Electrocyclic Aromatic Substitution by the Diazo-group. Part 3.[1,†] Studies on Substituent Directive Effects and on the Mechanism of Benzo-1,2-diazepine Formation by the Cyclisation of 1-Aryl-3-diazoalkenes

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The 1,7-cyclisation of diazo-compounds of type (4) which have an unsymmetrically placed substituent X gives both benzodiazepine isomers (6) and (8). The majority of substituents studied (X = R, OR, Cl) exert a directing effect which favours the formation of the less thermodynamically stable isomer (6) while only t-butyl and trifluoromethyl favour the formation of the *para*-isomer (8). A mechanistic study of the cyclisations of (6; X = Me and H) using ^{2}H-labelled substrates has shown that the electrocyclisation step is reversible (Scheme 1; $k_{-1} \neq 0$). However for other substituents (X = OR, CF$_3$, Cl) $k_{-2}(o) \neq 0$ and the *ortho*-isomers undergo slow thermal isomerisation at 80 °C to give the more stable *para*-isomers (8). The observed directing effects of the substituents X are exerted *via* their effects on k_1, k_{-1}, and k_2 and although it is not possible to separate these effects for the majority of the substituents it was shown from the labelling study that the k_2/k_{-1} ratio for the *ortho*-intermediate (5; X = Me) was markedly higher than that for the *para*-intermediate (7; X = Me).

We have shown in earlier work that the benzo-1,2-diazepine system (3) can be prepared in good yield by the cyclisation of the 1-aryl-3-diazoalkene (1).[2] It was proposed that this conversion took place in two steps, first ring closure *via* an 8π-electron 1,7-electrocyclisation to give the intermediate (2), followed by a 1,5-sigmatropic hydrogen migration giving the isolated product (3). The reaction is thus overall a substitution of an aryl hydrogen atom by the azo-group and provided the first example of electrocyclic aromatic substitution by a 1,3-dipolar intermediate. More recently we have extended this reaction to substitution in thiophene rings[3] and, using reactions of formally the same type, Padwa has reported the photochemical conversion of an azirine into a benzazepine[4] *via* a nitrile ylide intermediate and Eberbach has prepared 2-benzoxepines by the cyclisation of carbonyl ylides.[5]

The work described here was carried out to discover more about the mechanism of the (1) ⟶ (3) conversion and the factors affecting the rate of reaction. It is mainly concerned with the cyclisation of the *meta*-substituted diazo-compounds (4) which can in principle cyclise at either of positions 2′ or 6′ leading to (6) and (8) *via* substitution *ortho* or *para* to the group X. The general objective was to determine the directive effects of a range of X substituents and then to carry out a mechanistic study in an attempt to determine whether the substituents exert their directive effect in the cyclisation stage of the reaction or in the subsequent sigmatropic hydrogen shift.

Results and Discussion

(i) *Cyclisation of the Diazo-compounds* (4).—The diazo-compounds (4) were generated *in situ* in aprotic solvents at *ca.* 80 °C from tosylhydrazone salt precursors. Each of the preparative scale reactions, with the exception of that of (4g), gave two isomeric benzodiazepines (6) and (8) which were separated by column chromatography and whose isolated yields are given in Table 1. Their structures followed from a comparison of their ^{1}H and ^{13}C n.m.r. spectra (see Experimental section and Table 2) with those of the unsubstituted analogue (3).[2] The isomers were differentiated by means of their ^{1}H spectra; those of the unsubstituted compound and

(1) ⟶ (2)

[1,5]-H shift

(3)
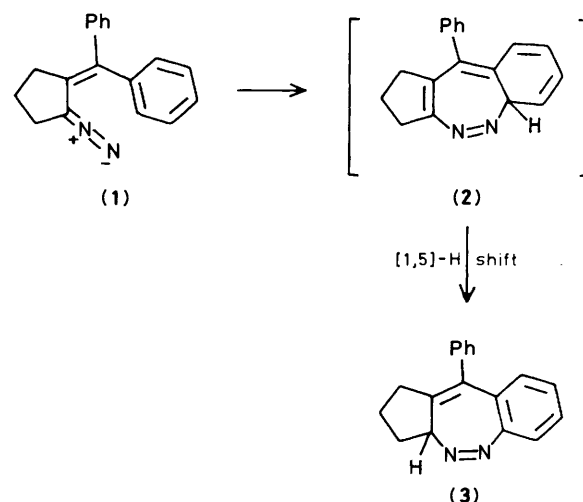
the 8-substituted isomers (8) showed a broad doublet due to the deshielded 6-proton which was absent in the spectra of the 6-substituted isomers (6).

The accurate (6)/(8) isomer ratios, in Table 3, were determined by h.p.l.c. on the products of separate small scale experiments done in cyclohexane and 1,2-dimethoxyethane.

(ii) *The Thermal Rearrangement of the 6-Substituted* (6) *to the 8-Substituted* (8) *Benzodiazepines.*—In all cases the isomer ratio was monitored by h.p.l.c. during the reaction to check on the stability of the benzodiazepines under the reaction conditions. In several cases (c—f) it was found that the (6) : (8) ratio diminished with time and control experiments on the isolated 6-isomers (6c—e) showed that they underwent slow isomerisation to the 8-isomers (8c—e) when heated in inert solvents at 80 °C. The occurrence and rate of this isomerisation was found to be dependent on the nature of the substituent X; it was fastest for X = OMe and OEt (*ca.* 14% in 17 h), slower for X = CF$_3$ (*ca.* 3% in 17 h), slowest for X = Cl (*ca.* 2% in 17 h), and did not occur at all for X = Me and Et. It seems likely that this rearrangement occurs *via* a reversal of the cyclisation mechanism (Scheme 1) with $k_2(o) \gg k_{-2}(o)$ so that although (6) is kinetically favoured in the forward

Table 1. $3H$-Benzo-1,2-diazepines (6) and (8) prepared by the cyclisation of diazo-compounds (4)

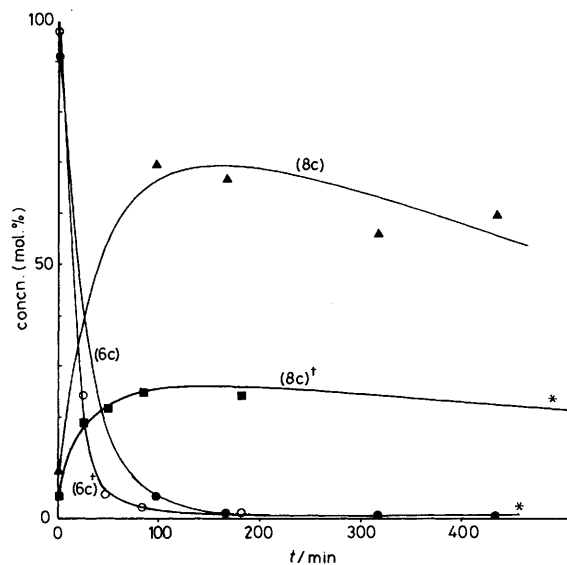|					Analysis					
		Yield *		Molecular	C (%)		H (%)		N (%)	
R	Compd.	(%)	M.p. (°C)	formula	Found	Calc.	Found	Calc.	Found	Calc.
Me	(6a)	67	119—121	$C_{20}H_{20}N_2$	83.5	83.3	7.1	7.0	9.6	9.7
	(8a)	8	111—112		83.5		7.0		9.8	
Et	(6b)	57	Yellow oil	$C_{22}H_{24}N_2$	83.3	83.5	7.8	7.6	8.75	8.85
	(8b)	17	105—106		83.7		7.8		9.1	
OMe	(6c)	62	164—166	$C_{20}H_{20}N_2O_2$	75.3	75.0	6.5	6.3	8.9	8.7
	(8c)	18	Yellow oil		Found: m/e, 320.151 172. $M^{+\cdot}$ requires 320.152 469					
OEt	(6d)	56	145	$C_{22}H_{24}N_2O_2$	75.7	75.8	7.0	6.9	8.1	8.0
	(8d)	22	100—101		75.6		7.0		7.85	
Cl	(6e)	55	99—100	$C_{18}H_{14}Cl_2N_2$	65.8	65.7	4.25	4.3	8.7	8.5
	(8e)	23	151—152		65.8		4.3		8.7	
CF₃	(6f)	17	108—109	$C_{20}H_{14}F_6N_2$	60.7	60.6	3.4	3.6	7.0	7.1
	(8f)	46	137—138		60.5		3.5		7.0	
Bu^t	(8g)	64	Yellow oil	$C_{26}H_{32}N_2$	83.9	83.8	8.7	8.7	7.4	7.5

