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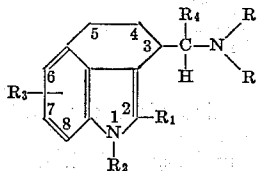
## 3,200,130 DERIVATIVES OF 1,3,4,5-TETRAHYDRO- BENZ[CD]INDOLES

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18 Claims. (Cl. 260-319)

The present invention relates to novel compounds and to processes for the preparation of the same. More particularly the invention relates to novel 3-(1-aminoalkyl)-1,3,4,5-tetrahydrobenz[cd]indoles, to intermediates in the preparation thereof, to derivatives thereof, and to novel processes for the preparation of the same.

The novel 3-(1-aminoalkyl)-1,3,4,5-tetrahydrobenz[cd]indoles of the invention can be presented by the following formula:



wherein R represents hydrogen and lower-alkyl, e.g., methyl, ethyl, propyl, butyl, amyl, hexyl, heptyl, octyl, and the isomeric forms thereof; R<sub>1</sub> represents hydrogen, alkyl of from 1 to 4 carbon atoms, inclusive, e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and the like, phenyl, hydroxyphenyl, e.g., p-hydroxyphenyl, m-hydroxyphenyl, 2,3-dihydroxyphenyl, 3,4-dihydroxyphenyl, 2,3,4-trihydroxyphenyl, and the like, alkoxyphenyl, wherein the alkoxy moiety is of from 1 to 4 carbon atoms, inclusive, e.g., p-methoxyphenyl, p-ethoxyphenyl, m-butoxyphenyl, o-propoxyphenyl, 2,3,4-triethoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, and the like, and halophenyl, e.g., p-chlorophenyl, p-bromophenyl, p-iodophenyl, p-fluorophenyl, 3,4-dichlorophenyl, 2,3,4-tribromophenyl, and the like; R<sub>2</sub> represents hydrogen, benzyl and halobenzyl, e.g., chloro-, bromo-, iodo-, and fluorobenzyl which can be substituted with alkyl or alkoxy of from 1 to 4 carbon atoms, inclusive, and alkyl of from 1 to 4 carbon atoms, inclusive, e.g., methyl, ethyl, propyl, butyl, isobutyl, and the like; R<sub>3</sub> represents from zero to 3 members of the group consisting of hydroxy, benzyloxy, alkyl of from 1 to 4 carbon atoms, inclusive, e.g., methyl, ethyl, propyl, butyl, isobutyl, and the like, halogen, e.g., fluorine, chlorine, and bromine, and alkoxy of from 1 to 4 carbon atoms, inclusive, e.g., methoxy, ethoxy, propoxy, butoxy, and the like; and R<sub>4</sub> represents hydrogen and alkyl of from 1 to 4 carbon atoms, inclusive.

The novel 3-(1-aminoalkyl)-1,3,4,5-tetrahydrobenz[cd]indoles of the invention exist either in the non-protonated (free base) form or the protonated form depending upon the pH of the environment. They form stable protonates (acid addition salts) on neutralization with suitable acids, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, thiocyanic, fluosilicic, acetic, benzoic, salicylic, glycolic, succinic, nicotinic, tartaric, maleic, malic, lactic, methanesulfonic, cyclohexanesulfamic acids, and the like. These acid addition salts are useful in upgrading the free base.

The novel compounds of Formula I where neither R is hydrogen also form alkyl quaternary ammonium salts by reaction with an alkyl halide, for example, an alkyl chloride, bromide, or iodide, or by reaction with an alkyl nitrate, an alkali metal alkyl sulfate, a dialkyl sulfate, an alkyl arylsulfonate, and the like. They can also be formed by metathesis or by neutralizing the quaternary ammonium hydroxide. The anion of the quaternary ammonium salt can be inorganic, for example, chloride, bromide, iodide, nitrate, sulfate, phosphate, thiocyanate, fluosilicate, perchlorate, and the like, or it can be organic, for example, methosulfate, p-toluene-sulfonate, 1-naphthalenesulfonate, acetate, benzoate, salicylate, hydrocinnamate, succinate, lactate, or the like. Examples of alkyl are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, and isomeric forms thereof.

The novel compounds of Formula I wherein neither R is hydrogen also form N-oxides on oxidation with peroxides, e.g., hydrogen peroxide. The N-oxides also form stable protonates (acid addition salts) on neutralization with suitable acids, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, thiocyanic, fluosilicic, acetic, benzoic, salicylic, glycolic, succinic, nicotinic, tartaric, maleic, malic, lactic, methanesulfonic, cyclohexanesulfamic acids, and the like. These acid addition salts are useful in upgrading the N-oxide free base.

The novel compounds of Formula I either in the free base form, as acid addition salts wherein the acid is pharmacologically acceptable, for example, hydrochloric acid or citric acid, as lower alkyl quaternary ammonium salts, i.e., alkyl of from 1 to 8 carbon atoms, inclusive, or as N-oxides have tranquilizing activity in mice and rats and can be used to calm agitated mammals, birds, humans, and other animals. They also exhibit characteristic absorption of light in the visible, ultraviolet, and infrared bands and accordingly are useful, in solutions or dispersed in plastic films, as light filters.

The higher alkyl quaternary ammonium salts, for example, wherein the alkyl group is of from 9 to 20 carbon atoms, inclusive, exhibit valuable surface-active and cation-active wetting and emulsifying properties, and also exhibit valuable bacteriostatic and bactericidal activity. These higher alkyl quaternary ammonium salts are useful as detergents and detergent-sanitizers and can be employed to clean and sanitize equipment used in the processing and preparation of foods, for example, fruit, meat, milk and the like.

The free base and the acid addition salt forms of compounds of Formula I wherein both R's are alkyl are useful as intermediates in the preparation of said alkyl quaternary ammonium salts.

