116. *Experiments on the Synthesis of Local Anæsthetics. Part III.*

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Esters of α-diethylamino- or α-piperidino-β-acyloxy-β-phenylpropionic acid have been prepared. The benzoyloxy-, cinnamoyloxy-, and β-phenylpropoxy-compounds described showed local anæsthetic activity.

SUBSTANCES of the formula (I) have been prepared in connexion with the problem whether an unsaturated centre is necessary for a compound to produce local anæsthesia.

(I.) (*p*)R·C_6H_4·CH(O·COR')·CHR''·CO_2R'''

α-Bromo-β-hydroxy-β-phenylpropionic acid was esterified with various alcohols, the resulting esters condensed with diethylamine or piperidine, and the α-diethylamino- or α-piperidino-β-hydroxy-β-phenylpropionates acylated. The hydrochlorides of the compounds (I) where R = H, R' = Ph, CH:CHPh, or CH_2·CH_2Ph, R'' = $C_5H_{10}N$, and R''' = Me were prepared. All the compounds had local anæsthetic properties in different degrees.

* M. p. not recorded in literature; we found 209—211°.

*iso*Propyl α-piperidino-β-cinnamoyloxy-β-phenylpropionate gives a *hydrochloride* which is not very stable to water and has only feeble local anæsthetic properties. The corresponding *benzoyloxy*-derivative shows much more activity, a drop of a 1% solution placed on the tip of the tongue causing a tingling sensation lasting for several minutes. The *hydrochloride* of methyl α-piperidino-β-β′-phenylpropoxy-β-phenylpropionate is a local anæsthetic markedly weaker than the corresponding *benzoyloxy*-derivative; the related cinnamoyloxy-compound is undoubtedly weaker than either of them, a drop of a 1% solution causing only a slight anæsthesia.

The detailed examination of these compounds will be described elsewhere.

Experimental.

α-Bromo-β-hydroxy-β-phenylpropionic acid was prepared by the method of Read and Williams (*J. Proc. Roy. Soc. N.S. Wales*, 1917, **51**, 558). From 55 g. of cinnamic acid, α-bromo-β-hydroxy-β-phenylpropionic acid (45 g.), αβ-dibromo-β-phenylpropionic acid (6 g.), and ω-bromostyrene (5 g.) can be obtained if the acid is brominated in a solution of sodium carbonate (27 g.) in water (800 c.c.). Departure from these relative proportions results in much diminished yields.

Methyl α-Bromo-β-hydroxy-β-phenylpropionate.—The acid (20 g.) was refluxed in dry methyl alcohol (45 c.c.) containing hydrogen chloride (*ca.* 3%) for 8 hours, matter volatile in a vacuum at 100° removed, and the residue washed with sodium bicarbonate solution. The *methyl* ester, isolated by means of ether, crystallised from light petroleum in plates (18·3 g.), m. p. 64° (Found: C, 46·6; H, 4·2; Br, 30·7. $C_{10}H_{11}O_3Br$ requires C, 46·3; H, 4·2; Br, 30·9%).

The ethyl, propyl, *iso*propyl, butyl, *iso*butyl, *iso*amyl, and benzyl esters, similarly prepared, were viscous liquids which could not be distilled in a high vacuum without decomposition. The crude esters were used after removal of unchanged acid and all matter volatile at 100° in a vacuum.

Methyl α-Piperidino-β-hydroxy-β-phenylpropionate.—A mixture of methyl α-bromo-β-hydroxy-β-phenylpropionate (10 g.), piperidine (7 g.), and benzene (50 c.c.) was heated on the steam-bath for 4 hours. The filtrate after the removal of piperidine hydrochloride was freed from the solvent, and the residue extracted with ether. The pasty mass obtained after the removal of ether solidified in contact with light petroleum at 0°; it then crystallised from this solvent in glancing needles, m. p. 142° (Found: N, 5·5. $C_{15}H_{21}O_3N$ requires N, 5·3%). The *hydrochloride*, prepared in ethereal solution, crystallised from acetone–ether in needles, m. p. 182° (Found: N, 4·35; Cl, 11·6. $C_{15}H_{21}O_3N$,HCl requires N, 4·7; Cl, 11·8%).

