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N-Quaternary Compounds

Part XII. Racemisation Studies

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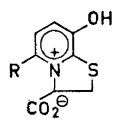
The rates for base-catalyzed racemisation and hydrogen-deuterium exchange of L-2-(3-hydroxypyridinium)propionates in NaOD were found to be similar. The carbanion generated from 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate was reprotonated with retention of configuration. The corresponding desmethyl derivative, however, is optically unstable.

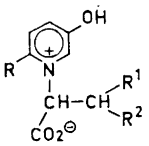
In preceding papers[1-3] the synthesis of pyridinium derivates from optically active amino acids have been described. Such compounds have now been subjected to racemisation studies. L-(—)-8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (Ia) was found to be optically stable on heating in dilute hydrochloric acid. This was also largely true for the monocyclic pyridinium acids (II, III). In alkaline solution, however, the activated methine proton on the chiral carbon is readily abstracted by a base eventually leading to racemisation. Loss of optical activity can also arise by decarboxylation whereby the asymmetric center is lost. The decarboxylation readily takes place due to the neighbouring quaternary nitrogen. The racemisation experiments, therefore, had to be chosen in such a way that the decarboxylation was kept to a minimum. This was checked continuously by chromatography.[2]



I

a) R = CH_3

b) R = H



II R = CH_3

a) $R^1 = R^2 = H$

b) $R^1 = R^2 = CH_3$

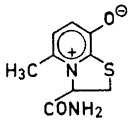
c) $R^1 = H$, $R^2 = C_6H_5$

III R = H

a) $R^1 = R^2 = H$

b) $R^1 = R^2 = CH_3$

c) $R^1 = H$, $R^2 = C_6H_5$



IV

Fig. 1 shows the rate of racemisation of Ia and II in aqueous 1 N NaOH at 35° measured at the sodium D-line. The NMR spectra of these compounds have been recorded in trifluoroacetic acid and in NaOD. The chemical shifts for the methine proton on the asymmetric carbon are given in Table 1. From

Table 1. Chemical shifts for the methine proton at the chiral carbon.

	Substituents			Chemical shift in τ values	
Comp.	R	R^1	R^2	CF_3CO_2H	0.4 N NaOD
IIIa	H	H	H	4.32	4.91
IIIb	H	CH_3	CH_3	4.95	5.57
IIIc	H	H	C_6H_5	4.2–4.3	4.84
IIa	CH_3	H	H	4.15	4.77
IIb	CH_3	CH_3	CH_3	4.77	5.31
IIc	CH_3	H	C_6H_5	4.04	4.57
Ia	CH_3	—	—	3.70	4.25
IV	—	—	—	3.70	3.90[a]

[a] Measured in D_2O.

Table 1 and Figs. 1 and 2 it is evident that the chemical shift of these protons is a good guide to the relative acidity as measured by the rate of racemisation. Furthermore, the relative rates of racemisation and proton acidity agree well

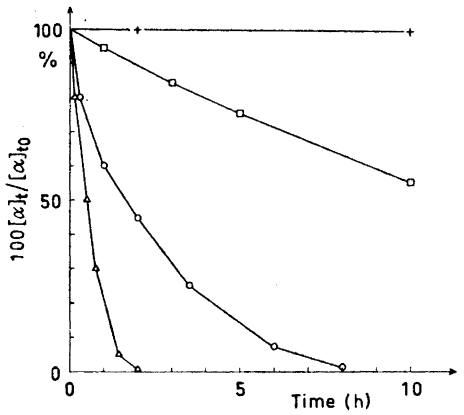


Fig. 1. Rate of racemisation in 1 N NaOH at 35°C. + Ia; ○ IIa; □ IIb; △ IIc.

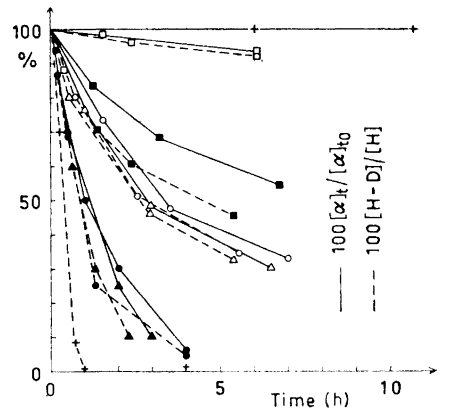


Fig. 2. Rate of racemisation and deuteration in 0.4 N NaOD at 40°C. + Ia; ○ IIa; ● IIIa; □ IIb; ■ IIIb; △ IIc; ▲ IIIc.

