyl)-4-methylpiperazine	1-benzyl-1-methyl-9-[4-(4-methyl-1-piperazinyl)-butyl]
908	815	1-(2-chloroethyl)-4-(3-hydroxypropyl)piperazine	1-benzyl-9-{2-[4-(hydroxypropyl)-1-piperazinyl]-ethyl}-1-methyl

EXAMPLE 909.

1,1-DIMETHYL-9-[2-(DIMETHYLAMINO)ETHYL]-1,3,4,9-TETRAHYDRO-PYRANO[3,4-b]INDOLE-6-OL (I, R^1 AND $Y = CH_2$, R^2, R^3, R^4 AND $R^5 = H$, $R^6 = OH$ AND $R^7 = CH_2CH_2N(CH_3)_2$]

5-Benzyloxy-3-tryptophol (II; R^2, R^3, R^4 and $R^5 = H$, $R^6 = 5$-benzyloxy and $X^1 =$ OH), m.p. 93—95°C., is prepared by lithium aluminum hydride reduction of ethyl 5-benzyloxy-3-indoleglyoxalate (British Patent 778,823) according to the procedure of Example 309. Subsequent treatment of 5-benzyloxy-3-tryptophol with the ketone, acetone, according to the procedure of Example 785 affords 6-benzyloxy-1,1-dimethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole (VII; R^1 M CH_3), nmr ($CDCl_3$) δ 1.53 (6H), 2.73 (t, 2H), 4.03 (t, 2H), 5.10 (2H), 6.67—7.83 (9H). The latter compound is then

N-alkylated with the organic halide, dimethylaminoethyl chloride, according to the procedure of Example 838 to afford 6-benzyloxy-1,1-dimethyl-9-[2-(dimethylamino)-ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole, which on treatment with hydrochloric acid gives the corresponding hydrochloric acid addition salt thereof, m.p. 209°C.

The latter compound, 6-benzyloxy-1,1-dimethyl-9-[2-(dimethylamino)ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole hydrochloride (11.5 g., 0.028M) in 600 ml. of absolute ethanol and 600 mg of 10% palladium on carbon is stirred at room temperature under a hydrogen atmosphere for 22 hrs. until no more hydrogen is taken up by the reaction. The catalyst is collected on celite and the filtrate concentrated to afford the corresponding hydrochloric acid addition salt of the title compound, m.p. 225—228°C., after recrystallization from ethanol-ether.

The title compound [free base, nmr ($CDCl_3$) δ 1.61 (6H), 2.57 (t, J = 5 cps, 2H), 3.86 (t, J = 5 cps, 2H)] is obtained by decomposing the hydrochloric acid addition salt, for example, by washing a chloroform solution of the salt with 10% sodium hydroxide solution and evaporating the solvent.

By replacing 5-benzyloxy-3-tryptophol with an equivalent amount of 7-benzyloxy-3-tryptophol in the procedure of this example, 1,1-dimethyl-9-[2-(dimethylamino)-ethyl]-1,3,4,9-tetrahydropyrano[3,4-b]indole-8-ol is obtained.

EXAMPLE 910.

1-(2-AMINOETHYL)-1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE (I; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7 = H$, $X = O$ AND $Y = CH_2NH_2$)

1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide (20.0 g., 0.817 mole), described in Example 126, is dissolved in dry methylene chloride (400 ml) and freshly prepared triethyloxonium fluoroborate (17.00 g., 0.894 mole) is added in one portion to the solution. The reaction mixture is stirred at room temperature for 2 hrs. The methylene chloride solution is washed with cold 30% aqueous potassium carbonate followed by brine and the dried organic layer is concentrated under reduced pressure. The residue is dissolved in ether (150 ml.). The solution is filtered and crystallization proceeds at room temperature to afford ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetimidate, m.p. 139.5—141°C.

The latter compound (4.79 g., 0.0176 mole) dissolved in dry THF (100 ml.) is added dropwise to a stirred and ice-cooled suspension of lithium aluminum hydride (1.75 g., 0.046 mole) in THF (50 ml.). The reaction mixture is stirred overnight at room temperature and then dilute sodium hydroxide is added dropwise to decompose excess hydride. The precipitate is collected by filtration and the filtrate is concentrated under reduced pressure thus affording a residue which is extracted with methylene chloride. The organic layers are washed with brine, dried ($MgSO_4$) and concentration of the solvent and crystallization from ether affords the title compound, m.p. 80—84°C., $\nu_{max}^{CHCl_3}$ 3455, 3280 cm^{-1}, identical with the compound of the same name described in Example 309.

