Polycyclic Fused Amidines. Part III.[1] An Unexpected Mode of Cyclisation of 2-Phenacylisoquinolinium Bromide[2]

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Treatment of 2-phenacylisoquinolinium bromide with ammonium acetate in acetic acid gave 5,10-dihydro-2-phenylimidazo[1,2-*b*]isoquinoline (4) by cyclisation at the 3-position of the isoquinoline ring. The mechanism of this reaction is discussed. On similar treatment 1-phenacylquinolinuim bromide gave 4,5-dihydro-2-phenylimidazo[1,2-*a*]quinoline (8).

NUCLEOPHILIC substitution of isoquinolines and their quaternary salts generally proceeds more readily at the 1- than at the 3-position.[3] Such a consideration led Kröhnke and Zecher [4] to suggest that the major product from the reaction between 2-phenacylisoquinolinium bromide (1) and ammonium acetate in acetic acid was the 2,3-dihydroimidazo[2,1-*a*]isoquinoline (3). It was felt that the intermediate enamine (2) would cyclise at the reactive 1-position, and this view was supported by the isolation of a small amount of 2-phenylimidazo-[2,1-*a*]isoquinoline from the reaction mixture. These authors assumed that the latter was formed by dehydrogenation during the reaction, although attempts to dehydrogenate the major product with lead tetra-acetate were unsuccessful. The analogous cyclisation of 1-phenacylquinolinium bromide (6) was thought to give the corresponding 1,2-dihydroimidazo[1,2-*a*]quinoline (7). Our interest in dihydroimidazo-fused systems [1,5] led us to repeat the cyclisations, and on the basis of n.m.r. spectra we have reformulated the major products as (4) and (8), respectively.

The ^{1}H n.m.r. spectrum of the product from the isoquinolinium salt (1) precludes the earlier formulation (3). As well as 10 aromatic protons, one of which is lost after bromination or deuterium exchange (in $CDCl_3$–D_2O), the compound possesses two distinct pairs of aliphatic protons as evidenced by triplets at δ 4.15 and 5.03. These signals are assigned to the protons on C-10 and C-5, respectively, in structure (4). These assignments were made by comparison of the chemical shifts of the methylene protons in (4) with those of 2-benzyl-4,5-diphenylimidazole (δ 4.14) and 1,2-dibenzyl-4,5-diphenylimidazole (δ 4.04 and 4.77).[6] On deuterium exchange in neutral CD_3OD, the signal at δ 4.15 is lost, and the other triplet collapses to a broad singlet. It seems reasonable that the potentially more acidic protons on C-10 should be exchanged in preference to those on C-5. The coupling between the protons on C-5 and C-10 was further demonstrated by spin-decoupling experiments. The size of the coupling constant (2.0 Hz) is consistent with homobenzylic coupling.[7]

Given the susceptibility of imidazoles to bromination,[8] the monobromo-derivative obtained on treatment of compound (4) with bromine must be reformulated as (5) rather than the previously suggested 2-bromo-derivative of (3). This conclusion explains the failure of attempts to dehydrobrominate the bromination product. Moreover it is also clear why the supposed 2,3-dihydro-compound (3) did not react with lead tetra-acetate.[4]

An obvious alternative formulation (12) for the product from 2-phenacylisoquinolinium bromide was eliminated by comparison with 5,6-dihydroimidazo-[2,1-*a*]isoquinoline (11). This compound was obtained from phenethyl isothiocyanate by reaction with triethyloxonium fluoroborate to give the 3,4-dihydroisoquinoline (10), which gave the known imidazo-compound (11) on treatment with aminoacetaldehyde dimethyl acetal.[9] The product (11) possesses two 2 H triplets in its ^{1}H n.m.r. spectrum at δ 3.05 and 4.10, with J 7.0 Hz, consistent with that expected from coupling between adjacent methylene groups.[10]

^{13}C N.m.r. data for compounds (4) and (11) provided further support for the structural assignments.

