

STRUCTURE OF BREVICOLLINE

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Previously, a probable structure for brevicolline has been proposed which makes it a derivative of harman. Additional studies were required to confirm the nature of the residue ($-C_5H_{10}N$) adjacent to the β -carboline system and the position of its attachment.

When this alkaloid was oxidized with chromic anhydride in sulfuric acid solution, three substances were obtained and identified, depending on the amount of oxidizing agent used: $C_{11}H_6O_3N_2$ (I)—1,3,4-trioxo-1,2,3,4-tetrahydro- β -carboline; $C_5H_7O_2N$ (II)—methylsuccinimide; and $C_{13}H_{10}O_2N_2$ (III)—harman-4-carboxylic acid.

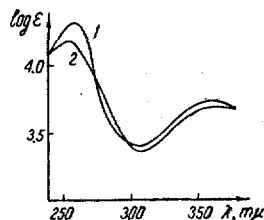


Fig. 1. UV spectra. 1) 1,3,4-trioxo-2-methyl-1,2,3,4-tetrahydro- β -carboline; 2) 1,3,4-trioxo-1,2,3,4-tetrahydro- β -carboline (I).

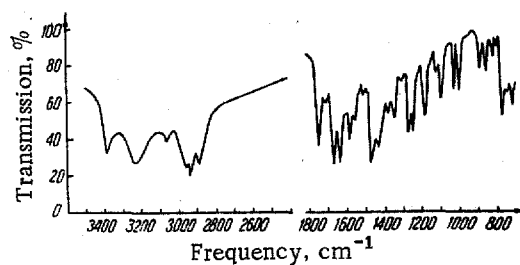


Fig. 2. IR spectrum of 1,3,4-trioxo-1,2,3,4-tetrahydro- β -carboline (suspension in paraffin oil).

Compound (I), which possesses the properties of an amide, is insoluble in water and dilute acids, but dissolves in alkalis. When alkaline solutions of the amide are heated, hydrolysis takes place with the liberation of ammonia and decarboxylation, giving indole-3-aldehyde (V).

The IR spectrum of (Fig. 2) exhibits three well-defined absorption bands at 1620 , 1660 , and 1740 cm^{-1} , which are characteristic for the $-CO-$ and $-CO-NH-CO-$ groupings.

A comparison of the UV spectrum of the substance $C_{11}H_6O_3N_2$ with the UV spectrum of 2-methyl-1,3,4-trioxo-1,2,3,4-tetrahydro- β -carboline (Fig. 1) which is given in Jonson's paper [2] clearly shows the similarity of these compounds. The results presented permit the conclusion that (I) is 1,3,4-trioxo-1,2,3,4-tetrahydro- β -carboline.

The compound $C_5H_7O_2N$ (II) was identified as N-methylsuccinimide.

The substance $C_{13}H_{10}O_2N_2$ (III) is an acid insoluble in water and alcohol but readily soluble in aqueous alkalis and concentrated ammonia. When an ammoniacal solution of (III) is evaporated, it crystallizes out in the form of lustrous yellow needles. When it is heated in vacuum to the melting point, decarboxylation takes place; a compound with the composition $C_{12}H_{10}N_2$, identical with harman (VI), is formed. Thus, III is a harmancarboxylic acid. Since the methyl ester of this acid (mp $194-195^\circ C$) is not identical with the methyl ester of harman-3-carboxylic acid synthesized for comparison (mp $247^\circ C$), the substance under study can only be harman-4-carboxylic acid. The results of a comparison of the IR spectra of these two acids (Fig. 3) confirm their similarity but not their identity.

On the basis of the results obtained, the structure of brevicolline can be illustrated by formula (IV) and its oxidation by the following scheme.

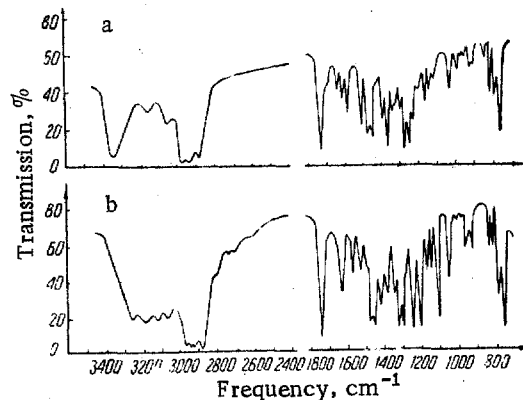
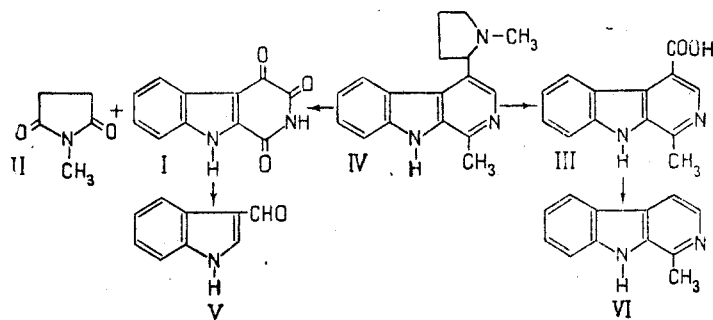
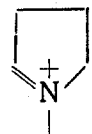


Fig. 3. IR spectra. a) Methyl ester of harman-3-carboxylic acid; b) methyl ester of harman-4-carboxylic acid. Suspensions in paraffin oil.