* Yields are for pure isolated products.
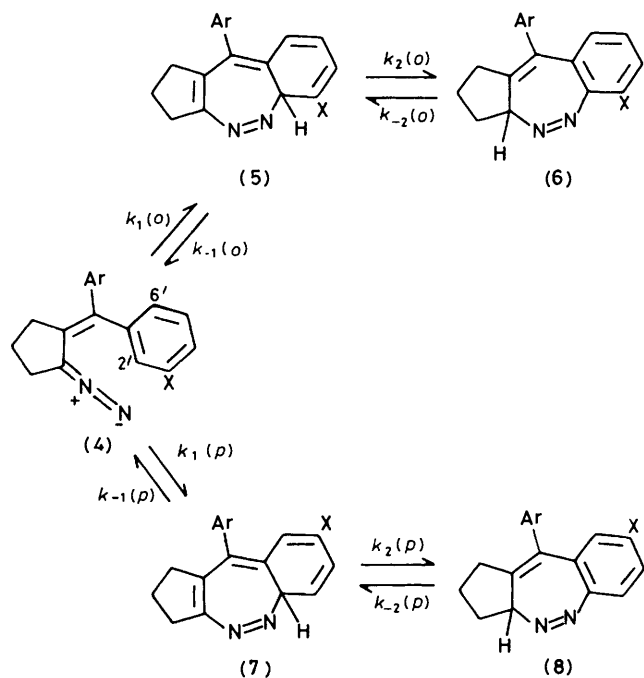
Scheme 1. X = Me, Et, OMe, OEt, Cl, CF₃, Bu^t (see Table 1), Ar = 3'-XC₆H₄

Thermal isomerisation at 130.1 °C of (6c) to (8c) in the absence and presence † of tributylphosphine [* values at 1 440 min for (6c) and (8c) were 18 and 9%, respectively]

reaction it can isomerise to (8) *via* a slow sigmatropic hydrogen shift to give (5) followed by retrocyclisation to give the diazo-compound (4) and subsequent conversion into the more stable 8-isomer (8) by the alternative reaction path. Some evidence supporting this mechanism was obtained by carrying out the isomerisation of (6c) to (8c) at 130 °C in the absence and presence of tributylphosphine. This reagent is known to react rapidly with diazo-compounds to give phosphazines and has been used previously to intercept diazo-compounds similar to (4).[2,6] The results are shown in the Figure; the observed reduction in the yield of (8c) and the faster consumption of (6c) in the presence of the phosphine are consistent with the interception of (4c). The slow decomposition of the diazepines at this temperature is due to extrusion of nitrogen and isomerisation to an indazole;[7] neither of these reaction paths is important at 80 °C.

It was suggested above that the motivation for the isomer-

isation is provided by the more crowded structure and consequent lower thermodynamic stability of the 6-isomer (6). This seems reasonable since Dreiding models show that in (6) the substituent X is closer to the azo N than the sum of their van der Waals radii but it provokes the question of why (6a and b) fail to isomerise when the Me and Et groups are more bulky than the substituents in (6c—e). The obvious answer to this is that the occurrence and rate of the isomerisation depends on the kinetic parameters of the system as well as on the relative stabilities of (6) and (8) and this will be considered further in part (iv) of the Discussion.

(iii) *The Directive Effects of the Substituents and the Mechanism of Cyclisation.*—It can be seen from Table 3* that in the cyclisation of (4a—e) the 6-isomer (6) is the major product and it can be inferred from its subsequent isomerisation to the 8-

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* The product ratios recorded in Table 3 are those after *ca.* 1 h reaction, so approximate closely to the true kinetically controlled ratio.

Table 2. ^{13}C N.m.r. data of 3*H*-benzo-1,2-diazepines and 3*H*-pyrazoles

Compd.	Chemical shift (p.p.m. from Me₄Si)
(6a)	C-1—C-3 26.8, 32.5br; C-3a 75.3; 2 × Me 18.3, 21.3; aromatic and olefinic 126.3, 126.7, 127.1, 128.1, 129.7, 130.7, 133.3 (tert), 135.3 (tert), 137.7 (tert), 139.8 (tert), 143.1 (tert), 150.8 (tert)
(8a)	C-1—C-3 26.7, 32.4, 32.8; C-3a 74.6; 2 × Me 21.4br; aromatic and olefinic 127.0, 127.2, 127.8, 128.1, 128.9, 130.7, 132.9 (tert), 137.0, 137.8 (tert), 139.6 (tert), 143.0 (tert), 150.4 (tert)
(6b)	C-1—C-3 25.1, 26.8, 28.8; C-3a 75.4; 2 × Me 15.2, 15.6; 2 × CH₂ 32.5 (resolved in C₆D₆ 29.97, 30.05); aromatic and olefinic 125.5, 126.8, 127.1, 127.4, 128.1, 129.6, 129.7, 133.5 (tert), 139.8 (tert), 141.3 (tert), 143.1 (tert), 144.1 (tert), 150.2 (tert)
(8b)	2 × Me 15.5, 15.6; 2 × CH₂ and C-1—C-3 26.8, 28.8, 32.5, 32.7; C-3a 74.5; aromatic and olefinic 125.8, 126.9, 127.4, 127.8, 128.0, 128.1, 129.7, 130.6, 133.0, 139.5, 142.9, 143.3, 144.2, 150.5
(6c)	C-1—C-3 26.7, 32.4, 32.7; 2 × Me 55.3, 56.2; C-3a 76.0; aromatic and olefinic 107.3, 113.1, 115.6, 121.0, 122.5, 127.4, 129.2, 130.6, 133.0, 141.1, 142.8, 144.0, 155.4, 159.6
(8c)	C-1—C-3 26.7, 32.5, 32.9; 2 × Me 55.3, 55.4; C-3a 74.4; aromatic and olefinic 111.7, 113.2, 114.0, 115.6, 122.5, 129.3, 130.3, 132.2, 132.5, 140.9, 143.1, 147.0, 157.8, 159.6
(6d)	C-1—C-3 26.7, 32.4, 32.6; C-3a 75.8; 2 × Me 14.8; 2 × CH₂ 63.4, 64.8; aromatic and olefinic 108.3, 113.6, 116.0, 120.9, 122.3, 127.4, 129.1, 130.6, 133.0, 141.0, 142.8, 143.8, 154.7, 158.8
(8d)	C-1—C-3 26.7, 32.5, 32.8; C-3a 74.3; 2 × Me 14.6, 14.8; 2 × CH₂ 63.5, 63.6; aromatic and olefinic 112.2, 113.7, 114.3, 116.1, 122.4, 129.3, 130.2, 132.3, 132.5, 140.8, 142.9, 146.9, 157.1, 158.9
(6e)	C-1—C-3 26.6, 32.2, 32.6; C-3a 76.1; aromatic and olefinic 127.0, 127.2, 127.7, 128.0, 128.9, 129.6, 129.8, 130.8, 131.4, 132.4, 134.2, 140.7, 145.3, 148.1
(8e)	C-1—C-3 26.7, 32.6, 32.6; C-3a 75.0; aromatic and olefinic 126.4, 128.0, 128.2, 129.5, 129.9, 130.7, 131.1, 132.8, 134.4, 140.4, 145.3, 150.3
(6f)	C-1—C-3 26.9, 32.4, 32.8; C-3a 76.4 *
(8f)	C-1—C-3 26.9, 32.6, 32.8; C-3a 75.7 *
(8g)	C-1—C-3 26.6, 32.4, 32.5; C-3a 74.3; 2 × Bu^t 30.8, 31.0, 34.4 (tert), 34.5 (tert); aromatic and olefinic 123.1, 123.8, 125.4, 126.8, 127.3, 127.5, 127.55, 130.0, 133.3, 138.8, 142.2, 149.6, 150.0, 150.5
(18; n = 3, R = Me)	C-1—C-3 26.5, 32.3, 32.4; C-3a 74.8; 4 × Me 18.15, 21.09br; aromatic and olefinic 126.45, 127.6, 128.3, 128.6, 129.6, 132.9, 135.1, 136.4, 137.3, 139.6, 142.5, 148.7
(16; n = 4, R = Me)	4 × Me 21.25; C-4—C-7 22.1, 22.3, 22.7, 23.3; C-3 104.2; aromatic and olefinic 125.4, 129.5, 137.2, 137.9, 150.6, 153.4

* The remainder of the spectrum complex because of C—F coupling.