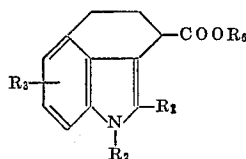
The thiocyanic acid addition and the alkyl quaternary ammonium salts when condensed with formaldehyde, form resinous materials useful as pickling inhibitors according to U.S. Patents 2,425,320 and 2,606,155. The fluosilicic acid addition salts and alkyl quaternary ammonium fluosilicates are useful as mothproofing agents according to U.S. Patents 1,915,334 and 2,075,359.

The free bases of the invention also form salts with penicillins. These salts have solubility characteristics which cause them to be useful in the isolation and purification of penicillins, particularly benzyl penicillin. Said

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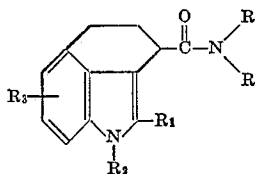
salts like the other salts specified above can be formed either by neutralization of the free base form of a compound of Formula I with the desired free acid, or by a metathetical exchange of the anion of a salt of a compound of Formula I, for example, the chloride ion of a hydrochloride, with the anionic form of the acid.

When  $R_4$  is hydrogen the novel compounds of Formula I can be prepared by amidating an acid or an ester of the formula:



(II)

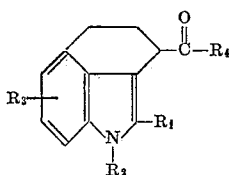
wherein  $R_1$ ,  $R_2$ , and  $R_3$  are as given above, and  $R_6$  is hydrogen or lower alkyl, to form an amide having the following formula:



(III)

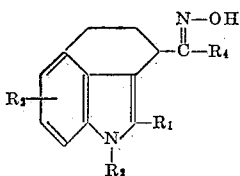
wherein  $R$ ,  $R_1$ ,  $R_2$ , and  $R_3$  are as given above, and reducing the amide with lithium aluminum hydride. The amidation advantageously is effected by converting an acid of Formula II to the corresponding acyl halide, for example, by reaction with thionyl halide, carbonyl halide, or oxalyl halide, and reacting the acid halide with a compound of the formula  $\text{HNRR}$  wherein  $R$  is as given above. Lithium aluminum hydride reduction can be effected in the manner usual for such reductions of amides, for example, according to U.S. Patent 2,781,348.

When  $R_4$  is alkyl the novel compounds of Formula I can be prepared by reacting an acid of Formula II wherein  $R_1$ ,  $R_2$ , and  $R_3$  are as given above, with an alkyl lithium to form a ketone of the formula:



(IV)

wherein  $R_4$  is alkyl and  $R_1$ ,  $R_2$ , and  $R_3$  are as given above; reacting the thus formed ketone with hydroxylamine to form an oxime of the formula:



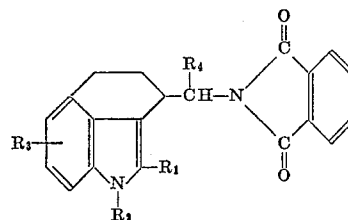
(V)

wherein  $R_1$ ,  $R_2$ ,  $R_3$ , and  $R_4$  are as given above; and reducing the thus formed oxime with sodium and ethanol. A mixture of two diastereoisomers is obtained.

If desired the mixture of isomers thus obtained can be separated. A suitable process is to react the mixture

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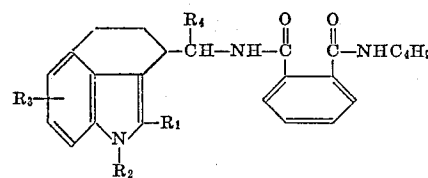
of diastereoisomers with phthalic anhydride to form the corresponding isomeric phthalimides of the formula:



(VI)

wherein  $R_1$ ,  $R_2$ ,  $R_3$ , and  $R_4$  are as given above, separating the isomeric phthalimides, for example, by chromatography, and subjecting the separated phthalimides to aminolysis, for example, with butylamine.

The aminolysis proceeds in two steps, yielding first an intermediate phthalamide of the formula:



(VII)

which on further aminolysis is converted to the desired amine of Formula I.

The compounds of Formula I wherein  $R_2$  is hydrogen can be alkylated at the 1-position by the usual procedures for alkylating indoles, e.g., they can be alkylated by reaction with an alkyl or aralkyl halide in the presence of an alkaline condensing agent such as an alkali metal amide or hydride.

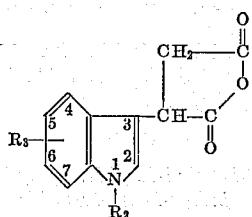
An  $R$  hydrogen in the compounds of Formula I can be substituted by lower-alkyl by acylation followed by reduction with lithium aluminum hydride. The acylation can be effected by conventional methods, such as, treatment with anhydride or acid chloride of a lower-alkanoic acid, e.g., acetic anhydride or acetyl chloride, or a lower-alkyl lower-alkanoate, e.g., ethyl formate. The lithium aluminum hydride reduction can be effected by the procedure given above. This procedure yields a secondary amine when both  $R$ 's in the compounds of Formula I are hydrogen, and a tertiary amine when only one  $R$  is hydrogen.

The starting compounds of Formula II are prepared by a Huang-Minlon reduction of the corresponding 1,3,4,5-tetrahydro-5-oxobenz[cd]indole-3-carboxylic acid wherein  $R_1$ ,  $R_2$ , and  $R_3$  are as given above, except that any hydroxy group will be acylated with alkanoyl of not more than 4 carbon atoms and  $R_2$  also can be alkanoyl of not more than 4 carbon atoms. These alkanoyls are the result of procedures used to make starting compounds, see below, but do not appear in the final products because any alkanoyl group is cleaved in the Huang-Minlon reduction. The 5-oxo group of the acid is reduced with hydrazine hydrate and potassium hydroxide or other alkali metal hydroxide. Advantageously, the reaction is carried out in an inert solvent, for example, diethylene glycol and triethylene glycol, at a temperature from about 180° C. to about 210° C. The desired 1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid is then obtained by acidifying the reaction mixture with hydrochloric acid or other strong acid and recovered by such processes as extraction and crystallization. It can then be esterified if the ester is desired as starting compound.

