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[28] 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 $C_{18}H_{23}NO_2$: 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]

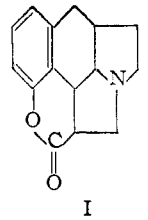
A Study of the Hydrogenation of Desmethoxy-β-erythroidine[1]

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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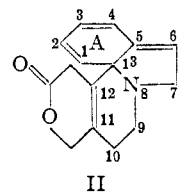


II

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.

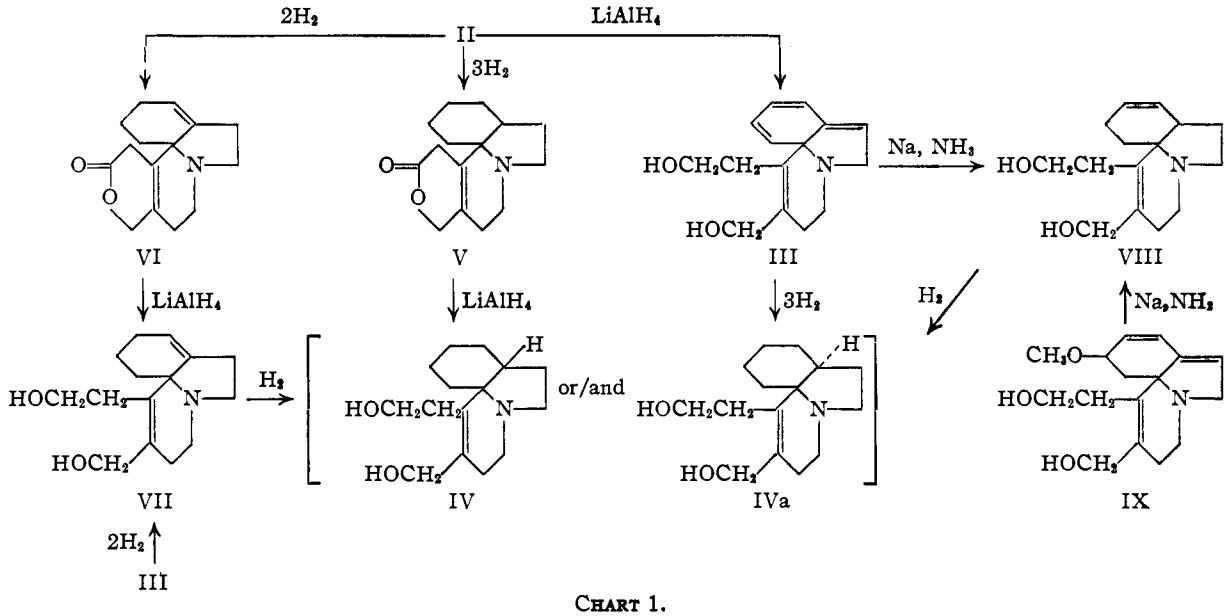


CHART 1.

dride are crystalline solids in all cases, whereas the simple hydrogenated derivatives are oils, the diols have been used as reference compounds throughout this series.

When desmethoxy-β-erythroidine was allowed to absorb three molar equivalents of hydrogen and the resulting hexahydro derivative[3,4] V was reduced with lithium aluminum hydride, a single homogeneous product, m.p. 185–187°, was obtained. The same material, identical in all respects, resulted when desmethoxy-β-erythroidine was first reduced with lithium aluminum hydride to its diol III and this in turn was allowed to absorb three molar equivalents of hydrogen. The fact that the same product resulted from both routes makes it quite unlikely that the lithium aluminum hydride reduction has any other effect on the molecule than reduction of the lactone ring. The hydrogenation over platinum is stereospecific, probably because of the rigid ring system, and gives only one of the possible diastereoisomers, either IV or IVa. As would be expected, the extremely high optical activity exhibited by desmethoxy-β-erythroidine ($[\alpha]^{25}D$ −789°) and its diol ($[\alpha]^{25}D$ −727°) is largely lost on hydrogenation and the diastereoisomer of hexahydrodesmethoxy-β-erythroidinol, obtained by reduction over platinum, shows a normal specific rotation (+30.1°). It should be noted that all of the diols in this series melt in the same general range and usually show no depression of melting point on mixing, so it has been necessary to rely principally on measurements of optical activity and infrared spectra for purposes of establishing identity.