Table 3. Isomer ratio of benzodiazepines (6) and (8)

Diazo-compound	Isomer ratio (6)/(8)		H.p.l.c. conditions * adsorbent–eluant
	Cyclo-hexane	1,2-Dimeth-oxyethane	
(4a)	4.31	3.62	S–3% D
(4b)	3.5	3.2	A and S–5% E
(4c)	1.63	1.75	A and S–25% D
(4d)	1.57	1.79	S–6% D, A–5% E
(4e)	1.86	2.73	A and S–5% E
(4f)	0.51	0.64	A and S–3% D
(4g)	(8g) only		
(4h)	17.1	13.4	S–3% D
(4i)	1.17	0.99	S–3% D

* A = alumina; S = silica; eluants are shown as vol. % of 1,4-dioxane (D) or ether (E) in hexane.

exerted in either (or both) of the two steps (Scheme 1) of the reaction it was necessary to find out something about their relative rates and whether either or both were reversible under the conditions of the cyclisation. This problem has been examined *via* ^{2}H labelling studies on the cyclisation of (4a). This substrate was selected for two reasons: (a) the methyl group has the strongest *ortho* directive effect and (b) the formation of (6a) and (8a) is irreversible so either k_{-1} or k_{-2} or both must be zero in both branches of the reaction. From the nature of the two steps and the failure to detect any measurable concentration of the intermediates it seems reasonable to assume that the second step at least is irreversible ($k_{-2} = 0$). The application of the steady-state approximation to the intermediates (5) and (7) then gives expressions (1a and b) for the rates of formation of the *ortho* (6 = O) and *para* (8 = P) isomers, where [S] = the concentration of the diazo-compound.

$$\frac{d[O]}{dt} = \frac{k_1(o)k_2(o)[S]}{k_{-1}(o) + k_2(o)} \tag{1a}$$

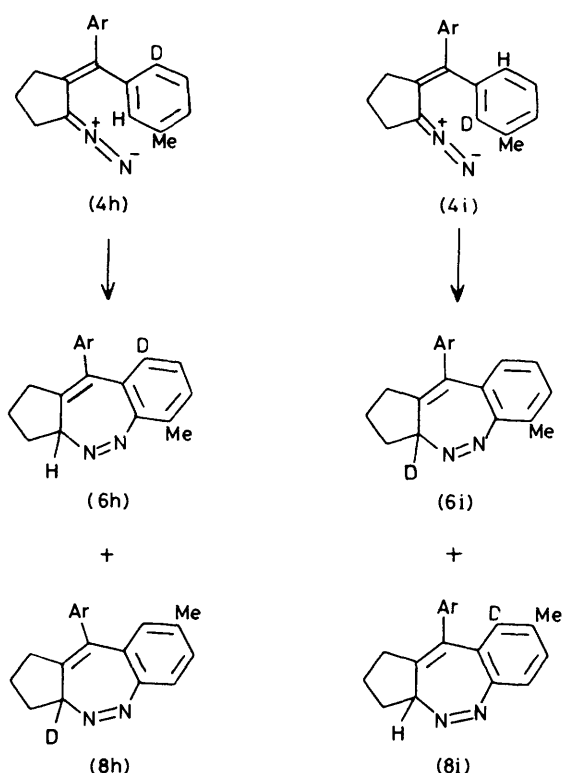$$\frac{d[P]}{dt} = \frac{k_1(p)k_2(p)[S]}{k_{-1}(p) + k_2(p)} \tag{1b}$$

The isomer ratio is then given by the expression in equation (2). Two extreme situations can be envisaged. (a) The substituent X could exert its directing influence only in the first step of the reaction in a slow irreversible cyclisation which is followed by a fast sigmatropic hydrogen shift (*i.e.* $k_{-1} = 0$ or $\ll k_2$); the isomer ratio would then depend only on $k_1(o)$ and $k_1(p)$ [equation (3)]. (b) The first step could be reversible ($k_{-1} \neq 0$) which would result in an isomer ratio dependent on k_1, k_{-1}, and k_2 [equation (2)] which in the extreme case of $k_{-1} \gg k_2$ would simplify to equation (4) where $K_1(o)$ and $K_1(p)$ are the equilibrium constants for the competing first steps.

$$(6)/(8) = \frac{k_1(o)k_2(o) \, [k_{-1}(p) + k_2(p)]}{k_1(p)k_2(p) \, [k_{-1}(o) + k_2(o)]} \tag{2}$$

$$(6)/(8) = \frac{k_1(o)}{k_1(p)} \tag{3}$$

$$(6)/(8) = \frac{k_2(o)K_1(o)}{k_2(p)K_1(p)} \tag{4}$$

To determine which of these situations obtain we have carried out cyclisations of substrates (4h and i) (Scheme 2) which are selectively deuteriated in, respectively, the positions *para* (6′) and *ortho* (2′) relative to the methyl group. The pres-

isomer (in some cases) that this preference for substitution *ortho* to X results from kinetic rather than thermodynamic control of the product ratio. This contra-thermodynamic *ortho*-favouring directive effect of the alkyl-, alkoxy-, and chloro-groups in (4a—e) was unexpected and contrasts with the *para*-directive effect of trifluoromethyl and t-butyl (4f and g). It was therefore of interest to attempt to discover the origin of these effects. Since the directing effect could be

Scheme 2.

Table 4. Deuterium content of tosylhydrazones and benzodiazepines

Compound	Composition (%)	
	Dideuteriated	Monodeuteriated
(10)	87	13
(9)	85	15
(6i)	83	17
(8i)	91	9
(6h)	85	15
(8h)	64	36

ence of the deuterium atom in such compounds should have little effect on the rates of the cyclisation steps $[k_1(o)$ and $k_1(p)]$ but should have a major effect on $k_2(p)$ in (4h) and $k_2(o)$ in (4i), diminishing them by a factor x due to the primary H–D isotope effect. Thus in the cyclisations of (4a) (Scheme 1; X = Me) and (4h and i) (Scheme 2) the product ratio should be unaffected by the presence of deuterium if mechanism (a) and equation (3) apply, i.e. the slow rate-determining cyclisation step followed by a fast sigmatropic hydrogen shift; but if the first step is reversible [mechanism (b)] then the ratio will depend to some degree on k_2 [equation (2)] and operation of the primary isotope effect should result in the diversion of the course of the reaction in favour of cyclisation at the non-deuteriated site. If the (6)/(8) isomer ratios from (4a, h, and i) are R, R^1, and R^2, respectively, and the primary isotope effect has a value x then from equation (2) we have (5).

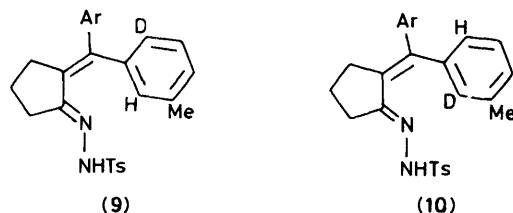$$\frac{R^i}{R} = \frac{k_{-1}(o) + k_2(o)}{xk_{-1}(o) + k_2(o)} \quad (5a)$$

$$\frac{R^2}{R} = \frac{xk_{-1}(p) + k_2(p)}{k_{-1}(p) + k_2(p)} \quad (5b)$$

Thus in the extreme case where $k_{-1} \gg k_2$, i.e. a fast pre-equilibrium followed by a relatively slow hydrogen shift the product ratio will change by a factor equal to the numerical value of the H–D primary isotope effect in the second step (assuming no significant secondary isotope effect in the first step).

