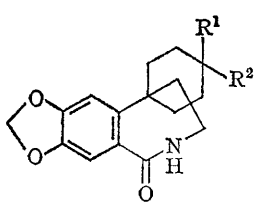
The Total Synthesis of Dihydrocrinine and Related Compounds

By HIROSHI IRIE, SHOJIRO UYEO, and AKIRA YOSHITAKE
(*Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan*)

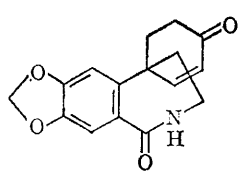
IN continuation of our earlier synthetic work[1] of tetrahydro-oxocrinine methine,[2] we now report the total synthesis of dihydrocrinine (X),[2] its epimer, and their enantiomers[3] starting from the acetoxy-lactam (I), an intermediate in the previous synthesis. Hydrolysis of the acetoxy-lactam (I) followed by oxidation with chromic acid–pyridine complex afforded the keto-lactam (II) which on bromination in chloroform with one mole of bromine at room temperature, and subsequent dehydrobromination with lithium chloride and lithium carbonate in dimethylformamide, gave the $\alpha\beta$-unsaturated keto-lactam (III).

Attempts were made first without much success to effect cyclisation of the lactam nitrogen to the β-position of the unsaturated double bond by the action of a strong base such as sodium amide, sodium hydride, or sodium t-butoxide in benzene, the yield of the desired compound (IV) in each case being very low.

On the other hand, ketalisation with ethylene glycol in the presence of toluene-*p*-sulphonic acid in benzene gave in 60% yield the cyclised ketal-lactam (V) which was basic in contrast to the neutral starting material (III) and, as expected, exhibited no AB-type quartet in the olefinic region in the n.m.r. spectrum. As an analogy with oxohaemanthidine,[4] the ketal-lactam (V) gave, on



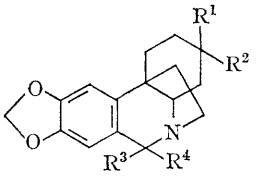
(I) R^1=OAc, R^2=H
(II) R^1R^2=O

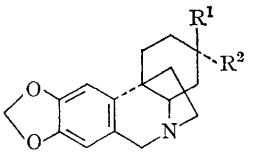


(III)

reduction with lithium aluminium hydride in tetrahydrofuran, the α-hydroxy-amine (VI) which was treated with thionyl chloride followed by lithium aluminium hydride, to give, after acid hydrolysis of the ketal grouping, (±)-dihydro-oxocrinine (VII), m.p. 171—173°. Resolution of this racemate was accomplished by using di-(*p*-tolyl)-D-tartaric acid in ethanol, giving dihydro-oxocrinine

(VIII), m.p. 158—160°, $[\alpha]$ −72·5° ($CHCl_3$) as its sparingly soluble salt.





(IV) $R^1R^2=R^3R^4=O$

(V) $R^1R^2=\overset{O}{O}$, $R^3R^4=O$

(VI) $R^1R^2=\overset{O}{O}$, $R^3=OH$, $R^4=H$

(VII) $R^1R^2=O$, $R^3=R^4=H$

(VIII) $R^1R^2=O$

(IX) Enantiomer of VIII

(X) $R^1=H$, $R^2=OH$

(XI) Enantiomer of X

(XII) $R^1=OH$, $R^2=H$,

(XIII) Enantiomer of XII

Addition of di-(*p*-tolyl)-L-tartaric acid to the mother liquor from this salt deposited the enantiomeric salt from which dihydro-oxovittatine (IX), m.p. 158—160°, $[\alpha]_D$ + 78·1° ($CHCl_3$) was isolated.

Meerwein–Ponndorf reduction of dihydro-oxocrinine and dihydro-oxovittatine furnished dihydrocrinine (X), m.p. 221—223°, $[\alpha]_D$ −21·0° ($CHCl_3$) and dihydrovittatine (XI), m.p. 221—223°, $[\alpha]_D$ +24·0° ($CHCl_3$), respectively. The former was identical in all respects with an authentic specimen of dihydrocrinine.* On the other hand, lithium aluminium hydride reduction of the above ketones (VIII) and (IX) gave dihydroepicrinine (XII), m.p. 101—102°, $[\alpha]_D$ −10·6° ($CHCl_3$) and dihydroepivittatine (XIII), m.p. 101—103°, $[\alpha]_D$ +12·3° ($CHCl_3$), respectively.

(*Received, August 2nd*, 1966; *Com.* 573.)

* Generously supplied by Dr. H. M. Fales, National Heart Institute, Bethesda, Md., U.S.A.

[1] S. Uyeo, H. Irie, A. Yoshitake, and A. Ito, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 427.
[2] W. C. Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2567.
[3] H.-G. Boit and H. Ehmke, *Chem. Ber.*, 1957, **90**, 369; E. R. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1960, **82**, 2620.
[4] S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2590.