of hydrogen and 190° for 8 hours gave 9.5 g. of 2-isopropylpyrrolidine, b.p. 48–51° (20 mm.), $n^{25}D$ 1.442, d^{25}_4 0.835, conversion 45.8%.

Anal. Calcd. for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 73.9, 74.1; H, 13.8, 13.5; N, 12.6, 12.1; chloroplatinate, m.p. 138–140°.

Anal. Calcd. for 2 $C_7H_{15}N \cdot H_2PtCl_6$: C, 26.42; H, 5.07, Pt, 30.68. Found: C, 26.0, 26.7; H, 5.5, 5.3; Pt, 30.8, 31.2.

2,5-Diisopropylpyrrolidine.—Fifteen grams of 2,5-diisopropylpyrrole, 3 g. of catalyst in 25 ml. of dioxane, were hydrogenated at 192 atm. and 185° for 5 hours. Fractional distillation gave 8.5 g. of 2,5-diisopropylpyrrolidine, b.p. 63–67° (10 mm.), $n^{25}D$ 1.442, d^{25}_4 0.826, conversion 55.2%.

Anal. Calcd. for $C_{10}H_{21}N$: C, 77.34; H, 13.63; N, 9.03. Found: C, 77.1, 77.0; H, 13.9, 13.5; N, 9.1; chloroplatinate, m.p.K. 198–200°.

Anal. Calcd. for 2 $C_{10}H_{21}N \cdot H_2PtCl_6$: C, 33.34; H, 6.16; Pt, 27.09. Found: C, 33.4; H, 5.8; Pt, 27.2.

2-Ethyl-5-isopropylpyrrolidine.—Eight and one-half grams of 2-ethyl-5-isopropylpyrrole, 3 g. of catalyst in 25 ml. of dioxane, were hydrogenated at 190° and 153 atm. for 4 hours; yield 4.5 g. of 2-ethyl-5-isopropylpyrrolidine, b.p. 171–172° (743 mm.), $n^{25}D$ 1.442, d^{25}_4 0.832, conversion 53.0%.

Anal. Calcd. for $C_9H_{19}N$: C, 76.52; H, 13.56; N, 9.92. Found: C, 76.3, 76.2; H, 13.6, 13.5; N, 9.8, 9.8. Hydrochloride, m.p. 195–200°.

Anal. Calcd. for $C_9H_{19}N \cdot HCl$: C, 60.82; H, 11.35; N, 7.88; Cl, 19.95. Found: C, 60.7, 60.7; H, 11.5, 11.6; N, 7.7, 7.8; Cl, 19.6, 19.8.

Acknowledgment.—One of us (CLG) is indebted to the Kettering Foundation for the Fellowship which made this study possible. The generous loan of hydrogenation and fractionation equipment, by the Chemistry Department of Antioch College, is gratefully acknowledged.

YELLOW SPRINGS, OHIO, AND
COLUMBUS, OHIO

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

The Structure of α-Erythroidine[1]

BY JOHN C. GODFREY,[2] D. S. TARBELL AND V. BOEKELHEIDE

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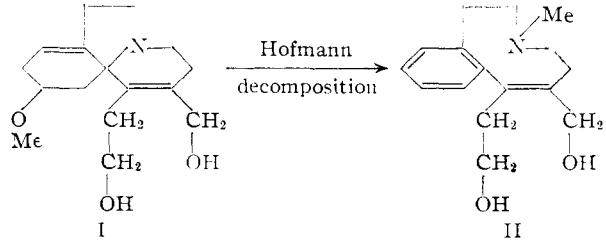
α-Erythroidine has been carried through a sequence of degradations which provides convincing evidence that the original molecule contains the partial structure shown by formula III. The key reaction in this sequence was the rearrangement and aromatization that occurred when dihydro-α-erythroidinol (V) was subjected to the conditions of the Hofmann exhaustive methylation procedure. From III, it can be seen that α-erythroidine possesses the same carbon skeleton as β-erythroidine but differs from it in the arrangement of the lactone ring. Although the positions of the methoxyl group and the two aliphatic double bonds in rings A and B remain uncertain, formula XV is tentatively proposed for the over-all structure of α-erythroidine.

In a previous publication,[3] the characterization of α-erythroidine was described and evidence was presented emphasizing the differences between α- and β-erythroidine in their behavior and properties. Although these two alkaloids had been named on the supposition that they were diastereoisomers,[4] the conclusion drawn in our previous study was that this was unlikely. In order to investigate this point further, we have now made a study of the Hofmann degradation of dihydro-α-erythroidinol following the same general approach which had been used successfully in the case of β-erythroidine.[5]

In the previous studies on β-erythroidine it was found that when dihydro-β-erythroidinol (I) was subjected to the conditions of the Hofmann exhaustive methylation procedure, rupture of the carbon–nitrogen bond was accompanied by aromatization with loss of the elements of methanol to give compound II.[5,6] Since this transformation removes the features responsible for optical activity, it would be expected that, if α-erythroidine were a diastereoisomer of β-erythroidine, a similar degradation of α-erythroidine would lead to the identical product II.



To test this hypothesis it was necessary to prepare dihydro-α-erythroidinol and this was accomplished as follows. α-Erythroidine was treated with lithium aluminum hydride to effect reduction of the lactone ring and give the corresponding diol, α-erythroidinol. This, on hydrogenation using Raney nickel as catalyst, gave the desired dihydro-α-erythroidinol in good yield. Although it was also shown that α-erythroidine could be catalytically reduced to dihydro-α-erythroidine following the same procedure, the further reduction of dihydro-α-erythroidine with lithium aluminum hydride as an alternate route to dihydro-α-erythroidinol was not investigated.

When dihydro-α-erythroidinol was subjected to the conditions of the Hofmann exhaustive methylation procedure, a smooth reaction occurred to give the corresponding des-base as a light yellow gum in 89% yield. From the analytical data, it was appar-

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

(2) Du Pont Postgraduate Fellow, 1953–1954.