The 1,3,4,5-tetrahydro-5-oxobenz[cd]indole-3-carboxyl-

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ic acids are prepared by cyclizing 1-substituted-3-indolesuccinic anhydrides of the formula:

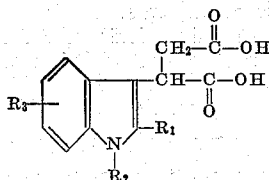


(VIII)

wherein  $R_2$  is other than hydrogen and can be alkanoyl of not more than 4 carbon atoms. The cyclization can be effected with aluminum chloride. The reaction is advantageously effected in a Friedel-Crafts solvent, for example, ethylene dichloride, sym.-tetrachloroethane, nitrobenzene, carbon disulfide, and the like. The reaction can be carried out at room temperature (about 24–30° C.), although in some cases gentle heating can be used. Advantageously the reagents are brought together at room temperature with or without cooling as may be desired and then heated on a steam bath until the reaction is complete. A molar excess of condensing agent, for example, 3 moles of aluminum chloride for each mole of anhydride, is advantageously used. The amount of condensing agent, however, can be varied over a wide range without affecting the reaction other than in the matter of yield. Ordinarily it will not be necessary or desirable to use more than about 5 moles or less than about 1 mole of condensing agent for each mole of anhydride. The product can be recovered from the reaction mixture and purified by recrystallization in a conventional manner. Advantageously, the reaction mixture is cooled and treated with concentrated hydrochloric acid to insure effective precipitation of the product. Other strong acids, for example, sulfuric acid and phosphoric acid can be used.

The 1-substituted-3-indolesuccinic anhydrides used as starting materials in the process of the invention can be prepared by reacting the corresponding 1-substituted-3-indolesuccinic acid with isopropenyl lower-alkanoate, for example, isopropenyl formate, acetate, propionate, and butyrate. The 1-lower-alkanoyl-3-indolesuccinic anhydrides can also be obtained by reacting the corresponding 1-substituted-3-indolesuccinic anhydrides with isopropenyl lower-alkanoate. Advantageously, the reaction is carried out in the presence of an inert solvent which may be an excess of the isopropenyl lower-alkanoate and in the presence of an acidic catalyst, for example, p-toluenesulfonic acid, methanesulfonic acid, sulfuric acid, sulfonic acid ion-exchange resins, and the like. The acetone formed in the reaction is distilled off to complete the reaction and the product can be recovered from the solution in any suitable manner, for example, by crystallization with or without recrystallization. The 1-alkanoyl group and any other alkanoyl group which may be introduced in this reaction will be cleaved in the subsequent Huang-Milon reduction.

The starting 3-indolesuccinic acids can be represented by the formula:



(IX)

wherein  $R_1$ ,  $R_2$ , and  $R_3$  have the significance defined above. They are prepared by two procedures depending on whether  $R_1$  is hydrogen or other than hydrogen. For example, when  $R_1$  is other than hydrogen, the 3-indolesuccinic acids can be prepared by condensing the corresponding 3-unsubstituted indole with maleic anhydride or maleic acid in accordance with the procedure of Diels and Alder,

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Ann. 490, 277, 1931. When maleic anhydride is used, it is sometimes unnecessary to go through the succinic acid stage. However, because of the difficulty of isolating the anhydride in most cases, and the possibility of competing side reactions, it is ordinarily desirable to hydrolyze the anhydride and to recover the 3-indolesuccinic acid for use as starting material. In such case the reaction mixture is allowed to stand for about 15 to 120 minutes and aqueous alkali, e.g., sodium hydroxide, potassium hydroxide, sodium carbonate, and the like, is added to the mixture. The alkaline mixture is heated, suitably to between about 50° C. and about 100° C., for a period between about 30 minutes to about 1 hour, cooled, and decanted. The aqueous solution thus obtained is acidified, e.g., with hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid, and the like. After standing for several hours, e.g., 2 to 12 hours, the 3-indolesuccinic acid is recovered by filtration.

When  $R_1$  is hydrogen the 3-indolesuccinic acids are prepared by the procedure of Perron et al., J. Org. Chem. 24, 1165, 1959, which involves condensing a 3-indolecarboxaldehyde with ethyl cyanoacetate or diethyl malonate, reacting the condensed product with potassium cyanide in ethanol, and hydrolyzing the resulting cyano derivative with aqueous potassium hydroxide solution.

The 3-indolecarboxaldehydes can be prepared by reacting a 3-unsubstituted indole with dimethylformamide, in the presence of phosphorus oxychloride, using essentially the procedure described by Smith, J. Chem. Soc. 1954, 3842.

The starting indoles utilized to prepare 3-indolesuccinic acids can be prepared by the processes disclosed in U.S. Patent 2,825,734.

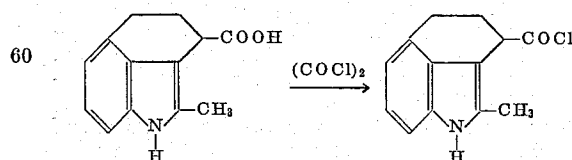
When hydroxy-substituted compounds ( $R_3$ =hydroxy) are desired the corresponding benzyloxy-substituted compounds should be used. The benzyloxy group can be converted to hydroxy by hydrogenolysis which can be advantageously carried out in the presence of a palladium catalyst such as palladium black, palladium-barium sulfate, palladium-charcoal and the like, in the manner more fully disclosed in U.S. Patent 2,708,197.

