(by previous standardization) was passed through a solution of 190 mg. of desazadesoxyhexahydro-β-erythroidinol in 15 ml. of ethyl chloride maintained at 0°. The solvent was then allowed to evaporate and 15 ml. of water, 100 mg. of zinc dust, 10 mg. of silver nitrate and a few crystals of hydroquinone were added to the residue. The mixture was boiled for 15 minutes and then allowed to distil until 5 ml. of distillate had collected. This was treated with a prepared reagent made of 200 mg. of 2,4-dinitrophenylhydrazine in ethanol. An orange solid immediately separated from solution and, after crystallization from ethanol, this gave 27.5 mg. (12.5%) of orange crystals, m.p. 106–110°. On further recrystallization from ethanol, this gave orange crystals, m.p. 114–116°. A mixed melting point determination with an authentic sample of the 2,4-dinitrophenylhydrazone of methyl ethyl ketone (m.p. 114–116°) showed no depression of melting point. Also, the infrared spectra of the authentic and naturally-derived samples were identical.

ROCHESTER, N. Y.

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

The Structure of β-Erythroidine and its Derivatives[1,2]

BY V. BOEKELHEIDE, JOSEPH WEINSTOCK, M. F. GRUNDON, G. L. SAUVAGE AND E. J. AGNELLO

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A study of the Hofmann decomposition of β-erythroidinol has led to the isolation of N-methyl-3-methoxyphthalimide. This result establishes the location of the aliphatic methoxyl in β-erythroidine and makes possible a complete assignment of structure for this alkaloid. The degradative evidence regarding β-erythroidine and its derivatives is summarized and interpretations of the rearrangements occurring in the formation of apo-β-erythroidine and in the formation of des-N-methyldihydro-β-erythroidinol are given. A possible scheme for the biogenesis of β-erythroidine is suggested.

The isolation of a physiologically active crystalline principle from a species of *Erythrina* was first reported by Folkers and Major in 1937.[3] Later, it was shown that this material, which was a mixture of two isomers, α- and β-erythroidine, constituted the principal alkaloidal fraction of seeds from *Erythrina americana*,[4] *Erythrina berteroana*,[4] *Erythrina peoppiginana*[4] and *Erythrina tholloniana*.[5] The more active of the two isomers, β-erythroidine, attracted interest because, in contrast to curare, it retained the ability to block neuromuscular transmission even when administered orally.[6] Fundamental interest in the structure of β-erythroidine was also evoked by the unusual fact that the alkaloid was a considerably more active curarizing agent as a tertiary base than as a quaternary salt.[6] In addition β-erythroidine was found to be converted by acid to an apo-derivative which possessed central depressant activity of long duration.[7]

Previous investigations[7–11] of the structure of β-erythroidine have yielded much information regarding the molecule but the structures, which have thus far been proposed,[8,10] have proved unsatisfactory in the light of later evidence. It is the purpose of this paper to summarize the degradative evidence relating to β-erythroidine and its derivatives and to suggest structures which will logically explain the evidence at hand and which will show, for the first time, the correlation between β-erythroidine and the other alkaloids isolated from the various species of Erythrina.[12,13]

The Structure of β-Erythroidine

In preceding papers in this series[2,14,15] it is shown that apo-β-erythroidine must have structure III and that des-N-methyldihydro-β-erythroidinol must have structure VI. In considering possible formulas for β-erythroidine, therefore, it is necessary to provide a structure that will explain the origin of these two important degradation products. Of the various possibilities the only logical arrangement which accounts satisfactorily for their formation, is a spiro structure of the type shown by formula I. Thus, such a spiro structure would be expected to undergo a carbonium ion rearrangement[16] to yield a 7-substituted indoline, as required for apo-β-erythroidine; yet, it would also be expected that, on Hofmann decomposition, elimination of the nitrogen would be accompanied by aromatization to give an *o*-disubstituted benzene, as required for des-N-methyl-dihydro-β-erythroidinol. These transformations, based on formula I for β-erythroidine, are illustrated below. An important advantage of the spiro structure is that it clearly explains why β-erythroidine is not dehydrogenated by the usual catalytic methods to an aromatic compound.

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

(2) Paper VIII in this series, for the preceding communication see J. Weinstock and V. Boekelheide, THIS JOURNAL, **75**, 2546 (1953). A portion of this paper was presented previously in preliminary form (*ibid.*, **74**, 1866 (1952)).

(3) K. Folkers and R. T. Major, *ibid.*, **59**, 1580 (1937).

(4) K. Folkers and R. T. Major, U. S. Patents 2,373,952 and 2,412,256; British Patent 543,187.

(5) (a) C. Lapiere, Dissertation on Erythrina Alkaloids, University of Liege, March 25, 1952; (b) C. Lapiere and G. Coppee, *Experientia*, **4**, 387 (1948).

(6) K. Unna and J. G. Greslin, *J. Pharmacol.*, **80**, 53 (1944); K. Unna, M. Kniazuk and J. G. Greslin, *ibid.*, **80**, 39 (1944).

(7) G. L. Sauvage, F. M. Berger and V. Boekelheide, *Science*, **109**, 627 (1949).

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

(9) F. Koniuszy and K. Folkers, *ibid.*, **73**, 333 (1951).

(10) C. Lapiere and R. Robinson, *Chem. and Ind.*, 150 (1951).

(11) See ref. 2 and the previous papers in this series.

(12) M. Carmack, B. C. McKusik and V. Prelog, *Helv. Chim. Acta*, **34**, 1601 (1951).

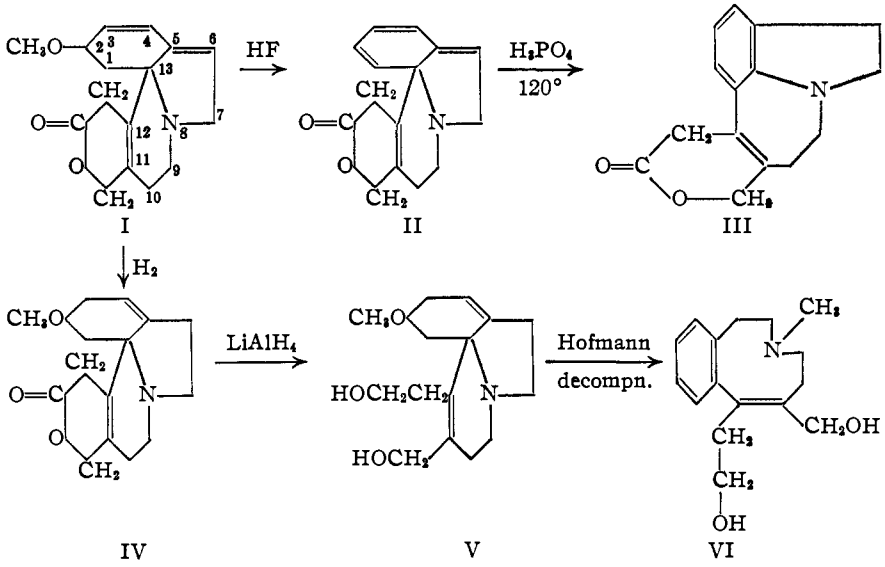
(13) G. W. Kenner, H. G. Khorana and V. Prelog, *ibid.*, **34**, 1969 (1951).

(14) M. F. Grundon and V. Boekelheide, THIS JOURNAL, **75**, 2537 (1953).

