THE ERGOT ALKALOIDS*

XVI. FURTHER STUDIES OF THE SYNTHESIS OF SUBSTANCES RELATED TO LYSERGIC ACID

By WALTER A. JACOBS and R. GORDON GOULD, Jr.

(*From the Laboratories of The Rockefeller Institute for Medical Research, New York*)

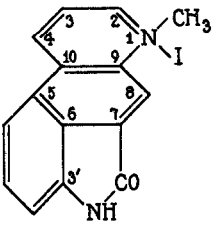
(Received for publication, July 28, 1938)

In a previous communication (1) we have described the synthesis of ergoline, a substance consisting of an unsubstituted, tetracyclic indole nucleus which is at the same time a derivative of a decahydroquinoline and is the ring system that has been derived for lysergic acid (2). Attempts have since been made to extend the program of synthesis to include the substituting groups present in lysergic acid; namely, the N-methyl group in Ring D and the carboxyl group which had been assumed to be in position 7 in Ring D. However, in view of the recent evidence, which we have presented elsewhere (3, 4), that the carboxyl group of lysergic acid is in position 8, it has now become more urgent to extend the study in this direction. We wish at this point to record our experience in the attempt to introduce a carboxyl group only in position 7.

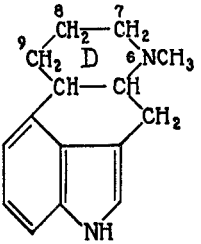
It has been possible by the following series of steps to synthesize *6-methyl ergoline* (Formula II). In order to avoid the formation of a mixture of methylated derivatives which would be expected if methylation were attempted after reduction to the polyhydroquinoline stage, methylation was directly accomplished with the quinoline derivative itself. Thus the *lactam of 3′-amino-5, 6-benzoquinoline-7-carbonic acid* (1) gave smoothly the *quinolinium methiodide* (Formula I). This salt on catalytic hydrogenation gave the hydroiodide of the *1-methyl-2,3,4-trihydroquinoline derivative* which was studied as the free base. When the latter was further reduced with sodium in butyl alcohol *6-methyl ergoline* (Formula II) resulted, owing to further reduction of the quinoline

* Reference (4) should have been designated Paper XV.

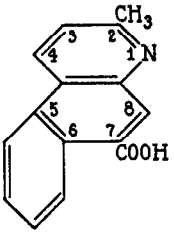
nucleus and the lactam group. Although this synthesis should result in a mixture of two racemic isomers since there are two centers of asymmetry in methyl ergoline, the properties of the substance obtained after recrystallization suggested homogeneity.



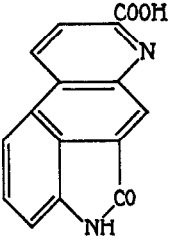
I



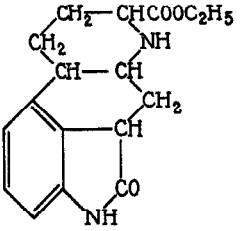
II



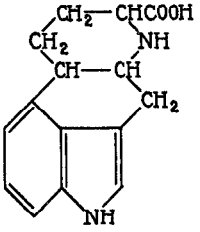
III



IV



V



VI

It gave color reactions which were very close to those given by lysergic acid itself. At this stage the attempt was made to obtain N-methyl ergoline by decarboxylation of dihydrolysergic acid but, as reported elsewhere (4), the latter was found not to decar-

boxylate on pyrolysis but to rearrange to a lactam with cleavage of Ring D. On the other hand, pyrolysis of lysergic acid itself has been found to result not only in loss of CO_2 but also of methylamine.

Parallel with the above studies a series of substances was synthesized leading to ergoline-7-carbonic acid as follows: *5,6-Benzoquinaldine-7-carbonic acid* (Formula III) was prepared by the Doebner reaction from 3-amino-1-naphthoic acid and acetaldehyde. It was further characterized as the *methyl* and *ethyl* esters. The 2-methyl group of this acid was smoothly oxidized to carboxyl by selenium dioxide (5) with formation of *5,6-benzoquinoline-2,7-dicarbonic acid.* The nature of the latter was confirmed by its ready decarboxylation at the melting point with formation of the previously described monobasic 5,6-benzoquinoline-7-carbonic acid (1).

