## Some Derivatives of 1,2,3,6-Tetrahydro-4-phenylpyridine

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The synthesis of some 1-substituted 1,2,3,6-tetrahydro-4-phenylpyridines, including xylocholine and bretylium analogues, is reported.

THESE derivatives were made during a search for compounds suitable for the study of the relationship between molecular planarity and pharmacological activity. The 1,2,3,6-tetrahydro-4-phenylpyridine molecule was chosen because the degree of planarity of its styrenoid system may readily be altered through ortho-substitution of the 4-phenyl group.<sup>1</sup> The tetrahydropyridine (Ia) gave the urethane (Ib) with ethyl chloroformate, and the diol (Ic) with 2,3-epoxypropanol. The sequence (Id)-(If), requiring the reagents ethylene chlorohydrin, thionyl chloride, and sodium 2,6-dimethylphenoxide, led to an ether which, with methyl iodide, gave the xylocholine analogue (IIa). The bretylium analogue (IIb) was obtained from 2-bromobenzyl bromide and the tetrahydropyridine (I; R = Me). Treatment of the tetrahydropyridine (Ia) with a molar proportion



of phosgene in benzene gave the urea (III) rather than the carbamoyl chloride (Ig), required for the preparation of unsymmetrical ureas. The diethylcarbamoyl derivative (Ih) was obtained by reaction between the tetrahydropyridine (Ia) and diethylcarbamoyl chloride. Some pharmacological properties of the derivatives (Ib), (Ic), (IIa), and (IIb) were investigated but no significant activities were detected.

## EXPERIMENTAL

## Ethyl 1,2,3,6-Tetrahydro-4-phenylpyridine-1-carboxylate

(Ib).—Ethyl chloroformate (11 g.) in chloroform was added to a stirred cooled mixture of 1,2,3,6-tetrahydro-4-phenylpyridine<sup>2</sup> (8 g.), sodium hydrogen carbonate (14 g.), and chloroform (30 ml.). Next day the product was filtered, and the filtrate, after being washed with aqueous hydrochloric acid, was dried and concentrated. The residual oil (8.9 g.) was distilled, to give the *urethane* (Ib) (6.8 g.), b. p. 134–138°/0·1 mm.,  $n_{\rm D}^{20}$  1·5549,  $\nu_{\rm max}$  1700 cm.<sup>-1</sup> (C=O) (Found: C, 72·6; H, 7·4; N, 6·1. C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub> requires C, 72·7; H, 7·4; N, 6·1%).

1-(2,3-Dihydroxypropyl)-1,2,3,6-tetrahydro-4-phenyl-

pyridine (Ic).—A mixture of 2,3-epoxypropanol (5 g.), the tetrahyropyridine (Ia) (9.6 g.), and benzene (10 ml.) was heated under reflux for 2 hr., evaporated, and the residue distilled to give the *diol* (Ic) (11.2 g.), b. p. 175°/0·3 mm. It gave a *hydrochloride*, m. p. 148° (from ethanolether) (Found: C, 61.9; H, 7.6; N, 5.8%; Equiv., 269.  $C_{14}H_{20}$ CINO<sub>2</sub> requires C, 62·3; H, 7·4; N, 5·2%; Equiv., 270).

1,2,3,6-Tetrahydro-1-(2-hydroxyethyl)-4-phenylpyridine (Id).—A mixture of ethylene chlorohydrin (8 g.), the tetrahydropyridine (Ia) (16 g.), sodium carbonate (6 g.), and ethyl acetate (50 ml.) was heated under reflux for 2.5 hr.

and filtered. The filtrate was evaporated and the residual oil (18 g.) treated with ethanolic hydrogen chloride, to give the hydroxyethyl-base (Id) *hydrochloride* (13 g.), m. p. 178° (from ethanol-ether) (Found: C,  $65 \cdot 5$ ; H,  $7 \cdot 8\%$ ; Equiv., 237. C<sub>13</sub>H<sub>18</sub>ClNO requires C,  $65 \cdot 1$ ; H,  $7 \cdot 5\%$ ; Equiv., 240).

