Cyclisation of Benzylamino-nitriles. Part 4.[1] Rearrangement with Cyclisation to a Benzyl or Phenethyl Substituent

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Methoxybenzylamino-acetonitriles with benzyl or phenethyl substituents attached to the nitrile α-carbon undergo spiro-cyclisation in concentrated sulphuric acid followed by rearrangement with cyclisation to the benzene ring of the substituent. The product is a tetrahydroisoquinoline or a 2-benzazepine depending on the substituent.

We have shown[1] that methoxybenzylamino-acetonitriles produce a range of products when treated with concentrated sulphuric acid, all consistent with an initial spiro-cyclisation. One observation which led us to propose this mechanism was the production of a 3-benzoyltetrahydroisoquinoline (2a) rather than the expected 3-benzylisoquinolin-4(3*H*)-one (3a) from the nitrile (1a) (Scheme 1). Here we describe further examples of this kind of rearrangement, and details of the original example.[2]

If the spiro-intermediate (4) is formed as described, only the *para*-methoxy substituent should be required to produce a rearrangement product. This was confirmed by cyclisation of four nitriles (1b—e) which all gave the expected products (2b—e) in moderate to good yield and a high state of purity. As in the case of the original dimethoxybenzoyl rearrangement product (2a), spectral data were unambiguous. The presence of the methoxybenzoyl moiety is clear from the ^{1}H n.m.r. spectra, with typical AA'XX' coupling in the case of the monomethoxy-compounds, and fragmentation with loss of this moiety provides the base peak in the mass spectra.

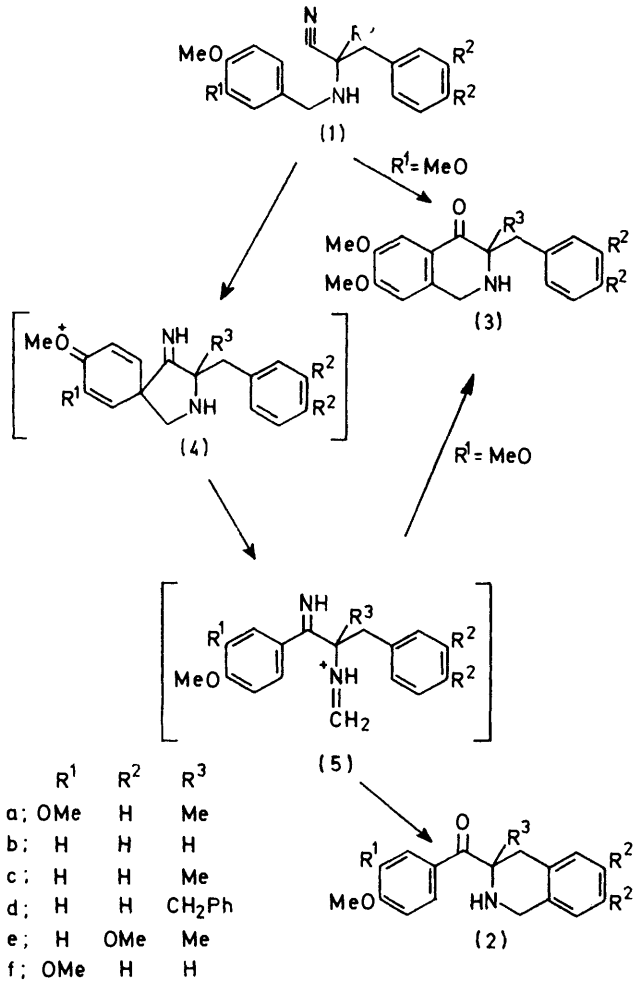
Where the amino-nitrile is derived from veratrylamine [*i.e.* (1; R^1 = OMe)] there is a possibility of straightforward *ortho*-cyclisation to give an isoquinolone (3). It is also possible to arrive at the same product after spiro-cyclisation, if the cyclisation to the imino- and methoxy-substituted ring is energetically comparable with cyclisation to the competing alternative. For an isoquinolone derived from an unlabelled C_α-achiral or C_α-racemic veratrylamine it is not possible to distinguish between the two mechanisms. The amino-nitrile (1f) produced equal amounts of the two products (2f) and (3f), the latter probably[1] by a combination of both mechanisms. Alteration of reaction conditions (temperature, concentration of acid) did not greatly affect the proportions of the two products. Separation was achieved by fractional crystallisation of the hydrobromide salts, other approaches having failed.