As isoquinolines and their quaternary salts are unlikely to undergo simple nucleophilic substitution at the 3-position in preference to the more reactive 1-position, the mechanism of this novel cyclisation is of interest. It is known that 1,2-dihydroisoquinolines are susceptible to nucleophilic substitution at the 3-position; [11] therefore it is suggested that the present reaction involves initial attack by acetate ion at the 1-position of either compound (1) or (2), followed by nucleophilic substitution at the 3-position of the resultant 1,2-dihydroisoquinoline (14). In this system such attack is aided by loss of acetate ion. A prototropic shift would then assist aromatisation of the imidazole ring.

The product from 1-phenacylquinolinium bromide (6)

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[1] Part II, R. F. Cookson and R. E. Rodway, *J.C.S. Perkin I*, 1975, 1854.

[2] Preliminary communication, R. F. Cookson, D. P. Nowotnik, and R. T. Parfitt, *Chem. Comm.*, 1974, 911.

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[4] F. Kröhnke and W. Zecher, *Chem. Ber.*, 1962, **95**, 1128.

[5] R. F. Cookson and R. E. Rodway, *J.C.S. Perkin I*, 1975, 1850.

[6] M. Weiss, *J. Amer. Chem. Soc.*, 1952, **74**, 5193.

[7] See for example A. M. Abd-Elfattah, S. M. Hussain, and M. I. Ali, *Tetrahedron*, 1974, **30**, 987. V. C. Kim, *Canad. J. Chem.*, 1969, **47**, 3259.

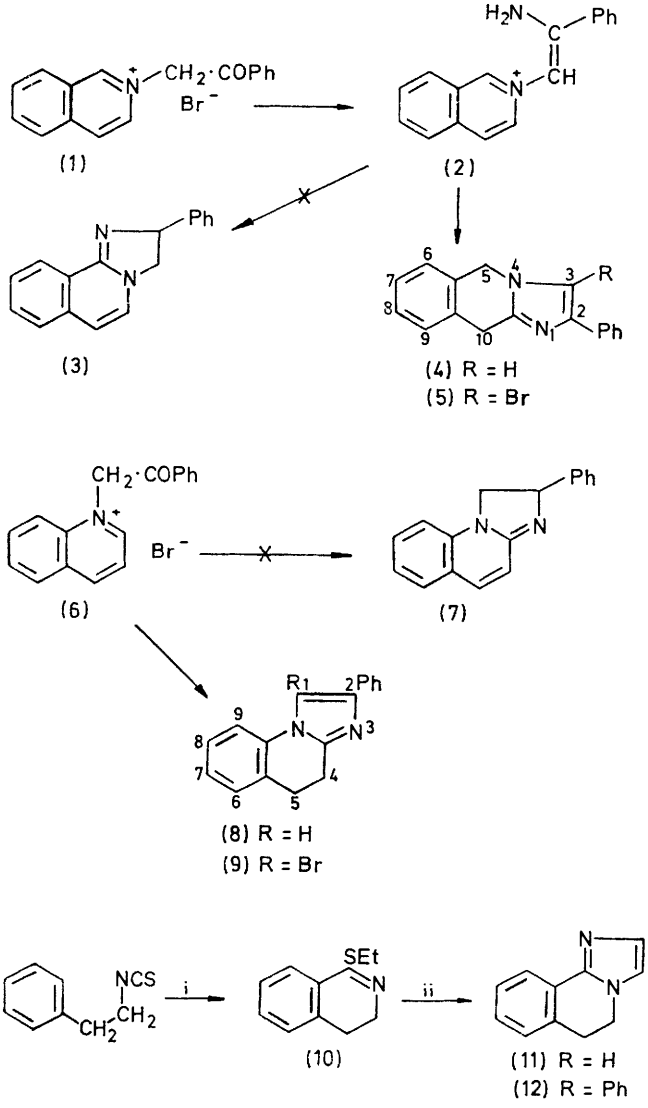
[8] K. Hofmann, 'Imidazole and its Derivatives,' Wiley–Interscience, New York, 1953, p. 111.

