Syntheses of Heterocyclic Compounds. Part XXXII.[1] Intramolecular 1,3-Dipolar Cycloadditions of 2-Allyloxy- and 2-Prop-2-ynyloxy-aromatic Aldehyde Azines

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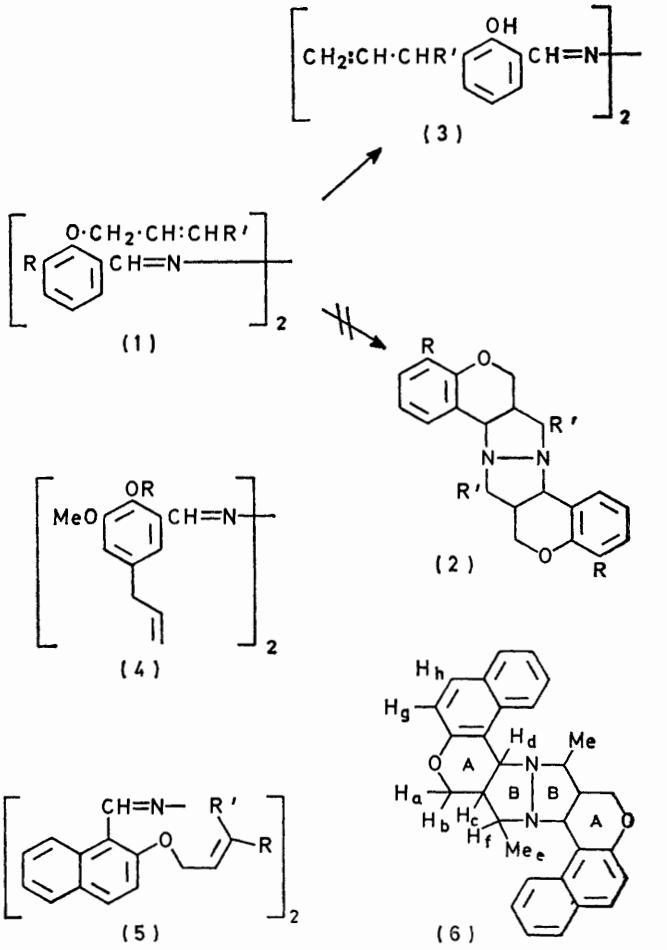
Thermolysis of 2-prop-2-ynyloxy-benzaldehyde and -1-naphthaldehyde azines as well as 2-allyloxy-1-naphthaldehyde azines in *NN*-diethylaniline causes intramolecular cycloaddition in a bis-[3 + 2] or ' criss-cross ' fashion of the prop-2-ynyl or allyl group to the azine side-chain.

FEW intramolecular 1,3-dipolar cycloadditions have so far been reported although they would be expected to be a thermodynamically favourable pathway to heterocycles. Nitrones have been found to add intramolecularly to an olefinic bond to give various isoxazoles,[2] and azomethineimines with internal double bonds give pyrazolidines;[3] more recently nitrilimines have been shown to combine intramolecularly with an acetylenic group to afford pyrazoles.[4]

