Syntheses in the Piperidine Series. Part II. The Preparation of Piperidyl Ethers and Related Compounds.*

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The preparation of ethers from secondary alcohols and 4-fluoronitrobenzene by use of potassium *tert.*-butoxide is described.

THE object of this work was to prepare various ethers, containing basic nitrogenous groups, for evaluation as anti-tubercular compounds.

In Part I * methods of synthesising piperidin-4-ol and related compounds, required for this work, were described. Another route to piperidin-4-ol has been investigated, involving hydrolysis of 4-pyridylpyridinium dichloride (Koenigs and Greiner, *Ber.*, 1931, **64**, 1052) to 4-hydroxypyridine, followed by hydrogenation. Contrary to the findings of these workers, the crude pyridylpyridinium dichloride was found to be unsatisfactory as starting material for hydrolysis and the recommended purification of it, involving evaporation at ordinary pressure, led to decomposition. Purification of 4-pyridylpyridinium dichloride employing evaporation under reduced pressure gives a satisfactory product which may be hydrolysed to 4-hydroxypyridine in excellent yields, without the aid of an autoclave. This is achieved by working with concentrated aqueous solutions and thereby raising the boiling point.

Hydrogenation of 4-hydroxypyridine in absolute alcohol, in presence of Raney nickel, did not proceed below 200°/100 atm., under which conditions the product was essentially 1-ethylpiperidin-4-ol, formed by interaction with the solvent. Use of Adams catalyst did not lead to hydrogenation. When water was used as a solvent the hydrogenation gave the required piperidin-4-ol, but only in poor yields. As some of the secondary alcohols, from which the required ethers were to be prepared, were difficult to obtain in quantity, a method of preparing ethers from secondary alcohols was needed which did not require an excess of the alcohol.

*cyclo*Hexyl *p*-nitrophenyl ether may be readily prepared from 4-fluoronitrobenzene and the potassium salt of *cyclo*hexanol, with *cyclo*hexanol as a solvent, but if benzene is used as a solvent no ether is formed. Although Whalley (*J.*, 1950, 2241) found that 1-fluoro-2 : 4-dinitrobenzene reacts with primary, secondary, and tertiary alcohols in benzene in the presence of triethylamine, no similar reaction took place between 4-fluoronitrobenzene and *cyclo*hexanol in the presence of triethylamine when benzene, chlorobenzene, or *cyclo*hexanol was used as solvent.

Eventually, it was found that ethers could be prepared from equimolecular proportions of *p*-fluoronitrobenzene and a secondary alcohol in the presence of potassium *tert.*-butoxide in *tert.*-butanol, indicating that the equilibrium

$$Me_3C{\cdot}O^- + >CH{\cdot}OH \rightleftharpoons Me_3C{\cdot}OH + >CH{\cdot}O^-$$

lies so far to the right that it may be utilised for preparative purposes. In the absence of *cyclo*hexanol, *p-tert.*-butoxynitrobenzene was formed.

Both *cyclo*hexyl and *tert.*-butyl *p*-nitrophenyl ether were reduced to the corresponding amino-ethers and these yielded stable acetyl derivatives. Similarly, *p*-acetamidophenyl

* Part I, *J.*, 1952, 1164.

1-methyl- and 1-acetyl-4-piperidyl ether were prepared from 1-methyl- and 1-acetylpiperidin-4-ol respectively.

If *p*-fluoronitrobenzene is replaced by 4-chloropyridine, pyridyl ethers are formed by this method, *e.g.*, *cyclo*hexyl 4-pyridyl ether. This compound gave a picrate but attempts to obtain a hydrochloride or methiodide from it yielded oils. *n*-Alkyl 4-pyridyl ethers normally give solid salts (Koenigs and Neumann, *Ber.*, 1915, **48**, 959; Renshaw and Conn, *J. Amer. Chem. Soc.*, 1937, **59**, 297), and the possibility that this substance might be 1-*cyclo*hexyloxypyrid-4-one was examined. According to Haitinger and Lieben (*Monatsh.*, 1885, **6**, 317), 4-methoxypyridine readily undergoes fission on treatment with hydriodic acid, whilst the isomeric 1-methylpyrid-4-one remains unchanged. The product formed from 4-chloropyridine and *cyclo*hexanol gave *cyclo*hexyl iodide and 4-hydroxypyridine, indicating that it was the *cyclo*hexyl ether.