(3) V. Boekelheide and M. F. Grundon, THIS JOURNAL, **75**, 2563 (1953).

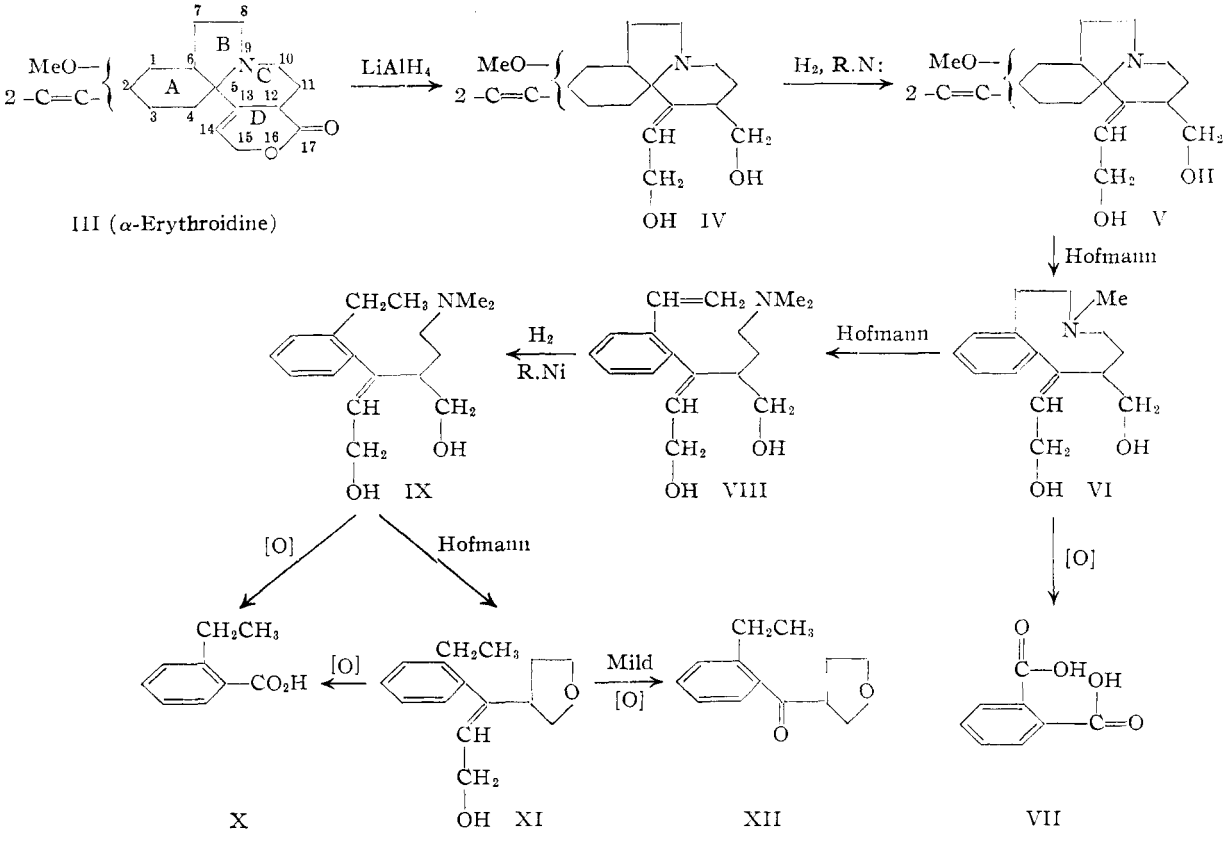
(4) K. Folkers and R. T. Major, British Patent 543,187; K. Folkers and R. T. Major, U. S. Patent 2,373,952.

(5) J. Weinstock and V. Boekelheide, THIS JOURNAL, **75**, 2546 (1953).

(6) The style of representing the formulas of these alkaloids has been changed from that used in our previous publications in order to obtain a uniform presentation for *all* of the erythrina alkaloids (see Boekelheide and Prelog, "Progress in Organic Chemistry," Vol. III, Academic Press, Inc., New York, N. Y., 1955.

CHART I

DEGRADATION OF α-ERYTHROIDINE



ent that this des-base no longer contained a methoxyl group and was isomeric with the analogous des-base II from β-erythroidine. However, seeding of the gummy des-base with crystals of II had no effect and, further, its infrared spectrum, although similar to that of II, showed distinct differences. When the des-base was converted to the corresponding methiodide derivative, it gave beautiful white crystals, m.p. 220–221°, whereas the methiodide of II melts at 149–150°.[5] Thus, it can be safely concluded that the two des-bases derived from dihydro-α-erythroidinol and dihydro-β-erythroidinol are not identical and, with the assumption that the changes occurring during the Hofmann degradations are the same in both cases, it becomes certain that α-and β-erythroidine are not diastereoisomers.

Because of its importance to later discussions of structure, it should be mentioned at this stage that the des-base from dihydro-α-erythroidinol as well as its various derivatives were found to be optically active. Since this contrasts sharply with compound II and its related derivatives in the β-erythroidine series, which are all optically inactive, α-erythroidine must have an additional source of asymmetry not present in β-erythroidine.

To gain further insight into these structural relationships, the des-base from dihydro-α-erythroidinol was subjected to a series of further degradations, the results of which are summarized in Chart I. For purposes of clarity, Chart I has been drawn to indicate the formulas now being assigned these degradation products; justification for these assignments will become apparent as the discussion develops.

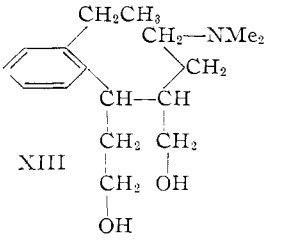
A comparison of the ultraviolet absorption spectrum of VI, the des-base from dihydro-α-erythroidinol (V), showed it to be almost identical with that of II, indicating the probable presence of an *ortho* substituted styryl nucleus in the molecule. The infrared spectrum of VI also supported this deduction since it possessed absorption peaks at 8.82, 9.26, 9.52 and 13.15 μ as is normal for an *ortho* disubstituted benzene derivative.[7] This relationship was then established chemically by subjecting the methohydroxide of VI to permanganate oxidation which produced phthalic acid, isolated as its N-methylphthalimide derivative VII, in good yield.

