The Synthesis of Apo-β-erythroidine[1]

James Blake,[2] James R. Tretter, Gabor J. Juhasz,[3] William Bonthrone, and Henry Rapoport

Contribution from the Department of Chemistry, University of California, Berkeley, California. *Received April 23, 1966*

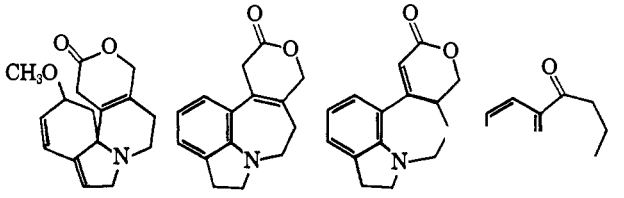
Abstract: The synthesis of apo-β-erythroidine (II) and isoapo-β-erythroidine (III) is reported. A major intermediate in this synthesis was 7-phenacylindoline (IXa) which was obtained from 4-phenyl-5-ethoxycarbonyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (VIIIa) by an interesting acid-catalyzed ring opening of the indole. Conversion of IXa to the 7-indolineacetic acid (XIVa) by the action of hydrazoic acid, followed by esterification, alkylation with methyl β-bromopropionate, cyclization, and decarboxylation, gave the tricyclic compound containing the fused seven-membered ring, 6-oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (XVII). The unsaturated δ-lactone necessary to complete the tetracycle was formed by first condensation with *t*-butyl glyoxylate to give the 7-*t*-butoxycarbonylmethylene derivative XXVIb. Then treatment of the latter with dimethyloxosulfonium methylide produced the epoxide rearrangement product, 6-hydroxymethyl-7-carboxymethylene-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]-indole δ-lactone (XXX). Hydrogenation of the diene lactone XXX gave both apo-β-erythroidine (II) and isoapo-β-erythroidine (III).

The compound β-erythroidine is a physiologically active alkaloid which has been isolated from several species of *Erythrina*, and has been assigned structure I by Boekelheide and co-workers[4] on the basis of spectral and degradative evidence. Treatment of β-erythroidine with phosphoric acid gave a rearranged demethoxy derivative, apo-β-erythroidine, which was isomerized on alumina to give isoapo-β-erythroidine;[5] structures II and III, respectively, were assigned to these products. Apo-β-erythroidine (II) is of interest because of its own physiological activity, for its relationship to the parent alkaloid, and because of its unusual fused tetracyclic structure, containing five-, six-, and seven-membered rings and an unsaturated δ-lactone.

The parent alkaloid, β-erythroidine, has not been synthesized, although the synthesis of anhydro-α-hexahydrodemethoxy-β-erythroidinol, which has the spiro system intact and which was also obtained directly from β-erythroidine, has been reported.[6,7]

More extensive work has been directed toward the synthesis of apo-β-erythroidine (II) and models thereof.[8-11] These efforts were unsuccessful, most notably owing to (1) the inability to synthesize appropriate 7-substituted indolines which in turn prevented synthesis of ketone IV,[8] (2) the lack of normal carbonyl reactivity in 1-methyl-2,3,4,5-tetrahydro-5-oxo-1H-1-benzazepine[9] (presumably because of nitrogen–carbonyl resonance interaction; see below for a further discussion of the carbonyl reactivity of vinylogous amides), and (3) the poor yields obtained in Friedel–Crafts ring closures.[8,10]

We now report the synthesis of apo-β-erythroidine (II) and isoapo-β-erythroidine (III). This synthesis was made possible, in part, by a partial reversal of the Fischer indole ring closure in the 1,2-dihydropyrrolo-[3,2,1-*hi*]indole series which constitutes a practical synthesis of 7-substituted indolines.



I II III

Discussion

The synthesis of apo-β-erythroidine (II) and isoapo-β-erthyroidine (III) will be considered in three stages: (A) formation of the 6,5,7-tricyclic ring system, (B) addition of the two-carbon fragment of the lactone ring, and (C) introduction of the one-carbon fragment and lactonization to give the final 6,5,7,6 tetracycle.

A. Formation of 6,5,7-Tricyclic Ring System. Previously the synthesis of 2,2a,3,4-tetrahydro-1H-cyclopent[*cd*]indene was reported,[12] and evidence of strain in this tricycle was noted. We then became interested in the nitrogen analog V, which in analogy to the carbocyclic system was also expected to evidence strain. Indeed, such strain should be more readily detectable owing to its effect on the p*K* and ultraviolet absorption spectrum of heterocycle V. Accordingly, 4-ethoxycarbonyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole was synthesized by Fischer ring closure of the hydrazone of 1-aminoindoline and ethyl pyruvate, although the main

(1) Part of these results have been reported in a preliminary communication: J. Blake, J. R. Tretter, and H. Rapoport, *J. Am. Chem. Soc.*, **87**, 1397 (1965).

(2) National Institutes of Health Predoctoral Fellow, 1962–1965.

(3) Deceased July 25, 1963.

(4) (a) See V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage, and E. J. Agnello, *J. Am. Chem. Soc.*, **75**, 2550 (1953), for a summary of the structural work on β-erythroidine; (b) also see V. Boekelheide in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp 201–227, for a recent summary of the structural work on the *Erythrina* alkaloids.

(5) (a) G. L. Sauvage and V. Boekelheide, *J. Am. Chem. Soc.*, **72**, 2062 (1950). (b) F. Koniuszy and K. Folkers, *ibid.*, **73**, 333 (1951), also isolated a derivative of β-erythroidine which they called apo-β-erythroidine. The latter differed in melting point and particularly in optical rotation from the apo-β-erythroidine isolated by Sauvage and Boekelheide,[5a] and thus was apparently impure or not the same compound.

(6) M. Muller, T. T. Grossnickle, and V. Boekelheide, *ibid.*, **81**, 3959 (1959).

(7) See A. Mondon and H. U. Menz, *Tetrahedron*, **20**, 1729 (1964), and A. Mondon and H. J. Nestler, *Angew. Chem.*, **76**, 651 (1964), for recent syntheses in the aromatic *Erythrina* series.

(8) W. G. Gall, B. D. Astill, and V. Boekelheide, *J. Org. Chem.*, **20**, 1538 (1955).

(9) B. D. Astill and V. Boekelheide, *J. Am. Chem. Soc.*, 77, 4079 (1955).

(10) B. D. Astill and V. Boekelheide, *J. Org. Chem.*, **23**, 316 (1958).

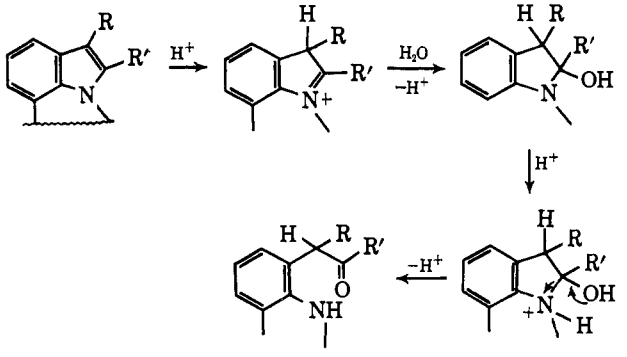
(11) V. Boekelheide and W. G. Gall, *ibid.*, **19**, 504 (1954).

(12) H. Rapoport and J. Pasky, *J. Am. Chem. Soc.*, **78**, 3788 (1956).

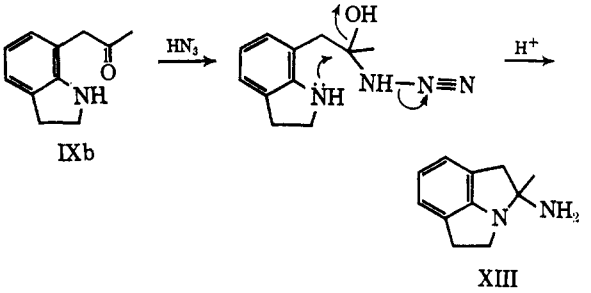
product of this reaction was the lactam, 1,2-dihydro-5-hydroxy-4H-pyrrolo[3,2,1-*ij*]quinolin-4-one.[13]

In an effort to increase the yield of pyrroloindole, we then studied the ring closure of the hydrazones (VI) of 1-aminoindoline and β-keto esters. Since the expected intermediate VII indicated that lactam formation would give a 6,5,5 tricycle, compared to the 6,5,6-lactam obtained from the pyruvate hydrazone,[13] lactam should not be as favored over normal indole ring closure, which also gives a 6,5,5 system. Indeed, when hydrazones VIa–c were treated with sulfuric acid in absolute ethanol, we obtained 4-phenyl-5-ethoxycarbonyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (VIIIa), the 4-methyl analog (VIIIb), and the 4-anisyl analog (VIIIc) in 83, 54, and 53% yields, respectively. In no case could we find evidence for the corresponding lactam (oxindole) formation.

