Erythrina Alkaloids. A Study of the Configurational Interrelationships[1]

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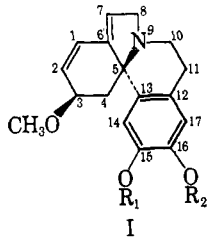
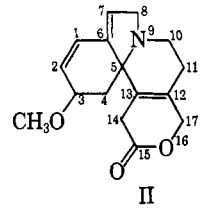
By the method of molecular rotation differences and by optical rotatory dispersion measurements the aromatic erythrina alkaloids and the erythroidines are shown to have the same configuration at the spiro carbon atom (position 5). Studies directed toward a chemical proof of the configurational interrelationships are described.

The nine known erythrina alkaloids fall into two classes: the aromatic erythrina alkaloids and the erythroidines.[5] The general structure representing most of the aromatic erythrina alkaloids is shown by I and that of β-erythroidine is given by II. α-Erythroidine differs from β-erythroidine in having the aliphatic double bond linking the 13–14- rather than the 12–13-positions, but, since α-erythroidine has been isomerized to β-erythroidine, the configurations at C-3 and C-5 for both α- and β-erythroidine are the same.[6] Likewise, with the exception of erythratine, all of the aromatic erythrina alkaloids have been interrelated and shown to have the same configuration of the spiro carbon atom, C-5.[7] Further, from an X-ray crystallographic study of erythraline hydrobromide[8] and from chemical studies of erysodine and the proof of its structure through synthesis,[9] the relative configurations at C-3 and C-5 are known for the aromatic erythrina alkaloids and the methoxyl and spiro amine groups have a *cis* relationship as shown by I.



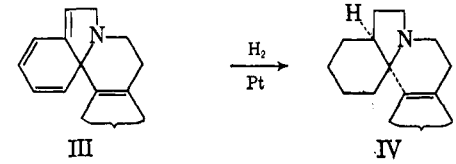
I



II

Thus, for a complete assignment of absolute configurations to essentially all of the erythrina alkaloids only two pieces of information are lacking: (1) a correlation of configuration between the aromatic erythrina alkaloids and the erythroidines, and (2) a determination of the absolute configuration of C-3 or C-5 in one of the alkaloids. The present paper is concerned with the correlation of configuration between the two groups of alkaloids and an accompanying paper describes the determination of the absolute configuration of C-3 in β-erythroidine.[10]

One of the typical reactions encountered in the degradation studies of both the aromatic erythrina alkaloids and the erythroidines was the loss of methanol on treatment with acid to give the corresponding conjugated triene as shown by partial structure III.[11,12] All of the derivatives represented by III have very high negative rotations and on hydrogenation over a platinum catalyst the corresponding saturated derivatives, as represented by partial structure IV, are formed. Since the various molecules represented by structure IV possess only one asymmetric carbon atom, the spiro



III IV

carbon at C-5, and since hydrogenation over platinum leads to a single product which should have the same stereochemistry in each case, all of the requirements for determining the configurational relationships at C-5 by the method of molecular rotation differences[13,14] are met in an ideal fashion. In Table I, the molecular rotations of various examples of both the aromatic erythrina alkaloids and the erythroidines are summarized with regard to those derivatives containing the structural features of III and IV. It is readily apparent that in each case the molecular rotation difference has the same sign and is a large value. Thus, it is safe to conclude that the absolute configuration

TABLE I

MOLECULAR ROTATIONS OF ERYTHRINA DERIVATIVES

Parent alkaloid	Molecular rotation of derivative Structure III	Structure IV	Molecular rotation difference
Erythraline	−2107[a,b]	−95[a]	−2012
Erysodine	−2577[a]	−92[a]	−2485
β-Erythroidine	−1901[c]	−128[c]	−1773
α-Erythroidine	−1952[a,d]	−136[a,e]	−1816

[a] Measured in water. [b] Measured as the hydrobromide. [c] Measured in ethanol. [d] Measured as the perchlorate. [e] This value is for the hexahydrodesmethoxy-β-erythroidine perchlorate which corresponds to the reduction product in this case (see ref. 6).

(1) Paper XVIII in this series. For the preceding communication, see ref. 5.

