SOME DERIVATIVES OF 1,2,3,6-TETRAHYDROPYRIDINE

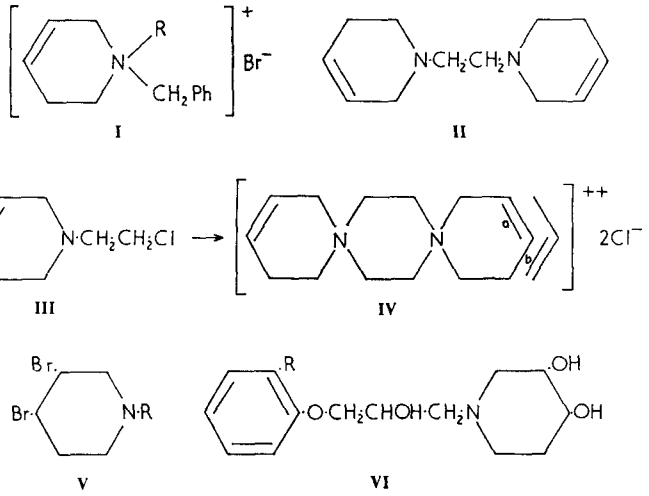
By V. Petrow and O. Stephenson

*From The British Drug Houses Ltd., Graham Street, London, N.*1

Received January 12, 1962

The preparation of some derivatives of 1,2,3,6-tetrahydropyridine and hydroxylation of certain of these to *cis*- and *trans*-piperidine-3,4-diols is described.

1-Benzyl-1,2,3,6-tetrahydropyridine reacted with benzyl bromide and with phenethyl bromide to yield the quaternary salts (Ia, R = ·CH_2·Ph) and (Ib, R = ·CH_2·CH_2·Ph) respectively. The latter compound, more readily prepared by reaction of 1,2,3,6-tetrahydro-1-phenethylpyridine with benzyl bromide, was only obtained in one isomeric form (compare Beasley, Petrow and Stephenson, 1958). 1,2,3,6-Tetrahydropyridine reacted slowly with 1,2-dichloroethane at reflux temperature to yield the dihydrochloride of 1,2-di(1,2,3,6-tetrahydropyridino)ethane (II). With ethylene oxide the tetrahydropyridine gave a high yield of 2-(1,2,3,6-tetrahydropyridino)ethanol, smoothly converted by reaction with thionyl chloride [compare Chabrier, Najer, Giudicelli and Joannic (1957)] into the hydrochloride of the chloride (III). The last compound was converted into the free base, which dimerised on prolonged heating in ethanolic solution to give the di*spiro*piperazine derivative (IVa or IVb), which again was obtained in only one form.



I II III IV V VI

Bromination of 1,2,3,6-tetrahydropyridine hydrobromide in acetic acid gave a high yield of the hydrobromide of the 3,4-dibromo-compound, smoothly converted into the urea (Va, R = ·CO·NH_2). Corresponding 3,4-dibromoderivatives were prepared from 1-benzoyl- (Vb, R = ·CO·Ph), and 1-benzyl-1,2,3,6-tetrahydropyridine (Vc, R = ·CH_2·Ph), the former

yielding two isomers, one of which passed slowly into the higher-melting form on storage. Neither of the isomers proved suitable for conversion into piperidine-3,4-diols by means of reaction with potassium acetate-acetic acid.

Only one mention of piperidine-3,4-diols has been found in the literature. McElvain and Safranski (1950) obtained 1-methyl-4-phenyl-piperidine-3,4-diol by hydrolysis of 3-bromo-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a reaction involving conversion of the bromine atom into a hydroxyl group followed by hydration at the double bond.

1-Benzoyl-1,2,3,6-tetrahydropyridine was readily converted by peracetic acid into *trans*-1-benzoylpiperidine-3,4-diol in good yield. With ethereal perphthalic acid, the benzoyl derivative gave an epoxide, obtained only in the form of a *gum*, which yielded the foregoing *trans*-diol on hydration. Hydrolysis of *trans*-1-benzoyl-piperidine-3,4-diol with ethanolic hydrochloric acid gave *trans*-piperidine-3,4-diol hydrochloride, subsequently obtained more readily by hydrolysis of *trans*-1-acetylpiperidine-3,4-diol, though the acetyl derivative itself could not be obtained pure. Hydrolysis of *trans*-1-benzoylpiperidine-3,4-diol with hot alkali, followed by reaction of the resultant base *in situ* with 1,2-epoxy-3-phenoxypropane gave *trans*-1-(2-hydroxy-3-phenoxypropyl)piperidine-3,4-diol (VI; R = H). The *o*-tolyl analogue (VI; R = Me) was similarly prepared. *trans*-1-Carbamoylpiperidine-3,4-diol was obtained by reaction of the diol hydrochloride with aqueous sodium cyanate.

