Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 72.88; H, 8.56. Found: C, 73.24; H, 8.59.

***allo*-Octahydrodesmethoxy-β-erythroidine Methiodide.**—A mixture containing 200 mg. of *allo*-dihydrodesmethoxy-β-erythroidine, 200 mg. of prereduced Adams catalyst, 12 drops of 12 *N* hydrochloric acid and 100 ml. of ethanol was subjected to hydrogenation at room temperature and 35 lb. pressure. Hydrogen uptake proceeded slowly and was complete after three days. The catalyst and solvent were removed, leaving a residue which was dissolved in an aqueous sodium bicarbonate solution. The bicarbonate solution was extracted repeatedly with benzene, and then the combined benzene extracts were concentrated. The oily residue did not crystallize and so it was dissolved in methanol and treated with an excess of methyl iodide. The solid which formed was recrystallized from absolute ethanol and yielded 260 mg. (81%) of white plates, m.p. 244–245° dec.

Anal. Calcd. for $C_{16}H_{26}NO_2I$: C, 49.10; H, 6.69. Found: C, 48.83, 49.15; H, 6.70, 6.80.

Permanganate Oxidation of *allo*-Dihydrodesmethoxy-β-erythroidine (XII).—A solution was prepared by dissolving 1.00 g. of *allo*-dihydrodesmethoxy-β-erythroidine in 20 ml. of water containing 1.0 g. of potassium hydroxide. This was then diluted to 50 ml. and maintained just below boiling while 182 ml. of a 4% aqueous potassium permanganate solution was added dropwise with stirring over a period of 11 hr. Sulfur dioxide was then bubbled through the solution until it became clear, sufficient hydrochloric acid was added to bring the *p*H of the solution to 4, and then it was extracted with seven 100-ml. portions of ether. The combined ether extracts were washed with water, dried and concentrated. The resulting residue was dissolved in aqueous sodium bicarbonate solution; this was extracted with ether, acidified and then extracted with ether again. The final ether extract on concentration, gave 155 mg. (23%) of a white solid, having the properties of phthalic acid. The solid was sublimed to give white needles, m.p. 120–125°, which were then treated with an aqueous methylamine solution. This mixture was evaporated to dryness, and the residue, on sublimation, gave white needles, m.p. 129–130°, alone or mixed with an authentic sample of N-methylphthalimide. The infrared spectra of the authentic and naturally-derived samples of N-methylphthalimide were identical.

Desmethoxy-β-erythroidinol Methiodide.—A solution of 400 mg. of desmethoxy-β-erythroidinol in 25 ml. of methanol was treated with an excess of methyl iodide and the solution was boiled under reflux for 0.5 hour. After removal of the methanol, ethyl acetate was added, causing the separation of 570 mg. of a white solid. This, after recrystallization from absolute ethanol, gave white plates, m.p. 168–169°.

Anal. Calcd. for $C_{16}H_{22}NO_2I$: C, 49.62; H, 5.72. Found: C, 49.75; H, 5.83.

Conversion of Desmethoxy-β-erythroidinol Methochloride (XIII) to Des-N-methyldihydro-β-erythroidinol (XIV).—A solution of 500 mg. of the methiodide of desmethoxy-β-erythroidinol in 25 ml. of ethanol was passed over an ion-exchange column (Amberlite IRA-400-Cl) to convert the methiodide to the corresponding methochloride derivative. To the eluate there was then added 40 mg. of Adams catalyst, and the mixture was subjected to hydrogenation at room temperature and atmospheric pressure. One molar equivalent of hydrogen was absorbed in 23 minutes and then hydrogen uptake ceased. After removal of the catalyst and solvent, the residue was dissolved in an aqueous sodium bicarbonate solution and extracted thoroughly with benzene. The combined benzene extracts were dried and then concentrated. When the resulting oil solidified, it was taken up in hexane and recrystallized. This gave 240 mg. (71%) of white crystals, m.p. 93–95°. This was shown to be identical with des-N-methyldihydro-β-erythroidinol (XIV)[10] by a mixed melting point determination and by a comparison of the infrared spectra of the two samples.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

