757. 8-*Phenylisoquinolines.*

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Methods for the preparation of 8-phenylisoquinolines have been explored. Three members of this class have been prepared.

In an attempt to fine new routes for the syntheses of the aporphine alkaloids, attention has been devoted to the preparation of isoquinolines substituted in the 8-position by a phenyl or substituted phenyl group. The interposition of a methylene group between the 1-position in the isoquinoline structure and the 2'-position in the phenyl group results in the formation of the aporphine ring system. Derivatives of 8-substituted isoquinoline are not easily accessible. Neither 8-phenylisoquinoline nor any of its substituted derivatives have been previously described.

Nitration of 7-methoxyisoquinoline by Kulka's method [1] gave 7-methoxy-8-nitroisoquinoline, which on reduction with Albert and Linnell's stannous chloride reagent [2] gave 8-amino-7-methoxyisoquinoline in 80% yield. Catalytic hydrogenation of the nitro-compound over palladium–charcoal gave the same base in almost quantitative yield. Successive acetylation and nitrosation gave 7-methoxy-8-nitrosoacetamidoisoquinoline, which decomposed in benzene solution to give 7-methoxy-8-phenylisoquinoline together with a little biphenyl.

5-Aminoisoquinoline was converted into 5-chloroisoquinoline and 5-chloro-8-nitroisoquinoline by Manske and Kulka's method.[3] Catalytic reduction of the latter gave 8-amino-5-chloroisoquinoline in quantitative yield. For larger batches it was more convenient to use Albert and Linnell's reagent,[2] which gave the base in 90% yield. Successive acetylation and nitrosation gave 5-chloro-8-nitrosoacetamidoisoquinoline, which decomposed in benzene solution to give 5-chloro-8-phenylisoquinoline.

The application of Mosby's method [4] of dehalogenation of aromatic compounds with ethanolic hydrazine hydrate in the presence of a palladium–charcoal catalyst to 5-chloro-8-nitroisoquinoline resulted in the smooth removal of chlorine with simultaneous reduction of the nitro-group to give 8-aminoisoquinoline in 81% yield. In similar manner, 8-amino-5-chloroisoquinoline was dehalogenated to 8-aminoisoquinoline in 98% yield. This method is superior to that of Osborn, Schofield, and Short,[5] who prepared 8-aminoisoquinoline from 5-chloro-8-nitroisoquinoline by hydrogenation over palladium–calcium carbonate in the presence of ammonium acetate. The latter method in our hands generally gave good yields on the small scale, but when it was applied to larger batches the results were not reproducible. Successive acetylation and nitrosation of 8-aminoisoquinoline gave 8-nitrosoacetamidoisoquinoline, which decomposed in benzene solution to give 8-phenylisoquinoline in low yield. 8-Phenylisoquinoline was also obtained in 85% yield by dehalogenation of 5-chloro-8-phenylisoquinoline with hydrazine hydrate in the presence of palladium–charcoal.

Condensation of *o*-phenylbenzaldehyde with aminoacetal gave *o*-phenylbenzylideneaminoacetal, but attempts to effect cyclisation to 8-phenylisoquinoline failed. Benzylideneaminoacetals substituted in the *ortho*-position are known to give poor results in the Pomeranz–Fritsch reaction.[6]

Experimental

M. p.s are uncorrected. For chromatography activated alumina (type "H," 100—200 mesh; Peter Spence and Sons Ltd.) was used. The light petroleum used had b. p. 40—60°.

8-*Amino-7-methoxyisoquinoline.*—(*a*) A solution of 7-methoxy-8-nitroisoquinoline [1] (4·1 g.)

[1] Kulka, *J. Amer. Chem. Soc.*, 1953, **75**, 3597.
[2] Albert and Linnell, *J.*, 1936, 1617.
[3] Manske and Kulka, *Canad. J. Res.*, 1949, **27***B*, 163.
[4] Mosby, *Chem. and Ind.*, 1959, 1348.
[5] Osborn, Schofield, and Short, *J.*, 1956, 4191.
[6] Gensler, *Org. Reactions*, 1951, **6**, 191.

