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

Hofmann Degradation Studies on β-Erythroidine. The Structure of Des-N-methyldihydro-β-erythroidinol[1,2]

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The Hofmann decomposition of dihydro-β-erythroidinol yields a stable aromatic compound, des-N-methyldihydro-β-erythroidinol, of fundamental importance in the elucidation of structure of the parent alkaloid, β-erythroidine. In the present paper, it is shown that all the evidence at hand leads to the conclusion that des-N-methyldihydro-β-erythroidinol has structure II. The critical evidence supporting structure II can be summarized as follows: (1) des-N-methyldihydro-β-erythroidinol has an ultraviolet absorption spectrum indicative of an *o*-substituted styrene derivative and on oxidation it yields phthalic acid. (2) When des-N-methyldihydro-β-erythroidinol is subjected to successive Hofmann decompositions followed by hydrogenation and oxidation, it yields *o*-ethylbenzoic acid. (3) Hydrogenolysis of des-N-methyldihydro-β-erythroidinol followed by successive Hofmann decompositions, hydrogenation and ozonolysis gives methyl ethyl ketone.

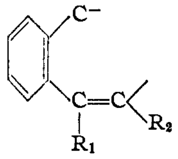
In a previous study,[3] it was observed that the Hofmann decomposition of dihydro-β-erythroidine gave both a normal methine base, $C_{17}H_{23}NO_3$, and an abnormal product of molecular formula, $C_{15}H_{19}N$. Furthermore, it was shown that, in the formation of the $C_{15}H_{19}N$ base, loss of the oxygen functions was accompanied by aromatization and the $C_{15}H_{19}N$ base was considered to be an *o*-substituted styrene derivative. When the Hofmann decomposition reaction was repeated with dihydro-β-erythroidinol, the lithium aluminum hydride reduction product of dihydro-β-erythroidine, it was found that aromatization again occurred with loss of the methoxyl function but that the diol grouping, derived from the lactone function, was retained.

The aromatization occurring during the Hofmann decompositions of dihydro-β-erythroidine and its diol appeared to offer a valuable lead in obtaining evidence regarding the structure of the parent alkaloid, β-erythroidine. We have, therefore, investigated the Hofmann products in some detail. In particular, we have given our attention to the Hofmann product from dihydro-β-erythroidinol, since in this case a single product is formed in high yield which still contains the diol grouping marking the position of the lactone ring.

In the Hofmann reaction leading to des-N-methyldihydro-β-erythroidinol, as well as in the other Hofmann reactions employed in this study, it was found advantageous to modify the usual procedure for conducting these decompositions. Instead of using the conventional silver oxide method for converting the quaternary ammonium salts to their corresponding ammonium hydroxides, we have accomplished this conversion by means of a basic ion-exchange resin.[4] This technique, in addition to being quicker and easier to perform, gives a cleaner product in higher yield than does the silver oxide procedure. Also, it avoids the undesirable oxidation which occurs when sensitive compounds are treated with silver oxide.

As indicated previously,[3] the infrared spectrum of des-N-methyldihydro-β-erythroidinol has absorption peaks at 6.25, 6.73 and 13.23 μ, which correspond to the usual peaks assigned to ortho disubstituted benzene derivatives.[5,6] For the purpose of establishing this deduction by chemical evidence, we subjected des-N-methyldihydro-β-erythroidinol to a permanganate oxidation and found, as expected, that phthalic acid was produced in high yield.[7] Thus, des-N-methyldihydro-β-erythroidinol must be an ortho disubstituted benzene derivative.

The character of these substituent groups is clearly indicated by the ultraviolet absorption spectrum of the compound. As shown in Fig. 1, des-N-methyldihydro-β-erythroidinol displays the broad general absorption typical of styrene derivatives and its over-all absorption curve agrees particularly well with that of 1-methyl-2-isopropenylbenzene.[6] Since its infrared spectrum lacks the usual peaks associated with mono-, di- or trisubstituted aliphatic double bonds,[8] des-N-methyldihydro-β-erythroidinol must have a tetrasubstituted double bond in conjugation with the benzene ring and a partial structure for the molecule can be written as shown by formula I.[9]



I

In order to determine the nature of the remaining portion of the molecule, des-N-methyldihydro-β-

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

(2) Paper VII in this series; for the preceding communication see M. F. Grundon, G. L. Sauvage and V. Boekelheide, THIS JOURNAL, **75**, 2541 (1953).

