Cyclisation of α-(*o*-Alkenylaryl)diazoalkanes: a Route to 2,3-Benzodiazepines *via* a Novel 1,7-Electrocyclic Ring Closure

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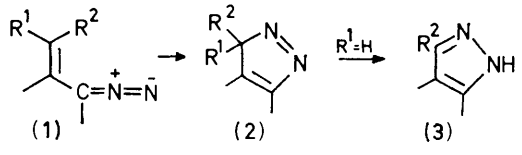
α-(*o*-Alkenylaryl)diazoalkanes, generated from tosylhydrazone salts, cyclise to 1*H*-2,3-benzodiazepines in high yield. These products isomerise to the 5*H*-isomers under basic conditions. The energy barriers to ring inversion for both isomers have been estimated from n.m.r. spectroscopic data.

αβ-UNSATURATED diazoalkanes (**1**) react by two main pathways, (i) *via* loss of nitrogen to give carbene- or carbonium ion-derived products, depending on solvent



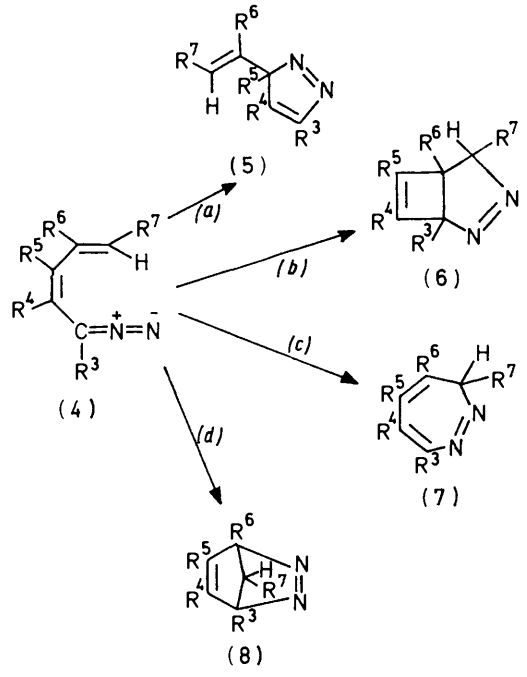
(1) (2) (3)

protonicity, and (ii) with retention of nitrogen to give 1*H*- and 3*H*-pyrazoles (**2**) and (**3**).[1-3] Brewbaker and Hart have examined the mechanism of pyrazole formation and concluded that ring closure occurs *via* an intramolecular 1,3-dipolar cycloaddition.[4] Recently, we have investigated the reactivity of related systems such as (**4**) where the conjugation is extended by one double bond. In such systems there are several possible modes of electrocyclic ring closure [(*a*)—(*d*), Scheme 1]. The isolated products would not necessarily be the primary products of cyclisation as shown but could be derived from them by rearrangement or nitrogen extrusion.

In reactions of diazoalkenes of type (**4**) in which the

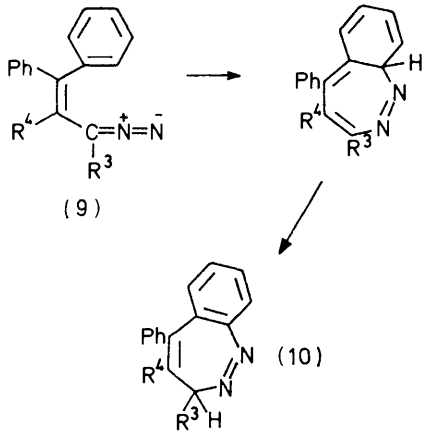
[1] G. L. Closs, L. E. Closs, and W. A. Böll, *J. Amer. Chem. Soc.*, 1963, **85**, 3796.
[2] R. H. Findlay, J. T. Sharp, and P. B. Thorogood, *Chem. Comm.*, 1970, 909.
[3] G. L. Closs and W. A. Böll, *Angew. Chem. Internat. Edn.*, 1963, **2**, 399.
[4] J. L. Brewbaker and H. Hart, *J. Amer. Chem. Soc.*, 1969, **91**, 711.

$\gamma\delta$-double bond forms part of an aromatic ring, *e.g.* (9), it has recently been shown [2] that the mode of cyclisation is greatly influenced by steric factors. For example when $R_3,R_4 = [CH_2]_3$, ring closure proceeds exclusively *via* mode (*c*) to give 1,2-benzodiazepines (10) (Scheme 2): however, when $R_3,R_4 = [CH_2]_4$, the cyclisation gives only



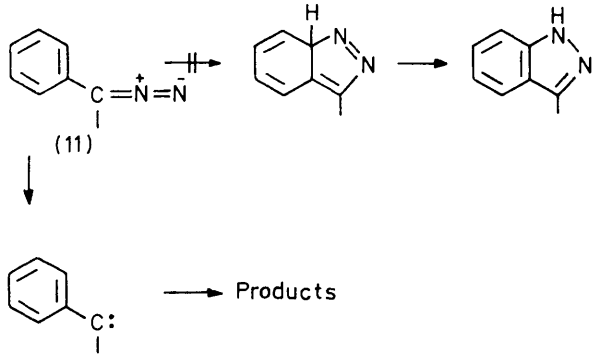
SCHEME 1

pyrazoles by a type (*a*) ring closure. These observations and those on related systems [5] indicate that mode (*a*) is generally preferred to (*c*) unless there is some constraint



SCHEME 2

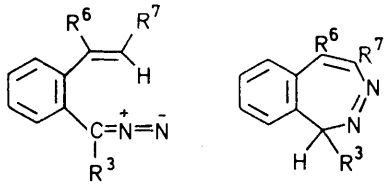
on pyrazole formation. Cyclisations *via* modes (*b*) and (*d*) have apparently not yet been observed, although it has recently been suggested that 2-azidobenzophenones cyclise by a mechanism analogous to (*d*) before eliminating nitrogen to give 3-phenylanthranils.[6] The synthesis



SCHEME 3

of (10; $R_3,R_4 = [CH_2]_3$) from (9) provided the first example of cyclisation *via* route (*c*) and it was therefore of interest to look for other structural features which might inhibit (*a*) and permit the extension of this synthesis to related seven-membered heterocyclic systems.

