RESEARCH PAPERS

OBSERVATIONS ON THE STEREOCHEMISTRY OF BENZAMINE

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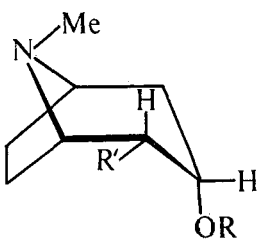
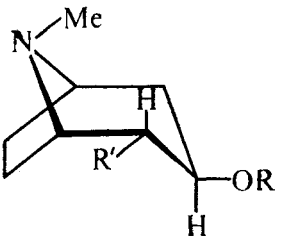
Conformations of the tropane alkaloids have recently been established as the result of the elegant acyl-migration studies of Fodor[1,2,3,4], and by application of the methods of conformational analysis[5,6,7]. Bose and Chaudhuri[6] have ascribed the following structures to cocaine (I, R = C_6H_5CO–, R′= COOMe) and ψ-cocaine (II, R = C_6H_5CO–, R′= COOMe) in which the piperidine ring has the *cyclo*hexane-like chair



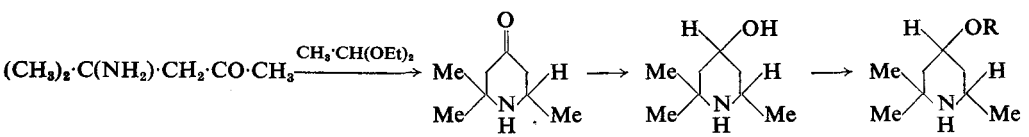
(I)



(II)

conformation, as in the other tropane alkaloids. The established configurations follow from the greater stability of the methyl ester of ψ-ecgonine (II, R = H, R′= COOMe) which is formed preferentially during the reduction of methyl tropinone-2-carboxylate, under equilibrating conditions.

Benzamine (β-eucaine) (VI, R = C_6H_5CO–) is a substituted piperidine related structurally to the piperidine fragment of cocaine. Its stereochemistry has not, until now, been completely elucidated, and although it is but little used as a local anæsthetic, it is of interest to formulate the finer details of its structure, in order to compare it with that of cocaine. Benzamine is synthesised from diacetoneamine (III) by the following reaction sequence[8]:

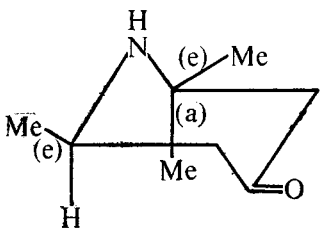


(III) (IV) (V) (VI)

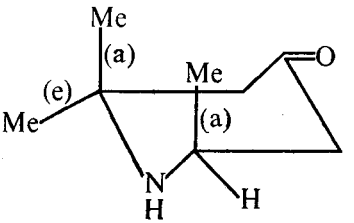
2:2:6-Trimethyl-4-piperidol (V) is obtained from IV in two stereoisomeric forms, one of which, according to Harries[8], is labile and convertible into its more stable epimer by refluxing with sodium amyloxide.

These two substances were regarded by Harries as possessing configurations comparable with those of cocaine and ψ-cocaine respectively, on account of the similar differences of stability between these last-named isomers. This conclusion was supported by the further observation that the epimeric mandelates (VI, R = C_6H_5·CHOH·CO–) derived from these two alcohols (V) exhibited minor differences in physiological activity, which were similar to those shown by cocaine and ψ-cocaine. That these inferred relationships are in fact correct can now be shown by the independent deduction of configuration to be described in the sequel.

It is accepted that simple piperidine derivatives exist as *cyclo*hexane-like *chair* structures[5,6,7], and on this basis the intermediate 2 : 2 : 6-trimethyl-4-piperidone (IV) may be represented by one of the two alternative conformations, (VII) or (VIII). Of these, (VII), in which two methyl

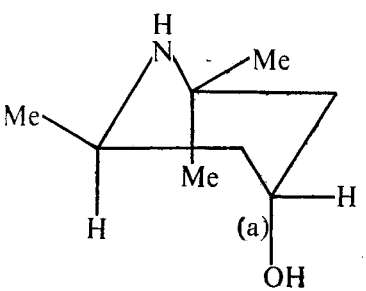


(VII)

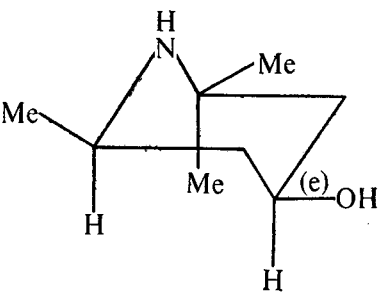


(VIII)

substituents are equatorial and only one axial[10], can be regarded as the preferred conformation, since, in the absence of other evidence to the contrary, that conformation with the greater number of equatorial substituents is regarded as the stable one. Reduction of the carbonyl groups of (VII) to the corresponding alcohol introduces a new centre of asymmetry, two disastereoisomers being produced in which the hydroxyl groups are respectively axial (IX) and equatorial (X). By virtue of



(IX)



(X)

the 1 : 3-non-bonded repulsive interactions between the $C_{(4)}$ axial hydroxyl group and the $C_{(2)}$ axial methyl group (IX), this isomer will be less stable than, and convertible under equilibrating conditions (sodium amyloxide), to (X). Thus the less stable isomer, of m.pt. 160° to 161° C. has the structure IX, whilst its more stable epimer, m.pt. 136° to 137° C. formed from

it by the action of sodium amyloxide has the structure (X). It is this latter, more stable isomer which is benzoylated to give benzamine. It follows, that as inferred by Harries, the stereochemical configuration of benzamine is related to that of ψ-cocaine, whilst that of the isomeric *iso*benzamine[9] is related to that of cocaine. It would appear, therefore, that the mydriatic activity, which is shown, in this series, by cocaine and *iso*benzamine only, is associated with the axial orientation of the $C_{(4)}$ hydroxyl group.

Summary

The stereochemical configurations of the two isomeric 2:2:6-trimethyl-4-piperidols and of benzamine and *iso*benzamine have been established by conformational analysis.

References

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