(3) V. Boekelheide and E. Agnello, *ibid.*, **73**, 2286 (1951).

(4) The idea for this modification was suggested by a discussion in "Ion Exchange Resins" by Kunin and Meyer, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 65.

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

(6) M. J. Murray and W. S. Gallaway, THIS JOURNAL, **70**, 3867 (1948).

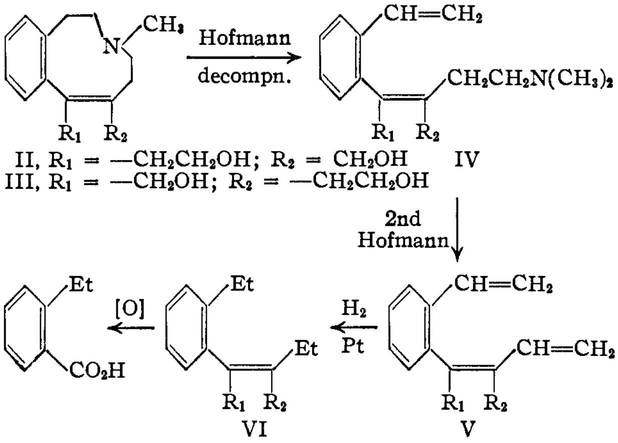
(7) The identity of the phthalic acid was established by converting it to N-methylphthalimide which was compared by means of mixed melting point determinations and infrared spectra with an authentic sample.

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

(9) It is worth noting at this stage that these deductions necessitate the revision of certain conceptions previously held regarding the extent of unsaturation and number of rings present in β-erythroidine. Since the Hofmann decomposition of dihydro-β-erythroidinol resulted in the elimination of the elements of methanol and water, it is logical to assume that only two double bonds were introduced during this decomposition and, therefore, dihydro-β-erythroidinol must originally have contained two double bonds instead of one, as formerly supposed. This, in turn, reduces from five to four the number of rings possible for the β-erythroidine skeleton. The hydrogenation experiments (Folkers and Koniuszy, British Patent 596,976) on which the previous conceptions were based, do not conflict with the present conclusions, since mild hydrogenation would not be expected to reveal a tetrasubstituted double bond.

erythroidinol was subjected to a second Hofmann decomposition. This gave an oily methine base which, in turn, was subjected to a third Hofmann descomposition. The resulting nitrogen-free product, desazadihydro-β-erythroidinol, was a crystalline solid which, on catalytic hydrogenation, readily absorbed two molar equivalents of hydrogen. Oxidation of this tetrahydro derivative with potassium permanganate gave *o*-ethylbenzoic acid in 10% yield.[10]

When the isolation of *o*-ethylbenzoic acid is considered in conjunction with other evidence available, it is possible to formulate a plausible reaction sequence to account for its formation, as is illustrated in Scheme I. The main points to be considered are: (1) Des-N-methyldihydro-β-erythroidinol is optically inactive and gives a negative result in the Kuhn–Roth determination for a C-methyl grouping. (2) The infrared spectrum of dihydro-β-erythroidine has a strong absorption peak at 5.78 μ,[11] which indicates the presence of a δ-lactone ring and, therefore, requires that des-N-methyldihydro-β-erythroidinol (II or III) have a 1,5-diol grouping, as shown. (3) The isolation of *o*-ethylbenzoic acid shows the nitrogen to be separated from the benzene ring by a $-CH_2-CH_2-$ grouping. (4) The absence of a C-methyl group requires that the heterocyclic ring be nine-membered.



II, R_1 = $-CH_2CH_2OH$; R_2 = CH_2OH

III, R_1 = $-CH_2OH$; R_2 = $-CH_2CH_2OH$

SCHEME I.