[9] M. W. Gittos, J. W. James, and J. P. Verge, U.S.P. 3,652,570/1972.

[10] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd edn., Pergamon New York, 1969, p. 288.

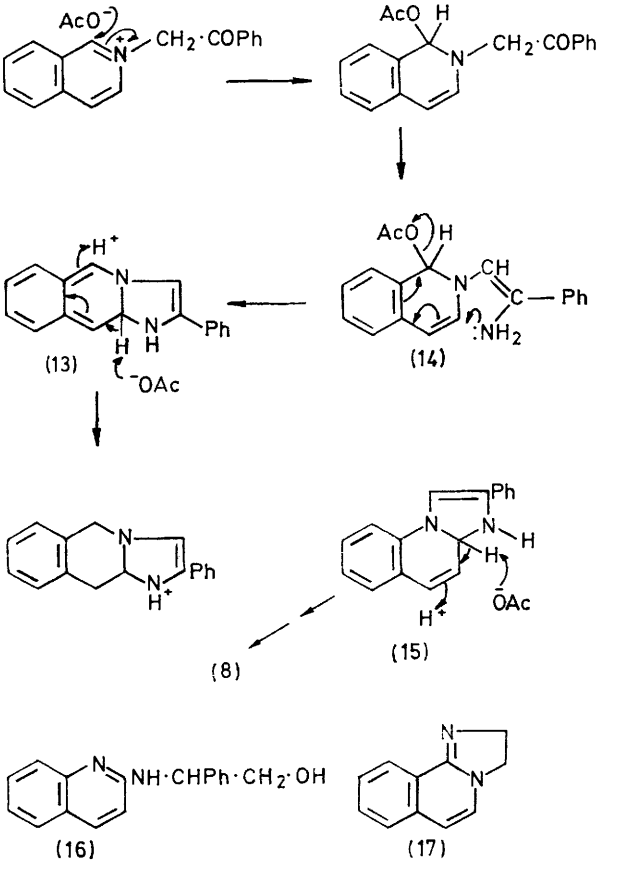
[11] S. F. Dyke, *Adv. Heterocyclic Chem.*, 1972, **14**, 279.

also possesses a ^1H n.m.r. spectrum which rules out the previously suggested structure. Integration data are compatible with the presence of 4 aliphatic and 10 aromatic protons, in contrast to the expected ratio of 3 : 11 in formula (7). Although in $CDCl_3$ the signal for the aliphatic protons appears as an apparent singlet at δ 3.0, in C_6D_6 the signal is resolved into a symmetrical AA'BB' multiplet. Treatment of the imidazoquinoline (8) with bromine in chloroform resulted in the mono-bromo-derivative (9), as evidenced by the loss of a 1 H singlet at δ 7.55. The reformulation of the product from 1-phenacylquinolinium bromide and ammonium acetate has recently been independently confirmed by Kröhnke and his colleagues.[12] Presumably the product



arises from prototropic shifts during partial aromatisation of the intermediate (15) in a manner reminiscent of the corresponding mechanism in the isoquinoline series (13).

Authentic 1,2-dihydro-2-phenylimidazo[1,2-*a*]quinoline (7) was synthesised by the reaction of 2-chloroquinoline with 2-amino-2-phenylethanol to give the hydroxyethylamino-compound (16), which was cyclised by treatment



with thionyl chloride. As expected, this compound is a stronger base (pK' 8.69; all pK' values were determined in 50% aqueous methyl Cellosolve) than the 5,6-dihydro-isomer (pK' 4.02). The latter is as weak a base as 5-phenylimidazo[1,2-*a*]quinoline (pK' 5.05). Similarly in the isoquinoline series the acidity constants of compounds (4) and (11) (pK' 5.04 and 5.55, respectively) are significantly lower than that found for 2,3-dihydroimidazo[2,1-*a*]isoquinoline (17) (pK' 9.74).

