in the ultracentrifuge,\(^4\)\(^1\) 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,\(^4\)\(^2\) electrophoretically\(^4\)\(^3\) and in amino acid composition\(^4\)\(^1\) 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.\(^4\)\(^4\)

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.\(^4\)\(^5\) 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.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES AND THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]  

**The Total Synthesis of Lysergic Acid**

BY EDMUND C. KORNFIELD, E. J. FORNEFELD, G. BRUCE KLINE, MARJORIE J. MANN, DWIGHT E. MORRISON, REUBEN G. JONES AND R. B. WOODWARD

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Lysergic acid, the basic fragment derived from the ergot alkaloids, has been synthesized in a fifteen-stage sequence beginning with \(\text{3-carboxyethylindole}\). The starting material was converted to the intermediate \(\text{1-benzoyl-5-keto-1,2,2a,3,4,5,5a,6,6a,7,8,8a-octahydroindolo[4,3-\text{fe}]}\quad\text{quinoline}\) (4), containing three of the four rings present in lysergic acid. This ketone in turn was transformed into the tetracyclic compound, \(\text{9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-\text{fe}]}\quad\text{quinoline}\) (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 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,\(^3\) 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 substance, lysergic acid (1).\(^4\) Of the natural bases, ergonovine (2) is a particularly simple representative; the others—ergotamine (3, \(R = H\); \(R' = -\text{CH}_2\)- \(\text{COCH}_3\)) and the corresponding derivatives (4) inherit the essential properties of ergonovine.

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\(^{(1)}\) Harvard University; other authors, The Lilly Research Laboratories.
\(^{(4)}\) W. Jacobs and L. Craig isolated lysergic acid *J. Biol. Chem.*, 104, 547 (1944) and 106, 393 (1944) 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, *Heit. Chem. Acta*, 25, 506 (1949); A. Stoll, Th. Petzalka, J. Rutschman 27, 2036 (1954)]. A complete account of the structural work is given in a review by A. Glenn.
ovlho

followed by a number of attempts directed at lysergic acid by Uhle and Jacobs was the first major accomplishment in the synthetic studies, and this was followed by a number of attempts directed at lysergic acid itself. More recently, interest in the synthesis of the dihydrolysergic acid and by the medical applications of the derived natural bases. The synthesis of dihydrolysergic acid by Uhle and Jacobs was the first major accomplishment in the synthetic studies, and this was followed by a number of attempts directed at lysergic acid itself. More recently, interest in the synthesis of dihydrolysergic acid has been heightened by the discovery of the corresponding diethylamide derivatives stability. This structure, which was deduced by Stoll on the basis of extensive studies, is unusual in that it represents the alkaloids as 

The presence of lysergic acid skeleton of a
diester group. It is of interest that the large-ring lactone structure is of interest that the large-ring lactone structure is unusual among the alkaloids as o"rbo amide derivatives containing a free hydroxyl group. No other authentic members of this class are known, and it may be questioned whether factors are present in these molecules which would confer on the o"rbo amide structures stability similar to the ring chain tautomeric isomers. It is of interest that the large-ring lactone structure,

β-substituted indole system and the ready availability of simple β-substituted indoles suggested such compounds as starting materials for synthetic work. However, the very high reactivity of the heteroring of indole compounds seemed incompatible with further extensive synthetic operations. Moreover, we were aware of the possibility that many tricyclic indole intermediates would be susceptible to ready and irreversible isomerization to the more stable naphthalenoid isomers.

In order to circumvent such problems we adopted the tricyclic ketone as starting material for synthetic work. Benzoyl-3 (β-carboxyethyl)-dihydroindole (5) was converted by thionyl chloride in ether solution to the corresponding acid chloride, and hence 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 unsuccessful; with polyphosphoric acid only a very small conversion was obtained. In another attempt to obtain useful tricyclic intermediates the oxalyldouble bond. Our presumption of the greater stability of the naphthalenoid isomers was based on the fact that the resonance energy of naphthalene is much greater than that of indole [L. Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1942]. It has been amply justified by subsequent events. Thus, indole acid itself falls into the above category, and has recently been found to suffer ready irreversible isomerization to iii in the presence of acids (ref. 7d). Furthermore, at least two attempts by other groups (ref. 7d and 7e) to synthesize indole acid were based apparently on the opposite presumption, i.e., isomerization of ii to i, but such an isomerization could not be effected after iii had been obtained by synthesis.

(10) We considered that this possibility would apply generally to any intermediate containing the tricyclic system (ii), and one additional double bond. Our presumption of the greater stability of the naphthalenoid isomers was based on the fact that the resonance energy of naphthalene is much greater than that of indole [L. Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N. Y., 1942]. It has been amply justified by subsequent events. Thus, indole acid itself falls into the above category, and has recently been found to suffer ready irreversible isomerization to iii in the presence of acids (ref. 7d). Furthermore, at least two attempts by other groups (ref. 7d and 7e) to synthesize indole acid were based apparently on the opposite presumption, i.e., isomerization of ii to i, but such an isomerization could not be effected after iii had been obtained by synthesis.

derivatives \((7, R = \text{Me or Et})\) 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 \(\alpha\)-keto acid \(8\), but no cyclization to a dihydronaphthalene (cf. \(9\)) was observed.\(^{12}\)

\[
\text{COOH} \quad \text{COOH}
\]
\[
\text{C}_6\text{H}_5\text{CON} - 8 \quad \text{C}_6\text{H}_5\text{CON} - 9
\]

The tricyclic ketone \(4\) was hydrolyzed readily by aqueous hydrochloric acid to the free base (\(10, R = \text{H}\)), which was dehydrogenated by palladium-charcoal in \(p\)-cymene to the known \(5\)-keto-\(1,3,4,5\)-tetrahydrobenz[cd]indole (\(11\)).\(^{7a,f}\) On the other hand, \(4\) itself, and the corresponding \(N\)-acetyl ketone (\(10, R = \text{Ac}\)), which was prepared either by acetylation of \(10 (R = \text{H})\), or by aluminum chloride-catalyzed cyclization of the chloride of \(N\)-acetyl-\(3\)-(\(\beta\)-carboxyethyl)-dihydroindole, were dehydrogenated under similar conditions to the naphthalenoid compounds (\(12, R = \text{Bz or Ac}\)). 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 dihydroindole 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 \(6.07\mu\) (amide carbonyl) in the infrared, and at \(235\) and \(326\) \(\text{mu}\) 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 unpromising. For instance, the reaction of the bromo ketone \(13\) with methylamine, even at room tempera-
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-wise unsuccessful. The side chain amine 15 was obtained by reaction of methylamine with either chloro- or bromoacetone ethylene ketal.\footnote{M. Kuhn, 	extit{J. prakt. Chem.}, 156, 103 (1940).} 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.\footnote{The Neber reaction, of which this is an example, has been studied recently by D. Cram and M. Hatch, 	extit{This Journal}, 75, 33 and 35 (1953).} 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.\footnote{Another acyl compound, the 4-acetyl derivative of 4, was prepared by condensation of the ketone with acetic anhydride in the presence of boron fluoride etherate, but was not further investigated.}

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 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.

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.\footnote{Some oxides of the type 25 have been reported by N. Leela, D. Fukushima and T. Gallacher, 	extit{This Journal}, 76, 2943 (1951) to be formed by the action of peracids on the enol acetates of the 17-keto-steroids.}

The simpler oxide 29 was prepared, however, by peroxidation of the olefin 28. The latter in turn was prepared from 4 by reduction to the alcohol (30, \(R = \text{OH}\)) with sodium borohydride, conversion to the bromide (30, \(R = \text{Br}\)) with phosphorus tribromide, and dehydrohalogenation with collidine. The olefin 28 contains the basic chromophoric system present in many subsequent compounds; its maxi-
mum absorption in the ultraviolet is at 264 m\(\mu\) (Fig. 2, curve A). The corresponding saturated compound 31, prepared from 28 by hydrogenation, absorbs at 267 and 292 m\(\mu\) (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 32 possesses bands at 241, 254, 307 and 316 m\(\mu\) (Fig. 2, curve B), while the bands of the saturated analog 33 are at 213, 253, 279 and 289 m\(\mu\) (Fig. 3, curve B).

The oxide 29 was typical of its class in that it was readily converted to a bromohydrin 34 with hydrogen bromide in benzene-ether, and rearranged to the \(\beta\)-tetralone (35) by magnesium bromide.\(^{(19)}\)

Of greater synthetic interest was the smooth reaction of 29 with amines. With methylamine at 100\(^{\circ}\)C, for example, the simple alkanolamine 36 was produced, while under similar conditions, methylaaminoacetone 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成功的. 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 \(\mu\) 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-1,3-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 = Me or Et) was obtained. The β,γ-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 = H), obtained by careful alkaline hydrolysis of either ester

\[ \text{CH}_{2}\text{COOH} \quad 40 \quad \text{C}_{6}\text{H}_{5}\text{CON} \quad 41 \]

(40, R = 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.

\[ \text{CH}_{2}\text{COOR} \quad 40 \quad \text{CH}_{2}\text{CH}_{2} \quad 41 \]

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 stereochi- mical control, and the availability of superior paths, led us not to make the effort.

Another attempt to utilize the Reformatsky ester (40, R = 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.

\[ \text{CHO} \quad 50 \quad \text{CHO} \]

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 = Et) obtained from the ketone by treatment with ethyl chloroacetate in the presence of potassium t-butoxide.21 The ester was smoothly hydrolyzed to the sodium salt (31, R = Na), which was converted to the saturated aldehyde 52 with mineral acids, or

\[ \text{CH}_{2}\text{COON} \quad 45 \quad \text{CH}_{2}\text{COOMe} \quad 46 \]

(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, 4993 (1953)].
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°

\[
\begin{align*}
\text{CHO} & \rightarrow \text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{CH}_2\text{CH}_2\text{COOH} \\
\text{CHO} & \rightarrow \text{CHO} \\
\text{CHO} & \rightarrow \text{CH}_2\text{CHO} \\
\end{align*}
\]

The dehydrobromination, induced by semicarbazide, follows well-explored paths [W. McGuckin and E. Kendall, *This Journal*, 74, 5811 (1952)].

(22) So far as we are aware, there are no previous instances of this reaction sequence, in which advantage is taken of the intermediacy of an enolate in the decarboxylation of glycidates.