On nitration of the dibasic acid a mixture of mononitro derivatives resulted which consisted essentially of *3′-nitro-5,6-benzoquinoline-2,7-dicarbonic acid.* This was not purified as such, but its reduction product because of ready lactam formation was easily separated from other substances as the *lactam of 3′-amino-5,6-benzoquinoline-2,7-dicarbonic acid* (Formula IV). The *methyl* and *ethyl* esters of the latter were also prepared. Hydrogenation of the lactam acid and its ester was then studied. When hydrogenation of the former was interrupted after absorption of 2 moles of H_2, an unstable 1,2,3,4-tetrahydro derivative resulted, which was isolated preferably as the hydrochloride. The *methyl* and *ethyl esters* proved to be more stable. The substance which was found to possess the most favorable properties of the series resulted from the complete hydrogenation of the ethyl ester. This product, since it proved to be the lactam of an amino group still of aromatic nature, must be *1,2,3,4,7,8,9,10-octahydro-3′-amino-5,6-benzoquinoline-2,7-dicarbonic ethyl ester lactam* (Formula V).

Because of the unfavorable solubility relationships shown by the original, fully aromatic benzoquinoline acid and its esters, reduction with sodium and butyl alcohol proved to be impracticable. The reduction of the tetrahydro and octahydro derivatives was therefore studied. In these cases substances were obtained which gave the Keller reaction. The reaction most studied was

the reduction of the tetrahydro methyl ester. In this case the reaction mixture, which gave strongly the Keller reaction, yielded by careful manipulation a substance that approximated in composition that of the desired *ergoline-7-carbonic acid* (Formula VI). Unfortunately the yields obtained and the properties of the substance made very difficult its final purification. Since it has now become evident that the properties of lysergic acid fit best with those of an N-methyl ergoline-8-carbonic acid, this particular synthesis of 7-carbonic acids has not been pressed further.

It is of interest to mention at this point that all attempts to add methyl iodide to the benzoquinoline lactam acid (Formula IV) and its esters, as well as to their tetra and octahydro derivatives (Formula V), were unsuccessful. In most cases starting material was practically quantitatively recovered. This is possibly due to steric hindrance and is interesting in contrast with the behavior of lysergic acid, dihydrolysergic acid, their esters, and the dihydrolysergols which have been found to add methyl iodide readily. On the other hand, *2-methyl-5,6-benzoquinoline-7-carbonic ethyl ester* added methyl iodide readily to give the corresponding benzoquinaldinium methiodide derivative.

Simultaneously with the above, we have had in progress among other related subjects the synthesis of substances leading to ergoline-8-carbonic acid and ergoline-9-carbonic acid and their derivatives. This work will be presented at a later time.

EXPERIMENTAL

3'-Amino-5,6-Benzoquinolinium Methiodide-7-Carbonic Acid Lactam—3 gm. of the lactam prepared as previously described (1) were treated in a bomb tube with 15 cc. of methyl iodide at 100° for 18 hours. The bright orange-red crystalline precipitate was collected with ether. The yield was quantitative. Recrystallized from a large volume of water, the substance formed needles which melted at 291–292° with decomposition.

$C_{15}H_{11}ON_2I$.	Calculated.	C 49.72, H 3.06,	N(CH_3) 4.14
	Found.	" 49.98, " 3.33,	" 2.12
			" 2.96

1-Methyl-2,3,4-Trihydro-3'-Amino-5,6-Benzoquinoline-7-Carbonic Acid Lactam—This substance was obtained by catalytic

hydrogenation of the methiodide. 0.285 gm. of the methiodide was suspended in 30 cc. of 0.5 per cent HCl and hydrogenated in the presence of 0.1 gm. of PtO_2 catalyst. The theoretical amount of hydrogen was absorbed in 3 to 4 hours. As the starting material dissolved, it was replaced by the hydrogenation product. The resulting suspension was heated at the end to dissolve the precipitate of colorless needles and the catalyst was filtered off. The clear solution was made slightly alkaline with ammonia and the precipitate of bright yellow crystals was collected. The yield was 90 per cent. The substance crystallizes from alcohol in plates which melted at 220–221°.