When the hydrogenation of desmethoxy-β-erythroidine in acid was interrupted after one molar equivalent of hydrogen was absorbed, it was possible to isolate a dihydro derivative which, with lithium aluminum hydride, gave the corresponding diol, dihydrodesmethoxy-β-erythroidinol. This same product could also be obtained by direct hydrogenation of desmethoxy-β-erythroidinol (III).

Similarly, when the catalytic hydrogenation of desmethoxy-β-erythroidine was interrupted after two molar equivalents of hydrogen had been absorbed, a tetrahydro derivative VI resulted. Furthermore, reduction of this tetrahydro derivative with lithium aluminum hydride gave the same isomer of tetrahydrodesmethoxy-β-erythroidinol (VII) as that which resulted when the direct hydrogenation of desmethoxy-β-erythroidinol was stopped after two molar equivalents of hydrogen was absorbed. Thus, as before, the two alternate routes led to the same hydrogenated diol. In addition, it was shown that on further hydrogenation over platinum, tetrahydrodesmethoxy-β-erythroidinol gave the same diastereoisomer of hexahydrodesmethoxy-β-erythroidinol (IV or IVa) as was obtained previously in the direct hydrogenation of desmethoxy-β-erythroidinol (III). Since all of the reactions utilized in the stepwise hydrogenation of desmethoxy-β-erythroidine proceeded in high yield, it is apparent that a structure such as II is needed to explain the hydrogenation data and aromatic ring structures such as I can no longer be seriously considered.

The fact that the same diastereoisomer of hexahydrodesmethoxy-β-erythroidinol was obtained as the end-product from the various hydrogenations over platinum leads to the conclusion that these catalytic hydrogenations in all cases are stereospecific and only one possible arrangement of the asymmetric center at C-5 is being formed. In order to obtain the other diastereoisomer, the Birch reduction procedure was reinvestigated. As reported previously,[5] the Birch reductions of β-erythroidinol (IX) and desmethoxy-β-erythroidinol (III), yielded isomeric mixtures of tetrahydrodesmethoxy-β-erythroidinol, which on catalytic hydrogenation gave the same hydrochloride of hexahydrodesmethoxy-β-erythroidinol. Further investigation of this hydrochloride has shown it to be a eutectic mixture of the two possible diastereoisomers (IV and IVa). The free base corresponding to this hydrochloride melted over a wide range and, by fractional crystallization, it was possible to separate the base into two isomers, A and B, of which isomer A was found

to be identical with the isomer of hexahydrodesmethoxy-β-erythroidinol obtained previously by hydrogenation of desmethoxy-β-erythroidinol over platinum. Since the specific rotation of isomer A has the smaller positive value, it can now be designated as β-hexahydrodesmethoxy-β-erythroidinol. Similarly, isomer B is best described as α-hexahydrodesmethoxy-β-erythroidinol.

This designation is consistent with the assignment made previously for the diastereoisomers of tetrahydro-β-erythroidine. Although the physical properties of α-tetrahydro-β-erythroidine have never been described, Folkers and Koniuszy have reported in the patent literature[6] that β-tetrahydro-β-erythroidine is produced by hydrogenation of β-erythroidine over platinum. Presumably, the α- and β-designations employed for the tetrahydro-β-erythroidines are likewise related to the optical rotations of these isomers. Since the formation of diastereoisomers in the case of tetrahydro-β-erythroidine involves the same center of asymmetry (C-5) that is formed in the hydrogenation of desmethoxy-β-erythroidine, it would be expected that, in both series, hydrogenation over platinum would lead to the same arrangement at this center. Our experimental observations of optical activity are, therefore, consistent with the structures which we have postulated.