Rather than the anticipated acids, aqueous acid hydrolysis of indoles VIIIa–c gave the 7-substituted indolines IXa,b,f in 90% yield; also, hydrolysis of indole IXe, which was available by saponification and decarboxylation of VIIIb, gave IXb. This hydrolytic opening of an indole ring is unknown for simple systems and has been previously observed only once, for the conversion of carbazole X to XI.[14] The mechanism is readily visualized as β protonation followed by nucleophilic attack of water at the resultant electron-deficient α position; the hydroxy intermediate, a carbinol amine, then opens under acid catalysis to give an amino ketone (indoline). The driving force for this reaction is presumably relief of steric strain, which results on ring opening. Since simple indoles do not have the necessary strain energy, they are not subject to hydrolytic ring opening, but instead remain closed in the indole form. In agreement with this explanation is the fact that the indole XII, which is a less strained homolog of VIIIb, could not be hydrolytically ring opened using the same (or even more forcing) conditions as were used to ring open VIIIb.



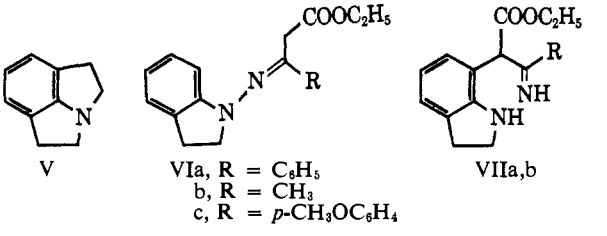
The synthesis of indolines IX suggested an application to the synthesis of apo-β-erythroidine which had suffered[8] from the difficulty in synthesizing 7-substituted indolines. Accordingly, IXb was treated with hydrazoic acid in chloroform, and the resulting mixture was hydrolyzed in alkali to give 7-indolineacetic acid (XIVa) and 7-aminomethylindoline. An accompanying neutral side product in this Schmidt reaction was the reindolization product, 4-methyl-1,2-dihydropyrrolo-[3,2,1-*hi*]indole (VIIIe). Its formation may be rationalized by nucleophilic attack of the indoline nitrogen on the developing positive carbon. Loss of nitrogen leads to the species XIII which may be considered the normal intermediate in indole formation and gives the indole *via* loss of ammonia. It is interesting in this regard that neither the 7-indolineacetic acid (XIVa) nor its methyl ester formed oxindole when heated at 200°.



IXb

XIII

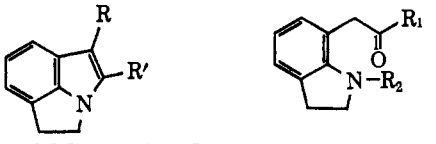
To prevent this side reaction, the indolines IXa,b, and f were acetylated. This resulted in a more easily isolated product, and subsequent Schmidt reaction gave no indole. The greatest migratory aptitude was shown by the phenyl group (in IXc) as compared to methyl (in IXd) and *p*-methoxyphenyl (in IXe), and 7-indolineacetic acid (XIVa) was obtained in 52% yield. Also, use of the Beckmann rearrangement gave a lower yield of 7-indolineacetic acid.



V

VIa, R = C_6H_5
b, R = CH_3
c, R = *p*-$CH_3OC_6H_4$

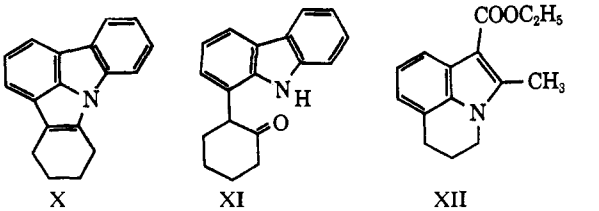
VIIa,b



VIIIa, R = $COOC_2H_5$; R′ = C_6H_5
b, R = $COOC_2H_5$; R′ = CH_3
c, R = $COOC_2H_5$; R′ = *p*-$CH_3OC_6H_4$
d, R = COOH; R′ = CH_3
e, R = H; R′ = CH_3

IX

IXa, R_1 = C_6H_5; R_2 = H
b, R_1 = CH_3; R_2 = H
c, R_1 = C_6H_5; R_2 = CH_3CO
d, R_1 = CH_3; R_2 = CH_3CO
e, R_1 = *p*-$CH_3OC_6H_4$; R_2 = CH_3CO
f, R_1 = *p*-$CH_3OC_6H_4$; R_2 = H



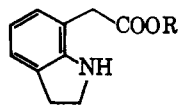
X XI XII

Alkylation of ester XIVb with methyl β-bromopropionate gave the diester XV, which on cyclization with potassium *t*-butoxide in benzene gave 6-oxo-7-methoxycarbonyl-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (XVI). The assignment of structure XVI to the keto ester product, rather than the 5-methoxycarbonyl alternative, was based on its nmr spectrum which showed a singlet at δ 4.5 corresponding to the benzylic

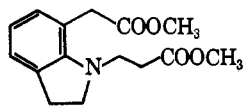
(13) H. Rapoport and J. R. Tretter, *J. Am. Chem. Soc.*, 80, 5574 (1958).
(14) D. Bowman, Dissertation, University of California, Berkeley.

7-hydrogen. Also, the nmr spectrum of the alkylated keto ester XVIIIb (see below) was in agreement with the assigned structure. Acid decarboxylation of keto ester XVI gave 6-oxo-1,2,4,5,6,7-hexahydroazepino-[3,2,1-*hi*]indole (XVII).

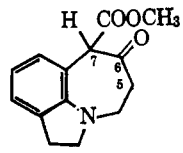
At this point we should mention that the 7-oxo analog IV of ketone XVII, in which the carbonyl is in conjugation with the nitrogen, was synthesized by ring closure of 1-indolinebutyric acid with polyphosphoric acid. Although the yield of ketone IV was low (5–10%), it was possible to recover about 80% of the starting material. Nevertheless, the low yield of ketone IV as well as its expected low carbonyl reactivity, due to nitrogen–carbonyl resonance,[15] led us to conclude that IV was not a practical intermediate in the synthesis of apo-β-erythroidine (II) and isoapo-β-erythroidine (III). Consequently, our attempts at the synthesis of II and III were based on succeeding reactions with ketone XVII (which contained the acidic 7-methylene hydrogens as well as a carbonyl not in conjugation with nitrogen and thus expected to show normal carbonyl reactivity) and keto ester XVI, both of which were now available in sufficient quantity.



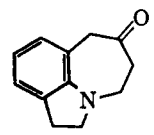
XIVa, R=H
b, R=CH_3



XV



XVI



XVII

B. Addition of the Two-Carbon Fragment. Simple alkylation was considered entirely feasible for introducing the two-carbon side chain, and for this purpose the azepinone XVII was treated with pyrrolidine, giving the eneamine. However, reaction of the latter with ethyl bromoacetate did not lead to any isolable keto ester XVIIIa, although sodium borohydride reduction of the crude reaction mixture yielded a small amount of lactone XXa. Similarly, β-keto ester XVI was readily alkylated with ethyl bromoacetate to give the keto diester XVIIIb, which on sodium borohydride reduction gave the lactone ester XXb. However, decarboxylation of XVIIIb and XXb gave mainly polymeric material, although a small amount of the desired lactone XXa was isolated from XXb.

