Tetrahedron Letters No.39, pp.3367-3370, 1969. Pergamon Press. Printed in Great Britain.

THE CONFORMATIONAL PREFERENCE OF SOME 4-THIA-1-AZA-BICYCLO[4.1.0]HEPT-2-ENES

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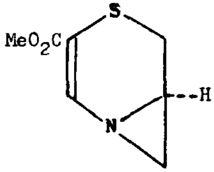
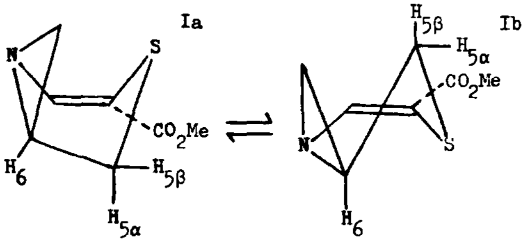
(Received in UK 6 July 1969; accepted for publication 14 July 1969)

Recently (1) we reported the preparation of (6L) 3-carbomethoxy-4-thia-1-azabicyclo[4.1.0] hept-2-ene (I). This compound is of interest since its ground- and excited-state properties should provide a measure of the interaction of the aziridine ring with the π-electrons. For example, the UV spectrum of I (EtOH) shows not only an absorption maximum at 230 nm (ε 6,500) attributable to the αβ-unsaturated ester chromophore (2), but also a maximum at 298 nm (ε 7,700) (3) indicating that either the nitrogen lone pair or the three-membered ring is extending the conjugation of the π-system.

I





Ib

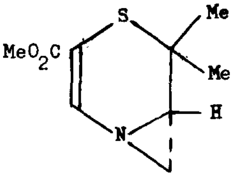
In principle I may exist in one of two conformations represented by Ia and Ib. Conjugation involving the hetero-atom lone pair is only possible in conformation Ib. Although this interaction is likely to be trivial in the ground state of the molecule, when the electron pair is expected to possess a considerable amount of s-orbital character (4), it could become important in an excited state in which the equilibrium geometry involves a near-planar, trigonal nitrogen. In conformation Ia the polarised electrons of the bent N-C bonds are well situated for overlap with the π-system (5), and this conjugation may become more effective in an excited species. Consequently a knowledge of the preferred conformation of I is of importance in an interpretation of its UV properties.

The NMR spectrum of I ($CDCl_3$) shows two quartets at τ 8.21 ($J_{5\alpha,5\beta}$ 12.7 Hz, $J_{5\beta,6}$ 7.6 Hz) and 6.67 ($J_{5\alpha,5\beta}$ 12.7 Hz, $J_{5\alpha,6}$ 5.7 Hz) for $H_{5\beta}$ and $H_{5\alpha}$ respectively; H_6 appears as a broad multiplet centred at 7.2, while the endo- and exo-protons of the aziridine ring are observed as doublets at 8.54 ($J_{6,7\text{-endo}}$ 3.0 Hz) and 7.52 ($J_{6,7\text{-exo}}$ 4.4 Hz) (6). The ester and vinylic protons are singlets at τ 6.25 and 2.25. The coupling constants of the 5β, 5α and 6 protons, which are solvent independent, are clearly in accord with conformation Ib, in which the dihedral angle between $H_{5\beta}$ and H_6 is estimated to be ~ 150° and that between $H_{5\alpha}$ and H_6 ~ 30°. Furthermore although the chemical shifts of $H_{5\beta}$ and $H_{5\alpha}$ vary with solvent ($\tau_{5\beta}$ 8.75 and $\tau_{5\alpha}$ 7.35 in C_6H_6) their chemical-shift differences are not changed markedly (7). Finally the chemical shift of $H_{5\beta}$ (8) suggests that it lies in the shielding zone of the three-membered ring (9).

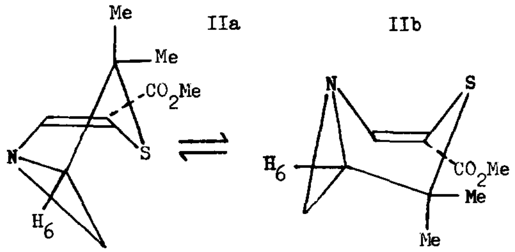
The evidence, therefore, strongly indicates that conformation Ib is preferred irrespective of solvent. Consequently the UV absorption at 298 nm is due to overlap of either the hetero-atom lone pair or the bent N1-C7 bond with the double-bond.