Although diazoalkanes with $\alpha\beta$-olefinic unsaturation generally cyclise readily to pyrazoles those with $\alpha\beta$-aromatic unsaturation do not likewise give indazoles (Scheme 3). Instead, the latter react principally *via* loss of nitrogen to give carbene-derived products such as azines and/or stilbenes,[7] although in cases where the aromatic ' double bonds ' are more localised, *e.g.* in (2-naphthyl)- and (9-phenanthryl)-diazomethanes, some



cyclisation does occur to give benzindazoles in useful yields (*ca.* 10% and 35% respectively).[8] Thus it seemed likely that in the system (12), *i.e.* as (4) with the $\alpha\beta$-double bond as part of an aromatic ring, cyclisation *via* (*a*) would be inhibited and reaction would occur either by an alternative mode of ring closure or *via* loss of nitrogen to give carbene-derived products. We found that experimental conditions could be chosen such that cyclisation by mode (*c*) was predominant, giving 1*H*-2,3-benzodiazepines (13) in high yield. A preliminary account of this work has been published.[9]

EXPERIMENTAL

N.m.r. spectra were obtained on a Varian HA100 spectrometer, and in the variable temperature experiments the probe temperature was determined from the chemical shift difference between the methylene and hydroxy protons of ethylene glycol. Cyclohexane and dimethoxyethane were

[5] J. T. Sharp and J. Dingwall, unpublished observations.
[6] J. H. Hall, F. E. Behr, and R. L. Reed, *J. Amer. Chem. Soc.*, 1972, **94**, 4952.
[7] W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 1952, 4735.
[8] J. T. Sharp, unpublished observations.
[9] J. T. Sharp and P. B. Thorogood, *Chem. Comm.*, 1970, 1197.

distilled under nitrogen from calcium hydride immediately before use.

trans-2-*Chlorostilbene*, m.p. 35—37° (lit.,[10] 39—40°), was prepared in 56% yield by the Wittig reaction from benzyltriphenylphosphonium chloride and *o*-chlorobenzaldehyde.

trans-2-*Cyanostilbene*, m.p. 65—66° (lit.,[10] 65—66°), was prepared in 85% yield by the reaction of *trans*-2-chlorostilbene with copper(I) cyanide and pyridine.

1-*Ethyl*-3,4-*dihydroisoquinoline*, b.p. 75° at 3·5 mmHg, was prepared from *N*-propionyl-2-phenylethylamine (m.p. 72—75°) by the method of Whaley and Hartung [11] in 72% yield (Found: C, 82·9; H, 8·6; N, 8·8. $C_{11}H_{13}N$ requires C, 83·0; H, 8·2; N, 8·8%).

Acylstyrenes.—The following compounds were prepared from 3,4-dihydroisoquinolines by Gensler's method: [12] 2-formyl-4,5-dimethoxystyrene, m.p. 46—48° (lit.,[12] 50—51°); 2-acetylstyrene, b.p. 82—85° at 2 mmHg (lit.,[12] 96—100° at 3 mmHg); 2-benzoylstyrene, b.p. 126° at 0·4 mmHg (lit.,[12] 159—161° at 2·5 mmHg); 2-benzoyl-4,5-dimethoxystryene, m.p. 66—67° (lit.,[12] 66—67°); 2-propionylstyrene (88%), b.p. 74° at 0·05 mmHg (Found: C, 82·6; H, 7·8. $C_{11}H_{12}O$ requires C, 82·5; H, 7·55%). 2-Formylstyrene, b.p. 59—62° at 0·5 mmHg (lit.,[13] 113—115° at 18 mmHg), was prepared by a similar method.[13]

Acylstilbenes.—trans-2-*Formylstilbene*, m.p. 80—82° (lit.,[14] 83°) was prepared by Natelson's method.[14]

trans-2-*Acetylstilbene*. A Grignard reagent was prepared from methyl iodide (13·2 g) and magnesium (2·5 g) in ether (35 ml). To this was added a solution of *trans*-2-cyanostilbene (6·33 g) in benzene (40 ml) and solvents were removed by distillation until the vapour temperature reached 62°. The mixture was boiled under reflux under nitrogen for 16 h, cooled, and evaporated to low volume under reduced pressure. After addition of hydrochloric acid (100 ml; 4M) the mixture was boiled under reflux for 4 h, cooled, and extracted with benzene (2 × 50 ml). The benzene solution was washed with water (3 × 100 ml), dried, and evaporated to give a purple oil (7·2 g) which was chromatographed on alumina. Elution with benzene gave an oil (5·1 g) which was distilled to give *trans*-2-acetylstilbene (4·1 g) as a pale yellow oil, b.p. 134—136° at 0·05 mmHg. The oil solidified and was recrystallised from ether–petroleum to give *crystals*, m.p. 67—68°. (Found: C, 86·5; H, 6·4. $C_{16}H_{14}O$ requires C, 86·45; H, 6·35%), $\nu_{max.}$ (Nujol) 1680 cm^{-1} (C=O).

trans-2-p-*Toluoylstilbene*. A similar reaction using the Grignard reagent from *p*-bromotoluene gave trans-2-p-*toluoylstilbene* (85%), m.p. 101—102° (Found: C, 88·5; H, 5·8. $C_{22}H_{18}O$ requires C, 88·6; H, 6·1%), $\nu_{max.}$ (Nujol) 1650 cm^{-1} (C=O).

Preparation of Tosylhydrazones.—The following compounds were prepared by the acid catalysed reactions of the carbonyl compounds with *p*-tosylhydrazine in ethanol or methanol. Full details of these preparations are described in Supplementary Publication No. SUP 20803 (6 pp.).*

2-*Formylstyrene tosylhydrazone* (14a), m.p. 115—116° (decomp.), $\nu_{max.}$ (Nujol) 3170 cm^{-1} (N–H).

2-*Formyl*-4,5-*dimethoxystyrene tosylhydrazone* (14b), m.p. 75—76° (decomp.), $\nu_{max.}$ (KBr) 3200 cm^{-1} (N–H).

2-*Acetylstyrene tosylhydrazone* (14c), m.p. 146—148°, $\nu_{max.}$ (Nujol) 3200 cm^{-1} (N–H).