At this point we decided to pursue further the synthesis of lactone XXa which was potentially capable of direct conversion to apo-β-erythroidine (II) and isoapo-β-erythroidine (III) by a Prins reaction.[16] Treatment of β-keto ester XVI with dimethyl sulfite gave the ester ketal XIX, which, on consecutive reactions with lithium aluminum hydride, tosyl chloride, and sodium cyanide gave the cyano ketal XXIIIc. Mild acid hydrolysis of the latter gave the cyano ketone XXIV, which on sodium borohydride reduction (with or without subsequent acid hydrolysis) gave the lactone XXa. Treatment of lactone XXa under Prins reaction conditions, which depended on the assumption of an equilibrium between the lactone and the β,γ-unsaturated acid XXI, gave no detectable apo-β-erythroidine (II) or isoapo-β-erythroidine (III). Thus, paraformaldehyde and trifluoroacetic acid gave only starting material as did paraformaldehyde and acetic–sulfuric acid. Forcing conditions using the latter catalyst system merely resulted in destruction of lactone XXa without formation of II or III.

Reaction of ketone XVII with *n*-butyl glyoxylate[17] in methanol gave a product whose ultraviolet spectrum and elemental analysis corresponded to the keto ester XXVIIc; however, the lack of reactivity of this product toward sodium borohydride and particularly its infrared spectrum, which showed just one carbonyl band at 1750 cm^{-1}, both indicated that the product was the lactol ether XXVa. Presumably lactol ether arose from XXVIIa by methanol attack on the ketone carbonyl followed by displacement of *n*-butoxide. Acid hydrolysis of XXVa, in an attempt to open the lactol ether to keto acid XXVIId, gave instead the lactol XXVb. Hydrogenation of XXVa gave a dihydro compound (XXVI), the hydrolysis of which gave no useful product.

Since the difficulty in the glyoxylate condensation of *n*-butyl glyoxylate was the result of lactol ether formation from keto ester XXVIIa, we decided to use *t*-butyl glyoxylate to synthesize XXVIIb; the latter was expected to be more resistant toward lactol ether formation owing to the well-known stability of *t*-butyl esters toward nucleophilic attack. To prepare *t*-butyl glyoxylate,[18] fumaric acid was first converted to its di-*t*-butyl ester with isobutylene. Oxidation of di-*t*-butyl fumarate by potassium permanganate gave di-*t*-butyl tartrate which was cleaved to *t*-butyl glyoxylate by the action of lead tetraacetate.[19] An attempt to obtain di-*t*-butyl tartrate directly from tartaric acid and isobutylene was unsuccessful owing to extensive *t*-butyl ether formation.

Condensation of the azepinone XVII with *t*-butyl glyoxylate gave 6-oxo-7-*t*-butoxycarbonylmethylene-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (XXVIIb) in 59% yield. The structure XXVIIb is consistent with the extended conjugation observed in the ultraviolet spectrum (λ_{max} 378, 251 mμ), the two carbonyl bands in the infrared spectrum (ν_{max} 1720, 1710 cm^{-1}), and the

(15) Actually the literature contains contrasting reports on the carbonyl activity of a vinylogous amide such as ketone IV. Thus, J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 3377 (1958), report the failure of α-methylene condensation of 1-methyl-2,3,4,5-tetrahydro-5-oxo-1H-1-benzazepine with *p*-dimethylaminobenzaldehyde and *p*-nitrosodimethylaniline, and Astill and Boekelheide[9] report the failure of condensation of methyl iodide with the same azepinone. On the other hand, P. I. Ittyerah and F. G. Mann, *ibid.*, 467 (1958), report the successful condensation of *p*-dimethylaminobenzaldehyde and *p*-nitrosodimethylaniline with 1-methyl-1,2,3,4-tetrahydro-4-quinolone which is also a vinylogous amide. Also, Rapoport and Tretter[24] report the condensation of 1-ketolilolidine with furfural, whereas Astill and Boekelheide[10] report the same compound to be unaffected by nitromethane or diazomethane.

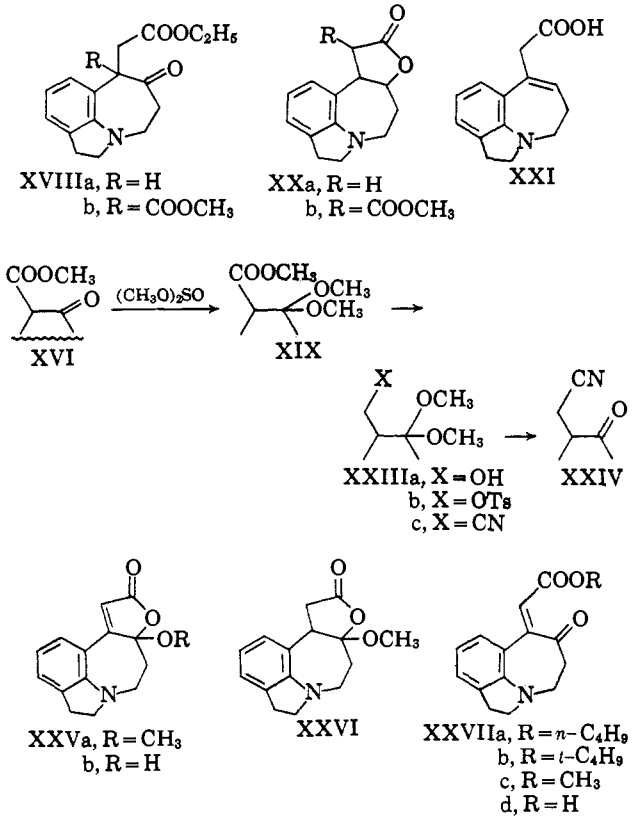
(16) B. Belleau, *Can. J. Chem.*, **35**, 673 (1957).

(17) See M. S. Newman, W. C. Sagar, and C. C. Cochran, *J. Org. Chem.*, **23**, 1832 (1958), for the use of glyoxylate condensations to add a two-carbon acid side chain to ketones.

(18) (a) E. Muller and H. Huber-Emden, *Ann.*, **660**, 54 (1962), have prepared *t*-butyl glyoxalate phenylhydrazone from *t*-butyl diazoacetate. (b) L. A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964), has isolated *t*-butyl glyoxalate as the hydrate and phenylhydrazone from hydrolysis of *t*-butyl α-bromo-α-alkoxyacetate. (c) Another potential method for the preparation of glyoxalate esters is that of N. Kornblum and H. W. Frazier, *J. Am. Chem. Soc.*, **88**, 865 (1966).

(19) F. J. Wolff and J. Weijlard, *Org. Syn.*, **35**, 18 (1955).

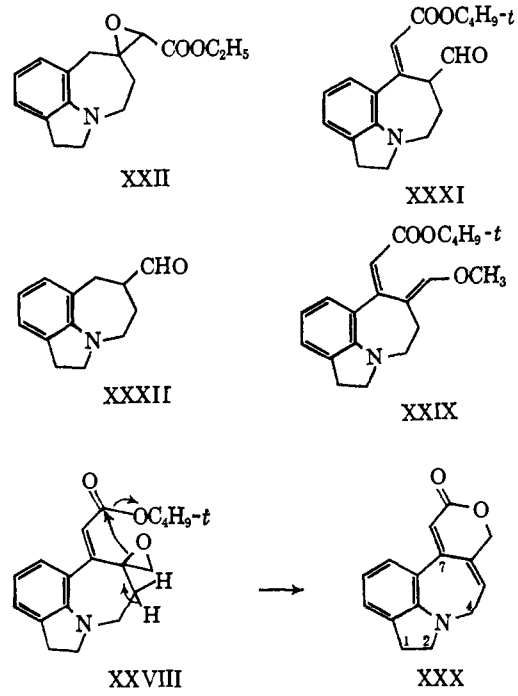
nmr spectrum which showed the *t*-butyl singlet and one vinyl proton. On the basis of the previous lactol ether formation observed with the *n*-butyl ester and subsequent cyclization to the lactone XXX, the stereochemistry of XXVIIb was assigned the *cis* configuration of *t*-butoxycarbonyl with respect to the ketone. Actually, although XXVIIb showed only one spot on thin layer chromatography, we cannot say with certainty that the *trans* isomer was not also present in the product of the *t*-butyl glyoxylate reaction.



C. **Introduction of the One-Carbon Fragment.** The final problem was the conversion of the ketone carbonyl of keto ester XXVIIb to an hydroxymethyl group. This transformation was visualized *via* a sodium borohydride reduction of the aldehyde XXXI which was potentially available from XXVIIb by a variety of procedures. Since the glycidic ester XXII, which was obtained by a Darzens condensation of ethyl chloroacetate with azepinone XVII, had not been convertible to the aldehyde XXXII, we did not investigate the Darzens condensation of keto ester XXVIb.