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

(16) The probable mechanism for this type of rearrangement has already been illustrated for the case of apo-erysopine (see ref. 12). This rearrrangement would appear to be a special example of the "semibenzene–alkylbenzene" rearrangement studied so extensively by v. Auwers (*Ann.*, **425**, 217 (1921)). Other examples of the rearrangement are given in ref. 15, and it is of interest that, when migration is accompanied by aromatization, there is no need for activation as is the case in the rearrangement of tetrahydro-erythraline.[12]

The assignment of the other structural features of β-erythroidine, as shown in formula I, have been deduced in the following way. The transformations of β-erythroidine to III and to VI determine quite definitely the nature of the carbon skeleton and the position and arrangement of the lactone ring. The presence of a δ-lactone ring is also corroborated by the infrared spectrum of β-erythroidine (see Fig. 1) which shows an absorption peak at 5.78 μ as would be expected for the carbonyl stretching vibration of a δ-lactone.[17]



I II III IV V VI

Also, from the formation of III and VI, it becomes evident that β-erythroidine must contain three aliphatic double bonds rather than two, as formerly thought.[8] The fact that β-erythroidine has been reported to form only di- and tetrahydro derivatives[18] on hydrogenation is not necessarily in disagreement. It is not uncommon for tetrasubstituted aliphatic double bonds to be either entirely resistant to hydrogenation or to undergo hydrogenation at a very slow rate.[19] Actually this behavior is observed for the tetrasubstituted double bond in compound VI. In this case, although hydrogenation does not reveal the presence of an aliphatic double bond, it can be shown that such a double bond is present by the ultraviolet absorption spectrum of the molecule as well as by ozonolysis experiments.[2] Furthermore, if one examines the hydrogenation of β-erythroidine to its tetrahydro derivative, it is observed that hydrogen absorption proceeds well beyond two molar equivalents before the rate becomes immeasurably slow. The infrared spectrum of the resulting isomeric mixture of tetrahydro derivatives shows a definite peak at 6.10 μ, which corresponds to the region where absorption related to C=C vibrations usually occurs.[20] Since there is nothing in the 9 to 12 μ region of the infrared spectrum to indicate the presence of a di- or trisubstituted double bond, it can be concluded that this absorption band is derived from a tetrasubstituted double bond. The only logical place for β-erythroidine to accommodate such a tetrasubstituted double bond is at the point of fusion of the lactone ring as indicated by I.[21]

The remaining questions regarding the structure of β-erythroidine are then the positions of the other two aliphatic double bonds and the position of the aliphatic methoxyl group. The ultraviolet absorption spectrum of β-erythroidine, as shown in Fig. 2, has a maximum at 238 mμ (log ε, 4.4) which is absent in the spectrum of its dihydro derivative.[22] According to the rules which have been developed for predicting the ultraviolet absorption spectra of conjugated dienes,[23] this would correspond to a trisubstituted conjugated diene in which the double bonds are not in the same ring.[24] Since β-erythroidine has the properties of neither a vinylamine nor an enol ether, the only possible arrangement for the conjugated diene system would appear to be that shown by formula I.

The final point, the position of the methoxyl group, has now been settled by a study of the Hofmann degradation of β-erythroidinol (VII), the lithium aluminum hydride reduction product of β-erythroidine. In contrast to dihydro-β-erythroidinol,[25] the Hofmann decomposition of β-erythroidinol led to aromatization without loss of the methoxyl group. The resulting des-N-methyl-β-erythroidinol (VIII) showed absorption peaks in the infrared at 11.4 and 12.2 μ, as is typical of 1,2,4-trisubstituted benzene derivatives,[26] and, on oxidation with permanganate, it gave 4-methoxyphthalic anhydride in good yield. The 4-methoxyphthalic anhydride was converted to its N-methylphthalimide derivative and this was identified by mixed melting point determinations and a comparison of its infrared spectrum with that of an authentic sample of N-methyl-4-methoxyphthalimide.[27] In view of the fact that β-erythroidine is not an enol ether, the isolation of 4-methoxyphthalic anhy-

(17) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, 71, 1073 (1949); *cf.* L. Zeftel, Ph.D. Thesis, University of Rochester, 1951.

(18) K. Folkers and F. Koniuszy, British Patent 596,976.

(19) H. L. Haller and F. B. La Forge, *J. Org. Chem.*, 2, 49 (1937).

(20) N. Sheppard and D. M. Simpson, *Quart. Rev.*, 6, 1 (1952).

(21) The possibility that the third aliphatic double bond is resistant to hydrogenation due to conjugation with the lactone carbonyl can be rejected on spectral grounds. The ultraviolet absorption spectrum of dihydro-β-erythroidine shows no maximum above 220 mμ (see Fig. 2) which would be required by such a system. Also, the ultraviolet absorption spectrum of β-erythroidinol (VII) is identical with that of β-erythroidine, indicating the absence of any conjugation with the lactone carbonyl.

(22) See also ref. 5 a.

(23) R. B. Woodward, THIS JOURNAL, 64, 72 (1942).

(24) The suggestion of Koniuszy and Folkers (refs. 8 and 9) that β-erythroidine contains a cyclohexadiene system is untenable, since such a system would absorb at 258 mμ or higher.

(25) V. Boekelheide and E. J. Agnello, THIS JOURNAL, 73, 2286 (1951).

(26) N. B. Colthup, *J. Optical Soc. Am.*, 40, 397 (1950).

(27) The authentic sample of 4-methoxyphthalic acid was prepared by the method of Grewe (*Ber.*, 71, 907 (1938)) and this was converted to N-methyl-4-methoxyphthalimide as described in the Experimental section.

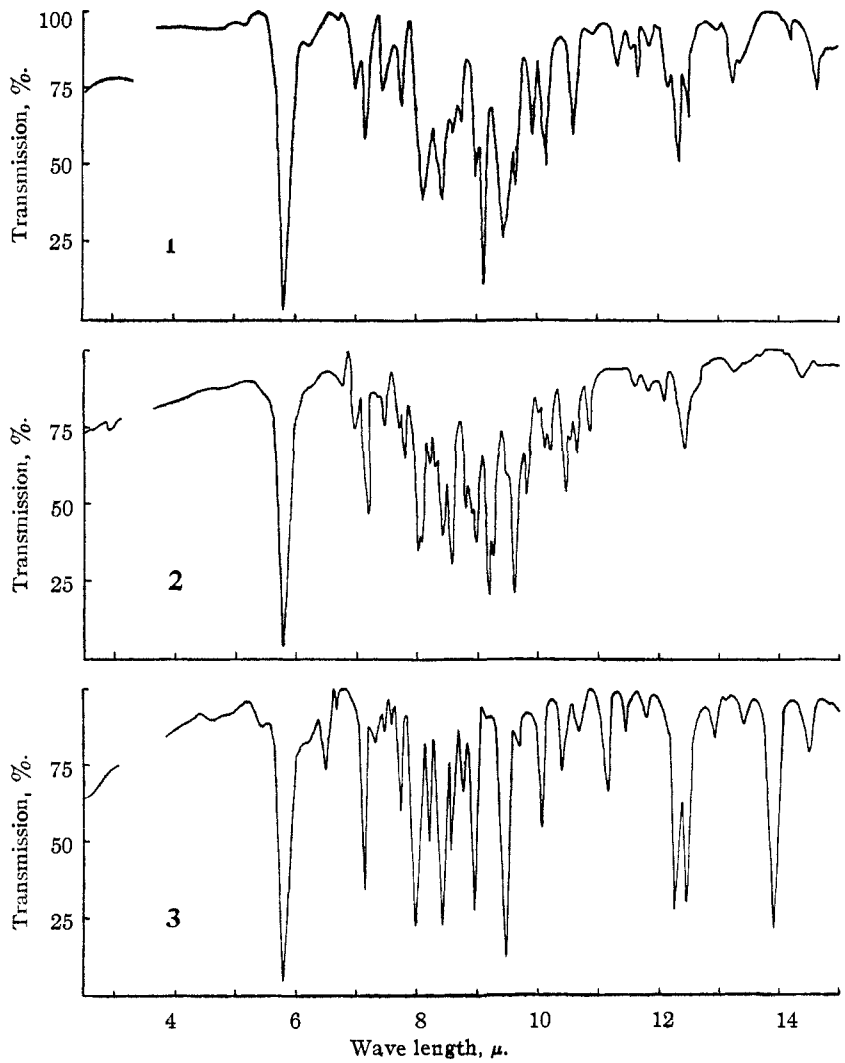
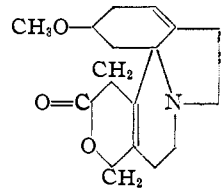
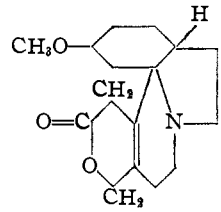