In an attempt to differentiate between these possibilities (6D) 3-carbomethoxy-5,5-dimethyl-4-thia-1-aza-bicyclo[4.1.0]hept-2-ene (II) was prepared. Since conformation IIb possesses an ~ eclipsed interaction corresponding to ~ 3 kcal/mole (10) between the 5α-methyl group and the C6-C7 bond of the aziridine ring, conformation IIa was expected to be favoured. Molecules present in the latter conformation should reflect the conjugative properties of the bent N1-C6 and N1-C7 bonds.

II



IIa IIb



The aziridine II, $[\alpha]_D$-220°(CHCl$_3$), was obtained from 3D,6-dicarbomethoxy-2,3-dihydro-2,2-dimethyl-1,4-thiazine (11) in a manner analogous to that used for the preparation of I (1). The UV spectrum of II (EtOH) is similar to that of I, showing maxima at 230 nm (ε 5,100) and 309 nm (ε 6,600) (12). Its NMR spectrum (CDCl$_3$) exhibits singlets at τ 8.98 and 8.39 for the *gem*-dimethyl group, at 6.30 for the ester and at 2.24 for the vinylic proton. The *endo*- and *exo*-protons appear as doublets at τ 8.18 ($J_{6,7\text{-}endo}$ 3.5 Hz) and 7.70 ($J_{6,7\text{-}exo}$ 4.6 Hz) respectively, due to coupling with H$_6$ which is a quartet at 7.25 (6). The shielding of the 5α-methyl group (13) implies that conformation IIb is still predominant. Moreover, although the chemical shifts of the methyl groups are solvent dependent (τ 9.27 and 8.74 in C$_6$H$_6$) their chemical-shift differences are quite similar (7), suggesting that the conformational equilibrium is not changed significantly by solvent. A study of internal nuclear Overhauser effects (14) in II provides further support that conformation IIb is preferred. Irradiation at the high-field methyl signal leads only to an increase in the integrated intensity (~ 45%) of the *endo*-hydrogen at position 7, while irradiation at the low-field methyl signal results in an intensity increase (~ 35%) for H$_6$. These observations indicate that the axial methyl group and the *endo*-hydrogen of the aziridine ring are in close proximity and that the equatorial methyl group is close to H$_6$, in accord with conformation IIb.

In seeking an explanation for the unexpected conformational behaviour of II we considered the possibility that conformations Ib and IIb possess some ground-state, conjugative stabilisation compared to Ia and IIa and that the latter conformations are destabilised by an unfavourable interaction between the sulphur atom and the *endo*-hydrogen of the aziridine ring.

There is little evidence to support the former interpretation. Thus the ester groups of I and II absorb at 1714 and 1710 cm^{-1} respectively in CCl$_4$, which is close to that observed for αβ-unsaturated esters (15). Furthermore both I and II are readily saponified by sodium hydroxide at similar rates to give the corresponding sodium salts. By contrast the 6-carbomethoxy group of (3L),6-dicarbomethoxy-2,3-dihydro-4-methyl-1,4-thiazine (III) (16), in which ground-state conjugation involving the nitrogen lone pair is considered to be important, absorbs at 1697 cm^{-1} (CCl_4) and it is resistant to alkaline hydrolysis. It is also pertinent that the sodium salts derived from I and II adopt conformations which are essentially unchanged from those of the parent esters (on the basis of NMR spectroscopy in D_2O).

According to Dreiding models of conformations Ia and IIa the distance between the endo-hydrogen of the aziridine ring and the sulphur atom is ~ 2.4 Å. An approximate calculation (17) suggests that this interaction is ~ 1.0 kcal/mole and consequently it does not appear to be a decisive factor in controlling the conformational equilibrium.