Reaction of keto ester XXVIIb with methoxymethylenetriphenylphosphorane gave unknown products and none of the desired enol ether XXIX.[20] Similarly, reaction with dimethylsulfonium methylide[21] gave no useful product, presumably owing to reaction at the ester carbonyl as reported for ethyl cinnamate, rather than at the ketone carbonyl to give the desired epoxide XXVIII. Also, diazomethane, which was potentially capable of giving the epoxide XXVIII,[22] gave no reaction. Finally, the reaction XXVIIb with dimethyloxosulfonium methylide was studied despite the reported reaction of this reagent with α,β-unsaturated ketones to form cyclopropanes and with α,β-unsaturated esters to give cyclic sulfur derivatives.[21] Indeed, when XXVIIb was treated with dimethyloxosulfonium methylide and the reaction mixture was analyzed by nmr, we observed a peak at δ 0.2 indicative of cyclopropane hydrogens. However, we were able to isolate a 51% yield of a compound whose properties allowed assignment of the structure 6-hydroxymethyl-7-carboxymethylene-1,2,4,7-tetrahydroazepino[3,2,1-*hi*]indole δ-lactone (XXX), presumably arising from rearrangement of the epoxide XXVIII. The following data are consistent with structure XXX: (1) elemental analysis, (2) mass peak at 239 in the mass spectrum, (3) single carbonyl band at 1723 cm,$^{-1}$ (4) extended conjugation in the electronic spectrum (λ_{max} 428, 300, 260 mμ). The nmr spectrum was conclusive. There were six protons at δ 2.5–3.5 corresponding to the three methylenes at C-1, -2 and -4; of these six protons, at the low-field end, there was a discernible two-proton doublet (the protons at position 4 are expected to be at lower field than those at 1 or 2). There was a two-proton singlet at δ 4.4 corresponding to the lactonic methylene, and two vinyl protons at δ 6 corresponding to a singlet superimposed on a triplet. In addition, the coupling constants of the C-5 vinyl triplet and the C-4 methylene doublet were the same, J = 6 cps, as they should be. Finally, there was a complex absorption in the region δ 6–7 which corresponded to three aromatic protons.

Hydrogenation of lactone XXX was studied at atmospheric pressure using platinum, Raney nickel, palladium on charcoal, and palladium on barium sulfate. All four catalysts resulted in complex mixtures which included apo-β-erythroidine (II), isoapo-β-erythroidine (III), lactone XXX, and at least three other products. The complexity of the reaction mixture was partly explained by the observation that apo-β-erythroidine (II) was partially destroyed under the reaction conditions, even when using palladium on barium sulfate in benzene. However, using palladium



(20) S. Trippett, *Quart. Rev.* (London), 17, 406 (1963).
(21) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 87, 1353 (1965), and earlier papers cited therein.
(22) C. D. Gutsche, *Org. Reactions*, 8, 364 (1954).

on barium sulfate in ethyl acetate, we were able to isolate apo-β-erythroidine (II) and isoapo-β-erythroidine (III) in 14 and 20% yields, respectively, along with a 13% recovery of lactone XXX. Separation was effected by thin layer chromatography, using acetic acid in the developing solvent to take advantage of the difference in basicity between apo-β-erythroidine and isoapo-β-erythroidine (weaker base because of conjugate interaction between nitrogen and lactone carbonyl). Crystalline samples of II and III were obtained, and these were shown to be identical with authentic samples by melting point, infrared and ultraviolet spectra, and thin layer chromatography.

Experimental Section[23]

N-Nitrosoindoline. Indoline[24] was dissolved in 10% sulfuric acid (4 g/ml) and the solution was cooled to 0°. Aqueous sodium nitrite (105 mole %, 1.5 g/ml) was then added dropwise with vigorous stirring under a nitrogen atomosphere so that the temperature did not rise above 5°. The mixture was stirred a few minutes after addition was complete, and the orange precipitate was filtered and washed well with carbonate solution followed by water. Sublimation at 75° (0.05 mm) gave a 95% yield of N-nitrosoindoline, mp 82.5–83° (lit.[25] mp 83–84°).

1-Aminoindoline. To a solution of 19 g (0.128 mole) of N-nitrosoindoline in 500 ml of dry ether, cooled as low as solubility would permit with an ice bath, was added 77 ml of 1.7 *M* ethereal lithium aluminum hydride, dropwise, with vigorous stirring under nitrogen. Fifteen minutes after addition was complete, 10 ml of ethyl acetate followed by 25 ml of water was cautiously added. The reaction mixture was filtered with minimum exposure to air, and the filtrate was evaporated to a residue which was fractionally distilled at 66–69° (0.25 mm) to give 12 g (70%) of an oil, 1-aminoindoline.

Anal. Calcd for $C_8H_8N_2$: C, 71.6; H, 7.5; N, 20.9. Found: C, 71.7; H, 7.7; N, 21.0.

4-Phenyl-5-ethoxycarbonyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (VIIIa). A few drops of glacial acetic acid, 5 g (37.3 mmoles) of 1-aminoindoline, and 7.3 g (37.3 mmoles) of ethyl benzoylacetate were heated on a steam bath for 45 min with stirring. The water which separated was removed by washing a benzene solution of the mixture with saturated sodium chloride solution and drying over sodium sulfate. Evaporation of the solvent gave the hydrazone VIa as an oil, which was taken up in 100 ml of absolute ethanol and treated dropwise with 10 ml of concentrated sulfuric acid under nitrogen. The resultant solution was refluxed for 3 hr and then cooled at −18° overnight. The crystals which had precipitated were washed with a small amount of cold ethanol and then thoroughly with water. Recrystallization from ethanol gave 9.1 g (83%) of 4-phenyl-5-ethoxycarbonyl-1,2-dihydropyrrolo[3,2,1-*hi*]-indole (VIIIa), mp 137–138°, $\lambda_{max}^{CH_3OH}$ 309 mμ (ε 9500) and 251 mμ (ε 18,000).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.4; H, 5.8; OC_2H_5, 15.5. Found: C, 78.6; H, 6.0; OC_2H_5, 15.4.

4-Methyl-5-ethoxycarbonyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (VIIIb). The synthesis of VIIIb from 1-aminoindoline and ethyl acetoacetate was achieved in 54% yield in the same manner as described for VIIIa: mp 89–90°; $\lambda_{max}^{CH_3OH}$ 297 mμ (ε 14,000), 240 (22,600), 220 (38,000).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.4; H, 6.6; N, 6.1; OC_2H_5, 19.6. Found: C, 73.5; H, 6.7; N, 6.3; OC_2H_5, 19.1.

4-(*p*-Methoxyphenyl)-5-ethoxycarbonyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (VIIIc). The synthesis of VIIIc from 1-aminoindoline and ethyl *p*-methoxybenzoylacetate was achieved in 53% yield in the same manner as described in VIIIa, mp 130–131°.

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.8; H, 5.9. Found: C, 74.5; H, 5.7.

7-Phenacylindoline (IXa) and 1-Acetyl-7-phenacylindoline (IXc). To a mixture of 500 ml of ethanol, 300 ml of water, and 200 ml of sulfuric acid was added 45 g of 4-phenyl-5-ethoxycarbonyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (VIIIa). The resultant mixture was refluxed under nitrogen until it became homogeneous; after an additional 30-min reflux, the solution was cooled and the alcohol was evaporated while periodically adding water to maintain a constant volume. Finally, the aqueous residue was diluted to 2 l., washed with ether, made alkaline with concentrated sodium hydroxide solution, and extracted with ether. The ether extract was dried and evaporated to an oily residue which crystallized on standing. An analytical sample was obtained by crystallization from petroleum ether and subsequent sublimation to give 7-phenacylindoline (IXa), mp 63–64°, $\lambda_{max}^{CH_3CH}$ 290 mμ (ε 3300) and 252 mμ (ε 19,700), $\nu_{max}^{CHCl_3}$ 3450 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO$: C, 81.0; H, 6.3; N, 5.9. Found: C, 80.8; H, 6.5; N, 6.1.

