Reactions of Ethyl Azepine-1-carboxylate with Heterodienophiles

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4-Phenyl-1,2,4-triazoline-3,5-dione and 2,3-phthalazine-1,4-dione react with ethyl azepine-1-carboxylate (EAC) to give [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] cycloadducts. Diethyl azodiformate reacts with EAC to give a [4 + 2]π cycloadduct also, contrary to the original report. No evidence has been found for a transient [6 + 2]π cycloaddition product. Structural assignments have been confirmed by ^{13}C n.m.r.

1*H*-AZEPINE (1) exhibits the marked polyene character predicted by Huckel molecular orbital calculations.[1] For example, ethyl azepine-1-carboxylate (EAC) has been shown to undergo a wide range of cycloaddition reactions wherein the triene system acts as a 2π,[2] 4π,[3] or 6π [4] component. In our preliminary report [5] we noted that EAC with a number of azo-dienophiles behaved predictably as a 4π component. With nitrosobenzene and diethyl azodiformate EAC reacted as a 6π component,[5] contrary to orbital symmetry rulings.[6] A previous apparent violation of the Woodward-Hoffmann rules, namely, the [6 + 2]π cycloaddition of EAC with tetracyanoethylene [7] was later corrected.[8] We have therefore reinvestigated our own work, and now present the full details.

Initially we reinvestigated the reaction of EAC with 4-phenyl-1,2,4-triazoline-3,5-dione in detail to confirm Sasaki's [3b] and our [5] identification of the product. We also intended to compare the spectral properties of other cycloadducts with those of this product. One product was obtained, a 1 : 1 cycloadduct (M^+ 340), showing no NH stretching band in the i.r. spectrum. Of the possible structures (2)—(4), structure (4) was discounted on the basis of the ^{1}H n.m.r. data, fully analysed by Sasaki.[3b] Further evidence in favour of structure (2) was obtained from ^{13}C n.m.r. data. Five ring carbon resonances were observed (see Table). Structure (3) has only three non-equivalent ring carbon atoms. The ^{13}C n.m.r. spectrum of the tetrahydro-derivative, obtained by catalytic hydrogenation in a Parr hydrogenator added confirmation. All six ring carbon resonances were resolved (see Table). The ^{1}H n.m.r. spectrum of the tetrahydro-derivative exhibited two non-equivalent bridgehead proton signals as broad singlets at τ 3.57 and 5.33, a result inconsistent with the symmetrical [6 + 2]π adduct structure (3). The i.r. spectrum of the cycloadduct had an absorption at 1 630 cm^{-1}, indicative of a vinylcarbamate grouping.[3a] Such a grouping is absent in structure (3). This absorption is absent in the i.r. spectrum of the tetrahydro-derivative of the cycloadduct. The u.v. difference curve between the cycloadduct and its tetrahydro-derivative [$\lambda_{max.}$ 250 nm (ε 4 588)] is in good agreement with that reported for the C=CH·NHAc system.[9]

The analogous reaction of phthalazine-1,4-dione was then investigated. A single product was isolated, a 1 : 1 cycloadduct showing no NH i.r. stretching band. Catalytic hydrogenation gave a mixture of the perhydro-derivative and starting material. The Brown hydro-

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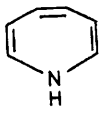
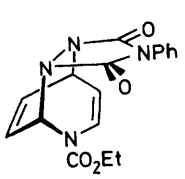
genator [10] was used in an attempt to prepare the tetrahydro-derivative, required for correlation. A range of products (t.l.c.) was formed which was not investigated further. On the same basis as structure (2), this cycloadduct was readily assigned structure (5). The ^{13}C n.m.r. spectrum had ring carbon signals (see Table) incompatible with a symmetrical [6 + 2]π cycloadduct. The chemical shifts are closely analogous to those of (2). The ^1H n.m.r. spectrum of the cycloadduct was similar to that of (2). The ^1H n.m.r. spectrum of the perhydro-derivative of (5) (M^+ 335) had two non-equivalent bridgehead proton signals at τ 2.91 and 4.60, incompatible with a symmetrical structure. The i.r. spectrum contained a vinylcarbamate band [3b] at 1 645 cm^{-1}. which was absent from that of the perhydro-derivative. The u.v. difference curve between the cycloadduct and its perhydro-derivative [$\lambda_{max.}$ 245 (ε 2 972) and 270 nm (1 090)] was ambiguous owing to the hydrogenation of the phenyl ring. However, the absorption at 245 nm is in good agreement [9] with that expected for the vinylcarbamate system.


