# 1,3-Dipolar Character of Six-membered Aromatic Rings. Part XVI.[1] Reactions of Benzyne with 3-Hydroxypyridine, 1-Methyl-3-oxidopyridinium, and Related Compounds

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3-Hydroxypyridine, its 6-methyl analogue, and 4-hydroxyisoquinoline all react with 2 mol. equiv. of benzyne; cycloadduct formation occurs across the 2- and 6-positions together with *N*-phenylation. 1-Methyl-3-oxidopyridinium and its 6-methyl analogue both react with 2 mol. equiv. of benzyne in two successive cycloadditions.

PREVIOUS parts of this series have shown that 1-substituted 3-oxidopyridinium betaines (1) react across the 2- and 6-positions with 2 π-electron dipolarophiles. 3-Hydroxypyridine (2) itself possesses[2] latent 1,3-dipolar character by virtue of significant contributions[3] from the zwitterionic tautomeric form (2b). We now report reactions of compound (2) and of related *N*-methyl betaines with benzyne. We have previously disclosed that *N*-phenyl betaines give the expected adduct with benzyne,[4] and that a benzyne precursor gives azacoumarins with β-hydroxypyridines.[5]
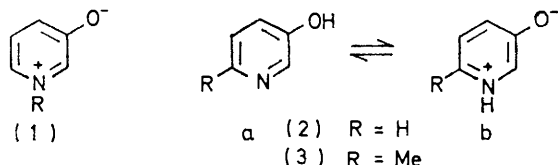
3-Hydroxypyridine (2) reacted with benzyne (from diazotised anthranilic acid[6]) to afford the cycloadduct (4), identical with the compound prepared from 3-oxido-1-phenylpyridinium and benzyne.[4] High yields of the
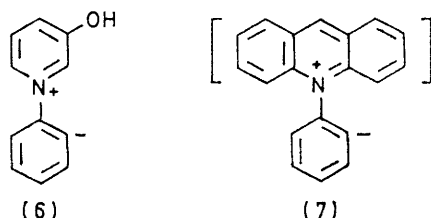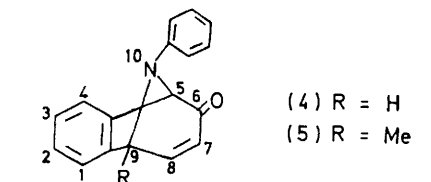
cycloadduct (4) were also obtained by treating 3-acetoxypyridine, 3-benzoyloxypyridine, 3-trifluoroacetoxypyridine, and 3-(2,4,6-trinitrophenoxy)pyridine, with

benzyne. We found earlier that 3-(2,4-dinitrophenoxy)-pyridine gives compound (4) with benzyne.[7]

The *N*-phenyl group in (4) could arise by initial reaction of the zwitterion (2b) to yield a cycloadduct with an NH group, which is subsequently phenylated by benzyne. Alternatively the *N*-phenyl betaine (1; R = Ph) could be an intermediate resulting from direct reaction of benzyne with the nitrogen atom of the substituted pyridine, with the initially formed zwitterion (6) tautomerising to the 1,3-dipolar betaine (1; R = Ph). A related species (7) has been postulated as an intermediate in the reaction of benzyne and acridine.[8] However, work in the phthalazinium series[9] indicates that cycloadduct formation probably occurs in the first step.

3-Hydroxy-6-methylpyridine (3) similarly reacts with benzyne to give the 9-methyl analogue (5), with similar

spectral characteristics. The mass spectrum shows the molecular ion at *m/e* 261; the base peak at *m/e* 220