Alternatively, the crude 7-phenacylindoline was treated with 100 ml of acetic anhydride, and the mixture was refluxed for 30 min under nitrogen. The reaction mixture was added to water, and the solid that separated was washed with water and recrystallized from alcohol or acetone to give a 90% yield of 1-acetyl-7-phenacylindoline (IXc), mp 136–137°, $\lambda_{max}^{CH_3OH}$ 243 mμ (ε 22,000).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.4; H, 6.1; N, 5.0. Found: C, 77.1; H, 6.0; N, 5.3.

The oxime of IXc was prepared by refluxing 8.4 g of IXc with 8.5 ml of pyridine and 8.4 g of hydroxylamine hydrochloride in 85 ml of ethanol for 3 hr under nitrogen. Most of the alcohol was removed by evaporation and the residue was added to ice–water which resulted in a 79% yield of crystalline oxime, mp 185–186°.

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.5; H, 6.1; N, 9.5. Found: C, 73.2; H, 5.9; N, 9.6.

1-Acetyl-7-(*p*-methoxyphenacyl)indoline (IXe). A mixture of 12.5 g of indole ester VIIIc, 125 ml of ethanol, 75 ml of water, and 50 ml of concentrated sulfuric acid was refluxed under nitrogen for 3 hr. The product was isolated and acetylated with 30 ml of acetic anhydride as described for the preparation of IXc. Recrystallization from ethanol gave 8.5 g (71%) of IXe, mp 138–139°.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2. Found: C, 74.1; H, 6.4.

7-Acetonylindoline (IXb). Ten grams of indole ester VIIIb in 100 ml of 6 *M* sulfuric acid was refluxed under nitrogen for 4 hr. After cooling, the reaction mixture was extracted with ether, made alkaline, and extracted with ether again. The second ether extract was dried and evaporated to a residue which was distilled at 110–112° (1.3 mm) to give 7.5 g (98%) of 7-acetonylindoline (IXb).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.4; H, 7.4; N, 8.0. Found: C, 75.4; H, 7.5; N, 8.2.

4-Methyl-5-carboxy-1,2-dihydropyrrolo[3,2,1-*hi*]indole (VIIId) and 4-Methyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (VIIIe). A mixture of 5.5 g of indole ester VIIIb and 4 g of potassium hydroxide in 50 ml of ethanol plus 20 ml of water was refluxed for 20 hr under nitrogen. After cooling, 900 ml of water was added and the reaction mixture was extracted with ether, filtered, and acidified. Indole acid VIIId precipitated in nearly quantitative yield and an analytical sample was obtained by sublimation at 170° (0.01 mm), mp 246°.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.8; H, 5.5; N, 7.1.

Indole acid VIIId was heated under a nitrogen atmosphere at 255–260° until carbon dioxide evolution ceased (*ca.* 10 min), then it was cooled and dissolved in ether. Extraction of the ether solution with aqueous bicarbonate followed by drying and evaporation of the solvent gave a nearly quantitative yield of indole VIIIe which was recrystallized from petroleum ether and sublimed at 70° (0.1 mm), mp 88–89°, $\lambda_{max}^{CH_3OH}$ 283 mμ (ε 4600) and 223 mμ (ε 15,600).

Anal. Calcd for $C_{11}H_{11}N$: C, 84.1; H, 7.0; N, 8.9. Found: C, 84.2; H, 7.0; N, 8.9.

7-Indolineacetic Acid (XIVa) and 7-Aminomethylindoline. To 30 g (0.108 mole) of 1-acetyl-7-phenacylindoline (IXc) in 300 ml of chloroform at 0° was added 20 ml of concentrated sulfuric acid, with stirring. Then, 125 ml of 1 *M* hydrazoic acid in chloroform was added dropwise over a period of 40 min. Vigorous stirring at 0° was continued for 4 hr, and the reaction mixture was added to 500 g of ice. After being shaken together in a separatory funnel, the two liquid layers were separated and more chloroform (four 150-ml portions) was used to extract the aqueous solution and to dissolve the gummy mass which had formed during the reaction. The combined organic extracts were washed with water, dried, and evaporated to a residue which was treated with 120 ml of 4 *M* potassium hydroxide at 175° in a steel bomb for 23 hr. After cooling, the reaction mixture was extracted with four 250-ml

(23) All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley; all evaporations were *in vacuo* using a rotary evaporator.

(24) H. Rapoport and J. R. Tretter, *J. Org. Chem.*, **23**, 248 (1958).

(25) G. Plancher and C. Ravenna, *Atti Reale Acad. Lincei*, [5] **14**, I 632 (1905).

portions of ether (fraction A), and then adjusted to pH 1 with sulfuric acid and extracted with five 130-ml portions of chloroform. To the remaining aqueous solution was added 8 g of trisodium phosphate, and the pH was adjusted to 4.3. Continuous extraction with ether, evaporation of the ether extract, and crystallization of the residue from acetone gave 9.97 g (52%) of 7-indolineacetic acid (XIVa). An analytical sample was obtained by recrystallization from acetone, mp 157–158°.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.2; N, 7.9. Found: C, 68.0; H, 6.2; N, 7.8.

Fraction A was extracted with 1 *M*, pH 6.1, phosphate buffer. The combined aqueous extracts were made alkaline with sodium hydroxide and the oil which separated was extracted into ether. The ether extracts were dried and evaporated to a residue which was distilled at 125° (3 mm) to give 2.0 g (12%) of 7-aminomethylindoline, ν_{max}^{neat} 3380 and 3300 cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2$: C, 73.0; H, 8.1; N, 18.9. Found: C, 73.0; H, 8.2; N, 19.1.

Methyl 7-Indolineacetate (XIVb). A mixture of 16 g of 7-indolineacetic acid, 170 ml of absolute methanol, and 16 ml of concentrated sulfuric acid was refluxed for 3.5 hr under nitrogen. After cooling, solid sodium bicarbonate was added to neutralize the acid present, the methanol was removed by evaporation, and the residue was distributed between 400 ml of ether and 300 ml of water. The aqueous layer was extracted with two 200-ml portions of ether, and the combined ether extracts were washed with 50 ml of water, dried, and evaporated to a residue which was distilled at 98–100° (0.2 mm) to give 15 g (87%) of methyl 7-indolineacetate (XIVb).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.1; H, 6.8; N, 7.3. Found: C, 69.1; H, 6.7; N, 7.3.

Methyl 7-Methoxycarbonylmethyl-1-indolinepropionate (XV). To 14.5 g (76 mmoles) of methyl 7-indolineacetate was added 6.34 g (38 mmoles) of methyl β-bromopropionate, and the mixture was heated at 100° for 24 hr under nitrogen. After cooling, the reaction mixture was taken up in 200 ml of benzene and 200 ml of water; solid sodium bicarbonate was added until the solid product had completely dissolved and gas evolution had ceased. The aqueous layer was further extracted with two 150-ml portions of benzene, and the combined benzene extracts were washed with 40 ml of water, dried, and evaporated to a residue which was fractionally distilled in the spinning-band column at 0.3-mm pressure. Methyl 7-indolineacetate (5.8 g, 40%) distilled at 115°; then, the residue was transferred to a Claisen flask and distilled at 150° (0.02 mm) to give 7.2 g (34%) of methyl 7-methoxycarbonylmethyl-1-indolinepropionate (XV).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1. Found: C, 65.0; H, 6.7; N, 5.3.

6-Oxo-7-methoxycarbonyl-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (XVI). Into a mixture of 15.9 mmoles of potassium *t*-butoxide in 100 ml of benzene, under nitrogen, was dropped a solution of 3.14 g (11.3 mmoles) of methyl 7-methoxycarbonylmethyl-1-indolinepropionate (XV) in 35 ml of benzene. The resultant mixture was stirred at room temperature for 21 hr, and then extracted with 50 ml of ice-water and four 50-ml portions of 0.2 *M* potassium hydroxide. The combined aqueous extracts were adjusted to pH 5.5 and extracted with four 100-ml portions of benzene; the combined benzene extracts were washed with 30 ml of water, dried, and evaporated to a residue which was sublimed at 85° (0.02 mm) to give 1.53 g (55%) of keto ester XVI. An analytical sample was obtained by recrystallization from benzene–hexane–ether, mp 91–93°, $\lambda_{max}^{C_2H_5OH}$ 253 mμ (ε 10,800) and 218 mμ (ε 16,600), $\lambda_{max}^{1NNaOH-C_2H_5OH}$ 285 mμ (ε 11,700) and 245 mμ (ε 16,000).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; OCH_3, 12.6. Found: C, 68.6; H, 6.3; OCH_3, 12.5.