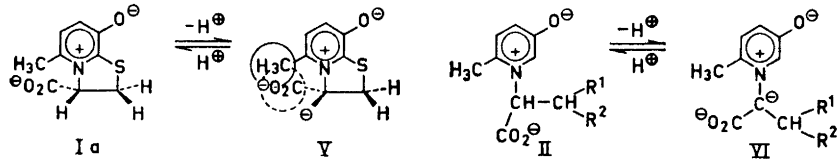
with the electronic properties of the β-substituents. Thus the compound with the two methyl groups on the β-carbon (IIb) is the most stable while the electronegative phenyl ring gives the least stable compound (IIc). The dihydrothiazolo[3,2-a]pyridinium derivative (Ia) behaves differently from the simple pyridinium derivatives. Its methine proton is more acidic than in any of the other compounds but its optical stability is remarkable. This is further discussed below.

Data for the rate of racemisation, measured at the sodium D-line, and deuterium incorporation on the chiral carbon at 40° in 0.4 N NaOD are recorded in Fig. 2. The rate of deuteration was determined by NMR. It is seen that the rate of racemisation corresponds roughly to the rate of deuterium exchange in the case of the simple pyridinium derivatives (II and III). The optical purities of the pyridinium derivatives used in these experiments are unknown. They have been synthesized from optically pure amino acids,[1-3] but no doubt have suffered racemisation to an unknown extent varying from compound to compound.

Racemisation in this case must take place by proton abstraction and the generation of a carbanion. In the absence of stabilizing groups carbanions are pyramidal, but possess a low activation energy for inversion. Asymmetric solvation, steric or electronic effects in the above compounds could well tend to preserve the normal pyramidal geometry. The annular quaternary nitrogen will strongly stabilize the carbanion, largely by induction. Since the rate of deuterium incorporation and the rate of racemisation are similar, the carbanion must be able to invert very much faster than it captures a deuteron from the solvent in any pyramidal geometry resulting in complete racemisation. Alternatively the deuterons could add to either side of a planar or nearly planar carbanion.

The methine proton in the bicyclic structure (Ia) was very rapidly exchanged with deuterium while the optical rotation remained practically constant. This shows that the optical rotation of the deuterated and non-deuterated compound is essentially the same. It also means that rapid inversion of the generated carbanion, or a nearly planar, partly resonance stabilized carbanion must be excluded. If the carbanion were to assume a planar state one would expect non-bonded interaction between the methyl group and the carboxylate group increasing the activation energy for inversion of the pyramidal carbanion. The latter, therefore, abstracts deuterons (protons) from the solvent faster than it can invert, *i.e.* from the same side as the proton was lost whereby the configuration is retained. Heating Ia in N NaOH at 80° for several hours led to partial racemisation and decarboxylation. The actual structure of the intermediate carbanion is difficult to picture. A molecule in which two excessive negative charges are placed closely together, the opposite charges on the annular nitrogen and the phenolic oxygen partially compensating each other, must require that these charges are largely dispersed by solvation. Nevertheless, this must be assumed to be the intermediate since the acidity of the carboxylic acid group is such that it is fully dissociated under the experimental conditions. The methine proton must thus be abstracted from the carboxylate anion. Since the carboxylate anion will decrease the electropositive character of the alpha carbon, the methine proton should be

less acidic than in the corresponding amide (IV). The NMR signals in TFA from the methine protons in both these compounds are found at the same field, *viz.* at 3.70 τ (Table 1). Therefore the amide should be deuterated much faster than the acid. Experimentally it was found under the above conditions that the methine proton in the amide was exchanged with deuteron before the NMR spectrum could be recorded.



Ia V II VI

In the above explanation the methyl group has been made responsible for the optical stability of this molecule. This was confirmed by the synthesis [3] of the desmethyl analogue (Ib) from L-cysteine under the same experimental conditions as used in the synthesis of Ia. While the latter was strongly levo rotatory, $[\alpha]_D = -150°$ (NaOH), the former was optically inactive.

The monocyclic pyridinium derivatives (II and III) are free to rotate around the C—N bond. Therefore they can assume such conformations that the non-bonded interaction in the planar transition state for the inversion of the carbanion is much reduced. Removal of the 6-methyl group (III) reduces the steric interaction further and thereby increases the rate of racemisation and deuteration.

REFERENCES

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