

Photochemical Conversion of α -Diazo-amides and -esters into β -Lactams and β - and γ -Lactones

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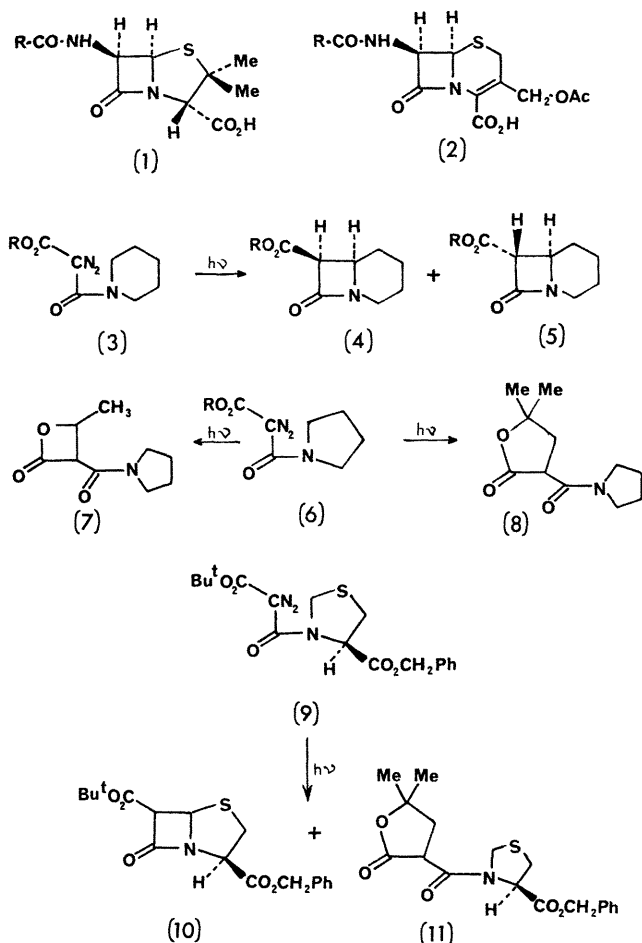
Summary *N*-[(Alkoxy-carbonyl)diazoacetyl]piperidines (**3**; R=Et and Bu^t) give both *cis*- and *trans*-fused β -lactams (**4** and **5**; R=Et and Bu^t) on photolysis, whereas *N*-[(alkoxy-carbonyl)diazoacetyl]pyrrolidines (**6**; R=Et) and (**6**; R=Bu^t) give the β - and γ -lactones (**7**) and (**8**) respectively; photolysis of the *N*-[(*t*-butoxycarbonyl)-diazoacetyl]-L-thiazolidine-4-carboxylic ester (**9**), however, gives both the β -lactams (**10**) and the γ -lactone (**11**).

THE photochemical conversion of α -diazo-amides into fused^{1,2} or monocyclic β -lactams³ provides a potential synthetic method for penicillins (**1**) and cephalosporins (**2**) or their nuclear analogues. However, this approach has

not yet yielded *cis*- β -lactams which are required for the production of effective β -lactam antibiotics nor have the substituents on the β -lactam been suitable for further synthetic manipulation. The photolysis of some diazo-malonic ester amides has now been found to give both *cis*- and *trans*-fused β -lactams, thus establishing the key step for the synthesis of new families of β -lactam antibacterial agents by this approach.

N-[(Ethoxycarbonyl)diazoacetyl]piperidine (**3**; R=Et) was prepared by coupling piperidine and ethyl malonyl chloride,⁴ followed by diazo-exchange with toluene-*p*-sulphonyl azide in the presence of diethylamine (*cf.* ref. 5). Photolysis of this diazo-compound in carbon tetrachloride

($c < 1\%$ w/v) with a medium-pressure mercury lamp in a Pyrex vessel for 2 h at room temperature gave, after chromatography on silica gel, a mixture of *cis*- and *trans*-7-ethoxycarbonyl-1-azabicyclo[4,2,0]octan-8-one (4 and 5; R=Et) in 80% yield, ν_{\max} (CCl₄) 1765 (β -lactam) and 1730 cm⁻¹ (ester), M^+ , m/e 197 (C₁₀H₁₅NO₃ = 197). The ¹H n.m.r. spectrum indicated that the *cis*-*trans* ratio was *ca.* 1:2.