Since azines are known to act as 1,3-dipoles[5] it was thought that aromatic aldehyde azines might undergo intramolecular bis-[3 + 2] or ' criss-cross ' cycloaddition with a suitably positioned internal dipolarophile. We thought that an *o*-allyloxy-group in an azine [as (1; R = H)] might undergo internal cycloaddition with the azine grouping (·CH:N·N:CH·) to give the fused six-ring system (2) in preference to a [3,3] sigmatropic (Claisen) rearrangement to the hydroxy-compound (3). However, heating a solution of (1; R = R′ = H) in diethylaniline for 4 h gave the Claisen product (3; R′ = H). The *ortho*-blocked 6-methoxy-compound (1; R = OMe, R′ = H) produced the rearranged phenol (4; R = H), and the *ortho,para*-blocked allyloxy-ether (4; R = CH_2·CH:CH_2) and the but-2-enyl derivative (1; R = OMe, R′ = Me) gave intractable mixtures. The failure to produce internal cycloadducts in the benzene series led us to study the analogous naphthaldehyde azine (5; R = Me, R′ = H) under similar conditions. Chromatography of the reaction mixture gave a white solid which did not show an allylic pattern in the ^{1}H n.m.r. spectrum, thus excluding any [3,3] sigmatropic rearrangement. Its spectral and analytical data were fully compatible with the diazabicyclo[3.3.0]octane structure (6) arising from intramolecular ' criss-cross ' cycloaddition between the ·CH:N·N:CH· chain and the two ·CH:CH_2· groups acting as 1,3-dipole and dipolarophile, respectively. The ^{1}H n.m.r. spectrum (in $CDCl_3$) indicated a symmetrical structure. Protons a (τ 5.9) and b (τ 6.05) coupled to H_c formed an ABX system which appeared as an eight-line pattern (J_{ab} 12, J_{ac} 6, J_{bc} 9 Hz). Proton c, being coupled to H_d (J_{cd} 9 Hz), H_f (J_{cf} 6 Hz), H_a, and H_b, appeared as a nine-line multiplet (overlapping triplet of triplets) at τ 7.7 with intensities roughly in the ratio 1 : 2 : 2 : 1 : 4 : 1 : 2 : 2 : 1. The H_f resonance is initially split by four interactions (J_{ef} 6, and J_{cf} 6 Hz) leading to a quintet at τ 6.8 (*ca.* 1 : 4 : 6 : 4 : 1). The methyl signal appeared as a doublet at τ 9.65, and that of H_d at τ 4.8 coupled to H_c (d, J_{cd} 9 Hz). The aromatic protons H_g and H_h gave rise to doublets at τ 3.0 and 2.4, respectively (J_{gh} 9 Hz) and the rest of the naphthalene protons



appeared as multiplet at τ 1.5—2.8. The mass spectral fragmentation was also consistent with the structure (6), showing a peak at 448(M^+) with sequential losses as indicated in Scheme 1 (R = Me). A prominent peak at

[1] Part XXXI, S. S. Mathur and H. Suschitzky, preceding paper.

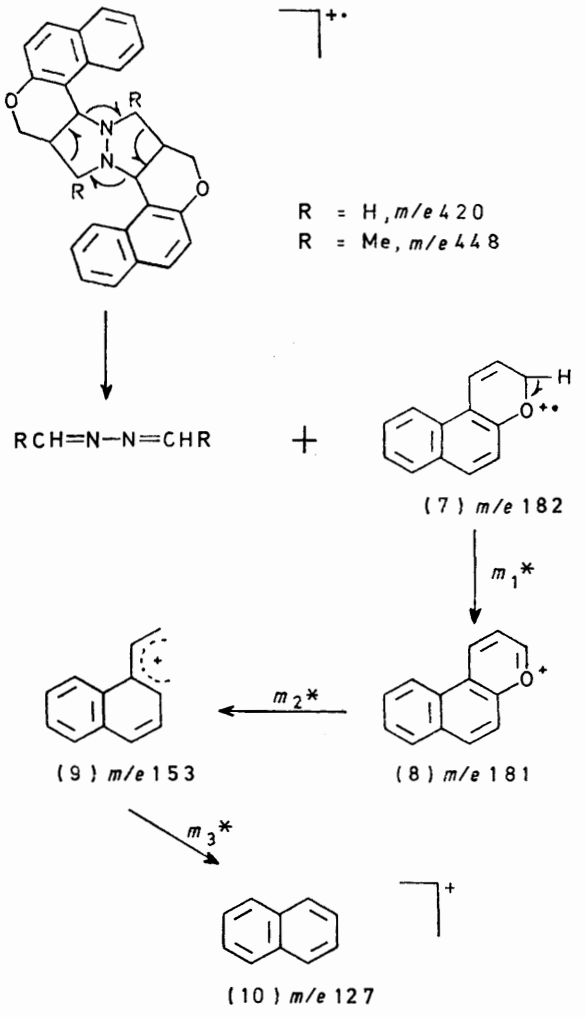
[2] (*a*) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Amer. Chem. Soc.*, 1964, **86**, 3759; (*b*) W. C. Lumma, jun., *ibid.*, 1969, **91**, 2820; (*c*) W. Oppolzer and K. Keller, *Tetrahedron Letters*, 1970, 1117, 1121, 4313.

[3] W. Oppolzer, *Tetrahedron Letters*, 1970, 3091; 1972, 1707.