Experimental

4-Pyridylpyridinium Dichloride.—The following procedure gave the best yield. Dry pyridine (200 g.) was gradually added to thionyl chloride (600 g.), cooled below 20°, and the whole set aside for 3 days at room temperature. Volatile materials were then removed at the water-pump, leaving a dark-brown crystalline mass. This was triturated with absolute alcohol (250 c.c.) at 0°, filtered off, washed with cold absolute alcohol (2 × 200 c.c.), and dried in vacuum. The crude product (183 g.) was dissolved in water (100 c.c.) and 2N-hydrochloric acid (300 g.), animal charcoal (10 g.) was added, and the mixture boiled for 5 min. After hot filtration, the filtrates were again treated with charcoal (10 g.), to give a light-orange solution which was evaporated at the water-pump to 200 c.c. Absolute alcohol (400 c.c.) was added and the mixture cooled to 0°. The product was filtered off, washed with absolute alcohol (200 c.c.), and dried in vacuum. The pale yellow crystals (167 g.) melted at 158—160°, softening between 153° and 158°. Recrystallisation from methanol (30 c.c.) gave material (113 g.), m. p. 158—160°. Concentration of the mother-liquor gave a further crop (25 g.) with the same m. p.

4-Hydroxypyridine.—Water was distilled from a solution of 4-pyridylpyridinium dichloride (120 g.) in water (54 c.c.) until the temperature of the mixture reached 130°. The solution was then refluxed for 24 hr. Water (150 c.c.) was added, followed by anhydrous sodium carbonate (75 g.), and the mixture was evaporated to dryness under reduced pressure. The resulting solid was extracted with absolute alcohol (3 × 100 c.c.), and the filtrates were treated with charcoal and then evaporated to a pale-yellow solid which was dried (P_2O_5). The yield of 4-hydroxypyridine (m. p. 120—130°) was 48 g. The nitrate, crystallised from 2N-nitric acid, melted at 204—205° (decomp.) (Found: C, 38·0; H, 3·8; N, 17·7. Calc. for $C_5H_6O_4N_2$: C, 38·0; H, 3·8; N, 17·7%). Bishop, Cavell, and Chapman (*J.*, 1952, 437) record m. p. 189—191°.

Catalytic Reductions of 4-Hydroxypyridine.—(*a*) 4-Hydroxypyridine (9·5 g.) in absolute alcohol (200 c.c.) with Raney nickel (1 g.) were hydrogenated at 200°/100 atm. Distillation, after removal of the catalyst, gave a viscous oil (7 g.), b. p. 98—102°/13 mm., which appeared to be 1-ethylpiperidin-4-ol (Emmert, D.-R.P. 292,871).

(*b*) 4-Hydroxypyridine (9·5 g.) in water (200 c.c.) with Raney nickel (1 g.) was hydrogenated at 170°/65 atm. The product was filtered, 2N-hydrochloric acid (75 c.c.) added, and the solution evaporated to dryness under reduced pressure. The resulting solid was dissolved in absolute alcohol (50 c.c.), filtered, and evaporated to dryness under reduced pressure. The solid was taken up in methanol (30 c.c.), and a solution of sodium methoxide [from sodium (2·3 g.) and methanol (30 c.c.)] was added. Sodium chloride was filtered off and the filtrates concentrated under reduced pressure to yield an oil which was distilled, giving piperidin-4-ol, b. p. 110—112°/14 mm. (1·3 g.), characterised as its sulphate, m. p. 66—68°. Unchanged 4-hydroxypyridine (7·0 g.) remained in the distillation flask.

cyclo*Hexyl* p-*Nitrophenyl Ether.*—(*a*) Powdered potassium hydroxide (2 g.) was heated with *cyclo*hexanol (20 c.c.) on the steam-bath until a clear solution was obtained. This was allowed to cool a little and then *p*-fluoronitrobenzene (5 g.) was gradually added, with shaking. The mixture was heated on the steam-bath for 15 min., cooled, and poured into dilute hydrochloric acid. The insoluble material was isolated with ether, washed with dilute sodium hydroxide solution, dried (Na_2SO_4), and distilled, giving cyclo*hexyl* p-*nitrophenyl ether*, b. p. 189—191°/12 mm. (3·6 g.) (Found: C, 65·0; H, 6·9; N, 6·8. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·8; N, 6·3%).

(*b*) Potassium (1·1 g.) and *cyclo*hexanol (20 c.c.) were heated together on the steam-bath until they had reacted. The mixture was allowed to cool, *p*-fluoronitrobenzene (5 g.) was added in

one portion, and the mixture was heated on the steam-bath for 15 min. The product was isolated by pouring the mixture into water, extracting with benzene, washing the benzene layer with alkali, drying the benzene layer (Na_2SO_4), and finally distilling it, to give *cyclo*hexyl *p*-nitrophenyl ether, b. p. 147—148°/0·3 mm. (4·5 g.).