Fig. 1.—Infrared spectra of: 1, β-erythroidine; 2, dihydro-β-erythroidine; 3, desmethoxy-β-erythroidine. All determined using Nujol mulls.

or 5,6-positions. This deduction is supported by the infrared spectrum of dihydro-β-erythroidine which shows a peak at 12.45 μ (see Fig. 1), as would be expected for a trisubstituted double bond, but lacks a peak in the 14.5 μ region where the *cis*-disubstituted double bond of β-erythroidine absorbs.[20] On the basis that reduction of a diene system is more likely to occur in a 1,4- than in a 1,2-manner, we have assigned structure IX to dihydro-β-erythroidine. Tetrahydro - β - erythroidine would then be expected to have structure X, and the α- and β-isomers of tetrahydro-β-erythroidine must correspond to the two possible ways of placing a hydrogen at C-5.



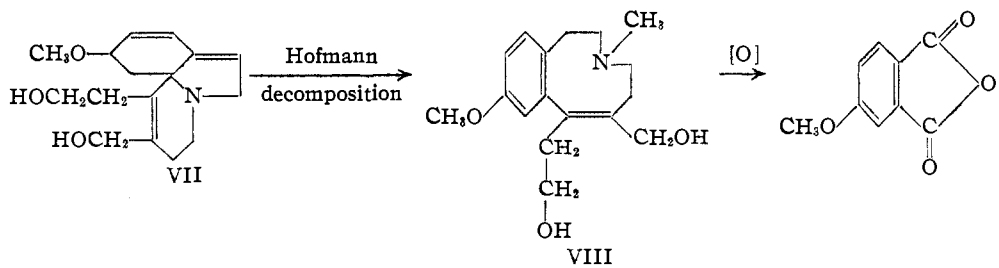
IX



X

dride establishes that the methoxyl group is located at the 2-position. Thus, all of the evidence at hand points strongly to formula I as the correct structure for β-erythroidine.

Desmethoxy-β-erythroidine.—Desmethoxy-β-erythroidine is formed from β-erythroidine by mild treatment with acid and its composition shows that it differs from β-erythroidine by the elements

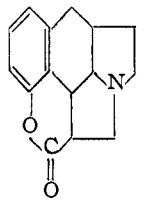


of methanol.[8,28] As shown by formula II, this transformation is pictured as a loss of the methoxyl group with concurrent introduction of a conjugated double bond. However, this postulation of desmethoxy-β-erythroidine, as given by structure II, is in disagreement with the work of Koniuszy and Folkers.[8] These authors reported that treatment

It is also possible to extend the previous arguments to deduce probable structures for dihydro-β-erythroidine and the isomeric tetrahydro-β-erythroidines. Since the dehydrogenation of β-erythroidine to its dihydro derivative gives a single homogeneous product, it is logical to assume that no new center of asymmetry is produced at C-5 during the reduction and, therefore, dihydro-β-erythroidine retains a double bond at either the 4,5-

(28) G. L. Sauvage and V. Boekelheide, THIS JOURNAL, **72**, 2062 (1950).

of desmethoxy-β-erythroidine with methyl sulfate and base followed by oxidation of the reaction mixture led to the isolation of 3-methoxyphthalic anhydride. On this basis they assumed that desmethoxy-β-erythroidine contained an aromatic ring and they suggested structure XI as a likely one for this molecule.



XI

Because the structure of desmethoxy-β-erythroidine is fundamental to our postulations regarding β-erythroidine, we have investigated in some detail the question of whether desmethoxy-β-erythroidine contains an aromatic ring or not. Neither desmethoxy-β-erythroidine nor its lithium aluminum hydride reduction product, desmethoxy-β-erythroidinol, gives a positive phenol test with ferric chloride solution, although it would be expected that XI and its reduction product should do so. Furthermore, the infrared spectrum of desmethoxy-β-erythroidine (Fig. 1) does not show the absorption bands in the 6 to 7 μ region which are characteristic of a benzenoid ring. Also, its ultraviolet absorption spectrum (Fig. 2) has a maximum at 312 mμ (log ε, 3.6) which corresponds well with what would be expected for a conjugated triene such as that represented by II but is not what would be expected for an aromatic lactone such as XI.[29] Likewise, the unusually high optical activity of desmethoxy-β-erythroidine ($[\alpha]^{20}D$ −789°) would be in accord with a highly unsaturated spiro system such as II but would seem unlikely for the molecule represented by XI.[29a]

In view of these considerations the procedure of Koniuszy and Folkers has been re-examined to see whether aromatization might not be a result of the conditions employed in their degradative experiment. Thus, the treatment of desmethoxy-β-erythroidine with dimethyl sulfate and sodium hydroxide solution at 40° might well be expected to effect a Hofmann decomposition which could lead to aromatization. However, if structure II were correct, it should be converted by such a Hofmann decomposition to XIV which, on oxidation, would yield phthalic anhydride rather than 3-methoxyphthalic anhydride. We have repeated the reaction sequence of Koniuszy and Folkers several times and it has been our experience that desmethoxy-β-erythroidine is converted in 36% yield to phthalic anhydride, as required by structure II.[30] The isolation of phthalic anhydride was established

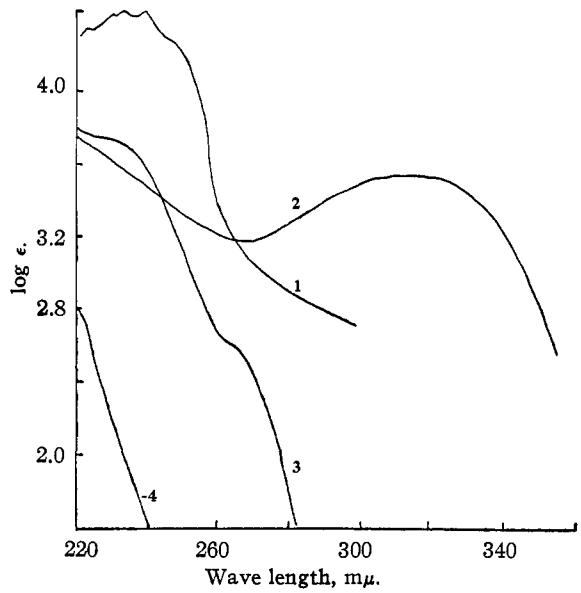


Fig. 2.—Ultraviolet absorption spectra of: 1, β-erythroidine hydrochloride; 2, desmethoxy-β-erythroidine; 3, hydrochloride of the $C_{15}H_{21}N$ base; and 4, dihydro-β-erythroidine hydrobromide. All determined using 95% ethanol as solvent.

