1 391 005

PATENT SPECIFICATION

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(54) 1,3,4,9-TETRAHYDRO(PYRANO OR THIOPYRANO)[3,4-b]-INDOLE DERIVATIVES

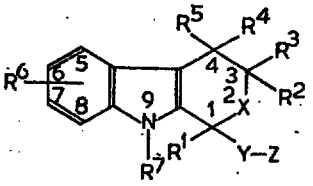
(71) We, AMERICAN HOME PRODUCTS CORPORATION, of 685 Third Avenue, New York, State of New York 10017, United States of America, a corporation organised and existing under the laws of the State of Delaware, United States of America, (assignee of CHRISTOPHER ALEXANDER DEMERSON, LESLIE GEORGE HUMBER, THOMAS ALBERT DOBSON and IVO LADISLAV JIRKOVSKY), 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 indole derivatives, and to processes for their preparation.

Notwithstanding the advances made during the last four decades in the development of agents for the treatment of inflammatory conditions, there still remains a need for effective agents without the side effects associated with the therapeutic agents presently used for this purpose.

The indole derivatives of this invention have been found to exhibit interesting and useful pharmacodynamic properties without eliciting undesirable side effects. Notable attributes of this effect are antiinflammatory and analgesic activities. In addition the compounds of this invention exhibit antibacterial and antifungal properties.

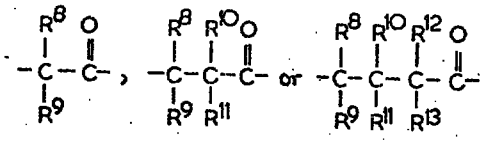
The present invention provides indole derivatives having a pyrano[3,4-b]indole or thiopyrano[3,4-b]indole nucleus bearing a substituent at position 1, said substituent incorporating an acid, ester or amide function therein. These derivatives may be represented by general formula:—



I.

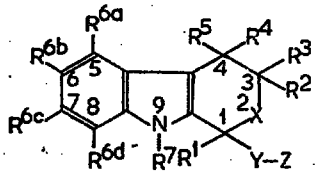
wherein R^1 is a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, phenyl, benzyl or 2-thienyl group, R^2, R^3, R^4 and R^5, which may be the same or different, are hydrogen atoms or lower alkyl groups, R^6 is a hydrogen or halogen atom, or a lower alkyl, hydroxy, lower alkoxy, benzyloxy, lower alkanoyloxy, or nitro group, R^7 is a hydrogen atom, or a lower alkyl or lower alkenyl group, X is an oxy or thio radical Y is a carbonyl,

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group in which each of R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} is a hydrogen atom or a lower alkyl group, and Z is a hydroxy, lower alkoxy, amino, lower alkylamino, di(lower)alkylamino or phenylamino group.

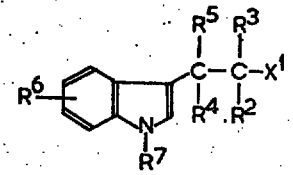
Also included within the scope of the present invention are pyrano[3,4-b]indole and thiopyrano[3,4-b]indole derivatives having general formula I but in which R^6 represents from one to four substituents, which may be present simultaneously, at positions 5, 6, 7 and 8 thereof. The exact nature of such substituents does not have to be limited necessarily by the above definitions of R^6, and R^6 may also include additional definitions, for example, mercapto, lower alkylthio, trifluoromethyl (or other halo(lower)alkyl), amino or sulfamoyl, provided that any two such substituents do not interfere with each other. Accordingly the indole derivatives of this invention are represented also by general formula Ia



Ia.

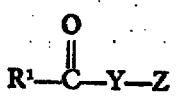
in which R^1, R^2, R^3, R^4, R^5, R^7, X, Y and Z are as defined hereinabove and R^{6a}, R^{6b}, R^{6c} and R^{6d}, which may be the same or different, are hydrogen or halogen atoms or lower alkyl, hydroxy, lower alkoxy, benzyloxy, lower alkanoyloxy, nitro, mercapto, lower alkylthio, halo(lower)alkyl (preferably trifluoromethyl), amino or sulfamoyl groups.

The indole derivatives of the present invention which have general formula I as hereinabove defined can be prepared by reacting a compound having the general formula:



II.

wherein R^2, R^3, R^4, R^5, R^6 and R^7 are as defined hereinabove and X' is a hydroxy or mercapto group with a compound having the general formula:



wherein R^1, Y and Z are as defined hereinabove in the presence of an acid catalyst.

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, and 2-methylpentyl.

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, and 2-ethyl-3-butenyl.

The term "lower alkynyl" as used herein contemplates both straight and branched chain alkynyl radicals containing from two to six carbon atoms and includes ethynyl, propargyl, and 1,1-dimethylpropargyl.

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

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, and isopropoxy.

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, and hexanoyloxy.

The term includes fluorine, chlorine, bromine and iodine.

Where the term "lower" is used herein as part of the description of alkylamino and dialkylamino, it contemplates one to six carbon atoms for each alkyl group of such a radical and includes methylamino, n-hexylamino, dimethylamino, and diethylamino.

The indole derivatives of formula I in which Z is hydroxy, the acid compounds of this invention, form addition salts with suitable inorganic and organic bases. These salts possess the same activities as the parent acid compound when administered to animals and may be utilized in the same manner. Suitable bases to form these salts include, for example, the hydroxides, lower alkoxides, carbonates and bicarbonates of sodium, potassium, calcium and magnesium, as well as the bases, ammonia, triethylamine, and benzylamine. The addition salts thus obtained are the functional equivalents of the parent acid compound in respect to their therapeutic use. Hence, these addition salts are included within the scope of this invention and are limited only by the requirement that the bases employed in forming the salts be pharmaceutically acceptable.

Also included within the scope of this invention are the isomers of the compounds of formula I resulting from the asymmetric centers contained therein.

Antiinflammatory and Analgesic Activity

The useful antiinflammatory and analgesic activities of the indole derivatives of this invention may be demonstrated in standard pharmacologic tests, for example, the tests described by R. A. Turner in "Screening Methods in Pharmacology", Academic Press, New York and London, 1965, pp. 152—163 and pp. 100—117, respectively.

More particularly, the antiinflammatory activity of the compounds of this invention may be readily demonstrated in a modification of the Freund's adjuvant test, the adjuvant induced acute oedema test as described by J. R. Boissier, *et al.*, Therapie, *25*, 43 (1970). This test is known to correlate well with data derived from clinical results with humans. Boissier *et al.* have demonstrated this correlation with such clinically active compounds as phenylbutazone, mefenamic acid, indomethacin, aspirin, hydrocortisone and prednisolone.

More particularly exemplified, a substantial antiinflammatory effect for the compounds listed below is demonstrable at oral doses of 100 mg/kg or less in this acute oedema test. In this test male rats are treated with the test compound one hour before the injection of Freund's adjuvant into the paw (day 0). The rats are then treated with the same dose of the test compound for the next three days. The antiinflammatory effect of the test compound is measured by the reduction of pedal inflammation, see Turner cited above, and expressed as a percent inhibition from adjuvant injected control rats on day 3.

COMPOUND	DAILY DOSE (MG/KG)	PERCENT INHIBITION
1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetic acid, Example No. 1	100	30
1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetic acid, Example No. 15	100	47
1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetic acid, Example No. 16	100	40
8-methyl-1-propyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid, Example No. 26	100	44
1-butyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetic acid, Example No. 25	100	40
1-*t*-butyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetic acid, Example No. 24	100	30
5-methyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]-indole-1-acetic acid, Example 32	100	44
1-ethyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole-1-acetic acid, Example No. 98	25	32

The lack of side effects for the compounds of this invention may be demonstrated by standard acute toxicity tests (see Turner cited above) and by prolonged administration of the compound to warm-blooded animals.

When the present indole derivatives of this invention are employed as antiinflammatory and analgesic agents in warm-blooded animals, e.g., rats, they may be administered orally, alone or in dosage forms, i.e., capsules or tablets, combined with pharmacologically acceptable excipients, such as starch and milk sugar. They may also be administered orally in the form of solutions in suitable vehicles such as vegetable oils.

The dosage of the indole derivatives of this invention will vary with the particular compound chosen and form of administration. Furthermore, it will vary with the particular host under treatment. Generally, the compounds of this invention are administered at a concentration level that affords protective effects without any deleterious side effects. These antiinflammatorily-analgesically effective concentration levels are usually obtained within a therapeutic range of 1.0 mg to 500 mg/kg per day, with a preferred range of 10 to 100 mg/kg per day.

Antibacterial and Antifungal Activity

The indole derivatives of this invention also exhibit utility as antibacterial agents against a number of gram-positive and gram-negative microorganisms, such as, *Staphylococcus pyogenes*, both penicillin sensitive and penicillin resistant, *Streptococcus faecalis, Escherichia coli, Aerobacter aerogenes, Salmonella pullorum, Pseudomonas aerugenosa, Proteus mirabilis, Proteus vulgaris, Klebsiella pneumoniae* and *Serratia marcescens* and as antifungal agents against a number of pathogenic fungi such as, *Candida albicans, Microsporum gypseum* and *Trichophyton granulosum*, in standard tests for antibacterial and antifungal activity, such as those described in "Antiseptics, Disinfectants, Fungicides and Sterilization", G. F. Reddish, Ed., 2nd ed., Lea and Febiger, Philadelphia, 1957 or by D. C. Grove and W. A. Randall in "Assay Methods of Antibiotics", Med. Encycl. Inc., New York 1955.

For example, by employing a test like the serial broth dilution test, see Grove and Randall, cited above, in which dilutions of the compounds of this invention in nutrient broth are inoculated with the microorganisms or fungi, described above, incubated at 37°C. for 2 days, respectively, and examined for the presence of growth, it may be shown that 1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-propionic acid is able to inhibit growth totally in this system of *Proteus vulgaris, Klebsiella pneumoniae* and *Serratia marcescens* at a concentration of 100 mcg/ml. or less.

When the compounds of this invention are employed as antibiotic or antifungal agents in warm-blooded animals, e.g. rats, they may be administered alone or in combination with pharmacologically acceptable carriers. The proportion of the compound 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, and certain types of clay. 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 as antibiotic or antifungal 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 antibacterially or antifungally effective results without causing any harmful or deleterious side effects and preferably at a level that is in a range of from 1.0 mg. to 1000 mg. per kilo per day, although as aforementioned variations will occur. However, a dosage level that is in the range of from 10 mg. to 500 mg. per kilo per day is most desirably employed in order to achieve effective results.

In addition, the agent may be employed topically. For topical application they may be formulated in the form of solutions, creams, or lotions in pharmaceutically acceptable vehicles containing 0.1—5 per cent, preferably 2 per cent, of the agent and may be administered topically to the infected area of the skin.

Also the antibacterial properties of the compounds of this invention may be utilized for washing equipment in hospitals, homes and farms, instruments used in

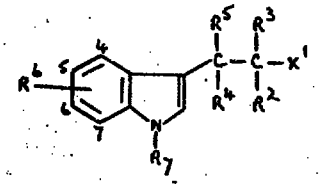
medicine and bacteriology, clothing used in bacteriological laboratories, and floors, walls and ceiling in rooms in which a background free of gram-positive and gram-negative microorganisms, such as those listed above, is desired. When employed in this manner the compounds of this invention may be formulated in a number of compositions comprising the active compound and an inert material. In such compositions, while the compounds of formula I of this invention may be employed in concentrations as low as 500 p.p.m., from a practical point of view, it is desirable to use from 0.10% by weight, to 5% by weight or more.

The formulations that may be used to prepare antiseptic wash solutions of the compounds of this invention are varied and may readily be accomplished by standard techniques, see for example, "Remington's Practice of Pharmacy", E. W. Martin *et al.*, Eds., 12 ed., Mack Publishing Company, Easton, Penn., 1961, pp. 1121—1150. In general, the compounds may be made up in stock solutions. They can also be formulated as suspensions in an aqueous vehicle. These make useful mixtures for decontaminating premises. Also, aqueous vehicles containing emulsifying agents, such as sodium lauryl sulfate, and relatively high concentrations, e.g., up to about 5% by weight, of the compounds may be formulated by conventional techniques.

A typical antiseptic preparation useful for disinfecting floors, walls, ceiling, and articles in a contaminated room may be prepared by adding 5 to 25 g. of N,N,1-trimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide to a mixture of 150 to 300 g. of polyethylene glycol 1540 and 150 to 300 g. of polyethylene glyol 300. The resulting mixture is stirred while a solution of 1 to 10 g. of sodium lauryl sulfate in 300 to 400 ml. of water is added portionwise. The article to be disinfected is coated or immersed in the preparation for a prolonged time, for example, one hour, and then rinsed with sterile water.

Preparation of Indole Derivatives.

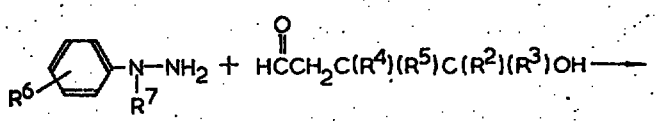
For the preparation of the indole derivatives of this invention we prefer to use as starting materials the compounds of the general formula II.



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′ is hydroxy or mercapto.

The starting materials of formula II in which X′ 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 may be obtained by the following process:



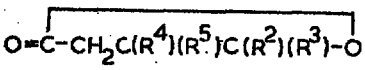
III. IV.

II (X′ = OH)

With reference to this process phenylhydrazines of formula III and the hydroxy-aldehyde 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′ = OH).