(*c*) Potassium (1·95 g.), *cyclo*hexanol (6 g.), and anhydrous benzene (50 c.c.) were heated under reflux until all the potassium had reacted. The benzene was removed under reduced pressure and *tert.*-butanol (25 c.c.) was added. The mixture was boiled on the water-bath under reflux for 10 min. after the last of the solid had dissolved and then cooled to 30° at which temperature *p*-fluoronitrobenzene (7 g.) was added in one portion. The temperature was held at 40° by cooling and, after the exothermic reaction had diminished, the mixture was heated on the steam-bath for 15 min. Excess of *tert.*-butanol was removed under reduced pressure and the residue was extracted with hot benzene (50 c.c.). The benzene solution was distilled, giving *cyclo*hexyl *p*-nitrophenyl ether, b. p. 145—147°/0·3 mm. (5·9 g.).

p-*Aminophenyl* cyclo*Hexyl Ether*.—(*a*) *cyclo*Hexyl *p*-nitrophenyl ether (3·6 g.) in 95% aqueous alcohol (20 c.c.) was stirred under reflux on the steam-bath with iron powder (8·2 g.) and concentrated hydrochloric acid (2 c.c.) for 3 hr. 95% Alcohol (30 c.c.) was then added and the mixture was allowed to cool. After neutralisation with concentrated aqueous ammonia, the mixture was centrifuged and the alcoholic solution concentrated under reduced pressure to give a semi-crystalline mass. This was dissolved in water (40 c.c.) and 2N-hydrochloric acid (20 c.c.), and the mixture was extracted with ether. The aqueous portion was made alkaline with 2N-sodium hydroxide, and the resulting oil extracted with ether, dried (Na_2SO_4), and distilled to give a colourless oil, b. p. 128°/0·2 mm. (2·1 g.).

(*b*) The amino-ether was also obtained by hydrogenation of *cyclo*hexyl *p*-nitrophenyl ether (9·8 g.) in absolute alcohol (80 c.c.) in the presence of Raney nickel at 60° and at atmospheric pressure. The yield was 6 g., b. p. 113—114°/0·004 mm. The *acetyl* derivative, crystallised from absolute alcohol, had m. p. 155° (Found : C, 72·4; H, 8·1; N, 6·05. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2; N, 6·0%).

tert.-*Butyl* p-*Nitrophenyl Ether*.—The ether, prepared from *tert.*-butanol (20 c.c.), potassium (1·4 g.), and *p*-fluoronitrobenzene (5 g.) by the above method, had b. p. 97°/0·2 mm. (4·3 g.) and a powerful odour.

p-*Aminophenyl* tert.-*Butyl Ether*.—Reduction of the nitro-ether (5 g.) as in (*a*) above gave the amino-ether (2·7 g.), b. p. 91—92·5°/0·4 mm., m. p. 73—74° [from light petroleum (b. p. 60—80°)]. The *acetyl* derivative crystallised from 66% aqueous alcohol as plates, m. p. 130° (Found : C, 69·8; H, 8·4; N, 6·95. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·3; N, 6·8%).

1-*Methyl*-4-*piperidyl* p-*Nitrophenyl Ether*.—A mixture of 1-methylpiperidin-4-ol (13·5 g.), *tert.*-butanol (75 c.c.), and potassium (3·4 g.) was heated under reflux until all the potassium had reacted. *p*-Fluoronitrobenzene (15·5 g.) was added in one portion at 30°. The mixture was shaken and the temperature was allowed to rise to 40°. When the exothermic reaction had abated the mixture was heated on the steam-bath for 15 min. The *tert.*-butanol was removed under reduced pressure and the residue was extracted with boiling benzene (100 c.c.), from which, on concentration under reduced pressure, orange crystals were deposited (23 g.). These were boiled with light petroleum (b. p. 60—80°; 150 c.c.), and the decanted solution gave orange-yellow plates, m. p. 96—98° (16 g.). The *ether* was finally crystallised from *iso*propyl ether, giving pale yellow crystals, m. p. 100—101° (Found : C, 61·1; H, 6·7; N, 11·9. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8; N, 11·9%). The *picrate* crystallised from 75% aqueous acetone as yellow needles, m. p. 204—205° (Found : C, 46·9; H, 3·8; N, 14·7. $C_{18}H_{19}O_{10}N_5$ requires C, 46·5; H, 4·1; N, 15·0%). The *methiodide* crystallised from 95% aqueous alcohol as pale yellow needles, m. p. 265—266° (Found : C, 41·0; H, 4·9; N, 7·5. $C_{13}H_{19}O_3N_2I$ requires C, 41·3; H, 5·1; N, 7·4%).