(2) University of Oregon, Eugene, Ore.

(3) Abstracted from the Ph.D. thesis of M. Y. Chang, University of Rochester, 1959.

(4) Research fellowship grants from the United Cerebral Palsy Association, the Elon Huntington Hooker Fund, the Smith, Kline and French Foundation, Chas. Pfizer and Co., and the Sherman Clarke Fund are gratefully acknowledged.

(5) For a summary of the chemistry of the erythrina alkaloids, see R. H. F. Manske, "The Alkaloids," Vol. VII, Academic Press, New York, N. Y., 1960, Chapter 11.

(6) V. Boekelheide and G. C. Morrison, *J. Am. Chem. Soc.*, **80**, 3905 (1958).

(7) The numbering of the erythrina alkaloids follows that devised earlier as a common numbering for all the erythina alkaloids [V. Boekelheide and V. Prelog, "Progress in Organic Chemistry," Vol. III, J. W. Cook, Ed., Butterworths, Scientific Publications, London, 1955, Chapter 5].

(8) W. Nowacki and G. F. Bonsma, *Z. Kryst.* **110**, 89 (1958).

(9) V. Prelog, A. Langemann, O. Rodig, and M. Ternbah, *Helv. Chim. Acta*, **42**, 1301 (1959).

(10) V. Boekelheide and G. Wenzinger, *J. Org. Chem.*, **29**, 1307 (1964).

(11) G. L. Sauvage and V. Boekelheide, *J. Am. Chem. Soc.*, **72**, 2062 (1950); V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage, and E. J. Agnello, *ibid.*, **75**, 2550 (1953); V. Boekelheide and M. F. Grundon, *ibid.*, **75**, 2563 (1953).

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

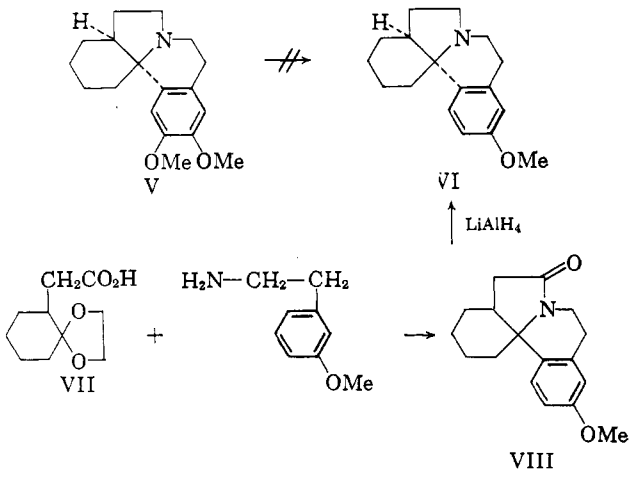
(13) K. Freudenberg, *Ber.*, **66**, 177 (1933).

(14) W. Klyne, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, Chapter 3.

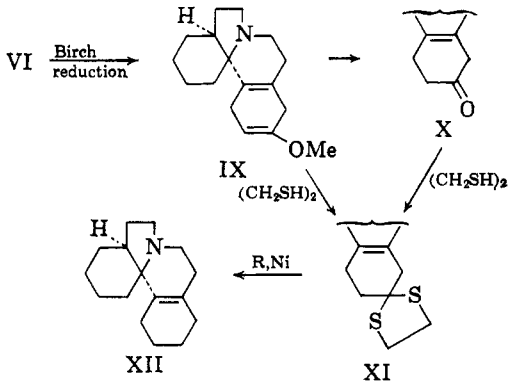
of the spiro carbon, C-5, is the same for both the erythroidines and the aromatic erythrina alkaloids.

Comparison by optical rotatory dispersion was also investigated. In the case of the aromatic erythrina alkaloids, hexahydroapoerysotrine (V) has been a key compound for interrelating the various alkaloids,[12] and its structure has been established by synthesis.[15-17] Mondon has clearly shown through an extension of his earlier synthetic studies that V has the *cis*-octahydroindole ring fusion shown by V.[18,19] The levorotatory enantiomorph of V, which corresponds to the natural series and is commonly designated as (−)-15,16-dimethoxy-*cis*-5,6-erythrinane, has been examined and its optical rotatory dispersion curve is almost superimposable with that of β-tetrahydro-β-erythroidine throughout the region of 320 to 650 mμ (see Experimental).[20] Although no Cotton effect is observed in this region, the close correspondence of the curves and the fairly large rotations observed strongly suggest that the two derivatives must have the same configuration at the spiro carbon atom, C-5, which is in agreement with the conclusions reached previously.

