172. *The Preparation of Some* iso*Quinoline Derivatives.*

By M. S. Gibson.

The picrates of 3 : 5-, 4 : 5-, 5 : 6-, 5 : 7-, and 5 : 8-dimethyl*iso*quinolines, required as reference substances, have been synthesised by standard methods.

During an investigation of gelsemine,[1] it became necessary to prepare as reference samples the picrates of the *x* : 5-dimethyl*iso*quinolines, of which only the 1 : 5-dimethyl compound was known.[2] The desired substances have been prepared by the Bischler–Napieralski reaction.

Condensing propylene oxide with *o*-tolylmagnesium bromide [3] gave only a poor yield of *o*-2-hydroxypropyltoluene and the isolation *via* the hydrogen phthalate was tedious. Accordingly, the desired carbon skeleton was constructed by Reformatsky condensation of *o*-tolualdehyde with ethyl α-bromopropionate, followed by dehydration of the hydroxy-ester, hydrolysis, and reduction to α-methyl-β-*o*-tolylpropionic acid. Degradation of the

[1] Gibson and Robinson, *Chem. and Ind.*, 1951, 93.
[2] Späth, Berger, and Kuntara, *Ber.*, 1930, **63**, 134.
[3] Cf. Levene and Walti, *J. Biol. Chem.*, 1931, **90**, 81.

amide of this acid with sodium hypochlorite under rather specific conditions gave the desired amine.

The phenethylamines required for the remaining syntheses were prepared by catalytic hydrogenation of the corresponding benzyl cyanides, that for 2-*o*-tolylpropylamine being prepared by direct methylation of *o*-xylyl cyanide with methyl iodide and potassamide in liquid ammonia, those for the remainder from the corresponding benzyl chlorides and potassium cyanide.

Each of the phenethylamines was converted into the formyl derivative, which was dehydrated with phosphoric anhydride in boiling tetralin. Dehydrogenation of the resulting dihydro*iso*quinolines gave the *iso*quinolines, which were characterised as picrates.

3-Methyl*iso*quinoline has also been prepared by the Bischler–Napieralski reaction; this route constitutes a more convenient preparation than the earlier method from *o*-cyanobenzyl cyanide.[4]

Experimental

Commercial tetralin was purified by washing it with concentrated sulphuric acid until the washings were only slightly discoloured. The hydrocarbon was then washed with water, dried, and distilled from phosphoric anhydride, the fraction of b. p. 210—212° being collected.

o-2-*Hydroxypropyltoluene*.—A solution of propylene oxide (7 g.) in ether (40 c.c.) was added to a stirred ice-cold solution of the Grignard reagent from *o*-bromotoluene (21 g.) and magnesium (3·2 g.) in ether (80 c.c.). After 12 hr., ice-cold hydrochloric acid was added to the mixture, and the products were isolated by means of ether. Fractionation afforded a considerable quantity of low-boiling material, and then material (5 g.), b. p. 125—150°/17 mm., which was heated in pyridine (9 c.c.) with phthalic anhydride (5 g.) on the steam-bath for 45 min. The resulting solution was poured on crushed ice, acidified, and extracted with chloroform. After being washed, the extract was evaporated, and the residue was treated with sodium carbonate solution. Oily impurites were removed by washing the residue with ether, and the alkaline solution was then acidified and extracted with ether. Evaporation afforded a pale yellow oil (4 g.), which solidified on trituration with light petroleum. Crystallisation from ether gave the *hydrogen phthalate* as cubes, m. p. 127—129° (Found : C, 72·4; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·0%). This ester (3 g.) was warmed with 10% sodium hydroxide solution (10 c.c.) for 20 min., yielding o-2-*hydroxypropyltoluene*, b. p. 139—142°/16 mm., n_D^{15} 1·5260 (Found : C, 79·9; H, 9·5. $C_{10}H_{14}O$ requires C, 80·0; H, 9·3%).

