# Reactions of Diene-conjugated 1,3-Dipolar Intermediates: the Formation of Cyclopropa[*c*]isoquinolines from Benzonitrile *o*-Alkenylbenzyl Ylides and their Rearrangements to Benzazepines[1]

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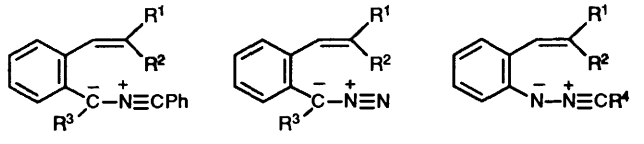
The diene-conjugated nitrile ylides **19**, generated by the 1,3-dehydrochlorination of imidoyl chlorides **18**, cyclise at room temperature to give the cyclopropa[*c*]isoquinolines **21** in a stereospecific reaction. Thermal decomposition of the latter when $R^1$ or $R^2$ = H involves an equilibration between *exo* and *endo* isomers (Scheme 4) accompanied by a slower ring expansion to give 1*H*-2-benzazepines. In cases where neither $R^1$ or $R^2$ = H the thermal decomposition follows another path (Scheme 5) to give 5*H*-2-benzazepines. In contrast **32** and **38**, the thiophene analogues of **19**, do not give cyclopropa[*b*]thienopyridines **33** and **39**, respectively but instead give the thienoazepines **35** and **41**.

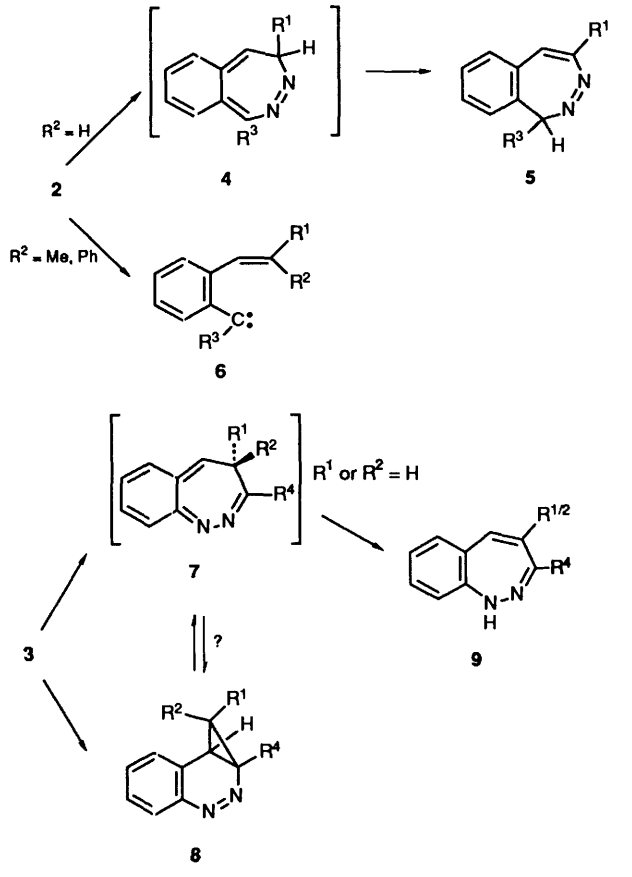
This paper is concerned with the reactions of diene-conjugated nitrile ylides in which the α,β-double bond is part of an aromatic ring—either a benzene ring **1** or a thiophene ring **32**, **36** and **38**.



**1** **2** **3**

The objective was to compare their reactions with those of analogous diazo compounds **2** and nitrile imines **3**. It has been shown that both **2** and **3** cyclise to give benzo fused seven-membered heterocycles, but they do so apparently by different reaction paths. The diazo compounds **2**, in cases where $R^2$ = H, cyclise at 80 °C to give 1*H*-2,3-benzodiazepines **5** *via* what is thought to be a [1.7] electrocyclisation process.[2–4] This cyclisation process is sensitive to the size of the $R^2$ group and fails when it is larger than hydrogen; the reaction then follows an alternative carbenic path *via* **6**.[4] The nitrile imines **3**, undergo a formally similar conversion at 80 °C into give 1*H*-1,2-benzodiazepines **9**, but in this case the cyclisation is not sensitive to the size of $R^2$ and occurs in cases where either $R^1$ *or* $R^2$ = H. However, when neither $R^1$ or $R^2$ = H the product is the tricyclic cyclopropa[*c*]cinnoline system **8**.[5,6] A subsequent investigation of the reactions of **3** at room temperature showed that it gave only **8** in a stereospecific reaction, irrespective of the nature of $R^1$ and $R^2$. When heated at 80 °C, **8** ($R^1$ or $R^2$ = H) gave the diazepines **9**.[7] Interestingly, the study of a diazo cyclisation similar to that of **2** at low temperature produced no evidence for an intermediate analogous to **8**.[8]

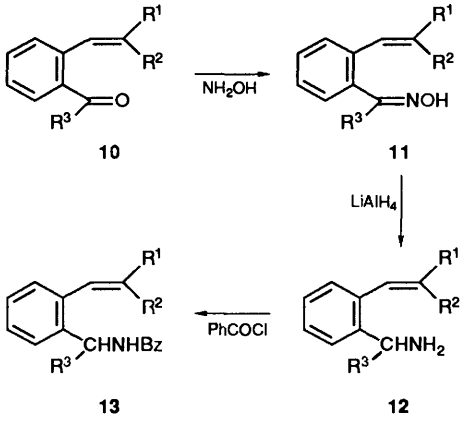
Only one example of a nitrile ylide of the type **1** had been studied before we undertook this work. The intermediate **1** ($R^1$, $R^2$, $R^3$ = H) was generated by Padwa and Ku by the photolysis of an azirine and gave **21** ($R^1$, $R^2$ = H).[9] Since nitrile ylides generated by this route have been shown to give non-stereospecific [1.1] cycloadditions in related systems,[10,11] our intention in this work was to use a non-photochemical method to generate a range of nitrile ylides of the type **1**. The objectives were to find out: (i) if the process was stereospecific like the nitrile imine reaction, (ii) if the reaction with the double bond was blocked when $R^2$ = H as it is in the diazo compound reaction, and (iii) if compounds of the type **21** would undergo thermal ring expansion and so provide a synthetic route to the fully unsaturated 2-benzazepine system, *e.g.* **25** and **26**, and to related systems in which the benzene ring was replaced by heteroaromatic rings.



## Results and Discussion

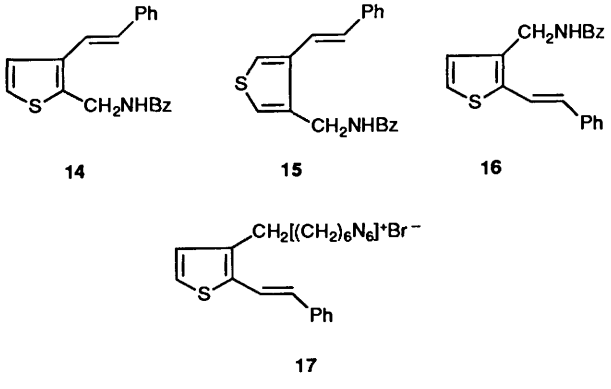
(*a*) *Preparation of Precursors and Generation of the Nitrile Ylides.*—The required nitrile ylides were generated by the 1,3-dehydrochlorination of the imidoyl chlorides **18** and analogues derived from the thiophene amides **14**–**16**. The imidoyl chlorides were prepared by the reaction of the appropriate amide with phosphorus pentachloride and were used without purification. The benzamides used as precursors **13a**–**i** and the analogous thiophene amides **14** and **15** were prepared from unsaturated

aldehydes and ketones, *e.g.* **10**, by the general method shown in Scheme 1. The amide **16** was prepared *via* the hexamine salt **17**.

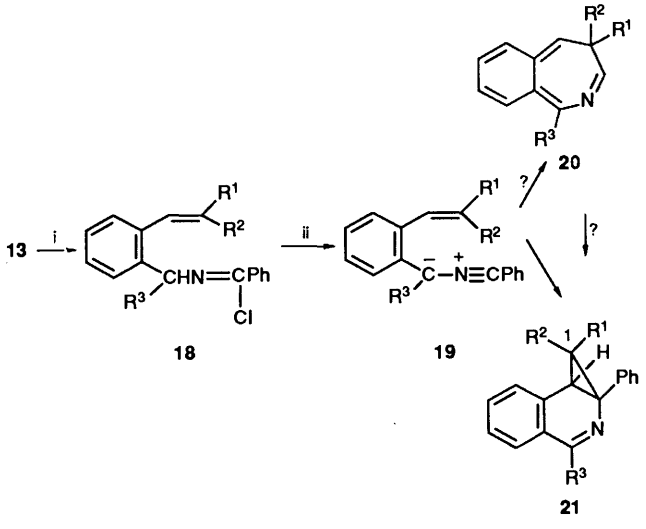



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **a** | Ph | H | H |
| **b** | H | Ph | H |
| **c** | Me | H | H |
| **d** | H | Me | H |
| **e** | Me | Me | H |
| **f** | Ph | Ph | H |
| **g** | Ph | Me | H |
| **h** | Me | Ph | H |
| **i** | Ph | H | Me |

**Scheme 1**




It was found that the nitrile ylides could be generated rapidly at room temperature or 0 °C using potassium *tert*-butoxide as the base in tetrahydrofuran (THF) as solvent (Scheme 2).




**Scheme 2** *Reagents:* i, $PCl_5$, $Et_2O$; ii, KOBu$^t$, THF

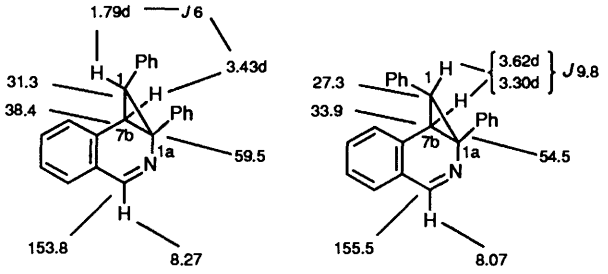
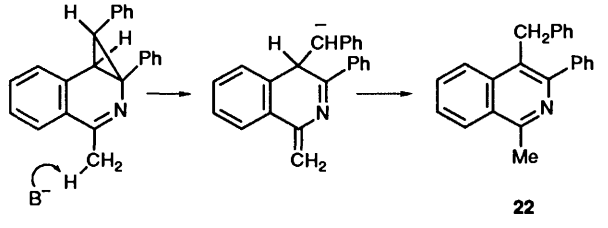



**Fig. 1**

Weaker bases such as triethylamine were ineffective. On addition of the base to the imidoyl chloride solution an intense red or brown colour was generated immediately which faded to yellow or orange after a few minutes. The origin of this colour is not certain, it was originally attributed to the nitrile ylide itself, but the lifetime of the colouration in this and a series of related reactions does not seem to correlate with the expected rate of cyclisation. This will be discussed in more detail in later papers but it is worthwhile to note here that the colour could be due to either the benzylic anion formed by deprotonation of **18** or to the presence of a quinonoid intermediate, *e.g.* **20**.