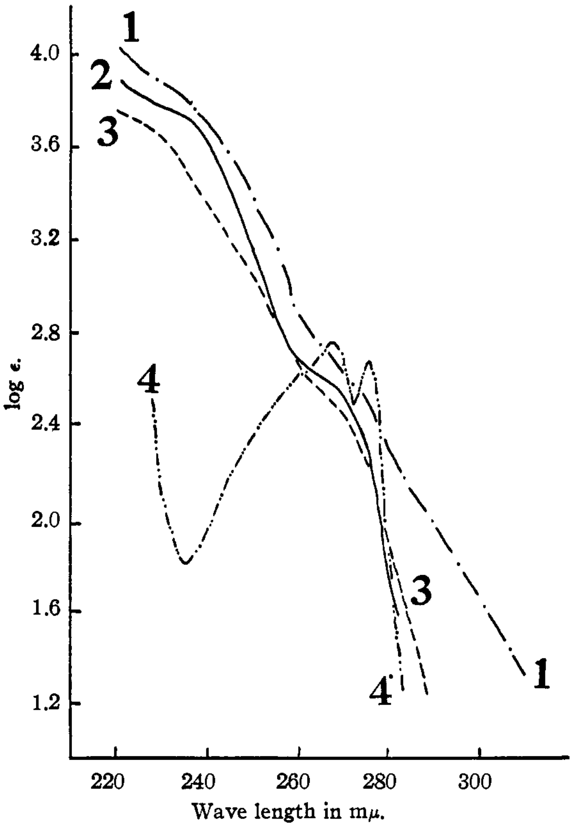


Fig. 1.—Ultraviolet absorption spectra of (1) des-N-methyldihydro-β-erythroidinol, II; (2) des-N-methyldesoxydihydro-β-erythroidinol, VII; (3) 1-methyl-2-isopropenylbenzene[6]; and (4) tetralin. The absorption spectra of 1, 2 and 4 were determined using ethanol as solvent.

Although this reaction scheme appeared very attractive, it did not distinguish between II and III as possible structures for des-N-methyldihydro-β-erythroidinol. We therefore examined other possible approaches which might both distinguish between II and III and also provide general evidence relating to the entire reaction scheme. Such an approach was discovered when it was found that careful hydrogenation of des-N-methyldihydro-β-erythroidinol could be conducted to effect hydrogenolysis of the allylic alcohol group in 57% yield. The resulting product, des-N-methyldesoxydihydro-β-erythroidinol, would be considered, on the basis of Scheme I, to have either structure VII or VIII. That hydrogenolysis had occurred without affecting the tetrasubstituted double bond was evident from the fact that the desoxy derivative retained the typical ultraviolet absorption spectrum (see Fig. 1) of an ortho substituted styrene derivative. As would be expected for structures VII and VIII, the desoxy derivative showed the presence of a C-methyl group in the Kuhn–Roth determination.

In order to decide between structures VII and VIII, the desoxy derivative was subjected to further Hofmann decompositions, as before. In this case, though, the methine base at each stage was examined spectroscopically and hydrogenated to obtain evidence regarding the type of double bond being produced. When subjected to the Hofmann decomposition, des-N-methyldesoxydihydro-β-erythroidinol gave in 84% yield a methine base IX, whose infrared spectrum showed absorption peaks at 10.03 and 11.00 μ. Since these peaks, which are in accord with those usually assigned to a terminal vinyl group of the type, $RCH=CH_2$,[8] disappeared on hydrogenation to the corresponding dihydro derivative X, it is fairly evident that there must be a $-CH_2-CH_2-$ group attached to the nitrogen atom.