When the aminonitrile α-substituent was increased in

[1] Part 2, D. N. Harcourt, N. Taylor, and R. D. Waigh, *J.C.S. Perkin I*, 1978, 722; Part 3, *J. Chem. Research*, 1978, (*S*) 154; (*M*) 1954.

[2] D. N. Harcourt, N. Taylor, and R. D. Waigh, *J.C.S. Chem. Comm.*, 1972, 644.

length to phenethyl, as in structures (6a and b), the rearrangement process and concomitant cyclisation gave a 2-benzazepine [(7a and b), respectively] (Scheme 2). It



SCHEME 1

is interesting that a perfectly straightforward alternative carbocyclic reaction is possible, particularly with the amino-nitrile (6b), which has a second activated ring, to give a 1-tetralone (8) (Scheme 2). Similar cyclisations in concentrated sulphuric acid are known,[3] but in the present example only the 2-benzazepine was isolated, indicating the surprisingly low energy associated with the nitrogen-containing five-membered spirocyclic system. It is significant in this respect that where the secondary cyclisation was not aided by an activating group, as in (6a), the major product was a sulphonic acid (9), produced by rearrangement but without secondary cyclisation.

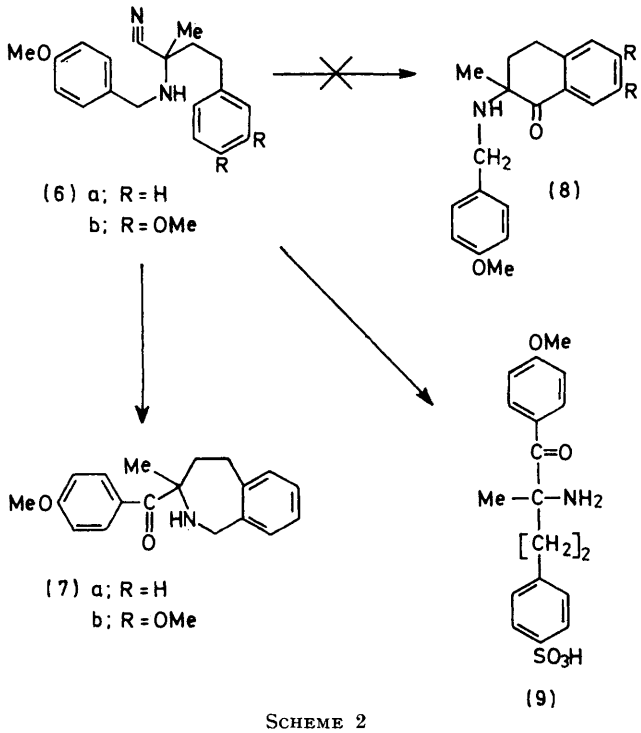
As with the other products reported here, the structures of the benzazepines (7a and b) are confirmed by n.m.r. and mass spectral data, elemental analysis, and i.r. data, while the sulphonic acid is assigned structure (9) from elemental analysis and i.r. and n.m.r. spectral data only, since it was not sufficiently volatile for mass spectrometry. In each case the most significant structural feature is the *p*-methoxybenzoyl moiety, which is clearly defined in both the ^{1}H n.m.r. and mass spectra (where feasible). The sulphonic acid (9) shows a second AA'XX' aromatic system in the ^{1}H n.m.r. spectrum, for the sulphonated ring.

