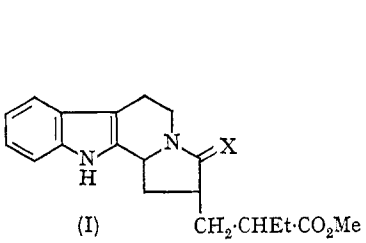
Total Synthesis of (±)-16-Hydroxydihydrocleavamines and Partial Synthesis of Demethoxycarbonyldeoxyvinblastine

By JOHN HARLEY-MASON* and ATTA-UR-RAHMAN
(*University Chemical Laboratory, Cambridge*)

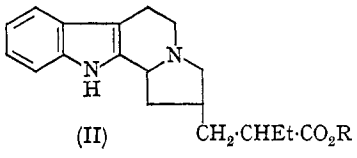
IN an earlier Communication[1] we described the synthesis of the tetracyclic amide (I; X = O). Treatment of this compound with phosphorus pentasulphide in xylene at 100° gave the thioamide (I; X = S), m.p. 155—158°, desulphurized by Raney nickel to the amine (II; R = Me). Alkaline hydrolysis then gave the amino-acid (II; R = H), m.p. 219—222°.

This, with acetic anhydride and sodium acetate at 80°, underwent an interesting skeletal rearrangement[2] yielding 16-acetoxy-21-oxodihydrocleavamine (III; R = Ac) m.p. 222°—223° as a mixture of two racemates only, demonstrated by layer chromatography. An examination of models and of the probable mechanism involved suggests that the acetoxy-group enters *trans* to the hydrogen atom at C-14 and that the isomers differ only in the configuration at C-20.

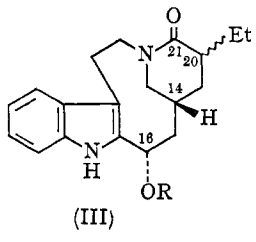
The skeletal structure of the product was proved by reduction of (III; R = Ac) with excess of lithium aluminium hydride, when hydrogenolysis of the acetoxy-group occurred yielding a mixture of α- and β-dihydrocleavamines identified by comparison with authentic materials. Alkaline hydrolysis of (III; R = Ac) gave the hydroxy-amide (III; R = H), m.p. 232—235°, which with lithium aluminium hydride gave a mixture of the C-20 epimers of 16-hydroxydihydrocleavamine (IV).



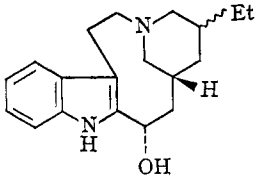
(I)

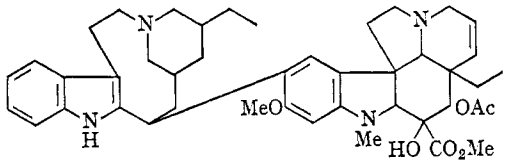


(II)



(III)





Oxidation of (III; R = H) with manganese dioxide gave the corresponding ketone, which exhibited the characteristic ultraviolet spectrum of a 2-acylindole, thus confirming the position of the hydroxyl group.

Compound (IV) reacted readily with vindoline (kindly supplied by Dr. N. Neuss of Eli Lilly, Inc.) in cold 1% methanolic hydrogen chloride[3] to give a product as two separable stereoisomers. That this product was the "dimeric" type (V) was shown by high-resolution mass spectrometry: found, M^+ 736·4211: calc., M^+ 736·4200. This material differs from vinblastine in that a hydroxyl group at C-20 and a methoxycarbonyl group at C-16 are lacking. It represents, however, the nearest synthetic approach so far to the oncolytic indole alkaloids, and work in this direction is continuing.†

(*Received, August 23rd*, 1967; *Com.* 906.)

[1] J. Harley-Mason, Atta-ur-Rahman, and J. A. Beisler, *Chem. Comm.*, 1966, 743.
[2] L. J. Dolby and S. Sakai (*J. Amer. Chem. Soc.*, 1964, **86**, 1890) have described a similar reaction in the corynantheine series, but the present case involves different ring sizes.
[3] *Cf.* G. Büchi and R. Manning, *J. Amer. Chem. Soc.*, 1964, **86**, 4640.

† We are informed by Dr. N. Neuss (private communication) that he has also prepared a "dimeric" type similar to ours from desacetylvindoline hydrazide.