(*b*) *Cyclisations of Benzonitrile* o-*Alkenylbenzyl Ylides* [α-(*Benzonitril*-N-*io*)-o-(*alkenyl*)*benzylides*] **19**.—In all cases where $R^3$ = H the cyclopropa[*c*]isoquinolines **21** (Scheme 2) were formed in substantial yields (Table 1). The products were separated by flash chromatography and identified by their elemental composition and $^1H$ and $^{13}C$ NMR spectra. Selected diagnostic data for compounds **21a** and **21b** are shown in Fig. 1. The formulation of the compounds as cyclopropa[*c*]isoquinolines, for example **21a** rather than the isomeric 1*H*-2-benzazepine **25**, is supported by the presence in the $^{13}C$ spectra of the saturated carbon signals attributed to the carbons of the cyclopropane ring, *e.g.* for **21a** at δ 31.3 (C-1), 38.4 (C-7b) and 59.5 (C-1a). In cases where there is a proton on C-3 the assignment of the stereochemistry at C-3 is based on the magnitude of the proton coupling constant $J_{1-7b}$. For example in **21a** and **21b** this is respectively 6 and 9.8 Hz, values typical of *trans* and *cis* couplings in cyclopropanes.[10,12] In other cases, nuclear Overhauser effects were used as noted in Table 1. These stereochemical assignments are supported by the chemical shifts of the groups on C-1, the *endo* group being shielded by its position above the π systems of the benzene ring and the imine bond.

Only one example has been studied of a nitrile ylide of type **19** in which $R^3$ is not hydrogen. The reaction of **19i** ($R^3$ = Me), when carried out under the usual conditions, gave a product whose $^1H$ and $^{13}C$ NMR spectra fitted neither the expected product **21** ($R^1$ = Ph, $R^2$ = H, $R^3$ = Me) nor the analogous benzazepine **23**. On the basis of spectroscopic evidence it has been formulated as the isoquinoline **22**, most likely formed by base catalysed isomerisation as shown in Scheme 3. The structure is based on a comparison of the NMR data with that for




**Scheme 3**

**Table 1** Spectroscopic data for 1,7b-dihydrocyclopropa[*c*]isoquinolines **21**

| 21 | Yield (%) | $R^1$ | $R^2$ | $R^3$ | | Spectroscopic data[a] |
|---|---|---|---|---|---|---|
| **a** | 85 | Ph | H | H | $\delta_H$ | 1.79 (d, *J* 6, $R^2$), 3.43 (d, *J* 6, 7b-H), 8.27 (s, $R^3$), 6.87–7.83 (m, 14 H) |
| | | | | | $\delta_C$ | 31.33 (C-1), 38.40 (C-7b), 59.54 (C-1a), 123.56 (q), 125.97, 126.55, 126.86, 127.35, 127.67, 127.90, 129.21, 129.34, 131.46, 135.85 (q), 136.44 (q), 139.65 (q), 153.84 (C-3) |
| | | | | | *m/z* | 295 (52), 294 (100), 218 (8), 192 (51), 191 (37), 165 (10), 115 (7) |
| **b** | 73 | H | Ph | H | $\delta_H$ | 3.30 (d, *J* 9.8, $R^1$), 3.62 (d, *J* 9.8, 7b-H), 8.07 (s, $R^3$), 6.74–7.66 (m, 14 H) |
| | | | | | $\delta_C$ | 27.32 (C-1), 33.92 (C-7b), 54.48 (C-1a), 126.09, 126.56, 127.40, 127.79, 128.01, 128.11, 128.42, 131.21, 132.13, 132.23, 133.52 (q), 144.57 (q), 155.45 (C-3) |
| | | | | | *m/z* | 295 (47), 294 (100), 218 (18), 192 (62), 191 (45), 165 (10), 115 (23) |
| **c** | 23[b] | Me | H | H | $\delta_H$ | 0.49 (dq, *J* 6.2 and 5.5, $R^2$), 1.08 (d, *J* 6.2, $R^1$), 2.66 (d, *J* 5.5, 7b-H), 8.16 (s, $R^3$), 7.25–7.55 (m, 9 H) |
| | | | | | $\delta_C$ | 14.43 (C-1), 28.12 ($R^1$), 31.76 (C-7b), 57.99 (C-1a), 123.44 (q), 126.03, 126.99, 127.20, 128.26, 129.15, 131.16, 136.72 (q), 140.94 (q), 153.02 (C-3) |
| | | | | | *m/z* | 233 (72), 232 (100), 218 (27), 130 (48), 115 (57) |
| **d** | 49[b] | H | Me | H | $\delta_H$ | 0.56 (d, *J* 6.2, $R^2$), 2.40 (dq, *J* 9.8 and 6.2, $R^1$), 2.85 (d, *J* 9.8, 7b-H), 8.51 (s, $R^3$), 7.18–7.55 (m, 9 H); 3% NOE enhancement of $R^2$ from $R^3$ |
| | | | | | $\delta_C$ | 5.31 ($R^2$), 15.48 (C-1), 33.13 (C-7b), 53.70 (C-1a), 125.49, 125.77 (q), 126.14, 128.19, 128.35, 131.15, 133.26 (q), 144.98 (q), 155.07 (C-3) |
| | | | | | *m/z* | 233 (89), 232 (100), 218 (50), 140 (95), 115 (66) |
| **e** | 79 | Me | Me | H | $\delta_H$ | 0.69 (s, $R^2$), 1.13 (s, $R^1$), 2.68 (s, 7b-H), 8.33 (s, $R^3$), 7.25–7.48 (m, 9 H) |
| | | | | | $\delta_C$ | 13.22 ($R^2$), 16.64 (C-1), 23.87 ($R^1$), 33.45 (C-7b), 60.93 (C-1a), 126.12, 126.68, 128.12, 128.24, 128.62, 128.79, 131.17, 134.23 (q), 142.74 (q), 154.74 (C-3) |
| | | | | | *m/z* | 247 (26), 246 (79), 232 (25), 144 (25), 129 (100), 128 (82), 103 (41), 77 (38) |
| **f** | 91 | Ph | Ph | H | $\delta_H$ | 3.95 (s, 7b-H), 8.01 (s, $R^3$), 6.51–7.72 (m, 19 H) |
| | | | | | $\delta_C$ | 34.24 (C-7b), 40.71 (C-1), 60.50 (C-7a), 125.70, 125.89, 126.26, 126.47, 127.31, 127.67, 127.75, 127.89, 128.13, 128.25, 129.45, 131.37, 132.42, 133.52 (q), 137.14 (q), 141.26 (q × 2), 156.02 (C-3) |
| | | | | | *m/z* | 371 (50), 294 (16), 268 (25), 165 (100), 102 (32) |
| **g** | 11[c] | Ph | Me | H | $\delta_H$ | 1.02 (s, $R^2$), 3.62 (s, 7b-H), 8.51 (s, R)[3]), 6.95–7.70 (m, 14 H); 2.7% NOE enhancement of $R^2$ from $R^3$ |
| | | | | | $\delta_C$ | 15.92 ($R^2$), 28.09 (C-1), 31.69 (C-7b), 59.57 (C-1a), 125.95, 126.77, 127.33, 127.50, 127.86, 128.47, 128.97, 129.20, 131.54, 133.37 (q), 141.83 (q), 142.40 (q), 155.85 (C-3) |
| | | | | | *m/z* | 309 (100), 308 (98), 294 (18), 204 (47), 191 (41) |
| **h** | 7[c] | Me | Ph | H | $\delta_H$ | 1.34 (s, $R^1$), 3.18 (s, 7b-H), 7.83 (s, $R^3$), 6.92–7.69 (m, 14 H); 9.7% NOE enhancement of $R^1$ from 7b-H) |
| | | | | | $\delta_C$ | 26.73 ($R^1$), 30.15 (C-1), 34.98 (C-7b), 61.26 (C-1a), 125.66, 126.05, 126.94, 127.45, 128.06, 128.32, 129.03, 131.15, 131.55, 134.42 (q), 138.15 (q), 142.10 (q), 154.65 (C-3) |
| | | | | | *m/z* | 309 (20), 308 (20), 206 (13), 192 (14), 105 (100) |

[a] *J* Values are given in Hz. [b] Separated from the mixture of **21c** and **21d** obtained from mixed *E*–*Z* precursor. [c] Separated from the mixture of **21g** and **21h** obtained from mixed *E*–*Z* precursor, overall yield = 56%.

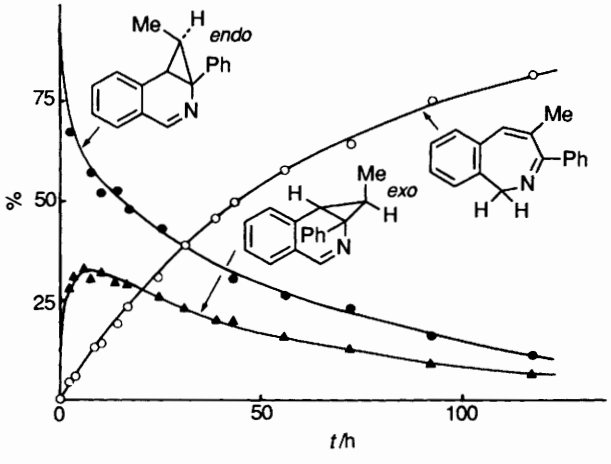



Fig. 2

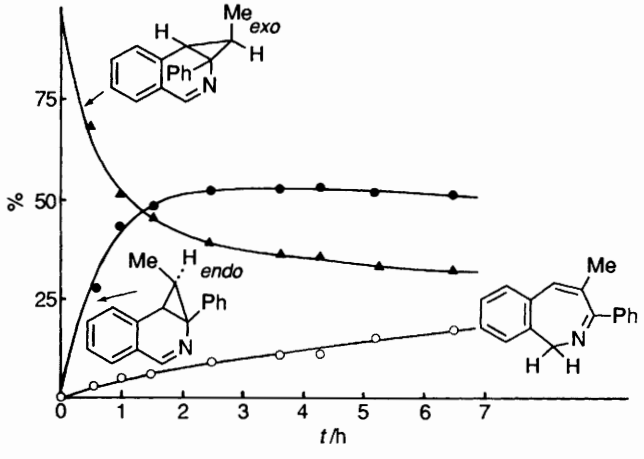
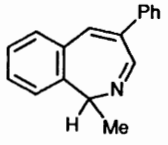
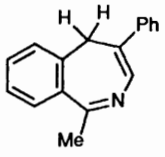



Fig. 3

1-methylisoquinoline.[13,14] The most likely alternative, the 5*H*-2-benzazepine **24**, was excluded because the methylene signal showed no change when the compound was heated or cooled.