EXPERIMENTAL

M.p.s were determined with a Gallenkamp apparatus. ^1H N.m.r. spectra were recorded on a Perkin-Elmer R12B instrument operating at 60 MHz (tetramethysilane as internal standard). ^{13}C N.m.r. spectra were obtained with a JEOL-PFT-100PC spectrometer, operating at 25 MHz with wide-band proton-noise decoupling. Mass spectra were recorded with an A.E.I. MS9 instrument operating at 70 eV. pK' Values were determined with a Metrohm recording pH meter/titrator, model EA 436 for solutions in 50% aqueous methyl Cellosolve at 25 °C. Solutions were dried over magnesium sulphate monohydrate.

2-Benzyl-4,5-diphenylimidazole and 1,2-dibenzyl-4,5-diphenylimidazole were prepared [6] from 2-benzamido-2-phenylacetophenone. The synthesis of 2,3-dihydroimidazo-

[12] U. Habermalz, B. Reinshagen, and F. Kröhnke, *Chem. Ber.*, 1975, **108**, 984.

[2,1-*a*]isoquinoline by the reaction of isoquinoline with ethylenediamine monotosylate has been reported previously.[1]

5,10-*Dihydro*-2-*phenylimidazo*[1,2-b]*isoquinoline* (4).—(i) *Free base*. A solution of 2-phenacylisoquinolinium bromide (13.1 g, 0.04 mol) and ammonium acetate (28 g, 0.36 mol) in acetic acid (36 ml) was heated under reflux for 2 h, cooled, and poured with stirring into water (500 ml). The precipitate was filtered off and washed with water. The solid was dissolved in methanol (20 ml) and added dropwise to a stirred solution of sodium hydroxide (1.6 g) in water (100 ml). More water (300 ml) was added to the suspension, and the solid was filtered off, washed with water, and dried. Crystallisation from methanol afforded yellow crystals of the imidazoisoquinoline (2.1 g, 21%), m.p. 195—197° (lit.,[4] 195—197°) (Found: C, 82.8; H, 6.0; N, 11.4. Calc. for $C_{17}H_{14}N_2$: C, 82.9; H, 5.7; N, 11.4%); δ_H ($CDCl_3$) 4.15 (2 H, t, *J* 2.0 Hz, 10-H_2), 5.03 (2 H, t, *J* 2.0 Hz, 5-H_2), 7.15 (1 H, s, 3-H), and 7.2—7.9 (9 H, m, aromatic); δ_C 28.13, 47.05, 113.40, 124.88, 126.22, 126.89, 127.74, 128.66, 129.09, 129.52, 131.22, 132.51, 134.09, 143.74, and 144.41; *m/e* 247 (11), 246 (100), 245 (75), 244 (7.5), 115 (10), and 102 (7.5); p*K'* 5.04.

(ii) *Hydrobromide*. A solution of 2-phenacylisoquinolinium bromide (3.28 g, 0.01 mol) and ammonium acetate (7.0 g, 0.09 mol) in glacial acetic acid (9 ml) was heated under reflux for 2 h, cooled, treated with aqueous 50% hydrobromic acid (25 ml), and poured into water (300 ml). The suspension was stirred and filtered, and the solid was washed with water and dried. Crystallisation from methanol–ether gave the imidazoisoquinoline hydrobromide (2.4 g, 74%), m.p. 246° (decomp.) (lit.,[4] 256—257°) (Found: C, 62.2; H, 4.7; N, 8.6; Br^-, 24.6. Calc. for $C_{17}H_{14}N_2$,HBr: C, 62.4; H, 4.6; N, 8.6; Br^-, 24.5%); δ_H [$(CD_3)_2SO$] 4.45 (2 H, t, *J* 2 Hz, 10-H_2), 5.45 (2 H, t, *J* 2 Hz, 5-H_2), 7.3—8.0 (9 H, m, aromatic), and 8.3 (1 H, s, 3-H); δ_C ($CDCl_3$) 28.7, 47.4, 113.2, 124.6, 126.0, 126.6, 127.6, 128.4, 128.9, 129.4, 131.3, 134.1, 141.5, and 143.6.