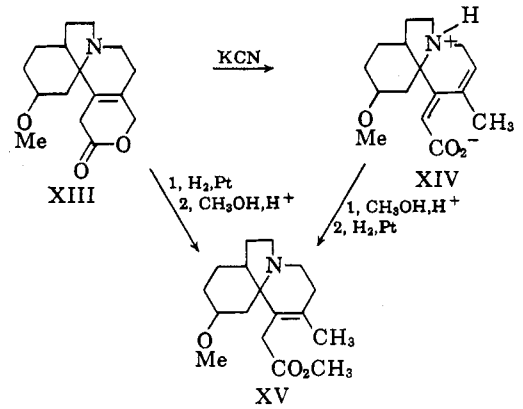
It was of interest to investigate a chemical correlation of the configuration at C-5 as well, both as a complement to the optical method and because of the intrinsic interest in these compounds. 14,15, 16,17-Tetrahydroerythrinane (XII) was the compound chosen for comparison. It was anticipated that the degradation of a member of the aromatic erythrina alkaloids to this compound and the synthetic elaboration of β-erythroidine to this stage would be tasks of comparable difficulty. Since the readily available (−)-15,16-dimethoxyerythrinane (V) has been shown to be identical with hexahydroapoerysotrine and, therefore, has the same configuration at C-5 as the naturally occurring aromatic erythrina alkaloids,[15,17] this was selected as a starting material. However, various attempts to convert it to a monomethoxyerythrinane such as VI were without success. The independent synthesis of VI was then carried out following the Mondon procedure.[16] Condensation of *m*-methoxyphenethylamine with the ketal acid VII occurred smoothly in 70% yield to give VIII which on lithium aluminum hydride reduction led to 16-methoxyerythrinane (VI) in essentially quantitative yield.



Resolution of 16-methoxyerythrinane was readily accomplished using dibenzoyl-L-(+)-tartaric acid. The levorotatory enantiomorph and (−)-15,16-dimethoxyerythrinane were compared through their dibenzoyl-L-(+)-tartrate derivatives and shown to have essentially superimposable optical rotatory dispersion curves. Thus, it is clear that (−)-16-methoxyerythrinane has the same configuration at C-5 as the natural series and so the remaining steps in the degradation to XII were explored. A Birch reduction of racemic 16-methoxyerythrinane proceeded cleanly in 80% yield to the dihydro derivative IX. Acid hydrolysis of IX gave the corresponding ketone X which could be isolated as the picrate but was rather unstable as the free base. Reaction of the ketone X with 1,2-ethanedithiol readily gave the thioketal XI. Later it was found that the enol ether IX was converted directly to the thioketal XI by treatment with 1,2-ethanedithiol and this is a more efficient procedure. Finally, Raney nickel desulfurization of the thioketal XI yielded 14,15,16,17-tetrahydroerythrinane (XII) identical in all respects with the racemic 14,15,16,17-tetrahydroerythrinane prepared previously by independent syntheses.[17]



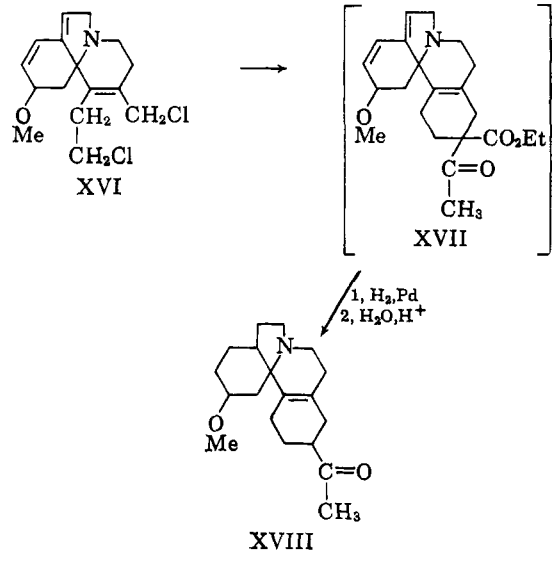
With a route thus available for obtaining optically active 14,15,16,17-tetrahydroerythrinane related to the aromatic alkaloids, attention turned to the conversion of β-erythroidine to an intermediate of the same structure. Although hexahydrodesmethoxy-β-erythroidine is the logical starting material for conversion to XII, the more readily accessible tetrahydro-β-erythroidine (XIII) was employed in the preliminary studies directed toward finding a suitable method for transform-