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

Chemical shifts (δ)	(4)[b]	(5)[b]	(10)[c]	(10)[c,d]	(21)[c]	(22)[e]
			Compound			
H-1			6.92[e]	6.16[e]		
H-5	5.27[f]	5.15	5.88[g]	5.21[g]		
H-6					4.31[f]	4.27[f]
H-7	5.42[e]	5.47[e]				
H-8	7.25[e]	7.03[f]				
H-9	5.46[f]					
H-9			6.82[e]	6.64[e]		
H-10			5.47[g]	3.49[g]		
H-11					6.54[e]	
H-12					5.44[h]	5.33[e]
H-13					4.26[i]	4.16[i]
H-2',6'				5.98[e]		
CMe		1.98[g]				2.16[f]
NMe					2.64[g]	2.64[g]

Coupling constants (Hz)	(4)[b]	(5)[b]			(21)[c]	(22)[c]
6, 13					1.5	1.5
5,7	2.0	2.0	11, 12		10.0	
7,8	10.0	10.0	11, 13		1.0	
8,9	4.5		12, 13		5.0	5.0
			Me, 12			1.5

[a] δ in p.p.m. relative to Me₄Si as internal standard. [b] In CCl₄. [c] In CDCl₃. [d] 0.013 4 g Pr(fod)₃ added. [e] Double doublet. [f] Doublet. [g] Singlet. [h] Quartet. [i] Complex.

[1] Part XV, N. Dennis, B. Ibrahim, and A. R. Katritzky, *J.C.S. Chem. Comm.*, 1975, 425.

[2] T. Banerji, N. Dennis, F. Frank, A. R. Katritzky, and T. Matsuo, *J.C.S. Perkin I*, 1976, 2334.

[3] A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1** 353.

[4] N. Dennis, A. R. Katritzky, T. Matsuo, S. K. Parton, and Y. Takeuchi, *J.C.S. Perkin I*, 1974, 746.

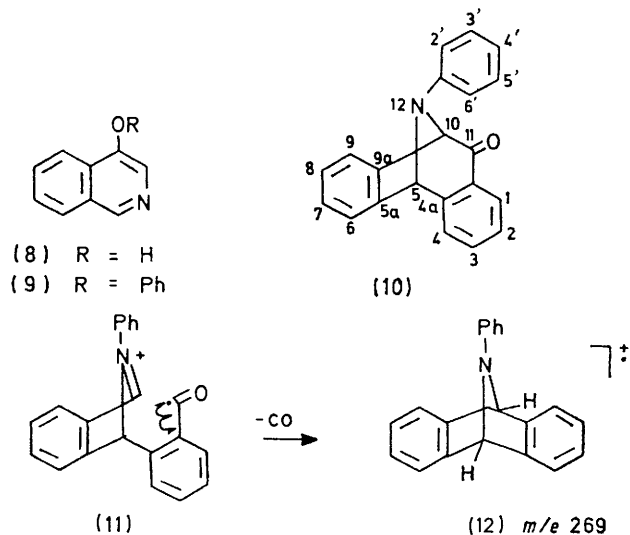[5] N. Dennis, A. R. Katritzky, and S. K. Parton, *J.C.S. Perkin I*, 1974, 750.

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

[7] N. Dennis, B. Ibrahim, A. R. Katritzky, and Y. Takeuchi, *J.C.S. Chem. Comm.*, 1973, 292.
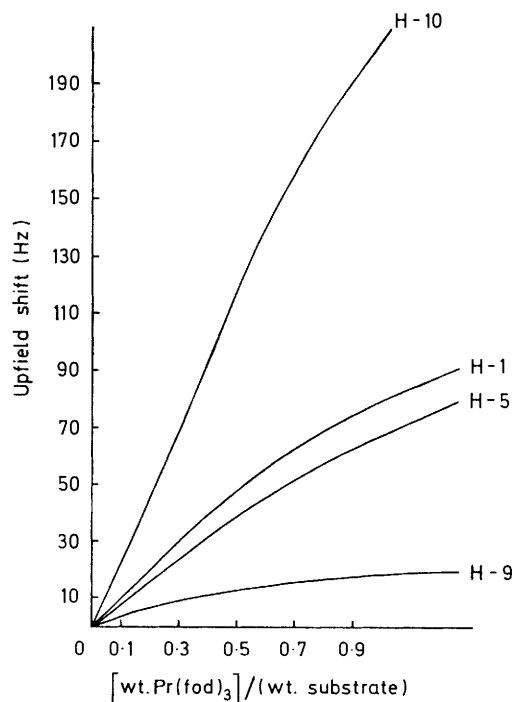
[8] G. Wittig and K. Niethammer, *Chem. Ber.*, 1960, **93**, 944.

