1,3-Dipolar Character of Six-membered Aromatic Rings. Part VII.[1] 1-Phenyl-3-oxidopyridinium

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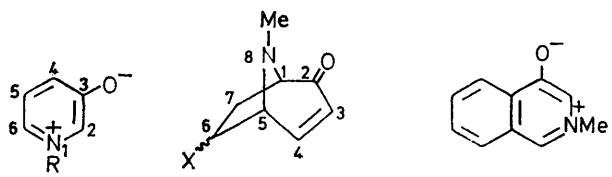
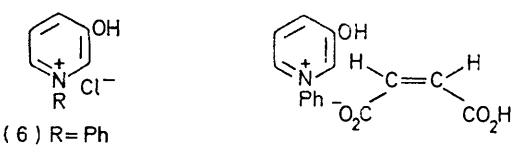
The title compound reacts as a 1,3-dipole with *N*-phenylmaleimide, acrylonitrile, methyl acrylate, and benzyne to give isomeric cycloadducts. The n.m.r. spectra of these products are discussed with particular reference to stereochemistry.

1-METHYL-3-OXIDOPYRIDINIUM (1) shows 1,3-dipolar reactivity across the 2- and 6-positions,[2,3] and gives cycloadducts [*e.g.* (3) and (4)] with electron-deficient olefins, convertible conveniently into tropones and tropolones.[2,4] 2-Methyl-4-oxidoisoquinolinium (5) reacts similarly;[5] we now report on 1-phenyl-3-oxidopyridinium (2).

3-Hydroxy-1-phenylpyridinium chloride (6) (prepared from aniline and 2-furaldehyde[6]) when treated with IRA-401 (OH) resin gives the hydrated betaine (2) (*m/e* 171), with an n.m.r. spectrum (Table 1) showing upfield shifts of the pyridine ring protons characteristic for the conversion of a halide into a betaine. The betaine (2) with maleic anhydride merely forms a salt (8), the n.m.r. spectrum of which showed only vinyl (δ 6·39) and aromatic CH absorptions. However with *N*-phenylmaleimide, acrylonitrile, and methyl acrylate the betaine (2) gave the expected cycloadducts as mixtures of *endo*- and *exo*-isomers (9)—(14) † in good



(1) R=Me
(2) R=Ph
(3) X=CN
(4) X=CO_2Me
(5)



(6) R=Ph
(7) R=Me
(8)

yields. Unlike the methyl series, the isomers were easily separable and the structures could be confirmed by i.r., mass, and n.m.r. spectra.

† The term *endo* is used to refer to the configuration in which the substituent is inside the cage formed by carbon atoms 2, 3, 4, 6, and 7; *exo* refers to the configuration in which the substituent is on the same side as the nitrogen bridge (see E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 295).

[1] Part VI, N. Dennis, B. Ibrahim, A. R. Katritzky, and Y. Takeuchi, *J.C.S. Chem. Comm.*, 1973, 292.
[2] A. R. Katritzky and Y. Takeuchi, *J. Amer. Chem. Soc.*, 1970, **92**, 4134.
[3] A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc.* (*C*), 1971, 874.
[4] A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc.* (*C*), 1971, 878.
[5] N. Dennis, A. R. Katritzky, and Y. Takeuchi, *J.C.S. Perkin I*, 1972, 2054.
[6] C. F. Koelsch and J. J. Carney, *J. Amer. Chem. Soc.*, 1950, **72**, 2285.

