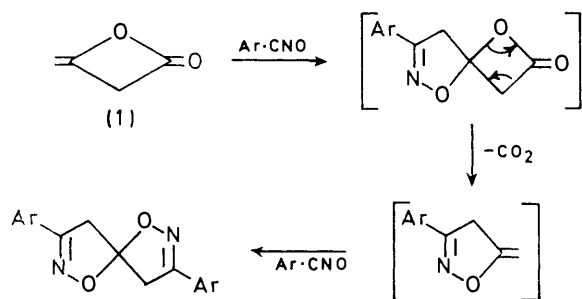


Cycloaddition Reactions of Cumulenes. Part III.¹ Diketen as an Allene-like System in the Reaction with an Azomethine Oxide

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The synthesis of 2-acetoacetyl-5-benzoyl-1-phenylpyrrolidin-3-one (5) from diketen and *C*-benzoyl-*N*-phenylazomethine oxide (benzoylmethyleneaniline *N*-oxide) is described. Its structure was elucidated by spectrometric methods, and its main mass spectral fragmentation path is presented. The formation of product (5) by a cycloaddition reaction followed by intramolecular rearrangement and acetoacetylation is discussed.

IN connection with our studies on the reactivity of cumulenes^{2,3} and cumulene-like¹ systems as dipolarophiles in electrocyclic reactions, we have recently reported that diketen (1) reacts with nitrile oxides to yield bi-isoxazolinic spiro-compounds with loss of carbon dioxide, according to Scheme 1.[†]



SCHEME 1

As we stated previously,¹ the behaviour of diketen in reactions with 1,3-dipoles closely resembles that of allenic systems in similar reactions. The reaction of allenes with azomethine oxides follows a different path from the reaction with other dipoles, the initial cycloaddition being followed by an intramolecular rearrangement;³ this result prompted us to extend the reaction of azomethine oxides to diketen.

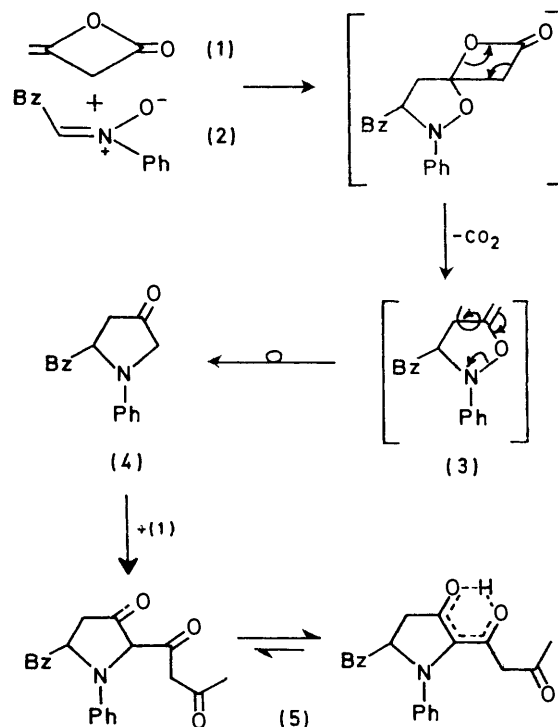
When a five-fold excess of (1) was allowed to react with *C*-benzoyl-*N*-phenylazomethine oxide (benzoylmethyleneaniline *N*-oxide) (2) in anhydrous benzene, a white solid was obtained which, after repeated crystallisations from acetone, gave a *ca.* 58% yield of a pure product. Structure (5) (Scheme 2) was assigned to this product on the basis of analytical and spectrometric data. The u.v. spectrum displays the characteristic absorption pattern of *N*-phenyl-substituted 3-pyrrolidinones.^{3,4} The i.r. spectrum shows absorption maxima for acetyl and benzoyl groups in addition to those of a β -diketone system.

[†] T. Sasaki and T. Yoshioka reported in *Bull. Chem. Soc. Japan*, 1969, **42**, 258 that a thermal cycloaddition between diketen and 5-nitrofuranyl-2-carbohydroxamoyl chloride gave the 3-(5-nitro-2-furyl)-5-methylisoxazole. Their statement: '... there have been no reports concerning the similar reactions of nitrile oxides with diketene, presumably because of its inertness' is clearly unsound, in the light of our previous findings.¹

¹ Part II, G. Stagno d'Alcontres, G. Cum, and M. Gattuso, *Ricerca sci.*, 1967, **37**, 750.

