Total Synthesis of α- and β-(±)-Dihydrocleavamines

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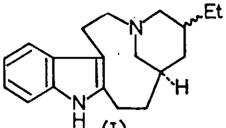
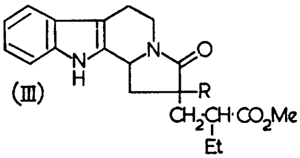
THE two dihydrocleavamines[1,2] (I; the two isomers differ in the disposition of the ethyl group) are key degradation products derived from reductive cleavage of the alkaloids leurosine and catharanthine, and are tetracyclic indolic bases isomeric with quebrachamine. The total synthesis of the racemates of the two stereoisomers is now described.

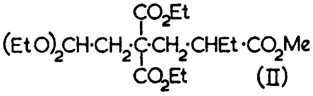
Michael addition of diethyl 2,2-diethoxyethylmalonate[3] to methyl α-ethylacrylate[4] gave the triester acetal (II). Reaction with tryptamine in boiling acetic acid gave the amide–ester (III; R = CO_2Et). Hydrolysis, followed by pyrolytic decarboxylation and re-esterification gave the amide–ester (III; R = H). Lithium aluminium hydride reduction gave the amine–alcohol (IV) which with methanesulphonyl chloride and triethylamine followed by heating yielded the pentacyclic quaternary salt (V). Reduction with sodium in liquid ammonia* yielded a mixture of α- and β-(±)-dihydrocleavamine (I), easily separated by thick-layer chromatography. Identity of the products was confirmed by direct comparison (mass spectra and t.l.c. in several solvent systems) with authentic (optically active) materials kindly supplied by Dr. N. Neuss of Eli Lilly Inc. It will be noted that the intermediates (III), (IV), and (V) contain three asymmetric centres and consequently are obtained as mixtures of four racemates. Separation at these earlier stages was found, however, to be unnecessary and the final separation of the two racemates of (I) gave no difficulty. Extensions of this synthesis are now in hand.



(I)

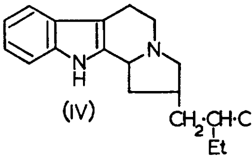


(III)

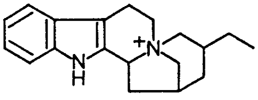


$$(EtO)_2CH\cdot CH_2\cdot\overset{CO_2Et}{\underset{CO_2Et}{C}}\cdot CH_2\cdot CHEt\cdot CO_2Me$$

(II)



(IV)



(V)

(*Received, September* 13*th*, 1966; *Com.* 686.)

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* After our work was complete a preliminary report (J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Veattas, *J. Amer. Chem. Soc.*, 1966, **88**, 5656) appeared of a similar cleavage of an isomeric pentacyclic quaternary salt leading to a synthesis of (±)-quebrachamine.

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