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Erythrina Alkaloids. XIX. Studies on the Structure of β-Erythroidine

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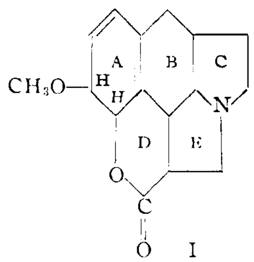
The isolation of erythroidine,[1] and the characterization of α- and β-erythroidine[2] have been reported. A review[3] of structural investigations on the *Erythrina* alkaloids included a discussion of structure I to account for the properties and reactions of β-erythroidine.

The methoxyl-, lactone, tertiary nitrogen and two double-bond functional groups permitted deduction of a pentacyclic nucleus for an alkaloid of composition $C_{16}N_{19}NO_3$. Among the degradation products[3] which led to considerations of structure I were 3-methoxyphthalic acid and 3,4-dimethoxyphthalic anhydride. These and other studies on the structure of β-erythroidine are described herein.



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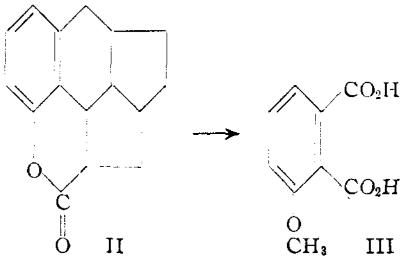


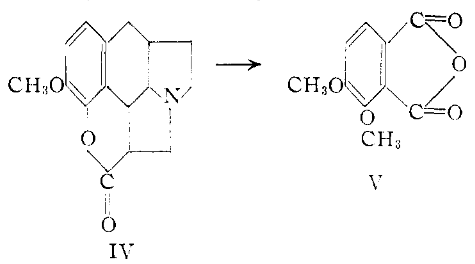
II III

After a solution of β-erythroidine in 35% sulfuric acid was heated at 100° for four hours, a new product having the composition $C_{15}H_{15}NO_2$ was obtained. This product was isolated as a crystalline perchlorate. It is designated desmethoxy-β-erythroidine,[4] and was considered to have structure II, primarily because its composition has decreased by CH_4O from that of β-erythroidine. The perchlorate was converted to the crystalline free base, m. p. 107–109°. Desmethoxy-β-erythroidine was also characterized by a crystalline hydrochloride and methiodide. Neither desmethoxy-β-erythroidine nor β-erythroidine contain a carbon–methyl group.

The hydrogenation of β-erythroidine yields dihydro and tetrahydro derivatives,[5] which are very potent in causing curare action.[6] As expected for structure II, desmethoxy-β-erythroidine in aqueous hydrochloric acid solution absorbed three moles of hydrogen over a platinum catalyst. Hexahydrodesmethoxy-β-erythroidine was not crystalline, but the analyses on sublimed material were satisfactory.

Desmethoxy-β-erythroidine was allowed to react with warm 10% sodium hydroxide solution to open the lactone ring. Dimethyl sulfate was then added to the alkaline solution for the formation of a methoxyl group at the position of the ring oxygen atom of the lactone. Probably the nitrogen atom was methylated also, but the subsequent oxidation with potassium permanganate removed this section of the molecule. 3-Methoxyphthalic acid (III) was obtained from the oxidation products in a yield of 30%; it was compared with an authentic specimen,[7] and it was converted into 3-methoxyphthalic anhydride and 3-methoxy-N-methylphthalimide for further identification. The degradation of β-erythroidine to 3-methoxyphthalic acid is in agreement with structures I and II.

Based on structure I for β-erythroidine, dehydrogenation might be expected to give dehydro-β-erythroidine (IV), and possibly additional hydrogen atoms might be removed from rings B, C or E. However, for the degradation of β-erythroidine (I) to 3,4-dimethoxyphthalic anhydride (hemipinic acid anhydride) (V), the dehydrogenation of ring A is essential, and the partial dehydrogenation of rings B, C or E is inconsequential. Dehydrogenation of β-erythroidine by the method of Cooke and Gulland[8] took place in aqueous solution with palladium chloride at the reflux temperature during eight hours. The recovered basic fraction of the products was allowed to react with sodium hydroxide in aque-



IV V

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[1] Folkers and Major, THIS JOURNAL, **59**, 1580 (1937).

[2] Folkers and Koniuszy, Abstracts of Papers, p. M15, 97th Meeting, American Chemical Society, Baltimore, Md., April 4, 1939. Folkers and Major, U. S. 2,373,952, 2,373,953.

