24. *A New Technique for the Reduction of Certain Heterocyclic Methiodides.*

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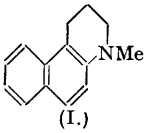
A convenient method, which is adaptable to large-scale operations, has been developed for the preparation of both simple and polynuclear 1-alkylpiperidine derivatives. It involves the hydrogenation of a quaternary salt of the pyridine over Raney nickel catalyst in the presence of a base, such as diethylamine. The corresponding *N*-methylpiperidines and tetrahydro-*N*-methyl-quinolines and -*iso*quinolines are readily obtained in excellent yield. The methosulphates are not suitable substrates because further methylation of the reduced compound occurs.

During the course of other investigations, it became necessary to prepare on a relatively large scale 1 : 2 : 3 : 4-tetrahydro-1-methyl-5 : 6-benzoquinoline (I). The methylation of 1 : 2 : 3 : 4-tetrahydro-5 : 6-benzoquinoline by formaldehyde and formic acid gave a somewhat impure specimen of (I) in 26% yield, whilst use of methyl iodide and potassium carbonate in acetone gave only 39% of the required product. In the hope of improving these yields we examined the reduction of 5 : 6-benzoquinoline methiodide.



(I.)

The standard techniques for reductions of this type leave much to be desired. Hydrogenation of heterocyclic methiodides over platinum oxide, because of the expense of the catalyst and the necessity of using it in relatively high concentrations, is, in general, limited to small-scale runs only. Reduction by dissolving metals, *e.g.* tin and hydrochloric acid or sodium and ethanol, gives yields that are variable and often poor, and the isolation of the product is frequently tedious. For these reasons, we decided to investigate the hydrogenation over Raney nickel catalyst, of heterocyclic methiodides in general, and 5 : 6-benzoquinoline methiodide in particular.

As a trial experiment, quinoline methiodide was hydrogenated, alone, in the presence of Raney nickel. From the resulting complex mixture, which contained free iodine, a substance which appeared to be *cis*-decahydro-1-methylquinoline was isolated in 17% yield. Since it appeared likely that the hydrogen iodide liberated in the course of the reduction, was interfering, a second hydrogenation was performed under identical conditions of temperature and pressure in the presence of 1 equivalent of potassium hydroxide. This led to the formation of 1 : 2 : 3 : 4-tetrahydro-1-methylquinoline in 54% yield. It seemed possible that the factor limiting the yield obtained in this experiment was the instability of the pseudo-base, formed by the interaction of the quaternary salt and the alkali. In order to minimise this effect, the potassium hydroxide was replaced by diethylamine. This modification was completely successful, tetrahydro-1-methylquinoline being obtained in over 90% yield.

This technique, when applied to the hydrogenation of 5 : 6-benzoquinoline methiodide, gave 1 : 2 : 3 : 4-tetrahydro-1-methyl-5 : 6-benzoquinoline (I) in 90% yield. In order to determine the scope of this process, the methiodides of a number of pyridines, quinolines, and *iso*quinolines were subjected to hydrogenation under similar conditions. The corresponding 1-methylpiperidines and tetrahydro-*N*-methyl-quinolines and *-iso*quinolines were obtained in yields varying between 78 and 95%. The lower yields associated with the piperidines are caused by mechanical losses consequent upon their extreme solubility in water.

Other secondary amines, such as piperidine, can be used in place of diethylamine with equal success, but the heterocyclic methosulphates appear to be unsuitable because the reduced compound is further methylated by the methosulphate anion at the high temperatures involved.

Experimental.

1 : 2 : 3 : 4-*Tetrahydro*-1-*methyl*-5 : 6-*benzoquinoline*.—(*a*) 1 : 2 : 3 : 4-Tetrahydro-5 : 6-benzoquinoline (10·8 g.) and formaldehyde (4·4 c.c.; 40%) were heated on the steam-bath and formic acid (8·8 c.c.; 85%) was added during 15 minutes. After being heated for 6 hours, the red mass was treated with concentrated hydrochloric acid (6 c.c.), and the whole evaporated to dryness *in vacuo*. The residue was dissolved in water, decolorised with charcoal, and basified, and the product isolated with ether and distilled. The *base* (3 g.) was collected at 212°/12 mm. as an oil, slowly setting to pearly flakes, m. p. 61°. The *picrate* crystallised from ethanol in yellow needles, m. p. 163° (Found: C, 56·5; H, 4·3. $C_{14}H_{15}N,C_6H_3O_7N_3$ requires C, 56·3; H, 4·2%).

(*b*) The tetrahydro-5 : 6-benzoquinoline (9 g.) in acetone (50 c.c.) was boiled under reflux with methyl iodide (7·5 g.) and potassium carbonate (16·5 g.) for 15 hours. The filtered solution, on evaporation, deposited an oil and a crystalline solid, which proved to be the *methiodide* of 1 : 2 : 3 : 4-tetrahydro-1-methyl-5 : 6-benzoquinoline. The oil, separated by solution in ether, was distilled; the tetrahydro-1-methyl-5 : 6-benzoquinoline (3·9 g.) was collected at 210°/10 mm. and was identified by means of its picrate, m. p. and mixed m. p. 163°. The methiodide crystallised from water in needles, m. p. 187° (Found: C, 51·9; H, 5·3; N, 3·9. $C_{15}H_{18}NI,\frac{1}{2}H_2O$ requires C, 51·7; H, 5·5; N, 4·0%).