(15) B. Belleau, *Can. J. Chem.*, **35**, 651 (1957).
(16) A. Mondon, *Angew. Chem.*, **68**, 578 (1956).
(17) V. Boekelheide, M. Müller, J. Jack, T. T. Grossnickle, and M. Chang, *J. Am. Chem. Soc.*, **81**, 3955 (1959).
(18) A. Mondon, *Ann.*, **628**, 123 (1959).
(19) A. Mondon and K. F. Hansen, *Tetrahedron Letters*, [**14**], 5 (1960).
(20) We are indebted to Professor W. C. Wildman for these measurements which were made at the National Heart Institute, Washington, D. C.

ing the δ-lactone ring to a cyclohexene ring. One method investigated for introducing the extra carbon needed was the SN2 displacement of the allylic ester grouping by cyanide ion. However, the expected displacement did not occur; instead, the cyanide ion served as a base effecting elimination with ring opening to give XIV. The structure of XIV is based on spectral data plus its conversion *via* esterification and hydrogenation to a product identical with that obtained by direct hydrogenolysis of XIII followed by esterification.

It has been shown previously that β-erythroidine on reduction with lithium aluminum hydride to the diol followed by reaction with thionyl chloride gives the dichloro derivative XVI.[21] This seemed an attractive starting material and, on treating it with ethyl acetoacetate in *t*-butyl alcohol using potassium *t*-butoxide as catalyst, condensation was effected to give XVII. This product was unstable and difficult to purify. It was, therefore, hydrogenated and then hydrolyzed directly to give the ketone XVIII. However, attempts to remove the acetyl group and to utilize this as a route for the conversion of β-erythroidine to 14,15,16,-17-tetrahydroerythrinane have been unsuccessful.



In view of the chemical determination of the absolute configuration of C-3 in β-erythroidine[22] and the recent X-ray crystallographic study of Hanson[23] defining the relative and absolute configurations of dihydro-β-erythroidine hydrobromide, the absolute configurations of both the erythroidines and the aromatic erythrina alkaloids can now be assigned[10] and work directed toward a chemical correlation of the two groups has been terminated.

Experimental[24]

16-Methoxy-8-oxoerythrinane (VIII).—A mixture of 388 mg. of *m*-methoxyphenethylamine hydrochloride[25] and 485 mg. of the ketal acid VII[17] was heated under a nitrogen atmosphere with stirring for 5 hr. The resulting viscous oil was dissolved in chloroform and washed successively with dilute aqueous hydrochloric acid, aqueous sodium carbonate, and then water. The chloroform solution was dried over sodium sulfate and then chromatographed over neutral alumina (Woelm, grade III). Concentration of the eluate gave an oil which crystallized on standing. This was recrystallized from ether to give 393 mg. (70%) of white crystals, m.p. 111–112°, $\gamma_{C=O}$ 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80. Found: C, 75.08; H, 7.65.

16-Methoxyerythrinane (VI).—A solution of 730 mg. of the lactam VIII in 100 ml. of dry benzene was added with stirring to a boiling solution of 2.0 g. of lithium aluminum hydride in 60 ml. of ether. After the mixture had boiled under reflux for 18 hr., it was cooled and the excess lithium aluminum hydride was destroyed with ethyl acetate. Dropwise addition of a saturated aqueous solution of sodium sulfate was continued until the metallic hydroxides separated as a granular precipitate. The precipitate was removed by filtration and the filtrate was extracted with 5 *N* hydrochloric acid. When the acidic solution was made basic, the oil that separated was extracted with ether and dried; the ether solution was concentrated. Distillation of the residue using a short-path still gave 688 mg. of a light yellow oil, b.p. 115–140° (10^{-2} mm.). This was converted directly to the picrate which, after recrystallization from acetone, melted at 171–173° dec.