1-(2-Chloroethyl)-1,2,3,6-tetrahydro-4-phenylpyridine(Ie).— Thionyl chloride (9 g.) was added to a suspension of the hydroxyethyl-base (Id) hydrochloride (16.8 g.) in benzene (200 ml.), and the mixture heated under reflux for 30 min. The cooled product was filtered and the recovered solid recrystallised from ethanol, to give the chloroethyl-base (Ie) hydrochloride (14 g.), m. p. 221° (Found: C, 60.4; H, 6.5; N, 5.8%; Equiv., 260.  $C_{13}H_{17}Cl_2N$  requires C, 60.5; H, 6.6; N, 5.4%; Equiv., 258).

1-[2-(2,6-Dimethylphenoxy)ethyl]-1,2,3,6-tetrahydro-

1-methyl-4-phenylpyridinium Iodide (IIa).—2,6-Dimethylphenol (5.5 g.), in benzene, was added to a suspension of sodium hydride (2 g.; 55% in mineral oil) in the same solvent; the mixture was heated under reflux for 15 min., and then treated with the chloroethyl-base (Ie) (10 g.) in benzene. After a further 1-hr. reflux period the mixture was filtered, and the filtrate washed with aqueous sodium hydroxide, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. The residue,

<sup>2</sup> C. J. Schmidle and R. C. Mansfield J. Amer. Chem. Soc., 1956, 78, 1702.

<sup>&</sup>lt;sup>1</sup> S. E. Fullerton, Ph.D. Thesis, London, 1960.

with excess of ethanolic hydrogen chloride, gave the ether (If) hydrochloride (3 g.), m. p. 203° (from ethanol) (Found: C, 72.9; H, 7.5; N, 3.95%; Equiv., 346.  $C_{21}H_{26}CINO$  requires C, 73.4; H, 7.6; N, 4.1%; Equiv., 344). The free base with methyl iodide gave the methiodide (IIa), m. p. 187° (from ethanol-ether) (Found: C, 58.6; H, 6.4; N, 3.1%; Equiv., 453.  $C_{22}H_{28}INO$  requires C, 58.8; H, 6.2; N, 3.1%; Equiv., 449).

1,2'-Bromobenzyl-1,2,3,6-tetrahydro-1-methyl-4-phenyl-

pyridinium Bromide (IIb).—2-Bromobenzyl bromide (1 mol.) in acetone was added to 1,2,3,6-tetrahydro-1-methyl-4-phenylpyridine (1 mol.) in the same solvent and the solid which separated recrystallised from acetone, to give the quaternary bromide (IIb), m. p. 206° (Found: C, 53·35; H, 4·9; N, 3·0.  $C_{19}H_{21}Br_2N$  requires C, 53·9; H, 5·0; N, 3·3%).

Reaction of the Tetrahydropyridine (Ia) with Phosgene.— The tetrahydropyridine (Ia) (8 g., 0.05 mole) in benzene was added to a stirred cooled solution of phosgene (6 g., 0.06 mole) in benzene (50 ml.). When addition was complete the product was heated under reflux for 10 min., cooled, and treated with excess of concentrated ammonia solution or 2-dimethylaminoethanol. In either case the sole product isolated was the *urea* (III) (8.5 g.), m. p. 188° (from ethanol),  $\nu_{max}$ . 1625 cm.<sup>-1</sup> (Found: C, 80.2; H, 7.0; N, 8.1.  $C_{23}H_{24}N_2O$  requires C, 80.2; H, 7.0; N, 8.1%).

1-Diethylcarbamoyl-1,2,3,6-tetrahydro-4-phenylpyridine (Ih).—A mixture of the tetrahydropyridine (Ia) (9.6 g.), diethylcarbamoyl chloride (9.5 g.), sodium carbonate (5 g.), and chloroform (100 ml.) was heated under reflux for 2 hr. The product was filtered, the filtrate concentrated, and the residue distilled, to give the diethylcarbamoyl derivative (Ih) (11 g.), b. p. 160—170°/0.5 mm.,  $n_{\rm D}^{25}$  1.5588,  $v_{\rm max}$ . 1640 cm.<sup>-1</sup> (Found: N, 10.6. C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>O requires N, 10.85%).

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