THE ERGOT ALKALOIDS

XII. THE SYNTHESIS OF SUBSTANCES RELATED TO LYSERGIC ACID*

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In a series of papers during the past few years Jacobs and Craig have shown that the ergot alkaloids are derivatives of a unique acid base, lysergic acid, in which the latter or an isomer is conjugated with certain amino acids or substances which can be derived from them, such as 2-aminopropanol-1, pyruvic acid, and isobutyrylformic acid. Since lysergic acid is thus the common characteristic constituent of these alkaloids, the determination of its structure became at once a major issue in the ergot alkaloid problem. Degradation studies combined with a study of its characteristic groupings and other properties made it possible to derive a very probable structure for lysergic acid, as given in Formula I.[1] This formula appears to explain satisfactorily all of the observations which have been made. An uncertainty, however, remains as to the exact position to which the carboxyl group can be assigned. All evidence in this case points to certain positions on Ring D, preferably (7) or (8). It has therefore been of importance and interest to obtain a direct check on the validity of this formulation by synthesis.

There appears to be no recorded experience in regard to the possibility of the formation of the tricyclic system represented by Rings A, B, and C, not to speak of the tetracyclic structure A, B, C, D given in Formula I. As a first step, the synthesis of *3,4-trimethylene indole* (Formula II) was attempted. This was accomplished by the reduction of naphthostyril with sodium and

* Jacobs, W. A., and Gould, R. G., Jr., *Science*, **85**, 248 (1937).

[1] Jacobs, W. A., and Craig, L. C., *J. Biol. Chem.*, **115**, 227 (1936).

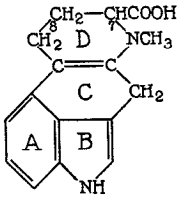
butyl alcohol. An expected by-product of the reaction was also encountered and was separated from the indole derivative by virtue of its basic properties, namely 1-hydroxymethyl-8-amino-1,2,3,4-tetrahydronaphthalene (Formula III). The identities of these substances were established by their production by a different procedure; namely, reduction of the methyl ester of 8-amino-1,2,3,4-tetrahydro-1-naphthoic acid, by the aromatic character of the amino group of the second (basic) reduction product, and by the characteristic indole reactions given by trimethylene indole. The latter, however, did not give the deep blue Keller test so characteristic of lysergic acid and its derivatives; instead a deep red-brown color was produced.

As a next step the attempt was made to realize the assumed 4-ring system of lysergic acid. This was actually accomplished as follows: The first objective was *5,6-benzoquinoline-7-carbonic acid* (Formula IV), which was obtained by a series of reactions beginning with 1,8-naphthalic acid. This acid was converted into 3-nitro-1-naphthoic acid according to Leuck, Perkins, and Whitmore,[2] and yielded 3-amino-1-naphthoic acid on reduction. The amino acid, when subjected to the Skraup synthesis, gave the desired benzoquinoline carbonic acid which was further characterized by its salts and *ethyl ester*. On nitration, benzoquinoline carbonic acid fortunately appeared to give mainly *3′-nitro-5,6-benzoquinoline-7-carbonic acid*. *3′-Amino-5,6-benzoquinoline-7-carbonic acid* resulted on reduction of the nitro acid. The amino acid readily formed the *benzoquinoline lactam* (Formula V).

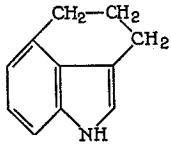
As in the case of naphthostyril, the lactam base on reduction with sodium in butyl alcohol gave a mixture of the desired tetracyclic indole derivative (Formula VI) and the by-product due to reductive cleavage of the lactam grouping to the aromatic amino alcohol, *viz. 3′-amino-7-hydroxymethyl-1,2,3,4,7,8,9,10-octahydro-5,6-benzoquinoline* (Formula VII). These substances were separated by virtue of their differential solubilities in ether.

