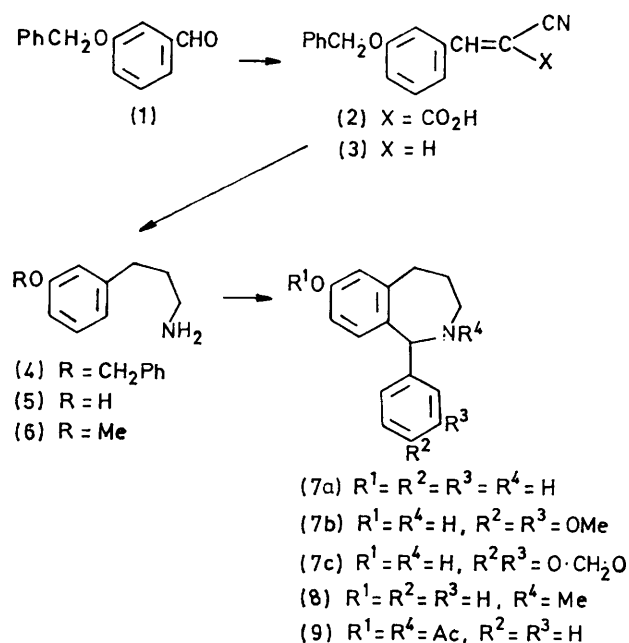


Studies on the Syntheses of Heterocyclic Compounds. Part DLXXVII.† Synthesis of 2,3,4,5-Tetrahydro-1*H*-benzazepine Derivatives by Phenolic Cyclisation

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Phenolic cyclisation of 3-(3-aminopropyl)phenol (5) with several carbonyl compounds gave 2,3,4,5-tetrahydro-1*H*-2-benzazepines (7).

PREVIOUSLY we have reported the novel synthesis of the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids by condensation of phenethylamine with various carbonyl compounds in the absence of an acidic catalyst. We referred



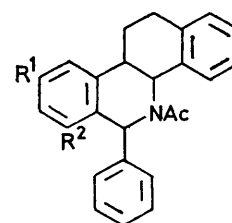
to this reaction as 'phenolic cyclisation' since the phenolic function played an important role in ring formation. Several isoquinoline derivatives, including 1,1-disubstituted compounds, have been synthesised by this method.¹⁻¹⁰ We now report a simple synthesis of 2,3,4,5-tetrahydro-1*H*-2-benzazepines (7) from 3-(3-aminopropyl)phenol (5).

The amino-phenol (5) was synthesised as follows. Condensation of 3-benzyloxybenzaldehyde (1) with cyanoacetic acid in benzene, followed by decarboxylation

of the resulting α -cyanocinnamic acid (2) in dimethylformamide gave 3-benzyloxycinnamionitrile (3). High pressure hydrogenation of this nitrile over Raney nickel afforded the phenylpropylamine (4), which was debenzylated with ethanolic hydrogen chloride.

Refluxing the amine (5) hydrochloride with benzaldehyde, veratraldehyde, and piperonal in butanol for 10 h afforded the corresponding 2,3,4,5-tetrahydro-1*H*-2-benzazepines (7a-c); however, in the corresponding reactions with the free amine (5) the products could not be isolated, although their presence was indicated by t.l.c. 3-Benzyloxy- (4) and 3-methoxyphenylpropylamine (6) hydrochlorides did not react with the carbonyl compounds in boiling butanol. Thus, the phenolic hydroxy group must play an important role in ring formation, indicating this reaction to be a type of phenolic cyclisation.

The structure of the benzazepine (7a) was determined by spectroscopic studies of some derivatives. Escheweiler-Clarke reaction of (7a) [δ 5.11 (1H, s, 1-H)] gave the *N*-methylated compound (8), *m/e* 253 (M^+), whose n.m.r. spectrum showed a one-proton singlet at δ 4.47. The *NO*-diacetyl derivative (9) [ν_{max} (CHCl₃) 1760 and 1642 cm⁻¹] revealed the acetoxy-resonance at δ 2.18, the



(10) $\text{R}^1 = \text{OAc}, \text{R}^2 = \text{H}$

(11) $\text{R}^1 = \text{H}, \text{R}^2 = \text{OAc}$

same value as for the 6-acetoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline derivative (10) but different from that of the 8-acetoxy-derivative (11) (δ 1.85; high-field

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shift due to the anisotropic effect of the 1-phenyl group).⁸

2,3,4,5-Tetrahydro-1H-2-benzazepines have been synthesised previously by a Bischler-Napieralski-type reaction, which is complicated by side reactions,¹¹ followed by reduction. Our synthetic route is preferable.

EXPERIMENTAL

N.m.r. spectra were taken with a JNM-MH-60 spectrometer, with tetramethylsilane as an internal standard. Mass spectra were measured with a Hitachi RMU-7 spectrometer.

