The Total Synthesis of Dihydrocrinine and Related Compounds*

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Racemic dihydro-oxocrinine (XVIII) was synthesized from the keto-lactam (X) by a sequence of reactions including the Michael-type cyclization of the αβ-unsaturated keto-lactam (XI) by the use of toluene-*p*-sulphonic acid. The racemic ketone (XVIII) was resolved into optically active dihydro-oxocrinine (XIX) and dihydro-oxovittatine (XX). The former gave dihydrocrinine (II) or dihydroepicrinine (IV) when reduced by the Meerwein-Ponndorf reaction or by lithium aluminium hydride, respectively. The latter (XX) afforded dihydrovittatine (III) or dihydroepivittatine (V) when similarly reduced.

CRININE [1] (I) and its enantiomer, vittatine,[1,2] are common *Amaryllidaceae* alkaloids with a 5,10b-ethanophenanthridine skeleton which have been synthesized recently in their racemic forms by two groups of investigators.[3,4] In a continuation of our recent studies involving the synthesis of dihydro-*N*-methyloxo-*N*-seocrinine (VI),[5] we now report the synthesis of the optically active forms of dihydrocrinine (II),[6,7] dihydrovittatine (III),[7,8] and certain related compounds (IV and V).

Our starting material was the acetal-lactam (VII),[5] previously prepared in our laboratory, which contained the C–N linkage appropriate for forming the 5,10b-ethanophenanthridine skeleton. As shown by Wildman,[6] dihydro-*N*-methyloxo-*N*-seocrinine can easily be converted into dihydro-oxocrinine methosalt by a transannular Michael addition. It was thought, therefore, that this reaction would result in a highly stereospecific intramolecular Michael-type cyclization between the αβ-unsaturated ketone produced from the acetal on the ring C and the secondary amine from the corresponding amide on ring B.

Several attempts were made to reduce the amide-carbonyl group of the acetal-lactam (VII) with lithium aluminium hydride, but the corresponding secondary amine was obtained in poor yields despite the use of various experimental conditions, although the *N*-methyl lactam (VIII) [5] was easily transformed into the tertiary amine (VI). We therefore attempted a Michael-type cyclization of the αβ-unsaturated ketone and the secondary amide function itself.

Attempts at the direct introduction of a double bond conjugated with the keto-function in (X) [5] by the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave only starting material even after prolonged heating in various solvents. In contrast, bromination and dehydrobromination of the keto-lactam (X) gave the αβ-unsaturated keto-lactam (XI) in 40% yield after chromatography on silica gel. The structure of this product was supported by its spectroscopic properties: $\nu_{max.}$ 3430 and 1650 (secondary amide) and 1680 (αβ-unsaturated carbonyl) cm.$^{-1}$, and δ 7·30 and 6·09 (AB-type quartet, *J* 10 c./sec., olefinic protons of the αβ-unsaturated ketone system). The compound possessed the required functions for an intramolecular Michael cyclization, but all attempts to obtain the desired skeleton by treating (XI) with base gave mainly starting material and less than 5% of the desired product (XII).

However, treatment of (XI) with ethylene glycol and toluene-*p*-sulphonic acid yielded a basic mixture of the mono- and di-acetals [(XIII) and (XIV)], separated by silica gel chromatography in chloroform.

The basic character of the mixture is explained by the influence of the bridgehead nitrogen in the molecule, analogous to that in oxohaemanthidine (XV) derived from haemanthidine (XVI).[9] The n.m.r. spectrum of the monoacetal (XIII), the major product, did not show an AB-type signal corresponding to the olefinic protons, in contrast with the starting material (XI), but did exhibit a singlet at δ 3·96 (4H) expected from an ethylene

* Preliminary communication, H. Irie, S. Uyeo, and A. Yoshitake, *Chem. Comm.*, 1966, 635.

[1] W. C. Wildman, 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1960, vol. VI, p. 289.

[2] S. Uyeo, K. Kotera, T. Okada, S. Takagi, and Y. Tsuda, *Chem. and Pharm. Bull. (Japan)*, 1966, **14**, 793.