It is now possible to formulate rules for the use of n.m.r. spectra for diagnostic purposes in this series. A characteristic pattern is observed for the olefinic protons

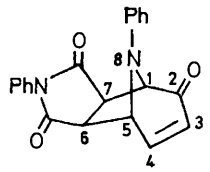
TABLE 1

^{1}H N.m.r. spectra (δ values) of pyridinium halides and betaines [a]

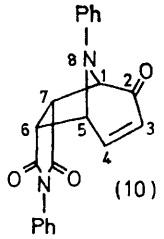
	Compound			
	(1) [b,c]	(2) [b]	(6) [b]	(7) [b,c]
H-2	7·30	7·50—7·65	8·91	8·63
H-4	6·90	7·08	8·35 [d]	8·16
H-5	7·21	7·40	8·08 [e]	8·16
H-6	7·35	7·50—7·65	8·78 [f]	8·63
NMe	3·73			4·48
NPh		*ca.* 7·50	*ca.* 7·75	

[a] Me_4Si as internal standard. [b] In $(CD_3)_2SO$. [c] Results from ref. 3. [d] Doublet ($J_{4,5}$ 9·0 Hz). [e] Quartet ($J_{4,5}$ = $J_{5,6}$ = 5·6 Hz). [f] Doublet ($J_{5,6}$ 5·6 Hz).

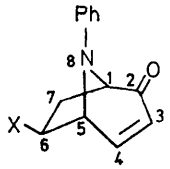
H-3 and H-4 [for numbering system see (3)] in the n.m.r. spectra (Table 2) of all the *N*-methyl and *N*-phenyl cycloadducts investigated: H-4 (δ 6·8—7·0 for NMe, δ 7·2—7·6 for NPh) forms a quartet with $J_{3,4}$ 10·0 and $J_{4,5}$ 5·0 Hz while H-3 (δ 6·06—6·15 for NMe and δ 6·0—6·1 for NPh) gives rise to a doublet of doublets with $J_{3,4}$ 10·0 and $J_{1,3}$ 1·4 Hz. The H-4 quartet



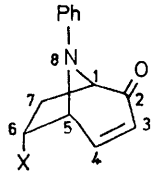
(9)



(10)



(11) X=CN
(12) X=CO_2Me



(13) X=CN
(14) X=CO_2Me

quartet ($J_{4,5}$ 5·0, $J_{5,6\text{-}exo}$ 7·0 Hz). The situation is similar for the acrylonitrile and methyl acrylate cycloadducts (11)—(14): here the H-1 signal appears as a

TABLE 2

Proton n.m.r. spectra of cycloadducts [a]

Chemical shifts (δ)	Compounds								
Proton(s)	(9) [b]	(10) [b]	(11) [c]	(12) [c]	(12) [d]	(13) [c]	(14) [c]	(14) [d]	(19) [e,f] †
1	4·76 [g]	5·00 [h]	4·55 [h]	4·48 [h]	4·30 [h]	4·46 [h]	4·42 [h]	4·24 [h]	5·27 [h]
3	6·00 [i]	6·12 [i]	5·98 [i]	5·93 [i]	5·59 [i]	6·14 [i]	5·92 [i]	5·71 [i]	5·42 [i]
4	7·55 [j]	7·31 [j]	7·28 [j]	7·13 [j]	6·19 [j]	7·18 [j]	7·03 [j]	6·50 [j]	7·25 [i]
5	5·17 [h]	5·32 [j]	4·92 [h]	5·09 [h]	4·76 [h]	4·88 [k]	4·92 [j]	4·45 [j]	5·46 [h]
6-*endo*	3·78 [j]		3·12 [j]	3·07 [j]	2·41 [j]				
6-*exo*		4·19				3·50 [l]	3·69 [l]	3·12 [l]	
7-*endo*	3·59 [j]		2·22 [j]	2·11 [m]	1·66 [m]	2·06 [j]	2·22 [n]	2·04 [n]	
7-*exo*		4·40	2·87 [n]	3·02 [n]	2·75 [n]	2·95 [n]	2·76 [m]	2·28 [m]	
CO_2Me				3·74 [g]	3·29 [g]		3·68 [g]	3·24 [g]	
NPh	6·9–7·7 [o]	6·8—7·6 [o]	6·7—7·3 [o]	6·7—7·3 [o]	6·6—7·2 [o]	6·7—7·4 [o]	6·6—7·3 [o]	6·4—7·2 [o]	6·0—6·8 [o]
Coupling constants (Hz)									
1,3	1·3	1·4	1·5	1·5	1·5	1·5	1·5	1·5	2·0
1,7-*endo*			1·0	0·8	0·8	1·0	1·5	1·5	
1,7-*exo*		8·2	8·0	7·8	7·6	8·0	8·0	7·5	
3,4	10·0	10·0	10·0	9·8	10·1	10·0	10·0	9·8	10·0
4,5	4·8	5·0	5·0	4·8	4·8	5·0	4·8	5·0	4·5
5,6-*endo*	*ca.* 0·5		0·8	*ca.* 0·4	*ca.* 0·4				
5,6-*exo*		7·0				6·0	6·0	6·0	
6-*endo*, 7-*endo*	7·5		9·4	9·4	9·8				
6-*endo*, 7-*exo*			3·4	3·4	3·2				
6-*exo*, 7-*endo*						6·0	6·1	6·5	
6-*exo*, 7-*exo*		8·0				10·4	10·0	9·8	
7-*endo*, 7-*exo*			13·8	13·8	13·4	13·8	13·8	13·8	