Ethyl β-*Hydroxy*-α-*methyl*-β-o-*tolylpropionate*.—Ethyl orthoformate (100 g.) was added with shaking to a cooled solution of the Grignard reagent from *o*-bromotoluene (107 g.) and magnesium (16 g.) in ether (300 c.c.). The mixture was refluxed for 6 hr., cooled, decomposed with sulphuric acid (750 c.c., 10%), and distilled in steam. *o*-Tolualdehyde (42 g.), collected by means of ether, was obtained as an oil, b. p. 94—96°/15 mm.

A solution of the aldehyde (11·2 g.) and ethyl α-bromopropionate (17 g.) in dry benzene (24 c.c.) was added to zinc turnings (6·2 g.) and benzene (8 c.c.) so that the mixture just boiled. After boiling for a further 2 hr., the complex was decomposed with sulphuric acid. *Ethyl* β-*hydroxy*-α-*methyl*-β-o-*tolylpropionate* (11 g.) was obtained as an oil, b. p. 160—162°/16 mm., n_D^{14} 1·5082 (Found : C, 70·2; H, 8·3. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%).

Ethyl α-*Methyl*-β-o-*tolylacrylate*.—Phosphoric anhydride (10 g.) was added during 2 hr. to a solution of the hydroxy-ester (11 g.) in boiling benzene (50 c.c.). After a further hour, the liquid was decanted, and the residue was extracted with hot benzene (2 × 30 c.c.), the extracts being added to the main solution, which was then treated with potassium carbonate (2 g.) to remove traces of phosphoric acid. Distillation afforded the *acrylate* (6 g.) as a yellow oil, b. p. 127—129°/15 mm., n_D^{14} 1·5361 (Found : C, 76·8; H, 8·1. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%).

α-*Methyl*-β-o-*tolylacrylic Acid*.—A solution of the unsaturated ester (5·8 g.) and potassium hydroxide (2 g.) in aqueous ethanol was boiled for 2 hr. Crystallised from water, the *acid* (4·3 g.) formed thread-like needles, m. p. 99—100° (Found : C, 75·1; H, 6·7. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%).

α-*Methyl*-β-o-*tolylpropionic Acid*.—The unsaturated acid (4 g.), in sodium carbonate solution, was shaken with 5% palladised barium sulphate (250 mg.) and hydrogen until absorption ceased (90 min.). Isolation by acidification and extraction with ether gave α-*methyl*-β-o-*tolylpropionic*

[4] Gabriel and Neumann, *Ber.*, 1892, **25**, 3563.

acid (3·8 g.), b. p. 112—114°/0·12 mm., n_D^{14} 1·5211 (Found : C, 74·4; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%).

The *amide* separated from aqueous ethanol in plates, m. p. 112° (Found : C, 74·5; H, 8·4; N, 7·7. $C_{11}H_{15}ON$ requires C, 74·5; H, 8·5; N, 7·9%).

Hofmann Degradation of α-Methyl-β-o-tolylpropionamide.—Chlorine, from potassium permanganate (4·1 g.) and concentrated hydrochloric acid, was passed into cold 10% aqueous sodium hydroxide (250 c.c.), and the amide (10 g.) was added to the resulting solution with shaking. The mixture was gradually heated to 70—80°, and kept at that temperature for an hour. Sodium hydroxide (50 g.) was then added, and the mixture was heated on the steam-bath for 5 hr. When cool, the liquid was extracted with ether, and the extract was dried and saturated with dry hydrogen chloride. The precipitated o-2-*aminopropyltoluene hydrochloride* (3·8 g.) was purified by crystallisation from ether–ethanol, from which it separated as colourless needles, m. p. 166—167° (Found : C, 64·3; H, 8·6; N, 7·8. $C_{10}H_{16}NCl$ requires C, 64·7; H, 8·6; N, 7·6%).