(1)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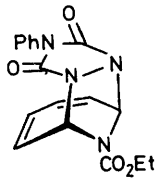
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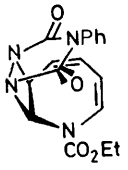
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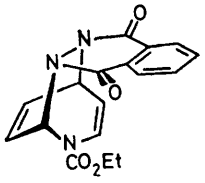
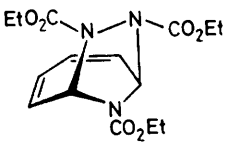
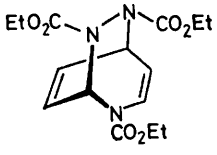

(5)


(6)

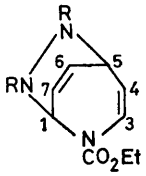

(7)

The reaction of EAC with diethyl azodiformate was extremely slow at room temperature. The product oil was a 1 : 1 cycloadduct (M^+ 339), showing no NH i.r. band. The tetrahydro-derivative was readily formed by catalytic hydrogenation in a Parr hydrogenator. All six ring carbon signals of both the cycloadduct and the tetrahydro-derivative were resolved in the ^{13}C n.m.r. spectrum (see Table). This pattern is incompatible with structure (6) and is consistent with (7). The chemical shifts are similar to those of (2) and (5), The ^1H n.m.r. spectrum, although not well resolved, was similar to those of (2) and (5) and exhibited *inter alia* the clear one-proton doublet of doublets at τ 4.02 characteristic of >HC·C*H*:CH–.[3b] The hydrogenated derivative showed two non-equivalent bridgehead proton signals at τ 3.99 and 5.40, compatible with structure (7)

^{13}C N.m.r. assignments (δ values; Me_4Si standard; $CDCl_3$ solvent)

Carbon no.	Structures (2)	(2)H_4 *	(5)	(7)	(7)H_4 *
1	60.49	61.20	59.39	60.12	61.66
3	129.20	38.39	128.00	132.20	38.79
4	102.98	33.78	103.24	96.96	29.69
5	47.43	47.95	45.42	50.45	52.30
6	118.58	22.41	119.87	117.31	20.47
7	118.58	23.71	119.87	125.52	23.97

* Corresponding tetrahydro-derivative



but not structure (6). The i.r. spectrum of the cycloadduct had a vinylcarbamate [3a] absorption at 1 628 cm^{-1}, absent from that of the tetrahydro-derivative. The u.v. difference curve between the cycloadduct and its tetrahydro-derivative [$\lambda_{max.}$ 249 nm (ε 5 401)] is similar to the two difference curves mentioned earlier and in good agreement with that expected for a vinylcarbamate.[9]

We reported previously [5] that the cycloadduct from the reaction of EAC with diethyl azodiformate had different spectra, consistent with structure (6). We have repeated this reaction three times, and the spectra of the product were invariably those of structure (7). The possibility remained that [6 + 2]π cycloaddition occurred initially, but that structure (6) rearranged to (7) by a [1,3] sigmatropic shift. Alternatively work-up may have been such as to effect rearrangement of the initially formed (7) to (6). There is precedent for this type of rearrangement. Paquette [11] has shown that the [6 + 4] dimer of EAC thermally rearranged, probably non-concertedly, to the [6 + 6] dimer. These possibilities were investigated by (*a*) a search for the transient formation of (6) and (*b*) a study of the thermal stability of (7). The reaction of EAC with diethyl azodiformate was followed by t.l.c. and by n.m.r. No evidence was found for an intermediate. The cycloadduct (7) was heated for 3 days at 100 °C. It remained virtually unchanged (t.l.c.; ^1H n.m.r.). Also the adduct (7) was

[10] C. A. Brown and H. C. Brown, *J. Org. Chem.*, 1966, **31**, 3989.
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unchanged when an ethereal solution was kept overnight in contact with either dilute aqueous acid or aqueous base. Thus, although we cannot explain the anomaly, we are satisfied that the original report was in error. The reaction of EAC with diethyl azodiformate is a conventional [4 + 2]π cycloaddition.

