in the ultracentrifuge, as are polysaccharides generally.

With respect to immunological homogeneity it has been established by several investigators that proteins which are non-homogeneous in the ultracentrifuge, electrophoretically and in amino acid composition may be immunochemically uniform.

The relationship of amino acid composition to specificity among the blood group substances is not clear from the data presented. Work on the inhibition by oligosaccharides of the precipitation of blood group substances with specific antibody suggests that the carbohydrate presents binding sites for the immunological reaction. In view of the general similarity of amino acid composition, it is possible that the amino acids function to maintain the structure of the blood group substances. This assumes that the samples are molecularly homogeneous. Because of the differences in amino acid composition among samples belonging to the same group, it is more likely that at least a part of the amino acids found are remnants of enzymatic digestion and play no role in specificity. A less appealing possibility is that a variety of protein-carbohydrate molecules are identically specific as blood group substances. The isolated samples would thus be molecules having a variety of compositions. Further elucidation of the function of the amino acids in blood group substances will have to await the preparation of more uniform materials or a demonstration of their inherent heterogeneity.

[Contribution from the Lilly Research Laboratories and the Converse Memorial Laboratory of Harvard University]

The Total Synthesis of Lysergic Acid

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Lysergic acid, the basic fragment derived from the ergot alkaloids, has been synthesized in a fifteen-stage sequence beginning with 33-carboxyethylindole. The starting material was converted to the intermediate 1-benzoyl-5-keto-1,2,2a,3,4,5,6,7,7a,8,8a,9-octahydroindolo[4,3-f][4,5,6,7,8,9]octahydroindolo[4,3-f][4,5,6,7,8,9]-octahydroindolodol(4a)-quinoline (69), and thence to lysergic acid. The synthetic acid was converted to dl-isolysergic acid hydrazide which had previously been resolved and converted to ergonovine. The present work, therefore, completes also the synthesis of this ergot alkaloid.

The striking physiological properties of ergot early directed attention to this remarkable product of the growth of the fungus Claviceps purpurea on rye grain. Pre-Christian allusions to its effects have been recorded, and it was identified in 1676 as the causative agent of the dreaded medieval gangrenous scourge, St. Anthony's Fire. The therapeutic powers of ergot were likewise recognized during the middle ages. Its capacity to induce uterine contractions was recorded as early as 1582, and crude preparations were introduced into orthodox medicine early in the nineteenth century. However, its present important position in medical practice was made possible only by the extensive researches of the past forty years on the isolation and characterization of the pure active principles. These elegant investigations, in which Arthur Stoll has played a dominant role, have led to the isolation of no less than six related bases all of which have been shown to be amides of the same key substructure, lysergic acid.

The present work, therefore, completes also the synthesis of this ergot alkaloid.

[1] Harvard University; other authors, The Lilly Research Laboratories.
[4] W. Jacobs and L. Craig isolated lysergic acid J. Biol. Chem., 104, 547 (1934) and 106, 393 (1934) and deserve the major credit for the determination of its structure. Their deductions were incomplete only in respect to the placing of one double bond, and stereochemical points. These final details were established by Stoll [A. Stoll, A. Hofmann and F. Troxler, Hei., Chem. Acta, 25, 506 (1949); A. Stoll, Th. Petrizlka, J. Rutschman, 37, 2039 (1944)]. A comprehensive account of the structural work is given in a review by A. Glenn.
The synthesis of dihydrolysergic acid was stimulated even before the structural issues were resolved in 1949. This attention was evoked by the unique polycyclic system present in the acid and by the medical applications of the derived natural bases. The synthesis of dihydrolysergic acid itself. More recently, interest in the synthesis has been heightened by the discovery of the large-ring lactone structure \(\text{LSD}\) to induce abnormal psychic states. In this communication we describe the synthesis of dihydrolysergic acid.

Benzoyl-3-(\(\alpha\)-carboxyethyl)-dihydroindole \(5\) \(\text{C}_5\text{H}_7\text{CON}\) was converted by thionyl chloride in ether solution to the corresponding acid chloride, and thence directly, by the action of aluminum chloride in carbon disulfide or ethylene dichloride, to the ketone \(4\). It is of some interest that when the Friedel-Crafts reaction was carried out in benzene solution, the sole product was the phenyl ketone \(6\). Attempts to effect direct cyclization of the acid \(5\) to \(4\) with sulfuric acid or hydrogen fluoride were un-

\[\begin{align*}
\text{CH}_3 & \quad \text{CO} \\
\text{COOH} & \quad \text{NCH}_3 \\
\text{CON} & \quad \text{NH} \\
\text{CH}_2 & \quad \text{CO} \\
\text{R} & \quad \text{N} \\
\text{CON} & \quad \text{CO}
\end{align*}\]
derivatives (7, R = Me or Et) were prepared by condensation of the appropriate oxalic ester with the corresponding ester of 5 in the presence of alkoxides. When these esters were heated with 80% sulfuric acid, hydrolysis and decarboxylation occurred smoothly, with the formation of the α-keto acid 8, but no cyclization to a dihydronaphthalene (cf. 9) was observed.12

The tricyclic ketone 4 was hydrolyzed readily by aqueous hydrochloric acid to the free base (10, R = H), which was dehydrogenated by palladium-charcoal in p-cymene to the known 5-keto-1,3,4,5-tetrahydrobenz[cd]indole (11).14 On the other hand, 4 itself, and the corresponding N-acetyl ketone (10, R = Ac), which was prepared either by acetylation of 10 (R = H), or by aluminum chloride-catalyzed cyclization of the chloride of N-acetyl-3-(β-carboxethyl)-dihydropindole, were dehydrogenated under similar conditions to the naphthalenoid compounds (12, R = Bz or Ac). The stabilization of the naphthalene system in the N-acetylated series as a result of the suppression of interaction between the nitrogen atom and the carbonyl group in the ketonic isomers (cf. 11, arrows) has been commented upon by Grob.13 These dehydrogenation studies early in the work tended to confirm the soundness of the synthetic approach based on dihydropindole derivatives. In addition they indicated that the conversion to the indole system would have to be carried out using compounds in which the nitrogen function was in the free base form.

Most of the substances described in the present work fell into one or another of several well-defined structural classes, which could be recognized readily by characteristic ultraviolet and infrared spectra, and liberal use was made of this valuable control. The chromophoric systems present in 4 gave rise to absorption at 5.91 (ketone carbonyl) and 6.07 μ (amide carbonyl) in the infrared, and at 235 and 326 μ in the ultraviolet (cf. Fig. 1).

All of our subsequent synthetic experiments were based upon the tricyclic ketone 4.

**Direct Introduction of Nitrogen at C.4.**—The presence, in the tricyclic ketone 4, of an activated methylene group at C.4, suggested that the construction of ring D of lysergic acid might be initiated by the attachment of the requisite nitrogen atom at the reactive position.

The 4-bromo derivative 13, an obvious intermediate for such studies, was obtained in excellent yield by bromination of the tricyclic ketone with either bromine or pyridine hydrobromide perbromide. However, early attempts to utilize this compound in the alkylation of amines were un promising. For instance, the reaction of the bromo ketone 13 with methylamine, even at room tem-
perature, took a complicated course and led in fairly good yield to the naphthalene derivative 14. In addition, initial experiments designed to obtain the potentially useful ketal-ketone 16 by alkylation of methylaminoacetone ethylene ketal 15 were like-

\[
\begin{align*}
\text{CH}_3 & \quad \text{NHCH}_3 \\
\text{C}_6\text{H}_5\text{CON} & \quad \text{15} \\
\end{align*}
\]

wise unsuccessful. The side chain amine 15 was obtained by reaction of methylamine with either chloro- or bromoacetone ethylene ketal.\(^\text{(14)}\) Further discussion of these alkylations and of the ketal-ketone 16 will be deferred until a later section.

Meanwhile, much of the early effort was directed toward the synthesis of the \(\alpha\)-amino ketone 17. The preparation of the \(\alpha\)-oximinoketone 18 by condensation of 4 with butyl nitrite in the presence of potassium ethoxide proceeded smoothly, but the desired reduction of 18 could not be brought about. On the other hand, treatment of the \(O\)-toluenesulfonyl derivative of the oxime of 4 with potassium ethoxide, followed by acid, gave the desired 17, as hydrochloride, in good yield.\(^\text{(15)}\) The free base, however, decomposed immediately on liberation from its salt, and in our hands was of little further synthetic utility. Another sequence of reactions which led into the 4-amino series was initiated by condensation of 4 with ethyl formate, or methyl oxalate, in the presence of sodium methoxide. These reactions afforded 19 and 20, respectively.\(^\text{(16)}\) When the hydroxymethylene compound 19 was treated with hydrazoic acid in trifluoroacetic acid in the presence of sulfuric acid, the major product was the cyano-ketone 21, though the desired 4-formylamino ketone 22 was formed concomitantly in low yield. Similar treatment of the

\[
\begin{align*}
\text{CH}_3 & \quad \text{NH}_2 \\
\text{C}_6\text{H}_5\text{CON} & \quad \text{17} \\
\end{align*}
\]

\[
\begin{align*}
18, R & = \text{NOH} \\
19, R & = \text{CHOH} \\
20, R & = \text{C} - \text{COOCH}_3 \\
\end{align*}
\]

\[
\begin{align*}
O & \quad R \\
\text{C}_6\text{H}_5\text{CON} & \quad \text{21, } R = \text{CN} \\
\text{C}_6\text{H}_5\text{CON} & \quad \text{22, } R = \text{NHCHO} \\
\end{align*}
\]

methoxalyl compound 20 gave the oxazole 23 in poor yield; the Schmidt reaction had evidently proceeded normally with subsequent cyclodehydration. Hydrolysis of either the ester 23, or the formylamino compound 22, gave the simple amino-ketone 24, which like 17 was deemed too sensitive to be useful.

\[
\begin{align*}
\text{COOMe} & \quad \text{20, } R = \text{CN} \\
\text{C}_6\text{H}_5\text{CON} & \quad \text{23} \\
\text{C}_6\text{H}_5\text{CON} & \quad \text{24} \\
\end{align*}
\]

In the hope that 4-alkylamino ketones might be prepared by the action of amines on oxides of the type 25, the ketone 4 was converted into the enol acetate (26, \(R = \text{Ac}\)) and the enol ethyl ether (26, \(R = \text{Et}\)) by the action of isopropenyl acetate and ethyl orthoformate, respectively. When these enol derivatives were treated with peracids, however, the product isolated was the hydroxyketone 27.\(^\text{(17)}\) Some oxides of the type 25 have been reported in \(19 \text{412}\) to be formed by the action of peracids on the enol acetates of the 17-keto-steroids.
The ultraviolet absorption is at 264 μm (Fig. 2, curve A). The corresponding saturated compound

![Graph showing ultraviolet absorption](image)

absorbs at 267 and 292 μm (Fig. 3, curve A). We further took advantage of having in hand these simple compounds of known structure by replacing the N-benzoyl groups by N-acetyl functions. The resulting amide II possesses bands at 241, 254, 307, and 316 μm (Fig. 2, curve B), while the bands of the saturated analog III are at 213, 253, 279, and 289 μm (Fig. 3, curve B).

The oxide II was typical of its class in that it was readily converted to a bromohydrin III with hydrogen bromide in benzene-ether, and rearranged to the β-tetralone (35) by magnesium bromide.\(^{(19)}\)

Of greater synthetic interest was the smooth reaction of 29 with amines. With methylvamine at 100\(^{\circ}\), for example, the simple alkanolamine 36 was produced, while under similar conditions, methylvaminoacetone ethylene ketal 15 gave the ketal alcohol 37.\(^{(20)}\) Numerous attempts to effect the oxidation of 37 to the corresponding amino-ketone 16 were un-

![Reaction scheme](image)

successful. Reaction of 36 with bromoacetone gave a substance which we formulate as the hemiketal 38 in view of the absence of a carbonyl band below 6 μ in its infrared spectrum, and its ready conversion to a methyl ether 39 with methanolic hydrogen chloride. The ether 39 was obtained also from 37 by treatment with hydrogen chloride in methanol. Like 37, 38 could not be oxidized to any well-defined product.

\(^{(20)}\) No rigorous proof of the direction of opening of this oxide with amines was obtained. However, in the 5-substituted-4,5-epoxy series described below reaction with amines takes place at the 4-position.
Addition of a Carbon Chain at C.5.—An obvious alternative for building ring D of lysergic acid involved the elaboration of a carbon chain at C.5. The capacity of the carbonyl group in the tricyclic ketone 4 to undergo addition reactions was therefore utilized.

The initial attempt in that direction involved the Reformatsky reaction. When 4 was treated with methyl or ethyl bromoacetate in the presence of zinc, and the resulting crude hydroxy-ester was warmed with formic acid, the unsaturated ester (40, \( R = \text{Me or Et} \)) was obtained. The \( \beta,\gamma \) position of the double bond in these esters was easily demonstrated by ultraviolet measurements (vide supra). It is of some interest that only the unconjugated isomers were isolated. The acid (40, \( R = \text{H} \)), obtained by careful alkaline hydrolysis of either ester (40, \( R = \text{Me or Et} \)), was then converted to the bromoketone 41 in excellent yield through successive treatments with oxalyl chloride in toluene, diazomethane in methylene chloride, and aqueous hydrobromic acid. Reduction of the bromoketone with sodium borohydride furnished directly the oxide 42; clearly the medium was sufficiently basic to effect dehydrobromination of the intermediary bromohydrin. Perbenzoic acid was then used to effect addition of an oxygen atom to the isolated double bond of 42, and the dioxide 43 was obtained.

With methylamine at 100°, the latter yielded an amorphous, tertiary, tetracyclic base, characterized as the crystalline methiodide. There is little doubt that the substance possesses the structure 44, and in view of its close relation to other tetracyclic substances, described below, it seems likely that intensive further investigation should have enabled us to connect this series with our other synthetic routes. However, the low over-all yield in the conversion of 4 to 44, which may be attributed in the main to an insufficient opportunity for stereochemical control, and the availability of superior paths, led us not to make the effort.

Another attempt to utilize the Reformatsky ester (40, \( R = \text{Me} \)) foundered early on a point of sufficient interest to merit description.

Conversion to the corresponding oxide 45 was easily effected by monoperphthalic acid. We hoped that 45 would yield the diester 46 on treatment with sarcosine methyl ester and were encouraged by the observation that methylamine at 100° gave the lactam 47. However, the changes depicted in (48, arrows) occurred so readily in the experiment with sarcosine ester that the lactone 49 was the sole product.