cis Hydroxylation of 1-acetyl- and 1-benzoyl-1,2,3,6-tetrahydropyridine was readily accomplished using aqueous sodium chlorate-osmium tetroxide at 50–60°, a procedure used by Böeseken and van Giffen (1920) and later by Clarke and Owen (1949). The *cis*-diol was also obtained, albeit in poor yield, using iodine-silver acetate in moist acetic acid as described by Ginsberg (1953), Gunstone and Morris (1957) and Woodward and Brutcher (1958). Hydrolysis of the l-acetyl- or -benzoyl- *cis*-diols with ethanolic hydrochloric acid yielded *cis*-piperidine-3,4-diol hydrochloride, which reacted with benzoyl chloride in the presence of alkali to yield the original benzoyl derivative and with sodium cyanate to give *cis*-1-carbamoylpiperidine-3,4-diol. *cis*-Piperidine-3,4-diol was converted by 1,2-epoxy-3-phenoxypropane into *cis*-1-(2-hydroxy-3-phenoxypropyl)-piperidine-3,4-diol.

Hydroxylation of 4-phenyl-1-toluene-*p*-sulphonyl-1,2,3,6-tetrahydropyridine with peracetic acid gave small yields of both the *cis*- and *trans*-3,4-diols. The former isomer alone was obtained using sodium chlorate-osmium tetroxide in aqueous ethanol.

Finally, the hydroxylation of 1-benzyl-1,2,3,6-tetrahydropyridine was studied. Possible complications due to the presence of a basic nitrogen centre were avoided by using the sulphate of the base in the sodium chlorate-osmium tetroxide procedure when *cis*-1-benzylpiperidine-3,4-diol was readily obtained. Reaction of this compound with methyl iodide furnished a difficultly separable mixture of isomeric methiodides. Their conversion into methochlorides permitted facile separation. 1-Benzyl-1,2,3,6-tetrahydropyridine was converted by peracetic acid into a mixture

of isomeric *trans*-1-benzyl-3,4-dihydroxypiperidine *N*-oxides which were readily separated as their hydrochlorides. Conversion of the corresponding *cis*-1-benzylpiperidine-3,4-diol to the *N*-oxides using acetone-hydrogen peroxide led to the isolation of only one pure isomer, which proved to be unstable on storage.

Pharmacological study of many of the above compounds by Dr. A. David and his colleagues gave no results worthy of comment.

Experimental

1-Benzyl-1,2,3,6-tetrahydropyridine. A solution of 1,2,3,6-tetrahydropyridine (91·5 g.) in water (400 ml.) containing potassium hydroxide (61·6 g.) was heated with stirring to 40° and benzyl chloride (126·5 g.) added during 10 min. Reaction was completed by heating to 70° for 2 hr. The *product* (151 g.), isolated with benzene, had b.p. 68° at 0·1 mm. Found: C, 83·6; H, 8·4; N, 7·8. $C_{12}H_{15}N$ requires C, 83·2; H, 8·7; N, 8·1 per cent.

1-Benzyl-3,4-dibromopiperidine hydrobromide. A solution of the foregoing base (86·5 g.) in acetic acid (200 ml.) was treated with stirring and water-cooling with 50 per cent w/v hydrogen bromide in acetic acid (90 ml.) followed by a solution of bromine (80 g.) in acetic acid (100 ml.) added during 20 min. The mixture was concentrated at reduced pressure and the residue dissolved in ethyl acetate (200 ml.) to yield the *product* (172 g.) m.p.184° (decomp.) (from ethanol-ethyl acetate). Found: C, 35·1; H, 4·0; Br, 57·5; N, 3·3. $C_{12}H_{16}Br_3N$ requires C, 34·8; H, 3·9; Br, 57·9; N, 3·4 per cent.