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

\[
\begin{align*}
\text{CHO} & \rightarrow \text{CHO} \\
\text{CHO} & \rightarrow \text{CHO} \\
\text{CHO} & \rightarrow \text{CHO} \\
\end{align*}
\]

methanolic hydrogen chloride, for example, the ester 57 was formed, while 6 N hydrochloric acid gave 58; hot 90% acetic acid removed the 6-cyanocethyl 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.

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\begin{align*}
\text{CHO} & \rightarrow \text{CHO} \\
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\text{CHO} & \rightarrow \text{CHO} \\
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\]

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Other instances are available of the difficulty of hydrolysing acetals and ketals neighbored by a basic nitrogen atom [R. Moggridge and A. Neuberger, *J. Chem. Soc.*, 745 (1938); C. Grob and H. Uebring, *Heil. Chim. Acta*, 37, 128 (1954)]. The basis for such behavior is reasonable: the usual easy heterolytic cleavage of the C-O bond in such substances involves the generation of a stabilized cation (cf. vi → vii) formation of which is strongly suppressed by a proximate N⁺. In the case at hand the positive pole engendered by the presence of a hydroxyl group, and perhaps also steric and hindrance effects, must enhance the difficulty. It will be noted, nevertheless, that an important later stage in our synthesis involves the hydrolysis of a basic ketal [vide infra, (16 → 68)].
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 Ponndorf 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 16 by slightly more than one mole of periodate in acid solution.

The important intermediate ketal-ketone 16 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 nonpolar 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.25 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.26

(25) 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 viii. 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.

(26)
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\(^\text{(27)}\) 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 -OH for -CN, it was transformed simply into the epimeric alcohol 71.\(^\text{(28)}\)

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 to the very smooth production of the formylamino compound 72.\(^\text{(29)}\)

\[\text{CH}_3\text{CON} - \quad 70\]
\[\text{OH} \quad 70\]
\[\text{NMe} \quad 70\]

Our attention was then directed to the preparation of the chloride 73, and after a series of experiments in a number of solvents it was found to be readily prepared as its hydrochloride, by the action of thionyl chloride on 70 in liquid sulfur dioxide. The chloride was extraordinarily susceptible to hydrolysis to the alcohol 71, and initial attempts to replace the chlorine atom by a cyano group in hydroxyl 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. Methanolation of 74 catalyzed by sulfuric acid gave the ester (75, R = Me), which was hy-

\[\text{CH}_3\text{CON} - \quad 70\]

\[\text{OH} \quad 70\]
\[\text{NMe} \quad 70\]

\[\text{CH}_3\text{CON} - \quad 71\]
\[\text{OH} \quad 71\]
\[\text{NMe} \quad 71\]

\[\text{CH}_3\text{CON} - \quad 72\]
\[\text{CH}_3\text{CON} - \quad 73\]

\[\text{OH} \quad 73\]

\[\text{NMe} \quad 73\]

\[\text{CH}_3\text{CON} - \quad 74\]
\[\text{HN} \quad 74\]
\[\text{NMe} \quad 74\]

\[\text{CH}_3\text{CON} - \quad 75\]
\[\text{OH} \quad 75\]
\[\text{NMe} \quad 75\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOR} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{CH}_3\text{CON} - \quad 76\]
\[\text{HN} \quad 76\]
\[\text{NMe} \quad 76\]

\[\text{NMe} \quad 76\]

\[\text{COOH} \quad 77\]

\[\text{COOCH}_3 \quad 77\]

\[\text{COOH} \quad 77\]

\[\text{NMe} \quad 77\]

\[\text{NMe} \quad 77\]
The synthetic dl-lysergic acid was converted, through its methyl ester, into dl-isolysergic acid hydrazide. The acid and the hydrazide were shown to be identical with samples prepared from natural materials by comparison of melting points, mixture melting points, infrared and ultraviolet spectra, X-ray powder diagrams, pKₐ's, and paper chromatographic behavior.

Since dl-isolysergic acid hydrazide has already been resolved and converted to ergonovine, the present work completes the synthesis of that alkaloid as well as that of lysergic acid.

Acknowledgments.—We wish to express our warmest appreciation to a number of people whose very cordial assistance during the course of the work was to a large measure responsible for its ultimate success: (1) to Drs. H. L. Breunig, A. W. Hubert and associates who provided more than adequate supplies of several of the early intermediates; (2) to Mr. W. L. Brown, Mr. G. Maciak, Mr. H. L. Hunter, Miss G. Beckmann and Mr. L. S. Hatfield who carried out all of the many analyses; (3) to Dr. H. E. Boaz, Mr. J. M. Forbes, Mr. D. O. Woolf, Miss M. Hofmann, Mrs. H. Arndt and Dr. H. A. Rose who recorded the numerous and very useful physical measurements; (4) to Dr. E. R. Shepard for helpful suggestions; and finally (5) to Dr. T. P. Carney for continued patient encouragement.

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 sequela, spectra are recorded ordinarily only for the substances in the main line of interest. Determinations were run at 0.15 molar concentration in chloroform solution except those designated with "M" on the curve. In the latter a mineral oil mull was used. Ultraviolet data were obtained in methanol solution using a Cary model 11 automatic recording spectrophotometer. Determinations were run at 0.15 molar concentration in chloroform solution except those designated with "M" on the curve.

1-Benzoyl-3-(3-carboxyethyl)-2,3-dihydroindole (5).—This was prepared by the modification of the method of Blount and Robinson, 13 3-Indolepropionic acid, 94.0 g. (0.5 mole), was dissolved in 600 ml. of water containing 20 g. of sodium hydroxide. The solution was mixed with about 100 g. of Kaney nickel catalyst and hydrogenated at room temperature in a stainless steel hydrogenation bomb at 3000 to 4000 pounds per square inch pressure. Reduction was usually complete in 20 to 30 hours, after which the catalyst was filtered and washed with a little water. Concentrated hydrochloric acid, 85 ml., was added to the filtrate, and the solution was cooled. If the reduction was incomplete, unreacted indolepropionic acid separated at this point and was removed by filtration. The filtrate was then benzoylated with benzoyl chloride in a 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° 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°.

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[a]indole (4).—1-Benzoyl-3-(3-carboxyethyl)-2,3-dihydroindole, 118 g. (0.4 mole), was mixed with 200 ml. of pure chionyl 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° 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-l. 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 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 condensation 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. Slow 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°. A sample was recrystallized from acetone; m.p. 147°.

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[a]indole Semiacetate.—A mixture of 1.5 g. of N-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[a]indole, 1.5 g. of semicarbazide hydrochloride and 2.25 g. of anhydrous sodium acetate was heated in 60 ml. of ethanol and 15 ml. of water to evaporate the water when warmed. The extract was filtered and washed with water, after which it was extracted with 4 l. of benzene. The resulting benzene solution was kept alkaline throughout the benzoylation, and the temperature was kept below 40° by cooling. The benzene took place rather than cyclization. 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. Slow addition of several volumes of ether caused the yellow ketone to crystallize. It was filtered and washed with ether; yield 7.7 g. (94%), m.p. 290-292° dec. It was recrystallized from dilute acetic acid.

Anal. Caled. for C₂₈H₂₃NO₄: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.05; H, 5.64; N, 16.08.

1-Benzoyl-3-β-benzoylthyl-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°, yield 39%. Anal. Caled. for C₂₈H₂₃NO₄: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.19; H, 6.14; N, 4.10.

1-Benzoyl-α-oxo-3-indolenebutyric Acid (8).—Diazomethane was prepared from 55 g. of nitromethylenes 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, and dried over magnesium sulfate, and concentrated in vacuo. The 1-benzoyl-3-[β-carboxymethyl]-2,3-dihydroindole so obtained did not crystallize but was adequately pure for use in the oxidation reaction below; yield 62.5 g. (99%).

The methyl ester was mixed with 300 ml. of dry ether, 36 g. of methyl oxalate and 12.5 g. of sodium methoxide, and the mixture was heated under reflux for 16 hours. The solution was poured onto an excess of ice, and the aqueous layer was separated from the neutral ether layer and then acidified with 7 ml. of concentrated sulfuric acid. The oil which separated was extracted with 500 ml. of ether in two portions, and the extracts were dried over magnesium sulfate.

The methoxyl ester was dissolved in 205 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 recrystallized from a mixture of benzene and diethyl ether; yield 18.4 g. (51%).

The methyl ester was prepared in dioxane solution by addition of an ether solution of diazomethane. It was crystallized from a mixture of benzene and ether, m.p. 145.5-147.5°.

The hydrochloride prepared in dioxane solution by addition of an ether solution of diazomethane was dissolved in 265 ml. of 77% sulfuric acid. The mixture was added, through one dropping funnel, a solution containing 58.6 g. (0.307 mole) of 3-[p-carboxyethyl]-2,3-dihydroindole, and the solution was refluxed for one hour, after which the solvent was removed in vacuo. The residual acid chloride was dissolved in 200 ml. of concentrated hydrochloric acid, 15.0 g. (0.375 mole) of sodium hydroxide, seven teaspoons 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. Unreduced 3-indolepropionic acid, 12.9 g., was recovered by filtration. The aqueous solution containing 58.6 g. (0.307 mole) of 3-[β-carboxyethyl]-2,3-dihydroindole was placed in a 1-l. three-necked flask equipped with a mechanical stirrer, two dropping funnels, a thermometer and a cooling bath. To the stirred mixture was added, through one dropping funnel, a solution of 92 g. (2.3 moles) of sodium hydroxide in 250 ml. of distilled water. When the reaction mixture became basic, simultaneous addition of 94 g. (0.921 mole) of acetic anhydride was begun, with continued stirring and cooling. At the completion of the additions, the reaction mixture was distilled with 100 ml. of concentrated hydrochloric acid, and the mixture was refrigerated overnight. The product which was collected on a funnel weighed 77.7 g. Recrystallization of the acid from 700 ml. of methanol gave 45.3 g. (63%), m.p. 157-158°.

The solution was filtered and washed with dilute hydrochloric acid and water and dried over magnesium sulfate. On concentration in vacuo and heating on a steam-bath for 15 minutes, the product was removed, and the residual acid chloride was dissolved in 200 ml. of concentrated hydrochloric acid. The hydrobromide prepared in similar fashion had a melting point of 92°.

