Photochemical and Thermal Addition of Methanol to 2-Phenyl-3,1-benzoxazepine-5-carboxylate: Reverse Stereoselectivities in the Two Reactions

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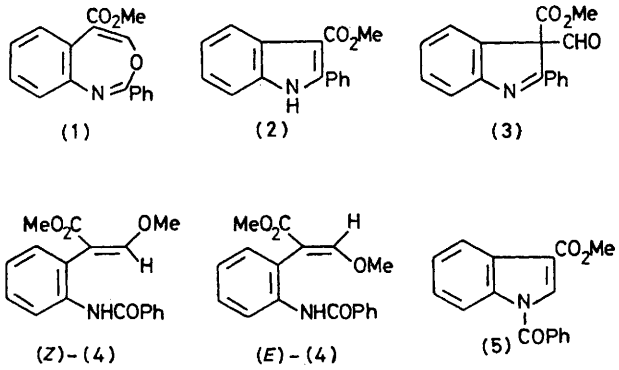
Summary Irradiation of methyl 2-phenyl-3,1-benzoxazepine-5-carboxylate (**1**) in methanol affords the (*Z*)-isomer of methyl 3-methoxy-2-(2-benzamidophenyl) acrylate (*Z*)-(**4**) as the major addition product, while thermal reaction of methanol with (**1**) in the presence of triethylamine gives the (*E*)-isomer (*E*)-(**4**), exclusively; reasons for the observed selectivities are discussed.

THE photochemical reaction of methyl 2-phenyl-1,3-benzoxazepine-5-carboxylate (**1**)† in aprotic solvents results in the almost quantitative formation of the indole-3-carboxylate (**2**) and has been explained in terms of the carboxylate (**3**) as a key intermediate.[1]

We now report a new reaction of the benzoxazepine (**1**), photochemical addition of methanol to form the acrylate (*Z*)-(**4**) which occurs in methanol much more rapidly than intramolecular ring-contraction leading to (**2**). Thus, irradiation‡ of a 2% solution of (**1**) in MeOH until it had been consumed completely (30 min for 1 l of solution) resulted in an 89% yield of a mixture of two 1 : 1 methanol adducts§ [ratio of (*Z*)- to (*E*)-(**4**) *ca.* 3 : 1], together with 4% of (**2**). Repeated recrystallization of the adducts afforded 45% of pure (*Z*)-(**4**),¶ m.p. 143·5—144·5 °C, λ_{max} (log ϵ): 229 (4·39) and 255 sh (4·22) nm. The mother liquor from the recrystallization was confirmed by n.m.r. spectroscopy to contain a *ca.* 1 : 1 mixture of the (*Z*)- and (*E*)-isomers.



† Obtained from 4-methoxycarbonyl-2-phenylquinoline 1-oxide in *ca.* 80% yield by irradiation in an aprotic solvent (*e.g.*, acetone or MeCN); m.p. 79·5—81·5 °C, λ_{max} (MeOH) (log ϵ) 255 (4·43) and 313·5 (3·82) nm.

‡ All irradiations were carried out under nitrogen with a Toshiba 400P high-pressure mercury lamp using a Pyrex filter ($\lambda >$ *ca.* 300 nm). Yields of the addition products (*Z*)- and (*E*)-(**4**) were calculated on the basis of the amount of (**1**).

§ Since the two isomers (*Z*)- and (*E*)-(**4**) behave identically on g.l.c., t.l.c., and column chromatography their proportions were determined by n.m.r. spectroscopy.

¶ Satisfactory microanalyses, and mass and other spectral data were obtained for all new compounds. Unless otherwise noted, n.m.r. spectra were recorded in $CDCl_3$ and u.v. spectra in 95% EtOH. M.p.s are uncorrected.

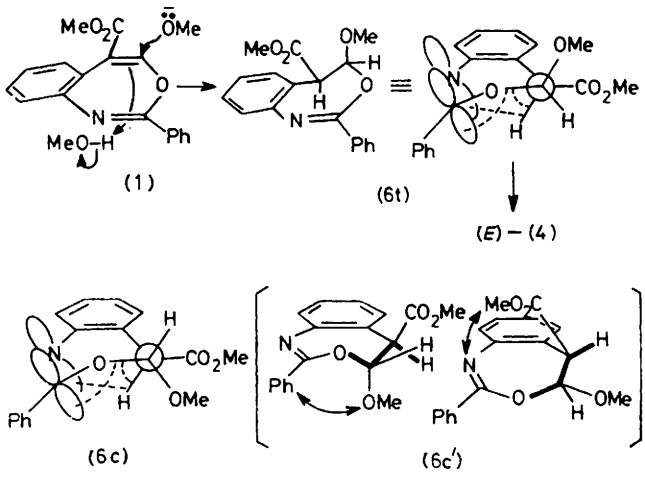
Irradiation of a 2%-methanolic solution of (*Z*)-(**4**) (2 h for 1 l of solution) produced a photostationary mixture of the isomers (*Z*)- and (*E*)-(**4**) in a ratio of *ca.* 1 : 2. This and the fact that almost pure (*Z*)-isomer was obtained if the irradiation of (**1**) [log ϵ values *ca.* 3 at 300 nm for (*Z*)- and (*E*)-(**4**)] in methanol was terminated when one-third of (**1**) had been consumed suggest that the formation of (*Z*)-(**4**) from (**1**) is highly stereoselective.