In considering the UV properties of the bicyclic aziridines we have employed III as a reference compound. Both the ground and excited states of this molecule are considered to possess a near-planar arrangement of nitrogen, olefin and ester, with the excited state being more polar than the ground state. Thus the UV spectrum of III (EtOH) shows a maximum at 320 nm (ϵ 11,000) which is shifted to 314 nm (ϵ 8,400) in cyclohexane. Consequently there is an increase in the energy difference between the ground and excited states of I and II compared to III (in EtOH) of ~ 6.6 and 3.2 kcal/mole respectively. These surprisingly small increases lead us to believe that the nitrogen lone pair is conjugatively interacting with the π-electron system in each compound. The decrease in energy between the ground and excited states of II compared to I corresponds to ~ 3.4 kcal/mole. Since this value is in good agreement with the anticipated increased compressional interaction present in conformation IIb compared to Ib we conclude that there is a substantial relief of ground-state strain in attaining excited-state geometry. It is of some interest that this strain is not reflected in enhanced reactivity of the aziridine ring of II over I. Thus in a competitive experiment an equimolar mixture of I and II was treated with a half equivalent of toluene-p-sulphonic acid in acetone. NMR analysis of the mixture revealed that II underwent ring-opening ~ 1.5 x faster than I.

It is difficult to estimate the energy involved in distorting the aziridine nitrogen toward trigonal geometry in the case of I and II because of the constraint imposed by the fused six-membered ring. However, it is worth noting that nitrogen inversion in aziridines probably involves a transition state in which the nitrogen is planar and so inversion barriers may serve as a crude model. Inversion is facilitated when the transition state is resonance-stabilised since the barrier of ~ 19 kcal/mole for 1-methylaziridine (18) is dramatically lowered to ~ 7.6 kcal/mole in the case of 1-carbomethoxyaziridine (19).

Acknowledgments We thank Mr. J.W. Akitt for determining the NMR spectra (measured at 90 MHz using a Bruker-Spectrospin spectrometer), and S.R.C. for a research studentship (to A.R.D.).

References and footnotes

1. A.R. Dunn and R.J. Stoodley, Tetrahedron Letters No. 35, 2979(1969).
2. A.T. Nielsen, J. Org. Chem. 22, 1539 (1957).
3. This maximum is shifted to 293 nm (ε 6,500) in cyclohexane.
4. H.A. Bent, Chem. Rev. 61, 275 (1965).
5. W.G. Dauben and G.H. Berezin, J. Amer. Chem. Soc. 89, 3499 (1967).
6. S.J. Brois and G.P. Beardsley, Tetrahedron Letters 5113 (1966).
7. We have examined several dihydro-1,4-thiazines and where solvent-induced conformational changes occur large chemical shift differences of these protons are observed.
8. In model compounds, which are considered to be conformationally homogeneous, the axial protons absorb at τ 7.44 - 7.66 ($CDCl_3$).
9. K. Tori, K. Kitahanoki, Y. Takana, H. Tanida and T. Tsuji, Tetrahedron Letters 869 (1965); K. Tori, K. Aono, K. Kitahanoki, R. Muneyuki, Y. Takana, H. Tanida and T. Tsuji, ibid 2921 (1966).
10. This value assumes that the interaction corresponds to a Me : Me interaction as in the eclipsed form of n-butane. See "Structures of Organic Molecules", N.L. Allinger and J. Allinger, Prentice-Hall, Inc., N.J. p. 96 (1965).
11. I. McMillan and R.J. Stoodley, J. Chem. Soc. (C) 2533 (1968).
12. This maximum is shifted to 305 nm (ε 6,300) in cyclohexane.
13. In model compounds, which are believed to be conformationally homogeneous, the high-field methyl groups (presumed to be axial) appear at τ 8.73 - 8.75 ($CDCl_3$).
14. F.A.L. Anet and A.J.R. Bourn, J. Amer. Chem. Soc. 87, 5250 (1965).
15. "The IR Spectra of Complex Molecules", L.J. Bellamy, Wiley, N.Y. p. 181-182 (1958).
16. A.R. Dunn, I. McMillan and R.J. Stoodley, Tetrahedron 24, 2985 (1968).
17. "Conformational Analysis", E.L. Eliel, N.L. Allinger, S.J. Angyal and G.A. Morrison, Interscience Publishers, N.Y. p. 451 (1965).
18. H.S. Gutowsky, Ann. N.Y. Acad. Sci. 82, 3599 (1960).
19. F.A.L. Anet and J.M. Osyany, J. Amer. Chem. Soc. 89, 352 (1967).