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Erythrina Alkaloids. VI. Studies on the Constitution of Erythramine

BY KARL FOLKERS AND FRANK KONIUSZY

The isolation and characterization of a new alkaloid, erythramine, from the seeds of *Erythrina sandwicensis* Deg. and *Erythrina subumbrans* (Hassk.) Merrill has been described.[1] The microanalyses on the crystalline erythramine base, hydriodide, hydrobromide, and the hydrochloride showed that erythramine has the empirical composition $C_{18}H_{21}NO_3$. The present paper reports the results of our studies of its constitution.

A Friedrich determination showed that one methoxy group is present, and that there is no group attached to the nitrogen atom. A Kuhn–Roth carbon-methyl determination gave a negative result. The presence of a methylenedioxy group was shown by hydrolysis with sulfuric acid and reaction of the formaldehyde with the added phloroglucinol. It follows that all three oxygen atoms of erythramine exist in ether linkage. This conclusion was confirmed by a lack of reaction between erythramine and acetic anhydride or with benzoyl chloride.

Methyl iodide reacted with the base to yield a crystalline erythramine methiodide; therefore, erythramine is a tertiary base. The negative methylimide group determination limits the probable alkaloidal formulations of the tertiary nitrogen to either a $-\overset{|}{C}=N-$ linkage of a ring or a ring system with the nitrogen atom common to two nuclei.

The presence of a methylenedioxy group presupposes the presence of one benzenoid nucleus.[2] Catalytic hydrogenation with Adams platinum catalyst under two atmospheres pressure resulted in the formation of a dihydroerythramine. This absorption of only two atoms of hydrogen was all that could be brought about, and considering the usual stability of alkaloidal oxygenated benzenoid nuclei to hydrogenation under such conditions, it seemed evident that the unsaturation of erythramine consisted of one benzenoid nucleus and one ethylenic double bond.

If the tertiary nitrogen atom were in the form of a $-\overset{|}{C}=N-$ linkage of a ring, then the hydrogenation would have produced a secondary nitrogen atom and dihydroerythramine would be a secondary base. However, a dihydroerythramine methiodide was readily formed, and this substance eliminates the formulation of the tertiary nitrogen atom of erythramine as a part of a $-\overset{|}{C}=N-$ linkage. These data lead to the formulation of the tertiary nitrogen atom of erythramine as being common to two nuclei. In this connection it is to be noted that three stages of Hofmann degradation proved that two other *Erythrina* alkaloids, α- and β-erythroidine, possessed tertiary nitrogen atoms common to two nuclei of the ring system.[3]

From this information concerning the nature of the three oxygen atoms, the nitrogen atom, and the unsaturation of erythramine, it has been deduced that this alkaloid possesses four nuclei, exclusive of the methylenedioxy bridge, which in all probability are six-membered rings.

It is now of interest to consider the relationship of alkaloids of known structure which have been isolated from species of genera belonging to the same subfamily, *Papilionaceae*, of the family *Leguminosae* to which the genus *Erythrina* belongs. From plants of this subfamily, the only alkaloids of known structure are represented by the "lupin" alkaloids, sparteine, and the related lupanine, anagyrine, cytisine, lupinine, matrine, and by the indole alkaloid, physostigmine. Although the "lupin" alkaloids possess a nitrogen atom common to two nuclei, they also possess a second nitrogen atom (except lupinine) so that there is this fundamental difference from erythramine and erythroidine ($C_{16}H_{19}NO_3$).[3,4] The subfamily, *Papilionaceae*, is quite large, and of the above alkaloids of known structure, only physostigmine is obtained from species of the genus *Physostigma* which is in the same tribe, *Phaseoleae*, with the genus *Erythrina*. The magnitude of even the tribe *Phaseoleae* is evident since forty-eight genera have been assigned to it by Bentham. Again, physostigmine possesses two nuclear nitrogen atoms and differs in other respects

(1) Folkers and Koniuszy, THIS JOURNAL, **61**, 1232 (1939).

(2) The ultraviolet absorption spectrum will be described at a future time in connection with other studies.

(3) Folkers and Koniuszy, Abstracts of Papers, 97th Meeting of the American Chemical Society, Baltimore, Md., April, 1939, Division of Organic Chemistry, page 17.

(4) Folkers and Major, THIS JOURNAL, **59**, 1580 (1937).

from erythramine. Thus, erythramine or α- and β-erythroidine cannot be compared readily with any of the alkaloids of known structure derived from plants of the same tribe or of a related tribe as the genus *Erythrina*. Furthermore, the indole character of hypaphorine, which has been found to occur[1] in many species of *Erythrina*, is not necessarily translatable into the properties of the accompanying erythramine.

One of the oldest known relationships between physiological action and chemical constitution is that of the curare action of quaternary ammonium compounds, as discovered by Crum-Brown and Fraser. Although erythramine is a tertiary base, it causes a selective and strong curare-like action at the threshold dose of 7 mg. of the hydrobromide per kilogram of frog. Dr. Klaus Unna, of the Merck Institute of Therapeutic Research, found that the synthetic quaternary erythramine methiodide was one-fifth as active as the tertiary base. Hydrogenation of erythramine to its dihydro derivative decreased the curare-like activity to about one-thirtieth of that for the natural alkaloid.

