THE ERGOT ALKALOIDS*

VIII. THE SYNTHESIS OF 4-CARBOLINE CARBONIC ACIDS

By WALTER A. JACOBS and LYMAN C. CRAIG

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

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In a previous preliminary note[1] the results were reported of attempts to synthesize substances closely related to the carboline formula originally suggested by us for lysergic acid. For this purpose we extended the method used by Tatsui[2] and by Akabori and Saito[3] in which tetrahydroharman was produced by the condensation of tryptamine with acetaldehyde. By the substitution of tryptophane itself in this reaction, it has been found possible to prepare in certain cases and with little difficulty 3-substituted tetrahydro-4-carboline-5-carboxylic acids. Thus, tryptophane and formaldehyde yielded *3,4,5,6-tetrahydro-4-carboline-5-carboxylic acid*. Acetaldehyde gave readily isomeric *3-methyl* derivatives due to the formation of a new center of asymmetry at carbon atom (3). The attempt was made to obtain only one of these in a form approaching homogeneity. This substance has also been described by Otani[4] who, however, did not correctly interpret its nature.

With the hope of obtaining a substance approaching the formula assumed for lysergic acid, crotonic aldehyde was then condensed with tryptophane. Although correct analytical figures for a propenyl derivative were obtained with the resulting substance, the latter could not be crystallized and possessed properties which

* The article (Jacobs, W. A., Craig, L. C., and Rothen, A., *Science*, **83**, 166 (1936)) on ergot alkaloids should have been designated Paper VII of this series.

[1] Jacobs, W. A., and Craig, L. C., *Science*, **82**, 421 (1935).

[2] Tatsui, G., *Chem. Centr.*, **2**, 668 (1928).

[3] Akabori, S., and Saito, K., *Ber. chem. Ges.*, **63**, 2245 (1930).

[4] Otani, S., *Z. physiol. Chem.*, **214**, 30 (1933).

suggested polymerization. By the use of paraldol, the *3-β-hydroxypropyl derivative* was prepared, which crystallized readily. Attempts to dehydrate this substance with formation of a propenyl derivative were unsuccessful. Finally, benzaldehyde gave a crystalline *3-phenyl derivative.*

As a next step in approaching the assumed formula of lysergic acid, which possesses an N-methyl group, methylation of several of these substances was attempted, but the reactions proceeded in undesired directions, giving amorphous products. Better results were obtained with N-methyltryptophane or abrine which was prepared from jequirity beans according to Hoshino.[5] With acetaldehyde, condensation readily occurred but the yield of crystalline 3-methyl-3,4,5,6-tetrahydro-4-methyl-4-carboline-5-carboxylic acid was only about 20 per cent. The major portion apparently remained as a more soluble, difficultly crystallizing stereoisomer which was not isolated as such. Its presence was indicated by oxidation to 4-methylharman as discussed below. Similarly, abrine and benzaldehyde gave a crystalline *3-phenyl derivative.*

Kermack, Perkin, and Robinson[6] have already assumed the intermediate formation of a tetrahydrocarboline derivative in the formation of harman by the condensation of tryptophane with acetaldehyde, but apparently made no attempt to isolate it. They were interested rather in the substance, harman, which was obtained by the additional step of oxidation. Since our tetrahydrocarboline acids were stable, it appeared that decarboxylation must accompany such oxidation. This was found to be the case for, on oxidation of 3-methyltetrahydrocarboline carbonic acid with chromic acid, the base, harman, was directly formed.

Lysergic acid is comparatively stable, requiring a temperature of 200° or more to decarboxylate it. Dihydrolysergic acid, however, shows still less tendency to decarboxylate, since it almost entirely sublimed unchanged at 25 mm. when heated above 300°. If lysergic acid or dihydrolysergic acid were carboline derivatives analogous to the above substances, they should on oxidation

[5] Hoshino, T., *Ann. Chem.*, **520**, 31 (1935).

[6] Kermack, W. O., Perkin, W. H., Jr., and Robinson, R., *J. Chem. Soc.*, **119**, 1616 (1921).

(assuming no complication from the previously assumed propenyl group) yield a harman derivative with decarboxylation. This, however, failed to be the case, since the resulting material, although amorphous, was acid in character. With the thought that the N-methyl group might prevent complete oxidation to the harman stage and therefore cause retention of the carboxyl group, a similar oxidation study was made with the above N-methylcarboline acid from abrine and acetaldehyde. Decarboxylation, however, occurred and the resulting product proved to be a strong, yellow base, *N-methylharman*, in which the second double bond, as assumed by Nishikawa, Perkin, and Robinson[7] in an analogous case, must lie between carbon atom (3) and a methylene group attached to it. Also, when the mother liquor which contained the majority of the non-crystallizing condensation product of abrine and acetaldehyde was oxidized, a copious yield of the same base was obtained. This indicated the presence of a more soluble stereoisomer due to asymmetry of carbon atom (3).

