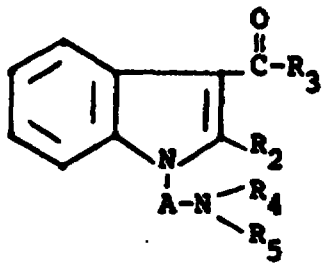
Description

This invention relates to the use of 3-arylcarbonyl-1-aminoalkyl-1H-indoles as medicaments useful for treating glaucoma and to novel compounds within this class.

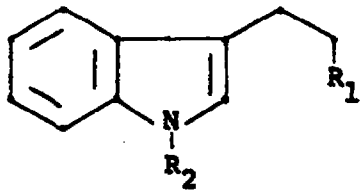
U.S. Patent 3,946,029 discloses compounds having the formula:



where A is alkylene; R_2 is one to four carbon alkyl, phenyl or phenyl substituted by fluorine, chlorine, bromine, methoxy or cyclohexyl; R_3 is a 2-, 3- or 4-pyridyl group; and R_4 and R_5 are either the same or different 1-5 carbon alkyl or R_4 and R_5 are joined together to form, with the nitrogen atom, a piperidino, pyrrolidino or morpholino group. The compounds are said to possess fibrinolytic and anti-inflammatory activities.

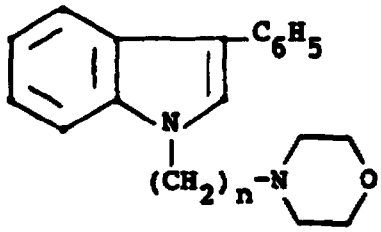
Essentially the same disclosure is found in Inion et al., Eur. J. of Med. Chem., 10 (3), 276-285 (1975). Specifically disclosed in both these references is the species, 2-isopropyl-3-(3-pyridylcarbonyl)-1-[2-(4-morpholinyl)ethyl] -indole.

U.S. Patent 3,489,770 generically discloses compounds having the formula:



where R_1 is "diloweralkylamino, pyrrolidinyl, piperidino and morpholino and R_2 is selected from the group consisting of cyclo(lower)alkanoyl and adamantanylcarbonyl". Although not within the ambit of the above-defined genus, the Herbst patent also discloses a variety of species where R_2 is an arylcarbonyl group. The compounds are said to possess anti-inflammatory, hypotensive, hypoglycemic and CNS activities.

Tambute, Acad. Sci. Comp. Rend., Ser. C, 278 (20), 1239-1242 (1974) discloses compounds of the formula:

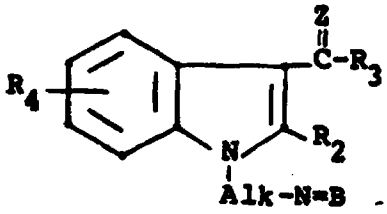


where n is 2 or 3. No utility for the compounds is given.

U.S. Patent 4,581,354 discloses 3-arylcarbonyl- and 3-cycloalkylcarbonyl-1-aminoalkyl-1H-indoles which are useful as analgesic, antirheumatic and anti-inflammatory agents.

US-A-4 634 776 discloses 3-arylcarbonyl- and 3-cycloalkylcarbonyl-1-aminoalkyl-1H-indoles, useful as analgesic, anti-rheumatic and anti-inflammatory agents.

The invention relates to the use for preparing a medicament useful for treating glaucoma of a 2-R_2-3-R_3-carbonyl-1-aminoalkyl-1H-indole having the formula:



I

where:

R_2 is hydrogen, lower-alkyl, chloro or fluoro;
R_3 is phenyl (or phenyl substituted by from one to three substitutents selected from halo, lower-alkoxy, lower-alkoxymethyl, hydroxy, lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino or lower-alkylmercapto), methylenedioxyphenyl, benzyl, styryl, lower-alkoxystyryl, 1- or 2-naphthyl (or 1- or 2-naphthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy, halo or cyano), (1H-imidazol-1-yl)-naphthyl, 2-(1-naphthyl)ethenyl, 1-(1,2,3,4-tetrahydronaphthyl), anthryl, phenanthryl, pyrenyl, 2-, 3-, 4-, 5-, 6- or 7-benzo[b]furyl, 2- or 3-benzo[b]thienyl, 5-(1H-benzimidazolyl) or 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl;
R_4 is hydrogen or lower-alkyl, hydroxy, lower-alkoxy or halo in the 4-, 5-, 6- or 7-positions;
Z is O or S;
Alk is lower-alkylene having the formula $(CH_2)_n$ where n is the integer 2 or 3, or such lower-alkylene substituted by a lower-alkyl group; and
N=B is N,N-di-lower-alkylamino, 4-morpholinyl, 2-lower-alkyl-4-morpholinyl, 3-lower-alkylmorpholinyl, 1-pyrrolidinyl, 1-piperidinyl or 3-hydroxy-1-piperidinyl.

Also within the ambit of the invention are certain novel compounds of formula I above where:

R_2 is hydrogen or lower-alkyl;
R_3 is lower-alkoxymethylphenyl, tri-lower-alkoxyphenyl, benzyl, lower-alkoxystyryl, (1H-imidazol-1-yl)-naphthyl, 2-(1-naphthyl)ethenyl, 1-(1,2,3,4-tetrahydronaphthyl), anthryl, phenanthryl or pyrenyl;
R_4 is hydrogen;
Z is O;
Alk is 1,2-ethylene; and
N=B is 4-morpholinyl.

As used herein, unless specifically defined otherwise, the terms lower-alkyl and lower-alkoxy mean monovalent, aliphatic radicals, including branched chain radicals, of from one to about four carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy and sec.-butoxy.

As used herein, the term halo means fluoro, chloro or bromo.

The compounds of formula I are prepared by the methods described in detail in U.S. Patent 4,581,354, and many of the compounds of formula I, as well as intermediates used in their preparation, are specifically disclosed therein.

In one method disclosed in said patent, the compounds of formula I where Z is O are prepared by reacting a 2-R_2-R_4-substituted-3-R_3-carbonyl-1H-indole with an amino-lower-alkyl halide or an amino-lower-alkyl tosylate, X-Alk-N=B, in the presence of an acid-acceptor, where X is a halogen atom or a toluenesulfonyloxy group and Alk and N=B have the meanings given above. The reaction is preferably carried out in an organic solvent inert under the conditions of the reaction, such as dimethylformamide (hereinafter DMF), dimethylsulfoxide (hereinafter DMSO), a lower-alkanol or acetonitrile. Suitable acid-acceptors are an alkali metal carbonate, such as sodium carbonate or potassium carbonate, or an alkali metal hydride, such as sodium hydride, an alkali metal amide, such as sodamide, or an alkali metal hydroxide, such as potassium hydroxide. Preferred solvents are DMF and DMSO, and preferred acid-acceptors are sodium hydride, potassium carbonate and potassium hydroxide. The reaction is carried out at a temperature in the range from around 0°C to the boiling point of the solvent used.

The 2-R_2-R_4-substituted-3-R_3-carbonyl-1H-indoles are in turn prepared by reacting a 2-R_2-R_4-substituted-indole with a lower-alkyl magnesium halide and reacting the resulting Grignard with an appropriate R_3-carboxylic acid halide. The reaction is carried out in an organic solvent inert under the conditions of the reaction, such as dimethyl ether, dioxane or tetrahydrofuran (hereinafter THF), at a temperature in the range from -5°C to the boiling point of the solvent used.

In another method, the compounds of formula I where Z is O are prepared by reacting a 2-R_2-R_4-substituted-1-aminoalkyl-1H-indole with an appropriate R_3-carboxylic acid halide (R_3-CO-X) in the presence of a Lewis acid, such as aluminum chloride, and in an organic solvent inert under the conditions of the reaction. Suitable solvents are chlorinated hydrocarbons such as methylene dichloride (hereinafter MDC) or ethylene dichloride (hereinafter EDC). The reaction is carried out at a temperature from 0°C to the boiling point of the solvent used.

The intermediate 2-R_2-R_4-substituted-1-aminoalkyl-1H-indoles are prepared by one of two methods. In one method, a 2-R_2-R_4-substituted-indole is reacted with an amino-lower-alkyl halide or an amino-lower-alkyl tosylate, X-Alk-N=B, where X, Alk and N=B have the meanings given above, in the presence of an acid-acceptor, in an organic solvent inert under the conditions of the reaction using the same conditions described above for the preparation of the compounds of formula I by alkylation of a 2-R_2-R_4-substituted-indole with an amino-alkyl halide or tosylate.

In a second method, a 2-R_2-R_4-substituted-indole is reacted with a halo-lower-alkanamide, X-Alk'CO-N=B, where Alk' is lower-alkylene, $(CH_2)_{n'}$, where n' is the integer 1 or 2, or such lower-alkylene substituted by a lower-alkyl group, and X and N=B have the meanings given above. The reaction is carried out in the presence of a strong base, and the resulting 2-R_2-R_4-substituted-IH-indole-I-alkanamide is then reduced with lithium aluminum hydride. The reaction of the

2-R_2-R_4-substituted-indole with the halo-lower-alkanamide is carried out in an appropriate organic solvent, such as DMF, at a temperature from -5°C to about 50°C. The reduction of the amides with lithium aluminum hydride is carried out in an inert organic solvent, such as diethyl ether, THF or dioxane, at a temperature from -5°C to about 50°C.

In another method for preparing the compounds of formula I where Z is O, a 2-R_2-R_4-substituted-3-R_3-carbonyl-1-(tosyloxy-lower-alkyl) - or 1-(halo-lower-alkyl) -1H-indole is reacted with a molar equivalent amount of an amine, H-N=B, in an organic solvent inert under the conditions of the reaction, such as acetonitrile, a lower-alkanol or DMF. The reaction is preferably carried out by heating a solution of the reactants at the boiling point of the mixture.

The 2-R_2-R_4-substituted-3-R_3-carbonyl-1-(2-tosyloxyethyl)- or 1-(2-haloethyl)-1H-indoles, where Alk is 1,2-ethylene, are in turn prepared by reaction of a 2-R_2-R_4-substituted-3-R_3-carbonyl indole with a lower-alkyl lithium, for example n-butyl lithium, in an inert organic solvent, such as THF, dioxane or diethyl ether, followed by reaction of the resulting lithium salt with ethylene oxide. Reaction of the resulting 2-R_2-R_4-substituted-3-R_3-carbonyl-1-(2-hydroxyethyl)-1H-indole with toluenesulfonyl chloride in the presence of an acid-acceptor affords the 1-(2-tosyloxyethyl)-1H-indoles, while reaction of the product with a phosphorus trihalide affords the corresponding 1-(2-haloethyl)-1H-indoles.

The 2-R_2-R_4-substituted-3-R_3-carbonyl-1-(halo-lower-alkyl)-1H-indoles, where Alk has the other possible meanings, are prepared by reaction of a 2-R_2-R_4-substituted-3-R_3-carbonyl indole with a dihalo-lower-alkane in the presence of a strong base, such as sodium hydride in an inert organic solvent, such as DMF. The reaction generally occurs at ambient temperature.

The compounds of formula I where Z is S are prepared by heating the corresponding compounds where Z is O with phosphorus pentasulfide in pyridine.

By further chemical manipulations of various functional groups in the compounds prepared by one or more of the above-described methods, other compounds within the ambit of formula I can be prepared. For example the compounds where R_3 is aminophenyl are advantageously prepared from the corresponding species where R_3 is nitrophenyl by reduction of the latter.

The reduction can be carried out either catalytically with hydrogen, for example over a platinum oxide catalyst at ambient temperature and in an appropriate organic solvent, such as a lower-alkanol, ethyl acetate or acetic acid or mixtures thereof, and at hydrogen pressures from around 30 to 60 p.s.i.g. Alternatively the reduction can be carried out chemically, for example with iron in the presence of hydrochloric acid in an appropriate organic solvent, for example a lower-alkanol. The reaction is carried out at temperatures from ambient to the boiling point of the solvent used for the reaction.

Other simple chemical transformations which are entirely conventional and well known to those skilled in the art of chemistry and which can be used for effecting changes in functional groups attached to the R_3-carbonyl group, (C=O) R_3, involve cleavage of aryl ether functions, for example with a pyridine hydrohalide salt to produce the corresponding phenolic compound (R_3 is hydroxyphenyl); preparation of compounds where R_3 is phenyl or naphthyl substituted by an amine or cyano function by reaction of the corresponding halophenyl or halonaphthyl species with an appropriate amine in the presence of a cuprous halide or with cuprous cyanide, respectively; catalytic debenzylation of benzyloxy-substituted species to prepare the corresponding phenolic compound (R_3 is hydroxyphenyl); or reductive alkylation of amino-substituted species to prepare the corresponding di-lower-alkylamino substituted species.