The structures assigned to the isomers of tetrahydrodesmethoxy-β-erythroidinol must be regarded as provisional insofar as the double bond of ring A is concerned. The Birch reduction products of β-erythroidinol (IX) and desmethoxy-β-erythroidinol (III) are now assumed to be mixtures of the two diastereoisomers corresponding to structure VIII. This assignment is based on the fact that the Birch reductions must affect the center of asymmetry at C-5. Also, the infrared spectra of these mixtures shows a strong peak at 13.90 μ, which is in the region usually assigned to *cis*-disubstituted aliphatic double bonds. The isomer of tetrahydrodesmethoxy-β-erythroidinol obtained by the platinum reduction of desmethoxy-β-erythroidinol has been assigned structure VII, because its infrared spectrum, which differs from those of the Birch products, has an absorption peak at 12.45 μ, where trisubstituted double bonds usually absorb.[7]

Hydrogenation in Neutral Solution

The hydrogenation of desmethoxy-β-erythroidine over platinum in neutral solution proceeded much more slowly than the hydrogenations in acid and a mixture of products resulted. From this mixture it was possible to isolate in 25% yield a white crystalline solid, m.p. 169–170°, having a composition corresponding to $C_{15}H_{17}NO_2$. Although this formula would agree with that of a dihydrodesmethoxy-β-erythroidine, the properties of this compound clearly indicate that a drastic change involving aromatization has occurred during hydrogenation and, to distinguish this product from the normal dihydro derivative, we have named it *allo*-dihydrodesmethoxy-β-erythroidine.

That *allo*-dihydrodesmethoxy-β-erythroidine is an aromatic compound was shown in several ways. First of all, its ultraviolet absorption spectrum has the typical fine structure of a simple benzene derivative, showing a very marked resemblance to the spectrum of 1,2,3,4-tetrahydroisoquinoline. Also, the infrared spectra of *allo*-dihydrodesmethoxy-β-erythroidine and its derivatives show absorption peaks at 6.25, 6.72 and 13.15 μ, which agrees well with the absorption pattern usually assigned to ortho disubstituted benzene derivatives.[8] Finally, it was found that when *allo*-dihydrodesmethoxy-β-erythroidine was oxidized with dilute alkaline permanganate, it gave phthalic acid in 23% yield. The identity of the phthalic acid was established by converting it to N-methylphthalimide and comparing this derivative with a synthetic sample.

Although *allo*-dihydrodesmethoxy-β-erythroidine resists further hydrogenation in neutral solution, it undergoes a very slow hydrogenation over platinum in acid to give a hexahydro derivative, which was isolated as the corresponding methiodide. This slow hydrogenation must be a reduction of the aromatic ring, since the reduced product no longer has an absorption maximum above 220 mμ in the ultraviolet and its infrared spectrum shows that the ortho disubstituted benzene peaks at 6.25, 6.72 and 13.15 μ have disappeared.

Before considering possible reaction pathways by which desmethoxy-β-erythroidine could undergo this unusual rearrangement to an ortho disubstituted benzene derivative, we should add several other observations bearing on the structure of the rearranged product. *allo*-Dihydrodesmethoxy-β-erythroidine gives a negative result in the Kuhn–Roth determination for a C-methyl group. Also, the lactone carbonyl does not show evidence of conjugation, since reduction of the lactone ring to the corresponding diol with lithium aluminum hydride has no effect on the ultraviolet absorption spectrum. The lactone ring can readily be opened by reaction with hydrazine or alkali; however, on acidification it does not readily reform the lactone ring. In this respect the behavior of the lactone ring more closely resembles a normal δ-lactone than it does the unsaturated δ-lactones present in β-erythroidine and desmethoxy-β-erythroidine.

To interpret the information at hand we would suggest that the conversion of desmethoxy-β-erythroidine to *allo*-dihydrodesmethoxy-β-erythroidine follows the course shown in Chart 2.