The Unsaturated Aldehyde 50.—The unsaturated aldehyde 50 containing as it does a very reactive carbonyl group, and a point of entry for the introduction of substituents at C.4, occupied a central position in many schemes for the elaboration of ring D. Furthermore, it was found to be readily preparable from the tricyclic ketone 4, through the corresponding glycidic ester (31, \( R = \text{Et} \)) obtained from the ketone by treatment with ethyl chloroacetate in the presence of potassium \( t \)-butoxide. The ester was smoothly hydrolyzed to the sodium salt (31, \( R = \text{Na} \)), which was converted to the saturated aldehyde 52 with mineral acids, or

\[
\text{(21) W. S. Johnson, J. S. Belew, L. J. Chinn and R. H. Hunt have independently discovered the superiority of this catalyst in the Darzens reaction [This Journal, 76, 4095 (1953)].}
\]
July 5, 1956  THE TOTAL SYNTHESIS OF LYSERGIC ACID  3093
directly to derivatives of that compound with appropriate carbonyl reagents. Our major interest in the sodium salt, however, was excited by the observation that it gave the semicarbazone of 50 simply and in high yield when it was treated successively, in acetonitrile solution, with pyridine hydrobromide perbromide and semicarbazide. The free aldehyde 50 was readily obtained from the derivative by exchange of the semicarbazide residue to pyruvic acid.

The synthetic opportunities presented by the unsaturated aldehyde were exploited, inter alia, in at least three directions: i. With ethylene glycol and toluenesulfonic acid, the aldehyde was converted to the ethylene acetal 53, which was smoothly oxidized by perbenzoic acid to the oxide 54. The latter reacted with methylamine at 120° to give the base 55, which in turn combined readily with acrylonitrile to give 56. It will not be difficult to imagine the uses to which we wished to put the nitrile 56; but the recalcitrance of the acetal function stood in the way of all of them. With methanolic hydrogen chloride, for example, the ester 57 was formed, while 6 N hydrochloric acid gave 58; hot 90% acetic acid removed the β-cyanoethyl chain, and gave the familiar 55. Attempts to remove the offending function by more brutal means led only to deep-seated changes of no utility.

ii. The unsaturated nitrile 59 was easily obtained from the aldehyde 50, through treatment of the corresponding oxime with thionyl chloride. Conversion of the 4,5-double bond to an oxide function, by means of alkaline hydrogen peroxide, was accompanied by hydration of the nitrile group, and the epoxyamide 60 was obtained in substantially quantitative yield. Like other 4,5-oxides, 60 was susceptible to attack by amines; with methylenamino...
acetone ethylene ketal, the base 61 was readily obtained. The remaining task in this series is the conversion of the α-hydroxyamide function to a carbonyl group. It remains undone; the most novel of the various results obtained in this effort was the formation of the pentacyclic lactone 62 when the amide was treated with red lead oxide in acetic acid, in an attempt to bring about oxidative cleavage of the group at C.5.

iii. The aldehyde 50 was converted to the epoxyalcohol 64 by either of two methods. In the first, and preferred method, alkaline hydrogen peroxide was used to convert the aldehyde to the corresponding oxide 63, which was then reduced with sodium borohydride. Alternatively, the latter reagent was used to convert 50 to the unsaturated alcohol 65, which was oxidized to 64 by perbenzoic acid. This method suffered from the concomitant formation of a certain amount of the dihydro alcohol 66 in the reduction step. Although this difficulty was overcome by the use of Ponnendorf reduction, the oxidation stage was relatively inefficient.

Reaction of the epoxyalcohol 64 with methylaminoacetone ethylene ketal 15 gave, although in poor yield, the desired amino glycol 67, which was very smoothly oxidized to the ketone 68 by slightly more than one mole of periodate in acid solution. The important intermediate ketal-ketone 68 thus became available in an eleven-stage sequence from the tricyclic ketone 4. However, both the length and the inefficiency of this route led us once again to re-examine the possible direct preparation of 16 from the bromoketone 13. In a new series of experiments it was discovered that reaction of 13 with methylaminoacetone ethylene ketal 15 in a non-polar solvent afforded the ketal-ketone 16 in excellent yield. The cumbersome earlier route, therefore, could be abandoned.

**The Tetracyclic Series.**—With the obtention of the ketone 16, the stage was set for entry into the tetracyclic phase of our work. Thus, it may be noted that the intermediate contains, actually or potentially, all of the functions necessary for closure of ring D, and for attachment of the lysergic acid carboxyl group as well.

The first step was taken with the hydrolysis of 16 to the diketone 68, best effected by treatment with 6 N hydrochloric acid. The diketone was then smoothly cyclized, by sodium methoxide in absolute ethanol, to the tetracyclic unsaturated ketone 69, which in turn was converted to the protected unsaturated alcohol 70, by successive treatments with acetic anhydride and sodium borohydride, or vice versa. It is worthy of note that the ketones of this series are susceptible to very ready aerial oxidation. Thus, in an attempt to effect the acetylation of 68 with acetic anhydride in methanol, the sole product isolated was 88. Special attention may be directed to the facile dehydrogenation of the N-acetyl derivative of the tetracyclic ketone 69 to the interesting betaine (ix), and the reduction of the latter by sodium borohydride to an unsaturated alcohol x isomeric with 70.
It was now necessary to replace the hydroxyl function in 70 by a carboxyl group. An initial attempt in that direction was based on the observation of Price and Krishnamurti\(^{(27)}\) that allyl alcohol is easily and directly converted to allyl cyanide by treatment with cuprous cyanide in concentrated hydrochloric acid. However, when the allylic alcohol 70 was treated under similar conditions with the aim of exchanging \(-\text{OH}\) for \(-\text{CN}\), it was transformed simply into the epimeric alcohol 71.\(^{(28)}\)

Nevertheless, the result was encouraging insofar as it suggested that carbonium ion reactions at C.9 were practicable. We next treated the alcohol 70 with liquid hydrogen cyanide in the presence of sodium borohydride. The chloride was extraordinarily susceptible to hydrolysis to the alcohol 71, and initial attempts to replace the chlorine atom by a cyano group in hydroxycarbonyl solvents were seriously complicated by the formation of the alcohol 71 and corresponding ethers. The difficulty was surmounted by treating the hydrochloride of 73 with excess sodium cyanide in anhydrous liquid hydrogen cyanide, under which conditions the desired nitrile 74 was formed in good yield. Methanolysis of 74 catalyzed by sulfuric acid gave the ester (75, \(R = \text{Me}\)), which was hydrolyzed by hydrochloric acid or by sodium hydroxide to the corresponding acid (75, \(R = \text{H}\)).

Two hydrogen atoms, placed by design at C.5 and C.5a to deprive our synthetic operations of the dangers attendant upon the presence of an indole ring, now alone remained to be eliminated. The position of these atoms, as components of a dihydroaromatic system, provided a basis for supposing that they should be relatively readily removed, and dehydrogenation studies were taken in hand. As was the case in our earlier experiences with related N-acyl derivatives (\textit{vide supra}, 10 \(\rightarrow\) 12), the N-acyl derivative of the ester (75, \(R = \text{Me}\)) was converted by palladium-charcoal in boiling xylene to the known naphthalenoid compound 76.\(^{(30)}\) On the other hand, when the sodium salt of the acid (75, \(R = \text{H}\)) was treated in boiling water with Raney nickel, disproportionation occurred, with formation of 77. Under these conditions generation of the desired indole system was accomplished, but reduction of the double bond in ring D took place as well.

Subsequent studies obviated these difficulties; in similar experiments in which heat-deactivated Raney nickel was used as dehydrogenation catalyst in the presence of sodium arsenate,\(^{(31)}\) \(dl\)-lysergic acid (78) was the sole product isolated.

\(^{[27]}\) C. Price and I. Krishnamurti, \textit{This Journal}, 72, 5334 (1950).
\(^{[28]}\) The stereochemistry implied in the formulas 70 and 71, and the complete solution, symbolized for 71 in xi, may be developed as follows: (a) The tightly fused A/B/C ring system can be constructed only with a quasi-axial hydrogen atom at C.5a. (b) C.6a will enjoy the stabler of the two possible orientations, i.e., that containing a quasi-equatorial C-N bond; since opportunities for equilibration have been provided in both the tricyclic and tetracyclic classes (cf. 68 and 69), by the proximity of a carbonyl or a vinylogous carbonyl function. (c) Sodium borohydride reduction of carbonyl groups ordinarily leads to equatorial alcohols (cf. 70); furthermore, the relative basicity of 70, \(pK_a\) 6.02 and 6.68 confirms our assignment, in that stabilization of the conjugate acid by hydrogen bonding is possible in the stronger base 71, but not in 70. A related case, that of quinine and epquinine, is discussed by R. Turner and R. Woodward (R. Manske and H. Holmes, "The Alkaloids," Academic Press, Inc., New York, N. Y., 1958, p. 32). Assignment of the configurations of the epimeric 10-hydroxydihydrodesoxycocaine was recently made in a similar fashion (H. Rapport and S. Masamune, \textit{This Journal}, 77, 4830 (1955)).

\(^{[29]}\) J. Ritter and J. Kalish, \textit{ibid.}, 70, 4048 (1948).
COOH

The synthetic dl-lysergic acid was converted, through its methyl ester, into dl-isolysergic acid hydrizide.\(^{12}\) The acid and the hydrizide were shown to be identical with samples prepared\(^{22,23}\) from natural materials by comparison of melting points, mixture melting points, infrared and ultraviolet spectra, X-ray powder diagrams, pK\(\alpha\)'s, and paper chromatographic behavior.

Since dl-isolysergic acid hydrizide has already been resolved and converted to ergonovine,\(^{24}\) the present work completes the synthesis of that alkaloid as well as that of lysergic acid.

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Experimental

Melting points were determined in soft glass capillary tubes and are uncorrected. Ultraviolet and infrared measurements were used for control purposes throughout the investigation, and spectra of all pure substances prepared were determined. However, in the sequel, spectra are recorded ordinarily only for the substances in the main line of the synthesis and for key model compounds. In each case, the infrared measurements, the abscissa is plotted in wave lengths (2.6–12 \(\mu\)) and the ordinate in percent transmission (0 to 100\%). The measurements were made on a Beckman IR 2-T automatic recording spectrophotometer. Determinations were run at 0.15 molar concentration in 20 to 30% hydroxide. The solution was mixed with about 100 g. of Raney nickel catalyst and hydrogenated at room temperature in a steel hydrogenation bomb at 3000 to 4000 pounds per square inch pressure. Reduction was usually complete, and the solution was cooled. If the reduction was incomplete, unreacted indole-propionic acid separated at this point and was removed by filtration. The filtrate was then benzoylated by the Schotten–Baumann procedure using 210 ml. of 12 N sodium hydroxide and 180 ml. of benzoyl chloride. The solution was kept alkaline throughout the benzoylation, and the temperature was kept below 40\(^{\circ}\) by cooling. When the benzoyl chloride was completely reacted, the mixture was cooled and acidified with 300 ml. of concentrated hydrochloric acid. The crude product was filtered and washed with water, after which it was extracted with four 1-l. portions of hot water to remove benzoic acid. The hot sirupy product, after decantation of the aqueous extract, was crystallized from a few volumes of methanol. The acid was filtered and washed with a little cold methanol; yield 103 g. (70%), m.p. 151–153\(^{\circ}\).

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[\(d\)]indole (4).—1-Benzoyl-3-(\(\beta\)-carboxyethyl)-2,3-dihydroindole, 118 g. (0.4 mole), was mixed with 200 ml. of pure thionyl chloride. The solution was allowed to stand for one-half hour, after which it was warmed gently for 15–20 minutes on the steam-bath. Excess thionyl chloride was evaporated completely below 30\(^{\circ}\) in vacuo, and the crude acid chloride was dissolved in 200 ml. of dry carbon disulfide. The solution of the acid chloride was then added in a thin stream to a vigorously stirred suspension of 240 g. of aluminum chloride in 1750 ml. of carbon disulfide contained in a 5-i. flask (hood!). A complex separated and stirring became difficult. The mixture was heated under reflux and stirred for one hour to complete the reaction, after which it was decomposed completely very carefully by adding 500 g. of ice, 250 ml. of concentrated hydrochloric acid and 500 ml. of water. During the decomposition, stirring was maintained, and cooling was effected by periodic distillation of the carbon disulfide in vacuo. When the decomposition was complete, any carbon disulfide remaining was removed completely in vacuo, and the product was extracted with 2 l. of benzene. The extract was washed thoroughly with 500 ml. of 2 N sodium hydroxide in three portions and then with water. It was dried over magnesium sulfate and then evaporated to small volume in vacuo. Show addition of several volumes of ether caused the yellow ketone to crystallize. It was filtered and washed with ether; yield 85.3 g. (77%, m.p. 146–147\(^{\circ}\)). A sample was recrystallized from benzene-ether.

Anal. Caled. for \(\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2\): C, 81.75; H, 5.64; N, 5.50. Found: C, 81.78; H, 5.59; N, 5.15.

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[\(d\)]indole Semicarbazone.—A mixture of 1.5 g. of N-benzyol-5-keto-1,2,2a,3,4,5-hexahydrobenz[\(d\)]indole, 1.5 g. of semicarbazide hydrochloride and 2.25 g. of anhydrous sodium acetate was added to 40 ml. of ethanol and 2 ml. of water. The solution was warmed with a little dilute sodium hydroxide, and the hot solution was cooled and acidified with 300 ml. of concentrated hydrochloric acid. After the indole was dissolved, a few volumes of methanol. The acid was filtered and washed with ether; yield 85.3 g. (77%), m.p. 146–147\(^{\circ}\). A sample was recrystallized from dilute acetic acid.

Anal. Caled. for \(\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2\): C, 68.25; H, 5.43; N, 5.86. Found: C, 68.05; H, 5.64; N, 5.86.

1-Benzoyl-3-benzoylethyl-2,3-dihydroindole (6).—In the above Friedel–Crafts cyclization procedure, if benzene was used as solvent in place of carbon disulfide, acylation of the benzene took place rather than cyclization. The product was crystallized from ethanol; m.p. 101–102\(^{\circ}\), yield 52%.


1-Benzoyl-o-oxo-3-indolinebutyric Acid (8).—Diazomethane was prepared from 55 g. of nitromethane and 150 ml. of 40% potassium hydroxide in 500 ml. of ether in the


usual way. The ether solution was dried over solid potassium hydroxide. Methanol (10 ml.) was added, and 60 g. of 1-benzoyl-3-β-carboxyethyl-2,3-dihydroindole was then added in portions with shaking and cooling in an ice-bath. When reaction was complete, the solution was concentrated in vacuo below 25°, and the residue was dissolved in 400 ml. of ether. The solution was washed well with dilute hydrochloric acid and with 5% aqueous sodium bicarbonate, then dried over magnesium sulfate, and concentrated in vacuo. The 1-benzoyl-3-β-carboxyethyl-2,3-dihydroindole so obtained did not crystallize but was adequately pure for use in isolation reaction below; yield 62.5 g. (90%).