For the above tetracyclic indole we propose the trivial name *ergoline* and have followed in Formula VI the same numbering used in the case of the formula for lysergic acid.[1] In the case both of the latter and of the amino alcohol simultaneously produced, it

[2] Leuck, G. L., Perkins, R. P., and Whitmore, F. C., *J. Am. Chem. Soc.*, **51**, 1834 (1929).



I



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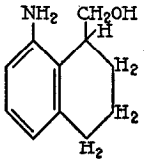

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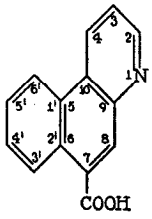

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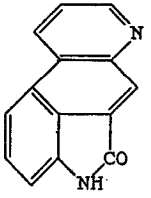

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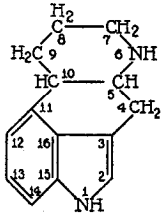

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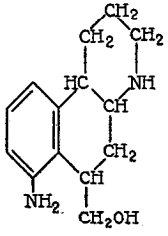

VII

is obvious that each contains several asymmetric centers. Therefore, although not certain, it is possible that the substances isolated

by us may still be non-homogeneous in the sense of being mixtures of epimers.

Of greatest interest, however, is not only the synthetic realization of the assumed tetracyclic system of lysergic acid (dihydrolysergic acid) but the color reactions produced by ergoline. The reactions with dimethylaminobenzaldehyde (as an indole) are identical with those given by lysergic acid. In the case of the Keller test there is a very close approach to that which is so characteristic of lysergic acid. In intensity and speed of development it is indistinguishable from the latter. However, instead of a deep pure blue, the color is more of a violet-blue. This slight difference could doubtlessly be caused either by the absence of the carboxyl group or of the N-methyl group of lysergic acid or of both.

Finally, catalytic hydrogenation of the above lactam base has resulted in only partial reduction to a tetrahydroquinoline derivative, *viz. 3′-amino-1,2,3,4-tetrahydro-5,6-benzoquinoline-7-carbonic acid lactam.* On reduction of this tetrahydro lactam with sodium and butyl alcohol, again a mixture of ergoline and the corresponding amino alcohol was obtained.

There is now in progress in this laboratory a logical extension of this synthetic work both in regard to methods of procedure and to the inclusion of substitution products of ergoline and finally, it is hoped, of the synthesis of lysergic acid or its derivatives.

EXPERIMENTAL

Reduction of Naphthostyril—10 gm. of sodium were added to a boiling solution of 2 gm. of naphthostyril in 200 cc. of dry butyl alcohol and the mixture was shaken vigorously. After the sodium had dissolved, water was added and the butyl alcohol was removed in a vacuum. The residual aqueous solution was extracted with ether, and the extract in turn was shaken with 2 per cent hydrochloric acid.

3,4-Trimethylene Indole—The above ether solution gave 0.8 gm. of the indole as a dark red oil, which crystallized when allowed to cool and scratched. It was purified by sublimation at 120–140° at 0.3 mm. pressure. The colorless, crystalline sublimate on recrystallization from low boiling petroleum ether separated as long, colorless prisms which melted at 58.5–59°.

$C_{11}H_{11}N$. Calculated. C 84.08, H 7.07, N 8.92
Found. " 84.18, " 7.18, " 8.97

Trimethylene indole has an odor resembling more that of α-naphthylamine than that of indole or skatole. It is very soluble in ether, alcohol, and benzene; moderately so in warm petroleum ether and ligroin; and practically insoluble in water and dilute acids. It gives an intense reddish violet color with *p*-dimethylaminobenzaldehye and hydrochloric acid. A reddish brown color is produced with Keller's reagent, which is quite different from the deep blue color given by lysergic acid and the ergot alkaloids.

Trimethylene indole picrate was obtained from alcohol as long, dull red needles which melted at 164–166°.