2-*Propionylstyrene tosylhydrazone* (14d), m.p. 141—143° (decomp.), $\nu_{max.}$ (Nujol) 3180 cm^{-1} (N–H).

2-*Benzoylstyrene tosylhydrazone* (14e), m.p. 116—120° (decomp.), $\nu_{max.}$ (Nujol) 3170 cm^{-1} (N–H).

2-*Benzoyl*-4,5-*dimethoxystyrene tosylhydrazone* (14f), m.p. 178—180° (decomp.), $\nu_{max.}$ (Nujol) 3180 cm^{-1} (N–H).

trans-2-*Formylstilbene tosylhydrazone* (14g), m.p. 145—146·5°, $\nu_{max.}$ (Nujol) 3210 cm^{-1} (N–H).

trans-2-*Acetylstilbene tosylhydrazone* (14h). Two isomeric tosylhydrazones were obtained, m.p. 149—150°, $\nu_{max.}$ (Nujol) 3184 cm^{-1} (N–H), and m.p. 134°, $\nu_{max.}$ (Nujol) 3190 cm^{-1} (N–H).

trans-2-p-*Toluoylstilbene tosylhydrazone* (14i), m.p. 176—177°, $\nu_{max.}$ (Nujol) 3300 cm^{-1} (N–H).

Cyclisation of Tosylhydrazone Sodium Salts.—The sodium salts were prepared and cyclised by the method described below for 2-formylstyrene tosylhydrazone (14a) and 2-acetylstyrene tosylhydrazone (14c). In all cases the cyclisations were carried out under nitrogen and in the dark in boiling dry dimethoxyethane, cyclohexane, or toluene as solvent as indicated below and in Table 1. In most cases

TABLE 1

p-Tosylhydrazone	Reaction solvent	Reaction time/h	Recrystallisation solvent
(14b)	DME*	0·33	EtOH
(14d)	DME	2	MeOH
(14e)	DME	0·5	EtOH
(14f)	DME	0·5	EtOH
(14g)	DME	0·33	EtOH
(14h)	DME	24	EtOH
(14i)	Cyclohexane	7	EtOH–$CHCl_3$

* DME = 1,2,-dimethoxyethane.

n.m.r. spectra of the crude products showed that only the 1*H*-2,3-benzodiazepine had been formed. The pure benzodiazepines were usually obtained by crystallisation of the crude products and the overall yields, m.p.s, and elemental analyses are given in Table 2.

2-*Formylstyrene tosylhydrazone* (14a). The tosylhydrazone (1·5 g, 0·005 mol) dissolved in dimethoxyethane (9 ml) was added to a solution of sodium (0·1149 g, 0·005 mol) in ethanol (50 ml) and the mixture was stirred for 30 min in the dark. After evaporation under reduced pressure at <40°, the residual salt was dried overnight in the reaction flask under high vacuum. Dry dimethoxyethane (100 ml) was added and the mixture was heated to reflux under nitrogen in the dark. After a few minutes sodium *p*-toluenesulphinate precipitated and the reaction was continued for 40 min until t.l.c. (alumina; 1 : 1 benzene–ether) showed that all the starting material had been consumed. The mixture was filtered through Celite and the solvent removed on a rotary evaporator using minimum heat to leave a viscous yellow oil (0·7 g). The n.m.r. spectrum of this crude product showed that it consisted almost entirely of 1*H*-2,3-benzodiazepine (17a). Attempts to crystallise this product from ethanol, methanol, and petroleum led only to dark oils; however, in

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1972, Index issue (items less than 10 pp. are supplied as full-size copies).

[10] D. F. De Tar and L. A. Carpino, *J. Amer. Chem. Soc.*, 1956, **78**, 475.

[11] W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, 1949, **14**, 650.

[12] W. J. Gensler, E. M. Healy, J. Onshuus, and A. L. Bluhm, *J. Amer. Chem. Soc.*, 1956, **78**, 1713.

[13] W. J. Dale, L. Starr, and C. W. Strobel, *J. Org. Chem.*, 1961, **26**, 2225.

[14] S. Natelson and S. P. Gottfried, *J. Amer. Chem. Soc.*, 1941, **63**, 487.

a subsequent reaction, the product was purified by sublimation onto a cold finger at 0·1 mmHg to give 1*H*-2,3-benzodiazepine (17a) as a yellow crystalline solid, m.p. 49—50°, in an overall yield of 41%.

2-*Acetylstyrene tosylhydrazone* (14c). The sodium salt was heated under reflux for 2 h in dimethoxyethane. After filtration the crude product was crystallised from ethanol at −20° to give 1-methyl-1*H*-2,3-benzodiazepine (64%).

Preparation of 5H-2,3-*Benzodiazepines*.—1-*Phenyl*-5H-2,3-*benzodiazepine* (30e). This was prepared by two methods. (a) 2-Benzoylstyrene tosylhydrazone (14e) (3·76 g) sodium salt was prepared in the usual way but using *ca.* 5% excess of sodium and heated under reflux under nitrogen in dry toluene (120 ml) for 12 h. The mixture was washed with water (2 × 50 ml) and the organic layer was dried over magnesium sulphate and evaporated to give an orange solid (2·10 g). This was recrystallised from ethanol to give the 5H-*benzodiazepine* (30e) (1·50 g, 69%), m.p. 152—153° (Found: C, 81·9; H, 5·6; N, 12·6. $C_{15}H_{12}N_2$ requires: C, 81·8; H, 5·5; N, 12·7%).

(b) 1-Phenyl-1*H*-2,3-benzodiazepine (17e) (0·050 g) and anhydrous potassium acetate (0·050 g) were heated under reflux under nitrogen in ethanol (20 ml) in the dark for 6 days. The solvent was evaporated off and the product was washed with water (10 ml) and extracted into benzene (30 ml). After drying ($MgSO_4$), the benzene was evaporated off to give a yellow solid (0·035 g) which was recrystallised from ethanol to give (30e) (0·023 g, 46%), m.p. 150—152°.