The methyl ester was mixed with 300 ml. of dry ether, 38 g. of methyl oxalate and 12.5 g. of sodium methoxide, and the mixture was heated under reflux for 16 hours. It was evaporated to dryness in vacuo, below 25°, and the residue was dissolved in 400 ml. of concentrated hydrochloric acid and heated on a steam-bath for 20 minutes, during which time the temperature was in the range of 68 to 92°. The solution was poured onto an excess of ice, and the product was filtered, washed with water, and dried in vacuo. It was crystallized from a mixture of benzene and diisopropylamine. The crystalline product was filtered, washed with water, and dried in vacuo. It was filtered and washed with dilute hydrochloric acid and then dried on carbon and 30 ml. of β-cymene. The mixture was placed in a 3-l., three-necked bomb which was placed in 71.0 g. (0.375 mole) of 3-indolepropionic acid, 15.0 g. (0.375 mole) of sodium hydroxide, seven teaspoonsful of (about 71 g.) of Raney nickel catalyst, and distilled water to make the volume 450 ml. This mixture was hydrogenated for about 20 hours at a pressure of 4300 lb. per square inch at room temperature. The catalyst was filtered, and the filtrate was acidified with 65 ml. of concentrated hydrochloric acid. Yield 18.4 g. (51%), m.p. 160-161° dec.

The solution was treated with carbon, filtered and excess potassium hydroxide solution, and then with distilled water until the filtrate was neutral. The nitrobenzene was steam distilled, and the residual crystalline product was filtered; yield 0.3 g. (15%), m.p. 157-158°. Anal. Calcd. for C_{11}H_{11}SO.HCl: C, 63.01; H, 5.77.

I-Acetyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole.-In a 1-l. round-bottomed flask was placed 71.0 g. (0.276 mole) of 3-indolepropionic acid, 15.0 g. (0.375 mole) of sodium hydroxide, seven teaspoonsful of (about 71 g.) of Raney nickel catalyst, and distilled water to make the volume 450 ml. This mixture was hydrogenated for about 20 hours at a pressure of 4300 lb. per square inch at room temperature. The catalyst was filtered, and the filtrate was acidified with 65 ml. of concentrated hydrochloric acid. Yield 18.4 g. (51%), m.p. 160-161° dec.

The methoxalyl ester was dissolved in 265 ml. of 77% sulfuric acid and heated on a steam-bath for 20 minutes, during which time the temperature was in the range of 68 to 92°. The solution was poured onto an excess of ice, and the product was filtered, washed with water, and dried in vacuo. It was crystallized from a mixture of benzene and diisopropylamine; yield 18.4 g. (51%), m.p. 160-161° dec.

The solution was treated with carbon, filtered and excess potassium hydroxide solution, and then with distilled water until the filtrate was neutral. The nitrobenzene was steam distilled, and the residual crystalline product was filtered; yield 0.3 g. (15%), m.p. 157-158°. Anal. Calcd. for C_{11}H_{11}SO.HCl: C, 63.01; H, 5.77.

5-Keto-1,2,2a,3,4,5-tetrahydrobenz[cd]indole (10).-1-Benzoyl-5-keto-1,2,2a,3,4,5-tetrahydrobenz[cd]indole, 30 g., was mixed with 300 ml. of concentrated hydrochloric acid and 225 ml. of glacial acetic acid, and the solution was heated under reflux for 16 hours. It was evaporated to dryness in vacuo, and the residue was dissolved in water. The solution was treated with carbon, filtered, and excess ammonium hydroxide was added to the filtrate. The crude yellow ketone was filtered and recrystallized from ethanol, m.p. 177.5-178.0 (yellow prisms). The solution was filtered, washed with water, and dried in vacuo. It was filtered and washed with dilute hydrochloric acid and then dried on carbon and 30 ml. of β-cymene. The mixture was placed in a 3-l., three-necked bomb which was placed in 71.0 g. (0.375 mole) of 3-indolepropionic acid, 15.0 g. (0.375 mole) of sodium hydroxide, seven teaspoonsful of (about 71 g.) of Raney nickel catalyst, and distilled water to make the volume 450 ml. This mixture was hydrogenated for about 20 hours at a pressure of 4300 lb. per square inch at room temperature. The catalyst was filtered, and the filtrate was acidified with 65 ml. of concentrated hydrochloric acid. Yield 18.4 g. (51%), m.p. 160-161° dec.

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1-Benzoyl-5-hydroxy-1,2-dihydrobenz[cd]indole (12).—A mixture of 20 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 20 g. of 5% palladium-on-carbon in 350 ml. of xylene was heated under reflux for 16 hours. The catalyst was filtered and washed with ethyl Cellosolve. The filtrate was concentrated, and the product was filtered; yield 8.45 g. (42%); m.p. 230–231°C. Recrystallization from a mixture of chloroform and methanol raised the melting point to 231–235°C.

Anal. Calcd. for C_{12}H_{10}O_{2}: C, 78.19; H, 5.90; O, 15.91. Found: C, 78.20; H, 5.92; O, 16.01.

1-Benzoyl-5-acetoxy-1,2-dihydrobenz[cd]indole. —1-Benzoyl-5-hydroxy-1,2-dihydrobenz[cd]indole (6.2 g.) was dissolved in a mixture of 60 ml. of acetic anhydride and 60 ml. of pyridine. The solution was warmed on a steam-bath for one hour, and the solvents were distilled under reduced pressure. The ester was crystallized from ethyl acetate; yield 2.05 g. (90%); m.p. 162–168°C. The ultraviolet absorption spectrum was identical to that reported by Grob and Voltz.41

Anal. Calcd. for C_{14}H_{13}O_{3}: C, 74.95; H, 5.59; O, 20.56. Found: C, 74.80; H, 5.60; O, 20.40.

1-Acetyl-5-hydroxy-1,2-dihydrobenz[cd]indole (12).—A mixture containing 2.0 g. of 1-acetyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 3.0 g. of 5% palladium-on-carbon in 30 ml. of p-cymene was heated under reflux for one hour. The solvent was distilled in vacuo, and the residue was extracted with hot methanol and chloroform. The evaporation of the chloroform was evaporated, and the residue was taken up in chloroform. The product was filtered (0.25 g.) and recrystallized from a mixture of acetic acid and methanol, m.p. 269–270°C. (Dec.)

Anal. Calcd. for C_{12}H_{10}O_{2}: C, 78.19; H, 5.90; O, 15.91. Found: C, 75.20; H, 4.01; O, 4.62.

The ultraviolet absorption spectrum was identical to that reported by Grob and Voltz.41

1-Benzoyl-4-isonitroso-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole. Potassium Salt. —A mixture of 100 ml. of anhydrous toluene and 0.5 ml. of absolute alcohol was added to a flask protected from atmospheric moisture. To this was added 0.9 g. (0.023 atom) of potassium with stirring and warming to speed solution. At this point, 5.55 g. (0.02 mole) of 1-benzoyl-5-keto-1,2a,3,4,5-hexahydrobenz[cd]indole suspended in 75 ml. of anhydrous toluene was added, and the mixture was warmed until the ketone had dissolved; immediately the solution was cooled; 5 ml. (0.0456 mole) of butyl nitrite was added, and the reaction mixture was stirred for 4 hours at room temperature, and allowed to stand for three days. The solid product obtained by filtration weighed 6.8 g. (100%); after washing with anhydrous ether, m.p. 167–169°C (Dec.). A sample was recrystallized from absolute ethanol, m.p. 159–160°C.

Anal. Calcd. for C_{26}H_{22}KNO_{3}: C, 67.25; H, 4.97; N, 5.10. Found: C, 67.34; H, 5.08; N, 5.09.

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole Oxime. —A mixture of 41.7 g. (0.15 mole) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole, 17.4 g. (0.25 mole) of hydroxylamine hydrochloride, 12 ml. (0.25 mole) of anhydrous potassium carbonate, 750 ml. of methanol and 20 ml. of distilled water was stirred and heated for one hour, cooled and placed in the refrigerator for a few days. The product was washed with anhydrous ether, and distilled water. Dilution of the filtrate with water gave additional product. After drying in vacuo at 50°C, the combined product had a m.p. of 210–212°C; yield 41.6 g. (95%).

Anal. Calcd. for C_{12}H_{13}NO: C, 71.43; H, 7.47; N, 11.90. Found: C, 71.43; H, 7.47; N, 11.90.

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole Tosylate. —Dry pyridine (1000 ml.) and 87.0 g. (0.30 mole) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole ethylene ketal were dissolved in 1000 ml. of anhydrous toluene. The solution was warmed on a steam-bath for 30 minutes; then the tosyl chloride was added, and the mixture was warmed on a steam-bath for 30 minutes. The tosyl chloride was filtered and washed thor-
mixture was cooled in ice to \(10^\circ\), a suspension of 8.8 g. (0.02 mole) of 1-benzoyl-5-isatinotro-1,2,3,4,5,6-hexahydrobenz[cd]indole tosylate in 200 ml. of absolute ethanol was added, and stirring and cooling were continued for eight hours, after which the reaction mixture was placed in the refrigerator for three days. Unchanged starting material, 3.09 g., was recovered by filtration, m.p. 156–157\(^\circ\). The filtrate was poured into 400 ml. of absolute ether, and the solution was extracted with a total of 225 ml. of \(N\) hydrochloric acid solution in several portions. The acid extract was concentrated to dryness in vacuo, and the residue was taken up in 250 ml. of hot absolute alcohol, from which the amino ketone hydrochloride, m.p. 240\(^\circ\) dec., crystallized. Additional product from the mother liquors brought the yield to 2.95 g. (80\%, based on starting material recovered). Material for analysis had a m.p. of 245–250\(^\circ\) dec.

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): C, 71.09; H, 5.08. **Found:** C, 71.09; H, 5.08.

The infrared spectrum (KBr) had bands at 5.83, 6.08, 6.27, 6.34, 6.78 and 7.19 \(\mu\).

1-Benzoyl-4-formyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole (19).-Sodium methoxide, 6.0 g., and 15 ml. of ether were added to 15 ml. of cold, dry chloroform. The mixture was stirred in an ice-bath, and 27.7 g. of 1-benzoyl-5-keto-1,2,3a,4,5-hexahydrobenz[cd]indole was added. The reaction mixture was stirred in the cold for 15 minutes, then at 25\(^\circ\) for two hours. The sodium chloride which separated was filtered and washed with benzene and ether; yield 28.0 g. (85\%). A sample of the salt was dissolved in water, and the solution was acidified with hydrochloric acid. The aqueous solution was decanted, and the gummy product was crystallized from a mixture of dimethylformamide and methanol; m.p. 142–145\(^\circ\) dec.

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): C, 74.74; H, 4.90. **Found:** C, 74.85; H, 4.91; N, 4.63.

1-Benzoyl-4-formamido-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole (22) and 1-Benzoyl-4-cyano-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole (21) from 1-Benzoyl-4-formyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole.-The crude sodium enolate of the 4-formyl derivative, 20 g., was dissolved in 15 ml. of concentrated sulfuric acid, and 1.0 g. of methyl oxazole-8-carboxylate was diluted with an equal volume of methanol, and the product was filtered, washed with water, and crystallized from ethanol; yield 0.69 g. (86\%, m.p. 270\(^\circ\) dec. It was insoluble in all the usual solvents.

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): C, 71.24; H, 5.03; N, 8.75. **Found:** C, 71.09; H, 5.08; N, 8.49.

The aqueous sodium hydroxide extract above, containing the acidic fraction, was acidified with hydrochloric acid and extracted with 150 ml. of chloroform. The chloroform solution was dried; the solvent was distilled, and the 4-cyano compound was methylated with methylation, yield 5.83 g. (32\%), m.p. 190–191\(^\circ\). A sample was recrystallized from a mixture of dimethylformamide and methanol; m.p. 190–191\(^\circ\).

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): C, 75.48; H, 4.67. **Found:** C, 75.73; H, 5.10; N, 9.01.

1-Benzoyl-5-keto-4-methoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (20).—To a solution of 30 g. of methyl oxalate in 800 ml. of cold benzene was added 15 g. of sodium carbonate powder with stirring and cooling in ice. The warm solution of 55.5 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole in 350 ml. of toluene was then added dropwise with continued stirring and cooling during 10 minutes. Stirring was maintained with the cooling bath removed for two hours, after which 400 ml. of ice-water was added. The aqueous solution containing the sodium enolate was separated and acidified with 30 ml. of concentrated hydrochloric acid. The product was extracted with 500 ml. of chloroform, and the solvent was distilled in vacuo. The residue was crystallized from a few volumes of ethanol, yield 52.5 g. (73\%). m.p. 282–284\(^\circ\) dec. A sample was recrystallized from a mixture of acetic acid and methanol.

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): C, 69.41; H, 4.72; N, 3.88. **Found:** C, 69.20; H, 4.77; N, 3.83.

Methyl 4-Benzoyl-4,5,5a,6-tetrahydroindole(4,3-fg)benzo[e]-8-carboxylate (23).—1-Benzoyl-4-keto-6-methyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole, 3.93 g., was dissolved in 15 ml. of concentrated sulfuric acid, and 1.0 g. of sodium azide was added with stirring. The mixture was warmed to 40\(^\circ\), at which time the reaction became exothermic, and the temperature rose spontaneously to 50\(^\circ\). The solution was cooled to 40\(^\circ\) and kept at that temperature for 15 minutes, after which it was poured onto ice. The amorphous product was filtered and washed with water, and the filtrate was decolorized with carbon, and evaporated to dryness in vacuo. The residue was crystallized from methanol; yield 0.26 g. (40\% based on ester not recovered), m.p. 226–227\(^\circ\) dec.

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): C, 69.99; H, 4.48; N, 7.77. **Found:** C, 70.03; H, 4.46; N, 7.70.

The infrared spectrum had carbonyl bands at 5.75 (ester) and 6.07 \(\mu\) (amide).

Methyl 4,5,5a,6-Tetrahydroindole(4,3-fg)benzo[e]-8-carboxylic Acid Hydrochloride.—A mixture of 1 g. of the 4-benzoyl derivative above and 50 ml. of methanol was saturated with 12 g. of dry hydrogen chloride while cooling. After the reaction mixture was kept for four days at 25\(^\circ\) and then at 35\(^\circ\) for two hours. The sodium chloride which separated was filtered and washed with benzene and ether; yield 22.6 g. (85\%). A sample was recrystallized from ethanol; yield 0.43 g. (86\%, m.p. 270\(^\circ\) dec. It was insoluble in all the usual solvents.

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): N, 15.55. **Found:** N, 15.07.

4-Amino-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole Di-hydrochloride (24).—A By Hydrolysis of Methyl 4-Benzoyl-4,5,5a,6-tetrahydroindole(4,3-fg)benzo[e]-8-carboxylic Acid Hydrazide.—One-half gram of the corresponding methyl ester was dissolved in 5.5 ml. of hot dimethylformamide. Pure hydrazine (7 ml.) was added, and in a few seconds the hydrazide crystallized. The mixture was diluted with an equal volume of methanol, and the product was filtered, washed with water, and crystallized from methanol and ether; yield 3.4 g. (62\%, m.p. above 300\(^\circ\).

