Formation of 3*H*-1,3-Benzodiazepines by Cycloaddition of 1,3-Oxazol-5-ones to 2-Phenylbenzazete

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Cycloaddition of 1,3-oxazol-5-ones (**2**) to 2-phenylbenzazete (**1**) gives 3*H*-1,3-benzodiazepines (**4**) which undergo thermal rearrangement to 3*H*-indoles.

There are only isolated reports of 5*H*-[1] and 3*H*-benzo-1,3-diazepines[2] and the first 1*H*-derivatives have recently been obtained by photolysis of isoquinoline *N*-imides.[3] We now report that 1,3-dipolar cycloaddition of 1,3-oxazol-5-ones (munchnones) (**2**) to 2-phenylbenzazete (**1**) provides a simple route to 3*H*-1,3-benzodiazepines (**4**).

The pyrolysate, isolated at −78 °C, from flash vacuum pyrolysis of 4-phenylbenzotriazine (440 °C, 10^{-1} Torr), which contains 2-phenylbenzazete[4] was dissolved in cold dichloromethane (−78 °C) and solid 3-methyl-2-*p*-tolyl-4-phenyl-1,3-oxazol-5-one (**2**; Ar^1 = *p*-tolyl, Ar^2 = Ph)‡ was added. After warming to room temperature, removal of the dichloromethane and extraction of the residue with hexane followed by chromatography on alumina gave the benzodiazepine§ (**4**;

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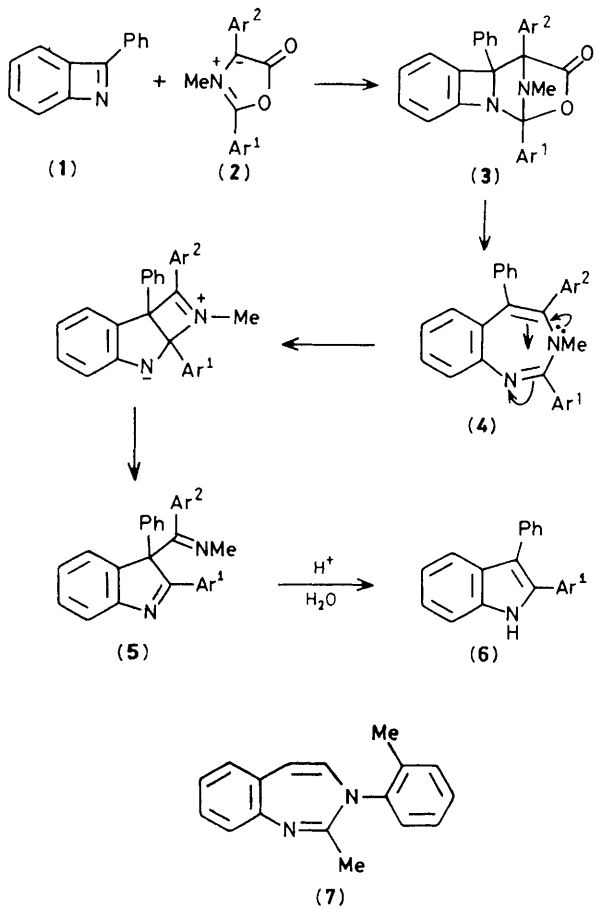
‡ Oxazolones (**2**; Ar^1 = *p*-tolyl, Ar^2 = Ph), m.p. 133—136 °C, and (**2**; Ar^1 = Ph, Ar^2 = *p*-tolyl), m.p. 136—137 °C, were prepared using the method of Huisgen and co-workers, ref. 5.

§ The benzodiazepine structures were fully supported by spectral data but combustion analyses were not obtained because of the instability of the compounds. All other new compounds gave satisfactory analytical and spectral data.



Ar¹ = *p*-tolyl, Ar² = Ph) (47%) as a yellow oil; ν_{max} 1640, 1605, and 1580 cm^{-1}; λ_{max} (EtOH) 275 nm; ^{13}C δ($CDCl_3$), singlets at 165.2, 149.5, 144.3, 140.1, 139.7, 136.7, 134.7, 134.9, 132.5; doublets at 130.0, 130.3, 129.8, 128.7, 127.5, 127.2, 126.7, 126.1, 123.8; and quartets at 37.6 and 21.3 p.p.m.; ^1H δ(CCl_4), 2.31 (ArMe) and 2.60 (NMe); *m/z* 400 (M^+ 16%), 283 (M^+ – tolylCN, 16%), 132 (tolylC$\overset{+}{N}$$CH_3$, 38%), and 118 (PhC$\overset{+}{N}$$CH_3$, 100%). This benzodiazepine presumably arises by extrusion of carbon dioxide accompanied by cleavage of the strained dihydroazete ring in the initial cycloadduct (**3**).