1,1-Dibenzyl-1,2,3,6-tetrahydropyridinium bromide, prepared by reaction of 1-benzyl-1,2,3,6-tetrahydropyridine with benzyl bromide in benzene, had m.p. 188–190° (from ethanol-ethyl acetate). Found: C, 66·5; H, 6·4; Br, 23·0; N, 3·8. $C_{19}H_{22}BrN$ requires C, 66·2; H, 6·4; Br, 23·2; N, 4·1 per cent. The *picrate* had m.p. 153–154° (from ethanol). Found: C, 60·8; H, 4·8; N, 11·1. $C_{25}H_{24}N_4O_7$ requires C, 60·9; H, 4·9; N, 11·4 per cent. A solution of the *bromide* (1·0 g.) in acetic acid (10 ml.) treated with the theoretical amount of bromine in acetic acid yielded *1,1-dibenzyl-3,4-dibromopiperidinium bromide* (1·5 g.) as light orange needles, (from ethanol). Found: C, 45·1; H, 4·3; Br, 47·2; N, 2·9. $C_{19}H_{22}Br_3N$ requires C, 45·2; H, 4·4; Br, 47·6; N, 2·8 per cent. *1,2,3,6-Tetrahydro-1-phenethylpyridine*, had b.p. 70° at 0·1 mm. Found: C, 83·5; H, 9·1; N, 7·4. $C_{13}H_{17}N$ requires C, 83·4; H, 9·2; N, 7·5 per cent.

1-Benzyl-1,2,3,6-tetrahydro-1-phenethylpyridinium bromide prepared (*a*) by reaction of the foregoing base with benzyl bromide at room temperature or in lower yield by (*b*) reaction of 1-benzyl-1,2,3,6-tetrahydropyridine with phenethyl bromide at 100° for 8 hr., had m.p. 195–197° (from ethanol-ethyl acetate). Found: C, 67·2; H, 6·7; Br, 22·3; N, 3·9. $C_{20}H_{24}BrN$ requires C, 67·0; H, 6·8; Br, 22·3; N, 3·9 per cent. Fractional crystallisation of a sample did not show the presence of an isomer. The *iodide* had m.p. 181–182° (from ethanol-ethyl acetate). Found: C, 59·0; H, 5·8. $C_{20}H_{24}IN$ requires C, 59·2; H, 6·0 per cent. The *picrate*, bright yellow crystals (from ethanol), had m.p. 136–138°. Found: C, 62·0;

H, 5·2; N, 10·8. $C_{26}H_{26}N_4O_7$ requires C, 61·6; H, 5·2; N, 11·1 per cent. A solution of the bromide in acetic acid treated with bromine in the same solvent yielded 1-*benzyl*-3,4-*dibromo*-1-*phenethyl-piperidinium bromide*, orange crystals (from ethanol), m.p. 92–94°. Found: C, 46·1; H, 4·9; Br, 46·3; N, 3·0. $C_{20}H_{24}Br_3N$ requires C, 46·3; H, 4·7; Br, 46·3; N, 2·7 per cent. 1,2-Di-(1,2,3,6-*tetrahydropyridino*)*ethane*. To a solution of 1,2,3,6-tetrahydropyridine (83 g.) in benzene (300 ml.) was added sodium carbonate (74·2 g.) followed by 1,2-dichloroethane (49·5 g.) and the mixture was heated under reflux for 20 hr. The *product* was obtained as an oil, b.p. 74° at 0·2 mm. Found: C, 74·9; H, 10·6; N, 14·8. $C_{12}H_{20}N_2$ requires C, 74·9; H, 10·5; N, 14·6 per cent. The *dihydrochloride* had m.p. 316° (decomp.) (from ethanol). Found: C, 54·6; H, 8·4; Cl, 26·8. $C_{12}H_{22}Cl_2N_2$ requires C, 54·3; H, 8·4; Cl, 26·8 per cent.

1,2,3,6-*Tetrahydro*-1-(2-*hydroxyethyl*)*pyridine* obtained in 72 per cent yield by reaction of 1,2,3,6-tetrahydropyridine with ethylene oxide in ethanolic solution, had b.p. 46° at 0·2 mm. Found: C, 65·8; H, 10·5; N, 10·8. $C_7H_{13}NO$ requires C, 66·1; H, 10·3; N, 11·0 per cent.

1-(2-*Chloroethyl*)-1,2,3,6-*tetrahydropyridine hydrochloride*. A solution of the foregoing base (100 g.) in benzene (500 ml.) was treated with thionyl chloride (141 g.), added during 30 min. with shaking and water cooling. The mixture was then heated under reflux for 1 hr. The *product* (141 g.) had m.p. 236° (decomp.) (from ethanol-ethyl acetate). Found: C, 46·4; H, 7·1; Cl, 38·6; N, 7·7. $C_7H_{13}Cl_2N$ requires C, 46·2; H, 7·2; Cl, 38·9; N, 7·7 per cent.