The deuteriated diazo-compounds (4h and i) were generated from tosylhydrazone precursors (9) and (10), respectively, which contained 85—87% of the dideuteriated species (two identical aromatic rings) (Table 4) and 13—15% of the species deuteriated in only one ring (equally distributed between the

cis- and trans-positions). They were cyclised under exactly the same conditions as (4a) and for the reaction of (4h) in cyclohexane the experimental value of the isomer ratio changed from 4.3 in the non-deuteriated case to 17.2 and the total yield of benzodiazepines (isolated) was 67% compared to 74% from the normal substrate. This shows that the presence of the deuterium atom has resulted not only in a decrease in the yield of (8) but in an almost corresponding increase in the yield of (6). This result was confirmed by cyclising the analogous diazo-compound (4i), deuteriated in the ortho (2') position, which gave an isomer ratio of 1.2 and a total benzodiazepine yield of 78%. If these isomer ratios are adjusted to compensate for the minor presence of the monodeuteriated diazo-compound the values for (4h and i) become 20.5 and 1.1, respectively, which represent changes of the ratio by factors of 4.8, and 3.9, respectively, due to the presence of deuterium.
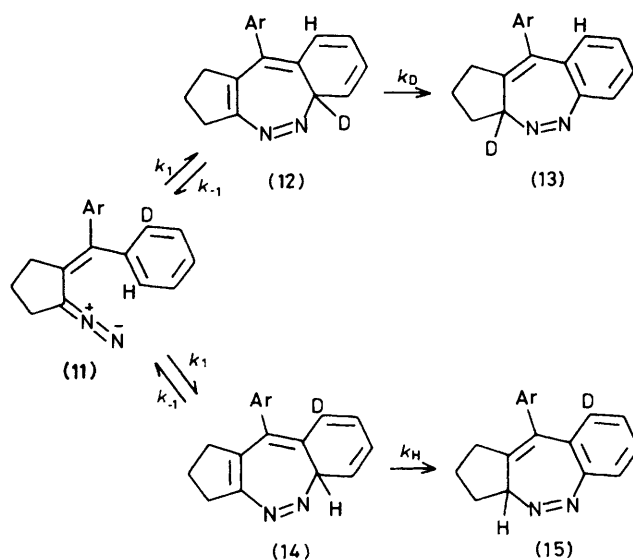
These results clearly exclude mechanism (a) and show that the cyclisation step is reversible. Thus the directive properties of the methyl group may be due to its influence on any or all of the cyclisation, retrocyclisation, or hydrogen migration steps. In Scheme 1 the two reaction intermediates are each subject to two competing bond cleavage processes at the saturated carbon atom: (a) N–C cleavage in the retro-cyclisation (k_{-1}), and (b) H–C cleavage in the [1,5] sigmatropic hydrogen shift (k_2). The way in which the position of the methyl group in (5a) and (7a) affects this partitioning, i.e. the k_{-1}/k_2 ratio, can be determined using equation (4) and an estimate of x, the k_H/k_D primary isotope effect. The latter cannot easily be measured (see later) but from this data must be greater than 4.8 (since $R^2/R \longrightarrow x$ when $k_{-1} \gg k_2$) which is consistent with the value of 5.0 determined for another example of a [1,5] hydrogen shift.[8] It can be seen from the values of R, R^1, and R^2 (4.3, 1.1, and 20.3, respectively) and equations (5) that $k_{-1}(p)/k_2(p) = 3.8/(x - 4.8)$ and $k_{-1}(o)/k_2(o) = 2.9/(x - 3.9)$. Therefore for the probable value of x (5.0—7.0) $k_{-1}(o)/k_2(o)$ is less than $k_{-1}(p)/k_2(p)$. For illustration, if $x = 5.0$ the $k_{-1}(p)/k_2(p)$ ratio is 19 so that for (7a) the retrocyclisation is considerably faster than the hydrogen shift, whereas for (5a) the $k_{-1}(o)/k_2(o)$ ratio is only 2.6, so it is clear that the o-methyl group has much altered the balance between the two competing processes in favour of the forward reaction either by accelerating the hydrogen shift or by slowing the retrocyclisation. Present knowledge about the effects of substituents on the rates of sigmatropic shifts and of electrocyclic ring opening

is scanty so it is not possible to say which of these is the more likely. This effect on the k_{-1}/k_2 ratio must be superimposed on whatever directive effect the methyl group exerts in the cyclisation step. This could in principle also be calculated using the above data and equation (2) giving $k_1(o)/k_1(p) = 4.3$ $(x - 4.8)/(x - 3.9)$. However, the range of probable values of x (5.0—7.0) leads to $k_1(o)/k_1(p)$ ratios of 0.8—3.1, so it is not possible at present to be certain whether the methyl group inhibits or promotes cyclisation at the *ortho-* compared to the *para-*sites.

These experiments using deuterium-labelled substrates have also served to confirm the intramolecular nature of the hydrogen shift. The 6- and 8-methyl isomers from each experiment were isolated and their deuterium content, determined by low eV mass spectrometry, is shown in Table 4 together with that of their tosylhydrazone precursors. The relative proportions of the di- and mono-deuteriated diazepines vary and differ from that of their precursors because half the monodeuteriated diazo-compound (*i.e.* that with the non-deuteriated ring *cis* to the diazo-group) will partition itself between the reaction paths leading to the 6- and 8-isomers in the ' normal ' ratio of 4.3 : 1 while the remainder will be subject to the isotope effect. The measured isotopic compositions are in accord with this fact ($\pm 1\%$) except for (8h) which apparently contains *ca.* 5% less of the dideuteriated species than expected. However, (8h) is a minor product, obtained in only 5% yield, and in both reactions the overall loss of deuterium was $<1\%$.

Returning to the reaction mechanism and directive effects of substituents other than methyl, it is very likely that the cyclisation step is reversible under the cyclisation conditions for (4b; X = Et) because of the similarity to (4a), and this must be so for (4c—f) as shown by the experimentally demonstrated slow isomerisation of (6c—f) to (8c—f). The directing effects of these substituents in both steps must therefore be important and it is not yet clear which properties of the alkyl, alkoxy-, and chloro-groups give rise to their moderate *ortho-*directing effect. However, it may be significant that all have the capability to release electrons by hyperconjugative or resonance effects while CF_3, the only group other than Bu^t to favour cyclisation at the *para-*site, has only a negative inductive effect. While rate studies on these cyclisations have yet to be carried out it appeared from the rate of disappearance of the colours of the diazo-compounds that CF_3 also had a marked effect in slowing down the overall rate of cyclisation. Reaction at the site *ortho* to Bu^t is no doubt sterically inhibited.

(iv) *Cyclisation Mechanism of the Unsubstituted Diazo-compound* (1) *and Factors affecting the Reversibility of the Sigmatropic Hydrogen Migration.*—The above results are consistent with a reaction mechanism for (4a; X = Me) as shown in Scheme 1 with $k_{-1} \neq 0$ but with $k_{-2}(o) = 0$. However for all the other substituents except alkyl groups the fact that the 6-isomers (6; X = OR, CF_3, Cl) undergo slow thermal isomerisation to the 8-isomers (8) shows that $k_{-2}(o) \neq 0$. This difference could be due either to the suppression of $k_{-2}(o)$ by the methyl group or to its enhancement by the alkoxy-, chloro-, and trifluoromethyl substituents. Differentiation between these alternatives required an investigation of the unsubstituted compound (1) to find out if the hydrogen migration step in its cyclisation was reversible under the normal cyclisation conditions at 80 °C.* It was also of interest to confirm the reversibility of the cyclisation step in a

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* The thermal extrusion of N_2 from (3) at higher temperatures almost certainly proceeds in part *via* a reversal of the cyclisation mechanism followed by loss of nitrogen from (1) to give carbene-derived products.[9]


Scheme 3.

molecule unperturbed by substituent effects. Both these problems were studied by the synthesis and cyclisation of the deuteriated substrate (11) (Scheme 3). Application of the steady-state approximation to (12) and (14) as above leads to equation (6) for the (15)/(13) product ratio where $x = k_H/k_D$.

$$(15)/(13) = (xk_{-1} + k_H)/(k_{-1} + k_H) \qquad (6)$$

Thus the ratio will be unity if $k_{-1} = 0$ and will tend to x when $k_{-1} \gg k_H$.