Propyl α-piperidino-β-hydroxy-β-phenylpropionate, prepared similarly, was a viscous liquid, which was characterised as its benzoyl derivative (below).

iso*Propyl α-piperidino-β-hydroxy-β-phenylpropionate* had m. p. 111° after crystallisation from light petroleum (Found: N, 4·7. $C_{17}H_{25}O_3N$ requires N, 4·8%). The *hydrochloride* of *iso*butyl α-piperidino-β-hydroxy-β-phenylpropionate had m. p. 141° (Found: N, 4·2; Cl, 10·2. $C_{18}H_{27}O_3N$,HCl requires N, 4·1; Cl, 10·4%). iso*Amyl α-piperidino-β-hydroxy-β-phenylpropionate* formed plates, m. p. 86°, from dilute methyl alcohol (Found: N, 4·45. $C_{19}H_{29}O_3N$ requires N, 4·4%). The *hydrochloride*, m. p. 159°, crystallised from acetone–ether (Found: N, 4·0; Cl, 9·9. $C_{19}H_{29}O_3N$,HCl requires N, 3·9; Cl, 9·9%). Benzyl α-piperidino-β-hydroxy-β-phenylpropionate was purified *via* its *hydrochloride*, which crystallised from acetone in needles, m. p. 187° (Found: N, 3·95; Cl, 9·45. $C_{21}H_{25}O_3N$,HCl requires N, 3·7; Cl, 9·2%).

Hydrochloride of Methyl α-Piperidino-β-benzoyloxy-β-phenylpropionate.—A mixture of methyl α-piperidino-β-hydroxy-β-phenylpropionate (1·0 g.), benzoyl chloride (0·5 c.c.), and benzene (5 c.c.) was heated for 4 hours. After the removal of the solvent, the residue was heated at 100° for 3 hours. The product was dissolved in acetone and precipitated with dry ether; the *hydrochloride* then crystallised from acetone–ether in clusters of radiating needles, m. p. 101° (Found: N, 2·7; Cl, 8·6. $C_{22}H_{25}O_4N$,HCl requires N, 2·8; Cl, 8·8%).

The *hydrochloride* of ethyl α-piperidino-β-benzoyloxy-β-phenylpropionate, prepared similarly and crystallised from acetone–ether, had m. p. 127° (Found: N, 3·4; Cl, 8·3. $C_{23}H_{27}O_4N$,HCl requires N, 3·35; Cl, 8·5%).

The *hydrochloride* of propyl α-piperidino-β-benzoyloxy-β-phenylpropionate, m. p. 112°, was purified by dissolving the crude product of benzoylation in dry acetone (charcoal) and precipitating it with dry ether; it crystallised from acetone–ether in clusters of rod-like needles (Found: N, 3·0; Cl, 8·0. $C_{24}H_{33}O_4N$,HCl requires N, 3·2; Cl, 8·2%).

The *hydrochloride* of butyl α-piperidino-β-benzoyloxy-β-phenylpropionate, crystallised from

acetone–alcohol, had m. p. 118° (Found : N, 3·0; Cl, 7·9. $C_{25}H_{31}O_4N$,HCl requires N, 3·1; Cl, 7·9%).

iso*Butyl α-piperidino-β-benzoyloxy-β-phenylpropionate* was prepared by heating the hydroxy-compound in pyridine solution with benzoyl chloride at 100° for 3 hours. The product, precipitated by water, solidified when kept at 0° for 12 hours. It crystallised from dilute methyl alcohol in needles, m. p. 82° (Found : N, 3·7. $C_{25}H_{31}O_4N$ requires N, 3·4%).

iso*Amyl α-piperidino-β-benzoyloxy-β-phenylpropionate*, prepared similarly, crystallised from dilute alcohol in needles, m. p. 79° (Found : N, 3·3. $C_{26}H_{33}O_4N$ requires N, 3·5%).

