298. *Amidines. Part XVI. A New Synthesis of* 1-*Alkyl- and* 1-*Aryl*-3 : 4-*dihydro*iso*quinolines.*

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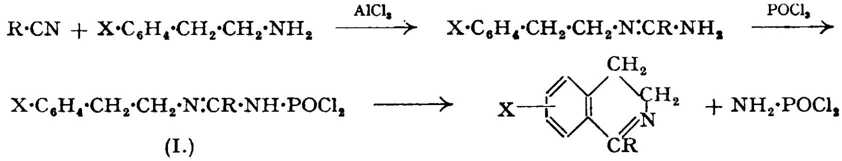
1-Alkyl- and 1-aryl-3 : 4-dihydro*iso*quinolines are produced by heating *N*-2-arylethyl derivatives of aliphatic and aromatic amidines and phosphoryl chloride in nitrobenzene solution.

The most important methods for the synthesis of *iso*quinolines start from 2-arylethylamines, which yield 3 : 4-dihydro*iso*quinolines on successive acylation and dehydration, and tetrahydro*iso*quinolines by ring closure of their alkylidene and arylidene derivatives. The first method, discovered by Bischler and Napieralski (*Ber.*, 1893, **26**, 1903) and generalised and improved by Pictet and his co-workers (*ibid.*, 1909, **42**, 1973, 1979), by Decker and Kropp (*ibid.*, p. 2075), by Decker, Kropp, Hoyer, and Becker (*Annalen*, 1913, **395**, 299), and by Whaley and Hartung (*J. Org. Chem.*, 1949, **14**, 650), has found considerable application in the synthesis of *iso*quinoline alkaloids. We find that a similar synthesis can be achieved by removing the elements of ammonia from the *N*-2-arylethyl derivatives of aliphatic and aromatic amidines, which are readily prepared from cyanides and 2-arylethylamines in presence of aluminium chloride (Part VII, *J.*, 1947, 1110) :



$$R{\cdot}CN + X{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2 \xrightarrow{AlCl_3} X{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}N{:}CR{\cdot}NH_2 \xrightarrow{POCl_3}$$

$$X{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}N{:}CR{\cdot}NH{\cdot}POCl_2 \longrightarrow$$

(I.)

An acid reagent and a high temperature are necessary for the reaction, and the best results are obtained with phosphoryl chloride (*ca.* 10 mols.) in boiling nitrobenzene. Derivatives of aminophosphonyl dichloride (I) are described in a subsequent communication. The following 3 : 4-dihydro*iso*quinolines were prepared from the corresponding amidines ; the yields recorded in parentheses are not necessarily the highest obtainable since a thorough examination of the experimental conditions was not made : 1-phenyl- (48%) ; 1-benzyl- (22%) ; 1-*p*-methylsulphonylphenyl- (80%) ; 1-*p*-methoxyphenyl- (31%) ; 6 : 7-dimethoxy-1-phenyl- (42%) ; 1-3′-pyridyl- (51%) ; and 1-amyl- (43·5%). The dihydro*iso*quinolines should not be distilled at atmospheric pressure since we have shown that they undergo disproportionation under these conditions (*J.*, 1949, 2587) ; they can be dehydrogenated or oxidised to *iso*quinolines by standard methods.

Experimental.*

Preparation of Amidines.—In the formation of the amidines the general procedure was that described for *N*-2-phenylethylbenzamidine, except that, in other cases, the melt was allowed to cool without further heating, the temperature in parentheses after the quantity of the reactants being the maximum attained. Usually a large volume of water was necessary to decompose the reaction mixture and dissolve the sparingly soluble amidine hydrochloride, which may be salted out as an oil.

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* See also B.P. 642,286/1948.

N-2-*Phenylethylbenzamidine.* Powdered anhydrous aluminium chloride (13·4 g., 1·0 mol.) was added during 20—30 seconds to a stirred mixture of phenyl cyanide (10·3 g., 1·0 mol.) and 2-phenylethylamine (12·1 g., 1·0 mol.). The temperature rose rapidly to 220° and then fell; the melt was finally heated to 165—175° for 30 minutes, then cooled to 130°, and poured into water (500 c.c.). The warm solution was filtered (Supercel) and the unchanged cyanide (0·2 g., 1·95%) extracted with ether. Aqueous sodium hydroxide was added to *ca.* pH 11 and the crude base isolated as a brown oil (18·9 g.) by extraction with benzene. The oil was dissolved in dry ether (300 c.c.) and treated with dry hydrogen chloride, and the sticky precipitate crystallised from methanol–ether to give thin, colourless prisms, m. p. 182—183°, of N-2-*phenylethylbenzamidinium chloride* (14·3 g., 55%) (Found : C, 68·65; H, 6·5; N, 11·0. $C_{15}H_{17}N_2Cl$ requires C, 69·1; H, 6·5; N, 10·75%). The *picrate* crystallised from ethanol in lemon-yellow prisms, m. p. 173—174° (Found : N, 15·6. $C_{21}H_{19}O_7N_5$ requires N, 15·45%), but the free amidine was only obtained as an oil.