6-Oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (XVII). A mixture of 1.64 g of keto ester XVI and 35 ml of concentrated hydrochloric acid was heated at 120–130°, under a nitrogen sweep, for 1.5 hr with stirring. After cooling, the reaction mixture was added to an ice-water mixture, the pH was adjusted to 9 with concentrated sodium hydroxide solution, and the aqueous mixture was extracted with four 100-ml portions of chloroform. The combined chloroform extracts were dried and evaporated to a residue which was sublimed twice at 80° (0.02 mm) to give 740 mg (59%) of azepinone XVII. Recrystallization from hexane gave an analytical sample, mp 82–83°, $\lambda_{max}^{CH_3OH}$ 257 mμ (ε 6400) and 300 mμ (sh) (ε 1500), $\nu_{max}^{CHCl_3}$ 1713 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO$: C, 77.0; H, 6.9; N, 7.5. Found: C, 76.8; H, 6.7; N, 7.5.

6-Oxo-7-methoxycarbonyl-7-ethoxycarbonylmethyl-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (XVIIIb). To a solution of 21 mmoles of potassium *t*-butoxide in 20 ml of *t*-butyl alcohol plus 80 ml of benzene was added 4.9 g (20 mmoles) of keto ester XVI. Then, 3.16 g (19 mmoles) of ethyl bromoacetate in 30 ml of benzene was added and the resultant mixture was refluxed under nitrogen for 3 hr. After cooling, the reaction mixture was shaken with 200 ml of ice-cold water, and the organic layer was extracted with eight 50-ml portions of 0.2 *M* potassium hydroxide solution, washed with water, and dried. Evaporation of solvent left a residue which was chromatographed on 40 g of activity I neutral alumina. Elution with benzene–ether gave a 45% yield of keto diester XVIIIb which was crystallized from methanol, mp 72–73°, $\lambda_{max}^{C_2H_5OH}$ 312 mμ (ε 2500) and 257 mμ (ε 6500).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.3; H, 6.4; N, 4.2; OR, 2/(331 mol wt). Found: C, 65.3; H, 6.4; N, 4.3; OR, 1.89/331.

7-Methoxycarbonyl-7-carboxymethyl-6-hydroxy-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole γ-Lactone (XXb). To a solution of 1.5 g of keto diester XVIIIb in 10 ml of methanol was added a solution of 100 mg of sodium borohydride in 7 ml of methanol. The solution was made basic to phenolphthalein by the addition of a few drops of sodium hydroxide and stirred at room temperature for 30 min; then, another solution of 100 mg of sodium borohydride in 5 ml of methanol was added, and the solution was refluxed for 45 min. After cooling, the solution was acidified with hydrochloric acid, concentrated to a volume of 15 ml, and added to 60 ml of a saturated ammonium chloride solution. The aqueous mixture was extracted with four 40-ml portions of benzene, and the combined extracts were washed with water and dried. Evaporation of the solvent gave a residue which was chromatographed on 25 g of neutral alumina; elution with benzene–ether gave 440 mg (34%) of lactone ester XXb, which was recrystallized from methanol, mp 142–145°, $\nu_{max}^{CHCl_3}$ 1792 and 1730 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.9; H, 6.0; OCH_3, 10.8. Found: C, 67.2; H, 6.2; OCH_3, 10.3.

7-Methoxycarbonyl-6,6-dimethoxy-1,2,4,5,6,7-hexahydroazepino-[3,2,1-*hi*]indole (XIX). To a solution of 5.91 g of keto ester XVI in 50 ml of methanol was added 4.25 ml of 5.88 *M* methanolic hydrogen chloride and 3 g of dimethyl sulfite, and the solution was refluxed for 27 hr under nitrogen. After cooling, most of the solvent was removed *in vacuo*, water was added, and the pH was adjusted to 7 with bicarbonate. The mixture was extracted with two 50-ml portions of benzene and the combined benzene extracts were washed with four 20-ml portions of 0.2 *M* potassium hydroxide solution and two 20-ml portions of water, and dried. Evaporation of the solvent and recrystallization of the residue from methanol gave an 82% yield of the ester ketal XIX, mp 121–122°, $\lambda_{max}^{C_2H_5OH}$ 302 mμ (ε 2600) and 257 mμ (ε 5500).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.9; H, 7.3; N, 4.8; OCH_3, 32.0. Found: C, 65.8; H, 7.3; N, 4.9; OCH_3, 31.2.

7-Hydroxymethyl-6,6-dimethoxy-1,2,4,5,6,7-hexahydroazepino-[3,2,1-*hi*]indole (XXIIIa). To a suspension of 1.2 g (30 mmoles) of lithium aluminum hydride in 40 ml of dry ether, under nitrogen, was added 8.73 g (30 mmoles) of ester ketal XIX in 50 ml of ether and 50 ml of benzene (slowly). The mixture was refluxed for 3 hr, and after cooling, water was cautiously added to destroy excess hydride. The ether layer was separated, washed with water, dried, and evaporated to a residue which crystallized on trituration with methanol giving 7.5 g (95%) of the alcohol XXIIIa. Recrystallization was achieved from methanol; mp 94–95°, $\lambda_{max}^{C_2H_5OH}$ 293 mμ (ε 2400) and 252 mμ (ε 7200).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.4; H, 8.0; N, 5.3; OCH_3, 23.6. Found: C, 68.3; H, 8.0; N, 5.4; OCH_3, 23.9.

7-Hydroxymethyl-6,6-dimethoxy-1,2,4,5,6,7-hexahydroazepino-[3,2,1-*hi*]indole *p*-Toluenesulfonate (XXIIIb). To a solution of 2.63 g (10 mmoles) of the alcohol XXIIIa in 40 ml of pyridine at −5° was added 2 g (11 mmoles) of *p*-toluenesulfonyl chloride, and the resulting mixture was stirred for 3.5 hr at 0°, under nitrogen. Then 4 ml of water was slowly added over a period of 10 min, and the solution was poured into 150-ml of ice-water. This solution was extracted with four 150-ml portions of chloroform, and the combined chloroform extracts were washed with six 50-ml portions of water, dried, and evaporated to a residue which was recrystallized from methanol to give 3.1 g (75%) of tosylate XXIIIb, mp 118–121°, $\lambda_{max}^{C_2H_5OH}$ 295 mμ (ε 2400) and 252 mμ (ε 9300).

Anal. Calcd for $C_{22}H_{27}NO_5S$: C, 63.3; H, 6.5; S, 7.7; OCH_3, 14.9. Found: C, 63.1; H, 6.3; S, 7.8; OCH_3, 14.7.

7-Cyanomethyl-6,6-dimethoxy-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (XXIIIc). A mixture of 1.25 g (3 mmoles) of the tosylate XXIIIb, 300 mg (6 mmoles) of sodium cyanide, and 3 ml of dimethyl sulfoxide was stirred for 2 hr at 120° under nitrogen. After cooling, 150 ml of water was added, and the aqueous mixture

was extracted with four 50-ml portions of chloroform. The combined chloroform extracts were washed with water, dried, and evaporated to a residue that crystallized on scratching with methanol. Recrystallization from methanol gave 571 mg (70%) of cyanoketal XXIIIc, mp 114–115°.

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.6; H, 7.4; N, 10.3; OCH_3, 22.8. Found: C, 70.5; H, 7.4; N, 10.1; OCH_3, 22.3.

7-Cyanomethyl-6-oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (XXIV). Cyanoketal XXIIIc (130 mg) was dissolved in 10 ml of 1 *M* hydrochloric acid, and the solution was stirred at 40° for 16 hr. The solution was then diluted with 30 ml of water, neutralized with bicarbonate, and extracted with four 80-ml portions of chloroform. The combined chloroform extracts were washed with water, dried, and evaporated to a residue which on crystallization from acetone–methanol gave 71 mg (70%) of cyano ketone XXIV, mp 144–146°.

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.3; H, 6.2; N, 12.4. Found: C, 74.3; H, 6.3; N, 12.3.

