Bredt's Rule. Part 6.[1] The Synthesis of 5-Phenyl-1-azabicyclo[3.3.1]nonan-2-one, a Bridgehead Amide

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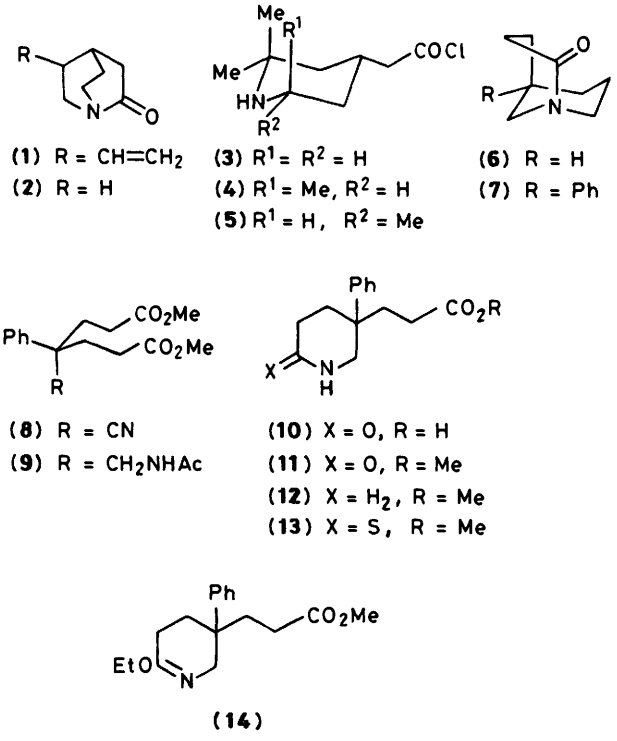
6-Oxo-3-phenylpiperidine-3-propanoic acid, prepared from dimethyl 4-cyano-4-phenylheptanedioate, has been reduced selectively to the corresponding amine and then cyclised thermally or *via* its acid chloride to 5-phenyl-1-azabicyclo[3.3.1]nonan-2-one.

The instability of bridgehead amides [*e.g.* (**1**)] arises from poor p–π–overlap and has long been recognised[2] as a manifestation of Bredt's rule.[3] This factor has also been held[2] to explain Koenigs' failure[4] to cyclise meroquinene to (**1**). However, more recently several *substituted* examples of the 1-azabicyclo-[2.2.2]octan-2-one ring system have been synthesised[5] from the amino-acid chlorides [*e.g.* (**3**), (**4**), and (**5**)] in good to excellent yields, although the parent molecule (**2**) has remained more elusive. At best, it has been isolated in trace amounts and in an impure state.[6,†] Bredt strain in the 1-azabicyclo[3.3.1]nonan-2-one system (**6**) will be less than in (**2**); nevertheless, the synthesis of this bridgehead amide by cyclisation of the appropriate amino acid or acid chloride has also proved to be difficult. After several failures, compound (**6**) was isolated[7] in low yield as the minor product of amino-acid pyrolysis: the main product was polymer. These differences cannot be attributed to Bredt strain, but we considered they might reflect the ease with which the molecules can attain the conformation of the transition state leading to ring closure. In an investigation of the conformation hypothesis we report here the synthesis of the 5-phenyl derivative (**7**) from the appropriate amino acid, 3-phenyl-piperidine-3-propanoic acid, in which it was expected that the acid side-chain would readily attain the axial conformation necessary for ring closure. In a preliminary report[8] of this work, we also established the boat–chair conformation of (**7**). More exact details of the geometry of the molecule were obtained later by *X*-ray crystallography.[9]

The cyano-diester (**8**) was reduced under acetylating conditions, to avoid side-reactions, and the product (**9**) was hydrolysed and cyclised by heat to the oxo piperidinepropanoic acid (**10**). Selective reduction of the amide function was achieved by esterification followed by Borch reduction[10] of the imino-ether (**14**). Alternatively, the reduction product (**12**) could be obtained by desulphurisation of the thio-amide (**13**), but in neither case could we isolate the amino-ester (**12**) in a pure state; the impurity appeared to be polymeric amide. Following hydrolysis of the crude amino-ester, cyclisation of the resulting amino acid to (**7**) was achieved either by heating *in vacuo* or by treating the corresponding acid chloride with triethylamine. In either case the yield was low and not significantly higher than that reported for (**6**). The inaccessibility of compounds (**2**) and (**6**) remains unexplained.



Experimental

6-Oxo-3-phenylpiperidine-3-propanoic Acid (**10**).—The cyano-diester (**8**)[11] (17.5 g) was shaken in acetic anhydride (35 ml) for 7 h at *ca.* 90—100 °C and 1 500 lb in^{-2} in the presence of Raney nickel (16 g) and anhydrous sodium acetate (4 g). After the addition of sufficient water and methanol, the catalyst was filtered off and the filtrate was concentrated to give a syrup. A small sample of the *diester* (**9**) solidified on trituration in water and crystallised from CCl_4, m.p. 110 °C (Found: C, 64.4; H, 7.3; N, 4.2. $C_{18}H_{25}NO_5$ requires C, 64.48; H, 7.46; N, 4.18%); $\nu_{max.}$(CCl_4) 1 740 and 1 680 cm^{-1}.