(*c*) 5 : 6-Benzoquinoline methiodide (25 g.), suspended in a mixture of ethanol (100 c.c.) and diethylamine (15 c.c.), was hydrogenated over Raney nickel catalyst at 180° and 75 atmospheres for 2 hours. The solution, filtered from catalyst, was distilled. The tetrahydro-1-methyl-5 : 6-benzoquinoline (11·8 g., 90%), m. p. and mixed m. p. 61°, was collected at 210°/10 mm. (Found: C, 85·3; H, 7·5; N, 7·1. $C_{14}H_{15}N$ requires C, 85·2; H, 7·6; N, 7·1%).

Hydrogenation of Quinoline Methiodide.—(*a*) Quinoline methiodide (13·6 g.), dissolved in ethanol (100 c.c.), was hydrogenated over Raney nickel catalyst at 135° and 75 atmospheres. After the catalyst had been removed by filtration, and the filtrate evaporated, a red oil was obtained which contained iodine. Distillation gave what appeared to be *cis*-decahydro-1-methylquinoline (1·3 g., 17%), b. p. 80°/15 mm. This gave a picrate, m. p. 199—200° (Found: C, 50·0; H, 5·5. Calc. for $C_{10}H_{19}N,C_6H_3O_7N_3$: C, 50·3; H, 5·8%). Ehrenstein and Bunge (*Ber.*, 1934, **67**, 1715) record m. p. 199—200°.

(*b*) Quinoline methiodide (13·6 g., 0·05 mol.), dissolved in ethanol (100 c.c.), was treated with potassium hydroxide (2·8 g., 0·05 mol.) and hydrogenated over Raney nickel catalyst under conditions identical with those described in (*a*). The filtered solution was evaporated and the product isolated with ether and distilled. 1 : 2 : 3 : 4-Tetrahydro-1-methylquinoline (4 g., 54%) was collected at 120°/15 mm. It was identified by m. p. and mixed m. p. of the picrate and methiodide.

(*c*) A solution of quinoline methiodide (30 g.) in ethanol (400 c.c.) was treated with diethylamine (25 c.c.) and hydrogenated over Raney nickel catalyst at 140° and 60 atmospheres. After the product had been worked up in the usual manner, 1 : 2 : 3 : 4-tetrahydro-1-methylquinoline (15 g., 94%), b. p. 115°/10 mm., was obtained. The picrate separated from ethanol in yellow needles, m. p. 125° alone, and when mixed with an authentic specimen (*lit.*, m. p. 125°).

1-*Methylpiperidine*.—Pyridine methiodide (38 g.), dissolved in ethanol, was treated with diethylamine (25 c.c.) and hydrogenated over Raney nickel catalyst for 3 hours at 140° and 75 atmospheres. The filtered solution was acidified, evaporated to dryness, and basified strongly, and the product isolated with ether. Fractionation over potassium hydroxide gave 1-methylpiperidine (13 g., 78%), b. p. 107° (Found: C, 72·6; H, 13·2. Calc. for $C_6H_{13}N$: C, 72·7; H, 13·1%). The picrate, m. p. 218°, formed yellow needles from ethanol (Found: C, 44·2; H, 5·1. Calc. for $C_6H_{13}N,C_6H_3O_7N_3$: C, 43·9; H, 4·9%).

1-*Methyl-α-pipecoline.*—α-Picoline methiodide (40 g.) dissolved in ethanol (400 c.c.) was treated with diethylamine (25 c.c.) and hydrogenated under the same conditions as those of the preceding experiment: 1-methyl-α-pipecoline (15·5 g., 80%), b. p. 118°, was obtained (Found: C, 74·2; H, 13·7. Calc. for $C_7H_{15}N$: C, 74·3; H, 13·3%). The picrate separated from ethanol in yellow needles, m p. 134° (*lit.*, m. p. 134°).

1 : 2 : 3 : 4-*Tetrahydro*-2-*methyl*iso*quinoline.*—*iso*Quinoline methiodide (8 g.), ethanol (120 c.c.), and diethylamine (5 c.c.) were hydrogenated for 2 hours at 180° and 75 atmospheres. Tetrahydro-2-methyl-*iso*quinoline (3·7 g., 86%), b. p. 123°/35 mm., was isolated. The methiodide separated from ethanol in prisms, m. p. 189° (Found: C, 45·9; H, 5·4. Calc. for $C_{11}H_{16}NI$: C, 45·7; H, 5·5%) (*lit.*, m. p. 189°).

1 : 2 : 3 : 4-*Tetrahydro*-1 : 6 : 8-*trimethylquinoline.*—6 : 8-Dimethylquinoline (3 g.) and methyl iodide (2 c.c.) were heated in a sealed tube for 1 hour at 100°. The methiodide (3 g.), dissolved in ethanol (100 c.c.), was hydrogenated in the presence of diethylamine (5 c.c.) for 2 hours at 140° and 75 atmospheres. 1 : 2 : 3 : 4-Tetrahydro-1 : 6 : 8-trimethylquinoline (1·5 g., 86%), b. p. 127°/15 mm., was obtained as an oil, which set to a solid, m. p. 48°. The mixed m. p. with an authentic specimen, prepared by Mr. S. L. Cosgrove (D. Phil. Thesis, Oxford, 1950), was 48°.

(±)-*Laudanosine.*—Papaverine methiodide (4·25 g.), dissolved in ethanol (100 c.c.), was treated with diethylamine (5 c.c.) and hydrogenated over Raney nickel catalyst for 3 hours at 180° and 60 atmospheres. The filtered solution was evaporated to dryness. The residual (±)-laudanosine, when crystallised from ethanol, formed fine needles (3 g., 95%), m. p. 114° alone and when mixed with an authentic specimen.

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