1,2,3,6-*Tetrahydropyridinium*-1-*spiro*-1′-*piperazine*-4′-*spiro*-1″-1″,2″,3″ (or 5″), 6″-*tetrahydropyridinium dichloride*. A solution of the foregoing hydrochloride (18·2 g.) in water (15 ml.) was treated with a solution of sodium hydroxide (5·5 g.) in water (10 ml.). The base was isolated with chloroform and the solvent distilled off. The residual oil was dissolved in ethanol (50 ml.) and the solution heated under reflux for 6 hr. The *product* which separated (10·1 g.) had m.p. 338° (decomp.) (from aqueous ethanol). Fractional crystallisation of a sample from the same solvent mixture yielded no sign of isomeric product. Found: C, 57·4; H, 8·3; N, 9·7. $C_{14}H_{24}Cl_2N_2$ requires C, 57·7; H, 8·3; N, 9·6 per cent.

3,4-*Dibromopiperidine hydrobromide* was obtained in 86 per cent yield by reaction of 1,2,3,6-tetrahydropyridine hydrobromide in acetic acid with a solution of bromine in the same solvent. It had m.p. 207° (decomp.) (from ethanol). Found: C, 18·9; H, 3·1; Br, 73·3; N, 4·4. $C_5H_{10}Br_3N$ requires C, 18·5; H, 3·1; Br, 74·1; N, 4·3 per cent.

3,4-*Dibromo*-1-*carbamoylpiperidine*. A solution of the foregoing hydrobromide (3·2 g.) in water (20 ml.) was treated with a solution of sodium cyanate (0·8 g.) in water (5 ml.) and the mixture warmed to 60–65° for 10 min. The product (2·8 g.) was collected and washed with a little cold water. It had m.p. 182–183° (decomp.) (from ethyl acetate). Found: C, 25·6; H, 3·5; N, 10·2. $C_6H_{10}Br_2N_2O$ requires C, 25·2; H, 3·5; N, 9·8 per cent.

1-*Benzoyl*-3,4-*dibromopiperidine*. A solution of 1-benzoyl-1,2,3,6-tetrahydropyridine (37·4 g.) in acetic acid (100 ml.) was treated with

stirring and water cooling with a solution of bromine (32 g.) in acetic acid (50 ml.). Dilution with water furnished a *product* (30·5 g.) having m.p. 86–89° after crystallisation from light petroleum (b.p. 60–80°) containing a small amount of ethyl acetate. Found: C, 41·3; H, 3·7; N, 4·2. $C_{12}H_{13}Br_2NO$ requires C, 41·5; H, 3·8; N, 4·0 per cent. The m.p. of the material after several weeks was 86–106°. Concentration of the mother liquors from the first crystallisation yielded a second *product* (12 g.), m.p. 106° (from aqueous methanol). Found: C, 41·5; H, 3·7; N, 3·7 per cent.

trans-1-*Benzoylpiperidine*-3,4-*diol* (*a*) 1-Benzoyl-1,2,3,6-tetrahydropyridine (37·4 g.) was melted and added with stirring to a solution of peracetic acid prepared from acetic acid (150 ml.) and 30 per cent hydrogen peroxide (46 ml.) and the mixture was heated at 85–90° for 10 hr. It was then concentrated to about one third bulk and neutralised with a concentrated solution of potassium hydroxide. The oil was isolated by extraction with chloroform and the extract washed with saturated salt solution when the chloroform was boiled off. The residue was dissolved in ethanol (150 ml.), sodium carbonate (10 g.) added and the mixture heated under reflux for 2 hr. It was filtered, concentrated to about 50 ml. and diluted with ethyl acetate. The product (29·2 g.) had m.p. 148–150° (from ethyl acetate containing a trace of methanol). Found: C, 65·2; H, 7·0; N, 6·5. $C_{12}H_{15}NO_3$ requires C, 65·1; H, 6·8; N, 6·3 per cent.