The proposed structure for brevicolline is also confirmed by the results of a mass-spectrometric investigation. The mass spectrum of the alkaloid (Fig. 4) has peaks of the molecular ion (M^+ ; m/e 265) and the ions $M-1$, $M-29$, and $M-43$

due to fragmentation of the pyrrolidine ring. The stringest peak (m/e 84) apparently belongs to the ion



formed by the rupture of the C-C bond between the pyrrolidine nucleus and the β -carboline system. This structure is also observed in the fragmentation of nicotine [3], in the mass spectrum of which the ion with m/e 84 also has the greatest intensity.

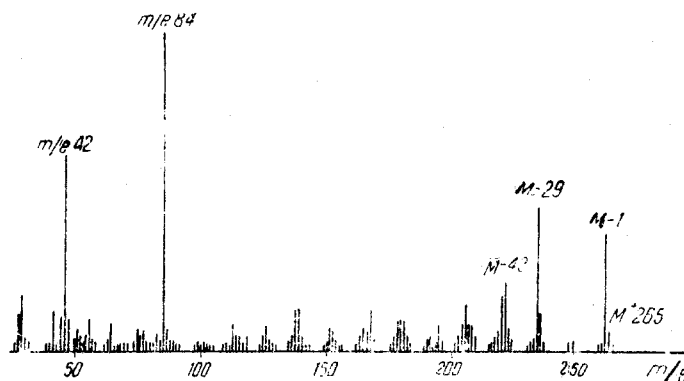


Fig. 4. Mass spectrum of brevicolline.

The integral curve of the NMR spectrum (Fig. 5) shows the presence of 19 protons in the brevicolline molecule. Of them we may note the three-proton singlets at 2.25 and 2.80 ppm, relating to $N-CH_3$ and aromatic $C-CH_3$ groups respectively. The peak at 10.70 ppm is characteristic for an indole NH and the peak at 8.50 ppm belongs to the α -hydrogen of a pyridine ring. Three two-proton signals and a one-proton triplet are present in the region of methylene groups (2-4 ppm). The hydrogens of a benzene nucleus are represented by a three-proton signal in the 7.50 ppm region and by a one-proton doublet at 8.5 ppm. Such a displacement to a weaker field is apparently due to the action of the currents not only of the aromatic ring itself but also of a second (pyridine) ring and the influence of the adjacent five-membered saturated ring.*

Experimental

Oxidation of brevicolline with an excess of chromic anhydride. A. Chromic anhydride (five 10-g portions) was added every 40-45 min to a solution of 10 g of brevicolline in 500 ml of water and 25 ml of concentrated sulfuric acid. The mixture was heated to a gentle boil. The yellow precipitate of brevicolline chromate that formed at first gradually dissolved, and the color of the solution changed from orange to the green characteristic for the trivalent chromium ion. After the addition of 50 g of chromic anhydride, a yellow precipitate of the oxidation product, 1,3,4-triketo-1,2,3,4-tetrahydro- β -carboline (I), separated. The precipitate was filtered off from the cooled solution and washed with water. The dried product was sublimed in vacuum. The sublimation temperature was 286°C. The IR spectra were taken on a UR-10 instrument in paraffin oil, and the UV spectrum on a SF-4 instrument.

Found, %: C 61.67; H 3.00; N 13.20. Calculated for $C_{11}H_6O_3N_2$, %: C 61.68; H 2.82; N 13.08.

*The mass spectrum and the NMR spectrum were taken and interpreted by Dr. Doleiš (AS CzSSR), and Dr. Šeřčovič (Slovak AS), and also by Prof. Yu. N. Sheinker (Chemical and Pharmaceutical Scientific Research Institute, Moscow).

The acidic mother liquors from the separation of substance (I) were extracted with three 70-ml portions of benzene. The combined extract was dried with sodium sulfate and the benzene was distilled off. The residual oil crystallized on cooling. Vacuum sublimation gave white crystals with mp 66–67° C. A mixture with an authentic sample of N-methylsuccinimide melted without depression.

Found, %: C 53.67; H 6.11; N 12.27. Calculated for $C_5H_7O_2N$, %: C 53.10; H 6.23; N 12.37.