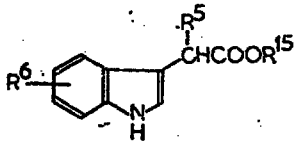
The phenylhydrazines of formula III are either known or may be prepared according to known methods. A convenient method involves the diazotization of the appropriately substituted aniline to give the corresponding diazo derivative. The latter compound is then reduced with stannous chloride or sodium 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 may be prepared according to known methods. A convenient method involves reduction of an appropriate lactone of formula



with bis-(3-methyl-2-butyl)borane, H. C. 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 reduction are either commercially available, for example, δ-valerolactone, α-methylbutyrolactone, 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′ is hydroxy may be 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 Specification No. 3,161,654, Dec. 15, 1964:

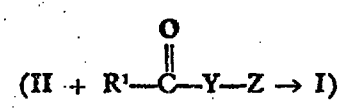


V.

wherein R^{15} is lower alkyl and R^5 and R^6 are as defined in the first instance.

The starting materials of formula II in which X′ is mercapto and R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in the first instance may be obtained by the following process: The appropriate compound of formula II (X′ = OH), described above, is treated with phosphorus tribromide in an inert solvent, for example, diethyl 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′ = SH) by a procedure similar to that described by N. N. Suvorov and V. N. Buyanov, Khim.-Farm. Zh., *1*, 4 (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, R^6 and R^7 = H and X′ = 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, which on treatment with strong alkali for example, sodium or potassium hydroxide, is transformed into 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.

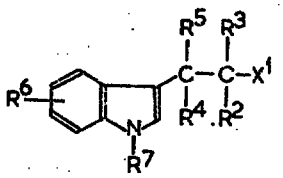
It should be noted that the preceding process is not entirely practical for the preparation of the compounds of formula II in which X′ is mercapto and R^6 is hydroxy or lower alkanoyloxy. For this reason, the preferred starting materials of formula II for the ultimate preparation of the compounds of 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, readily prepared by this process. The latter compounds of formula II in which R^6 is benzyloxy are employed as starting materials in the general process



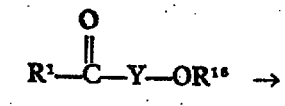
to give the corresponding compound of formula I in which R^6 is benzyloxy. Subsequently, the benzyloxy group is removed by hydrogenation, in the presence of a catalyst, for example, 10% palladium on carbon, to afford the corresponding com-

pound of formula I in which R^6 is hydroxy. The latter may be 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' 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 preferred.

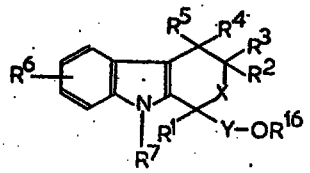
For the preparation of the acid and ester compounds of this invention of formula I in which Z is hydroxy or lower alkoxy and R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are as defined in the first instance, we have found that the following, hitherto undisclosed process is both practical and convenient:



II.



VI.



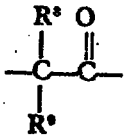
≡ I. (Z = OH or lower alkoxy)

VII.

in which R^1, R^2, R^3, R^4, R^5, R^6, R^7, X, Y and Z are as defined hereinabove. X' is hydroxy or mercapto and R^{16} is hydrogen or lower alkyl. (For convenience and clarity these particular acid and ester compounds of formula I are represented above as formula VII.)

With reference to the above scheme the starting material of formula II is condensed with a ketoacid (VI, R^{16} = H) or a ketoester (VI, R^{16} = lower alkyl) in the presence of a suitable acid catalyst to yield the compounds of formula VII.

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 acid compounds of formula VII in which Y is



and R^{16} is hydrogen, it is preferable with respect to yield 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 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 in which R^{16} is lower alkyl to their corresponding acids of formula VII is readily effected by treatment with a suitable alkali, for example, potassium hydroxide or sodium carbonate, in aqueous methanol or aqueous ethanol.

In practising the condensation (II + VI → VII) we have found it preferable to use a solvent as a reaction medium. Any solvent inert to the reaction conditions may be used. Suitable solvents include benzene, toluene, diethyl ether, dioxan, tetrahydrofuran,

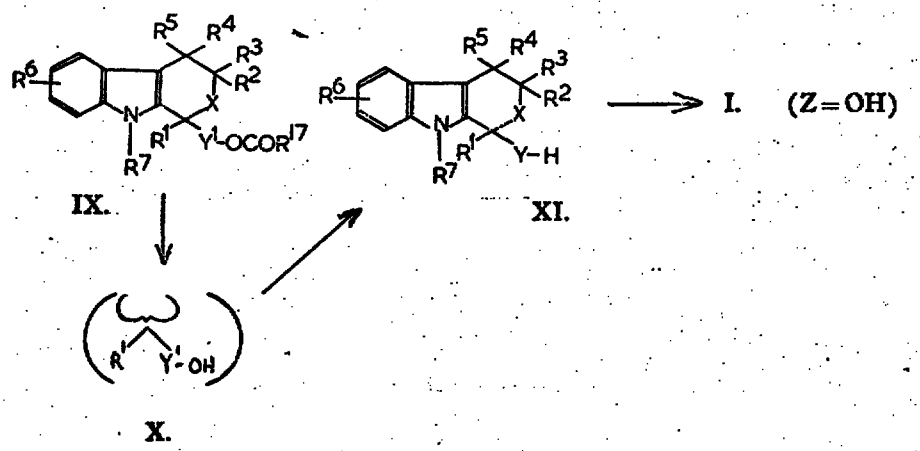
methylene dichloride, and carbon tetrachloride. Benzene and tetrahydrofuran are especially convenient and practical for this use. A variety of suitable acid catalysts may be used for this condensation, for example, the type of catalyst used in a Fischer Indole Synthesis, such as *p*-toluenesulfonic acid, phosphorus pentoxide, boron trifluoride, zinc chloride, hydrochloric acid and sulfuric acid. *p*-Toluenesulfonic acid, 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. 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.

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, β,β-dimethylevulinic acid and benzoylacetic acid or they may be 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. 1d, pp. 226—274.

Alternatively, the acid compounds of formula I in which Z is hydroxy and R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are as defined in the first instance may be prepared by the following process:

II. + $R^{17}CO—Y'—OCOR^{17}$ ⟶

VIII.



in which Y′ is CH_2, $C(R^8)(R^9)CH_2$, $C(R^8)(R^9)C(R^{10})(R^{11})CH_2$ or $C(R^8)(R^9)C(R^{10})(R^{11})C(R^{12})(R^{13})CH_2$, R^{17} is hydrogen or lower alkyl, Z is hydroxy and R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are as defined in the first instance.

With reference to this alternative process a starting material of formula II is condensed with an acylated ketoalcohol (VIII) in the presence of a suitable acid catalyst according to the conditions described above for the condensation (II + VI → VII). The acylated ketoalcohols are either known, for example, acetonyl acetate or 5-acetoxypentan-2-one, or may be prepared by known methods, for instance, see "Rodd's Chemistry of the Carbon Compounds", cited above, Vol. 1d, pp. 49—54. In this manner the condensation product of general formula IX is obtained. Hydrolysis of this product with an aqueous alcoholic solution of a suitable alkali, for example, sodium hydroxide in aqueous methanol, affords the corresponding primary alcohol X. The primary alcohol is then oxidized to the corresponding aldehyde of formula XI. 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 sul-

foxide in the presence of a suitable acid, for example, trifluoroacetic acid, to be both efficacious and convenient in this case. Subsequently the aldehyde XI may be converted to the desired acid compounds of formula I by a variety of oxidizing agents, including silver oxide, alkaline permanganate, hydrogen peroxide, and peracids. In this case we prefer to use silver oxide according to the method of M. Delépine and P. Bonnet, Compt. rend., *149*, 39 (1909).

The amide compounds of this invention of formula I in which Z is amino, lower alkylamino, di(lower)alkylamino and phenylamino and R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are as defined in the first instance, may be prepared from their corresponding acid compounds of formula I (compounds of formula VII in which R^{16} is hydrogen, described above) by treatment of the latter compounds 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, such as ammonia, aniline or a suitable alkylamine or dialkylamine, to the desired amide compound of formula I.

Alternatively, these amides of formula I may be prepared from the corresponding esters of formula I (compounds of formulae VII, in which R^{16} is lower alkyl, described above) by treatment of the latter compounds with the appropriate amine according to known methods, for example, see A. L. J. Beckwith in "The Chemistry of Amides", J. Zalicky, Ed., Interscience Publishers, New York, 1970, pp. 96—105.

Again alternatively, the amide compounds of formula I in which Z is amino, lower alkylamino, di(lower)alkylamino, and phenylamino and R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and Y are as defined in the first instance, may be prepared by the condensation of an appropriate starting material of formula II with an appropriate α-, β-, γ- or δ-ketoamide in the presence of a suitable acid catalyst according to the conditions described above for the condensation (II + VI → VII). The ketoamides required for this condensation are either known, for example, pyruvamide or α,α-dimethylacetoacetamide, or they may be prepared by known methods, for instance, see "Rodd's Chemistry of the Carbon Compounds", cited above, Vol. 1d, pp. 226—274.

The alkylated acid and ester compounds of this invention of formula I in which R^7 is lower alkyl or lower alkenyl and Z is hydroxy or lower alkoxy, are prepared readily from the above described, corresponding acid or ester compounds of formula I in which R^7 is hydrogen. This conversion involving the N-alkylation of the indolic nitrogen is effected by treatment of the latter compounds with an appropriate lower alkyl or lower alkenyl halide in an inert solvent in the presence of an acid acceptor. Preferred conditions for effecting this conversion include the use of sodium hydride as an acid acceptor and tetrahydrofuran as the inert solvent.

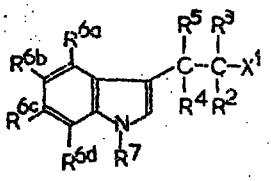
Finally, it is the intention to cover all changes and modifications of the embodiment of the invention herein chosen for the purpose of disclosure which are within the scope of this invention. Such changes and modification include those variations which depend on well known interconversions of acids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

For example, in preparing the N-alkylated acid, ester or amide compounds of formula I in which R^7 is lower alkyl or lower alkenyl, the changing of the order of the N-alkylation step, as depicted in the embodiment of this invention, by the act of N-alkylation of the starting materials of formula II and subjecting the products thereof to treatment with an appropriate ketoacid or ketoester of formula VI or a ketoamide, would not depart from the scope of this invention.

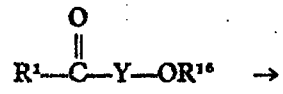
Likewise, N-alkylated amide compounds of formula I in which R^7 is lower alkyl or lower alkenyl and Z is di(lower)alkylamino may be prepared by N-alkylation of the corresponding compounds of formula I in which R^7 is hydrogen, or by treating the N-alkylated acid compounds of formula I, described above, with a lower alkyl chloroformate followed by treatment with the appropriate amine, or treating the N-alkylated ester compounds of formula I, described above, with an appropriate amine.

It will also be apparent to those skilled in the art that the processes described herein for the preparation of the indole derivatives of formula I are applicable likewise to the preparation of the indole derivatives of formula Ia, described above. In the latter case, the appropriate starting material of formula IIa, see below, prepared analogously to the starting material of formula II, is utilized.

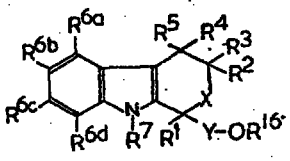
More specifically, the acid and ester compounds of formula Ia in which R^{6a}, R^{6b}, R^{6c}, R^{6d} and R^7 are as defined in the first instance, Z is hydroxy or lower alkoxy, and R^1, R^2, R^3, R^4, R^5, X and Y are as defined in the first instance, are readily prepared by the condensation (IIa + VI → VIIa), illustrated below, according to the conditions described previously for the condensation (II + VI → VII).



IIa.



VI.



VIIa.

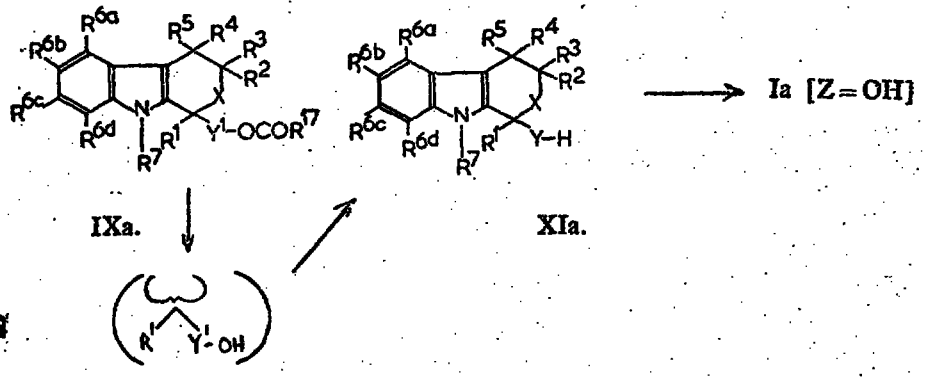
$\equiv$ Ia(Z = OH or lower alkoxy)

in which R^1, R^2, R^3, R^4, R^5, R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^7, X, Y and R^{16} are as defined in the first instance.

Likewise, the acid compounds of formula Ia in which R^{6a}, R^{6b}, R^{6c}, R^{6d} are as defined in the first instance, Z is hydroxy and R^1, R^2, R^3, R^4, R^5, R^7, X and Y are as defined in the first instance may be prepared by the following process:

IIa + $R^1CO—Y'—OCOR^{17}$ →

VIII.



IXa. XIa.

Ia [Z=OH]

in which R^1, R^2, R^3, R^4, R^5, X, Y, Y', R^{6a}, R^{6b}, R^{6c}, R^{6d}, R^7, and R^{17} are as defined in the first instance according to the process disclosed above for the conversion

{II + VIII → IX → X → XI → I (Z = OH)}.

Optional transformation of the above acid and ester compounds of formula Ia in which R^7 is hydrogen to their corresponding N-alkylated and amide derivatives of formula Ia is effected in the same manner for the similar conversions of the acid ester compounds of formula I, described herein.

Alternatively, the amide derivatives of formula Ia are prepared by the condensation of an appropriate starting material of formula IIa with an appropriate α-, β-, γ- or δ-ketoamide in the presence of a suitable acid catalyst according to the conditions described previously for the condensation (II + VI → VII).