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): N, 10.73; H, 7.25. **Found:** N, 10.30; H, 7.27.

Hydrolysis of the ester in aqueous hydrochloric acid gave about the same result.

B. By Hydrolysis of 1-Benzoyl-4-amino-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole Hydrochloride.—A solution of 1.11 g. of the amino ketone hydrochloride in 50 ml of concentrated hydrochloric acid was heated under reflux overnight. The mixture was treated with carbon, and the solvent was distilled in vacuo. The residual product was digested with a little ethanol, filtered, and washed with ethanol and ether; yield 0.6 g. (66%, m.p. above 300\(^\circ\).

**Analytical.**

**Calcd.** for \(C_{19}H_{16}O_2\): N, 10.19; H, 7.25. **Found:** N, 10.18; H, 7.27.

X-Ray diffraction patterns of the samples prepared by methods A and B were identical.

C. From 1-Benzoyl-4-formamido-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indoleHydrolysis in this case was run in hydrochloric acid exactly as above. Once again the m.p. was indistinct in the region of 280–300\(^\circ\) dec., and identity was proved by comparison of X-ray diffraction patterns.
1-Benzoyl-4-acetyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[d]indole.—A mixture of 18.8 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[d]indole in 100 ml. of acetic anhydride was cooled in an ice-bath. Boron trifluoride gas was bubbled into the solution for 20 minutes with stirring and continued cooling, during which time the temperature of the reaction mixture rose to 40°C. The solution was kept at 25°C for 1.5 hours, after which it was concentrated to small volume in a vacuum. The residue was dissolved in chloroform, and the solution was washed successively with water, 6 N sodium hydroxide, concentrated hydrochloric acid and water. It was dried over magnesium sulfate and concentrated under reduced pressure. The crude ketone was recrystallized from benzene; yield 6.0 g. (38%). m.p. 172-175°C. Anal. Calcd. for C_{19}H_{17}O_3: C, 78.66; H, 6.27; O, 15.11. Found: C, 78.57; H, 6.17; O, 15.13.

The infrared spectrum had carbonyl bands at 5.91 (ketone) and 6.07 μ (amide); ultraviolet λ_{max} 244 μm (ε 33300), 330 μm (ε 4400).

B. From 1-Benzoyl-5-ethoxy-1,2,2a,3-tetrahydrobenz[d]indole.—A solution of 18.53 g. (0.0602 mole) of perbenzoic acid in 200 ml. of ice-acetic acid was added to a mixture of 11.5 g. of 1-benzoyl-5-ethoxy-1,2,2a,3-tetrahydrobenz[d]indole dissolved in 200 ml. of ethyl alcohol. The solution was allowed to stand in the refrigerator overnight, after which it was washed with two 15-ml. portions of saturated sodium bicarbonate solution, and then with 15 ml. of water. It was then dried over anhydrous magnesium sulfate, and the chloroform was removed after leaving an oil. The crude ketone was recrystallized from ethyl acetate; yield 205-207°C. A mixture melting point with a sample of hydroxy ketone prepared from the enol acetate showed no depression.

1-Benzoyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[d]indole.—Twenty-five grams of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[d]indole was dissolved in 200 ml. of hot absolute ethanol. The solution was stirred and heated at reflux while a solution of 2.5 g. of sodium borohydride in 120 ml. of absolute alcohol was added dropwise during about 0.5 hour. Refluxing was continued for one hour, after which 50 ml. of 10% aqueous sodium hydroxide was added, and heating was continued for 0.5 hour. The solution was allowed to cool and then poured into 250 ml. of 0.6 N hydrochloric acid. Most of the ethanol was distilled in vacuo, and the product was extracted from the residue with 3 200-ml. portions of 1:1 ether-benzene. The extracts were washed with water, treated with charcoal and the solvents were removed. The crude alcohol, 20 g. (80%), was sufficiently pure to be used in the subsequent reaction. A sample was recrystallized from ethyl acetate-petroleum ether, m.p. 182-183°C. Anal. Calcd. for C_{19}H_{17}O_3: C, 75.43; H, 5.71; O, 4.47. Found: C, 75.41; H, 5.69; O, 4.48.

In another experiment the extraction was omitted and the crude product was simply added to 200 ml. of water, cold methanol and ether. The yield of crystalline material was 75%, m.p. 182-183°C.

Oxidation of 1-Benzoyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[d]indole to 1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[d]indole.—A mixture of 2.79 g. of the tricyclic alcohol in 100 ml. of acetic acid was added with shaking of 0.73 g. of chromic acid in 7 ml. of water and 9 ml. of acetic acid. The reaction mixture was kept at 25°C for two days, after which it was warmed on a steam-bath for four hours. The solvents were evaporated under reduced pressure, and the residue was washed with water, cold methanol and ether. The yield of crystalline material was 75%, m.p. 182-183°C. Recrystallization of the crude benzene and ether gave ketone with m.p. 145-146°C. A mixture melting point with authentic tricyclic ketone was not depressed.

1-Benzoyl-1,2a,2,3-tetrahydrobenz[d]indole (28).—Thirty-nine and one-half grams of crude 1-benzoyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[d]indole was dissolved in 400 ml. of benzene, and the mixture was cooled in an ice-bath while 25 ml. of phosphorus tribromide was added slowly with swirling. The solution was kept overnight at room temperature and was then boiled gently under reflux for four hours. It was cooled and poured into ice. The crystal layer was separated, and the aqueous layer was washed with a mixture of ether and benzene. The combined extracts were washed well with water, and the solvent was evaporated in vacuo. The residue of 1-benzoyl-5-bromo-1,2a,2,3,4,5-hexahydrobenz[d]indole weighed 86 g. (74%) and was pure enough for use in the next step.

The bromide was mixed with 150 ml. of 2,6-lutidine, and the solution was heated at reflux for 4 hours. The mixture was poured into 1000 ml. of ice-water containing 100 ml. of 2N hydrochloric acid. The product was extracted with 1:1 ether-benzene, and the extract was washed with aqueous sodium carbonate, dilute hydrochloric acid and finally with water. The solution was treated with deoxygenating carbide, and the solvents were distilled in vacuo. The residue 1-benzoyl-1,2a,2,3-tetrahydrobenz[d]indole was crystallized from benzene-petroleum ether; yield 15.2 g. (32%), based on the
tricyclic ketone), m.p. 91-95°. An analytical sample melted at 95.5-96.5°.

Anal. Caled. for C₈H₁₅NO: C, 82.72; H, 5.78; N, 5.31. Found: C, 82.66; H, 5.61; N, 5.32.

5.36. Found: C, 82.66; H, 5.61; N, 5.37.

An analytical sample of 1,2,2a,3,4,5-hexahydrobenz[cd]indole, m.p. 91-95°. An analytical sample of 1,2,2a,3,4,5-hexahydrobenz[cd]indole was crystallized from a benzene-petroleum ether mixture; yield 6.1 g. (74%), m.p. 104-105°; ultraviolet max 217 mp. 5.05. Found: C, 77.40; H, 7.61; N, 6.68.

The infrared spectrum had bands at 6.04, 6.21, 6.28, 6.86 and 7.14 μ.

1-Benzoyl-4-bromo-5-hydr oxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (34). A. From 1-Benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (32).—A solution of 2.63 g. of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole in 25 ml. of ethanol and 5 ml. of 50% aqueous sodium hydroxide solution was heated under reflux for 2.25 hours. The solution was concentrated to about 10 ml., and the residue was dissolved with 100 ml. of ether and 25 ml. of water. The ether layer was separated and washed with water. It was then extracted with dilute hydrochloric acid to remove basic material, and the extract was separated and neutralized with excess sodium bicarbonate. The crude derivative was crystallized from an ether–petroleum ether mixture; yield 1.54 g. (77%), m.p. 104-105°.

B. From 1-Benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (34).—The epoxide, 5.0 g., was dissolved in a mixture of absolute alcohol and benzene (3:1). 0.28 g. of sodium borohydride in 6.7 ml. of absolute alcohol was added to the mixture. The reaction mixture was kept at 25°C for 1.5 hours, after which the mixture was allowed to stand at 25°C for 18 hours. Solvents were distilled, and the acetyl derivative was crystallized from an ether–petroleum ether mixture; yield 1.54 g. (77%), m.p. 104-105°. The infrared spectrum had bands at 6.05, 6.13, 6.37, 6.85 and 7.12 μ.

1-Benzoyl-1,2,2a,3,4,5-tetrahydrobenz[cd]indole (32).—A suspension containing 2.61 g. of 1-benzoyl-1,2,2a,3,4,5-tetrahydrobenz[cd]indole and 4.0 ml. of 50% aqueous sodium hydroxide was heated under reflux for two hours. About half of the alcohol was distilled, and several volumes of water were added. The mixture was extracted with 100 ml. of ether, and the extract was washed with water. The ether solution was then extracted with dilute hydrochloric acid, and the acid extract was neutralized with sodium bicarbonate. The crude 1,2,2a,3,4,5-tetrahydrobenz[cd]indole was extracted with 100 ml. of ether, and the extract was dried over magnesium sulfate and concentrated to a volume of about 25 ml. Methanol, 25 ml., and 4.0 ml. of acetic anhydride were added, and the solution was kept at 25°C for 18 hours. The solvents were distilled, and the acid derivative was crystallized from a benzene–petroleum ether mixture; yield 1.58 g. (78%), m.p. 120.5-121.5°.

Anal. Caled. for C₂₀H₁₉NO: C, 78.27; H, 6.68; N, 6.79. Found: C, 78.27; H, 6.68; N, 6.79.

The infrared spectrum had bands at 6.05, 6.13, 6.37, 6.85 and 7.12 μ.

1-Benzoyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole (31).—1-Benzoyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole was hydrogenated at three atmospheres pressure in 150 ml. of ethanol using 4.1 g. of 5% palladium-on-carbon catalyst. The catalyst was filtered, the ethanol was distilled, and the residue was crystallized from a mixture of benzene and petroleum ether: yield 6.1 g. (74%), m.p. 104-105°. A sample for analysis was recrystallized from methanol.

Anal. Caled. for C₁₈H₁₅NO: C, 82.10; H, 6.51; N, 5.38. Found: C, 82.16; H, 6.09; N, 5.38.

The infrared spectrum had bands at 6.11, 6.20, 6.31, 6.85, 7.15, 7.37 and 7.72 μ.

1-Benzoyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole (31).—1-Benzoyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole was hydrogenated at three atmospheres pressure in 150 ml. of ethanol using 4.1 g. of 5% palladium-on-carbon catalyst. The catalyst was filtered, the ethanol was distilled, and the residue was crystallized from a mixture of benzene and petroleum ether: yield 6.1 g. (74%), m.p. 104-105°. A sample for analysis was recrystallized from methanol.

Anal. Caled. for C₁₈H₁₅NO: C, 82.10; H, 6.51; N, 5.38. Found: C, 82.16; H, 6.09; N, 5.38.

The infrared spectrum had bands at 6.11, 6.20, 6.31, 6.85, 7.15, 7.37 and 7.72 μ.
ness in vacuo. Dry toluene, 3 l., was added to the residue, and the resulting mixture was stirred and heated under reflux for 4 hours. It was then cooled and washed with ice-water. The organic layer was dried over magnesium sulfate, and the toluene was distilled under reduced pressure. The ketone was crystallized from a mixture of benzene and ether; yield 11.4 g.; m.p. 147-149°; second crop, 3.7 g.; m.p. 143-146°; total, 15.1 g. (75%). A sample for analysis had a m.p. of 149.5-151.5°; a mixture with the isomeric 5-keto compound was 120-141°.

The ultraviolet type was like Fig. 3, curve A.

The semicarbazone of the ketone was prepared in the usual way and was obtained as colorless prisms by recrystallization from aqueous acetic acid; m.p. 225-226°. Anal. Calcd. for C_{24}H_{22}N_{2}O_{4}: C, 70.56; H, 6.91; N, 5.47. Found: C, 70.75; H, 6.89; N, 5.67.

For isolation of the compound as the free base the following procedure was used. 1-Benzoyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[c]indole Ethylene Ketal Ethylene Ketal Hydrochloride (37) - A mixture of 155.5 g. of 1-benzoyl-5,6,9,2a,3,4,5-hexahydrobenz[c]indole and 310 ml. of methylaminoacetone ethylene ketal was heated on the steam-bath for 17 hours. Excess amine was recovered by distillation under reduced pressure, and the residue was dissolved in a little benzene. Several volumes of petroleum ether were added to precipitate the product, and the supernatant solution was concentrated. The residue was purified by recrystallization from 200 ml. of acetone; yield 98.5 g. (45%); m.p. 126-129°.

Anal. Calcd. for C_{16}H_{18}N_{2}O_{4}HCl: C, 59.14; H, 4.15; N, 5.07. Found: C, 59.10; H, 4.00; N, 5.07.

6-Hydroxy-1,2,2a,3,4,5-hexahydrobenz[c]indole Ethylene Ketal (38) - 1-Benzoyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[c]indole was dissolved in 250 ml. of ethanol, and 75 ml. of an aqueous solution containing 30 g. of sodium hydroxide was added. The reaction mixture was stirred and heated under reflux for eight hours. The mixture was cooled and extracted with benzene. The extract upon concentration gave material of ultraviolet type (38) - R. B. Woodward, N. L. Wendler and F. J. Brutschy, This Journal, 67, 1425 (1945).
extracted with chloroform, and the extract was dried over magnesium sulfate and concentrated.

**Analytical Calculations**

Anal. Calcd. for C_{6}\text{H}_{11}\text{NO}_{2}: C, 65.87; H, 7.57; N, 8.09.

B. From 1-Benzoyl-5-hydroxy-4-(N-methyl-N-acetonyl-amino)-1,2,2a,3,4,5-hexahydrobenz[e]indole Ethylene Ketals:—A solution of 0.5 g. of the ketals in 20 ml. of 90% acetic acid was warmed on a steam-bath for four and two-thirds hours. The reaction started, and the solution became cloudy. After 3 hours 20 min. of standing, the solution showed no depression.

**Analytical Calculations**

Anal. Calcd. for C_{16}\text{H}_{22}\text{N}_{2}\text{O}_{3} \text{HC}_{1}: C, 72.42; H, 7.98; N, 7.74; S, 5.74. Found: C, 72.42; H, 7.60; N, 7.64.

The ultraviolet type was like Fig. 3, curve B.

B. From 1-Benzoyl-5-hydroxy-4-(N-methyl-N-acetonyl-amino)-1,2,2a,3,4,5-hexahydrobenz[e]indole Ethylene Ketals:—A solution of 1.0 g. of the benzoyl derivative above in 40 ml. of 6 N hydrochloric acid was kept at room temperature for five days. The mixture was cooled, and 0.19 g. of benzoic acid was removed by filtration. The filtrate was concentrated to small volume, and the residue was dissolved in water and neutralized with sodium bicarbonate. The product was extracted with chloroform; the solution was dried over anhydrous magnesium sulfate. The concentrate was evaporated to dryness, and the residue was distilled.

