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The configuration of β-eucaine and β-isoeucaine

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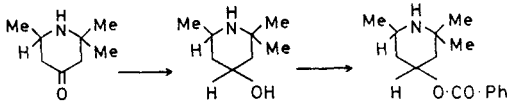
The configurations of the two isomers, β-eucaine (benzamine hydrochloride B.P.C. 1954) and β-isoeucaine have been deduced. As a result of a study of the nuclear magnetic resonance spectra and of catalytic hydrogenation and oxidation, the α-form has been assigned an equatorial hydroxyl group on C-4 and the β-form an axial hydroxyl group in this position.

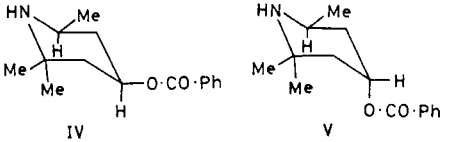
THE compound, β-eucaine (benzamine hydrochloride, B.P.C. 1954; 4-benzoyloxy-2,2,6-trimethylpiperidine hydrochloride) was prepared as a cocaine substitute by reduction of 2,2,6-trimethylpiperid-4-one (I) with sodium amalgam to yield a mixture of two isomers of 2,2,6-trimethyl-4-hydroxypiperidine (II) of melting points 137–138° and 160–163°.

The labile isomer of higher melting point was converted to the stable isomer by refluxing with sodium amylate (Harries, 1897), and this was then *O*-benzoylated to give β-eucaine (III).



I II III

King (1924) prepared and examined β-eucaine and its isomer, β-isoeucaine, in the four optically active and two racemic forms and Stenlake (1954) attempted to deduce the configurations of both β-eucaine and β-isoeucaine by conformational analysis, ascribing to them the structures (IV) for β-eucaine and (V) for β-isoeucaine.



IV V

No experimental evidence was provided to support this view, but it was deduced that the presence in both cocaine and β-isoeucaine of mydriatic activity was due to a similar configuration of the benzoyloxy-group in both molecules. Unfortunately the configuration of cocaine accepted at the time was that of Fodor (Fodor & Nador, 1953), where the benzoyloxy-group was assigned to the axial position. It has since been shown (Fodor, Kovacs & Weisz, 1954) that this group in cocaine occupies the equatorial position. The foregoing conclusions would therefore appear to be invalid and the present work outlines an attempt to deduce the configurations of both isomers of β-eucaine from experimental evidence.

The two isomers of II have melting points of 137–138° and 160–163° and are usually referred to in the literature as the α- and β-forms respectively. This practice is followed in the present report.

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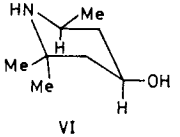
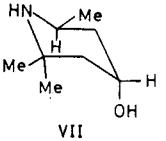
The usual conformational arguments would indicate that in each case the piperidine ring possesses the chair form and that, of the three methyl groups in positions 2 and 6, two will occupy equatorial positions for reasons of steric repulsion and 1,3 interactions. Hence the two possible conformations of 2,2,6-trimethyl-4-hydroxypiperidine will be as shown in VI and VII, i.e. the hydroxyl group in position 4 may be either axial or



VI

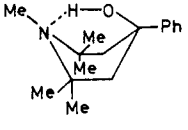


VII

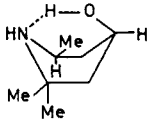
equatorial. The following techniques were employed in attempts to assign a definite configuration to each isomer.

Measurement of pK_a. These were made on a Cambridge pH meter using a glass electrode and calomel reference electrode. α-Form of II, $pK_a = 10{\cdot}0$; β form of II, $pK_a = 10{\cdot}6$, α-*O*-benzoyl derivative, $pK_a = 9{\cdot}4$; β-*O*-benzoyl derivative, $pK_a = 9{\cdot}8$. It might have been expected that the form possessing an equatorial hydroxyl group, i.e. the chair conformer corresponding to VI, would exhibit some degree of hydrogen bonding with the nitrogen atom which would enhance the base strength, but this is not indicated in the pK_a values of the two forms of II which therefore do not contribute any positive evidence to the configuration.

Infrared spectra. These were measured on a Unicam SP.100 I.R. Spectrometer. Lyle (1957) has shown that in 1,2,2,6,6-pentamethyl-4-phenyl-4-hydroxypiperidine (VIII) a band at 3350 cm^{-1} is due to an intramolecular bonded O–H stretch. Zenitz, Martini, Priznar & Nachod (1952) reported a similar band at 3390 cm^{-1} in pseudotropine.



VIII



IX

The fact that the infrared spectra of both forms of II show only a non-bonded –OH frequency at 3630–3640 cm^{-1} is taken to indicate that a stabilized boat structure IX is absent in each case, probably because the secondary amine is a weaker base than the tertiary amino-group of VIII.

$N \rightleftharpoons O$ acyl migrations. The migration of acyl groups such as acetyl and benzoyl from nitrogen to oxygen and vice-versa has been employed especially by Fodor & Kovacs (1952) in studies in the tropine series. Accordingly the α- and β-*O*-benzoyl derivatives and the β-*N*-benzoyl derivative of II were prepared (King, 1924) and acyl migrations were attempted (Nickon & Fieser, 1952). No evidence of migration of acyl group was found, the starting material being recovered unchanged.

Oxazine formation. Attempts to form an oxazine by refluxing either the α- or β-form of II with *p*-nitrobenzaldehyde in chlorobenzene (Hardegger & Ott, 1953) were unsuccessful.