3-*Bromo*-5,10-*dihydro*-2-*phenylimidazo*[1,2-b]*isoquinoline* (5).—Bromine (0.8 g, 0.002 mol) in chloroform (5 ml) was gradually added to a stirred solution of the imidazoisoquinoline (4) (1.22 g, 0.002 mol) in chloroform (5 ml). The solution was stirred for a further 5 min, and then evaporated to dryness. The residue was dissolved in methanol (15 ml) and added dropwise, with stirring to aqueous 0.1N-ammonia (200 ml). The precipitate was dissolved in chloroform (40 ml) and the solution was washed with water, dried, and evaporated to dryness. Crystallisation of the residue from methanol afforded the bromo-compound (0.6 g, 37%), m.p. 190—192° (lit.,[4] 203—205°) (Found: C, 62.6; H, 4.0; N, 8.6. Calc. for $C_{17}H_{13}BrN_2$: C, 62.8; H, 4.0; N, 8.6%); δ_H ($CDCl_3$) 4.25 (2 H, t, *J* 2 Hz, 10-H_2), 5.2 (2 H, t, *J* 2 Hz, 5-H_2), and 7.2—7.65 (9 H, m, aromatic).

4,5-*Dihydro*-2-*phenylimidazo*[1,2-a]*quinoline Hydrobromide* (8).—A solution of 1-phenacylquinolinium bromide (3.28 g, 0.01 mol) and ammonium acetate (5.0 g, 0.064 mol) in glacial acetic acid (8 ml) was heated under reflux for 1 h, treated hot with 50% hydrobromic acid (4 ml) in water (10 ml), and cooled to room temperature. The precipitate was filtered off, washed once with water (10 ml), and dried. Crystallisation of the solid from 50% aqueous ethanol gave the imidazoquinoline hydrobromide (1.4 g, 50.7%), m.p. 344—345° (lit.,[4] 355°) (Found: C, 62.4; H, 4.7; N, 8.4. Calc. for $C_{17}H_{13}N_2$,HBr: C, 62.4; H, 4.6; N, 8.6%), δ_H [$(CD_3)_2SO$] 3.3 (4 H, q, 4- and 5-H_2), 7.3—8.05 (9 H, m, aromatic), and 8.95 (1 H, s, 1-H); δ_H (free base in $CDCl_3$) 3.0 (4 H, s, 4- and 5-H_2), 7.0—7.9 (9 H, m, aromatic), and 7.55 (1 H, s, 1-H); δ_C (free base in $CDCl_3$) 22.58, 25.69, 108.82, 115.60, 125.00, 125.60, 125.98, 127.20, 127.32, 127.99, 128.78, 129.21, 133.67, and 145.94; *m/e* 247 (16), 246 (100), 245 (43), 244 (40), 206 (8), 143 (8), and 128 (12); p*K'* 4.02.

1-*Bromo*-4,5-*dihydro*-2-*phenylimidazo*[1,2-a]*quinoline Hydrobromide* (9).—Bromine (0.8 g, 0.002 mol) in chloroform (5 ml) was gradually added to a stirred solution of the imidazoquinoline (8) (1.1 g, 0.0018 mol) in chloroform (10 ml). The mixture was stirred for an additional ½ h, then evaporated to dryness. Crystallisation of the residue from methanol–ether provided the *bromo-compound* (0.6 g, 37%), m.p. 330—332° (Found: C, 50.1; H, 3.6; N, 6.8. $C_{17}H_{13}BrN_2$,HBr requires C, 50.3; H, 3.5; N, 6.9%), δ_H ($CDCl_3$) 2.9—3.8m (4 H, 4- and 5-H_2), and 7.2—8.4 (9 H, m, aromatic).