Together, these results suggest that spiro-cyclisation is often more favourable than the alternative *ortho*-cyclisation, even where the latter leads to a six-membered ring. This tends to support the assertion[4] that ' reactions which involve spirocyclic intermediates are general. Such reactions may be expected whenever a compound containing a suitably substituted aromatic ring is subjected to reaction conditions which allow for aromatic participation.'

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus. I.r. spectra were recorded with a Unicam SP 200 or Perkin-Elmer 137 spectrophotometer for potassium bromide discs or liquid films. N.m.r. spectra were determined for solutions in deuteriochloroform using Perkin-Elmer R12 or Varian HA 100 instruments. Mass spectra were obtained using A.E.I. MS12 or MS902 spectrometers. Mass spectral ion formulae were obtained by computer matching of accurate masses.

Cyclisations were performed as previously.[5] Hydrochlorides were prepared by addition of ethereal hydrogen chloride to an organic solution of the base.



SCHEME 2

Preparation of Amino-nitriles.—Compounds (1a—f) and (6a and b) were prepared as previously described.[5] All

[3] C. K. Bradsher, E. D. Little, and D. J. Beavers, *J. Amer. Chem. Soc.*, 1956, **78**, 2153.

[4] M. S. Newman, *Accounts Chem. Res.*, 1972, **5**, 354.

[5] D. N. Harcourt and R. D. Waigh, *J. Chem. Soc.* (*C*), 1971, 967.

free bases showed weak $-C\equiv N$ i.r. absorption at *ca.* 2 240 cm^{-1}; secondary bases had >NH absorption at *ca.* 3 300 cm^{-1}. ^1H N.m.r. data are given in Table 1, analyses in Table 2. The preparation of the amino-nitrile (6b) was carried out using a boiling water-bath, instead of at room temperature.

TABLE 1

^1H N.m.r. data for benzylamino-nitriles (δ values, *J* in Hz)

(1a)	1.45 (3 H), 1.59 (1 H), 3.00 (2 H), 3.85 (8 H), 6.84 (3 H, m), 7.30 (5 H)
(1b)	1.61 (1 H),* 2.94 (2 H, d, *J* 6 Hz), 3.53—4.05 (3 H, m), 3.67 (3 H), 6.78 (2 H, d, *J* 8 Hz), 7.17 (d, 2 H, *J* 8 Hz), 7.22 (5 H)
(1c)	1.34 (3 H), 1.54 (1 H),* 2.89 (2 H), 3.64 (3 H), 3.76 (2 H), 6.70—6.79 (2 H, d, *J* 9 Hz), 7.08—7.30 (7 H, m)
(1d)	2.64 (1 H),* 2.93 (4 H), 3.66 (3 H), 3.77 (2 H), 6.76 (2 H, d, *J* 8 Hz), 7.12 (2 H, d, *J* 8 Hz), 7.24 (10 H)
(1e)	1.45 (3 H), 2.25 (1 H),* 2.90 (2 H), 3.80 (2 H), 3.84 (3 H), 3.87 (6 H), 6.75—7.35 (7 H, m)
(1f) †	3.4—3.7 (2 H, m), 3.86 (6 H), 4.05—4.70 (3 H, m) 6.9—7.9 (8 H, m)
(6a)	1.47 (3 H), 1.50—1.65br (1 H),* 1.70—2.15 (2 H, m), 2.62—2.95 (2 H, m), 3.72 (3 H,) 3.80 (2 H), 6.75—7.30 (9 H, m)
(6b)	1.42 (1 H),* 1.48 (3 H), 2.0 (2 H, m), 2.7 (2 H, m), 3.6—3.84 (11 H, partly resolved), 6.6—7.30 (7 H, m)

* Exchangeable. † Hydrochloride, in C_5D_5N.