[3] H. W. Whitlock, jun., and G. L. Smith, *Tetrahedron Letters*, 1965, 1389; *J. Amer. Chem. Soc.*, 1967, **89**, 3600.

[4] J. B. Hendrickson, C. Foote, and N. Yoshimura, *Chem. Comm.*, 1965, 165.

[5] S. Uyeo, H. Irie, A. Yoshitake, and A. Ito, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 427.

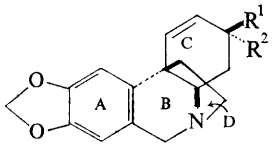
[6] W. C. Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2567.

[7] H-G. Boit and H. Ehmke, *Chem. Ber.*, 1957, **90**, 369.

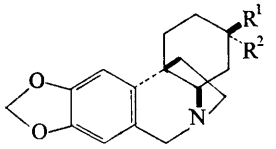
[8] R. E. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1960, **82**, 2620.

[9] S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1958, **80** 2590.

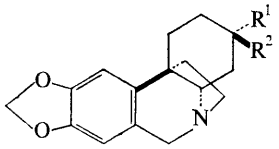
acetal. Moreover, its u.v. spectrum in ethanol showed absorption maxima at 234, 274, and 322 mμ (ε 23,000, 6100, and 5800), in close agreement with those of oxohaemanthidine (XV). The n.m.r. spectrum of the second



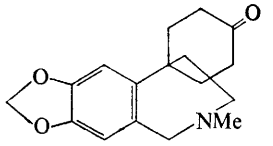
(I) $R^1 = H$; $R^2 = OH$



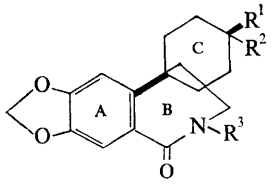
(II) $R^1 = H$; $R^2 = OH$
(IV) $R^1 = OH$; $R^2 = H$
(XIX) $R^1R^2 = O$



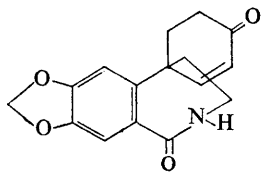
(III) $R^1 = H$; $R^2 = OH$
(V) $R^1 = OH$; $R^2 = H$
(XX) $R^1R^2 = O$



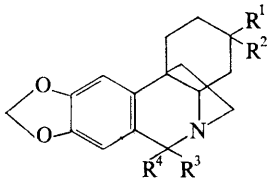
(VI)



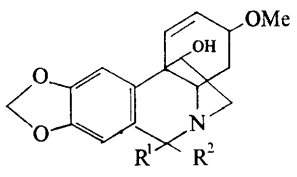
(VII) $R^1R^2 = \langle O O \rangle$; $R^3 = H$
(VIII) $R^1R^2 = \langle O O \rangle$; $R^3 = Me$
(IX) $R^1 = R^3 = H$; $R^2 = OH$
(X) $R^1R^2 = O$; $R^3 = H$



(XI)



(XII) $R^1R^2 = R^3R^4 = O$
(XIII) $R^1R^2 = \langle O O \rangle$; $R^3R^4 = O$
(XIV) $R^1R^2 = R^3R^4 = \langle O O \rangle$
(XVII) $R^1R^2 = \langle O O \rangle$; $R^3 = H$; $R^4 = OH$
(XVIII) $R^1R^2 = O$; $R^3 = R^4 = H$



(XV) $R^1R^2 = O$
(XVI) $R^1 = H$; $R^2 = OH$

basic product (XIV) did not exhibit an olefinic signal, but showed two broad singlets at δ 3·99 and 4·20, assigned to the protons of the two ethylene acetals. The formation of an ethylene acetal from the amide carbonyl at the benzylic position is also explained by the fact that the bridgehead nitrogen confers a ketonic character to this function.

By a procedure analogous to that used for oxohaemanthidine (XV), reduction of (XIII) with lithium aluminium hydride yielded the corresponding α-hydroxyamine (XVII). Treatment of (XVII) with thionyl chloride followed by lithium aluminium hydride and subsequent hydrolysis with hydrochloric acid gave (±)-dihydro-oxocrinine (XVIII), m.p. identical with that reported in the literature [8] and u.v., i.r. and n.m.r. spectra were in agreement with the expected structure.