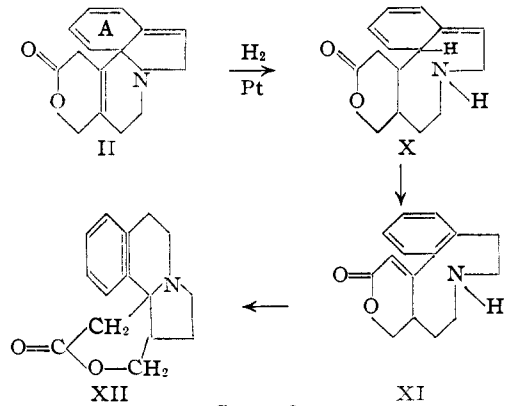


CHART 2.

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

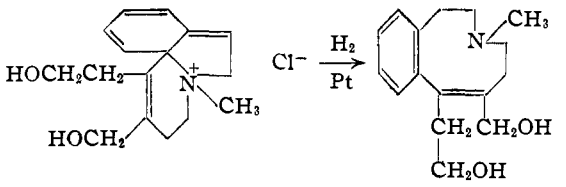
(7) N. Sheppard and D. M. Simpson, *Quart. Rev.*, **6**, 1 (1952).

(8) H. L. McMurry and V. Thornton, *Anal. Chem.*, **24**, 318 (1952).

The first step, which involves hydrogenolysis of the spiro carbon–nitrogen bond to form X, would be expected to be an easy one since the amino nitrogen is allylic with respect to three of the aliphatic double bonds in desmethoxy-β-erythroidine. This hydrogenolysis also provides a logical explanation for the complete loss of optical activity which occurs during the rearrangement. Since the only center of asymmetry in desmethoxy-β-erythroidine is the spiro carbon attached to the amino group, the rearrangement must affect this center.

With the removal of the amino group, there is no longer any hindrance to aromatization of ring A. As shown in structure XI, it is likely that aromatization would be accompanied by isomerization of the tetrasubstituted double bond to give a completely conjugated system. This type of isomerization has been shown to occur in the presence of platinum and has been described previously in the case of the isomerization of apo- to isoapo-β-erythroidine.[9] The final step in the formation of *allo*-dihydrodesmethoxy-β-erythroidine (XII) would be a simple 1,4-addition of the secondary amine to the conjugated lactone.

In support of the reaction scheme postulated in Chart 2, the following evidence can be cited. Desmethoxy-β-erythroidine was reduced with lithium aluminum hydride and the resulting diol was converted to the corresponding methochloride XIII. When this methochloride derivative was subjected to mild hydrogenation over platinum in neutral solution, it gave des-N-methyldihydro-β-erythroidinol (XIV) in high yield. It was shown that the product obtained in this way was identical in all respects with the Hofmann decomposition product from dihydro-β-erythroidinol, which previously has been shown to have structure XIV.[10]



XIII XIV

In the case of the methochloride derivative, therefore, it has been proved that the type of hydrogenolysis reaction proposed in our scheme does occur. In the absence of the conjugated lactone system, though, the nine-membered heterocyclic ring is stable and the final product is XIV. To our knowledge the use of quaternary ammonium salts in hydrogenolysis experiments has not previously been studied, although it would appear to be a reaction of general usefulness.

Because of the difficulties involved in obtaining the necessary natural material, we have concluded our degradative studies on *allo*-dihydrodesmethoxy-β-erythroidine at this point. Although structure XII has not been conclusively established as being the correct one for *allo*-dihydrodesmethoxy-β-erythroidine, it appears to be the only likely structure for explaining the present evidence. Further proof will need to await the synthesis of XII or a closely related derivative.

(9) M. F. Grundon and V. Boekelheide, THIS JOURNAL, **74**, 2637 (1952).

(10) J. Weinstock and V. Boekelheide, *ibid.*, **75**, 2546 (1953).

Experimental[11,12]

β-Hexahydrodesmethoxy-β-erythroidinol (IV or IVa). (a) From β-Hexahydrodesmethoxy-β-erythroidine (V).—The hydrogenation of desmethoxy-β-erythroidine over platinum in acid to a hexahydro derivative has been previously described.[3,4] The resulting oil can now be designated as β-hexahydrodesmethoxy-β-erythroidine and its conversion to the corresponding diol was accomplished as follows.