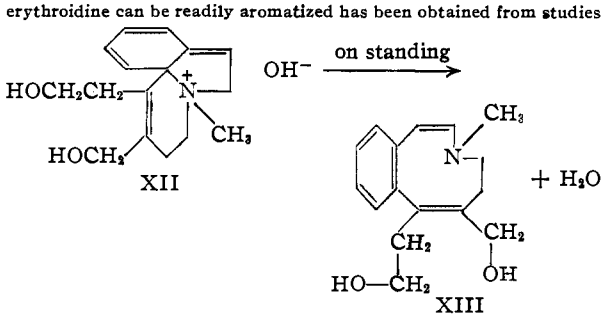
by converting the product to N-methylphthalimide and showing, by a mixed melting point determination and infrared spectral comparison, that this derivative was identical with an authentic specimen.

The importance of desmethoxy-β-erythroidine in the over-all degradative scheme prompted us to investigate an independent method for showing that no skeletal rearrangement had occurred in its preparation from β-erythroidine. The Birch procedure,[31] which has recently been applied to the reduction of allylic amines,[32] seemed particularly well suited for our purpose. When β-erythroidinol (XV) was subjected to a Birch reduction, loss of the aliphatic methoxyl group occurred and a tetrahydrodesmethoxy-β-erythroidinol XVI or XIX resulted.[33]

(29) For an excellent discussion of the ultraviolet absorption spectra of cyclic trienes, see Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., Inc., 1948, p. 185. Also see ref. 12.

(29a) For example, see D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).

(30) In an attempt to show that a Hofmann decomposition would occur under the conditions used by Koniuszy and Folkers,[5] a sample of the methodide of desmethoxy-β-erythroidinol was converted by means of an ion exchange column to the corresponding quaternary hydroxide XII. The aqueous solution of the methohydroxide quickly became cloudy and an oil separated. Although this oil was unstable and could not be purified satisfactorily, it had the properties of a vinyl amine, as evidence by a positive Schiff test, and would thus appear to be the product XIII of a Hofmann decomposition as shown below. Independent evidence that the double bond system of desmethoxy-β-erythroidine can be readily aromatized has been obtained from studies



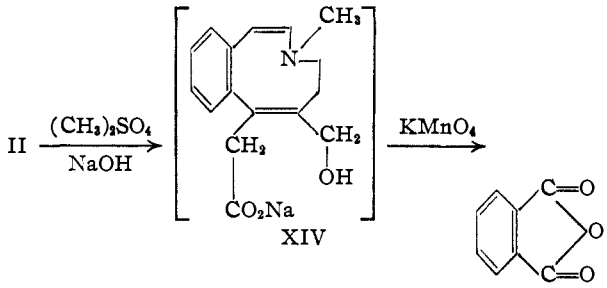
XII XIII

on the hydrogenation of this compound in neutral solution with Adams catalyst (V. Boekelheide, A. E. Anderson and G. L. Sauvage, THIS JOURNAL, 75, 2558 (1953)).

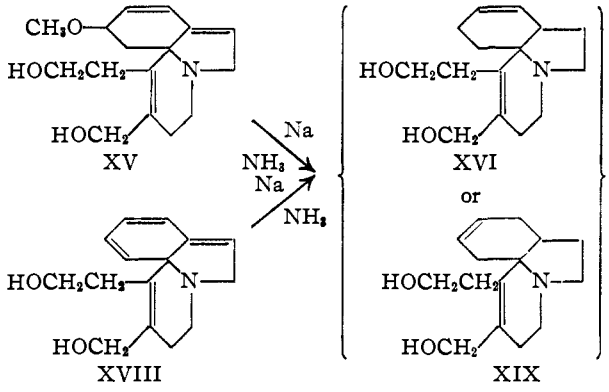
(31) A. J. Birch, *Quart. Rev.*, 4, 69 (1950).

(32) T. J. King, *J. Chem. Soc.*, 898 (1951).

(33) The hydrogenolysis of allylic ethers under the conditions of the Birch reduction has been noted previously (G. Stork, THIS JOURNAL, 74, 768 (1952)), and its occurrence in the present instance is supporting evidence that the position assigned to the methoxyl group is correct as shown by structure I.



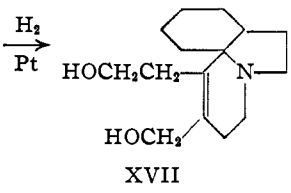
Under similar conditions desmethoxy-β-erythroidinol (XVIII) was likewise converted to a tetrahydro derivative XVI or XIX. Although the two samples of tetrahydrodesmethoxy-β-erythroidinol, obtained from the two different Birch reductions, had similar melting points and showed no depression of melting point on mixing, their infrared



spectra were not completely identical. Arbitrarily, the Birch reduction products have been assumed to have either structure XVI or structure XIX, and it appeared likely that the minor disparities observed in the infrared spectra were due to contamination of the Birch reduction product of desmethoxy-β-erythroidinol by a small amount of the alternate isomer. Therefore, both Birch reduction products were subjected to hydrogenation over Adams catalyst in the presence of hydrochloric acid and it was found that both gave the same hydrochloride of hexahydrodesmethoxy-β-erythroidinol (XVII), identical in all respects.[34] Thus, in view of their reduction to a common product, β-erythroidine and desmethoxy-β-erythroidine most probably have the same skeletal arrangement, as assumed in our postulations.

Apo-, Isoapo- and Dehydro-apo-β-erythroidine. —From the degradative evidence previously presented,[14,15,35] it is clear that apo-β-erythroidine has structure III. This structure readily accounts for the formation of dihydro- and octahydroapo-β-erythroidine.[9,35] Also, the dehydrogenation of apo-β-erythroidine to an indole derivative and its permanganate oxidation to 7-carboxyisatin and 3,8-dicarboxy-4-hydroxyquinoline are in agreement with structure III.[15,35] Finally, the complete loss of optical activity in passing from desmethoxy-β-erythroidine to apo-β-erythroidine is nicely explained by the transition from structure II to III.

When apo-β-erythroidine is passed over an alumina column, it is isomerized to a derivative named isoapo-β-erythroidine.[28] Permanganate oxidation of isoapo-β-erythroidine has now been found to yield 2-aminoisophthalic acid and 3,8-dicarboxy-4-hydroxyquinoline, indicating that there is no fundamental difference in structure between apo- and isoapo-β-erythroidine.[35a] Actually the difference between them must be one of double bond isomerism, since isoapo-β-erythroidine gives the same dihydro and octahydro derivatives as does apo-β-erythroidine. The nature of this isomerism becomes apparent on examination of the ultraviolet absorption spectra of apo- and isoapo-β-erythroidine and their corresponding diols obtained by reduction with lithium aluminum hydride. As shown in Fig. 3, apo-β-erythroidine and its diol have identical absorption spectra, whereas the reduction of isoapo-β-erythroidine to its diol (isoapo-β-erythroidinol) causes a marked shift in the absorption maxima to shorter wave lengths. This clearly indicates that the lactone carbonyl of isoapo-β-erythroidine is conjugated with the aromatic ring, and it is the formation of this conjugated system which serves as the driving force for the isomerization. The structure of isoapo-β-erythroidine is, therefore, best represented by formula XX.