The (15)/(13) product ratio was determined from the ^2H n.m.r. spectrum of the total benzodiazepine product (after chromatography) by measuring the ratio of the integrals of the bands at δ 2.8 and 7.2 due respectively to the aliphatic and aromatic deuterons. If the ratio (aromatic ^2H)/(aliphatic ^2H) $= R$ then $(15)/(13) = (R - 1)/2$. Two cyclisation experiments gave R 9.9 and 9.8 and thus a (15)/(13) product ratio of 4.4. The precision possible in the measurement of an integral ratio of this magnitude is not high and the resulting uncertainty in the product ratio is *ca.* ± 0.5, but it is clear that this result supports a mechanism with $k_{-1} \neq 0$ and $>k_H$. The reactant for this experiment consisted largely (80%) of the dideuteriated species (11; Ar $= o$-DC_6H_4) but because of the method of preparation it also contained *ca.* 18% of the species with only one deuteriated ring (equally distributed between the *cis-* and *trans-*positions) and *ca.* 2% of non-deuteriated material. Because of the equal abundance of the two isomers of the monodeuteriated reactant the (15; Ar $= C_6H_5$)/(13; Ar $= C_6H_5$) ratio produced in the cyclisation of (11; Ar $= C_6H_5$) is also given by $(R - 1)/2$, so the result is independent of the proportions of the mono- and di-deuteriated substrates in the reactant. Control experiments showed that the (15)/(13) ratio was unchanged by chromatography and recrystallisation from ethanol. The question of the reversibility of the hydrogen migration was determined by heating the (15)/(13) mixture for 20 h under reflux in cyclohexane. After this treatment the ^2H n.m.r. spectrum of the recovered benzodiazepine mixture was unchanged, thus excluding any interconversion between the isomers. Therefore it appears that the cyclisation of (4; X $= H$) parallels that of (4; X $= Me$) in having $k_{-2} = 0$. Thus it is clear that the effect of the alkoxy-, chloro-, and trifluoromethyl substituents in (6c—f) is to lower the activation energy

Ar Ar

(CH₂)ₙ

(16)

6π 1,5

Ar

(CH₂)ₙ

R

R

1,7
8π

(CH₂)ₙ

Ar

R

R

H

(17)   (18)

Ar = 3',5'- R₂C₆H₃
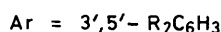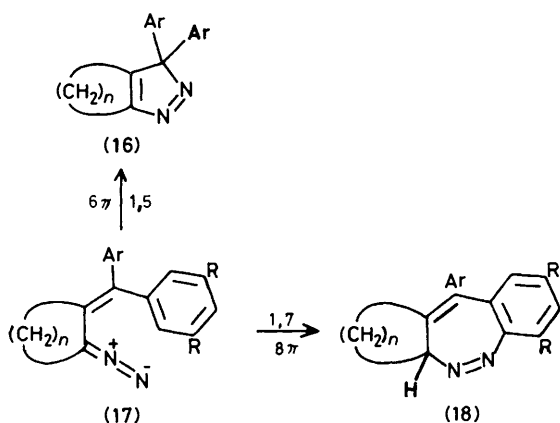
for the ' retro '-sigmatropic hydrogen shift which converts (6) into (5) and allows isomerisation to give (8). This could be due either to some effect of these substituents in destabilising (6) or conversely to their stabilisation of the transition state for hydrogen migration. Considering the stability of (6), it seems unlikely that any destabilisation could be purely steric in origin since Me, for which $k_{-2}(o) = 0$, is much bulkier than OR and Cl for which $k_{-2}(o) \neq 0$. The only common property of OR, Cl, and CF_3 is their negative inductive effect and it seems likely that it is this which raises the value of $k_{-2}(o)$ from zero. However, the results show that it is not this effect alone which controls the rate of the isomerisation since OR which produces the highest rate has the weakest inductive effect. This though is not surprising since the rate of isomerisation will depend not only on the magnitude of $k_{-2}(o)$ but also on that of all the other rate constants in the system and these will be affected differently by the different substituents.

(v) *The Effect of Methyl Substitution on the Periselectivity of Cyclisation of the Tosylhydrazone Salts of 2-Diphenylmethylenecyclanones.*—Finally since it appeared from the cyclisation experiments on (4a) that the methyl group had the strongest activating effect on *ortho*-substitution an attempt was made to utilise this effect to manipulate the periselectivity of cyclisation in the system (17). It had previously been shown that (17; $n = 3$, R = H) cyclises only by the 8π-electron 1,7 pathway as discussed above to give diazepines but that for (17; $n = 4$, R = H) the 6π-electron 1,5-electrocyclisation process is dominant and only the 3*H*-pyrazole (16) is obtained. It was thought to be of interest to find out if the presence of two methyl groups in the aromatic ring of (17; $n = 4$) would activate the ring enough to make the 1,7 cyclisation competitive with pyrazole formation. In the event it did not and although (17; $n = 3$, R = Me) as a model compound gave the diazepine (18; $n = 3$, R = Me) as expected, the cyclohexyl analogue (17; $n = 4$, R = Me) gave only the indazole (16; $n = 4$, R = Me) in *ca.* 67% conversion with no diazepine either isolable or detectable by t.l.c.*

(vi) *Summary of Results.*—This work has shown that unsymmetrically placed substituents in the aromatic rings of diazocompounds of type (4) exert an appreciable directive effect on the site of cyclisation. The (6)/(8) isomer ratios (Table 3) show that most of the substituents studied (alkoxy, alkyl, chloro) favour the formation of the less thermodynamically

stable *ortho*-isomers (6) while only t-butyl and trifluoromethyl favour formation of the *para*-isomer. The ^2H labelling studies on the cyclisation of (4; X = Me, X = H) have shown that the electrocyclisation step is reversible ($k_{-1} \neq 0$) but the sigmatropic hydrogen shift is not ($k_{-2} = 0$). However for other substituents (X = alkoxy, trifluoromethyl, chloro) $k_{-2}(o) \neq 0$ and the *ortho*-isomers (6) undergo slow thermal isomerisation at 80 °C to give the more stable *para*-isomers (8). The observed directive effects of the substituents X for reactions under kinetic control result from their effects on k_1, k_{-1}, and k_2 and although it is not possible to separate these effects for the majority of substituents the study of the ^2H-labelled compounds (4h and i) has shown that the k_2/k_{-1} ratio for the *ortho*-intermediate (5; X = Me) is markedly higher than that for the *para*-intermediate (7; X = Me). Further work on the measurement of actual rates of cyclisation rather than relative rates in internal competition is required to establish the k_H/k_D isotope effect and allow a better analysis of the effects of the methyl substituent on the two steps of the reaction.

Experimental

^1H N.m.r. spectra were obtained on a Varian HA 100 spectrometer and ^{13}C n.m.r. spectra on a Varian CFT 20 spectrometer. All samples were run as solutions in deuteriochloroform unless otherwise stated and chemical shifts are recorded as p.p.m. from internal tetramethylsilane. Preparative chromatography was carried out by the medium-pressure technique [10] (50—100 lb in⁻²) using either 1 000 × 15 or 1 000 × 25 mm columns packed with Merck Kieselgel 60. Mass spectra were obtained using an A.E.I. MS902.

Reagents and Starting Materials.—1,2-Dimethoxyethane, benzene, and cyclohexane were freshly distilled from calcium hydride as required. The following were prepared by literature methods: ethyl 1,4-dioxaspiro[4.4]nonane-5-carboxylate,[11] ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate,[11] 1-bromo-3-t-butylbenzene,[12] 1-bromo-3-ethoxybenzene,[13] 1-bromo-3-ethylbenzene,[12] 2-amino-3-bromotoluene,[14] 4-amino-3-bromotoluene,[15] deuteriohypophosphorous acid,[16] 1-bromo-3,5-dimethylbenzene.[17]

2-*Deuterio*-3-*bromotoluene* [18] prepared by the method of Renaud *et al.*[18] (56%) was 93% monodeuteriated. 4-*Deuterio*-3-*bromotoluene* similarly prepared by the deamination of 4-dideuterioamino-3-bromotoluene in deuteriohypophosphorous acid was 92% monodeuteriated. 2-*Deuteriobromobenzene* similarly prepared by the deamination of 2-dideuterioaminobromobenzene in deuteriohypophosphorous acid was 90% monodeuteriated.

Preparation of 2-Diarylmethylenecyclopentanones and their Tosylhydrazones.—The following ketones were prepared by the reactions of the appropriate aryl Grignard reagents with ethyl 1,4-dioxaspiro[4.4]nonane-6-carboxylate followed by hydrolysis and dehydration using very dilute aqueous–ethanolic mineral acid using the general method described earlier [2] for 2-diphenylmethylenecyclopentanone.