7,8-*Dimethoxy*-1-*phenyl*-5H-2,3-*benzodiazepine* (30f). This was prepared by two methods; (a) from 2-benzoyl-4,5-dimethoxystyrene tosylhydrazone (14f) (2·0 g) with a reaction time of 7 h by the method (a) described for (30e) above. The crude product (1·2 g) was recrystallised from ethanol to give the 5H-*benzodiazepine* (30f) (0·74 g, 57%), m.p. 162—163° (Found: C, 73·1; H, 5·9; N, 9·8. $C_{17}H_{16}N_2O_2$ requires C, 72·8; H, 5·75; N, 10·0%).

(b) 7,8-Dimethoxy-1-phenyl-1*H*-2,3-benzodiazepine (17f) (0·20 g) dissolved in ethanol (50 ml) containing an equimolar amount of sodium ethoxide was boiled under reflux under nitrogen in the dark for 3 h. The solvent was removed and benzene (60 ml) was added. The solution was washed with water (2 × 20 ml), dried ($MgSO_4$), and evaporated to give a pale yellow solid (0·19 g) which was recrystallised from ethanol–petroleum to give the 5*H*-benzodiazepine (30f) (0·165 g, 82%), as colourless crystals, m.p. 162—163°.

4-*Phenyl*-1-p-*tolyl*-5H-2,3-*benzodiazepine* (30i). 4-Phenyl-1-*p*-tolyl-1*H*-2,3-benzodiazepine (17i) (0·25 g) dissolved in ethanol (50 ml) containing an equimolar amount of sodium ethoxide was boiled under reflux under nitrogen in the dark for 4 h. On cooling, crystals were deposited (0·22 g), m.p. 256—257°, and these were recrystallised from benzene–ethanol to give the 5H-*benzodiazepine* (30i) (0·186 g, 84%), m.p. 269—270° (Found: C, 84·8; H, 5·9; N, 9·0. $C_{22}H_{18}N_2$ requires C, 85·1; H, 5·85; N, 9·0%). In a duplicate reaction carried out in the absence of base the 1*H*-benzodiazepine was unchanged.

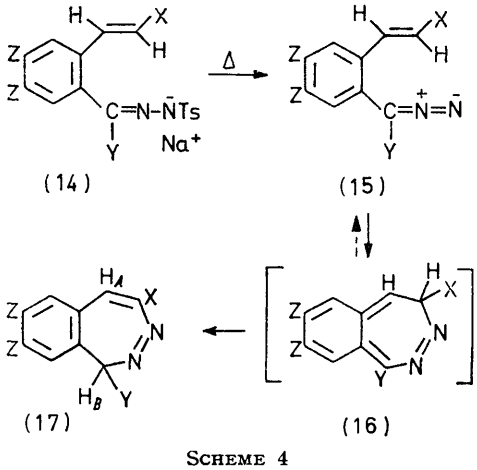
DISCUSSION

The diazo-compounds (15) (Scheme 4) were generated by the thermal decomposition of sodium salts of the *p*-tosylhydrazones (14) of a series of *o*-acyl-styrenes and stilbenes. The tosylhydrazones were generally readily prepared from the acyl-styrenes and -stilbenes but in a few cases mixtures of *syn*- and *anti*-isomers were formed.

TABLE 2

1*H*-2,3-Benzodiazepines

Compound	Molecular formula	Analysis C % Found	C % Calculated	H % Found	H % Calculated	N % Found	N % Calculated	Yield (%)	m.p. (°C)
(17a)	$C_9H_8N_2$	75·0	75·0	5·6	5·6	19·2	19·4	41	49—50
(17b)	$C_{11}H_{12}N_2O_2$	64·6	64·7	6·0	5·9	13·4	13·7	70	89—91
(17c)	$C_{10}H_{10}N_2$	75·7	75·9	6·5	6·4	17·8	17·7	64	47
(17d)	$C_{11}H_{12}N_2$	76·2	76·7	7·2	7·0	16·15	16·3	68	40—41
(17e)	$C_{15}H_{12}N_2$	81·8	81·8	5·5	5·5	12·9	12·7	62	101—102
(17f)	$C_{17}H_{16}N_2O_2$	72·8	72·8	5·8	5·75	10·0	10·0	84	112—113
(17g)	$C_{15}H_{12}N_2$	81·6	81·8	5·6	5·5	12·5	12·7	71	132—133
(17h)	$C_{16}H_{14}N_2$	82·1	82·0	6·0	6·0	11·8	12·0	88	92—93
(17i)	$C_{22}H_{18}N_2$	84·8	85·1	6·0	5·85	9·25	9·0	67	146—147

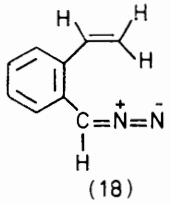


SCHEME 4

	X	Y	Z
a;	H	H	H
b;	H	H	OMe
c;	H	Me	H
d;	H	Et	H
e;	H	Ph	H
f;	H	Ph	OMe
g;	Ph	H	H
h;	Ph	Me	H
i;	Ph	*p*-Tolyl	H

This usually caused no problems other than a complication of the i.r. and n.m.r. spectra but in the case of *o*-acetylstilbene the mixture of isomers initially was very difficult to crystallise, and in this case the isomers were

separated and then characterised. The salt of the minor isomer, presumed to be the *syn*-aryl isomer, decomposed to diazo-compound much faster than the other, probably owing to higher steric compression. The decomposition of the tosylhydrazone salts was generally carried out in boiling cyclohexane or dimethoxyethane for the minimum time required to consume all the starting material. The reactions gave only a single cyclised product, a 1*H*-2,3-benzodiazepine (17) as listed in Table 2. These products were usually isolated by filtering off the precipitated sodium toluenesulphinate and then removing the solvent by evaporation under reduced pressure to leave an oil or solid from which the pure benzodiazepine



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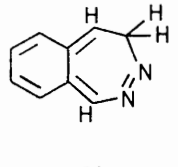

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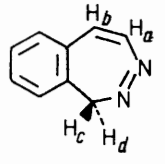

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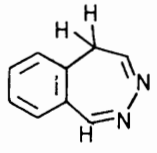

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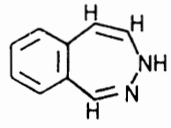


(22)

was obtained by crystallisation. The benzodiazepines obtained from the *o*-diazoalkylstilbenes were higher melting and more stable to handling and recrystallisation than were those from the *o*-diazoalkylstyrenes, which tended to darken during recrystallisation unless this was done quickly under nitrogen.