The *picrate* crystallised from aqueous ethanol in yellow needles, m. p. 162—163° (Found : C, 51·2; H, 5·0; N, 14·6. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%).

Addition of a few drops of aqueous sodium carbonate solution to a solution of sodium nitroprusside and the free base in aqueous acetone produced a purple colour which slowly faded to pale yellow.

3 : 4-*Dihydro*-3 : 5-*dimethyl*isoquinoline *Picrate.*—95% Formic acid (4 c.c.) was heated with *o*-2-aminopropyltoluene (from the hydrochloride, 3·4 g.) at 140—150° for 4 hr. in an open flask. The formyl derivative was dissolved in tetralin (80 c.c.), and phosphoric anhydride (15 g.) was added to the boiling solution during 30—40 min. When the mixture was cool, an excess of hydrochloric acid was added, and tetralin was removed in steam. The residue was strongly basified and again distilled in steam. Isolated by extraction with ether and precipitation with picric acid, 3 : 4-*dihydro*-3 : 5-*dimethyl*isoquinoline *picrate* (900 mg.) crystallised from acetone in yellow needles, m. p. 166—168° (Found : C, 52·4; H, 4·1; N, 14·6. $C_{17}H_{16}O_7N_4$ requires C, 52·6; H, 4·1; N, 14·3%).

3 : 5-*Dimethyl*isoquinoline *Picrate.*—3 : 5-Dimethyl-3 : 4-dihydro*iso*quinoline, regenerated from the picrate (400 mg.), was heated with 30% palladised charcoal (200 mg.) at 220° for 30 min. The residue was extracted with warm dilute hydrochloric acid; addition of aqueous picric acid precipitated 3 : 5-*dimethyl*isoquinoline *picrate* (350 mg.), which separated from ethanol as pale yellow needles, m. p. 219—220° (Found : C, 53·0; H, 3·7; N, 14·5. $C_{17}H_{14}O_7N_4$ requires C, 52·9; H, 3·7; N, 14·5%).

α-o-*Tolylpropionitrile.*—A solution of *o*-xylyl cyanide [5] (20 g.) in ether (60 c.c.) was added to a stirred solution of potassamide (from potassium, 6 g.) in liquid ammonia (400 c.c.). A solution of methyl iodide (22 g.) in ether (50 c.c.) was then cautiously added. When the ammonia had evaporated, ethanol (10 c.c.) and then water were added. Fractionation of ether-soluble material furnished α-o-*tolylpropionitrile* (15 g.), b. p. 150—152°/20 mm. (Found : C, 82·4; H, 7·6; N, 9·8. $C_{10}H_{11}N$ requires C, 82·8; H, 7·6; N, 9·6%).

α-o-*Tolylpropionamide* crystallised from aqueous ethanol in needles, m. p. 125—126° (Found : C, 73·7; H, 8·1; N, 8·5. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%).

Under analogous conditions, methylation of benzyl cyanide (20 g.) gave α-phenylpropionitrile (16 g.), b. p. 114—116°/13 mm. (Found : C, 82·4; H, 6·9. Calc. for C_9H_9N : C, 82·4; H, 6·9%).

β-o-*Tolylpropylamine.*—α-*o*-Tolylpropionitrile (9 g.) in ethanol (100 c.c.), saturated with ammonia at 0°, was hydrogenated at 100°/80—100/atm. in the presence of Raney nickel. The β-*o*-tolylpropylamine (8 g.) obtained, b. p. 117—120°/15 mm., yielded a *picrate*, yellow needles (from aqueous methanol), m. p. 175—176° (Found : C, 51·0; H, 4·7; N, 15·1. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%). In the sodium nitroprusside test described above, the base gave a fine violet colour, which slowly faded to yellow.