[4] R. Fusco, L. Garanti, and G. Zecchi, *Tetrahedron Letters*, 1974, 269.

[5] T. Wagner-Jauregg, *Ber.*, 1930, 3213; M. Haring and T. Wagner-Jauregg, *Helv. Chim. Acta*, 1957, **40**(99), 852.

m/e 182 is assigned to benzo[*f*]chromen (7), converted by loss of a hydrogen atom into the chromenyl cation (8),



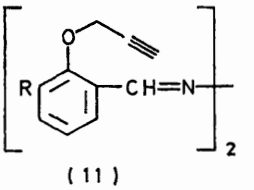
SCHEME 1 m_1* m_2*, and m_3*: metastable peaks at *m/e* 180, 129, and 105 were observed for these fragmentations

appearing as the base peak at *m/e* 181. The fragment ion at *m/e* 127 corresponds to the naphthyl cation (10). 2*H*-Chromen [6] itself is known to give the chromenyl cation by a similar fragmentation pattern leading to the analogous phenyl cation.

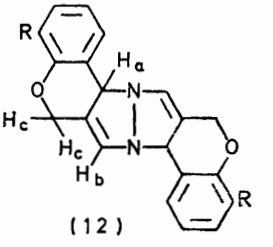
Thermolysis of the azine (5; R = R′ = H) under similar conditions gave the corresponding diazabicyclo-octane (6; H for Me) (12%) with ^{1}H n.m.r. and mass spectral data analogous to those of its methyl homologue. Each cycloadduct (6) was isolated in one form only, indicating stereospecificity of the cycloaddition, but the spectral data did not enable us to distinguish with certainly between several possible conformations. Models (Dreiding) suggest *cis*-fusion between A and B [see (6)] on the basis of least strain, which is also compatible with the observed coupling (J_{cd} 9 Hz) and that reported for the isosteric heterocyclic part in benzopyrano[4,3-*c*]isoxazole.[2c] The slightly high-field methyl resonance (τ 9.65) suggests shielding, presumably owing to the alkyl group lying over the plane of the aromatic rings which is only possible if both naphthopyran units are in an *endo*-position relative to the two folded pyrazolidine rings (B).

Thermolysis of the 2-methylbut-2-enyl ether (5; R′ = R = Me) gave only the dealkylated product, in high yield (82%).

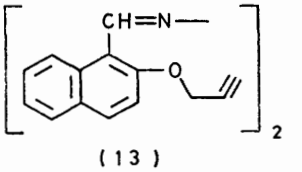
We extended our studies to the azine (11; R = OMe) with an *ortho*-prop-2-ynyloxy-group. Its thermolysis in *NN*-diethylaniline at 200 °C for 1—2 h gave, on cooling, a solid (50%) which on the basis of its spectra is identified as the diazabicyclo-octadiene (12; R = OMe), rather than an internal Diels–Alder product as obtained from some 2,6-disubstituted aryl prop-2-ynyl ethers when treated in a similar way.[7] Its significant ^{1}H n.m.r. signals (in $CF_3 \cdot CO_2D$) were at 2.5 (s, H_a), 1.5 (s, H_b), and 4.8 (s, 2 H_c) with the methyl signal at τ 6.15 (s). The low-field position of the H_a signal as compared with H_d in (6) may be regarded as due to the combined deshielding effect of the double bond and the adjacent nitrogen atom (quaternised by the solvent). The mass spectrum showed peaks which can be rationalised as set out in Scheme 2. The adduct undergoes fission to give the azine (14) which suffers N–N cleavage.[8] Loss of HCN gives the fragment ion (16) which by a symmetry-allowed suprafacial 1,2 H-shift affords the chromenyl cation (17). Further changes are due to loss of CO (18) and acetylene to give fragment ion (19) (*m/e* 107).



(11)



(12)



(13)

Prolonged heating (6—7 h) of the adduct (12; R = MeO) in diethylaniline gave a new adduct with a complex ^{1}H n.m.r. spectrum possibly formed by migration of the double bond. However, no conclusive evidence for an alternative structure was obtained.