Structure of the Cyclisation Products.—Elemental analyses and mass spectra of the products showed that they were isomeric with their diazoalkene precursors. A large number of structures having the required composition can be envisaged as products of the cyclisation, *i.e.* compounds (5)—(8) and isomers derived from them. For example if the cyclisation of *o*-diazomethylstyrene (18) occurred by route (*c*) to give (19) as a primary product then the isolated product could be (19), (20), (21), or (22) or the diazanorcaradienes derived from them by ring contraction, *e.g.* (23). Other possible products could be derived from (23) and its analogues by sequential [1,5] sigmatropic migrations of the methylene group and electrocyclic ring expansion and contraction.[15,16]

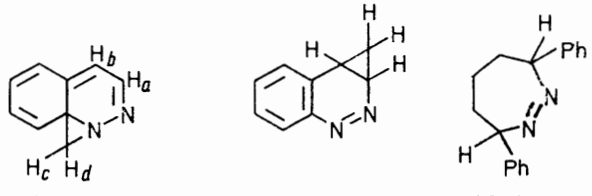
The mass spectra of all the cyclisation products (17) (Table 3) showed only a small peak due to the parent ion and a larger peak due to an (*M* − 28) ion. This ready loss of 28 mass units (N_2) from the parent ion is typical of cyclic azo-compounds and supports formulations containing an −N=N− group, *e.g.* structures (19), (20), or (24) rather than (21)—(23); and although it would be possible for ring expansion in compounds like (23) to precede fragmentation, this was not observed for (27).[17] The mass spectrum of (17a) also shows that the indene

TABLE 3

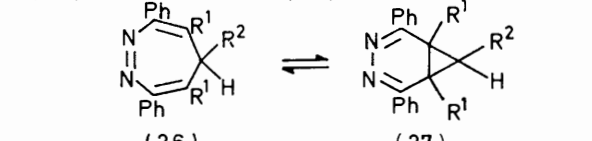
Mass spectra of 1*H*- and 5*H*-2,3-benzodiazepines

Compound	*m/e* (% Relative abundance)
(17a)	39(10), 63(14), 89(12), 115(100), 116(74), 144(16)
(17b)	39(43), 50(33), 51(47), 62(22), 63(58), 64(25), 77(44), 89(65), 90(100), 91(22), 102(29), 103(53), 105(75), 115(56), 118(93), 131(22), 133(83), 161(92), 162(14), 176(100), 177(17), 204(31)
(17c)	39(12), 51(24), 63(18), 64(25), 77(12), 89(10), 115(100), 116(22), 128(25), 129(89), 130(84), 131(13), 158(42)
(17d)	115(37), 127(12), 128(37), 129(100), 130(12), 144(29), 172(19)
(17e)	114(15), 164(20), 189(24), 191(91), 192(100), 193(15), 220(4)
(17f)	44(11), 115(15), 165(31), 178(14), 191(13), 194(12), 206(16), 209(10), 221(15), 237(37), 252(100), 280(5)
(17g)	115(20), 164(20), 189(21), 191(80), 192(100), 193(16), 220(1)
(17h)	89(15), 91(34), 101(12), 103(10), 128(24), 129(13), 165(18), 189(24), 191(99), 192(22), 205(38), 206(100) 207(19), 234(4)
(17i)	(at 70eV) 265(12), 267(15), 281(12), 282(100), 283(26), 310(<1); (at 20eV) 282(100), 283(18), 310(2)
(30e)	51(17), 77(28), 89(26), 90(23), 91(13), 115(13), 116(17), 165(32), 179(19), 191(36), 192(55), 193(68), 194(36), 219(34), 220(100)
(30f)	51(12), 77(21), 165(15), 237(12), 238(14), 249(10), 252(19), 253(16), 280(100)
(30h)	89(20), 90(11), 103(11), 116(35), 130(50), 131(37), 234(100)
(30i)	91(24), 120(20), 121(23), 165(12), 206(22), 207(53), 208(11), 282(20), 310(100)

fragment ion formed by loss of N_2 readily loses H· to give the base peak at *m/e* 115; this process parallels the ready loss of H· from the parent ion of indene itself (intensity ratio *m/e* 116 : 115 = 100 : 73).



(23) (24) (25)



(26) (27)

a; $R^1 = R^2 = Ph$ b; $R^1 = R^2 = H$

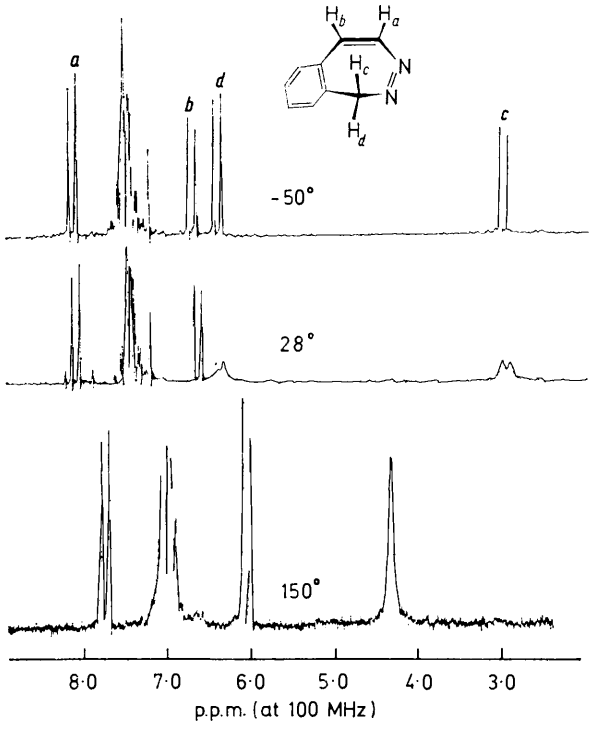
More definitive information on the structure of the cyclisation products was obtained from their n.m.r. spectra; that for the parent compound is shown in the Figure and others are recorded in Table 4. Apart from the aromatic multiplet, the low temperature spectrum in the Figure shows four doublets each integrating for one

[15] J. A. Berson and M. R. Willcott, *J. Amer. Chem. Soc.*, 1965, **87**, 2751, 2752; 1966, **88**, 2494.