4 : 5-*Dimethyl*isoquinoline *Picrate.*—Boiling 95% formic acid (7 c.c.) converted the above amine (6 g.) into the formyl derivative which was dehydrated with phosphoric anhydride (27 g.) in boiling tetralin (110 c.c.). As it gave a gummy picrate, the crude dihydro*iso*quinoline was dehydrogenated with 30% palladised charcoal (400 mg.) at 200—220° for 30 min. 4 : 5-*Dimethyl*isoquinoline *picrate* (800 mg.) separated from acetone in yellow needles, m. p. 234—235° (Found : C, 52·6; H, 3·9; N, 14·4%).

2 : 3-*Dimethylbenzyl Cyanide.*—A solution of 2 : 3-dimethylbenzyl chloride [6] (21 g.) and

[5] Atkinson and Thorpe, *J.*, 1907, 1687.
[6] Smith and Spillane, *J. Amer. Chem. Soc.*, 1940, **62**, 2639.

potassium cyanide (15 g.) in aqueous ethanol was boiled for 4 hr. The *nitrile* (14 g.), b. p. 136—144°/17 mm., crystallised from ether in rhombs, m. p. 55—56° (Found : C, 82·8; H, 7·6. $C_{10}H_{11}N$ requires C, 82·8; H, 7·6%).

The nitrile (0·5 g.) was hydrolysed by boiling aqueous-ethanolic potassium hydroxide (0·4 g.) for 6 hr. 2 : 3-*Dimethylphenylacetic acid* (0·4 g.) crystallised from aqueous ethanol in plates, m. p. 113—114° (Found : C, 73·0; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%).

2 : 3-*Dimethylphenethylamine.*—Reduced as was 1-*o*-tolylpropionitrile, 2 : 3-dimethylbenzyl cyanide (8 g.) yielded 2 : 3-*dimethylphenethylamine* (7 g.), b. p. 116—118°/17 mm. The *picrate* crystallised from aqueous ethanol in yellow needles, m. p. 219—220° (decomp.) (Found : C, 50·8; H, 4·6; N, 14·9. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%). The 3 : 5-*dinitrobenzoate* crystallised from aqueous ethanol in needles, m. p. 182—183° (Found : C, 56·6; H, 5·1. $C_{17}H_{19}O_6N_3$ requires C, 56·5; H, 5·3%). The sodium nitroprusside colour was intense magenta, which faded to pale yellow.

5 : 6-*Dimethyl*iso*quinoline Picrate.*—The amide, from the above amine (5 g.) and 98—100% formic acid (6 c.c.) was dehydrated with phosphoric anhydride (25 g.) in tetralin (100 c.c.). 3 : 4-*Dihydro*-5 : 6-*dimethyl*iso*quinoline picrate* (1·5 g.) separated from ethanol in yellow platelets, m. p. 199—200° (Found : C, 52·9; H, 4·1; N, 13·9%). Obtained as in the previous cases, 5 : 6-*dimethyl*iso*quinoline picrate* (950 mg.; from 1·1 g.) formed pale yellow needles (from ethanol), m. p. 246° (decomp.) (Found : C, 52·5; H, 3·7; N, 14·6%).

2 : 4-*Dimethylphenethylamine.*—Reduction of 2 : 4-dimethylbenzyl cyanide [7] (12 g.) under the conditions employed for the 2 : 3-isomer afforded 2 : 4-dimethylphenethylamine (10 g.), b. p. 116—122°/16 mm. The *hydrochloride* crystallised from ethyl acetate–ethanol in needles, m. p. 172—173° (Found : C, 64·6; H, 8·9; N, 7·4. $C_{10}H_{16}NCl$ requires C, 64·7; H, 8·6; N, 7·6%), and the 3 : 5-*dinitrobenzoate* from aqueous ethanol in needles, m. p. 181—182° (Found : C, 56·4; H, 5·1; N, 11·6. $C_{17}H_{19}O_6N_3$ requires C, 56·5; H, 5·3; N, 11·6%).

In the sodium nitroprusside test, the base gave a deep magenta colour, which finally faded to pale yellow.