The racemic dihydro-oxocrinine (XVIII) was resolved by use of di-(*p*-toluoyl)-D- and -L-tartaric acids to give dihydro-oxocrinine (XIX) and dihydro-oxovittatine (XX), respectively.

Finally, the ketone was reduced to the corresponding axial alcohol. It was previously reported [5] that hydride reduction of dihydro-oxocrinine gave only dihydroepicrinine (IV), isomeric with the dihydro-derivative of the naturally-occurring alkaloid, crinine. We have confirmed this and obtained the same product (IV), $[\alpha]_D$ −10·0°, m.p. 101—103°, by treatment of the ketone (XIX) with lithium aluminium hydride. However, Meerwein-Ponndorf reduction of the ketone (XIX) afforded dihydrocrinine (II), $[\alpha]_D$ −21·0°, m.p. 221—223°, identical with an authentic specimen of (II). No isomeric alcohol was detected in the reaction product by t.l.c.

Dihydro-oxovittatine (XX) was reduced similarly to dihydrovittatine (III), $[\alpha]_D$ +24·0°, m.p. 221—223° by a Meerwein-Ponndorf reaction and to dihydroepivittatine [7] (V), $[\alpha]_D$ +12·3°, m.p. 101—103°, when treated with lithium aluminium hydride.

EXPERIMENTAL

The αβ-Unsaturated Keto-lactam (XI).—Bromine (60 mg.) in chloroform (10 ml.) was added to a mixture of the keto-lactam (X) [5] (100 mg.) and calcium carbonate (20 mg.) in chloroform (10 ml.) with stirring at room temperature. After 30 min. the mixture was diluted with chloroform, washed with aqueous sodium carbonate and water, dried, and evaporated to dryness to leave an oil (150 mg.). A solution of this oil in dimethylformamide (45 ml.) was heated under reflux with lithium chloride (250 mg.) and lithium carbonate (50 mg.) under nitrogen for 15 hr. The mixture was diluted with water and extracted with chloroform; the extract was washed with water, dried, and evaporated to dryness to leave an oil. Chromatography of this oil in chloroform on silica gel gave the *αβ-unsaturated keto-lactam* (XI) (80 mg.) as prisms, m.p. 104—105° (from chloroform) (Found: C, 65·3; H, 5·6; N, 4·4. $C_{16}H_{15}NO_4$,1/2H_2O requires C, 65·3; H, 5·4; N, 4·7%), $\nu_{max.}$ ($CHCl_3$) 3430, 1680, and 1650 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 213, 261, and 295 mμ (ε 30,600, 4800, and 3800).

Treatment of the αβ-Unsaturated Keto-lactam (XI) *with Sodium Hydride*.—The αβ-unsaturated keto-lactam (XI) (80 mg.) and sodium hydride (50% in mineral oil) (80 mg.) in toluene (20 ml.) were heated under reflux for 5 hr. and cooled. Acetic acid (1 ml.) was added, and the mixture was washed with aqueous sodium carbonate and water, dried, and evaporated to dryness under reduced pressure. The residue (60 mg.) was chromatographed in chloroform over silica gel. The initial chloroform eluate gave the keto-lactam (XII) (3 mg.), which gave needles, m.p. 126—127° (from ethanol), $\nu_{max.}$ ($CHCl_3$) 1715 and 1685 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 237, 276, and 320 mμ (ε 15,000, 6800, and 6600). Further elution gave the unchanged αβ-unsaturated keto-lactam (XI) (50 mg.), m.p. and mixed m.p. 104—105°.