[9] N. Dennis, A. R. Katritzky, and M. Ramaiah, *J.C.S. Perkin I*, 1975, 1506.

corresponds to loss of the fragment -CHCO*. Loss of CH$_3$ gives m/e 246 (8.9%). The n.m.r. spectrum (Table) is simplified to first order by the shift reagent Pr(fod)$_3$ and plots [10] of chemical shift difference against the weight ratio of Pr(fod)$_3$ show that H-5 and -7 are affected to a greater extent than H-8 and the methyl group.

(10) (Table) discloses the signals for H-2′ and -6′ which are buried in the aromatic envelope in the absence of lanthanide. Plots of the chemical shift difference ($\delta\Delta$) $vs.$ the weight ratio of Pr(fod)$_3$ added (Figure) show H-10, adjacent to the carbonyl group, to be affected most. The mass spectrum affords further evidence for structure (10). The base peak at m/e 268 could arise by cleavage of the 10,11-bond to give (11), which is further cleaved to give the radical ion (12) (m/e 269) with expulsion of carbon monoxide. Further removal of a hydrogen atom then occurs (m/e 268).

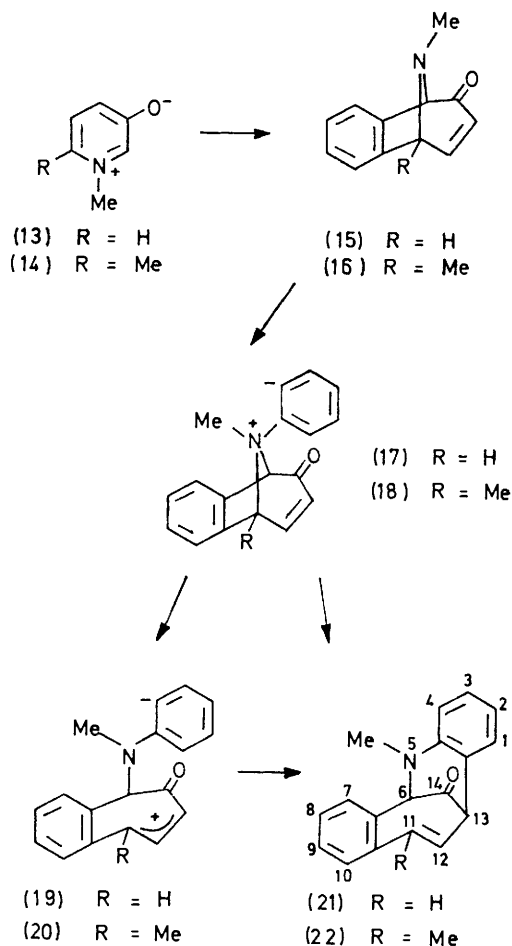(8) R = H
(9) R = Ph

(10)

(11)

(12) m/e 269

4-Hydroxyisoquinoline (8) reacts with benzyne to form 4-phenoxyisoquinoline (9) and 5,5a,9a,10-tetra-hydro-12-phenyl-5,10-iminodibenzo[a,d]cyclohepten-11-one (10) which was again identified by spectral evidence. The first-order [Pr(fod)$_3$-modified] n.m.r. spectrum of

(13) R = H
(14) R = Me

(15) R = H
(16) R = Me

(17) R = H
(18) R = Me

(19) R = H
(20) R = Me

(21) R = H
(22) R = Me

Effect of lanthanide shift reagent on proton resonances of the cycloadduct (10)