[a] Me_4Si as internal standard. [b] In $(CD_3)_2SO$. [c] In $CDCl_3$. [d] In C_6D_6. [e] In CCl_4. [f] $Pr(fod)_3$ (0·0134 g) added. [g] Singlet. [h] Doublet. [i] Doublet of doublets. [j] Quartet. [k] Triplet. [l] Doublet of triplets. [m] Doublet of quartets. [n] Octet. [o] Complex.

† For numbering system (non-systematic) see illustrated formula.

for the *N*-phenyl derivatives overlaps with the aromatic proton signals, but is revealed by expansion of that region of the spectrum.

The splitting patterns of the two bridgehead protons, H-1 and H-5 characterise the stereochemistry of the cycloadducts, since $J_{5,6\text{-}endo}$ is negligibly small whereas $J_{5,6\text{-}exo}$ is relatively large (6—8 Hz). Thus the *exo*-*N*-phenylmaleimide adduct (9) shows the H-1 signal as a doublet ($J_{1,7\text{-}exo}$ 8·0 Hz) irrespective of the stereochemistry, and H-5 gives rise to a doublet ($J_{4,5}$ 5·0 Hz) for the *exo*-isomers and a quartet ($J_{4,5}$ 5·0, $J_{5,6\text{-}exo}$ 6·0 Hz) for the *endo*-isomers.

The 6- and 7-protons of *exo*-(9) form a typical AB quartet whereas the signals corresponding to the same protons of the isomeric *endo*-(10) can be analysed as a pair of quartets on a first-order basis. For the

exo-isomers, (11) and (12), H-6-*endo* gives a quartet ($J_{6\text{-}endo,7\text{-}exo}$ and $J_{6\text{-}endo,7\text{-}endo}$), but for the *endo*-isomers (13) and (14), H-6-*exo* gives a doublet of triplets because of significant additional coupling ($J_{5,6\text{-}exo}$ 6·0 Hz). In all four isomers (11)—(14), H-7-*exo* gives an octet and H-7-*endo* a quartet. All these assignments were confirmed by double irradiation experiments: *e.g.* on irradiation at the frequency of H-5 in all the cycloadducts, the H-4 quartet (hidden in the aromatic proton region) collapsed to a doublet allowing the quartet to be distinguished from the complex aromatic multiplet.

The phenylbetaine (2) gives comparable amounts of *exo*- and *endo*-isomers whereas the methylbetaine (1) gives predominantly, if not exclusively, the *exo*-isomer. *endo*-Cycloaddition transition states entail steric and electronic interactions between the oxido-group of (1) and the polar group of the dipolarophile; hence the favoured formation of the *exo*-isomer (17) from the methylbetaine. In the *N*-phenyl case these repulsions are balanced by repulsions between the phenyl group and the polar group in the *exo*-transition state (18).