2-(*Bis*-m-*tolylmethylene*)*cyclopentanone* (24%) had m.p. 124—125 °C (from ethanol) (Found: C, 86.8; H, 7.2. $C_{20}H_{20}O$ requires C, 86.9; H, 7.3%), $\nu_{max.}$ (Nujol) 1 690 cm⁻¹ (C=O). *Tosylhydrazone* (79%) had m.p. 165—166 °C (decomp.) (from 1 : 1 ethanol–ethyl acetate) (Found: C, 73.2; H, 6.5; N, 6.6. $C_{27}H_{28}N_2O_2S$ requires C, 72.9; H, 6.3; N, 6.3%), $\nu_{max.}$ (Nujol) 3 200 cm⁻¹ (NH).

2-{*Bis*-([2-²H]-3-*methylphenyl*)*methylene*}*cyclopentanone* (27%) had m.p. 126—127 °C (from ethanol), shown by mass

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* This work was carried out as an undergraduate project by C. B. Argo.

spectrometry (12 eV) to contain 87% di- and 12% mono-deuteriated product. Tosylhydrazone (93%) had m.p. 166—168 °C (decomp.) (from ethanol), $v_{max.}$ (Nujol) 3 200 cm^{-1} (NH).

2-{Bis-([2-^{2}H]-5-methylphenyl)methylene}cyclopentanone (with I. D. Thomson) (18%) had m.p. 122—123 °C (from ethanol), shown by mass spectrometry (12 eV) to contain 85% di- and 15% mono-deuteriated product. Tosylhydrazone (80%) had m.p. 163—164 °C (decomp.) (from ethanol), $v_{max.}$ (Nujol) 3 200 cm^{-1} (NH). 2-[Bis-(3-ethylphenyl)methylene]-cyclopentanone (31%) had m.p. 48—50 °C (from light petroleum at —50 °C) (Found: C, 86.6; H, 8.0. $C_{22}H_{24}O$ requires C, 86.8; H, 7.95%), $v_{max.}$ (Nujol) 1 720 cm^{-1} (C=O). Tosylhydrazone (87%) had m.p. 180—181 °C (decomp.) (from ethanol) (Found: C, 73.85; H, 6.9; N, 5.9. $C_{29}H_{32}N_2O_2S$ requires C, 73.7; H, 6.8; N, 5.9%), $v_{max.}$ (Nujol) 3 160 cm^{-1} (NH).

2-[Bis-(3-methoxyphenyl)methylene]cyclopentanone (27%) had m.p. 104—105 °C, (lit.,[2] 106 °C). Tosylhydrazone (62%) had m.p. 147—148 °C (lit.,[2] 148—149 °C), $v_{max.}$ (Nujol) 3 210 cm^{-1} (NH).

2-[Bis-(3-ethoxyphenyl)methylene]cyclopentanone (21%) had m.p. 82—84 °C (from ethanol) (Found: C, 78.6; H, 7.2. $C_{22}H_{24}O_3$ requires C, 78.5; H, 7.2%), $v_{max.}$ (Nujol) 1 710 cm^{-1} (C=O). Tosylhydrazone (62%) had m.p. 145—147 °C (decomp.) (from ethanol) (Found: C, 68.7; H, 6.3; N, 5.7. $C_{29}H_{32}N_2O_4S$ requires C, 69.0; H, 6.4; N, 5.55%), $v_{max.}$ (Nujol) 3 190 cm^{-1} (NH).

2-[Bis-(3-chlorophenyl)methylene]cyclopentanone. The usual procedure gave (2-oxocyclopentyl)bis-(3-chlorophenyl)methanol (18%) as white crystals, m.p. 109—110 °C (Found: C, 64.8; H, 4.9. $C_{18}H_{16}Cl_2O_2$ requires C, 64.5; H, 4.8%), $v_{max.}$ (Nujol) 3 440 (OH) and 1 730 cm^{-1} (C=O). This compound (4.0 g) and toluene-4-sulphonic acid (0.4 g) in dry benzene (200 ml) were boiled under reflux for 1 h using a Dean and Stark water separator. The usual work-up gave 2-[bis-(3-chlorophenyl)-methylene]cyclopentanone (2.65 g, 70%) as yellow crystals, m.p. 80—81 °C (from ethanol) (Found: C, 68.1; H, 4.4. $C_{18}H_{14}Cl_2O$ requires C, 68.15; H, 4.45%), $v_{max.}$ (Nujol) 1 710 cm^{-1} (C=O). Tosylhydrazone (89%) had m.p. 181—182 °C (decomp.) (from ethanol) (Found: C, 61.95; H, 4.5; N, 5.7. $C_{25}H_{22}Cl_2N_2O_2S$ requires C, 61.85; H, 4.6; N, 5.8%), $v_{max.}$ (Nujol) 3 180 cm^{-1} (NH).

2-[Bis-(3-t-butylphenyl)methylene]cyclopentanone (27%) was a yellow oil (Found: C, 86.5; H, 8.9. $C_{26}H_{32}O$ requires C, 86.6; H, 8.95%), $v_{max.}$ (film) 1 715 cm^{-1} (C=O). Tosylhydrazone (72%) had m.p. 183 °C (decomp.) (from methanol) (Found: C, 74.8; H, 7.6; N, 5.4. $C_{33}H_{40}N_2O_2S$ requires C, 75.0; H, 7.6; N, 5.3%), $v_{max.}$ (Nujol) 3 200 cm^{-1} (NH).

2-[Bis-(3-trifluoromethylphenyl)methylene]cyclopentanone (53%) had m.p. 65—66 °C (from light petroleum–ethanol) (Found: C, 62.8; H, 3.7. $C_{20}H_{14}F_6O$ requires C, 62.5; H, 3.7%), $v_{max.}$ (Nujol) 1 695 cm^{-1} (C=O). Tosylhydrazone (64%) had m.p. 179—180 °C (decomp.) (from ethanol–ethyl acetate) (Found: C, 58.9; H, 4.0; N, 5.2. $C_{27}H_{22}F_6N_2O_2S$ requires C, 58.7; H, 4.0; N, 5.1%), $v_{max.}$ (Nujol) 3 200 cm^{-1} (NH).

2-{Di-([2-^{2}H]phenyl)methylene}cyclopentanone (27%) had m.p. 115—116 °C (from ethanol) (lit.,[2] 115—116 °C). Tosyl-hydrazone (90%) had m.p. 167—168 °C (decomp.) (from ethanol–ethyl acetate) (lit.,[2] 166 °C).

2-[Bis-(3,5-dimethylphenyl)methylene]cyclopentanone (with C. B. Argo) (10%) had m.p. 114—115 °C (from ethanol) (Found: C, 87.0; H, 8.0. $C_{22}H_{24}O$ requires C, 86.8; N, 7.95%), $v_{max.}$ (Nujol) 1 695 cm^{-1} (C=O). Tosylhydrazone (63%) had m.p. 185—187 °C (decomp.) (from ethanol) (Found: C, 73.5; H, 6.9; N, 5.7. $C_{29}H_{32}N_2O_2S$ requires C, 73.7; H, 6.8; N, 5.9%); $v_{max.}$ (Nujol) 3 160 cm^{-1} (NH).

2-[Bis-(3,5-dimethylphenyl)methylene]cyclohexanone (with C. B. Argo). The reaction of the Grignard reagent from 1-bromo-3,5-dimethylbenzene and ethyl 1,4-dioxaspiro[4.5]-decane-6-carboxylate and the usual work-up gave (2-oxo-cyclohexyl)bis-(3,5-dimethylphenyl)methanol (30%), m.p. 149—150 °C (from ethanol) (Found: C, 81.95; H, 8.4. $C_{23}H_{28}O_2$ requires C, 82.1; H, 8.4%); $v_{max.}$ (Nujol) 3 480 (OH) and 1 690 cm^{-1} (C=O). This compound (2.83 g) and toluene-4-sulphonic acid (0.02 g) in dry benzene (40 ml) were boiled under reflux for 30 min. The usual work-up gave 2-[bis-(3,5-dimethylphenyl)methylene]cyclohexanone (2.59 g, 97%) as pale yellow crystals, m.p. 105—106 °C (from ethanol) (Found: C, 86.5; H, 8.2. $C_{23}H_{26}O$ requires C, 86.75; H, 8.2%); $v_{max.}$ (Nujol) 1 680 cm^{-1} (C=O). Tosylhydrazone (41%) had m.p. 174—175 °C (decomp.) (from ethanol) (Found: C, 73.9; H, 7.0; N, 5.7. $C_{30}H_{34}N_2O_2S$ requires C, 74.05; H, 7.0; N, 5.8%); $v_{max.}$ (Nujol) 3 170 cm^{-1} (NH).