1-Methyl-3-oxidopyridinium (13) reacted with benzyne from diazotised anthranilic acid [6] to yield 6,13-dihydro-5-methyl-6,13-methano-5H-5-azadibenzo[a,e]cyclononen-14-one (21) in place of the expected cycloadduct (15). The structure of (21) was substantiated by spectroscopic data. The i.r. spectrum showed saturated ν(C=O) (1 720 cm^{-1}), olefinic ν(C=C) (1 640 cm^{-1}), and aromatic (1 600 cm^{-1}) bands. The u.v. spectrum shows absorption at 247.5 nm for an $n \longrightarrow \pi$ transition characteristic of NN-dimethylaniline (251 nm).[11]

The n.m.r. assignment (Table) is supported by the

[10] For full details see S. K. Parton, Ph.D. Thesis, University of East Anglia, 1975.
[11] V. Baliah and T. Rangarajan, $Naturwiss.$, 1959, 46, 107.

results of double irradiation studies. Irradiation at the frequency of (i) H-13 causes collapse of the double doublet and quartet due to H-11 and H-12 to doublets; (ii) H-12 causes collapse of the double doublet due to H-11 and the multiplet due to H-13 to a doublet and a quartet, respectively; (iii) H-11 causes collapse of the quartet due to H-12 to a doublet and the multiplet due to H-13 to a double doublet. The signals for H-6 and H-13 are too close for mutual decoupling. The n.m.r assignment was further supported by a plot of upfield shift vs. weight ratio of Pr(fod)₃, which confirmed that the bridgehead protons H-6 and H-13 are the most sensitive with H-12, H-11, and N–CH₃ successively less so, as expected for structure (21).

Structure (21) is also supported by the low resolution mass spectrum, with a molecular ion at m/e 261. The base peak at m/e 232 is envisaged as formed by loss of CO to give m/e 233 (confirmed by a metastable peak at m/e 206.5, due to the transition 261 ⟶ 233) and then loss of a hydrogen atom. Subsequent losses of a methyl group and a hydrogen atom give m/e 217 and 216, respectively. The fragment ion at m/e 233 alternatively loses methyl (to m/e 218) and then a hydrogen atom (to m/e 217). The mass spectrum of the similar bridged carbonyl compound (23) shows an analogous loss of carbon monoxide.[12]

1,6-Dimethyl-3-oxidopyridinium (14) was prepared from 3-hydroxy-6-methylpyridine via the methiodide (24); it reacted with benzyne similarly to give compound (22), which showed i.r. and u.v. spectral characteristics almost identical with those for compound (21). The n.m.r. spectrum showed similar chemical shifts for the corresponding protons H-6, H-12, and H-13. Differences from compound (21) were the replacement of the signal for H-11 by that for a second methyl group, which occurred as a doublet (δ 2.16) owing to allylic coupling with H-12, and appearance of the H-12 signal as a doublet of doublets (Table). The low-resolution mass spectrum of (22) shows the base peak at m/e 275 for the molecular ion and prominent fragments corresponding to successive losses of carbon monoxide (m/e 247) and a hydrogen atom (m/e 246). The former fission is confirmed by the metastable peak (m/e 221.5) due to the transition 275 ⟶ 247. Further fragment ions occurred at m/e 231 and 216, which correspond to two subsequent methyl radical losses. A methyl radical is also lost from the molecular ion to give m/e 260. Loss of carbon monoxide gives m/e 232, which can then fragment to give either m/e 231 or 217 (loss of hydrogen atom or methyl radical, respectively).

The reaction of 2-methyl-4-oxidoisoquinolinium with benzyne gave no isolable products.