Reaction of the betaine (2) with benzyne gives the adduct (19),[7] previously prepared from 3-(2,4-dinitrophenoxy)pyridine [1,8] and benzyne.[9] The structure was supported by i.r. and u.v. absorption characteristic of an αβ-unsaturated carbonyl group (see Experimental section), analytical figures, and the mass spectrum, with a base peak at *m/e* 206 envisaged as being formed by loss of the fragment –CHCO·, which is confirmed by the presence of a metastable peak at *m/e* 171·8. The

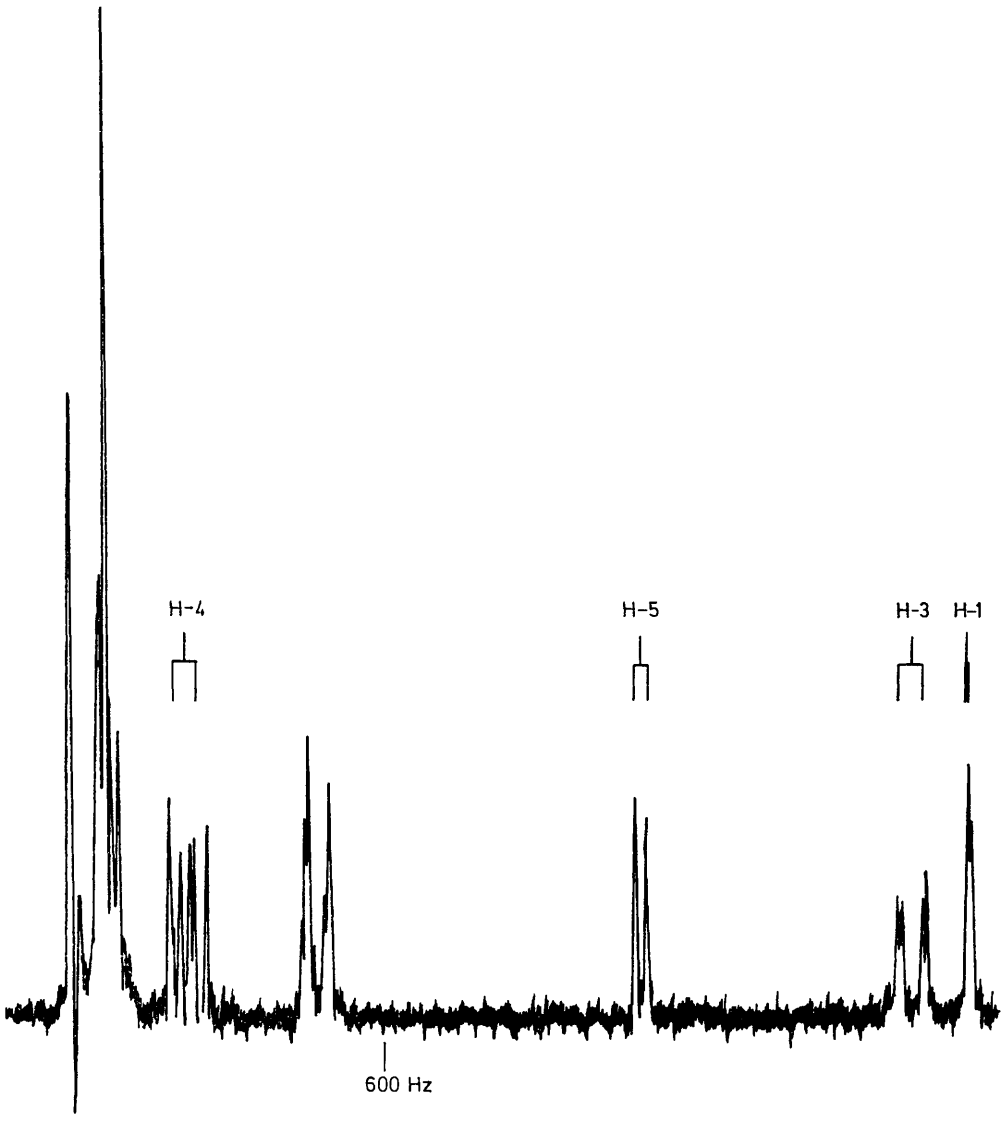


FIGURE 1 N.m.r. spectrum of the benzyne adduct (19) after addition of $Pr(fod)_3$ (0·0134 g)

[7] N. Dennis, A. R. Katritzky, S. K. Parton, and Y. Takeuchi, *J.C.S. Chem. Comm.*, 1972, 707.