TABLE 2

Benzylamino-nitriles

	Yield	M.p.	Found (%)			Required (%)		
	(%)	(*T*/°C)	C	H	N	C	H	N
(1a)	80	82	73.6	6.8	4.3	73.4	6.7	4.5
(1b)	56	166 [a]	67.2	6.1	9.2	67.4	6.3	9.3
(1c)	80	80	76.9	7.2	9.7	77.1	7.1	10.0
(1d)	65	153 [b]						
(1e)	75	*c*, *d*						
(1f)	33	175 [a]	64.8	6.2	8.7	65.0	6.3	8.4
(6a)	65	220 [a]	69.1	6.9	8.3	69.0	7.0	8.5
(6b)	65	*c*	71.4	7.5	8.1	71.2	7.3	7.9

[a] Hydrochloride, from ethanol–ether (m.p. with decomp.). [b] Crude hydrochloride, decomposed on warming in ethanol. [c] Semi-solid. [d] Thermolabile; hydrochloride unstable.

Isoquinolines.—3-(3,4-*Dimethoxybenzoyl*)-3-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (2a) crystallised from light petroleum (b.p. 60—80°); yield 33%, m.p. 138°, $\nu_{max.}$ 1 660 and 3 260 cm^{-1}, δ 1.55 (3 H), 1.95 (1 H, exchangeable), 2.65 and 3.55 (2 H, ABq, *J* 20 Hz), 3.9 (8 H), 6.85 (1 H, d, *J* 8 Hz), 6.8—7.25 (4 H, m), 7.8 (d, *J* 2 Hz), and 8.25 (dd, *J* 8, 2 Hz), *m/e* 311 (2%, $C_{19}H_{21}NO_3$, M^+), 165 (15, $C_9H_9O_3$), 146 (100, ($C_{10}H_{12}N$), and 144 (20) (Found: C, 73.6; H, 6.8; N, 4.3. $C_{19}H_{21}NO_3$ requires C, 73.6; H, 6.8; N, 4.5%).

3-(4-*Methoxybenzoyl*)-1,2,3,4-*tetrahydroisoquinoline* (2b) was obtained as a pale yellow solid after extraction with ether and recrystallisation from light petroleum (b.p. 80—100°); m.p. 110°, yield 42%, $\nu_{max.}$ 1 675 and 3 300 cm^{-1}, δ 2.23 (1 H), 2.6—3.1 (2 H, m), 3.83 (3 H), 4.12 (2 H), 4.53 (1 H, dd, *J* 6, 10 Hz), 6.90 (2 H, d, *J* 9 Hz), 6.90—7.25 (4 H, m), and 7.95 (2 H, d, *J* 9 Hz), *m/e* 267 (2.2%, $C_{17}H_{17}NO_2$, M^+), 135 (21.2, $C_8H_7O_2$), 132 (100, $C_9H_{10}N$), and 130 (21.3, C_9H_8N) (Found: C, 76.4; H, 6.5; N, 5.2. $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%).

3-(4-*Methoxybenzoyl*)-3-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (2c) was obtained as white needles from light petroleum (b.p. 60—80°) in 73% yield; m.p. 125°, $\nu_{max.}$ 1 660 and 3 400 cm^{-1}, δ 1.55 (3 H), 1.90 (1 H, exchangeable), 2.65 (1 H, d, *J* 16 Hz), 3.50 (1 H, d, *J* 16 Hz), 3.82 (3 H), 3.91 and 3.94 (2 H, outer lines of AB quartet not discernible), 6.85 (2 H, d, *J* 10 Hz), 6.90—7.20 (4 H, m), and 8.33 (2 H, d, *J* 10 Hz) (Found: C, 76.8; H, 6.7; N, 4.8. $C_{18}H_{19}NO_2$ requires C, 76.9; H, 6.8; N, 5.0%).