3-Benzoyloxy- α -cyanocinnamic Acid (2).—A solution of 3-benzoyloxybenzaldehyde (1) (50 g), cyanoacetic acid (21 g), and ammonium acetate (3 g) in benzene (150 ml) was refluxed for 12 h, and cooled. The yellow solid was filtered off and gave the α -cyanocinnamic acid (2) (63.2 g, 96.1%) as needles, m.p. 190–191° (from ethanol) (Found: C, 72.85; H, 4.5; N, 4.85. $C_{17}H_{13}NO_3$ requires C, 73.1; H, 4.7; N, 5.0%), ν_{\max} (KBr) 2220 (CN) and 1700 cm^{-1} (CO).

3-Benzoyloxy- α -cyanocinnamitrile (3).—A solution of the α -cyanocinnamic acid (2) (196 g) in dimethylformamide (300 ml) was heated at 130° for 1 h and then refluxed for 2 h. To this solution was added water and the mixture was extracted with ether. The extract was washed with 5% sodium hydroxide solution and water, dried (K_2CO_3), and evaporated to leave a pale yellow oil, which was distilled *in vacuo* to give the cinnamitrile (3) (130 g, 80%) as an oil, b.p. 168–175° at 0.5 mmHg (Found: C, 81.7; H, 5.55; N, 6.15. $C_{16}H_{13}NO$ requires C, 81.7; H, 5.55; N, 5.95%), ν_{\max} (neat) 2220 cm^{-1} (CN), δ (CCl_4) 5.12 (2H, s, OCH_2), 5.50 and 5.92 (1H, d, J 12 Hz, $CH=CH-CN$, mixture of *cis* and *trans* cinnamitriles; the lower field portion was obscured by other resonances), 7.05–7.45 (5H, m, ArH and $CH=CH-CN$), and 7.55 (5H, s, ArH).

3-(3-Benzoyloxyphenyl)propylamine (4).—To a mixture of the nitrile (3) (55.3 g), Raney nickel (5 g), and ethanol (40 ml) was added ethanol (10 ml) saturated with ammonia gas, and the mixture was subjected to high pressure hydrogenation (100 kg cm^{-2}) at 100° for 4 h to give the amine (4) (4.22 g, 74.4%) as an oil, b.p. 165–170° at 0.5 mmHg, δ ($CDCl_3$) 1.35–1.77 (2H, m, $CH_2-CH_2-CH_2-NH_2$), 2.50 (4H, two t, J 6.75 Hz, $ArCH_2-CH_2-CH_2-NH_2$), 4.84 (2H, s, $PhCH_2-O$), 6.04–7.03 (4H, m, ArH), and 7.17 (5H, s, ArH). The hydrochloride formed needles, m.p. 168–170° (from ethanol-ether) (Found: C, 69.55; H, 7.25; N, 5.25. $C_{16}H_{19}NO, HCl$ requires C, 69.2; H, 7.25; N, 5.05%), ν_{\max} (KBr) 1600 cm^{-1} (benzene).

3-(3-Aminopropyl)phenol (5).—A solution of the amine (4) (37.3 g) in ethanol (100 ml) saturated with hydrogen chloride gas was refluxed for 6 h and the solvent was distilled off. The residue was dissolved in aqueous 10% sodium hydroxide and washed with ether. After acidification of the aqueous layer with 10% hydrochloric acid, this was basified with 28% ammonia and extracted with chloroform. The extract was evaporated to give the amine (5) (22 g), which was converted into the hydrochloride (24.5 g, 84.5%), obtained as needles, m.p. 105–107° (from propan-2-ol-chloroform) (Found: C, 57.4; H, 7.5; N, 7.4. $C_9H_{13}NO, HCl$ requires C, 57.6; H, 7.5; N, 7.45%), ν_{\max} (KBr) 1600 cm^{-1} (benzene),

δ (D_2O ; H_2O internal standard) –2.41 to –1.98 (4H, m, ArH), 1.83 (2H, t, J 7.88 Hz, CH_2-N), 2.19 (2H, t, J 7.50 Hz, $ArCH_2-CH_2$), and 2.68–3.18 (2H, m, $CH_2-CH_2-CH_2$), δ (free base in $CDCl_3$) 1.57–2.0 (2H, m, $CH_2-CH_2-CH_2$), 2.55 (2H, distorted t, J 7.95 Hz, $ArCH_2$), 2.72 (2H, t, J 7.5 Hz, CH_2NH_2), 3.98 (3H, s, NH_2 , OH, disappeared on D_2O exchange), and 6.40–7.20 (4H, m, ArH).