If the starting indole compound contains an N-hydrogen ( $R_2$ =hydrogen) the reaction with isopropenyl lower-alkanoate will acylate the nitrogen with a lower-alkanoyl group. The same or a different acyl group can be present in the starting 3-indolesuccinic acids. These acyl groups can, when desired, be removed from the 1,3,4,5-tetrahydro-5-oxobenz[cd]indole-3-carboxylic acid by simple hydrolysis or they can be carried on in further processing of the compound and removed when and if desired by simple hydrolysis.

The following examples are illustrative of the process and products of the invention, but are not to be construed as limiting.

#### EXAMPLE 1

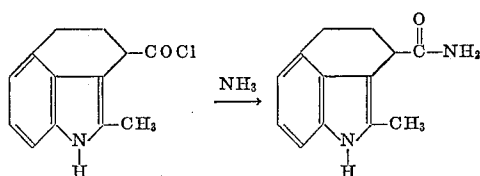
##### A. 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carbonyl chloride



The acid (4.3 g.; 0.02 mole) was dissolved in 200 ml. of hot benzene. The solution was cooled in ice and oxalyl chloride (20 ml.) was added during 5 minutes while swirling. The dark solution was allowed to stand at about 25° C.; gas evolution started after a few minutes. After two hours the solution was evaporated at 40–45° C. in vacuo. Benzene (50 ml.) was added and the solution was evaporated to give 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carbonyl chloride as an oily brown liquid which was used directly in Part B.

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B. 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxamide



Fifty ml. of aqueous ammonium hydroxide (29%) was added to one-half of the oily acid chloride of Part A (cooled in ice). An oily product separated which was broken up to give a precipitate. The suspension was cooled in ice, then filtered and the solid washed with cold water; 1.25 g. (58.5% yield), M.P. 210–212° C. (darkened at 200° C.). Crystallization from methanol-benzene treated with decolorizing carbon afforded 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxamide as pale yellow leaflets melting at 213–215° C. For analysis a sample was recrystallized from benzene containing a trace of methanol; M.P. 214–215.5° C.

*Analysis.*—Calcd. for  $C_{13}H_{14}N_2O$ : C, 72.87; H, 6.59; N, 13.08. Found: C, 72.86; H, 6.67; N, 12.72.

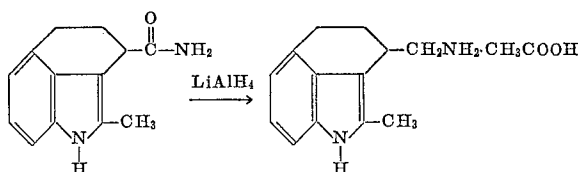
U.V.: 224.5 (33,900); 274 (7,200); 278 (7,300);  $\epsilon$  289 (5,150).

In all the ultraviolet determinations, the first figure is the wave length in millimicrons and the second in parentheses is the molar absorptivity; the letter "f" stands for flex; and unless otherwise specified, the solvent was 95% ethanol.

I.R.: NH, 3410, 3320, 3180; C=O, 1665; amide II, 1642; C=C, 1587; aromatic, 775, 752.

All the infrared determinations were carried out in a mineral oil mull, and are expressed as reciprocal centimeters. The letters "sh" stand for shoulder and "w" stands for weak.

C. 3-aminomethyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole and its acetic acid salt



A solution of the amide of Part B (0.86 g.; 4 mmoles) in 35 ml. of warm tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added during 5 minutes with stirring to a solution of lithium aluminum hydride (1 g.) in 100 ml. of ether. The mixture was then refluxed for 5 hours and allowed to stand for two days. It was cooled in ice and decomposed by the successive addition of 1 ml. of water, 1 ml. of 15% aqueous sodium hydroxide solution, and 3 ml. of water. The suspension was filtered, the precipitate was washed well with ether, and the combined filtrate and washings were evaporated to dryness at about 25° C. to give 0.83 g. of 3-aminomethyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole as a yellow oil. It showed only a trace of residual amide infrared absorption band at 1670  $cm^{-1}$ .

The yellow oil (0.794 g.) was dissolved in 25 ml. of warm ether and the solution was decanted from a small amount of undissolved amorphous material. A solution of acetic acid (0.36 g.) in 3 ml. of ether was added. The resulting precipitate was filtered and washed with ether, yielding 0.9 g. of 3-aminomethyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole acetic acid salt; M.P. 190–192.5° C. (dec. starting at 189° C.). The salt was dissolved in about 10 ml. of methanol, 40 ml. of ether was added, and crystallization allowed to proceed in the cold overnight; clusters of needles; 0.75 g. melting at 195–198° C. (dec.), darkens at 185° C.

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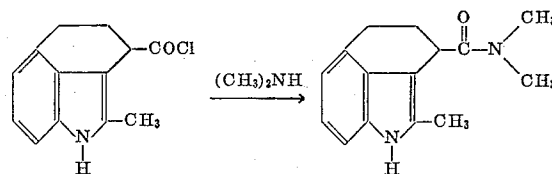
*Analysis.*—Calcd. for  $C_{15}H_{20}N_2O_2$ : C, 69.20; H, 7.74; N, 10.76. Found: C, 68.89; H, 7.44; N, 10.49.

U.V.: 226 (34,900); 274 (7,250); 279 (7,300);  $\epsilon$  290 (5,150).

I.R.: NH, 3260;  $NH_3^+$  (salt), 3000, 2770, 2700, 2640, 2560, 2460, 2190; COO<sup>-</sup>/C=C, 1635, 1575 sh, 1560 sh, 1538, 1415; ring, 735, 680.