$C_{15}H_{14}ON_2$.	Calculated.	C 75.59, H 5.93, N(CH_3) 6.30
	Found.	" 75.48, " 5.61, " 4.94

6-Methyl Ergoline—A solution of 0.7 gm. of the previous N-methyl derivative in 100 cc. of dry *n*-butyl alcohol was treated with 5 gm. of sodium at the boiling point. After all the metal had dissolved, 100 cc. of water were added, and the butyl alcohol was removed *in vacuo*. The residual aqueous solution was extracted with benzene. The residue from the benzene extract was dissolved in a few cc. of ether. 2.5 cc. of water were added, followed by dilute HCl until the aqueous layer was just acid to Congo red. Beautifully crystalline 6-methyl ergoline hydrochloride separated on standing. The yield of crude salt was 75 mg. It was recrystallized several times from water with norit, and separated as glittering leaflets.

$C_{15}H_{18}N_2 \cdot HCl$.	Calculated.	C 68.54, H 7.29, N(CH_3) 5.71
	Found.	" 68.18, " 7.54, " 2.90

The free base was obtained by addition of alkali to an aqueous solution of the salt. It separated as a flocculent white precipitate. Recrystallized from methyl alcohol or chloroform, it melted at 210–212°. The pure substance is practically insoluble in ether, whereas the crude mixture of products obtained by the sodium-butyl alcohol reduction is readily soluble. The substance, although a racemic mixture, appeared to be otherwise homogeneous.

$C_{15}H_{18}N_2$.	Calculated.	C 79.59, H 8.02, N(CH_3) 6.64
	Found.	" 79.54, " 7.57, " 5.97

6-Methyl ergoline gives the Keller test but there is a suggestion that the color shade in the acetic acid layer is a little more in the purple than that given by lysergic acid. It gave a definite melting point depression with ergoline itself. It may be mentioned at this point that *ergoline* more recently purified by repeated recrystallization of its hydrochloride has since been found to melt at 201–203° instead of at 175–183° as previously given (1).

5,6-Benzoquinaldine-7-Carbonic Acid—This acid was prepared by the Doebner reaction. 30 gm. of the finely powdered sulfate of 3-amino-1-naphthoic acid were mixed with 30 gm. of paraldehyde and 60 cc. of HCl (sp. gr. 1.19) and the mixture was heated under a reflux at 110–120°, with mechanical stirring, for 6 to 8 hours. The reaction mixture was diluted with 500 cc. of water, brought to a boil, and then filtered. The filtrate was neutralized to Congo red with NaOH solution and, after cooling, the precipitate was filtered. The crude product was recrystallized several times from dilute HCl as the hydrochloride. The latter was finally decolorized with norit in dilute HCl solution and then neutralized with NaOH as before to give the free quinaldine acid. The yield was about 9 gm.

For analysis it was recrystallized from a small volume of pyridine and separated as transparent rods which melted at 313–315° with decomposition.

$C_{15}H_{11}O_2N$. Calculated, C 75.92, H 4.68; found, C 76.15, H 4.65

The hydrochloride formed needles from dilute HCl, which melted at 314–316° with decomposition.

$C_{15}H_{11}O_2N \cdot HCl$. Calculated, C 65.80, H 4.42; found, C 65.77, H 4.75

The Methyl Ester—The finely powdered hydrochloride of the acid was suspended in a large volume of absolute methyl alcohol and refluxed with a continuous stream of HCl until a clear solution resulted. The resulting HCl salt was converted as usual into the free quinaldine ester. Recrystallized from alcohol, it formed needles melting at 114–116°.

$C_{16}H_{13}O_2N$. Calculated, C 76.46, H 5.22; found, C 76.44, H 4.96

The Ethyl Ester—The ethyl ester prepared in the same manner after recrystallization from alcohol melted at 103–104°.

$C_{17}H_{15}O_2N$. Calculated, C 76.94, H 5.70; found, C 77.32, H 6.07

5,6-Benzoquinaldinium Methiodide-7-Carbonic Ethyl Ester—The ethyl ester when heated at 100° with an excess of methyl iodide gave the methiodide in good yield. Recrystallized from water, it melted at 201–203° with decomposition.

$C_{18}H_{18}O_2NI$. Calculated, C 53.06, H 4.46; found, C 52.5, H 4.45

5,6-Benzoquinoline-2,7-Dicarbonic Acid—The 2-methyl group in the benzoquinaldine acid was readily oxidized to carboxyl by selenium dioxide, either as the ester in amyl alcohol or xylene solution, or better as the free acid in pyridine solution. Ordinary so called C.P. pyridine contains homologous methyl pyridines which were oxidized to the corresponding pyridine acids (5) at the same time, but this did not affect the main reaction and the products could be easily separated.