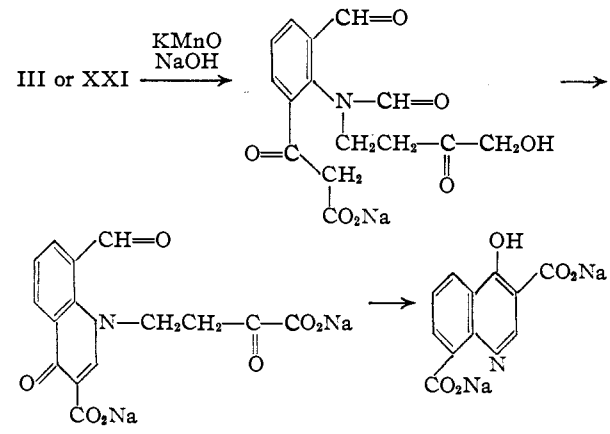


The assignment of formula XX to isoapo-β-erythroidine is also supported by many other incidental observations. For example, isoapo-β-erythroidine is yellow and is too weakly basic to form a methiodide. That these properties are the result

(34) The identity of the two samples of hydrochlorides was established by mixed melting point determinations and by infrared spectral comparison. As is shown in an accompanying paper (V. Boekelheide, A. E. Anderson and G. L. Sauvage, THIS JOURNAL, **75**, 2558 (1953)) the hydrochloride, so produced, is a eutectic mixture of the two possible diastereoisomers of hexahydrodesmethoxy-β-erythroidinol (XVII).

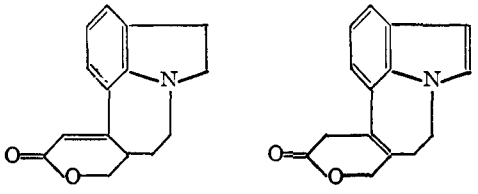
(35) M. F. Grundon and V. Boekelheide, *ibid.*, **74**, 2637 (1952).

(35a) The formation of 2-aminoisophthalic acid from apo-β-erythroidine and its derivatives during oxidation is fairly obvious from the structures proposed for these derivatives (III, XX and XXI). The formation of 3,8-dicarboxy-4-hydroxyquinoline in these oxidations, however, must involve a basic condensation of the type observed in the Camps reaction (Witkop, Patrick and Rosenblum, THIS JOURNAL, **73**, 2641 (1951)) and a possible scheme for its formation from apo- and dehydroapo-β-erythroidine can be written as



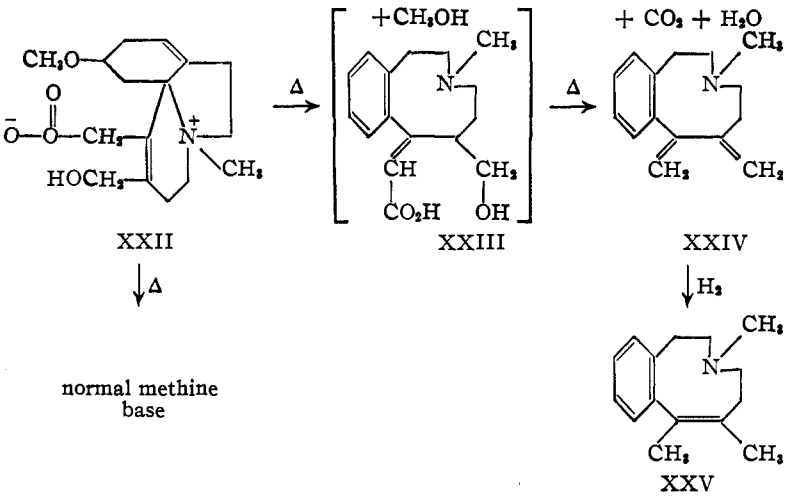
of conjugation of the lactone carbonyl with the amine is evident from the fact that both apo-β-erythroidine and isoapo-β-erythroidinol are white and readily give methiodide derivatives. Furthermore, the absorption peak in the infrared for the lactone carbonyl of isoapo-β-erythroidine occurs at appreciably longer wave lengths (5.89 μ[35]) than is true for the other erythroidine derivatives, indicating again that the lactone carbonyl has become conjugated.

The formation of dehydroapo-β-erythroidine from apo-β-erythroidine can readily be accomplished either by heating apo-β-erythroidine in ethanol in the presence of Adams catalyst[35] or by oxidizing it with sodium peroxide.[5a,10] As indicated previously, it is evident that this transformation corresponds to the conversion of an indoline to an indole derivative and thus dehydroapo-β-erythroidine can be assigned formula XXI. Lapiere and Robinson[10] have remarked on the similarity of the ultraviolet absorption spectrum of dehydroapo-β-erythroidine (see Fig. 3) to that of lysergic acid and the basis for this similarity is readily apparent from structure XXI.



XX XXI

The $C_{15}H_{19}N$ Base.—In a previous paper in this series,[25] it was reported that the Hofmann decomposition of dihydro-β-erythroidine gave both a normal methine base and an abnormal product of molecular formula, $C_{15}H_{19}N$. The $C_{15}H_{19}N$ base was shown by oxidation studies to be an ortho substituted derivative. Additional evidence, which has now been obtained from hydrogenation studies on the $C_{15}H_{19}N$ base, gives a good indication of the structure of this molecule and its probable mode of formation. Reduction of the $C_{15}H_{19}N$ base in the presence of Adams catalyst gave a dihydro derivative whose infrared absorption spectrum lacks the terminal methylene peak at 11.12 μ characteristic of the parent base. However the ultraviolet absorption spectrum of this dihydro derivative (see Fig. 2) is only slightly altered from that of the $C_{15}H_{19}N$ base and it still retains the typical absorption spectrum of a substituted styrene. This anomalous behavior becomes understandable if structure XXIV is accepted for the $C_{15}H_{19}N$ base and its reduction is presumed to occur in a 1,4-manner to yield XXV. The Hofmann decomposition of dihydro-β-erythroidine can then be formulated as



XXII XXIII XXIV

normal methine base

XXV

The starting compound used in the Hofmann decomposition is neutral and is therefore represented as a betaine XXII rather than as a quaternary hydroxide.[36] During the Hofmann decomposition rupture of the spiro nitrogen linkage would lead to an intermediate such as XXIII which, as a cinnamic acid derivative, might be expected to undergo decarboxylation and dehydration to give the $C_{15}H_{19}N$ base XXIV. The normal methine base would result from rupture of either of the other two carbon–nitrogen linkages, but no attempt has been made to decide to which of these two possibilities our product corresponds.

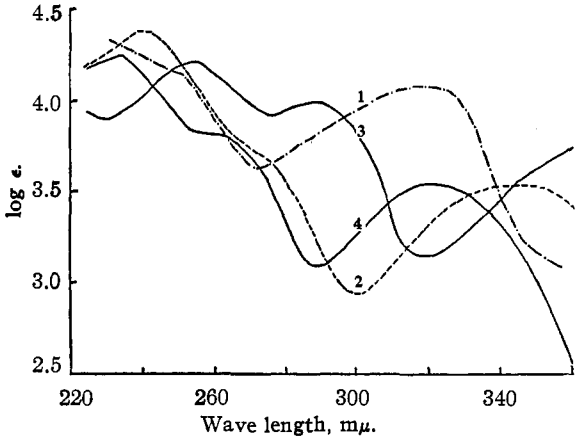


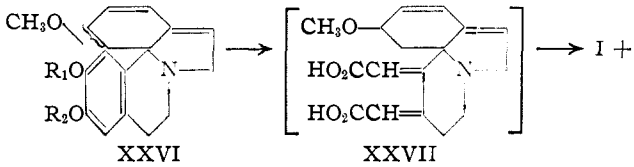
Fig. 3.—Ultraviolet absorption spectra of: 1, dehydroapo-β-erythroidine -.-.-; 2, apo-β-erythroidine ---; 3, isoapo-β-erythroidine —; and 4, isoapo-β-erythroidinol —. All determined using 95% ethanol as solvent.