[8] N. Dennis, B. Ibrahim, A. R. Katritzky, Y. Takeuchi, and I. G. Taulov, submitted to *J.C.S. Perkin I*.

[9] L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, 1963, **85**, 1549.

n.m.r. spectrum (Table 2) affords further evidence, in particular, doublets for the bridgehead protons H-1 and H-5 and double doublets for the vinyl protons H-3 and H-4. Considerable overlap in the n.m.r.

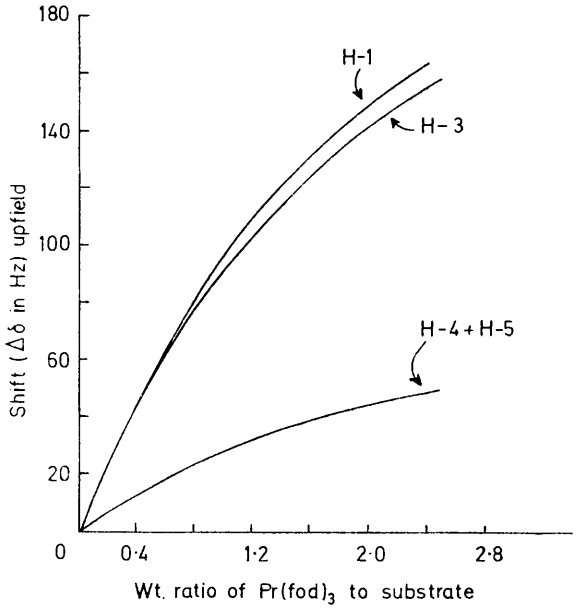
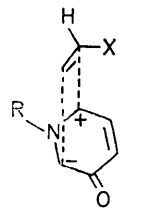
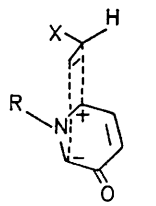


FIGURE 2 Graph of Δδ against wt. ratio of $Pr(fod)_3$ to substrate for the benzyne adduct

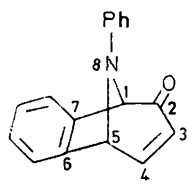
spectrum, in particular the signals of H-2 with those of H-4 and the signals of H-3 with those of the aromatic protons, is resolved (Figure 1) by use of the lanthanide



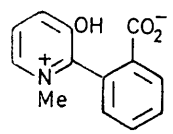
(15) R=Me
(16) R=Ph



(17) R=Me
(18) R=Ph



(19)



(20)

shift reagent, tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-octane-4,6-dionato)praeseodymium(III) $[Pr(fod)_3]$.[10]

[10] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.
[11] P. Bélanger, C. Freppel, D. Tizané, and J. C. Richer, *Chem. Comm.*, 1971, 266.
[12] Z. W. Wolkowski, *Tetrahedron Letters*, 1971, 821.

Plots of upfield shifts (Δδ) *vs.* weight ratio of $Pr(fod)_3$ to substrate (Figure 2) show that H-1 and H-3 are influenced much more than H-4 and H-5; the shift reagent complexes with the ketonic carbonyl group as expected.[11,12] This contrasts with the methylbetaine (1),[13] which is attacked by the intermediate benzenediazonium-2-carboxylate [14] to give the betaine (20).

Attempted quaternisation of the cycloadducts (9)—(14) with methyl iodide failed, probably because of the large steric requirements of the *N*-phenyl group. Attempts to convert these cycloadducts into cycloheptatrienones by the other methods are in progress.