EXAMPLE 2

A. N,N,2-trimethyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxamide



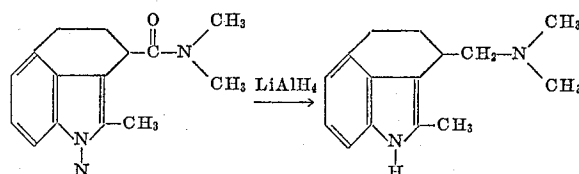
Fifty ml. of aqueous dimethylamine (40%) was added to the remaining half of the acid chloride of Part A, Example 1 (cooled in ice). The resulting suspension was stirred for a few minutes. It was then cooled in ice, filtered, and the precipitate was washed with cold water, yielding 2.15 g. (89% yield) of N,N,2-trimethyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxamide, M.P. 231–233° C. Crystallization from methanol treated with decolorizing carbon gave pale yellow plates; M.P. 232.5–234° C. (darkens at 220° C.), unchanged on further recrystallization.

*Analysis.*—Calcd. for  $C_{15}H_{18}N_2O$ : C, 74.35; H, 7.49; N, 11.56. Found: C, 73.96; H, 7.73; N, 11.83.

U.V. 227 (62,800);  $\epsilon$  274 (6,750); 280 (6,950);  $\epsilon$  290 (5,100).

I.R.: NH, 3190; C=O, 1620 sh, 1612; C=C, 1578, 1500; aromatic, 757, 745, 723.

B. 3-dimethylaminomethyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole



A solution of the amide of Part A (1.55 g.; 6.4 mmoles) in 100 ml. of hot tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added with stirring to a solution of lithium aluminum hydride (2 g.) in 150 ml. of ether so that mild reflux resulted. The mixture was then refluxed for 6 hours and allowed to stand overnight. It was decomposed by the successive addition of 2 ml. of water, 2 ml. of 15% aqueous sodium hydroxide solutions, and 6 ml. of water. The suspension was filtered, the cake was washed with ether, and the combined filtrate and washings were evaporated to dryness in vacuo to give 1.48 g. (quantitative yield) of 3-dimethylamino-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole as a solid melting at 111.5–113.5° C. (it showed no residual amide band in the infrared). For analysis, a sample was recrystallized from technical hexane (Skellysolve B); prisms, M.P. 113.5–115° C.

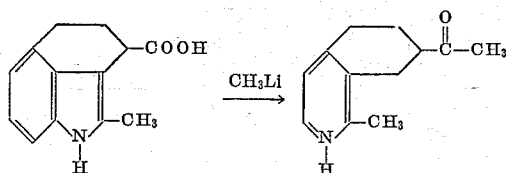
*Analysis.*—Calcd. for  $C_{15}H_{20}N_2$ : C, 78.90; H, 8.83; N, 12.27. Found: C, 78.59; H, 8.57; N, 12.43.

U.V.: 227 (32,150);  $\epsilon$  274 (6,900); 280 (6,950);  $\epsilon$  290 (5,100).

I.R.: NH, 3140; tert. amine, 2780, 2740 sh, 2700; C=C, 1623, 1606, 1575, 1507, 1495 sh; ring, 860, 846, 800, 780, 738.

## EXAMPLE 3

## A. 3-acetyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole



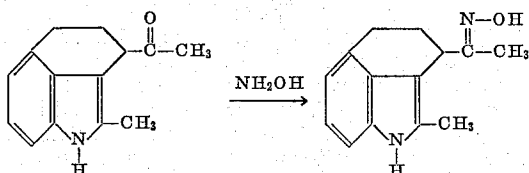
A solution of methyl lithium containing 15 mmoles of the reagent in 23 ml. of ether was added during 10 minutes to a solution of 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid (1.08 g.; 5 mmoles) dissolved in 50 ml. of ether under nitrogen at room temperature. Immediate precipitation occurred accompanied by mild reflux. The mixture was then refluxed for 35 minutes. It was cooled in ice, 50 ml. of water was added, and the ether layer was washed with water. The combined aqueous solution was extracted twice with ether. The combined ether extracts and original ether layer were washed twice with saturated sodium chloride solution, dried with sodium sulfate, and evaporated to give 0.335 g. of 3-acetyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole as a pale viscous oil. Crystallization from ether-Skellysolve B (technical hexane) afforded 0.235 g. of prisms (22% yield); M.P. 96.5–97.5° C. Recrystallization from the same solvent mixture using decolorizing carbon raised the melting point to 97–98° C.

*Analysis*.—Calcd. for  $C_{14}H_{15}NO$ : C, 78.84; H, 7.09; N, 6.57. Found: C, 79.20; H, 7.00; N, 6.66.

U.V.: 225 (35,200); 274 (7,450);  $\epsilon$  280 (7,400);  $\epsilon$  289 (5,300).

I.R.: NH, 3320; C=O, 1688; C=C, 1620, 1608, 1575.

## B. Oxime of 3-acetyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole



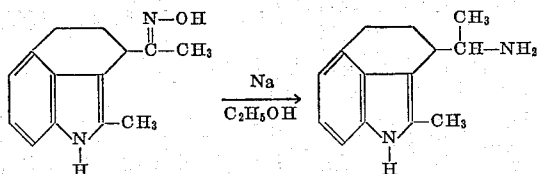
A solution of the ketone of Part A (6.3 g.; 0.296 mole) in 40 ml. of 95% ethanol was added to a solution of hydroxylamine hydrochloride (10.4 g.; 0.15 mole) and sodium acetate (18.5 g.; 0.225 mole) in 40 ml. of water. The mixture was refluxed for 1 hour and the resulting yellow solution was evaporated until an oily product separated. Water (50 ml.) was added and the mixture was cooled and filtered to give 6.38 g. (94.5% yield) of the oxime of 3-acetyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole; M.P. 163–171° C. (sintering at 145° C.). One crystallization from benzene-petroleum ether gave clusters melting at 167–174° C. (sintering at 154° C.).