When the hydrogenated product, des-N,N-dimethyldesoxytetrahydro-β-erythroidinol (X), was again subjected to a Hofmann decomposition, it gave a nitrogen-free product XI in 69% yield. This material, desazadesoxytetrahydro-β-erythroidinol,

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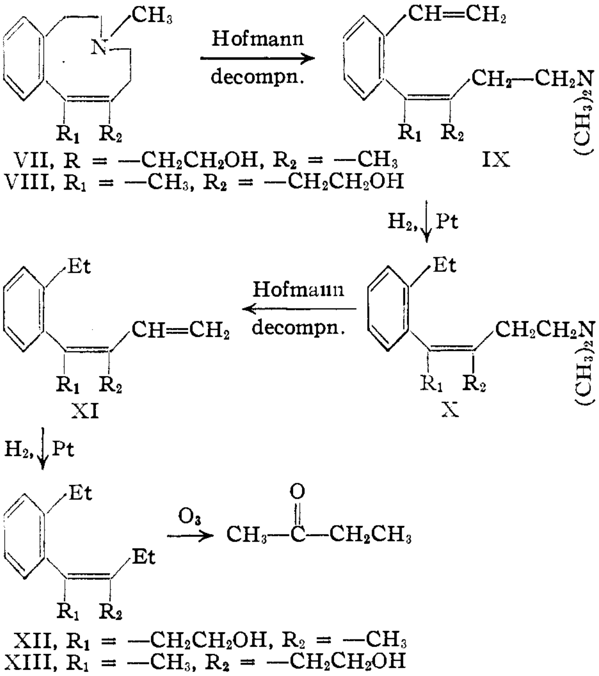
[10] The *o*-ethylbenzoic acid isolated from the oxidation experiment was shown to be identical with a synthetic sample by a comparison of their infrared spectra and by mixed melting point determinations.

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

possessed strong absorption peaks at 10.01 and 11.10 μ, which again disappeared on hydrogenation to the corresponding dihydro derivative (XII or XIII). The spectroscopic evidence, therefore, clearly shows that once again a terminal vinyl group of the type, R—CH=CH$_2$, was produced and that there must be a second –CH$_2$CH$_2$– group attached to the nitrogen atom, as postulated in Scheme I.



VII, R = —CH$_2$CH$_2$OH, R$_2$ = —CH$_3$

VIII, R$_1$ = —CH$_3$, R$_2$ = —CH$_2$CH$_2$OH

XII, R$_1$ = —CH$_2$CH$_2$OH, R$_2$ = —CH$_3$

XIII, R$_1$ = —CH$_3$, R$_2$ = —CH$_2$CH$_2$OH

SCHEME II.

The Hofmann studies on the desoxy derivative are summarized in Scheme II. It is apparent that the final hydrogenation product, desazadesoxyhexahydro-β-erythroidinol, must have either structure XII or XIII. To decide between these two possibilities, the product was subjected to ozonolysis. In the case of structure XII, ozonolysis followed by reductive hydrolysis should yield methyl ethyl ketone, whereas structure XIII should lead to *o*-ethylacetophenone. The accompanying β-hydroxyethyl ketone from either structure would be expected to be too unstable for isolation on the scale the ozonolysis experiment was conducted. When the steam distillate, resulting from hydrolysis of the ozonide, was treated with 2,4-dinitrophenylhydrazine reagent, a 2,4-dinitrophenylhydrazone was formed in 12.5% yield. This was shown to be identical with an authentic sample of the dinitrophenylhydrazone of methyl ethyl ketone by a mixed melting point determination and by a comparison of their infrared spectra. This result establishes the correctness of structure XII and, in turn, demonstrates that des-N-methyldihydro-β-erythroidinol must have structure II.

In the reaction schemes formulated to explain the Hofmann decomposition reactions, the first carbon–nitrogen cleavage has been assumed to occur on the side toward the benzene ring. Although the scheme presented appears to be the more likely course for these decompositions to take, it is quite possible that the order of rupture of the carbon–nitrogen bonds should be reversed. However, whether or not the order of bond rupture is correct, the arguments leading to XII for the structure of desazadesoxyhexahydro-β-erythroidinol and II for the structure of des-N-methyldihydro-β-erythroidinol are unaffected.

The implications of these results in relation to possible structures for β-erythroidine and dihydro-β-erythroidine are discussed in an accompanying paper.[11] Confirmation for the conclusions presented is also being sought through investigations directed toward the synthesis of II or a closely related derivative.