7-Carboxymethyl-6-hydroxy-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole γ-Lactone (XXa). A mixture of 170 mg of cyano ketone XXIV, 500 mg of sodium borohydride, and 18 ml of methanol was stirred for 24 hr at 40°. Most of the solvent was then removed by evaporation, water was added, and the aqueous mixture was extracted with three 100-ml portions of chloroform. The combined extracts were washed with water, dried, and evaporated to a residue that was chromatographed on 5.5 g of neutral activity I alumina. Elution with benzene–ether gave 51 mg (30%) of lactone XXa which was recrystallized from acetone–petroleum ether, mp 166–168°. Treatment of the chromatographic fractions containing intermediate cyano alcohol with 70% sulfuric acid at 70° for 45 min gave another 50% of lactone XXa, $\nu_{max}^{CHCl_3}$ 1765 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.3; H, 6.5; N, 6.1.

Lactone XXa was also obtained from lactone ester XXb by treating the latter with 6 *M* hydrochloric acid at reflux for 3 hr under nitrogen. The reaction mixture was then made alkaline and extracted with benzene. The combined benzene extracts were washed with bicarbonate and water, dried, and evaporated to a residue that was chromatographed on alumina to give 5–10% of lactone XXa.

Similarly, treatment of ketone XVII with pyrrolidine in benzene at reflux under nitrogen for 1.5 hr and evaporation of the solvent gave the eneamine, which was dissolved in benzene and treated with ethyl bromoacetate for 10 hr at room temperature and 1 hr at reflux. The residue from this solution was chromatographed on alumina and treated with sodium borohydride in methanol. After 3 hr, potassium hydroxide was added and the solution was refluxed for 4 hr, concentrated, diluted with water, and extracted with ether. After a second extraction at pH 1, the aqueous phase was buffered to pH 4.3 and continuously extracted with ether. Evaporation of the ether solution gave a residue which was sublimed at 60° (0.01 mm) to give 3% of lactone XXa.

Di-*t*-butyl Fumarate. A mixture of 80 ml of dry diglyme, 10 ml of concentrated sulfuric acid, 10 g of fumaric acid, and 100 ml of isobutylene in a pressure bottle was shaken for 16 hr at room temperature, and then added to 250 ml of 2 *M* potassium hydroxide. The aqueous solution was extracted with three 100-ml portions of ether, and the combined ether extracts were washed with seven 100-ml portions of water. The ether solution was dried and evaporated to a residue which was recrystallized from ether to give 12.5 g (64%) of di-*t*-butyl fumarate, mp 69–70° (lit.[18a] 46°).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.1; H, 8.8. Found: C, 63.1; H, 8.9.

Di-*t*-butyl Tartrate. To a solution of 17.1 g (75 mmoles) of di-*t*-butyl fumarate in 500 ml of *t*-butyl alcohol was added (dropwise) 8.2 g (52 mmoles) of potassium permanganate in 500 ml of water, with vigorous stirring. After an additional 10 min of stirring at room temperature, the reaction mixture was extracted with two 1000-ml portions of ether; the combined ether extracts were washed with three 500-ml portions of water, dried, and evaporated to a residue which was recrystallized from petroleum ether to give 8.6 (44%) of di-*t*-butyl tartrate, mp 84–85°.

Anal. Calcd for $C_{12}H_{22}O_6$: C, 55.0; H, 8.4. Found: C, 55.2; H, 8.3.

***t*-Butyl Glyoxylate.** To a cold solution of 2.54 g (9.7 mmoles) of di-*t*-butyl tartrate in 12 ml of dry benzene was added 4.95 g (11.1 mmoles) of lead tetraacetate, and the mixture was stirred at room temperature under nitrogen for 3 hr. Then, 50 ml of petroleum ether was added and the mixture was stirred 5 min and decanted. This procedure was repeated with another 50-ml portion of petroleum ether, and the mixture was filtered. The combined filtrates were evaporated to a residue which was taken up in 25 ml of petroleum ether and allowed to stand overnight at 0°; then the resultant mixture was filtered, the filtrate was evaporated, and the residue was dissolved in 10 ml of petroleum ether and shaken with a small amount of phosphorus pentoxide. Filtration and evaporation gave another residue which was distilled at 49° (12 mm) to give 780 mg (31%) of *t*-butyl glyoxylate as a colorless, viscous oil. In phosphorus pentoxide dried chloroform solution, *t*-butyl glyoxylate showed two carbonyl bands in the infrared at 1745 and 1715 cm^{-1}; vpc analysis showed the product to be >95% pure, the impurities being benzene, petroleum ether, and acetic acid.

6-Oxo-7-*t*-butoxycarbonylmethylene-1,2,4,5,6,7-hexahydroazepino-[3,2,1-*hi*]indole (XXVIIb). To a solution of 120 mg (0.64 mmole) of ketone XVII plus 194 mg (1.49 mmoles) of *t*-butyl glyoxylate in 1.5 ml of dry *t*-butyl alcohol was added 0.16 ml of piperidine and 0.04 ml of glacial acetic acid. After 3 hr of refluxing under nitrogen, the reaction mixture was cooled and distributed between 75 ml of benzene and 15 ml of water. The benzene extract was washed with 10 ml of 1 *M* sodium bicarbonate solution and two 10-ml portions of water, dried, and evaporated to a residue which was chromatographed on 80 g of activity III acid-washed alumina. Elution was achieved with benzene–hexane and gave 113 mg (59%) of XXVIIb, pure by tlc, $\lambda_{max}^{C_2H_5OH}$ 378 mμ (ε 5200) and 251 mμ (ε 15,200), $\nu_{max}^{CCl_4}$ 1720 and 1710 cm^{-1}.

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.2; H, 7.1; N, 4.7. Found: C, 72.0; H, 6.7; N, 4.6.

6-Methoxy-6-hydroxy-7-carboxymethylene-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole γ-Lactone (XXVa). To a solution of 3.45 g (18.5 mmoles) of ketone XVII and 2.4 g (18.5 mmoles) of *n*-butyl glyoxylate[19] in 25 ml of dry methanol was added 3 ml of piperidine and 1 ml of glacial acetic acid. After a 3-hr reflux under nitrogen, the solution was cooled to −10°. It deposited 2.1 g of lactol ether XXVa which was recrystallized from methanol and sublimed at 140° (0.01 mm): mp 176°, $\lambda_{max}^{CH_3OH}$ 402 mμ (ε 5500), 290 (9000), 255 (16,300); ν_{max}^{KBr} 1750 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.4; H, 5.8; N, 5.5; OCH_3, 12.1. Found: C, 70.4; H, 5.8; N, 5.3; OCH_3, 11.5.

Acid Hydrolysis of Lactol Ether XXVa. A mixture of 200 mg of lactol ether XXVa, 4 ml of glacial acetic acid, and 3 ml of concentrated hydrochloric acid was heated on a steam bath for 2 hr under nitrogen. The resultant solution was diluted with water and extracted with benzene. The aqueous acid solution was made alkaline, extracted with benzene, and finally buffered at pH 4.5 and continuously extracted with ether. Evaporation of the ether gave solid lactol XXVb, which was crystallized from acetone and sublimed at 160° (0.01 mm), mp 192°, ν_{max}^{KBr} 1720 and 3250 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.1; H, 5.4. Found: C, 68.8; H, 5.5.

Hydrogenation of Lactol Ether XXVa. A solution of 1 g of lactol ether XXVa in 250 ml of methanol was hydrogenated on the Parr apparatus at 30 psi for 24 hr with 300 mg of platinum oxide catalyst. Filtration of the reaction mixture and concentration of the filtrate gave 240 mg of a solid which was recrystallized from methanol and sublimed at 160° (0.01 mm) to give dihydro lactol ether XXVI, mp 214–215°, $\lambda_{max}^{CH_3OH}$ 292 mμ and 253 mμ, ν_{max}^{KBr} 1775 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.6; OCH_3, 12.0. Found: C, 69.6; H, 6.5; OCH_3, 12.0.

