

EQUILIBRATION OF 3-OXOTROPANIUM SALTS

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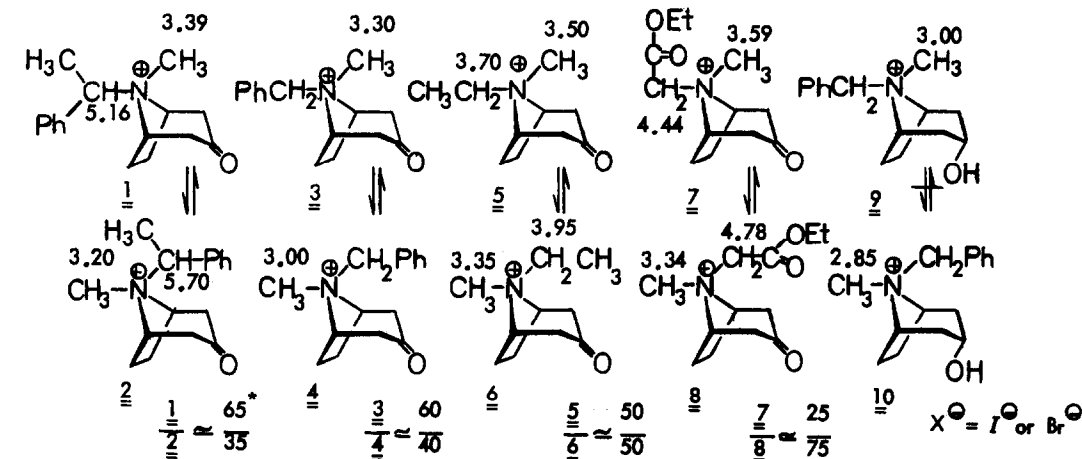
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While investigating the CD behaviour of optically active piperidone-like compounds, we have found that N-isomeric (S)-N-(1-phenethyl)-3-oxotropanium iodides undergo equilibration in aqueous solution at room temperature¹. The equilibrium was followed by CD (290 nm Cotton effect) and by NMR, which showed that the two N-isomers lead to the same equilibrium mixture.

A literature survey revealed that equilibration of quaternary tropanes and related systems was already attempted, for structure assignment purposes². Whereas camphidines and other piperidonic compounds containing N-benzyl groups undergo equilibration (though in drastic conditions)², tropanium salts do not³. Of the various mechanisms proposed², the most important one assumes iodide ion attack on the N-substituent. Fodor et al.⁴, on the other hand, found that N-methoxycarbonylmethyl-3-oxo-tropanium bromides undergo equilibration on boiling in the presence of a strong base such as aluminium t-butoxide. Two mechanisms were proposed, assuming either a spiroazetidione or a Hoffman product intermediate.

We were interested to investigate: a) the role of the keto-group and the N-substituent in the equilibration, b) the applicability of our mild equilibration procedure to other compounds, c) the mechanism which governs this reaction. In this context we have studied the equilibration of five pairs of N-isomeric quaternary tropanic compounds⁵ (Scheme I) in aqueous solution.

Scheme I



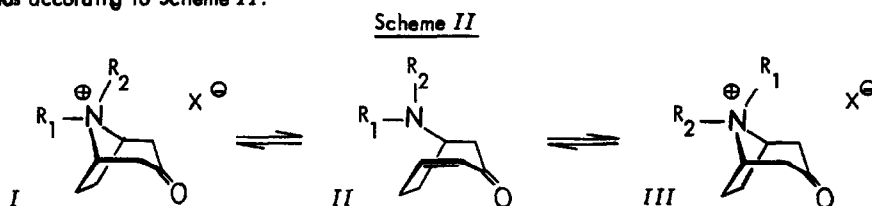
* Equilibrium composition by NMR, according to N-CH₃, N-CH₂-signals.

Comparing the behaviour of the compounds studied by us and the literature data, we have reached the following conclusions:

1. The equilibration process does not affect the optical activity in compounds 1 and 2, i.e., the chiral center is not involved. 2. N-Benzyl-3-oxotropanium salts (3, 4) undergo equilibration, while the tropanium analogues do not³. 3. N-Ethyl-3-oxotropanium salts (5, 6), though lacking any easily displaceable N-substituent nevertheless undergo equilibration. 4. Fodor's compounds (7, 8) undergo equilibration even in our mild conditions and the presence of a strong base is not essential. 5. Compounds lacking a keto-group (such as 9, 10) do not equilibrate.

On examining the NMR spectra of the D₂O equilibrium mixtures it became evident that four protons which may be accounted for the 2,2,4,4 protons α - to carbonyl, were exchanged for deuterium during the process. This is clearly observed in the case of N-ethyl-3-oxotropanium salts (5, 6); the ethyl and methyl moieties were not deuterated. Such an exchange would be expected to occur, if the intermediate in this process were of type *II* (Scheme *II*). The existence of such intermediates was already postulated for 3-oxotropanium salts⁶ and similar systems^{7,8}.

Based on the above observations, it seems likely that the equilibration of the 3-oxotropanium salts in water proceeds according to Scheme *II*:



In the case of camphidinium and piperidinium salts lacking a keto group, the mechanism must be different, and the possibility of the equilibration depends on the N-substituent.

Equilibrations of additional optically active 3-oxotropanium salts are presently investigated for structure assignment by CD and NMR.

Footnotes and References

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3. J. McKenna in "Topics in Stereochemistry" Vol. V., E.L. Eliel and N.L. Allinger Eds., Interscience, N.Y. 1970, p 275.
4. G. Fodor, R.V. Chastain, Jr., D. Frehel, M.J. Cooper, N. Mandava and E.L. Gooden, *J. Am. Chem. Soc.*, 93, 403 (1971).
5. The quaternary compounds were prepared from the corresponding tropane base in acetone and a halo-compound. The products were of >90% purity by NMR, and structures were assigned assuming preferred equatorial steric course of the quaternization⁴. Usually equilibrations are complete after several days at 20°-55°. (Equilibrations conducted at higher temperatures are accompanied by decomposition). The NMR spectra were taken on a JEOL JNM-C-60HL spectrometer.
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