Possible Biogenesis of β-Erythroidine.—In contrast to α- and β-erythroidine all of the other erythrina alkaloids, which have thus far been investigated, show the presence of an aromatic ring. The isolation and characterization of these "aromatic" erythrina alkaloids were accomplished by Folkers and his collaborators,[37] who also established

(36) This is apparently a common phenomenon and has been discussed in detail in the case of apo-β-erythroidine.[18]

(37) (a) See K. Folkers, F. Koniuszy and J. Shavel, Jr., THIS JOURNAL, **73**, 589 (1951), and the earlier papers in this series. (b) For a leading reference to the work of Deulofeu and his collaborators, see *J. Org. Chem.*, **16**, 90 (1951).

many of the structural features and interrelationships of these alkaloids. Recently, Prelog and his co-workers have shown that the structures of the members of the aromatic series are best represented by the general formula XXVI shown below.[12,13] The principal "aromatic" alkaloids differ only in the nature of the oxygen function attached to the benzenoid ring or in their degree of unsaturation.



XXVI XXVII

erysopine, $R_1 = R_2 = -H$
erysovine R_1 or $R_2 = -H$ and
erysodine R_1 or $R_2 = -CH_3$
erythraline, R_1 and $R_2 = -CH_2-$

The close relationship between structure XXVI and our formula I for β-erythroidine is readily apparent. If erysopine were to undergo oxidative fission of the general type proposed by Woodward in the case of strychnine[38] and later applied by Robinson to emetine,[39] it would be expected to yield XXVII, as an intermediate. This, on decarboxylation and lactonization, could readily give β-erythroidine, as illustrated. Although the position of the aliphatic methoxyl has not been established for erysopine and the other "aromatic" erythrina alkaloids, the present scheme would suggest that it probably occupies the allylic position as is the case for β-erythroidine.

It would seem quite possible that the starting material for the biogenesis of the erythrina alkaloids is 3,4-dihydroxyphenylalanine, since an appropriate union of two molecules of this amino acid can lead directly to a structure representative of the "aromatic" alkaloids.[39a] If erysopine is first formed in the plant and then converted enzymatically to the other alkaloids, including β-erythroidine, the extent to which this would occur would depend on the enzyme systems possessed by a particular plant species. It is of interest, therefore, that erysopine apparently occurs in all species of erythrina except those producing erythroidine.[40]

If erysopine were being exhausted in these plants because of its conversion to erythroidine, it would be expected that α- and β-erythroidine would be very similar chemically. The two compounds have very similar physical properties so, apparently, it was assumed on this basis that they were diasteroisomers and they were given the α- and β-designations.[41] Although the structure of α-erythroidine is still unknown, recent work would suggest that it cannot be a diasteroisomer, but rather it must be either a position or structural isomer of β-erythroidine.[5a,42] Further investigations of α-erythroidine are in progress.

(38) R. B. Woodward, *Nature*, **162**, 155 (1948).

(39) R. Robinson, *ibid.*, **162**, 524 (1948).

(39a) For an alternate suggestion, see B. Witkop and S. Goodwin, *Experientia*, **8**, 377 (1952).

(40) K. Folkers and F. Koniuszy, U. S. Patent 2,391,013.

(41) (a) K. Folkers and R. T. Major, U. S. Patent 2,385,266 and R. T. Major, British Patent 543,187.

(42) V. Boekelheide and M. F. Grundon, THIS JOURNAL, **75**, 2537 (1953).

The pharmacological data thus far obtained provide very little basis for correlation of chemical structure and pharmacological activity. These results, which will be presented elsewhere in detail,[43] can be briefly summarized as follows. β-Erythroidine, desmethoxy-β-erythroidine and all of their derivatives containing the spiro amine grouping show curariform activity to some degree, even though in many cases it is masked by other effects such as ganglionic blockade. On the other hand, apo-β-erythroidine and its derivatives all show central depressant activity to some degree and are lacking in curariform activity.

Experimental[44,45]

β-Erythroidinol Methiodide.—A solution of 3.1 g. of β-erythroidinol[15] (VII) and excess methyl iodide in 25 ml. of methanol was boiled under reflux for three hours. The solution was then concentrated, a small amount of absolute ethanol was added and the mixture was refrigerated. There separated 4.4 g. (93.5%) of a white solid, m.p. 171–174°, which on crystallization from absolute ethanol gave white crystals, m.p. 173.5–175°.

Anal. Calcd. for $C_{17}H_{26}NO_3I$: C, 48.69; H, 6.25. Found: C, 48.57; H, 6.19.

Des-N-methyl-β-erythroidinol (VIII).—A solution of 1.82 g. of β-erythroidinol methiodide in 15 ml. of water was passed over an ion-exchange column (Amberlite IRA-400-OH). The eluate was concentrated and then the residual oil was distilled in a molecular still to give 880 mg. (70%) of a viscous colorless oil, b.p. (pot temperature) 150–170° at 0.05 mm.

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; $-OCH_3$, 10.65. Found: C, 69.81; H, 8.58; $-OCH_3$, 10.30.

The hydrochloride of VIII was prepared in ethanol and, after two crystallizations from the same solvent, it was obtained as white crystals, m.p. 195–197°.

Anal. Calcd. for $C_{17}H_{26}NO_3Cl$: C, 62.28; H, 8.00. Found: C 62.21; H, 8.20.

Permanganate Oxidation of Des-N-methyl-β-erythroidinol.—A solution of 405 mg. of the hydrochloride of des-N-methyl-β-erythroidinol (VIII) in 5 ml. of 10% aqueous sodium hydroxide was heated at 80° and a 4% aqueous solution of potassium permanganate was added slowly until the permanganate color was no longer discharged. The oxidation mixture was made acidic with hydrochloric acid and sulfur dioxide was bubbled through the solution until the manganese dioxide dissolved. The solution was then extracted five times with 100-ml. portions of ether, the combined extracts were concentrated to 100 ml., and the concentrate was extracted twice with 20-ml. portions of a saturated sodium bicarbonate solution. The bicarbonate extracts were acidified and extracted with ether. The residue resulting from concentration of the ethereal extract was sublimed under reduced pressure to give 40 mg. (18%) of a white solid. This was treated with methylamine and again sublimed to give 33 mg. of a white solid, m.p. 135–145°. Recrystallization of this solid from water gave white needles, m.p. 151–154°. A mixed melting point determination of this specimen with an authentic sample of N-methyl-4-methoxyphthalimide (see below) showed no depression of melting point. Also, the infrared spectra of the authentic and naturally-derived samples were identical.

N-Methyl-4-methoxyphthalimide.—4-Methoxyphthalic acid was prepared by the permanganate oxidation of 3,4-

(43) We are indebted to Dr. I. H. Slater, University of Rochester School of Medicine and Dentistry, Rochester, N. Y., for the pharmacological testing.

(44) The β-erythroidine hydrochloride employed in this and most of the related studies was isolated by S. B. Penick and Co. from seeds of *Erythrina berteroana*, Urban obtained from Nicaragua. The accompanying α-erythroidine was found to be present to almost the same extent as the β-isomer in this particular sample of seeds.