2-(2-*Hydroxy*-1-*phenylethylamino*)*quinoline* (16).—A stirred mixture of 2-chloroquinoline (1.63 g, 0.01 mol) and 2-amino-2-phenylethanol[13] (5.48 g, 0.04 mol) was heated at 180—200 °C (oil-bath temp.) for 1½ h. The cooled mixture was treated with ethanol (50 ml), and the suspension was heated to reflux. The resultant solution was poured into a stirred solution of sodium hydroxide (0.4 g, 0.01 mol) in water (150 ml). The suspension was stirred for 10 min, and the solid was filtered off, washed with water, and dried. Crystallisation from industrial methylated spirits afforded white crystals of the *aminoquinoline* (1.8 g, 68%), m.p. 190—191° (Found: C, 77.1; H, 5.9; N, 10.5. $C_{17}H_{16}N_2O$ requires C, 77.3; H, 6.1; N, 10.6%); δ_H [$(CD_3)_2SO$] 3.75 (2 H, t, *J* 5 Hz, CH_2), 4.8—5.6 (2 H, m, CH and NH), 6.9 (1 H, d, *J* 9 Hz, 3-H), 7.0—7.9 (9 H, m, aromatic), and 7.85 (1 H, d, *J* 9 Hz, 4-H).

1,2-*Dihydro*-2-*phenylimidazo*[1,2-a]*quinoline* (7).—A solution of 2-(2-hydroxy-1-phenylethylamino)quinoline (7.8 g, 0.03 mol) in thionyl chloride (80 ml) was heated under reflux for 1 h, cooled, and evaporated to dryness. The residue was treated with ethanol (100 ml), and the resultant solution was heated under reflux for 3 h, cooled, and poured into stirred 5N-sodium hydroxide (25 ml) in water (600 ml). The resultant oil was dissolved in chloroform (200 ml), and the solution was separated, washed with water, dried, and evaporated to dryness. Crystallisation of the residue from cyclohexane gave pale yellow crystals of the *imidazoquinoline* (4.2 g, 58%), m.p. 121—122° (Found: C, 82.8; H, 5.8; N, 11.1. $C_{17}H_{14}N_2$ requires C, 82.9; H, 5.7; N, 11.4%); δ_H ($CDCl_3$) 3.6—4.4 (2 H, oct, 1-H_2), 5.2—5.55 (1 H, q, 2-H), and 6.5—7.6 (11 H, m, aromatic); p*K'* 8.69.

5-*Phenylimidazo*[1,2-a]*quinoline Hydrogen Maleate*.—A solution of 2-chloro-4-phenylquinoline (29.1 g, 0.121 mol) and aminoacetaldehyde dimethyl acetal (25.5 g, 0.243 mol) in bis-(2-methoxyethyl)ether (150 ml) was heated under reflux for 17 h, then poured into water, and extracted with ether. The extract was washed, dried, and evaporated to dryness. The residue (21.1 g) was boiled with 5N-hydrochloric acid (300 ml) for 2 h, and basified. Extraction with chloroform gave an oil (14.6 g), which on treatment with ether left an insoluble solid (5.4 g) shown to be 4-phenyl-2-quinolone. The crude base was purified by preparation of its hydrochloride with ethereal hydrogen chloride, followed by basification of a filtered aqueous solution of the salt. Extraction with chloroform gave an oil (7.4 g), which was dissolved in ether and added slowly to ethereal maleic acid

[13] A. J. Castro, D. K. Brain, H. D. Fisher, and R. K. Fuller, *J. Org. Chem.*, 1954, **19**, 1444.

(3.88 g). The precipitate was filtered off and crystallised from acetone to give *5-phenylimidazo*[1,2-a]*quinolinium hydrogen maleate* (2.5 g, 6%), m.p. 164—166° (Found: C, 70.1; H, 4.5; N, 7.7. $C_{17}H_{12}N_2,C_4H_4O_4$ requires C, 70.0; H, 4.5; N, 7.8%).

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