**Analytical Calculations**

Anal. Calcd. for C_{6}\text{H}_{10}\text{N}_{2}O_{3}: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.31; H, 7.98; N, 10.32.

4.5.5a.6a.6b.9a.10a-Octahydro-7,9-dimethyl-7H-indolo-[3,4-g] [1.4]-benzoxazin-9-ol (38).—A solution of 1.0 g. of the benzyl derivative above in 40 ml. of 6 N hydrochloric acid was kept at room temperature for five days. The mixture was cooled, and 0.19 g. of benzoic acid was removed by filtration. The filtrate was concentrated to small volume, and the residue was dissolved in water and neutralized with sodium bicarbonate. The product was extracted with chloroform; the solution was dried over anhydrous magnesium sulfate, and the solvent was distilled. The hemiketal was crystallized from ethanol; yield 0.15 g., m.p. 120-122°.

**Analytical Calculations**

Anal. Calcd. for C_{6}\text{H}_{10}\text{N}_{2}O_{3}: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.31; H, 7.98; N, 10.32.

1-Benzoyl-5-carboxymethyl-1,2,2a,3-tetrahydrobenz[e]indole (40, R = Me).—A mixture of 500 g. of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[e]indole and 1100 ml. of absolute alcohol was brought to reflux, and with efficient stirring 250 ml. of 9 N sodium hydroxide was added over a period of 3 hours. After heating for an additional 1.5 hours, the mixture was concentrated to about 600 ml. in vacuo and diluted with 2 l. of water. After extracting with anhydrous ether, the combined chloroform extracts were washed with 250 ml. of water and dried over anhydrous magnesium sulfate.
After removal of the chloroform in vacuo, 550 ml. of hot ethyl acetate and several grams of decolorizing carbon were added to the residual oil, and the mixture was allowed to boil for 20 minutes. The carbon was filtered, and the filtrate was allowed to stand in a refrigerator overnight. The crystalline product was collected and washed with a small amount of cold ethyl acetate. The ether was removed by distillation, and the residual oil was dissolved in chloroform and extracted with two 50-ml portions of dilute hydrochloric acid. Any residual extract was washed with distilled water and dried over anhydrous magnesium sulfate and concentrated to dryness in vacuo leaving 3.2 g. of crude, amorphous tetracyclic dioxolane, m.p. 95-105°C. Secondary amine impurities were removed by dissolving the product in about 100 ml. of ice-cold 6 N hydrochloric acid and adding slowly and with stirring 70 ml. of 20% sodium nitrite solution. The insoluble neutral material which formed was extracted with chloroform, and the aqueous layer was made basic with sodium hydroxide, and the basic product was extracted with water and dried over potassium carbonate. The solvent was removed, and the product was triturated with petroleum ether and filtered, m.p. 102-110°C. It was not obtained in crystalline form.

Anal. Caled. for C_{21}H_{19}N_O: C, 77.19; H, 5.48; N, 5.33. Found: C, 75.34; H, 5.49; N, 5.48. The ultraviolet type was like Fig. 3, curve A. Although the product was not analytically pure, it was suitable for conversion to the crystalline methiodide below. 

4-Benzoyl-9,10a-dihydroxy-7,7-dimethyl-4,5,5a,6,6a,7,8,9,10a-decahydrobenz[d]indole dodecyl chloride (43).—A mixture of 3.2 g. (0.0105 mole) of 4-benzoyl-9,10a-dihydroxy-7,7-dimethyl-4,5,5a,6,6a,7,8,9,10a-decahydrobenz[d]indole and 30 ml. of chloroform, and a solution of 0.205 g. (0.000561 mole) of oxalyl chloride in 10 ml. of ethyl acetate and 20 minutes. The carbon was filtered, and the filtrate was concentrated to dryness in vacuo leaving 2.9 g. of crude benzyl alcohol was treated with 4.56 g. Calcd. for C_{21}H_{19}N_O: C, 77.19; H, 5.48; N, 5.33. The ultraviolet type was like Fig. 3, curve A. Although the product was not analytically pure, it was suitable for conversion to the crystalline methiodide below.

4-Benzoyl-9,10a-dihydroxy-7,7-dimethyl-4,5,5a,6,6a,7,8,9,10a-decahydrobenz[d]indole dodecyl chloride (43).—A mixture of 3.2 g. (0.0105 mole) of 4-benzoyl-9,10a-dihydroxy-7,7-dimethyl-4,5,5a,6,6a,7,8,9,10a-decahydrobenz[d]indole and 30 ml. of chloroform, and a solution of 0.205 g. (0.000561 mole) of oxalyl chloride in 10 ml. of ethyl acetate and 20 minutes. The carbon was filtered, and the filtrate was concentrated to dryness in vacuo leaving 2.9 g. of crude benzyl alcohol was treated with 4.56 g. Calcd. for C_{21}H_{19}N_O: C, 77.19; H, 5.48; N, 5.33. The ultraviolet type was like Fig. 3, curve A. Although the product was not analytically pure, it was suitable for conversion to the crystalline methiodide below. 

4-Benzoyl-9,10a-dihydroxy-7,7-dimethyl-4,5,5a,6,6a,7,8,9,10a-decahydrobenz[d]indole dodecyl chloride (43).—A mixture of 3.2 g. (0.0105 mole) of 4-benzoyl-9,10a-dihydroxy-7,7-dimethyl-4,5,5a,6,6a,7,8,9,10a-decahydrobenz[d]indole and 30 ml. of chloroform, and a solution of 0.205 g. (0.000561 mole) of oxalyl chloride in 10 ml. of ethyl acetate and 20 minutes. The carbon was filtered, and the filtrate was concentrated to dryness in vacuo leaving 2.9 g. of crude benzyl alcohol was treated with 4.56 g. Calcd. for C_{21}H_{19}N_O: C, 77.19; H, 5.48; N, 5.33. The ultraviolet type was like Fig. 3, curve A. Although the product was not analytically pure, it was suitable for conversion to the crystalline methiodide below.
distilled in vacuo, and the residual oil was crystallized from aqueous ethanol. The unsaturated lactone crystallized; with potassium had dissolved the solution was evaporated to under nitrogen in a 22-l. round-bottom flask. After the potassium metal, 179 g., was added to dry t-butyl alcohol and 4900 ml. of dry benzene contained an atmosphere of nitrogen it was cooled to -5°. Pre-
keeping the reaction mixture protected continuously under
The cake was broken up by mechanical stirring, and while mixed with 3700 ml. of dry benzene and 4900 ml. of toluene.
rapidly to 70-75° and was kept at that temperature for a few minutes. It was then cooled rapidly below room tempera-
ture by evaporation
further crop of less pure material, 109 g. (llyo), was ob-
The sodium salt crystallized, and the mixture was kept at 25° for two hours, and then cooled. The bisulfite
The enol acetate could be prepared also, but less con-
veniently, from either 1-benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole or its sodium bisulfite addition product.
Sodium Salt of 1-Benzoyl-5-carboxymethyl-5-epoxy-1,2a,2,3,4,5-hexahydrobenz[cd]indole (51, R = Na).—Potassium metal, 179 g., was added to a mixture of 3700 ml. of dry benzyl alcohol and 4900 ml. of dry benzene containing 71.5 g. of t-butyl alcohol and 4900 ml. of toluene.
The cake was broken up by mechanical stirring, and while the mixture was kept at 25° for 18 hours, after which it was passed through a filter paper. The filtrate was evaporated in vacuo, and the residue was mixed with 12 l. of water. The crude semicarbazone was filtered and washed well with water. It was purified by recrystallization from methanol; yield 8 g. (55%), m.p. 168-170°.
Infrared carbonyl bands were at 5.84 (lactone) and 6.09 (amide).

Anal. Calcd. for C_{19}H_{17}NO_2: N, 4.91.
Found: N, 4.86.

1-Benzoyl-5-oxo-1,2a,3,4,5-hexahydrobenz[cd]indole Oxime.—A solution containing 17.9 g. of the sodium salt of 1-benzoyl-5-carboxymethyl-5-epoxy-1,2a,2,3,4,5-hexahydrobenz[cd]indole, 21.9 g. of hydroxylamine hydrochloride, and 21.9 g. of anhydrous sodium acetate in 270 ml. of water and 180 ml. of ethanol was heated at reflux for two hours. It was then concentrated to about 250 ml., and 500 ml. of cold water was added. The product was filtered, washed with water and crystallized from methanol; yield 8.5 g. (55%), m.p. 168-170°.

Anal. Calcd. for C_{19}H_{17}NO_2: N, 4.91.
Found: N, 4.86.

1-Benzoyl-5-carboxymethyl-5-epoxy-1,2a,2,3,4,5-hexahydrobenz[cd]indole and 25 g. of anhydrous sodium acetate in 800 ml. of acetic anhydride and 150 ml. of acetic acid was refluxed for one hour and then concentrated to small volume in vacuo. An excess of methanol was added slowly to decompose any remaining acetic anhydride, and the solution was decanted and again evaporated. Water (2 l.) was added slowly with shaking, and the product was filtered and then recrystallized from acetic acid; yield 49.6 g. (74.5%). The compound showed a double melting point at 125-130° and 185-189°. The higher melting form could be obtained by recrystallization from ethanol.

Anal. Calcd. for C_{20}H_{20}O_3: N, 5.07; S, 6.22.
Found: C, 82.40; H, 5.07; N, 6.44.

The infrared carbonyl bands were at 5.70 (ester) and 6.10 (amide). The sodium salt of 1-benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole was dissolved in 150 ml. of water and treated with 25 ml. of acetic acid. The reaction mixture was illuminated with two 250-watt heat lamps and stirred for 12-15 minutes, during which time the temperature rose to about 63°. The illumination was re-

Semicarbazone.—Ten liters of acetonitrile in a 224-l. round-bottom flask was warmed to 88°. The solvent was stirred while 500 g. of the sodium salt of 1-benzoyl-5-carboxymethyl-
1,2a,2,3,4,5-hexahydrobenz[cd]indole and 448 g. of pyridine-2-pyridine 2-pyridine hydrobromide was added. The reaction mixture was illuminated with two 250-watt heat lamps and stirred for 12-15 minutes, during which time the temperature rose to about 63°. The illumination was re-

1-Benzoyl-5-oxo-1,2a,3,4,5-hexahydrobenz[cd]indole and 50 g. of anhydrous sodium acetate in 250 ml. of water was heated at reflux for 1.25 hours, and then concentrated under reduced pressure to a volume of 75 ml. Five per cent. sodium carbonate solution (100 ml.) was added, and the semicarbazone was filtered and recrystallized from 200 ml. of methanol; yield 22.5 g. (45%), m.p. 200-202° dec.; ultraviolet \( \lambda_m = 255 \times 10^2 \) (e 18000), 267 \( \times 10^2 \) (e 12000), 293 \( \times 10^2 \) (e 8050).

Anal. Calcd. for C_{19}H_{17}NO_2: C, 71.71; H, 5.79; N, 10.85.
Found: C, 71.82; H, 5.79; N, 10.77.

1-Benzoyl-5-formyl-1,2a,2,3,4,5-hexahydrobenz[cd]indole

Semicarbazone.—A mixture of acetic acid and methanol; yield 426 g. (87%), m.p. 231-232° dec., ultraviolet \( \lambda_m = 257 \times 10^2 \) (e 24200).
methano!, chilled and filtered; yield 130 g. (SOTc), m.p. 
ture of ethyl acetate and petroleum ether melted at 153-
1,2,2a,3-tetrahydrobenz[cd]indole (53).-A mixture of 140 g. of 1-benzoyl-5-formyl-
magnesium sulfate. The solvents were distilled under re-
was kept at 0-5° for 23 hours, after which it was washed 
was kept at 0-5° for 23 hours, after which it was washed 
the original toluene solution, and the mixture was dried over 
and the residual acetal was taken 

1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[cd]indole, 83.5 g. (0.25 mole), was 
3,2a,3-tetrahydrobenz[cd]indole, 83.5 g. (0.25 mole), was 

anal. Calcd. for C₃₁H₂₇N₂O₆: C, 75.65; H, 5.74; N, 
Calcd. for C₃₁H₂₇N₂O₆: C, 75.65; H, 5.74; N, 
Calcd. for C₃₁H₂₇N₂O₆: C, 75.65; H, 5.74; N, 
Calcd. for C₃₁H₂₇N₂O₆: C, 75.65; H, 5.74; N, 

The unsaturated semicarbazone was also prepared by 
this was prepared from the aldehyde and 
phenyldrazine in ethanol solution using a little acetic acid as 
it was recrystallized from a benzene-
ethanol mixture; m.p. 210-212°.

anal. Calcd. for C₃₁H₂₇N₂O₆: C, 75.65; H, 5.74; N, 

The pike from several runs, 82.0 g., was dissolved by 
shaking in a mixture of 500 ml. of 40% aqueous ethanalamine 
and 400 ml. solution was a mixture of chloroform and 
and the aqueous amine layer was washed with two 200-ml. 

1-Benzoyl-5-[2'-dioxolanyl]-1,2,2a,3-tetrahydrobenz[cd] 
A mixture of 140 g. of 1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[cd]indole, 250 ml. of ethylene 
glycol, 480 ml. of toluene and 0.4 g. of p-toluensulfonic 
acid was heated under reflux for 7.5 hours using a water 
separator to collect water formed in the reaction. The 
reaction mixture was washed thoroughly with aqueous sodium 
bicarbonate, and the aqueous was extracted once with 
chloroform. Then the ethyl alcohol was extracted with 
the original toluene solution, and the mixture was dried over 
magnesium sulfate. The solvents were distilled under re-
duced pressure, and the residue was taken up in water and 
separated, after which they were dried over magnesium sulfate, 
and the residual acetal was taken in 60% acetic acid. 