Though (**1**) was stable in methanol at room temperature in the dark, the presence of triethylamine caused slow stereospecific addition of methanol to (**1**). Thus, a 1% methanolic solution of (**1**) in the presence of 3% of Et_3N at room temperature for 5 h afforded (*E*)-(**4**) (75% yield), m.p. 99—101 °C, λ_{max} (log ϵ): 226 (4·38) and 251 sh (4·30) nm. Irradiation of (*E*)-(**4**) in methanol also produced a *ca.* 2 : 1 photostationary mixture of (*E*)- and (*Z*)-(**4**) within an irradiation time comparable with that for (*Z*)-(**4**). The adducts (*Z*)- and (*E*)-(**4**) were not interconvertible in Et_3N–MeOH. [Under these conditions, slow addition of methanol to (*E*)- and (*Z*)-(**4**) to give 1 : 2 methanol adducts of (**1**) was observed.] Hence, the stereochemical routes to each isomer are clearly different. Both isomers gave the indole (**5**), m.p. 124·5—125·5 °C, in *ca.* 90% yield upon short treatment in refluxing MeOH–10% aq. HCl.

The n.m.r. signals of (*Z*)- and (*E*)-(**4**) are not very different, except for the olefinic protons: (*Z*)-(**4**) δ 6·70 (s); (*E*)-(**4**) δ 7·73, (s). The olefinic proton in the *E*-isomer only would be deshielded by the carbonyl function, so leading to a resonance at lower field than in the (*Z*)-isomer.[2]

Although additional work is required for detailed mechanistic proposals, our preliminary results are consistent with the premise that the formation of (*E*)-(**4**) proceeds by *trans*-addition of methanol (either concerted or stepwise)[3] to give the tetrahedral intermediate (**6t**) which undergoes a *cis*-elimination through a retro-ene reaction.[4] The converse mechanism, *trans*-elimination from an intermediate arising from *cis*-addition would be prohibited on stereochemical grounds [see conformers (**6c**′)]

For the photochemical formation of (*Z*)-(**4**), the stereochemistry of the adduct formally requires one of two pathways: (i) *trans*-addition followed by *trans*-elimination, or (ii) *cis*-addition followed by *cis*-elimination. We prefer pathway (ii) for two reasons. First, it is difficult to explain why the (*E*)-isomer would not be formed, if it is assumed that the *trans*-addition product (**6t**) is an intermediate. Secondly, concerted addition of a $_{\sigma}2_s$-component to a $_{\pi}2_s$-component is a photochemically allowed pericyclic reaction[5,6] and if the *cis*-addition product were formed, it would be expected to give (*Z*)-(**4**) by retro-ene reaction *via* the conformer (**6c**) in its ground state, just as (**6t**) gave (*E*)-(**4**).



Since such a Michael-type addition of a nucleophile to the 4,5-double bond in oxazepine derivatives has not been observed previously, an essential requisite for its occurrence seems to be the presence of an alkoxycarbonyl group (a strong electron-withdrawing group) at the 5-position in the oxazepine system. While more thorough experiments are needed to clarify the mechanism, it is worth noting that photolysis of 4-carboxy-2-phenylquinoline 1-oxide in methanol also gave a minor amount (7%) of a similar type of addition product [CO_2H replaces CO_2Me in (*Z*)-(**4**)] with the (*Z*)-configuration of the double bond, m.p. 183—185 °C, δ [$(CD_3)_2SO$] 6·80 (1H, s, =C*H*OMe).

We have obtained similar results for the photochemical addition of other alcohols to (**1**) and related oxazepines. Details will be reported elsewhere.

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[1] R. Kitamura, H. Fujii, K. Hashiba, M. Somei, and C. Kaneko, *Tetrahedron Letters*, 1977, 2911.

[2] Calculations (assuming the 2-benzamidophenyl group is an aryl group) using the equation derived by C. Pascual, J. Meier, and W. Simon (*Helv. Chim. Acta*, 1966, **49**, 164) indicate that the olefinic proton in the (*E*)-isomer should appear at δ 7·38, and that in the (*Z*)-isomer at δ 7·16.

[3] Reaction of the (*E*)-isomer of *O*-methylbenzohydroximoyl chloride with methoxide ion under comparable conditions leads to essentially complete inversion, the product being the (*Z*)-isomer of methyl-*O*-methylbenzohydroximate. A mechanism involving *trans*-addition of methanol to the (*E*)-isomer [as in the formation of (**6t**) from (**1**)] followed by *trans*-elimination of HCl was proposed: J. E. Johnson, E. A. Nalley, and C. Weidig, *J. Amer. Chem. Soc.*, 1973, **95**, 2051.

[4] Pyrolyses of esters and xanthogens are classic examples of this class of reaction. The reaction becomes more feasible when heteroatoms and other functions are involved in the system: H. M. R. Hoffmann, *Angew. Chem.*, 1969, **81**, 597.

[5] Photochemical Michael-type additions of alcohols to related compounds, *e.g.*, $\alpha\beta$-unsaturated ketones (T. Matsuura and K. Ogura, *J. Amer. Chem. Soc.*, 1966, **88**, 2602), their enol esters (P. De Mayo and J. S. Wasson, *Chem. Comm.*, 1967, 970), and $\alpha\beta$-unsaturated carboxylic acids (R. Stoermer and H. S. Stockmann, *Ber.*, 1914, **47**, 1786) are known. However, stereochemical aspects of these reactions have not been studied.

[6] It was reported recently that photochemical additions of methanol or acetic acid to cycloheptenone were stereospecific giving *trans*-products. Photoisomerization of cycloheptenones to *trans*-cycloheptenones was assumed to be the key step. A similar mechanism is ruled out in this case, since the presence of two other double bonds in the oxazepine system would result in too much strain in the corresponding 4,5-*trans*-oxazepine system: E. Dunkelblum and H. Hart, *J. Amer. Chem. Soc.*, 1977, **99**, 644.

[7] The isolation and structure determination of the other products in this experiment have already been reported: C. Kaneko and R. Kitamura, *Heterocycles*, 1977, **6**, 117.

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