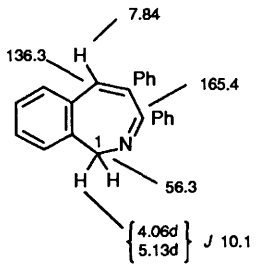



**23**




**24**

(*i*) *Stereospecificity*. Looking first at cases (a) and (b), where the alkenyl group is respectively *E*- and *Z*-phenylethenyl: reaction of **19a** and of **19b** at room temperature gave, respectively, the *exo*- and *endo*-isomers of 1,7b-diphenylcyclopropa[*c*]isoquinoline **21a** and **21b** in stereospecific reactions. Two other tests for stereospecificity were carried out using the analogues *E*- and *Z*-propenyl **19c**/**19d**, and *E*- and *Z*-2-phenylpropenyl **19g**/**19h**. In both cases the *E* and *Z* isomers of the nitrile ylide precursors could not be separated at any stage of the synthesis but in the final *E*–*Z* mixture of the amides **13** the stereoisomers were identified using the nuclear Overhauser effect (see Experi-




**27**

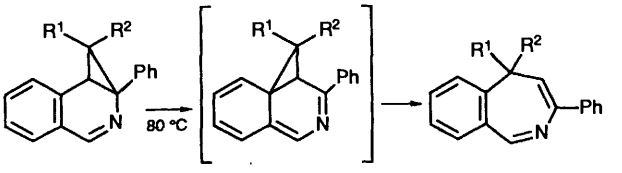
**Fig. 4**

mental section) and their ratio was measured by integration. In each case cyclisation gave a mixture of *exo* and *endo* isomers of **21** in a ratio which was, within experimental error, the same as the *E*:*Z* ratio in the amide precursor. In the case of the amide with the *E*/*Z* propenyl group **19c**/**19d** the reaction was carried out at two different temperatures, the first was at room temperature using an amide *Z*:*E* ratio of 2.2:1. In the second, the reaction was carried out briefly at 67 °C in refluxing THF followed by rapid quenching in ice. In the latter reaction an amide mixture richer in the *E* isomer (*Z*:*E* = 1:3.7) was used and it was found that the reaction was still stereospecific at the higher temperature even though the *exo* isomer of the product **21c** is less stable than the *endo* isomer **21d** (see thermolysis study below and Figs 2 and 3). In all cases the product ratio was measured by $^1$H NMR spectrometry on the crude product mixture and the two isomers were then separated by chromatography for identification as discussed above.

(*ii*) *The effect on cyclisation of the nature of the* cis *substituent* $R^2$ *in* **19**. The results here are clear, as shown by the reactions of **19d** and **19e** ($R^2$ = Me) and of **19b**, **19f** and **19h** ($R^2$ = Ph). These groups had no observable inhibiting effect on the conversion of **19** into **21** whereas the same groups totally prevented the diazo cyclisation **2** ⟶ **5**.

(*c*) *Thermal Rearrangement of Cyclopropa*[c]*isoquinolines* **21**.—The reactions of **21** ($R^3$ = H) fall into two distinct categories depending on the nature of the substitution at C-1 of the reactant. In cases where one of the substituents was hydrogen, **21a**/**b** and **21c**/**d**, then the reaction gave the 1*H*-2-benzazepines **25** and **26** respectively, apparently *via* the path shown in Scheme 4. These benzazepines were identified by comparison of their $^1$H and $^{13}$C NMR spectra with the analogous diazepine systems.[2–4] For example, some diagnostic signals from the spectra of **25** are shown in structure **27** (Fig. 4). At room temperature the 1-$CH_2$ group showed a broad AB pattern which sharpened as the compound was cooled (*J* 10.1 Hz), and coalesced as it was heated ($T_c$ = 62 °C). Studies on the course of this thermal rearrangement were carried out using the *exo* and *endo* isomers **21a** and **21b** ($R^1$ = Ph) and **21c** and **21d** ($R^1$ = Me). The *exo* isomer **21a** ($R^1$ = Ph) when heated under reflux for 12 h in benzene gave the benzazepine **25** in 92% yield. The rearrangement of the *endo* isomer **21b** was carried out at 50 °C in perdeuteriobenzene with NMR monitoring. This showed that an equilibrium between the *exo* and *endo* isomers is established fairly rapidly and that they are then slowly converted into the benzazepine. Thermal decomposition of the 1-Me analogues **21c** and **21d** showed similar results. A mixture of the two isomers when heated under reflux in benzene gave the benzazepine **26** in 92% yield. In this case an attempt was made to trap any possible 4π electron intermediate, *e.g.* **20** or **19c**/**19d**, by carrying out the reaction in the presence of three types of alkenes–diethyl fumarate, norbornene and butyl vinyl ether. However, no adducts were obtained from these reactions, even when the decomposition was carried out in norbornene as solvent; in all cases the benzazepine **26** only was obtained in yields of 75–90%. Pure samples of the *exo* **21c** and *endo* **21d** isomers were also thermolysed at 69 °C in perdeuteriobenzene with NMR monitoring, the results were similar to that for the 3-phenyl analogue and are shown in Figs. 2 and 3. It seems very likely that these interconversions occur *via* the mechanism shown in Scheme 4. The 1,5-hydrogen shift giving the 1*H*-2-benzazepine is probably a sigmatropic migration.

The thermolysis of the cyclopropa[*c*]isoquinolines which have no hydrogen at C-1 follows a different path (Scheme 5).



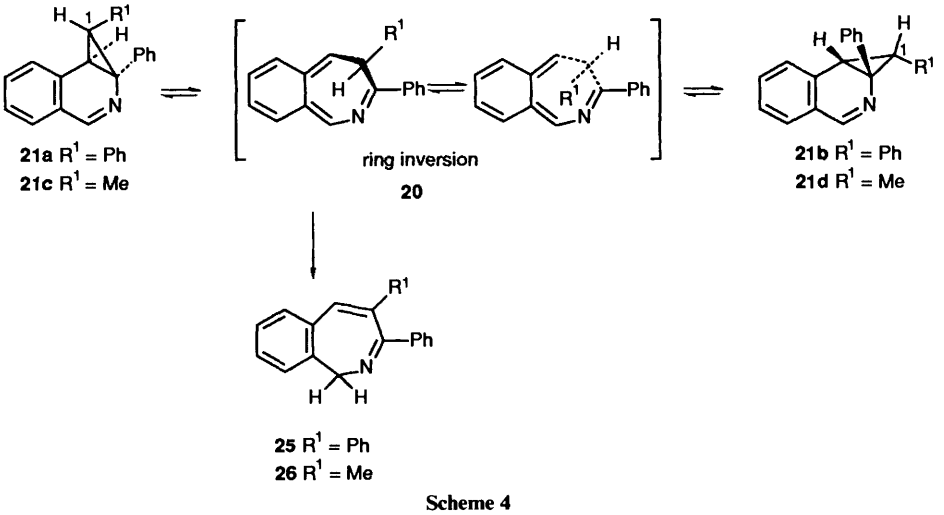

**21g/h** $R^1/R^2$ = Me/Ph
**21f** $R^1$ and $R^2$ = Ph

**28**

**29** $R^1/R^2$ = Me/Ph
**30** $R^1$ and $R^2$ = Ph

**Scheme 5**

Two examples were studied, **21g**/**21h** as a mixture, and **21f**. The reactions were much slower than those of **21a**/**21b** and **21c**/**21d** and gave the 5*H*-2-benzazepines **29** and **30** respectively in moderate yields (Scheme 5). It was not possible to determine the structure of the products by spectroscopy alone since the $^1$H and $^{13}$C NMR spectra were also consistent with the 3*H*-2-benzazepine structures **31**. However, X-ray crystallography on




**21a** $R^1$ = Ph
**21c** $R^1$ = Me

ring inversion

**20**

**21b** $R^1$ = Ph
**21d** $R^1$ = Me

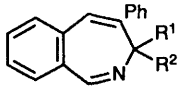
**25** $R^1$ = Ph
**26** $R^1$ = Me

**Scheme 4**

**Table 2** Spectroscopic data for benzazepines **25**, **26**, **29** and **30** and thienoazepines **35** and **41**

| Compound | | Spectroscopic data[a] |
|---|---|---|
| **25** | $\delta_H$ | (−23 °C) 4.06 (d, *J* 10.1, 1-$H_{ax}$), 5.13 (d, *J* 10.1, 1-$H_{eq}$), 7.84 (s, 5-H), 7.10–7.56 (m, 14 H); $T_c$ ($CH_2$) 62 °C |
| | $\delta_C$ | 56.31 (C-1), 127.06, 127.57, 128.01, 128.39, 128.65, 128.87, 135.71 (q). 136.31 (C-5), 137.98 (q), 139.33 (q), 139.72 (q), 140.06 (q), 165.42 (C-3) |
| | *m/z* | 295 (60), 294 (100), 192 (40), 191 (40) |
| **26** | $\delta_H$ | (−37 °C) 1.82 (d, *J* 1.4, Me), 3.87 (d, *J* 10.2, 1-$H_{ax}$), 4.96 (d, *J* 10.2, 1-$H_{eq}$), 7.20–7.66 (m, 10 H); $T_c$($CH_2$) 39 °C |
| | $\delta_C$ | 22.67 (Me), 56.12 (C-1), 126.93, 127.50, 127.67, 127.99, 128.41, 128.92, 135.50 (q), 135.91 (q), 136.51, 137.21 (q), 139.30 (q), 168.17 (C-3) |
| | *m/z* | 233 (45), 232 (100), 129 (15), 115 (23) |
| **29** | $\delta_H$ | 1.65 (s, Me), 5.95 (d, *J* 1.1, 4-H), 6.92–7.34 (m, 12 H), 7.84–7.96 (m, 2 H), 8.46 (d, *J* 1.1, H-1) |
| | $\delta_C$ | 31.62 (Me), 46.40 (C-5), 124.25, 124.39, 126.29, 126.79, 127.05, 127.52, 128.00, 128.48, 129.69, 130.99, 132.75 (q), 139.70 (q), 145.97 (q), 146.92 (q), 148.84 (q), 161.06 (C-1) |
| | *m/z* | 309 (88), 308 (100), 294 (15), 206 (59), 191 (47) |
| **30** | $\delta_H$ | 6.66–7.77 (m, 20 H), 8.59 (s, H-1) |
| | $\delta_C$ | 56.64 (C-5), 126.28, 126.42, 126.68, 127.02, 127.68, 127.83, 128.16, 129.52, 129.71, 130.66, 132.77 (q), 139.39 (q), 145.30, 149.68, 161.46 (C-1) |
| | *m/z* | 371 (78), 370 (26), 294 (22), 268 (50), 267 (22), 191 (20), 165 (100), 149 (22) |
| **35** | $\delta_H$ | (−60 °C) 3.71 (d, *J* 10.8, 4-$H_{ax}$), 5.20 (d, *J* 10.8, 4-$H_{eq}$), 7.78 (s, 8-H), 7.06–7.49 (m, 12 H); $T_c$($CH_2$) 7 °C |
| | $\delta_C$ | 50.96 (C-4), 127.08, 127.36, 127.61, 127.71, 127.93, 128.51, 128.73, 128.79 129.24, 136.69 (q), 139.59 (q), 140.50 (q), 140.61 (q), 166.34 (C-6) |
| | *m/z* | 301 (25), 300 (55), 197 (67), 165 (30), 105 (39), 84 (69), 83 (100) |
| **41** | $\delta_H$ | (−40 °C) 3.98 (d, *J* 10.8, 3-$H_{ax}$), 5.45 (d, *J* 10.8, 3-$H_{eq}$), 8.02 (s, H-7), 7.28–7.68 (m, 12 H); $T_c$($CH_2$) 19 °C |
| | $\delta_C$ | 51.02 (C-3), 127.08, 127.35, 127.63, 127.70, 127.87, 128.03, 128.51, 128.70, 129.23, 129.72, 136.71 (q), 139.66 (q), 140.64 (q), 166.30 (C-5) |
| | *m/z* | 301 (22), 300 (43), 197 (70), 165 (22), 105 (22), 84 (62), 83 (100) |

