542. *Synthesis of 2-Pyridyl-, 2-Quinolyl-, and* 1-iso*Quinolyl-carbinols.*

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The Hammick reaction (Dyson and Hammick, *J.*, 1937, 1724; Mislow, *J. Amer. Chem. Soc.*, 1947, **69**, 2559) has been applied to non-aromatic ketones. 3-1′-iso*Quinolylpentan*-3-*ol*, 1-1′-iso*quinolyl*cyclo*hexanol* and several 2-pyridylcarbinols and 2-quinolyl ketones have been synthesised by this method. 8-Nitroquinaldinic and quinoxaline-2-carboxylic acid do not undergo the Hammick reaction. Bromination of 2 : 3-dimethylquinoline and 9-methylphenanthridine yielded 3-*methyl*-2-*tribromomethylquinoline* and 9-*tribromomethylphenanthridine*. A new preparation of 2-acetylquinoline by the bromination of 2-ethylquinoline is described.

Recently Tilford, Shelton, and Campen (*J. Amer. Chem. Soc.*, 1948, **70**, 4001) and Sperber, Papa, Schwenk, and Sherlock (*ibid.*, 1949, **71**, 887) described the preparation of 2-pyridylcarbinols by two methods : (1) condensation of pyridine and an aldehyde or a ketone in the presence of aluminium, mercuric chloride, and mercury (Emmert and Asendorf, *Ber.*, 1939, **72**, 1188; Emmert and Pirot, *ibid.*, 1941, **74**, 714); and (2) decarboxylation of picolinic acid in an aromatic aldehyde or ketone (Ashworth, Daffern, and Hammick, *J.*, 1939, 809).

The latter method, the Hammick reaction (Mislow, *loc. cit.*), has now been extended and used with non-aromatic carbonyl compounds. Decarboxylation of picolinic, quinaldinic, and *iso*quinaldinic acid in *cyclo*hexanone has yielded 30% of 1-2′-pyridyl-, 1-2′-quinolyl-, and 1-1′-iso*quinolyl*-cyclo*hexanol*, and that of *iso*quinaldinic acid in diethyl ketone gave a 20% yield of 3-1′-iso*quinolylpentan*-3-*ol*.

The bromination of 2 : 3-dimethylquinoline, 2-methylquinoxaline, and 9-methylphenanthridine in a sodium acetate–acetic acid buffer (Hammick, *J.*, 1923, 2882) gave 3-*methyl*-2-*tribromomethylquinoline*, 2-tribromomethylquinoxaline, and 9-*tribromomethylphenanthridine*, respectively. Hydrolysis of the first two bromo-compounds was used as a convenient route to the corresponding acids. 9-Tribromomethylphenanthridine was unchanged after being boiled with sulphuric acid for 20 hours.

Syntheses of miscellaneous carbinols have been carried out using the Hammick reaction. It appears to be a general rule that secondary 2-quinolyl alcohols are very readily autoxidised, since when these compounds should result from the reaction the corresponding ketone is invariably obtained. On the other hand, 2-pyridyl- and 1-*iso*quinolyl-carbinols of this type are quite stable in air.

8-Nitroquinaldinic and quinoxaline-2-carboxylic acid are decarboxylated in benzaldehyde, acetophenone, or benzophenone to yield only the parent bases. No alcoholic products could be detected.

A brief examination of the synthetic method of Emmert *et al.* (*locc. cit.*) by the new technique of Tilford, Shelton, and Campen (*loc. cit.*) has indicated that the reaction is generally applicable to the synthesis of 2-quinolylcarbinols (*e.g.*, of phenyl-2-quinolylmethylcarbinol), but no success has been achieved by using *iso*quinoline with either aldehydes or ketones.

2-Ethylquinoline smoothly absorbs two molecules of bromine. Direct hydrolysis of the product, without isolation of the intermediate dibromo-compound, provides a good method for the preparation of 2-acetylquinoline.

Experimental.

(M. p.s and b. p.s are uncorrected. Analyses are by Mr. F. C. Hall and by Drs. Weiler and Strauss of Oxford).

1-2′-*Pyridyl*cyclo*hexanol*.—Picolinic acid (5·0 g.) was heated under reflux with *cyclo*hexanone (50 ml.) for 58 hours. The solution was then extracted with equal volumes of 15% hydrochloric acid and ether, and the acid layer made alkaline. Ether-extraction yielded a basic yellow oil which was distilled at atmospheric pressure. 1-2′-Pyridyl*cyclo*hexanol was collected at 260°, as a colourless oil which solidified. Recrystallisation from light petroleum (b. p. 80—100°) yielded colourless rectangular prisms (2·4 g., 33%), m. p. 41—42° (Found : 74·8; H, 8·4. Calc. for $C_{11}H_{15}ON$: C, 74·6; H, 8·4%). Emmert and Pirot (*loc. cit.*) record m. p. 43°. The *picrate* separated from alcohol–ether as small yellow prisms, m. p. 82—83° after softening (Found : N, 13·0. $C_{17}H_{18}O_7N_4,C_2H_6O$ requires N, 12·9%).