The compounds of formula I in free base form are converted to the acid-addition salt form by interaction of the base with an acid. In like manner, the free base can be regenerated from the acid-addition salt form in conventional manner, that is by treating the salts with cold, weak aqueous bases, for example alkali metal carbonates and alkali metal bicarbonates. The bases thus regenerated can be interacted with the same or a different acid to give back the same or a different acid-addition salt. Thus the bases and all of their acid-addition salts are readily interconvertible.

It will thus be appreciated that formula I not only represents the structural configuration of the bases of formula I but is also representative of the structural entities which are common to all of the compounds of formula I whether in the form of the free base or in the form of the acid-addition salts of the base. It has been found that, by virtue of these common structural entities, the bases of formula I and their acid-addition salts have inherent pharmacological activity of a type to be more fully described hereinbelow. This inherent pharmacological activity can be enjoyed in useful form for pharmaceutical purposes by employing the free bases themselves or the acid-addition salts formed from pharmaceutically acceptable acids, that is acids whose anions are innocuous to the animal organism in effective doses of the salts so that beneficial properties inherent in the common structural entity represented by the free bases are not vitiated by side effects ascribable to the anions.

In utilizing this pharmacological activity of the salts of formula I, it is preferred, of course, to use pharmaceutically acceptable salts. Although water insolubility, high toxicity or lack of crystalline character may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water-insoluble or toxic salts can be converted to the corresponding pharmaceutically acceptable bases by decomposition of the salts with aqueous base as explained above, or alternatively they can be converted to any desired pharmaceutically acceptable acid-addition salt by double decomposition reactions involving the anion, for example by ion-exchange procedures.

Moreover, apart from their usefulness in pharmaceutical applications, the salts are useful as characterizing or iden-

tifying derivatives of the free bases or in isolation or purification procedures. Like all of the acid-addition salts, such characterizing or purification salt derivatives can, if desired, be used to regenerate the pharmaceutically acceptable free bases by reaction of the salts with aqueous base, or alternatively they can be converted to a pharmaceutically acceptable acid-addition salt by, for example, ion-exhange procedures.

The acid-addition salts are prepared by reacting the free base and the acid in an organic solvent and isolating the salt directly or by concentration of the solution.

In standard pharmacological test procedures, the compounds of formula I have been found to possess cannabinoid receptor agonist activity and are thus indicated to be useful as anti-glaucoma agents.

It has been shown previously that smoking marijuana reduces intraocular pressure in man [Helper and Frank, Marijuana Smoking and Intraocular Pressure., J. Am. Med. Assoc. 217, 1392 (1971)]. Topical application or systemic injection of delta-9 tetrahydrocannabinol, a principal active ingredient in marijuana, also reduces intraocular pressure [Purnell and Gregg, delta-9 Tetrahydrocannabinol, Euphoria and Intraocular Pressure in Man., Ann. Opth. 7, 921-923 (1975); Green and Pederson, Effect of delta-9 Tetrahydro-cannabinol on Aqueous Dynamics and Ciliary Body Permeability in the Rabbit Eye., Exptl. Eye Research 15, 499-507 (1973); Colasanti, Craig and Allara, Intraocular Pressure, Ocular Toxicity and Neurotoxicity after Administration of Cannabinol or Cannibigerol, Exptl. Eye Research 39, 252-259 (1984)]. Similarly, synthetic cannabinoids also reduce intraocular pressure [Green, Symunds, Oliver and Elijah, Intraocular Pressure Following Systemic Administration of Cannabinoids, Curr. Eye Research 2, 247-253 (1982); Tiedeman, Shields, Weber, Crow, Coccetto, Harris and Howes, Ophthalmology, 88, 270-277 (1981); Colasanti et al., supra]. Cannabinoid receptor binding sites can be defined as those to which radiolabelled 4-(1,1-dimethylheptyl)-2,3'-dihydroxy-6'alpha-(3-hydroxypropyl)-1',2',3',4',5',6'-hexahydrobiphenyl (CP 55940) binds in a specific and saturable manner, and the binding sites are heterogeneously distributed in the brain [Devane, Dysarz, Johnson, Melvin and Howlett, Determination and Characterization of a Cannabinoid Receptor in Rat Brain, Molecular Pharm. 34, 605-613 (1988)]. Natural and synthetic cannabinoids and representative examples of the compounds of the present invention bind to CP 55940 binding sites. Classification of whether a molecule is an agonist or an antagonist can be made using a mouse vasa deferentia (MVD) preparation in vitro, compounds which inhibit contractions in the MVD preparation being considered active as agonists and those which do not inhibit contractions being considered antagonists. It is believed that agonist activity at the cannabinoid receptor mediates the anti-glaucoma actions of cannabinoids, and that agonist activity at this receptor correlates with ocular pressure lowering actions in man. Accordingly the cannabinoid receptor agonist activity of the compounds of formula I indicate their usefulness in reducing ocular pressure and hence in treating glaucoma.

The compounds of formula I can be prepared for pharmaceutical use by incorporating them in unit dosage form as tablets or capsules for oral administration either alone or in combination with suitable adjuvants such as calcium carbonate, starch, lactose, talc, magnesium stearate, gum acacia and the like. Still further, the compounds can be formulated for oral or topical administration either in aqueous solutions of the water soluble salts or in aqueous alcohol, glycol or oil solutions or oil-water emulsions in the same manner as conventional medicinal substances are prepared.

The percentages of active component in such compositions may be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is variable, depending upon the clinician's judgment using as criteria: the route of administration, the duration of treatment, the size and physical condition of the patient, the potency of the active component and the patient's response thereto. An effective dosage amount of the active component can thus be determined by the clinician after a consideration of all criteria and using his best judgment on the patient's behalf.

The molecular structures of the compounds of formula I were assigned on the basis of study of their infrared, ultraviolet and NMR spectra. The structures were confirmed by the correspondence between calculated and found values for elementary analyses for the elements.

The following examples will further illustrate the invention without, however, limiting it thereto. All melting points are uncorrected.

Preparation of Intermediates

A. The 2-R_2-R_4-Substituted-3-R_3-carbonyl indoles

Preparation 1A

To a solution of 0.05 mole of methyl magnesium bromide in about 45 ml. of anhydrous diethyl ether at 0°C under a nitrogen atmosphere was added, dropwise, a solution containing 6.0 g. (0.04 mole) of 2,7-dimethylindole in 30 ml. of anhydrous ether. When addition was complete, the reaction mixture was stirred at room temperature for one hour, then cooled in an ice bath and treated dropwise with a solution of 8.53 g. (0.05 mole) of 4-methoxybenzoyl chloride in 20 ml. of anhydrous ether. The mixture was stirred at room temperature for approximately twelve hours, then on a steam bath for two hours and then treated with ice water. Excess ammonium chloride was added, and the ether layer was separated, dried and evaporated to dryness to give a solid which was collected by filtration and washed thoroughly with water and

ether to give 8.5 g. (76%) of 2,7-dimethyl-3-(4-methoxybenzoyl)indole, m.p. 182-184°C.

Preparations 1B - 1BN

Following a procedure similar to that described above in Preparation 1A, substituting for the 2,7-dimethylindole and the 4-methoxybenzoyl chloride used therein an appropriate 2-R_2-R_4-subtituted-indole and an appropriate aroyl chloride (R_3CO-Cl), the following 2-R_2-R_4-substituted-3-arylcarbonyl indoles listed in Table A were prepared. In some instances the products, without further purification, were used directly in the next step of the synthesis of the final products of formula I, and no melting points were taken. In a few cases, the weight of the products was not obtained, and so calculation of yields of products in those instances are not possible. Here and elsewhere in the tables included with this specification, the melting point of the product (in °C) and the recrystallization solvent are given in columns headed "m.p./Solv.", and the yield, in percent, of product is given in columns headed "Yield".

Table A

Prepn.	R_2	R_3	R_4	m.p./Solv.	Yield
1B	CH_3	4-$CH_3C_6H_4$	--	215-217/DMF-H_2O	85
1C	CH_3	4-$CH_3SC_6H_4$	--		
1D	CH_3	4-$NO_2C_6H_4$	--		23
1E	CH_3	4-$CH_3OC_6H_4$	5-F	199-202/i-PrOH	
1F	CH_3	4-$CH_3OC_6H_4$	7-F	204-205/H_2O	42
1G	CH_3	4-$CH_3OC_6H_4$	7-CH_3O		68
1H	CH_3	4-$CH_3OC_6H_4$	5-/7-F (a)		55
1I	CH_3	4-FC_6H_4	--	199-201/EtOH	38
1J	CH_3	3,4-$\overline{OCH_2O}C_6H_3$	--	210-213/i-PrOH	60
1K	CH_3	3-benzo[b] thienyl	--	181-183	64
1L	CH_3	2-benzo[b] furyl	--	218-220/i-PrOH	62
1M	CH_3	2-$CH_3OC_6H_4$	--	203-206/i-PrOH	75
1N	CH_3	3-F-4-$CH_3OC_6H_3$	--	160-165/EtOH	39
1-O	CH_3	2-naphthyl	--	208-213/i-PrOH	57
1P	H	4-$CH_3OC_6H_4$	5-CH_3	189-192/EtOH	42
1Q	CH_3	3-FC_6H_4	--		64
1R	CH_3	2-FC_6H_4	--	216-218/i-PrOH	44
1S	CH_3	4-CNC_6H_4	--	211-213/EtOAc	7
1T	CH_3	C_6H_5	4-CH_3	176-179/EtOAc	65
1U	CH_3	4-$C_2H_5C_6H_4$	--	199-201/EtOAc	70
1V	CH_3	3-$NO_2C_6H_4$	--	218-221/DMF-H_2O	20
1W	CH_3	4-$CH_3C_6H_4$	--	207-209/EtOH	60
1X	CH_3	3-$CH_3OC_6H_4$	--	163-164/EtOAc	63
1Y	H	4-$CH_3OC_6H_4$	--		46
1Z	H	C_6H_5	5-CH_3O		46
1AA	CH_3	4-$CH_3OC_6H_4$	6-CH_3O		53
1AB	CH_3	4-$NO_2C_6H_4$	6-CH_3O		73
1AC	CH_3	C_6H_5	--	185-186/MeOH	64
1AD	H	C_6H_5	--	241-242/MeOH	38
1AE	CH_3	4-ClC_6H_4	--	183-185/MeOH	34
1AF	CH_3	4-$CH_3OC_6H_4$	6-Cl		58
1AG	CH_3	4-$CH_3OC_6H_4$	6-$C_6H_5CH_2O$		51
1AH	CH_3	2,3-$\overline{OCH_2O}C_6H_3$	--	239.5-240/CH_3CN	98

Table A (cont'd)

Prepn.	R_2	R_3	R_4	m.p./Solv.	Yield
1AI	CH_3	1-naphthyl	--	223-224/i-PrOH	69
1AJ	CH_3	2,3-$(CH_3O)_2C_6H_3$	--	185-187	87
1AK	CH_3	3,5-$(CH_3O)_2C_6H_3$	--	182-184	85
1AL	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	--	176-178/EtOAc-ether	44
1AM	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	5-F	173-175	11
1AN	CH_3	2-FC_6H_4	5-F	247-249/i-PrOH	10
1AO	CH_3	4-CH_3O-1-naphthyl	--	286-289/i-PrOH	24
1AP	CH_3	4-$CH_3OC_6H_4$	--	200-203	97
1AQ	H	1-naphthyl	5-Br	250-252/i-PrOH	26
1AR	H	4-$CH_3OC_6H_4$	6-F		78
1AS	CH_3	3,4,5-$(CH_3O)_3C_6H_2$	--		
1AT	CH_3	2,3,4-$(CH_3O)_3C_6H_2$	--		
1AU	H	1-naphthyl	5-F		54
1AV	CH_3	9-phenanthryl	--	370(dec.)/EtOH	51
1AW	CH_3	1-anthryl	--	280(dec.)/AcOH	9
1AX	H	4-ClC_6H_4	--	239-241	58
1AY	CH_3	3,4-$(CH_3O)_2C_6H_3$	--	162-165/EtOAc	19
1AZ	CH_3	4-$C_2H_5OC_6H_4$	--	214-217/i-PrOH	73
1BA	H	C_6H_5	7-CH_3		58
1BB	CH_3	4-$CH_3OC_6H_4$	4-F (b)		55
1BC	CH_3	6-CH_3O-2-naphthyl	--		40
1BD	CH_3	1-naphthyl	6-CH_3	270-271/EtOH	29
1BE	H	1-naphthyl	--		87
1BF	CH_3	4-$CH_3OC_6H_4$	--	142-144/EtOAc	59
1BG	H	4-$CH_3OC_6H_4$	5-F	200-202	100
1BH	CH_3	C_6H_5	5-F	223-225	67
1BI	CH_3	4-$CH_3OC_6H_4$	5-Cl	167-169	41
1BJ	CH_3	2,3-$F_2C_6H_3$	--		
1BK	CH_3	2,6-$(CH_3)_2C_6H_3$	--		95
1BL	CH_3	4-$CH_3OC_6H_4$	5,7-F_2		26
1BM	CH_3	4-ClC_6H_4	6-CH_3O	206-208	61
1BN	CH_3	3,4-$Cl_2C_6H_3$	--	229-230	44

(a) Product consisted of a mixture of the 5-fluoro and the 7-fluoro isomers.