(45) Analyses by Mrs. G. L. Sauvage and Miss Claire King. The infrared spectra were recorded by Mr. Carl Whiteman using a Perkin-Elmer instrument, model 12B.

dimethylanisole according to the procedure of Grewe.[27] A portion of this acid was treated with methylamine and the resulting solid was sublimed as before. The sublimate, on repeated crystallization from water, gave white needles, m.p. 155–156°.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75. Found: C, 62.78; H, 4.90.

Isolation of Phthalic Anhydride from the Stepwise Hydrolysis, Methylation and Oxidation of Desmethoxy-β-erythroidine.—This was performed essentially as described by Koniuszy and Folkers[8] but with slight modifications because of the smaller quantity of desmethoxy-β-erythroidine employed. A solution containing 400 mg. of desmethoxy-β-erythroidine, 10 ml. of aqueous 10% sodium hydroxide solution and 1.3 ml. of dimethyl sulfate was warmed at about 60° for 10 minutes. To this there was then added dropwise a 4% aqueous solution of potassium permanganate until the purple color was no longer discharged by warming to 80° (114 ml. required). The mixture was acidified with hydrochloric acid, and sulfur dioxide was bubbled into the mixture until the manganese dioxide dissolved. Continuous extraction of the aqueous solution with ether for 17 hours was followed by concentration of the ether extract. Sublimation of the residue at atmospheric pressure gave 87 mg. (36%) of white needles, m.p. 85–126°. A recrystallization of this from a toluene–heptane mixture gave needles, m.p. 120–129.5°. A methoxyl determination on the crude product showed the complete absence of this group. The crude product was then treated with aqueous methylamine and warmed at 160° for 10 minutes. Sublimation of the residue gave white needles, m.p. 128–131.5°. This, on recrystallization from an ethanol–water mixture, gave a sample of crystals melting at 130–132°.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38. Found: C, 67.29; H, 4.59.

A mixture of the above sample and synthetic N-methylphthalimide showed no depression of melting point. Also the infrared spectrum of this material was identical with that of authentic N-methylphthalimide.

In order to eliminate the possibility that an aromatic ring was initially present in desmethoxy-β-erythroidine the oxidation was repeated in the same manner as above except that the dimethyl sulfate was omitted. Under these conditions a Hofmann decomposition could not occur to introduce an aromatic ring. When a 500-mg. sample of desmethoxy-β-erythroidine was subjected to this oxidation procedure, nothing could be isolated from the ether extract corresponding to an aromatic acid.

Desmethoxy-β-erythroidinol (XVIII).—To a solution of 500 mg. of desmethoxy-β-erythroidine[28] in 250 ml. of dry ether there was added 2 ml. of a 1 *M* ethereal solution of lithium aluminum hydride. The reaction mixture was stirred at room temperature for 2 hours and then was decomposed by addition of moist ether. The mixture was filtered and the precipitate of inorganic hydroxides was washed with 5 ml. of absolute ethanol. The combined ether and ethanol filtrates were concentrated until crystals of desmethoxy-β-erythroidinol began to form, whereupon the solution was put aside to cool. There separated 510 mg. (96%) of pure white crystals, m.p. 179–180° with a change in crystalline form at 145–150°.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.29; H, 7.75.

The methiodide of desmethoxy-β-erythroidinol was prepared in ethanol using an excess of methyl iodide. After recrystallization from ethanol, it was obtained as white crystals, m.p. 169–170° dec.

Anal. Calcd. for $C_{16}H_{22}NO_2I$: C, 49.62; H, 5.72. Found: C, 49.79; H, 5.92.

Attempted Preparation of Desmethoxy-β-erythroidinol Methohydroxide.—A solution of 500 mg. of desmethoxy-β-erythroidinol methiodide in 20 ml. of water was passed over an ion-exchange column (Amberlite IRA-400-OH). The eluate quickly became cloudy and slowly deposited a light yellow solid. This solid (approximately 300 mg.) was collected but it proved to be rather unstable. Attempts to purify it by recrystallization were unsuccessful and, on attempted distillation under high vacuum, it resinified. It is assumed that this material is the vinylamine represented by formula XIII. In support of this it was found that an acidic solution of the yellow solid gave a positive fuchsin–aldehyde test.

When desmethoxy-β-erythroidinol methiodide was converted to the corresponding quaternary hydroxide by treating it directly with a cold aqueous solution of 10% sodium hydroxide, the same phenomenon was observed. The solution became cloudy and deposited an unstable yellow solid. Attempts to convert this yellow solid to a more stable derivative by catalytic hydrogenation in ethanol over Adams catalyst were also unsuccessful.

Tetrahydrodesmethoxy-β-erythroidinol (XVI or XIX). (a) **By the Birch Reduction of β-Erythroidinol.**—To a solution of 2.0 g. of β-erythroidonol[15] and 4 ml. of absolute ethanol in 50 ml. of liquid ammonia small pieces of metallic sodium were added until a permanent blue color was obtained. The mixture was then treated with a small quantity of cracked ice and the resulting solution was extracted four times with 100-ml. portions of chloroform. After the chloroform extracts were concentrated *in vacuo*, the residual oil was taken up in benzene and allowed to stand in the cold. There separated from solution 1.0 g. (55%) of a white solid, m.p. 181–185°. This, on crystallization from a benzene–methanol mixture, gave white crystals, m.p. 185–187° dec.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; $-OCH_3$, 0.00. Found: C, 72.40; H, 8.97; $-OCH_3$, 0.00

(b) **By the Birch Reduction of Desmethoxy-β-erythroidinol.**—To a solution of 2.0 g. of desmethoxy-β-erythroidinol (XVIII) and 5 ml. of absolute ethanol in 100 ml. of liquid ammonia small pieces of sodium were added until the blue color no longer faded. A small quantity of cracked ice was then added and the mixture was extracted three times with 100-ml. portions of chloroform. After concentration of the combined chloroform extracts, the residue was dissolved in an ethanol–benzene mixture and allowed to stand in the cold. The solution deposited 1.25 g. (62%) of a white solid, m.p. 183–193° dec. The melting point behavior was not affected appreciably by recrystallization of the material from a benzene–ethanol mixture. Also, the melting point range was not affected by admixture of the Birch reduction product of β-erythroidinol. In contrast to desmethoxy-β-erythroidine, its Birch reduction product shows a normal rotation, $[\alpha]^{25}D$ −88.4 (*c*, 1.64% in ethanol).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 72.53; H, 8.93.

When the crystals obtained above were subjected to a prolonged series of fractional crystallizations from benzene, it was possible to obtain a sample melting at 194–197° dec. This sample showed the same composition (Found: C, 72.68; H, 9.11) as the main body of crystals. It is presumed that the higher-melting sample represents a fairly pure specimen of one of the isomers XVI or XIX whereas the Birch reduction product of β-erythroidinol (m.p. 185–187° dec.) represents a fairly pure sample of the other isomer. The infrared spectra of the two samples, although they show only minor differences, would appear to support this conclusion.

Hydrochloride of Hexahydrodesmethoxy-β-erythroidinol. (a) **From the Birch Reduction Product of β-Erythroidinol.**—A mixture containing 500 mg. of the Birch reduction product of β-erythroidinol, 0.25 ml. of 12 *N* hydrochloric acid, 200 mg. of Adams catalyst and 15 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. When hydrogen absorption was complete, the catalyst and solvent were removed and a mixture of absolute ethanol and ethyl acetate was added to the residue. This caused the separation of 150 mg. (26%) of white crystals, m.p. 158–163°. Recrystallization of this from an ethanol–ethyl acetate mixture gave 116 mg. of crystals, m.p. 163–166°.