20 gm. of benzoquinaldine-7-carbonic acid were dissolved in 150 cc. of boiling pyridine and cooled. 40 gm. of selenium dioxide dissolved in 20 cc. of warm water were added in small portions and the mixture was then refluxed for 8 hours. The precipitated selenium was collected and found to weigh 11.5 gm.; calculated, 10 gm. The clear filtrate was concentrated *in vacuo*. The residue formed a crystalline cake which was dissolved in water. Dilute HCl was added until slightly acid to Congo red, and the precipitate was filtered off. The crude dibasic acid was washed with water and dried *in vacuo* at 100°. The yield was practically theoretical. It melted at 258° with evolution of CO_2, resolidifying as the monobasic 7-carbonic acid which melted at about 300° as previously described (1).

$C_{15}H_9O_4N$. Calculated, C 67.40, H 3.40; found, C 67.66, H 3.19

The substance formed a beautifully crystalline monosodium salt from an acetic acid-sodium acetate buffer.

3'-Nitro-5,6-Benzoquinoline-2,7-Dicarbonic Acid—The nitration was performed as described for the monocarbonic acid, with fuming nitric acid (sp. gr. 1.58) at 0°, and the resulting solution was poured into ice water. It was purified by reprecipitation from alkaline solution with dilute HCl.

$C_{15}H_8O_6N_2$. Calculated, C 57.68, H 2.58; found, C 57.74, H 3.06

The substance was presumably not homogeneous.

3'-Amino-5,6-Benzoquinoline-2,7-Dicarbonic Acid Lactam—10 gm. of the above nitro derivative were dissolved in a mixture of 50 cc. of water and 15 cc. of concentrated ammonium hydroxide. The solution was added slowly with shaking to a suspension of ferrous hydroxide prepared from a mixture of 100 gm. of ferrous sulfate in 250 cc. of water and 100 cc. of ammonium hydroxide. The mixture was heated to about 70° and treated with 65 cc. of 50 per cent NaOH. It was then boiled for 5 minutes and filtered. The clear, light red filtrate was acidified to Congo red with HCl which produced a flocculent red precipitate gradually turning to a tan color. After the mixture was boiled for 5 minutes to complete lactamization and cooled, the crude product was collected with water. The yield was 7.8 gm., which represented an over-all yield from benzoquinaldine-7-carbonic acid of about 70 per cent. The substance was soluble only in concentrated H_2SO_4 and dilute aqueous pyridine or piperidine solutions. It was purified through the sparingly soluble ammonium salt, and by precipitation from solution in dilute pyridine with HCl.

The ammonium salt melted with decomposition at 273–276°.

$C_{15}H_{11}O_3N_3$.	Calculated.	C 64.03, H 3.94, N 14.95
	Found.	" 63.9 , " 3.51, " 14.93

The free acid, which was yellow in color, was dried at 100° *in vacuo* and melted at 270–271° with evolution of CO_2 and then resolidified. The resulting benzoquinoline lactam melted at 280–281° as previously described (1).

$C_{15}H_8O_3N_2$. Calculated, C 68.16, H 3.05; found, C 67.9, H 3.17

The Methyl Ester—The free acid was esterified by passing HCl through the boiling methyl alcoholic suspension or by refluxing in methyl alcohol containing 6 per cent of H_2SO_4. The resulting sparingly soluble methyl ester salts were hydrolyzed when treated with water. The bright yellow ester was recrystallized from pyridine and melted at 305–307°.

$C_{16}H_{10}O_3N_2$. Calculated, C 69.04, H 3.62; found, C 68.30, H 3.62
" " 68.23, " 3.52

The Ethyl Ester—This ester was prepared in the same way. Recrystallized from pyridine or glacial acetic acid, it melted at 275–277°.

$C_{17}H_{12}O_3N_2$. Calculated, C 69.84, H 4.14; found, C 69.24, H 4.18
" " 69.56, " 4.58

1,2,3,4-Tetrahydro-3'-Amino-5,6-Benzoquinoline-2,7-Dicarbonic Acid Lactam—1.5 gm. of the previous benzoquinoline lactam acid suspended in about 50 cc. of acetic acid were hydrogenated at 60° with 0.5 gm. of PtO_2 catalyst. The solution absorbed 460 cc. of H_2 in 1 hour, and the absorption which had slowed down was interrupted at this point. Calculated for 2 moles of H_2, 413 cc. The clear solution was filtered from the catalyst and enough HCl was added to cause complete precipitation of the acid salt. The yield of hydrochloride of the tetrahydro compound was 1.3 gm.