(b) Product consisted of a mixture of the 4- and 6-fluoro isomers.

B. The 2-R_2-R_4-Substituted-1-aminoalkyl-1H-indoles

(a) By Alkylation of a 2-R_2R_4-Substituted-indole

Preparation 2A

To a stirred suspension of 229.5 g. (1.22 moles) of 4-(2-chloroethyl)morpholine hydrochloride in 300 ml. of DMSO at ambient temperature was added 200 g. (3.03 moles) of 85% potassium hydroxide pellets, and the suspension was stirred for five minutes and then treated dropwise at ambient temperature with a solution of 133.7 g. (1.0 mole) of 2-methylindole in 140 ml. of DMSO. The temperature of the reaction mixture gradually rose during the addition of the 2-methylindole as well as on stirring after addition was complete. When the temperature reached 78°C , the mixture was cooled in a water bath until the temperature subsided to 75°C , and the mixture was stirred for a total of three and a half hours while the temperature subsided to ambient. The mixture was then diluted with 1 liter of water and extracted with toluene. The extracts were washed with water, dried over magnesium sulfate and taken to dryness in vacuo, and the residual dark oil was crystallized from heptane to give 224 g. (92%) of 2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 63-65°C.

Preparation 2B

Following a procedure similar to that described in Preparation 2A above, 60 g. (0.4 mole) isatin was reacted with 102 g. (0.54 mole) of 4-(2-chloroethyl)morpholine hydrochloride in 100 ml. of dry DMF in the presence of 120 g. (0.87 mole) of potassium carbonate to give 52 g. of 1-[2-(4-morpholinyl)ethyl]-2,3-dioxo-1H-indole.

The latter (0.2 mole) was dissolved in 200 ml. of MDC and the solution treated all at once with 40 ml. of phosphorus oxychloride and then treated dropwise with cooling with 55 g. of phosphorus pentachloride. The reaction mixture was stirred at ambient temperature for about forty-eight hours and then added dropwise with stirring to 500 ml. of 3N hydrochloric acid containing zinc dust, additional zinc dust being added with addition of the reaction mixture, a total of 168 g. of zinc dust being added. The reaction mixture was then stirred at ambient temperature for about one hour, filtered, the filter washed several times with water and the combined filtrates evaporated to remove the MDC. The mixture was filtered, the filtrate neutralized by the addition of solid potassium carbonate, and the resulting mixture extracted with ethyl acetate. The combined extracts, on drying and evaporation to dryness, afforded 29.2 g. of 1-[2-(4-morpho-linyl) ethyl]-2-oxo-1H-indole, as an oil.

A mixture of the latter (40 g., 0.139 mole) and 100 ml. of phosphorus oxychloride was heated on the steam bath for several days and the reaction mixture then taken to dryness in vacuo. The residue was dissolved in MDC, and the solution poured slowly onto an ice/potassium carbonate/ethyl acetate mixture. The organic layer was separated from the mixture, dried and taken to dryness and the residue taken into a 15% solution of ethyl acetate in toluene and the solution chromatographed on silica gel, the product being eluted with the same solution. The initial cuts were discarded and the final cuts combined and evaporated to dryness to give the product in the form of the free base which was converted to the hydrochloride salt to give 9.9 g. of 2-chloro-1-[2-(4-morpholinyl)ethyl]-1H-indole hydrochloride.

Preparations 2C - 2-O

Following a precedure similar to that described in Preparation 2A above, substituting for the N-(2-chloroethyl)morpholine hydrochloride and the 2-methylindole used therein an appropriate N-(haloalkyl)morpholine and an appropriate 2-R_2-R_4-substituted-indole, the following 2-R_2-R_4-substituted-1-[(4-morpholinyl)alkyl]-1H-indoles listed in Table B were prepared.

Table B

Prepn.	R_2	R_4	Alk	m.p./Solv.	Yield
2C	H	--	CH_2CH_2	--	46
2D	CH_3	7-CH_3O	CH_2CH_2	--	31
2E	H	5-F	$(CH_2)_3$	oil b.p. 150-170/0.01mm.	84
2F	H	5-F	CH_2CH_2	oil b.p. 153-159/0.04mm.	92
2G	H	6-F	$(CH_2)_3$	152-154 (HCl) MDC/Et_2O	81
2H	H	--	$(CH_2)_3$	yellow oil	66
2I	H	6-CH_3	CH_2CH_2	yellow oil	100
2J	H	5-BzO	CH_2CH_2	oil	80
2K	H	4-BzO	CH_2CH_2	--	98
2L	H	7-BzO	CH_2CH_2	--	75
2M	CH_3	5-F	$(CH_2)_3$	165-167(c)	81
2N	CH_3	5-F	CH_2CH_2	oil	100
2-O	C_2H_5	--	CH_2CH_2	59-60/hexane	54

(c) Maleate

(b) Via the 2-R_2R_4-Substituted-1H-indole-alkanamides Preparation 3A

Following a procedure similar to that described in Preparation 2A above, 32.8 g. (0.25 mole) of 2-methylindole in 160 ml. of dry DMF was reacted with 13.4 g. (0.28 mole) of a 50% mineral oil dispersion of sodium hydride in 200 ml. of dry DMF, and the resulting sodium salt was then reacted with 62 g. (0.28 mole) of 4-(α-bromopropionyl)morpholine in 160 ml. of DMF to give 55.3 g. (59%) of 4-[α-(2-methyl-1H-indol-1-yl)-propionyl]morpholine.

The latter (130 g., 0.48 mole), dissolved in 900 ml. of THF, was added to 80 ml. (0.80 mole) of a solution of boron methyl sulfide complex in THF under nitrogen while cooling in an ice bath. When addition was complete, the mixture was stirred for eighteen hours at room temperature, heated under reflux for four hours, quenched by addition of about 1 liter of methanol, boiled for about fifteen minutes, concentrated essentially to dryness and then diluted with aqueous 6N hydrochloric acid. The mixture was extracted with methylene dichloride, and the raffinate was basified with 35% sodium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated to dryness to give 42.6 g. (34%) of 2-methyl-1-[1-methyl-2-(4-morpholinyl)ethyl]-1H-indole as an oil. A portion of the latter was reacted with methanesulfonic acid to give the monomethanesulfonate as the 4:1 hydrate, m.p. 154-157°C.

Preparation 3B

Following a procedure similar to that described in Preparation 3A above, 29.29 g. (0.25 mole) of indole in 200 ml. of dry DMF was reacted with 13.4 g. (0.28 mole) of a 50% mineral oil dispersion of sodium hydride in 200 ml. of dry DMF and the resulting sodium salt reacted with 62.0 g. (0.28 mole) of 4-(α-bromopropionyl)morpholine in 200 ml. of dry DMF and the product recrystallized from isopropanol to give 13.7 g. (21%) of 4-[α-(1H-indole-1-yl)propionyl]morpholine, m.p. 92-94°C. The latter (20 g., 0.078 mole) in 300 ml. of diethyl ether was reduced with 3.12 g. (0.078) mole of lithium aluminum hydride in 100 ml. of diethyl ether to give 17 g. (90%) of 1-[1-methyl-2-(4-morpholinyl)ethyl]-1H-indole, m.p. 35-37°C.

Preparation 3C

Following a procedure similar to that described in Preparation 3B, 83 g. (0.63 mole) of 2-methylindole was reacted with 30 g. (0.75 mole) of a 60% mineral oil dispersion of sodium hydride, and the resulting sodium salt was reacted with a molar equivalent amount of 4-(α-bromobutyryl)-morpholine in 100 ml. of DMF. The crude product thus obtained was reduced with 25 g. (0.66 mole) of lithium aluminum hydride in 500 ml. of THF. The product was isolated in the form of the hydrochloride to give 53.4 g. (27%) of 2-methyl-1-[1-ethyl-2-(4-morpholinyl)ethyl]-1H-indole hydrochloride, m.p. 159-162°C. (from ethyl acetate-ether).

Preparation 3D

Following a procedure similar to that described in Preparation 3A above, 25 g. (0.19 mole) of 7-methylindole in 150 ml. of dry DMF was reacted with 8.6 g. (0.21 mole) of a 60% mineral oil dispersion of sodium hydride in 150 ml. of dry DMF and the resulting sodium salt reacted with 65 g. (0.21 mole) of 4-(α-bromopropionyl)morpholine in 150 ml. of DMF to give 40.5 g. of 4-[α-(7-methyl-1H-indol-1-yl)propionyl]morpholine. The latter (0.15 mole) in 200 ml. of diethyl ether was reduced with 5.6 g. (0.15 mole) of lithium aluminum hydride in 200 ml. of diethyl ether to give 26.3 g. (68%) of 1-[1-methyl-2-(4-morpholinyl)ethyl]-7-methyl-1H-indole as a yellow oil.

C. The 2-R_2-R_4-Substituted-3-R_3-carbonyl-1-halo- or tosyloxyalkyl-1H-indoles

Preparation 4A

To a suspension of 24.8 g. (0.087 mole) of 2-methyl-3-(1-naphthylcarbonyl)indole (Preparation 1AM) in 300 ml. of THF was added, dropwise with stirring, 35 ml. (0.09 mole) of a 2.6M solution of n-butyl lithium in hexane while maintaining the temperature at 2-4°C. The reaction mixture was stirred for one and a quarter hours at 2-4°C, then at room temperature for forty-five minutes, recooled to 0°C and treated dropwise, over a forty minute period, with a solution of 5.6 ml. (0.15 mole) of a 2.6 M solution of ethylene oxide in THF. The reaction mixture was gradually allowed to warm to room temperature, treated with a saturated ammonium chloride solution and the aqueous layer extracted with ethyl acetate. The combined organic extracts were evaporated to dryness in vacuo, and the residual solid was recrystallized from cyclohexane to give 22.6 g. of 2-methyl-3-(1-naphthylcarbonyl)-1-(2-hydroxyethyl) -1H-indole (64%).

Reaction of the latter (0.065 mole) with 18.5 g. (0.097 mole) of p-toluenesulfonyl chloride in 400 ml. of methylene dichloride in the presence of 340 ml. of 35% sodium hydroxide and 0.6 g. (0.0026) mole of benzyl trimethyl ammonium chloride afforded 20.1 g. (64%) of 2-methyl-3-(1-naphthylcarbonyl)-1-(2-p-toluenesulfonyloxyethyl)-1H-indole as a viscous oil.

Preparation 4B

Following a procedure similar to that described above in Preparation 4A, 40 g. (0.015 mole) of 2-methyl-3-(4-methoxybenzoyl)indole in 320 ml. of THF was reacted with 61 ml. of a 2.6 M solution of butyl lithium in hexane and 45.8 ml. of ethylene oxide to give 33.6 g. (72%) of 2-methyl-3-(4-methoxybenzoyl)-1-(2-hydroxyethyl)-1H-indole. Reaction of 17 g. (0.06 mole) of the latter with 72 g. (0.06 mole) of p-toluenesulfonyl chloride in 250 ml. of pyridine afforded 2-methyl-3-(4-methoxybenzoyl)-1-(2-p-toluenesulfonyloxyethyl)1H-indole as an oil.

Preparation 4C

Following a procedure similar to that described in Preparation 4A above, 75 g. (0.26 mole) of 2-methyl-3-(1-naphthylcarbonyl)indole in 900 ml. of THF was reacted with 105 ml. of a 2.6 M solution of butyl lithium in hexane and 98 ml. of ethylene oxide to give 101.1 g. of 2-methyl-3-(1-naphthylcarbonyl)-1-(2-hydroxyethyl)-1H-indole as an amber oil, 21.3 g. (0.0647 mole) of which in 200 ml. of MDC, together with 0.6 g. of benzyl trimethyl ammonium chloride and 40 ml. of 35% sodium hydroxide was treated with 18.5 g. (0.097 mole) of p-toluenesulfonyl chloride in MDC. There was thus obtained 20.1 g. (64%) of 2-methyl-3-(1-naphthylcarbonyl)-1-(2-p-toluenesulfonyloxyethyl)-1H-indole as an amber oil.

Preparation 4D

Following a procedure similar to that described above in Preparation 4A, 20 g. (0.1 mole) of 2-methyl-3-(4-ethylbenzoyl)indole in 200 ml. of THF was reacted with 51 ml. of a 2.15 M solution of n-butyl lithium in hexane and 6.16 g. of ethylene oxide to give 18 g. (73%) of 2-methyl-3-(4-ethylbenzoyl)-1-(2-hydroxyethyl)-1H-indole, which was dis-

solved in 480 ml. of MDC and 50 ml. of 35% sodium hydroxide and reacted with 14.32 g. of p-toluenesulfonyl chloride in the presence of 1.6 g. of benzyl trimethyl ammonium chloride. There was thus obtained 25 g. of 2-methyl-3-(4-ethylbenzoyl)-1-(2-p-toluenesulfonyloxyethyl)-1H-indole.