² G. Lo Vecchio, G. Cum, and G. Stagno d'Alcontres, *Tetrahedron Letters*, 1964, 3495.

In the mass spectrum of (5) (Figure 1), the base peak is at m/e 160 ($C_{10}H_{10}NO^+$). This ion, *a*, follows the same



SCHEME 2

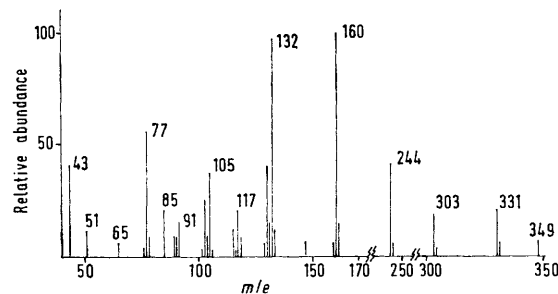


FIGURE 1 Mass spectrum of 2-acetoacetyl-5-benzoyl-1-phenylpyrrolidin-3-one (5)

fragmentation path as the corresponding ion (m/e 160, $C_{10}H_{10}NO^+$) in the mass spectrum of 5-benzoyl-1-phenylpyrrolidin-3-one.³

³ M. C. Aversa, G. Cum, and N. Uccella, *Chem. Comm.*, 1971, 188.

⁴ P. L. Southwick, D. I. Sapper, and L. A. Pursglove, *J. Amer. Chem. Soc.*, 1950, **72**, 4940; P. L. Southwick and H. L. Dimond, *ibid.*, 1954, **76**, 5667.

phenylpyrrolidin-3-one (4) (Figure 2). Ion *a* is formed from the molecular ion, *m/e* 349 ($C_{21}H_{19}NO_4^+$) by loss of benzoyl radical followed by expulsion of acetylketen

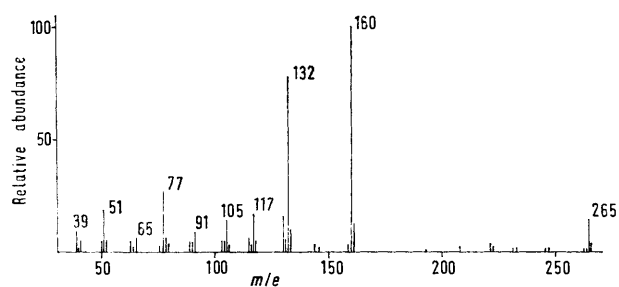


FIGURE 2 Mass spectrum of 5-benzoyl-1-phenylpyrrolidin-3-one (4)

Loss of the methyl radical has been interpreted as loss of the *N*-methyl to yield the indole molecular ion tautomer, *m/e* 117. Elimination of H_2 from *b* probably follows an initial ring expansion and yields the resonance-stabilised ion *c*, *m/e* 130, which then loses HCN to form the styryl cation. Loss of $CH_3\cdot CN$ results in formation of the tropylium ion, *m/e* 91. In the mass spectrum of 1,2-dimethylindoline ⁷ (*d*, Scheme 3 and Figure 3), the ion at