The mother-liquors from the crystallisation of the hydrochloride were evaporated and the residue was treated with an aqueous solution of sodium picrate to give mixed picrates (5·9 g.), m. p. 100—120°, a portion (1·5 g.; m. p. 167—170°) remaining undissolved on extraction with warm ethanol (50 c.c.). Crystallisation from a large volume of ethanol gave yellow prisms, m. p. 170—171°, of NN′-*bis*-2-*phenylethylbenzamidinium picrate* (Found : C, 62·0; H, 4·9; N, 12·7. $C_{29}H_{27}O_7N_5$ requires C, 62·5; H, 4·85; N, 12·6%). Fractional crystallisation of the product obtained from the ethanol liquors yielded the picrate of the *N*-monosubstituted amidine.

In an experiment in which poor-quality aluminium chloride was inadvertently used the only product isolated was the *NN′*-disubstituted picrate (3·5%), together with unchanged cyanide (74%) and amine (60%).

The amidine hydrochloride was also prepared by the Pinner route in 47% yield; the low yield may be due to the incidental access of moisture, since benzo-2-phenylethylamide was isolated as a by-product.

α-*Phenyl*-N-2-*phenylethylacetamidine.* Benzyl cyanide (23·4 g.), 2-phenylethylamine (24·2 g.), and aluminium chloride (26·8 g.) (240°) afforded α-*phenyl*-N-2-*phenylethylacetamidinium chloride* (15·5 g., 28%) as colourless prisms, m. p. 173·5—174·5° (Found : N, 10·1. $C_{16}H_{19}N_2Cl$ requires N, 10·2%). The *picrate* crystallised from ethanol in needles, m. p. 113—114° (Found : N, 15·35, 15·4. $C_{22}H_{21}O_7N_5$ requires N, 15·0%).

In another experiment the melt was further heated at 185° for 45 minutes; the yield of hydrochloride was then 21%, and benzyl cyanide (13%), contaminated with a small amount of an unidentified substance, m. p. 82—84°, was recovered unchanged.

p-*Methylsulphonyl*-N-2-*phenylethylbenzamidine.* Powdered *p*-cyanophenyl methyl sulphone (18·1 g.), 2-phenylethylamine (12·1 g.), and aluminium chloride (13·4 g.) (190°) afforded unchanged cyanide (0·47 g., 2·6%) and crude amidine as a brown, viscous gum (28 g.). It was converted into the *hydrochloride* by trituration with 2N-hydrochloric acid (110 c.c.) and recrystallising the insoluble material from methanol–ether as colourless plates, m. p. 264—265° (uncorr.) (18·5 g., 55%) (Found : N, 8·4. $C_{16}H_{19}O_2N_2ClS$ requires N, 8·3%). The *picrate* crystallised from ethanol in elongated plates, m. p. 168—168·5° (Found : N, 13·2. $C_{22}H_{21}O_9N_5S$ requires N, 13·2%).

p-*Methoxy*-N-2-*phenylethylbenzamidine.* The reaction mixture from *p*-methoxyphenyl cyanide (13·3 g.), 2-phenylethylamine (12·1 g.), and aluminium chloride (13·4 g.) (140°) was cooled and triturated with water (25 c.c.). The insoluble solid consisted of unchanged cyanide (2·94 g., 22%), removed by repeated extraction with ether, and p-*methoxy*-N-2-*phenylethylbenzamidinium chloride* (15·26 g., 52·5%) which was obtained as needles, m. p. 223—223·5°, on crystallisation from methanol–ether (Found : C, 66·1; H, 6·4; N, 9·7. $C_{16}H_{19}ON_2Cl$ requires C, 66·1; H, 6·5; N, 9·6%).