EXAMPLE 911.

1-[2-(DIMETHYLAMINO)ETHYL]-9-ETHYL-1-METHYL-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]INDOLE [I; $R^1 = CH_3$, R^2, R^3, R^4, R^5, AND $R^6 = H$, $R^7 = C_2H_5$, $X = S$ AND $Y = CH_2CH_2N(CH_3)_2$]

The compound of formula I in which R^7 = H and Y = amino(lower)alkyl, 1-[2-(dimethylamino)ethyl]-1-methyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole (822 mg), described in Example 398, is dissolved in 15 ml of DMF and 15 ml of benzene. To remove all possible traces of water, a portion of this benzene is distilled. After cooling to 0°, 140 mg of sodium hydride (54% suspension in mineral oil) is added, and the mixture stirred for 15 mins. Alkylation is accomplished by addition of 350 mg of ethyl bromide and stirring the reaction mixture at 0° for 20 mins. The resulting suspension is poured onto cracked ice, extracted with chloroform, the organic layer washed repeatedly with water and evaporated. Chromatography of the residue on silica gel (20 g) using chloroform-methanol (0—10%) affords the title compound, which after crystallization from ether hexane has m.p. 86—88°C., $\nu_{max}^{CHCl_3}$ 2820, 2765, 1600, 1568, 1537 cm^{-1}, nmr ($CDCl_3$) δ 2.20 (s, 6H), 2.30 (m, 4H).

The corresponding hydrochloric acid addition salt of the title compound, 1-[2-

(dimethylamino)ethyl] - 9 - ethyl - 1 - methyl - 1,3,4,9 - tetrahydrothiopyrano-[3,4-b]indole hydrochloride, has m.p. 220—222°C.

By following the procedure of Example 911 and using an appropriate compound of formula I in which R^7 is hydrogen and Y is an amino(lower)alkyl, for instance those described in Example 309 to 487, together with the appropriate organic halide, then other compounds of formula I in which R^7 is lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl or amino(lower)alkyl are obtained.

For example, the use of the same compound of formula I as described in Example 911 with an equivalent amount of methyl bromide, instead of ethyl bromide, in the procedure of Example 911 gives 1,9-dimethyl-1-[2-(dimethylamino)ethyl]-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole, nmr ($CDCl_3$) δ 3.72 (s, 6H), 6.40 (s, 3H), identical to the product of Example 732. The corresponding hydrochloric acid addition salt of this latter compound, 1,9-dimethyl-1-[2-(dimethylamino)ethyl]-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole hydrochloride has m.p. 244—246°C.

Likewise, the use of the same compound of formula I as described in Example 911 with an equivalent amount of propyl bromide, instead of ethyl bromide, gives 1 - [2 - (dimethylamino)ethyl] - methyl - 9 - propyl - 1,3,4,9 - tetrahydrothiopyrano-[3,4- b]indole, nmr ($CDCl_3$) δ 1.03 (t, 3H), 1.83 (S, 3H), 2.22 (S, 6H), 4.14 (m, 2H), 7.22 (m, 4H); corresponding hydrochloric acid addition salt has m.p. 243—245°C.

EXAMPLE 912.

1-[(2-DIMETHYLAMINO)ETHYL]-1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE [I; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7 = H$, $X = O$ AND $Y = CH_2CH_2N(CH_3)_2$]

To a solution of *p*-toluenesulfonic acid (2.28 g) in toluene (40 ml), the starting material of formula II, triptophol (1.61 g), and the aminoketone, 4-(dimethylamino)-2-butanone (1.27 g) are added. The mixture is evaporated under reduced pressure and the residue stirred under nitrogen at 130°C (bath temperature) for 45 mins. The mixture is cooled, water (20 ml) added and the mixture extracted with toluene. The toluene extract is washed with 5% sulfuric acid (5 ml) and with water (5 ml). The aqueous layer containing a dark heavy oil is combined with the aqueous washes. Conc. NH_4OH (10 ml) is added and the mixture extracted with toluene (10 ml and 2 × 5 ml). The combined toluene solution is washed with water (2 × 5 ml), dried (Na_2SO_4), treated with charcoal and evaporated under reduced pressure. The residue is recrystallized from ether to afford the pure title compound, identical to the product of the same name described in Example 309.