*Analysis*.—Calcd. for  $C_{14}H_{16}N_2O$ : C, 73.65; H, 7.06; N, 12.27. Found: C, 73.55; H, 7.36; N, 12.63.

U.V.: 227 (36,150); 274 (7,100); 280 (7,200);  $\epsilon$  290 (5,100).

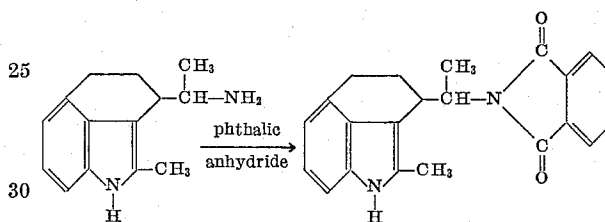
I.R.: NH, 3350; OH, 3200; C=N, 1660 w; C=C, 1605, 1505, 1570; =N—OH, 963, 940, 906, 860.

## C. Reduction of the oxime of 3-acetyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole



Sodium (78 g.) was added during 20 min. to a refluxing solution of the oxime of Part B (12.1 g.; 0.053 mole) in 800 ml. of absolute ethanol without external heating. The solution was then refluxed for one hour. The resulting brown solution was cooled in ice, 800 ml. of water was added, and the solution was evaporated in vacuo until about 800 ml. of distillate was collected and an oil separated. The mixture was extracted with ether and the ethereal layer was washed with water, and then extracted six times with a total of 175 ml. of 10% hydrochloric acid. The acidic extracts were washed once with ether and basified with 15% aqueous sodium hydroxide solution. The resulting oil was extracted with ether. The ether was evaporated to give 9.88 g. of 2-methyl-3-(1-aminoethyl)-1,3,4,5-tetrahydrobenz[cd]indole as an oily brown solid, this product being a mixture of diastereoisomers.

## D. Reaction with phthalic anhydride



A mixture of phthalic anhydride (7.8 g.; 0.0526 mole) and the crude amine of Part C (7.53 g.; 0.0352 mole) was heated in an oil bath. The temperature was raised to 210° C. during 15 minutes and then kept at 210–220° C. for 15 min. The mixture was allowed to cool, 350 ml. of absolute ethanol was added, and the mixture was refluxed for 1 hour and 40 minutes. It was evaporated in vacuo to a small volume, diluted with 250 ml. of ethyl acetate, and washed three times with dilute aqueous sodium bicarbonate solution. The bicarbonate washes were extracted with ethyl acetate and the combined organic layer was filtered, washed with water, then twice with 10% hydrochloric acid, followed by saturated salt solution. The washed solution was dried with sodium sulfate, and evaporated, to give 11.5 g. of a brown solid.

The solid was dissolved in 100 ml. of benzene and chromatographed on 1,150 g. of magnesium silicate. Elution with 6% acetone-Skellysolve B (8 l.) gave 124.3 mg. (discarded). Further elution (10 l.) gave a total of 7.07 g. of product varying in M.P. from 184° to 187° C. It was crystallized from methanol using decolorizing carbon to give isomer A of the phthalimido derivative of the above structure; 3.32 g. of yellow clusters, M.P. 180–181° C. The second crop amounted to 0.48 g., M.P. 179–180° C. The analytical sample melted at 182–182.5° C. (from methanol).

*Analysis*.—Calcd. for  $C_{22}H_{20}N_2O_2$ : C, 76.72; H, 5.85; N, 8.13. Found: C, 77.01; H, 5.94; N, 8.10.

U.V.: 222 (71,850);  $\epsilon$  242 (11,400); 275 (9,150); 279 (9,250); 290 (7,250).

I.R.: NH, 3400, 3360; C=O, 1768, 1700; C=C, 1622 sh, 1615, 1575, 1508.

Further elution (18 l.) gave 5.3 g. of product melting from 166° to 170° C. Crystallization from methanol afforded isomer B of the phthalimido derivative of the above structure; 2.08 g. of yellow rods, M.P. 169–170° C. The second crop (0.46 g.) melted at 167–168° C.

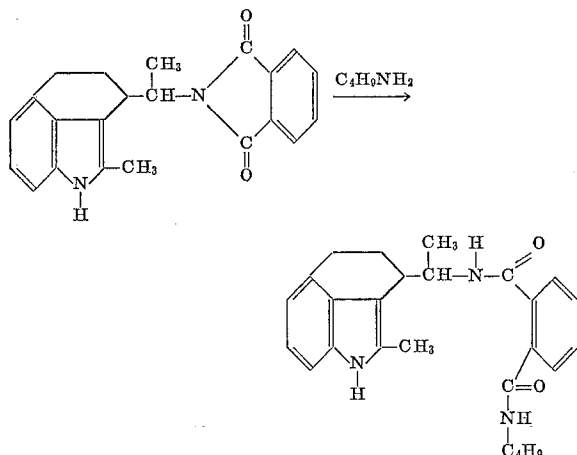
*Analysis*.—Calcd. for  $C_{22}H_{20}N_2O_2$ : C, 76.72; H, 5.85; N, 8.13. Found: C, 76.92; H, 5.98; N, 8.17.

U.V.: 225 (71,250);  $\epsilon$  240 (12,800); 275 (8,050); 280 (8,150);  $\epsilon$  289 (6,600).

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I.R.: NH, 3350, C=O, 1771, 1695; C=C, 1615, 1605 sh, 1579, 1510.

E. Cleavage of isomer A with butylamine



A solution of the phthalimido derivative (isomer A of Part D, M.P. 180–181° C.) (3.8 g.; 0.011 mole) in 100 ml. of methanol and 11 ml. of butylamine was refluxed for 20.5 hours under nitrogen. It was evaporated to dryness in vacuo to give a pale yellow gum. Water (50 ml.) and ether (50 ml.) were added and the mixture was stirred until a fine suspension resulted. Filtration (filtrate worked up below) gave 2.65 g. of a colorless precipitate, M.P. 209–213° C. (sintering at 155° C.) Crystallization from aqueous methanol afforded colorless needles of the partial aminolysis product of the above structure: M.P. 217–218° C., unchanged on further crystallization.