The ultraviolet absorption spectrum was identical with that reported by Uhle.35

1-Butyryl-5-keto-1,2,3,4,5-tetrahydrobenz[e][inden]-10(11).—The in-dene derivative, 2.0 g., was treated with 2 g. of 5% palladium-on-carbon and 30 ml. of p-cymene. The mixture was refluxed for one hour, after which the solvent was removed in vacuo, and the residue was taken up in 200 ml. of benzene. The solution was filtered and washed with dilute hydrochloric acid and water and dried over magnesium sulfate. On concentration in vacuo to about 10 ml., the indene derivative crystallized; yield 0.3 g. (15%), m.p. 157-158°. Recrystallization from a few ml. of benzene gave the pure ketone, m.p. 150-150.5°.
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 off. Yield 8.45 g. (42%); m. 230-231°C. Recrystallization from a mixture of chloroform and methanol raised the melting point to 231-235°C dec.

Anal. Calcd. for C21H19BrNO3: C, 71.03; H, 5.29; N, 5.09; Br, 18.62. Found: C, 70.98; H, 5.47; N, 5.09; Br, 18.55.

1-Benzoyl-5-acetoxy-1,2-dihydrobenz[cd]indole (13).—A mixture of 20 g. of 1-benzoyl-5-hydroxy-1,2-dihydrobenz[cd]indole and 20 ml. of glacial acetic acid was warmed to 40°C. While stirred to small volume the solution was decanted and dried over potassium hydroxide to remove all water, and the ether was distilled. The crude product was distilled to yield 3210 g., b.p. 50-80°C at 12 mm., of a mixture still containing 25-30% of unchanged benzoyl-5-hydroxy-1,2-dihydrobenz[cd]indole, which was removed as follows. The crude product was distilled in 201. of dry ether, and the hydrochloride of the product was precipitated with hydrochloric acid. The salt was filtered and washed thoroughly with ether to remove all chloroformate; m. 105-107°C.


1-Benzoyl-4-is(onitroso)-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 0.5 ml. of a flask protected by a nitrogen atmosphere. 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. (0.01 mole) of 1-benzoyl-5-keto-1,2,2a,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. (0.045 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. 157-159°C dec. A sample was recrystallized from absolute ethanol, m. 145-150°C dec. and reprecipitated from methanol.

1-Benzoyl-4-is(onitroso)-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, 12.75 g. (0.25 mole) of anhydrous potassium carbonate, 730 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 filtered and washed with 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 210-211°C, yield 41.6 g. (95%).

1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole Tosylate.—Dry pyridine (1000 ml.) and 87.0 g. (0.80 mole) of 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole oxime were cooled in an ice-bath. To the reaction mixture was added with stirring a cold solution of 128.1 g. (1.2 moles) of tosyl chloride in 500 ml. of dry pyridine, and the solution was stirred and kept at 5°C for two days. Methylation was allowed to evaporate, and the residue was recrystallized from about 10 ml. of ethanol, yield 9.5 g. (35%); m. 197-202°C dec. For a sample for analysis was recrystallized twice from toluene, m. 205-209°C dec.; ultraviolet max. 248 mc (e, 21000), 278 mc (e, 41000), 370 mc (e, 4400).

1-Benzoyl-4,5-di-methylaminol-1,2-dihydrobenz[cd]indole (14).—A mixture of 10 g. of 1-benzoyl-4,5-di-methylaminol-1,2-dihydrobenz[cd]indole and 10 ml. of glacial acetic acid was dissolved in 300 ml. of liquid methylamine. The solution was cooled to 2°C. Addition was at such a rate that the temperature remained at 1-2°C. When the addition was complete, stirring was continued at 0°C for 2 hours, and the reaction mixture was placed in the refrigerator overnight. The solution was poured onto ice, and the product was filtered, washed with water, and recrystallized from ethanol; yield 10.7 g. (85%); m. 152-155°C dec.

Methylaminocarboxy Ethylene Ketal (15).—A mixture of 3718 g. of chloroacetic ethylene ketal and 7150 g. of liquid methylamine was heated at 155-157°C for 48 hours (pressure 750 to 800 pounds per square inch). Methylamine was vented, and the residue was mixed with several volumes of ether. A warm solution of 1400 g. of potassium hydroxide in 560 ml. of water was then added slowly with thorough agitation, after which excess solid potassium hydroxide was added to form a thick sludge as a bottom layer. The ether solution was decanted and dried over potassium hydroxide to remove all water, and the ether was distilled. The crude product was distilled to yield 3210 g., b.p. 50-80°C at 12 mm., of a mixture still containing 25-30% of unchanged chloroacetic ethylene ketal, which was removed as follows. The crude product was distilled in 201. of dry ether, and the hydrochloride of the product was precipitated with hydrochloric acid. The salt was filtered and washed thoroughly with ether to remove all chloroformate; m. 105-107°C.


1-Benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole Hydrochloride (17).—Potassium metal, 9.86 g. (0.022 gram atom), was added to 50 ml. of absolute ethanol protected from atmospheric moisture, and the mixture was stirred until solution was complete. After the reaction
mixture was cooled in ice to \(10^\circ\), a suspension of 8.8 g. (0.02 mole) of 1-benzoyl-5-isonitroso-1,2a,3a,4,5,6-hexahydrobenz-
\(\text{cd} \) indole tosylate in 250 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, after which the reaction mixture was placed in the refrigerator, was recovered by filtration, m.p. 155-157\(^\circ\). 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 250 g. (72\%, based on starting material consumed). Material for analysis had a m.p. of 248-250\(^\circ\) dec.

Analytical. Calcd. for C\(_{16}\)H\(_{14}\)N\(_2\)O\(_2\): C, 73.85; H, 4.91; N, 4.62. Found: C, 74.81; H, 4.91; N, 4.67.

The infrared spectrum (null) had bands at 8.49, 9.01, 15.97, 16.47, and 17.81 \(\mu\). The ultraviolet spectrum was like that in Fig. 1.

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The aqueous sodium hydroxide extract above, containing the acidic fraction, was acidified with hydrochloric acid and extracted with 150 ml. of chloroform. The chloroform fraction was dried; the solvent was distilled off. The mixture was then cooled to 25\(^\circ\) for two hours. The sodium enolate of the 4-formyl derivative, 20 g., was dissolved in 250 ml. of chloroform. The chloroform 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\(_{16}\)H\(_{14}\)N\(_2\)O\(_2\): C, 72.76; H, 4.96; N, 5.86. Found: C, 72.73; H, 4.91; N, 5.89.

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1-Benzoyl-4-formyl-5-keto-1,2a,3a,4,5,6-hexahydrobenz-
\(\text{cd} \) indole (21).—A mixture of 4-toluene carboxylic acid and 1-benzoyl-4-cyano-5-keto-1,2a,3a,4,5,6-
hexahydrobenz-
\(\text{cd} \) indole was 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 52.3 g. (72\%), m.p. 202-204\(^\circ\) dec. A sample was recrystallized from a mixture of dimethylformamide and methanol; m.p. 237-238\(^\circ\)

Analytical. Calcd. for C\(_{16}\)H\(_{14}\)N\(_2\)O\(_2\): C, 69.41; H, 4.46; N, 7.70. Found: C, 70.05; H, 4.46; N, 7.70.

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The infrared spectrum had carbonyl bands at 270 (ester) and 1670 \(\mu\) (amide).

Methyl 4-Benzoyl-4,5,5a,6-tetrahydroidole[4,3-fg]benzoxazole-8-carboxylate Hydrochloride.—A mixture of 1 g. of the benzoyl derivative above and 50 ml. of methanol was saturated with 12 g. of dry hydrogen chloride while cooling. The reaction mixture was heated to 25\(^\circ\), which time 0.34 g. (34\%) of unchanged starting material was filtered. The filtrate was decolorized with carbon, and evaporated to dryness in vacuo. The residue was crystallized from methanol; yield 0.26 g. (49\% based on ester not recovered), m.p. 226-227\(^\circ\) dec.

Analytical. Calcd. for C\(_{16}\)H\(_{14}\)N\(_2\)O\(_2\): C, 69.99; H, 4.48; N, 7.77. Found: C, 70.05; H, 4.46; N, 7.70.

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4-Benzoyl-4,5,5a,6-tetrahydroidole[4,3-fg]benzoxazole-8-
carboxylic Acid Hydrochloride.—One-half gram of the corresponding methyl ester was dissolved in 5.5 ml. of hot dimethylformamide. Pure hydrazine dihydride (7 ml.) was added, and in a few seconds the hydrazide crystallized. The mixture was filtered, 0.43 g. (86\%), m.p. 270\(^\circ\) dec. It was insoluble in all the usual solvents.


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4-Amino-5-keto-1,2a,3a,4,5,6-hexahydrobenz-
\(\text{cd} \) indole Di-
hydrochloride (24).—A. By Hydrolysis of Methyl 4-Benzoyl-4,5,5a,6-
tetrahydroidole[4,3-fg]benzoxazole-8-carboxylate. A mixture of the oxazole ester, 7.6 g., in 400 ml. of absolute ethanol with dry hydrogen chloride, and the solution was heated at reflux while a continuous stream of dry hydrogen chloride was bubbled in during 4.5 hours. The solution was digested with carbon, and the solvent was distilled in vacuo. The residual product was taken up in methanol, filtered and washed with methanol and ether; yield 3.4 g. (62\%); m.p. above 300\(^\circ\).

B. By Hydrolysis of 1-Benzoyl-4-amino-5-keto-1,2a,3a,4,5,6-
hexahydrobenz-
\(\text{cd} \) indole.—The hydrolysis 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.

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X-Ray diffraction patterns of the samples prepared by methods A and B were identical.
1-Benzoyl-4-acyethyl-5-keto-1,2,2a,3,4,5-hexahydrobenz[d]indole.—A mixture of 15.8 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 in through the solution for 20 minutes with stirring and continued cooling, during which time the temperature of the reaction mixture rose to 40°. The solution was kept at 25° for 1.5 hours, after which it was concentrated to small volume in a stream of nitrogen and the residue was dissolved in 10 ml. of 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 residual ketone was recrystallized from benzene; yield 6.0 g. (38%), m.p. 172-175°.