[3] Folkers, Koniuszy, and Shavel, Abstracts of Papers, p. M30, 102nd Meeting, American Chemical Society, Atlantic City, N. J., September 10, 1941.

[4] Or o-desmethyl-erythroidene,[3] initially.

[5] Folkers and Koniuszy, U. S. Patent 2,370,651; Major and Folkers, U. S. 2,280,837.

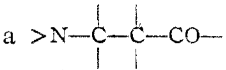
[6] Unna, Kniazuk and Greslin, *J. Pharmacol. Exp. Therap.*, **80**, 39 (1944).

[7] Corbellini and Rossi, *Gazz. chim. ital.*, **61**, 281 (1931).

[8] Cooke and Gulland, *J. Chem. Soc.*, 872 (1939).

ous solution to open the lactone ring, and then dimethyl sulfate was added for methylation. Oxidation by potassium permanganate and fractionation of the resulting products yielded 3,4-dimethoxyphthalic anhydride (V), which was also characterized as an N-methyl imide. Both the anhydride and the imide of 3,4-dimethoxyphthalic acid were identical with synthetic specimens which were derived[9] from narcotine.

The degradation of β-erythroidine to indole was accomplished by a fusion reaction with potassium hydroxide. The derivation of indole from β-erythroidine, as interpreted on the basis of structure I, undoubtedly comes from rings B and C rather than rings B and E, because the weakness of the nitrogen–carbon bond in a

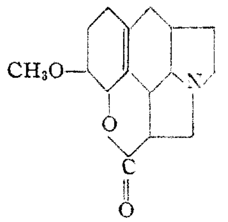


$>N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-CO-$

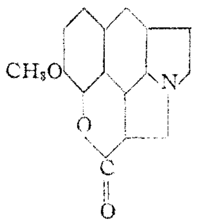
grouping would lead to rupture of ring E with alkali.

Sauvage, Berger and Boekelheide[10] have prepared desmethoxy-β-erythroidine by reaction of β-erythroidine with hydrogen fluoride at room temperature or with phosphoric acid at 80°, and have reported on some interesting properties of this compound and related degradation products.

Based upon structure I, dihydro-β-erythroidine and tetrahydro-β-erythroidine could be expected to have structures VI and VII, respectively.



VI



VII

Experimental

Desmethoxy-β-erythroidine Perchlorate.—One gram of β-erythroidine hydrochloride was dissolved in 20 ml. of 35% sulfuric acid and the solution was heated on the steam-bath for four hours. After cooling, the solution was diluted with an equal volume of water, made alkaline with sodium bicarbonate and extracted with ten 25-ml. portions of chloroform. Evaporation of the chloroform extract gave 713 g. of a pale yellow sirup which did not give a color reaction with ferric chloride solution. The sirup was dissolved in absolute ethanol, and perchloric acid solution was added until the mixture was just acidic. After refrigeration overnight, 620 mg. of crystalline product was obtained which melted at 195–196.5° (dec.). After three recrystallizations from ethanol, the desmethoxy-β-erythroidine perchlorate melted constantly at 209–210°; $[\alpha]^{25}D$ −528 (*c*, 0.5% in H_2O).

Anal. Calcd. for $C_{15}H_{15}NO_2 \cdot HClO_4$: C, 52.71; H, 4.71. Found: C, 52.50, 52.63; H, 5.01, 4.72.

Desmethoxy-β-erythroidine.—A 200-mg. sample of desmethoxy-β-erythroidine perchlorate was dissolved in water. The solution was made alkaline with sodium bicarbonate and extracted with ten 10-ml. portions of chloroform. Evaporation of the chloroform extract gave 144 mg. of desmethoxy-β-erythroidine. This free base was distilled at 2 × 10^{-3} mm. and a bath temperature of 100–125°. The sublimate crystallized, m. p. 107–109°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.65; H, 6.26. Found: C, 74.74; H, 6.22; C-CH_3, none.

Desmethoxy-β-erythroidine Hydrochloride.—A 150-mg. sample of desmethoxy-β-erythroidine was dissolved in absolute ethanol, and a freshly prepared solution of hydrogen chloride in ethanol was added. After refrigeration overnight, the crystalline desmethoxy-β-erythroidine hydrochloride was collected on a filter; m. p. 214–216° (dec.). When this product was recrystallized from alcohol–ethyl ether, the melting point was unchanged.