1-Benzoyl-5-formyl-1,2,2a,3-tetrahydrobenz[cd]indole from 1-Benzoyl-5-[2'-dioxolanyl]-1,2,2a,3-tetrahydrobenz[cd]indole (54).-A mixture of 10 g. of 1-Benzoyl-5-[2'-dioxolanyl]-1,2,2a,3-tetrahydrobenz[cd]indole, 80.5 g. (0.25 mole), was 
dissolved in a cold solution containing 0.3 mole of perben-
zoic acid in 600 ml. of chloroform. The reaction mixture 
was kept at 0-5° for 23 hours, after which it was washed 
twice with 5% aqueous sodium bicarbonate solution. 
The aqueous layer was washed with 200 ml. of excess so-

The unsaturated semicarbazone was also prepared by 
a similar procedure starting with 1-Benzoyl- 
Formyl-1,2,2a,3-tetrahydrobenz[cd]indole, 83.5 g. (0.25 mole), was 
recrystallized from methanol. The solution was decolorized 
with carbon. The filtrate after removal of carbon was then 
mixed with a hot solution of 9.3 g. of picric acid in 600 ml. of 
ethanol. The picrate salt which crystallized was 
filtered and washed with acetone; yield 13.2 g. (51%), m.p. 230° dec. 
A sample was recrystallized for analysis from a mixture 
of dimethylformamide and methanol; m.p. 245° dec.

anal. Calcd. for C₃₁H₂₇N₂O₆: C, 75.65; H, 5.74; N, 

1-Benzoyl-5-[2'-dioxolanyl]-5-hydroxy-4-methylamino-
1,2,2a,3,4,5-hexahydrobenz[cd]indole (55) A. From 1-
1-Benzoyl-5-[2'-dioxolanyl]-5-hydroxy-4-methylamino-
1,2,2a,3,4,5-hexahydrobenz[cd]indole (55) A. From 1-

1-Benzoyl-5-[2'-dioxolanyl]-5-hydroxy-4-methylamino-
1,2,2a,3,4,5-hexahydrobenz[cd]indole. — A mixture of 15 g. of the epoxy acetal 
and 500 ml. of liquid methyamine was heated in a 
autoclave at 120° for 14 hours. The methyamine was 
evaporated completely, and the dark amorphous product 
was dissolved in 250 ml. of methanol, and the solution was 
decolorized with carbon. The filtrate after removal of carbon 
was treated with a hot solution of 9.3 g. of picric acid in 
600 ml. of ethanol. The picrate salt which crystallized was 
filtered and washed with acetone; yield 13.2 g. (51%), m.p. 230° dec. 
A sample was recrystallized for analysis from a mixture 
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in 250 ml. of methanol, and the solution was decolorized 
with carbon. The filtrate after removal of carbon was then 
mixed with a hot solution of 9.3 g. of picric acid in 600 ml. of 
ethanol. The picrate salt which crystallized was filtered 
and washed with acetone; yield 13.2 g. (51%), m.p. 230° dec. 
A sample was recrystallized for analysis from a mixture 
of dimethylformamide and methanol; m.p. 245° dec.

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at 120° for 14 hours. The methyamine was evaporated 
completely, and the dark amorphous product was dissolved 
in 250 ml. of methanol, and the solution was decolorized 
with carbon. The filtrate after removal of carbon was then 
mixed with a hot solution of 9.3 g. of picric acid in 600 ml. of 
ethanol. The picrate salt which crystallized was filtered 
and washed with acetone; yield 13.2 g. (51%), m.p. 230° dec. 
A sample was recrystallized for analysis from a mixture 
of dimethylformamide and methanol; m.p. 245° dec.

anal. Calcd. for C₃₁H₂₇N₂O₆: C, 75.65; H, 5.74; N, 

1-Benzoyl-5-[2'-dioxolanyl]-5-hydroxy-4-methylamino-
1,2,2a,3,4,5-hexahydrobenz[cd]indole. — A mixture of 15 g. of the epoxy acetal 
500 ml. of liquid methyamine was heated in an autoclave 
at 120° for 14 hours. The methyamine was evaporated 
completely, and the dark amorphous product was dissolved 
in 250 ml. of methanol, and the solution was decolorized 
with carbon. The filtrate after removal of carbon was then 
mixed with a hot solution of 9.3 g. of picric acid in 600 ml. of 
ethanol. The picrate salt which crystallized was filtered 
and washed with acetone; yield 13.2 g. (51%), m.p. 230° dec. 
A sample was recrystallized for analysis from a mixture 
of dimethylformamide and methanol; m.p. 245° dec.

anal. Calcd. for C₃₁H₂₇N₂O₆: C, 75.65; H, 5.74; N, 

1-Benzoyl-5-[2'-dioxolanyl]-5-hydroxy-4-methylamino-
1,2,2a,3,4,5-hexahydrobenz[cd]indole. — A mixture of 15 g. of the epoxy acetal 
500 ml. of liquid methyamine was heated in an autoclave 
at 120° for 14 hours. The methyamine was evaporated 
completely, and the dark amorphous product was dissolved 
in 250 ml. of methanol, and the solution was decolorized 
with carbon. The filtrate after removal of carbon was then 
mixed with a hot solution of 9.3 g. of picric acid in 600 ml. of 
ethanol. The picrate salt which crystallized was filtered 
and washed with acetone; yield 13.2 g. (51%), m.p. 230° dec. 
A sample was recrystallized for analysis from a mixture 
of dimethylformamide and methanol; m.p. 245° dec.
The dihydrochloride salt was prepared and crystallized from a methanol-acetic mixture; m.p. 250° dec.

Anal. Calcd. for C_{12}H_{20}N_4O_4: C, 51.58; H, 6.35; N, 12.18. Found: C, 51.56; H, 6.32; N, 12.18.

B. By Acid Hydroyisation.-A solution of 1.0 g. of the 1-benzoyl-5-hydroxy-4-methylamino-5-acetil in 50 ml. of methanol containing 1 ml. of concentrated sulfuric acid was refluxed for 16 hours. Most of the methanol was distilled, and the residue was mixed with 20 ml. of 6 N sodium hydroxide. The product was extracted with chloroform in three portions and isolated as above; yield 0.3 g. (41%), m.p. 228-229° dec. A mixture m.p. with a sample obtained by alkaline hydrolysis showed no depression. Hydrolysis of the benzoyl compound with aqueous acid gave similar results.

1-Benzoyl-5-(2'-dioxolanyl)-5-hydroxy-4-methylaminoethylenin-1,2,2a,3,4,5-hexahydrobenz[cd]indole (57).—A mixture of 6.5 g. of 1-benzoyl-5-(2'-dioxolanyl)-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 50 ml. of acrylonitrile was warmed briefly to 50° until homogeneous and then kept at 25° for 16 hours. Excess acrylonitrile was distilled in vacuo, and the residue was crystallized from ethyl acetate; yield 5.0 g. (88%), m.p. 150-151° dec.
The infrared carbonyl band was at 5.20 (unsubstituted amide).—A solution containing 20 g. of 1-benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 650 ml. of liquid methylamine was sealed in a steel autoclave and heated in a steam-bath, 50 ml. of water was added to dissolve all sodium carbonate, and the crude product, m.p. 224.5-225.5° dec., was filtered; yield 3.12 g. (94.8%). Crystalization from methanol gave the analytical sample, m.p. 225.5-230° dec., containing 0.6 mole of water of crystallization.

The compound had an infrared band at 4.38 μ (nitrite).

1-Benzoyl-5-formyl-1,2,2a,3,4,5-tetrahydrobenz[cd]indole Oxime.—To a suspension of 1.0 g. of 1-benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole oxime in 200 ml. of dry benzene was added 20 ml. of thionyl chloride during 15 minutes while stirring and cooling in an ice-bath. Stirring at 0-5° continued for 0.5 hour, after which the solvent was distilled in vacuo at room temperature. The residue was dissolved in ethyl methylether ether mixture; yield 10.7 g. (91%), m.p. 142-144° dec.

The infrared spectrum had bands at 4.48, 6.05, 6.15, 6.52, 7.15 and 7.34 μ.

1-Benzoyl-5-carbamyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (60).—To 2.80 g. (0.01 mole) of 1-benzoyl-5-cyano-1,2,2a,3,4,5-tetrahydrobenz[cd]indole was added 11.3 g. of 30% hydrogen peroxide (0.1 mole H_2O_2), in 22.6 g. of water, 150 ml. of acetone and 2.7 ml. of 10% sodium carbonate. Stirring was continued for 10 hours at room temperature, after which the reaction mixture was refluxed for 2.5 hours. Then, after concentration in vacuo on the steam-bath, 50 ml. of water was added to dissolve all sodium carbonate, and the crude product, m.p. 224.5-225.5° dec., was filtered; yield 3.12 g. (94.8%). Crystalization from methanol gave the analytical sample, m.p. 225.5-230° dec., containing 0.6 mole of water of crystallization.

The ultraviolet type was like Fig. 3, curve A. The infrared spectrum had carbonyl bands at 6.89 (unsubstituted amide) and at 0.07 μ (substituted amide).

1-Benzoyl-5-cyano-1,2,2a,3,4,5-hexahydrobenz[cd]indole.—To a suspension of 1.0 g. of 1-benzoyl-5-cyano-1,2,2a,3,4,5-hexahydrobenz[cd]indole was added 11.3 g. of 30% hydrogen peroxide (0.1 mole H_2O_2), in 22.6 g. of water, 150 ml. of acetone and 2.7 ml. of 10% sodium carbonate. Stirring was continued for 10 hours at room temperature, after which the reaction mixture was refluxed for 2.5 hours. Then, after concentration in vacuo on the steam-bath, 50 ml. of water was added to dissolve all sodium carbonate, and the crude product, m.p. 224.5-225.5° dec., was filtered; yield 3.12 g. (94.8%). Crystalization from methanol gave the analytical sample, m.p. 225.5-230° dec., containing 0.6 mole of water of crystallization.

The solvent-free form was obtained by drying in vacuo and recrystallizing from benzene, m.p. 191-193°

Anal. Calcd. for C_{12}H_{20}N_4O_4: C, 51.58; H, 6.35; N, 12.18. Found: C, 51.56; H, 6.32; N, 12.18.

Anal. Calcd. for C_{12}H_{20}N_4O_4HCl: N, 9.37; Cl, 18.81. Found: N, 9.37; Cl, 18.06.

The free base was obtained by dissolving the salt in water and adding excess sodium bicarbonate. It was extracted with chloroform and the solution was dried over magnesium sulfate and concentrated in vacuo. The product was crystallized from benzene; m.p. 150-152°.

Anal. Calcd. for C_{12}H_{20}N_4O_2: C, 56.53; H, 7.04; N, 12.76. Found: C, 56.55; H, 7.31; N, 12.87.

Carbonyl bands in the infrared were at 5.93 (unsubstituted amide) and 6.08 μ (substituted amide).

S-Carbamyl-5-hydroxy-4-methylamino-1,2a,3,4,5,hexahydrobenz[cd]indole Dihydrochloride.—To 100 ml. of methanol saturated with dry hydrogen chloride was added 1 g. (0.008 mole) of 1-benzoyl-5-carbamyl-5-hydroxy-4-methylamino-1,2a,3,4,5-hexahydrobenz[cd]indole, and the mixture was allowed to stand for three days. Crystals had formed, m.p. 223-226° dec., yield 0.46 g. (51%). Recrystallization from a methylmethylether mixture gave an analytical sample, m.p. 223-226° dec.


1-Benzoyl-5-carbamyl-4-dimethylamino-5-hydroxy-1,2a,3,4,5-hexahydrobenz[cd]indole.—In a glass autoclave liner was placed 1.0 g. (0.008 mole) of 1-benzoyl-5-carbamyl-
and then kept at room temperature for one week. The yield was 0.94 g. (58.7%).

Acid Lactone (62).-Treatment of 1.8 g. (0.004 mole) of 1-benzoyl-5-hydroxymethyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole with 30% aqueous hydrogen peroxide gave a 10% yield of crude amide, which was separated and washed with ether; yield 0.7 g. (61%).

The infrared spectrum had carbonyl bands at 5.57 (lactone) and 6.08 (amide), m.p. 198–200° dec., was obtained. Recrystallization from ethyl acetate gave the analytical sample, m.p. 200.5–203° dec.

The ultraviolet type was like that in Fig. 3, curve A. A larger run (100 g.) gave a 60% yield of the anhydrous form from the hydrate, and the filtrates on evaporation left a solid which gave a 2% yield of 1-benzoyl-5-hydroxy-5-aminomethyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole. The compound was a monohydrate. The sample for analysis was recrystallized from methanol.

The ultraviolet spectrum was very similar to that in Fig. 3, curve A.

The anhydrous epoxycyclopentadiene could be obtained by vacuum drying of the hydrate at 140° or better as follows: A mixture of the hydrate, 0.98 g., in 2.5 g. of ethyl orthoformate and 0.46 ml. of absolute ethanol containing a trace of sulfuric acid was refluxed for 2.5 hours. The solution was cooled, and the ethyl alcohol was filtered and washed with ether; yield 0.5 g. (54%), m.p. 168–171° dec. A sample was recrystallized from ethyl acetate; m.p. 173–174°. The ultraviolet spectrum was very similar to that in Fig. 3, curve A.

The infrared spectrum had carbonyl bands at 5.57 (lactone) and 6.08 (amide) and no bands in the OH or NH regions. The ultraviolet type was like that in Fig. 2, curve A.

The infrared spectrum had carbonyl bands at 6.57 (lactone) and 6.08 μ (amide) and no bands in the OH or NH regions.

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The ultraviolet spectrum was like that in Fig. 3, curve A.

The ultraviolet spectrum was like that in Fig. 2, curve A.

The infrared spectrum had carbonyl bands at 6.57 (lactone) and 6.08 μ (amide) and no bands in the OH or NH regions.
with water and dilute sodium bicarbonate solution, after which it was dried over magnesium sulfate and concentrated under reduced pressure. The residue was taken up in wet ether, and the crystalline alcohol-hydrate was filtered and washed with ether; yield 2.66 g. (89%). Recrystallization from dilute acetic acid gave pure alcohol with m.p. 108-111° dec. A mixture melting point with a sample prepared by sodium borohydride reduction showed no depression.

1-Benzoyl-5-acetoxyethyl-1,2,2a,3-tetrahydrobenz[cd]indole.—One gram of 1-benzoyl-5-hydroxyethyl-1,2,2a,3-tetrahydrobenz[cd]indole was dissolved in 50 ml. of chloroform containing 4.14 g. of perbenzoic acid. The solution was kept at 0-5° for 16 hours, after which it was washed with aqueous sodium bicarbonate solution and dried over magnesium sulfate. The chloroform was distilled and the epoxy ester was crystallized from an ethyl acetate-petroleum ether mixture; yield 2.03 g. (24%). A sample for analysis was recrystallized from a mixture of ethyl acetate and methanol; m.p. 177-179° dec.

Anal. Calcd. for C19H17N03: C, 78.96; H, 5.35; N, 5.68. Found: C, 78.52; H, 5.11; N, 5.78.

1-Benzoyl-5-hydroxy-5-hydroxymethyl-4-[N-methyl-N-acetoxymino]-1,2,2a,3,4,5-hexahydrobenz[cd]indole Ethylene Ketal (67).—A mixture of 12.0 g. of 1-benzoyl-5,5-epoxy-5-hydroxyethyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 50 ml. of methylaminoacetone ethylene ketal was heated under nitrogen in an oil-bath at 125° for 16 hours. Excess amine was distilled in vacuo, and the residue was taken up in a little benzene. The crude product was precipitated as a gum by addition of petroleum ether. The supernatant liquid was decanted, and the gum was taken up in chloroform. The resulting solution was extracted with cold dilute hydrochloric acid to remove all the basic material, and the acid extracts were neutralized with sodium bicarbonate. The product was extracted with chloroform; the solution was then dried over magnesium sulfate, and the solvent was distilled. The crude product was precipitated as a gum by addition of petroleum ether. The amorphous gum was dissolved in 10 ml. of chloroform and the solution was kept at 0-5° for 16 hours. The mixture was then poured into cold water, and the gummy residuum was collected, washed with water, and then dried over magnesium sulfate; yield 0.88 g. (88%).