The following examples will illustrate further this invention.

EXAMPLE 1.

1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-ACETIC ACID (I; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND R^7 = H, X = O, Y = CH_2CO AND Z = OH)

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 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% diethyl 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, $\gamma_{max}^{CHCl_3}$ 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., $\gamma_{max}^{CHCl_3}$ 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 (I; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7 = H$, $X = O$, $Y = CH_2CH_2CO$ AND $Z = OH$)

A. 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 diethyl 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), 2.18 (4H), 2.74 (2H), 3.96 (2H), 7.18 (4H), 7.85 (1H), 9.60 (1.H).

B. 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., $\gamma_{max}^{CHCl_3}$ 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 (I; $R^1 = CH_3$, R^2, R^3, R^4, R^5, R^6 AND $R^7 = H$, $X = S$, $Y = CH_2CO$ AND $Z = OH$)

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*-Toluene-sulfonic 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 a 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-tetra-hydrothiopyrano[3,4-b]indole-1-acetic acid methyl ester, as a semi-solid, $\gamma_{max}^{CHCl_3}$ 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

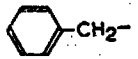
(23)

($CDCl_3$) δ 1.86 (S, 3H), 3.06 and 8.12 (6H), 7.35 (multiplet, 4H), 8.71 (1H), 10.31 (1H), after recrystallization from benzene-hexane.

The procedures of Examples 1, or 3 may be followed to prepare other compounds of formula I in which R^1, R^2, R^3, R^4, R^5, R^6, X and Y are as defined in the first instance, R^7 is hydrogen and Z is hydroxy. Examples of such compounds of formula I are listed 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 the corresponding ester compound of formula I of the product listed therein, the alkyl portion of said lower alkoxy being derived from the R^{16} portion of the ketoester of formula VI employed therein.

By following the procedure of Example 2A and using as starting material, an equivalent amount of one of the compounds of formula II listed in Tables I and II, instead of tryptophol, and using an equivalent amount of an appropriate ketoacid of formula VI derived from a ketoester of formula VI listed in Tables I and II instead of levulinic acid, the products listed in Tables I and II may be obtained.

TABLE I.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—C(=O)—Y—OR^{16})			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	Y	R^{16}	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	$CH_3CH=CH$	CO	CH_3	3,3-dimethyl-6-hydroxy-1-(1-propenyl)//carboxylic acid
8	H	H	H	H	7-C_2H_5	O	HC≡C	CO	CH_3	8-ethyl-1-ethynyl//carboxylic acid
9	H	H	2-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	H	H	H	O		CO	CH_3	1-phenyl//carboxylic acid
12	CH_3	C_2H_5	H	H	H	O		CO	CH_3	1-benzyl-3-ethyl-3-methyl//carboxylic acid
13	H	H	H	H	6-Cl	O		CO	CH_3	7-chloro-1-(2-thienyl)//carboxylic acid
14	H	H	CH_3	H	H	O	CH_3	CH_2CO	C_2H_5	1,4-dimethyl//acetic acid m.p. 163—164°C.
15	H	H	H	H	H	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl//acetic acid, m.p. 137—140°C.
16	H	H	H	H	H	O	n-C_3H_7	CH_2CO	C_2H_5	1-propyl//acetic acid, m.p. 148—151°C.

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TABLE I—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—CO—Y—OR^{16})			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	Y	R^{16}	PREFIX//SUFFIX
17	H	H	H	H	H	O	i-C_3H_7	CH_2CO	C_2H_5	1-isopropyl//acetic acid, m.p. 150—152°C.
18	CH_3	H	H	H	H	O	$CH_2=CHCH_2$	CH_2CO	C_2H_5	1-allyl-3-methyl//acetic acid
19	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)
20	CH_3	H	C_2H_5	CH_3	H	O	HC≡C	CH_2CO	C_2H_5	4-ethyl-1-ethynyl-3-methyl//acetic acid, $\nu_{max}^{CHCl_3}$ 3300, 2135, 1710 cm^{-1}
21	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)
22	H	H	H	H	H	O		$C(CH_3)_2CO$	C_2H_5	1-cyclohexyl-α,α-dimethyl//acetic acid
23	H	H	H	H	H	O		CH_2CO	C_2H_5	1-phenyl//acetic acid, m.p. 148—150°C.
24	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.
25	H	H	H	H	H	O	n-C_4H_9	CH_2CO	C_2H_5	1-butyl//acetic acid, m.p. 124—127°C.
26	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.
27	H	H	H	H	H	O		CH_2CO	C_2H_5	1-(2-thienyl)//acetic acid m.p. 127—130°C.
28	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.

TABLE I—continued

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—CO—Y—OR^{16})			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	Y	R^{16}	PREFIX//SUFFIX
29	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.
30	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.
31	H	H	H	H	5-benzyloxy	O	CH_3	CH_2CO	C_2H_5	6-Benzyloxy-1-methyl//acetic acid, m.p. 163.5°C.
32	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.
33	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.
34	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.
35	i-C_3H_7	H	i-C_3H_7	H	5-NO_2	O	$CH_2=CH$	$CH(CH_3)CO$	C_2H_5	3,4-diisopropyl-α-methyl-6-nitro-1-vinyl//acetic acid
36	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.
37	H	H	C_2H_5	H	7-CH_3	O	$HC\equiv C$	$C(i\text{-}C_3H_7)_2CO$	C_2H_5	α,α-diisopropyl-4-ethyl-1-ethynyl-8-methyl//acetic acid
38	CH_3	CH_3	H	H	5-OC_2H_5	O		$C(C_2H_5)_2CO$	C_2H_5	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy//acetic acid
39	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
40	CH_3	H	n-C_3H_7	n-C_3H_7	4-n-C_3H_7	O		$CH(CH_3)CO$	C_2H_5	α,3-dimethyl-1-phenyl-4,4,5-tripropyl//acetic acid

TABLE I—continued.

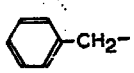
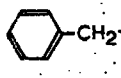
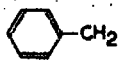
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—CO—Y—OR^{16})			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{16}	PREFIX//SUFFIX
41	H	H	H	H	H	O		$C(CH_3)_2CO$	C_2H_5	α,α-dimethyl-1-phenyl//acetic acid
42	C_2H_5	C_2H_5	C_2H_5	C_2H_5	4-C_2H_5	O		$C(i\text{-}C_3H_7)_2CO$	C_2H_5	1-benzyl-α,α-diisopropyl-3,3,4,4,5-pentaethyl//acetic acid
43	CH_3	H	H	H	7-OCC_2H_5 (O)	O		$C(CH_3)_2CO$	C_2H_5	1-benzyl-8-propionoxy-α,α,3-trimethyl//acetic acid
44	H	H	CH_3	H	H	O		$CH(CH_3)CO$	C_2H_5	α,4-dimethyl-1-(2-thienyl)// acetic acid
45	H	H	H	H	H	O		$C(CH_3)_2CO$	C_2H_5	α,α-dimethyl-1-(2-thienyl)// acetic acid
46	H	H	H	H	4-I	O	i-C_3H_7	CH_2CH_2CO	C_2H_5	5-iodo-1-isopropyl//propionic acid
47	CH_3	CH_3	CH_3	CH_3	7-$OCCH_3$ (O)	O	$CH_2=CH$	$CH_2CH(CH_3)CO$	C_2H_5	8-acetoxy-α,3,3,4,4-pentamethyl-1-vinyl//propionic acid
48	H	H	H	H	6-OH	O	$HC\equiv C-CH_2$	$C(C_2H_5)_2CH_2CO$	C_2H_5	β,β-diethyl-7-hydroxy-1-(2-propynyl)//propionic acid
49	CH_3	H	H	H	7-NO_2	O		$CH_2CH(n\text{-}C_3H_7)CO$	C_2H_5	1-cyclobutyl-3-methyl-8-nitro-α-propyl//propionic acid
50	H	H	CH_3	H	5-CH_3	O		$C(CH_3)_2C(CH_3)_2CO$	C_2H_5	$\alpha,\alpha,\beta,\beta$,4,6-hexamethyl 1-phenyl//propionic acid
51	i-C_3H_7	H	H	H	7-Br	O		$CH(CH_3)CH(C_2H_5)CO$	C_2H_5	1-benzyl-8-bromo-α-ethyl-3-isopropyl-β-methyl//propionic acid

TABLE I—continued.

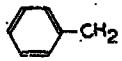
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—CO—Y—OR^{10})			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{10}	PREFIX//SUFFIX
52	C_2H_5	H	C_2H_5	H	7-Cl	O		CH_2CH_2CO	C_2H_5	8-chloro-3,4-diethyl-1-(2-thienyl)//propionic acid
53	CH_3	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
54	CH_3	H	C_2H_5	C_2H_5	H	O	$CH_2=C(CH_3)-CH_2$	$CH(CH_3)C(CH_3)_2CO$	CH_3	4,4-diethyl-1-methallyl-$\alpha,\alpha,\beta,3$-tetramethyl//propionic acid
55	H	H	CH_3	CH_3	H	O	$HC\equiv C$	$C(CH_3)_2CH_2CO$	CH_3	1-ethynyl-$\beta,\beta,4,4$-tetramethyl//propionic acid
56	H	H	n-C_3H_7	H	4-OCC_2H_5 (O)	O		$C(C_2H_5)_2CH(C_2H_5)CO$	CH_3	1-cyclopentyl-5-propionoxy-4-propyl-α,β,β-triethyl//propionic acid
57	n-C_3H_7	H	H	H	4-OCH_3	O		$CH_2CH(CH_3)CO$	C_2H_5	5-methoxy-α-methyl-1-phenyl-3-propyl//propionic acid
58	H	H	i-C_3H_7	H	6-benzyloxy	O		$CH_2CH(C_2H_5)CO$	C_2H_5	1-benzyl-7-benzyloxy-α-ethyl-4-isopropyl//propionic acid
59	CH_3	CH_3	CH_3	CH_3	7-Cl	O		$CH(CH_3)CH_2CO$	C_2H_5	8-chloro-β,3,3,4,4-pentamethyl-1-(2-thienyl)//propionic acid
60	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
61	C_2H_5	C_2H_5	H	H	5-F	O	$CH_2=CHCH_2$	$CH(C_2H_5)CH(CH_3)CO$	C_2H_5	1-allyl-6-fluoro-α-methyl-β,3,3-triethyl//propionic acid
62	C_2H_5	C_2H_5	H	H	4-C_2H_5	O	$CH_3C\equiv C$	$CH(n\text{-}C_3H_7)CH_2CO$	CH_3	β-propyl-1-(1-propynyl)-3,3,5-triethyl//propionic acid
63	H	H	H	H	5-OC_2H_5	O		$CH(C_2H_5)CH(C_2H_5)CO$	C_2H_5	1-cyclopropyl-α,β-diethyl-6-ethoxy//propionic acid

TABLE I—continued.

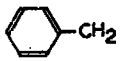
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—CO—Y—OR^{16})			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{16}	PREFIX//SUFFIX
64	CH_3	CH_3	CH_3	CH_3	6-O-*n*-C_3H_7	O		$C(CH_3)_2CH(CH_3)CO$	C_2H_5	$\alpha,\beta,\beta,3,3,4,4$-heptamethyl-1-phenyl-7-propoxy//propionic acid
65	C_2H_5	C_2H_5	H	H	5-CH_3	O		$C(CH_3)_2C(CH_3)_2CO$	C_2H_5	1-benzyl-3,3,-diethyl-$\alpha,\alpha,\beta,\beta,6$-pentamethyl//propionic acid
66	n-C_3H_7	H	H	H	4-OH	O		$C(CH_3)_2C(CH_3)_2CO$	C_2H_5	5-hydroxy-3-propyl-$\alpha,\alpha,\beta,\beta$-tetramethyl-1-(2-thienyl)//propionic acid
67	H	H	H	H	H	O	CH_3	$CH_2CH_2CH_2CO$	C_2H_5	1-methyl//butyric acid, m.p. 132—135°C.
68	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
69	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
70	CH_3	CH_3	n-C_3H_7	H	H	O	$CH_2=CH$	$C(n\text{-}C_3H_7)_2CH(n\text{-}C_3H_7)CH_2CO$	C_2H_5	3,3-dimethyl-$\beta,\gamma,\gamma,4$-tetrapropyl-1-vinyl//butyric acid
71	H	H	H	H	H	O	$CH_2=CHCH_2$	$[C(CH_3)_2]_2CH_2CO$	C_2H_5	1-allyl-$\beta,\beta,\gamma,\gamma$-tetramethyl//butyric acid
72	H	H	C_2H_5	C_2H_5	6-Cl	O	$CH_2=CH-$	$[C(C_2H_5)_2]_2CH(C_2H_5)CO$	C_2H_5	7-chloro-$\alpha,\beta,\beta,\gamma,\gamma,\gamma,4$-heptaethyl-1-vinyl//butyric acid
73	H	H	CH_3	H	4-CH_3	O	$HC\equiv C$	$[C(CH_3)_2]_2CO$	C_2H_5	1-ethynyl-$\alpha,\alpha,\beta,\beta,\gamma,\gamma,4,5$-octamethyl//butyric acid
74	C_2H_5	C_2H_5	C_2H_5	H	5-$OCCH_3$ (O)	O	$CH_3C\equiv C$	$CH(C_2H_5)[C(C_2H_5)]_2CO$	C_2H_5	6-acetoxy-$\alpha,\alpha,\beta,\beta,\gamma,3,3,4$-octaethyl-1-(1-propynyl)//butyric acid