General Method of Decarboxylation.—The conditions used by Dyson and Hammick (*loc. cit.*) and Ashworth, Daffern, and Hammick (*loc. cit.*) were employed. The acid was heated in 6—10 times its weight of carbonyl compound at such a temperature that the decarboxylation usually took about 4 hours. When easily oxidisable aldehydes were used the reaction was carried out under nitrogen. The basic products were isolated by means of 15% hydrochloric acid. The method is described in full in the following example. In succeeding examples the procedure is described in full after isolation of the basic products.

3 : 4-*Dimethoxyphenyl-2′-pyridylcarbinol.*—Picolinic acid (4·0 g.) was slowly decarboxylated by heating it in redistilled veratraldehyde (30 g.) under nitrogen for 4 hours. Basic products were extracted with 15% hydrochloric acid and ether. The acid layer was made alkaline, and the resulting oil isolated by means of ether. This oil separated from light petroleum (b. p. 80—100°) in the form of stout colourless prisms (1·2 g., 15%), m. p. 92—93° (Found : C, 69·0; H, 6·1. Calc. for $C_{14}H_{15}O_3N$: C, 68·6; H, 6·1%). Sperber *et al.* (*loc. cit.*) recorded a yield of 2·5%, but give no m. p. for their product. The *picrate* separated from alcohol as yellow needles, m. p. 137—138° (Found : N, 11·5. $C_{20}H_{18}O_{10}N_4$ requires N, 11·8%).

3-1′-iso*Quinolylpentan*-3-*ol.*—Steam-distillation of the basic products from *iso*quinaldinic acid and diethyl ketone yielded first *iso*quinoline and then a colourless oil which crystallised in the distillate. Recrystallisation from dilute aqueous alcohol yielded 3-1′-iso*quinolylpentan*-3-*ol* (20%) as colourless irregular plates, m. p. 56—57° (Found : C, 78·2; H, 8·1. $C_{14}H_{17}ON$ requires C, 78·1; H, 7·9%). The compound has a pleasant, slightly camphoric odour. It is slightly soluble in hot water from which it crystallises. Attempts to prepare a picrate and a benzoyl derivative were unsuccessful.

1-1′-iso*Quinolyl*cyclo*hexanol.*—Distillation in a vacuum removed *iso*quinoline from the basic products derived from *iso*quinaldinic acid and *cyclo*hexanone. Crystallisation of the residue from light petroleum (b. p. 40—60°) yielded 1-1′-iso*quinolyl*cyclo*hexanol* (28%) as long narrow plates, m. p. 92—93° (Found : C, 79·2; H, 7·65. $C_{15}H_{17}ON$ requires C, 79·3; H, 7·5%).

2-*Acetylquinoline.*—A mixture of 2-ethylquinoline (12·8 g., 1 mol.), acetic acid (80 ml.), and anhydrous sodium acetate (30 g.) was treated at 90° during 10 minutes with bromine (8·2 ml., 2 mols.) in acetic acid (50 ml.). The bromine was completely absorbed, and sodium bromide separated. The mixture was kept at 90° for 30 minutes, then heated under reflux with 2N-sulphuric acid (100 ml.) for 30 minutes, and made just alkaline with aqueous sodium carbonate. Distillation with steam yielded a colourless oil (8·7 g., 62%) which slowly solidified. After several recrystallisations from dilute alcohol to constant m. p., the ketone was obtained as fine colourless needles, m. p. 46° [Kaufmann and Dändliker (*Ber.*, 1913, **46**, 2942) record m. p. 52°]. The phenylhydrazone separated from alcohol as slender yellow needles, m. p. 153—154° (Kaufmann *et al.* record m. p. 154°).