Preparation 4E

A solution of 120 g. (0.42 mole) of 5-fluoro-2-methyl-3-(4-methoxybenzoyl) indole in 240 ml. of DMF was treated first with 427 g. (2.12 mole) of 1,3-dibromopropane and then with 25.8 g. of a 60% mineral oil dispersion of sodium hydride added in portions while cooling in an ice bath. The mixture was stirred for about twelve hours, taken to dryness and the residue partitioned between MDC and water. The organic layer was separated, washed with water, dried and taken to dryness and the residue recrystallized from ethyl acetate/hexane to give 51 g. (30%) of 5-fluoro-2-methyl-3-(4-methoxybenzoyl)-1-(3-bromopropyl)-1H-indole, m.p. 131-134.

Preparation 4F

Following a procedure similar to that described in Preparation 4E above, 100 g. (0.38 mole) of 2-methyl-3-(4-methoxybenzoyl)-1H-indole in 250 ml. of DMF was reacted with 22.6 g. (0.57 mole) of a 60% mineral oil dispersion of sodium hydride and 381 g. (1.9 mole) of 1,3-dibromopropane to give 30 g. (21%) of 2-methyl-3-(4-methoxybenzoyl)-1-(3-bromopropyl)-1H-indole.

Preparation 4G

Following a procedure similar to that described in Preparation 4E above, 15 g. (0.053 mole) of 5-fluoro-2-methyl-3-(4-methoxybenzoyl) indole in 200 ml. of DMF was reacted with 3.1 g. of a 60% mineral oil dispersion of sodium hydride and 9.18 g. (0.058 mole) of 1-bromo-3-chloropropane to give 15.3 g. (80%) of 5-fluoro-2-methyl-3-(4-methoxybenzoyl)-1-(3-chloropropyl)-1H-indole.

Preparation of the Final Products

A. From the 2-R_2-R_4-Substituted-3-R_3-carbonylindoles

Example 1A

Following a procedure similar to that described in Preparation 2A above, 25 g. (0.10 mole) of 3-(4-methoxybenzoyl) indole (Preparation 1Y) in 100 ml. of DMF was reacted with 5.76 g. (0.12 mole) of a 50% dispersion of sodium hydride in mineral oil in 120 ml. of DMF, and the resulting sodium salt was reacted with 0.14 mole of 4-(2-chloroethyl)-morpholine (freed from 26.06 g. of the corresponding hydrochloride) in 120 ml. of DMF to give 42 g. of the crude product as an oil which, on trituration with ethyl acetate/diethyl ether/hexane, gave a yellow crystalline solid which was converted to the methanesulfonate salt to afford 9.5 g. (20%) of 3-(4-methoxybenzoyl)-1-[2-(4-morpholinyl)ethyl]1H-indole methanesulfonate monohydrate, m.p. 110-112°C.

Examples 1B - 1CJ

Following a procedure similar to that described in Example 1A above, the following species of formula I in Table 1 were prepared by reaction of a 2-R_2-R_4-substituted-3-R_3-carbonyl-1H-indole with an appropriate haloalkylamine or tosyloxyalkylamine. The acid-acceptor and reaction solvent used in the reactions are given in the column headed "Cat./Solv.". Here and elsewhere in the tables, the form in which the product was isolated, either as the free base or as an acid-addition salt, is given in columns headed "Base/Salt", and the abbreviations "Morph.", "Pip." and "Pyr." in the columns headed N=B represent the 4-morpholinyl, 1-piperidinyl and 1-pyrrolidinyl groups, respectively. In Table 1, unless noted otherwise, an appropriate chloroalkylamine was used as the alkylating agent. Here and elsewhere in the specification and the claims, the alkylene groups, Alk, are depicted as they would appear with the 1-indolyl moiety attached to the carbon atom at the left end of the alkylene chain and with the amine group, N=B, attached to the carbon at the right end of the chain.

Table 1

Example	R_2	R_3	R_4	Alk	N=B	Cat./Solv.	Base/Salt	m.p./Solv.	Yield
1B	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base (d)	104-105/EtOAc-hexane	37
1C	CH_3	4-$CH_3SC_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	125-126/EtOAc-hexane	36
1D	CH_3	4-$CH_3OC_6H_4$	7-CH_3	$(CH_2)_2$	Morph.	NaH/DMF	Base	149-151/i-PrOH	83
1E	CH_3	4-$CH_3OC_6H_4$	5-F	$(CH_2)_2$	Morph.	NaH/DMF	HCl	198-200/MeOH-ether	59
1F	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	Morph.	NaH/DMF	HCl	248-249/MeOH-ether	53
1G	CH_3	4-$CH_3OC_6H_4$	5-F	$(CH_2)_3$	Morph.	NaH/DMF	HCl	222-224/i-PrOH-ether	50
1H	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_3$	Morph.	NaH/DMF	HCl	202-203/i-PrOH-ether	53
1I	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	Pip.	NaH/DMF	CH_3SO_3H	228-230/MeOH-ether	31
1J	CH_3	4-$CH_3OC_6H_4$	7-F	$(CH_2)_2$	Morph.	NaH/DMF	Base	120-121/i-PrOH	23
1K	CH_3	4-$CH_3OC_6H_4$	7-CH_3O	$(CH_2)_2$	Morph.	NaH/DMF	HCl	203-204	25
1K	CH_3	4-$CH_3OC_6H_4$	6-Cl	$(CH_2)_2$	Morph.	NaH/DMF	Base	138-139/i-PrOH	3
1M	CH_3	4-$CH_3OC_6H_4$	4-/6-F (e)	$(CH_2)_2$	Morph.	NaH/DMF	Base	127-128/DMF	39
1N	CH_3	4-FC_6H_4	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	CH_3SO_3H	209-211/i-PrOH	70
1-O	CH_3	3,4-$\overline{OCH_2O}C_6H_3$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	CH_3SO_3H	142-145/i-PrOH	33
1P	CH_3	2-benzo[b] furyl	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	CH_3SO_3H	194-198/EtOH	60
1Q	CH_3	3-benzo[b] thienyl	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	$CH_3SO_3H.H_2O$	155-158/EtOH	55
1R	CH_3	2-$CH_3OC_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	CH_3SO_3H	199-214/i-PrOH	65

(d) The corresponding methanesulfonate has m.p. 162-164 (from isopropanol-ether); the hydrochloride, m.p. 178-182 (from water); the fumarate, m.p. 178-182 (from water); the fumarate, m.p. 184-187 (from methanol-ether); and the maleate, 146-149 (from methanol-ether). A higher melting polymorph of the maleate, m.p. 163-166, was obtained on crystallization from methanol alone.

(e) Consists of a 4:1 mixture of the 4-fluoro and 6-fluoro isomers.

Table 1 (cont'd)

Example	R_2	R_3	R_4	Alk	N=B	Cat./Solv.	Base/Salt	m.p./Solv.	Yield
1S	CH_3	2-naphthyl	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	CH_3SO_3H	195-198/i-PrOH	35
1T	H	4-$CH_3OC_6H_4$	5-CH_3	$(CH_2)_2$	Morph.	K_2CO_3/DMF	CH_3SO_3H	150-151/i-PrOH	45
1U	CH_3	3-FC_6H_4	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	130-131/i-PrOH	77
1V	CH_3	2-FC_6H_4	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	112-114/i-PrOH	65
1W	CH_3	C_6H_5	4-CH_3	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	116-117.5/EtOAc	46
1X	CH_3	4-$C_2H_5C_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	124-126-EtOAc	70
1Y	CH_3	3-$NO_2C_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	141-143/EtOAc	67
1Z	CH_3	4-$CH_3C_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	120.5-121.5/EtOAc	60
1AA	CH_3	3-$CH_3OC_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	130-131/EtOAc	84
1AB	CH_3	3,4-$(CH_3O)_2C_6H_3$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	HCl	230-233/i-PrOH	64
1AC	H	C_6H_5	5-CH_3O	$(CH_2)_2$	Morph.	NaH/DMF	Base	98-101	55
1AD	CH_3	4-$CH_3OC_6H_4$	6-CH_3O	$(CH_2)_2$	Morph.	NaH/DMF	HCl	222-224/EtOAc-MDC-ether	63
1AE	CH_3	C_6H_5	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	111-112/EtOAc-hexane	78
1AF	H	C_6H_5	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	101-103/EtOAc-hexane	69
1AG	CH_3	4-ClC_6H_4	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	148-150/EtOAc	54
1AH	H	4-ClC_6H_4	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	136-138/EtOAc-hexane	60
1AI	CH_3	3,4-$Cl_2C_6H_3$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	128-130/EtOAc-hexane	44
1AJ	CH_3	4-ClC_6H_4	6-CH_3O	$(CH_2)_2$	Morph.	K_2CO_3/DMF	HCl	275-285/EtOH-H_2O	52
1AK	CH_3	C_6H_5	--	$CHCH_3CH_2$	Morph.	K_2CO_3/DMF	Base	137-139/EtOAc-hexane	1.3
1AL (f)	CH_3	C_6H_5	--	CH_2CHCH_3	Morph.	K_2CO_3/DMF	Base	108-110-EtOAc-hexane	48

(f) Prepared by reaction of 4-(2-tosyloxypropyl)morpholine with appropriate indole.

Table 1 (cont'd)

Example	R_2	R_3	R_4	Alk	N=B	Cat./Solv.	Base/Salt	m.p./Solv.	Yield
1AM (g)	H	C_6H_5	--	$CHCH_3CH_2$	Morph.	K_2CO_3/DMF	Base	123-125/EtOAc-hexane	7
1AN (g)	H	C_6H_5	--	CH_2CHCH_3	Morph.	K_2CO_3/DMF	Base	97-100/EtOAc-hexane	48
1AO	H	C_6H_5	7-CH_3	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	131-133/EtOAc-hexane	80
1AP	CH_3	1-naphthyl	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	122-124/i-PrOH	40
1AQ	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	$N(CH_3)_2$	NaH/DMF	HCl	237-240/MeOh	56
1AR	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	$N(C_2H_5)_2$	NaH/DMF	HCl	209-211/EtOAc-ether	62
1AS	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	Morph.	NaH/DMF	Base.1/4H_2O	127-128/DMF	38
1AT	CH_3	4-$PrOC_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	104.5-105.5/EtOAc	39
1AU	CH_3	4-$EtOC_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	93-97/i-PrOH	68
1AV	CH_3	4-CH_3O-1-naphthyl	--	$(CH_2)_2$	Morph.	K_2CO_3DMF	CH_3SO_3H. 0.4i-PrOH	145-147/i-PrOH	26
1AW	CH_3	6-CH_3O-2-naphthyl	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	159-160/EtOAc	4.9
1AX	H	4-$CH_3OC_6H_4$	5-F	$(CH_2)_3$	Morph.	NaH/DMF	HCl	172-174/i-PrOH	67
1AY	CH_3	4-$CH_3OC_6H_4$	5-F	$(CH_2)_3$	Pip.	NaH/DMF	HCl	199-201/MeOH-ether	40
1AZ	CH_3	C_6H_5	5-F	$(CH_2)_3$	Morph.	NaH/DMF	HCl	244-245/MeOH-ether	81
1BA	CH_3	4-$CH_3OC_6H_4$	5-F	$(CH_2)_3$	$N(C_2H_5)_2$	NaH/DMF	HCl	124-126/MeOH-ether	52
1BB	CH_3	4-$CH_3OC_6H_4$	5-Cl	$(CH_2)_3$	Morph.	NaH/DMF	HCl	160-162/MeOH-ether (h)	64
1BC	CH_3	4-$CH_3OC_6H_4$	5,7-F	$(CH_2)_3$	Morph.	NaH/DMF	HCl	231-233/i-PrOH	79
1BD	CH_3	4-$CH_3OC_6H_4$	7-F	$(CH_2)_3$	Morph.	NaH/DMF	HCl	209-211/MDC-ether	59

(g) Prepared by reaction of 4-(bromopropyl)morpholine with appropriate indole.

(h) A higher melting polymorph of the hydrochloride has m.p. 217-218 from isopropanol.