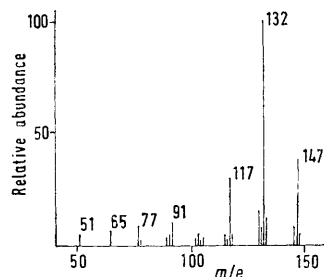
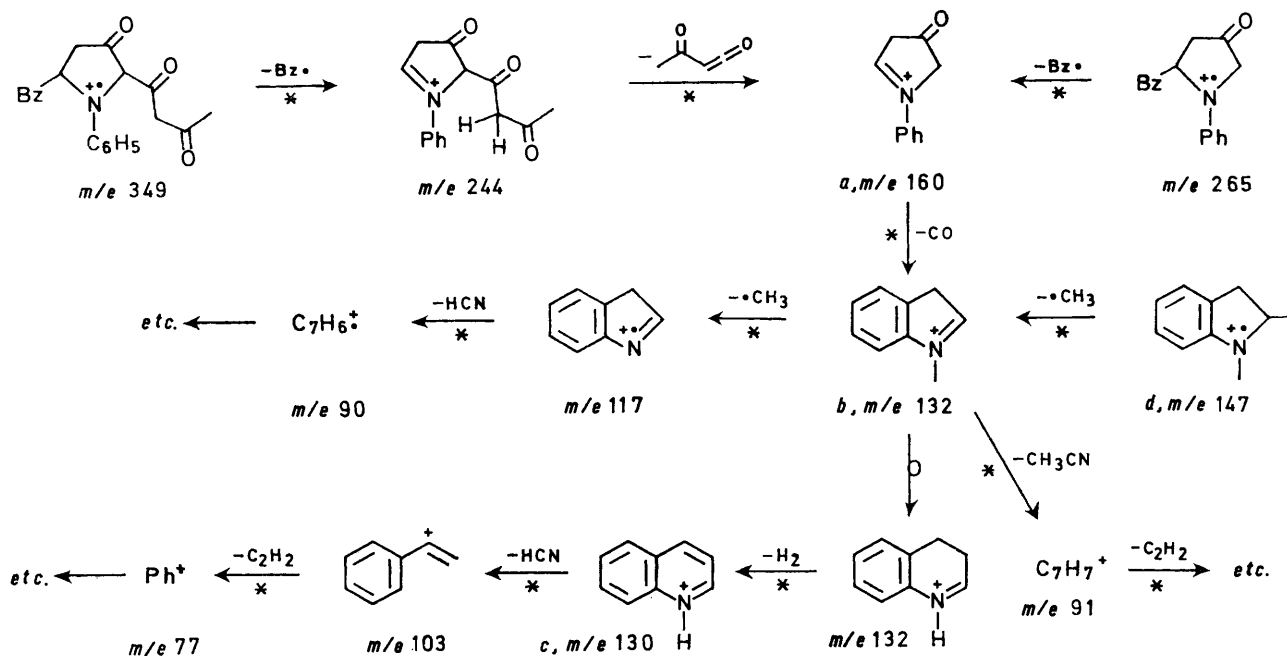


FIGURE 3 Mass spectrum of 1,2-dimethylindoline

from the intermediate ion, *m/e* 244 (Scheme 3). Accurate mass measurements show that *a* fragments with loss of CO, probably to form *b* (*m/e* 132, $C_9H_{10}N^+$) (*vide infra*), as was also observed in the mass spectrum of (4). In each case the second drift region metastable peak is 'flat-topped', corresponding to a release of *ca.* 0.2 eV of kinetic energy.⁵ This is strong evidence that the two reactions are proceeding *via* the same potential surface,

m/e 132, formed by loss of a methyl radical from the molecular ion, undergoes the same fragmentations and has the same elemental composition as *b* (*m/e* 132) in the



SCHEME 3

and that the two precursor ions (*m/e* 160) are reacting from the same structure or mixture of structures in the second drift region. Metastable refocusing experiments⁶ show that *b* undergoes three competing reactions in the first drift region, loss of $CH_3\cdot$, H_2 , and $CH_3\cdot CN$.

mass spectra of (4) and (5). This is further strong evidence for structure *b*. An additional feature in the mass spectrum of (5) is the presence of the acetoacetyl ion which, together with *a* and the benzoyl ion, constitutes its fundamental structural fragments.

The ¹H n.m.r. spectrum showed the presence of a $-CH_2-$ (AB quartet), a $>CH-CH_2-$ (ABX system), in

⁵ J. H. Beynon, R. A. Saunders, and A. E. Williams, *Z. Naturforsch.*, 1965, **20a**, 180.

⁶ K. R. Jennings in 'Some Newer Physical Methods in Structural Chemistry,' eds. R. N. Bonnet and J. G. Davies, United Trade Press, London, 1967, p. 105.

⁷ J. von Braun, O. Bayer, and G. Blessing, *Ber.*, 1924, **57**, 397.

addition to an acetyl singlet and aromatic absorptions. The enolised proton resonance on C-2 is clearly seen in the expected downfield position. The presence of the ABX system indicates that the acetoacetyl group must be situated on C-2. The AB quartet can be explained if the mode of enolisation is as shown.