EXPERIMENTAL

The m.p.s were determined with a Reichert apparatus. Spectra were recorded with a Perkin-Elmer 257 grating spectrophotometer, a Unicam SP 800A spectrophotometer, a Hitachi–Perkin-Elmer RMU-6E mass spectrometer, and a Varian HA-100 n.m.r. spectrometer. Compounds were purified until they were observed as single spots on t.l.c. (*a*) with Kieselgel G and either light petroleum–dichloromethane (50 : 50) or ethanol–ether (5 : 95) as eluant, or (*b*) with Kieselgel PF 254 and benzene–ethanol (80 : 20) as eluant.

1-*Phenyl*-3-*oxidopyridinium* (2).—Amberlite IRA-401 (OH) resin was generated in the normal manner.[15] 3-Hydroxy-1-phenylpyridinium chloride (6) [6] (53 g, 0·25 mol) was dissolved in distilled water (50 ml) and filtered through a column of resin. Elution with distilled water (2 l), concentration of the eluate *in vacuo* on a steam-bath (45°; 10 mmHg), and freeze-drying afforded a white deliquescent solid, the *betaine* (2) (10·5 g, 24·5%), which formed needles (from EtOH), m.p. 160° (decomp.) (Found: C, 73·6; H, 5·7; N, 7·7. $C_{11}H_9NO,0{\cdot}5H_2O$ requires C, 73·3; H, 5·6; N, 7·8%), $\nu_{max.}$ (Nujol) 1365 and 760 cm^{-1}.

2-*Oxo*-N,8-*diphenyl*-8-*azabicyclo*[3.2.1]*oct*-3-*ene*-6,7-endo-*and* 6,7-exo-*dicarboximide* [(10) *and* (9)].—The betaine (2) (3·42 g, 0·02 mol) and *N*-phenylmaleimide (3·42 g, 0·019 mol) were heated under reflux in dry tetrahydrofuran (100 ml) for 15 h. The solvent was evaporated off *in vacuo* and the cycloadducts (5·6 g, 81%) (*exo* : *endo* ratio *ca.* 4 : 5 by n.m.r.) were separated by fractional crystallisation from EtOH. The less soluble endo-*adduct* (10) crystallised as yellow plates, m.p. 209—210° (Found: C, 73·4; H, 4·8; N, 8·1. $C_{21}H_{16}N_2O_3$ requires C, 73·2; H, 4·7; N, 8·1%); $\nu_{max.}$ (Nujol) 1715 (amide C=O), 1686 (αβ-unsaturated C=O), 1600, and 1500 (arom.) cm^{-1}; $\lambda_{max.}$ (EtOH) 235 nm (log ε 4·27); *m/e* 344; and the exo-*adduct* (9) as yellow needles, m.p. 219—220·5° (Found: C, 73·0; H, 4·8; N, 8·2%); $\nu_{max.}$ (Nujol) 1715 (amide C=O), 1680 (αβ-unsaturated C=O), 1600, and 1500 (arom.) cm^{-1}; $\lambda_{max.}$ (EtOH) (log ε 4·19) 230 nm; *m/e* 344.

2-*Oxo*-8-*phenyl*-8-*azabicyclo*[3.2.1]*oct*-3-*ene*-6-exo- *and* 6-endo-*carbonitrile* [(11) *and* (13)].—The betaine (2) (3·42 g, 0·02 mol) was heated with an excess of acrylonitrile (80 ml) for 16 h. The acrylonitrile was removed *in vacuo* and the resultant yellow solid washed with cold MeOH (20 ml) to

[13] Y. Takeuchi, N. Dennis, A. R. Katritzky, and I. Taulov, 3rd International Congress of Heterocyclic Chemistry, Sendai, Japan, 1971.
[14] J. Nakayama, O. Simamura, and M. Yoshida, *Chem. Comm.*, 1970, 1222.
[15] The British Drug Houses Ltd., B.D.H. Laboratory Chemicals Division, 'Ion Exchange Resins,' Poole, 1965, 5th edn., p. 20.

give a mixture (*exo* : *endo* ratio 4 : 5 by n.m.r.) of two stereoisomers (3·49 g, 76%), which was chromatographed on alumina [light petroleum–CH_2Cl_2 (2 : 1)].