Table 1 (cont'd)

Example	R_2	R_3	R_4	Alk	N=B	Cat./Solv.	Base/Salt	m.p./Solv.	Yield
1BE	CH_3	4-$CH_3OC_6H_4$	5-F	$CHCH_3$-CH_2CH_2	Morph.	NaH/DMF	HCl	178-180/i-PrOH-ether	72
1BF	CH_3	2-FC_6H_4	--	CH_2CHCH_3	Morph.	NaH/DMF	Base	107-109	53
1BG	CH_3	4-$CH_3OC_6H_4$	--	CH_2CHCH_3	Morph.	NaH/DMF	Base	128-130/EtOAc-hexane	45
1BH	CH_3	2-FC_6H_4	5-F	$CHCH_3$-CH_2CH_2	Morph.	NaH/DMF	Base	124-126-EtOAc-hexane	50
1BI	CH_3	4-$CH_3OC_6H_4$	--	$CHCH_3$-CH_2CH_2	Morph.	NaH/DMF	HCl	164-166/MeOH-ether	24
1BJ	CH_3	2,3-$\overline{OCH_2OC_6H_3}$	--	CH_2CH_2	Morph.	K_2CO_3/DMF	Base	173-174/$CHCl_3$	81
1BK	CH_3	2-FC_6H_4	--	$CHCH_3$-CH_2CH_2	Morph.	NaH/DMF	HCl.1/4H_2O	147-150/MDC-ether	36
1BL	CH_3	2-naphthyl	--	CH_2CH_2	$N(C_2H_5)_2$	NaH/DMF	Base	106-107/EtOAc	34
1BM	H	C_6H_5	--	$(CH_2)_2$	$N(CH_3)_2$	NaH/DMF	Base	65-67	43
1BN	CH_3	2,3-$F_2C_6H_3$	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	165-167/MDC	37
1BO	CH_3	2,6-$(CH_3)_2C_6H_3$	--	$(CH_2)_2$	Morph.	NaH/DMF	HCl	275-280	100
1BP	CH_3	2,3-$(CH_3O)_2C_6H_3$	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	126-128	77
1BQ	CH_3	3,5-$(CH_3O)_2C_6H_3$	--	$(CH_2)_2$	Morph.	NAH/DMF	Base	88-90	64
1BR	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	151-153/EtOAc-ether	42
1BS	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	--	$(CH_2)_3$	Morph.	NaH/DMF	Base	90-92	42
1BT	CH_3	4-$NO_2C_6H_4$	--	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	173-175	49
1BU	CH_3	1-naphthyl	--	$(CH_2)_3$	Morph.	NaH/DMF	Base	135-138/ether	50

Table 1 (cont'd)

Example	R_2	R_3	R_4	Alk	N=B	Cat./Solv.	Base/Salt	m.p./Solv.	Yield
1BV	CH_3	1-naphthyl	6-CH_3	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	154.5-156/EtOAc	74
1BW	H	1-naphthyl	5-Br	$(CH_2)_2$	Morph.	K_2CO_3/DMF	Base	153-155/EtOAc	37
1BX	H	1-naphthyl	--	CH_2CHCH_3	Morph.	NaH/DMF	Base	145-147/EtOAc-hexane	35
1BY	H	4-$CH_3OC_6H_4$	6-F	$(CH_2)_3$	Morph.	NaH/DMF	HCl.1/2H_2O	190-192/MeOH-ether	7
1BZ	H	4-$CH_3OC_6H_4$	--	$(CH_2)_3$	Morph.	NaH/DMF		131-135/EtOAc-hexane	31
1CA	CH_3	2,3,4-$(CH_3O)_3C_6H_2$	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	127-128/EtOAc	80
1CB	CH_3	3,4,5-$(CH_3O)_3C_6H_2$	--	$(CH_2)_2$	Morph.	NaH/DMF	HCl	156-158/EtOH-ether	30
1CC	H	4-$CH_3OC_6H_4$	7-CH_3	$(CH_2)_2$	Morph.	NaH/DMF	Base	146-149/EtOAc-hexane	75
1CD	H	4-$CH_3OC_6H_4$	7-CH_3	$(CH_2)_3$	Morph.	NaH/DMF	Base	139-142	44
1CE	H	1-naphthyl	5-F	$(CH_2)_2$	Morph.	NaH/DMF	CH_3SO_3H	210-212	
1CF	CH_3	1-anthryl	--	$(CH_2)_2$	Morph.	KOH/DMSO	Base	126-128	67
1CG	CH_3	9-phenanthryl	--	$(CH_2)_2$	Morph.	KOH/DMSO	HCl	180-182/$CHCl_2$-ether	62
1CH	H	C_6H_5	--	$(CH_2)_2$	Morph.	NaH/DMF	Base	76-78/EtOAc-hexane	42
1CI	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	Pyr.	NaH/DMF	HCl	233-235/MeOH-ether	41
1CJ	CH_3	4-$CH_3OC_6H_4$	--	$(CH_2)_3$	Pyr.	NaH/DMF	CH_3SO_3H	152-153/i-PrOH	77

B. From the 2-R_2-R_4-Substituted-1H-indoles

Example 2A

To a stirred, refluxing solution of 13.2 g. (0.054 mole) of 1-[1-methyl-2-(4-morpholinyl)ethyl]-1H-indole (Preparation 3B) in 150 ml. of ethylene dichloride was added, over a period of about one hour, a mixture of 17.35 g. (0.13 mole) of aluminum chloride and 10.08 g. (0.065 mole) of 4-methylbenzoyl chloride in 200 ml. of ethylene dichloride. When addition was complete, the mixture was heated under reflux under a nitrogen atmosphere for three and a half hours and then poured, with stirring, into 1 liter of ice and water containing 300 ml. of 5N sodium hydroxide. The mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was washed with an additional 300 ml. of ethylene dichloride. The combined organic extracts were then washed with brine, filtered, dried over magnesium sulfate, filtered again and evaporated to dryness to give a viscous oil (22.55 g.) which solidified on cooling. The latter was recrystallized, after charcoaling, from isopropanol to give 15.78 g. (81%) of 3-(4-methylbenzoyl)-1-[1-methyl-2-(4-morpholinyl)ethyl]-1H-indole, m.p. 116.5-118°C.

Examples 2B - 2CJ

Following a procedure similar to that described in Example 2A above, the following species of formula I in Table 2 below were prepared by reaction of a 2-R_2-R_4-substituted-1-aminoalkyl-1H-indole with an appropriate acid chloride (R_3CO-Cl) in the presence of aluminum chloride. The solvent used to carry out the reaction, methylene dichloride (MDC) or ethylene dichloride (EDC), is given in the column headed "Solv."

Table 2

Example	R_2	R_3	R_4	Alk	N=B	Solv.	Base/Salt	m.p./Solv.	Yield
2B	CH_3	4-$CH_3C_6H_4$	--	$CHCH_3CH_2$	Morph.	EDC	Base	163-165/i-PrOH	69
2C	CH_3	2-FC_6H_4	--	$CHCH_3CH_2$	Morph.	EDC	Base	126-128/i-PrOH	62
2D	H	4-FC_6H_4	--	$CHCH_3CH_2$	Morph.	EDC	Base	153-155/i-PrOH	83
2E	H	2-FC_6H_4	--	$CHCH_3CH_2$	Morph.	EDC	Base	145-147/i-PrOH	65
2F	CH_3	4-FC_6H_4	--	$CHCH_3CH_2$	Morph.	EDC	Base	95-98/heptane	23
2G	CH_3	4-$CH_3OC_6H_4$	--	$CHCH_3CH_2$	Morph.	EDC	Base (i)	yellow-orange powder	13
2H	H	C_6H_5	7-CH_3	$CHCH_3CH_2$	Morph.	EDC	HCl.1/2C_2H_5OH	amorphous, off white solid	62
2I	CH_3	4-t-$C_4H_9C_6H_4$	--	$(CH_2)_2$	Morph.	MDC	HCl	235-236	57
2J	CH_3	2-benzo[b] thienyl	--	$(CH_2)_2$	Morph.	MDC	Base	134-135	23
2K	CH_3	2-$CH_3C_6H_4$	--	$(CH_2)_2$	Morph.	MDC	HCl	245-247/i-PrOH-ether	25
2L	CH_3	3,4-$(CH_3)_2C_6H_3$	--	$(CH_2)_2$	Morph.	MDC	Base	145-147/i-PrOH	41
2M	CH_3	$C_6H_5CH=CH_2$	--	$(CH_2)_2$	Morph.	MDC	Base	127-128/EtOH	29
2N	CH_3	3-benzo[b] furyl	--	$(CH_2)_2$	Morph.	MDC	Base	134-135/EtOH	28
2O	H	2-$CH_3C_6H_4$	--	$(CH_2)_2$	Morph.	MDC	Base	129-131/i-PrOH	100
2P	C_2H_5	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	Morph.	MDC	Base	143-145.5/EtOAc-ether	88
2Q	Cl	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	Morph.	MDC	HCl	170-173/EtOH	58
2R	CH_3	4-$C_3H_7C_6H_4$	--	$(CH_2)_2$	Morph.	MDC	Base	86.5-87.5/EtOAc-ether	68
2S	CH_3	2-$CH_3C_6H_4$	5-F	$(CH_2)_3$	Morph.	MDC	HCl	215.5-219.5/EtOH	78
2T	CH_3	4-FC_6H_4	5-F	$(CH_2)_3$	Morph.	MDC	HCl	223.0-225.0/EtOH	43
2U	CH_3	$C_6H_5CH=CH_2$	5-F	$(CH_2)_3$	Morph.	MDC	HCl	223.5-226.5/MeOH	44
2V	CH_3	2,4-$F_2C_6H_3$	5-F	$(CH_2)_2$	Morph.	MDC	Base	118-120/i-PrOH	24
2W	CH_3	2-FC_6H_4	--	$CHC_2H_5CH_2$	Morph.	MDC	Base	162-165/EtOAc-hexane	52

(i) The hydrochloride has m.p. 193-197 (from methanol-t-butyl methyl ether).

Table 2 (cont'd)

Example	R_2	R_3	R_4	Alk	N=B	Solv.	Base/Salt	m.p./Solv.	Yield
2X	CH_3	4-$CH_3OC_6H_4$	--	$CHC_2H_5CH_2$	Morph.	MDC	HCl	153-157/i-PrOH-ether	39
2Y	CH_3	1-naphthyl	--	$CHCH_3CH_2$	Morph.	EDC	Maleate	87/t-butyl methyl ether	36
2Z	H	1-naphthyl	--	$(CH_2)_2$	Morph.	EDC	Base	105-107/ether	44
2AA	CH_3	5-benzo[b]furyl	--	$(CH_2)_2$	Morph.	MDC	Base	165.5-167/EtOAc-acetone	46
2AB	CH_3	2,4-$F_2C_6H_3$	--	$(CH_2)_2$	Morph.	MDC	Base	121-123.5/i-PrOH	30
2AC	CH_3	2,4-$F_2C_6H_3$	5-F	$(CH_2)_3$	Morph.	EDC	HCl	212-216/EtOH	33
2AD	CH_3	2-F-4-$CH_3OC_6H_3$	--	$(CH_2)_2$	Morph.	EDC	HCl	258-260/EtOH	25
2AE	CH_3	2-F-4-$CH_3OC_6H_3$	5-F	$(CH_2)_3$	Morph.	EDC	HCl	221-223.5/EtOH	16
2AF	CH_3	4-BrC_6H_4	5-F	$(CH_2)_3$	Morph.	MDC	HCl	238-240/i-PrOH	64
2AG	CH_3	2,6-$F_2C_6H_3$	--	$(CH_2)_2$	Morph.	EDC	Base	117-119/EtOAc	53
2AH	CH_3	2,3-$(CH_3)_2C_6H_3$	--	$(CH_2)_2$	Morph.	EDC	HCl.3/4H_2O	241-243/EtOH	35
2AI	CH_3	3,5-$Cl_2C_6H_3$	--	$(CH_2)_2$	Morph.	MDC	Base	145-146	55
2AJ	CH_3	3,5-$(CH_3)_2C_6H_3$	--	$(CH_2)_2$	Morph.	MDC	Base	142-144/EtOH-hexane	51
2AK	CH_3	3-$CH_3C_6H_4$	--	$(CH_2)_2$	Morph.	MDC	Base	125-127	44
2AL	CH_3	3-ClC_6H_4	--	$(CH_2)_2$	Morph.	MDC	Base	116-118/EtOAc-ether	38
2AM	CH_3	3-FC_6H_4	--	$CHCH_3CH_2$	Morph.	EDC	Base	85-87	27
2AN	CH_3	2-ClC_6H_4	--	$CHCH_3CH_2$	Morph.	EDC	HCl	150(dec.)/EtOAc	37
2AO	CH_3	1-naphthyl	7-CH_3O	$(CH_2)_2$	Morph.	EDC	Base	225-227/EtOAc-ether	11
2AP	CH_3	2-FC_6H_4	5-F	$(CH_2)_3$	Morph.	MDC	HCl	224-226/EtOH	20
2AQ	CH_3	2-FC_6H_4	5-F	$CHCH_3CH_2$	Morph.	MDC	HCl	208-211/EtOAc	49
2AR	CH_3	4-BrC_6H_4	--	$(CH_2)_2$	Morph.	EDC	HCl.1/2H_2O	257-260	13
2AS	CH_3	5-(1H-benzimidazolyl)	--	$(CH_2)_2$	Morph.	MDC	Base	173.5-175.5/EtOAc	25