$C_{11}H_{11}N \cdot C_6H_3O_7N_3$. Calculated. C 52.8, H 3.65, N 14.5
Found. " 52.93, " 3.46, " 14.43

1-Hydroxymethyl-8-Amino-1,2,3,4-Tetrahydronaphthalene—This by-product in the formation of trimethylene indole was contained in the 2 per cent hydrochloric acid solution described above. After the dissolved ether was removed and the solution made alkaline, the product crystallized. The yield was 0.8 gm. of crude substance from 2 gm. of naphthostyril. Crystallized from alcohol and then from ether, it formed square, colorless platelets which melted at 111–112°.

$C_{11}H_{15}ON$. Calculated, C 74.6, H 8.53; found, C 74.38, H 8.58

The fact that the amino alcohol after diazotization coupled to form dyes showed that the ring containing the amino group is aromatic. Attempts to transform the amino alcohol into trimethylene indole were unsuccessful.

The hydrochloride was obtained from a small volume of dilute hydrochloric acid.

$C_{11}H_{15}ON \cdot HCl$. Calculated, C 61.9, H 7.54; found, C 62.12, H 7.56

The picrate formed light yellow prisms from alcohol, which melted at 206–207°.

The *N-benzoyl derivative* was prepared by treatment of the amino alcohol in benzene solution with excess benzoyl chloride and

potassium carbonate. After recrystallization from alcohol it melted at 195.5–197°.

$C_{18}H_{19}O_2N$.	Calculated.	C 76.9, H 6.84, N 4.98
	Found.	" 76.50, " 6.78, " 5.25

The properties of the substance made it apparent that acylation occurred on the amino group.

Both trimethylene indole and hydroxymethyl amino tetrahydronaphthalene were obtained also from the methyl ester of 8-amino-1,2,3,4-tetrahydro-1-naphthoic acid. This substance was prepared according to Schroeter and Rössler[3] who reported a melting point of 53–54°. Our preparation, however, after repeated recrystallization from petroleum ether melted at 75–76°.

$C_{12}H_{15}O_2N$. Calculated, C 70.30, H 7.36; found, C 70.30, H 7.47

The ester was reduced with sodium and butyl alcohol, as described above for naphthostyril, and gave the same reduction products. 0.2 gm. of the ester gave 70 mg. of trimethylene indole and 100 mg. of the amino alcohol.

5,6-Benzoquinoline-7-Carbonic Acid—3-Nitro-1-naphthoic acid was prepared from 1,8-naphthalic acid according to Leuck, Perkins, and Whitmore.[2] After recrystallization from glacial acetic acid it was then reduced to the amino acid with ferrous sulfate and ammonia. Since the free amino acid is unstable, it was found advantageous to isolate it as the sparingly soluble sulfate.

22 gm. of nitronaphthoic acid were dissolved in 300 cc. of 15 per cent ammonia, and 180 gm. of ferrous sulfate in 300 cc. of water were added. The mixture was brought to a boil and then filtered. The clear, light yellow filtrate on acidification with sulfuric acid yielded the sulfate which was collected in almost theoretical yield.

A mixture of 19 gm. of the sulfate, 13 gm. of sulfuric acid, 25 gm. of dry glycerol, and 5 gm. of nitrobenzene was heated for 5 hours at 170–180°. The reaction mixture after dilution with 200 to 300 cc. of water was boiled and filtered. The acid filtrate was extracted with ether, then made alkaline, filtered, and again

[3] Schroeter, G., and Rossler, H., *Ber. chem. Ges.*, **35**, 4222 (1902).

extracted with ether. Finally, the aqueous solution was made just acid to litmus with acetic acid, and quickly filtered, or decanted, from precipitated tar. The benzoquinoline carbonic acid then crystallized when scratched and allowed to stand. Occasionally, however, the substance crystallized immediately with the tar. In such a case, repeated recrystallization as the hydrochloride from dilute hydrochloric acid proved necessary.

In either case, final purification was accomplished by treatment of the dilute hydrochloric acid solution with norit, followed by cautious addition of sodium acetate solution. The colorless, microcrystalline powder so obtained melted with decomposition at 298–300°, and with the appearance of the odor of benzoquinoline.