EXAMPLE 913.

1,9-DIMETHYL-1-[2-(DIMETHYLAMINO)ETHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE [I; R^1 AND $R^7 = CH_3$, R^2, R^3, R^4, R^5, AND $R^6 = H$, $X = O$ AND $Y = CH_2CH_2N(CH_3)_2$]

To a mixture of the starting material of formula II, N-methyltryptophol (0.50 g), and the aminoketone, 4-dimethylamino-2-butanone (0.363 g), *p*-toluene-sulfonic acid (0.650 g) is added in portions and the mixture stirred under nitrogen at 130°C for 1½ hrs. After cooling water is added (10 ml) and the mixture is extracted with toluene (2 × 5 ml). The combined toluene solution is backwashed with water and discarded. The aqueous phase, containing a heavy brown oil, is made alkaline with conc. ammonium hydroxide (10 ml) and extracted with benzene (3 × 10 ml). The combined benzene extract is washed with water (2 × 10 ml), dried (Na_2SO_4), treated with charcoal and evaporated under reduced pressure to yield the title compound, identical to the product of the same name described in Example 674.

EXAMPLE 914.

1,9-DIMETHYL-1-[2-(DIMETHYLAMINO)ETHYL]-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]INDOLE [I; R^1 AND $R^7 = CH_3$, R^2, R^3, R^4, R^5 AND $R^6 = H$, $X = S$ AND $Y = CH_2CH_2N(CH_3)_2$]

A mixture of the starting material of formula II, 1-methylindole-3-ethanethiol (0.75 g), 4-dimethylamino-2-butanone hydrochloride (0.72 g), toluene (ca. 1 ml) and *p*-toluenesulfonic acid (1.00 g), is stirred under nitrogen at 125°C for ½ hr. After cooling, water (20 ml) and conc. hydrochloric acid (0.5 ml) are added and the mixture is then extracted with toluene (3 × 10 ml). The combined toluene solution is backwashed with water. The aqueous phase containing a brown oil is rendered alkaline with conc. NH_4OH and extracted with toluene (3 × 15 ml). The combined toluene solution

is washed with water, dried (Na_2SO_4), treated with charcoal and evaporated under reduced pressure to yield the title compound, identical to the product of the same name described in Example 732.

EXAMPLE 915.

1-[2-(DIMETHYLAMINO)ETHYL]-9-ETHYL-1-METHYL-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]INDOLE [I, R^2 CH_3, R^3, R , R^4, R , AND $R^6=H$, $R^7=C_2H_5$, $X=S$ AND $Y=CH_2CH_2N(CH_3)_2$]

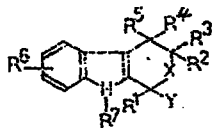
To a stirred solution of *p*-toluenesulfonic acid monohydrate (57.0 g) in toluene (400 ml) at 80°C. under nitrogen, the aminoketone, 4-(dimethylamino)-2-butanone (13.8 g), is added. Thereafter, the starting material of formula II, sodium 1-ethylindole-3-ethyl thiosulfate (30.7 g), prepared from 1-ethylindole-3-ethanol according to the procedure of Sururov and Buyanov, cited above, is added portionwise over a period of 5 minutes. The mixture is maintained at 80°C. for 1½ hrs. with stirring then cooled and diluted with 20% sodium hydroxide (66 ml) followed by water (100 ml) and extracted with toluene. The toluene extract is washed with 20% sulfuric acid (5 × 30 ml) and with water (5 × 30 ml). The combined aqueous phases plus solid precipitating therefrom are rendered alkaline with 20% sodium hydroxide and then extracted with toluene (4 × 50ml). The combined toluene solution is washed with water, dried (Na_2SO_4), and evaporated. The residue is recrystallized from ether-hexane to give the title compound, identical to the product of Example 911. The corresponding hydrochloric acid addition salt of the title compound has m.p. 225—227°C. after recrystallization from isopropanol.

In the same manner but using an equivalent amount of potassium 1-ethylindole-3-ethyl thiosulfate the title compound is also obtained.

By following the procedure of Examples 912, 913, 914 or 915 and using an appropriate starting material of formula II together with the appropriate aminoketone, then other compounds of formula I, for example, those described in Examples 309—487 and 675—775, are obtained.