On heating in carbon tetrachloride at 76 °C for 30 h, the benzodiazepine (**4**; Ar¹ = *p*-tolyl, Ar² = Ph) rearranged to the 3*H*-indole (**5**; Ar¹ = *p*-tolyl, Ar² = Ph) (92%); m.p. 161—163 °C; ν_{max} 1632 and 1601 cm^{-1}; ^{13}C δ($CDCl_3$) 77.5 p.p.m. (C-3); ^1H δ(CCl_4) 2.38 (ArMe) and 2.98 (NMe). On hydrolysis with aqueous acid or by adsorption on silica gel this gave 2-*p*-tolyl-3-phenylindole (**6**; Ar¹ = *p*-tolyl).

The isomeric munchnone (**2**; Ar¹ = Ph, Ar² = *p*-tolyl)‡ similarly gave benzodiazepine (**4**; Ar¹ = Ph, Ar² = *p*-tolyl) (44%); m.p. 159—160 °C, which on heating gave the isomeric 3*H*-indole (**5**; Ar¹ = Ph, Ar² = *p*-tolyl) (88%); m.p. 140—142 °C, and ultimately 2,3-diphenylindole (83%) on hydrolysis. Thus the regioselectivity of the initial cycloaddition is consistent with that observed for the addition of munchnones to other electron deficient dipolarophiles.[6] The diphenyl munchnone (**2**; Ar¹ = Ar² = Ph) also gave an analogous series of products. Interestingly the addition of munchnones (**2**) to less reactive acyclic imines proceeds *via* the ring opened oxazolone to give a different type of product.[7]

The thermal rearrangement of the 3*H*-1,3-benzodiazepines (**4**) to 3*H*-indoles (**5**) has precedent in the isomerisation of 3,1-benzoxazepines to 3-acylindoles,[8] and possibly proceeds as indicated. It is also catalysed by acid since direct hydrolysis of the benzodiazepines (**4**) gives the same indoles (**6**) as hydrolysis after thermal rearrangement to 3*H*-indoles (**5**). In this respect the 3-alkylbenzodiazepines (**4**) differ from the previously reported *N*-arylbenzodiazepine (**7**) which was hydrolysed by nucleophilic attack at C-2 followed by ring opening and reclosure.[2]

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References

1 U. Stauss, H. P. Härter, M. Neunschwander, and O. Schindler, *Helv. Chim. Acta*, 1972, **55**, 771.
2 F. M. F. Chen and T. P. Forrest, *Can. J. Chem.*, 1973, **51**, 881.
3 T. Tsuchiya, M. Enkaku, J. Kurita, and H. Sawanishi, *J. Chem. Soc., Chem. Commun.*, 1979, 534; T. Tsuchiya, M. Enkaku, and S. Okajima, *Chem. Pharm. Bull.*, 1980, **28**, 2602; see also H. Plieninger and I. Nógrádi, *Chem. Ber.*, 1955, **88**, 1965.
4 B. M. Adger, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Perkin Trans.* 1, 1975, 45.
5 H. O. Bayer, R. Huisgen, R. Knorr, and F. C. Schaefer, *Chem. Ber.*, 1970, **103**, 2581.
6 R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber.*, 1970, **103**, 2611; H. Gotthardt and R. Huisgen, *ibid.*, p. 2625; R. Huisgen, E. Funke, H. Gotthardt, and H.-L. Panke, *ibid.*, 1971, **104**, 1532.
7 E. Funke and R. Huisgen, *Chem. Ber.*, 1971, **104**, 3222.
8 O. Buchardt, P. L. Kumler and C. Lohse, *Acta Chem. Scand.*, 1969, **23**, 2149; R. Kitamura, H. Fujii, K. Hashiba, M. Somei, and C. Kaneko, *Tetrahedron Lett.*, 1977, 2911.