$C_{14}H_9O_2N$.	Calculated.	C 75.4, H 4.04, N 6.3
	Found.	" 75.38, " 3.85, " 6.44
	"	" 75.17, " 4.22

Benzoquinoline carbonic acid is soluble in dilute mineral acid and alkali, and in pyridine; it is sparingly soluble in acetic acid and alcohol. It is a stronger acid than base and is almost completely precipitated at a pH just acid to Congo red.

The hydrochloride crystallized from dilute hydrochloric acid in microscopic needles.

$C_{14}H_9O_2N \cdot HCl$. Calculated, C 65.00, H 3.91; found, C 65.10, H 3.81

The ethyl ester was prepared by refluxing a suspension of the acid in absolute alcohol saturated with HCl for several hours and until solution was complete. Although on concentration the ester hydrochloride separated in transparent rhombs, it was not isolated as such but converted into the free ester. The latter, after recrystallization from alcohol, melted at 104–105°.

$C_{16}H_{13}O_2N$. Calculated, C 76.50, H 5.21; found, C 76.40, H 5.25

3′-Nitro-5,6-Benzoquinoline-7-Carbonic Acid—4 gm. of finely powdered benzoquinoline carbonic acid were gradually added to 16 cc. of fuming nitric acid (sp. gr. 1.58) cooled in ice, and the mixture was then allowed to stand at room temperature overnight.

Concentration of the solution *in vacuo* at room temperature gave large, colorless crystals of the nitrate of the nitro compound. The salt, however, hydrolyzed on washing with water. The nitro

compound was then dissolved in dilute sodium hydroxide solution and reprecipitated with acetic acid, as a colorless microcrystalline powder melting at 310°.

$C_{14}H_8O_4N_2$.	Calculated.	C 62.7, H 3.01, N 10.45
	Found.	" 62.84, " 3.37, " 10.20

Nitrobenzoquinoline carbonic acid gives silvery leaflets of the sodium salt from dilute sodium hydroxide solution. The hydrochloride crystallizes from 15 per cent hydrochloric acid as long needles.

For the next step, however, it was found advantageous to pour the nitration mixture directly onto ice, and to collect the precipitate with water. The material thus obtained was light tan in color and practically pure. The yield was almost theoretical.

3′-Amino-5,6-Benzoquinoline-7-Carbonic Acid Lactam—The above nitro derivative was reduced with ferrous sulfate and alkali to the amino acid which was then lactamized by treatment with hydrochloric acid in the following steps.

2.7 gm. of nitro compound were dissolved in 130 cc. of 5 per cent sodium hydroxide and warmed. A hot solution of 20 gm. of ferrous sulfate in 50 cc. of water was then added, and the mixture was brought to a boil and then filtered. The iron precipitate was reextracted with hot dilute sodium hydroxide solution. The combined clear, yellow filtrates were made strongly acid with hydrochloric acid. On standing, the hydrochloride of the lactam crystallized as red needles. The salt was recrystallized from dilute hydrochloric acid.

$C_{14}H_8ON_2 \cdot HCl$. Calculated, C 65.50, H 3.54; found, C 65.51, H 3.58

The lactam base obtained by decomposition of the salt was purified by recrystallization from alcohol with bone-black. It separated as long, silky, bright yellow needles which melted at 280°.

$C_{14}H_8ON_2$. Calculated, C 76.40, H 3.66; found, C 76.47, H 3.53

The over-all yield from 5,6-benzoquinoline-7-carbonic acid was about 65 per cent, which indicates that the nitration must give mainly the 3′-nitro derivative.

The lactam ring is readily opened by heating with strong alkali

and is again closed on acidification with mineral acids even at room temperature.

The free amino acid was obtained, however, from the sodium salt with dilute acetic acid in the cold. The dry acid which is carmine-red in color changes to the yellow lactam on heating. It can be diazotized and coupled with α-naphthol, whereas the lactam gives a negative diazo reaction.