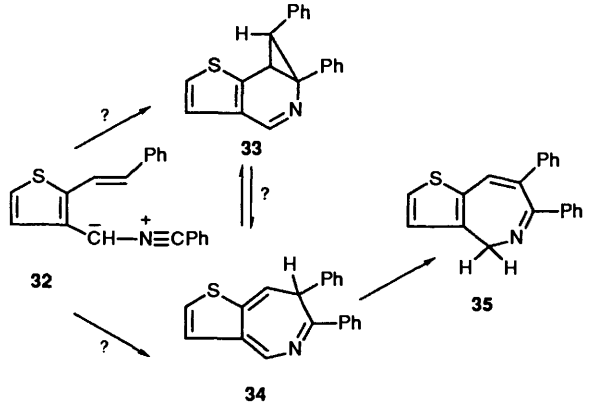
[a] *J* Values are given in Hz.




**31**

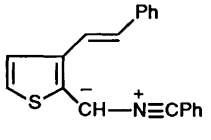
the product of **21g**/**21h** confirmed the structures as **29** (Fig. 3). In the case of **21f**, when refluxed in toluene an equilibrium was established between the reactant and the 5*H*-2-benzapepine **30** in the ratio *ca.* 2:1 after *ca.* 24. h. Thermolysis of **21f** at a higher temperature in refluxing *m*-xylene gave after 6 days the recovered azepine (23%), **30** (19%) and an isomeric compound (28%) tentatively formulated as 1,3,4-triphenyl-3*H*-2-benzapine on the basis of its $^1$H NMR spectrum.

(*d*) *Cyclisation of Benzonitrile Alkenylthiophenemethyl Ylides* **32**, **36** *and* **38**.—These nitrile ylides, all having the thiophene ring as the α,β-unsaturated moiety, showed considerable differences

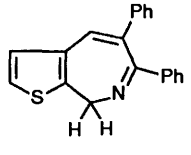



in their pattern of reactivity from their benzene analogues **19**. The intermediate **32**, generated in the usual way at 0 °C, gave after work-up and chromatography at room temperature the thieno[3,2-*c*]azepine **35**, not the expected cyclopropa[*b*]thieno[2,3-*d*]pyridine **33**. The structure of the thienoazepine followed from its molecular formula and the close similarity of its $^1$H and $^{13}$C NMR spectra to those of the benzo-fused analogues **25** and **26** (Table 2). In an attempt to find out whether compound **33** was a precursor for **35** the reaction was carried out in perdeuteriotetrahydrofuran in an NMR tube at low temperature with NMR monitoring. The imidoyl chloride and the base were mixed at −78 °C with the production of the usual intense colour. The $^1$H spectrum showed a complex aromatic region and multiplets in the δ 4.5–5.3 region. It was clear that the thienoazepine was absent and there were no doublets in the regions expected for the cyclopropyl protons of **33**. The spectrum showed no change over 2 h at −78 °C and the sample was then allowed to warm up slowly to 0 °C. Not much change was visible until the sample was at 0 °C when the signals in the range δ 4.5–5.3 began to diminish and those due to the thienoazepine began to appear. The reaction was complete after storage overnight at 0 °C giving the thienoazepine as the only product. At no stage were there any signals visible which could be attributed to compound **33** although it is possible that they could have been masked by those at δ 1.9 and 3.8 due to non-deuteriated solvent.

The analogous nitrile ylide **36** was generated in the usual way, however work-up gave only a multi-component mixture from



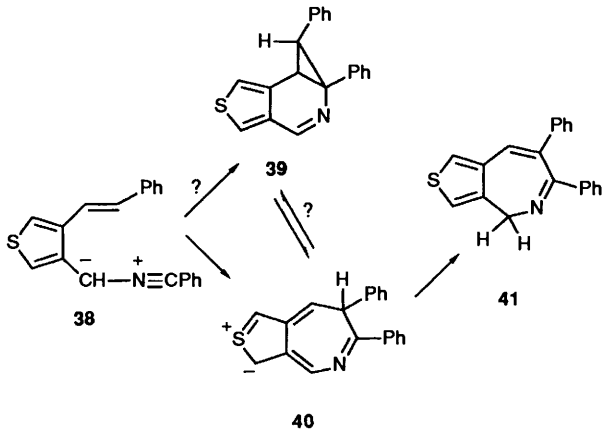

**36**




**37**

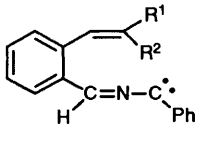
which no pure material could be isolated. The $^1$H NMR spectrum of the crude reaction mixture before chromatography showed the presence of a broad singlet at δ 4.6, possibly due to the methylene group of the thienoazepine **37** but, if present, this compound was not stable enough to survive preparative thin-layer chromatography.

The third nitrile ylide in this series was **38**, which has the 1,3-dipole and the alkenyl group attached at the 3 and 4 positions of the thiophene ring. The product of this reaction, carried out and worked-up at room temperature, was predominantly the



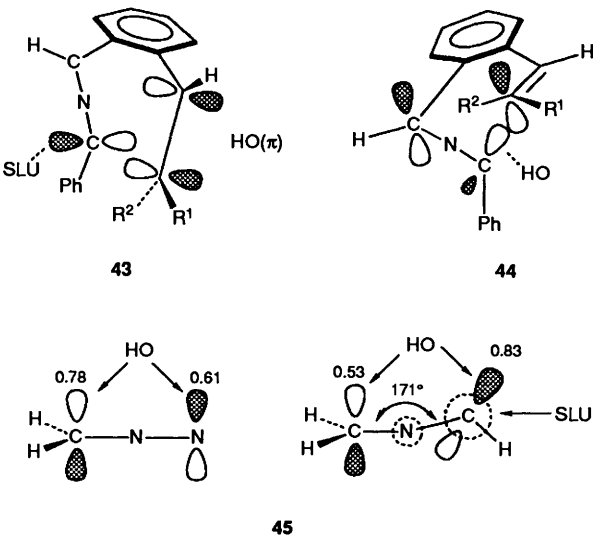
thieno[3,4-*c*]azepine **41**. The structure is based on the similarity of its NMR spectra, Table 2, to those of **35** and the benzene analogues **25** and **26**. However, it should be noted that the $^1$H NMR spectrum of the crude product, before chromatography, showed in addition to the peaks due to **41** two small doublets at $\delta$ 3.70 and 2.26 ($J$ 5.8 Hz), *possibly* due to the presence of compound **39** (*ca.* 10%). This compound could not be isolated.

(*e*) *The Mechanism of the Cyclisations.*—The results presented above show that the reactions of nitrile ylides of the type (**1**) (**19** in Scheme 2) generally parallel those of the nitrile imines **3**. They cyclise to give the cyclopropa[*c*]isoquinolines **21** in a reaction which is stereospecific at room temperature and at 67 °C. This reaction differs from that of the diazo compounds **2** not only in the nature of the product but also in the effect of the *cis* substituent $R^2$. When this is larger than hydrogen, *e.g.* Me or Ph, it totally inhibits the diazo cyclisation[4,15] but has no observable effect on the conversion of the nitrile imines into **8** and the nitrile ylides into **21**. These observations would seem to indicate the diazo compound **2** and the nitrilium betaines **1** and **3**, although formally similar in structure, cyclise by different reaction mechanisms. The diazo cyclisations are consistent with a [1.7] electrocyclisation process, while the nitrilium betaine reactions can be most simply rationalised as one-step [1.1]-cycloaddition reactions in which the terminal carbon of the nitrile ylide reacts in the manner of a singlet carbene—as in the canonical form **42**. Such a process would require a transition state geometry as shown in **43** in which the terminal carbon of



**42**

the nitrile ylide presents the large lobe of the SLUMO to the $\pi$ system of the double bond.[16] This is quite different from the geometry of the helical transition state required for [1.7] electrocyclisation[15,17] **44** and would account for the difference in the effect of the size of $R^2$ on the two reactions. This, the most straightforward explanation for the differences between the two reactions, is probably correct and there is nothing in the results obtained which is inconsistent with it. However the more complicated alternative, in which **19** also reacts by a [1.7] electrocyclisation to give **20** as the primary product, cannot be completely ruled out, particularly in view of the results in the thiophene series. The experimental observations can be accommodated by this mechanism as follows. The formation of the cyclopropa[*c*]isoquinolines **21** rather than the 1*H*-2,3-benzazepines *e.g.* **25** as the isolated product in cases where $R^2$ = H



(*cf.* the formation of **5** from **4**) could be due to a much slower rate for the sigmatropic hydrogen shift in **20** ($R^2$ = H) than in **4**. In support of this it is clear from Figs. 2 and 3 that azepine formation, Scheme 4, *via* the hydrogen shift is relatively slow compared to the rate at which equilibrium is established between the *exo* and *endo* isomers of **21**. The inhibiting effect of large $R^2$ groups on the cyclisation of **2** but not of **1**, could be due to the difference in the nature and geometry of the two 1,3-dipoles rather than a difference in mechanism. The diazo compound has open to it an alternative pathway of relatively low activation energy *via* the loss of nitrogen to give the carbene **6**. The nitrilium betaines have no equivalent escape route and so, although their rate of cyclisation may be slowed down by larger $R^2$ groups, they are less likely to be diverted into another path. The difference in geometry between diazo compounds and nitrile ylides may also be important here. The nature of the steric interactions involved in the diazo cyclisation has been discussed elsewhere[4,15] but these would be slightly different for nitrile ylides since this species has a bent structure and the orbital lobe at the terminal carbon of the HOMO is angled as shown in **45**.[16] These properties should allow a better orbital overlap in the helical transition state for electrocyclisation with less steric interaction between the nitrogen atom and the $R^2$ group. The complete stereospecificity observed in the formation of **21**, even at a temperature as high as 67 °C is difficult evidence to evaluate. At first sight it appears to provide clear support for the concerted formation of **21** *via* a [1.1] cycloaddition. However, it would be consistent with [1.7] electrocyclisation as the first step if the ring contraction of **20** to give **21** is very much faster than its rate of ring inversion.