A Characterization of α-Erythroidine[1]

BY V. BOEKELHEIDE AND M. F. GRUNDON

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Of the two isomers of erythroidine only β-erythroidine has been subjected to chemical investigation. In the present paper the purification and characterization of α-erythroidine are described. The results of preliminary chemical studies on α-erythroidine suggest that it is not a diastereoisomer of β-erythroidine and, therefore, the present manner of designating these two isomers is probably inappropriate.

As an outgrowth of our studies on β-erythroidine,[2] we became interested in the accompanying isomeric alkaloid, α-erythroidine, and its possible structural relationship to β-erythroidine. These two alkaloids, which constitute the "erythroidine" fraction from various species of Erythrina, were first isolated by Folkers and Major who gave them the α- and β-designations in conformity with the usual practice for diastereoisomers (α-erythroidine hydrochloride has a specific rotation of +118°, whereas the specific rotation of β-erythroidine hydrochloride is +109°).[3] Although Folkers and Major reported the melting points of a number of salts of α-erythroidine (hydrochloride, m.p. 227–228°; hydrobromide, m.p. 220–222°; hydroiodide, m.p. 210–212°; perchlorate, m.p. 208–208.5°; and the flavinate, m.p. 216°),[3] no further information regarding this alkaloid was available until the recent publication of the excellent dissertation by Lapière.[4] It is the purpose of the present paper to present some independent observations bearing on the characterization of α-erythroidine and its possible structural relationship to β-erythroidine.

The crude α-erythroidine hydrochloride fraction obtained from isolation studies is usually badly contaminated with β-erythroidine hydrochloride. Since the solubility properties of these two hydrochlorides, as well as those of the other common salts of the α- and β-erythroidines, are very similar, it is not easily possible to effect complete separation of these two alkaloids by fractional crystallization. Although samples of α-erythroidine hydrochloride, obtained by fractional crystallization, were found to show the same melting point and rotation, as described by Folkers and Major,[3] these samples in-

(1) Aided by a grant from the United Cerebral Palsy Association.

(2) This is paper X in this series; for the preceding communication see V. Boekelheide, A. E. Anderson and G. L. Sauvage, THIS JOURNAL, 75, 2558 (1953).

(3) K. Folkers and R. T. Major, British Patent 543,187; K. Folkers and R. T. Major, U. S. Patent 2,373,952.

(4) C. Lapière, Dissertation on the Erythrina Alkaloids, University of Liege (1952).