Anal. Calcd. for $C_{23}H_{26}N_4O_8$: C, 56.78; H, 5.39. Found: C, 56.77; H, 5.44.

The **resolution** of VI was carried out by adding dropwise a solution of dibenzoyl-L-(+)-tartaric acid in ethyl acetate to a solution of the amine (regenerated from the picrate) in ethyl acetate. The precipitate was recrystallized from acetone several times until its melting point remained constant. It was obtained as white crystals, m.p. 126–127°, $[\alpha]^{26}D$ −91.46° (*c* 1.04, ethanol).

Anal. Calcd. for $C_{35}H_{37}NO_9$: C, 68.28; H, 6.06. Found: C, 68.16; H, 6.01.

In a similar manner treatment of the amine with dibenzoyl-D-(−)-tartaric acid yielded, after recrystallization from acetone, white crystals, m.p. 124–125°, $[\alpha]^{29}D$ +92.61° (*c* 1.04, ethanol).

Anal. Calcd. for $C_{35}H_{37}NO_9$: C, 68.28; H, 6.06. Found: C, 67.98; H, 6.42.

Optical Rotatory Dispersion Studies.[20]—The general comparison of the optical rotatory dispersion curves and the indication of their close correspondence is described in the discussion. This information is presented in Table II for selected points from the curve.

14,17-Dihydro-16-methoxyerythrinane (IX).—To a stirred solution of 620 mg. of 16-methoxyerythrinane (VI) in 55 ml. of anhydrous ether there was added 70 ml. of liquid ammonia followed by 160 mg. of lithium as small pieces. After 10 min., absolute ethanol was added dropwise at such a rate that the blue color was discharged in about 10 min. The ammonia was allowed to evaporate and water was added to the residue. Then, the basic aqueous solution was extracted with ether and the combined ether extracts, after washing with water, were dried over sodium sulfate. Concentration of the ether solution gave a solid which was sublimed at 70–80° (0.1 mm.). This gave 500 mg. (80%) of white crystals, m.p. 84–86°.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.72. Found: C, 78.33; H, 9.58.

The **picrate** of **IX** was prepared in ethanol and, after recrystallization from acetone, was isolated as yellow crystals, m.p. 157–160° dec.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.55; H, 5.78. Found: C, 56.54; H, 5.97.

14,15,16,17-Tetrahydro-16-oxoerythrinane (X).—Sufficient methanol was added to dissolve 149 mg. of 14,17-dihydro-16-methoxyerythrinane (IX) and then a solution of 500 mg. of oxalic acid dihydrate in 6.5 ml. of water was added dropwise with swirling until the solution became cloudy. The mixture was allowed to stand at room temperature for 1 hr. and then it was cooled in an ice bath and made basic by addition of sodium bicarbonate.

(21) M. F. Grundon, G. L. Sauvage, and V. Boekelheide, *J. Am. Chem. Soc.*, **75**, 2541 (1953).

(22) G. R. Wenzinger and V. Boekelheide, *Proc. Chem. Soc.*, 53 (1963).

(23) A. W. Hanson, *ibid.*, 52 (1963).

(24) Analyses were by A. Smith, T. Montzka, and the Micro-Tech Laboratories. All melting points are corrected.

(25) L. Helfer [*Helv. Chim. Acta*, **7**, 948 (1924)] has previously reported the preparation of *m*-methoxyphenethylamine but gives the melting point of the hydrochloride as 145–146°. Our sample of *m*-methoxyphenethylamine, prepared by the catalytic hydrogenation [K. Kindler, B. Hedemann, and E. Scharfe, *Ann.*, **560**, 215 (1948)] of 3-methoxy-β-nitrostyrene [J. B. Shoesmith and R. H. Connor, *J. Chem. Soc.*, 2232 (1927)] in 61% yield, agreed with Helfer's description in other respects but the hydrochloride melted at 136–137°. (*Anal.* Calcd. for $C_9H_{14}NOCl$: C, 57.60; H, 7.52. Found: C, 57.83; H, 7.43.)