Although it is known that α -diazo-*t*-alkyl esters can give rise to some $\gamma\gamma$ -dialkylbutyrolactones,⁹ this did not seem to outweigh the advantage of *t*-butyl esters in subsequent transformations. In the event, the photolysis of *N*-[(*t*-butoxycarbonyl)diazoacetyl]piperidine (3; R=Bu^t), m.p. 79–80°, ν_{\max} (CCl₄) 2130 (CN₂), 1710 (ester), and 1630

cm⁻¹ (amide), for 1 h as above, gave after chromatography on silica gel only *cis*-7-*t*-butoxycarbonyl-1-azabicyclo[4,2,0]octan-8-one (4; R=Bu^t) (14%), M^+ , m/e 225 (C₁₂H₁₉NO₃ = 225); ν_{\max} (CCl₄) 1765 (β -lactam) and 1730 cm⁻¹ (ester); τ (CCl₄) 6.10 (1H, dd, $J_{6,7}$ 5 Hz, $J_{5,7}$ 1.5 Hz, H-7 α) and its *trans*-isomer (5; R=Bu^t) (40%), m.p. 108.5–109.5°, M^+ , m/e 225 (C₁₂H₁₉NO₃ = 225); ν_{\max} (CCl₄) 1765 (β -lactam) and 1730 cm⁻¹ (ester); τ (CCl₄) 6.57 (1H, d, $J_{6,7}$ 2 Hz, 7 β -H). The stereochemical assignments were made on the basis of the coupling constant $J_{6,7}$,⁸ and the long range W-coupling, $J_{5,7}$, observed for the *cis*-isomer (*cf.* ref. 9). There was no evidence of γ -lactone formation.

The utility of this photochemical reaction for the generation of fused β -lactam-pyrrolidine systems was also investigated. *N*-[(Ethoxycarbonyl)diazoacetyl]pyrrolidine (6; R=Et) was photolysed for 1.5 h as above. The i.r. spectrum of the mixture showed no evidence of β -lactam, but the β -lactone (7) was isolated by chromatography on silica gel, M^+ , m/e 183 (C₉H₁₃NO₃ = 183); ν_{\max} (CHCl₃) 1810 (β -lactone) and 1645 cm⁻¹ (amide); τ (CDCl₃) 4.90 (1H, m, CH-CHMe), 5.93 (1H, d, J 5 Hz, CH-CH-CO), 6.58 [4H, m, N(CH₂)₂], 8.06 [4H, m, N(CH₂CH₂)₂], and 8.41 (3H, d, J 8 Hz, CHMe). By analogy with β -lactams the coupling constant of 5 Hz for the τ 5.93 signal suggests that the β -lactone may have the *cis*-configuration. In view of this, it was not surprising to find that photolysis of *N*-[(*t*-butoxycarbonyl)diazoacetyl]pyrrolidine (6; R=Bu^t) gave after chromatography only the dimethylbutyrolactone (8), ν_{\max} (CCl₄) 1750 (γ -lactone) and 1650 cm⁻¹ (amide).

Intramolecular C-H bond insertions have not hitherto been found with carbenes generated by the photolysis of α -diazo-esters, except for the formation of γ -lactones from *t*-alkyl esters,⁹ and diethyl diazomalonate in the presence of thiobenzophenone.¹⁰ Certainly there does not appear to be any previous report of the formation of β -lactones from the photolysis of α -diazo-esters.

Although the β -lactam-pyrrolidine system has been generated by photolysis of *N*-[(phenyl)diazoacetyl]pyrrolidine,² β - or γ -lactone formation appears to be favoured when this is possible. The expectation that the 2-CH₂ group in a thiazolidine would be more susceptible to carbene insertion was justified when photolysis of benzyl *N*-[(*t*-butoxycarbonyl)diazoacetyl]-*L*-thiazolidine-4-carboxylate (9) for 1 h as above gave mixed stereoisomers of 2-benzyloxy-carbonyl-6-*t*-butoxycarbonyl-1-aza-4-thiabicyclo[3,2,0]heptan-7-one (10), ν_{\max} (CCl₄) 1790 (β -lactam) and 1745 cm⁻¹ (ester) in 50% yield, together with the γ -lactone (11), ν_{\max} (CHCl₃) 1750 (γ -lactone and ester) and 1655 cm⁻¹ (amide).

The synthesis of nuclear analogues of the penicillin-cephalosporin antibiotics is in progress.

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