*Analysis*.—Calcd. for  $C_{26}H_{31}N_3O_2$ : C, 74.79; H, 7.48; N, 10.06. Found: C, 74.68; H, 7.59; N, 10.15.

U.V.: 227 (45,950); 273.5 (8,400); f 278 (8,200); f 290 (5,550).

I.R.: NH, 3350, 3260, 3180; =CH, 3030; C=O, 1625; C=C, 1600, 1580, 1507 sh, 1480 sh; amide II, 1560 sh.

The above filtrate was separated into layers and the aqueous layer was extracted once with ether. The combined ether extract and ether layer were washed four times with 10% hydrochloric acid (85 ml.) and the acid extract was basified with 15% aqueous sodium hydroxide solution. The mixture was extracted three times with ether and the combined ether extract was evaporated to give 1.048 g. (44.6% yield) of a pale yellow oil. Crystallization from benzene-petroleum ether (B.P. 30–60° C.) gave 0.912 g. of isomer A of 2-methyl-3-(1-aminoethyl)-1,3,4,5-tetrahydrobenz[cd]indole; M.P. 123–125° C. Recrystallization from ether-Skellysolve B raised the M.P. to 126–127° C.

*Analysis*.—Calcd. for  $C_{14}H_{18}N_2$ : C, 78.46; H, 8.47; N, 13.07. Found: C, 78.23; H, 8.45; N, 13.03.

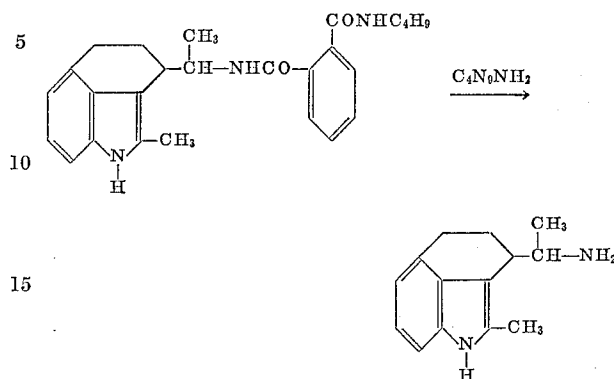
U.V.: 228 (35,050); f 275 (7,050); 280 (7,150); f 290 (5,200).

I.R.: NH, 3130, 3020; C=C/NH def., 1620, 1597, 1575.

The neutral ether fraction remaining after acid extraction was worked up to give 1.187 g. of a gummy solid which was crystallized from benzene to give N,N'-dibutylphthalimide.

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F. Cleavage of the partial aminolysis product with butylamine



A solution of the partial aminolysis product of Part E (2.45 g.; 5.9 mmoles) in 50 ml. of ethanol and 17 ml. of butylamine was refluxed under nitrogen for 22.5 hours. The solution was evaporated to dryness in vacuo to give a gum. Water and ether were added (50 ml. of each) and the mixture was stirred. A solution resulted at first and then a white precipitate separated, and was filtered off. The filtrate was separated into layers and the ether layer was extracted four times with 10% hydrochloric acid (total 100 ml.). The acidic extract was washed with ether and then basified with potassium hydroxide. The mixture was extracted with ether and the ether extract was evaporated to give 0.810 g. (64.5% yield) of the crude isomer A. It was triturated with ether-petroleum ether (B.P. 30–60° C.) to give 0.588 g. of isomer A of 2-methyl-3-(1-aminoethyl)-1,3,4,5-tetrahydrobenz[cd]indole; M.P. 126–127° C.

G. Cleavage of isomer B with butylamine

A solution of the phthalimido derivative (isomer B of Part D, M.P. 169–170° C.) (2.54 g.; 7.4 mmoles) in 63 ml. of ethanol and 22 ml. of butylamine was refluxed for 72 hrs. under nitrogen. The pale yellow solution was evaporated to dryness in vacuo. Ether (100 ml.) and 10% hydrochloric acid (100 ml.) were added and the mixture was stirred for about an hour to give almost complete solution. The layers were separated and the aqueous acidic layer was extracted with ether. The acidic solution was cooled and basified with 30% aqueous potassium hydroxide solution. The mixture was extracted with benzene and the extract was evaporated to give 1.583 g. of a pale yellow oil. It was crystallized from benzene-petroleum ether (B.P. 30–60° C.) to give 0.13 g. of N,N'-dibutylphthalimide.

The filtrate obtained in the above crystallization from benzene-petroleum ether was evaporated to dryness, the residue was dissolved in ether, and the same acid extraction procedure was followed as above, the only difference being that ethyl acetate was used to extract neutral material from the acidic layer. The product amounted to 1.038 g. and showed no residual amide according to I.R. It was crystallized from ether-Skellysolve B to give 0.82 g. of isomer B of 2-methyl-3-(1-aminoethyl)-1,3,4,5-tetrahydrobenz[cd]indole; M.P. 101–102.5° C., unchanged on further recrystallization.

*Analysis*.—Calcd. for  $C_{14}H_{18}N_2$ : C, 78.46; H, 8.47; N, 13.07. Found: C, 78.52; H, 8.69; N, 12.87.

U.V.: 227 (35,400); 274 (6,950); 279 (7,050); f 289 (5,000).

I.R.: NH, 3160, 3100, 3050; C=C/NH def., 1623, 1663, 1585, 1510.