The crude diester was refluxed for 5 h with 6M HCl (120 ml). Some water (*ca.* 50 ml) was distilled off and the solution, at 0 °C, was neutralised to yield the amino acid (8.38 g) which cyclised on heating at 230 °C for 35 min. The *piperidone* (**10**) was extracted into alkali and reprecipitated with acid (7.47 g, 90%), m.p. 204 °C (from water) (Found: C, 67.9; H, 7.1; N, 5.75. $C_{14}H_{17}NO_3$ requires C, 68.02; H, 6.88; N, 5.67%). It afforded its *methyl ester* (**11**) by reaction with CH_2N_2, in near quantitative yield; $\nu_{max.}$(CCl_4) 1 740 and 1 673 cm^{-1}; m.p. 117—118 °C [from benzene–light petroleum (b.p. 40—60 °C)] (Found: C, 69.3; H, 7.5; N, 5.3. $C_{15}H_{19}NO_3$ requires C, 68.96; H, 7.28; N, 5.36%).

Methyl 3-Phenyl-6-thioxopiperidine-3-propionate (**13**).—The ester (**11**) (1.04 g), P_2S_5 (1.3 g), and K_2S (1.3 g) were refluxed in

† A Russian claim to have synthesised compound (**2**) (L. N. Yakhontov and M. W. Rubzov, *J. Gen. Chem. USSR*, 1957, **27**, 83) is probably mistaken; see ref. 6, p. 2266.

dry pyridine (40 ml) for 2 h. Water (3 ml) was then added and the mixture was refluxed for a further 2 h. The solvent was then removed under reduced pressure, water (40 ml) containing $NaHCO_3$ (2 g) was added, and the mixture was kept overnight. After work-up, a solution of the gummy product in benzene was washed with water till neutral and the solvent removed. The resulting red oil was chromatographed in chloroform on dry silica (30 g) and afforded the thio-amide (**13**) (0.99 g), $\nu_{max.}(CHCl_3)$ 1 735 and 1 540 cm^{-1}, which distilled as a yellow oil, b.p. 210—220 °C (bath)/0.1 mmHg (Found: C, 64.4; H, 7.3; N, 4.9. $C_{15}H_{19}NO_2S$ requires C, 64.89; H, 6.86; N, 5.05%).

When this product (84 mg), dissolved in dry benzene (5 ml), was heated to reflux with W-4 Raney nickel for 8 h, the colourless product (**12**) obtained by evaporation ($\nu_{max.}$ 1 735 cm^{-1}) was strongly basic but unstable. On keeping or on heating this ester, a 1 670 absorption band appeared and grew stronger and the substance became only partially soluble in acid. Purification *via* acid extraction did not yield a stable product.

5-Phenyl-1-azabicyclo[3.3.1]*nonan-2-one* (**7**).—(*a*) A solution of the amide ester (**11**) (0.55 g, 2.1 mmol) and triethyloxonium tetrafluoroborate (1.1 g, 5.8 mmol) in dry methylene dichloride (15 ml) was stirred at room temperature for 7 h and, after being kept overnight, the solvent was removed under reduced pressure and replaced by ethanol (30 ml). This solution was stirred at 0 °C and treated with $NaBH_4$ (0.7 g, 18 mmol) in portions, then stirred for a further 1 h at 0 °C and at room temperature for 4 h, and finally was flooded with water and extracted with ether. The resulting oil on work-up (**12**) showed acid solubility as well as an i.r. spectrum identical with that of the desulphurisation product and yielded an oily picrate. With time, it became partly insoluble in acid. The non-basic by-product [$\nu_{max.}(CCl_4)$ 1 742 and 1 675 cm^{-1}] was shown (g.l.c.) to differ from the amide ester (**11**).

Following abortive attempts to obtain a number of crystalline derivatives, the residue (0.35 g) was dissolved in 6M-HCl (12 ml) and the solution was boiled under reflux for 7 h then evaporated to dryness. The residue, in an excess of $SOCl_2$, was kept overnight, then taken to dryness under reduced pressure, and dry benzene was added and removed under reduced pressure to leave the crude acid chloride ($\nu_{max.}$ 1 800 cm^{-1}). This material and Et_3N (5 ml) in dry benzene (15 ml) were kept for 20 h at room temperature, filtered, and reconcentrated under reduced pressure to afford an oil (0.32 g) [$\nu_{max.}$ 1 670 and 1 630 cm^{-1} (CO)] which was chromatographed in $CHCl_3$ on dry silica (17 g) to yield the *bicyclic amide* (**7**) (45 mg) (10% overall) which sublimed at 130—160 °C/0.08 mmHg and gave needles m.p. 74 °C [from light petroleum (40—60 °C)]; *m/z* 215.1305 (M^+). $C_{14}H_{17}NO$ requires *M*, 215.1306; $\nu_{max.}(CCl_4)$ 1 693 cm^{-1} (Found: C, 78.0; H, 8.0; N, 6.35. $C_{14}H_{17}NO$ requires C, 78.14; H, 7.91; N, 6.51%). Consistent ^1H and ^{13}C n.m.r. data have already been published.[8]

A specimen which was crystallised from water had m.p. 85 °C but was shown to be identical with the above material (i.r. and mass spectrum fragmentation) and thereafter *all* samples, recrystallised from light petroleum or from water, had the higher m.p.

(*b*) The methyl ester (**12**), prepared as above from the amide (**11**) (1 g), distilled unchanged at 125—140 °C (bath)/0.1 mmHg. It was boiled under reflux with 6M-HCl (28 ml) for 7 h and the solution was left overnight, adjusted to pH 6, and evaporated to dryness. The colourless residue was extracted with methanol and the filtered extract was concentrated and distilled at 210—230 °C/0.1 mmHg to yield the amide (**7**) (150 mg) which crystallised with time and recrystallised from light petroleum (40—60 °C), m.p. 85—86 °C (0.138 g, 16.8%). The non-volatile residue showed $\nu_{max.}(CHCl_3)$ 3 100—2 500br, 1 720, and 1 670s cm^{-1}.

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