Anal. Calcd. for C24H19NO4: C, 73.70; H, 5.16; N, 4.78. Found: C, 73.61; H, 5.07; N, 4.79.

The infrared spectrum had carbonyl bands at 5.91 (ketone) and 6.07 μ (amide); ultraviolet λ max 244 μm (ε 23300), 330 μm (ε 4400).

B. From 1-Benzoyl-5-ethoxy-1,2,2a,3,4,5-hexahydrobenz[d]indole.—A solution of 1.8 (0.0052 mole) of benzyl alcohol and 1 ml. of 15% of chloroform was cooled in an ice-bath, and mixed with 22 ml. of cold chloroform containing 0.86 g. (0.0052 mole) of perbenzoic acid. 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 in vacuo. The crude hydroxy ketone was recrystallized from ethyl acetate and then dried over anhydrous magnesium sulfate. The sample of hydroxy ketone prepared from the enol acetate was recrystallized from ethyl acetate-petroleum ether, m.p. 205-207°. A melting point mixture 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 cooled, and then poured into 250 ml. of 8 N hydrochloric acid. Most of the ethanol was distilled in vacuo, and the product was extracted with 3 200-ml. portions of 1:1 ether-benzene. The extract was washed with water, treated with carbon 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°.


In another experiment the extraction was omitted, and the crude product was simply filtered and then washed with water, cold methanol and ether. The yield of crystalline material was 72%, m.p. 182-183°.

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.—To a mixture of 2.79 g. of the tricyclic alcohol in 100 ml. of acetic anhydride was added with shaking a solution of 0.79 g. of chromic acid in 7 ml. of water and 9 ml. of acetic acid. The reaction mixture was kept at 25° 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 dissolved in 20 ml. of absolute alcohol and ether, filtered and then washed with water. The solution was dried over magnesium sulfate; the solvent was distilled, and the ketone was crystallized from ethyl acetate-petroleum ether, m.p. 158-161°. Recrystallization from ethyl acetate and ether gave ketone with m.p. 145-146°. A mixture melting point with authentic tricyclic ketone was not depressed.

1-Benzoyl-1,2,2a,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 refluxed with 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 onto ice. The organic layer was separated, and the aqueous layer was washed with a mixture of ether and benzene. The combined extracts were washed well with 15% sodium carbonate solution, and the solvents were evaporated in vacuo.

The residue of 1-benzoyl-5-bromo-1,2,2a,3,4,5-hexahydrobenz[d]indole weighed 36 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 concentrated to 400 ml. of ice-water solution of 160° 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 deproteinizing carbon, and the solvents were distilled in vacuo. The residual 1-benzoyl-1,2,2a,3-tetrahydrobenz[d]indole was crystallized from benzene-petroleum ether; yield 15.2 g. (52%), based on the
tricyclic ketone), m.p. 91-95°. An analytical sample melted at 95.5-96.5°.

Anal. Caled. for C16H15NO2: C, 77.95; H, 5.45; N, 4.88. Found: C, 78.27; H, 6.59; N, 6.73.

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

An analytical sample

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1-Benzoyl-1,2,2a,3,4,5-hexahydrobenzene[cd]indole (31).—1-Benzoyl-1,2,2a,3,4,5-hexahydrobenzene[cd]indole, 3.0 g., was dissolved in 50 ml. of hot absolute alcohol, and to the solution was added 4 ml. of 4% sodium borohydride in absolute ethanol. The mixture was heated under reflux for ten minutes, after which another 4 ml. of the sodium borohydride solution was added, and heating was continued for 0.5 hour. Water, 25 ml., was added, and the solution was heated for ten minutes, cooled, acidified with 2 ml. of concentrated hydrochloric acid, and the residue was diluted with several volumes of water. The product was extracted with 75 ml. of chloroform, and the extract was washed with dilute hydrochloric acid and with 5% sodium bicarbonate solution. The solution was dried over magnesium sulfate, decolorized with carbon, and concentrated to small volume. Petroleum ether was added, and the product was filtered; yield 2.7 g. (88%).

The infrared spectrum had bands at 6.05, 6.13, 6.37, 6.89, and 7.12 μ.

Anal. Caled. for C16H15NO2: C, 77.40; H, 7.61; N, 6.68. 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-1,2,2a,3-tetrahydrobenzene[cd]indole (29).—A solution of perbenzoic acid in chloroform was prepared in the usual fashion and standardized against sodium thiosulfate. Twenty-four grams of 1-benzoyl-1,2,2a,3-tetrahydrobenzene[cd]indole was added in portions with swirling to a cold solution of perbenzoic acid containing a 20% excess of the oxidizing agent. The solution was allowed to stand for 44 hours at 0°, after which it was washed several times with 5% sodium hydroxide solution and then with water. It was dried over sodium sulfate, and the solvent was removed in vacuo. The epoxide compound was crystallized from a mixture of ethyl acetate and petroleum ether, m.p. to 104-105°; ultraviolet λmax 217 μ (ε 3450), 265 μ (ε 4050).

Anal. Caled. for C13H12NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.37; H, 6.68; N, 6.75.

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-hexahydrobenzene[cd]indole (32).—A solution of 2.63 g. of 1-benzoyl-1,2,2a,3,4,5-hexahydrobenzene[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., 100 ml. of ether, and 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 1,2,2a,3,4,5-hexahydrobenzene[cd]indole (32) was extracted with 100 ml. of ether, and the solution was dried and concentrated to 25 ml. Methanol, 25 ml., and 5 ml. of acetic anhydride were added, and the mixture was kept at 25° 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°.

Anal. Caled. for C18H16NO5: C, 78.27; H, 6.59; N, 6.73. Found: C, 78.40; H, 6.58; N, 6.75.
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 m.p. with the isomeric 5-keto compound was 120-141°.

Anal. Calcd. for CaH11NO2: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.80; H, 5.61; N, 5.01.

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. 184-185°.

Anal. Calcd. for C18H18N2O4: C, 68.24; H, 7.05; N, 16.75. Found: C, 68.00; H, 5.95; N, 16.11.

1-Benzoyl-4-methylamino-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (36).—Twenty grams of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole was placed in an autoclave with 200 ml. of liquid methylamine, and the mixture was kept at 98° for 8 hours. Excess amine was distilled, and the residue was crystallized from benzene with benzene and petroleum ether; yield 25 g. (90%), m.p. 93-95°. The amino alcohol crystallized from benzene with one mole of solvent of crystallization.

Anal. Calcd. for C19H18N2O4: C, 70.56; H, 6.91; N, 5.80. Found: C, 70.75; H, 6.73; N, 6.76.

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

1-Benzoyl-4-acetylmethylamino-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole. Two-hundredths of a mole of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole was placed in a mixture of 155.5 g. of sodium hydroxide, 15.0 g., was dissolved in 250 ml. of ethanol, and dry hydrogen chloride was added. The mixture was kept at 25° for 16 hours. The hydrochloride crystallized from dilute ethanol, from which it deposited as crystals containing one mole of ethanol of crystallization, m.p. 184-185°.

Anal. Calcd. for C24H20N2O4: C, 70.56; H, 6.91; N, 5.80. Found: N, 5.10; S, 6.00.

5-Hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[cd]indole Ethylene Ketal (37).—One mole of 5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[cd]indole ethylene ketal was heated on the steam-bath for 19 hours. Excess amine was distilled, and the residue was dissolved in 10 ml. of methanol and 60 ml. of ether, and dry hydrogen chloride was added. The reaction mixture was kept at room temperature for one hour, cooled, and the product was filtered and washed with cold acetone and ether: yield 81%, m.p. 156-158° dec. It contained one mole of acetic of crystallization.

Anal. Calcd. for CaH18N2O4.HCl.C2H5O: N, 5.57; Cl, 7.05. Found: N, 5.54; Cl, 7.22; pK4 in 0.6% dimethylformamide, 4.4.

Larger runs gave yields up to 88%.

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[cd]indole. A mixture of 155.5 g. of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 310 ml. of methylamine was heated on the steam-bath for 17 hours. Excess amine was removed 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 decanted. The residue was crystallized from 300 ml. of acetone; yield 98.5 g. (48%), m.p. 120-129°.

Anal. Calcd. for C19H18N2O4: C, 70.56; H, 6.91; N, 5.80. Found: C, 70.75; H, 7.23; N, 6.76.

The filtrates were treated with dry hydrogen chloride, and the hydrochloride of the product was filtered and recrystallized from a mixture of ethanol and acetone; yield 88 g. (31%), m.p. 160-160° dec. The total yield of product as free base and salt was thus 74%.

The sulfuric acid addition salt was prepared from the above free base in ethanol solution and was recrystallized from dilute ethanol, from which it deposited as crystals containing one mole of ethanol of crystallization, m.p. 184-185°.


5-Hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[cd]indole Ethylene Ketal (37).—One mole of 5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[cd]indole ethylene ketal hydrochloride, 15.0 g., was dissolved in 250 ml. of ethanol, and 0.5 ml. of an aqueous solution containing 30 g. of sodium hydroxide was added. The mixture was kept at 25° for 19 hours, after which it was concentrated in vacuo to small volume. The residue was mixed with water and extracted three times with benzene. The extracts were dried over magnesium sulfate, and the hydrochloride was precipitated with dry hydrogen chloride. The solvent was decanted, and the gummy product was crystallized from a mixture of ethanol and acetone; yield 5.2 g. (40%). A sample was recrystallized from the same solvents, m.p. 166-167° dec. It crystallized with one molecule of acetone of crystallization.

Anal. Calcd. for C19H18N2O4.2HCl.C2H5OH: N, 6.44; Cl, 10.29. Found: N, 6.49; Cl, 10.37.

The same debenzyolated ketal-alcohol dichlorohydrochloride was isolated in about 35% yield in an attempt to oxidize the benzoylketal-alcohol by a modified Oppenauer procedure using potassium t-butoxide and benzaldehyde. 1-Acetyl-5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[cd]indole Ethylene Ketal. One gram of the dichlorohydrochloride salt of 5-hydroxy-4-[N-methyl-N-acetonylamino]-1,2,2a,3,4,5-hexahydrobenz[cd]indole ethylene ketal was dissolved in 10 ml. of methanol, and 0.5 g. of anhydrous sodium acetate, 5 ml. of ether and 1 ml. of acetic anhydride were added. The reaction mixture was kept at 25° for three days, after which it was evaporated to dryness in vacuo, and the residue was mixed with excess aqueous sodium bicarbonate. The acetyl derivative was

extracted with chloroform, and the extract was dried over magnesium sulfate and concentrated in vacuo. The product was taken up in ether, and filtered; yield, 0.705 g. (89%), m.p. 150-151°. A sample was recrystallized from acetone; m.p. 152-153°.