In the thiophene series the isolation of the thienoazepines **35** and **41** rather than the cyclopropa[*b*]thieno[*d*]pyridines **33** and **39** respectively is surprising in view of the relatively high stability of the benzene fused analogues **21**. The failure to isolate the tricyclic products does not necessarily indicate a difference of mechanism but more likely reflects changes in the relative stability of the species involved and in the rate constants of the reactions which interconvert them. The tricyclic systems **33** and **39** apparently have lower thermodynamic or kinetic stability than **21**. This could be due to any or several of the following factors: (i) the incorporation of the thiophene ring in **33** and **39** increases angle strain, (ii) the activation energy for the conversion of *e.g.* **33** into **34**, must be lower than that for **21** into **20** (Scheme 4) because of the lower aromatic stabilisation energy of thiophene (*ca.* 122 kJ mol$^{-1}$ *cf.* 150 for benzene), (iii) the rate constant for the sigmatropic hydrogen migrations **34** ⟶ **35** and **40** ⟶ **41** may be higher than for **20** ⟶ **25**/**26** (Scheme

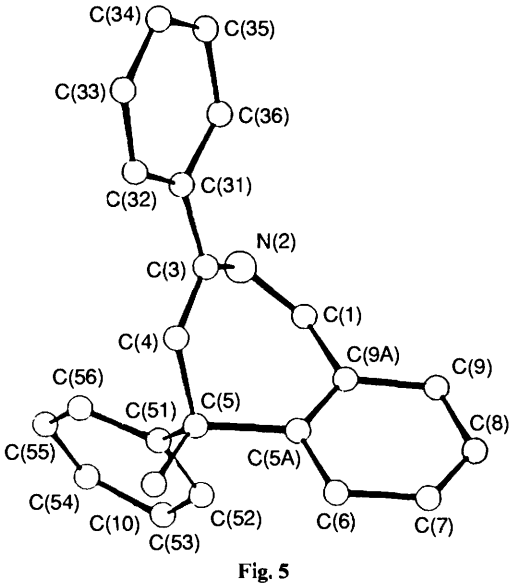



Fig. 5

**Table 3** Selected torsion angles and interplanar angles for 3-methyl-3,5-diphenyl-5*H*-2-benzazepine **29** (estimated standard deviation 1.5°)

| | Molecule 1 | Molecule 2 |
|---|---|---|
| C(9A)–C(1)–N(2)–C(3) | 5.9 | −1.7 |
| C(1)–N(2)–C(3)–C(4) | −53.6 | −44.9 |
| N(2)–C(3)–C(4)–C(5) | 10.8 | 8.7 |
| C(3)–C(4)–C(5)–C(5A) | 60.5 | 61.1 |
| C(4)–C(5)–C(5A)–C(9A) | −65.5 | −63.1 |
| C(5)–C(5A)–C(9A)–C(1) | 5.1 | 1.6 |
| C(5A)–C(9A)–C(1)–N(2) | 37.0 | 42.6 |
| N(2)–C(3)–C(31)–C(36) | −17.8 | −3.9 |
| C(4)–C(5)–C(51)–C(56) | −37.4 | −38.6 |
| Interplanar angle[a] 1/2 | 36.5 | 35.1 |
| Interplanar angle[a] 1/3 | 51.3 | 51.0 |

[a] Plane 1: C(4), C(3), C(9A), C(5A); plane 2: C(3), C(9A), N(2), C(1); plane 3: C(4), C(5), C(5A).

4) either because of the incorporation of another heteroatom into the system or because of a change in geometry. The conversion of **38** into the thieno-azepine **41** at room temperature is perhaps even more surprising than the formation of **35** from **32**, since it depends on a sufficiently high degree of 'double-bond character' for the 3,4 bond. Apparently the dipolar nature of **40** is not sufficiently destabilising to inhibit the electrocyclisation, if that is the primary step; or the ring expansion of **39** if it is the primary product. It is noteworthy that the diazo analogue of **38** failed to cyclise and instead reacted *via* a carbenic path.[3] That **38** did cyclise provides another illustration of the higher reactivity of nitrile ylides than diazo compound in reactions of this type.[18]

Further work involving the generation of the nitrile ylides at very low temperature with spectroscopic monitoring is required to establish whether the first step in these cyclisations is [1.1] cycloaddition or [1.7] electrocyclisation.

(*f*) *The Crystal Structure of* 3-*Methyl*-3,4-*diphenyl*-3H-2-*benzazepine* **29**.—There are two crystallographically unrelated molecules in the asymmetric unit. The poor quality weak diffraction data resulted in rather large estimated standard deviations. Bond lengths and angles are, however, within the expected ranges and show no significant differences between the two independent molecules. The wide intra-ring angles of 129.1

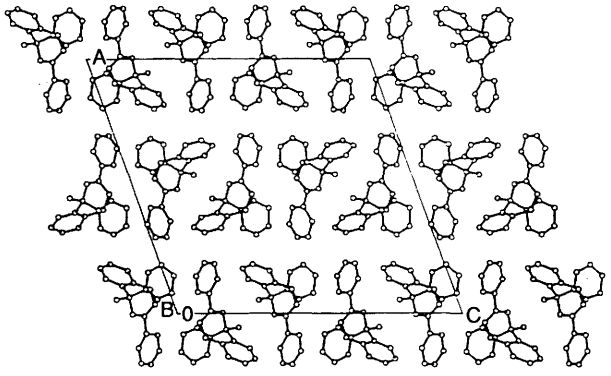



Fig. 6

and 128.4° at C(1) and C(5), Fig. 5, is a common feature of azepine and diazepine rings. Both molecules adopt very similar boat-shaped conformations as defined by the torsion angles in Table 3. The interplanar angles, Table 3, are similar to those found in related diazepine structures.[19,20] The major difference between the two molecules is the orientation of the phenyl substituent on C(3) which shows a conformational difference of 14° about the C-(3)–C(31) bond, presumably caused by differences in the intermolecular environments. Fig. 6 shows the sheet-like packing of the crystallographically unrelated molecules. Intra-sheet contacts (between the molecules) are very similar with shortest contacts of C(4)–C(10) = 3.500 and C(4′)–C(10′) = 3.494 Å. The shortest inter-sheet contact is longer, C(33)–C(52′) = 3.615 Å.

## Experimental

NMR spectra were run as solutions in deuteriochloroform unless otherwise stated. Chemical shifts are recorded as $\delta$ values. *J* Values are given in Hz. In the $^{13}C$ spectra carbon multiplicity was established by single frequency off resonance decoupling or by DEPT. Mass spectra were obtained using an AEI MS902 spectrometer with electron ionisation at 70 eV unless otherwise stated. Preparative chromatography was carried out by the medium pressure technique[21] (< 100 psi) using either 1000 × 15 × 1000 or 25 mm columns packed with Merck Kieselgel 60, or by flash chromatography.[22] Eluting solvents were based on light petroleum (b.p. 40–60 °C), referred to as petroleum. Ether refers to diethyl ether. Evaporation of solvents indicates evaporation under reduced pressure using a rotary evaporator. All solutions were dried using anhydrous magnesium sulfate.

(1) *Preparation of the Amides* **13**–**16**.—All the amides except **16** were prepared from carbonyl compounds,[3,4] *e.g.* **10**, by the general route which is given in detail for the first example. Attempted distillation of some of the amines **12** resulted in decomposition and they were used without purification either as the crude reaction product or after precipitation as the hydrochloride salt. In the preparation of **13 c**/**d** and **13 g**/**h** the *E*/*Z* isomers could not be separated at any stage and were used as mixtures. The yields and physical data for the oximes **11** and the amides **13**–**16** are given in Table 4, and their spectroscopic data in Table 5.

(E)-N-*Benzoyl*-2-(2-*phenylvinyl*)*benzylamine* **13a**. (i) (E)-*o*-(2-*Phenylvinyl*)*benzaldehyde oxime* **11a**. A mixture of (*E*)-*o*-(2-phenylvinyl)benzaldehyde[4] **10a** (5.38 g, 25.8 mmol), hydroxylamine hydrochloride (5.38 g, 77.4 mmol), pyridine (5 $cm^3$) and ethanol (50 $cm^3$) was heated under reflux for 30 min. After evaporation of solvent and dilution with water (60 $cm^3$) and dichloromethane (100 $cm^3$), the aqueous phase was separated, extracted with dichloromethane (2 × 50 $cm^3$). The combined organic extracts were dried and evaporated to give a brown oil

**Table 4** Yields and physical data on oximes **11** and amides **13** and 14–16

| Compound | Yield (%) | Cryst. solvent[a] | M.p. (°C) | Molecular formula | C (%) Found | C (%) Calc. | H (%) Found | H (%) Calc. | N (%) Found | N (%) Calc. | *m/z* ($M^+$) Found | *m/z* ($M^+$) Calc. | Yield of **12** (unpurified %) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **11a** | 78 | E | 127–129 | $C_{15}H_{13}NO$ | 80.5 | 80.7 | 5.7 | 5.9 | 6.5 | 6.3 | | | 86[b] |
| **11b** | 67 | E–LP | 81–83 | $C_{15}H_{13}NO$ | 80.9 | 80.7 | 6.0 | 5.9 | 6.5 | 6.3 | | | 85[b] |
| **11c–11d** 1:2[c] | 84 | | oil, b.p. 110–112 12 mmHg | $C_{10}H_{11}NO$ | | | | | | | 161.083 551 | 161.084 064 | 71 |
| **11e** | 73 | | oil, b.p. 96–98 0.3 mmHg | $C_{11}H_{13}NO$ | 75.5 | 75.4 | 7.5 | 7.5 | 8.1 | 8.0 | | | 84 |
| **11f** | 91 | E–LP | 133–135 | $C_{21}H_{17}NO$ | | | | | | | 299.131 007 | 299.131 014 | 84 |
| **11g–11h** | 66 | | mixture semi-solid | $C_{16}H_{15}NO$ | | | | | | | 237.113 207 | 237.115 364 | 75 |
| **11h** | | E–LP | 96–97 | $C_{16}H_{15}NO$ | 80.7 | 81.0 | 6.2 | 6.4 | 5.7 | 5.9 | | | |
| **11i** | 79 | E–P | 109–110 | $C_{16}H_{15}NO$ | 81.1 | 81.0 | 6.3 | 6.4 | 5.75 | 5.9 | | | 91 |
| **13a** | 89 | E–P | 142–144 | $C_{22}H_{19}NO$ | 84.05 | 84.3 | 6.1 | 6.1 | 4.7 | 4.5 | | | |
| **13b** | 84 | E–LP | 139–141 | $C_{22}H_{19}NO$ | 84.2 | 84.3 | 6.1 | 6.1 | 4.6 | 4.5 | | | |
| **13c–13d** 1:2.2 | 83 | E–LP | 91–93 | $C_{17}H_{17}NO$ | 81.0 | 81.2 | 7.0 | 6.8 | 5.7 | 5.6 | | | |
| **13e** | 68 | E–LP | 96–98 | $C_{18}H_{19}NO$ | 81.3 | 81.5 | 7.4 | 7.2 | 5.5 | 5.3 | | | |
| **13f** | 88 | E | 110–112 | $C_{28}H_{23}NO$ | 86.5 | 86.3 | 5.8 | 6.0 | 3.65 | 3.6 | | | |
| **13g–13h** 1:1.7 | 86 | | gum | $C_{23}H_{21}NO$ | | | | | | | 327.160 862 | 327.162 314 | |
| **13i** | 88 | E–P | 186–187 | $C_{23}H_{21}NO$ | 84.1 | 84.4 | 6.6 | 6.5 | 4.2 | 4.3 | | | |
| **14** | 76 | E–LP | 122–123 | $C_{20}H_{17}NOS$ | | | | | | | 319.102 889 | 319.103 086 | |
| **15** | 60 | E–LP | 95–96 | $C_{20}H_{17}NOS$ | | | | | | | 319.102 889 | 319 103 086 | |
| **16** | 71 | E–LP | 147–148 | $C_{20}H_{17}NOS$ | 75.1 | 75.2 | 5.35 | 5.4 | 4.3 | 4.4 | | | |

[a] E = ethanol, P = pentane, LP = light petroleum, b.p. 60–80 °C. [b] As hydrochloride. [c] Partial separation by flash chromatography gave a mixture *E*:*Z* = 3.7:1.

