Thiazepine Photochemistry. Ready 1,3-Hydrogen Shifts from a Side-chain Amide

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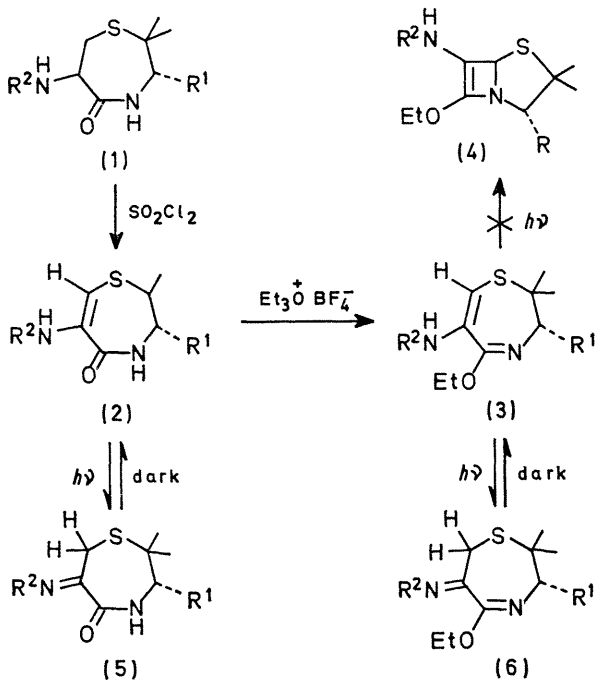
Summary An unusual, thermally reversible, 1,3-hydrogen shift occurs during irradiation of 6-benzyloxycarbonylamino-2,3-dihydro-1,4-thiazepines (2, 3, and the corresponding sulphoxide and sulphone of 3b); this is a special case of imine-enamine tautomerism, arising from the singlet excited state.

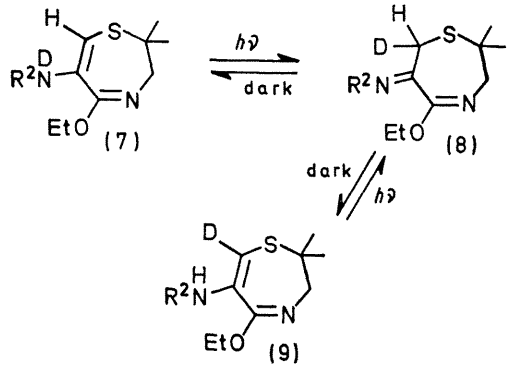
PHOTOCHEMICAL ring closure of cyclohepta-1,3-diene derivatives is a general and direct route to the bicyclo[3,2,0]-hept-6-ene ring system.[1] By analogy, the thiazepine (3) would lead to a thiazabicyclo[3,2,0]hept-6-ene (4) closely



a; $R^1 = MeOCO$; $R^2 = PhCH_2OCO$
b; $R^1 = H$; $R^2 = PhCH_2OCO$

related to penicillin, and thus is an intriguing potential precursor of new penicillins.[2] We report the preparation and behaviour on irradiation of (3a), a simpler model system, (3b), and related heterocycles. Ring closure has not been observed for these compounds; an unusual, thermally reversible 1,3-hydrogen transfer dominates the reactions of the singlet excited state.

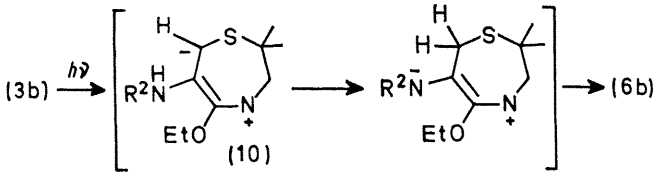
The syntheses are direct and efficient, beginning with the known general route to tetrahydrothiazepinones[3] followed by chlorination and dehydrochlorination, and finally *O*-alkylation using triethyloxonium fluoroborate.[4] For example, treatment of (1b) with sulphuryl chloride in dichloromethane at −30°, followed by stirring at 25°, gives the unsaturated lactam, (2b), directly in 72% yield (m.p. 118–120°).† Triethyloxonium fluoroborate (slight excess) in dichloromethane at 0° reacts remarkably selectively at the lactam carbonyl to afford (after washing with aqueous sodium carbonate) the dihydrothiazepine (3b) in high purity and 94% yield.† In the same way the analogues (2a) and (3a) of unknown optical purity were prepared from D-(+)-penicillamine; $[\alpha]_D^{25}$ +74·2° ($CHCl_3$)† for (2a), $[\alpha]_D^{25}$ −9·24° ($CHCl_3$)† for (3a).