Formation of the 2-acetoacetyl-5-benzoyl-1-phenylpyrrolidin-3-one (5) can be interpreted as an initial $[3 + 2 \rightarrow 5]$ cycloaddition reaction of the dipole to the exocyclic double bond of diketene (Scheme 2). Under the reaction conditions (room temperature) diketene does not eliminate carbon dioxide to give allene, as has already been shown in the analogous reaction with nitrile oxides¹ (Scheme 1), thus confirming that it is diketene and not allene that acts as the dipolarophile. Elimination of carbon dioxide follows the addition (*cf.* Scheme 1) to give the intermediate alkylidene-isoxazolidine (3) which was not isolated. Intramolecular rearrangement of (3) gives 5-benzoyl-1-phenylpyrrolidin-3-one (4), which has previously been synthesised by the cycloaddition of allene and azomethine oxide.³ Unchanged diketene acts on (4) as an acetoacetylating agent at C-2, which is activated by the 3-keto-functionality and the ring nitrogen atom, and is probably favoured over C-5 because of the steric hindrance of the benzoyl group. The intermediacy of (4) in the reaction has been demonstrated by its isolation from the reaction mixture by preparative t.l.c., and its identification by n.m.r. and i.r. spectroscopy. After concentration of the reaction mixture the main product was always compound (5), compound (4) being detectable in only small traces by t.l.c. Further support for Scheme 2 is the synthesis of (5) from the pyrrolidone (4) and diketene under experimental conditions identical with those for the reaction between compounds (1) and (2).

To try to stop the reaction between diketene and the azomethine oxide at the formation of compound (4), different ratios of starting materials, including 1 : 1, were used; they gave only compound (5) in reduced yields, most of the dipole being recovered unchanged. These experiments show that acetoacetylation is a faster reaction than the initial cycloaddition. In the latter cases the poor yields of (5) are also due to the competitive formation of diketene oligomers, which is induced by the basicity of the 3-pyrrolidinones formed.

Thus, the formation of compound (5) indicates an analogous pattern of behaviour between diketene and allene as the dipolarophile in 1,3-dipolar cycloaddition reactions. The same dipole when treated with both diketene and allene results in the formation of an identical heterocyclic system, *e.g.* with benzonitrile oxides spirobi-isoxazolines are formed^{1,2} whereas azomethine oxide yields 3-pyrrolidinones.³ Furthermore, when the same dipolarophile is treated with different dipoles, although the initial cycloaddition reactions are similar, the final product is dependent on the dipole and the nature of the intermediate; competition between cycloaddition and rearrangement processes of the proposed exocyclic alkylidene derivative occurs.

EXPERIMENTAL

I.r. spectra were taken in Nujol mulls on a Perkin-Elmer Model 225 instrument. N.m.r. spectra were recorded on a Varian A-60 spectrometer in CDCl_3 solution; chemical shifts are given in p.p.m. units (δ) downfield from internal Me_4Si and coupling constants (J) in Hz. Mass spectra were determined on Varian MAT CH-5 single-focusing and AEI MS-9 double-focusing mass spectrometers, operating at 70 eV; samples were introduced *via* direct-inlet systems, the source temperature being in the region of the melting points of the products and through a heated inlet system for the liquid sample. Empirical formulae of all ions were determined at 10,000 resolution power. Metastable peaks were observed in all cases for transition marked with an asterisk, and first drift region measurements were done using the technique devised by K. R. Jennings.⁶ Analytical and preparative t.l.c. was carried out on silica gel G with benzene-ether (1 : 1) as eluant.

Reactions between Diketen (1) and C-Benzoyl-N-phenylazomethine Oxide (Benzoylmethyleneaniline N-Oxide) (2).—Preparation of C-benzoyl-N-phenylazomethine oxide (2) was by a modification of the Kröhnke reaction.⁸

A cooled solution of nitrosobenzene (5.35 g., 50 mmole) in acetone (70 ml.) was added to phenacylpyridinium bromide (13.90 g., 50 mmole) in water (30 ml.). To the mixture, kept at -2°C , *m*-sodium hydroxide (50 ml.) was added very slowly and with vigorous stirring, until pH 7 was reached: the bright green solution turned to yellow and was left at -20° for 30 min. The deep yellow precipitate was filtered off and washed with water and then light petroleum. Recrystallisation from ethanol yielded 85% of the product m.p. 109–110°.