2,3,4,5-Tetrahydrophenyl-1H-2-benzazepin-7-ol (7a).—A mixture of the aminophenol (5) hydrochloride (5 g), benzaldehyde (10 g), and butanol (10 ml) was refluxed for 10 h and the solvent was evaporated off. The residue was washed with ether and then chromatographed on silicic acid (150 g) [benzene-chloroform-ethanol (5 : 5 : 1 v/v) as eluant] to give the benzazepine (7a) hydrochloride (3.3 g, 22.4%) as needles, m.p. 261° (decomp.) (from ethanol) (Found: C, 69.45; H, 6.55; N, 5.1. $C_{16}H_{17}NO, HCl$ requires C, 69.7; H, 6.6; N, 5.1%), δ ($CDCl_3$; for free amine) 1.4–1.9 (2H, $CH_2-CH_2-CH_2$), 2.5–3.3 (4H, $PhCH_2-CH_2-CH_2-N$), 5.11 (1H, s, $ArCH-N$), 6.2–6.55 (3H, m, ArH), and 7.43 (5H, s, ArH).

1-(3,4-Dimethoxyphenyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-7-ol (7b).—A mixture of the amine (5) hydrochloride (5 g), veratraldehyde (10 g), and butanol (10 ml) was treated as above to give the 1-(3,4-dimethoxyphenyl)-2-benzazepine (7b) hydrochloride (0.5 g, 5.6%) as needles, m.p. 261° (decomp.) (from propan-2-ol) (Found: C, 64.1; H, 6.5; N, 4.4. $C_{18}H_{21}NO_3, HCl$ requires C, 64.3; H, 6.3; N, 4.15%), δ ($CDCl_3$; for free amine) 1.4–1.9 (2H, $CH_2-CH_2-CH_2$), 2.5–3.3 (4H, $PhCH_2-CH_2-CH_2-N$), 3.66 (3H, s, OMe), 3.73 (3H, s, OMe), 4.97 (1H, s, $ArCHN$), 6.2–6.50 (3H, m, ArH), and 6.75–6.88 (3H, m, ArH).

2,3,4,5-Tetrahydro-1-(3,4-methylenedioxyphenyl)-1H-2-benzazepin-7-ol (7c).—A mixture of the amine (5) hydrochloride (5 g), piperanol (10 g), and butanol (10 ml) was treated as above to afford the 2-benzazepine (7c) hydrochloride (1.1 g, 12.9%) as needles, m.p. 265° (decomp.) (from propan-2-ol) (Found: C, 63.7; H, 5.65; N, 4.55. $C_{17}H_{17}NO_3, HCl$ requires C, 63.85; H, 5.35; N, 4.4%), δ ($CDCl_3$; for free amine) 1.4–1.9 (2H, $CH_2-CH_2-CH_2$), 2.5–3.3 (4H, $PhCH_2-CH_2-CH_2-N$), 4.96 (1H, s, $ArCHN$), 5.84 (2H, s, $O-CH_2-O$), 6.19–6.55 (3H, m, ArH), and 6.73 (6.77 (3H, m, ArH).

2,3,4,5-Tetrahydro-2-methyl-1-phenyl-1H-2-benzazepin-7-ol (8).—To a stirred solution of the benzazepine (7a) (2 g) and 37% formalin (7 ml) in methanol (100 ml) at room temperature, sodium borohydride (10 g) was added in portions during 0.5 h. After stirring for a further 1 h, the mixture was acidified with 10% hydrochloric acid and methanol was distilled off *in vacuo*. The residue was basified with 28% ammonia and extracted with chloroform, and the extract was dried ($MgSO_4$) and evaporated to leave the 2-methyl-2-benzazepine (8) as a pale yellow syrup, which was characterised as the hydrochloride (1.95 g, 91.1%) as needles, m.p. 244–246° (from ethanol) (Found: C, 70.4; H, 7.05; N, 5.1. $C_{17}H_{19}NO, HCl$ requires C, 70.45; H, 6.6; N, 4.85%), ν_{\max} (KBr) 1600 cm^{-1} (benzene), δ ($CDCl_3$; for free amine) 2.28 (3H, s, NMe), 4.47 (1H, s, $ArCHN$), 6.40–6.86 (3H, m, ArH), and 7.20 (5H, s, ArH).

7-Acetoxy-2-acetyl-2,3,4,5-tetrahydro-1-phenyl-1H-2-benzazepine (9).—A mixture of the benzazepine (7a) (260 mg) and acetic anhydride (2 ml) was refluxed for 2 h and then the excess of reagent was distilled off *in vacuo* to give the NO-diacetyl derivative (9) (347 mg, 98.9%) as needles, m.p. 163–164° (from benzene-petroleum) (Found: C, 74.5; H, 6.4; N, 4.35. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.55; N, 4.35%), ν_{\max} (KBr) 1760 (OAc) and 1642 cm^{-1} (Nac), δ

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(CDCl₃) 2.08 and 2.12 (3H, each s, NAc in two conformations) and 2.18 (3H, s, OAc).

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