Irradiation of (3b) (u.v. max 294 nm, ϵ 5300, *ca.* 10^{-3} M, under argon) with a 450 w Hanovia medium-pressure mercury arc and Pyrex filter in hexane, dichloromethane, ether, acetonitrile, or methyl alcohol at temperatures ranging from −55° to +45° gave complete conversion into the same single product, which is assigned structure (6b) from spectral and chemical data, including a labelling experiment. Compound (6b) is thermodynamically very unstable, returning to (3b) by a thermal 1,3-hydrogen shift

† The n.m.r. and i.r. spectral data of this compound are in complete accord with the structure. Elemental composition has been verified by combustion analysis or by high-resolution mass spectrometry (AEI model MS-902).

which is dependent on concentration and solvent polarity as well as acid and base catalysis. The ^{1}H n.m.r. signal due to the $-CH_2-S$ group is a sharp singlet (δ 3·30, 2H) at 20° but broadens significantly at 0° indicating a temperature dependence consistent with inversion about the side-chain imino-group in (6b). The coalescence temperature cannot be determined simply, because of broadening of all signals from (6b) at temperatures below −20°, probably due to slow ring inversion. At *ca.* 0·3M and 25° in $CDCl_3$ solution



the half-life of (6b) is 2 h, but in dilute n-pentane solution (*ca.* 2×10^{-3} M), the photoproduct has a much longer lifetime ($t_{\frac{1}{2}}$ 100 h). Addition of triethylamine (5×10^{-4} M) to the dilute n-pentane solution reduced the half-life of (6b) to 0·5 h; acetic acid produced the same effect but only at higher concentrations. We feel that the sensitivity of the lifetime of (6b) to base, acid, and concentration of (6b) and (3b) is in accord with the imine–enamine relationship suggested for these isomers.

Exchange of the side-chain N–H for N–D (as in 7) followed by irradiation, gave a photoproduct for which the ^{1}H n.m.r. spectrum at 20° showed a broad singlet at δ 3·30 (1H) consistent with structure (8) (1D at C-7). On standing at 25°, thermal reversal occurred to give approximately equal amounts of (7) and an isomer (9), with deuterium at C-7. This indicates that the thermal 1,3-shift occurs with approximately equal probability of hydrogen or deuterium transfer, and is completely consistent with the structure assigned to the photoproduct.

The corresponding sulphoxide and sulphone derived from (3b) with appropriate amounts of *m*-chloroperbenzoic acid give exactly parallel results upon irradiation. The non-bonding electrons on sulphur thus play no important part in the photochemical 1,3-hydrogen shift. Surprisingly, the lactam (2b) gives a single photoproduct for which the ^{1}H n.m.r. spectrum and chemical behaviour are consistent with the product (5b) from 1,3-hydrogen shift. Preliminary results indicate that the photochemistry of (3a) and (2a) closely parallels that of the simpler analogues, (3b) and (2b). The major photoproducts (6a, 5a) show appropriate ^{1}H n.m.r. spectra and are thermally unstable, reverting to (3a) and (2a), respectively, with half-lives of the order of several hours at 25°.

A polar singlet excited state (represented by valence bond structure 14), which has been suggested[5] for very similar dihydro-1,4-thiazepines, would provide a simple ionic pathway for the conversion (3 → 6). Alternative mechanisms involving radical or concerted pathways cannot be ruled out at present. The triplet excited state of (3b) (from photosensitization using thioxanthone, E_T = 65·5 kcal/mole[6]) does not give (6b); instead, a mixture of *thermally stable* products, apparently dimers, is formed.

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