in a minimum of glacial acetic acid was added slowly, with stirring and cooling, to the anhydrous stannous chloride reagent (160 ml.), prepared as described by Albert and Linnell.[2] The solution was left overnight at room temperature. The white complex was filtered off and washed with a little glacial acetic acid. The precipitate was suspended in a little ice-cold water and decomposed with 30% aqueous sodium hydroxide. The amine was collected, washed with cold water, and dried (2·8 g.). Crystallisation from benzene (charcoal) gave yellow needles, m. p. 155—156° (Kulka [1] reported m. p. 156—157°). (*b*) The nitro-compound (2·04 g.) in acetone (50 ml.) was hydrogenated at room temperature and pressure in the presence of palladium–charcoal (5%; 0·4 g.). On filtration, the yellow solution of the amine exhibited a green fluorescence. Evaporation gave the amine (1·74 g.), which separated from benzene as yellow needles, m. p. 155—156°. The base (1·74 g.) was acetylated with acetic anhydride (8 ml.) and a drop of perchloric acid by boiling for 5 min. and then at room temperature for 2 hr. The mixture was then poured on crushed ice and neutralised. Crystallisation of the solid (2·0 g.) from acetone (charcoal) gave 8-*acetamido*-7-*methoxyisoquinoline* as prisms, m. p. 193—194° (Found: C, 66·4; H, 5·7. $C_{12}H_{12}N_2O_2$ requires C, 66·6; H, 5·6%).

7-*Methoxy*-8-*phenylisoquinoline*.—To a well stirred mixture of 8-acetamido-7-methoxyisoquinoline (4·0 g.), fused potassium acetate (12·0 g.), glacial acetic acid (16 ml.), acetic anhydride (12 ml.), and phosphoric oxide (0·4 g.), was added dropwise a solution of nitrosyl chloride in acetic anhydride (13 ml.; 25%) at 0—5°. The thin yellow paste was stirred for another 20 min. and then poured on crushed ice containing aqueous alkali (32·0 g. of sodium hydroxide). On vigorous stirring a yellow oil separated, which solidified. It was quickly filtered off, washed with ice-cold water, and dried *in vacuo* (KOH) below 5° (4·0 g.). Crystallisation of a small portion from cold dry ether (charcoal) gave 7-*methoxy*-8-*nitrosoacetamidoisoquinoline* as pale yellow microneedles, m. p. 82—83° (decomp.) (Found: C, 55·3; H, 5·0. $C_{12}H_{11}N_3O_3,H_2O$ requires C, 54·7; H, 4·9%). The nitroso-compound decomposed when kept at room temperature for a few days. A solution of the nitroso-compound (3·5 g.) in "AnalaR" benzene (100 ml.) was boiled for 20 hr. with exclusion of moisture. Nitrogen was evolved and the solution became dark red; removal of benzene gave a dark-red residue, which was distilled with steam. A very small quantity of biphenyl was collected, m. p. and mixed m. p. 68—69° after crystallisation from benzene. The steam-involatile residue was collected, dried, and extracted with chloroform. The dried (Na_2SO_4) extract, after removal of excess of the solvent, was passed down a column of alumina, which was eluted with light petroleum–benzene (1 : 1). 7-*Methoxy*-8-*phenylisoquinoline* (0·8 g.) was obtained, which crystallised from the same solvent as needles, m. p. 134—135° (Found: C, 81·5; H, 5·8; N, 5·8. $C_{16}H_{13}NO$ requires C, 81·7; H, 5·5; N, 5·9%). Its solution in dilute mineral acids or organic solvents exhibited a green fluorescence. Its *picrate* separated from benzene as bright yellow microneedles, m. p. 221·5—223·5° (Found: C, 56·9; H, 3·5. $C_{16}H_{13}NO,C_6H_3N_3O_7$ requires C, 56·9; H, 3·45%).