Finally, contrary to lysergic acid and its dihydro derivative, none of these carboline derivatives gives with dimethylaminobenzaldehyde and hydrochloric acid the reaction generally produced by indole derivatives with α or β positions free. This proved to be the case likewise with yohimbine. As regards the Keller reaction, so characteristic of lysergic acid, only the crotonic aldehyde condensation product gave a color approaching it. The significance of such color reactions, however, is not certain, but the behavior of lysergic acid on oxidation as well as the nature of its degradation products, discussed elsewhere,[8] has caused us to discard the carboline formula for the ergot acid which we had first suggested.

EXPERIMENTAL

3,4,5,6-Tetrahydro-4-Carboline-5-Carboxylic Acid—0.5 gm. of *l*-tryptophane was treated with 2.5 cc. of N H_2SO_4, 8 cc. of water, and then 2.5 cc. of 40 per cent formaldehyde solution. After a few minutes a copious precipitate developed in the clear solution which first formed. After 1.5 hours at room temperature, a

[7] Nishikawa, N., Perkin, W. H., Jr., and Robinson, R., *J. Chem. Soc.*, **125**, 657 (1924).

[8] Jacobs, W. A., and Craig, L. C., *Science*, **83**, 38 (1936).

slight excess of ammonia was added and the mixture was allowed to stand overnight. The precipitate after collection with water was dissolved in 50 per cent alcohol with sufficient ammonia. After diluting somewhat, the alcohol and ammonia were boiled off, when suddenly the crystalline condensation product separated. On repetition of this recrystallization, the substance separated as lustrous leaflets which were anhydrous and melted with effervescence at 310°. Contrary to tryptophane, it gives no color reaction when HCl (1.19) is run down beneath its solution in 1 per cent dimethylaminobenzaldehyde.

$C_{12}H_{12}O_2N_2$. Calculated, C 66.64, H 5.60; found, C 66.94, H 5.37

3,4,5,6-Tetrahydro-3-Methyl-4-Carboline-5-Carboxylic Acid—1 gm. of *l*-tryptophane was warmed with 5 cc. of N H_2SO_4 and 25 cc. of 10 per cent acetaldehyde at 40° for 30 minutes. The clear solution was then heated on the steam bath for 1.5 hours during which crystallization occurred. On evaporation of the solution to remove excess aldehyde, crystallization became copious, especially after addition of sufficient ammonia. The collected material was recrystallized by solution in hot dilute ammonia and boiling off most of the ammonia after clearing with bone-black. The acid separated as cream-colored needles which decomposed at 297° after softening and darkening above 282°. For analysis it was dried at 110° and 15 mm.

$[\alpha]_D^{25} = -115°$ ($c = 0.505$ in 50 per cent pyridine)
$C_{13}H_{14}O_2N_2$. Calculated, C 67.79, H 6.13; found, C 67.66, H 5.96

No attempt was made to fractionate a possible stereoisomer from the mother liquor.

That decarboxylation accompanied oxidation with formation of harman was shown under the following comparatively gentle conditions.

70 mg. of the above carboline acid were dissolved in 18 cc. of boiling water. 3.5 cc. of 10 per cent $K_2Cr_2O_7$ solution were added. A cloudiness soon appeared. 0.7 cc. of acetic acid was added, which appeared to hasten the reaction, and some gas evolution became apparent. The heating was not longer than 1 minute, when the mixture was cooled and then treated with dilute sodium sulfite to reduce the excess reagent. After making alka-

line with sodium carbonate, the mixture was extracted with ether. The latter on concentration gave crystalline prisms and needles which were collected with ether. After recrystallization from dilute alcohol it melted at 234° (uncorrected).

$C_{12}H_{10}N_2$. Calculated, C 79.08, H 5.53; found, C 78.95, H 5.36

3,4,5,6-Tetrahydro-3-β-Hydroxypropyl-4-Carboline-5-Carboxylic Acid—0.1 gm. of tryptophane was dissolved in a mixture of 0.5 cc. of N H_2SO_4 and 1.5 cc. of water. 0.1 gm. (an excess) of paraldol was added and the mixture was warmed a moment on the bath. A yellow color developed and the reaction was evident from the disappearance of the tryptophane reaction. On addition of dilute sodium acetate solution crystallization occurred. Recrystallization was accomplished from dilute ammonia. The acid formed needles which melted at 261°, depending upon the rate of heating.

The substance gave negative dimethylaminobenzaldehyde and Keller reactions. It contained solvent and was dried for analysis at 100° and 15 mm.