Table I—continued

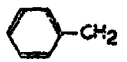
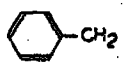
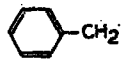
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—CO—Y—OR^{16})			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{16}	PREFIX//SUFFIX
75	H	H	CH_3	CH_3	7-OCH_3	O		$CH_2[C(CH_3)_2]_2CO$	C_2H_5	1-cyclobutyl-α,α,β,β,4,4-hexamethyl-8-methoxy//butyric acid
76	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
77	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
78	H	H	H	H	7-C_2H_5	O		$CH_2CH_2CH(CH_3)CO$	C_2H_5	8-ethyl-α-methyl-1-phenyl//butyric acid
79	CH_3	CH_3	CH_3	H	5-F	O		$[CH(CH_3)]_3CO$	C_2H_5	6-fluoro-α,β,γ,3,3,4-hexamethyl-1-phenyl//butyric acid
80	CH_3	CH_3	H	H	4-CH_3	O		$CH(C_2H_5)CH_2CH(C_2H_5)CO$	C_2H_5	α,γ-diethyl-1-phenyl-3,3,5-trimethyl//butyric acid
81	C_2H_5	H	H	H	6-NO_2	O		$[CH(CH_3)]_3CO$	C_2H_5	1-benzyl-3-ethyl-7-nitro-α,β,γ-trimethyl//butyric acid
82	CH_3	CH_3	H	H	4-n-C_3H_7	O		$CH_2[CH(C_2H_5)]_2CO$	C_2H_5	1-benzyl-α,β-diethyl-3,3-dimethyl-5-propyl//butyric acid
83	H	H	H	H	7-OH	O		$C(CH_3)_2CH_2C(CH_3)_2CO$	C_2H_5	1-benzyl-8-hydroxy-α,α,γ,γ-tetramethyl//butyric acid
84	CH_3	H	CH_3	H	4-OC_2H_5	O		$[C(CH_3)_2]_3CO$	C_2H_5	5-ethoxy-α,α,β,β,γ,γ,3,4-octamethyl-1-(2-thienyl)//butyric acid
85	C_2H_5	H	C_2H_5	C_2H_5	6-Cl	O		$CH_2CH_2C(C_2H_5)_2CO$	C_2H_5	7-chloro-α,α,3,4,4-pentaethyl-1-(2-thienyl)//butyric acid
86	CH_3	CH_3	CH_3	CH_3	4-Br	O		$CH_2CH_2CH(CH_3)CO$	C_2H_5	5-bromo-α,3,3,4,4-pentamethyl-1-(2-thienyl)//butyric acid

TABLE II

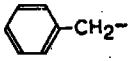
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $(R^1—\overset{O}{\overset{\|}{C}}—Y—OR^{10})$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIO-PYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{10}	PREFIX//SUFFIX
87	H	H	H	H	H	S	CH_3	CO	C_2H_5	1-methyl//carboxylic acid
88	CH_3	H	H	H	H	S	C_2H_5	CO	C_2H_5	1-ethyl-3-methyl//carboxylic acid
89	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
90	CH_3	CH_3	H	H	5-OH	S	$CH_3CH=CH$	CO	CH_3	3,3-dimethyl-6-hydroxy-1-(1-propenyl)//carboxylic acid
91	H	H	H	H	7-C_2H_5	S	$HC\equiv C$	CO	CH_3	8-ethyl-1-ethynyl//carboxylic acid
92	H	H	i-C_3H_7	H	H	S		CO	CH_3	1-cyclopropyl-4-isopropyl//carboxylic acid
93	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
94	H	H	H	H	H	S		CO	CH_3	1-phenyl//carboxylic acid
95	CH_3	C_2H_5	H	H	H	S		CO	CH_3	1-benzyl-3-ethyl-3-methyl//carboxylic acid
96	H	H	H	H	6-Cl	S		CO		7-chloro-1-(2-thienyl)//carboxylic acid
97	H	H	CH_3	H	H	S	CH_3	CH_2CO	C_2H_5	1,4-dimethyl//acetic acid
98	H	H	H	H	H	S	C_2H_5	CH_2CO	C_2H_5	1-ethyl//acetic acid, m.p. 138°C.
99	H	H	H	H	H	S	n-C_3H_7	CH_2CO	C_2H_5	1-propyl//acetic acid, m.p. 127—129°C.
100	H	H	H	H	H	S	i-C_3H_7	CH_2CO	C_2H_5	1-isopropyl//acetic acid
101	CH_3	H	H	H	H	S	$CH_2=CHCH_2$	CH_2CO	C_2H_5	1-allyl-3-methyl//acetic acid
102	CH_3	H	H	H	H	S	n-C_3H_7	CH_2CO	C_2H_5	3-methyl-1-propyl//acetic acid

TABLE II—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $(R^1—\overset{O}{\overset{\|}{C}}—Y—OR^{10})$			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	Y	R^{10}	PREFIX//SUFFIX
103	CH_3	H	C_2H_5	CH_3	H	S	$HC\equiv C$	CH_2CO	C_2H_5	4-ethyl-1-ethynyl-3,4-dimethyl//acetic acid
104	H	H	H	H	H	S	CH_3	$CH(CH_3)CO$	C_2H_5	α,1-dimethyl//acetic acid
105	H	H	H	H	H	S		$C(CH_3)_2CO$	C_2H_5	1-cyclohexyl-α,α-dimethyl//acetic acid
106	H	H	H	H	H	S		CH_2CO	C_2H_5	1-phenyl//acetic acid
107	H	H	H	H	H	S	t-C_4H_9	CH_2CO	C_2H_5	1-t-butyl//acetic acid
108	H	H	H	H	H	S	n-C_4H_9	CH_2CO	C_2H_5	1-butyl//acetic acid
109	H	H	H	H	7-CH_3	S	n-C_3H_7	CH_2CO	C_2H_5	8-methyl-1-propyl//acetic acid
110	H	H	H	H	H	S		CH_2CO	C_2H_5	1-(2-thienyl)//acetic acid
111	H	H	H	H	5-Br	S	n-C_3H_7	CH_2CO	C_2H_5	6-bromo-1-propyl//acetic acid
112	H	H	H	H	5-OCH_3	S	CH_3	CH_2CO	CH_3	6-methoxy-1-methyl//acetic acid
113	H	H	H	H	5-$OCOCH_3$	S	CH_3	CH_2CO	C_2H_5	6-acetoxy-1-methyl//acetic acid
114	H	H	H	H	5-benzyloxy	S	CH_3	CH_2CO	C_2H_5	6-benzyloxy-1-methyl//acetic acid
115	H	H	H	H	4-CH_3	S	n-C_3H_7	CH_2CO	C_2H_5	5-methyl-1-propyl//acetic acid
116	H	H	H	H	6-CH_3	S	n-C_3H_7	CH_2CO	C_2H_5	7-methyl-1-propyl//acetic acid
117	H	H	H	H	7-F	S	$CH_2=CH$	$C(C_2H_5)_2CO$	C_2H_5	α,α-diethyl-8-fluoro-1-vinyl//acetic acid
118	i-C_3H_7	H	i-C_3H_7	H	5-NO_2	S	$CH_2=CH$	$CH(CH_3)CO$	C_2H_5	3,4-diisopropyl-α-methyl-6-nitro-1-vinyl//acetic acid
119	CH_3	CH_3	H	H	5-Cl	S	$CH_3C\equiv C$	$CH(i\text{-}C_3H_7)CO$	C_2H_5	6-chloro-3,3-dimethyl-α-isopropyl-1-(1-propynyl)//acetic acid

TABLE II—continued.

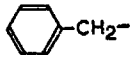
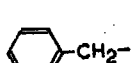
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $(R^1—\overset{O}{\overset{\|}{C}}—Y—OR^{16})$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIO-PYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{16}	PREFIX//SUFFIX
120	H	H	C_2H_5	H	7-CH_3	S	$HC\equiv C$	$C(i\text{-}C_3H_7)_2CO$	C_2H_5	α,α-diisopropyl-4-ethyl-1-ethynyl-8-methyl//acetic acid
121	CH_3	CH_3	H	H	5-OC_2H_5	S		$C(C_2H_5)_2CO$	C_2H_5	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy//acetic acid
122	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
123	CH_3	H	n-C_3H_7	n-C_3H_7	4-n-C_3H_7	S		$CH(CH_3)CO$	C_2H_5	α,3-dimethyl-1-phenyl-4,4,5-tripropyl//acetic acid
124	H	H	H	H	H	S		$C(CH_3)_2CO$	C_2H_5	α,α-dimethyl-1-phenyl//acetic acid
125	C_2H_5	C_2H_5	C_2H_5	C_2H_5	4-C_2H_5	S		$C(i\text{-}C_3H_7)_2CO$	C_2H_5	1-benzyl-α,α-diisopropyl-3,3,4,4,5-pentaethyl//acetic acid
126	CH_3	H	H	H	7-$OC\overset{O}{\overset{\|}{C}}C_2H_5$	S		$C(CH_3)_2CO$	C_2H_5	1-benzyl-8-propionoxy-α,α,3-trimethyl//acetic acid
127	H	H	CH_3	H	H	S		$CH(CH_3)CO$	C_2H_5	α,4-dimethyl-1-(2-thienyl)//acetic acid
128	H	H	H	H	H	S		$C(CH_3)_2CO$	C_2H_5	α,α-dimethyl-1-(2-thienyl)//acetic acid
129	H	H	H	H	H	S	CH_3	CH_2CH_2CO	C_2H_5	1-methyl//propionic acid
130	CH_3	CH_3	CH_3	CH_3	7-$OC\overset{O}{\overset{\|}{C}}CH_3$	S	$CH_2=CH$	$CH_2CH(CH_3)CO$	C_2H_5	8-acetoxy-α,3,3,4,4-pentamethyl-1-vinyl//propionic acid
131	H	H	H	H	6-OH	S	$HC\equiv C—CH_2$	$C(C_2H_5)_2CH_2CO$	C_2H_5	β,β-diethyl-7-hydroxy-1-(2-propynyl)//propionic acid

TABLE II—continued.

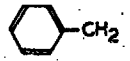
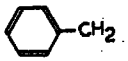
EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—C(=O)—Y—OR^{10})			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROTHIOPYRANO-[3,4-b]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{10}	PREFIX//SUFFIX
132	CH_3	H	H	H	7-NO_2	S		$CH_2CH(n\text{-}C_3H_7)CO$	C_2H_5	1-cyclobutyl-3-methyl-8-nitro-α-propyl//propionic acid
133	H	H	CH_3	H	5-CH_3	S		$C(CH_3)_2C(CH_3)_2CO$	C_2H_5	α,α,β,β,4,6-hexamethyl-1-phenyl//propionic acid
134	i-C_3H_7	H	H	H	7-Br	S		$CH(CH_3)CH(C_2H_5)CO$	C_2H_5	1-benzyl-8-bromo-α-ethyl-3-isopropyl-β-methyl//propionic acid
135	C_2H_5	H	C_2H_5	H	7-Cl	S		CH_2CH_2CO	C_2H_5	8-chloro-3,4-diethyl-1-(2-thienyl)//propionic acid
136	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
137	CH_3	H	C_2H_5	C_2H_5	H	S	$CH_2=C(CH_3)CH_2$	$CH(CH_3)C(CH_3)_2CO$	CH_3	4,4-diethyl-1-methallyl-α,α,β,3-tetramethyl//propionic acid
138	H	H	CH_3	CH_3	H	S	$HC\equiv C$	$C(CH_3)_2CH_2CO$	CH_3	1-ethynyl-β,β,4,4-tetramethyl//propionic acid
139	H	H	n-C_3H_7	H	4-O(C=O)C_2H_5	S		$C(C_2H_5)_2CH(C_2H_5)CO$	CH_3	1-cyclopentyl-5-propionoxy-4-propyl-α,β,β-triethyl//propionic acid
140	n-C_3H_7	H	H	H	4-OCH_3	S		$CH_2CH(CH_3)CO$	C_2H_5	5-methoxy-α-methyl-1-phenyl-3-propyl//propionic acid
141	H	H	i-C_3H_7	H	5-benzyloxy	S		$CH_2CH(C_2H_5)CO$	C_2H_5	1-benzyl-6-benzyloxy-α-ethyl-4-isopropyl//propionic acid
142	CH_3	CH_3	CH_3	CH_3	7-Cl	S		$CH(CH_3)CH_2CO$	C_2H_5	8-chloro-β,3,3,4,4-pentamethyl-1-(2-thienyl)//propionic acid

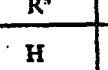
TABLE II—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $(R^1—\overset{O}{\overset{\|}{C}}—Y—OR^{10})$			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	Y	R^{10}	PREFIX//SUFFIX
143	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-$\alpha,\alpha,\beta,\beta,3$-pentaethyl//propionic acid
144	C_2H_5	C_2H_5	H	H	5-F	S	$CH_2=CHCH_2$	$CH(C_2H_5)CH(CH_3)CO$	C_2H_5	1-allyl-6-fluoro-α-methyl-$\beta,3,3$-triethyl//propionic acid
145	C_2H_5	C_2H_5	H	H	4-C_2H_5	S	$CH_3C\equiv CH$	$CH(n\text{-}C_3H_7)CH_2CO$	CH_3	β-propyl-1-(1-propynyl)-3,3,5-triethyl//propionic acid
146	H	H	H	H	5-OC_2H_5	S		$CH(C_2H_5)CH(C_2H_5)CO$	C_2H_5	1-cyclopropyl-α,β-diethyl-6-ethoxy//propionic acid
147	CH_3	CH_3	CH_3	CH_3	6-O-n-C_3H_7	S		$C(CH_3)_2CH(CH_3)CO$	C_2H_5	$\alpha,\beta,\beta,3,3,4,4$-heptamethyl-1-phenyl-7-propoxy//propionic acid
148	C_2H_5	C_2H_5	H	H	5-CH_3	S		$C(CH_3)_2C(CH_3)_2CO$	C_2H_5	1-benzyl-3,3-diethyl-$\alpha,\alpha,\beta,\beta,6$-pentamethyl//propionic acid
149	$n\text{-}C_3H_7$	H	H	H	4-OH	S		$C(CH_3)_2C(CH_3)_2CO$	C_2H_5	5-hydroxy-3-propyl-$\alpha,\alpha,\beta,\beta$-tetramethyl-1-(2-thienyl)//propionic acid
150	H	H	H	H	H	S	CH_3	$CH_2CH_2CH_2CO$	C_2H_5	1-methyl//butyric acid
151	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
152	CH_3	CH_3	H	H	H	S	$n\text{-}C_3H_7$	$C(C_2H_5)_2CH_2CH_2CO$	C_2H_5	γ,γ-diethyl-3,3-dimethyl-1-propyl//butyric acid
153	CH_3	CH_3	$n\text{-}C_3H_7$	H	H	S	$CH_2=CH$	$C(n\text{-}C_3H_7)_2CH(n\text{-}C_3H_7)CH_2CO$	C_2H_5	3,3-dimethyl-$\beta,\gamma,\gamma,4$-tetrapropyl-1-vinyl//butyric acid
154	H	H	H	H	H	S	$CH_2=CHCH_2$	$[C(CH_3)_2]_2CH_2CO$	C_2H_5	1-allyl-$\beta,\beta,\gamma,\gamma$-tetramethyl//butyric acid
155	H	H	C_2H_5	C_2H_5	6-Cl	S	$CH_2=CH—$	$[C(C_2H_5)_2]_2CH(C_2H_5CO$	C_2H_5	7-chloro-$\alpha,\beta,\beta,\gamma,\gamma,4,4$-heptaethyl-1-vinyl//butyric acid