Anal. Calcd. for $C_{15}H_{15}NO_2 \cdot HCl$: C, 64.84; H, 5.80. Found: C, 64.77; H, 5.81.

Desmethoxy-β-erythroidine Methiodide.—A 262-mg. sample of desmethoxy-β-erythroidine was dissolved in 1 ml. of dry benzene. Addition of a few drops of methyl iodide caused the immediate separation of a gummy precipitate. Evaporation of the benzene and excess methyl iodide left 438 mg. of residue, which crystallized from absolute ethanol solution; m. p. 167–169°.

Anal. Calcd. for $C_{16}H_{18}NO_2I$: C, 50.14; H, 4.73. Found: C, 50.10; H, 4.77.

Hexahydrodesmethoxy-β-erythroidine.—A 189-mg. sample of desmethoxy-β-erythroidine was added to a mixture of 25 ml. of water and 1 ml. of concd. hydrochloric acid. The solution was diluted with 25 ml. of water and 25 mg. of Adams platinum catalyst was added. The hydrogenation was carried out at atmospheric pressure. Hydrogen absorption ceased after 61 ml. had been used; the calculated hydrogen absorption was 58 ml. After catalyst removal, the filtrate was made alkaline with sodium bicarbonate and extracted with ten portions of chloroform. Evaporation of the chloroform gave 162 mg. of hexahydrodesmethoxy-β-erythroidine which was distilled at 1 × 10^{-3} mm. and a bath temperature of 75–100°.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.55; N, 5.66. Found: C, 72.75; H, 8.77; N, 5.69.

3-Methoxyphthalic Acid, 3-Methoxyphthalic Anhydride and 3-Methoxy-N-methylphthalimide from the Oxidation of Desmethoxy-β-erythroidine.—Nine grams of desmethoxy-β-erythroidine was dissolved in 50 ml. of 10% sodium hydroxide solution at 40°, and this solution was stirred mechanically while 10 ml. of dimethyl sulfate was added dropwise. With continued stirring, 4% potassium permanganate solution was added until a persistent red color could be observed. The mixture was acidified with hydrochloric acid, and sulfur dioxide was bubbled into the solution until the manganese dioxide was gone. Continuous extraction of the aqueous solution with ethyl ether for thirty-six hours yielded 3.06 g. of crude oxidation product. This product was extracted with two liters of petroleum ether at the reflux temperature. The residue which was insoluble in petroleum ether was dissolved in ethyl ether. The crystals which separated from the ethereal solution weighed 2.2 g. and melted at 184–185°. After one recrystallization from ethyl ether, this product melted at 186–188°; when a specimen was mixed with synthetic 3-methoxyphthalic acid (m. p. 186–188°) the melting point of the mixture was unchanged. A specimen of the oxidation product was melted, and the cooled melt was recrystallized twice from toluene–petroleum ether; m. p. 161–163°.

A mixture of this product with synthetic 3-methoxyphthalic anhydride (m. p. 161–162°) also melted at 161–163°.

Anal. Calcd. for $C_9H_6O_4$: C, 60.72; H, 3.39. Found: C, 60.69; H, 3.57.

A 15-mg. sample of oxidation product (m. p. 186–188°) in ethereal solution was treated with methylamine. The precipitate was freed of solvent by evaporation, and heated at 160° for ten minutes. The residue was sublimed, and the sublimate was crystallized from methanol–petroleum ether; m. p. 143°.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.87; H, 4.74. Found: C, 62.86; H, 4.95.

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[9] Wegscheider, *Monatsh.*, **3**, 348 (1882).

[10] Sauvage, Berger and Boekelheide, *Science*, **109**, 627 (1949).

The melting point of a mixture of this product with synthetic 3-methoxy-N-methylphthalimide (m. p. 143°) was unchanged.

3,4-Dimethoxyphthalic Anhydride and 3,4-Dimethoxy-N-methylphthalimide from β-Erythroidine.—Eleven grams of palladium chloride was added to 1500 ml. of dilute hydrochloric acid (*p*H 2) and the solution was warmed to about 90° when all of the solid had dissolved. After cooling, 14 g. of β-erythroidine hydrochloride was dissolved in this solution, and the temperature was raised to boiling and maintained there for eight hours. The yield of palladium was 6.948 g. The theoretical yield of palladium is 4.8 g. for loss of H_2 from β-erythroidine. The filtrate was extracted with chloroform, but only 240 mg. of material was removed. The aqueous solution was made alkaline with sodium bicarbonate. More palladium separated and was removed. After eighteen extractions with chloroform, 7.5 g. of basic material was obtained. During the extractions, residual palladium was removed by filtration.