To a solution of 500 mg. of β-hexahydrodesmethoxy-β-erythroidine[3,4] in 1000 ml. of dry ether there was added dropwise with stirring 5 ml. of a 0.75 *M* ethereal solution of lithium aluminum hydride. The mixture was boiled under reflux with stirring for one hour and was then decomposed by addition of moist ether. After removal of the precipitated hydroxides, the ether solution, on concentration *in vacuo*, gave a white solid. This, on recrystallization from benzene containing a trace of ethanol, gave 430 mg. of white crystals, m.p. 184–186°, $[\alpha]^{25}D$ +30.1° (*c* 2.0% in ethanol).

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 71.66; H, 9.96. Found: C, 71.66; H, 9.45.

(b) From Desmethoxy-β-erythroidinol (III).—A mixture containing 500 mg. of desmethoxy-β-erythroidinol,[5] 340 mg. of prereduced Adams catalyst, 0.4 ml. of concentrated hydrochloric acid and 100 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. Three molar equivalents of hydrogen were absorbed in about 45 minutes and then hydrogen uptake ceased. After removal of the catalyst and solvent, the residue was taken up in aqueous sodium carbonate solution and extracted with five 100-ml. portions of chloroform. When the combined chloroform extracts were dried and concentrated, there separated 410 mg. of a white solid. This was recrystallized three times from a benzene–ethanol mixture to give white crystals, m.p. 186–188°. A sample of these crystals was shown to be identical with those obtained in (a) by a mixed melting point determination and by comparison of their infrared spectra and optical activity.

Anal. Calcd. for $C_{16}H_{25}NO_2$: C, 71.66; H, 9.96. Found: C, 71.82; H, 9.88.

Dihydrodesmethoxy-β-erythroidinol. (a) From Desmethoxy-β-erythroidine (II).—A mixture containing 1.00 g. of desmethoxy-β-erythroidine,[3] 500 mg. of prereduced Adams catalyst, 1 ml. of concentrated hydrochloric acid and 100 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. One molar equivalent of hydrogen was absorbed in 11 minutes and the hydrogenation was stopped at this point. After removal of the catalyst and solvent, there remained a gum which was then suspended in 2000 ml. of dry ether. To this dry ethereal suspension there was then added dropwise with stirring 10 ml. of a 0.75 *M* ethereal solution of lithium aluminum hydride. After the mixture had boiled under reflux for one hour with stirring, moist ether was added, the precipitated hydroxides were removed, and the ether solution was concentrated. This caused the separation of 372 mg. of a light brown solid. On recrystallization from benzene containing ethanol this gave almost white crystals, m.p. 178–181°, $[\alpha]^{25}D$ −302° (*c* 1.0% in ethanol).

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.92; H, 8.67.

(b) From Desmethoxy-β-erythroidinol (III).—A mixture containing 460 mg. of desmethoxy-β-erythroidinol,[5] 300 mg. of prereduced Adams catalyst, 0.5 ml. of concentrated hydrochloric acid and 100 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. After one molar equivalent of hydrogen had been absorbed, the reaction was stopped and the catalyst was removed. The solution was then concentrated, an aqueous solution of sodium carbonate was added, and the resulting solution was thoroughly extracted with chloroform. Concentration of the combined chloroform extracts caused the separation of 142 mg. of straw-colored crystals. After recrystallization from benzene containing a trace of ethanol, this gave crys-

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

(12) All melting points are corrected.

tals melting at 176–180°. A mixture of the crystals from (a) and (b) showed no depression of melting point and the infrared spectra of the two samples were identical.

Tetrahydrodesmethoxy-β-erythroidinol (VII). (a) From Desmethoxy-β-erythroidinol by Reduction over Platinum.—A mixture containing 337 mg. of desmethoxy-β-erythroidinol,[5] 200 mg. of prereduced Adams catalyst, 0.5 ml. of 12 *N* hydrochloric acid and 50 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. When two molar equivalents of hydrogen had been absorbed, the reaction was stopped and the catalyst and solvent were removed. The residue was dissolved in an aqueous sodium carbonate solution and extracted with chloroform. Concentration of the combined chloroform extracts gave 306 mg. (90%) of a white solid. After recrystallization from benzene containing ethanol, this gave white crystals, m.p. 176–179°, $[\alpha]^{25}D$ −4.1° (*c* 2.0% in ethanol).