Preparation of the Benzo-1,2-diazepines (6) *and* (8).—The tosylhydrazone sodium salts were prepared by the addition of the solid tosylhydrazone (ca. 5% molar excess) to a solution of sodium ethoxide in dry ethanol. The solution was stirred in the dark for 1 h and then the ethanol was evaporated using a rotary evaporator with a bath temperature of <45 °C. The salt was then dried, in the flask, under high vacuum over phosphoric oxide for at least 12 h in the dark. The reaction solvent (benzene, cyclohexane, or 1,2-dimethoxyethane) was added and the mixture was boiled under reflux, with stirring, under nitrogen, in the dark until t.l.c. showed that all the reactant had been consumed. After cooling and filtration to remove the precipitated sodium toluene-4-sulphinate the filtrate was evaporated under reduced pressure and the products obtained by chromatography on silica. The yields are given in Table 1, the ¹H n.m.r. data below, and the ¹³C n.m.r. data in Table 2.

¹H *N.m.r. data for* 6- *and* 8-*substituted* 1,2,3,3a-*tetrahydro-*10-*arylbenzo*[c]*cyclopenta*[f][1,2]*diazepines* (6) *and* (8). 6-Substituted compounds (6). (6a), δ 2.0—2.8 (m, 6 H), 2.28 (s, Me), 2.53 (s, Me), 3.14br (m, 1 H), and 6.7—7.4 (m, 7 H); (6b), δ 1.18 (t, *J* 7 Hz, Me), 1.20 (t, *J* 7 Hz, Me), 2.0—3.3 (m, 11 H), and 6.9—7.3 (m, 7 H); (6c), δ 2.0—3.4 (m, 7 H), 3.75 (s, Me), 4.00 (s, Me), and 6.6—7.4 (m, 7 H); (6d), δ 1.35 (t, *J* 7 Hz, CH₃), 1.50 (t, *J* 7 Hz, Me), 1.9—2.8 (m, 6 H), 3.15br (m, 1 H), 3.95 (q, *J* 7 Hz, CH₂), 4.20 (q, *J* 7 Hz, CH₂), and 6.6—7.3 (m, 7 H); (6e), δ 2.1—2.8 (m, 6 H), 3.20br (m, 1 H), and 6.9—7.5 (m, 7 H); (6f), δ 2.0—3.0 (m, 6 H), 3.26br (m, 1 H), and 7.0—7.7 (m, 7 H).

8-Substituted compounds (8). (8a), δ 2.25 (s, Me), 2.30 (s, Me), 2.0—2.9 (m, 6 H), 3.12 (br m, 1 H), 6.85—7.3 (m, 6 H), and 7.65 (d, *J* 8 Hz, 6-H); (8b), δ 1.13 (t, *J* 7 Hz, Me), 1.21 (t, *J* 7 Hz, Me), 2.0—2.9 (m, 6 H), 1.15 (br m, 1 H), 6.9—7.3 (m, 6 H), 7.69 (d, *J* 8 Hz, 6-H); (8c), δ 2.0—2.9 (m, 6 H), 3.13 (br m, 1 H), 3.64 (s, Me), 3.73 (s, Me), 6.5—7.5 (m, 6 H), 7.71 (d, *J* 9 Hz, 6-H); (8d), δ 1.30 (t, *J* 7 Hz, Me), 1.37 (t, *J* 7 Hz, Me), 2.0—2.9 (m, 6 H), 3.10 (br m, 1 H), 3.87 (q, *J* 7 Hz, CH₂), 3.96 (q, *J* 7 Hz, CH₂), 6.5—7.3 (m, 6 H), 7.69 (d, *J* 8 Hz, 6-H); (8e), δ 2.0—2.9 (m, 6 H), 3.18 (br m, 1 H), 6.9—7.4 (m, 6 H), 7.70 (d, *J* 8 Hz, 6-H); (8f), δ 2.0—2.9 (m, 6 H), 3.25 (br m, 1 H), 7.2—7.7 (m, 6 H), 7.90 (d, *J* 8 Hz, 6-H); (8g), δ 1.19 (s, Bu^t), 1.27 (s, Bu^t), 2.0—2.9 (m, 6 H), 3.15 (br m, 1 H), 7.1—7.5 (m, 6 H), and 7.73 (d, *J* 8 Hz, 6-H).

1,2,3,3a-*Tetrahydro*-6,8-*dimethyl*-10-(3,5-*dimethylphenyl*)-*benzo*[c]*cyclopenta*[f][1,2]*diazepine* (18; n = 3, R = Me) (with C. B. Argo). This was prepared from the sodium salt of 2-[bis-(3,5-dimethylphenyl)methylene]cyclopentanone tosyl-hydrazone in 66% yield, m.p. 169—170 °C (from ethanol) (Found: C, 83.3; H, 7.7; N, 8.85. $C_{22}H_{24}N_2$ requires C, 83.5; H, 7.6; N, 8.85%), δ_H 2.15 (s, Me), 2.19 (br s, 2 × Me), 2.47 (s, Me), 2.0—2.6 (m, 4 H), 3.15 (m, 3 H), 6.69 (s, 2 H), 6.73 (s, 1 H), 6.85 (s, 1 H), and 6.91 (s, 1 H).

Cyclisation of the Sodium Salt of the Tosylhydrazone of 2-[Bis-(3,5-dimethylphenyl)methylene]cyclohexanone.—The sodium salt of the tosylhydrazone (1.0 g, 2.05 mmol) was heated under reflux in 1,2-dimethoxyethane (50 ml) for 1 h, during which no red colour was observed, cooled, and filtered to give sodium toluene-4-sulphinate (0.21 g, 57%). Evaporation of the filtrate gave a white solid which was chromatographed on silica to give 4,5,6,7-*tetrahydro*-3,3-*bis*-(3,5-*dimethylphenyl)indazole* (16; n = 4, R = Me) (0.25 g, 44%), m.p. 130 °C (from light petroleum–ethanol) (Found: C, 83.35; H, 7.9; N, 8.3. $C_{23}H_{26}N_2$ requires C, 83.6; H, 7.9; N, 8.5%); δ_H 1.75—2.95 (m, 8 H), 2.25 (s, 4 × Me), 6.75 (br s, 4 H), and 6.90 (br s, 2 H).

Measurement of Isomer Ratios (6)/(8).—Solutions of the tosylhydrazone sodium salts in ethanol were prepared in the usual way using ca. 1 g of the tosylhydrazone in ca. 75 ml of ethanol. Portions (25 ml) of this solution were pipetted into separate flasks and each was evaporated to dryness under reduced pressure and dried in the usual way. Freshly distilled dry cyclohexane or 1,2-dimethoxyethane (25 ml) was added to each flask and the reactions were carried out in an oil-bath at 80 ± 0.2 °C. All reactions and control experiments were done under nitrogen and in the dark.

The product mixtures were analysed by h.p.l.c. using 10 or 15 cm × 0.5 cm columns packed with 5 μm Spherisorb silica or alumina and eluants as indicated in Table 3. A u.v. detector operating at 254 nm was used and peak areas were measured by electronic integration. In all cases at least three injections of each sample were made and peak area ratios were concordant to ±3%. In each case the correction factor relating the peak area ratio to molar ratio was determined using calibration mixtures made up from the diazepines isolated in the preparative experiments. In all cases the reactions were carried out in duplicate and the peak assignments checked on both silica and alumina columns. The molar ratios given in Table 3 have confidence limits of ca. ±5%.

2-[*Bis*-(3-*methoxyphenyl)methylene*]*cyclopentanone Tosylhydrazone.*—(i) *Cyclisation of the tosylhydrazone.* Samples taken during the reaction showed that the (6c)/(8c) ratio decreased as the reaction progressed. The results are given as: molar ratio (reaction time). (a) In cyclohexane: 1.63 (1.0 h), 1.53 (8.0 h), 1.01 (17.0 h). (b) In 1,2-dimethoxyethane: 1.75 (1.0 h), 1.64 (2.0 h), 0.82 (17.0 h).