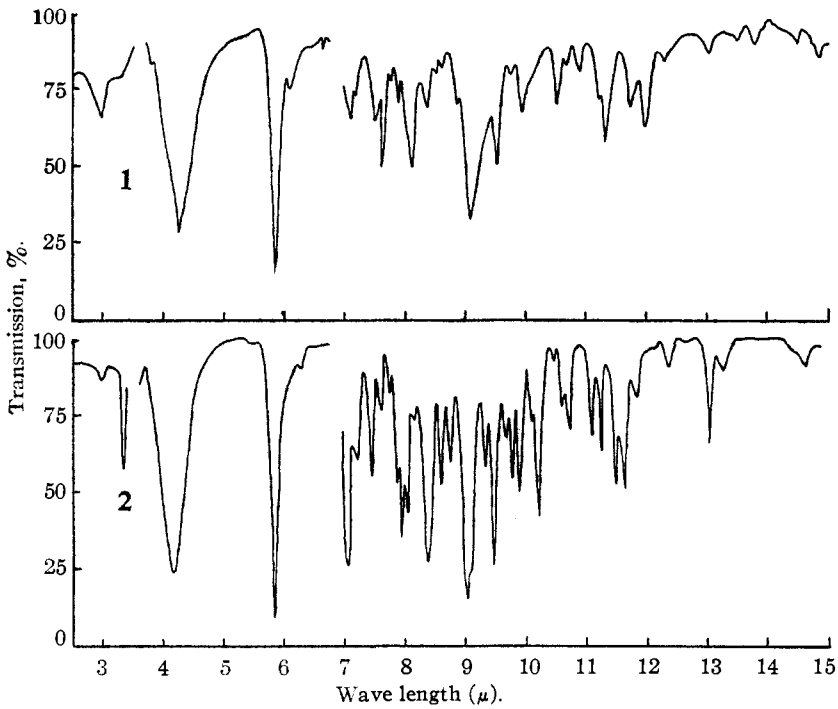


Fig. 1.—The infrared absorption spectra of: 1, α-erythroidine hydrochloride; 2, β-erythroidine hydrochloride. Both determined using Nujol mulls.

variably gave a positive result in the color test devised by Dietz and Folkers for β-erythroidine.[5] This test, as well as the more sensitive acetic anhydride–ferric chloride test devised by Lapière,[4] is extremely useful for determining whether samples of salts of α-erythroidine are contaminated by traces of the corresponding β-erythroidine derivative.

To obtain α-erythroidine free of the β-isomer we have found it most convenient to subject the free base to chromatography over alumina. When a sample of α-erythroidine, purified in this way, was converted to the corresponding hydrochloride, this derivative had the same physical properties reported by Folkers and Major for α-erythroidine hydrochloride and it also gave negative results in the previously mentioned color tests for β-erythroidine hydrochloride. α-Erythroidine, as the free base, separated from benzene or pentane as beautiful white crystals, m.p. 58–60°; however, on exposure to the atmosphere, the alkaloid was extremely unstable and decomposed so rapidly that it has not been possible to obtain satisfactory analyses of its composition.[6] In contrast, the salts of α-erythroidine are reasonably stable and, in addition to the hydrochloride, we have prepared the perchlorate, methiodide and picrolonate derivatives. As expected, the compositions of these derivatives are in accord with an empirical formula of $C_{16}H_{19}NO_8$ for α-erythroidine.

The behavior of α-erythroidine toward alkali would suggest that it contains a lactone ring whose cleavage by hydrolysis can readily be reversed. The presence of a lactone ring is supported by Lapière's results on the electrometric titration of α-erythroidine hydrochloride and also by our experiments, to be discussed later, on the lithium aluminum hydride reduction of α-erythroidine. Furthermore, a comparison of the infrared spectra of the α- and β-erythroidine hydrochlorides (see Fig. 1) reveals that the lactone carbonyl peaks for both of these alkaloids occur at the same wave length (5.85 μ).[7] In view of the evidence previously presented suggesting that β-erythroidine contains an unsaturated δ-lactone ring,[8] it appears likely that this structural unit is also present in α-erythroidine.

The physical properties of corresponding derivatives of the α- and β-erythroidines are surprisingly similar. In addition to the difficulty of separating these derivatives by fractional crystallization, it should be noted that in most cases mixtures of similar derivatives of the two alkaloids show no depression of melting point. It is an obvious hypothesis, therefore, to suppose that the α- and β-erythroidines are diastereoisomers. However, further examination of α-erythroidine has led us to the conclusion that this is not the case. For example, if the hydrochlorides of the α- and β-erythroidines were diastereoisomers, they should possess very similar ultraviolet and infrared absorption spectra. But, in fact, the ultraviolet absorption spectrum of α-erythroidine hydrochloride (see Fig. 2) is different from that of β-erythroidine hydrochloride, its absorption maximum occurring at considerably shorter wave lengths (224 mμ for the α-isomer compared to 238 mμ for β-erythroidine hydrochloride).