The formation of compounds (21) and (22) is considered to proceed through initial cycloadducts (15) and (16), which were not isolated even when less than molar quantities of the benzyne precursor were used. The initial cycloadducts (15) and (16) react as tertiary amines

with further benzyne to give intermediate zwitterions (17) and (18), which cyclise to (21) and (22) either directly or via the ring-opened species (19) and (20), in which there is some stabilisation of the positive charge by conjugation with the benzene ring. Somewhat analogous reactions have been reported [13,14] between benzyne and N-substituted pyrroles, to give first the

(23) (24)

(25) (26)
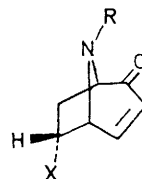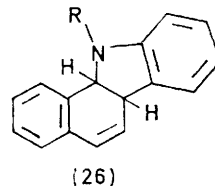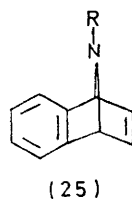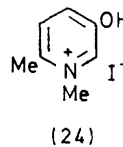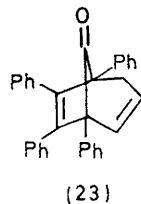
(27) R = Me, X = CN
(28) R = Me, X = CO₂Me
(29) R = Ph, X = Ph

Diels–Alder adduct (25) and then (with further benzyne) (26). Isoindoles give rearranged 1 : 2 adducts with dimethyl acetylenedicarboxylate, and benzyne with certain napthalen-1,4-imines forms N-methylcarbazoles.[15] Attempts to bring about reactions of N-methyl and N-phenyl cycloadducts (27)—(29) with benzyne failed.

EXPERIMENTAL

M.p.s. were determined with a Reichert apparatus. Spectra were recorded with a Perkin-Elmer 257 grating i.r. spectrophotometer, a Unicam SP 800A u.v. spectrophotometer, a Hitachi–Perkin-Elmer RMU-6E mass spectrometer, and a Varian HA-100 MHz n.m.r. spectrometer. Compounds were purified until they were obtained as single spots on t.l.c. [Kieselgel PF 254 and C₆H₆–EtOH (80 : 20)]

5,9-Dihydro-10-phenyl-5,9-iminobenzocyclohepten-6-one (4).—3-Hydroxypyridine (9.0 g, 0.081 mol), n-pentyl nitrite (4 ml + 3 × 6 ml), and 1,2-dichloroethane (100 ml) were heated to reflux (76 °C) with stirring. Anthranilic acid (14 g, 0.102 mol) in bis-(2-methoxyethyl) ether (50 ml) was added dropwise to the solution under reflux during 3 h, and the heating was continued for a further 3 h. Water (100 ml) was added and the mixture was extracted with CHCl₃.

¹² D. C. Dittmer, K. Ikura, J. M. Balquist, and N. Takashina, J. Org. Chem., 1972, **37**, 225.

¹³ G. Wittig and B. Reichel, Chem. Ber., 1963, **96**, 2851.
¹⁴ G. Wittig and W. Behnisch, Chem. Ber., 1958, **91**, 2358.
¹⁵ L. J. Kricka and J. M. Vernon, J.C.S. Perkin I, 1973, 766.

After drying (Na_2SO_4), the extract was evaporated *in vacuo*. The brown residue, on preparative thick-layer chromatography [Kieselgel PF 254; C_6H_6–EtOH (80 : 20)], gave a yellow solid which crystallised from light petroleum (b.p. 60—80 °C) as the *cycloadduct* (4) in yellow prisms (2 g, 20%), m.p. 192—193 °C (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%); $v_{max.}$ (Nujol) 1 685 ($\alpha\beta$-unsaturated ketone C=O) and 1 603 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 240 (log ε 3.38) and 208 nm (3.30); *m/e* 247.

3-Acetoxypyridine,[16] 3-benzoyloxypyridine,[16] 3-trifluoro-acetoxypyridine, and 3-(2,4,6-trinitrophenoxy)pyridine [17] were treated with benzyne as described for 3-hydroxypyridine to yield the cycloadduct (4) in 32, 23, 45, and 89% yields, respectively.

