A Synthetic Approach to Lycopodium Alkaloids

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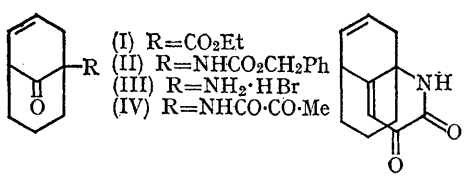
THE recent interest in the establishment of synthetic pathways to the lycopodium alkaloids[1,2] prompts us to report our pilot experiments on this theme. Our endeavours differ from those hitherto reported in that they involve the elaboration of a preformed bicyclo[3,3,1]nonane derivative. The approach is illustrated by the synthesis of a member (IX) of the hitherto unreported 5,8a-propanoperhydroquinoline system which comprises three of the rings of the tetracyclic system of lycopodine (X).

Ethyl bicyclo[3,3,1]non-3-en-9-one-1-carboxylate[3] (I) was converted, *via* the acid, acid azide, and isocyanate, into the benzylcarbamate (II). Cleavage with hydrogen bromide in acetic acid afforded an amino-ketone, which was isolated as its hydrobromide (III) in order to preclude dimerisation. Treatment of the hydrobromide with a mixture of phosphorus oxychloride and pyruvic acid, in the presence of triethylamine, proved to be a very efficient acylation procedure,[4] leading to the pyruvamide (IV), which was then cyclised in high yield by means of sodium hydride in tetrahydrofuran, to the crystalline tricyclic enone-lactam (V).[5] The application of selective reduction methods to the plethora of functionality in (V) obviously admits of many permutations.

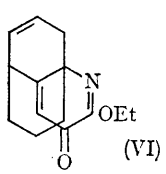
For our synthetic purposes, the following route



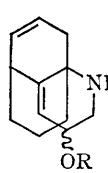
(I) R=CO_2Et
(II) R=$NHCO_2CH_2Ph$
(III) R=$NH_2 \cdot HBr$
(IV) R=$NHCO \cdot CO \cdot Me$

(V)

was found to be the most efficient. The lactim ether (VI), obtained by treatment of the lactam (V) with triethyloxonium tetrafluoroborate[6] in methylene chloride, was reduced with lithium aluminium hydride in ether, to the carbinolamine (VII) as the sole product. The corresponding



(VI)

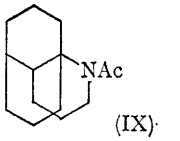


(VII) R=H
(VIII) R=Ac

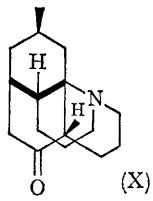
diacetate (VIII) gave mixtures of products under most conditions of catalytic hydrogenation; however the necessary combination of hydrogenolysis and hydrogenation was smoothly effected

in ethanolic perchloric acid when palladium–charcoal was used as catalyst to produce a quantitative yield of the desired *N*-acetyl-5,8a-propanoperhydroquinoline (IX).

The novel and efficient ring-annelation technique successfully evolved in the above model experiments is now being incorporated into a sequence designed to produce lycopodine[7] (X) itself.



(IX)



(X)

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