When VI was further degraded by the Hofmann exhaustive methylation procedure, it gave VIII which was still optically active having a specific rotation of +22°. In agreement with its assigned structure, VIII possessed an ultraviolet absorption spectrum very similar to that of *o*-divinylbenzene.[8] That a terminal vinyl group had been produced during this second Hofmann degradation was evident both from ozonolysis and infrared spectral studies. Thus, VIII on ozonolysis gave formaldehyde, isolated as its dimedon derivative, in 28% yield, while its infrared spectrum showed absorption peaks at 9.93 and 11.00 μ which disappeared when VIII was converted by hydrogenation over Raney nickel catalyst to the corresponding dihydro

(7) H. L. McMurry and V. Thornton, *Anal. Chem.*, **24**, 318 (1952).
(8) K. Fries and H. Bestian, *Ber.*, **69**, 715 (1936).

derivative IX. From the extensive spectral studies on olefins,[9] it may be assumed by analogy that the terminal vinyl group present in VIII is of the type —CH=CH_2. Final evidence regarding the position and nature of this group was obtained through the discovery that the methiodide of IX, in contrast to VI, underwent permanganate oxidation to give *o*-ethylbenzoic acid. The ethyl group in this instance must correspond to the vinyl group produced during the second Hofmann reaction.

It was of interest that when the hydrogenation of VIII was investigated using Adams catalyst the product obtained was not the dihydro derivative IX but a tetrahydro derivative to which we assign structure XIII. This indicated that the second aliphatic double bond in VIII was not highly resistant to hydrogenation and was probably trisubstituted rather than tetrasubstituted as is the case in the β-erythroidine series (*i.e.*, as in II). Support for this view was also found during attempts to hydrogenate VI using Adams catalyst. In the case of II, hydrogenation under these conditions led cleanly to hydrogenolysis of the allylic hydroxyl without affecting the tetrasubstituted double bond. However, with VI the resulting mixture of products indicated that hydrogenation of the aliphatic double bond was the predominant reaction.



XIII

The next step in the degradation sequence was the removal of the nitrogen atom by subjecting IX to a third Hofmann degradation. This final elimination proceeded with exceptional ease to give a nitrogen-free product of the expected composition in 87% yield. However, attempts to determine by means of ozonolysis and spectral data the type of unsaturation which had been introduced during the Hofmann reaction were fruitless. A prolonged consideration of the infrared absorption spectrum of this product led to the observation that there was a striking similarity between its spectrum (absorption peaks at 6.87, 7.31, 8.31, 8.43, 9.11, 9.44 and 11.13 μ) and that considered to be characteristic of tetrahydrofuran derivatives (absorption peaks at 6.85, 7.4, 8.4–8.5, 9.1–9.3 and 11.0 μ).[10] It seemed possible, therefore, that one of the oxygens was now present in a tetrahydrofuran nucleus due to an internal displacement of the trimethylamino group by hydroxyl. That only one free hydroxyl group remained was borne out by the conversion of XI to the corresponding *mono p*-phenylazobenzoate derivative. This derivative no longer showed absorption in the hydroxyl region of its infrared spectrum, a result to be expected from the hypothesis that the second oxygen is now involved in a tetrahydrofuran ring.[11]

Additional facts bearing on the assignment of structure XI to the product of the final Hofmann degradation were the observations (a) that it retained the ultraviolet absorption spectrum typical of an *ortho* substituted styrene derivative and (b) that it was converted on strong permanganate oxidation to *o*-ethylbenzoic acid (X).

On the other hand when XI was subjected to mild oxidation with dilute permanganate in acetone, the resulting product had a composition corresponding to the empirical formula $C_{13}H_{16}O_2$, indicating the loss of a simple two carbon fragment. The infrared absorption spectrum of this product still possessed the characteristic tetrahydrofuran peaks, but no longer showed hydroxyl absorption. Instead there was a strong peak at 5.98 μ indicative of a carbonyl group conjugated with an aromatic system.[12] In addition the ultraviolet absorption spectrum of this compound was found to be closely similar to that of 2,4-dimethylacetophenone.[13] If consideration is given to the fact that this final degradation product still retains optical activity, the only satisfactory structure for this substance in accord with our experimental data is that given by XII. Once XII is accepted as being correct the earlier structures in the series VI to XII become a logical consequence.

From VI the chain of reasoning leading back to III, as the correct partial structure for α-erythroidine, is essentially the same as that given in detail previously for β-erythroidine.[5,14] Our experimental evidence substantiates, therefore, prior expectations that α-erythroidine has the same type of spiro structure as do all the other erythrina alkaloids.[6] It should be stated, though, that before this conclusion was accepted various alternate formulations, ranging from biogenetically favorable structures to unusual bridged-ring types, were considered and found to be unsatisfactory.[15]

A comparison of β-erythroidine (XIV) and partial structure III for α-erythroidine reveals that both have the same carbon skeleton but they differ in the arrangement of their lactone rings. Justification for the assignment of the lactone ring arrangement for α-erythroidine as given by III follows from several considerations. The oxidation of XI with loss of a two-carbon fragment and introduction of a carbonyl group adjacent to the aromatic ring must represent the oxidation of the aliphatic double bond originally present in ring D and thus this double bond has to be placed between C_{13} and C_{14}. That the lactone carbonyl group is at C_{17} and not at C_{15} follows from a comparison of the ultraviolet absorption spectra of III and IV, which are essentially identical. Had the lactone carbonyl been at C_{15}, it would have been conjugated

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

(10) G. M. Barrows and S. Searles, THIS JOURNAL, **75**, 1175 (1953).

(11) The ease with which such internal displacements occur to give tetrahydrofuran ring systems is well illustrated by the case of isomethadone (N. R. Easton and V. B. Fish, *ibid.*, **76**, 2836 (1954)).