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 72.36; H, 9.54.

(b) **From Desmethoxy-β-erythroidine.**—A mixture containing 1.00 g. of desmethoxy-β-erythroidine, 700 mg. of prereduced Adams catalyst, 1.0 ml. of 12 *N* hydrochloric acid and 50 ml. of ethanol was subjected to hydrogenation at room temperature and pressure. The hydrogenation was interrupted after 2 molar equivalents of hydrogen had been absorbed, and the catalyst and solvent were removed. The residue was crystallized from a mixture of absolute alcohol and ether and gave 950 mg. of white needles, m.p. 228–230° dec. The composition of this material showed it to be the hydrochloride of tetrahydrodesmethoxy-β-erythroidine (VI).

Anal. Calcd. for $C_{18}H_{20}NO_2Cl$: C, 63.93; H, 7.15. Found: C, 64.17; H, 7.34.

When a sample of this hydrochloride was reduced with lithium aluminum hydride in the same manner previously described for the hydrochloride of dihydrodesmethoxy-β-erythroidine, it gave crystals which were identical in melting point, infrared spectrum and optical activity with the crystals of tetrahydrodesmethoxy-β-erythroidinol obtained in (a). Neither of the isomeric samples of tetrahydrodesmethoxy-β-erythroidinol, VII or VIII, show an absorption maximum above 220 mμ in the ultraviolet region.

When a 630-mg. sample of tetrahydrodesmethoxy-β-erythroidinol (VII) was hydrogenated over platinum in the presence of hydrochloric acid in the same manner previously described for the other hydrogenations, it readily absorbed one molar equivalent of hydrogen. From the reaction mixture there was obtained 317 mg. of white crystals, m.p. 183.5–184.5°, which were shown by a mixed melting point determination and a comparison of infrared spectra to be identical with the isomer of hexahydrodesmethoxy-β-erythroidinol obtained previously by direct hydrogenation of desmethoxy-β-erythroidinol.

Separation of the Diastereoisomers of Hexahydrodesmethoxy-β-erythroidinol.—The Birch reductions of β-erythroidinol (IX) and desmethoxy-β-erythroidinol (III) have previously been described.[5] It is now believed that the mixture of isomers of tetrahydrodesmethoxy-β-erythroidinol, which are isolated in each case from the Birch reductions, represent mixtures of the two diastereoisomers corresponding to structure VIII. Previously, it was shown that hydrogenation of the Birch products over platinum in acid gave a sharp melting hydrochloride and it was thought, therefore, that the mixture of isomers was the result of double bond isomerism.[6] However, this hydrochloride, when converted to its free base, gave crystals melting from 110 to 165°, indicating that the hydrochloride was a eutectic mixture of the two diastereoisomers of hexahydrodesmethoxy-β-erythroidinol (IV and IVa). The most satisfactory procedure for separating these two diastereoisomers was found to be the following.

A solution containing 475 mg. of the Birch reduction product from β-erythroidinol, m.p. 184–187°,[5] in 25 ml. of ethanol was added to a mixture of 300 mg. of prereduced Adams catalyst, 0.5 ml. of 12 *N* hydrochloric acid and 25 ml. of ethanol. When the resulting mixture was subjected to hydrogenation at room temperature and pressure, one molar equivalent of hydrogen was quickly absorbed (17 min.) and then hydrogenation stopped. After removal of the catalyst and solvent, the residue was dissolved in an aqueous sodium carbonate solution and extracted with chloroform. The combined chloroform extracts were dried and then concentrated under reduced pressure. The residue was dissolved in 25 ml. of benzene and from the benzene solution there separated, on standing, 176 mg. of white crystals, m.p. 110–165°. These crystals were again dissolved in benzene, a few drops of ethanol were added and the mixture was seeded with a crystal of the isomer of hexahydrodesmethoxy-β-erythroidinol obtained previously from the platinum reduction of desmethoxy-β-erythroidinol. The solution was allowed to stand overnight and then the white crystals, which had separated, were removed. These crystals (isomer A) weighed 27 mg. and appeared to be quite homogeneous, since they melted at 184–186°. That isomer A was identical with the isomer of hexahydrodesmethoxy-β-erythroidinol obtained previously by the platinum reductions was shown by a mixed melting point determination and by a comparison of the infrared spectra of the two samples.