[16] R. B. Woodward and R. Hoffmann, *Angew. Chem. Internat. Edn.*, 1969, **8**, 831.

[17] M. A. Battiste and T. J. Barton, *Tetrahedron Letters*, 1967, 1227.

proton; decoupling experiments (at −50°) showed coupling between the *a*–*b* pair and the *c*–*d* pair. An examination of the temperature dependence of the



N.m.r. spectra of 1*H*-2,3-benzodiazepine at − 50° and 28° (in [^{2}H]chloroform) and at 150° (in [$^2H_8$]toluene)

spectrum showed that the *c* and *d* doublets broadened with increasing temperature and eventually coalesced to give a singlet.* The original spectrum was restored on cooling, provided that the compound was not held at the high temperature long enough for extensive thermolysis to occur. We consider that this spectrum best fits structure (20) and the n.m.r. peaks are assigned as shown in the Figure. These assignments are based on the effects of group substitution on the spectrum, on the chemical shifts, and on the variable temperature study. An unexpected feature of this spectrum is the very large chemical shift difference between the methylene protons (*ca.* 3·4 p.p.m.). The azo-group is known to have a strong deshielding effect on the protons attached to α-carbon atoms, *e.g.* the methine proton in (25) absorbs at τ 5·06 [18] and experimental data have shown [19] that protons at positions *in* the –C–N=N– plane are deshielded relative to those in positions above or below this plane. The mechanism for this effect is not fully understood but it is thought that it does not derive solely from magnetic anisotropy.[19] A Dreiding model of (20) shows that the H_d proton is located almost in the plane of the azo-group and should therefore be more deshielded than H_c which lies well above the plane. H_d Also lies virtually in the plane of the benzene ring at *ca.* 3·4 Å from its centre and will therefore also be deshielded by 0·6—0·7 p.p.m. due to ring current effects; [20] H_c will also experience some deshielding from the same source. The H_c proton lying out of the plane of the azo-group would be expected to absorb at higher field and will additionally be shielded by the C(4)–C(5) double bond although since it is *ca.* 2·1 Å above the plane of the bond and *ca.* 2·5 Å from the bond axis this effect would be expected to be small.[20] On the basis of existing data it would therefore be predicted that H_d would absorb at lower field than H_c; however, the magnitude of the separation is surprising. H_a Absorbing at τ 1·83 is also strongly deshielded by the azo-group.

These assignments are supported by the variable temperature study; the spectra of all compounds having a methylene group at C(1) showed a similar temperature dependence to (20) consistent with the predictable

TABLE 4

^{1}H N.m.r. spectra of 1*H*-2,3-benzodiazepines [a]

Compound	τ_A	τ_X	J_{AX} (Hz)	τ_B (*endo*)	τ_Y (*exo*)	J_{BY} (Hz)	τ_Z	Aromatic protons	Temperature (°C)
(17a)	3·30(d, 1H)	1·85(d, 1H)	9	7·01(d, 1H)	3·59(d, 1H)	9		2·3—2·8(m, 4H)	−50
(17b)	3·40(d, 1H)	1·91(d, 1H)	9	7·24(d, 1H)	3·72(d, 1H)	9	6·14br (s,[b] 6H)	3·08(s, 1H) 3·14(s, 1H)	−50
(17c)	3·34(d, 1H)	1·90(d, 1H)	9	7·19(q,[c] 1H)	7·70(d, 3H)	6		2·3—2·8(m, 4H)	28
(17d)	3·36(d, 1H)	1·90(d, 1H)	9	6·7—7·1(m, 1H)	8·77(t, *J* 7 Hz, CH_3) 7·2—7·4(m, CH_2)			2·3—2·8(m, 4H)	28
(17e)	3·19(d, 1H)	1·75(d, 1H)	9	6·11(s, 1H)				2·0—3·1(m, 9H)	28
(17f)	3·30(d, 1H)	1·84(d, 1H)	9	6·29(s, 1H)			6·14(s, 3H) 6·40(s, 3H)	2·1—2·7(m, 5H) 3·08(s, 1H) 3·64(s, 1H)	28
(17g)	3·05(s, 1H)			6·95(d, 1H)	3·60(d, 1H)	9		2·0—2·7(m, 9H)	28
(17h)	3·06(s, 1H)			7·10(q,[c] 1H)	7·71(d, 3H)	6		2·0—2·8(m, 9H)	28
(17i)	2·95(s, 1H)			6·07(s, 1H)	7·59(s, CH_3) + aromatics			2·0—3·1(m, 13H)	28

[a] The spectra were recorded of solutions in $CDCl_3$ at 100 MHz with field sweep. [b] Resolved into two singlets at 28°. [c] Distorted due to small $\Delta\nu_{BY}$.

* The low temperature spectra were run in [^{2}H]chloroform and the high temperature one in [$^2H_8$]toluene. The singlet observed at high temperatures does not appear at the midpoint of the *c*–*d* doublets owing to solvent induced shifts. In low temperature spectra run in [$^2H_8$]toluene the *b* and *d* doublets overlapped.

[18] C. G. Overberger, J.-P. Anselme, and J. R. Hall, *J. Amer. Chem. Soc.*, 1963, **85**, 2752.

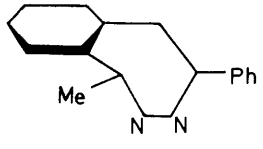
[19] S. N. Ege and R. R. Sharp, *J. Chem. Soc.* (*B*), 1971, 2014.

[20] L. M. Jackman and S. Sternhell, 'Applications of N.m.r. Spectroscopy in Organic Chemistry,' 2nd Edn., Pergamon, Oxford, 1969, pp. 85—95.

temperature dependent ring inversion of the diazepine ring. Similar temperature dependence has been observed in the n.m.r. spectra of 4*H*-1,2-diazepines.[21] The large difference in chemical shift between the *c* and *d* protons prevents an accurate measurement of the coalescence temperature; however for (20), in [$^2H_8$]-toluene as solvent, this lies in the region 60 ± 20 °C which gives a free energy of activation at the coalescence temperature of $\Delta G_c^{\ddagger} = 15 \pm 1$ kcal mol^{-1} assuming the transmission coefficient to be unity.[22] The n.m.r. spectra of compounds in which one of the C(1) hydrogens is substituted by a methyl or phenyl group showed no variation with temperature; these molecules are apparently locked in the least hindered conformation with the substituent group in the *exo*-position.