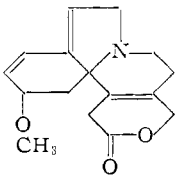
(12) V. Boekelheide and J. Godfrey, *ibid.*, **75**, 3679 (1953).

(13) M. T. O'Shaughnessy and W. H. Rodebush, *ibid.*, **62**, 2906 (1940).

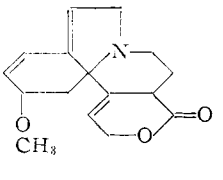
(14) V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage and E. J. Agnello, *ibid.*, **75**, 2550 (1953).

(15) John C. Godfrey, Ph.D. Thesis, University of Rochester, 1954.

with the aliphatic double bond and would have shown an absorption band in the region between 220 and 240 mμ. The fact that removal of the lactone carbonyl by lithium aluminum hydride reduction had no effect on the ultraviolet absorption spectrum of the molecule shows that no such conjugated system is present and the carbonyl group must, therefore, be at C_{17}. Finally, the fact that optical activity is not lost in the transition of V to VI, whereas in the analogous transformation in the β-erythroidine series it is, is readily explained by the asymmetric carbon atom at C_{12} which is made possible through the different arrangement of the lactone ring in α-erythroidine. Actually, it is the retention of configuration at C_{12} that is responsible for the optical activity present in the compounds VI through XII.



XIV



XV

Although the degradative evidence pointing to partial structure III appears reasonably conclusive, experimental evidence regarding the positions to be assigned the methoxyl group and the two remaining aliphatic double bonds is still incomplete. If these groups have the same arrangement that prevails in the case of β-erythroidine (XIV), some reconciliation of the differences in the ultraviolet absorption spectra of the two alkaloids is necessary. Whereas β-erythroidine hydrochloride has its absorption maximum at 238 mμ (log ε, 4.4) that of α-erythroidine hydrochloride occurs at 224 mμ (log ε, 4.5). The shorter wave length at which α-erythroidine has its maximum has led us to consider whether some conjugated system other than a diene might be responsible for the ultraviolet absorption spectrum of α-erythroidine.[16] Of the alternative possibilities the only two which seem at all likely are those of a vinyl ether or a vinyl amine system. For this reason various attempts were made to effect a hydrolysis of such a linkage by prolonged heating of α-erythroidine hydrochloride with aqueous mineral acid; however, in each case the alkaloid was recovered unchanged. This result renders most unlikely the possibility of a vinyl ether group being present, although a cyclic vinyl amine might possibly survive such treatment.

To investigate further the possibility of a vinyl amine system a study was made of the acid dissociation constants of the hydrochlorides of α-erythroidinol (IV) and dihydro-α-erythroidinol (V). The diols were chosen for this study rather than the parent compounds so that the lactone ring would not be a complicating influence during the potentiometric titrations. Also, since the reduction of α-erythroidinol to dihydro-α-erythroidinol results in the elimination of the absorption peak at 224–225 mμ, it can be assumed that the catalytic reduction affects the conjugated system in question. The pK_a values which have been determined are given in Table I with accompanying values from the β-erythroidine series for comparison.

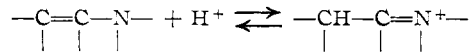
TABLE I

pK_a VALUES OF HYDROCHLORIDE SALTS[a]

	pK_a
α-Erythroidinol	7.79
Dihydro-α-erythroidinol	8.42
β-Erythroidinol	7.80
Dihydro-β-erythroidinol	8.69
Desmethoxy-β-erythroidinol	7.71

[a] Determinations made by potentiometric titration using water as solvent.

It can be seen from Table I that the pK_a values for both the α- and β-erythroidine series are very similar and argue strongly against the possibility of a vinyl amine grouping. As indicated from the work of Adams and Mahan,[17] vinyl amines enter into an equilibrium with acids as illustrated below and are therefore more basic than the corresponding saturated amines. Since in the case of both α-



XVI

and β-erythroidinol, their dihydro derivatives are more basic than the parent compounds, the order of basicity is the reverse of that to be expected for vinyl amine derivatives. Furthermore the arguments against a vinyl system supported by the comparison of pK_a values cannot be circumvented by invoking a structure of the neostrychnine type in which the restrictions of Bredt's rule prevent formation of the immonium ion XVI. As Prelog and Häfliger have shown,[18] the pK_a value for the vinyl amine group in neostrychnine is 3.6, a very low basicity quite outside the range of any of the compounds in Table I.

Recently, Witkop has made a study of the infrared spectra of the salts of various vinyl and saturated tertiary amines and has shown that these spectra have diagnostic value for distinguishing between these two possibilities.[19] Investigation of the infrared spectra of both α- and β-erythroidine hydrochlorides revealed that both these alkaloids have an absorption peak at 4.25 μ corresponding to absorption for an ammonium ion but neither has absorption peaks where an immonium ion such as XVI would be expected to absorb. Thus, the spectral evidence is likewise against the presence of a vinyl amine grouping in α-erythroidine.

With the elimination of the alternate possibilities it is necessary to reconsider whether α-erythroidine is not best represented by structure XV in which it is given the same heteroannular diene system as β-erythroidine (XIV). In order to explain the difference in their ultraviolet absorption spectra it would then be necessary to assume that a difference in configuration at C_3 would have sufficient influence on the conjugated diene system to account for the shift in spectra. There is recent evidence to in-

(16) Since homoannular dienes have their absorption maxima at longer wave lengths than do heteroannular dienes (L. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Pub. Corp., New York, N. Y., 1949, p. 185), any alternate manner of placing the diene system in rings A and B is even less satisfactory.

(17) R. Adams and J. E. Mahan, THIS JOURNAL, **64**, 2588 (1942).

(18) V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **32**, 1851 (1949).