WHAT WE CLAIM IS:—

1. A compound having the general formula



I.

in which R^1 is lower alkyl or lower cycloalkyl; R^2, R^3, R^4 and R^5 are the same or different and are hydrogen or lower alkyl; R^6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, nitro or halo; R^7 is hydrogen, lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl or an amino(lower)alkyl radical of formula

—Alk—NR^8R^9

wherein Alk is an alkylene group having the formula

$CR^{10}R^{11}CR^{12}R^{13}$, $CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}$ or
$CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}CR^{16}R^{17}$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are hydrogen or lower alkyl and R^8 and R^9 are either the same or different and are hydrogen or lower alkyl, or R^8 and R^9 together with the nitrogen atom to which they are joined form a heterocyclic amine radical which is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-(lower alkyl)-1-piperazinyl or 4-[hydroxy(lower)alkyl]-1-piperazinyl; X is oxy or thio; and Y is lower alkyl, phenyl(lower)alkyl or an amino(lower)alkyl radical of formula —Alk—NR^8R^9 wherein Alk is an alkylene which is

$CH^{10}R^{11}$, $CR^{10}R^{11}CR^{12}R^{13}$, $CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}$ or
$CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}CR^{16}R^{17}$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are hydrogen or lower alkyl and R^8 and R^9 are as defined hereinabove; with the proviso that at least one of R^7 and Y is

is washed with water, dried (Na_2SO_4), treated with charcoal and evaporated under reduced pressure to yield the title compound, identical to the product of the same name described in Example 732.

EXAMPLE 915.

1-[2-(DIMETHYLAMINO)ETHYL]-9-ETHYL-1-METHYL-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]INDOLE [I; $R^1 = CH_3$, R^2, R, R^4, R, AND $R^6 = H$, $R^7 = C_2H_5$, $X = S$ AND $Y = CH_2CH_2N(CH_3)_2$]

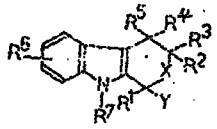
To a stirred solution of *p*-toluenesulfenic acid monohydrate (57.0 g) in toluene (400 ml) at 80°C. under nitrogen, the aminoketone, 4-(dimethylamino)-2-butanone (13.8 g), is added. Thereafter, the starting material of formula II, sodium 1-ethylindole-3-ethyl thiosulfate (30.7 g), prepared from 1-ethylindole-3-ethanol according to the procedure of Suvorov and Buyanov, cited above, is added portionwise over a period of 5 minutes. The mixture is maintained at 80°C. for 1¼ hrs. with stirring then cooled and diluted with 20% sodium hydroxide (66 ml) followed by water (100 ml) and extracted with toluene. The toluene extract is washed with 20% sulfuric acid (5 × 30 ml) and with water (5 × 30 ml). The combined aqueous phases plus solid precipitating therefrom are rendered alkaline with 20% sodium hydroxide and then extracted with toluene (4 × 50ml). The combined toluene solution is washed with water, dried (Na_2SO_4), and evaporated. The residue is recrystallized from ether-hexane to give the title compound, identical to the product of Example 911. The corresponding hydrochloric acid addition salt of the title compound has m.p. 225—227°C. after recrystallization from isopropanol.

In the same manner but using an equivalent amount of potassium 1-ethylindole-3-ethyl thiosulfate the title compound is also obtained.

By following the procedure of Examples 912, 913, 914 or 915 and using an appropriate starting material of formula II together with the appropriate aminoketone, then other compounds of formula I, for example, those described in Examples 309—487 and 675—775, are obtained.

WHAT WE CLAIM IS:—

1. A compound having the general formula



I.

in which R^1 is lower alkyl or lower cycloalkyl; R^2, R^3, R^4 and R^5 are the same or different and are hydrogen or lower alkyl; R^6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy, nitro or halo; R^7 is hydrogen, lower alkyl, lower alkenyl, propargyl, phenyl(lower)alkyl or an amino(lower)alkyl radical of formula

$$—Alk—NR^8R^9$$

wherein Alk is an alkylene group having the formula

$$CR^{10}R^{11}CR^{12}R^{13}, \quad CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15} \quad \text{or}$$
$$CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}CR^{16}R^{17}$$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are hydrogen or lower alkyl and R^8 and R^9 are either the same or different and are hydrogen or lower alkyl, or R^8 and R^9 together with the nitrogen atom to which they are joined form a heterocyclic amine radical which is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-(lower alkyl)-1-piperazinyl or 4-[hydroxy(lower)alkyl]-1-piperazinyl; X is oxy or thio; and Y is lower alkyl, phenyl(lower)alkyl or an amino(lower)alkyl radical of formula —Alk—NR^8R^9 wherein Alk is an alkylene which is

$$CH^{10}R^{11}, \quad CR^{10}R^{11}CR^{12}R^{13}, \quad CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15} \quad \text{or}$$
$$CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}CR^{16}R^{17}$$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are hydrogen or lower alkyl and R^8 and R^9 are as defined hereinabove; with the proviso that at least one of R^7 and Y is