Analytical. Calcd. for C31H38N2O3: C, 75.65; H, 7.74; N, 6.82. Found: C, 75.62; H, 7.69; N, 6.82.

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

4-Benzoyl-4,5,5a,6,9,10a-octahydro-7,9-dimethyl-7H-indolo[3,4-gh]benzoxazin-9-ol.-A solution of 1.0 g. of the benzoylated 4-ethyl-4-aminomethyl-1,2,2a,3-tetrahydrobenz[cd]-indole (39). A mixture of 1.0 g. of the hemiketal in 40 ml. of methanol was saturated with dry hydrogen chloride and kept at 25° for 16 hours. The mixture was evaporated in vacuo, and the residue was washed with ether to remove methyl benzoate. The crude dihydrochloride was then crystallized from a mixture of absolute ethanol and ether; yield 0.3 g. (31%), m.p. 193-195°. An analytical sample recrystallized from the same mixture had a m.p. of 199-201°.

Analytical. Calcd. for C31H38N2O3: C, 75.65; H, 7.74; N, 6.82. Found: C, 75.62; H, 7.69; N, 6.82.

The infrared bands were at 5.74 (ester) and 6.08 μ (amide).

1-Benzoyl-5-carboxymethyl-1,2,2a,3-tetrahydrobenz[cd]indole (40, R = H).—A mixture of 190 g. of 1-benzoyl-5-carboxymethyl-1,2,2a,3-tetrahydrobenz[cd]indole and 1100 ml. of absolute alcohol was brought to reflux, and with efficient stirring 200 ml. of 8 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 extraction of the benzene solution with two 250 ml. portions of chloroform, the aqueous solution was acidified with 75 ml. of concentrated hydrochloric acid, and the product was extracted with four 200 ml. portions of chloroform. The combined chloroform extracts were washed with 200 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 min. 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 chloroform and methanol. The analysis was obtained from material, m.p. 128-132°, redried in 960 ml. of methanol and 40 ml. of water was added to the mixture and then the layers were separated. The or- 

d or 

 called filtrate was concentrated to dryness in vacuo. The residue was dissolved in dry benzene and again crystallized from methylene chloride. The reaction mixture was allowed to stand overnight with ice-bath cooling and vigorous stirring. The solid product was collected and washed with a small amount of cold ethyl acetate. The yield of acid, m.p. 166-170° dec., was 170 g. (86%).

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.

1-Benzoyl-5-(3,5-bromomethyl)-1,2,2a,3-tetrahydrobenz-

c(d) indole (48).—A mixture of 1 g. of 1-benzoyl-

The combined chloroform extracts were washed successively with 1 N hydrochloric acid, 150 ml. of 1N sodium hydroxide and water. The solution was dried over anhydrous magnesium sulfate and concentrated to dryness in vacuo to yield a tan solid. The yield of crude bromoketone, m.p. 127-129°, was 48 g. (77%). The best analytical sample was obtained from a mixture of 0.128-129°, recrystallized from benzene-petroleum ether. The crude acid chloride was dissolved in 11. of dry benzene, and the solution was added dropwise over a period of 2 hours to an ice-cold well-stirred solution of diazomethane (from 75 g. of nitrosomethylenes) in methanol. The reaction mixture was allowed to stir at room temperature overnight. After adding 500 ml. of chloroform (to diminish emulsion formation), 300 ml. of 48% hydrobromic acid was added over a period of one hour. The mixture was heated at bath-cooling and vigorous stirring. The mixture was allowed to stir an additional 3 hours at room temperature, and then the layers were separated. The organic layer was washed with two 50-ml. portions of water and then dried over potassium carbonate. The solution was made alkaline with sodium hydroxide, and the basic product was extracted with two 50-ml. portions of chloroform. The acid solution was made alkaline with sodium hydroxide and concentrated in vacuo leaving 3.8 g. of crude, amorphous tetracyclic dialcohol, m.p. 95-105°. Secondary amine impurities were removed by dissolving the product in about 100 ml. of ice-cold 6% 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 alkaline with sodium hydroxide and concentrated in vacuo and then dried over potassium carbonate. The solid was removed, and the product was triturated with petroleum ether, m.p. 102-110°. It was not obtained in crystalline form.

1-Benzoyl-5-carboxymethyl-1,2,2a,3-tetrahydro-7-
methyl-4H-indole (49).—A mixture of 3.5 g. (0.0105 mole) of 1-benzoyl-5-carboxymethyl-1,2,2a,3-tetrahydrobenz[d]indole, 30 ml. of chloroform, and a solution of 2.2 g. (0.012 mole) of monoperphthalic acid in 70 ml. of water was allowed to stand at room temperature for one hour. The supernatant solution was decanted and washed successively with saturated sodium bicarbonate solution and water. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to a viscous oil, which solidified upon trituration with benzene. The yield of the epoxide was 2.0 g. (53%).

The ultraviolet type was like Fig. 3, curve A. A mixture of 1 g. of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[d]indole (47). The ultraviolet type was like Fig. 2, curve A. 

1-Benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz-[d]indole (48).—A mixture of 5.3 g. (0.0131 mole) of 1-benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz-[d]indole and a large excess of liquid methylamine was heated to 100° for 2.5 hours. Semicrystalline ester was heated at 100° for 2.5 hours. Semicrystalline ester was
distilled in vacuo, and the residual oil was crystallized from aqueous ethanol. The unsaturated lactone crystallized with one mole of water. To a mixture of crystalline ethanol, and 21,0 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. 108-107°.

**Anal.** Calcd. for \( \text{C}_{19}\text{H}_{18}\text{NNaO}_5\): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.15; H, 6.16; N, 9.20.

1-Benzoyl-5-acetoxyethylene-1,2,2a,3,4,5-hexahydrobenz[cd]indole—Ten liters of acetonitrile in a 22-1. round-bottom flask was warmed to 85°. The solution of the sodium salt of 1-benzoyl-5-acetoxyethylene-1,2,2a,3,4,5-hexahydrobenz[cd]indole was added slowly with shaking, and the product was filtered and then recrystallized from acetone; yield 49.6 g. (74.6%). The compound showed a double melting point at 125-130° and 196-198°. The higher melting form could be obtained by recrystallization from ethanol.

**Anal.** Calcd. for \( \text{C}_{20}\text{H}_{18}\text{NSaO}_4\): C, 75.65; H, 5.74; N, 4.45. Found: C, 75.50; H, 5.77; N, 4.45.

The results obtained are expressed only as acidifying aqueous solutions of the Darzens sodium salt.

1-Benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole Oxime—A solution containing 17.9 g. of the sodium salt of 1-benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole, 21,0 g. of hydrazinocarboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole, and 21,0 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. 108-107°.

**Anal.** Calcd. for \( \text{C}_{19}\text{H}_{18}\text{NNaO}_5\): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.15; H, 6.16; N, 9.20.

1-Benzoyl-5-acetoxyethylene-1,2,2a,3,4,5-hexahydrobenz[cd]indole—Three hundred and thirty-five grams of 1-benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole was mixed with 4400 ml. of chloroform, 1050 ml. of pure, freshly distilled pyruvic acid and 15 ml. of water. The solution was kept at 25° for 18 hours, after which it was diluted with 11.0 of chloroform and washed three times with 1500-ml. portions of water and once with 1000 ml. of 5% sodium bicarbonate. The chloroform solution was dried over magnesium sulfate, and the solvent was distilled in vacuo. The crystalline aldehyde was digested with a little hot methanol, and the mixture was cooled, and the product was filtered and washed with methanol and ether; yield 293.4 g. (83.5%); m.p. 179.5-180.8°. Similar runs gave yields in the range of 80 to 89%. A sample for analysis was recrystallized from ethanol.

**Anal.** Calcd. for \( \text{C}_{20}\text{H}_{18}\text{NO}_{5}\): C, 78.87; H, 5.23; N, 4.84. Found: C, 78.40; H, 5.07; N, 4.44.

The infrared carbonyl bands were at 24200 and 23400.

Similar results were obtained simply by acidifying aqueous solutions of the Darzens sodium salt.

1-Benzoyl-5-formyl-1,2,2a,3,4,5-hexahydrobenz[cd]indole Sodium Salt—Ten liters of acetonitrile in a 22-1. round-bottom flask was warmed to 85°. The solution of the sodium salt of 1-benzoyl-5-carboxymethyl-α,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole was added slowly with shaking, and the product was filtered and then recrystallized from acetic acid; yield 49.6 g. (74.6%). The compound showed a double melting point at 125-130° and 196-198°. The higher melting form could be obtained by recrystallization from ethanol.

**Anal.** Calcd. for \( \text{C}_{20}\text{H}_{18}\text{NSaO}_4\): C, 75.65; H, 5.74; N, 4.45. Found: C, 75.50; H, 5.77; N, 4.45.
4.20. Found: C, 75.54; H, 5.88; methano!, chilled and filtered; yield 130 g. (SOTc), m.p. of ethyl acetate and petroleum ether melted at 153-174-176'. Recrystal1iza:ion from methanol raised the melting point to 178-180°. A mixture melting point with authentic aldehyde was unchanged.

1-Benzoyl-5-formyl-1,2a,3-tetrahydrobenz[cd]indole (53).—A mixture of 140 g. of 1-benzoyl-5-formyl-1,2a,3-tetrahydrobenz[cd]indole, 250 ml. of ethylene glycol, 480 ml. of toluene and 0.4 g. of p-toluenesulfonic 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 three times with aqueous sodium bicarbonate solution. It was then dried over magnesium sulfate, and the solvent was kept at 0-5° for 23 hours, after which it was washed 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.