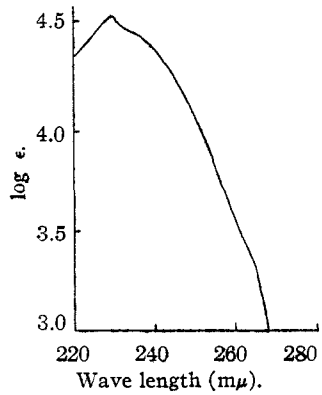


Fig. 2.—The ultraviolet absorption spectrum of α-erythroidine hydrochloride in ethanol.

(5) E. M. Dietz and K. Folkers, *J. Am. Pharm. Ass., Sci. Ed.*, **35**, 48 (1946).

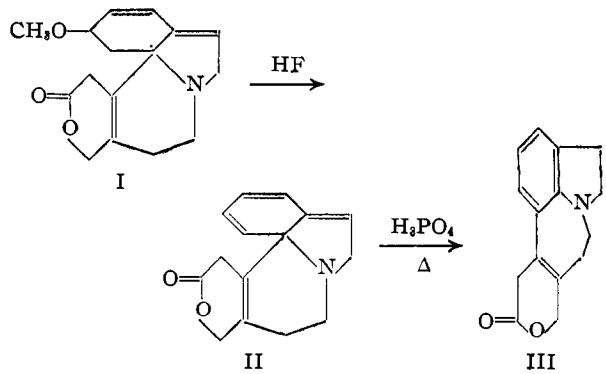
(6) Lapière (ref. 4) has likewise isolated α-erythroidine as a crystalline compound and found it too unstable to determine accurately either its melting point or composition.

(7) It is of interest that the lactone carbonyl peak for β-erythroidine hydrochloride occurs at somewhat longer wave lengths (5.85 μ) than it does in the case of the free base (5.78 μ).

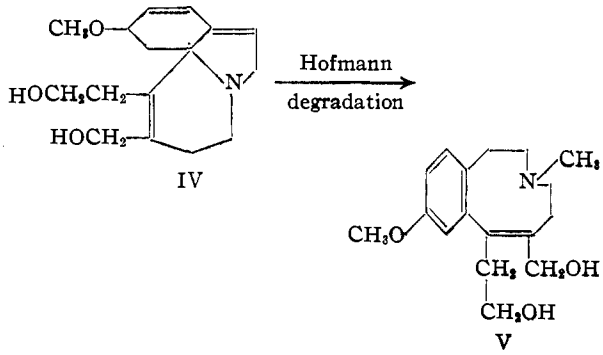
(8) V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage and E. J. Agnello, THIS JOURNAL, **75**, 2550 (1953).

As discussed elsewhere,[8] we have recently concluded that β-erythroidine is best described by formula I. One of the characteristic reactions of β-erythroidine is its conversion, on treatment with hydrogen fluoride, to desmethoxy-β-erythroidine (II). Since this reaction presumably removes one of the two centers of asymmetry present in β-erythroidine, a comparable reaction with α-erythroidine, if it were diastereoisomeric, should lead either to the identical desmethoxy derivative or its enantiomorph. When α-erythroidine hydrochloride was treated with hydrogen fluoride, loss of the elements of methanol occurred, but the resulting product was neither identical with nor the enantiomorph of desmethoxy-β-erythroidine. The non-identity of the two desmethoxy derivatives is evident from a comparison of their physical properties and the infrared absorption spectra of their perchlorate derivatives.

Further evidence that the two desmethoxy derivatives are structurally different was provided from a study of their optical activity. Desmethoxy-α-erythroidine perchlorate has a specific rotation of −810°, which is an even greater negative value than that of the perchlorate of desmethoxy-β-erythroidine (−528°).[9] The abnormally high negative rotation of desmethoxy-α-erythroidine would suggest that it might have an unsaturated spiro system similar to that present in desmethoxy-β-erythroidine (II). In the case of both β-erythroidine and desmethoxy-β-erythroidine, it has previously been shown that these spiro systems undergo a rearrangement on heating with phosphoric acid to give an aromatic compound, apo-β-erythroidine (III).[10,11] It was of interest, therefore, to subject separately both α-erythroidine hydrochloride and desmethoxy-α-erythroidine perchlorate to the conditions employed in the apo-rearrangement. In neither case was it possible to isolate a product having the properties to be expected for an apo-derivative. Although this does not remove the possibility that desmethoxy-α-erythroidine contains a spiro structure, it does emphasize the fact that there are significant structural differences between the two series of compounds.[12]