The 6-exo-*carbonitrile* (11) was eluted first and crystallised from light petroleum–CH_2Cl_2 (2 : 1) as yellow plates, m.p. 123—124° (Found: C, 74·8; H, 5·4; N, 12·4. $C_{14}H_{12}N_2O$ requires C, 75·0; H, 5·4; N, 12·5%); $\nu_{max.}$ (Nujol) 2250 (C≡N), 1682 (αβ-unsaturated C=O), 1600, and 1500 (arom.) cm^{-1}; $\lambda_{max.}$ (EtOH) 237 nm (log ε 4·14); *m/e* 224.

The second fraction afforded yellow needles of the 6-endo-*carbonitrile* (13), m.p. 170—171° (Found: C, 75·3; H, 5·4; N, 12·6%); $\nu_{max.}$ (Nujol) 2250 (C≡N), 1682 (αβ-unsaturated C=O), 1600, and 1502 (arom.) cm^{-1}; $\lambda_{max.}$ (EtOH) 237 nm (log ε 4·14); *m/e* 224.

Methyl 2-*Oxo*-8-*phenyl*-8-*azabicyclo*[3.2.1]*oct*-3-*ene*-6-endo-*and* 6-exo-*carboxylate* [(14) *and* (12)].—The betaine (2) (8·6 g, 0·05 mol) was heated under reflux during 15 h with an excess of methyl acrylate (120 ml). The yellow oil obtained by evaporation *in vacuo* was purified by column chromatography (alumina) to give a mixture of two stereoisomers (9·3 g, 72%). Fractional recrystallisation of the mixture (MeOH) gave the less soluble isomer, the 6-endo-*carboxylate* (14) as yellow prisms, m.p. 97—98° (Found: C, 70·1; H, 5·9; N, 5·3. $C_{15}H_{15}NO_3$ requires C, 70·0; H, 5·9; N, 5·4%); $\nu_{max.}$ (Nujol) 1740 (ester C=O), 1680 (αβ-unsaturated C=O), 1600, and 1500 (arom.) cm^{-1}; $\lambda_{max.}$ (EtOH) 237 nm (log ε 4·16); *m/e* 257.

The filtrate slowly deposited the 6-exo-*carboxylate* (12) as yellow plates, m.p. 80—90° (from MeOH) (Found: C, 69·8; H, 5·8; N, 5·4%); $\nu_{max.}$ (Nujol) 1735 (ester C=O), 1685 (αβ-unsaturated C=O), 1600, and 1502 (arom.) cm^{-1}, $\lambda_{max.}$ (EtOH) 236 nm (log ε 4·02); *m/e* 257.

5,9-*Dihydro*-10-*phenyl*-5,9-*iminobenzocyclohepten*-6-*one* (19).—The betaine (2) (5 g, 0·03 mol), pentyl nitrite (3 ml), and 1,2-dichloroethane (50 ml) were heated under reflux (76°) with stirring. Anthranilic acid [8] (4·4 g, 0·03 mol), and bis-(2-methoxyethyl) ether (20 ml) were added dropwise to the solution under reflux during 2 h. After a further 3 h under reflux, NaOH solution (4%; 20 ml) was added and the mixture shaken and extracted with $CHCl_3$ (200 ml). After drying (Na_2SO_4), the extract was evaporated *in vacuo*. The brown residue, on preparative thick-layer chromatography [Kieselgel PF254; benzene–EtOH (80 : 20)] gave a yellow solid. Crystallisation from light petroleum (b.p. 60—80°) gave the *cycloadduct* (19) as yellow prisms (1·1 g, 35%), m.p. 192—193° (decomp.) (Found: C, 82·2; H, 5·3; N, 5·5. $C_{17}H_{13}NO$ requires C, 82·5; H, 5·6; N, 5·3%); $\nu_{max.}$ (Nujol) 1685 (αβ-unsaturated C=O) and 1603 (C=C) cm^{-1}; $\lambda_{max.}$ (EtOH) 240 (log ε 4·38) and 208 nm (4·30); *m/e* 247.

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