The possibility of formulating the products as compounds of type (23) had to be considered in view of recent structural work on analogous 1,2-diazepines not annulated to benzene rings.[17,23-26] It has been shown by *X*-ray structural analysis [25] and by n.m.r. studies [24-26] that compounds of type (26)/(27) exist entirely in the bicyclic diazanorcaradiene form (27). This structure is thought to be more stable than (26) because of the much lower bond energy of nitrogen–nitrogen double bonds compared with carbon–carbon or carbon–nitrogen double bonds.[26] The n.m.r. spectrum in the Figure might possibly be fitted to structure (23) with the assignments shown and with the temperature dependence of the spectrum explained by interconversion of diastereotopes *via* (20).[23] This formulation is however ruled out on the basis of the chemical shift of the *d* proton which occurs at much lower field than would be predicted for (23) and by the coupling constant $J_{c,d}$ (9 Hz) which is much higher than that expected for an aziridine ring.[27]

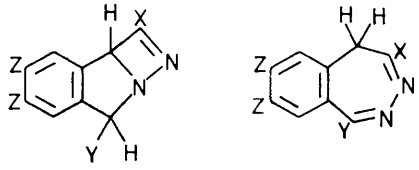
The formulation of the cyclisation products as diazepines (17) has been confirmed [28] by an *X*-ray structure determination on (17h), as shown in structure (28) which



(28)

also confirms that the preferred conformation for this molecule has the methyl group in the *exo*- rather than the *endo*-position, as suggested above on the basis of n.m.r. data. The existence of these compounds as diazepines and not as diazanorcaradienes suggests that the loss of aromatic stabilisation energy which would be involved in the transformation of, *e.g.*, (20) ⟶ (23) outweighs the gain in stability which would result from the absence of the nitrogen–nitrogen double bond in (23).

Some Reactions of the 1H-2,3-*Benzodiazepines.*—These compounds are readily isomerised by light [29] to the tricyclic compounds (29) [*e.g.* a sample of (17h) was quantitatively isomerised on standing in daylight for 48 h]. They also decompose on heating [8] either by loss of nitrogen or by isomerisation to the 5*H*-isomers (30). These



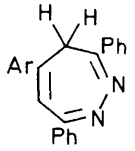
(29) (30)

	X	Y	Z
a;	H	H	H
b;	H	H	OMe
c;	H	Me	H
d;	H	Et	H
e;	H	Ph	H
f;	H	Ph	OMe
g;	Ph	H	H
h;	Ph	Me	H
i;	Ph	*p*-Tolyl	H

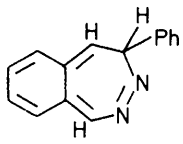
reactions will be reported in full elsewhere. It has also been shown that the 1*H*-benzodiazepines (17) are readily isomerised to the 5*H*-isomers (30) under basic conditions; so readily that the inadvertent use of a slight excess of base when preparing the sodium salts of the tosylhydrazones (14) can lead to the isolation of the 5*H*-isomers from the cyclisation reactions rather than the first formed 1*H*-isomers. This base-catalysed rearrangement has not been studied extensively, although several examples of the 5*H*-isomers (30) have been prepared (Table 5). No attempt has been made to optimise reaction conditions for the isomerisation, which has been carried out with both potassium acetate and sodium ethoxide. Sodium ethoxide–ethanol has provided a convenient and adequate base–solvent combination in two cases, *e.g.* (17i) gave (30i) in 74% yield on boiling under reflux with an equimolar amount of sodium ethoxide in ethanol for 4 h while a blank reaction in the absence of base left (17i) unchanged. The structures of the 5*H*-isomers follow from their mass and n.m.r. spectra (Tables 3 and 5). The mass spectrum of (30h) shows the parent ion as the base peak, fragmenting *via* loss of PhCN to give an isoindole fragment which loses H· to give the peak at *m/e* 130 or Me· to give the *m/e* 116 peak. The 4*H*-1,2-diazepines (31) also gave large peaks corresponding to loss of PhCN from the molecular ion.[21] The mass spectrum of (30i) similarly showed loss of PhCN from the parent ion as a major fragmentation path but also showed a loss of 28 mass units to give a peak at *m/e* 282; this may

[21] O. Buchardt, C. L. Pedersen, U. Svanholm, A. M. Duffield, and A. T. Balaban, *Acta Chem. Scand.*, 1969, **23**, 3125.
[22] G. J. Bishop, B. J. Price, and I. O. Sutherland, *Chem. Comm.*, 1967, 672, and references cited therein.
[23] J. Sauer and G. Heinrichs, *Tetrahedron Letters*, 1966, 4979.
[24] G. Maier and U. Heep, *Chem. Ber.*, 1968, **101**, 1371.
[25] G. Heinrichs, H. Krapf, B. Schröder, A. Steigel, T. Troll, and J. Sauer, *Tetrahedron Letters*, 1970, 1617.
[26] A. Steigel, J. Sauer, D. A. Kleier, and G. Binsch, *J. Amer. Chem. Soc.*, 1972, **94**, 2770.
[27] H. Booth, *Prog. Nuclear Magn. Res.*, 1969, **5**, 192.
[28] R. O. Gould and S. Gould, unpublished observations.
[29] A. A. Reid, J. T. Sharp, and S. J. Murray, *J.C.S. Chem. Comm.*, 1972, 827.

reflect some isomerisation to (17i) either of the molecular ion of (30i) or of the compound itself prior to ionisation.