The chloroform was distilled and the epoxy ester was crystallized from an ethyl acetate-petroleum ether mixture; yield 2.03 g. (24%). A sample for analysis was recrystallized from a mixture of ethyl acetate and methanol; m.p. 177-179° dec.

Anal. Calcd. for C19H17N03: C, 78.96; H, 5.35; N, 5.68. Found: C, 78.52; H, 5.11; N, 5.78.

Analytical data for 1-benzoyl-5-trifluoroacetoxymethyl-1,2,2a,3-tetrahydrobenz[cd]indole and 50 ml. of methylaminoacetone ethylene ketal was heated under nitrogen in an oil-bath at 125° for 16 hours. Excess amine was distilled in vacuo, and the residue was taken up in a little benzene. The crude product was precipitated as a gum by addition of petroleum ether. The supernatant liquid was decanted, and the gum was taken up in chloroform. The resulting solution was extracted with cold dilute hydrochloric acid to remove all the basic material, and the acid extracts were neutralized with sodium bicarbonate. The product was extracted with chloroform; the solution was then dried over magnesium sulfate, and the solvent was distilled. The crude product was precipitated as a gum by addition of petroleum ether. The amorphous gum was dissolved in 10 ml. of chloroform and the solution was kept at 0-5° for 16 hours. The mixture was then poured into cold water, and the gummy residuum was collected, washed with water, and then dried over magnesium sulfate; yield 0.88 g. (88%).

The chloroform was distilled and the epoxy ester was crystallized from an ethyl acetate-petroleum ether mixture; yield 2.03 g. (24%). A sample for analysis was recrystallized from a mixture of ethyl acetate and methanol; m.p. 177-179° dec.

Anal. Calcd. for C19H17N03: C, 78.96; H, 5.35; N, 5.68. Found: C, 78.52; H, 5.11; N, 5.78.

The hydrochloride was prepared using dry hydrogen chloride in acetone. The salt crystallized with one mole of acetone; m.p. 155-158° dec.


The sulfate acid addition salt, prepared in methanol containing a little water, analyzed for a trihydrate, m.p. 159-162° dec.

Anal. Calcd. for C19H17N03·3H2O·H2SO4: C, 51.61; H, 6.14; N, 5.02; S, 5.74. Found: C, 51.24; H, 6.09; N, 4.78; S, 5.46.

By Alkylation with the Bromo Ketone 12.—A solution of 270 g. (0.76 mole) of 1-benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 307 g. (2.35 moles) of sodium borohydride in chloroform was refluxed for two hours. The mixture was then poured into cold water, and the gummy residuum was collected, washed with water, and then dried over magnesium sulfate; yield 0.88 g. (88%).

The chloroform was distilled and the epoxy ester was crystallized from an ethyl acetate-petroleum ether mixture; yield 2.03 g. (24%). A sample for analysis was recrystallized from a mixture of ethyl acetate and methanol; m.p. 177-179° dec.

Anal. Calcd. for C19H17N03: C, 78.96; H, 5.35; N, 5.68. Found: C, 78.52; H, 5.11; N, 5.78.

The ultraviolet spectrum closely resembled that of Fig. 3, curve A.
mole) of methylaminoacetone ethylene ketal in 4500 ml. of dry benzene was refluxed under nitrogen for 21 hours. The mixture was cooled, and 151 g. (90.4%) of methylaminoacetone ethylene ketal hydrobromide was filtered, m.p. 158-159°.

Anal. Caled. for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}: C, 67.98; H, 6.71; N, 11.66. Found: C, 74.97; H, 6.71; N, 11.78.

The ultraviolet curve was like that in Fig. 1.

3-Keto-4-[N-methyl-N-acetonyl]amino\textsubscript{1}-2,2a,3,4,5-hexahydrobenz[cd]indole (69). - Twenty grams of 1-benzoyl-2,2a,3,4,5-hexahydrobenz[cd]indole, filtered and the filtrate was concentrated to small volume. The residue was treated with excess of ice-cold dilute sodium hydroxide. The product was filtered on a 6.5-inch buchner funnel and washed with a little cold ethanol and ether. With the very minimum exposure to air (contains sodium methoxide!) the crude ketal was immediately slurried with a little ice-water and refiltered. It was washed with ice-water, ethanol and ether; yield 16.2 g. (69%), m.p. 155-157°. An analytical sample was recrystallized from dilute ethanol; m.p. 165-167°.

Anal. Caled. for C\textsubscript{15}H\textsubscript{17}N\textsubscript{3}O: C, 70.43; H, 6.55; N, 16.30.

The dihydrochloride was prepared and recrystallized from aqueous acetone; m.p. 270° dec.

Anal. Caled. for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}.HCl: C, 57.51; H, 5.79; N, 8.65. Found: C, 67.60; H, 6.18; N, 8.05.

The oxime was prepared in dilute ethanol and was recrystallized from a mixture of dimethylformamide and ether, m.p. 250-255° dec.

Anal. Caled. for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}: C, 70.60; H, 6.72; N, 16.49. Found: C, 70.43; H, 6.55; N, 16.30.

The semicarbazone recrystallized likewise from dimethylformamide-ether melted at 225° dec.

Anal. Caled. for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O: C, 68.44; H, 6.08; N, 9.33. Found: C, 67.60; H, 6.03; N, 9.08.

The ultraviolet curve was like that in Fig. 1.

4-Acetyl-4,5,8,9-tetrahydro-7,9-dimethyl-7H-indole (64). - Twenty-five grams of 5-keto-4-[N-methyl-N-acetonyl]amino\textsubscript{1}-2,2a,3,4,5-hexahydrobenz[cd]indole was mixed with 550 ml. of absolute ethanol. The mixture was cooled, and the product was filtered and washed with ether; yield 20.5 g. (76%), m.p. 167-170°. A second crop was obtained by evaporation of the filtrate; this raised the total yield to 82%. A sample was recrystallized from acetone-ether; m.p. 169-170°; ultraviolet \( \lambda_{\text{max}} \) 216 m\( \mu \) (6400), 289 m\( \mu \) (21000), 301 m\( \mu \) (17600); \( \lambda_{\text{K}} \) in 60% dimethylformamide, 4.30.

Anal. Caled. for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.60; H, 6.03; N, 9.08.
The hydrochloride was prepared in ethanol and was recrystallized from aqueous ethanol; m.p. 230° dec.

Anal. Calcd. for C$_{17}$H$_{18}$N$_2$O$_2$·HCl: N, 8.79. Found: N, 8.80.

The oxime was prepared in the usual fashion, m.p. 230° dec., after recrystallization from dimethylformamide-ether.

Anal. Calcd. for C$_{18}$H$_{20}$N$_2$O$_2$: C, 68.74; H, 6.48; N, 9.42. Found: C, 68.74; H, 6.70; N, 9.41.

The semicarbazone melted at 245-246° dec. after crystallization from aqueous ethanol.

Anal. Calcd. for C$_{18}$H$_{22}$N$_2$O$_2$: C, 67.51; H, 6.24; N, 9.58. Found: C, 67.51; H, 6.18; N, 9.58.

2-Hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline. Ten grams of 9-keto-7-methyl-4,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline in a mixture of 200 ml. of methanol and 10 ml. of water was treated with 1.5 g. of sodium borohydride. The mixture was stirred for two hours, after which it was diluted with 150 ml. of methanol and 25 ml. of water, heated to boiling, treated with concentrated sulfuric acid, and the solution was separated, dried over magnesium sulfate and the chloroform was distilled. The residue was recrystallized twice from a nitromethane-ethyl acetate mixture; yield 0.2 g. (21%); m.p. 193-196° dec.

10-Hydroxy-7-methyl-4,5,5a,6-tetrahydro-9-hydroxy-7-methylindolo[4,3-fg]quinolinium Hydroxide Betaine (ix).—A mixture of 1.0 g. of 4-acetyl-9-keto-7-methyl-4,5,5a,6,7,8,9-octahydroindolo[4,3-fg]quinoline, 10 g. of 5% palladium-on-carbon, and 35 ml. of xylene was heated under reflux for four hours. The catalyst was filtered and extracted with hot methanol and chloroform. The combined filtrates were evaporated under reduced pressure, and the residue was recrystallized from water: yield 0.1 g. (57%); m.p. 295-296° dec. The compound was a monohydrate; ultraviolet A$_{max}$ 246 mp (e 29000), 331 mp (e 66000); $pK'_a$ in 66% dimethylformamide, 9.06; $pK'_a$ in water, 4.82.

The hydrochloride was obtained by treating the methiodide with silver acetate, filtering the silver iodide, and then adding hydrochloric acid to the filtrate. It was crystallized from a mixture of methanol and ethyl acetate; m.p. 240-241° dec.

Ana1. Calcd. for C$_{17}$H$_{19}$N$_2$O$_2$: C, 71.72; H, 7.20; N, 9.73. Found: C, 71.72; H, 7.20; N, 9.73.

The free base was obtained by neutralization of the hydrochloride with aqueous sodium bicarbonate. It was extracted with chloroform; the solution was dried over magnesium sulfate and the chloroform was distilled. The crude product was crystallized from ethyl acetate; m.p. 192-194°; ultraviolet A$_{max}$ 245 mp (e 33600), 251 mp (e 38700), 306 mp (e 3500), 318 mp (e 3000); $pK'_a$ in 66% dimethylformamide, 6.02.

Ana1. Calcd. for C$_{17}$H$_{18}$N$_2$O$_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.72; H, 7.20; N, 9.73.

The hydrochloride was prepared and recrystallized from dilute ethanol; m.p. 243-244° dec.

Ana1. Calcd. for C$_{17}$H$_{19}$N$_2$O$_2$·HBr: C, 55.90; H, 5.80; N, 7.67. Found: C, 55.83; H, 5.84; N, 8.23.

The acetate ester of the alcohol was prepared using excess acetic anhydride (15 ml.) with 0.5 g. of the alcohol at 25° for 12 hours. The acetic anhydride in vacuo was recrystallized in vacuo, and the hydrochloride of the acetate was prepared in methanol and recrystallized from dilute ethanol; m.p. 186-187° dec.

Ana1. Calcd. for C$_{17}$H$_{19}$N$_2$O$_2$: H, 6.39; N, 7.72. Found: C, 68.71; H, 6.38; N, 7.72.

The methodide of the unsaturated alcohol was obtained using 1.5 parts of methyl iodide in 1:1 nitromethane-methanol as solvent. It was recrystallized from water, m.p. 257-258° dec.

Ana1. Calcd. for C$_{17}$H$_{20}$N$_2$O$_2$: C, 50.71; H, 5.44; N, 6.57; I, 29.77. Found: C, 50.25; H, 5.12; N, 6.68; I, 29.03.

The methochloride was obtained by treating the methiodide with silver acetate, filtering the silver iodide, and then adding hydrochloric acid to the filtrate. It was crystallized from a mixture of methanol and ethyl acetate; m.p. 240-241° dec.

Ana1. Calcd. for C$_{17}$H$_{18}$N$_2$O$_2$: C, 68.74; H, 6.60; N, 9.39. Found: C, 68.47; H, 6.33; N, 9.39.

The free base was obtained by neutralization of the hydrochloride with aqueous sodium bicarbonate. It was extracted with chloroform; the solution was dried over magnesium sulfate and the chloroform was distilled. The crude product was crystallized from ethyl acetate; m.p. 192-194°; ultraviolet A$_{max}$ 245 mp (e 33600), 251 mp (e 38700), 306 mp (e 3500), 318 mp (e 3000); $pK'_a$ in 66% dimethylformamide, 6.02.

Ana1. Calcd. for C$_{17}$H$_{18}$N$_2$O$_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.87; H, 7.23; N, 9.80.

Four-tenths of a gram of starting betaine was recovered from the aqueous layer.

4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,7,8,9-octahydroindolo[4,3-fg]quinoline (71). From the 9-Chloro Compound.—One gram of 4-acetyl-9-chloro-7-methyl-4,5,5a,6,7,8,9-octahydroindolo[4,3-fg]quinoline hydrochloride below was dissolved in 2 ml. of water, and the solution was refrigerated overnight. The crystalline product which separated was filtered and washed with cold water and ethyl alcohol; yield 0.4 g. (42%). It was recrystallized from aqueous ethanol; m.p. 195° dec.
The free base was obtained by neutralization of the hydrochloride with aqueous sodium bicarbonate. It was crystallized from ethanol or ethyl acetate; m.p. 195-197°. The mass spectrum showed no depression.

When the epimeric 8-alcohol was used as starting material in place of the normal alcohol above, the same amide was obtained in the same yield. m.p. 267-268°. A mixture m.p. showed no depression.

The infrared spectrum (mull) had bands at 3.05, 3.09, and 3.20 (C-H). The ultraviolet spectrum (ethanol) had maxima at 243, 250, and 334 (E). The ultraviolet spectrum (methanol) had maxima at 243, 250, and 334 (E). The ultraviolet spectrum (methanol) had maxima at 243, 250, and 334 (E).

**4-Acetyl-9-3-acetoxy-7-methyl-4,5,6,7,8,9-octahydronindolo[4,3-fg]quinoline.**—A solution of 0.4 g. of 9-formamido-7-methyl-4,5,5a,6,6a,7,8,9-octahydronindolo[4,3-fg]quinoline in 125 ml. of concentrated hydrochloric acid was heated at reflux under nitrogen for 4.5 hours. The solution was decomposed with carbon and concentrated until a thick slurry of the product was deposited. The mixture was filtered and washed with alcohol and ether; yield 5.2 g. (81%), m.p. 303-305°. A sample was recrystallized from aqueous methanol; ultraviolet λmax 245 μ (ε 3600), 230 μ (ε 1500), 330 μ (ε 1240).

**Anal.** Caled. for C17H20N202: C, 71.80; H, 7.09; N, 14.95. Found: C, 71.53; H, 7.50; N, 14.95.

**9-Amino-7-methyl-4,5,5a,6,7,8,9-octahydronindolo[4,3-fg]quinoline.**—A solution of 5 g. of 9-formamido-7-methyl-4,5,5a,6,6a,7,8,9-octahydronindolo[4,3-fg]quinoline in 50 ml. of concentrated hydrochloric acid was heated at reflux under nitrogen for 18 hours. The solution was evaporated to dryness under reduced pressure, and the residue was crystallized from methyl alcohol and ether; yield 0.01 g. (2%), m.p. 196-197°.