—Alk—NR^8R^9, and the corresponding acid addition salt with a pharmaceutically acceptable acid.

2. 1 - [2 - (Dimethylamino)ethyl] - 1 - methyl - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

3. 1 - (2 - Aminoethyl) - 1 - methyl - 1,3,4,9 - tetrahydropyrano[3,4 - b]indole.

4. 1 - Methyl - 1 - [2 - (methylamino)ethyl] - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

5. 1 - Methyl - 1 - [2 - (1 - pyrrolidinyl)ethyl] - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

6. 1 - Methyl - 1 - (2 - piperidinoethyl) - 1,3,4,9 - tetrahydropyrano[3,4 - b]-indole.

7. 1 - Methyl - 1 - (2 - morpholinoethyl) - 1,3,4,9 - tetrahydropyrano[3,4 - b]-indole.

8. 1 - Methyl - 1 - [2 - (4 - methyl - 1 - piperazinyl)ethyl] - 1,3,4,9 - tetra-hydropyrano[3,4-b]indole.

9. 1 - Methyl - 1 - [3 - (methylamino)propyl] - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

10. 1 - Methyl - 1 - [3 - (dimethylamino)propyl] - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

11. 1 - (Aminomethyl) - 1 - methyl - 1,3,4,9 - tetrahydropyrano[3,4 - b]indole.

12. 1 - [(Ethylamino)methyl] - 1 - methyl - 1,3,4,9 - tetrahydropyrano[3,4-b]-indole.

13. 1 - [2 - (Dimethylamino)ethyl] - 1 - propyl - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

14. 1 - [2-(Dimethylamino)ethyl] - methyl - 1,3,4,9 - tetrahydrothiopyrano-[3,4-b]indole.

15. 1,9 - Dimethyl - 1 - [2 - (dimethylamino)ethyl] - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

16. 1 - [2 - (Diethylamino)ethyl] - 1,9 - dimethyl - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

17. 1 - [2 - (Dimethylamino)ethyl] - 9 - ethyl - 1 - methyl - 1,3,4,9 - tetra-hydropyrano[3,4-b]indole.

18. 1 - [2 - (Dimethylamino)ethyl] - 1 - methyl - 9 - propyl - 1,3,4,9 - tetra-hydropyrano[3,4-b]indole.

19. 1,9 - Dimethyl - 1 - [3 - (dimethylamino)propyl] - 1,3,4,9 - tetrahydro-pyrano[3,4-b]indole.

20. 1,9 - Dimethyl - 1 - [2 - (1 - pyrrolidinyl)ethyl] - 1,3,4,9 - tetrahydro-pyrano[3,4-b]indole.

21. 1,9 - Dimethyl - 1 - (2 - piperidinoethyl) - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

22. 1,9 - Dimethyl - 1 - [2 - (4 - methyl - 1 - piperazinyl)ethyl] - 1,3,4,9-tetrahydropyrano[3,4-b]indole.

23. 1,9 - Dimethyl - 1 - {2 - [4 - (2 - hydroxyethyl) - 1 - piperazinyl] - ethyl}-1,3,4,9-tetrahydropyrano[3,4-b]indole.

24. 1,1 - Dimethyl - 9 - [2-(dimethylamino)ethyl] - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

25. 1,1 - Dimethyl - 9 - [3 - (dimethylamino)propyl] - 1,3,4,9 - tetrahydro-pyrano[3,4-b]indole.

26. 1 - Benzyl - 9 - [2 - (dimethylamino)ethyl] - 1 - methyl - 1,3,4,9 - tetra-hydropyrano[3,4-b]indole.

27. 1,1 - Dimethyl - 9 - [2 - (dimethylamino)ethyl] - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole-6-ol.

28. 1 - [2 - (Dimethylamino)ethyl] - 9 - ethyl - 1 - methyl - 1,3,4,9 - tetra-hydrothiopyrano[3,4-b]indole.