**Table 5** Spectroscopic data for oximes **11** and amides **13** and **14–16**

| Compound | NMR[a] $\delta_H$ | IR ($\nu_{max}$/cm$^{-1}$)[b] O–H | N–H | C=O |
|---|---|---|---|---|
| **11a** | 6.97 (d, *J* 16, 1 H), 7.25–7.67 (m, 10 H), 7.75 (br s, 1 H), 8.52 (s, 1 H) | 3200br | | |
| **11b** | 6.76 (s, 2 H), 7.12–7.78 (m, 9 H), 8.41 (s, 1 H), 8.99 (br s, 1 H) | 3200br | | |
| **11c–11d** | 1.74 (dd, *J* 7.0 and 1.8) and 1.94 (dd, *J* 6.6 and 1.7), total integral 3 H; 5.89–6.19 (2 × dq, 1 H); 6.60–6.82 (2 × dd, 1 H); 7.25–7.94 (m, 4 H); 8.50 (s) and 8.64 (s), total integral 1 H | 3300br | | |
| **11e** | 1.64 (d, *J* 1.2, 3 H), 1.91 (d, *J* 1.5, 3 H), 6.30 (br s, 1 H), 7.07–7.82 (m, 5 H), 8.32 (s, 1 H) | 3300br | | |
| **11f** | 6.93–7.85 (m, 16 H), 8.41 (s, 1 H) | 3240br | | |
| **11h** | 2.07 (d, *J* 1.3, 3 H), 6.94 (br q, 1 H), 7.24–7.90 (m, 9 H), 8.37 (s, 1 H), 8.2–8.9 (br s, 1 H) | 3300br | | |
| **11i** | 2.22 (s, 3 H), 7.02 (d, *J* 16, 1 H), 7.19–7.65 (m, 10 H), 9.00 (br s, 1 H) | 3260br | | |
| **13a** | 4.74 (d, *J* 5, 2 H), 6.36 (br d, NH), 6.95 (d, *J* 16, 1 H), 7.35–8.20 (m, 15 H) | | 3325 | 1630 |
| **13b** | 4.79 (d, *J* 5.3, 2 H), 6.31 (br d, 1 H), 7.05–7.74 (m, 16 H) | | 3340 | 1633 |
| **13c–13d*** | 1.72* (dd, *J* 7.0 and 1.8) and 1.86 (dd, *J* 6.6 and 1.7) total integral 3 H; 4.57* (d, *J* 5.5) and 4.64 (d, *J* 5.3) total integral 2 H; 5.93* (dq, *J* 11.3 and 7.0) and 6.15 (dq, *J* 15.5 and 6.6) total integral 1 H; 6.35 (br, NH); 6.60*(dq, *J* 11.3 and 1.8) and 6.70 (dq, *J* 15.5 and 1.7) total integral 1 H; 7.16–8.11 (m, 9 H) minor isomer confirmed as *E* by NOE (2.3%) between Me and adjacent *cis* H | | 3300 | 1635 |
| **13e** | 1.69 (d, *J* 1.1, 3 H), 1.88 (d, *J* 1.3, 3 H), 4.60 (d, *J* 5.4, 2 H), 6.32 (br, 2 H), 7.18–7.80 (m, 9 H) | | 3300 | 1640 |
| **13f** | 4.63 (d, *J* 5.7, 2 H), 6.15 (br, 1 H), 6.96–7.69 (m, 20 H) | | | |
| **13g–13h*** | 2.11 (d, *J* 1.5) and 2.24* (d, *J* 1.5) total integral 3 H; 4.58* (d, *J* 5.5) and 4.67 (d, *J* 5.5) total integral 2 H; 6.10* (br d) and 6.47 (br d, NH); 6.63* (br m, *Z*-CH); 6.94–7.71 (m, 29 H) isomers identified by NOE of Me on olefinic proton (2.5% for *Z* and 0.1% for *E*) | | 3150 | 1680 |
| **13i** | 1.63 (d, *J* 6.8, 3 H), 5.78 (quin, *J* 6.8, 1 H), 6.32 (br d, 1 H), 6.95 (d, *J* 16, 1 H), 7.19–7.77 (m, 15 H) | | 3315 | 1635 |
| **14** | 4.71 (d, *J* 5.4, 2 H), 6.45 (br, 1 H), 6.93 (d, *J* 16, 1 H), 6.99–7.78 (m, 13 H) | | 3290 | 1645 |
| **15** | 4.72 (d, *J* 5.4, 2 H), 6.30 (br, 1 H), 6.56–7.82 (m, 14 H) | | 3050 | 1630 |
| **16** | 4.46 (d, *J* 5.4, 2 H), 6.26 (br, 1 H), 6.49 (d, *J* 16, 1 H), 6.74–7.42 (m, 13 H) | | 3060 | 1640 |

[a] *J* Values are given in Hz. [b] IR spectra of solids as Nujol mulls, of oils as films.

which was purified by flash chromatography (silica, ether–petroleum, 1:2) to give a white solid which was crystallised from ethanol to give the oxime **11a** (4.48 g, 78%).

(ii) *o-(2-Phenylvinyl)benzylamine* **12a**. The oxime **11a** (7.30 g, 33 mmol) in dry ether was added dropwise over 1 h, with stirring, to lithium aluminium hydride (13.2 g, 33 mmol) in dry ether (400 cm$^3$) cooled in an ice-bath. The mixture was stirred for 2 h at room temperature and then heated under reflux for 1 h. The mixture was then cooled to *ca.* −20 °C and hydrolysed by the careful addition of saturated aqueous sodium sulfate (200 cm$^3$). The solid was filtered off and washed with ether. The aqueous layer of the filtrate was separated and extracted with ether and the combined ether extracts were dried. Treatment with hydrogen chloride gave the amine **12a** hydrochloride (7.01

**Table 6** Physical data for 1,7b-dihydrocyclopropa[*c*]isoquinolines **21**, benzazepines **25**, **26**, **29** and **30** and thienoazepines **35** and **41**

| Compound | Cryst. solvent[a] | M.p. (°C) | Molecular formula | C (%) | | H (%) | | N (%) | | *m/z* ($M^+$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Found | Calc. | Found | Calc. | Found | Calc. | Found | Calc. |
| **21a** | E–P | 117–119 | $C_{22}H_{17}N$ | 89.2 | 89.5 | 5.6 | 5.8 | 4.7 | 4.7 | | |
| **21b** | | Oil | $C_{22}H_{17}N$ | | | | | | | 295.134 970 | 295.136 010 |
| **21c** | | Oil | $C_{17}H_{15}N$ | | | | | | | 233.118 920 | 233.120 450 |
| **21d** | C | 72–74 | $C_{17}H_{15}N$ | | | | | | | 233.119 380 | 233.120 450 |
| **21e** | C | 56–58 | $C_{18}H_{17}N$ | 87.2 | 87.40 | 6.8 | 6.9 | 5.7 | 5.7 | | |
| **21f** | EA–P | 247–248 | $C_{28}H_{21}N$ | | | | | | | 371.167 391 | 371.167 400 |
| **21g** | E–P | 128–130 | $C_{23}H_{19}N$ | 89.0 | 89.3 | 6.4 | 6.2 | 4.7 | 4.5 | | |
| **21h** | | Oil | $C_{23}H_{19}N$ | | | | | | | 309.150 409 | 309.151 750 |
| **25** | E | 136–137 | $C_{22}H_{17}N$ | | | | | | | 295.134 533 | 295.136 100 |
| **26** | LP | 110–111 | $C_{17}H_{15}N$ | 87.8 | 87.5 | 6.7 | 6.5 | 6.0 | 6.0 | | |
| **29** | EA–P | 172–173 | $C_{23}H_{19}N$ | 89.1 | 89.3 | 6.1 | 6.2 | 4.6 | 4.5 | | |
| **30** | C | 185–187 | $C_{28}H_{21}N$ | | | | | | | 371.1678 | 371.167 400 |
| **35** | | Oil | $C_{20}H_{15}NS$ | | | | | | | 301.092 634 | 301.092 521 |
| **41** | | Oil | $C_{20}H_{15}NS$ | | | | | | | 301.0909 | 301.092 521 |

[a] C = chloroform, E = ethanol, EA = ethyl acetate, P = pentane, LP = light petroleum, b.p. 60–68 °C.