3-Trifluoroacetoxypyridine.—3-Hydroxypyridine (9.5 g, 0.1 mol) and trifluoroacetic anhydride (25 g, 0.12 mol) were heated under reflux for 1 h. $NaHCO_3$ (1.3 g, 0.14 mol) was added and the mixture was stirred for 24 h at room temperature, then extracted with dry diethyl ether. The solvent was removed and the residue distilled to yield the *product* (1.2 g, 8.3%) as an oil, b.p. 70—72 °C at 14 mmHg (Found: C, 48.5; H, 2.1; N, 7.3. $C_4H_4F_3NO_2$ requires C, 48.2; H, 2.0; N, 7.2%); $v_{max.}$ (film) 1 768 cm^{-1} (ester C=O).

5,9-Dihydro-9-methyl-10-phenyl-5,9-iminobenzocyclohepten-6-one (5).—3-Hydroxy-6-methylpyridine (3) (9.0 g, 0.094 mol) was treated with benzyne as above. The crude product was purified by thick-layer chromatography. Crystallisation from light petroleum (b.p. 60—80 °C) gave the *cycloadduct* (5) as yellow prisms (1.8 g, 10%), m.p. 129 °C (Found: C, 82.8; H, 5.8; N, 5.4. $C_{18}H_{15}NO$ requires C, 82.7; H, 5.8; N, 5.4%); $v_{max.}$ (Nujol) 1 675 ($\alpha\beta$-unsaturated ketone C=O) and 1 600 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 238.5 (log ε 3.28) and 204.0 nm (3.34); *m/e* 261 (22.6), 246 (8.9), and 220 (100%).

5,5a,9a,10-Tetrahydro-12-phenyl-5,10-iminodibenzo[a,d]-cyclohepten-11-one (10).—4-Hydroxyisoquinoline (8) (9 g, 0.03 mol) was treated with benzyne as described above. The crude product was purified by thick-layer chromatography. Crystallisation from EtOH gave the *cycloadduct* (10) as yellow prisms (2.5 g, 12%), m.p. 196—198 °C (Found: C, 84.5; H, 5.1; N, 4.7. $C_{21}H_{15}NO$ requires C, 84.8; H, 5.1; N, 4.7%); $v_{max.}$ (Nujol) 1 685 ($\alpha\beta$-unsaturated ketone C=O) and 1 600 cm^{-1} (C=C); $\lambda_{max.}$ (EtOH) 208 (log ε 3.47), 226.5 (3.43), and 240 nm (3.37); *m/e* 297 (55), 269 (60), and 268 (100%).

The thick-layer chromatography also gave 4-*phenoxyisoquinoline* (9) (2.0 g, 12%) as hexagons, m.p. 66—67 °C (from MeCN) (Found: C, 81.4; H, 5.0; N, 6.1. $C_{15}H_{11}NO$ requires C, 81.4; H, 5.0; N, 6.3%); $v_{max.}$ (Nujol) 1 635, 1 625, 1 220, and 1 065 cm^{-1}; $\lambda_{max.}$ (EtOH) 208 (log ε 3.26), 274 (2.97), 284 (2.86), 311.5 (2.61), and 323.5 nm (2.60); *m/e* 221.

3-Hydroxy-1,6-dimethylpyridinium Iodide (24).—3-

Hydroxy-6-methylpyridine (3) 10.9 g, 0.1 mol) and methyl iodide (130 ml) were heated under reflux in benzene-acetone (50 : 50) (160 ml) for 8 h to give the *iodide* (24) (17.5 g, 70%) as pale yellow hexagonal prisms, m.p. 202—203 °C (from MeCN) (Found: C, 33.4; H, 4.2; N, 5.7. $C_7H_{10}INO$ requires C, 33.5; H, 4.0; N, 5.6%); $v_{max.}$ (Nujol) 3 320 (OH) and 1 590 cm^{-1} (aromatic); *m/e* 123.