29. 1,9 - Dimethyl - 1 - [2 - (dimethylamino)ethyl] - 1,3,4,9 - tetrahydrothio-pyrano[3,4-b]indole.

30. 1 - [2 - (Diethylamino)ethyl] - 1 - methyl - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

31. 1,9 - Dimethyl - 1 - [2 - (methylamino)ethyl] - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

32. 1 - (2 - Aminoethyl) - 1,9 - dimethyl - 1,3,4,9 - tetrahydropyrano[3,4 - b]-indole.

33. 1,9 - Dimethyl - 1 - [3 - (methylamino)propyl] - 1,3,4,9 - tetrahydro-pyrano[3,4-b]indole.

34. 1,9 - Dimethyl - 1 - [2 - (dimethylamino)ethyl] - 6 - methoxy - 1,3,4,9-tetrahydropyrano[3,4-b]indole.

35. 1,9 - Dimethyl - 1 - (2 - morpholinoethyl) - 1,3,4,9 - tetrahydropyrano-[3,4-b]indole.

36. 1 - [2 - Dimethylamino)ethyl] - 1,5,9 - trimethyl - 1,3,4,9 - tetrahydropyrano[3,4-b]indole.

37. 6 - Benzyloxy - 1 - [2 - (dimethylamino)ethyl] - 9 - ethyl - 1 - methyl-1,3,4,9 - tetrahydropyrano[3,4-b]indole.

38. 5 - Chloro - 1 - [2 - (dimethylamino)ethyl] - 1,9 - dimethyl-1,3,4,9 - tetrahydropyrano[3,4-b]indole.

39. 6 - Benzyloxy - 1,9 - dimethyl - 1 - [2 - (dimethylamino)ethyl] - 1,3,4,9-tetrahydropyrano[3,4-b]indole.

40. 1 - [2 - (Dimethylamino)ethyl] - 9 - ethyl - 1 - methyl - 1,3,4,9 - tetrahydropyrano[3,4-b]indol-6-ol.

41. 1,9 - Dimethyl - 1 - [2 - (dimethylamino)ethyl] - 1,3,4,9 - tetrahydropyrano[3,4-b]indol-6-ol.

42. 9 - [2 - (Dimethylamino)ethyl] - 1 - methyl - 1 - propyl - 1,3,4,9 - tetrahydropyrano[3,4-b]indole.

43. 1 - [2 - (Dimethylamino)ethyl] - 1 - methyl - 9 - propyl - 1,3,4,9 - tetrahydrothiopyrano[3,4-b]indole.

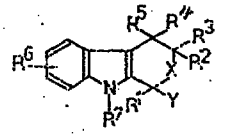
44. (+) and (−) - 1,9 - Dimethyl - [2 - (dimethylamino)ethyl] - 1,3,4,9-tetrahydropyrano[3,4-b]indole.

45. A compound as claimed in claim 1 and substantially as hereinbefore described with reference to any one of Examples 309 to 487, 674 to 731, 732 to 775, 778, 780 to 782 or 838 to 909.

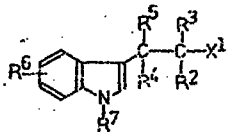
46. A compound as claimed in claim 1 and substantially as hereinbefore described with reference to any one of Examples 912 to 915.

47. A compound as claimed in claim 1 and substantially as hereinbefore described with reference to any one of Examples 731a, 731b, 731c, 731d, 910 or 911.

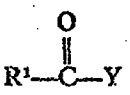
48. A process for preparing a compound having the general formula



in which R^1, R^2, R^3, R^4, R^5, R^6, R^7 and X are as defined in claim 1, and Y is: lower alkyl, phenyl (lower) alkyl or ALK—NR^8R^9 in which ALK, R^8 and R^9 are as defined in claim 1, which comprises treating a compound having the general formula:



in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim 1 and X^1 is hydroxy, mercapto, —S—SO_3—Na or —S—SO_3—K with a compound having the general formula



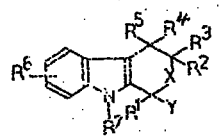
in which R^1 is lower alkyl or lower cycloalkyl and Y is as defined hereinabove, in the presence of an acid catalyst; with the proviso that when Y is lower alkyl or phenyl (lower alkyl R^7 is —Alk—NR^8R^9.