In the β-erythroidine series, it has been shown that β-erythroidinol (IV) on Hofmann degradation undergoes aromatization to give a des-base having structure V.[8] It might be expected, if α-erythroidine were closely related structurally to β-erythroidine, that a comparable series of reactions in the α-series would lead to a des-base similar to V. Of course, if the α- and β-erythroidinols were diastereoisomers, the same des-base V should result. With this in mind, we subjected α-erythroidine to a lithium aluminum hydride reduction and readily obtained the corresponding diol, α-erythroidinol. This derivative, in contrast to α-erythroidine, was relatively stable as the free base and could be handled in the usual manner without difficulty. When α-erythroidinol was converted to the corresponding methiodide and then subjected to a Hofmann degradation, resinification occurred and no useful product could be isolated.



It can be concluded from these studies that α-erythroidine and β-erythroidine are not diastereoisomers and, in this regard, the present method of designating these alkaloids is probably inappropriate. Although it would seem only reasonable, from biological considerations,[8] that the α- and β-erythroidines should be related structurally, the present investigation suggests that there are significant differences between the two alkaloids. Certainly, the approaches utilizing the Hofmann degradation and the apo-rearrangement, which were so useful in elucidating the structure of β-erythroidine,[8] have given only negative results in the case of the α-isomer. Rather unexpectedly, α-erythroidine presents itself as a new and possibly independent structural problem.

Experimental[13]

Purification and Characterization of α-Erythroidine.—The α-erythroidine used in this study was obtained from S. B. Penick and Co., who supplied us with the crude "α-erythroidine hydrochloride fraction" isolated from seeds of *Erythrina berteroana*, Urban grown in Nicaragua. The principal contaminant in this fraction was β-erythroidine hydrochloride. When a sample of this crude fraction was subjected to fractional recrystallization from an ethanol–ether mixture, it gave a sample of white prisms, m.p. 226–228°, with decomposition beginning at 200°; $[\alpha]^{25}D$ +118°. When this sample of crystals was tested for the presence of β-erythroidine using either the Dietz–Folkers color test or the acetic anhydride color test of Lapière,[14] it gave a strongly positive result.

(9) F. Koniuszy and K. Folkers, THIS JOURNAL, **72**, 5579 (1950).

(10) G. L. Sauvage and V. Boekelheide, *ibid.*, **72**, 2062 (1950).

(11) M. F. Grundon, G. L. Sauvage and V. Boekelheide, *ibid.*, **75**, 2541 (1953).

(12) The negative results in the attempted apo-rearrangement of α-erythroidine were not unexpected since α-erythroidine gives a negative Dietz–Folkers color test and this test is dependent on the intermediate formation of apo-β-erythroidine.

(13) Analyses by Miss Claire King and Miss Viola Williams.

(14) Lapière's procedure for this test is as follows: a sample of the material to be tested is dissolved in 1 ml. of chloroform and to this there is added 1 ml. of acetic anhydride. After this mixture has been

To purify α-erythroidine the following procedure, which is closely related to that used by Lapière,[4] was found to be most convenient. A solution containing 10.0 g. of crude α-erythroidine hydrochloride in 100 ml. of water was brought to a *p*H of 8 by addition of sodium bicarbonate and then extracted four times with 20-ml. portions of benzene. After the combined benzene extracts had been concentrated under reduced pressure to a total volume of 20 ml., it was introduced on a column of activated alumina (25 g.). When the column was eluted with benzene, the first 10 ml. of eluate and the next 40 ml. of eluate were saved as separate fractions. Concentration of the first fraction of eluate gave a crystalline residue which was taken up in ethanol and treated with dry hydrogen chloride. There separated from the ethanolic solution 0.35 g. of white crystals. After recrystallization from ethanol, a sample of the hydrochloride of α-erythroidine was obtained as colorless, irregular prisms, m.p. 226–228° dec., darkening beginning *ca.* 200°; $[\alpha]^{32}D$ +118° (*c* 0.5% in water). This sample of the hydrochloride gave negative results in both the Dietz–Folkers and Lapière color tests for β-erythroidine.