(*b*) A solution of 1-benzoyl-1,2,3,6-tetrahydropyridine (9·35 g.) in ether (20 ml.) was treated with a solution of perphthalic acid in ether (100 ml., 0·05 M.). The mixture was allowed to stand for 12 days when chloroform was added and the solution, after washing free from acid and peroxide, was concentrated. The resultant gum failed to crystallise. It was heated with acetic acid (10 ml.) at 95° for 3 hr. when the acid was distilled off at reduced pressure and the product dissolved in ethanol (30 ml.) and the solution heated under reflux with sodium carbonate (2 g.) for 3 hr. The solution was filtered and concentrated. Crystallisation of the residue from ethyl acetate furnished the product (2·2 g.) m.p. 147–149°. The melting point was not depressed on admixture with the compound prepared in (*a*). Reaction of the diol (1·5 g.) with two equivalents of benzoyl chloride in pyridine yielded trans-1-*benzoyl*-3,4-*benzoyloxypiperidine*, m.p. 140–141° [from ethyl acetate-light petroleum (b.p. 60–80°)]. Found: C, 72·5; H, 5·1; N, 3·1. $C_{26}H_{23}NO_5$ requires C, 72·7; H, 5·4; N, 3·3 per cent.

trans-*Piperidine*-3,4-*diol hydrochloride*. A solution of *trans*-1-benzoylpiperidine-3,4-diol (50 g.) in concentrated hydrochloric acid (80 ml.) was boiled under reflux for 6 hr. after which excess of acid was removed under reduced pressure. The residual solid was crystallised from ethanol-ethyl acetate to yield the product (28·6 g.) m.p. 138–140°. Found: C, 39·3; H, 7·8; Cl, 23·6; N, 9·4. $C_5H_{12}ClNO_2$ requires C, 39·1; H, 7·9; Cl, 23·1; N, 9·1 per cent.

trans-1-*Carbamoylpiperazine*-3,4-*diol*, prepared by reaction of the foregoing hydrochloride with sodium cyanate in concentrated aqueous solution, had m.p. 131–133° (from ethanol-ethyl acetate). Found:

C, 44·7; H, 7·5; N, 17·2. $C_6H_{12}N_2O_3$ requires C, 45·0; H, 7·6; N, 17·5 per cent.

trans-1-(2-p-*Acetamidophenoxyethyl*)*piperidine*-3,4-*diol hydrochloride.* A mixture of *trans*-piperidine-3,4-diol hydrochloride (6·14 g.), 2-*p*-acetamidophenoxyethyl bromide (10 g.)and sodium carbonate (4·7 g.) in ethanol (50 ml.) was heated under reflux for 8 hr. and filtered. Treatment of the filtrate with hydrogen chloride yielded the *product*, m.p. 192° (from ethanol-ethyl acetate). Found: Cl, 10·8; N, 8·4. $C_{15}H_{23}ClN_2O_4$ requires Cl, 10·7; N, 8·5 per cent.

trans-1-(2-*Hydroxy*-3-*phenoxypropyl*)*piperidine*-3,4-*diol.* 1-Acetyl-1,2,3,6-tetrahydropyridine (25 g.) was added to a solution of peracetic acid prepared from 30 per cent hydrogen peroxide (46 ml.) and acetic acid (120 ml.) and the solution was heated at 90° for 2 hr. It was then concentrated to about one-fifth volume at reduced pressure and just basified with 25 per cent aqueous potassium hydroxide. The solution was saturated with sodium chloride and extracted with t-butanol. The extract was concentrated and the residual oil hydrolysed by heating with a solution of potassium hydroxide (11·2 g.) in water (20 ml.) for 2 hr. Ethanol (50 ml.) was then added, followed by 1,2-epoxy-3-phenoxypropane (16 g.) and the mixture heated under reflux for 30 min. The solution was concentrated at reduced pressure and the residual solid crystallised from ethyl acetate containing a trace of ethanol to yield the *product* (10·4 g.) m.p. 166–168°. Found: C, 62·9; H, 7·6; N, 4·8. $C_{14}H_{21}NO_4$ requires C, 62·9; H, 7·9; N, 5·2 per cent.

trans-1-(2-*Hydroxy*-3-o-*tolyloxypropyl*)*piperidine*-3,4-*diol*, had m.p. 150–152° (from ethyl acetate). Found: C, 63·5; H, 8·1; N, 5·1. $C_{15}H_{23}NO_4$ requires C, 64·0; H, 8·2; N, 5·0 per cent.