3-*Benzyl*-3-(4-*methoxybenzoyl*)-1,2,3,4-*tetrahydroisoquinoline* (2d) was obtained by extraction with chloroform, followed by crystallisation from aqueous ethanol, in 38% yield; m.p. 136°, $\nu_{max.}$ 1 665 and 3 300 cm^{-1}, δ 1.86 (1 H), 2.66 (1 H, d, *J* 16 Hz), 2.98—3.36 (2 H, ABq, *J* 13 Hz), 3.38 (1 H, d, *J* 16 Hz), 3.77 (3 H), 3.85 (2 H), 6.81 (2 H, d, *J* 9 Hz), 6.7—7.3 (9 H, m), and 8.37 (2 H, d, *J* 9 Hz), *m/e* 357 (0.8%, $C_{24}H_{23}NO_2$, M^+), 266 (39.8, $C_{17}H_{16}NO_2$), 222 (100, $C_{16}H_{16}N$), 135 (41.6, $C_8H_7O_2$), 131 (14.3, C_9H_9N), 130 (44.4, C_9H_8N), 91 (21.0, C_7H_7), and 77 (13.4, C_6H_5) (Found: C, 79.8; H, 6.6; N, 4.1. $C_{24}H_{23}NO_2$ requires C, 80.2; H, 6.7; N, 4.1%).

6,7-*Dimethoxy*-3-(4-*methoxybenzoyl*)-3-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (2e) was obtained as white needles in 30% yield; m.p. 116° [from light petroleum (b.p. 60—80°], $\nu_{max.}$ 3 400 cm^{-1}, δ 1.50 (3 H), 1.74 (1 H), 2.55 (1 H, d, *J* 16 Hz), 3.39 (1 H, d, *J* 16 Hz), 3.74 (2 H), 3.79 (9 H), 6.40 (1 H), 6.56 (1 H), 6.84 (2 H, d, *J* 8 Hz), and 8.37 (2 H, d, *J* 8 Hz), *m/e* 341 (<1%, M^+), 206 (100), and 77 (20) (Found: C, 70.5; H, 6.8; N, 4.3. $C_{20}H_{23}NO_4$ requires C, 70.4; H, 6.7; N, 4.1%).

3-(3,4-*Dimethoxybenzoyl*)-1,2,3,4-*tetrahydroisoquinoline* (2f) *and* 3-*Benzyl*-6,7-*dimethoxy*-1,2-*dihydroisoquinolin*-4(3H)-*one* (3f) were obtained as a 1 : 1 mixture (n.m.r.) (0.74 g, m.p. 84°) from cyclisation of the amino-nitrile hydrochloride (2g). Conversion into hydrobromide salts with gaseous hydrogen bromide in chloroform and precipitation with ether, followed by crystallisation from ethanol, gave crystals, m.p. 240°, which dissolved in water. Basification and extraction produced a gum which after trituration with ether and crystallisation from light petroleum (b.p. 80—100°) gave the *isoquinolinone* (3f), m.p. 120°, $\nu_{max.}$ 1 670 and 3 270 cm^{-1}, δ 2.04 (1 H), 2.65—3.85 (3 H, m), 3.94 (6 H), 4.06 (2 H), 6.65 (1 H), 7.36 (5 H), and 7.62 (1 H) (Found: M^+, 297.138 9. $C_{18}H_{19}NO_3$ requires *M*, 297.136 5), *m/e* 297 (8.3%) and 206 (100, $C_{11}H_{12}NO_3$).

Addition of ether to the mother liquor gave, over several days, a second crop of crystals, m.p. 228°, which after treatment as above and recrystallisation from light petroleum (b.p. 60—80°) gave the *tetrahydroisoquinoline* (2f), m.p. 103°, $\nu_{max.}$ 1 675 and 3 300 cm^{-1}, δ 2.83 (1 H), 2.80—3.10 (2 H, m), 3.93 (6 H), 4.19 (2 H), 4.62 (1 H, dd, *J* 6, 10 Hz), 6.91 (1 H, d, *J* 9 Hz), 7.12 (4 H, m), and 7.54—7.78 (2 H, m) (Found: M^+, 297.135 6. $C_{18}H_{19}NO_3$ requires *M*, 297.136 5), *m/e* 297 (6.2%), 165 (8.4, $C_9H_9O_3$), 132 (100, $C_9H_{10}N$), 131 (11.5, C_9H_9N), and 130 (29.4, C_9H_8N). A peak at *m/e* 206 (13.3%, $C_{11}H_{12}NO_3$) was presumed to arise from a small amount of isoquinolinone (3).