TABLE II—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI $(R^1—\overset{O}{\overset{\|}{C}}—Y—OR^{16})$			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	Y	R^{16}	PREFIX//SUFFIX
156	H	H	CH_3	H	4-CH_3	S	$HC\equiv C$	$[C(CH_3)_2]_3CO$	C_2H_5	1-ethynyl-$\alpha,\alpha,\beta,\beta,\gamma,\gamma$-4,5-octamethyl//butyric acid
157	C_2H_5	C_2H_5	C_2H_5	H	5-$OCCH_3$ (O)	S	$CH_3C\equiv CH$	$CH(C_2H_5)[C(C_2H_5)]_2CO$	C_2H_5	6-acetoxy-$\alpha,\alpha,\beta,\beta,\gamma$,3,3,4-octaethyl-1-(1-propynyl)//butyric acid
158	H	H	CH_3	CH_3	7-OCH_3	S	□	$CH_2[C(CH_3)_3]_2CO$	C_2H_5	1-cyclobutyl-$\alpha,\alpha,\beta,\beta$,4,4-hexamethyl-8-methoxy//butyric acid
159	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
160	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
161	H	H	H	H	7-C_2H_5	S	⬡	$CH_2CH_2CH(CH_3)CO$	C_2H_5	8-ethyl-α-methyl-1-phenyl//butyric acid
162	CH_3	CH_3	CH_3	H	5-F	S	⬡	$[CH(CH_3)]_3CO$	C_2H_5	6-fluoro-α,β,γ,3,3,4-hexamethyl-1-phenyl//butyric acid
163	CH_3	CH_3	H	H	4-CH_3	S	⬡	$CH(C_2H_5)CH_2CH(C_2H_5)CO$	C_2H_5	α,γ-diethyl-1-phenyl-3,3,5-trimethyl//butyric acid
164	C_2H_5	H	H	H	6-NO_2	S	⬡—CH_2	$[CH(CH_3)]_3CO$	C_2H_5	1-benzyl-3-ethyl-7-nitro-α,β,γ-trimethyl//butyric acid
165	CH_3	CH_3	H	H	4-n-C_3H_7	S	⬡—CH_2	$CH_2[CH(C_2H_5)]_2CO$	C_2H_5	1-benzyl-α,β-diethyl-3,3-dimethyl-5-propyl//butyric acid
166	H	H	H	H	7-OH	S	⬡—CH_2	$C(CH_3)_2CH_2C(CH_3)_2CO$	C_2H_5	1-benzyl-8-hydroxy-$\alpha,\alpha,\gamma,\gamma$-tetramethyl//butyric acid

TABLE II—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II						KETOESTER OF FORMULA VI (R^1—C(=O)—Y—OR^{16})			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	Y	R^{16}	PREFIX//SUFFIX
167	CH_3	H	CH_3	H	4-OC_2H_5	S		$[C(CH_3)_2]_3CO$	C_2H_5	5-ethoxy-$\alpha,\alpha,\beta,\beta,\gamma,\gamma,3,4$-octomethyl-1-(2-thienyl)//butyric acid
168	C_2H_5	H	C_2H_5	C_2H_5	6-Cl	S		$CH_2CH_2C(C_2H_5)_2CO$	C_2H_5	7-chloro-$\alpha,\alpha,3,4,4$-pentaethyl-1-(2-thienyl)//butyric acid

EXAMPLE 169.

1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-CARBOXYLIC ACID (XI; R^1 = CH_3, R^2, R^3, R^4, R^5 AND R^6 = H, AND Y = CO AND Z = OH)

A mixture of the starting material of formula II, 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 (X; R^1 = CH_3, R^2, R^3, R^4, R^5 and R^6 = H, Y = CH_2 and R^{17} = H), 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 diethyl 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% diethyl ether in benzene affords 1-methyl,1,3,4,9-tetrahydropyrano[3,4-b]-indole-1 carboxaldehyde (XI; R^1 = CH_3, R^2, R^3, R^4, R^5 and R^6 = H and Y = CO) 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).

Oxidation of the latter compound 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 procedure of Example 169 but using as starting material an equivalent amount of the appropriate starting material of formula II, for example, those described in Examples 1 to 168, inclusive, and using an equivalent amount of the appropriate acylated ketoalcohol of formula VIII, then the acid compounds of formula I in which Z is hydroxy, for example, the respective products of Examples 1 to 168, inclusive, are obtained.

More specifically exemplified, according to the procedure of Example 169 the use of indole-3-ethanethiol and acetonyl acetate affords 1-methyl-1,3,4,9-tetrahydro-thiopyrano[3,4-b]indole-1-acetic acid, identical to the product of Example 3. Similarly the use of tryptophol and 5-acetoxypentan-2-one affords 1-methyl-1,3,4,9-tetrahydro-pyrano[3,4-b]indole-1-propionic acid, identical to the product of Example 2.

EXAMPLE 170.

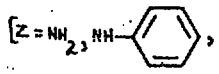
N,N,1-TRIMETHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-ACETAMIDE (I; R^1 = CH_3 R^2, R^3, R^4, R^5, R^6 AND R^7 = H, X = O, Y = CH_2CO AND Z = $N(CH_3)_2$)

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., $\gamma_{max}^{CHCl_3}$ 3375, 1634 cm^{-1}.

In the same manner but replacing dimethylamine with an equivalent amount of ammonium hydroxide (concentrated), methylamine (30% aqueous solution), n-hexyl-amine (20% aqueous solution), diethylamine (30% aqueous solution), or aniline (20% aqueous solution),

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, and
N-phenyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide, m.p. 205—208°C, are obtained respectively.

By following the procedure of Example 170 but using as a starting material an equivalent amount of one of the acid compounds of formula I, described in Examples 2 to 168, 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 170, then the corresponding amide compound of formula I



$NHCH_3$, $N(CH_3)_2$, $NH(n\text{-}C_6H_{13})$ or $N(C_2H_5)_2$] is obtained. Examples of such amides are listed as products in Tables III and IV 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.

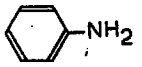
EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
171	2	CH_3NH_2	N,1-dimethyl//propionamide, m.p. 149—150°C.
172	2	NH_3	1-methyl//propionamide
173	2	$(CH_3)_2NH$	N,N,1-trimethyl//propionamide
174	2	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//propionamide
175	2	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//propionamide
176	4	CH_3NH_2	N,1-dimethyl//carboxamide
177	4	NH_3	1-methyl//carboxamide, m.p. 188—189°C.
178	4	$(CH_3)_2NH$	N,N,1-trimethyl//carboxamide
179	4	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//carboxamide
180	4	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//carboxamide
181	5	CH_3NH_2	N,3-dimethyl-1-ethyl//carboxamide
182	8		8-ethyl-1-ethynyl-N-phenyl//carboxamide
183	9	$(CH_3)_2NH$	1-cyclopropyl-N,N-dimethyl-4-isopropyl//carboxamide
184	11	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-phenyl//carboxamide
185	12	$(C_2H_5)_2NH$	1-benzyl-3-methyl-N,N,3-triethyl//carboxamide
186	14	$(CH_3)_2NH$	N,N,1,4-tetramethyl//acetamide
187	15	CH_3NH_2	1-ethyl-N-methyl//acetamide

TABLE III—continued.

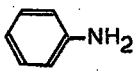
EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
188	15	NH_3	1-ethyl//acetamide
189	15	$(CH_3)_2NH$	N,N-dimethyl-1-ethyl//acetamide
190	15	$n\text{-}C_6H_{13}NH_2$	1-ethyl-N-hexyl//acetamide
191	15	$(C_2H_5)_2NH$	N,N,1-triethyl//acetamide
192	16	CH_3NH_2	N-methyl-1-propyl//acetamide
193	16	NH_3	1-propyl//acetamide
194	16	$(CH_3)_2NH$	N,N-dimethyl-1-propyl//acetamide
195	16	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-propyl//acetamide
196	16	$(C_2H_5)_2NH$	N,N-diethyl-1-propyl//acetamide
197	17	CH_3NH_2	1-isopropyl-N-methyl//acetamide
198	17	NH_3	1-isopropyl//acetamide
199	17	$(C_2H_5)_2NH$	N,N-diethyl-1-isopropyl//acetamide
200	19	CH_3NH_2	N,3-dimethyl-1-propyl//acetamide
201	19		3-methyl-N-phenyl-1-propyl//acetamide
202	19	$(CH_3)_2NH$	1-propyl-N,N,3-trimethyl//acetamide
203	19	$n\text{-}C_6H_{13}NH_2$	N-hexyl-3-methyl-1-propyl//acetamide
204	19	$(C_2H_5)_2NH$	N,N-diethyl-3-methyl-1-propyl//acetamide
205	21	CH_3NH_2	N,α,1-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
206	21	NH_3	α,1-dimethyl//acetamide
207	21	$(CH_3)_2NH$	N,N,α,1-tetramethyl//acetamide
208	21	$n\text{-}C_6H_{13}NH_2$	α,1-dimethyl-N-hexyl//acetamide
209	21	$(C_2H_5)_2NH$	N,N-diethyl-α,1-dimethyl//acetamide
210	22	CH_3NH_2	1-cyclohexyl-N,α,α-trimethyl//acetamide
211	23	$(C_2H_5)_2NH$	N,N-diethyl-1-phenyl//acetamide
212	26	CH_3NH_2	N,8-dimethyl-1-propyl//acetamide
213	31	NH_3	6-benzyloxy-1-methyl//acetamide
214	32	$(CH_3)_2NH$	1-propyl-N,N,5-trimethyl//acetamide
215	38	$n\text{-}C_6H_{13}NH_2$	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy-N-hexyl//acetamide
216	43	$(CH_3)_2NH$	1-benzyl-N,N,α,α,3-pentamethyl-8-propionoxy//acetamide
217	46	CH_3NH_2	5-iodo-1-isopropyl-N-methyl//propionamide
218	49	NH_3	1-cyclobutyl-3-methyl-8-nitro-α-propyl//propionamide
219	54	$(CH_3)_2NH$	4,4-diethyl-N,N,α,α,β,3-hexamethyl-1-methallyl//propionamide
220	57	$(C_2H_5)_2NH$	N,N-diethyl-5-methoxy-α-methyl-1-phenyl-3-propyl//propionamide
221	62	CH_3NH_2	N-methyl-β-propyl-1-(1-propynyl)-3,3,5-triethyl//propionamide

TABLE III—continued.

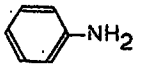
EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
222	63		1-cyclopropyl-α,β-diethyl-6-ethoxy-N-phenyl//propionamide
223	67	$(CH_3)_2NH$	N,N,1-trimethyl//butyramide
224	67	CH_3NH_2	N,1-dimethyl//butyramide
225	67	NH_3	1-methyl//butyramide
226	67	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//butyramide
227	70	CH_3NH_2	β,γ,γ,4-tetrapropyl-N,3,3-trimethyl-1-vinyl//butyramide
228	71	$(C_2H_5)_2NH$	1-allyl-N,N-diethyl-β,β,γ,γ-tetramethyl//butyramide
229	73	$(CH_3)_2NH$	N,N,α,α,β,β,γ,γ,4,5-decamethyl-1-ethynyl//butyramide
230	76	NH_3	5-bromo-1-cyclopentyl-α,α,β-trimethyl//butyramide
231	78	CH_3NH_2	8-ethyl-N,α-dimethyl-1-phenyl//butyramide
232	80	$(C_2H_5)_2NH$	1-phenyl-N,N,α,γ-tetraethyl-3,3,5-trimethyl//butyramide
233	82	$n\text{-}C_6H_{13}NH_2$	1-benzyl-α,β-diethyl-3,3-dimethyl-N-hexyl-5-propyl//butyramide

TABLE IV.

