The Mechanism of Racemisation of 2,3-Dihydro-3*R*-iodomethyl-6-methoxycarbonyl-1,4-thiazine: A Novel Bond-switching

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Summary 2,3-Dihydro-3*R*-iodomethyl-6-methoxycarbonyl 1,4-thiazine undergoes a thermally-induced racemisation during which the 2- and the exocyclic-methylene groups become equivalent.

IN connection with some work related to the conformational behaviour of dihydro-1,4-thiazines,[1,2] we had occasion to prepare the title compound (II) by two routes. In method *A* the methylsulphonate (I), m.p. 85—86°, $[\alpha]_D + 230°$ ($CHCl_3$), was converted with sodium hydride in tetrahydrofuran into the aziridine[2] (VII), which gave (II), m.p. 125—126°, $[\alpha]_D + 93°$ ($CHCl_3$), with dilute hydriodic acid In method *B*, (I) was heated in refluxing ethyl methyl ketone with an equivalent of sodium iodide. The reaction was monitored by t.l.c. and after 22 hr. the iodide, which appeared to be the only component present, was isolated (95%) m.p. 125—126°, $[\alpha]_D + 54°$ ($CHCl_3$). The lower optical rotation of the iodide prepared by route *B* indicated that some racemisation had occurred, and indeed if the reaction was left for 10 days the derived iodide was optically inactive.

In a control experiment the optically-pure iodide was heated in refluxing ethyl methyl ketone for 10 days. Complete loss of optical activity was observed, indicating that the racemisation was thermally induced. Furthermore, when the experiment was repeated using ethyl methyl ketone saturated with deuterium oxide, the derived optically-inactive iodide contained no detectable deuterium† (on the basis of mass spectrometry). This established that the racemisation was not occurring by any mechanism involving a reversible elimination–addition of hydriodic acid.

In seeking an explanation for this curious behaviour we considered the possibility of bond-switching between the sulphur and iodine atoms. To test this pathway the dideuteriated iodide (III), $[\alpha]_D + 87°$ ($CHCl_3$), was prepared by route *A*. The mass spectrum of (III) indicated that it contained *ca.* 15% of monodeuteriated and <1% of undeuteriated material. Moreover, in common with (II), the deuteriated iodide exhibited a strong peak at *m/e* 158 ($M^+ - CD_2I$), which confirmed that the isotope was confined to the iodomethylene group. N.m.r. spectroscopy at 90 MHz substantiated the latter result since the octet centred at τ 6·68 ($CDCl_3$), due to the exocyclic methylene group, was absent.

On heating in ethyl methyl ketone for 10 days the optical rotation of the iodide (III) fell to zero, and, on the basis of n.m.r. and mass spectroscopy, the deuterium was equally distributed between the 2- and the exocyclic-methylene groups. This result, which demonstrated the

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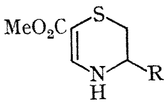
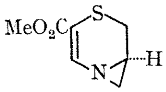
† The exchangeable deuterium (*i.e.* N–D) was removed by shaking a chloroform solution of the iodide with water.

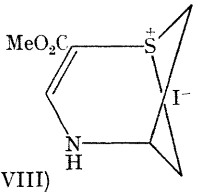
equivalence of the methylene groups during the reaction, may be accommodated by a symmetrical, ion-pair intermediate such as (VIII) or by a concerted reorganisation *via* a transition state such as (IX). The stereochemical consequences of these pathways are distinct: the former requires a 1,3-sulphur migration with inversion of configuration at the exocyclic-methylene group, while the latter demands retention of configuration at the latter site. As yet the stereospecific introduction of a single deuterium atom into the iodide, which would distinguish the mechanisms, has not been accomplished. However, it is worth pointing out that the rate of racemisation is only slightly sensitive to solvent polarity,‡ implying that little ionic character is developed at the transition state. Furthermore, if the ion-pair (VIII) is involved internal return of the iodide ion is remarkably efficient, since none of the ether (IV) was detected when the racemisation was performed in refluxing ethanol.



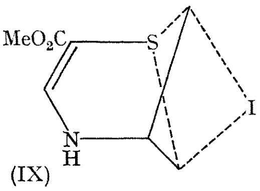
(I) R=CH$_2$OSO$_2$Me
(II) R=CH$_2$I
(III) R=CD$_2$I
(IV) R=CH$_2$OEt
(V) R=Me
(VI) R=CH$_2$Cl



(VII)



(VIII)



(IX)

We have recently commented upon the unusual conformational properties of some 2,3-dihydro-6-methoxycarbonyl-1,4-thiazines which are substituted with polar groups at position 3.[2] For example, while the 3-methyl group of (V) shows no preference for the axial or equatorial environment the 3-methylsulphonoxymethyl and the 3-chloromethyl groups of (I) and (VI) display a marked preference for the axial orientation. Similarly the iodide exists predominantly in the conformation with the iodomethyl group axial. We have suggested that the axial preference may be associated with a dipolar attraction between the sulphur and the electrophilic carbon of the 3-substituent. It is of added interest, therefore, that bond-making and bond-breaking processes involving these centres have now been demonstrated.

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‡ The relative rates in benzene, ethyl methyl ketone and ethanol (80°) were *ca.* 0·4 : 1·0 : 1·4 respectively.

[1] A. R. Dunn, I. McMillan and R. J. Stoodley, *Tetrahedron*, 1968, **24**, 2985.
[2] A. R. Dunn and R. J. Stoodley, *Tetrahedron Letters*, 1969, 2979.