The Synthesis of Macronecine, a Hexahydropyrrolizine-2,9-diol

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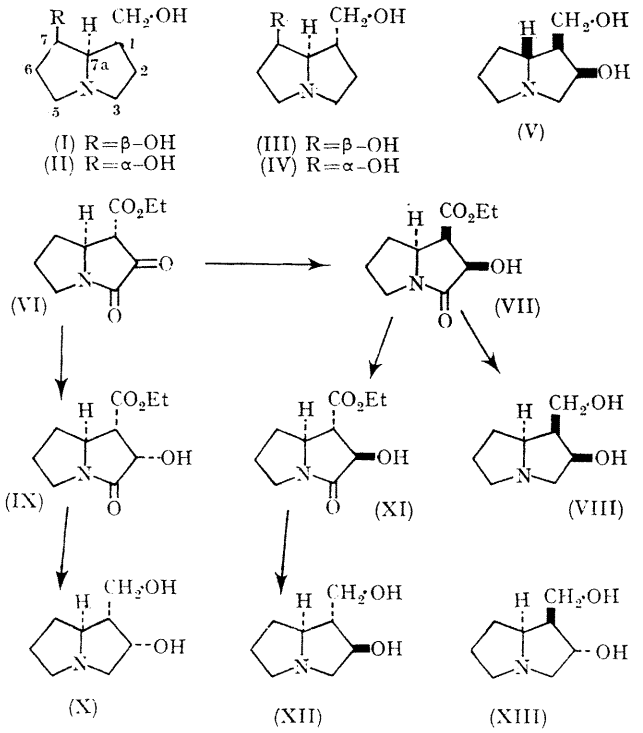
OF the six hexahydropyrrolizinediols which have been obtained as derivatives of alkaloids, the configuration of platynecine (I) and dihydroxyheliotridane (II) are the only ones to have been well established.[1] The other four, hastanecine,[2] turneforcidine,[3] macronecine,[4] and the amino-alcohol from retusine,[5] have not been accessible for detailed study. Untch and Martin[6] prepared the 7,9-diols (III) and (IV) by a reaction sequence which effected epimerization of platynecine at C-7 and C-8. With the identification of the products as hastanecine and turneforcidine, these workers concluded that macronecine was not a 7,9-diol.



Macronecine has been shown to be a derivative of 1β-hydroxymethyl-7aβ-hexahydropyrrolizine by conversion of its parent alkaloid into laburnine,[7] but the location of the other hydroxy-group has remained unknown. A gift of samples of hastacine and macrophylline† enabled one of us to make a comparative spectral study of these two alkaloids, retusine, and their respective amino-alcohols.[8] From this we were able to confirm that hastanecine and turneforcidine were 7,9-diols which allowed identification of the amino-alcohol from retusine as turneforcidine; this showed that macronecine is a 2,9-diol, probably 2β-hydroxy-1β-hydroxymethyl-7aβ-hexahydropyrrolizine (V). This structure for macronecine has now been confirmed by total synthesis.

The mass spectra of hastanecine and the amino-alcohol from retusine are closely similar to those of platynecine and dihydroxyheliotridane, whereas the spectrum of macronecine differs considerably from these but is closely similar to the spectra of the 2-hydroxy-1-hydroxymethyl hexahydropyrrolizine of Adams *et at.*[9] and 2α-hydroxy-1β-hydroxymethyl-7aα-hexahydropyrrolizine prepared[10] by catalytic reduction of 1β-hydroxymethyl-1α,2α-epoxy-7aα-pyrrolizine. The two groups of spectra have base peaks of *m/e* 82 and *m/e* 83 respectively. The n.m.r. spectrum of macronecine shows the C*H*OH multiplet as a rough triplet, width *ca.* 12 c./sec., suggesting two couplings of 5—6 c./sec. and one of *ca.* 1 c./sec.; this is in best accord with the 2β-OH configuration (V).

In undertaking a synthesis of (V) to confirm this structure, the racemic form of the dioxo-ester (VI) of Adams *et at.*[9] was taken as starting point [formulae (VI)—(XII), drawn to illustrate relative configuration, represent the 7aαH-series which is more commonly encountered]. These authors reduced (VI) catalytically to an alcohol which was further reduced with lithium aluminium hydride to give a 2,9-diol. From n.m.r. data, we concluded that these products have the relative configuration of the 1β,2β,7aα-derivatives (VII) and (VIII), consistent with (VII) being formed by *cis*-addition of hydrogen to the enol-form of (VI) from the least-hindered side. Proof of the configuration of (VIII) was obtained by degradation to (±)-heliotridane (1β-methyl-7aα-hexahydropyrrolizine), and by finding that (VIII) differed from the 1β,2α,7aα-diastereoisomer (XIII).[10] Reduction of (VI) with zinc–acetic acid gave the alcohol of 1α,2α-7aα-configuration (IX) which was reduced further with lithium aluminium hydride to give (±)-macronecine (X), which had an n.m.r. spectrum identical with the authentic amino-alcohol. Compound (X) was resolved *via* the (+)-α-bromocamphorsulphonate salts giving (+)-macronecine (V), m.p. 129°, $[\alpha]_D^{18}$ + 42·6° (lit.,[4] m.p. 126—128°, $[\alpha]_D$ + 49·29°), (+)-macronecine

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hydrochloride, m.p. 152—152·5°, $[\alpha]^{18}$ + 40·5° (lit.,[4] m.p. 152—153°, $[\alpha]_D$ + 49·37°), (−)-macronecine, m.p. 128—128·5° $[\alpha]_D^{18}$ − 42·1°, and (−)-macronecine hydrochloride, m.p. 151·5—153·5° $[\alpha]_D^{18}$ − 41·3° (all rotations in EtOH). The n.m.r. and mass spectra of synthetic and natural macronecine were identical, but a mixed m.p. with natural macronecine could not be carried out because of the decomposition of a sample of macronecine used in the spectral study. The relative stereochemistry of (IX), and hence of macronecine (X), follows from the preparation of the lactam (XI) and the diol (XII), both of 1α-configuration. Naturally occurring macronecine, being of 7aβH-configuration, therefore has the absolute configuration (V). Epimerization of (VII) in alkaline solution gave the thermodynamically more stable 1α,2β,7aα-isomer (XI), which yielded the 1α,2β,7aα-diol (XII) on hydride reduction. Thus the four diastereoisomeric 2,9-diols have now been prepared.

(*Received, September 4th,* 1968; *Com.* 1188.)

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