**Anal.** Caled. for C17H20N3O: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.43; H, 7.64; N, 17.43.

**9-Formamido-7-methyl-4,5,5a,6,7,8,9-octahydronindolo[4,3-fg]quinoline.**—To a solution of 0.4 g. of 9-formamido-7-methyl-4,5,5a,6,6a,7,8,9-octahydronindolo[4,3-fg]quinoline in 100 ml. of methanol was added 10 ml. of a saturated solution of sodium bicarbonate. The mixture was warmed briefly until it was homogeneous, and the mixture was then kept at 25° for 2 hours. The reaction was then cooled, and the mixture was then filtered and washed with water; yield 0.44 g. (82%).

**Anal.** Caled. for C17H20N3O: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.43; H, 7.64; N, 17.43.

**9-Acetamido-4-acetyl-7-methyl-4,5,5a,6,7,8,9-octahydronindolo[4,3-fg]quinoline.**—A solution of 0.2 g. of 9-acetamido-4-acetyl-7-methyl-4,5,5a,6,7,8,9-octahydronindolo[4,3-fg]quinoline in 100 ml. of acetic anhydride was heated at reflux under nitrogen for 4.5 hours. The solution was decolorized with carbon and concentrated until a thick slurry of the product was deposited. The mixture was filtered and washed with alcohol and ether; yield 5.2 g. (81%), m.p. 303-305°. A sample was recrystallized from aqueous methanol; ultraviolet λmax 245 μ (ε 3600), 230 μ (ε 1500), 330 μ (ε 1240).

**Anal.** Caled. for C17H20N3O: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.43; H, 7.64; N, 17.43.

**9-Formamido-7-methyl-4,5,5a,6,7,8,9-octahydronindolo[4,3-fg]quinoline.**—A. By Acid Hydrolysis of the 9-Formamido Compound.—A solution of 0.88 g. of 9-formamido-7-methyl-4,5,5a,6,6a,7,8,9-octahydronindolo[4,3-fg]quinoline in 300 ml. of liquid hydrogen cyanide, and 200 ml. of methylformamide-methanol; ultraviolet λmax 243 μ (ε 3800), 249 μ (ε 4100), 304 μ (ε 3100), 315 μ (ε 2700).

**Anal.** Caled. for C17H20N3O: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.43; H, 7.64; N, 17.43.

**B. By Acid Hydrolysis of the 4-Acetyl-9-formamido Compound.**—A solution of 2 g. of the formamido compound in 125 ml. of liquid hydrogen cyanide and 100 ml. of water was heated at reflux under nitrogen for 16 hours. The solution was evaporated to dryness under reduced pressure, and the residue was crystallized from water; yield 0.11 g. (24%). It was then recrystallized from methanol-ether; yield 0.44 g. (82%). The crude acetate was dissolved in methanol, and the hydrochloride was precipitated with dry hydrogen chloride. It was recrystallized from methanol-ethyl acetate, m.p. 176-177° dec., and the melting point was depressed when mixed with the α-anomer described above.

**Anal.** Caled. for C17H20N3O: C, 74.65; H, 7.94; N, 17.41. Found: C, 74.43; H, 7.64; N, 17.43.

**C. By Basic Hydrolysis of the 9-Formamido Compound.**—A mixture of 2.5 g. of the formamido compound, 5.0 g. of potassium hydroxide and 100 ml. of water was heated at reflux under nitrogen for 17 hours. The solution was cooled, and the product was filtered and washed with water; yield 1.96 g. (88%), m.p. 165-166°. A mixture melting point with the sample obtained by acid hydrolysis above showed no depression.

**9-Acetamido-4-acetyl-7-methyl-4,5,5a,6,7,8,9-octahydronindolo[4,3-fg]quinoline.**—The 9-amino-4-deacetyl compound, 0.4 g., was dissolved in 10 ml. of acetic anhydride, and the solution was kept at 25° for 0.5 hour. Excess acetic anhydride was removed in vacuo, and the residue was crystallized from methanol-ether; yield 0.44 g. (82%). The diacetyl derivative was recrystallized from aqueous methanol, m.p. 215-217° dec.; ultraviolet λmax 245 μ (ε 4200), 250 μ (ε 4500), 305 μ (ε 3200), 315 μ (ε 2900).

**Anal.** Caled. for C17H20N3O: C, 74.43; H, 7.64; N, 17.29. Found: C, 70.78; H, 7.27; N, 12.87.

**7-Methyl-4-[3',4',5'-trimethoxybenzoyl]-9-3',4',5'-trimethoxybenzamido-4,5,5a,6,7,8,9-octahydronindolo[4,3-fg]quinoline.**—To a solution of 1.88 g. of 9-amino-4-[3',4',5'-trimethoxybenzamido]-4,5,5a,6,7,8,9-octahydronindolo[4,3-fg]quinoline in 10 ml. of pyridine was added 0.88 g. of 3,4,6-trimethoxybenzoyl chlo-
ride. The solution was kept at 0° for 17 hours, after which it was poured into an excess of aqueous sodium bicarbonate solution. The mixture was extracted three times with chloroform, and the extracts were washed with water and dried over magnesium sulfate. The solvent was distilled, and the product was crystallized from methanol; yield 0.9 g. (97%). A sample for analysis was recrystallized from a mixture of dimethylformamide and methanol; m.p. 275°-280° dec.

Anal. Calcld. for C_{67}H_{57}N_{20}O_{2}: C, 66.78; H, 6.24; N, 10.07. Found: C, 66.53; H, 6.30; N, 10.48.

4-Acetyl-9-chloro-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline (73).—4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline hydrochloride. 5.1 g., was dissolved in 75 ml. of liquid sulfur dioxide contained in a glass liner in a steel autoclave. Thiophenol chloride, 1.2 ml., was added, and the vessel was sealed and kept at 25° for 6 hours. The autoclave was vented, and the reaction mixture was removed. The mixture was extracted three times with chloroform, and the extracts were washed with water and dried over magnesium sulfate. The solvent was distilled under reduced pressure below about 10°. The residue was added. Stirring was continued for 30 minutes, after which the hydrogen cyanide was quickly distilled under reduced pressure below about 10°. The residue was washed with chloroform and ice-water, and the resulting mixture was filtered. The organic layer was separated, and the aqueous phase was extracted twice with chloroform. The combined extracts were dried over magnesium sulfate, decolorized and the solvent was distilled in vacuo. The product was crystallized from ethyl acetate; yield 3.3 g. (54% over-all based on the alcohol hydrochloride), m.p. 172-174°.

Anal. Calcld. for C_{67}H_{57}N_{20}O_{2}: C, 66.76; H, 6.24; N, 10.07. Found: C, 66.51; H, 6.19; N, 10.20.

4-Acetyl-9-carboxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline (77).—Recrystallization from the same solvent raised the m.p. to 275°-280° dec. Methanalysis under the same conditions using hydrogen chloride as catalyst gave the ester in lower yield. Methanalysis under milder conditions gave mixtures containing the above ester along with some deacetylated nitrile, m.p. 170-171°.

Anal. Calcld. for C_{67}H_{57}N_{20}O_{2}: C, 76.48; H, 6.82; N, 16.72. Found: C, 76.08; H, 6.67; N, 16.15.

4-Acetyl-9-carboxybenzoxo-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline. —Acetylation of one part of the tetracyclic ester using four parts of acetic anhydride in about 25 parts of methanol gave the acetyl derivative, m.p. 140-142° (from benzene-ether).

Anal. Calcld. for C_{67}H_{57}N_{20}O_{2}: C, 69.92; H, 6.79; N, 14.57. Found: C, 70.00; H, 6.88; N, 14.70.

9-Carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline (76).—Acetylation of one part of the tetracyclic ester using four parts of acetic anhydride in about 25 parts of methanol gave the acetyl derivative, m.p. 140-142° (from benzene-ether).

Anal. Calcld. for C_{67}H_{57}N_{20}O_{2}: C, 59.78; H, 6.29. Found: C, 59.51; H, 6.19; N, 6.20.

4-Acetyl-9-carboxybenzoxo-7-methyl-4,5,5a,6,6a,7,8,9,10-hexahydroindolo[4,3-fg]quinoline (70).—A mixture of 0.575 g. of 4-acetyl-9-carboxybenzoxo-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline, 15 ml. of xylene and 1 ml. of 5% palladium-on-carbon was heated at reflux under nitrogen for 16 hours. The catalyst was filtered, and the filtrate was cooled. The first crop of yellow crystalline product was collected and washed with benzene; yield 0.20 g. (35%). Some less pure ester could be obtained by concentrating the filtrates. The melting point after recrystallization from benzene was 177-178°.

Anal. Calcld. for C_{67}H_{57}N_{20}O_{2}: C, 70.35; H, 6.22; N, 8.84. Found: C, 70.25; H, 6.30; N, 8.64.

The ultraviolet spectrum was identical to that reported by Stoll^{4} and by Atherton.^{5}

9-Carboxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline (75, R = Me).—A solution of 1.0 g. of 9-carboxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline in 30 ml. of concentrated hydrochloric acid and 5 ml. of water was heated under reflux for three hours. The light yellow solution was evaporated completely to dryness under reduced pressure. A sample of the dihydrochloride salt, obtained thus in quantitative yield, was dissolved in a little water, and the solution was passed through a column of ion exchange resin IR 45 to remove hydrochloric acid.
acid. The eluate was evaporated to give the amino acid, m.p. above 300°. A sample was recrystallized from water for analysis.

Anal. Caled. for C\textsubscript{13}H\textsubscript{11}N\textsubscript{2}O\textsubscript{2}: C, 71.08; H, 6.71; N, 10.36. Found: C, 70.76; H, 6.87; N, 10.40.

9-Carboxy-7-methyl-4,5,6a,7,8,9,10,10a-octahydroindolo-[4,3-fg]quinoline (77).—A mixture of 1.0 g. of 9-carbomethoxy-7-methyl-4,5,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinoline and 40 ml. of N sodium hydroxide solution was heated under reflux for 19 hours. The solution was treated with decolorizing carbon, filtered and 10 g. of wet Raney nickel was added. Refluxing was continued for three hours under nitrogen. The catalyst was filtered, and the pH was adjusted to 5.8 by addition of dilute hydrochloric acid. The crude product which separated, 0.5 g., contained inorganic impurities was purified by reprecipitation from dilute ammonium hydroxide solution with carbon dioxide, m.p. 315-316° dec. The compound retained water of crystallization when dried at 120°, and was not completely anhydrous after drying at 180°.

Anal. Caled. for C\textsubscript{12}H\textsubscript{12}O\textsubscript{3}N\textsubscript{2}H\textsubscript{2}O: C, 66.64; H, 6.69; N, 9.72. Caled. for C\textsubscript{13}H\textsubscript{12}O\textsubscript{3}N\textsubscript{2}: C, 71.09; H, 6.71; N, 10.36. Found, dried at 120°: C, 69.40; H, 7.10; N, 9.79. Found, dried at 180°: C, 69.20; H, 6.77.

The same dihydrolagrymic acid was formed when 4-acetyl-9-cyano-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline was hydrolyzed with alkali and the hydrolysate was treated with Raney nickel.

The infrared spectrum (mull) had bands at 2.9, 3.1, 6.20, 6.38, 6.89 and 7.30 p. The ultraviolet spectrum was that of an unconjugated indole system; 

\[
\lambda_{\max} = 222 \text{ nm} \quad (e = 30000), \quad 238 \text{ nm} \quad (e = 20500), \quad 310 \text{ nm} \quad (e = 9100).
\]

The unreacted portion was treated with Raney nickel (16 g. wet), previously deactivated by boiling in xylene suspension,\textsuperscript{41} was added, and the mixture was heated under reflux and stirred in a nitrogen atmosphere for 20 hours. The solution was treated with carbon, and the crude lyseric acid was precipitated by neutralization to pH 5.8. It was filtered and washed with water; yield 1.04 g., m.p. 242-243° dec. A second crop, 0.16 g., m.p. 293-295° dec., was also obtained; total yield 20%. The acid could be purified by dissolving it in dilute ammonium hydroxide, treating with decolorizing carbon, and reprecipitating with carbon dioxide, m.p. 242-243° dec.; a mixture m.p. with dl-lyseric acid made from natural dl-lyseric acid\textsuperscript{42} was likewise 242-243° dec.

Anal. Caled. for C\textsubscript{13}H\textsubscript{11}N\textsubscript{2}O\textsubscript{2}H\textsubscript{2}O: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.07; H, 6.50; N, 9.91.

The anhydrous acid was obtained by drying in vacuo for several hours at 150°.

Anal. Caled. for C\textsubscript{13}H\textsubscript{11}N\textsubscript{2}O\textsubscript{2}: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 6.10; N, 10.52.

The ultraviolet spectrum in dilute aqueous alkaline solution was identical with that of the sample derived from natural sources, \(\lambda_{\max} = 222 \text{ nm} \quad (e = 30000), \quad 238 \text{ nm} \quad (e = 20500), \quad 310 \text{ nm} \quad (e = 9100). \) The \(K\epsilon\) of 66% dimethylformamide (4.92 and 8.94) was the same for both samples, and the X-ray diffraction patterns and paper chromatographic behavior were identical.

\textit{dl}-Lysergic Acid Hydrazide from Ergocristine.—A sample was obtained by reaction of anhydrous hydrazine with ergocristine in the usual manner.\textsuperscript{12} It was recrystallized from a mixture of dimethylformamide and methanol; 226-228° dec.; \(\lambda_{\max} = 226 \text{ nm} \quad (e = 18000), \quad 240 \text{ nm} \quad (e = 18300), \quad 310 \text{ nm} \quad (e = 7830). \)

Anal. Caled. for C\textsubscript{13}H\textsubscript{11}N\textsubscript{2}O\textsubscript{2}: C, 68.06; H, 6.43; N, 19.85. Found: C, 67.90; H, 6.52; N, 19.62.

\textit{dl}-Lysergic Acid Hydrazide.—Crude synthetic \textit{dl}-lysergic acid, 0.4 g., was powdered and mixed with 25 ml. of benzene, 2 ml. of methanol and 25 ml. of approximately 2.5% diazomethane in cold ether. The mixture was shaken periodically during 45 minutes. Solvents were evaporated under reduced pressure, after which the residue was taken up in about 20 ml of 1:1 benzene–methanol and decolorized with carbon. Solvents were again evaporated, and the \textit{dl}-methyl lysergate was dissolved in 10 ml. of methanol and 2 ml. of anhydrous hydrazine. The solution was heated at reflux under nitrogen for 1.5 hours, after which solvents were removed in vacuo, and the \textit{dl}-lyseregic acid hydrazide was crystallized from methanol; yield 0.050 g., m.p. 224-227° dec. A mixture melting point with natural \textit{dl}-lysergic acid hydrazide showed no depression. Ultraviolet and infrared spectra and X-ray diffraction patterns for natural and synthetic specimens were identical in every respect.

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