Experimental[12]

Dihydro-β-erythroidine.—The preparation of dihydro-β-erythroidine hydrobromide has been previously described.[3,13] The free base employed in this study was obtained by treating the hydrobromide salt (m.p. 227–229° (dec.), $[\alpha]^{25}D$ +103.6° (*c* 1.6% in ethanol)) with an aqueous sodium bicarbonate solution followed by extraction with chloroform. Concentration of the chloroform extract followed by crystallization of the residue from an ethyl acetate–hexane mixture gave dihydro-β-erythroidine as colorless crystals, m.p. 85–86°. The dihydro-β-erythroidine hydrobromide was shown to be homogeneous by subjecting it to a countercurrent distribution between an acetic acid–sodium acetate buffered solution (*p*H 5.24) and ethylene dichloride using a 24-tube Craig machine.[14] The distribution of the dihydro-β-erythroidine hydrobromide was followed spectroscopically by observing the intensity of the absorption peak at 220 mμ.

Des-N-methyldihydro-β-erythroidinol (II).—Utilization of the ion-exchange procedure made it possible to increase the yield in this Hofmann decomposition reaction from 40%, as previously described,[3] to 78%.

A solution of 1.29 g. of dihydro-β-erythroidinol[3] and 3 ml. of methyl iodide in 15 ml. of methanol was allowed to stand overnight and was then boiled under reflux for one hour. After removal of the solvent *in vacuo*, the residue was taken up in 15 ml. of water and passed over a column of Amberlite IRA-400-OH. The column was eluted with an additional 15 ml. of water and the combined eluates were concentrated under reduced pressure. Distillation of the residue in a molecular still at 0.03 mm. (pot temp. 130–150°) gave a viscous oil, which was taken up in methanol and treated with hexane. This caused the separation of 0.95 g. (78%) of a white solid, m.p. 93–97°. Recrystallization of this material from hexane gave white crystals, m.p. 96–98°, $[\alpha]^{25}D$ 0.00° (*c* 5% in ethanol), –C–Me negative.

The methiodide of des-N-methyldihydro-β-erythroidinol formed readily in methanol and was obtained, after crystallization from a methanol–ethyl acetate mixture, as white plates, m.p. 149–151°.

Anal. Calcd. for $C_{17}H_{26}NO_2I$: C, 50.63; H, 6.50. Found: C, 51.08; H, 6.60.

It should be noted that the infrared spectrum of des-N-methyldihydro-β-erythroidinol, which was previously presented,[3] has been redetermined with greater resolution and the broad peak at 13.12 μ has been separated into two peaks having their maxima at 13.23 and 13.05 μ.

Permanganate Oxidation of Des-N-methyldihydro-β-erythroidinol.—To a suspension of 500 mg. of des-N-methyldihydro-β-erythroidinol and 300 mg. of potassium hydroxide in 20 ml. of water a solution of 3% aqueous potassium permanganate was added until the permanganate color was no longer discharged on warming the reaction mixture to 80° (150 ml. required). The resulting mixture was made strongly acidic with hydrochloric acid and air was bubbled through the solution to remove the chlorine gener-

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(12) Analyses by Miss Claire King and W. Manser. The infrared spectra were recorded by Mr. Carl Whiteman using a Perkin–Elmer instrument, model 12 B.

(13) K. Folkers and F. R. Koniuszy, U. S. Patent 2,370,651.

(14) L. C. Craig and D. Craig, "Technique of Organic Chemistry," Vol. III, edited by A. Weissberger, Interscience Publishers, Inc., New York, N. Y., 1950, p. 265.

ated. The solution was then extracted continuously with ether for 15 hours. After removal of the solvent followed by a brief washing with chloroform, there remained 195 mg. (61%) of crude acid, m.p. 175–190° dec. Sublimation of 80 mg. of this material at atmospheric pressure gave 50 mg. of white needles, m.p. 120–130°. The sublimate was heated with aqueous methylamine and then sublimed to give a white solid which, after two crystallizations from an ethanol–water mixture, melted at 130.5–132.7°. The melting point of this product was not depressed by admixture of an authentic sample of N-methylphthalimide (m.p. 132–132.7°). Also, the infrared spectra of the authentic and naturally-derived samples of N-methylphthalimide were identical.