(19) B. Witkop, THIS JOURNAL, **76**, 5597 (1954).

dicate that such an assumption is not unreasonable. Investigations in the steroid field have shown that a difference in configuration of an oxygen function adjacent to a conjugated diene system may result in the shift of the absorption maximum by as much as 5 mμ.[20] Furthermore, the prediction of absorption maxima for heterocyclic systems appears to be far more uncertain than is the case for carbocyclic systems. Both Georgian[21a] and Marchant and Pinder[21b] have observed that the absorption maxima for the α,β-unsaturated ketone grouping in certain octahydroisoquinolines is at shorter wave lengths by 10 to 15 mμ than would be predicted from Woodward's rules for carbocyclic systems.[22] Presumably this is due to interaction of the nitrogen atom with the absorbing system. It is conceivable, therefore, that in the case of α- and β-erythroidine the configuration at C_3 can control the degree of interaction between the nitrogen atom and the absorbing diene system. Since this appears to be the best explanation at hand for correlating the spectral and other properties of α- and β-erythroidine, we tentatively propose structure XV to represent the complete α-erythroidine molecule.

Further studies relating to the structure and synthesis of α-erythroidine and its derivatives are in progress.

Experimental[23]

α-Erythroidine.—The α-erythroidine hydrochloride used in this study was purified by the same general chromatographic technique described earlier and showed a negative Dietz-Folker's test for the presence of β-erythroidine.[3] A typical sample of this hydrochloride melted at 233–234° dec. and showed a specific rotation of +118° (0.0208, water). Also, a Kuhn-Roth determination for C-methyl was negative.

Dihydro-α-erythroidinol (V).—A mixture of 1.70 g. of α-erythroidinol[3] in 400 ml. of absolute ethanol was subjected to hydrogenation at atmospheric pressure and room temperature using Raney nickel as catalyst. When one mole of hydrogen was absorbed (7 min.), the hydrogenation was stopped even though the uptake of hydrogen was continuing. After removal of the catalyst and solvent, the residual gum was dissolved in warm ethyl acetate. The ethyl acetate solution on concentration to a volume of 20 ml. followed by chilling deposited 1.15 g. (67%) of crystals, m.p. 142–144°. Recrystallization of this material from ethyl acetate gave 1.03 g. of white prisms, m.p. 145–148°. The sample for analysis was obtained from a mixture of absolute ethanol–hexane as white prisms, m.p. 148.5–149°.

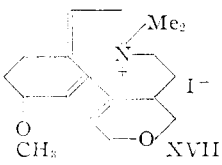
Anal. Calcd. for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02. Found: C, 68.59; H, 9.11.

The **methiodide of dihydro-α-erythroidinol** was obtained by dissolving 9.38 g. of dihydro-α-erythroidinol in 120 ml. of absolute ethanol containing 30 ml. of methyl iodide and heating the mixture under reflux for exactly one-half hour. When the mixture was cooled, there separated 12.3 g. (87%) of crystals. These, on recrystallization from 135 ml. of absolute ethanol, gave 11.8 g. of white crystals, m.p. 192.5–194°. These were recrystallized from ethanol once more to give a sample m.p. 194–195°, $[\alpha]^{25}D$ +128° (*c* 0.0632, ethanol).

Anal. Calcd. for $C_{17}H_{28}NO_3I$: C, 48.46; H, 6.70. Found: C, 48.49; H, 6.70.

When the period of heating used in the preparation of the methiodide of dihydro-α-erythroidinol was extended, a different product resulted. Thus, a sample of 100 mg. of dihydro-α-erythroidinol when heated for 20 hours in an absolute ethanol–methyl iodide mixture gave, on working up the reaction mixture in the same manner as before, 121 mg. of light yellow prisms, m.p. 236–238°. This same product also could be obtained by heating the original methiodide (m.p. 194–195°) with an ethanol–methyl iodide mixture, although boiling ethanol alone had no effect on the original methiodide. A sample of this second product, when purified by recrystallization from absolute ethanol, melted at 241–242° and showed a specific rotation of +107° (*c* 0.0496, water). The ultraviolet absorption spectrum of this substance showed a maximum at 227 mμ (log ε 4.1). These data combined with the empirical formula required to fit its composition make it seem likely that this product has structure XVII. The transformation of the methiodide of V to XVII would merely require an easy Hofmann elimination coupled with an acid-catalyzed ring closure to the cyclic ether, a reaction which apparently goes with some ease.[24] As yet no further investigation has been made of this compound.

Anal. Calcd. for $C_{18}H_{28}NO_2I$: C, 51.80; H, 6.76; N, 3.36. Found: C, 51.85, 51.94; H, 6.73, 6.77; N, 3.74.



XVII

Dihydro-α-erythroidine.—For this reduction of α-erythroidine, it was necessary to obtain the alkaloid as the free base. For this purpose a 500-mg. sample of α-erythroidine hydrochloride was dissolved in chloroform and treated with an aqueous paste of sodium bicarbonate. After the chloroform layer was separated, the solvent was removed *in vacuo* and the residual alkaloid, as the free base, was taken up in 100 ml. of absolute ethanol. This solution was subjected to hydrogenation at room temperature and atmospheric pressure using Raney nickel as catalyst. When one mole of hydrogen had been absorbed, the hydrogenation was stopped and the catalyst and solvent were removed. The residue was taken up in 10 ml. of ethyl acetate, treated with Norite and the solvent again removed. Treatment of the residue with hexane resulted in the deposition of 270 mg. (61%) of crystals, m.p. 127–129°. These, after recrystallization from an ethanol–hexane mixture, gave large flat needles; m.p. 138.5–139.5°, $[\alpha]^{32}D$ +115° (*c* 0.055, ethanol).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.61; H, 7.89.

The **methiodide of dihydro-α-erythroidine** was obtained by boiling a solution of 100 mg. of dihydro-α-erythroidine and 3 ml. of methyl iodide in 5 ml. of absolute ethanol under reflux for one hour. Removal of the solvent and addition of hexane gave 150 mg. of a yellow solid, m.p. 220–222° dec. This, after recrystallization from ethanol, gave white crystals, m.p. 221.5–223.5° dec.