The dried product can be stored at -25° in a sealed bottle for more than 60 days, without any appreciable decomposition.

(a) Freshly distilled diketene (1) (12.5 ml., 162 mmole) was slowly added to a stirred solution of C-benzoyl-N-phenylazomethine oxide (2) (7.20 g., 32 mmole) in anhydrous benzene (90 ml.). The resulting yellow mixture was stirred in the dark at room temperature, for 120 hr. Carbon dioxide was evolved and trapped by $\text{Ba}(\text{OH})_2$ solution. After the elimination of solvent under reduced pressure, the brown residue was triturated with cold methanol and recrystallised from acetone to give 2-acetoacetyl-5-benzoyl-1-phenylpyrrolidin-3-one (7.3 g., 58%) (5), m.p. 162–163°, as colourless plates (Found: C, 72.2; H, 5.45; N, 3.95. $\text{C}_{21}\text{H}_{19}\text{NO}_4$ requires C, 72.2; H, 5.5; N, 4.0%); *M*, *m/e* 394; λ_{max} (cyclohexane) 272 (log ϵ 3.97) and 245 nm. (4.21); ν_{max} 1706s (acetyl), 1686s (benzoyl), 1650s and 1637s (enolised β -diketone), 1597, 1580, 1495, 1453s, 1425, 1366s, 1269, 1239, 1220s, 1171, 1148, 986, 770s, and 669 cm^{-1} ; δ (CDCl_3) 13.75 (s, 1H, enolic OH), 8.1–7.1 (m, 10H, ArH), 6.36 (dd, 1H, $J_{54} = 5.1$ Hz and $J_{54'} = 11.9$ Hz, 5-CH), 4.08 and 3.46 (*gem* AB quartet, 2H, $J_{\text{gem}} = 17.0$ Hz, CO-CH₂-CO), 2.77 and 2.63 (ddd, 2H, $J_{44'} = 12.5$ Hz, $J_{45} = 5.1$ Hz, $J_{4,5} = 11.9$ Hz, by ABX analysis, 4-CH₂), 1.98 p.p.m. (s, 3H, -CH₃); dd and ddd constitute an ABX system.

(b) A solution of diketene (1) (1.7 ml., 22 mmole) in anhydrous benzene (10 ml.) was added dropwise to a solution of (2) (2.25 g., 10 mmole) in anhydrous benzene (70 ml.)–chloroform (15 ml.); the reaction was kept in the dark for 110 hr. and followed by t.l.c. The presence of 5-benzoyl-1-phenylpyrrolidin-3-one³ ($R_F = 0.71$) and (5)

⁸ F. Kröhnke and E. Börner, *Ber.*, 1936, **63**, 2006.

($R_F = 0.56$) was indicated by t.l.c. using authentic samples as standards. Two other spots, near the solvent front, were also detected and their identity was established likewise as the two diketene oligomers, m.p. 131—133° and m.p. 258°.⁹ Preparative t.l.c. allowed isolation of (4), m.p. 119° (40 mg.) and (5) m.p. 162—163° (600 mg., 11%). Their i.r. and n.m.r. spectra were identical with those of authentic samples.

(c) Under experimental conditions similar to those reported above, equimolecular amounts (15 mmole) of (1) and (2) in anhydrous benzene (50 ml.) or benzene-chloroform 5:1 (30 ml.) gave (5) in lower yields (8%), together with starting materials and other by-products.

Reaction between Diketene (1) and 5-Benzoyl-1-phenylpyrrolidin-3-one.—Compound (4) (0.53 g., 2 mmole) and

diketene (1) (0.80 ml., 10 mmole) were dissolved in anhydrous benzene (30 ml.) at room temperature, and stirred in the dark for 120 hr. The solvent was removed at reduced pressure and an n.m.r. of the oily residue showed the presence of (5) and an excess of (1). T.l.c. confirmed the presence of (5), together with traces of unchanged (4).

The residue was dissolved in ether, washed with water, and dried ($MgSO_4$). Ether was removed under reduced pressure and the yellow solid was recrystallised to give the product m.p. 162—163° (yield 52%).

We thank the C.N.R., Rome, for financial support.

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⁹ E. Marcus and J. K. Chan, *J. Org. Chem.*, 1967, **32**, 2881.