8-*Amino*-5-*chloroisoquinoline*.—(*a*) Freshly prepared palladium–charcoal (5%; 0·2 g.) in acetone was shaken with hydrogen for ½ hr. 5-Chloro-8-nitroisoquinoline [3] (1·0 g.) in acetone (50 ml.) was added, and shaking was continued until the theoretical quantity of hydrogen had been absorbed (about 1 hr.). Removal of solvent from the filtered solution left 8-amino-5-chloroisoquinoline in almost quantitative yield. Crystallisation from benzene (charcoal) gave pale yellow needles, m. p. 201—202° (decomp.). Manske and Kulka [3] recorded m. p. 201—202°. (*b*) A solution of 5-chloro-8-nitroisoquinoline (21·0 g.) in the minimum of glacial acetic acid was added with stirring to the anhydrous stannous chloride reagent (600 ml.).[2] The yellow solution, on being kept overnight, deposited the stannic chloride complex, which was filtered off, washed with a little glacial acetic acid, suspended in ice-cold water, and decomposed with aqueous sodium hydroxide. The free amine (16·0 g.) was collected, washed with cold water, and dried. Crystallisation from benzene (charcoal) gave pale yellow needles, m. p. 201—202° (decomp.). 8-Amino-5-chloroisoquinoline exhibits an intense blue fluorescence when dissolved in organic solvents or dilute mineral acids. The *monopicrate* separated from ethanol as bright red microneedles, m. p. 234—235° (decomp.) (Found: N, 17·3. $C_9H_7ClN_2,C_6H_3N_3O_7$ requires N, 17·2%). Acetylation of the base (9·0 g.) with boiling acetic anhydride (50 ml.) gave 8-*acetamido*-5-*chloroisoquinoline* (9·5 g.), which crystallised from benzene (charcoal) as microneedles, m. p. 209—210° (Found: C, 59·9; H, 3·8; Cl, 16·2. $C_{11}H_9ClN_2O$ requires C, 59·8; H, 4·0; Cl, 16·3%).

5-*Chloro*-8-*phenylisoquinoline*.—A 25% solution of nitrosyl chloride in acetic anhydride 25·6 ml.) was added dropwise to a well-stirred mixture of 8-acetamido-5-chloroisoquinoline

(8·0 g.), fused potassium acetate (24·0 g.), glacial acetic acid (32 ml.), acetic anhydride (24 ml.), and phosphoric oxide (0·8 g.), at 0—5°. Stirring was continued for another 20 min. and then the yellow mixture was poured on crushed ice containing aqueous sodium hydroxide (40%; 160 ml.). On vigorous stirring a yellow solid separated, which was quickly filtered off, washed with ice-cold water, and dried (KOH) *in vacuo* at 0—5° for 24 hr., to give the crude product (8·0 g.). A small portion, on rapid crystallisation from cold dry ether (charcoal), gave 5-*chloro*-8-*nitrosoacetamidoisoquinoline* in light yellow microneedles, which decomposed at 78—79° (Found: C, 53·3; H, 3·5. $C_{11}H_8ClN_3O_2$ requires C, 52·9; H, 3·2%). A solution of the crude nitroso-compound (7·5 g.) in dry "AnalaR" benzene (200 ml.) was boiled for 24 hr. under moisture-proof conditions. The benzene was then removed and the residue was taken up in the minimum of chloroform and passed down a column of activated alumina, which was eluted with light petroleum. 5-*Chloro*-8-*phenylisoquinoline* (2·51 g.) was obtained in long silky needles. After one crystallisation from light petroleum it melted at 103—104° (Found: C, 75·4; H, 4·2; N, 6·1. $C_{15}H_{10}ClN$ requires C, 75·1; H, 4·1; N, 5·8%). When the column was eluted further with benzene–chloroform and finally with ethanol, some unchanged 8-acetamido-5-chloroisoquinoline was obtained. The *picrate* of 5-chloro-8-phenylisoquinoline separated from benzene as yellow needles, m. p. 193—194° with previous shrinking (Found: N, 11·8. $C_{15}H_{10}ClN,C_6H_3N_3O_7$ requires N, 11·9%). Solutions of 5-chloro-8-phenylisoquinoline in organic solvents or in dilute hydrochloric acid exhibit a green fluorescence.

8-*Aminoisoquinoline*.—(*a*) *From* 5-*chloro*-8-*nitroisoquinoline*. 5-Chloro-8-nitroisoquinoline (3·0 g.) was dissolved in warm ethanol (300 ml.) and 5% palladium–charcoal (1 g.) was added, followed by dropwise addition of hydrazine hydrate (99—100%; 24 ml.). A rapid evolution of gas occurred with each addition. A gentle reflux was maintained throughout the operation and then the mixture was boiled overnight. The catalyst was filtered off and washed with a little ethanol. The residue obtained after removal of the solvent from the combined filtrate and washings was taken up in a little water, made alkaline by the addition of a few drops of ammonia, and exhaustively extracted with chloroform. The chloroform solution (charcoal) was dried (Na_2SO_4) and the solvent was removed. The residue (1·67 g.) was precipitated from chloroform solution by addition of light petroleum. 8-Aminoisoquinoline was obtained as pale yellow microneedles, m. p. 173—174° with previous shrinking at 171°. (Robinson [7] recorded m. p. 174°.) 8-Aminoisoquinoline gave a *monopicrate*, which separated from benzene as bright yellow microneedles, m. p. 231—232° (decomp.), with previous darkening and shrinking (Found: C, 47·8; H, 2·9; N, 18·9. $C_9H_8N_2,C_6H_3N_3O_7$ requires C, 48·2; H, 2·9; N, 18·7%).