When the mother liquor from which isomer A had separated was concentrated to 10 ml. and refrigerated overnight, the solution deposited 29 mg. of white crystals (isomer B), m.p. 162–170°. Mixtures of isomer B with either isomer A or the hexahydro derivative from the platinum reduction of desmethoxy-β-erythroidinol showed a large depression of melting point, melting over a range from 136–173°. Although isomer B is undoubtedly not entirely pure, its specific rotation ($[\alpha]^{25}D$ +205° (*c* 0.5% in ethanol)) is considerably more dextrorotatory than any other compound in this series and this establishes that isomer B should be designated as α-hexahydrodesmethoxy-β-erythroidinol.

Anal. (Isomer B). Calcd. for $C_{18}H_{25}NO_2$: C, 71.66; H, 9.96. Found: C, 71.73; H, 9.61.

***allo*-Dihydrodesmethoxy-β-erythroidine (XII).**—A mixture containing 1.60 g. of desmethoxy-β-erythroidine, 200 mg. of prereduced Adams catalyst and 250 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. Hydrogen uptake ceased after about 36 hr. and corresponded to about 2.8 molar equivalents of hydrogen. After removal of the catalyst, the solution was concentrated to 10 ml. and allowed to stand. The white crystals, which deposited, were removed and recrystallized from alcohol. This gave 415 mg. of white prisms, m.p. 169–170°, $[\alpha]^{25}D$ 0.0° (*c* 5% in ethanol).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.75; -C-Me, 0.0. Found: C, 74.00, 73.96; H, 7.45, 7.50; N, 5.65; -C-Me, 0.0.

The **methiodide** of *allo*-dihydrodesmethoxy-β-erythroidine was prepared in ethanol and was obtained, after recrystallization from the same solvent, as white crystals, m.p. 218–219°.

Anal. Calcd. for $C_{16}H_{20}NO_2I$: C, 49.88; H, 5.26. Found: C, 49.86; H, 5.41.

The mother liquor from which *allo*-dihydrodesmethoxy-β-erythroidine had separated was investigated but the residue, after evaporation, proved to be a complex mixture which we were unable to separate into pure components. The fact that these residues were optically active showing low negative rotation, suggests that the residue is not related to *allo*-dihydrodesmethoxy-β-erythroidine but, rather, is a mixture of the normal tetra- and hexahydrodesmethoxy-β-erythroidine derivatives.

Hydrazide of *allo*-Dihydrodesmethoxy-β-erythroidine.—A solution of 300 mg. of *allo*-dihydrodesmethoxy-β-erythroidine and 0.6 ml. of hydrazine hydrate (85%) was boiled under reflux for one hour. Then, 10 ml. of ethanol was added and the solution was heated an additional hour. The ethanol was removed and 5 ml. of warm benzene was added together with a few drops of cyclohexane. A solid separated, which after several recrystallizations from benzene, gave 290 mg. (85%) of white needles, m.p. 138–139°.

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 65.43; H, 7.69. Found: C, 65.40; H, 7.94.

***allo*-Dihydrodesmethoxy-β-erythroidinol.**—To a solution of 178 mg. of *allo*-dihydrodesmethoxy-β-erythroidine (XII) in 200 ml. of ether there was added dropwise with stirring 3 ml. of a 1.0 *M* ethereal solution of lithium aluminum hydride and the mixture was boiled under reflux for one hour. Moist ether was then added and the precipitated hydroxides were removed. Concentration of the ether gave a solid residue, which was recrystallized from an ether–ethanol mixture. There was obtained 160 mg. (85%) of white needles, m.p. 99–100°.

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]

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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-

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(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).