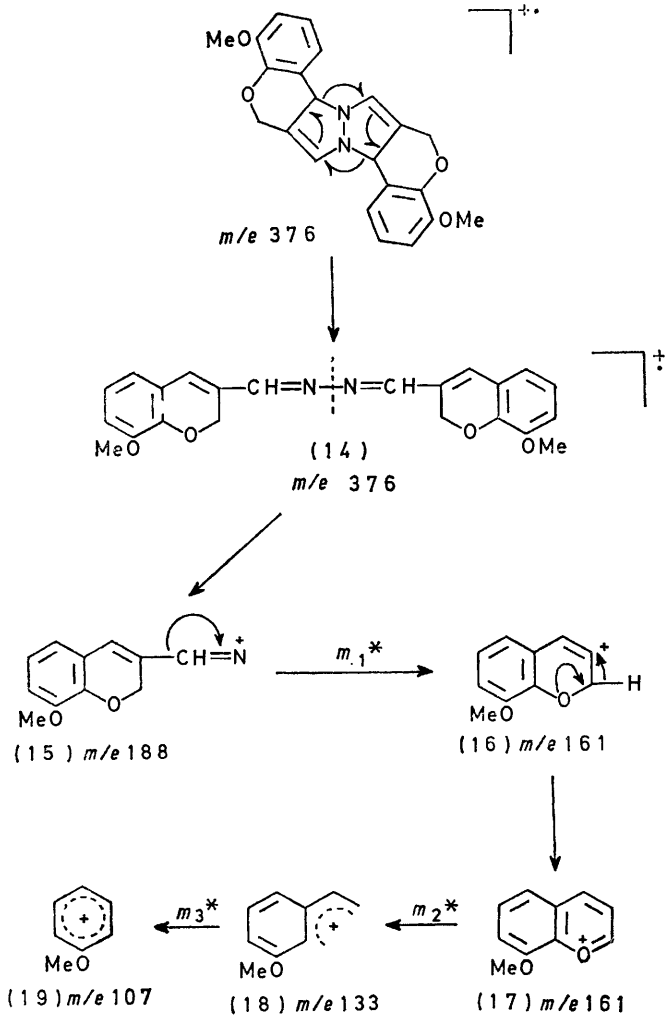
[6] B. Willhalm, A. F. Thomas, and F. Gautschi, *Tetrahedron*, 1964, **20**, 1185.

[7] I. Iwai and H. Ide, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 1042; J. Zsindely and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 1510.

[8] R. G. Cooks and S. W. Tam, *Org. Mass Spectrometry*, 1968, **1**, 583; B. Zeeh and R. Beutler, *ibid.*, p. 791.

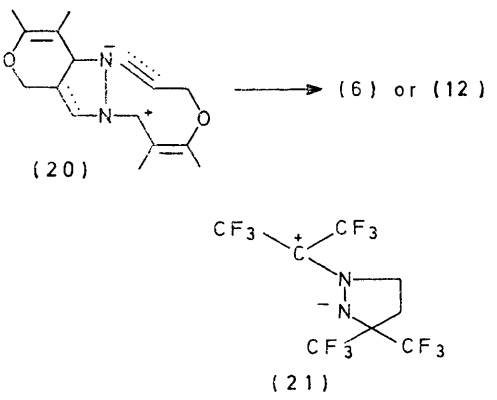
Thermolysis of the *o*-prop-2-ynyloxy-azine (11; R = H) gave the criss-cross cycloadduct (12; R = H) as expected and not a chromen [8] as is usual with prop-2-ynyl ethers under Claisen conditions. The structure is consistent with the ^{1}H n.m.r. and i.r. data (see Experimental section) as well as with its mass spectrum, which showed a peak at 316 (M^+) and a fragmentation pattern analogous to that of its methoxy-derivative (*cf.* Scheme 2). Thermolysis of the naphthaldehyde azine (13) in *NN*-diethylaniline gave the cycloadduct analogous to (12).

We presume that the observed intramolecular cycloadditions follow a pathway analogous to that postulated for the usual intermolecular ' criss-cross ' additions of azines with dipolarophiles.[9] A zwitterionic intermediate (20) is formed arising from the intramolecular cycloaddition of one of the double or triple bonds of the unsaturated ether side-chain onto the azine group. This



SCHEME 2 m_1*, m_2*, and m_3*: metastable peaks at *m/e* 137, 109, and 86 were observed for these fragmentations

is followed by a second intramolecular cycloaddition leading to the described adduct [(6) or (12)]. The intermediacy of the dipole (20) is given some credence by the recent isolation of the dipolar compound [10] (21).