TABLE II. OPTICAL ROTATORY DISPERSION, $[\alpha]_\lambda^{25}$

Compound	c	λ[a] 650	589	460	380	320
(+)-15,16-Dimethoxyerythrinane dibenzoyl-D-(−)-tartrate	0.89	+68	+90	+180	+345	+765
(−)-15,16-Dimethoxyerythrinane dibenzoyl-L-(+)-tartrate	0.95	−70	−93	−180	−350	−760
(−)-16-Methoxyerythrinane dibenzoyl-L-(+)-tartrate	0.79	−70	−90	−177	−350	−740
(−)-Tetrahydro-β-erythroidine dibenzoyl-L-(+)-tartrate	0.80	−60	−77	−157	−333	−710

[a] Run in ethanol, λ in mμ.

The basic solution was extracted with ether, the ether extracts were dried, and the solvent was removed under reduced pressure. This left 139 mg. of a yellow oil (carbonyl absorption at 1720 cm.$^{-1}$) which was unstable and purification attempts indicated rapid decomposition. It was, therefore, treated directly with ethanolic picric acid and the resulting solid, after recrystallization from ethanol, gave yellow crystals, m.p. 189–193 dec.

Anal. Calcd. for $C_{22}H_{26}N_4O_8$: C, 55.69; H, 5.52. Found: C, 55.38; H, 5.57.

14,15,16,17-Tetrahydro-16-oxoerythrinane Ethylene Thioketal (XI).—A solution of 130 mg. of X (regenerated from the picrate) in 200 mg. of 1,2-ethanedithiol was cooled in an ice bath and dry hydrogen chloride was bubbled through the mixture. At the end of 3 hr., the mixture was diluted with ether and the whole was made basic with a concentrated aqueous sodium hydroxide solution. The ether layer was separated, dried, and concentrated to give 147 mg. of a clear viscous oil (no carbonyl absorption in the infrared). This was converted directly to the picrate which, after recrystallization from methanol, was obtained as yellow crystals, m.p. 180–182°, liquid crystals, 186–189°. This melting point behavior was reproducible and unchanged by further recrystallization from methanol.

Anal. Calcd. for $C_{24}H_{30}N_4O_7S_2$: C, 52.35; H, 5.49; N, 10.18. Found: C, 52.30; H, 5.31; N, 10.21.

When 165 mg. of IX was treated directly with 1,2-ethanedithiol in the same manner as described above, it was converted in essentially quantitative yield to XI, isolated as the picrate. The picrates from the two preparations were shown to be identical by a mixture melting point determination and by comparison of their infrared spectra.

14,15,16,17-Tetrahydroerythrinane (XII).—An ethanolic solution of 231 mg. of XI containing prepared Raney nickel catalyst was boiled under reflux under 1 atm. of hydrogen for 11 hr. After removal of the catalyst, the solution was concentrated under reduced pressure to give 163 mg. of a colorless oil. This was converted to the picrate which, after recrystallization from ethanol, melted at 152–155°. This was shown to be identical with an authentic sample of the picrate of racemic 14,15,16,17-tetrahydroerythrinane prepared previously[17] by a mixture melting point determination and a comparison of infrared spectra.

Reaction of Tetrahydro-β-erythroidine (XIII) with Potassium Cyanide to Give XIV.[26]—A mixture of 1.05 g. of tetrahydro-β-erythroidine[11b] and 1.0 g. of potassium cyanide was slowly warmed without solvent under a nitrogen atmosphere. The mixture melted and at 160° some effervescence occurred. The temperature was allowed to rise to 200° before the mixture was removed and allowed to cool. It was then extracted with chloroform and examination of the chloroform extract in the infrared indicated the presence of the $\equiv NH^+$, $-OCH_3$, and $-C{=}CCOO^-$ functional groups as required by XIV. For ease of handling, the zwitterion XIV was then converted to the corresponding methyl ester by removing the chloroform and heating the residue with methanolic hydrogen chloride. After removal of the methanol the residue was subjected to chromatography over powdered cellulose using a series of aqueous citrate–phoshate buffers starting at a pH of 6 and extending to a pH of 2.5. The main product was isolated from the eluate at pH 4 by treatment with ammonia and extraction with ether. The ether extract, after drying and concentration, gave a pale yellow oil, b.p. 148–156° (0.003 mm.), R_f (pH 4.0) 0.36. As would be expected for the methyl ester of XIV, the n.m.r. spectrum in deuteriochloroform showed signals at τ 6.22 and 6.72 corresponding to the ester and ether methoxyls, signals at τ 4.15 and 4.35 corresponding to the vinyl protons, and a signal at τ 8.19 corresponding to the allylic methyl protons.