Alkaline hydrolysis of 1,3,4-trioxo-1,2,3,4-tetrahydro- β -carboline (I). A mixture of 0.5 g of (I) and 20 ml of 10% caustic soda solution was boiled under reflux for 1 hr. Then the solution was evaporated to half bulk and, after being cooled, was carefully acidified to an acid reaction to Congo Red. The yellow precipitate of acid that deposited was dissolved in 10 ml of N-dimethylaniline containing a small amount of aniline and, to decarboxylate it, the mixture was boiled for 1 hr, after which time the evolution of carbon dioxide had ceased. Then 10 ml of water was added and the solvent was distilled off with steam. The residue in the distillation flask was decolorized with activated carbon and left to crystallize. The crystals that separated after some days were filtered off, mp 196° C. A mixture with an authentic sample of indole-3-aldehyde melted without depression.

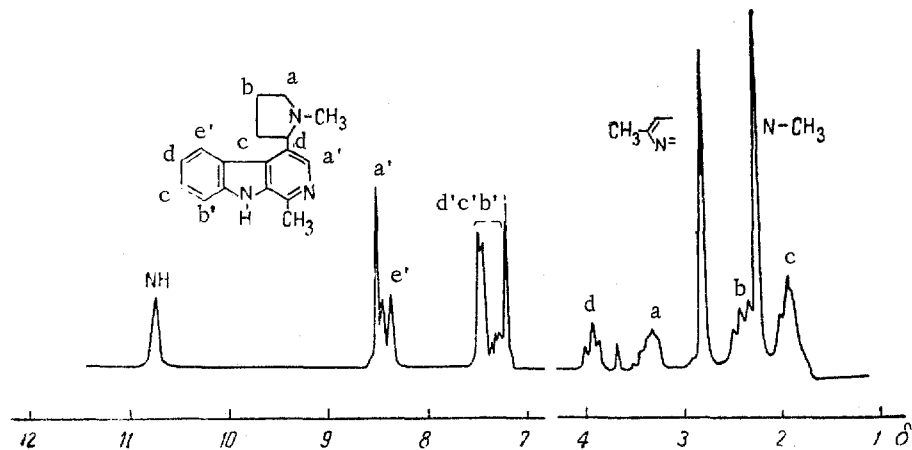


Fig. 5. NMR spectrum of brevicolline (solvent $CDCl_3$; standard TMSO, instrument—JNM-4H-100, 100 MHz).

Oxidation of brevicolline. B. A solution of 1.2 g of brevicolline in 150 ml of water containing 2 ml of concentrated sulfuric acid was heated to the boil, and 2.5 g of chromic anhydride was added. The mixture was boiled for 1 hr. To eliminate chromium salts, the cooled solution was treated with barium hydroxide, and the precipitate that deposited was filtered off. The excess of barium ions in the filtrate was precipitated with ammonium carbonate. The filtered solution was carefully acidified with sulfuric acid. The oxidation product, III, separated out in the form of a yellow flocculent precipitate. It was dissolved in concentrated ammonia and the solution was evaporated to incipient crystallization. Yellow needle-like crystals of harman-4-carboxylic acid, mp 205° C, separated out from the cooled solution.

Methyl ester of harman-4-carboxylic acid. A suspension of 1 g of harman-4-carboxylic acid in 20 ml of absolute methanol and 5 ml of concentrated sulfuric acid was boiled in the water bath for 2 hr. Then the mixture was diluted with 50 ml of water and the methanol was distilled off. The aqueous solution, after filtration from unchanged acid, was treated with a saturated sodium carbonate solution. The precipitate of ester that deposited was filtered off, washed with water, dried, and recrystallized from benzene. This gave white silky crystals, mp 194–195° C.

Found, %: C 69.77; H 5.03; N 11.39. Calculated for $C_{14}H_{12}N_2O_2$, %: C 69.99; H 5.04; N 11.68.

Decarboxylation of harman-4-carboxylic acid. In an apparatus for vacuum sublimation, 0.5 g of the acid was heated until it began to melt. The evolution of gas ceased after 20 min. A sublimate condensed on the cooled walls. It was resublimed and was then crystallized from benzene. The harman obtained in this way had mp 237° C and gave no depression of the melting point with an authentic sample of harman.

Found, %: C 78.93; H 5.53; N 15.30. Calculated for $C_{12}H_{10}N_2$, %: C 79.09; H 5.53; N 15.38.

Methyl ester of harman-3-carboxylic acid. The acid was synthesized from tryptophan by the method of Snyder et al. [4], mp 247° C. A mixture with methyl harman-4-carboxylate showed a depression in the melting point.

Summary

The results of a study of the oxidation of brevicolline has shown that the structural formula of the alkaloid is 1-methyl-4-(N-methyl-2'-pyrrolidyl)- β -carboline. The formula has been confirmed by mass spectroscopy and NMR.

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