EXPERIMENTAL

Microanalyses were performed in this Department. Spectra were recorded with a Perkin-Elmer 257 i.r. spectrophotometer for KBr discs, a Unicam SP 800 u.v. spectrophotometer for solutions in ethanol, a Perkin-Elmer R20A-60 MHz ^{1}H n.m.r. spectrometer, a JEOL FX60 ^{13}C n.m.r. spectrometer and an A.E.I. MS 902 mass spectrometer.

EAC,[12] 4-phenyl-1,2,4-triazoline-3,5-dione,[13] and phthalazine-1,4-dione [14] were prepared by published procedures.

For n.m.r. assignments, atoms are numbered as shown in the Table.

Cycloaddition Reactions of EAC.—(a) *4-Phenyl-1,2,4-triazoline-3,5-dione.* To a suspension of the triazoline (4.0 g) and EAC (4.29 g) in methylene chloride (100 ml) at 0 °C was added slowly a cold solution of lead tetra-acetate (13.4 g) in methylene chloride (100 ml). The red colour disappeared on stirring for 24 h. The usual work-up [13] afforded the white crystalline cycloadduct (2) (3.2 g, 40%), m.p. 137—138° (lit.,[3b] 137—139°) (Found: C, 60.1; H, 5.1; N, 16.5. Calc. for $C_{17}H_{16}N_4O_4$: C, 60.0; H, 4.7; N, 16.5%); $\nu_{max.}$ 1 760, 1 705, and 1 630 cm^{-1}; $\lambda_{max.}$ 239 (ε 5 852) and 254 nm (4 882); τ 2.60 (5 H, s, Ph), 3.10 (1 H, m, H-1 + -3), 3.40 (1 H, dd, *J* 7.5 Hz, H-6), 3.80 (1 H, dd, *J* 7.5 Hz, H-7), 4.65 (1 H, dd, *J* 7.5 Hz, H-4), 5.04 (1 H, t, *J* 7.5 Hz, H-5), 5.75 (2 H, q, *J* 8 Hz, OCH_2), and 8.70 (3 H, t, *J* 8 Hz, CH_3); *m/e* 340 (M^+, 100%), 165 (30), and 92 (66).

The product (2) (0.78 g) in methanol (30 ml) was hydrogenated in a Parr hydrogenator at 47 lb in^{-2} over platinum dioxide (0.1 g). The product (0.78 g, 99%) which solidified during 4 days, had m.p. 166—167° (from methanol) (lit.,[3b] 166—167°) (Found: C, 59.5; H, 6.1; N, 16.5. Calc. for $C_{17}H_{20}N_4O_4$: C, 59.3; H, 5.9; N, 16.3%); $\nu_{max.}$ 2 920, 1 770, and 1 695—1 585 cm^{-1}; $\lambda_{max.}$ 233 nm (ε 5 000); τ 2.60 (5 H, s, Ph), 3.57br (1 H, s, H-1), 5.33br (1 H, s, H-5), 5.82 (2 H, q, *J* 8 Hz, OCH_2), 7.86br (8 H, s, 4 × CH_2), and 8.72 (3 H, t, *J* 8 Hz, CH_3); M^+ 276.

(b) *Phthalazine-1,4-dione.* To a suspension of 2,3-dihydrophthalazine-1,4-dione [14] (3.72 g) and EAC (3.78 g) in methylene chloride (100 ml) at 0.5 °C was added a cooled solution of lead tetra-acetate (13.7 g) in methylene chloride (100 ml). The initially formed red colour had faded within 24 h. One product was formed (t.l.c.). The usual work-up [13] followed by four recrystallisations, afforded pure *ethyl 2,5,7,12-tetrahydro-7,12-dioxo-1,5-etheno-1H-[1,2,4]triazepino[1,2-b]phthalazine-2-carboxylate* (5) (0.5 g, 20%), m.p. 216.5—217.5° (Found: C, 62.4; H, 4.7; N, 12.6. $C_{17}H_{15}N_3O_4$ requires C, 62.8; H, 4.7; N, 12.9%); $\nu_{max.}$ 3 018, 1 720, 1 645, and 1 575 cm^{-1}; $\lambda_{max.}$ 220sh (ε 11 800), 241 (16 700), and 312 nm (4 060); τ 1.75 (2 H, m, Ph), 2.20 (3 H, m, Ph + H-3), 3.30 (2 H, dd, *J* 8 Hz, H-1 + -6), 3.85 (1 H, dd, *J* 8 Hz, H-7), 4.19 (1 H, dd, *J* 8 Hz, H-4), 4.75 (1 H, t, *J* 8 Hz, H-5), 5.60 (2 H, q, *J* 8 Hz, OCH_2), and 8.64 (3 H, t, *J* 8 Hz, CH_3).