1-Benzoyl-5'-[2'-dioxolanyl]-5-hydroxy-4-methylamino-1,2a,3,4,5-hexahydrobenz[cd]indole (55). A. From 1-Benzoyl-5'-[2'-dioxolanyl]-5-hydroxy-1,2a,3,4,5-hexahydrobenz[cd]indole. —A mixture of 15 g. of the epoxy acetal and 500 ml. of liquid methanol was heated in an autoclave at 120° for 14 hours. The methanol 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.

1-Benzoyl-5'-[2'-dioxolanyl]-5-hydroxy-4-methylamino-1,2a,3,4,5-hexahydrobenz[cd]indole. —A mixture of 15 g. of the epoxy acetal and 500 ml. of liquid methanol was heated in an autoclave at 120° for 14 hours. The methanol 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.

1-Benzoyl-5'-[2'-dioxolanyl]-5-hydroxy-4-methylamino-1,2a,3,4,5-hexahydrobenz[cd]indole. —A mixture of 15 g. of the epoxy acetal and 500 ml. of liquid methanol was heated in an autoclave at 120° for 14 hours. The methanol 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-acetone mixture; m.p. 250° dec.

Anal. Caled. for \( C_{24}H_{33}N_2O_2 \cdot 2HCl \): C, 51.58; H, 6.35; N, 8.18. Found: C, 51.36; H, 6.22; N, 8.15.

B. By Acid Hydrolysis.—A solution of 1.0 g. of the 1-benzoyl-5-hydroxy-4-methylamino-5-acetal in 20 ml. of 6 N sodium hydroxide was added. The solution was kept at 25° for 16 hours. Excess sodium hydroxide was then back-titrated with 2 N HCl to give a neutral solution. The mixture was then concentrated in vacuo, and the residue was mixed with ether; m.p. 224.5-225.5° dec., yield 0.46 g. (51%).

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

1-Benzoyl-5-formyl-1,2,2a,3-tetrahydro benz[cd]indole Dihydrochloride.—A solution containing 20 g. of 1-benzoyl-5-formyl-1,2,2a,3-tetrahydro benz[cd]indole dihydrochloride was refluxed in 50 ml. of water for 5 hours. The mixture was then cooled overnight, and the product was filtered and recrystallized from benzene–methanol; m.p. 195-197° dec., yield 12.5 g. (82%).

Anal. Caled. for \( C_{26}H_{22}N_2O_2 \cdot 2HCl \): C, 57.70; H, 4.50; N, 8.94. Found: C, 58.02; H, 4.58; N, 8.94.

1-Benzoyl-5-cyano-1,2,2a,3-tetrahydro benz[cd]indole Dihydrochloride.—To a suspension of 12.5 g. of 1-benzoyl-5-cyano-1,2,2a,3-tetrahydro benz[cd]indole oxide in 200 ml. of dry benzene was added 20 ml. of thionyl chloride dropwise during 15 minutes while stirring and cooling in an ice-bath. Stirring was continued for 0.5 hour, after which the solvent was distilled in vacuo at room temperature. The residue was allowed to stand for three days. Crystals had formed, m.p. 223-226° dec., yield 0.46 g. (51%). Recrystallization from a methanol–ether mixture gave an analytical sample, m.p. 223-226° dec., containing 0.6 mole of water of crystallization.

Anal. Caled. for \( C_{24}H_{22}N_3O_2 \cdot 0.5H_2O \): C, 57.91; H, 4.60; N, 9.79. Found: C, 58.03; H, 4.54; N, 9.56.

The infrared spectrum had bands at 4.48, 6.05, 6.15, 6.82, 7.15 and 7.34 μ.

1-Benzoyl-5-carbamyl-4,5-epoxy-1,2,2a,3,4,5-hexahydro benz[cd]indole Dihydrochloride.—To 2.80 g. (0.01 mole) of 1-benzoyl-5-cyano-1,2,2a,3-tetrahydro benz[cd]indole was added 11.3 ml. 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%). Crystallization from methanol gave the analytical sample, m.p. 229.5-230° dec., containing 0.6 mole of water of crystallization.

Anal. Caled. for \( C_{24}H_{22}N_3O_2 \cdot 2HCl \): C, 57.92; H, 4.50; N, 9.79. Found: C, 58.09; H, 4.54; N, 9.56.

The ultraviolet type was like Fig. 3, curve A. The infrared spectrum had bands at 5.89 (unsubstituted amide) and at 6.07 μ (substituted amide).

1-Benzoyl-5-carbamyl-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydro benz[cd]indole.—A mixture of 24.5 g. of 1-benzoyl-5-carbamyl-4,5-epoxy-1,2,2a,3,4,5-hexahydro benz[cd]indole and 650 ml. of liquid methylamine was sealed in a steel autoclave and heated in a steam-bath for 18 hours. The methylamine was vented, and the residue digested with a few volumes of hot methanol. The mixture was cooled, and the product was filtered and washed with methanol and ether; yield 25.4 g. (89%), m.p. 140-142° dec. A sample was recrystallized from a mixture of methylformamide and methanol, m.p. 141-143° dec. The amide contained one mole of methanol of crystallization.

Anal. Caled. for \( C_{24}H_{22}N_3O_2 \cdot CH_2O \): C, 55.78; H, 6.37; N, 10.96. Found: C, 55.89; H, 6.35; N, 10.89.

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

Anal. Caled. for \( C_{24}H_{22}N_3O_2 \): C, 68.38; H, 6.03; N, 11.96. Found: C, 68.61; H, 6.29; N, 12.27.

Carbamyl bands in the infrared were at 5.03 μ (unsubstituted amide) and 6.08 μ (substituted amide).

5-Carbamyl-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydro benz[cd]indole Dihydrochloride.—To 100 ml. of methanol saturated with dry hydrogen chloride was added 1.0 g. (0.008 mole) of 1-benzoyl-5-carbamyl-5-hydroxy-4-methylamino-1,2,2a,3,4,5-hexahydro benz[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 methanol–ether mixture gave an analytical sample, m.p. 223-226° dec.

Anal. Caled. for \( C_{24}H_{22}N_3O_2 \cdot 2HCl \): C, 13.12. Found: C, 12.69.
4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 150 ml. of anhydrous dimethylamine. The liner and contents were placed in the bomb, which was sealed and heated on the steam-bath at 100°C for 16 hours. After the bomb was opened and the excess dimethylamine was evaporated, the residue was recrystallized from benzene to give the product, m.p. 204-205°C, yield 0.7 g. (61%).

**Anal.** Calcd. for C_{19}H_{19}N_{2}O_{3}: C, 77.79; H, 6.40; N, 5.30. Found: C, 77.58; H, 6.40; N, 5.30.

1-Benzoyl-5-carbamyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[cd]indole Ethylene Ketal (61).—A mixture of 1.0 g. (0.002 mole) of 1-benzoyl-5-carbamyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[cd]indole and 60.0 g. (0.3 mole) of methylacetoacetone ethylene ketal was heated on the steam-bath overnight. Excess ethylene ketal was distilled in vacuo, and 1.0 g. (71%) of crude amide, m.p. 198-200°C dec., was obtained. Recrystallization from benzene gave the analytical sample, m.p. 200.5-203°C.

**Anal.** Calcd. for C_{21}H_{23}N_{3}O_{3}: N, 11.50. Found: N, 11.71.

The ultraviolet type was like that in Fig. 3, curve A. The pK'/n of dimethylformamide was 4.7.

**Anal.** Calcd. for C_{25}H_{29}N_{8}O_{6}: C, 66.50; H, 6.47; N, 13.47. Found: C, 66.35; H, 6.48; N, 13.50.

The anhydrous epoxaldehyde could be obtained by vacuum drying of the hydrate at 140°C or better as follows: A mixture of the hydrate, 0.98 g., in 2.5 g. of ethyl orthoformate and 0.45 ml. of absolute ethanol containing a trace of sulfuric acid was refluxed for 2.5 hours. The solution was cooled, and the aldehyde was filtered and washed with ether; yield 0.5 g. (54%), m.p. 168-171°C. A sample was recrystallized from ethyl acetate; m.p. 173-174°C.

**Anal.** Calcd. for C_{25}H_{29}N_{8}O_{6}: C, 66.50; H, 6.47; N, 13.47. Found: C, 66.35; H, 6.48; N, 13.50.

The ultraviolet spectrum was very similar to 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-carbamyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3,4,5-hexahydrobenz[cd]indole ethylene ketal. Recrystallization from methanol gave the analytical sample, m.p. 210.5-203°C.

**Anal.** Calcd. for C_{25}H_{29}N_{8}O_{6}: C, 66.50; H, 6.47; N, 13.47. Found: C, 66.35; H, 6.48; N, 13.50.

The ultraviolet type was like Fig. 2, curve A. The infrared spectrum had carbonyl bands at 5.57 (lactone) and 5.30 (amide) and no bands in the OH or NH regions.

**Anal.** Calcd. for C_{25}H_{29}N_{8}O_{6}: C, 66.50; H, 6.47; N, 13.47. Found: C, 66.35; H, 6.48; N, 13.50.

1-Benzoyl-5-hydroxy-4,5,5a,6,8,9-hexahydro-9-hydroxy-7,9-dimethoxy-2,3-tetrahydrobenz[cd]indole (66).—Filtrates from the preparation of 1-benzoyl-5-carbamyl-5-hydroxy-4-(N-methyl-N-acetonylamino)-1,2,2a,3-tetrahydrobenz[cd]indole were then added during 20 minutes to a stirred solution of 7.32 g. of sodium borohydride in 330 ml. of absolute ethanol. The warm mixture was then stirred at room temperature for two hours, after which 800 ml. of water was added. The product which separated upon cooling was filtered and washed with acetone; yield 64.5 g. (74%), m.p. 108-110°C dec. The compound was a monohydrate.

**Anal.** Calcd. for C_{31}H_{35}N_{3}O_{3}.H_{2}O: C, 73.76; H, 6.19; N, 4.35; loss on drying at 120°C, 5.82. Found: C, 73.95; H, 6.09; N, 4.56; loss on drying at 120°C, 6.46.

The ultraviolet type was like that in Fig. 2, curve A. The infrared spectrum had carbonyl bands at 5.67 (lactone) and 6.08 (amide) and no bands in the OH or NH regions.