(ii) *Control experiment on the diazepine* (6c) The 6-isomer (6c) (0.0055 g) in cyclohexane (2.6 ml) was heated under reflux for 17 h. H.p.l.c. analysis then showed the presence of (6c) and (8c) in the ratio 86 : 14.

(iii) *Thermolysis of the diazepine* (6c) *at* 130.1 °C. (a) In chlorobenzene.The diazepine (6c) (0.252 g) in dry chlorobenzene (30 ml) was heated under reflux for 3 h when h.p.l.c. showed that only ca. 5% of (6c) remained. Evaporation of the solvent under vacuum and chromatography of the residue on alumina gave the 8-isomer (8c) (0.070 g, 28%) as a yellow glass with identical ^1H and ^{13}C n.m.r. spectra to those of the sample prepared directly by the cyclisation of (4c). Further elution gave a mixture of the 8-methoxydiazepine (8c) and 3-cyclopent-1-enyl-7-methoxy-3-*m*-methoxyphenylindazole * (0.120 g, 48%) in a 5 : 1 ratio (by h.p.l.c.) 3-Cyclopent-1-enyl-5-methoxy-*m*-methoxyphenylindazole (ca. 2%) was also detected by h.p.l.c.

(b) Rate study. A diazepine sample (0.10 g) containing (6c) and (8c) in a 91 : 9 ratio, and diethyl phthalate (0.140 g)

(as an internal standard) in hexadecane (10.0 ml) were heated at 130.1 ± 0.2 °C in an oil-bath. Samples (40—50 μl) were taken at intervals, diluted with dichloromethane, stored at −20 °C, and subsequently analysed by h.p.l.c. Concentrations of reactants and products were determined by the internal standard method using correction factors determined from calibration mixtures. The results are shown in the Figure.

(c) Rate study for thermolysis of (6c) in the presence of tributylphosphine. A study similar to (b) above was carried out on a reaction mixture containing a diazepine sample, containing (6c) and (8c) in a 96 : 4 ratio, and tributylphosphine in two-fold molar excess. The results are shown in the Figure.

2-[*Bis*-(3-*ethoxyphenyl)methylene*]*cyclopentanone Tosylhydrazone.*—(i) *Cyclisation of the tosylhydrazone.* Samples taken during the reaction showed that the (6d)/(8d) ratio decreased as the reaction progressed. The results are given as: molar ratio (reaction time). (a) In cyclohexane: 1.57 (1.25 h), 1.32 (8.0 h), 1.10 (17.0 h). (b) In 1,2-dimethoxyethane: 1.79 (1.0 h), 1.70 (1.92 h), 0.97 (17.0 h). In the experiment in cyclohexane, after 17 h the reaction mixture was cooled, filtered, evaporated under high vacuum and dissolved in deuteriochloroform for ^{13}C n.m.r. examination. The integral ratio of the C-3a peaks showed a (6d)/(8d) ratio of 1.0.

(ii) *Control experiments on the diazepines* (6d) *and* (8d). The 6-isomer (6d) (0.0123 g) in dry cyclohexane (10 ml) was heated under reflux for 17 h. H.p.l.c. analysis then showed the presence of both (6d) and (8d) in the ratio 87 : 13. In a similar experiment in 1,2-dimethoxyethane the ratio after 19 h was 79 : 21, and after 43 h 54 : 46.

In a similar experiment with the 8-isomer (8d), none of the 6-isomer was formed.

2-[*Bis*-(3-*chlorophenyl)methylene*]*cyclopentanone Tosylhydrazone.*—(i) *Cyclisation of the tosylhydrazone.* The (6e)/(8e) ratio did not change significantly during the reaction and after 17 h the ratio was 1.86 for the reaction done in cyclohexane and 2.73 for the reaction in 1,2-dimethoxyethane.

(ii) *Control experiment on the diazepine* (6e). The 6-isomer (6e) (0.019 g) in cyclohexane was heated under reflux and sampled over 6 days. H.p.l.c. analysis showed the ratio (8e)/(6e) to be 2 : 98 (17 h), 4 : 96 (40 h), and 15 : 85 (136 h).

2-[*Bis*-(3-*methylphenyl)methylene*]*cyclopentanone.*—(i) *Cyclisation of the tosylhydrazone.* The (6a)/(4a) ratio did not change during the reaction and after 17 h the ratio was 4.31 for the reaction in cyclohexane and 3.62 for the reaction in 1,2-dimethoxyethane.

(ii) *Control experiments on the diazepines* (6a) *and* (8a). These were separately heated under reflux in cyclohexane for 17 h after which h.p.l.c. analysis showed no isomerisation.

2-{*Bis*-([2-^2H]-3-*methylphenyl)methylene*}*cyclopentanone Tosylhydrazone.*—The tosylhydrazone (10) salt (2.1 mmol) was prepared, divided, and dried in the usual way and cyclised in cyclohexane and 1,2-dimethoxyethane for 5 h when t.l.c. showed that reaction was complete. The (6i)/(8i) ratios were 1.17 for the reaction in cyclohexane and 0.99 for the reaction in 1,2-dimethoxyethane.

After h.p.l.c. analysis the reaction mixtures were combined, filtered to remove sodium toluene-4-sulphinate, evaporated under vacuum, and chromatographed on silica (1.5 × 100 cm) to give the 6-isomer (6i) (0.26 g, 43%), m.p. 122—123 °C (from ethanol) and the 8-isomer (8i) (0.20 g, 33%), m.p. 117 °C (from ethanol), both identified by comparison of their ^1H n.m.r. spectra with the non-deuteriated analogues. The deuterium content of the tosylhydrazone (10) and the two products was determined by mass spectrometry and is shown in Table 4.

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* The preparation of these indazoles and details of the rate studies on the thermal interconversion of 3*H*-benzo-1,2-diazepines and 3*H*-indazoles will be given in a subsequent paper.[19]

2-{Bis-([2-²H]-5-methylphenyl)methylene}cyclopentanone Tosylhydrazone (with I. D. Thomson).—The tosylhydrazone (9) salt (1.96 mmol) was prepared and cyclised as above. The (6h)/(8h) ratios were 17.1 for the reaction in cyclohexane and 13.4 for the reaction in 1,2-dimethoxyethane. The reaction mixtures were combined and worked up as above to give the 6-isomer (6h) (0.34 g, 60%), m.p. 122—124 °C (from ethanol), and the 8-isomer (8h) (0.03 g, 5%), m.p. 90 °C. The deuterium content of the tosylhydrazone and the two products was determined by mass spectrometry and is shown in Table 4.

2-[Bis-(3-trifluoromethylphenyl)methylene]cyclopentanone Tosylhydrazone.—(i) Cyclisation of the tosylhydrazone. Samples taken during the reaction showed that the (6f)/(8f) ratio decreased as the reaction progressed. The following results for the cyclisation in cyclohexane are given as molar ratio (reaction time); 0.51 (2.0 h), 0.44 (20.5 h), and 0.36 (42 h).

2-(Di-[2-²H]phenylmethylene)cyclopentanone Tosylhydrazone (11).—(i) Cyclisation of the tosylhydrazone. The tosylhydrazone (1.76 mmol) was cyclised in 1,2-dimethoxyethane (40 ml) for 7 h when t.l.c. showed that reaction was complete. The reaction mixture was filtered and chromatographed on deactivated alumina to give the diazepine mixture (13) + (15) (0.25 g, 55%), m.p. 161—162 °C (lit.,² 159—160 °C for non-deuteriated sample). The ²H n.m.r. spectrum (CHCl₃) showed two peaks at δ 7.42 and 2.98 with an integral ratio of 9.8 : 1. A similar reaction in cyclohexane gave the diazepine in 56% yield and an integral ratio in the ²H n.m.r. spectrum of 9.9 : 1. Mass spectrometry showed that the product contained dideuteriated (79%), monodeuteriated (18%), and non-deuteriated material (3%).

(ii) Control experiments. (a) The deuteriated diazepine product of the previous experiment (0.087 g) in cyclohexane was heated under reflux for 20 h. The solvent was removed by evaporation under vacuum and the residue was recrystallised from ethanol to give the unchanged diazepine (0.061 g) whose ²H n.m.r. spectrum was identical with that obtained before heating. (b) A sample of the deuteriated diazepine was re-chromatographed on deactivated alumina and recrystallised twice from ethanol. Its ²H n.m.r. spectrum was identical with the original material.

Acknowledgements

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