(*b*) *From* 8-*amino*-5-*chloroisoquinoline*. The above procedure was repeated with 8-amino-5-chloroisoquinoline. Boiling for 15 min. was sufficient to dehalogenate the compound. 8-Aminoisoquinoline, m. p. 171°, was obtained in 93% yield. Acetylation of the base with acetic anhydride gave, in almost quantitative yield, 8-*acetamidoisoquinoline* as needles, m. p. 168—169° (with previous shrinking), from acetone (charcoal) (Found: C, 70·2; H, 5·4; N, 15·3. $C_{11}H_{10}N_2O$ requires C, 70·9; H, 5·4; N, 15·1%).

8-*Phenylisoquinoline*.—(*a*) To a mixture of 5-chloro-8-phenylisoquinoline (200 mg.), ethanol (40 ml.), and 5% palladium–charcoal (70 mg.) under a gentle reflux, was added hydrazine hydrate (99—100%; 2 ml.). There was an immediate evolution of gas. Heating was continued for 2 hr. The catalyst was then filtered off and washed with a little ethanol. The solvent was removed under reduced pressure from the combined filtrate and washing. The residue was taken up in a little water, made alkaline with a few drops of ammonia, and then extracted with ether. Removal of solvent from the dried (Na_2SO_4) ether solution left a very pale yellow viscous oil (146 mg.). Treatment with charcoal in ether solution removed the colour. 8-*Phenylisoquinoline* was obtained as a viscous oil (Found: C, 87·5; H, 5·6; N, 6·9. $C_{15}H_{11}N$ requires C, 87·8; H, 5·4; N, 6·8%). The *picrate* crystallised from benzene as yellow prismatic needles, m. p. 205—206° (decomp.) (Found: C, 58·3; H, 3·2; N, 12·65. $C_{15}H_{11}N,C_6H_3N_3O_7$ requires C, 58·1; H, 3·2; N, 12·9%). The *methiodide*, prepared by the normal method, crystallised from benzene–ethanol as yellow microneedles, m. p. 210—211° with previous shrinking at 204° (Found: C, 55·8; H, 4·2. $C_{16}H_{14}IN$ requires C, 55·3; H, 4·0%). (*b*) 8-Acetamidoisoquinoline (1·0 g.) was nitrosated according to the procedure described above for the nitrosation of 8-acetamido-5-chloroisoquinoline. 8-Nitrosoacetamidoisoquinoline separated as an unstable yellow oil, which was immediately dissolved in "AnalaR" benzene (100 ml.); the dried (Na_2SO_4) yellow solution was then boiled for about 24 hr. Removal of the solvent

[7] Robinson, *J. Amer. Chem. Soc.*, 1947, **69**, 1944.

left a dark residue, which was re-dissolved in a minimum of benzene and put on a column of activated alumina. Elution with light petroleum gave 8-phenylisoquinoline (0·14 g.) as a pale yellow viscous oil which gave a picrate, m. p. and mixed m. p. with a sample prepared by method (*a*) 205—206° (decomp.).

o-*Phenylbenzylideneaminoacetal.*—A mixture of freshly prepared *o*-phenylbenzaldehyde (9·0 g.; Zaheer and Faseeh [8]) and aminoacetal (7·0 g.) was heated on a water-bath until most of the water formed in the reaction had evaporated (about 3 hr.). The product was distilled under reduced pressure. After a little water and some unchanged aminoacetal had been removed, the fraction of b. p. 218—224°/16 mm. was collected as a pale yellow viscous oil (14·0 g.). Redistillation gave o-*phenylbenzylideneaminoacetal* as a viscous oil, b. p. 222—224°/16 mm., n^{20} 1·5615 (Found: C, 77·2; H, 7·9; N, 4·7. $C_{19}H_{23}NO_2$ requires C, 76·8; H, 7·7; N, 4·7%). Attempted cyclisation with 76%, 80%, and finally concentrated, sulphuric acid, gave products from which no basic material could be isolated.

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[8] Zaheer and Faseeh, *J. Indian Chem. Soc.*, 1944, **21**, 38.