cis-1-*Acetylpiperidine*-3,4-*diol.* 1-Acetyl-1,2,3,6-tetrahydropyridine (87·6 g.) was dissolved in water (700 ml.) containing sodium chlorate (97 g.) and a solution of osmium tetroxide (0·25 g.) in water (25 ml.) added at once with stirring. The temperature of the mixture rose spontaneously to 48° over about 45 min. and was then kept at 45–50° for 1 hr. The mixture was cooled, extracted with benzene and the aqueous layer evaporated to dryness at reduced pressure. The residual solid was extracted with four 250 ml. portions of boiling chloroform, the chloroform extracts were concentrated, and diluted with ethyl acetate. The *product* (83·5 g.) had m.p. 119–120° after crystallisation from ethyl acetate containing a little methanol. Found: C, 52·9; H, 8·2; N, 9·0. $C_7H_{13}NO_3$ requires C, 52·8; H, 8·2; N, 8·8 per cent.

cis-1-*Benzoylpiperidine*-3,4-*diol*, was prepared by hydroxylation of 1-benzoyl-1,2,3,6-tetrahydropyridine (37·4 g.) in water (500 ml.) containing sodium chlorate (34 g.) and osmium tetroxide (0·2 g.) at 50° for 5 hr. The *product* (30 g.) had m.p. 151–152° after crystallisation from ethyl acetate containing a trace of methanol. Found: C, 64·7; H, 6·8; N, 6·5. $C_{12}H_{15}NO_3$ requires C, 65·1; H, 6·8; N, 6·3 per cent. A mixture of the diol (2·21 g.) and *p*-nitrobenzaldehyde (1·51 g.) in benzene (40 ml.) and dioxan (20 ml.) was treated with toluene *p*-sulphonic acid (50 mg.) and heated on the steam-bath for 1 hr., to yield a p-*nitrobenzylidene*

derivative (2·1 g.) m.p. 138–139° (from aqueous methanol). Found: C, 64·6; H, 5·6; N, 7·8. $C_{19}H_{18}N_2O_5$ requires C, 64·4; H, 5·1; N, 7·9 per cent. Treatment of the diol with 2 mole equivs. of benzoyl chloride in pyridine yielded a *gum* which failed to crystallise.

cis-*Piperidine*-3,4-*diol hydrochloride.* A solution of *cis*-1-acetylpiperidine-3,4-diol (79·5 g.) in ethanol (200 ml.) containing concentrated hydrochloric acid (100 ml.) was heated under reflux for 5 hr. and the mixture evaporated to dryness at reduced pressure. The *product* (63 g.) had m.p. 224–225° (from methanol-ether). Found: C, 39·1; H, 7·8; Cl, 23·5; N, 9·2. $C_5H_{12}ClNO_2$ requires C, 39·1; H, 7·9; Cl, 23·1; N, 9·1 per cent. A solution of the hydrochloride (7·7 g.) in water (40 ml.) was stirred and treated successively with 40 per cent caustic soda solution (10 ml.) and benzoyl chloride (7 g.). After 4 hr. the product was isolated with chloroform to yield *cis*-1-benzoylpiperidine-3,4-diol, m.p. 150–151°, identical with the compound described earlier.

cis-1-*Carbamoylpiperidine*-3,4-*diol*, obtained in 70 per-cent yield, had m.p. 176° (from methanol). Found: C, 44·6; H, 7·8; N, 17·9. $C_6H_{12}N_2O_3$ requires C, 45·0; H, 7·6; N, 17·5 per cent.

cis-1-(2-*p*-*Acetamidophenoxyethyl*)*piperidine*-3,4-*diol*, was prepared by reaction of *cis*-piperidine-3,4-diol hydrochloride (6·14 g.) with 2-*p*-acetamidophenoxyethyl bromide (10 g.) in ethanol (50 ml.) containing sodium carbonate (4·7 g.) at reflux temperature for 8 hr. It (8·6 g.) had m.p. 139–140° [from ethanol-light petroleum (b.p. 60–80°)]. Found: C, 61·5; H, 7·5; N, 9·6. $C_{15}H_{22}N_2O_4$ requires C, 61·2; H, 7·5; N, 9·5 per cent.