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
234	3	CH_3NH_2	N,1-dimethyl//acetamide
235	3	NH_3	1-methyl//acetamide
236	3	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//acetamide
237	3	$(CH_3)_2NH$	N,N,1-trimethyl//acetamide
238	3	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//acetamide
239	129	CH_3NH_2	N,1-dimethyl//propionamide
240	129	NH_3	1-methyl//propionamide
241	129	$(CH_3)_2NH$	N,N,1-trimethyl//propionamide
242	129	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//propionamide
243	129	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//propionamide
244	87	CH_3NH_2	N,1-dimethyl//carboxamide
245	87	NH_3	1-methyl//carboxamide
246	87	$(CH_3)_2NH$	N,N,1-trimethyl//carboxamide
247	87	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//carboxamide
248	87	$(C_2H_5)_2NH$	N,N-diethyl-1-methyl//carboxamide
249	88	CH_3NH_2	N,3-dimethyl-1-ethyl//carboxamide
250	91	NH_3	8-ethyl-1-ethynyl//carboxamide
251	92	$(CH_3)_2NH$	1-cyclopropyl-N,N-dimethyl-4-isopropyl//carboxamide

TABLE IV—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
252	94	$n\text{-}C_{10}H_{13}NH_2$	N-hexyl-1-phenyl//carboxamide
253	95	$(C_2H_5)_2NH$	1-benzyl-3-methyl-N,N,3-triethyl//carboxamide
254	97	$(CH_3)_2NH$	N,N,1,4-tetramethyl//acetamide
255	98	CH_3NH_2	1-ethyl-N-methyl//acetamide
256	98	NH_3	1-ethyl//acetamide
257	98	$(CH_3)_2NH$	N,N-dimethyl-1-ethyl//acetamide
258	98	$n\text{-}C_6H_{13}NH_2$	1-ethyl-N-hexyl//acetamide
259	98	$(C_2H_5)_2NH$	N,N,1-triethyl//acetamide
260	99	CH_3NH_2	N-methyl-1-propyl//acetamide
261	99	NH_3	1-propyl//acetamide
262	99	$(CH_3)_2NH$	N,N-dimethyl-1-propyl//acetamide
263	99	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-propyl//acetamide
264	99	$(C_2H_5)_2NH$	N,N-diethyl-1-propyl//acetamide
265	100	CH_3NH_2	1-isopropyl-N-methyl//acetamide
266	100	NH_3	1-isopropyl//acetamide
267	100	$(C_2H_5)_2NH$	N,N-diethyl-1-isopropyl//acetamide
268	102	CH_3NH_2	N,3-dimethyl-1-propyl//acetamide
269	102	NH_3	3-methyl-1-propyl//acetamide
270	102	$(CH_3)_2NH$	1-propyl-N,N,3-trimethyl//acetamide

TABLE IV—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
271	102	$n\text{-}C_6H_{13}NH_2$	N-hexyl-3-methyl-1-propyl//acetamide
272	102	$(C_2H_5)_2NH$	N,N-diethyl-3-methyl-1-propyl//acetamide
273	104	CH_3NH_2	N,α,1-trimethyl//acetamide
274	104	NH_3	α,1-dimethyl//acetamide
275	104	$(CH_3)_2NH$	N,N,α,1-tetramethyl//acetamide
276	104	$n\text{-}C_6H_{13}NH_2$	α,1-dimethyl-N-hexyl//acetamide
277	104	$(C_2H_5)_2NH$	N,N-diethyl-α,1-dimethyl//acetamide
278	105	CH_3NH_2	1-cyclohexyl-N,α,α-trimethyl//acetamide
279	106	$(C_2H_5)_2NH$	N,N-diethyl-1-phenyl//acetamide
280	109	CH_3NH_2	N,8-dimethyl-1-propyl//acetamide
281	111	NH_3	6-bromo-1-propyl//acetamide
282	117	$(CH_3)_2NH$	α,α-diethyl-N,N-dimethyl-8-fluoro-1-vinyl//acetamide
283	121	$n\text{-}C_6H_{13}NH_2$	1-cyclopropyl-α,α-diethyl-3,3-dimethyl-6-ethoxy-N-hexyl//acetamide
284	126	$(CH_3)_2NH$	1-benzyl-N,N,α,α,3-pentamethyl-8-propionoxy//acetamide
285	128	CH_3NH_2	1-(2-thienyl)-N,α,α-trimethyl//acetamide
286	132	NH_3	1-cyclobutyl-3-methyl-8-nitro-α-propyl//propionamide
287	137	$(CH_3)_2NH$	4,4-diethyl-N,N,α,α,β,3-hexamethyl-1-methallyl//propionamide

TABLE IV—continued.

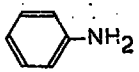
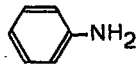
EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	AMINE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
288	140	$(C_2H_5)_2NH$	N,N-diethyl-5-methoxy-α-methyl-1-phenyl-3-propyl//propionamide
289	145	CH_3NH_2	N-methyl-β-propyl-1-(1-propynyl)-3,3,5-triethyl//propionamide
290	146		1-cyclopropyl-α,β-diethyl-6-ethoxy-N-phenyl//propionamide
291	150	$(CH_3)_2NH$	N,N,1-trimethyl//butyramide
292	150	CH_3NH_2	N,1-dimethyl//butyramide
293	150		1-methyl-N-phenyl//butyramide
294	150	$n\text{-}C_6H_{13}NH_2$	N-hexyl-1-methyl//butyramide
295	153	CH_3NH_2	β,γ,γ,4-tetrapropyl-N,3,3-trimethyl-1-vinyl//butyramide
296	154	$(C_2H_5)_2NH$	1-allyl-N,N-diethyl-β,β,γ,γ-tetramethyl//butyramide
297	155	$(CH_3)_2NH$	7-chloro-N,N-dimethyl-α,β,β,γ,γ,4,4-heptaethyl-1-vinyl//butyramide
298	159	NH_3	5-bromo-1-cyclopentyl-α,α,β-trimethyl//butyramide
299	161	CH_3NH_2	N,α-dimethyl-8-ethyl-1-phenyl//butyramide
300	163	$(C_2H_5)_2NH$	1-phenyl-N,N,α,γ-tetraethyl-3,3,5-trimethyl//butyramide

TABLE IV—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
301	165	$n\text{-}C_6H_{13}NH_2$	1-benzyl-α,β-diethyl-3,3-dimethyl-N-hexyl-5-propyl//butyramide
302	168	CH_3NH_2	7-chloro-N-methyl-α,α,3,4,4-pentaethyl-1-(2-thienyl)//butyramide

EXAMPLE 303.

1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-CARBOXAMIDE (I; R^1 = CH_3, R^2, R^3, R^4, R^5, R^6 AND R^7 = H, X = O, Y = CO AND Z = NH_2)

By following the procedure of Example 1 but using 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 177, 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 may be obtained. For example, by using tryptophol (II; R^2, R^3, R^4, R^5, R^6 = H and X' = OH) and the β-ketoamide, N,N-dimethyl-acetoacetamide, in the procedure of this Example, N,N,1-trimethyl-1,3,4,9-tetrahydro-pyrano[3,4-b]indole-1-acetamide, identical with the product of Example 170, is obtained.

EXAMPLE 304.

1,9-DIMETHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-ACETIC ACID (I; R^1 AND R^7 = CH_3, R^2, R^3, R^4, R^5 AND R^6 = H, X = O, Y = CH_2CO AND Z = OH)

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% dispresion) 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 partition 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 diethyl 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 9-ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid, m.p. 134—136°C., and 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 304 but using as the starting material an equivalent amount of the appropriate acid compounds of formula I, in which R^7 is hydrogen and Z is hydroxy, described in Examples 1 to 168, inclusive, and using an equivalent amount of an appropriate lower alkyl or lower alkenyl halide, then the corresponding N-alkylated acid compounds of formula I in which R^7 is lower alkyl or lower alkenyl are obtained. Examples of these latter compounds are listed as products in Tables V and VI together with the appropriate starting material and alkyl or alkynyl halide used for their preparation. In each case the starting material is noted by the Example in which it is prepared.

TABLE V.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ALKYL OR ALKENYL HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
305	1	$CH_2=CHCH_2Br$	9-allyl-1-methyl//acetic acid, m.p. 103—105°C.
306	1	$CH_2=CHBr$	1-methyl-9-vinyl//acetic acid
307	1	$CH_2=C(CH_3)CH_2Br$	1-methyl-9-methallyl//acetic acid
308	2	$n\text{-}C_3H_7I$	1-methyl-9-propyl//propionic acid
309	2	CH_3I	1,9-dimethyl//propionic acid
310	2	$CH=CHBr$	1-methyl-9-vinyl//propionic acid
311	2	$CH_2=CHCH_2Cl$	9-allyl-1-methyl//propionic acid
312	4	CH_3I	1,9-dimethyl//carboxylic acid
313	4	$CH_2=CHBr$	1-methyl-9-vinyl//carboxylic acid
314	7	CH_3I	6-hydroxy-1-(1-propenyl)-3,3,9-trimethyl//carboxylic acid
315	9	$CH_3CH=CHBr$	1-cyclopropyl-4-isopropyl-9-(1-propenyl)//carboxylic acid
316	11	$i\text{-}C_3H_7I$	9-isopropyl-1-phenyl//carboxylic acid
317	15	CH_3I	1-ethyl-9-methyl//acetic acid
318	15	C_2H_5Cl	1,9-diethyl//acetic acid
319	15	$CH_2=CHCH_2Br$	9-allyl-1-ethyl//acetic acid
320	15	$CH_2=CHBr$	1-ethyl-9-vinyl//acetic acid
321	16	CH_3I	9-methyl-1-propyl//acetic acid
322	16	$n\text{-}C_3H_7Cl$	1,9-dipropyl//acetic acid

TABLE V—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ALKYL OR ALKENYL HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
323	16	$CH_2=CHCH_2Br$	9-allyl-1-propyl//acetic acid
324	16	$CH_2=C(CH_3)CH_2Br$	9-methallyl-1-propyl//acetic acid
325	17	CH_3I	9-methyl-1-isopropyl//acetic acid
326	17	$CH_2=CHBr$	1-isopropyl-9-vinyl//acetic acid
327	19	$n\text{-}C_3H_7Cl$	1,9-dipropyl-3-methyl//acetic acid
328	19	$CH_2=CHCH_2Br$	9-allyl-3-methyl-1-propyl//acetic acid
329	21	CH_3I	α,1,9-trimethyl//acetic acid
330	21	$CH_2=CHBr$	α,1-dimethyl-1-vinyl//acetic acid
331	22	$n\text{-}C_3H_7Cl$	1-cyclohexyl-α,α-dimethyl-9-propyl//acetic acid
332	27	$CH_2=CHCH_2I$	9-allyl-1-(2-thienyl)//acetic acid
333	29	CH_3Cl	1,9-dimethyl-6-methoxy//acetic acid
334	34	$CH_2=CHBr$	6-nitro-1-propyl-9-vinyl//acetic acid
335	40	C_2H_5Cl	α,3-dimethyl-9-ethyl-11-phenyl-4,4,5-tripropyl//acetic acid
336	42	$CH_2=CHCH_2Br$	9-allyl-1-benzyl-α,α-diisopropyl-3,3,4,4,5-pentaethyl//acetic acid
337	48	C_2H_5I	7-hydroxy-1-(2-propynyl)-β,β,9-triethyl//propionic acid
338	49	CH_3I	1-cyclobutyl-3,9-dimethyl-8-nitro-α-propyl//propionic acid

TABLE V—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ALKYL OR ALKENYL HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
339	54	$CH_2=C(CH_3)CH_2Cl$	4,4-diethyl-1,9-dimethallyl-α,α,β,3-tetramethyl//propionic acid
340	59	$CH_2=CHCH_2Br$	9-allyl-8-chloro-β,3,3,4,4-pentamethyl-1-(2-thienyl)//propionic acid
341	60	$CH_2=CHCl$	1-methyl-6-nitro-$\alpha,\alpha,\beta,\beta$,3-pentaethyl-9-vinyl//propionic acid
342	63	C_2H_5Cl	1-cyclopropyl-6-ethoxy-α,β,9-triethyl//propionic acid
343	67	CH_3I	1,9-dimethyl//butyric acid
344	67	$CH_2=CHCH_2Cl$	9-allyl-1-methyl//butyric acid
345	68	C_2H_5Cl	1,9-diethyl-γ,3-dimethyl//butyric acid
346	70	$CH_2=CHBr$	3,3-dimethyl-1,9-divinyl-β,γ,γ,4-tetrapropyl//butyric acid
347	72	$CH_2=CHBr$	7-chloro-1,9-divinyl-$\alpha,\beta,\beta,\gamma,\gamma$,4-heptaethyl//butyric acid
348	78	C_2H_5I	8,9-diethyl-α-methyl-1-phenyl//butyric acid
349	82	CH_3I	1-benzyl-α,β-diethyl-5-propyl-3,3,9-trimethyl//butyric acid
350	85	C_2H_5Br	7-chloro-α,α,3,4,4,9-hexaethyl-1-(2-thienyl)//butyric acid

TABLE VI.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ALKYL OR ALKENYL HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
351	3	$CH_2=CHCH_2Br$	9-allyl-1-methyl//acetic acid
352	3	CH_3I	1,9-dimethyl//acetic acid
353	3	$CH_2=C(CH_3)CH_2Br$	1-methyl-9-methallyl//acetic acetic acid
354	129	$n\text{-}C_3H_7I$	1-methyl-9-propyl//propionic acid
355	129	CH_3I	1,9-dimethyl//propionic acid
356	129	$CH_2=CHBr$	1-methyl-9-vinyl//propionic acid
357	129	$CH_2=CHCH_2Cl$	9-allyl-1-methyl//propionic acid
358	87	CH_3I	1,9-dimethyl//carboxylic acid
359	87	$CH_2=CHBr$	1-methyl-9-vinyl//carboxylic acid
360	90	CH_3I	6-hydroxy-1-(1-propenyl)-3,3,9-trimethyl//carboxylic acid
361	92	$CH_3CH=CHBr$	1-cyclopropyl-4-isopropyl-9-(1-propenyl)//carboxylic acid
362	94	$2\text{-}C_3H_7I$	9-isopropyl-1-phenyl//carboxylic acid
363	98	CH_3I	1-ethyl-9-methyl//acetic acid
364	98	C_2H_5Cl	1,9-diethyl//acetic acid
365	98	$CH_2=CHCH_2Br$	9-allyl-1-ethyl//acetic acid
366	98	CH_2CHBr	1-ethyl-9-vinyl//acetic acid
367	99	CH_3I	9-methyl-1-propyl//acetic acid
368	99	$n\text{-}C_3H_7Cl$	1,9-dipropyl//acetic acid

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TABLE VI—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ALKYL OR ALKENYL HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
369	99	$CH_2=CHCH_2Br$	9-allyl-1-propyl//acetic acid
370	99	$CH_2=C(CH_3)CH_2Br$	9-methallyl-1-propyl//acetic acid
371	100	CH_3I	9-methyl-1-isopropyl//acetic acid
372	100	$CH_2=CHBr$	1-isopropyl-9-vinyl//acetic acid
373	102	n-C_3H_7Cl	1,9-dipropyl-3-methyl//acetic acid
374	102	$CH_2=CHCH_2Br$	9-allyl-3-methyl-1-propyl//acetic acid
375	104	CH_3I	α,1,9-trimethyl//acetic acid
376	104	$CH_2=CHBr$	α,1-dimethyl-1-vinyl//acetic acid
377	105	n-C_3H_7Cl	1-cyclohexyl-α,α-dimethyl-9-propyl//acetic acid
378	110	$CH_2=CHCH_2I$	9-allyl-1-(2-thienyl)//acetic acid
379	112	CH_3Cl	1,9-dimethyl-6-methoxy//acetic acid
380	117	$CH_2=CHBr$	α,α-diethyl-1,9-divinyl-8-fluoro//acetic acid
381	123	C_2H_5Cl	α,3-dimethyl-9-ethyl-1-phenyl-4,4,5-tripropyl// acetic acid
382	125	$CH_2=CHCH_2Br$	9-allyl-1-benzyl-α,α-diisopropyl-3,3,4,4,5-pentaethyl//acetic acid
383	131	C_2H_5I	7-hydroxy-1-(2-propynyl)-β,β,9-triethyl// propionic acid
384	132	CH_3I	1-cyclobutyl-3,9-dimethyl-8-nitro-α-propyl// propionic acid
385	137	$CH_2=C(CH_3)CH_2Cl$	4,4-diethyl-1,9-dimethallyl-α,α,β,3-tetramethyl// propionic acid

TABLE VI—continued.