**Anal.** Calcd. for C_{21}H_{23}N_{3}O_{3}: N, 11.50. Found: N, 11.71.
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-ether 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-1,2,3,4,5-tetrahydrobenz[cd]-indole. — Benzoyl-5-hydroxymethyl-1,2,3,4,5-tetrahydrobenz[cd]indole hydrate (2.0 g.) was dried at 120° in vacuo. The resulting amorphous product was dissolved in 10 ml. of acetic anhydride and treated with six drops of boron fluoride etherate. The mixture was kept at room temperature for three days and was then concentrated in vacuo below 40°. The product was taken up in chloroform, and the solution was washed with aqueous sodium bicarbonate. The chloroform solution was then poured into cold water, and the gummy material, and the acid extracts were neutralized with sodium bicarbonate solution. 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 dried over magnesium sulfate, and the solvent was evaporated. The yield was unsatisfactory. The epoxide alcohol was also prepared by treatment of 1-benzoyl-5-hydroxymethyl-1,2,3,4,5-tetrahydrobenz[cd]indole with perbenzoic acid in chloroform solution; however, the yield was unsatisfactory.

1-Benzoyl-5-acetoxyethyl-4,5-epoxy-1,2,3,4,5-hexahydrobenz[cd]indole. — Benzoyl-5-acetoxyethyl-1,2,3,4,5-hexahydrobenz[cd]indole (8.0 g.) was dissolved in 60 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 solution was evaporated, and the residue was crystallized from ethyl acetate-petroleum ether mixture; yield 2.05 g. (24%). A sample for analysis was recrystallized from a mixture of ethyl acetate and methanol; m.p. 177-179°.


1-Benzoyl-5-hydroxy-3-hydroxymethyl-4-[N-methyl-N-(acetoxyamino)]-1,2,3,4,5-tetrahydrobenz[cd]indole Ethylene Ketal (67). — A mixture of 12.0 g. of 1-benzoyl-4,5-epoxy-5-hydroxymethyl-1,2,3,4,5-hexahydrobenz[cd]indole and 50 ml. of methylaminocetone 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 dried over magnesium sulfate, and the solvent was distilled. The residual amino-glycol was crystallized from ethyl acetate; m.p. 149-150° yield 1.2 g. (7.0%).

Anal. Calcd. for C26H22NO5: C, 68.47; H, 6.30; N, 6.39. Found: C, 68.54; H, 7.14; N, 6.55.

The pircate prepared in methanol melted at 185-186° dec.

Anal. Calcd. for C26H25NO2.C6H2NO2: C, 55.77; H, 4.98; N, 10.49. Found: C, 55.65; H, 5.14; N, 10.38.

1-Benzoyl-2,2a,3,4-tetrahydro-4-[methyl-2-methyl-1,3-dioxolan-2-yl-methyl]-amino]benz[cd]indol-5(1H)-one (16). A. By Oxidation of the Glycol (67). — A mixture (0.002 mole) of 1-benzoyl-5-hydroxy-5-hydroxymethyl-1,2,3,4,5-hexahydrobenz[cd]indole and 0.44 g. (0.0022 mole) of sodium periodate in 10 ml. of water was treated with 0.2 ml. of concentrated sulfuric acid. The mixture was shaken occasionally during 0.5 hour at 35-37°. The solution was neutralized with sodium bicarbonate, and the amorphous product was filtered and washed with water; yield almost theoretical. The crude product was crystallized from acetone, m.p. 155-156°.

Anal. Calcd. for C26H22NO5: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.85; H, 6.49; N, 6.95.

The hydrochloride was prepared using dry hydrogen chloride in acetone. The salt crystallized with one mole of acetone; m.p. 138-139°.

Anal. Calcd. for C26H25NO2·C6H2HCl: C, 64.72; H, 6.46; N, 5.59. Found: C, 65.27; H, 6.51; N, 5.61.

The sulfonic acid addition salt, prepared in methanol containing a little water, analyzed for a trihydrate, m.p. 155-157° dec.

Anal. Calcd. for C26H22NO5.H2SO4.3H2O: C, 51.51; 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 Brome 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 mol) of the pircate in methanol melted at 185-186° dec.
mole) of methylaminoacetone ethylene ketal in 4500 ml. of dry benzene was refluxed under nitrogen for 21 hours. The mixture was cooled, and 161 g. (93.4%) of methylaminoacetone ethylene ketal hydrobromide was filtered, m.p. 158-159°.

**Anal.** Caled. for C_{17}H_{18}BrN_2O_3: C, 57.98; H, 6.71; N, 11.78. 
Found: C, 58.05; H, 6.67; N, 11.83.

The ultraviolet curve was like that in Fig. 1.

5-Keto-4-[N-methyl-N-acetonylamo]-1,2,3,4,5-hexahydrobenzoc[cd]indole (89).—Twenty grams of 1-benzoyl-2,3,4,5-tetrahydrobenzoc[cd]indole was mixed with 550 ml. of absolute ethanol. The mixture was cooled, and the product was filtered 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. 145-147°. An analytical sample was recrystallized from dilute ethanol; m.p. 155-157°; ultraviolet λ_{max} 210 μm (ε 10000); 266 μm (ε 18000); 306 μm (ε 20000).

**Anal.** Caled. for C_{17}H_{18}N_2O_2HBr: N, 10.91. 
Found: N, 10.85. 
Calcd. for C_{17}H_{18}N_2O_2: N, 10.85. 
Found: N, 10.75.

The diketone was crystallized from acetone; m.p. and mixture m.p. 135-136°, yield 220 g. (71%).

The diketone was mixed with 550 ml. of absolute ethanol. The mixture was cooled, and the product was filtered 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. 145-147°. An analytical sample was recrystallized from dilute ethanol; m.p. 155-157°; ultraviolet λ_{max} 210 μm (ε 10000); 266 μm (ε 18000); 306 μm (ε 20000).

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Found: N, 10.85. 
Calcd. for C_{17}H_{18}N_2O_2: N, 10.85. 
Found: N, 10.75.

The diketone was crystallized from acetone; m.p. and mixture m.p. 135-136°, yield 220 g. (71%).

The diketone was mixed with 550 ml. of absolute ethanol. The mixture was cooled, and the product was filtered 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. 145-147°. An analytical sample was recrystallized from dilute ethanol; m.p. 155-157°; ultraviolet λ_{max} 210 μm (ε 10000); 266 μm (ε 18000); 306 μm (ε 20000).

**Anal.** Caled. for C_{17}H_{18}N_2O_2HBr: N, 10.91. 
Found: N, 10.85. 
Calcd. for C_{17}H_{18}N_2O_2: N, 10.85. 
Found: N, 10.75.

The diketone was crystallized from acetone; m.p. and mixture m.p. 135-136°, yield 220 g. (71%).

The diketone was mixed with 550 ml. of absolute ethanol. The mixture was cooled, and the product was filtered 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. 145-147°. An analytical sample was recrystallized from dilute ethanol; m.p. 155-157°; ultraviolet λ_{max} 210 μm (ε 10000); 266 μm (ε 18000); 306 μm (ε 20000).

**Anal.** Caled. for C_{17}H_{18}N_2O_2HBr: N, 10.91. 
Found: N, 10.85. 
Calcd. for C_{17}H_{18}N_2O_2: N, 10.85. 
Found: N, 10.75.
The hydrochloride was prepared in ethanol and was recrystallized from aqueous ethanol; m.p. 250° dec.


The oxime was prepared in the usual fashion, m.p. 250° dec., after recrystallization from dimethylformamide-ether.

Anal. Calcd. for C18H19N2O2: C, 68.88; H, 6.44; N, 14.15. Found: C, 68.74; H, 6.70; N, 14.41.

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

Anal. Calcd. for C18H19N2O2: C, 63.70; H, 6.24; N, 10.64. Found: C, 63.71; H, 6.18; N, 10.58.

9-Hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline.-Ten grams of 9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinoline was subjected to hydrogenation over 1 g. of platinum black in 500 ml. of methanol, 15 ml. of acetic acid, and 15 ml. of water. The solution was filtered, evaporated under reduced pressure, and the residue was recrystallized from chloroform; m.p. 267-268° dec.

Anal. Calcd. for C16H19N2O2: C, 71.80; H, 7.09; N, 9.85. 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. 182-184° dec.; ultraviolet \( \lambda_{\text{max}} = 285 \text{ nm} \) (3350), 251 nm (3870), 306 nm (3500), 328 nm (3000); \( pK' \) 4.06 in 60% dimethylformamide, 6.02.

Anal. Calcd. for C18H20N2O2: C, 66.47; H, 6.81; N, 8.86. Found: C, 68.47; H, 6.81; N, 8.86.

The acetate acid salt was prepared by crystallization from acetic acid; m.p. 175° dec.

Anal. Calcd. for C18H20N2O2: C, 66.78; H, 6.28; N, 8.25. Found: C, 66.23; H, 5.48; N, 8.49.

The hydrochloride was recrystallized from water as a hemihydrate, m.p. 267-268° dec.


The acetic acid salt was separated, dried over magnesium sulfate and the hydrochloride was recrystallized from aqueous ethanol; m.p. 195° dec.


4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinolinium Hydroxide Betaine (f).—A mixture of 0.1 g. of 4-acetyl-9-keto-7-methyl-4,5,5a,6,6a,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. 253-256° for 12 hours. The product was dissolved in water, and the solution was separated, dried over magnesium sulfate and the hydrochloride was recrystallized from a mixture of methanol and ethanol; m.p. 240-241° dec.

Anal. Calcd. for C18H20N2O2.HCl: C, 59.67; H, 6.92; N, 8.30; Cl, 10.58. Found: C, 64.47; H, 7.15; N, 8.44; Cl, 10.34.

The methiodide 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.


4-Acetyl-4,5,5a,6-tetrahydro-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinolinium Hydroxide Betaine.—A mixture of 0.1 g. of 4-acetyl-9-keto-7-methyl-4,5,5a,6,6a,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. 253-256° for 12 hours. The compound was a monohydrate; ultraviolet \( \lambda_{\text{max}} = 246 \text{ nm} \) (3200), 351 nm (6000); \( pK' \) 4.06 in 60% dimethylformamide, 6.06; \( pK' \) 4 in water, 4.82.

The methiodide 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.

The starting betaine was recovered from the reaction mixture. 

