

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

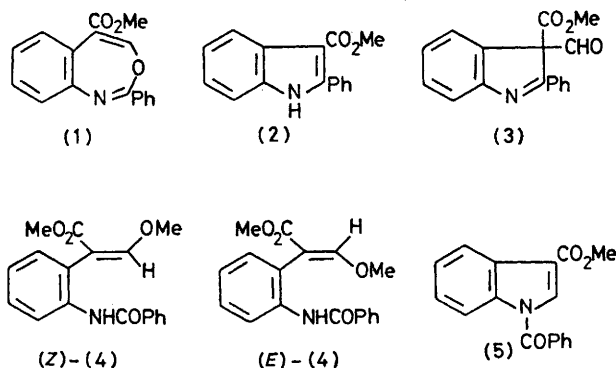
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Summary Irradiation of methyl 2-phenyl-3,1-benzoxazepine-5-carboxylate (**1**) in methanol affords the (*Z*)-isomer of methyl 3-methoxy-2-(2-benzamidophenyl) acrylate (*Z*)-(4) as the major addition product, while thermal reaction of methanol with (**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-3,1-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 CDCl₃ 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.

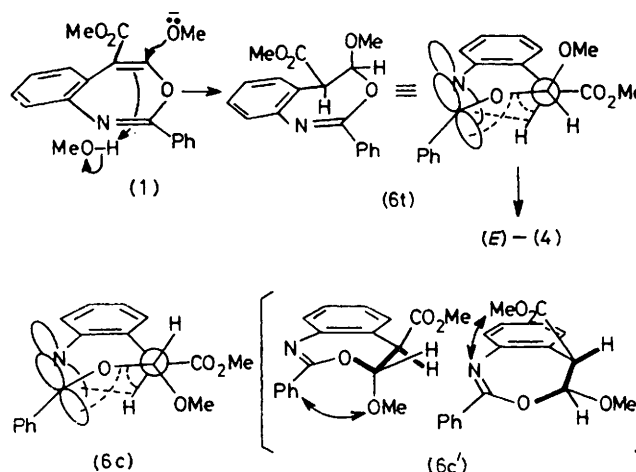
Though (1) was stable in methanol at room temperature in the dark, the presence of triethylamine caused slow stereospecific addition of methanol to (1). Thus, a 1% methanolic solution of (1) in the presence of 3% of Et₃N at room temperature for 5 h afforded (E)-(4) (75% yield), m.p. 99–101 °C, λ_{max} (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 Et₃N-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 σ_2 -component to a π_2 -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 [CO₂H replaces CO₂Me in (Z)-(4)] with the (Z)-configuration of the double bond, m.p. 183–185 °C, δ [(CD₃)₂SO] 6.80 (1H, s, =CHOMe).

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.