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SYNTHESIS OF /-/CORYNANTHEIDINE

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The alkaloid corynantheidine /I/ was isolated from Pseudocinchona africana and its structure elucidated by Janot et al.[1] The only synthesis of its racemic form was published by Weisbach and al.[2] We wish to report a new and convenient route leading to the natural product.

The easily available[3] keton II was condensed with cyanoacetic acid methyl ester in boiling toluene in the presence of ammonium acetate to yield III (66%, m.p. 183°, ν_{max}^{KBr} 2230,1735 and 1600 cm^{-1}). During this reaction epimerization occurs at the position 3 of the indolo-quinolizidine system, as it was shown in a similar case in the benzo-quinolizidine series[4,5].

The adduct III was reduced by sodium borohydride in methanol[cf.6] to IV isolated as hydrochloride [yield 85%, m.p. 210°, ν_{max}^{KBr} 2250 and 1740 cm^{-1}]. After keeping IV at room temperature for 3 days in methanol previously saturated with hydrogen chloride, the solution was refluxed for 10 hours. As a result diester V was obtained in 45% yield (m.p. 156-157°, ν_{max}^{KBr} 1760 and 1715 cm^{-1}, $\nu_{max}^{CCl_4}$ 1740 and 1760 cm^{-1}). Reduction of V by lithium aluminium hydride in ether at -50° for about 6 hours furnished VI, isolated in form of its sodium salt /40%/. The free α-hydroxymethylene ester VI had a m.p. of 93-97°, ν_{max}^{KBr} 1740, 1720, 1665 and 1625 cm^{-1}, $\lambda_{max}^{CH_3OH}$ 280 mμ /log ε 3.857/ and 225 /4.418/.

We tried to methylate compound VI with diazomethane as reported[2]. The reaction of base in ether gave only traces of rac. corynantheidine as was proved on TLC /silicagel G, benzene: EtOAc 3.5:1/. One of the main products had a somewhat higher R_f value and a quite different IR spectrum, the other one a lower R_f value than the natural corynantheidine and a similar but clearly distinguishable IR spectrum. The methylation of the hydrochloride of VI under ethylacetate gave a little more rac. I but the yield was still very low and the purification could be performed only with the aid of laborious chromatography. So in our hands diazomethane was inadequate for the preparation of rac. I in an amount suitable for resolvation.

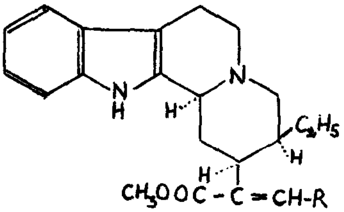
We succeeded, however, in methylating directly the sodium salt of VI with dimethylsulfate in benzene, i.e. in heterogenious phase, in almost quantitative yield. Using this method we could prepare the desired rac. I (m.p. of perchlorate 244°, of picrate 212°, IR,UV spectra and its thin layer behavior in several system was indistinguishable from that of the natural product).

The racemate was resolved with dibenzoyl-d-tartaric acid. The free base, regenerated from the crystalline salt (m.p. 152-153° from methanol-water), gave the same ORD curve as the natural I, thus the first total synthesis of /-/corynantheidine was achieved.

The above reaction sequence was also carried through with benzo/a/quinolizidine derivatives as model compounds.

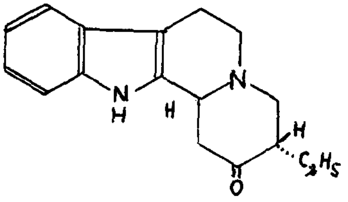
All new compounds reported here have given satisfactory elemental /C,H,N/ microanalysis.

Experiments using the mentioned methylation procedure to improve our earlier synthetic approache to dihydrocorynantheine[7] and other syntheses of alkaloids having the α-methoxymethylene ester structural feature are in progress.

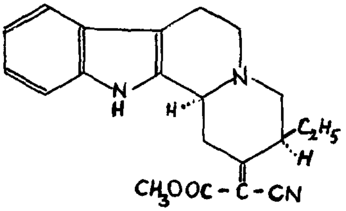


I $R=OCH_3$

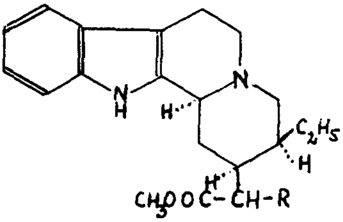
VI R=H



II



III



IV R=CN

V $R=COOCH_3$

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