The product (5) (0.31 g) was hydrogenated (Parr hydrogenator) at 43 lb in^{-2} in methanol for 48 h platinum dioxide (0.05 g). A viscous oil (0.30 g) was isolated which consisted of (5) and the *perhydro-derivative*. Separation was effected by column chromatography. Unchanged (5) (0.20 g, 66%) was recovered. The product (0.032 g, 10%) was isolated as white crystals, m.p. 157—158° (Found: C, 61.1; H, 7.0; N, 12.4. $C_{17}H_{25}N_3O_4$ requires C, 60.9; H, 7.5; N, 12.5%); $\nu_{max.}$ 1 720 and 1 620 cm^{-1}; $\lambda_{max.}$ 229 (ε 14 700), 250sh (3 560), and 321 nm (ε 5 900); τ 2.92br (1 H, s, H-1), 4.60br (1 H, s, H-5), 5.90 (2 H, q, *J* 8 Hz, OCH_2), 6.68 (2 H, quint, *J* 8 Hz, 2 × CH), 7.30—8.50 (16 H, m, 8 × CH_2), and 8.76 (3 H, t, CH_3); M^+ 335.

(c) *Diethyl azodiformate.* A solution of EAC (1.98 g) in diethyl azodiformate (2.08 g) was kept in a stoppered flask for 12 weeks. The reaction was monitored by t.l.c. Unchanged EAC was removed by column chromatography and the thick oily *triethyl 2,6,7-triazabicyclo[3.2.2]nona-3,8-diene-2,6,7-tricarboxylate* (7) (2.0 g, 50%) was isolated (Found: C, 52.6; H, 6.1; N, 12.0. $C_{15}H_{21}N_3O_6$ requires C, 53.1; H, 6.2; N, 12.4%); $\nu_{max.}$ 1 711br and 1 630 cm^{-1}; $\lambda_{max.}$ 229sh (ε 2 900) and 249 nm (5 100); τ 3.15—3.61 (3 H, m, poorly resolved, H-1 + -3 + -6), 4.02 (1 H, dd, *J* 8 Hz, H-7), 4.86—5.40 (2 H, m, poorly resolved, H-4 + -5), 5.60—6.04 [6 H, 2 × q, *J* 7.5 Hz, ratio 1 : 2, 3 × OCH_2 (the first finely split)], and 8.50—8.90 [9 H, 2 × t, *J* 7.5 Hz, ratio 1 : 2, 3 × CH_3 (the first finely split)]; *m/e* 339 (M^+, 65%), 165 (73), and 92 (100).

The adduct (7) (2.62 g) was hydrogenated over platinum dioxide (0.05 g) in methanol (40 ml) at 50 lb in^{-2} (Parr hydrogenator). The *tetrahydro-derivative* (2.6 g, 98%) was an oil which contained no (7) (t.l.c.) (Found: C, 52.2; H, 7.5; N, 12.2. $C_{15}H_{25}N_3O_6$ requires C, 52.5; H, 7.3; N, 12.2%); $\nu_{max.}$ 1 735 and 1 700br cm^{-1}; $\lambda_{max.}$ 217 nm (ε 1 150); τ 3.99 (1 H, s, H-1), 5.40 (1 H, m, H-5), 5.60—6.10 [6 H, 2 × q, *J* 7.5 Hz (ratio 1 : 2), 3 × OCH_2], 6.45 (2 H, m, H_2-3), 7.70—8.40 (6 H, m, 3 × CH_2), and 8.60—8.90 [9 H, 2 × t, *J* 7.5 Hz (ratio 1 : 2), 3 × CH_3]; M^+ 343.

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