49. A process as claimed in claim 48 where R^7 is hydrogen or lower alkyl.

50 A process as claimed in claim 49 where R^7 is hydrogen.

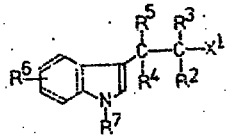
51. A process as claimed in claim 49 wherein R^6 is hydrogen, lower alkyl, hydroxy, lower alkoxy, lower alkanoyloxy or halo and Y is Alk—NR^8R^9.

52. A process for preparing a compound having the general formula



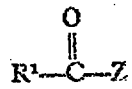
I.

in which R^1, R^2, R^3, R^4, R^5, R^6, R^7 and Y are as defined in claim 1 which comprises treating in the presence of an acid catalyst acompound having the general formula:



II.

in which R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim 1 and X^1 is hydroxy, mercapto, —S—SO_3—Na or —S—SO_3—K with a compound having the general formula



in which R^1 is lower alkyl or lower cycloalkyl and Z is:

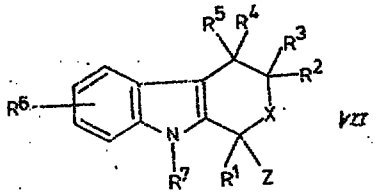
(a) $COOR^{19}$ or Alk^1—$COOR^{19}$ in which R^{19} is hydrogen or lower alkyl and Alk^1 is an alkylene group which is

$$CR^{10}R^{11},\ CR^{10}R^{11}CR^{12}R^{13} \text{ or } CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}$$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are hydrogen or lower alkyl, with the proviso that when R^{19} is hydrogen then Alk^1 is

$$CR^{10}R^{11}CR^{12}R^{13} \text{ or } CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15},$$

to obtain the corresponding compound having the general formula:



VII

in which Z is $COOR^{19}$ or Alk^1—$COOR^{19}$ as defined hereinabove subjecting the last-named compound to optional N-alkylation with an appropriate organic halide to the extent required and desired to obtain the corresponding compound having the general formula VII as defined herein in which Z is $COOR^{19}$ or Alk^1—$COOR^{19}$, subjecting the latter compound to amidation with an appropriate amine of formula NHR^8R^9 in which R^8 and R^9 are as defined in Claim 1 to give the corresponding amide, reducing the amide with a suitable complex metal hydride to give the corresponding compound having the general formula I as defined in Claim 1 in which Y is an amino-(lower)alkyl having the general formula Alk—NR^8R^9 in which Alk is CH_2 or Alk^1—CH_2 wherein Alk^1 is as defined hereinabove and R^8 and R^9 are as defined in Claim 1;

(b) $CONR^8R^9$ or Alk^1—$CONR^8R^9$ in which R^8 and R^9 are as defined in Claim 1 and Alk^1 is as defined hereinabove to obtain the corresponding compound having the general formula VII in which Z is $CONR^8R^9$ or Alk^1—$CONR^8R^9$ as defined hereinabove, subjecting the last-named compound in optional order and to the extent required and desired, to (1) N-alkylation of the indolic nitrogen with an appropriate halide and (2) reduction with a suitable complex metal hydride to give the corresponding compound having the general formula I as defined in Claim 1 in which Y is an amino (lower) alkyl having the general formula Alk—NR^8R^9 in which Alk is CH_2 or Alk^1—

CH_2 wherein Alk^1 is as defined hereinabove and R^8 and R^9 are as defined in Claim 1;

(c) CH_2OCOR^{20} or Alk^1—CH_2OCOR^{20} in which R^{20} is hydrogen or lower alkyl and Alk^1 is as defined hereinabove, to obtain the corresponding compound having the general formula VII in which Z is CH_2OCOR^{20} or Alk^1—CH_2OCOR^{20} as defined hereinbefore, subjecting the last-named compound to hydrolysis with a suitable alkali to give the corresponding primary alcohol; reacting said primary alcohol with

(i) a suitable oxidizing agent to give the corresponding aldehyde, treating the aldehyde with an amine of formula HNR^8R^9 in which R^8 and R^9 are as defined in Claim 1 to give the corresponding Schiff base, reducing the Schiff base with sodium borohydride to give the corresponding amine, and subjecting said corresponding amine to optional N-alkylation on the indolic nitrogen to the extent required and desired with an appropriate organic halide, or