N-2-(3 : 4-*Dimethoxyphenyl*)*ethylbenzamidine.* Phenyl cyanide (8·8 g.), homoveratrylamine (14·32 g.), and aluminium chloride (10·4 g.) (210°) (frothing then occurred, probably owing to demethylation, so the melt was cooled rapidly) afforded recovered cyanide (3·6 g., 41%) and crude amidine (7·55 g.) (isolated with chloroform). It was dissolved as far as possible in aqueous lactic acid and extracted with benzene to remove insoluble material, and the dry, benzene solution of the regenerated base treated with dry hydrogen chloride. The *hydrochloride* was recrystallised several times from methanol–ether as colourless plates, m. p. 200·5—201·5° (3·5 g., 13%) (Found : C, 63·5; H, 6·8; N, 8·9. $C_{17}H_{21}O_2N_2Cl$ requires C, 63·65; H, 6·55; N, 8·7%). The *picrate* crystallised from ethanol in orange-yellow needles, m. p. 165—166° (Found : N, 13·8. $C_{23}H_{23}O_9N_5$ requires N, 13·65%).

N-2-*Phenylethylnicotinamidine.* 3-Cyanopyridine (10·4 g.), 2-phenylethylamine (12·1 g.), and aluminium chloride (13·4 g.) (210°) gave the crude amidine as a gum (14·0 g.), which crystallised on treatment with ether. The brown solid (8·1 g., 36%; m. p. *ca.* 118—129°) afforded dense prisms of N-2-*phenylethylnicotinamidine*, m. p. 131—131·5°, on crystallisation first from benzene and then from ethyl acetate (Found : C, 74·8; H, 6·5; N, 18·8. $C_{14}H_{15}N_3$ requires C, 74·7; H, 6·7; N, 18·7%). With alcoholic picric acid it formed the *dipicrate*, rosettes of prisms (from ethanol), m. p. 174—175° (Found : C, 45·7; H, 3·1. $C_{26}H_{21}O_{14}N_9$ requires C, 45·7; H, 3·1%).

N-2-*Phenylethylhexanamidine* (with D. A. FIRTH). The reaction mixture from amyl cyanide (8 g.), 2-phenylethylamine (10 g.), and aluminium chloride (11 g.) (170°) was treated with ice-water (50 c.c.) and extracted with benzene. The insoluble oil which formed at the interface was dissolved in water (600 c.c.) and treated with aqueous benzenesulphonic acid [20 c.c. of 70% (w/v)]. The amidine *benzenesulphonate* which separated crystallised from water in white plates, m. p. 74—75° (6·9 g., 22%) (Found : N, 7·6. $C_{20}H_{28}O_3N_2S$ requires N, 7·45%).

*Preparation of Dihydro*isoquinolines.—3 : 4-*Dihydro*-1-*phenyl*isoquinoline. *N*-2-Phenylethylbenzamidinium chloride (7·8 g.) was refluxed with nitrobenzene (81 c.c.) and phosphoryl chloride (27 c.c.) for 2·5 hours. Hydrogen chloride was evolved and the internal temperature rose from about 150° to 170°.

The excess of phosphoryl chloride and nitrobenzene were removed by distillation at 1 mm. (bath, 100°), and the residue was heated with excess of aqueous sodium hydroxide. The insoluble oil was extracted with benzene and distilled to give 3 : 4-dihydro-1-phenyl*iso*quinoline, b. p. 145—155°/1—2 mm. (2·68 g., 43%) (the forerun containing nitrobenzene gave a further 4·8% as picrate). After dilution with light petroleum (2 volumes) it was filtered from a small amount of solid and then distilled at 139—142°/0·75 mm. (Found : C, 86·4; H, 6·2; N, 6·65. Calc. for $C_{15}H_{13}N$: C, 86·95; H, 6·3; N, 6·8%). The identity of the product was confirmed by comparison of the properties of the base (absorption spectrum and disproportionation on heating at atmospheric pressure), the picrate, m. p. 173—174° (Found : C, 57·8; H, 3·4; N, 12·9. Calc. for $C_{21}H_{16}O_7N_4$: C, 57·8; H, 3·7; N, 12·8%), and the hydrochloride, m. p. 236—238° (Found : C, 73·4; H, 6·0; N, 5·6. Calc. for $C_{15}H_{14}NCl$: C, 73·9; H, 5·75; N, 5·75%), with authentic specimens, prepared as described by Brodrick and Short (*loc. cit.*) (Whaley and Hartung, *loc. cit.*, record m. p. 178° for the picrate and 245—248° for the hydrochloride).