Anal. Calcd. for $C_{15}H_{26}NO_2Cl$: C, 62.59; H, 9.11. Found: C, 62.69; H, 9.18.

(b) **From the Birch Reduction Product of Desmethoxy-β-erythroidinol.**—A mixture containing 250 mg. of the Birch reduction product of desmethoxy-β-erythroidinol, 0.12 ml. of 12 *N* hydrochloric acid, 100 mg. of Adams catalyst and 10 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure until hydrogen absorption was complete. After removal of the catalyst and solvent, the residue was taken up in ethyl acetate. This caused the separation of 166 mg. (51%) of white crystals, m.p. 161–165°. Recrystallization of this sample from an ethanol–ethyl acetate mixture gave 150 mg. of white crystals, m.p. 165–166°.

Anal. Calcd. for $C_{15}H_{26}NO_2Cl$: C, 62.59; H, 9.11. Found: C, 62.71; H, 9.28.

The two samples of the hydrochloride of hexahydrodesmethoxy-β-erythroidinol obtained in (a) and (b) showed no depression of melting point on mixing. Also, the infrared absorption spectra of the two samples were completely identical.

Permanganate Oxidation of Isoapo-β-erythroidine (XX).—A solution of 690 mg. of isoapo-β-erythroidine[23] in 10 ml. of warm aqueous 10% sodium hydroxide was diluted by addition of 50 ml. of water and a 3% aqueous potassium permanganate solution was added dropwise until the permanganate color remained for 30 minutes. The solution was then clarified with sulfur dioxide, strongly acidified with sulfuric acid and extracted 8 times with 40-ml. portions of ether. The combined ether extracts were concentrated to 20 ml. and then allowed to stand at 0°. From the solution 18 mg. of white crystals was deposited and these, on recrystallization from aqueous ethanol, were obtained as fine, colorless needles, m.p. > 360°. The properties of these crystals agreed with those previously found for 3,8-dicarboxy-4-hydroxyquinoline[35] and that they were truly identical was established by a comparison of their infrared spectra.

After removal of the quinoline compound, the ether solution was evaporated and the residue was dissolved in warm chloroform. A colorless solid (8 mg.), m.p. 280° with sublimation, separated from the cold chloroform solution and this shown to be identical with a synthetic sample of 2-aminoisophthalic acid by comparison of their infrared spectra.

Hydrogenation of the $C_{15}H_{19}N$ Base.—To a solution of 650 mg. of the $C_{15}H_{19}N$ base[25] in 25 ml. of ethanol there were added 100 mg. of Adams catalyst and 4 molar equivalents of hydrochloric acid and the mixture was hydrogenated at room temperature and atmospheric pressure. One molar equivalent of hydrogen was rapidly absorbed and then hydrogenation stopped. The catalyst was removed and a small quantity of ether was added to the solution. This caused the separation of 500 mg. (65%) of white crystals, m.p. 216–218° softening at 204°. A sample, on recrystallization from an isopropyl alcohol–ether mixture, melted at 234–236°. When the free base was liberated from its hydrochloride, it gave an oil which did not crystallize.

Anal. Calcd. for $C_{15}H_{22}NCl$: C, 71.56; H, 8.80. Found: C, 71.14; H, 8.82.

Tetrahydro-β-erythroidine (X).—To a solution of 2.5 g. of β-erythroidine hydrochloride in 125 ml. of water there were added 400 mg. of Adams catalyst and 1 ml. of concentrated hydrochloric acid. The mixture was subjected to hydrogenation at room temperature and atmospheric pressure until two molar equivalents of hydrogen were absorbed. In experiments in which hydrogenation was allowed to proceed to completion, 2.3 to 2.5 molar equivalents of hydrogen were absorbed. Likewise in the hydrogenation of β-erythroidine in alkaline solution with Raney nickel as catalyst, 2.5 molar equivalents of hydrogen was absorbed before hydrogenation was complete.

After the mixture had absorbed two molar equivalents of hydrogen, the catalyst was removed and the solution was concentrated under reduced pressure to 50 ml. The solution was then brought to a *p*H of 8.0 by addition of sodium bicarbonate and it was extracted 10 times with 50-ml. portions of chloroform. After the chloroform extracts had been dried over Drierite the chloroform was removed *in vacuo* and the residue was distilled in a molecular still. This gave 1.8 g. of a light yellow oil, b.p. (pot temperature) 200–230° at 0.03 mm. The infrared spectrum of this oil, presumably a mixture of the α- and β-isomers of tetrahydro-β-erythroidine,[18] showed a definite peak at 6.10 μ, corresponding to absorption by an aliphatic double bond.[20]

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 69.28; H, 8.36. Found: C, 69.27; H, 8.29.

The picrate of tetrahydro-β-erythroidine was prepared for purposes of characterization. After recrystallization from absolute ethanol, it was obtained in 80% yield as fine yellow needles, m.p. 205–207°. This probably is the picrate of β-tetrahydro-β-erythroidine.[18]

Anal. Calcd. for $C_{22}H_{26}N_4O_{10}$: C, 52.17; H, 5.17. Found: C, 52.38; H, 5.11.

ROCHESTER, N. Y.

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

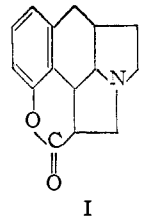
A Study of the Hydrogenation of Desmethoxy-β-erythroidine[1]

BY V. BOEKELHEIDE, A. E. ANDERSON, JR.,[2] AND G. L. SAUVAGE

RECEIVED DECEMBER 19, 1952

The hydrogenation of desmethoxy-β-erythroidine over platinum in an acidic medium can be controlled to give di-, tetra- and hexahydro derivatives. The formation and interrelationships of these derivatives provide additional evidence that structure II correctly represents desmethoxy-β-erythroidine. In neutral solution hydrogenation of desmethoxy-β-erythroidine results in an unusual rearrangement and gives a product named *allo*-dihydrodesmethoxy-β-erythroidine. An interpretation is offered for the formation of this unexpected product from desmethoxy-β-erythroidine.

Desmethoxy-β-erythroidine is formed by the treatment of β-erythroidine with acid under mild conditions.[3,4] Koniuszy and Folkers, on the basis of their degradative work, have concluded that desmethoxy-β-erythroidine contains an aromatic ring and they have suggested I as a probable structure for the molecule. Recently, we summarized the chemistry of β-erythroidine and presented evidence to show that desmethoxy-β-erythroidine is best represented by formula II.[5] It is the purpose of the present paper to present information regarding the hydrogenation of desmethoxy-β-erythroidine and to show that these results are in good accord with structure II and are strong evidence against the possibility that desmethoxy-β-erythroidine contains an aromatic ring.



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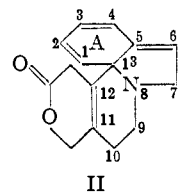

II

Hydrogenation Studies in Acid

The hydrogenation studies on desmethoxy-β-erythroidine in acid over platinum are summarized in Chart 1. Since the diols resulting from reduction of the lactone ring with lithium aluminum hy-

(1) Paper IX in this series; for the preceding communication see V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage and E. J. Agnello, THIS JOURNAL, **75**, 2550 (1953).

(2) Union Carbide and Carbon Fellow, 1952–1953.

(3) G. L. Sauvage and V. Boekelheide, THIS JOURNAL, **72**, 2062 (1950).

(4) F. Koniuszy and K. Folkers, *ibid.*, **72**, 5579 (1950).

(5) See the preceding communication cited in ref. 1.