Anal. Calcd. for $C_{17}H_{24}NO_3I$: C, 48.93; H, 5.80. Found: C, 48.98; H, 5.80.

Des-N-methyldihydro-α-erythroidinol (VI).—A solution of 11.8 g. of the methiodide of dihydro-α-erythroidinol in 100 ml. of water was passed over an ion-exchange column (Amberlite I.R. A-400-OH) to convert it to the corresponding methohydroxide derivative. The eluate was combined with the washings (1,500 ml. of water) from the column and concentrated *in vacuo*, after which the residue was distilled using a short-path still to give 6.50 g. (89%) of a pale yellow gum; b.p. (pot temperature) 160–220° at 0.03 mm., $[\alpha]^{25}D$ +55.2° (*c* 0.07, ethanol).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87. Found: C, 73.13; H, 9.02.

The **methiodide of des-N-methyldihydro-α-erythroidinol** was obtained by boiling a solution of 6.50 g. of des-N-methyldihydro-α-erythroidinol and 50 ml. of methyl iodide

(20) K. Florey and M. Ehrenstein (*J. Org. Chem.* **19**, 1331 (1954)) have found that the two epimers, Δ⁴-pregnene-6α,17α,21-triol-3,20-dione and Δ⁴-pregnene-6β,17α,21-triol-3,20-dione, show a difference of 5 mμ in the wave length of their absorption maximum; see also, L. Dorfman, *Chem. Revs.*, **53**, 72 (1953).

(21) (a) V. Georgian, *Chemistry and Industry*, 930 (1954); (b) A. Marchant and A. R. Pinder, *ibid.*, 1261 (1954).

(22) R. B. Woodward, THIS JOURNAL, **64**, 76 (1942).

(23) All melting points are corrected. Analyses by V. Williams, A. E. Smith, W. Manser and the Micro-Tech Laboratories. Infrared spectra were determined by C. Whiteman, Jr.

(24) V. Boekelheide and T. T. Grossnickle, unpublished results.

in 50 ml. of absolute ethanol under reflux for 15 minutes. Removal of the solvent gave 6.38 g. (63%) of a white solid. This, on recrystallization from absolute ethanol, yielded 6.12 g. of white crystals; m.p. 220–221°, $[\alpha]^{27}D$ −7.2° (*c* 0.06, water).

Anal. Calcd. for $C_{17}H_{26}NO_2I$: C, 50.63; H, 6.50; N, 3.47; $-OCH_3$, 0.00. Found: C, 50.82; H, 6.78; N, 3.15; $-OCH_3$, 0.00.

Oxidation of the Methohydroxide of Des-N-methyldihydro-α-erythroidinol to *o*-Phthalic Acid.—A sample of 414 mg. of the methiodide of des-N-methyldihydro-α-erythroidinol was converted to the corresponding methohydroxide by passage over an ion-exchange column as described above. The resulting gummy methohydroxide was oxidized using 75 ml. of an aqueous 3% solution of potassium permanganate following the general procedure given previously for the oxidation of des-N-methyldihydro-β-erythroidinol.[5] There was obtained 110 mg. (64%) of *o*-phthalic acid, m.p. 165–180°, which on sublimation gave 56 mg. of *o*-phthalic anhydride, m.p. 124–128°. This, after treatment with an aqueous methylamine solution followed by sublimation, gave 27 mg. of white needles, m.p. 132–132.5°. A mixture of this material and authentic N-methylphthalimide showed no depression of melting point and the infrared spectra of the naturally-derived sample and the synthetic sample were identical.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38. Found: C, 66.83; H, 4.65.

Des-N,N-dimethyldihydro-α-erythroidinol (VIII).—A solution of 6.28 g. of the methiodide of des-N-methyldihydro-α-erythroidinol in 150 ml. of water was converted to the corresponding methohydroxide derivative by passage over an ion-exchange column as before. Concentration of the eluate followed by distillation of the residue using a short-path still gave 3.88 g. (90%) of a colorless, viscous oil; b.p. (pot temperature) 180–210° at 0.01 mm., $[\alpha]^{26}D$ +21.4° (*c* 0.06, ethanol).

Anal. Calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.24; H, 9.26; N, 5.04.

Ozonolysis of Des-N,N-dimethyldihydro-α-erythroidinol.—A stream of oxygen containing about 2% ozone was passed through a solution of 110 mg. of des-N,N-dimethyldihydro-α-erythroidinol (VIII) in 20 ml. of ethyl chloride maintained at 0° until there was evidence that ozone was no longer being rapidly absorbed. The ethyl chloride solution was then added to a mixture of 10 ml. of water and 300 mg. of zinc dust and warmed to remove the ethyl chloride. After the mixture remaining had been warmed for 5 minutes on a steam-bath, it was steam distilled and the first 10 ml. of aqueous distillate was added to a hot solution of 300 mg. of 5,5-dimethyldihydroresorcinol (dimedon) in 30 ml. of 50% aqueous ethanol. There separated 33 mg. (28%) of white needles, m.p. 187–188.5°. A mixture of this sample and an authentic sample of the dimedon derivative of formaldehyde showed no depression of melting point.

Des-N,N-dimethyltetrahydro-α-erythroidinol (IX).—A solution of 970 mg. of des-N,N-dimethyldihydro-α-erythroidinol (VIII) in 260 ml. of absolute ethanol was hydrogenated at room temperature and atmospheric pressure using Raney nickel as catalyst. After one mole of hydrogen was absorbed (3 min.), the hydrogenation was stopped and the catalyst and solvent were removed. The residual oil was dissolved in ethyl acetate, treated with Norite and then concentrated. This gave an oil which was apparently a mixture of basic and non-basic material. Therefore, the residue was taken up in 12 ml. of 3 *N* hydrochloric acid and extracted with chloroform. The chloroform extracts yielded 65 mg. of a non-basic oil, presumably the result of internal elimination of the dimethylamino group. Neutralization of the acid solution with aqueous sodium carbonate solution followed by chloroform extraction gave 915 mg. (93%) of a colorless oil, $[\alpha]^{25}D$ +19.8 (*c* 0.04, ethanol). Attempts to purify this oil by distillation led to decomposition and so the oil was converted directly to the corresponding methiodide derivative.