3 : 4-*Dihydro*-1-p-*methylsulphonylphenyl*iso*quinoline*. (i) When *p*-methylsulphonyl-*N*-2-phenylethylbenzamidinium chloride (6·8 g.) was treated similarly for 4 hours the product solidified on evaporation of the benzene extract. Crystallisation from methanol gave brownish prisms, m. p. 152—154° (4·02 g., 70%), and further crystallisation from ethyl acetate–light petroleum afforded the pure dihydro*iso*quinoline as almost colourless prismatic needles, m. p. 156·5° (Found : C, 67·5; H, 5·35; N, 5·0. $C_{16}H_{15}O_2NS$ requires C, 67·4; H, 5·3; N, 4·9%). The methanolic mother-liquor, with picric acid, gave the *picrate* (1·0 g., 9·7%; m. p. 186—189°), which crystallised from methanol–acetone in yellow plates and needles, m. p. 192—192·5° (Found : N, 10·85. $C_{22}H_{18}O_9N_4S$ requires N, 10·9%). The *hydrochloride* formed almost colourless prisms (from methanol–ether), m. p. 267—268°, sintering slightly at 262° (Found : N, 4·4. $C_{16}H_{16}O_2NClS$ requires N, 4·35%).

(ii) The amidine hydrochloride (2·3 g.), nitrobenzene (21 c.c.), and phosphoric oxide (4·6 g.) were refluxed for 1 hour. The solid was separated by decantation and cautiously decomposed with water. The dihydro*iso*quinoline, m. p. 156—157° (yield, 15%), and picrate, m. p. 193—194°, were identical with the products obtained in (i).

(iii) By use of xylene and phosphoryl chloride the dihydro*iso*quinoline was obtained in 31% yield.

3 : 4-*Dihydro*-1-p-*methoxyphenyl*iso*quinoline*. Reaction of *p*-methoxy-*N*-2-phenylethylbenzamidinium chloride (2·9 g.) under the usual conditions for 5 hours gave an oil which was converted into the *hydrochloride*, crystallising from methanol–ether in colourless prisms (0·95 g., 31%), containing solvent of crystallisation, m. p., if entered at *ca.* 80° and heated slowly, 199—200° (Found, on air-dried substance : C, 67·2; H, 5·8; N, 4·7. $C_{16}H_{16}ONCl,CH_3{\cdot}OH$ requires C, 66·8; H, 6·55; N, 4·6%). When the material was dried at 100° it melted at 212—214° (entering at 204°) (Found : C, 70·5; H, 5·4; N, 5·2. $C_{16}H_{16}ONCl$ requires C, 70·2; H, 5·85; N, 5·1%), but when kept it was readily converted into the *dihydrate* (Found : loss at 100°/1 mm., 11·7; on dried material, C, 70·3; H, 6·1. $C_{16}H_{16}ONCl,2H_2O$ requires H_2O, 11·6%). The *picrate* formed fine, hair-like needles (from methanol), m. p. 161·5° (Found : N, 12·3, 12·35. $C_{22}H_{18}O_8N_4$ requires N, 12·0%).

3 : 4-*Dihydro*-6 : 7-*dimethoxy*-1-*phenyl*iso*quinoline*. Prepared similarly from the amidine hydrochloride (2·7 g.) by reaction for 2 hours, this dihydro*iso*quinoline crystallised from benzene–light petroleum in almost colourless, prismatic needles, m. p. 119·5—120·5° (0·95 g., 42%) (Found : N, 5·5. Calc. for $C_{17}H_{17}O_2N$: N, 5·25%) (Harwood and Johnson, *J. Amer. Chem. Soc.*, 1934, **56**, 468, record m. p. 120·5—121·5°, and Sugasawa, *J. Pharm. Soc. Japan*, 1935, **55**, 224, m. p. 120—121°).

3 : 4-*Dihydro*-1-3′-*pyridyl*iso*quinoline*. The amidine (2·84 g.) was allowed to react for 3 hours and worked up as usual. Distillation of the benzene extract gave the *dihydro*iso*quinoline* as a colourless oil, b. p. 155—159°/0·8 mm. (1·33 g., 51%), which was redistilled (b. p. 155°/0·5 mm.) for analysis (Found : C, 80·7; H, 5·5; N, 13·5. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8; N, 13·5%). The *dipicrate* crystallised from ethanol–acetone in clusters of fine, prismatic needles, m. p. 196—197° (Found : C, 46·7; H, 2·7; N, 16·9. $C_{26}H_{18}O_{14}N_8$ requires C, 46·85; H, 2·7; N, 16·8%).

1-*Amyl*-3 : 4-*dihydro*iso*quinoline* (with D. A. FIRTH). *N*-2-Phenylethylhexanamidine (0·75 g.), prepared as an oil from the benzenesulphonate, was allowed to react by the general method for 2·5 hours. The crude 1-amyl-3 : 4-dihydro*iso*quinoline was obtained as a gum (0·3 g., 43·5%) which was converted into the *picrate*, needles (from ethanol), m. p. 112·5—113° (Found : N, 13·4. $C_{20}H_{22}O_7N_4$ requires N, 13·0%).

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