1-2′-*Quinolyl*cyclo*hexanol.*—Steam-distillation of the basic products from quinaldinic acid and *cyclo*hexanone yielded first quinoline and then the carbinol (29%) as colourless waxy plates, m. p. 67° (Found : C, 78·9; 7·5. Calc. for $C_{15}H_{17}ON$: C, 79·3; H, 7·5%). Emmert and Pirot (*loc. cit.*) record m. p. 66°. The compound has a characteristic camphoric odour. The *picrate* separated from methyl alcohol as yellow rods, m. p. 150—151° (Found : C, 55·0; H, 4·4. $C_{21}H_{20}O_8N_4$ requires C, 55·3; H, 4·4%). Emmert and Pirot record m. p. 145°, but give no analysis.

m-*Methoxyphenyl 2-Quinolyl Ketone.*—Interaction of quinaldinic acid and *m*-methoxybenzaldehyde and the usual extraction procedure, followed by steam-distillation from alkaline solution, yielded a residual brown viscous oil, which was isolated by means of ether. Extraction with hot dilute acetic acid (charcoal) gave colourless needles (38%). Recrystallisation from light petroleum (b. p. 60—80°) gave the *ketone* as colourless silky needles, m. p. 70—71° (Found : C, 77·95; H, 4·95. $C_{17}H_{13}O_2N$ requires C, 77·6; H, 4·9%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as small orange-coloured needles, m. p. 249° (Found : N, 15·6. $C_{23}H_{17}O_5N_5$ requires N, 15·8%).

m-*Methoxyphenyl-2-decahydroquinolylcarbinol.*—*m*-Methoxyphenyl 2-quinolyl ketone (1·1 g.) was hydrogenated in ethyl alcohol (80 ml.) in the presence of Raney nickel (1·0 g.) at 100° and 100 atmospheres (3 hours). Removal of the catalyst, treatment with charcoal, and evaporation of the solvent yielded a colourless viscous oil (1·0 g.) which partly crystallised overnight. Attempts to separate the racemates by fractional crystallisation from light petroleum were unsuccessful. Crystallisation from 4N-hydrochloric acid yielded colourless crystals (0·1 g.) of the *hydrochloride* of one racemate. This compound crystallised from alcohol as small colourless prisms, m. p. 256—258° (decomp.) (Found : C, 65·6; H, 8·25. $C_{17}H_{25}O_2N,HCl$ requires C, 65·5; H, 8·35%). An aqueous solution of the hydrochloride gives no colour with ferric chloride.

3 : 4-*Dimethoxyphenyl 2-Quinolyl Ketone.*—Quinaldinic acid and veratraldehyde, by interaction, extraction, and crystallisation of the resulting basic oil from dilute acetic acid and then from light petroleum (b. p. 60—80°), yielded the *ketone* (24%) as small colourless needles, m. p. 104° (Found : C, 73·75; H, 5·0. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1%). The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in the form of very small red needles, m. p. 246—247° (Found : N, 14·3. $C_{24}H_{19}O_6N_5$ requires N, 14·8%).

2-*Furyl 2-Quinolyl Ketone.*—The hydrochloric acid extract of the products obtained from quinaldinic acid and furfuraldehyde was filtered through charcoal, made alkaline, and distilled in steam to remove quinoline. The residual black solid was extracted with light petroleum (b. p. 80—100°). The extract yielded sandy yellow needles (16%; m. p. 84—85°). Two recrystallisations from the same solvent yielded 2-*furyl 2-quinolyl ketone* as colourless needles, m. p. 88—89° (Found : C, 75·1; H, 4·0. $C_{14}H_9O_2N$ requires C, 75·4; H, 4·0%). The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid as red micro-crystals, m. p. 222—223° (Found : C, 57·7; H, 3·35. $C_{20}H_{13}O_5N_5$ requires C, 58·1; H, 3·15%).

Phenyl-2-quinolylmethylcarbinol (cf. Emmert and Pirot, *loc. cit.*).—A mixture of quinoline (20 g.), acetophenone (20 g.), aluminium foil (5 g.), mercuric chloride (5 g.), a few drops of mercury, and a crystal of iodine was heated until a vigorous reaction ensued. Toluene (20 ml.) was then added, and the mixture kept at 90° and stirred vigorously for 5 hours. Treatment of the reaction mixture with aqueous sodium hydroxide yielded a semi-solid brown product which was dissolved in ether. Basic compounds were extracted with 10% hydrochloric acid, the acid layer was made alkaline, and quinoline removed in steam. The remaining brown oil was dissolved in hot light petroleum (b. p. 80—100°). The crystals which separated on cooling were crystallised several times from light petroleum to give the carbinol (7·3 g., 19%) as colourless needles, m. p. 101—102°. Dyson and Hammick (*loc. cit.*) give m. p. 100°. The *picrate* crystallised from alcohol as yellow needles, m. p. 168—169° (Found : N, 11·4. $C_{23}H_{18}O_8N_4$ requires N, 11·7%) (Dyson and Hammick record m. p. 169°, but give no analysis).