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81; $-OCH_3$, 21.31. Found: C, 69.89; H, 8.75; N, 4.71; $-OCH_3$, 20.89.

The above experiment was repeated but, instead of subjecting the ester to chromatography over powdered cellulose, it was hydrogenated using platinum as a catalyst. This was then followed by purification through countercurrent distribution using chloroform and a citrate–phosphate buffer (pH 4.2) with 40 exchanges. The main product, isolated from tubes 30–38, was obtained as a solid in 47% yield. This, after recrystallization from acetone, gave white crystals, m.p. 135–136°. By a mixture melting point determination and comparison of infrared spectra, this was shown to be identical with XV obtained in the hydrogenolysis experiment following.

Hydrogenolysis of Tetrahydro-β-erythroidine to Give XV.—A solution of 5.0 g. of β-erythroidine hydrochloride in 50 ml. of water containing 600 mg. of platinum oxide catalyst was subjected to hydrogenation at 3-atm. pressure and room temperature for 36 hr. After removal of the catalyst, the solution was made basic and extraction with chloroform. Concentration of the chloroform extract followed by conversion of the residue to its picrate derivative gave yellow crystals, m.p. 213–214°. These were shown to be identical with tetrahydro-β-erythroidine picrate and corresponded to a 22% yield.[27]

The aqueous basic solution was then evaporated to dryness and the residue was taken up in methanolic hydrogen chloride. This solution was boiled under reflux for 4 hr. to convert the acid to the corresponding methyl ester. It was then concentrated, the residue was treated with aqueous ammonia, and the solution was extracted with chloroform. Concentration of the chloroform gave 3.1 g. (68%) of a light tan solid. This, after recrystallization from acetone, yielded white prisms, m.p. 135–136°.

Anal. Calcd. for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.79; H, 8.88; N, 4.90.

16-Acetyl-3-methoxyl-14,15,16,17-tetrahydroerythrinane (XVIII).[28]—To a solution of 440 mg. of potassium in 75 ml. of dry *t*-butyl alcohol there was first added 1.46 g. of ethyl acetoacetate and then dropwise with stirring a solution of 3.53 g. of dichlorodesoxy-β-erythroidinol (XVI)[21] in 200 ml. of dry *t*-butyl alcohol. The solution was boiled under reflux for 20 min. and then, after an additional 440 mg. of potassium in 75 ml. of *t*-butyl alcohol was added, it was boiled under reflux for 6 hr. The precipitate was removed and the solution was concentrated to give 3.99 g. of an oil, which gave a negative Beilstein test for chloride. This oil was dissolved in 330 ml. of ethanol containing 2.5 ml. of concentrated hydrochloric acid and was subjected to hydrogenation using 2.5 g. of a 5% palladium-on-charcoal catalyst at room temperature and atmospheric pressure. After removal of the catalyst and solvent, the residual oil was dissolved in 150 ml. of 3 *N* hydrochloric acid and boiled under reflux for 5 hr. The cooled solution was made alkaline and extracted with benzene and then ether. The combined extracts were washed with water and then concentrated leaving 1.86 g. (58%) of an oil showing a strong carbonyl absorption at 5.85 μ. This was

(26) We thank Dr. K. Butler for working out the experimental details of this reaction.

(27) V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage, and E. J. Agnello, *J. Am. Chem. Soc.*, **75**, 2550 (1953).

(28) We thank Dr. T. T. Grossnickle for working out the experimental details of this reaction.

treated with ethanolic picrolonic acid to give 2.1 g. of yellow crystals, m.p. 213–215° dec. After recrystallization from ethanol, the picrolonate of XVIII was obtained as yellow crystals, m.p. 216–217° dec.