The free tetrahydro acid was found to be very sensitive to air, as in the case of tetrahydroquinaldinic acid (6). It was obtained by treating an aqueous suspension of the hydrochloride with sodium acetate solution. The substance melted at 237–239°, and was lemon-yellow in color. However, it has been very difficult to obtain satisfactory analytical figures with the acid itself. Better results were obtained with the esters.

The Methyl Ester—This ester was obtained with methyl alcohol and HCl, and also by catalytic reduction of the parent benzoquinaldinic acid ester. Recrystallized from methyl alcohol, the yellow tetrahydro ester melted at 234–236°.

$C_{16}H_{14}O_3N_2$. Calculated, C 68.05, H 5.00; found, C 68.38, H 5.06

The Ethyl Ester—Both methods of preparation were also used in this case. Recrystallized from ethyl alcohol or pyridine, the substance melted at 240–242°.

$C_{17}H_{16}O_3N_2$. Calculated, C 68.88, H 5.44; found, C 69.43, H 5.38
" " 68.46, " 5.15

1,2,3,4,7,8,9,10-Octahydro-3'-Amino-5,6-Benzoquinoline-2,7-Dicarbonic Acid Lactam Ethyl Ester—When the above catalytic hydrogenation in the case of the ethyl ester was continued for a long time (30 to 40 hours), a crystalline substance was isolated in about 30 per cent yield. Analysis showed it to be an octahydro derivative. Over this long period the apparent absorption of H_2 corresponded to about 5 moles, possibly due to leakage. It formed long, pale yellow needles from ethyl alcohol, which melted at 232–236°.

$C_{17}H_{20}O_3N_2$. Calculated, C 67.96, H 6.72; found, C 68.29, H 6.80

This substance, after cleavage with alkali, gave the usual reactions of an aromatic amino derivative. On reduction with sodium and alcohol the formation of an indole derivative also demonstrates the aromatic character of the amino group.

Ergoline-7-Carbonic Acid—0.7 gm. of *1,2,3,4-tetrahydro-3'-amino-5,6-benzoquinoline-2,7-dicarbonic acid lactam methyl ester* was dissolved in 100 cc. of dry *n*-butyl alcohol and brought to a boil. 5 gm. of sodium were added and the mixture was shaken vigorously. The color changed to an orange-red at first and finally a clear, almost colorless solution resulted. After addition of water and removal of butyl alcohol *in vacuo*, the residual aqueous alkaline solution was extracted successively with benzene and ether to remove by-products and then filtered. The solution was then made just acid to Congo red with H_2SO_4, which caused precipitation of dark colored, amorphous material that was filtered off. Sodium carbonate solution was added to the filtrate until just alkaline to phenolphthalein. On concentration a residue was obtained which was dried and ground. This material was extracted three times with 25 cc. of boiling alcohol, and the combined extracts were concentrated *in vacuo*. The red, resinous residue was dissolved in a few cc. of water. Dilute HCl was cautiously added until just acid to Congo red and after standing at 0° the solution was filtered from a dark colored, amorphous precipitate. The filtrate was concentrated *in vacuo* to a thick syrup, and a few drops of HCl (1:1) were added. After standing at 0° for several days, crystalline material separated, which was collected. The yield was only 10 mg. After recrystallization from dilute HCl it formed glittering leaflets. Its color reactions were practically identical with those given by lysergic acid.

$C_{15}H_{16}O_2N_2 \cdot HCl$. Calculated, C 61.52, H 5.86; found, C 60.9, H 5.14

BIBLIOGRAPHY

1. Jacobs, W. A., and Gould, R. G., Jr., *J. Biol. Chem.*, **120**, 141 (1937).
2. Jacobs, W. A., and Craig, L. C., *J. Biol. Chem.*, **115**, 227 (1936).
3. Craig, L. C., Shedlovsky, T., Gould, R. G., Jr., and Jacobs, W. A., *J. Biol. Chem.*, **125**, 289 (1938).
4. Jacobs, W. A., and Craig, L. C., *J. Am. Chem. Soc.*, **60**, 1701 (1938).
5. Henze, M., *Ber. chem. Ges.*, **67**, 750 (1934).
6. Wieland, H., Hettche, O., and Hoshino, T., *Ber. chem. Ges.*, **61**, 2371 (1928).