Epimerization of II. The α- and β-forms of II were separately refluxed with (*a*) amyl alcohol and (*b*) sodium in amyl alcohol, and the results examined by thin-layer chromatography. With both forms the use of amyl alcohol alone produced no change, but refluxing the β-form with sodium in amyl alcohol produced a virtually quantitative conversion to the α-form. This was confirmed by its nmr and infrared spectra, and by melting point and mixed melting point determination.

Catalytic hydrogenation of 2,2,6-*trimethylpiperidine*-4-*one* (*I*). Catalytic hydrogenation of the ketone (I) in methanol using Adams catalyst gave the β-form of II as shown by thin-layer chromatography, melting point and mixed melting points, and by nmr and infrared spectra. Since the reacting hydrogen atom will attack from the non-hindered side, this is interpreted as indicating that the β-form has an axial hydroxyl group and an equatorial hydrogen atom as in VII.

Oxidation of α- and β-forms of II. It has already been reported (Harries, 1918) that for the *N*-methyl derivatives of II, the α-form is very resistant to oxidation by chromate to the *N*-methyl derivative of the ketone I, whereas the β-form is very readily oxidized. In sterically hindered secondary alcohols it is usual that those isomers having axial hydroxyl groups are more readily oxidized by chromate (Barton, 1964) and this again, indicates that the β-form has the axial hydroxyl group.

Catalytic oxidation. The α- and β-forms of II were catalytically oxidized using platinum catalyst prepared by reduction of Adams platinum dioxide. The β-form absorbed the calculated amount of oxygen in 4 hr, whereas the α-form had only taken up 10% of this after 24 hr. This indicates that the β-form has the more readily oxidizable axial hydroxyl group, which is supported by the observations of Angyal (1963) and Anderson & Post (1963), for the inositols.

Nuclear magnetic resonance. This was measured in pyridine and D_2O solutions on a Perkin Elmer R.10 nmr spectrometer.

Assuming that the structures VI and VII represent the preferred conformations of the α- and β-isomers, the hydrogen atom on C-4 should be readily distinguishable in the nmr spectrum, because of the presence of the hydroxyl group and might be expected to occur at $\tau = 5$ to 6.

On the assumption that a first order approach can be made we would expect VII to show splitting of the hydrogen atom at C-4 by the four H atoms on C-3 and C-5, all at a 60° dihedral angle and hence all being identically coupled. This would be expected to result in a quintuplet of relative magnitudes 1, 4, 6, 4, 1 at regular intervals (J = 3 to 5) and for the *O*-benzoyl ester, structure V, a similar prediction is made. Structure VI would be expected to show more complex splitting of the hydrogen atom on C-4 due to: (*a*) coupling with the axial hydrogen atoms on C-3 and C-5 at a dihedral angle of 180° ($J' = 10$ to 12), (*b*) coupling with the equatorial hydrogen atoms on C-3 and C-5, dihedral angle of 60° ($J'' =$ 3 to 5), resulting in a nonet of relative magnitudes 1, 2, 1, 2, 4, 2, 1, 2, 1

with intervals of J'', J'', J' − 2J'', J'', J'', J' − 2J'', J'', J''. Again, the corresponding *O*-benzoyl ester, structure IV, will show a similar pattern.

Results

The α-form of II gave a nonet centred at 5·85 τ and an expanded trace showed relative magnitudes of 1, 2, 1, 2, 4, 2, 1, 2, 1 at intervals of 4·75, 4·5, 2·1, 4·75, 4·8, 2·25, 4·3 and 5·0 cycles/sec at 60 Mcycles/sec giving J'' = 4·5 to 5·0 cycles/sec and J' = 11·35 cycles/sec. The *O*-benzoyl derivative of the α-form of II (benzamine) also gave a similar pattern of relative magnitudes, 1, 2, 1, 2, 4, 2, 1·3, 2·3, 1 centred at 4·7 τ, at intervals of 4·5, 4·75, 2, 4·5, 4·5, 1·75, 4·75, 4·5 cycles/sec giving J'' = 4·5–4·75 cycles/sec and J' = 11–11·5 cycles/sec.

The β-form of II was much less soluble in pyridine and D_2O than the α-form and hence gave a spectrum of rather poorer resolution which showed a quintuplet of relative magnitudes 1, 2·5, 3·25, 2·5, 1 at intervals of 3, 3·1, 3·1, 3 cycles/sec, J = 3 cycles/sec. The *O*-benzoyl ester of the β-form of II (β-isoeucaine) also gave a quintuplet centred at 4·5 τ, of relative magnitudes 1, 4, 6, 4, 1 at intervals of 3, 3, 3, 3 cycles/sec, giving J = 3 cycles/sec. Whilst this work was in progress Chen & LeFevre (1965) published the results of an nmr study of 2,2,6,6-tetramethylpiperidin-4-ol which are in agreement with the foregoing observations.

Discussion

The methods of pK_a measurements, infrared spectra, acyl migration and oxazine formation are inconclusive, the clearest evidence being that obtained by a study of the nmr spectra of the α- and β-forms of II, and of their *O*-benzoyl derivatives. These clearly indicate that the α-form has configuration VI (equatorial hydroxyl) and the β-form that of VII (axial hydroxyl) and that β-eucaine and β-isoeucaine therefore have configurations IV and V respectively.

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