1,6-Dimethyl-3-oxidopyridinium (14).—3-Hydroxy-1,6-dimethylpyridinium iodide (50.2 g, 0.2 mol) was treated with Amberlite IRA-401 (OH^-) resin (500 g) to give an oil. This crystallised from hot acetonitrile to give the *betaine* (14) (6.3 g, 78.9%) as off-white plates, m.p. 134—136 °C (decomp.) (Found: C, 58.4; H, 7.5; N, 9.5. C_7H_9NO,H_2O requires C, 59.6; H, 7.9; N, 9.9%); $v_{max.}$ (Nujol) 3 400, 3 260 (OH), and 1 600 cm^{-1} (aromatic); $\lambda_{max.}$ (MeOH) 336 (log ε 3.45), 255.5 (3.65), and 220 nm (3.96); δ (D_2O) 2.54 (3 H, s, CMe), 4.07 (3 H, s, NMe), and 7.41, 7.44, 7.70, and 7.73 (3 H, aromatic).

6,13-Dihydro-5-methyl-6,13-methano-5H-5-azadibenzo-[a,e]cyclononen-14-one (21).—1-Methyl-3-oxidopyridinium[18] (13) (6.0 g, 0.055 mol), n-pentyl nitrite (6 ml + 4 × 5 ml) and 1,2-dichloroethane (100 ml) were heated to reflux (76 °C) with stirring. Anthranilic acid (8.0 g, 0.06 mol) in bis-(2-methoxyethyl) ether (30 ml) was added dropwise during 3 h to the solution. After a further 4 h under reflux, the cooled mixture was extracted with chloroform (3 × 50 ml) and the organic layer washed with distilled water (3 × 15 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The brown residue on thick-layer chromatography [Kieselgel PF 254; benzene–ethanol (80 : 20)] gave the *cycloadduct* (21) (2.5 g, 21%) as hexagonal prisms, m.p. 172—173° (from MeCN) (Found: C, 82.5; H, 5.8; N, 5.4. $C_{18}H_{15}NO$ requires C, 82.7; H, 5.8; N, 5.4%); $v_{max.}$ (CHBr$_3$) 1 720 (sat. C=O), 1 640 (C=C), and 1 600 cm^{-1} (aromatic); $\lambda_{max.}$ (EtOH) 247.5 (log ε 4.31) and 275 nm (4.33); *m/e* 261 (77), 233 (50), 232 (100), 218 (31), 217 (42), and 216 (20%).

6,13-Dihydro-5,11-dimethyl-6,13-methano-5H-5-azadi-benzo[a,e]cyclononen-14-one (22).—1,6-Dimethyl-3-oxido-pyridinium (14) (6.8 g, 0.055 mol) was treated with benzyne as above. The chloroform extracts (3 × 40 ml) were combined, dried (Na_2SO_4), and evaporated *in vacuo*. The dark-brown residue was purified by thick-layer chromatography [Kieselgel PF 254; benzene–ethanol (80 : 20)] to yield the *cycloadduct* (22) (3.9 g, 25%) as hexagonal prisms, m.p. 208—209 °C (from MeCN) (Found: C, 82.8; H, 6.3; N, 5.2. $C_{19}H_{17}NO$ requires C, 82.9; H, 6.2; N, 5.1%); $v_{max.}$ (CHBr$_3$) 1 725 (sat. C=O), 1 640 (C=C), and 1 600 cm^{-1} (aromatic); $\lambda_{max.}$ (EtOH) 247 (log ε 4.30) and 275 nm (4.33); *m/e* 275 (100), 260 (72), 247 (96), 246 (98), 232 (98), 231 (89), 217 (93), and 216 (84%).

[16] H. Bojarska-Dahlig and T. Urbánski, *Prace Placówek Nauk-Badawcz. Ministerstwa Przemyslu Chem.*, 1952, No. 1, 1—15 *Chem. Abs.*, 1954, **48**, 1337.

[17] A. R. Katritzky and T. Matsuo, unpublished results.
[18] A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc.* (C), 1971, 874.