Treatment of the αβ-Unsaturated Keto-lactam (XI) *with Ethylene Glycol in the Presence of Toluene-p-sulphonic Acid.*—A mixture of the αβ-unsaturated keto-lactam (XI) (100 mg.), benzene (70 ml.), ethylene glycol (1 ml.) and toluene-*p*-sulphonic acid (50 mg.) was fractionally distilled with occasional addition of benzene to remove an azeotropic mixture of benzene and the water produced by acetal formation. After 5 hr. the mixture was poured into aqueous sodium carbonate and extracted with chloroform. The extract was washed with water, dried, and evaporated under reduced pressure to give a residue which was chromatographed in chloroform over silica gel. The first chloroform eluate gave the *acetal-lactam* (XIII) (60 mg.) as needles, m.p. 230—231° (from chloroform–ether) (Found: C, 63·4; H, 5·9; N, 4·0. $C_{18}H_{19}NO_5,2/3H_2O$ requires C, 63·4; H, 6·0; N, 4·1%), $\nu_{max.}$ ($CHCl_3$) 1685 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 234, 274, and 322 mμ (ε 23,000, 6100, and 5800), δ ($CDCl_3$) 7·47 (1H, s), 6·80 (1H, s), 6·03 (2H, s), and 3·96 (4H, s). Further elution with the same solvent gave the *diacetal* (XIV) (5 mg.) as needles, m.p. 205—207° (from ethanol) (Found: C, 64·5; H, 6·3; N, 3·8. $C_{20}H_{23}NO_6$ requires C, 64·3; H, 6·2; N, 3·8%).

Reduction of the Acetal-lactam (XIII) *with Lithium Aluminium Hydride.*—The acetal-lactam (XIII) (95 mg.) was treated with lithium aluminium hydride (50 mg.) in tetrahydrofuran (20 ml.) for 3 hr. The product was the *acetal α-hydroxy-amine* (XVII) (70 mg.), obtained as needles, m.p. 267—269° (from chloroform–ethanol) (Found: C, 64·4; H, 6·4; N, 4·0. $C_{18}H_{21}NO_5,1/4H_2O$ requires C, 64·5; H, 6·4; N, 4·2%), $\nu_{max.}$ (Nujol) 3300 cm.$^{-1}$. The *acetyl derivative*, prepared with acetic anhydride–pyridine had m.p. 253—254° (Found: C, 64·6; H, 6·5; N, 3·8. $C_{20}H_{23}NO_6$ requires C, 64·3; H, 6·2; N, 3·8%), $\nu_{max.}$ (Nujol) 1725 cm.$^{-1}$, δ ($CDCl_3$) 6·20 (1H, s), 3·99 (4H, s), and 2·11 (3H, s).

(±)-*Dihydro-oxocrinine* (XVIII).—The acetal α-hydroxy-lactam (XVII) (100 mg.) in freshly distilled thionyl chloride (5 ml.) was kept at room temperature for 30 min. and then heated under reflux for 15 min. Concentration of the mixture left a residue which was taken up in tetrahydrofuran (20 ml.) and treated with lithium aluminium hydride (50 mg.) under reflux for 6 hr. The solution was cooled, and the excess of the reagent was decomposed with a few drops of water. The mixture was filtered and evaporated to dryness to leave an oil which was heated on a water-bath in dilute hydrochloric acid for 1 hr., basified with aqueous ammonia and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness. The resulting oil was chromatographed in benzene over alumina (Brockmann, grade III). The benzene–chloroform (95 : 5) eluate gave (±)-dihydro-oxocrinine (XVIII) (45 mg.) as needles, m.p. 171—173° (from benzene-ether) (lit.,[8] 171—173°) (Found: C, 70·7; H, 6·5; N, 5·0. $C_{16}H_{17}NO_3$ requires C, 70·8; H, 6·3; N, 5·2%), $\nu_{max.}$ ($CHCl_3$) 1715 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 237 and 294 mμ (ε 3560 and 5070), δ ($CDCl_3$) 4·41 (1H, d, *J* 17 c./sec.) and 3·77 (1H, d, *J* 17 c./sec.).