p-*Aminophenyl* 1-*Methyl*-4-*piperidyl Ether*.—The nitro-ether (9·4 g.) was hydrogenated in absolute alcohol (150 c.c.) in the presence of Raney nickel (4 g.) at 20°/5 atm. The catalyst was filtered off and the solvent removed under pressure to give a pale-brown oil which slowly crystallised. Difficulty was experienced in recrystallising this material, a small amount of crystals being obtained, m. p. 74—76°, from ether, but these appeared to be hygroscopic. The acetyl derivative crystallised from water as a hydrate, m. p. 107°, which was converted into an acetyl compound, m. p. 130°, on drying ($CaCl_2$). This compound reverted to that melting at 107° when kept in air. Both compounds gave the same *methiodide*, m. p. 226° (from methanol) (Found : C, 46·1; H, 5·9; N, 7·2; I, 32·7. $C_{15}H_{23}O_2N_2I$ requires C, 46·1; H, 5·9; N, 7·2; I, 32·5%).

1-*Acetyl*-4-*piperidyl* p-*Nitrophenyl Ether* —To potassium *tert* -butoxide prepared from potas-

sium (1 g.) and *tert.*-butanol (25 c.c.) was added 1-acetylpiperidin-4-ol (4 g.). The resulting solution was boiled for 15 min. and then cooled to 35°; then *p*-fluoronitrobenzene (4 g.) was added in one portion, with shaking. The temperature was held at 45° until the exothermic reaction had ceased and was finally raised to 80° and held at this temperature for 15 min. After removal of the *tert.*-butanol under reduced pressure, the *nitro-ether* was isolated by benzene-extraction, forming yellow crystals, m. p. 94—95° (3·8 g.), from diethylamine (Found: C, 58·9; H, 6·4; N, 10·8. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6%).

1-*Acetyl*-4-*piperidyl* p-*Aminophenyl Ether*.—Hydrogenation of the nitro-ether (2·64 g.) in absolute alcohol (50 c.c.) in the presence of Raney nickel (1·0 g.) at 45°/1 atm. gave a pale brown oil (2·3 g.) which slowly crystallised. This was converted into the *acetyl* derivative (1·8 g.), m. p. 158° (from hot water) (Found: C, 65·3; H, 7·1; N, 10·4. $C_{15}H_{20}O_3N_2$ requires C, 65·2; H, 7·3; N, 10·1%).

cyclo*Hexyl* 4-*Pyridyl Ether*.—(*a*) Potassium (1·3 g.) and *cyclo*hexanol (20 c.c.) were heated together until the reaction was complete. 4-Chloropyridine (3·8 g.) was added in one portion, and when the exothermic reaction had ceased, the mixture was boiled for 3 hr. Sodium chloride was deposited from the hot solution but redissolved on cooling. The product was isolated in the usual way with benzene, and distilled to give a colourless oil, b. p. 139—142°/10 mm. (5·1 g.). The substance was insoluble in water, but readily dissolved in dilute acids from which it could be regenerated. Dry hydrogen chloride in ether reacted with it, as did methyl iodide, to give an oil. With alcoholic picric acid a *picrate* was formed, m. p. 148° (from absolute alcohol) (Found: C, 50·3; H, 4·4; N, 14·0. $C_{17}H_{18}O_8N_4$ requires C, 50·3; H, 4·5; N, 13·8%). The base (2 g.), heated on the steam-bath for 3 hr. with concentrated hydriodic acid (15 g.), gave *cyclo*hexyl iodide (1·3 g.), b. p. 71°/14 mm., and 4-hydroxypyridine (1·2 g.) characterised as the nitrate, m. p. 204—205° (decomp.).

(*b*) Potassium (1·4 g.) and *tert.*-butanol (25 c.c.) were heated together until completion of the reaction, and *cyclo*hexanol (4 g.) was then added and the mixture boiled for 15 min. 4-Chloropyridine (4 g.) was added and the mixture heated in a sealed tube at 150° for 15 hr. The product was isolated in the usual manner, giving 4 g. of material identical with that obtained as in (*a*).

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