3-(4-*Methoxybenzoyl*)-3-*methyl*-2,3,4,5-*tetrahydro*-1H-2-*benzazepine* (7a).—This was obtained from the amino-nitrile (6a) in 5% yield as a *semi-solid* which would not crystallise, $\nu_{max.}$ 1 665 and 3 400 cm^{-1}, δ 1.10 (3 H), 1.20—1.30 (1 H, m), 1.50 (1 H, exchangeable), 2.3—3.3 (3 H, m), 3.48 (2 H), 3.60 (3 H), 6.69 (2 H, d, *J* 9 Hz), 6.70—7.0 (4 H, m), and 8.30 (2 H, d, *J* 9 Hz), *m/e* 295 (<1%, M^+), 160 (100), and 135 (20) (Found: C, 77.3; H, 7.2; N, 4.5. $C_{19}H_{21}NO_2$ requires C, 77.3; H, 7.1; N, 4.75%).

4-[3-*Amino*-3-(4-*methoxybenzoyl*)*butyl*]*benzenesulphonic Acid* (9).—This was obtained from the amino-nitrile (6a) by reacidification of the cyclisation medium to pH 6.5 with

hydrochloric acid after basification and extraction. After several days white crystals were filtered off and recrystallised from water to yield the *sulphonic acid* (9), 30%, m.p. 220° (decomp.), $\nu_{max.}$ 690, 850, 1 010, 1 170, 1 665, and 3 400 cm^{-1}, $\delta(D_2O–CF_3CO_2H)$ 2.0 (3 H), 2.30—3.00 (4 H, m), 3.94 (3 H), 7.0—7.2 (4 H, 2d overlapping, *J* 8.5 Hz), 7.75 (2 H, d, *J* 8.5 Hz), and 8.05 (2 H, d, *J* 8.5 Hz) (Found: C, 57.6; H, 5.85; N, 3.5; S, 8.8. $C_{18}H_{21}NO_5S,0.5H_2O$ requires C, 58.05; H, 6.0; N, 3.8; S, 8.6%).

7,8-*Dimethoxy*-3-(4-*methoxybenzoyl*)-3-*methyl*-2,3,4,5-*tetrahydro*-1H-2-*benzazepine* (7b).—This was obtained from the amino-nitrile (6b) in 50% yield as fine white needles [from light petroleum (b.p. 60—80°)], m.p. 116°, $\nu_{max.}$ 1 665 and 3 400 cm^{-1}, δ 1.42 (3 H), 1.50—1.61 (1 H, m and 1 H, exchangeable), 2.60—3.0 (3 H, m), 3.63 (2 H), 3.82 (3 H), 3.86 (6 H), 6.56 (1 H), 6.70 (1 H), 6.92 (2 H, d, *J* 9 Hz), and 8.28 (2 H, d, *J* 9 Hz) [irradiation of the multiplet (δ 2.60—3.0) reduced the signal at δ 1.50—1.61 to a singlet], *m/e* 355 (1% M^+, $C_{21}H_{25}NO_4$), 312 (6, $C_{19}H_{22}NO_3$), 220 (100, $C_{13}H_{18}NO_2$), 203 (16, $C_{13}H_{15}O_2$), and 135 (24) (Found: C, 71.4; H, 7.1; N, 3.7%. $C_{21}H_{25}NO_4$ requires C, 71.0; H, 7.4; N, 3.9%).

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