**Table 7** Fractional coordinates of atoms with standard deviations

| | *x* | *y* | *z* |
|---|---|---|---|
| C(1) | −0.0947(9) | 0.564(3) | 0.5678(9) |
| N(2) | −0.0354(7) | 0.6058(22) | 0.5681(7) |
| C(3) | 0.0129(8) | 0.664(3) | 0.6240(9) |
| C(4) | 0.0061(9) | 0.807(3) | 0.6632(9) |
| C(5) | −0.0638(9) | 0.894(3) | 0.6518(8) |
| C(5A) | −0.1084(9) | 0.731(3) | 0.6622(9) |
| C(6) | −0.1353(10) | 0.750(3) | 0.7112(10) |
| C(7) | −0.1780(11) | 0.604(3) | 0.7170(10) |
| C(8) | −0.1960(10) | 0.464(3) | 0.6742(11) |
| C(9) | −0.1690(10) | 0.443(3) | 0.6235(11) |
| C(9A) | −0.1235(9) | 0.583(3) | 0.6197(9) |
| C(10) | −0.0525(10) | 1.041(3) | 0.7000(10) |
| C(31) | 0.0800(9) | 0.594(3) | 0.6357(9) |
| C(32) | 0.1368(11) | 0.655(3) | 0.6831(9) |
| C(33) | 0.1970(9) | 0.567(4) | 0.6933(11) |
| C(34) | 0.2020(12) | 0.417(4) | 0.6599(12) |
| C(35) | 0.1464(13) | 0.350(4) | 0.6109(12) |
| C(36) | 0.0844(11) | 0.436(3) | 0.5991(11) |
| C(51) | −0.0943(7) | 0.9722(23) | 0.5850(8) |
| C(52) | −0.1639(9) | 0.9725(24) | 0.5554(9) |
| C(53) | −0.1922(9) | 1.061(3) | 0.4959(10) |
| C(54) | −0.1519(10) | 1.137(3) | 0.4651(10) |
| C(55) | −0.0833(11) | 1.137(3) | 0.4956(10) |
| C(56) | −0.0556(11) | 1.059(3) | 0.5545(11) |
| C(1′) | 0.4067(8) | 0.0576(25) | 0.8697(9) |
| N(2′) | 0.4647(7) | 0.0876(23) | 0.9098(7) |
| C(3′) | 0.5170(8) | 0.158(3) | 0.8878(8) |
| C(4′) | 0.5087(8) | 0.2943(23) | 0.8453(8) |
| C(5′) | 0.4409(8) | 0.376(3) | 0.8078(8) |
| C(5A′) | 0.3972(8) | 0.2241(25) | 0.7660(11) |
| C(6′) | 0.3775(9) | 0.229(3) | 0.7025(9) |
| C(7′) | 0.3387(11) | 0.093(3) | 0.6671(11) |
| C(8′) | 0.3176(10) | −0.055(4) | 0.6977(12) |
| C(9′) | 0.3393(9) | −0.066(3) | 0.7654(11) |
| C(9A′) | 0.3825(7) | 0.081(3) | 0.7981(8) |
| C(10′) | 0.4538(8) | 0.534(3) | 0.7679(9) |
| C(31′) | 0.5810(7) | 0.061(3) | 0.9225(8) |
| C(32′) | 0.6403(8) | 0.130(3) | 0.9110(8) |
| C(33′) | 0.7010(11) | 0.037(3) | 0.9409(11) |
| C(34′) | 0.7031(11) | −0.101(3) | 0.9806(10) |
| C(35′) | 0.6474(11) | −0.160(3) | 0.9933(11) |
| C(36′) | 0.5844(10) | −0.078(3) | 0.9643(10) |
| C(51′) | 0.4062(8) | 0.4563(24) | 0.8540(8) |
| C(52′) | 0.3349(8) | 0.457(3) | 0.8345(10) |
| C(53′) | 0.3087(8) | 0.541(3) | 0.8741(10) |
| C(54′) | 0.3447(12) | 0.629(3) | 0.9315(11) |
| C(55′) | 0.4148(12) | 0.636(3) | 0.9485(10) |
| C(56′) | 0.4444(10) | 0.547(3) | 0.9099(9) |

g, 86%) as a white solid, which was converted into the amide without further purification.

(iii) (E)-N-*Benzoyl*-o-(2-*phenylvinyl*)*benzylamine* **13a**. The amine **12a** hydrochloride (7.01 g, 28 mmol), benzoyl chloride (8.47 g, 60 mmol), pyridine (60 $cm^3$) and benzene (100 $cm^3$) were heated under reflux for 40 min. After cooling the mixture was diluted with water and the organic layer was separated, washed with aqueous sodium carbonate and dried. Evaporation gave a brown oil which was purified by chromatography (silica, ethyl acetate–petroleum, 1:2) to give the amide **13a**, m.p. 142–144 °C (from ethanol–pentane).

(E)-2-*Benzamidomethyl*-3-(2-*phenylvinyl*)*thiophene* **14**. (i) (E)-3-(2-Phenylvinyl)thiophene-2-carbaldehyde [3] gave its oxime (15 min, 70%), m.p. 116–119 °C (from ethanol) (Found: *m/z* 229.056 093. $C_{13}H_{11}NOS$ requires *m/z* 229.056 136); $\nu_{max}$(Nujol)/$cm^{-1}$ 3250 (br, OH); $\delta_H$ 6.91 (d, *J* 16, 1 H), 7.04–7.53 (m, 8 H), 7.91 (br s, 1 H) and 8.51 (s, 1 H). (ii) Reduction gave (*E*) 2-aminomethyl-3-(2-phenylvinyl)thiophene (84%), m.p. 73–75 °C (from chloroform) (Found: *m/z* 215.076 826. $C_{13}H_{13}NS$ requires *m/z* 215.076 871; $\delta_H$ 1.88 (2 H, br s), 4.11 (2 H, s) and 6.78–7.57 (9 H, m). (iii) Benzoylation gave the amide **14**.

(E)-2-*Benzamidomethyl*-4-(2-*phenylvinyl*)*thiophene* **15**. (i) (*E*)-3-Formyl-4-(2-phenylvinyl)thiophene [3] gave its oxime (15 min, 73%), m.p. 109–111 °C (Found: *m/z* 229.056 0934. $C_{13}H_{11}NOS$ requires *m/z* 229.056 136); $\nu_{max}$(Nujol)/$cm^{-1}$ 3350 (OH); $\delta_H$ 7.00 (d, *J* 16, 1 H), 7.14–7.60 (m, 8 H), 8.27 (br, 1 H) and 8.46 (s, 1 H). (ii) Reduction gave (*E*)-3-aminomethyl-4-(2-phenylvinyl)-thiophene (79%) as an oil (Found: *m/z* 215.076 7687. $C_{13}H_{13}NS$ requires *m/z* 215.076 871); $\nu_{max}$(Nujol)/$cm^{-1}$ 3350 and 3290 ($NH_2$); $\delta_H$ 1.76 (br, 2 H), 4.00 (s, 2 H), 6.80–7.75 (m, 9 H). (iii) Benzoylation gave the amide **15**.

(E)-3-*Benzamidomethyl*-2-(2-*phenylvinyl*)*thiophene* **16**. The hexamine salt of (*E*)-3-bromomethyl-2-(2-phenylvinyl)thiophene [3] (30.02 g, 71.6 mmol) was dissolved in warm ethanolic hydrochloric acid [from 10 mol $dm^{-3}$ hydrochloric acid (78 $cm^3$), ethanol (270 $cm^3$) and water (54 $cm^3$)] and the solution allowed to stand overnight. After filtration and evaporation the residue was dissolved in water (100 $cm^3$), cooled to 0 °C and made alkaline to pH 13 with aqueous sodium hydroxide. Extraction with ether, drying and evaporation gave (*E*)-3-aminomethyl-2-(2-phenylvinyl)thiophene (10.19 g, 66%) as a brown oil which was used without further purification; $\nu_{max}$(film)/$cm^{-1}$ 3360 and 3300 ($NH_2$); $\delta_H$ 1.76 (br, 2 H), 3.75 (s, 2 H) and 6.79–7.50 (m, 9 H). The amine was benzoylated as above; chromatography (12% deactivated alumina, ethyl acetate–petroleum 1:4) and crystallisation from ethanol–petroleum gave the amide **16**.

(2) *Preparation of the Imidoyl Chlorides and their Base-*

*promoted Cyclisation.—Preparation of the imidoyl chlorides.* The imidoyl chlorides were prepared by heating under reflux a mixture of the appropriate amide and phosphorus pentachloride (*ca.* 1.15 mol per mol of amide) in dry ether (*ca.* 50 $cm^3$ per mmol of amide) for 16–22 h. Evaporation of the ether left an oil which was kept at 30–40 °C on a high-vacuum (<0.1 mmHg) rotary evaporator for *ca.* 4 h to remove phosphorus oxychloride. In a number of cases the conversion into the imidoyl chloride was confirmed by removing a small sample for $^1H$ NMR spectroscopy. The crude benzimidoyl chlorides were used without further purification.

*Generation and Cyclisation of the Nitrile Ylides* **19**, **32**, **36** and **38**.—The crude benzimidoyl chlorides were dissolved in dry THF (*ca.* 30 $cm^3$ per mmol of reactant) and the solution was kept at either room temperature or 0 °C under nitrogen. Addition of dry potassium *tert*-butoxide (*ca.* 2 mol per mol of benzimidoyl chloride) in one batch produced a deep red or purple colour which faded over times ranging from *ca.* 15 s to 20 min to give a yellow solution. After *ca.* 2 h at room temperature water was added to the mixture which was then extracted with methylene dichloride. The organic extract was dried and evaporated to give the crude product which was then purified by flash chromatography. The $^1H$ and $^{13}C$ NMR spectra and the mass spectra of the products **21** are shown in Table 1, and of the thienoazepines **35** and **41** in Table 2. The physical data are given in Table 6.

(i) (E)-α-(*Benzonitril*-N-*io*)-o-(2-*phenylvinyl*)*benzylide* **19a** gave 1,7b-dihydro-1-*exo*-phenyl-1a-phenylcyclopropa[*c*]isoquinoline **21a** (85%) and recovered amide (7%).

(ii) (Z)-α-(*Benzonitril*-N-*io*)-o-(2-*phenylvinyl*)*benzylide* **19b** gave 1,7b-dihydro-1-*endo*-phenyl-1a-phenylcyclopropa[*c*]isoquinoline **21b** (73%). $^1H$ NMR spectroscopy of the crude product showed the absence of any of the *exo* isomer.

(iii) α-(*Benzonitril*-N-*io*)-o-(*prop*-1-*enyl*)*benzylide* **19c/d** *as an* E/Z *mixture.* (*a*) *Reaction at room temperature.* A reaction using the amides **13c/d** (*Z*:*E* 2.2:1 by $^1H$ NMR) gave 1,7b-dihydro-1-*endo*-methyl-1a-phenylcyclopropa[*c*]isoquinoline **21d** (49%) and the *exo* isomer **21c** (23%). $^1H$ NMR spectroscopy of the crude product showed the *endo*:*exo* ratio to be 2.2:1.

(b) *Reaction at* 67 °C. The amide (*Z*:*E* 1:3.7 by $^1H$ NMR; 0.093 g, 0.37 mmol) was converted into the imidoyl chloride in the usual way and the product was dissolved in THF (4 $cm^3$). This solution was injected through a septum into THF (15 $cm^3$) boiling under reflux under nitrogen. The solution was brought back to reflux (*ca.* 1 min) and a solution of potassium *tert*-butoxide (0.056 g, 0.50 mmol) in THF (1 $cm^3$) was injected in one batch. The mixture was cooled immediately in an ice-bath and water (20 $cm^3$) was added. After the usual work-up $^1H$ NMR spectroscopy showed the presence of **21c** and **21d** in the ratio 3.7:1. Chromatography gave the product as an *exo–endo* mixture (67 mg, 78%).

(iv) α-(*Benzonitril*-N-io)-o-(2-*methylprop*-1-*enyl*)*benzylide* **19e** gave 1,1-dimethyl-1a-phenyl-7b*H*-cyclopropa[*c*]isoquinoline **21e** (79%) and recovered amide (11%).

(v) α-(*Benzonitril*-N-*io*)-o-(2,2-*diphenylvinyl*)*benzylide* **19f** gave 1,1,1a-triphenyl-7b*H*-cyclopropa[*c*]isoquinoline **21f** (91%).