EXAMPLE	NO. OF THE EXAMPLE IN WHICH STARTING MATERIAL IS PREPARED	ALKYL OR ALKENYL HALIDE	PRODUCT: [(*PREFIX LISTED BELOW*-1,3,4,9-TETRAHYDROTHIOPYRANO[3,4-b]-INDOLE-1-(*SUFFIX LISTED BELOW*)] PREFIX//SUFFIX
386	142	$CH_2=CHCH_2Br$	9-allyl-8-chloro-β,3,3,4,4-pentamethyl-1-(2-thienyl)//propionic acid
387	143	$CH_2=CHCl$	1-methyl-6-nitro-α,α,β,β,3-pentaethyl-9-vinyl//propionic acid
388	146	C_2H_5Cl	1-cyclopropyl-6-ethoxy-α,β,9-triethyl//propionic acid
389	150	CH_3I	1,9-dimethyl//butyric acid
390	150	$CH_2=CHCH_2Cl$	9-allyl-1-methyl//butyric acid
391	151	C_2H_5Cl	1,9-diethyl-γ,3-dimethyl//butyric acid
392	153	$CH_2=CHBr$	3,3-dimethyl-1,9-divinyl-β,γ,γ,4-tetrapropyl//butyric acid
393	155	$CH_2=CHBr$	7-chloro-1,9-divinyl-α,β,β,γ,γ,4,4-heptaethyl//butyric acid
394	161	C_2H_5I	8,9-diethyl-α-methyl-1-phenyl//butyric acid
395	165	CH_3I	1-benzyl-α,β-diethyl-5-propyl-3,3,9-trimethyl//butyric acid
396	168	C_2H_5Br	7-chloro-α,α,3,4,4,9-hexaethyl-1-(2-thienyl)//butyric acid

EXAMPLE 397.

By following the procedure of Example 304 but using as the starting material an equivalent amount of the ester compounds of formula I in which R^7 is hydrogen and Z is lower alkoxy, obtained prior to hydrolysis in Example 1 and 3 to 168, 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 lower alkyl or lower alkenyl halide, then the corresponding N-alkylated ester compounds of formula I in which R^7 is lower alkyl or lower alkenyl, are obtained.

For example, when following the procedure of Example 304, 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 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 170 but using as the starting material an equivalent amount of one of the N-alkylated acid compounds of formula I, described in Examples 304 to 396, 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 170, then the corresponding amide compound of formula I in which R^7 is lower alkyl or lower alkenyl and Z is amino, lower alkyl amino, di(lower)alkylamino or phenylamino, is obtained. Examples of such amides are listed as products in Tables VII and VIII 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 VII.

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
398	304	$(CH_3)_2NH$	N,N,1,9-tetramethyl//acetamide
399	304	CH_3NH_2	N,1,9-trimethyl//acetamide, m.p. 136—138°C.
400	304	NH_3	1,9-dimethyl//acetamide, m.p. 105—106°C.
401	304	$n\text{-}C_6H_{13}NH_2$	1,9-dimethyl-N-hexyl//acetamide
402	304	$(C_2H_5)_2NH$	N,N-diethyl-1,9-dimethyl//acetamide
403	305	CH_3NH_2	9-allyl-N,1-dimethyl//acetamide
404	305	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//acetamide
405	309	CH_3NH_2	N,1,9-trimethyl//propionamide
406	309	$(C_2H_5)_2NH$	1,9-dimethyl-N,N-diethyl//propionamide
407	311	NH_3	9-allyl-1-methyl//propionamide
408	311	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//propionamide
409	313	CH_3NH_2	N,1-dimethyl-9-vinyl//carboxamide
410	314	$(C_2H_5)_2NH$	N,N-diethyl-6-hydroxy-1-(1-propenyl)-3,3,9-trimethyl//carboxamide
411	316	$n\text{-}C_6H_3NH_2$	N-hexyl-9-isopropyl-1-phenyl//carboxamide
412	317	CH_3NH_2	N,9-dimethyl-1-ethyl//acetamide
413	319	$(C_2H_5)_2NH$	9-allyl-N,N,1-triethyl//acetamide
414	320	$(CH_3)_2NH$	N,N-dimethyl-1-ethyl-9-vinyl//acetamide
415	321	CH_3NH_2	N,9-dimethyl-1-propyl//acetamide

TABLE VII—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
416	323	$(C_2H_5)_2NH$	9-allyl-N,N-diethyl-1-propyl//acetamide
417	331	CH_3NH_2	1-cyclohexyl-9-propyl-N,α,α-trimethyl//acetamide
418	332	$n\text{-}C_6H_{13}NH_2$	9-allyl-N-hexyl-1-(2-thienyl)//acetamide
419	333	$(CH_3)_2NH$	6-methoxy-N,N,1,9-tetramethyl//acetamide
420	335	CH_3NH_2	9-ethyl-1-phenyl-4,4,5-tripropyl-N,α,3-trimethyl//acetamide
421	341	$(C_2H_5)_2NH$	N,N,α,α,β,β,3-heptaethyl-1-methyl-6-nitro-9-vinyl//propionamide
422	342	$(C_2H_5)_2NH$	1-cyclopropyl-6-ethoxy-N,N,α,β,9-pentaethyl//propionamide
423	343	CH_3NH_2	N,1,9-trimethyl//butyramide
424	344	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//butyramide
425	345	NH_3	1,9-diethyl-γ,3-dimethyl//butyramide
426	349	CH_3NH_2	1-benzyl-α,β-diethyl-5-propyl-N,3,3,9-tetramethyl//butyramide

TABLE VIII

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
427	352	$(CH_3)_2NH$	N,N,1,9-tetramethyl//acetamide
428	352	CH_3NH_2	N,1,9-trimethyl//acetamide
429	352	NH_3	1,9-dimethyl//acetamide
430	352	$n\text{-}C_6H_{13}NH_2$	1,9-dimethyl-N-hexyl//acetamide
431	352	$(C_2H_5)_2NH$	N,N-diethyl-1,9-dimethyl//acetamide
432	351	CH_3NH_2	9-allyl-N,1-dimethyl//acetamide
433	351	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//acetamide
434	355	CH_3NH_2	N,1,9-trimethyl//propionamide
435	355	$(C_2H_5)_2NH$	1,9-dimethyl-N,N-diethyl//propionamide
436	357	NH_3	9-allyl-1-methyl//propionamide
437	357	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//propionamide
438	359	CH_3NH_2	N,1-dimethyl-9-vinyl//carboxamide
439	360	$(C_2H_5)_2NH$	N,N-diethyl-6-hydroxy-1-(1-propenyl)-3,3,9-trimethyl//carboxamide
440	362	$n\text{-}C_6H_{13}NH_2$	N-hexyl-9-isopropyl-1-phenyl//carboxamide
441	363	CH_3NH_2	N,9-dimethyl-1-ethyl//acetamide
442	365	$(C_2H_5)_2NH$	9-allyl-N,N,1-triethyl//acetamide
443	366	$(CH_3)_2NH$	N,N-dimethyl-1-ethyl-9-vinyl//acetamide
444	367	CH_3NH_2	N,9-dimethyl-1-propyl//acetamide

TABLE VIII—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
445	369	$(C_2H_5)_2NH$	9-allyl-N,N-diethyl-1-propyl//acetamide
446	377	CH_3NH_2	1-cyclohexyl-9-propyl-N,α,α-trimethyl//acetamide
447	378	$n\text{-}C_6H_{13}NH_2$	9-allyl-N-hexyl-1-(2-thienyl)//acetamide
448	379	$(CH_3)_2NH$	6-methoxy-N,N,1,9-tetramethyl//acetamide
449	381	CH_3NH_2	9-ethyl-1-phenyl-4,4,5-tripropyl-N,α,3-trimethyl//acetamide
450	387	$(C_2H_5)_2NH$	N,N,α,α,β,β,3-heptaethyl-1-methyl-6-nitro-9-vinyl//propionamide
451	388	$(C_2H_5)_2NH$	1-cyclopropyl-6-ethoxy-N,N,α,β,9-pentaethyl//propionamide
452	389	CH_3NH_2	N,1,9-trimethyl//butyramide
453	390	$(CH_3)_2NH$	9-allyl-N,N,1-trimethyl//butyramide
454	391	NH_3	1,9-diethyl-γ,3-dimethyl//butyramide
455	395	CH_3NH_2	1-benzyl-α,β-diethyl-5-propyl-N,3,3,9-tetramethyl//butyramide

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EXAMPLE 456.

6-HYDROXY-1-METHYL-1,3,4,9-TETRAHYDROPYRANO[3,4-b]INDOLE-1-ACETIC ACID (I; R^1 = CH_3, R^2, R^3, R^4, R^5 AND R^7 = H, R^6 = 6-OH, X = O, Y = CH_2CO AND Z = OH)

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 31, 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, ["Celite" is a registered Trade Mark]) 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-tetrahydropyrano[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 diethyl 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 30.

Table IX provides further examples of the compounds of this invention. The remarks relating to procedure, starting material and product applied to Table I are applicable also to Table IX. Note also that starting materials of both formulae II and IIa are utilized.

TABLE IX

EXAMPLE	STARTING MATERIAL OF FORMULA II or IIa						KETOESTER OF FORMULA VI $(R^1—C(=O)—Y—OR^{16})$			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-d]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{16}	PREFIX//SUFFIX
457	H	H	CH_3	H	H	O	n-C_3H_7	CH_2CO	C_2H_5	4-methyl-1-propyl//acetic acid, m.p. 191—195°C.
458	H	H	H	H	5-CH_3	O	n-C_3H_7	CH_2CO	C_2H_5	6-methyl-1-propyl//acetic acid, m.p. 126—129°C.
459	H	H	H	H	4-i-C_3H_7	O	n-C_3H_7	CH_2CO	C_2H_5	5-isopropyl-1-propyl//acetic acid, 164.5—165°C.
460	H	H	H	H	4-Cl	O	n-C_3H_7	CH_2CO	C_2H_5	5-chloro-1-propyl//acetic acid, m.p. 166—169°C.
461	H	H	H	H	6-OCH_3	O	n-C_3H_7	CH_2CO	C_2H_5	7-methoxy-1-propyl//acetic acid, m.p. 164—166°C.
462	H	H	CH_3	H	H	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-4-methyl//acetic acid, m.p. 153—156°C., (Isomer A), m.p. 132—133°C. (Isomer B)
463	H	H	H	H	4-Cl	O	CH_3	CH_2CO	C_2H_5	5-chloro-1-methyl//acetic acid, m.p. 183—184°C.
464	H	H	H	H	4-C_2H_5	O	n-C_3H_7	CH_2CO	C_2H_5	5-ethyl-1-propyl//acetic acid, m.p. 130—131°C.
465	H	CH_3	H	H	H	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-3-methyl//acetic acid, m.p. 147—148°C., (Isomer A), m.p. 145—146°C., (Isomer B)
466	H	H	H	H	4-CH_3	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-5-methyl//acetic acid, m.p. 170—172°C.
467	H	H	H	H	4-CH_3	O	CH_3	CH_2CO	C_2H_5	1,5-dimethyl//acetic acid, m.p. 150—151°C.
468	H	H	H	H	4-Cl	O	C_2H_5	CH_2CO	C_2H_5	5-chloro-1-ethyl//acetic acid, m.p. 154—157°C.