Thermolysis of *o*-allylamino- or *o*-allylthio-benzaldehyde azine gave only intractable mixtures.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 257 instrument, ^{1}H n.m.r. spectra with a Varian A60 or A100 instrument (Me_4Si as standard), and mass spectra with an A.E.I. MS 12 or MS 9 (for high resolution work) instrument.

Preparation of 2-Alkoxy-aromatic Aldehydes.—In a typical procedure a mixture of the 2-hydroxy-aldehyde (0.1 mol) and allyl, but-2-enyl, or prop-2-ynyl bromide (0.1 mol) and finely powdered anhydrous potassium carbonate (0.1 mol) in dry acetone was heated under reflux for 12—24 h. After cooling, water was added and the mixture extracted with ethyl acetate. The extract was washed with aqueous sodium hydroxide (10%) followed by water, dried ($MgSO_4$), and evaporated, leaving the aldehyde which was purified by distillation or recrystallisation (Table 1).

Preparation of Aromatic Aldehyde Azines.—By a conventional method the aldehyde (0.1 mol) in ethanol (20 ml) was treated with hydrazine hydrate (0.05 mol) and the resulting solution was kept on a water-bath for 0.5—1 h. The solution was cooled and the product filtered off and recrystallised from ethanol or chloroform as yellow needles. Some physical data are listed in Table 2. ^{1}H N.m.r. spectra were in accord with the proposed structures.

3-Methoxy-5-(prop-2-enyl)-2-(prop-2-enyloxy)benzaldehyde Azine (4; R = CH_2:CH·CH_2).—A mixture of the hydroxy-azine (1.0 g) obtained from the Claisen rearrangement of (1; R = MeO, R′ = H) (see below), prop-2-enyl bromide (2.4 g) and finely powdered anhydrous potassium carbonate (3 g) in dry acetone was heated under reflux for 20 h. The mixture was cooled, diluted with water (50 ml), and extracted with ethyl acetate (2 × 20 ml). The extract was washed with aqueous sodium hydroxide (10%), dried, and evaporated. Chromatography of the residue over alumina with light petroleum–ethyl acetate (1 : 4) gave the yellow *azine* (4; R = CH_2:CH·CH_2) (1.0 g, 80%), m.p. 90° (Found: C, 72.8; H, 7.1; N, 5.8. $C_{28}H_{32}N_2O_4$ requires C, 73.1; H, 7.0; N, 6.0%). Thermolysis in *NN*-diethylaniline gave tars.

2-(Prop-2-enylamino)benzaldehyde Azine.—A mixture of

[9] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565.
[10] K. Burger, W. Thenn, and A. Gieren, *Angew. Chem. Internat. Edn.*, 1974, **7**, 474.

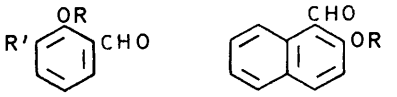
2-aminobenzaldehyde azine[11] (1.6 g), allyl bromide (4.0 g), and anhydrous potassium carbonate (2.0 g) in dry butanol was heated under reflux for 24 h. Work-up as described above gave the *azine* as yellow needles (0.4 g, 26%), m.p. 145° (Found: C, 75.2; H, 6.7; N, 17.5. $C_{20}H_{22}N_4$ requires C, 75.5; H, 6.9; N, 17.6%). Thermolysis in diethylaniline gave only tars.

m.p. 70° (Found: C, 68.7; H, 5.4; N, 7.4. $C_{20}H_{20}N_2S_2$ requires C, 68.2; H, 5.7; N, 7.9%). Thermolysis in diethylaniline gave intractable tars.