$C_{15}H_{18}O_3N_2$. Calculated, C 65.65, H 6.62; found, C 65.32, H 6.57

3,4,5,6-Tetrahydro-3-Phenyl-4-Carboline-5-Carboxylic Acid — Benzaldehyde was similarly condensed with tryptophane, just sufficient alcohol to cause complete solution being used. The mixture was heated for 15 minutes. The substance was recrystallized from hot dilute ammonia. The phenyl derivative formed needles which melted at 223–226°. It contained solvent and was dried for analysis at 100° and 15 mm.

$C_{18}H_{16}O_2N_2$. Calculated, C 73.94, H 5.52; found, C 73.85, H 5.45

3,4,5,6-Tetrahydro-3-Methyl-4-Methyl-4-Carboline-5-Carboxylic Acid—5 gm. of methyl tryptophane (abrine) were treated with 25 cc. of N H_2SO_4 and 110 cc. of 10 per cent acetaldehyde. On warming at 40° for several hours, a clear solution formed. The mixture was heated an additional 30 minutes on the steam bath and then evaporated on the bath to small volume to remove excess aldehyde. A slight excess of ammonia was then added and the concentration continued. Crystallization slowly occurred, especially after seeding. After the material was collected with water, the yield was 0.8 gm. Attempts to obtain more crystalline ma-

terial from the mother liquor were fruitless, except after oxidation, as given below.

After crystallization by concentration of the dilute ammonia solution, the carboline acid formed colorless needles which contained solvent and effervesced at 248° after preliminary softening and darkening.

For analysis it was dried at 120° and 15 mm.

$C_{14}H_{16}O_2N_2$. Calculated, C 68.81, H 6.60; found, C 68.79, H 6.79

4-Methyl-4-Carboline (*4-N-Methylharman*)—0.1 gm. of the previous carboline derivative was dissolved in 2.5 cc. of water, and to the boiling solution 5 cc. of 10 per cent $K_2Cr_2O_7$ were added. After a moment, a slight change in color appeared with development of a slight cloudiness. 1 cc. of acetic acid was added, which hastened the reaction and induced separation of yellow needles. After 2 minutes the solution was cooled. The substance which was recrystallized from water proved to be the bichromate of methylharman. On exposure to light and air it darkened to a gray-green.

$(C_{13}H_{12}N_2)_2 \cdot H_2Cr_2O_7$.	Calculated.	C 51.13, H 4.29
	Found.	" 51.69, " 4.32

In another experiment the base was isolated as the acid sulfate as follows. After oxidation as above, an excess of 10 per cent H_2SO_4 was added to the cooled mixture and all chromate ions were reduced with an excess of SO_2. After boiling off the latter and cooling, the acid sulfate crystallized after addition of H_2SO_4 to about 10 per cent. The salt was recrystallized by solution in a small volume of hot water and addition of an equal volume of acetone. It formed practically colorless, lustrous platelets and needles which melted with decomposition at 273°.

$C_{13}H_{12}N_2 \cdot H_2SO_4$. Calculated, C 53.03, H 4.80; found, C 53.52, H 4.45

The free base proved to be a strong base, since it was not precipitated from solutions of its salts by ammonia or sodium carbonate. NaOH, however, caused a change in color to deep yellow with immediate precipitation of the base as yellow needles.

In the preparation of the above crystalline carboline acid from abrine, only 0.8 gm. was obtained from 5 gm. of abrine. The mother

liquor of the crude crystalline product was diluted to 800 cc. and then after heating to 100° was oxidized with 300 cc. of 10 per cent $K_2Cr_2O_7$ and 40 cc. of acetic acid. After cooling, the excess chromate was reduced with SO_2 and the mixture was strongly acidified with H_2SO_4 to about 10 per cent. The acid sulfate crystallized copiously. After collection it was converted into the free base by precipitation of its aqueous solution with alkali. The yield of the latter was 2.3 gm.

The base was recrystallized from chloroform-petroleum ether and formed yellow needles which melted at 180° after preliminary darkening.

$C_{13}H_{12}N_2$. Calculated, C 79.55, H 6.17; found, C 79.35, H 6.12

3,4,5,6-Tetrahydro-3-Phenyl-4-Methyl-4-Carboline-5-Carboxylic Acid—In the case of benzaldehyde and abrine, 50 per cent alcohol was employed as solvent. Heating on the steam bath for about 18 hours was required before the dimethylaminobenzaldehyde reaction disappeared. The reaction product crystallized on standing. It was dissolved in dilute ammonia and after removal of excess benzaldehyde with ether the solution was acidified with acetic acid. A slight voluminous precipitate was rapidly removed by filtration and the carboline derivative then crystallized as minute needles. It decomposed at 199–201° after preliminary sintering and darkening. It retained solvent tenaciously, and for analysis it was necessary to dry the substance at 140° and 15 mm.

$C_{19}H_{18}O_2N_2$. Calculated, C 74.47, H 5.93; found, C 73.70, H 6.13