3-*Methyl-2-tribromomethylquinoline*.—This was obtained by the method used by Hammick (*J.*, 1923, 2882) for the preparation of ω-tribromoquinaldine. 2 : 3-Dimethylquinoline (1·4 g.) yielded 3-*methyl*-2-*tribromomethylquinoline* (3·0 g., 86%), which crystallised from acetic acid as stout colourless needles, m. p. 157—158° (Found : Br, 61·1. $C_{11}H_8NBr_3$ requires Br, 60·9%). The compound liberates iodine from acidified potassium iodide solution.

3-*Methylquinoline*-2-*carboxylic Acid*.—3-Methyl-2-tribromomethylquinoline (2·0 g.) was heated under reflux with 10% sulphuric acid (25 ml.) for 16 hours. The acid was isolated through its copper salt. Recrystallisation from benzene yielded colourless needles, m. p. 141—142° (decomp.) (0·5 g., 53%). Koenigs and Stockhausen (*Ber.*, 1901, **34**, 4332) report m. p. 144° (decomp.).

Phenyl-3-*methyl*-2-*quinolylmethylcarbinol*.—Decarboxylation of 3-methylquinoline-2-carboxylic acid (0·4 g.) in excess of acetophenone, followed by the usual extraction procedure, yielded a yellow basic oil, a solution of which in light petroleum (b. p. 60—80°) deposited *phenyl*-3-*methyl*-2-*quinolylmethylcarbinol* (0·3 g., 54%) as colourless rods, m. p. 115—116° (Found : C, 82·1 ; H, 6·4. $C_{18}H_{17}ON$ requires C, 82·2 ; H, 6·45%). The *picrate* separated from alcohol as fine yellow needles, m. p. 181—182° (Found : C, 58·6; H, 4·1. $C_{24}H_{20}O_8N_4$ requires C, 58·6; H, 4·1%).

2-*Tribromomethylquinoxaline*.—This compound separated from ethyl alcohol as pink plates, m. p. 109° (77%) (Bennett and Willis, *J.*, 1928, 1960, record m. p. 109° and a yield of 10%).

2-*Dibromomethylquinoxaline*.—A hot solution of 2-tribromomethylquinoxaline (4·0 g., 1 mol.) in alcohol (40 ml.) was treated with a solution of silver nitrate (4·0 g., 2·2 mols.) in a mixture of alcohol (7 ml.) and water (15 ml.) and warmed for 5 minutes. Excess of dilute hydrochloric acid was added and the silver halides separated. On cooling, the yellow filtrate deposited almost colourless needles (1·2 g., 40%). Recrystallisation from alcohol yielded 2-*dibromomethylquinoxaline* as colourless needles, m. p. 118° (Found : C, 35·8; H, 2·4; N, 9·15. $C_9H_6N_2Br_2$ requires C, 35·8; H, 2·0; N, 9·3%).

Quinoxaline-2-*carboxylic Acid*.—A hot solution of 2-tribromomethylquinoxaline (11·8 g., 1 mol.) in alcohol (80 ml.) was treated with a solution of silver nitrate (20·0 g., 3·7 mols.) in aqueous alcohol and heated under reflux for 15 minutes. Excess of dilute hydrochloric acid was added, the silver halides were removed, and the filtrate was evaporated under reduced pressure to remove alcohol. The yellow crystals of the acid separated from water as fine colourless needles (2·7 g., 50%), m. p. 209° (decomp.) (Found : N, 15·8. Calc. for $C_9H_6O_2N_2$: N, 16·1%). Maurer, Schiedt, and Schroeter (*Ber.*, 1935, **68**, 1716) record m. p. 210°. The *copper* salt was precipitated from an aqueous solution of the acid as green needles (Found : Cu, 15·9. $C_{18}H_{10}O_4N_4Cu$ requires Cu, 15·5%).

9-*Tribromomethylphenanthridine*.—9-Methylphenanthridine (1·9 g., 1 mol.) (Morgan and Walls, *J.*, 1931, 2450) in a mixture of acetic acid (15 ml.) and anhydrous sodium acetate (5 g.) was treated at 90° with a solution of bromine (1·5 ml., 3 mols.) in acetic acid (10 ml.). The *tribromo*-compound separated during the experiment in the form of almost colourless needles. The reaction mixture was cooled, and the mixture of product and sodium bromide separated and washed with acetic acid and then with water until free from bromide. Recrystallisation from much alcohol yielded slender colourless needles (2·7 g., 63%), which were dried at 100° in a vacuum and then had m. p. 181—182° (Found : Br, 55·75. $C_{14}H_8NBr_3$ requires Br, 55·8%). The compound liberates iodine from acidified potassium iodide solution, and is unaffected by being boiled with 10% sulphuric acid for 20 hours.

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