cis-1-2-*Hydroxy*-3-*phenoxypropyl*)*piperidine*-3,4-*diol.* A mixture of *cis*-piperidine-3,4-diol hydrochloride (15·36 g.) and 1,2-epoxy-3-phenoxypropane (15 g.) in methanol (25 ml.) was treated with a solution of potassium hydroxide (5·8 g.) in methanol (25 ml.) and the mixture heated under reflux for 30 min. It was then concentrated, diluted with water and extracted with chloroform. The extract was washed with salt solution, concentrated, and diluted with light petroleum (b.p. 60–80°) to yield the *product* (19·3 g.), m.p. 123–124° (from ethanol). Found: C, 63·0; H, 7·8; N, 5·1. $C_{14}H_{21}NO_4$ requires C, 62·9; H, 7·9; N, 5·2 per cent.

trans-1-*Benzylpiperidine*-3,4-*diol* N-*oxide hydrochloride.* 1-Benzyl-1,2,3,6-tetrahydropyridine (31·8 g.) was added to a solution of peracetic acid prepared from 30 per cent hydrogen peroxide (46 ml.) and acetic acid (150 ml.) and the mixture heated at 75–80° for 5 hr., when it was concentrated to about one fifth of its volume at reduced pressure. The viscous residue was neutralised with concentrated aqueous sodium carbonate, saturated with salt and extracted with chloroform. The extracts were concentrated, the residue dissolved in ethanol (50 ml.) and treated with a slight excess of hydrogen chloride. Dilution with ether furnished two products, (A) 8 g. m.p. 152–154° (decomp.) and (B) 1·5 g., m.p. 140–142°. Repeated crystallisation from ethanol-ether yielded *isomer* (A), m.p. 158° (decomp.) Found: C, 55·4; H, 6·8; N, 5·2 and *isomer* (B), m.p. 168–170°. Found: C, 55·3; H, 6·8; N, 5·6. $C_{12}H_{18}ClNO_3$ requires C, 55·5; H, 7·0; N, 5·4 per cent. Mixtures of the two isomers melted at 140–146°.

cis-1-*Benzylpiperidine*-3,4-*diol.* (*a*) A solution of 1-benzyl-1,2,3,6-tetrahydropyridine (34·6 g.) in water (400 ml.) was brought to pH 7 by addition of concentrated sulphuric acid (6·5 ml.). The solution was stirred and treated with sodium chlorate (34 g.), followed by osmium tetroxide (0·2 g.), and the mixture left at 30–35° for 2 hr. and then heated to 75° for 10 min. It was cooled, extracted with benzene and the aqueous fraction saturated with solid sodium carbonate. The resultant oil was isolated with chloroform and distilled at reduced pressure to yield unchanged material (14·3 g.), b.p. 75–80° at 0·5 mm., along with *product* (21·1 g.) b.p. 150–155° at 0·5 mm. The latter had m.p. 98–100° [from ethyl acetate-light petroleum (b.p. 60–80°)]. Found: C, 69·7; H, 8·2; N, 6·6. $C_{12}H_{17}NO_2$ requires C, 69·5; H, 8·3; N, 6·8 per cent.

(*b*) A mixture of *cis*-piperidine-3,4-diol hydrochloride (30·72 g.), benzyl chloride (25·3 g.) and sodium hydroxide (20 g.) in water (110 ml.) was stirred at 35° for 6 hr. The *product* (31·5 g.) isolated with chloroform had b.p. 150–153° at 0·5 mm. and m.p. 98–100° [from ethyl acetate-light petroleum (b.p. 60–80°)].

cis-1-*Benzylpiperidine*-3,4-*diol* N-*oxide hydrochloride.* A solution of the foregoing diol (10·35 g.) in acetone (50 ml.) was treated with 30 per cent hydrogen peroxide solution (8·5 ml.) and kept at 20–25° for 4 days, when the mixture was evaporated to dryness at reduced pressure. The residual gum, treated with ethanolic hydrogen chloride, yielded the product (7·2 g.), m.p. 145–146° (from ethanol-ethyl acetate). Found: C, 55·7; H, 7·3; Cl, 13·6; N, 5·6. $C_{12}H_{18}ClNO_3$ requires C, 55·5; H, 7·0; Cl, 13·7; N, 5·4 per cent. The compound decomposed slowly on storage.

cis-1-*Benzyl*-3,4-*dihydroxy*-1-*methylpiperidinium chloride.* A mixture of *cis*-1-benzylpiperidine-3,4-diol (20·7 g.) and methyl iodide (17 g.) in ethanol (60 ml.) was heated under reflux for 1 hr., when dilution with ethyl acetate furnished the *methiodides* (30 g.). Conversion into the *methochlorides* yielded two readily separable isomers, the less-soluble *isomer* (A) (5·1 g.) had m.p. 239–240° (from ethanol). Found: C, 60·6; H, 8·3; Cl, 13·8; N, 5·3. $C_{13}H_{20}ClNO_2$ requires C, 60·5; H, 7·8; Cl, 13·8; N, 5·4 per cent. The more-soluble *isomer* (B) (4·9 g.) had m.p. 184–186° (from ethanol-ethyl acetate). Found: C, 60·5; H, 8·0; Cl, 13·8; N, 5·5 per cent.