The **methiodide of des-N,N-dimethyltetrahydro-α-erythroidinol (IX)** was prepared by treating 2.89 g. of the above oil in 20 ml. of absolute ethanol with 20 ml. of methyl iodide at room temperature for 20 hr. After removal of the solvent, the residual solid was dissolved in absolute ethanol, treated with Norite and then the solution was concentrated to a volume of 17 ml. and allowed to stand. There separated 3.67 g. (84%) of cream-colored prisms; m.p. 93–94°, $[\alpha]^{24}D$ −8.7 (*c* 0.05, water).

Anal. Calcd. for $C_{18}H_{30}NO_2I$: C, 51.55; H, 7.21; N, 3.34; I, 30.27. Found: C, 50.95; H, 7.14; N, 3.14; I, 30.70.

When 54 mg. of the methiodide of des-N,N-dimethyltetrahydro-α-erythroidinol was oxidized with a solution of 370 mg. of potassium permanganate in 10 ml. of water following the same general procedure used previously in the β-erythroidine series,[5] there resulted after sublimation a minute quantity of a crystalline acid. That this product was *o*-ethylbenzoic acid was established by comparative paper chromatography with an authentic sample of this acid. The R_f values determined for the synthetic and naturally-derived samples of *o*-ethylbenzoic acid were 0.713 and 0.716, respectively.

Des-N,N-dimethylhexahydro-α-erythroidinol (XIII).—To 100 ml. of ethanol containing 50 mg. of prereduced platinum oxide catalyst there was added 1 ml. of concentrated hydrochloric acid and 287 mg. of des-N,N-dimethyldihydro-α-erythroidinol (VIII). When this mixture was subjected to hydrogenation at room temperature and atmospheric pressure, absorption of two moles of hydrogen was complete in 42 minutes. After removal of the catalyst and solvent, the residual oil was taken up in water and extracted with chloroform to remove non-basic material. Concentration of the chloroform extracts and distillation of the residue gave 109 mg. of an oil which from its composition and physical properties appeared to be identical with desazahexahydro-α-erythroidinol (XVIII). The aqueous solution was then made basic with an aqueous solution of sodium carbonate and again extracted with chloroform. Concentration of this chloroform extract followed by distillation of the residue gave 150 mg. of a colorless oil; b.p. (pot temperature) 150° at 0.005 mm., $[\alpha]^{25}D$ +4.7 (*c* 0.059, ethanol).

Anal. Calcd. for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.48. Found: C, 72.51; H, 10.03.

When 381 mg. of des-N,N-dimethyltetrahydro-α-erythroidinol (IX) was subjected to hydrogenation following the same procedure described above, hydrogen absorption corresponded to one mole after 75 minutes. From the reaction mixture there was isolated 174 mg. of an oil having the same physical properties and ultraviolet absorption spectrum as XIII and 163 mg. of an oil having the same physical properties as desazahexahydro-α-erythroidinol (XVIII). The fact that so large a fraction of the starting material should be converted to XVIII under the rather mild conditions of hydrogenation is quite surprising. It should be pointed out that the hydrogenation product of this reaction, des-N,N-dimethylhexahydro-α-erythroidinol (XIII), has an ultraviolet absorption spectrum very similar to that of *o*-xylene as would be expected from the assigned structure.

Desazatetrahydro-α-erythroidinol (XI).—A solution of 3.02 g. of the methiodide of des-N,N-dimethyltetrahydro-α-erythroidinol in 50 ml. of water was passed over an ion-exchange column to convert it to the corresponding methohydroxide derivative in the same manner previously described. The combined eluate and aqueous washings from the column were concentrated and the residual oil was distilled using a short-path still. This gave 1.45 g. (87%) of a colorless oil; b.p. (pot temperature) 80–100° at 0.001 mm., $[\alpha]_D^{25}$ +21.9 (*c* 0.064, ethanol).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.64, 77.47; H, 8.90, 8.98.

The **mono *p*-phenylazobenzoate of desazatetrahydro-α-erythroidinol** was obtained by treating 103 mg. of the above oil with 123 mg. of *p*-phenylazobenzoyl chloride[25] in 2 ml. of pyridine at 60° for 10 minutes. When the resulting solution was poured into 8 ml. of water, a precipitate separated which was filtered and washed with aqueous sodium carbonate. This gave 177 mg. (94%) of orange crystals, m.p. 89–93°. Several recrystallizations of this product from an ethanol–water mixture gave 58 mg. of fine orange needles; m.p. 101–102°, $[\alpha]^{25}D$ +17.3 (*c* 0.02, diethyl ketone).

Anal. Calcd. for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.56; H, 6.65; N, 6.65.

(25) G. H. Coleman, G. H. Nichols, C. M. McKloskey and H. D. Anspon, *Org. Syntheses*, **25**, 87 (1945).

Oxidation of Desazatetrahydro-α-erythroidinol (XI) to *o*-Ethylbenzoic Acid (X).—A suspension of 283 mg. of desazatetrahydro-α-erythroidinol (XI) in 12 ml. of water was treated with a solution of 1.17 g. of potassium permanganate in 35 ml. of water. The mixture was warmed until the permanganate color disappeared, after which it was acidified with hydrochloric acid and clarified by bubbling sulfur dioxide through the solution. The resulting solution was extracted several times with ether and the combined ether extracts were then extracted in turn with two 5-ml. portions of 10% aqueous sodium bicarbonate solution. Acidification of the alkaline extract precipitated 14 mg. (8%) of a white solid, m.p. 58–62.5°. Treatment of an ethanol solution of this solid with Norite followed by recrystallization of the product from an ethanol–water mixture gave white crystals, m.p. 63.5–65°. A mixture of this sample and an authentic sample of *o*-ethylbenzoic acid (X) showed no depression of melting point. Also, the infrared spectra of the naturally-derived and synthetic samples of *o*-ethylbenzoic acid were identical.