Anal. Calcd. for $C_{16}H_{20}NO_3Cl$: C, 62.04; H, 6.36; N, 4.52; $-OCH_3(1)$, 10.01. Found: C, 62.15; H, 6.70; N, 4.53; $-OCH_3$, 9.55.

When the second fraction of benzene eluate was concentrated and converted to the hydrochloride salt in the same manner as above, there resulted 4.75 g. of white prisms, which showed the same melting point and rotation as the hydrochloride from the first fraction of eluate. Although the hydrochloride from the second fraction of eluate gave a negative result in the Dietz–Folkers test, it did give a faintly positive result in the test devised by Lapière, indicating the presence of trace amounts of β-erythroidine hydrochloride.

A solution of 1.30 g. of the pure α-erythroidine hydrochloride in 20 ml. of water was made basic with sodium bicarbonate and then extracted six times with 10-ml. portions of benzene. When the combined benzene extracts were concentrated to a small volume and then refrigerated, the free α-erythroidine base separated as hygroscopic white crystals, m.p. 52–55°. A sample of this material, on recrystallization from pentane, gave colorless needles; m.p. 58–60°, $[\alpha]^{27}D$ +136 (*c* 0.5% in H_2O). Although samples of α-erythroidine were relatively stable in solution, the pure crystals were extremely hygroscopic and turned brown immediately on exposure to the atmosphere.

The **methiodide of α-erythroidine** formed readily when methyl iodide was added to an ethanolic solution of α-erythroidine and the resulting solution was allowed to stand at room temperature. The solid, which separated, was recrystallized from ethanol giving faintly yellow prisms, m.p. 219–220°, sintering at 217°.

Anal. Calcd. for $C_{17}H_{22}NO_3I$: C, 49.16; H, 5.30. Found: C, 49.35; H, 5.52.

The **picrolonate of α-erythroidine** was prepared in ethanol and was obtained, after recrystallization from the same solvent, as orange-brown needles, m.p. 207.5–208° dec.

Anal. Calcd. for $C_{26}H_{27}N_5O_3$: C, 58.09; H, 5.06. Found: C, 58.24; H, 5.55.

The perchlorate of α-erythroidine was prepared by treating a solution of 300 mg. of α-erythroidine hydrochloride in 10 ml. of ethanol with a slight excess of perchloric acid. The white solid, which separated, was recrystallized from ethanol to give 300 mg. of colorless needles, m.p. 195–197° dec. Although this is somewhat lower than the melting point reported by Folkers and Major (208–208.5°),[3] the manner in which these crystals decompose makes comparison difficult.

Anal. Calcd. for $C_{16}H_{20}NO_7Cl$: C, 51.41; H, 5.36. Found: C, 51.12; H, 5.59.

For comparison the corresponding derivatives were prepared from a pure sample of β-erythroidine (m.p. 99–100°, $[\alpha]^{28}D$ +85° (*c* 0.3% in water)). The hydrochloride of β-erythroidine was obtained as white needles; m.p. 228–231° dec., blackening beginning at 200°; $[\alpha]^{27}D$ +107° (*c* 0.5% in water).[4] The methiodide of β-erythroidine formed as white crystals, m.p. 208–211° dec.[10]

The **picrolonate of β-erythroidine** formed readily in ethanol and was obtained as yellow needles, m.p. 209.5–210.5° dec.