Resolution of (±)-*Dihydro-oxocrinine* (XVIII).—A solution of di-(*p*-toluoyl)-D-tartaric acid (143 mg.) in ethanol (10 ml.) was added to a solution of (±)-dihydro-oxocrinine (XVIII) (100 mg.) in ethanol (5 ml.). Fine crystals were immediately deposited. After 3 hr. at room temperature, the crystals were filtered off and washed with boiling ethanol (20 ml.). The resulting dihydro-oxocrinine di-(*p*-toluoyl)-D-tartarate (70 mg.), m.p. 231—232°, was suspended in dilute aqueous potassium hydroxide and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness to leave dihydro-oxocrinine (XIX) (20 mg.). The base gave prisms, m.p. 158—160° (from benzene–ether) $[\alpha]_D$ −72·5° (*c* 1·1 in $CHCl_3$) (Found: C, 70·9; H, 6·6; N, 4·9. $C_{16}H_{17}NO_3$ requires C, 70·8; H, 6·3; N, 5·2%), physical properties identical with those of the natural compound.[6] The mother liquors from dihydro-oxocrinine di-(*p*-toluoyl)-D-tartarate were concentrated to *ca.* 5 ml., diluted with water (50 ml.), basified with 10% aqueous potassium hydroxide, and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness to give a crude (+)-base (30 mg.). This was treated with di-(*p*-toluoyl)-L-tartaric acid (36 mg.) as described above to afford dihydro-oxovittatine di-(*p*-toluoyl)-L-tartarate (15 mg.), which gave dihydro-oxovittatine (XX) when basified. The *base* formed prisms, m.p. 158—160° (from benzene–ether), $[\alpha]_D$ + 78·1° (*c* 0·7 in $CHCl_3$), i.r. and mass spectra and optical rotation (except for direction) identical with those of dihydro-oxocrinine [6] (Found: C, 70·9; H, 6·6; N, 4·9. $C_{16}H_{17}NO_3$ requires C, 70·8; H, 6·3; N, 5·2%.)

Dihydrocrinine (II).—Freshly prepared aluminium isopropoxide (100 mg.) was added to a solution of dihydro-oxocrinine (XIX) (30 mg.) in propan-2-ol (40 ml.), and the whole was fractionally distilled for 40 min. During this time, the volume of the reaction mixture was kept at *ca.* 40 ml. by the occasional addition of propan-2-ol. After 30 ml. of the distillate had collected, the mixture was concentrated under reduced pressure to *ca.* 5 ml., diluted with ice–water, and extracted with chloroform. The extract was washed with water, dried, and evaporated to dryness to leave an oil. This was chromatographed in benzene over alumina (Brockmann, grade III) and eluted with benzene–chloroform (1 : 1) to give dihydrocrinine (II) (16 mg.) as prisms, m.p. 221—223° (from acetone), $[\alpha]_D$ −21·0° (*c* 0·7 in $CHCl_3$), $\nu_{max.}$ 3170 cm.$^{-1}$, M^+, 273, identical with an authentic sample of dihydrocrinine.

Dihydrovittatine (III).—In a similar manner dihydro-oxovittatine (XX) (32 mg.) was converted into dihydrovittatine (III) (13 mg.) which gave prisms, m.p. 221—223° (from acetone), $[\alpha]_D$ +24·0° (*c* 0·7 in $CHCl_3$), i.r. (KBr) and mass spectra superimposable upon those of dihydrocrinine (II).

Dihydroepicrinine (IV).—Dihydro-oxocrinine (20 mg.) (XIX) and lithium aluminium hydride (40 mg.) were heated under reflux in tetrahydrofuran (10 ml.) for 4 hr. The product was an oil which was chromatographed in benzene over alumina (Brockmann, grade III). The benzene–chloroform (1 : 1) eluate afforded dihydroepicrinine (IV) (12 mg.) as prisms, m.p. 101—103° (from aqueous acetone), $[\alpha]_D$ −10·6° (*c* 0·7 in $CHCl_3$), $\nu_{max.}$ (KBr) 3200 cm.$^{-1}$, M^+, 237.

Dihydroepivittatine (V).—In the same way dihydro-oxovittatine (XX) (18 mg.) was reduced with lithium aluminium hydride (40 mg.) in tetrahydrofuran (10 ml.) to give dihydroepivittatine (V) (11 mg.) as prisms, m.p. 101—103° (from aqueous acetone), $[\alpha]_D$ +12·3° (*c* 1·2 in $CHCl_3$), i.r. (KBr) and mass spectra superimposable upon those of dihydroepicrinine (IV).

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