Des-N,N-dimethyldihydro-β-erythroidinol (IV).—A solution of 5.6 g. of the methiodide of des-N-methyldihydro-β-erythroidinol in 50 ml. of water was passed over a column of Amberlite IRA-400-OH. After concentration of the combined eluate and wash liquors under reduced pressure, the residue was distilled to give 3.4 g. (90%) of a viscous oil, b.p. (pot temperature) 160–170° at 0.03 mm.

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.14; H, 9.15; C–Me, 0.00. Found: C, 74.13; H, 9.17; C–Me, 0.00.

Desazadihydro-β-erythroidinol (V).—A methanolic solution of 3.4 g. of des-N,N-dimethyldihydro-β-erythroidinol was allowed to stand with a fivefold excess of methyl iodide for one hour and then the mixture was boiled under reflux for two hours. After removal of solvent *in vacuo*, the oily methiodide was taken up in 30 ml. of water and passed over a column of Amberlite IRA-400-OH. The combined eluate and wash liquors were concentrated and the residue was distilled to yield a colorless oil, b.p. (pot temperature) 150–160° at 0.001 mm. When the distillate was dissolved in ether and then the ether was replaced by hexane, there separated 2.37 g. (84%) of a white solid, m.p. 78–85°. Recrystallization of this from hexane gave 1.85 g. of white needles, m.p. 83–85°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.25; H, 7.88. Found: C, 78.18; H, 7.58.

Desazahexahydro-β-erythroidinol (VI).—A suspension of 350 mg. of desazadihydro-β-erythroidinol and 100 mg. of platinum oxide in 15 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. The hydrogen uptake was complete in five minutes and corresponded to two molar equivalents of hydrogen. After removal of the catalyst and solvent, the residue was distilled yielding 340 mg. (95%) of a colorless oil, b.p. (pot temperature) 150° at 0.1 mm.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 76.79; H, 9.56.

Oxidation of Desazahexahydro-β-erythroidinol to Give *o*-Ethylbenzoic Acid.—To a suspension of 340 mg. of desazahexahydro-β-erythroidinol in 15 ml. of water there was added a calculated quantity (35 ml.) of aqueous 4% potassium permanganate and the mixture was warmed until the permanganate color was discharged. The mixture was then made acidic with hydrochloric acid and sulfur dioxide was bubbled through the solution until the manganese dioxide dissolved. The solution was then extracted three times with equivalent volumes of ether and the combined ether extracts were washed twice with an aqueous sodium bicarbonate solution. Acidification of the bicarbonate extract followed by chilling caused the separation of 22 mg. (10%) of white crystals, m.p. 52–58°. This was crystallized from water, then from hexane, and finally sublimed to give white needles, m.p. 63.5–64.5°. The melting point of these crystals was not depressed by admixture of a synthetic sample of *o*-ethylbenzoic acid (m.p. 63.5–64.5°).[15,16] Also, the infrared spectra of the synthetic and naturally derived samples of *o*-ethylbenzoic acid were identical.

Des-N-methyldesoxydihydro-β-erythroidinol (VII).—A suspension of 4.5 g. of des-N-methyldihydro-β-erythroidinol, 300 mg. of platinum oxide and 4.5 ml. of 12 *N* hydrochloric acid in 35 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. The hydrogen uptake at the end of five hours corresponded to 1.25 molar equivalents and the hydrogenation was then stopped, since the rate of absorption had become very slow. After removal of the catalyst and solvent, the residue was treated with aqueous potassium carbonate and the solution was extracted repeatedly with benzene. The combined benzene extracts were concentrated and the residue was taken up in hexane. This caused the separation of 2.3 g. (55%) of a white solid, m.p. 85–89°. Recrystallization of this from hexane gave 2.1 g. of white crystals, m.p. 88–89.5°.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; –C–Me, 6.39. Found: C, 78.24; H, 9.36; –C–Me, 2.66.