Table 2 (cont'd)

Example	R_2	R_3	R_4	Alk	N=B	Solv.	Base/Salt	m.p./Solv.	Yield
2AT	CH_3	4-Br-1-naphthyl	--	$(CH_2)_2$	Morph.	MDC	Base	126.5-128.5/EtOAc-ether	35
2AU	H	4-$CH_3OC_6H_4$	--	$CHCH_3CH_2$	Morph.	EDC	$HCl.H_2O$	140	54
2AV	CH_3	2-naphthyl	--	$CHC_2H_5CH_2$	Morph.	MDC	CH_3SO_3H	214-216/i-PrOH	32
2AW	H	4-Br-1-naphthyl	--	$(CH_2)_2$	Morph.	MDC	Base	164-166/acetone	43
2AX	H	1-naphthyl	--	$(CH_2)_3$	Morph.	MDC	Base	143-144/EtOAc	57
2AY	H	1-naphthyl	6-CH_3	$(CH_2)_2$	Morph.	MDC	Base	163-165/EtOAc	54
2AZ	CH_3	6-quinolyl	--	$(CH_2)_2$	Morph.	MDC	Base	138-139/EtOAc	55
2BA	CH_3	7-quinolyl	--	$(CH_2)_2$	Morph.	MDC	Base	174-175	38
2BB	CH_3	8-quinolyl	--	$(CH_2)_2$	Morph.	MDC	Base	158-159/EtOAc	28
2BC	CH_3	3-quinolyl	--	$(CH_2)_2$	Morph.	MDC	Base	165-166/MDC-MeOH	34
2BD	CH_3	2-quinolyl	--	$(CH_2)_2$	Morph.	MDC	Base	163-164/MDC-MeOH	51
2BE	CH_3	4-quinolyl	--	$(CH_2)_2$	Morph.	MDC	Base	142-143/EtOH	63
2BF	H	6-quinolyl	--	$(CH_2)_2$	Morph.	MDC	Base	123-124	37
2BG	Cl	1-naphthyl	--	$(CH_2)_2$	Morph.	MDC	Base	144-145/EtOAc	48
2BH	CH_3	7-quinolyl	--	$(CH_2)_2$	Morph.	MDC	Base	125-126	41
2BI	CH_3	7-benzo[b] furyl	--	$(CH_2)_2$	Morph.	MDC	Base	161-162/EtOAc-hexane	27
2BJ	H	4-benzo[b] furyl	--	$(CH_2)_2$	Morph.	MDC	Base	160-162/EtOAc	59
2BK	H	6-benzo[b] furyl	--	$(CH_2)_2$	Morph.	MDC	Base	125-126	61
2BL	H	7-benzo[b] furyl	--	$(CH_2)_2$	Morph.	MDC	Base	145-147/EtOAc	80
2BM	CH_3	benzyl	--	$(CH_2)_2$	Morph.	MDC	HCl	220-226/i-PrOH	30
2BN	CH_3	4-CH_3O-styryl	--	$(CH_2)_2$	Morph.	MDC	Base	108.5-111/EtOH	59
2BO	CH_3	2-(1-naphthyl)-ethenyl	--	$(CH_2)_2$	Morph.	MDC	Base	152-155.5/EtOAc	40

Table 2 (cont'd)

Example	R_2	R_3	R_4	Alk	N=B	Solv.	Base/Salt	m.p./Solv.	Yield
2BP	H	1-(tetra-H-naphthyl)	--	$(CH_2)_2$	Morph.	MDC	HCl	198-200	59
2BQ	H	2-FC_6H_4	--	$(CH_2)_2$	Morph.	MDC	HCl	210-212/i-PrOH	14
2BR	H	5-benzo[b] furyl	--	$(CH_2)_2$	Morph.	MDC	Base	158-159/EtOAc	36
2BS	H	4-$CH_3OC_6H_4$	6-F	$(CH_2)_3$	Morph.	MDC	HCl	201-203/MDC-ether	37
2BT	H	C_6H_5	5-F	$(CH_2)_3$	Morph.	MDC	Base	102-103/Me-t-Bu-ether	34
2BU	H	3-$CH_3OC_6H_4$	5-F	$(CH_2)_3$	Morph.	MDC	Maleate	150-151/EtOH	17
2BV	H	4-$CH_3OC_6H_4$	5-F	$(CH_2)_2$	Morph.	MDC	Base	141-142/CH_3CN	80
2BW	CH_3	4-$CH_3OCH_2C_6H_4$	--	$(CH_2)_2$	Morph.	MDC	HCl.1/2H_2O	194-195/CH_3CN	13
2BX	H	1-naphthyl	--	$CHCH_3CH_2$	Morph.	EDC	Base	115-118	26
2BY	H	1-naphthyl	5-Bzl-O	CH_2CH_2	Morph.	EDC	Base	195-200/EtOAc	24
2BZ	H	3,4-$(CH_3O)_2C_6H_3$	5-HO (j)	CH_2CH_2	Morph.	EDC	Base	223-226/EtOAc	6
2CA	CH_3	4-CH_3-1-naphthyl	--	CH_2CH_2	Morph.	MDC	Base	171-173	75
2CB	H	4-CH_3-1-naphthyl	--	CH_2CH_2	Morph.	MDC	Base	158.5-160.5	76
2CC	H	4-$CH_3OC_6H_4$	4-HO	CH_2CH_2	Morph.	MDC	Base	169-172/CH_3CN	18
2CD	H	4-$CH_3OC_6H_4$	7-Bzl-O	CH_2CH_2	Morph.	MDC	Base	*oil*	36
2CE	H	6-Cl-1-naphthyl	--	CH_2CH_2	Morph.	MDC	Base	173-173.5	60
2CF	CH_3	2,4-$Cl_2C_6H_3$	--	CH_2CH_2	Morph.	MDC	Base	114-116	20
2CG	CH_3	2-pyrenyl	--	CH_2CH_2	Morph.	MDC	Base	157-159/EtOAc	30
2CH	CH_3	2-ClC_6H_5	--	CH_2CH_2	Morph.	EDC	Base	104-107	64
2CI	CH_3	2-BrC_6H_5	--	CH_2CH_2	Morph.	EDC	Base	108-110/EtOAc-ether	20
2CJ	H	2-naphthyl	--	$(CH_2)_2$	Morph.	MDC	Base	170-172/EtOAc	48

(j) Starting material was the corresponding 5-benzyloxy compound which was debenzylated during the reduction.

C. From the 2-R_2-R_4-Substituted-1-halo or 1-tosyloxy-1H-indoles

Example 3A

A solution of 20 g. (0.41 mole) of 2-methyl-3-(1-naphthylcarbonyl)-1-[2-(p-toluenesulfonyloxy)ethyl]-1H-indole (Preparation 4A) and 8.5 g. (0.1 mole) of piperidine in 50 ml. of dry DMF was heated under reflux for about twenty-four hours, and the mixture was then diluted with ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate, filtered and concentrated to dryness to give the product, in the form of the free base, as a brown oil which was dissolved in ethyl acetate and chromatographed on silica gel, the product being eluted with 1:1 ethyl acetate:hexane. There was thus obtained 5.2 g. (32%) of 2-methyl-3-(1-naphthylcarbonyl)-1-[2-(1-piperidinyl)ethyl]-1H-indole, m.p. 119-121°C.

Examples 3B - 3K

Following a procedure similar to that described in Example 3A above, the following 2-R_2-R_4-substituted-3-R_3-carbonyl-1-amino-lower-alkyl-1H-indoles in Table 3 below were prepared by reaction of a 2-methyl-3-R_3-carbonyl-1-(2-toxyloxyethyl)-1H-indole or a 2-methyl-3-R_3-carbonyl-1-(halo-lower-alkyl)-1H-indole with an appropriate amine, HN=B, where R_2, in each instance, is CH_3. The starting material in each of Examples 3B-3F and 3K was the corresponding 1-(2-tosyloxyethyl)-1H-indole; in Example 3G the corresponding 1-(3-chloro-propyl)-1H-indole; and in each of Examples 3H, 3I and 3J the corresponding 1-(bromo-lower-alkyl)-1H-indole.

Table 3

Example	R_3	R_4	Alk	N=B	Solv.	Base/Salt	m.p./Solv.	Yield
3B	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	3-HO-1-piperidinyl	CH_3CN	HCl.1/2H_2O (k)	160	31
3C	4-$C_2H_5C_6H_4$	--	$(CH_2)_2$	3-HO-1-piperidinyl	CH_3CN	Base	139-141	57
3D	1-naphthyl	--	$(CH_2)_2$	3-HO-1-piperidinyl	DMF	HCl.H_2O. 1/6i-PrOH	175-180/i-PrOH-ether	24
3E	1-naphthyl	--	$(CH_2)_2$	2-CH_3-4-morpholinyl	DMF	Base	144-145/ether	21
3F	4-$CH_3OC_6H_4$	--	$(CH_2)_2$	2-CH_3-4-morpholinyl	DMF	maleate.1/2EtOAc	135-140/EtOAc	52
3G	4-$CH_3OC_6H_4$	5-F	$(CH_2)_3$	3-HO-1-piperidinyl	DMF	HCl	126-128/MeOH-ether	69
3H	4-$CH_3OC_6H_4$	5-F	$(CH_2)_3$	2-CH_3-4-morpholinyl	DMF	HCl	216-217/i-PrOH	85
3I	4-$CH_3OC_6H_4$	--	$(CH_2)_3$	1-piperidinyl	DMF	HCl	201-203/i-PrOH-ether	80
3J	4-$CH_3OC_6H_4$	--	$(CH_2)_3$	$N(C_2H_5)_2$	DMF	HCl	179-181/CH_3CN	11
3K	1-naphthyl	--	$(CH_2)_2$	3-CH_3-4-morpholinyl	DMF	HCl	149-154	5

(k) The anhydrous hydrochloride has m.p. 224-226 (from ethanol).

D. Miscellaneous Processes

Example 4A

2-Methyl-3-(3-nitrobenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole (8.0 g., 0.02 mole) dissolved in 175 ml. of ethyl acetate and 75 ml. of acetic acid was reduced with hydrogen in a Parr shaker over 0.3 g. of platinum oxide. The product was isolated in the form of the free base and recrystallized from ethyl acetate to give 6.0 g. (83%) of 2-methyl-3-(3-aminobenzoyl) -1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 167-169°C.

Example 4B

Following a procedure similar to that described in Example 4A above, 28 g. (0.07 mole) of 2-methyl-3-(4-nitrobenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole in 100 ml. of glacial acetic acid and 100 ml. of ethyl acetate was reduced with hydrogen over platinum oxide and the product, in the form of the free base, was recrystallized from ethyl acetate to give 19.05 g. (75%) of 2-methyl-3-(4-aminobenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 154-156°C.

A small amount of the free base was reacted with methanesulfonic acid and the product recrystallized from ethanol to give the corresponding methanesulfonate as an orange powder, m.p. 221-223°C.

Example 5A

A mixture of 5 g. (0.012 mole) of 2-methyl-3-(2,3-dimethoxybenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole and 7.1 g. (0.061 mole) of pyridine hydrochloride was heated under reflux under a nitrogen atmosphere for three hours, allowed to stand at ambient temperature for about forty-eight hours and then poured into an ice/water mixture and extracted with MDC. The combined organic extracts were washed with sodium carbonate, then with water, dried and taken to dryness to give 1.8 g. (39%) of 2-methyl-3-(2,3-dihydroxybenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 119-121°C.

Example 5B

To a solution of 5.17 g. (0.01 mole) of 5-benzyloxy-3-(1-naphthylcarbonyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole in 225 ml. of absolute ethanol was added 1 g. of 10% palladium-on-charcoal catalyst, and the mixture was reduced with hydrogen at ambient temperature and 55 p.s.i.g hydrogen pressure. When reduction was complete, the catalyst was removed by filtration, the filtrate taken to dryness and the residue partitioned between chloroform and aqueous sodium bicarbonate. The organic layer was separated, dried and taken to dryness to give 2.4 g. (60%) of 5-hydroxy-3-(1-naphthylcarbonyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 200-202°C.

Example 5C

To a solution of 2.0 g. (0.0043 mole) of 7-benzyloxy-3-(4-methoxybenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole in 25 ml. of ethanol was added two small scoops of 10% palladium-on-charcoal catalyst, and the mixture was heated under reflux and then treated cautiously with 2.02 g. (0.032 mole) of ammonium formate. The mixture was heated under reflux for about one half hour, cooled, diluted with water and extracted with MDC. The combined organic extracts were dried, taken to dryness and the residue recrystallized from acetonitrile to give 1.6 g. (97%) of 7-hydroxy-3-(4-methoxybenzoyl) -1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 203-205°C.