Thermolysis of the Azines in NN-*Diethylaniline.*—A suspension of the finely powdered azine [(III) or (IV); see Table 2] (*ca.* 3.0 g) in diethylaniline (15 ml) was heated under reflux for 3 h. After cooling, the mixture was poured onto

TABLE 1

2-Alkoxy-benzaldehydes and -1-naphthaldehydes



(I) (II)

R	R′	Yield (%)	M.p. (°C) [B.p. (°C); mmHg]	Found (%) C	Found (%) H	Formula	Required (%) C	Required (%) H
(I)								
CH_2:CH·CH_2	H	75	[135; 10] [a]			$C_{10}H_{10}O_2$		
CH_2:CH·CH_2	MeO	55	[165; 12] [a]			$C_{11}H_{12}O_3$		
CHMe:CH·CH_2	MeO	65	*b*	69.5	6.3	$C_{12}H_{14}O_3$	69.9	6.8
CH:C·CH_2	H	66	64	75.4	5.2	$C_{10}H_8O_2$	75.0	5.0
CH:C·CH_2	MeO	60	*b*	69.0	4.9	$C_{11}H_{10}O_3$	69.5	5.3
(II)								
CH_2:CH·CH_2		77	77 [c]			$C_{14}H_{12}O_2$		
CHMe:CH·CH_2		70	49	79.3	6.0	$C_{15}H_{14}O_2$	79.7	6.2
CMe_2:CH·CH_2		82	64	79.5	6.5	$C_{16}H_{16}O_2$	80.0	6.7
CH:C·CH_2		76	116	80.5	5.0	$C_{14}H_{10}O_2$	80.0	4.8

[a] Ref. 7. [b] The aldehyde was obtained as an oil by chromatography [Al_2O_3; light petroleum–ethyl acetate (1 : 2)]. [c] L. Claisen and O. Eisleb, *Annalen*, 1913, **401**, 21.

TABLE 2

2-Alkoxy-benzaldehyde and -1-naphthaldehyde azines

(III) (IV)

R	R′	Yield (%)	M.p. (°C)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(III)										
a; CH_2:CH·CH_2	H	84	108	75.5	6.5	8.9	$C_{20}H_{20}N_2O_2$	75.0	6.3	8.7
b; CH_2:CH·CH_2	MeO	62	100	69.2	6.8	7.5	$C_{22}H_{24}N_2O_4$	69.5	6.3	7.3
c; CHMe:CH·CH_2	MeO	80	164	70.2	6.7	6.8	$C_{24}H_{28}N_2O_4$	70.6	6.9	6.8
d; CH:C·CH_2	H	84	174 [a]				$C_{20}H_{16}N_2O_2$			
e; CH:C·CH_2	MeO	52	210	69.8	5.6	7.4	$C_{22}H_{20}N_2O_4$	70.2	5.3	7.4
(IV)										
a; CH_2:CH·CH_2		83	160	79.9	5.9	6.6	$C_{28}H_{24}N_2O_2$	80.0	5.7	6.6
b; CHMe:CH·CH_2		88	131	80.3	6.2	6.5	$C_{30}H_{28}N_2O_2$	80.4	6.3	6.2
c; CMe_2:CH·CH_2		66	135	80.8	6.7	6.8	$C_{32}H_{32}N_2O_2$	80.7	6.7	5.8
d; CH:C·CH_2		76	186	80.5	5.0	7.0	$C_{28}H_{20}N_2O_2$	80.8	4.8	6.7

[a] E. G. Brain, F. P. Doyle, M. D. Mehta, D. Miller, J. H. C. Nayler, and E. R. Stove, *J. Chem. Soc.*, 1963, 491.

2-(*Prop*-2-*enylthio*)*benzaldehyde Azine.*—A mixture of *o*-fluorobenzaldehyde (12.0 g), prop-2-ene-1-thiol (10 g), powdered potassium carbonate, and butanol (50 ml) was kept under reflux for 24 h. Dilution with water was followed by extraction with chloroform. The extract was dried ($MgSO_4$) and evaporated *in vacuo*. The resulting oil was purified on silica with light petroleum–ethyl acetate (1 : 1) as eluant. The resulting oily 2-(prop-2-enylthio)-benzaldehyde was converted into the *azine* (6.5 g, 73%) with hydrazine as described above for the preparation of azines; an alumina column and the solvent was eluted with light petroleum. The products obtained by further elution with other solvents (in parentheses) and recrystallised from ethanol were as follows. (*a*) The azine (IIIa) rearranged to give 2-*hydroxy*-3-(*prop*-2-*enyl*)*benzaldehyde azine* (chloroform) (3; R′ = H), m.p. 124° (46%) (Found: C, 75.2; H, 6.7; N, 8.2. $C_{20}H_{20}N_2O_2$ requires C, 75.0; H, 6.3; N, 8.7%). (*b*) The azine (IIIb) rearranged to 2-*hydroxy*-3-*methoxy*-5-(*prop*-2-*enyl*)*benzaldehyde azine* (4; R = H),