The methiodide of des-N-methyldesoxydihydro-β-erythroidinol was prepared by treating the base with an excess of methyl iodide in methanol at room temperature for one hour followed by heating under reflux for another 1.5 hours. Removal of the solvent followed by addition of ethyl acetate gave a white solid in 90% yield. This was recrystallized from a mixture of methanol and ethyl acetate to give white plates, m.p. 174.5–177°.

Anal. Calcd. for $C_{17}H_{26}NOI$: C, 52.71; H, 6.77. Found: C, 52.75; H, 6.83.

Des-N,N-dimethyldesoxydihydro-β-erythroidinol (IX).—An aqueous solution containing 1.61 g. of the methiodide of des-N-methyldesoxydihydro-β-erythroidinol was passed over a column of Amberlite IRA-400-OH. After concentration of the eluate under reduced pressure, the residue was distilled yielding 930 mg. (84%) of a colorless oil, b.p. (pot temperature) 110–120° at 0.003 mm.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.72; H, 9.72. Found: C, 78.48; H, 9.64.

Des-N,N-dimethyldesoxytetrahydro-β-erythroidinol (X).—A mixture of 930 mg. of des-N,N-dimethyldesoxydihydro-β-erythroidinol, 100 mg. of platinum oxide, 1 ml. of 12 *N* hydrochloric acid and 15 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure. The hydrogen uptake was complete in 15 minutes and corresponded to one molar equivalent of hydrogen. After removal of the catalyst and solvent, the residue was treated with aqueous sodium carbonate and the resulting mixture was extracted five times with benzene. Concentration of the combined benzene extracts followed by distillation of the residue gave 900 mg. (97%) of a colorless oil, b.p. (pot temperature) 110° at 0.013 mm.

Anal. Calcd. for $C_{17}H_{27}NO$: C, 78.10; H, 10.41. Found: C, 77.99; H, 10.50.

The hydrochloride of des-N,N-dimethyldesoxytetrahydro-β-erythroidinol was obtained by repeating the hydrogenation described above and adding ether to the residue resulting after removal of the catalyst and solvent. The solid so obtained was crystallized from an ether–ethanol mixture and then from an isopropyl alcohol–ether mixture to give white crystals, m.p. 150–153°. The fact that a single hydrochloride formed in high yield is evidence that the Hofmann decomposition must have occurred almost exclusively in one direction.

Anal. Calcd. for $C_{17}H_{28}NOCl$: C, 68.55; H, 9.47. Found: C, 68.32; H, 9.33.

Desazadesoxytetrahydro-β-erythroidinol (XI).—A methanolic solution of 840 mg. of des-N,N-dimethyldesoxytetrahydro-β-erythroidinol and excess methyl iodide was allowed to stand for one hour and then the mixture was boiled under reflux for an additional 1.5 hours. After removal of the methanol, the residual oil was taken up in water and passed over a column of Amberlite IRA-400-OH. Concentration of the eluate was followed by distillation of the residue to give 480 mg. (69%) of a colorless oil, b.p. (pot temperature) 120° at 0.02 mm.

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 82.78; H, 9.24.

Desazadesoxyhexahydro-β-erythroidinol (XII).—A mixture of 418 mg. of desazadesoxytetrahydro-β-erythroidinol and 100 mg. of platinum oxide in 15 ml. of ethanol was subjected to hydrogenation at room temperature and atmospheric pressure. One molar equivalent of hydrogen was quickly absorbed. After removal of the catalyst and solvent, the residue was distilled yielding 380 mg. (90%) of a colorless oil, b.p. (pot temperature) 100° at 0.01 mm.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.30; H, 10.19.

Ozonolysis of Desazadesoxyhexahydro-β-erythroidinol.—A stream of oxygen containing three equivalents of ozone

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(15) S. F. Birch, R. A. Dean, F. A. Fidler and R. A. Lowry, THIS JOURNAL, **71**, 1362 (1949).

(16) R. Riemschneider, *Gazz. chim. ital.*, **77**, 607 (1947).

(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.

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

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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.

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(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)).

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(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).

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

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

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(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 rearrangement 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]