In place of dimethylamine in the amidation reaction there can be substituted other alkylamines, for example, methylamine, ethylamine, propylamine, butylamine, pentylamine, hexylamine, heptylamine, octylamine, diethylamine, ethylmethylamine, dipropylamine, dibutylamine,

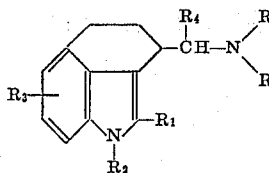
dipentylamine, dihexylamine, diheptylamine, dioctylamine, and the isomeric forms thereof. In place of the 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid, there can be substituted

- 1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1,2-dimethyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-(p-anisyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-methyl-2-(p-anisyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-(3,4,5-trimethoxy-phenyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-(p-hydroxyphenyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-(p-fluorophenyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-ethyl-2-(p-ethoxyphenyl)-6-benzyloxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-propyl-2-(p-propoxyphenyl)-7-methoxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-butyl-2-(p-butoxyphenyl)-8-benzyloxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1,2-diethyl-6-ethoxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-propyl-7-propoxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1,2-dibutyl-6-butoxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-(3,4-diethoxyphenyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-methyl-2-(3,4-dipropoxyphenyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-methyl-2-(p-chlorophenyl)-6-benzyloxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-methyl-2-(p-chlorophenyl)-6-hydroxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-(3,4-dibromophenyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-propyl-2-(3,4-diiodophenyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-ethyl-2-(3,4-dihydroxyphenyl)-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-phenyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6-benzyloxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6-hydroxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-methyl-6-benzyloxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 2-methyl-6-hydroxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 1-benzyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6-chloro-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6,7,8-trimethyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6,8-dichloro-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6,7-dimethoxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6,7,8-trimethoxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6,7-dibromo-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid,
- 6-ethoxy-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid, and
- 6-fluoro-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxylic acid.

In place of the acids in the amidation reaction there can be substituted the lower-alkyl esters. In place of methyl lithium there can be substituted ethyl, propyl, and butyl lithium.

I claim:

1. A compound of the formula:

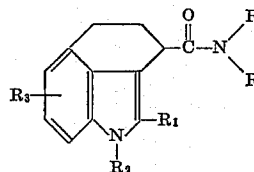


(I)

- wherein R is selected from the group consisting of hydrogen and loweralkyl; R<sub>1</sub> is selected from the group consisting of hydrogen, alkyl of from 1 to 4 carbon atoms, inclusive, phenyl, hydroxyphenyl, alkoxyphenyl wherein alkoxy is of not more than 4 carbon atoms, and halo-phenyl; R<sub>2</sub> is selected from the group consisting of hydrogen, benzyl and halobenzyl which can be substituted with alkyl or alkoxy of from 1 to 4 carbon atoms, inclusive, and alkyl of from 1 to 4 carbon atoms, inclusive; R<sub>3</sub> is selected from zero to three members of the group consisting of hydroxy, benzyloxy, alkyl of not more than 4 carbon atoms, halogen, and alkoxy of not more than 4 carbon atoms; and R<sub>4</sub> is selected from the group consisting of hydrogen and alkyl of not more than 4 carbon atoms.

2. 2-aminomethyl - 2 - methyl-1,3,4,5-tetrahydrobenz[cd]indole.
3. 3-dimethylaminomethyl - 2 - methyl-1,3,4,5-tetrahydrobenz[cd]indole.
4. 2-methyl-3-(1-aminoethyl)-1,3,4,5 - tetrahydrobenz[cd]indole.

5. A compound of the formula:



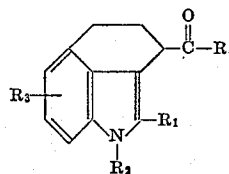
(III)

wherein R, R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub> are as given in claim 1.

6. 2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxamide.

7. N,N-2-trimethyl-1,3,4,5-tetrahydrobenz[cd]indole-3-carboxamide.

8. A compound of the formula:



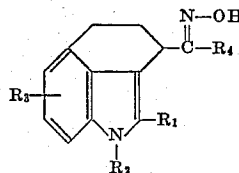
(IV)

wherein R<sub>4</sub> is alkyl of not more than 4 carbon atoms and R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub> are as given in claim 1.

9. 3 - alkanoyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole wherein the alkanoyl is from 2 to 5 carbon atoms, inclusive.

10. 3-acetyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole.

11. A compound of the formula:



(V)

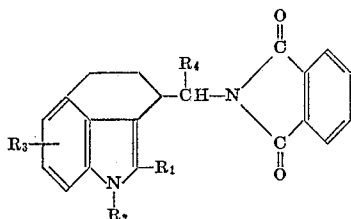
15

wherein  $R_4$  is alkyl of not more than 4 carbon atoms, and  $R_1$ ,  $R_2$ , and  $R_3$  are as given in claim 1.

12. 3-alkanoyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole oxime wherein alkanoyl is from 2 to 5 carbon atoms, inclusive.

13. 3-acetyl-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole oxime.

14. A compound of the formula:



(VI)

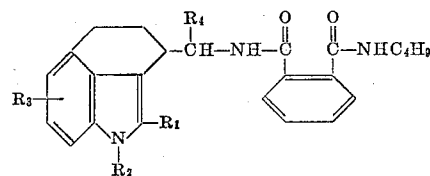
wherein  $R_4$  is alkyl of not more than 4 carbon atoms and  $R_1$ ,  $R_2$ , and  $R_3$  are as given in claim 1.

15. 3-(1-phthalimidoalkyl)-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole wherein the alkyl of phthalimidoalkyl is of from 2 to 5 carbon atoms, inclusive.

16. 2-(1-phthalimidoethyl)-2-methyl-1,3,4,5-tetrahydrobenz[cd]indole.

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17. A compound of the formula:



(VII)

18. N-[2-methyl-1,3,4,5-tetrahydrobenz[cd]indole-3-(1-alkyl)]-N'-butylphthalamide wherein the 1-alkyl is of from 2 to 5 carbon atoms, inclusive.

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