5 : 7-*Dimethyl*iso*quinoline Picrate.*—The above base (5 g.) was formylated, and the product was dehydrated with phosphoric anhydride in boiling tetralin. 3 : 4-*Dihydro*-5 : 7-*dimethyl*iso*quinoline picrate* (1·1 g.) crystallised from ethanol in yellow needles, m. p. 222—224° (Found : C, 52·9; H, 4·0; N, 14·4%).

Obtained as in the earlier cases, 5 : 7-*dimethyl*iso*quinoline picrate* (650 mg.; from 750 mg.) crystallised from ethanol in yellow needles, m. p. 261—262° (decomp.) (Found : C, 53·0; H, 3·7; N, 14·5%).

2 : 5-*Dimethylphenethylamine.*—2 : 5-Dimethylbenzyl cyanide [8] (11 g.) was reduced under the same conditions as the 2 : 3-isomer to give the amine (9 g.), b. p. 110—112°/13 mm., whose *picrate* crystallised from aqueous ethanol in yellow needles, m. p. 169—170° (Found : C, 50·8; H, 4·8; N, 15·1. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%). The *hydrogen oxalate* separated from aqueous ethanol in needles, m. p. 199—200° (Found : C, 60·4; H, 7·2; N, 5·9. $C_{12}H_{17}O_4N$ requires C, 60·3; H, 7·1; N, 5·9%). The sodium nitroprusside colour was intense plum-red which passed through purple to pale yellow.

5 : 8-*Dimethyl*iso*quinoline Picrate.*—The formyl derivative of the above base (5 g.) was dehydrated with phosphoric anhydride (23 g.) in tetralin (100 c.c.). 3 : 4-*Dihydro*-5 : 8-*dimethyl*iso*quinoline picrate* (1·4 g.) separated from acetone in yellow columns, m. p. 182—183° (Found : C, 52·5; H, 4·0; N, 14·2%).

Prepared in the usual manner, 5 : 8-*dimethyl*iso*quinoline picrate* (720 mg.; from 850 mg.) crystallised from ethanol in yellow needles, m. p. 231—233° (decomp.) (Found : C, 53·1; H, 3·9; N, 14·6%).

2′-*Formamidopropylbenzene.*—Crystallised ammonium formate (19 g.) was slowly distilled until the internal temperature reached 165°. Phenylacetone [9] (10 g.) was added and the temperature was raised during 3 hr. to 185—190°. After a further hour at 190°, the mixture was poured into water and extracted with benzene. The amide (7 g.) was obtained as an oil, b. p. 119—121°/0·12 mm. (Found : C, 73·5; H, 8·1; N, 8·5. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·0; N, 8·6%).

3-*Methyl*iso*quinoline Picrate.*—The amide (4 g.) was dehydrated with phosphoric anhydride (20 g.) in tetralin (90 c.c.). 3 : 4-*Dihydro*-3-*methyl*iso*quinoline picrate* (1 g.) crystallised from

[7] Bogert and Stamatoff, *Rec. Trav. chim.*, 1933, **52**, 584.
[8] Bardhan and Sengupta, *J.*, 1932, 2520.
[9] Magidson and Garkusha, *J. Gen. Chem.* (*U.S.S.R.*), 1941, **11**, 339.

ethanol in yellow platelets, m. p. 139—141° (Found : C, 51·5; H, 3·9; N, 15·2. $C_{16}H_{14}O_7N_4$ requires C, 51·3; H, 3·8; N, 15·0%).

3-Methyl*iso*quinoline picrate (430 mg.; from 500 mg.) separated from ethanol in yellow needles, m. p. 197—198° (Found : C, 51·9; H, 3·3; N, 14·8. Calc. for $C_{16}H_{12}O_7N_4$: C, 51·6; H, 3·2; N, 15·0%). Gabriel and Neumann [4] give m. p. 197—198°.

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