Anal. Calcd. for $C_{26}H_{27}N_5O_8$: C, 58.09; H, 5.06. Found: C, 58.33; H, 5.31.

The **perchlorate of β-erythroidine** separated from ethanol as colorless needles, m.p. 190–191° dec.

Anal. Calcd. for $C_{16}H_{20}NO_7Cl$: C, 51.41; H, 5.36. Found: C, 51.08; H, 5.58.

Desmethoxy-α-erythroidine Perchlorate.—A sample of 3.00 g. of α-erythroidine hydrochloride was added in small portions to 30 ml. of anhydrous hydrogen fluoride. After the solution had stood at room temperature until almost all of the hydrogen fluoride had evaporated, the brown residue was taken up in 50 ml. of water. The resulting solution was made alkaline by addition of sodium bicarbonate and then extracted six times with 30-ml. portions of benzene. Concentration of the combined benzene extracts gave a brown gum which did not crystallize. The gum was therefore taken up in 20 ml. of benzene and chromatographed over Florisil. When the benzene eluate was concentrated it gave a pale yellow oil, which again did not crystallize. A solution of this oil in ethanol was then treated with perchloric acid. The solid which separated was crystallized from ethanol and gave 296 mg. of colorless prisms; m.p. 142–143.5°, $[\alpha]^{25}D$ −810° (*c* 0.15% in water).

Anal. Calcd. for $C_{15}H_{16}NO_6Cl$: C, 52.70; H, 4.72; $-OCH_3(O)$, 0.00. Found: C, 52.31; H, 4.70; $-OCH_3$, 0.00.

When samples of either desmethoxy-α-erythroidine perchlorate or α-erythroidine hydrochloride were subjected to the conditions employed for preparing apo-β-erythroidine,[10,11] there was no indication of the formation of an apo-derivative even when the reaction time was increased to 3 hours. In several instances, where impure samples of α-erythroidine hydrochloride were employed, apo-β-erythroidine was isolated in minute yield. Its appearance was shown to be a result of contamination by β-erythroidine.

α-Erythroidinol.—A solution of α-erythroidine (obtained from 6.00 g. of α-erythroidine hydrochloride without direct isolation) in 500 ml. of dry ether was treated with 25 ml. of a 1 *M* ethereal solution of lithium aluminum hydride. The mixture was stirred at room temperature for 12 hours and then decomposed by addition of moist ether. After removal of the inorganic precipitate, the ethereal solution was allowed to stand at 0°, whereupon it deposited 1.42 g. of colorless crystals, m.p. 149–154°. A sample of this material, on recrystallization from benzene, gave white plates, m.p. 155–156°.

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.24; H, 8.35. Found: C, 69.62; H, 8.50.

The **methiodide of α-erythroidinol** was prepared by treating 1.20 g. of α-erythroidinol in 20 ml. of methanol with 5 ml. of methyl iodide. The resulting solid, after recrystallization from an ethanol–ether mixture, gave 1.38 g. of colorless plates, m.p. 197–199°.

Anal. Calcd. for $C_{17}H_{26}NO_3I$: C, 48.70; H, 6.25. Found: C, 48.61; H, 6.50.

The Hofmann degradation of α-erythroidinol was attempted in the same manner employed previously for β-erythroidinol.[8] An aqueous solution of 2.4 g. of the methiodide of α-erythroidinol was passed over a column of Amberlite IRA-400-OH; the eluate was collected and concentrated under reduced pressure. The residual oil, on attempted distillation, completely resinified.

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well shaken, it is carefully added to 1 ml. of a prepared solution of sulfuric acid (this solution is prepared by adding one drop of a 29% aqueous ferric chloride solution to 100 ml. of concentrated sulfuric acid). If β-erythroidine is present, a violet ring appears at the zone separating the two layers and, with more concentrated solutions, this color may spread throughout the chloroform layer. Lapière estimates that this test is sufficiently sensitive to detect the presence of 1 microgram of β-erythroidine (ref. 4).