Further insight on the constitution of erythramine will be described by experiments made on another new *Erythrina* alkaloid, erythraline, which is very closely related to erythramine.

Experimental Part

Functional Groups of Erythramine.—A sample of erythramine hydriodide (m. p. 249°; $(\alpha)_D$ + 220°) from *Erythrina sandwicensis* Deg. was used.

Anal. Calcd. for $C_{18}H_{21}NO_3 \cdot HI$: C, 50.60; H, 5.15. Found: C, 50.66; H, 5.13. The micro Friedrich determination showed: OCH_3, 7.17%; N-CH_3, negative. Calcd. for one OCH_3, 7.26%.

In three separate test-tubes were placed 20-mg. samples, respectively, of erythramine base, hydrastine base, and hydrocotarnine base; the fourth tube was a blank. In each of the four tubes were added 5 ml. of 40% sulfuric acid and 60 mg. of phloroglucinol. When all had dissolved, the tubes were heated in a beaker of boiling water for twenty minutes. Erythramine, hydrastine, and hydrocotarnine each gave a heavy red precipitate of a phloroglucide while the blank remained colorless. Thus, erythramine contains a methylenedioxy group.[5] The methoxy and methylenedioxy groups account for the three oxygen atoms in the molecule and are in agreement with the failure of erythramine to react with acetic anhydride or benzoyl chloride.

Stability of Erythramine.—The free base cannot be stored satisfactorily under ordinary conditions because of progressive decomposition. Small samples were kept in evacuated vials at dry-ice temperature. When the free base was required, it generally was obtained from the hydriodide just before the experiment.

Erythramine hydrohalide salts were stable either dry or in solution.

The stability of erythramine in alkaline solution was tested as follows. A quantity of 106 mg. of pure erythramine hydriodide was dissolved in 30 ml. of water, heated to 100° on the steam-bath, and when 1 ml. of 5% sodium hydroxide was added, white globules of insoluble erythramine base formed. After the addition of 1.5 ml. of ethanol to cause homogeneity, the solution was refluxed for two hours. The cooled solution was diluted to 50 ml. and extracted with chloroform. The yield of base (gum) after solvent removal was 74 mg. (99.9%). It was converted to the hydrobromide, which had the established properties.

Purity of Erythramine.—It was found essential that erythramine hydriodide show a melting point of 245° (slow bath) or 249° (normal bath) and an optical rotation of +220–221° before use. In one instance, a sample of hydriodide showing m. p. 241–242° (slow bath) and $(\alpha)_D$ +219° would not yield crystalline dihydroerythramine hydriodide after hydrogenation. The same sample yielded a hydrobromide which melted at 204–205° instead of the established 228°.

Erythramine Methiodide.—A quantity of 200 mg. of erythramine base was dissolved in 1.5 ml. of absolute methanol and treated with 1 ml. of redistilled methyl iodide. The solution was warmed on the steam-bath and then concentrated until the volume was 1.5 ml. After standing overnight at 10°, a crystalline methiodide derivative separated as yellowish-white gleaming platelets; m. p. 96–98°, $(\alpha)^{28}_D$ +176°, C = 0.355, H_2O.

Anal. Calcd. for $C_{18}H_{21}NO_3 \cdot CH_3I$: C, 51.69; H, 5.48. Found: C, 51.61; H, 5.22.

Dihydroerythramine Hydriodide.—In the first experiment, erythramine hydriodide (322.5 mg.) in 50 ml. of water could not be hydrogenated with Adams platinum catalyst (25 mg.) at atmospheric pressure.

When 814 mg. of erythramine base was dissolved in 50 ml. of water containing 2 ml. of concentrated hydrochloric acid, and hydrogenated over 100 mg. of Adams platinum catalyst at two atmospheres pressure, the absorption of hydrogen stopped (one mole) after one hour. After filtration, the solution was made alkaline with sodium bicarbonate and extracted ten times with chloroform. Distillation of the solvent yielded 820 mg. of gum. This was treated with 348 mg. of sodium iodide in 5 ml. of absolute ethanol, and acidified with acetic acid. A first crop of 622.4 mg. of dihydroerythramine hydriodide was obtained. After crystallizations from absolute ethanol, the melting point was constant at 214–215° with decomposition. Analyses made on this material after drying at 25° *in vacuo* indicated non-stoichiometric solvation. Therefore, the salt was dried at 140° and 2 mm. for two hours: $(\alpha)_D$ 0°; C = 0.500, H_2O.

Anal. Calcd. for $C_{18}H_{23}NO_3 \cdot HI$: C, 50.35; H, 5.65. Found: C, 50.28; H, 5.48.