[11] C. E. Pawloski, U.S.P. 3,235,595.

m.p. 182° (55%) (Found: C, 69.8; H, 6.7; N, 7.8. $C_{22}H_{24}N_2O_4$ requires C, 69.5; H, 6.3; N, 7.3%), τ [$(CD_3)_2SO$–$CDCl_3$)] 6.6 (4 H, s), 6.1 (2 MeO, s), 4.6 (4 H, m), 3.8 (2 H, m), 3.1 (4 H, s), 1.25 (2 H, s), and −1.3 (OH, s, collapsed on addition of D_2O). (c) Thermolysis of the azine (IIIc) gave tarry material. (d) The azine (IVa) gave 8a,9b,-17a,18b-*tetrahydro*-8H,9H,17H,18H-7,16-*dioxa*-9a,18a-*diazapentaleno*[2,1-c:5,4-c′]*diphenanthrene* (6; H for Me) (from ethyl acetate) as white needles (12%), m.p. 275—276° (Found: C, 79.6; H, 5.7; N, 6.4. $C_{28}H_{24}N_2O_2$ requires C, 80.0; H, 5.7; N, 6.6%), τ (CF_3·CO_2D) 6.15 (4 H, m), 5.65 (8 H, m), 4.25 (2 H, d, J_{cd} 8 Hz), 3.1 (2 H, d), and 2.2—2.8 (10 H, m). (*e*) The azine (IVb) gave the 9,18-*dimethyl derivative* (6) of the foregoing compound (from diethyl ether), m.p. 243—245° (17%) (Found: C, 80.2; H, 6.0; N, 6.1. $C_{30}H_{28}N_2O_2$ requires C, 80.4; H, 6.3; N, 6.2%); for ^1H n.m.r. data see Discussion section. (*f*) When the azine (IIId) was heated, 6H,7bH,13H,14bH-5,12-*dioxa*-7a,14a-*diazapentaleno*[2,1-c:5,4-c′]*dinaphthalene* (12; R = H) separated on cooling; m.p. 254° (from dimethylformamide) (33%) (Found: C, 76.2; H, 5.2; N, 8.5. $C_{20}H_{16}N_2O_2$ requires C, 76.0; H, 5.1; N, 8.8%), τ (CF_2·CO_2D) 4.65 (2 H, s), 2.35—2.95 (8 H, m), 2.25 (2 H, s), and 1.4 (2 H, s). (*g*) The azine (IIIe) gave the 4,11-*dimethoxy-derivative* (12; R = OMe) in a similar manner; m.p. 252—253° (50%) (Found: C, 70.2; H, 5.4; N, 7.2. $C_{22}H_{20}N_2O_4$ requires C, 70.2; H, 5.3; N, 7.4%) (see Discussion section for ^1H n.m.r. spectrum). (*h*) From the aldazine (IVd) 8H,-9H,17H,18H-7,16-*dioxa*-9a,18a-*diazapentaleno*[2,1-c:5,4-c′]-*diphenanthrene* separated on cooling (35%); m.p. 285—287° (from dimethylformamide) (Found: C, 80.7; H, 4.8; N, 6.6. $C_{28}H_{20}N_2O_2$ requires C, 80.8; H, 4.8; N, 6.7%). (*i*) When the aldazine (IVc) was heated, 2-hydroxy-1-naphthaldehyde azine (IV; R = H) (82%), m.p. 290° (decomp.) (lit.,[12] 290°), was deposited on cooling.

We thank Allen and Hanbury for a studentship (to S. S. M.), Dr. D. Bishop for discussions, and Mr. T. McC. Paterson for experimental assistance.

[5/680 *Received*, 10*th April*, 1975]

[12] I. Heilbron and H. M. Bunbury, 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965.