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. 182-184° dec.; ultraviolet \( \lambda_{\text{max}} = 285 \text{ nm} \) (3350), 251 nm (3870), 306 nm (3500), 328 nm (3000); \( pK' \) 4.06 in 60% dimethylformamide, 6.02.

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

4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-fg]quinolinium Hydroxide Betaine.—A mixture of 0.1 g. of 4-acetyl-9-keto-7-methyl-4,5,5a,6,6a,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. 253-256° for 12 hours. The compound was a monohydrate; ultraviolet \( \lambda_{\text{max}} = 246 \text{ nm} \) (3200), 351 nm (6000); \( pK' \) 4.06 in 60% dimethylformamide, 6.06; \( pK' \) 4 in water, 4.82.

The methiodide 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.
The free base was obtained by neutralization of the hyd- 
drochloric acid with aqueous sodium bicarbonate. It was 
crystallized from ethanol or ethyl acetate; m.p. 195-197° 
dec. The infrared spectrum was like the epimeric alcohol 
above; pK', 6.58. 

A. By Acid Hydrolysis of the 9-Formamido Compound. —A solution of 9 g. of 9-formamido-4-methyl- 
4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline in 150 
ml. of concentrated hydrochloric acid was heated at reflux 
under nitrogen for 17 hours. The solution was cooled 
and the solnuiion was kept at 25° for 0.5 hour. Excess acetic 
acid was removed in vacuo, and the residue was crystallized 
from ethyl acetate; m.p. 195-197° dec. 

Anal. Caled. for C₂₉H₂₅N₃O₂: C, 71.85; H, 6.98; N, 
13.50. Found: C, 71.69; H, 6.92; N, 13.49.

When the epimeric 3-alcohol was used as starting material 
in place of the normal alcohol above, the same amide was 
generated in the same yield. m.p. 297-298° dec. A mixture 
m.p. showed no depression.

The infrared spectrum (nall) had bands at 3.15, 6.03, 
6.82, 6.57, 6.83 and 7.13 μ. 

4-Acetyl-9-amino-7-methyl-4,5,5a,6,6a,7,8,9-octahydro 
indolo[4,3-f]quinoline.-A mixture of the 4-acetyl-9-form-
amido compound, 0.5 g., and 10 ml. of anhydrous hydra-
lic acid was heated under reduced pressure. The solnuiion 
was concentrated to a thick sirup. Water and methanol 
were added, and the residue was crystallized from aqueous 
methanol; m.p. 291-292° dec. A sample was recrystallized 
from aqueous ethanol; ultraviolet λmax 245 μe (ε 27000), 
290 μe (ε 1900), 380 μe (ε 1240). 

Anal. Caled. for C₂₉H₂₅N₃O₂: C, 71.85; H, 6.98; N, 
11.92. Found: C, 71.81; H, 6.31; N, 11.99.

B. By Acid Hydrolysis of the 4-Acetyl-9-formamido Com-
pound.—A solution of 2 g. of the formamido compound 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 residual 
hydrochloride salt was recrystallized from water and meth-
anol, m.p. 215-217° (dec.). 

The salt from either A or B (2.2 g.) was dissolved in 
50 ml. of methanol and was heated at reflux under nitrogen for 17 
hours. The solution was cooled, and the product was filtered and 
washed with methanol and water; yield 1.6 g. (90%). After recrystallization from ethyl acetate it melted at 165- 
167° dec.
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 9.8 g. (57%). A sample for analysis was recrystallized from a mixture of dimethylformamide and methanol; m.p. 275°-280° dec.

**Anal.** Caled. for C62H50N1O5; C, 66.78; H, 6.24; N, 6.67. Found: C, 66.83; H, 6.30; N, 6.48.

4-Acetyl-9-chloro-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline Hydrochloride (73).—4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline hydrochloride, 5.1 g., was dissolved in 75 ml. of liquid sulfur dioxide contained in a glass liner in a steel autoclave. Thionyl 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. Sulfur dioxide was allowed to evaporate while the volume of the solution was kept constant by slow addition of dry ether. The amorphous chloro hydrochloride was filtered, washed with ether, and dried in vacuo, m.p. 190°-195° dec., yield 3.5 g.

**Anal.** Caled. for C35H30ClN2O4·HCl: Cl, 20.95; N, 8.26. Found: Cl, 21.61; N, 7.79.

Use of the 9-p-epimeric alcohol in this reaction gave the same chloride in comparable yield.

4-Acetyl-9-cyano-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline (74).—Dry, powdered sodium cyanide, 40 g., was added to 300 ml. of ice-cold liquid hydrogen cyanide, and the mixture was stirred and cooled in ice, and 7.5 g. of the crude amorphous 4-acetyl-9-chloro-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline hydrochloride 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 mixed with chloroform and ice-water, and the resulting mixture was filtered. The organic layer was separated, and the aqueous layer was again extracted with chloroform. The combined extracts were dried over magnesium sulfate, and the residue was filtered. A light yellow solution was evaporated completely to dryness under reduced pressure. A sample of the dihydroindolo[4,3-f]quinoline, 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, and then dissolved in a mixture of chloroform (30 ml.), ice and 2 ml. of concentrated hydrochloric acid. The mixture was treated with decolorizing carbon and then sulfuric acid was added slowly. The solution was sealed in a glass tube under nitrogen and heated at 100° for 24-25 hours. The mixture was treated with decolorizing carbon and then concentrated in vacuo to about 10 ml. It was poured onto a mixture of chloroform (30 ml.), ice and 10 g. of sodium bicarbonate. The chloroform 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 recrystallized from ethyl acetate; yield 3.3 g. (54% same chloride in comparable yield.

**Anal.** Caled. for C44H38Na: C, 76.46; H, 6.82; N, 5.85. Found: C, 76.08; H, 6.97; N, 6.70.

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

**Anal.** Caled. for C44H38O: C, 69.92; H, 6.79; N, 5.85. Found: C, 70.06; H, 6.88; N, 6.70.

4-Acetyl-9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline.-Acetylation of the above ester along with some deacetylated nitrile, m.p. 170°-171°.

**Anal.** Caled. for C43H36N2O4: C, 75.41; H, 6.38; N, 9.17. Found: C, 75.80; H, 6.50; N, 9.85.

Recrystallization from the same solvent raised the m.p. to 181°-182°; ultraviolet λmax 243 μm (ε 37000), 249 μm, (ε 29000), 258 μm (ε 14200), 313 μm (ε 3210). The ultraviolet spectrum was identical to that reported by Stoll and by Atherton.

**Anal.** Caled. for C43H36N2O4: C, 70.35; H, 6.22; N, 9.84. Found: C, 70.28; H, 6.36; N, 8.84.

The ultraviolet spectrum was identical to that reported by Stoll and by Atherton.

9-Carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline (75, R = Me).—A solution of 1.0 g. of 9-carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline, 15 ml. of xylene and 0.5 g. of 5% palladium-on-carbon catalyst 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.** Caled. for C43H36N2O4: C, 70.35; H, 6.22; N, 9.84. Found: C, 71.80; H, 7.19; N, 10.06.
acid. The eluate was evaporated to give the amino acid, m.p. above 300°. A sample was recrystallized from water for analysis.

Anal. Calcd. for C_{10}H_{13}NO_{4}: C, 71.09; H, 6.71; N, 10.35. Found: C, 70.76; H, 6.87; N, 10.40.

9-Carboxy-7-methyl-4,5,6,6a,7,8,9,10,10a-octahydroindololo[4,3-f]quinoline (77).—A mixture of 1.0 g. of 9-carboxymethoxy-7-methyl-4,5,6,6a,7,8,9-octahydroindolo[4,3-f]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 3.8 by addition of dilute hydrochloric acid. The crude product which separated, 0.5 g., containing 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. Calcd. for C_{10}H_{13}NO_{4}·H_{2}O: C, 66.64; H, 6.90; N, 9.72. Found, dried at 120°: C, 67.49; H, 7.10; N, 9.79. Found, dried at 180°: C, 69.20; H, 6.77.

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

The infrared spectrum (nul) had bands at 3.9, 3.1, 6.20, 6.28, 6.89 and 7.61 μ. The ultraviolet spectrum was that of an unconjugated indole system; λ_{max} 222 μ (ε 30000), 281 μ (ε 2600), 291 μ (ε 5100).

Synthetic dl-Lysergic Acid (78).—A mixture of 9-carboxymethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo[4,3-f]quinoline, 3.9 g., and 78 ml. of 1.5% potassium hydroxide solution was refluxed for 30 minutes under nitrogen. Hydrated sodium arsenate, 8.5 g., and Raney nickel (16 g. wet), previously deactivated by boiling in xylen suspension, 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 lysergic 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. 233-235° dec., was also obtained; total yield 30%. 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-lysergic acid made from natural dl-lysergic acid was likewise 242-243° dec.

Anal. Calcd. for C_{10}H_{13}NO_{4}·H_{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. Calcd. for C_{10}H_{13}NO_{4}: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 6.10; N, 10.32.

The ultraviolet spectrum in dilute aqueous alkaline solution was identical with that of the sample derived from natural sources, λ_{max} 222 μ (ε 30000), 281 μ (ε 2600), 291 μ (ε 5100). The P.Kₐ in 65% dimethylformamide (4.92 and 8.04) was the same for both samples, and the X-ray diffraction patterns and paper chromatographic behavior were identical.

dl-Isolysergic Acid Hydrazide from Ergocristine.—A sample was obtained by reaction of anhydrous hydrazine with ergocristine in the usual manner. It was recrystallized from a mixture of dimethylformamide and methanol; 225-228° dec.; λ_{max} 259 μ (ε 18000), 240 μ (ε 18300), 210 μ (ε 7630).

Anal. Calcd. for C_{10}H_{13}NO_{4}: C, 68.06; H, 6.43; N, 19.85. Found: C, 67.90; H, 6.52; N, 19.62.

Synthetic dl-Isolysergic Acid Hydrazide.—Crude synthetic dl-lysergic acid, 0.4 g., was powdered and mixed with 23 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 benzene–methanol and decolorized with carbon. Solvents were again evaporated, and the crude dl-methyl ergylate 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 dl-isolysergic acid hydrazide was crystallized from methanol; yield 0.050 g., m.p. 224-227° dec. A mixture melting point with natural dl-isolysergic 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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