Oxidation of Desazatetrahydro-α-erythroidinol to *o*-Ethylphenyl 3-Tetrahydrofuranyl Ketone (XII).—To a solution of 398 mg. of desazatetrahydro-α-erythroidinol (XI) in 30 ml. of acetone there was added 500 mg. of magnesium sulfate and 110 ml. of a 1% solution of potassium permanganate in acetone. The oxidation was allowed to proceed at 0° for 8.5 hours before it was stopped by adding a solution of 6.0 g. of sodium thiosulfate in 17 ml. of water. After the precipitated manganese dioxide had been removed by filtration, the acetone solution was concentrated to a small volume and 1.0 g. of potassium hydroxide was added. The resulting solution was extracted with ether; the combined ether extracts were washed with base, dried over magnesium sulfate, and concentrated *in vacuo*. This gave 215 mg. of a residual yellow oil which was taken up in benzene and chromatographed over Florisil. From the first 30 ml. of eluate there was obtained 164 mg. of an oil which was then purified by distillation using a short-path still. There was obtained 70 mg. of a colorless, mobile oil; b.p. (pot temperature) 45° at 0.001 mm., $[\alpha]^{26}D$ +7.2 (*c* 0.013, ethanol).

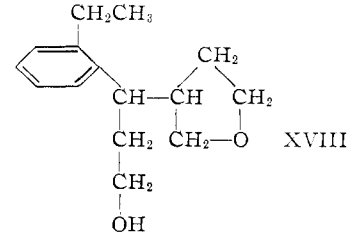
Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.31, 76.41; H, 8.07, 8.10.

Although several attempts were made to obtain solid derivatives of XII, these were unsuccessful. This is not too surprising in view of the hindered nature of the carbonyl group. However, as discussed in the previous section, the ultraviolet and infrared absorption spectra of this material are so characteristic that no alternative structure appears suitable.

Desazahexahydro-α-erythroidinol (XVIII).—A solution of 162 mg. of des-N,N-dimethylhexahydro-α-erythroidinol (**XIII**) in 5 ml. of absolute ethanol containing 5 ml. of methyl iodide was boiled under reflux for 1.5 hours. After removal of the solvent, the resulting methiodide was obtained as a gum which failed to crystallize and so it was converted directly to the corresponding methohydroxide derivative by passage of an aqueous solution of the gum over an ion exchange column (Amberlite I.R. A-400-OH). Concentration of the combined eluate and washings from the column gave an oil which was distilled using a short-path still. There was obtained 83.6 mg. of a colorless, mobile oil; b.p. (pot temperature) 150° at 0.02 mm., $[\alpha]^{25}D$ +13.2° (*c* 0.009, ethanol).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 76.83, 76.22; H, 10.15, 9.58.

The ultraviolet absorption spectrum of this compound was almost identical with that of XIII and was very similar to that of *o*-xylene. Its infrared absorption spectrum does not show the expected peaks for a terminal vinyl group but instead has absorption peaks at 6.91, 7.33, 8.29, 9.41 and 11.06 μ, indicating the presence of a tetrahydrofuran ring. For these reasons this product has been assigned structure XVIII. Thus, this is a second instance in which the Hofmann elimination proceeds by internal displacement of the trimethylamino group with formation of a tetrohydrofuran ring and shows that this type of elimination is not unusual or peculiar to the ring system present in IX.



XVIII

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, AYERST, MCKENNA AND HARRISON, LTD.]

Some New Hypotensive Ester Alkaloids from *Veratrum viride*

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The isolation from commercial *Veratrum viride* of the five hypotensive ester alkaloids isogermidine, germbudine, neogermbudine, desacetylneoprotoveratrine and veratetrine (neoprotoveratrine) is described. Isogermidine is the diester germine monoacetate-mono-α-methylbutyrate. Germbudine is a diester of the alkamine germine which gives on hydrolysis germine, α-methylbutyric acid and the high melting diastereoisomer of α,β-dihydroxy-α-methylbutyric acid (m.p. 99–100°). Neogermbudine is a new diester of germine in which the esterifying groups are α-methylbutyric acid and the low-melting diastereoisomer of α,β-dihydroxy-α-methylbutyric acid. Desacetylneoprotoveratrine is a known triester of protoverine which gives on hydrolysis one mole each of acetic acid, α-methylbutyric acid and the high melting isomer of α,β-dihydroxy-α-methylbutyric acid. Veratetrine has been shown to be a tetraester of protoverine in which the esterifying acids are two moles of acetic acid and one mole each of α-methylbutyric acid and the high melting α,β-dihydroxy-α-methylbutyric acid. It has been shown to be identical to the alkaloid neoprotoveratrine. The structures of the naturally occurring high and low melting isomeric α,β-dihydroxy-α-methylbutyric acids obtained by hydrolysis of some of these ester alkaloids, have been confirmed by the synthesis of the racemic form of the former and both the racemic and resolved optical isomers of the latter, from hydroxylation of tiglic acid. The infrared absorption spectra of these hypotensive alkaloids are recorded for identification purposes.

Previous communications have disclosed the isolation of the hypotensive ester alkaloids germbudine, isogermidine, veratetrine[1] and desacetylneoprotoveratrine[2] from commercial *Veratrum viride*. This report presents further findings on their constitution together with the isolation of the new hypotensive ester neogermbudine.

The benzene-extractable alkaloids obtained from the ground roots and rhizomes of commercial *Veratrum viride* using the procedure of Jacobs and Craig[3]

(1) G. S. Myers, W. L. Glen, P. Morozovitch, R. Barber and G. A. Grant, THIS JOURNAL, **74**, 3198 (1952).

(2) M. W. Klohs, M. D. Draper, F. Keller, W. Malesh and F. J. Petracek, *ibid.*, **75**, 3595 (1953).

(3) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **160**, 555 (1945).