Example 6

A solution of 15 g. (0.04 mole) of 2-methyl-3-(4-aminobenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole, 12 g. (0.4 mole) of formaldehyde and 7.5 g. (0.119 mole) of sodium cyanoborohydride in 250 ml. of acetonitrile was stirred for thirty minutes and then treated dropwise with acetic acid until acidic. The mixture was stirred for about eighteen hours, then poured into aqueous potassium hydroxide and the mixture extracted with ether. The organic extracts, on drying over magnesium sulfate and concentration to dryness, afforded a yellow solid which was recrystallized from isopropanol to give 7.5 g. (48%) of 3-(4-dimethylaminobenzoyl)-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 152-154°C.

Example 7A

A mixture of 9.54 g. (0.02 mole) of 3-(4-bromo-1-naphthylcarbonyl)-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole and 4.4 g. (0.48 mole) of cuprous cyanide in 50 ml. of DMF containing 5 drops of pyridine was heated under reflux for eight hours and the mixture then poured into 10% ammonium hydroxide. The solid which separated was collected by

filtration, dissolved in MDC and the solution passed through a column of silica gel. The eluate was diluted with ethyl acetate, and the solid which separated on standing was collected and dried to give 4.8 g. (56%) of 2-methyl-3-(4-cyano-1-naphthylcarbonyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 180.5-183.5°C.

Examples 7B - 7D

Following a procedure similar to that described in Example 7A above, reaction of a 2-R_2-3-(4-bromo-1-naphthylcarbonyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole either with a molar equivalent of cuprous cyanide in DMF in the presence of a small amount of pyridine (to prepare the corresponding 4-cyano-1-naphthylcarbonyl compound) or with molar equivalent amounts of cuprous bromide and imidazole in DMF in the presence of a molar excess of potassium carbonate (to prepare the corresponding 1-[4-(1-imidazolyl)]naphthylcarbonyl compounds) afforded the species of formula I in Table 5 where, in each instance, R_4 is H; Alk is CH_2CH_2; and N=B is 4-morpholinyl. All products were isolated in the form of the free bases.

Table 4

Example	R_3	R_2	m.p./Solv.	Yield
7B	1-[4-(1-imidazolyl)naphthyl]	CH_3	173.5-177/EtOAc	5
7C	1-[4-(1-imidazolyl)naphthyl]	H	198-200/EtOAc	78
7D	4-cyano-1-naphthyl	H	186.5-189.0/EtOAc	77

Example 8

A solution of 4 g. (0.01 mole) of 2-chloro-3-(4-methoxybenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole and 10 g. of potassium fluoride in 100 ml. of DMF was heated under reflux for about twenty hours and then poured into an ice/ water mixture and extracted with ethyl acetate. The combined organic extracts were washed with water, then with brine, dried and taken to dryness and the residue recrystallized from ethanol to give 1.7 g. of 2-fluoro-3-(4-methoxybenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole, *m.p.* 134-135°C.

Example 9

A solution of 18 g. (0.05 mole) of 2-methyl-3-(4-methoxybenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole, 6 g. (0.042 mole) of phosphorus pentasulfide in 100 ml. of pyridine was heated on a steam bath for one hour, then cooled and poured into 300 ml. of water, and an aqueous solution containing 11.5 g. (0.108 mole) of sodium carbonate was added with stirring. Extraction of the mixture with ethyl acetate and drying and evaporation of the extracts to dryness afforded 18 g. (91%) of 2-methyl-3-(4-methoxyphenylthiocarbonyl)-1-[2-(4-morpholinyl)-ethyl]-1H-indole, m.p. 138-139°C.

Example 10

To a solution of 20 g. (0.055 mole) of 2-methyl-3-(4-aminobenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole (Example 4B) in 200 ml. of MDC was added 14.4 g. (0.068 mole) of trifluoroacetic anhydride, the solution was allowed to stand at ambient temperature for fifteen minutes and then taken to dryness in vacuo. Recrystallization of the solid residue from pentane gave 22 g. (92%) of 2-methyl-3-(4-trifluoroacetylaminobenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole.

A mixture of the latter (0.049 mole), 35.9 g. (0.19 mole) of iodobutane and 48 g. (0.343 mole) of potassium carbonate in 250 ml. of acetone was heated under reflux until no unreacted starting material could be detected by thin layer chromatography and then taken to dryness in vacuo. The mixture was partitioned between water and MDC, the aqueous layer extracted with additional MDC and the combined organic extracts washed with brine, dried and taken to dryness in vacuo. The residue was dissolved in diethyl ether, the solution treated with excess ethereal hydrogen chloride, and the solid which separated was collected and dried to give 24 g. (95%) of 2-methyl-3-[4-(N-butyl-N-trifluoroacetylamino) benzoyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole.

The latter (0.047 mole) was dissolved in 100 ml. of ethanol and 500 ml. of 10% sodium hydroxide, the solution was heated under reflux for two hours, taken to dryness in vacuo, and the residue chromatographed on silica gel, eluting with 25% acetone/hexane. The higher R_f fraction was collected and recrystallized from ethyl acetate to give 2.6 g. (13%) of 2-methyl-3-(4-butylaminobenzoyl)-1-[2-(4-morpholinyl)ethyl]-1H-indole, m.p. 129.0-130.0°C.

BIOLOGICAL TEST RESULTS

Data obtained in the mouse vas deferens test (MVD) and in the CP55490 binding assay (CP), expressed as the IC_{50} in μM, for the compounds described above, identified by the example number where their preparations are described, are given in Table 5 below. Compounds are considered active in the MVD test at IC_{50} levels of 5.0 μM or less.

Table 5

Example	MVD	CP
1A	0.1	59%I/1μM
1B	0.5	3-10
1C	0.61	
1D	0.178	
1E	0.12	
1F	1.4	
1H	0.36	
1J	0.073	
1K	0.26	
1L	0.54	
1M	0.28	
1-O	1.3	
1P	0.32	
1Q	0.018	≈50
1R	0.09	
1S	0.05	
1U	1.9	
1X	0.071	
1Z	0.44	
1AA	0.2	
1AB	0.068	
1AE	0.7	
1AF	1.1	
1AG	0.56	
1AK	0.9	
1AP	0.015	51.0
1AV	0.026	
1AW	0.46	
1AX	>10	
1BJ	0.31	
1BO	1.6	
1BP	0.26	
1BQ	0.42	
1BU	0.111	
1BV	0.015	
1BW	0.02	
1BX	0.06	
1BZ	4.3	
1CA	0.07	70%I/1μM
1CB	0.09	
1CD	0.04	
1CE	0.007	
1CF	0.06	
1CG	0.17	
1CH	1.6	
1CI	0.24	
1CJ	>10	

Table 5 (cont'd)

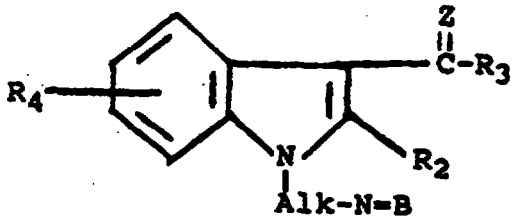
Example	MVD	CP
2C	0.49	
2E	2.4	
2G	1.3	
2H	0.177	
2K	0.71	
2N	0.052	
2Q	0.176	
2Y	0.01	
2Z	0.006	88.0
2AA	0.125	
2AD	0.18	
2AG	0.37	
2AJ	0.39	
2AM	0.86	
2AR	0.62	
2AT	0.034	
2AU	3.7	
2AV	0.091	
2AW	0.005	
2AX	0.01	
2AY	0.002	
2AZ	0.102	
2BA	0.093	
2BB	0.129	
2BC	0.57	
2BD	0.099	
2BE	0.115	
2BF	0.142	
2BG	0.006	
2BH	0.088	
2BI	0.017	
2BJ	0.007	
2BK	0.040	
2BL	0.004	
2BM	0.174	
2BN	0.138	
2BO	0.13	
2BP	0.01	
2BQ	0.5	
2BR	0.03	
2BW	0.9	
1BZ	0.2	
2CA	0.009	
2CB	0.003	
2CE	0.088	
2CF	0.2	
2CG	0.04	
2CH	0.091	
2CJ	0.031	

Table 5 (cont'd)

Example	MVD	CP
3A	0.066	
3B	>10	
3D	0.236	200-500
3E	0.21	
3J	>10	
3K	0.03	
4A	0.7	
4B	0.52	
5A	0.18	
5B	0.02	
5C	0.4	
7A	0.014	
7B	0.005	
7C	0.008	
7D	0.005	
9	0.11	

Claims

1. The use for preparing a medicament useful for treating glaucoma of a compound having the formula:



wherein:

R_2 is hydrogen, lower-alkyl, chloro or fluoro;
R_3 is phenyl (or phenyl substituted by from one to three substituents selected from halo, lower-alkoxy, lower-alkoxymethyl, hydroxy, lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino or lower-alkylmercapto), methylenedioxyphenyl, benzyl, styryl, lower-alkoxystyryl, 1- or 2-naphthyl (or 1- or 2-naphthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy, halo or cyano), (1H-imidazol-1-yl)naphthyl, 2-(1-naphthyl)ethenyl, 1-(1,2,3,4-tetrahydronaphthyl), anthryl, phenanthryl, pyrenyl, 2-, 3-, 4-, 5-, 6- or 7-benzo[b]furyl, 2- or 3-benzo[b]-thienyl, 5-(1H-benzimidazolyl) or 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl;
R_4 is hydrogen or lower-alkyl, hydroxy, lower-alkoxy or halo in the 4-, 5-, 6- or 7-positions;
Z is O or S;
Alk is lower-alkylene having the formula $(CH_2)_n$ where n is the integer 2 or 3, or such lower-alkylene substituted by a lower-alkyl group; and
N=B is N,N-di-lower-alkylamino, 4-morpholinyl, 2-lower-alkyl-4-morpholinyl, 3-lower-alkyl-4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl or 3-hydroxy-1-piperidinyl; or an acid-addition salt thereof.

2. The use according to claim 1, wherein Z is O.

3. The use according to claim 1, wherein Z is S.

4. The use according to any one of the preceding claims, wherein N=B is 4-morpholinyl.

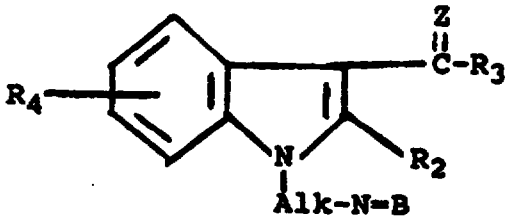
5. The use according to any one of the preceding claims, wherein:

Table 5 (cont'd)

Example	MVD	CP
3A	0.066	
3B	>10	
3D	0.236	200-500
3E	0.21	
3J	>10	
3K	0.03	
4A	0.7	
4B	0.52	
5A	0.18	
5B	0.02	
5C	0.4	
7A	0.014	
7B	0.005	
7C	0.008	
7D	0.005	
9	0.11	

Claims

1. The use for preparing a medicament useful for treating glaucoma of a compound having the formula:



wherein:

R_2 is hydrogen, lower-alkyl, chloro or fluoro;
R_3 is phenyl (or phenyl substituted by from one to three substituents selected from halo, lower-alkoxy, lower-alkoxymethyl, hydroxy, lower-alkyl, amino, lower-alkylamino, di-lower-alkylamino or lower-alkylmercapto), methylenedioxyphenyl, benzyl, styryl, lower-alkoxystyryl, 1- or 2-naphthyl (or 1- or 2-naphthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy, halo or cyano), (1H-imidazol-1-yl)naphthyl, 2-(1-naphthyl)ethenyl, 1-(1,2,3,4-tetrahydronaphthyl), anthryl, phenanthryl, pyrenyl, 2-, 3-, 4-, 5-, 6- or 7-benzo[b]furyl, 2- or 3-benzo[b]-thienyl, 5-(1H-benzimidazolyl) or 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl;
R_4 is hydrogen or lower-alkyl, hydroxy, lower-alkoxy or halo in the 4-, 5-, 6- or 7-positions;
Z is O or S;
Alk is lower-alkylene having the formula $(CH_2)_n$ where n is the integer 2 or 3, or such lower-alkylene substituted by a lower-alkyl group; and
N=B is N,N-di-lower-alkylamino, 4-morpholinyl, 2-lower-alkyl-4-morpholinyl, 3-lower-alkyl-4-morpholinyl, 1-pyrrolidinyl, 1-piperidinyl or 3-hydroxy-1-piperidinyl; or an acid-addition salt thereof.