Anal. Calcd. for $C_{29}H_{37}N_5O_7$: C, 61.36; H, 6.57; N, 12.34. Found: C, 61.32; H, 6.28; N, 12.51.

Regeneration of the free base (XVIII) from the picrolonate followed by distillation using a short-path still gave a pale yellow oil, b.p. 150° (10^{-4} mm.), $[\alpha]^{25}$ +126.0°, $\lambda_{C=O}$ 5.85 μ.

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62 $-OCH_3$, 10.23. Found: C, 75.21; H, 9.40; N, 4.51; $-OCH_3$ 10.35.

The Absolute Configurations of the Erythrina Alkaloids[1]

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A degradation of β-erythroidine has been accomplished which allows a correlation between the absolute configuration of the asymmetric atom at C-3 of β-erythroidine and the levorotatory (3*S*)-3-methoxyadipic acid. This combined with other available data allows the assignment of the absolute configuration of β-erythroidine as 3*R*,5*S*. Further, the implications of these results with respect to the other erythrina alkaloids are discussed and absolute configurational assignments are made for these as well.

Although the erythrina alkaloids have been subjected to extensive degradative and synthetic investigations,[5] the relative and absolute configurations of these alkaloids have largely remained as important problems to be settled. In attempting to resolve these questions, we have approached the over-all problem from two points of view. First, the configurational relationships existing among the various erythrina alkaloids have been studied.[1] Secondly, we have undertaken the determination of the absolute configuration of one of the asymmetric atoms of one of the key alkaloids. The combination of data would thus allow complete configurational assignments for all the important erythrina alkaloids. The present communication presents the details of the accomplishment of these objectives.[6]

Of the asymmetric atoms present in the various erythrina alkaloids the most feasible one from the point of view of degradation and ease of correlation with a molecule of known absolute configuration appeared to be the asymmetric carbon at C-3 of β-erythroidine (I). From previous studies,[7,8] it was known that the spiro amine nitrogen is readily removed through a series of Hofmann degradations and by starting with tetrahydro-β-erythroidine (II) such a degradation might yield a derivative having the general features shown by III. Oxidation of III could then yield optically active β-methoxyadipic acid (IV) for which the absolute configuration of each enantiomorph is known[9] because of its role in the elucidation of the absolute configuration of steroids.[10,11]

Preliminary studies on the Hofmann degradation of tetrahydro-β-erythroidine (II), however, led to a mixture of products indicating that, in part, opening of the lactone ring was occurring followed by decarboxylation. To circumvent this the corresponding diol (V) was employed, but in this case the Hofmann reaction was accompanied by some dehydration, leading again to a mixture of products. Treatment of the diol V with phosphoric acid readily converted it to the dihydropyran derivative VI and this now underwent the Hofmann reaction smoothly and cleanly to give VII. The formation of VII being favored in the first step of the Hofmann reaction could be predicted by analogy to the behavior of tetrahydroerythraline[12] as well as from theoretical considerations.[13] The spectral properties of VII are in full accord with this assignment. In the infrared the characteristic absorption bands of a vinyl group are present at 900–915 and at 1000 $cm.^{-1}$. These disappear on hydrogenation. The ultraviolet absorption spectrum of VII has a broad maximum at 238 mμ (log ε 3.97) as would be expected.[14] Finally the n.m.r. spectrum of VII shows a clear quartet at τ 2.64 corresponding to the lone internal vinyl hydrogen and a pair of doublets centered at τ 5.07 corresponding to the terminal methylene protons. The approximate coupling constants for the *cis* and *trans* protons are 10.0 and 16.4 c.p.s.

(1) Paper XIX in this series. For the preceding communication, see V. Boekelheide and M. Chang, *J. Org. Chem.*, **29**, 1303 (1964).

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(3) Abstracted from the Ph.D. thesis of G. R. Wenzinger, University of Rochester, 1960.

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(5) For a summary of the chemistry of the erythrina alkaloids, see R. H. F. Manske, "The Alkaloids," Vol. VII, Academic Press, New York, N. Y., 1960, Chapter 11.

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