Dihydroerythramine Base.—When 100 mg. of dihydroerythramine hydriodide was dissolved in water, treated with sodium bicarbonate, extracted with chloroform, etc., 53.5 mg. of a colorless gummy base was obtained.

(5) Gadamer and Winterfeld, *Arch. pharm.*, **262**, 601 (1924).

This was dissolved in 5 ml. of dry ethyl ether and then treated with 10 ml. of petroleum ether. After filtration to remove flocculent material, the filtrate was concentrated by gentle warming to a volume of *ca.* 2 ml. The concentrate was cooled in an ice-bath and the sides of the flask were scratched. Tiny white crystals separated, which melted at 89–90°.

Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.75; H, 7.69. Found: C, 71.82; H, 7.60.

Dihydroerythramine Hydrobromide Monohydrate.—A quantity of 99 mg. of pure dihydroerythramine hydriodide yielded 64 mg. of gummy base by the usual procedure. It was dissolved in 1 ml. of absolute ethanol, treated with 0.3 ml. of 40% hydrobromic acid, and a little dry ether was added. After filtration of flocculent precipitate, the solution was allowed to stand overnight at 10°. The hydrobromide (34 mg. yield) melted constantly at 240° after recrystallization from ethanol. For analysis, the salt was dried at 25° *in vacuo*.

Anal. Calcd. for $C_{18}H_{23}NO_3 \cdot HBr \cdot H_2O$: C, 54.00; H, 6.54. Found: C, 54.26; H, 6.04.

Drying of 5 mg. of this monohydrate at 140° and 2 mm. for two hours caused a decrease in weight of only 0.04 mg. (0.8%). The anhydrous hydrobromide could not be obtained. Longer drying periods initiated thermal decomposition.

Dihydroerythramine Methiodide Hemihydrate.—A quantity of 52 mg. of dihydroerythramine base was dissolved in 1 ml. of methanol and 1 ml. of redistilled methyl iodide. Ethyl ether was added to the point of turbidity. Crystals of the methiodide separated after refrigeration overnight; m. p. 160–161°. The substance was dried at 78° and 2 mm. for two hours before analysis.

Anal. Calcd. for $C_{18}H_{23}NO_3 \cdot CH_3I \cdot {}^1/_2H_2O$: C, 50.45; H, 6.01. Found: C, 50.61; H, 6.13.

This substance could not be dehydrated at 140° *in vacuo* without decomposition.

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Summary

Erythramine, which has the empirical composition $C_{18}H_{21}NO_3$, contains one methoxy group and one methylenedioxy group. The nitrogen atom is tertiary and in all probability is common to two nuclei of the molecule. The unsaturation consists of one benzenoid nucleus and one ethylenic double bond. The molecule appears to contain four six-membered nuclei exclusive of the methylenedioxy bridge.

Erythramine methiodide was about one-fifth as active and dihydroerythramine was about one-thirtieth as active as the natural erythramine for curare-like action in frogs.

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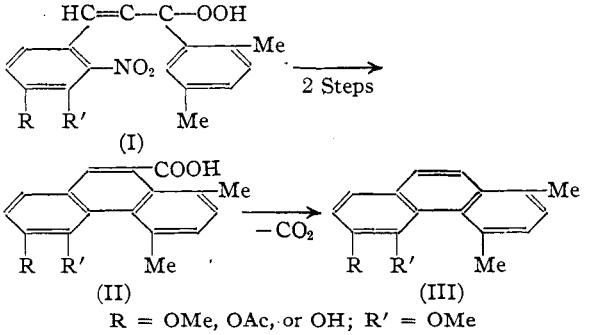
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Some New 1,4-Dimethylphenanthrenes Structurally Related to Morphol

BY JACK TARKINGTON CASSADAY[1] AND MARSTON TAYLOR BOGERT

In a recent communication,[2] we described the preparation of 1,4-dimethyl-6,7-dihydroxyphenanthrene from *p*-xylylacetic acid and 6-nitroveratraldehyde by the Pschorr reaction. The work recorded in the present paper consists of the extension of that investigation by substituting 2-nitroveratraldehyde and 2-nitroacetovanillin for the 6-nitroveratraldehyde, resulting in the production of the 5,6-dimethoxy and 5-methoxy-6-hydroxy derivatives of 1,4-dimethylphenanthrene, and their 10-carboxylic acids.

In the case of the 1,4-dimethyl-5,6-dimethoxyphenanthrene, or 1,4-dimethyl-5-methoxy-6-hydroxyphenanthrene, the methoxyl groups could not be hydrolyzed by the process which proved



R = OMe, OAc, or OH; R′ = OMe

effective with the 6,7-dimethoxy isomer,[2] or by any of the other methods used. This is in agreement with the experience of other investigators. Pschorr and Sumuleanu[3] found it impossible to demethylate 3,4-dimethoxyphenanthrene. Mo-

(1) Ferguson Fellow at Columbia University, 1938–1939.

(2) Cassaday and Bogert, THIS JOURNAL, **61**, 2461 (1939).

(3) Pschorr and Sumuleanu, *Ber.*, **33**, 1810 (1900).