6-Hydroxymethyl-7-carboxymethylene-1,2,4,7-tetrahydroazepino-[3,2,1-*hi*]indole δ-Lactone (XXX). To 1.10 mmoles of sodium hydride (51 mg of a 51.8% dispersion in oil which had been washed with hexane to remove the oil) was added 265 mg (1.20 mmoles) of trimethyloxosulfonium iodide and 1.7 ml of dry dimethyl sulfoxide, and the mixture was stirred for 20 min at room temperature under nitrogen. To the resulting solution was added 314 mg (1.05 mmoles) of keto ester XXVIIb in 3.1 ml of dimethyl sulfoxide, and stirring was continued for 1 hr at room temperature. Then, 40 ml of pH 7 phosphate buffer was added, and the mixture was extracted with one 150-ml portion plus three 50-ml portions of chloroform. The combined chloroform extracts were washed with four 25-ml portions of water, dried, and evaporated to a residue which was chromatographed on 30 g of activity III acid-washed alumina. Elution was achieved with benzene–hexane and benzene, and gave 129 mg (51%) of XXX, pure by tlc: $\lambda_{max}^{C_2H_5OH}$ 428 mμ (ε 5000), 300 (11,000), 260 (10,000); $\nu_{max}^{CCl_4}$ 1723 cm^{-1}; nmr spectrum in acetone-d_6 (δ values, TMS = 0) 2.5–3.5 (m) (C-1, -2, -4, H_6), 4.4 (s) (—$COOCH_2$—), 6 [(s) =CHCO—, (t) C-5 H], 6–7 (m) (ArH_3).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.5; N, 5.8; mol wt, 239. Found: C, 75.0; H, 5.7; N, 5.6; mol wt, 239 (mass spectrometry).

Apo-β-erythroidine (II) and Isoapo-β-erythroidine (III). A mixture of 118 mg of lactone XXX plus 69 mg of 5% palladium on barium sulfate in 70 ml of ethyl acetate was stirred at room temperature for 55 min under hydrogen at atmospheric pressure. After filtration, the filtrate was evaporated to a residue which was chromatographed on 14 g of Decalso (>150 mesh) with benzene and benzene–ether elution. Thin layer chromatographic analysis of the eluent showed only II, III, and XXX. This mixture was then purified by preparative thin layer chromatography on silica gel (benzene–acetone–acetic acid, 10:2:2.7). The bands corresponding to each compound were shaken with a mixture of 20 ml of aqueous bicarbonate (0.5 *M*) and 40 ml of ether. The mixture of silica gel in aqueous bicarbonate was extracted with two more 30-ml portions of ether, and the combined ether extracts were washed with three 10-ml portions of aqueous bicarbonate and 10 ml of water and dried. Evaporation of solvent gave 17 mg (14%) of apo-β-erythroidine[26] (II), 24 mg (20%) of isoapo-β-erythroidine (III), and 16 mg (13%) of recovered lactone XXX. Crystallization of II and III was achieved from acetone–water and ethanol–water, respectively. Apo-β-erythroidine had mp 128–129° (lit.[5a] 132–132.5°), $\nu_{max}^{CHCl_3}$ 1737 cm^{-1}, $\lambda_{max}^{C_2H_5OH}$ 345 mμ (ε 3500) and 240 mμ (ε 24,500).[27] Isoapo-β-erythroidine had mp 146–148° (lit.[5a] 146–147°), $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}, $\lambda_{max}^{C_2H_5OH}$ 379 mμ (ε 6500), 288 (10,800), 253 (16,800).[27] In addition, both synthetic samples were shown to be pure and identical with authentic specimens[28] of apo-β-erythroidine (II) and isoapo-β-erythroidine (III) by thin layer chromatography.

1-Indolinebutyronitrile. Indoline (32 g) and 18.5 g of ω-bromobutyronitrile were heated at 75° for 2 hr under nitrogen. The reaction mixture was then taken up in a benzene–water mixture, and solid sodium bicarbonate was added until gas evolution ceased and the solid product had dissolved. The benzene layer was separated, and the aqueous solution was extracted with more benzene. The combined extracts were washed with water, dried, and evaporated to a residue which was fractionally distilled to give 15 g of indoline and 20.2 g (94%) of 1-indolinebutyronitrile, bp 128° (0.25 mm).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.4; H, 7.5; N, 15.1. Found: C, 77.3; H, 7.7; N, 14.8.

7-Oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (IV). Eighteen grams of 1-indolinebutyronitrile and 15 g of potassium hydroxide were dissolved in 150 ml of 10% ethanol–water and refluxed for 7 hr under nitrogen. After cooling, the solution was washed with ether, and the pH was adjusted to 4.0. A second extraction with ether gave 21 g of 1-indolinebutyric acid which was not purified. Instead, 5 g of 1-indolinebutryic acid was treated with 150 g of polyphosphoric acid at 100° for 40 hr to give a 5–10% yield of ketone IV after distillation at 160° (5 mm): $\lambda_{max}^{C_2H_5OH}$ 376 mμ (ε 3000), 315 (830), 242 (12,600).

Anal. Calcd for $C_{10}H_{13}NO$: C, 77.0; H, 7.0; N, 7.5. Found: C, 76.7; H, 7.3; N, 7.2.

In addition, 70–80% of starting 1-indolinebutyric acid was recovered from the reaction mixture.

Glycidic Ester XXII. To a solution of 84 mmoles of potassium *t*-butoxide in 10 ml of *t*-butyl alcohol was added 40 ml of benzene, and then 30 ml of solvent was distilled. After cooling, 1.5 g (80 mmoles) of azepinone XVII plus 1.08 g (84 mmoles) of ethyl chloroacetate in 10 ml of benzene were added. The resultant solution was stirred under nitrogen at room temperature for 2 hr and refluxed for 1 hr. The reaction mixture was then distributed between 250 ml of water and 100 ml of ether; the ether solution was washed with 15 25-ml portions of 0.2 *M* sodium hydroxide solution and two 50-ml portions of water, dried, and evaporated to a residue that was chromatographed on activity I neutral alumina. Elution with benzene and benzene–chloroform gave a residue that was dissolved in 2 ml of methanol and allowed to stand overnight at 0°. The 9 mg of crystalline material, mp 238–241°, that separated was removed by filtration and not further investigated. Evaporation of the filtrate gave 1.28 g (59%) of oily glycidic ester XXII, ν_{max} 1742 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.3; H, 7.0; N, 5.1; OC_2H_5, 16.5. Found: C, 70.3; H, 7.0; N, 5.2; OC_2H_5, 16.5.

(26) We have observed that apo-β-erythroidine is partially decomposed on silica gel using acetic acid as one of the developing solvents; hence, the true yield of II may be considerably higher than that isolated.

(27) (a) See ref 4a for the ultraviolet spectra of authentic II and III isolated from β-erythroidine. (b) In ref 9, the ultraviolet spectrum of II is reported to be slightly different from that reported in ref 4a and obtained by us for authentic apo-β-erythroidine; since no solvent is mentioned in ref 9, we presume a difference in solvent may be the explanation for the slight disagreement in reported spectra.

(28) Prepared[5a] from a sample of β-erythroidine hydrochloride kindly supplied by Dr. Karl Folkers.

Synthesis in the Emetine Series. XIII.[1] Structure and Synthesis of Psychotrine and 6′-O-Methyl-7′-desmethylpsychotrine

S. Teitel and A. Brossi

Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received May 19, 1966*

Abstract: The 6′ position for the free hydroxyl group in psychotrine (I) has been established by an unequivocal synthesis. The related 6′-O-methyl-7′-desmethylpsychotrine (XIII) has also been prepared. Acid hydrolysis of O-methylpsychotrine (II) gave a complex mixture containing both I and XIII.

The two phenolic Ipecac alkaloids psychotrine (I) and cephaeline (III) have been related to each other by reduction.[2] Their absolute configuration has been established since O-methylation yielded O-methylpsychotrine (II)[3] and emetine (IV),[2] respectively, two other Ipecac alkaloids of known absolute configuration.[4] However, the assignment of the free hydroxy group to the 6′ position in psychotrine (I) and cephaeline (III) has not been rigidly established since it is primarily based on the assumption by Brindley and Pyman[5] that the 6′-methoxyl in O-methylpsychotrine (II) is the most labile of the four methoxyls in the molecule and is preferentially cleaved on acid hydrolysis to give psychotrine (I) with a 6′-hydroxyl group. Pailer and Porschinski[6] lent support to this assumption when they subjected O-ethylcephaeline (V) to a lengthy degradation and obtained a semicarbazone which gave

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