(31)



(32)

The n.m.r. spectra (Table 5) showed temperature dependence as reported for (31).[21] The coalescence temperatures and free energies of activation for ring inversion ($\Delta G_c^{\ddagger}$) are also given in Table 5; the latter were calculated using the formula [22]

$$k_c = \frac{\pi(\Delta\nu_{AB}^2 + 6J_{AB}^2)^{\frac{1}{2}}}{\sqrt{2}}$$

and the Eyring equation, assuming the transmission coefficient to be unity. The energy barriers to ring inversion are slightly higher than those recorded for the isolated product, the 1*H*-benzodiazepine, is clearly not the most thermodynamically stable isomer and must therefore be produced by a kinetically controlled route. The most likely mechanism on present evidence is shown in Scheme 4 and involves a type (*c*) electrocyclic ring closure to give the intermediate (16). This is *a priori* a reversible reaction and the sequence is probably driven to the right under these reaction conditions by the symmetry allowed [1,5] *supra*-facial sigmatropic hydrogen migration which gives (17) and restores the aromaticity of the benzene ring. Evidence for the sigmatropic nature of the hydrogen migration is provided by the fact that only a [1,5] migration is observed and not a [1,7] migration which would have produced the more stable 5*H*-isomer (30) or the as yet unprepared eight π-electron N–H isomer [*e.g.* (22)] but would have required the inaccessible transition state necessitated by an *antara*-facial migration.* Further work in progress on the mechanism of this reaction is concerned with the reactions of analogues of (14) which have groups other than hydrogen at the terminus of the double bond, *i.e.* compounds with no hydrogen to migrate in the last stage of

TABLE 5

^{1}H N.m.r. spectra of 5*H*-2,3-benzodiazepines at 28°

Compound	τ_X	τ_Y	τ_Z	Aromatic protons	τ_{CH_2}	T_c (°C)*	$\Delta G_c^{\ddagger}$(kcal mol^{-1})
(30e)	In aromatic multiplet			2·2—2·8(m, 10H)	AB part of ABX; τ_A 6·58, τ_B 6·98 J_{AB} 12·5 Hz; $J_{AX} = J_{BX} = 5$ Hz	120 ± 5 (ODCB)	19·5 ± 0·3
(30f)	In aromatic multiplet		6·09(s, 1H); 6·32(s, 1H)	2·2—3·3(m, 8H)	AB part of ABX; τ_A 6·65, τ_B 7·05 J_{AB} 12·5 Hz; $J_{AX} = J_{BX} = 5$ Hz	110 ± 5 (ODCB) and DPE)	19·0 ± 0·3
(30h)		7·43(s, 3H)		2·0—2·8(m, 9H)	AB: τ_A 5·97, τ_B 6·87 J_{AB} 12·5 Hz	137 ± 5 (DPE)	19·9 ± 0·3
(30i)		7·62(s, CH_3) + aromatics		2·0—2·8(m, 13H)	AB: τ_A 5·87, τ_B 6·75 J_{AB} 12·5 Hz	180 ± 5 (N)	22·1 ± 0·3

* Temperature of coalescence. The 28° spectra used deuteriochloroform as solvent and the variable temperature studies used *o*-dichlorobenzene (ODCB) and diphenyl ether (DPE) as indicated, and nitrobenzene (N) was used for (30i) for solubility reasons.

monocyclic diazepines (31).[21] Increasing the bulk of both the substituents X and Y increases $\Delta G_c^{\ddagger}$ most probably because of increased steric interaction in the transition state between the methylene group and X, and between Y and the *peri*-hydrogen on the aromatic ring.

Mechanism of the Cyclisation Reaction.—The inference that diazocompounds are involved in the cyclisation step rather than their precursors, the tosylhydrazone salts, is drawn from the deep red colouration observed in the early stages of several of the cyclisations and from the trapping of the diazoalkene in a related reaction.[2] The Scheme 4. Work is also in progress on the extension of this new synthetic principle to related seven-membered heterocyclic systems.

Since the preliminary account of this work was published another example of this cyclisation has been reported.[31] The cyclisation of (14g) was carried out under conditions very similar to our own and gave a product with an identical melting point which was formulated *not* as the 1*H*-benzodiazepine (17g) but as (32), the compound suggested by us to be an intermediate in the reaction. The ^{1}H n.m.r. spectrum of the product is given in Table 4. Considered in isolation and in the absence of a variable temperature study this spectrum *could* be fitted to the suggested structure; however this formulation is clearly ruled out by com-

* In respect of the ' allowedness ' of the sigmatropic migrations discussed above it is assumed that the diazapolyene system present in these molecules behaves in the manner predicted[16] for an all carbon polyene system. It has recently been shown that the electrocyclic reactions of 2,4- and 2,5-diazahexatrienes take similar paths to those of their hydrocarbon analogues.[30]

[30] Z. Neiman, *J.C.S. Perkin II*, 1972, 1746.
[31] V. I. Bendall, *J.C.S. Chem. Comm.*, 1972, 823.

parison of the ^1H n.m.r. spectrum with those of other compounds in the series (Table 4) and by the variable temperature study which showed that the doublets at τ 3·6 and 6·95 broadened with increase in temperature and eventually coalesced to a singlet at the midpoint with a coalescence temperature of 100 ± 15° ($\Delta G_c^{\ddagger} = 17{\cdot}1 \pm 0{\cdot}7$ kcal mol^{-1}). As with other compounds in the series, the original spectrum was restored on cooling. We therefore emphasise that the cyclisation of *o*-diazomethylstilbene (15g) is similar to that of the other compounds of this type and that the isolated product of m.p. 131—132° is the 1*H*-2,3-benzodiazepine (17g) and *not* compound (32) as suggested elsewhere.[31] Bendall also reported the formation of a compound of m.p. 82—83° which he formulated as (17g) which was produced by keeping the primary product in solution for several days or by irradiating the original diazoalkene. This product is clearly not (17g), but in the absence of spectroscopic data it is impossible to be certain of its structure: however, we surmise that it is the photoisomer (29; X = Ph, Y = Z = H), the formation of which we have reported previously.[27]

The cyclisation of *o*-diazoalkyl styrenes and stilbenes thus exemplifies a new mode of intramolecular cyclisation of diazoalkenes and provides a useful route to the previously unknown 1*H*-2,3-benzodiazepines.

We thank the Wellcome Foundation Ltd. and the S.R.C. for the award of a CAPS studentship (to A. A. R.), Dr. H. Openshaw of the Wellcome Foundation Ltd. for discussions and gifts of compounds, and Drs. S. and R. O. Gould for their *X*-ray structure determination on (17h).

[3/702 *Received*, 3*rd April*, 1973]