Reduction of 3′-Amino-5,6-Benzoquinoline-7-Carbonic Acid Lactam—2 gm. of sodium were added to a boiling solution of 0.45 gm. of the lactam in 40 cc. of dry butyl alcohol and the mixture was shaken vigorously. The latter changed instantly to a brilliant scarlet and then finally became colorless. After addition of water the butyl alcohol was removed *in vacuo*. The yellowish or brownish yellow oil was dissolved in chloroform, washed with water, and the solvent removed *in vacuo*. About 0.4 gm. of a partly crystalline residue was obtained, from which the following two substances were isolated.

Ergoline—The above residue was extracted with two 10 cc. portions of warm ether. After standing at 0°, the ether solution was filtered and concentrated to small volume. On chilling, crude ergoline crystallized. It was recrystallized from 60 per cent methyl alcohol and then from ether. The base was obtained as a white crystalline powder, melting over a rather wide range, *i.e.* 175–183°, and possibly consisted of stereoisomers.

It gave an intense indole color test with *p*-dimethylaminobenzaldehyde and hydrochloric acid. With this reagent and concentrated sulfuric acid (the van Urk test), it gave colors indistinguishable from those given by lysergic acid. With Keller's reagent a test very similar to, but not identical with that given by lysergic acid was obtained, in which the color was a deep blue-violet instead of the usual deep blue.

Ergoline is unstable to air and to acids. It is very soluble in alcohol, chloroform, and benzene; but moderately soluble in ether; and insoluble in water and petroleum ether.

$C_{14}H_{16}N_2$.	Calculated.	C 79.2, H 7.58, N 13.2
	Found.	" 78.96, " 7.20, " 13.12
	"	" 78.84, " 7.44

The hydrochloride was obtained from the crude as well as the pure base by crystallization from 10 per cent hydrochloric acid.

When recrystallized from dilute methyl alcohol, it formed a colorless microcrystalline powder which is practically insoluble in water.

$C_{14}H_{16}N_2 \cdot HCl$.	Calculated.	C 67.60, H 6.88
	Found.	" 67.60, " 6.56
	"	" 67.43, " 6.68

3'-Amino-7-Hydroxymethyl-1,2,3,4,7,8,9,10-Octahydro-5,6-Benzoquinoline—This by-product of the preparation of ergoline was obtained from the fractions less soluble in ether. This residue described above was dissolved in a large volume (300 to 400 cc.) of ether. On concentration to half volume and cooling, the amino alcohol separated in fairly pure form. It gave negative indole color tests, and after diazotization coupled with α-naphthol. It melted at 80–85° and possibly consisted of stereoisomers.

$C_{14}H_{20}ON_2$. Calculated, C 72.5, H 8.7; found, C 71.88, H 8.5

The dihydrochloride separated from a small volume of dilute hydrochloric acid as silvery leaflets. It was recrystallized from acetone containing a little dilute hydrochloric acid.

$C_{14}H_{20}ON_2 \cdot 2HCl \cdot H_2O$.	Calculated.	C 52.00, H 7.50
	Found.	" 51.39, " 7.64

3'-Amino-1,2,3,4-Tetrahydro-5,6-Benzoquinoline-7-Carbonic Acid Lactam—220 mg. of the above amino lactam were dissolved in hot dilute HCl and kept warm to prevent crystallization of the hydrochloride. The solution was hydrogenated with 50 mg. of Adams and Shriner's catalyst. 2 moles of H_2 were absorbed in about an hour, during which the color of the solution changed from red to yellow. Cautious neutralization with sodium acetate solution caused crystallization of the tetrahydro compound as pale yellow needles. After crystallization from alcohol, it melted at 248–249°.

$C_{14}H_{12}ON_2$. Calculated, C 75.00, H 5.40; found, C 74.61, H 5.23

The hydrochloride crystallized as yellow needles from dilute hydrochloric acid.