TABLE IX—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II or IIa						KETOESTER OF FORMULA VI ($R^1—C(=O)—Y—OR^{16}$)			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-d]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{16}	PREFIX//SUFFIX
469	H	H	CH_3	H	H	O	t-C_4H_9	CH_2CO	C_2H_5	1-t-butyl-4-methyl//acetic acid, m.p. 179—181°C.
470	H	H	H	H	4-OCH_3	O	n-C_3H_7	CH_2CO	C_2H_5	5-methoxy-1-propyl//acetic acid, m.p. 148—151°C.
471	H	H	H	H	7-CH_3	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-8-methyl//acetic acid, m.p. 160—161°C.
472	H	H	CH_3	H	7-CH_3	O	C_2H_5	CH_2CO	C_2H_5	4,8-dimethyl-1-ethyl//acetic acid, m.p. 129—131°C.
473	H	H	CH_3	H	7-CH_3	O	CH_3	CH_2CO	C_2H_5	1,4,8-trimethyl//acetic acid, m.p. 157—159°C.
474	H	H	H	H	7-Cl	O	C_2H_5	CH_2CO	C_2H_5	8-chloro-1-ethyl//acetic acid, m.p. 168—171°C.
475	H	H	H	H	6-Cl	O	C_2H_5	CH_2CO	C_2H_5	7-chloro-1-ethyl//acetic acid, m.p. 182—183°C.
476	H	H	H	H	6-Cl	O	n-C_3H_7	CH_2CO	C_2H_5	7-chloro-1-propyl//acetic acid, m.p. 182—183°C.
477	H	H	H	H	7-C_2H_5	O	C_2H_5	CH_2CO	C_2H_5	1,8-diethyl//acetic acid, m.p. 145—148°C.
478	H	H	H	H	7-OCH_3	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-8-methoxy//acetic acid, m.p. 132°C.
479	H	H	H	H	4-CH_3, 7-CH_3	O	C_2H_5	CH_2CO	C_2H_5	5,8-dimethyl-1-ethyl//acetic acid
480	H	H	H	H	4-Cl, 7-Cl	O	C_2H_5	CH_2CO	C_2H_5	5,8-dichloro-1-ethyl//acetic acid
481	H	H	H	H	6-Cl, 7-Cl	O	n-C_3H_7	CH_2CO	C_2H_5	7,8-dichloro-1-propyl//acetic acid

TABLE IX—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II or IIa						KETOESTER OF FORMULA VI O ‖ (R^1—C—Y—OR^{16})			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-d]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{16}	PREFIX//SUFFIX
482	H	H	H	H	4-Cl, 6-Cl	O	CH_3	CH_2CO	C_2H_5	5,7-dichloro-1-methyl//acetic acid
483	H	H	H	H	4-CH_3, 7-Cl	O	C_2H_5	CH_2CO	C_2H_5	8-chloro-1-ethyl-5-methyl//acetic acid
484	H	H	H	H	4-Cl, 7-CH_3	O	C_2H_5	CH_2CO	C_2H_5	5-chloro-1-ethyl-8-methyl//acetic acid
485	H	H	CH_3	H	4-C_2H_5, 6-Br	O	C_2H_5	CH_2CO	C_2H_5	7-bromo-1,5-diethyl-4-methyl//acetic acid
486	H	H	H	H	6-Cl, 7-CH_3	O	CH_3	CH_2CO	C_2H_5	7-chloro-1,8-dimethyl//acetic acid
487	H	H	CH_3	H	4-Cl, 6-Cl, 7-Cl	O	CH_3	CH_2CO	C_2H_5	1,4-dimethyl-5,7,8-trichloro//acetic acid
488	H	H	H	H	4-OCH_3, 5-OCH_3, 6-OCH_3, 7-OCH_3	O	n-C_3H_7	CH_2CO	C_2H_5	1-propyl-5,6,7,8-tetramethoxy//acetic acid
489	H	H	H	H	4-OCH_3, 7-Cl	O	C_2H_5	CH_2CO	C_2H_5	8-chloro-1-ethyl-5-methoxy//acetic acid
490	H	H	CH_3	H	4-OCH_3, 6-Cl, 7-Cl	O	CH_3	CH_2CO	C_2H_5	7,8-dichloro-1-methyl-5-methoxy//acetic acid
491	H	H	H	H	4-OCH_3, 7-OCH_3	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-5,8-dimethoxy//acetic acid, m.p. 167—169°C.
492	CH_3	H	H	H	4-F, 7-Cl	O	n-C_3H_7	CH_2CO	C_2H_5	8-chloro-5-fluoro-3-methyl-1-propyl//acetic acid

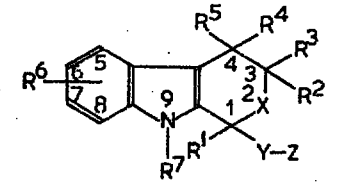
TABLE IX—continued.

EXAMPLE	STARTING MATERIAL OF FORMULA II or IIa						KETOESTER OF FORMULA VI O ‖ (R¹—C—Y—OR¹⁶)			PRODUCT: [(*PREFIX LISTED BELOW*)-1,3,4,9-TETRAHYDROPYRANO-[3,4-d]INDOLE-1-(*SUFFIX LISTED BELOW*)]
	R^2	R^3	R^4	R^5	R^6	X	R^1	Y	R^{16}	PREFIX//SUFFIX
493	H	H	H	H	4-F, 6-Cl, 7-Cl	O	C_2H_5	CH_2CO	C_2H_5	7,8-dichloro-5-fluoro-1-ethyl// acetic acid
494	C_2H_5	H	CH_3	H	4-CF_3, 7-CH_3	O	CH_3	CH_2CO	C_2H_5	3-ethyl-5-trifluoromethyl-1,4,8-trimethyl//acetic acid
495	H	H	H	H	6-CF_3	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-7-trifluoromethyl// acetic acid
496	H	H	CH_3	H	7-CF_3	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-4-methyl-8-trifluoro-methyl//acetic acid
497	H	H	C_2H_5	H	5-CH_3, 7-NO_2	O	CH_3	CH_2CO	C_2H_5	1,6-dimethyl-4-ethyl-8-nitro// acetic acid
498	CH_3	H	H	H	4-NO_2, 7-Cl	O	n-C_3H_7	CH_2CO	C_2H_5	8-chloro-3-methyl-5-nitro-1-propyl//acetic acid
499	H	H	H	H	5-SH	O	CH_3	CH_2CO	C_2H_5	6-mercapto-1-methyl//acetic acid
500	H	H	CH_3	H	7-SCH_3	O	CH_3	CH_2-CH_2CO	C_2H_5	1,4-dimethyl-8-methyl-thio// propionic acid
501	H	H	H	H	6-SC_2H_5	O	C_2H_5	CH_2CO	C_2H_5	1-ethyl-7-ethylthio//acetic acid
502	H	H	H	H	4-NH_2	O	C_2H_5	CH_2CO	C_2H_5	5-amino-1-ethyl//acetic acid
503	H	H	H	H	6-NH_2	O	C_2H_5	CH_2CO	C_2H_5	7-amino-1-ethyl//acetic acid
504	H	H	H	H	4-SO_2NH_2	O	n-C_3H_7	CH_2CO	C_2H_5	1-propyl-5-sulfamoyl//acetic acid
505	H	H	H	H	6-SO_2NH_2	O	CH_3	CH_2CO	C_2H_5	1-methyl-7-sulfamoyl//acetic acid

* C L M S *

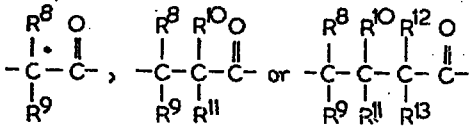
WHAT WE CLAIM IS:—

1. An indole derivative having the general formula:—



I.

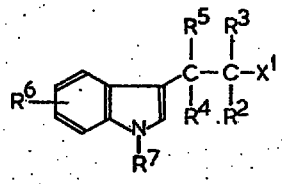
wherein R^1 is a lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, phenyl, benzyl or 2-thienyl group, R^2, R^3, R^4 and R^5, which may be the same or different, are hydrogen atoms or lower alkyl groups, R^6 is a hydrogen atom, or a lower alkyl, hydroxy, lower alkoxy, benzyloxy, lower alkanoyloxy, or nitro group or a halogen atom, R^7 is a hydrogen atom, or a lower alkyl or lower alkenyl group, X is an oxy or thio radical Y is a carbonyl.



group in which each of R^8, R^9, R^{10}, R^{11}, R^{12} and R^{13} is a hydrogen atom or a lower alkyl group, and Z is a hydroxy, lower alkoxy, amino, lower alkylamino, di(lower)alkylamino or phenylamino group, the terms "lower alkyl", "lower alkenyl", "lower alkynyl", "lower cycloalkyl", "lower alkoxy", "lower alkanoyloxy", "lower alkylamino", "di(lower)-alkylamino" being as hereinbefore defined.

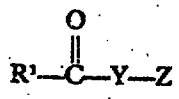
2. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid ethyl ester.
3. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
4. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid methyl ester.
5. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-propionic acid.
6. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-propionic acid ethyl ester.
7. 1-Methyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole-1-acetic acid methyl ester.
8. 1-Methyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole-1-acetic acid.
9. 1-Ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
10. 1-Propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
11. 1-Isopropyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
12. 3-Methyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
13. 4 - Ethyl - 1 - ethynyl - 3 - methyl - 1,3,4,9 - tetrahydropyrano[3,4 - b]-indole-1-acetic acid.
14. α,1-Dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
15. 1-Phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
16. 1-t-Butyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
17. 1-Butyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
18. 8-Methyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
19. 1-(2-Thienyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
20. 6-Bromo-1-ethyl-1,3,4,9,tetrahydropyrano[3,4-b]indole-1-acetic acid.
21. 6-Methoxy-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
22. 6-Acetoxy-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
23. 6-Benzyloxy-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
24. 5-Methyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
25. 7-Methyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
26. 6-Nitro-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
27. 4,4-Dimethyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
28. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-butyric acid.
29. 1-Ethyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole-1-acetic acid.
30. 1-Propyl-1,3,4,9-tetrahydrothiopyrano[3,4-b]indole-1-acetic acid.
31. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-carboxylic acid.
32. N,N,1-Trimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide.
33. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide.
34. N,1-Dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide.
35. N-Phenyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide.
36. N,1-Dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-propionamide.

37. 1-Methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-carboxamide.
38. 1,9-Dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
39. 9-Allyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
40. 6-Hydroxy-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
41. 6-Hydroxy-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid benzylamine salt.
42. 1,4-Dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
43. N,N-Diethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide.
44. 9-Ethyl-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
45. 1-Methyl-9-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
46. N,1,9-Trimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide.
47. 1,9-Dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetamide.
48. 4-Methyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
49. 6-Methyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
50. 5-Isopropyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
51. 5-Chloro-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
52. 7-Methoxy-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
53. 1-Ethyl-4-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
54. 5-Chloro-1-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
55. 5-Ethyl-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
56. 1-Ethyl-3-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
57. 1-Ethyl-5-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
58. 1,5-Dimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
59. 5-Chloro-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
60. 1-t-Butyl-4-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
61. 5-Methoxy-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
62. 1-Ethyl-8-methyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
63. 4,8-Dimethyl-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
64. 1,4,8-Trimethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
65. 8-Chloro-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
66. 7-Chloro-1-ethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
67. 7-Chloro-1-propyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
68. 1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
69. 1-Ethyl-8-methoxy-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.
70. A process for the production of an indole compound having the general formula I as defined in claim 1 which comprises reacting a compound having the general formula:



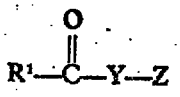
II.

wherein R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim 1 and X' is a hydroxy or mercapto group with a compound having the general formula



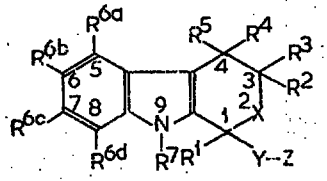
wherein R^1, Y and Z are as defined in claim 1, in the presence of an acid catalyst.

71. A process as claimed in claim 70 in which the compound having general formula II is reacted with a compound of formula



wherein R^1 and Y are as defined in claim 1 and Z is a lower alkoxy group, and the corresponding compound of formula I wherein Z is a lower alkoxy group is obtained.

72. An indole derivative having the general formula Ia



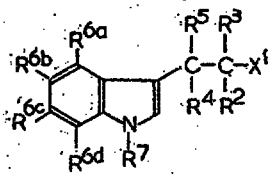
Ia.

wherein R^1, R^2, R^3, R^4, R^5, R^7, X, Y and Z are as defined in claim 1, R^{6a}, R^{6b}, R^{6c}, and R^{6d}, which may be the same or different, are hydrogen or halogen atoms, or lower alkyl, hydroxy, lower alkoxy, benzyloxy, lower alkanoyloxy, nitro, mercapto, lower alkylthio, halo(lower)alkyl, amino or sulfamoyl groups.

73. An indole derivative as claimed in claim 72 in which at least one of R^{6a}, R^{6b} R^{6c} and R^{6d} is trifluoromethyl.

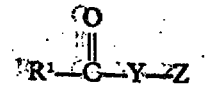
74. 1-Ethyl-5,8-dimethoxy-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid.

75. A process for the production of an indole derivative having the general formula Ia as defined in claim 72 which comprises reacting a compound having the general formula



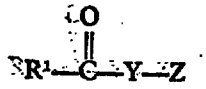
IIa.

wherein R^2, R^3, R^4, R^5, R^7, R^{6a}, R^{6b}, R^{6c}, and R^{6d} are as defined in claim 72 and X' is a hydroxy or mercapto group with a compound having the general formula



wherein R^1, Y and Z are as defined in claim 1, in the presence of an acid catalyst.

76. A process as claimed in claim 75 in which the compound having the general formula IIa is reacted with a compound having the general formula



wherein R^1 and Y are as defined in claim 1 and Z is a lower alkoxy group, and the corresponding compound of formula Ia in which Z is a lower alkoxy group is obtained.

77. An indole derivative of general formula I or *Ia* substantially as hereinbefore described with particular reference to any of the foregoing Examples.

78. A process for the production of an indole derivative of general formula I or *Ia* substantially as hereinbefore described with particular reference to any of the foregoing Examples.

79. Addition salts of indole derivatives having the general formula I or Ia substantially as hereinbefore described.

80. A pharmaceutical composition which comprises an indole derivative having the general formula I or Ia or an addition salt thereof, and a pharmaceutically acceptable carrier.

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* C L M S *

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ERRATUM

SPECIFICATION No. 1,391,005

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THE PATENT OFFICE
23rd June, 1975