1,2,3,6-*Tetrahydro*-4-*phenyl*-1-*toluene*-p-*sulphonylpyridine* was obtained in 90 per cent yield by reaction of 1,2,3,6-tetrahydro-4-phenylpyridine with toluene-*p*-sulphonyl chloride in pyridine. It had m.p. 203–205° (from benzene). Found: C, 68·7; H, 5·8; N, 4·3; S, 10·5. $C_{18}H_{19}NO_2S$ requires C, 69·0; H, 6·1; N, 4·5; S, 10·2 per cent.

cis-4-*Phenyl*-1-*toluene*-p-*sulphonylpiperidine*-3,4-*diol.* A suspension of the foregoing tetrahydropyridine (10·45 g.) in ethanol (300 ml.) was treated with a solution of sodium chlorate (5·33 g.) in water (100 ml.). Aqueous osmium tetroxide (20 ml., 1 per cent w/v) was then added and the mixture stirred at 60–65° for 4 hr. The insoluble solid (8·6 g.; unchanged material) was filtered off, the filtrate concentrated to remove ethanol and extracted with four 50 ml. portions of chloroform. Concentration of the chloroform extract furnished the *product* (2·0 g.) m.p.

168–169° [from ethyl acetate-light petroleum (b.p. 60–80°)]. Found: C, 62·1; H, 6·1; N, 4·2; S, 9·5. $C_{18}H_{21}NO_4S$ requires C, 62·2; H, 6·1; N, 4·0; S, 9·2 per cent.

trans-4-*Phenyl*-1-*toluene*-p-*sulphonylpiperidine*-3,4-*diol*. A suspension of 1,2,3,6-tetrahydro-4-phenyl-1-toluene-*p*-sulphonylpyridine (6·26 g.) in acetic acid (40 ml.) was added to a solution of peracetic acid prepared from acetic acid (15 ml.) and 30 per cent hydrogen peroxide (5 ml.) and the mixture (homogeneous after 1 hr.) heated at 90–95° for 2 hr. The solution was diluted with water, the viscous material isolated with chloroform, the chloroform distilled off and the residual gum refluxed in ethanol (50 ml.) containing sodium carbonate (2 g.) for 1 hr. The ethanolic suspension was filtered, concentrated and diluted with light petroleum (b.p. 60–80°). The crystalline material which separated (1·0 g.) had m.p. 196–198° (from aqueous methanol). Found: C, 62·4; H, 5·9; N, 4·2; S, 9·1. $C_{18}H_{21}NO_4S$ requires C, 62·2; H, 6·1; N, 4·0; S, 9·2 per cent. The mother-liquors from the crystallisation were concentrated, the residual gum dissolved in ethanol (30 ml.) containing concentrated hydrochloric acid (5 drops) and the solution heated under reflux for 30 min. After removal of the ethanol, the product was isolated with chloroform. It (0·7 g.) had m.p. 168–169° [from ethyl acetate-light petroleum (b.p. 60–80°)]. The m.p. was not depressed on admixture with the *cis*-isomer described earlier.

References

Beasley, Y. M., Petrow, V. and Stephenson, O. (1958). *J. Pharm. Pharmacol.*, **10**, 103–111.
McElvain, S. M. and Safranski, J. C. (1950). *J. Amer. chem. Soc.*, **72**, 3134–3138.
Böeseken, J. and van Giffen, J. (1920). *Rec. Trav. chim.*, **39**, 183–186.
Chabrier, P., Najer, H., Giudicelli, R. and Joannic, M. (1957), *Bull. Soc. chim. France*, 1365–1369.
Clarke, M. F. and Owen, L. N. (1949). *J. chem. Soc.*, 315–320.
Ginsberg, D. (1953). *J. Amer. chem. Soc.*, **75**, 5746–5747.
Gunstone, F. D. and Morris, L. J. (1957). *Ibid.*, **79**, 487–490.
Woodward, F. B. and Brutcher, F. V. (1958). *Ibid.*, **80**, 209–211.