The basic material was dissolved in 300 ml. of 5% potassium hydroxide solution, 10 ml. of dimethyl sulfate was added, and the mixture was stirred for an hour. Then, 10 g. of potassium hydroxide and 10 ml. of dimethyl sulfate were added, and the mixture was stirred one hour; 2 g. of potassium hydroxide was added and the stirring was continued for thirty minutes.

A solution of 30 g. of potassium permanganate in 300 ml. of hot water was made and added dropwise to the mixture until a purple color remained. The mixture was acidified with hydrochloric acid, and sulfur dioxide was bubbled through the solution until the manganese dioxide was gone. The solution was extracted continuously with ethyl ether for two hours, and 805 mg. of material was obtained. This material was dissolved in 50 ml. of 5% ammonium hydroxide and, after filtration, 5 ml. of saturated calcium chloride solution was added. The precipitate was removed, and the filtrate was acidified with hydrochloric acid and extracted continuously with ether for two hours. The yield of ether residue was 310 mg.; it partially crystallized. One-half of this residue was fractionally sublimed at 10^{-4} mm. That part which sublimed as the bath temperature was slowly raised to 100° was discarded. That part which sublimed at 125° was a mixture of oil and solid on the cold surface. The gum was quickly removed with a drop or two of ether, and the solid was heated in a micro-tube at 160–165° for five minutes to ensure complete anhydride formation. Sublimation at a bath temperature of 130° *in vacuo* of the solidified melt yielded a white crystalline sublimate. Recrystallization of this sublimate from ether gave 3,4-dimethoxyphthalic anhydride, m. p. 166–167°.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.69; H, 3.87. Found: C, 57.97; H, 3.92.

The melting point of a mixture of this material with 3,4-dimethoxyphthalic anhydride (m. p. 166–167°, obtained from narcotine by oxidation[9]) was 166–167°.

The mother liquor of the ether recrystallization was saturated with methylamine and then evaporated. The residue weighed 6.8 mg. and was heated at 140–145° for five minutes and then sublimed *in vacuo*. The sublimate of 3,4-dimethoxy-N-methylphthalimide melted at 167–168° and when mixed with a synthetic specimen, the melting point of the mixture was 167–168°.

The synthetic 3,4-dimethoxy-N-methylphthalimide was made similarly and found to melt at 167–168°.

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01. Found: C, 59.89; H, 5.01.

Degradation of β-Erythroidine to Indole.—Ten grams of β-erythroidine hydrochloride was mixed with 50 g. of powdered potassium hydroxide. The mixture was heated in an open porcelain dish until it became molten. After stirring and heating the melt for one hour, it was poured into a 400-ml. mixture of ice and water. The aqueous solution was extracted with twelve 100-ml. portions of ethyl ether, and the ethereal extract yielded 2.4 g. of a dark-red colored residue, after distillation. The residue was dissolved in 500 ml. of ethyl ether, and this solution was washed with three 120-ml. portions of 20% hydrochloric acid, and then with 100 ml. of water. The ethereal solution was passed through a column (14 inches × 0.75 inch) of alumina to yield 975 mg. of an amber-colored gum. Sublimation of 300 mg. of this gum at 70° and 0.01 mm. gave 145 mg. of crystalline material which melted at 49–50°. Recrystallization of this material from petroleum ether gave indole; m. p. 51–52°. A mixture of this sample with authentic indole showed no melting-point depression.

Anal. Calcd. for C_8H_7N: C, 82.04; H, 6.03. Found: C, 82.04; H, 6.20.

Acknowledgment.—We are indebted to Messrs. D. F. Hayman, W. Reiss and H. C. Clark for the microanalytical data.

Summary

β-Erythroidine has been degraded to desmethoxy-β-erythroidine by reaction in sulfuric acid solution. Desmethoxy-β-erythroidine has been characterized as a free base, perchlorate, hydrochloride and methiodide.

Desmethoxy-β-erythroidine has been hydrogenated to a hexahydro derivative, and oxidized to 3-methoxyphthalic acid.

β-Erythroidine has been degraded to 3,4-dimethoxyphthalic anhydride by stepwise dehydrogenation, hydrolysis, methylation and oxidation. β-Erythroidine has been degraded to indole by fusion with alkali.

Interpretation of these reactions and products of β-erythroidine permits structure formulations.

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