(ii) a suitable halogenating, mesyiating or tosylating agent and reacting the intermediate obtained thereby with an amine of formula HNR^8R^9 in which R^8 and R^9 are as defined in Claim 1 to give the corresponding amine and subjecting said corresponding amine to optional N-alkylation to the extent required and desired with an appropriate organic halide,

to obtain the corresponding compound having the general formula I as defined in Claim 1 in which Y is amino(lower)alkyl having the general formula Alk—NR^8R^9 in which Alk is CH_2 or Alk^1—CH_2 wherein Alk^1 is as defined hereinabove and R^8 and R^9 are as defined in Claim 1;

(d) Alk^2—L in which Alk^2 is an alkylene group which is

$$CR^{10}R^{11}CHR^{12}, \quad CR^{10}R^{11}CR^{12}R^{13}CHR^{14} \quad \text{or} \quad CR^{10}R^{11}CR^{12}R^{13}CR^{14}R^{15}CHR^{16}$$

wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} are hydrogen or lower alkyl and L is halo, to obtain the corresponding compound having the general formula VII in which Z is Alk^2—L as defined hereinabove, reacting the last-named compound with an amine of formula HNR^8R^9 in which R^8 and R^9 are as defined in Claim 1 to give the corresponding amine, subjecting said amine to optional N-alkylation on the indolic nitrogen to the extent required and desired with an appropriate organic halide to give the corresponding compound having the general formula I as defined in Claim 1 in which Y is an amino(lower) alkyl having the general formula Alk—NR^8R^9 in which Alk is Alk^2 as defined hereinabove and R^8 and R^9 are as defined in Claim 1;

(e) Alk—NR^8COR^{21} in which Alk is as defined in Claim 1, R^8 is hydrogen or lower alkyl and R^{21} is hydrogen or lower alkyl containing one to five carbon atoms, to obtain the corresponding compound having the general formula VII in which Z is Alk—NR^8COR^{21} as defined hereinabove, reducing the last-named compound with a suitable complex metal hydride to give the corresponding amine, subjecting said corresponding amine to optional N-alkylation to the extent required and desired with an appropriate organic halide to obtain a compound having the general formula I as defined in Claim 1 in which Y is an amino(lower)alkyl having the general formula Alk—NR^8R^9 in which Alk is as defined hereinabove, R^8 is hydrogen or lower alkyl and R^9 is lower alkyl;

(f) Alk—NO_2 in which Alk is as defined in Claim 1, to obtain the corresponding compound having the general formula VII in which Z is Alk—NO_2 as defined hereinabove, reducing the last-named compound with a suitable complex metal hydride to give to corresponding amine, subjecting said amine to optional N-alkylation with an appropriate organic halide to the extent required and desired to give the corresponding compound having the general formula I as defined in Claim 1 in which Y is an amino(lower)alkyl having the general formula Alk—NR^8R^9 in which Alk, R^8 and R^9 are as defined in Claim 1; or

(g) lower alkyl or phenyl(lower)alkyl, to obtain the corresponding compound having the general formula VII in which Z is lower alkyl or phenyl(lower)alkyl, and subjecting the last-named compound to N-alkylation with an appropriate amino(lower)alkyl halide to give the corresponding compound having the general formula I as defined in Claim 1 in which Y is lower alkyl or phenyl(lower)alkyl and R^7 is an amino(lower)alkyl radical as defined in Claim 1;

and if desired forming the acid addition salt of the hereinabove compound having the general formula I as defined in Claim 1, with a pharmaceutically acceptable acid.

53. A process as claimed in claim 52 in which R^7 is hydrogen or lower alkyl.

54. A process as claimed in claim 48 or 52 and substantially as hereinbefore

described with particular reference to any of Examples 309 to 487, 674 to 731, 732 to 775, 778, 780 to 482 or 838 to 909.

55. A process as claimed in claim 48 or 52 and substantially as hereinbefore described with reference to any one of Examples 912 to 915.

56. A process as claimed in claim 48 or 52 and substantially as hereinbefore described with reference to any one of Examples 731a, 731b, 731c, 731d, 910 or 911.

57. A product whenever obtained by a process as claimed in any one of claims 48 to 57.

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Chartered Patent Agents.

ERRATA

SPECIFICATION No. 1,391,234

Page 2, line 16, and page 90, line 47, *for* $CH^{10}R^{11}$, *read* $CR^{10}R^{11}$,

Page 91, line 25, *after* ethyl]- *insert* 1-

THE PATENT OFFICE
13th June, 1975