(vi) α-(*Benzonitrilio*)-o-(2-*phenylprop*-1-*enyl*)*benzylide* **19g/h** as an *E–Z* mixture, generated from the amide **13g/h** (*E*:*Z* 1:1.7), gave 1,7b-dihydro-1-methyl-1-*exo*-phenyl-1a-phenylcyclopropa[*c*]isoquinoline **21g** (11%), the *endo* isomer **21h** (7%) as an oil, a mixture of the *exo* and *endo* isomers (38%), and recovered amide (20%). $^1H$ NMR spectroscopy of the crude product gave the *exo*:*endo* ratio as 1:1.5.

(vii) (E)-α-(*Benzonitril*-N-*io*)-α-*methyl*-o-(2-*phenylvinyl*)*benzylide* **19i** gave 4-benzyl-1-methyl-3-phenylisoquinoline **22** (63%) as an oil (Found: *m*/*z* 309.150 114. $C_{23}H_{19}N$ requires *m*/*z* 309.151 750); $\delta_H$ 3.05 (s, 3 H), 4.45 (s, 2 H) and 7.07–8.17 (m, 14 H); $\delta_C$ 22.45 (Me), 34.72 (C-5), 123.86 (q), 125.07, 125.78, 125.99, 126.20, 126.69, 127.52, 128.02, 128.38, 129.23, 129.88, 136.00 (q), 141.05 (q), 141.31 (q), 152.01 (q) and 156.97 (C-1); $\lambda_{max}$(EtOH)/nm 330 (log ε 3.65), 316 (3.66), 291 (3.91), 281 (3.94) and 238 (4.52).

(viii) (E)-α-(*Benzonitril*-N-*io*)-2-(2-*phenylvinyl*)-3-*thenylide* **32**. (a) Generation at 0 °C and work-up at room temperature gave 6,7-diphenyl-4*H*-thieno[3,2-*c*]azepine **35** (59%) as an oil. (b) *With NMR monitoring.* The imidoyl chloride (13 mg) was dissolved in perdeuteriotetrahydrofuran ([$^2H_8$]THF) (0.3 $cm^3$) in an NMR tube equipped with a septum cap and cooled to −78 °C. Potassium *tert*-butoxide (10 mg) in [$^2H_8$]THF (0.2 $cm^3$) was added by syringe and the solutions were mixed by shaking. The reaction mixture was kept at −78 °C for 2 h and then allowed to warm to 0 °C over 45 min with $^1H$ NMR monitoring at 10 min intervals. Finally the mixture was kept at 0 °C overnight. The results are described in the Results and Discussion section.

(ix) (E)-α-(*Benzonitril*-N-*io*)-3-(2-*phenylvinyl*)-2-*thenylide* **36** gave the usual red colouration which faded over 3 h at 0 °C. The usual work-up gave a red oil (Found: *m*/*z* 301.0927. $C_{20}H_{15}NS$ requires 301.092 521) which decomposed on attempted purification by chromatography on both silica and alumina.

(x) (E)-α-(*Benzonitril*-N-*io*)-4-(2-*phenylvinyl*)-3-*thenylide* **38**, at room temperature gave after the usual work-up and preparative TLC on silica 5,6-diphenyl-3*H*-thieno[3,4-*c*]azepine **41** (65%) as an oil.

(3) *Thermal Isomerisation of* 1,7b-*Dihydro*-1a-*phenylcyclopropa*[c]*isoquinolines* **21**.—All reactions were carried out in dry solvents, under nitrogen and in the dark. The $^1H$ and $^{13}C$ NMR spectra and the mass spectra of the benzazepines **25**, **26**, **29** and **30** are given in Table 2, and their physical data in Table 6.

(i) Isoquinolines **21a** and **21b**. (a) The *exo* isomer **21a** (204 mg) in dry benzene (30 $cm^3$) was heated under reflux for 12 h. Evaporation of the solvent gave a brown oil which was purified by flash chromatography (silica, ethyl acetate–petroleum 1:9) to give 3,4-diphenyl-1*H*-2-benzazepine **25** (188 mg, 92%).

(b) The *endo* isomer **21b** (24 mg) in $C_6D_6$ (0.5 $cm^3$) was heated at 50 °C with monitoring by $^1H$ NMR until complete (20 days). Results: [time (h), % *endo*, % *exo*, % azepine] 0, 95, 5, 0; 74, 54, 31, 14; 100, 52, 31, 17; 125, 53, 31, 15; 293, 32, 25, 43; 340, 28, 20, 52; 388, 26, 17, 57; 483, 22, 13, 65; 526, 19, 12, 68; 617, 16, 12, 72; 777, 10, 7, 83; 1023, 3, 2, 95. Evaporation of the solvent and crystallisation of the residue gave 3,4-diphenyl-1H-2-benzazepine **25** (87%) identical with the product from (a) above.

(ii) *Isoquinolines* **21c** *and* **21d**. (a) A mixture of the *endo* and *exo* isomers (103 mg, *endo*:*exo* 2.15:1) in toluene (20 $cm^3$) was heated under reflux for 20 h. Evaporation of the solvent and crystallisation from petroleum (b.p. 60–80 °C) gave 4-methyl-3-phenyl-1*H*-2-benzazepine **26** (95 mg, 92%).

(b) Isomerisation in the presence of 2π electron trapping agents. Similar experiments were carried out with the addition of a five-fold excess of each of the following: diethyl fumarate, norbornene and butyl vinyl ether. The reactant **21c/d** was also heated under reflux in neat norbornene. No adduct was obtained in any of these reactions and work-up gave only benzazepine **26** in 75–90% yields.

(c) *endo* Isomer **21d** with NMR monitoring. The pure *endo* isomer **21d** (13 mg) in perdeuteriotoluene (0.5 $cm^3$) in an NMR tube was heated at 69 ± 0.1 °C for 135.5 h. The composition was measured periodically by $^1H$ NMR (80 MHz), and the results are shown in Fig. 1.

(d) *exo* Isomer **21c** with NMR monitoring. The results of a similar experiment using the pure *exo* isomer **21c** (10 mg) in perdeuteriotoluene (0.5 $cm^3$) are shown in Fig. 2.

(iii) *Isoquinolines* **21g** and **21h** as a mixture of *endo*/*exo*

isomers (182 mg) in benzene (50 $cm^3$) was heated under reflux for 61 h. Evaporation of the solvent and flash chromatography (silica, ethyl acetate–petroleum 1:9) gave 3-methyl-3,4-diphenyl-3*H*-2-benzazepine **29** (92 mg, 51%).

(iv) Isoquinoline **21f**. (a) The reactant (82 mg) in toluene was heated under reflux. Monitoring showed that an equilibrium between the reactant and a single product had been established after *ca.* 24 h. After 95 h, evaporation and flash chromatography (silica, ether–petroleum 1:19) of the residue give 3,5,5-triphenyl-5*H*-2-benzazepine **30** (22 mg, 27%) and recovered reactant (57%).

(b) A similar reaction carried out in *m*-xylene under reflux for 6 days gave recovered reactant (23%), 3,5,5-triphenyl-5*H*-2-benzazepine **30** (19%) and an unidentified isomeric product as an oil (Found: *m/z* 371.167 41. $C_{28}H_{21}N$ requires *m/z* 371.167 400) (28%); $\delta_H$ 5.45 (1 H, d, *J* 1.7), 6.27 (1 H, d, *J* 1.7), 6.89–7.39 (17 H, m), 7.77–7.80 (2 H, m).

(4) *The Crystal Structure of* 3-*Methyl*-3,5-*diphenyl*-5*H*-2-*benzazepine* **29**.—*Crystal data* $C_{23}H_{19}N$ $M_r$ = 309.4, monoclinic $P2_1/c$, $a$ = 21.449(6), $b$ = 7.468(3), $c$ = 22.351(6) Å, $\beta$ = 109.772(23)°, $U$ = 3369.1 $Å^3$, $Z$ = 8, $D_c$ = 1.22 g $cm^{-3}$, $\lambda$(Mo-K$\alpha$) = 0.710 69 Å, $\mu$ = 0.66 $cm^{-1}$, $F(000)$ = −1312, $T$ = 293 K. Final $R$ = 0.11 from 1422 observed reflections.

Poorly diffracting crystal of dimensions 0.3 × 0.4 × 0.12 mm; intensities of 4117 unique reflections measured out to $\theta$ = 22° using a Nonius CAD-4 diffractometer with graphite monochromator; 1422 reflections with $I > 2.5\sigma(I)$ were used in refinement; structure solved by direct methods (SHELX84, Sheldrick 1984). All non hydrogen atoms were refined anisotropically. No attempt was made to include hydrogen atoms in the refinement as only about 50% were located on the final Fourier difference maps. The maximum ratio of least squares fit to error in the final refinement cycle = 0.02. Maximum and minimum peak heights in the final difference map were 0.5 and 0.3 $eÅ^{-3}$, respectively and most of the higher peaks could indeed be assigned as hydrogen. A unit weighting scheme was applied. Fractional coordinates are given in Table 4. Thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.*

* For details of the CCDC deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1992, Issue 1.

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## References

1 Preliminary communication, K. R. Motion, I. R. Robertson and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 1984, 1531.
2 A. A. Reid, J. T. Sharp, H. R. Sood and P. B. Thorogood, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2543.
3 D. P. Munro and J. T. Sharp, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1718.
4 D. P. Munro and J. T. Sharp, *J. Chem. Soc., Perkin Trans. 1*, 1984, 849.
5 L. Garanti and G. Zecchi, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2092.
6 L. Garanti and G. Zecchi, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1195.
7 A. Padwa and S. Nahm, *J. Org. Chem.*, 1981, **46**, 1402.
8 I. R. Robertson and J. T. Sharp, *Tetrahedron*, 1984, **40**, 3113.
9 A. Padwa and A. Ku, *J. Am. Chem. Soc.*, 1978, **100**, 2181.
10 A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, 1976, **98**, 2006; 1977, **99**, 1514.
11 A. Padwa, A. Ku, A. Mazzu and S. I. Wetmore, *J. Am. Chem. Soc.*, 1976, **98**, 1048.
12 J. W. Emsley, J. Feeney and L. H. Sutcliffe, *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, Oxford, 1966, vol. 2.
13 J. A. Su, E. Siew, E. V. Brown and S. L. Smith, *Org. Magn. Reson.*, 1977, 122.
14 F. Balkau and M. L. Heffernan, *Aust. J. Chem.*, 1971, **24**, 2311.
15 I. R. Robertson and J. T. Sharp, *Tetrahedron*, 1984, **40**, 3095.
16 P. Caramella and K. N. Houk, *J. Am. Chem. Soc.*, 1976, **98**, 6397.
17 K. N. Houk and J. C. Evanseck, personal communication.
18 P. W. Groundwater, C. Struthers-Semple and J. T. Sharp, *J. Chem. Soc., Chem. Commun.*, 1987, 1367.
19 R. O. Gould and S. E. B. Gould, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1075.
20 R. O. Gould and M. D. Walkinshaw, *Cryst. Struct. Commun.*, 1981, **10**, 1139.
21 A. I. Meyer, J. Slade, R. K. Smith, E. D. Mihelich, F. M. Hershenson and C. D. Liang, *J. Org. Chem.*, 1979, **44**, 2247.
22 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

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