2. The use according to claim 1, wherein Z is O.

3. The use according to claim 1, wherein Z is S.

4. The use according to any one of the preceding claims, wherein N=B is 4-morpholinyl.

5. The use according to any one of the preceding claims, wherein:

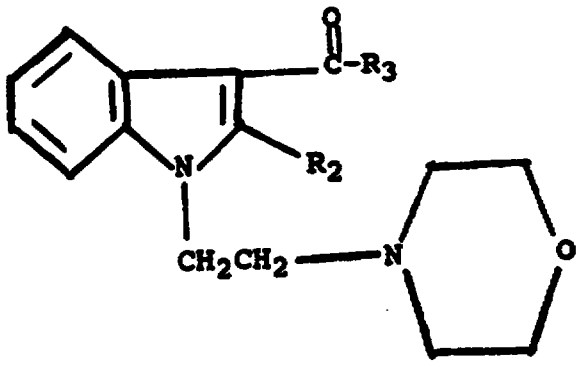
* C L M S *

R_2 is hydrogen, lower-alkyl or chloro; and
R_3 is phenyl substituted by from one to three substituents selected from halo, lower-alkoxy or lower-alkyl, 1- or 2-naphthyl (or 1- or 2-naphthyl substituted by from one to two substituents selected from lower-alkyl, lower-alkoxy, halo or cyano), (1H-imidazol-1-yl)naphthyl, 1-(1,2,3,4-tetrahydronaphthyl), anthryl, pyrenyl, 2-, 3-, 4-, 5-, 6- or 7-benzo[b]furyl, 2- or 3-benzo[b]thienyl or 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl.

6. The use according to claim 5, wherein:

R_3 is 1- or 2-naphthyl (or 1- or 2-naphthyl substituted by lower-alkyl, halo or cyano), (1H-imidazol-1-yl)-naphthyl or 2-, 3-, 4-, 5-, 6- or 7-benzo[b]furyl;
R_4 is hydrogen, lower-alkyl or fluoro; and
Alk is 1,2-ethylene.

7. A compound having the formula:



wherein:

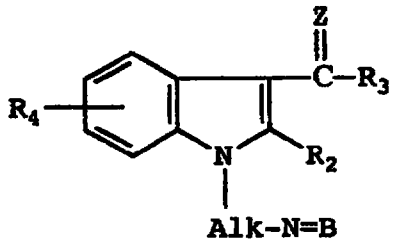
R_2 is hydrogen or lower-alkyl; and
R_3 is lower-alkoxymethylphenyl, tri-lower-alkoxy-phenyl, benzyl, lower-alkoxystyryl, (1H-imidazol-1-yl)-naphthyl, 2-(1-naphthyl)ethenyl, 1-(1,2,3,4-tetrahydronaphthyl), anthryl, phenanthryl or pyrenyl; or an acid-addition salt thereof.

8. A compound according to claim 8, wherein R_2 is hydrogen.

9. A compound according to claim 8, wherein R_2 is lower-alkyl.

Patentansprüche

1. Verwendung einer Verbindung zur Herstellung eines zur Behandlung von Glaukom nützlichen Medikaments, welche Verbindung die Formel hat:



worin sind:

R_2 Wasserstoff, niederes Alkyl, Chlor oder Fluor;
R_3 Phenyl (oder Phenyl, substituiert mit einem bis drei Substituenten, ausgewählt aus: Halogen, niederes Alkoxy, niederes Alkoxymethyl, Hydroxy, niederes Alkyl, Amino, niederes Alkylamino, Di-(niederes alkylamino) oder niederes Alkylmercapto), Methylendioxyphenyl, Benzyl, Styryl, niederes Alkoxystyryl, 1-Naphthyl oder 2-Naphthyl (oder 1-Naphthyl oder 2-Naphthyl, substituiert mit einem bis zwei Substituenten, ausgewählt aus: niederes Alkyl, niederes Alkoxy, Halogen oder Cyano), (1H-Imidazol-1-yl)naphthyl, 2-(1-naphthyl)vinyl, 1-

* C L M S *

(1,2,3,4-Tetrahydronaphthyl), Anthryl, Phenanthryl, Pyrenyl, 2-, 3-, 4-, 5-, 6- oder 7-Benzo-[b]furyl, 2- oder 3-Benzo[b]thienyl, 5-(1H-Benzimidazolyl) oder 2-, 3-, 4-, 5-, 6-, 7- oder 8-Chinoyl;
R_4 Wasserstoff oder niederes Akyl, Hydroxy, niederes Alkoxy oder Halogen in den Stellungen 4, 5, 6 oder 7;
Z Sauerstoff oder S;
Alk niederes Alkylen der Formel $(CH_2)_n$, worin n die ganze Zahl 2 oder 3 ist, oder ein solches niederes Alkylen, das durch eine niedere Alkylgruppe substituiert ist; sowie N=B N,N-Di-(niederes alkylamino), 4-Morhpolinyl, 2-niederes Alkyl-4-morhpolinyl, 1-Pyrrolidinyl, 1-Piperidinyl oder 3-Hydroxy-1-piperidinyl; oder ein Säureanlagerungssalz davon.

2. Verwendung nach Anspruch 1, worin Z Sauerstoff ist.

3. Verwendung nach Anspruch 1, worin Z Schwefel ist.

4. Verwendung nach einem der vorgenannten Ansprüche, worin N=B 4-Morhpolinyl ist.

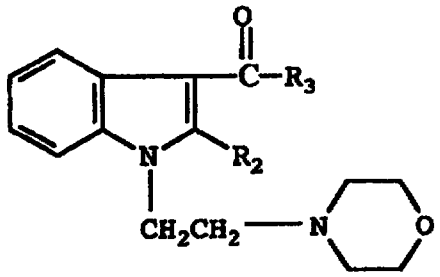
5. Verwendung nach einem der vorgenannten Ansprüche, worin sind:

R_2 Wasserstoff, niederes Alkyl oder Chlor;
R_3 Phenyl, substituiert mit einem bis drei Substituenten, ausgewählt aus: Halogen, niederes Alkoxy, niederes Alkyl, 1-Naphthyl oder 2-Naphthyl (oder 1-Naphthyl oder 2-Naphthyl, substituiert mit einem bis zwei Substituenten, ausgewählt aus: niederes Alkyl, niederes Alkoxy, Halogen oder Cyano), (1H-Imidazol-1-yl)naphthyl, 1-(1,2,3,4-Tetrahydronaphthyl), Anthryl, Pyrenyl, 2-, 3-, 4-, 5-, 6- oder 7-Benzo[b]furyl, 2- oder 3-Benzo[b]thienyl, oder 2-, 3-, 4-, 5-, 6-, 7- oder 8-Chinoyl.

6. Verwendung nach Anspruch 5, worin sind:

R_3 1-Naphthyl oder 2-Naphthyl (oder 1-Naphthyl oder 2-Naphthyl, substituiert durch niederes Alkyl, Halogen oder Cyano), (1H-Imidazol-1-yl)naphthyl oder 2-, 3-, 4-, 5-, 6- oder 7-Benzo[b]furyl;
R_4 Wasserstoff oder niederes Akyl oder Fluor sowie Alk 1,2-Ethylen.

7. Verbindung der Formel:



worin sind:

R_2 Wasserstoff oder niederes Alkyl;
R_3 niederes Alkoxymethylphenyl; Tri-(niederes alkoxy)phenyl, Benzyl, niederes Alkoxystyryl, (1H-Imidazol-1-yl) naphthyl, 2-(1-naphthyl)vinyl, 1-(1,2,3,4-Tetrahydronaphthyl), Anthryl, Phenanthryl oder Pyrenyl, oder ein Säureanlagerungssalz davon.

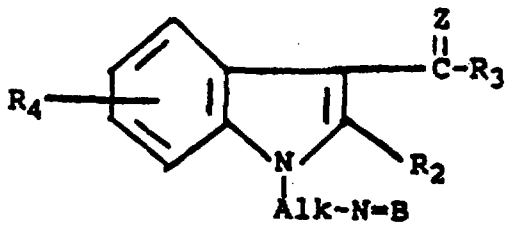
8. Verbindung nach Anspruch 8, worin R_2 Wasserstoff ist.

9. Verbindung nach Anspruch 8, worin R_2 niederes Alkyl ist.

Revendications

1. Utilisation pour la préparation d'un médicament utile au traitement du glaucome d'un composé ayant la formule :

* C L M S *



où

R_2 est un hydrogène, alkyle inférieur, chloro ou fluoro ;
R_3 est un phényle (ou phényle substitué par 1 à 3 substituants choisis parmi halo, alcoxy inférieur, alcoxyméthyle inférieur, hydroxy, alkyle inférieur, amino, alkylamino inférieur, dialkylamino inférieur ou alkylmercapto inférieur), méthylène-dioxyphényle, benzyle, styryle, alcoxystyryle inférieur, 1- ou 2-naphtyle (ou 1- ou 2-naphtyle subtitué par 1 à 2 substituants choisis parmi alkyle inférieur, alcoxy inférieur, halo ou cyano), (1H-imidazol-1-yl)naphtyl, 2-(1-naphtyl)éthényle, 1-(1,2,3,4-tétrahydronaphtyl), anthryle, phénanthryle, pyrényle, 2-, 3-, 4-, 5-, 6- ou 7-benzo[b]furyle, 2- ou 3-benzo[b]-thiényle, 5-(1H-benzimidazolyl) ou 2-, 3-, 4-, 5-, 6-, 7- ou 8-quinolyle;
R_4 est un hydrogène ou alkyle inférieur, l'hydroxy, alcoxy inférieur ou halo en position 4-, 5-, 6- ou 7- ;
Z est O ou S ;
Alk est un alkylène inférieur ayant la formule $(CH_2)_n$ où n est un entier qui est 2 ou 3, ou un alkylène inférieur substitué par un groupe alkyle inférieur ; et
N=B est un N,N-di-alkylamino inférieur, 4-morpholinyle, 2-alkyl-4-morpholinyle inférieur, 3-alkyl-4-morpholinyle inférieur, 1-pyrrolidinyle, 1-pipéridinyle ou 3-hydroxy-1-pipéridinyle; ou un de leurs sels d'addition d'acide.

2. Utilisation selon la revendication 1, où Z est O.

3. Utilisation selon la revendication 1, où Z est S.

4. Utilisation selon l'une quelconque des revendications précédentes, où N=B est le 4-morpholinyle.

5. Utilisation selon l'une quelconque des revendications précédentes, où:

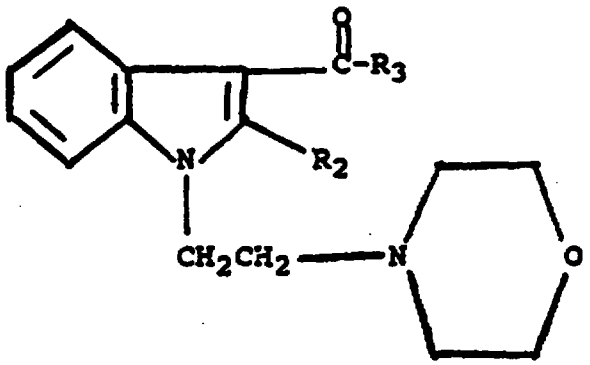
R_2 est un hydrogène, alkyle inférieur ou chloro ; et
R_3 est un phényle substitué par 1 à 3 substituants choisis parmi halo, alcoxy inférieur ou alkyle inférieur, 1- ou 2-naphtyle (ou 1- ou 2-naphtyle substitué par 1 à 2 substituants choisis parmi alkyle inférieur, alcoxy inférieur, halo ou cyano), (1H-imidazol-1-yl)naphtyle, 1-(1,2,3,4-tétrahydronaphtyle), anthryle, pyrényle, 2-, 3-, 4-, 5-, 6- ou 7-benzo[b]furyle, 2- ou 3-benzo[b]thiényle ou 2-, 3-, 4-, 5-, 6-, 7- ou 8-quinolyle.

6. Utilisation selon la revendication 5, où :

R_3 est un 1- ou 2-naphtyle (ou 1- ou 2-naphtyle substitué par alkyle inférieur, halo ou cyano), (1H-imidazol-1-yl) -naphtyle ou 2-, 3-, 4-, 5-, 6- ou 7-benzo[b]furyle;
R_4 est un hydrogène, alkyle inférieur ou fluoro ; et
Alk est un 1,2-éthylène.

7. Composé ayant la formule :

* C L M S *



où

R_2 est un hydrogène ou alkyle inférieur ; et
R_3 est un alcoxyméthylphényle inférieur ; tri-alcoxyphényle inférieur, benzyle, alcoxystyryle inférieur, (1H-imidazol-1-yl)naphtyle, 2-(1-naphtyl)éthényle, 1-(1,2,3,4-tétrahydronaphtyl), anthryle, phénanthryle ou pyrényle ; ou un de leurs sels d'addition d'acides.

8. Composé selon la revendication 7, où R_2 est un hydrogène.

9. Composé selon la revendication 7, où R_2 est un alkyle inférieur.

* C L M S *