The *hydrochloride* of benzyl α-piperidino-β-benzoyloxy-β-phenylpropionate had m. p. 175° (Found : N, 3·0; Cl, 7·3. $C_{28}H_{29}O_4N$,HCl requires N, 2·9; Cl, 7·3%).

Hydrochloride of Methyl α-Piperidino-β-β′-phenylpropoxy-β-phenylpropionate.—A mixture of methyl α-piperidino-β-hydroxy-β-phenylpropionate (0·5 g.) and β-phenylpropionyl chloride (1 c.c.) was heated at 120—130° for 4 hours. The product was cooled in ice and stirred with dry ether. The precipitated *hydrochloride*, crystallised from acetone–ether, had m. p. 197° (decomp.) (Found : N, 3·1; Cl, 8·1. $C_{24}H_{29}O_4N$,HCl requires N, 3·2; Cl, 8·2%).

The related cinnamoyloxy-compound, prepared as above, could not be satisfactorily crystallised on account of its highly hygroscopic nature.

The *hydrochloride* of *iso*propyl α-piperidino-β-benzoyloxy-β-phenylpropionate, prepared in an analogous manner, had m. p. 190° (decomp.) after crystallisation from ethyl acetate–ether (Found : N, 3·05; Cl, 8·1. $C_{24}H_{29}O_4N$,HCl requires N, 3·2; Cl, 8·2%).

The related cinnamoyloxy-derivative was prepared by heating a mixture of *iso*propyl α-piperidino-β-hydroxy-β-phenylpropionate (0·5 g.) and cinnamoyl chloride (0·7 g.) at 175° for 3 hours. The *hydrochloride*, isolated in the usual manner, crystallised from acetone–dry ether in fine needles, m. p. 223° (Found : N, 2·7; Cl, 8·0. $C_{26}H_{31}O_4N$,HCl requires N, 3·0; Cl, 7·8%).

α-Bromo-β-hydroxy-β-p-nitrophenylpropionic Acid.—To a solution of sodium carbonate (12 g.) in water (400 c.c.), well-powdered *p*-nitrocinnamic acid (25 g.) was added with stirring, the solution was cooled to 0°, and bromine (15 c.c.), vaporised with air, was led in. After 2 hours, the separated ω-bromo-*p*-nitrostyrene was removed, and the aqueous filtrate shaken with light petroleum to remove free bromine. The acidified solution furnished the *bromo-hydroxy-acid*, which crystallised from water in needles (22 g.), m. p. 179° (Found : N, 4·8; Br, 27·7. $C_9H_8O_5NBr$ requires N, 4·8; Br, 27·5%). The *ethyl* ester, m. p. 95°, crystallised from ligroin (Found : N, 4·6; Br, 25·3. $C_{11}H_{12}O_5NBr$ requires N, 4·6; Br, 25·1%).

Ethyl α-piperidino-β-hydroxy-β-*p*-nitrophenylpropionate was prepared by a method similar to that used for methyl α-piperidino-β-hydroxy-β-phenylpropionate and purified by conversion into its *hydrochloride*, m. p. 205° (decomp.) after crystallisation from acetone–ether (Found : N, 7·8; Cl, 9·8. $C_{16}H_{22}O_5N_2$,HCl requires N, 7·8; Cl, 9·9%).

The foregoing substance was benzoylated in pyridine solution at 100° for 3 hours. The *benzoyl* derivative crystallised from alcohol in pale yellow needles, m. p. 139° (Found : N, 6·5. $C_{23}H_{26}O_6N_2$ requires N, 6·6%); its *hydrochloride* had m. p. 193° (Found : N, 5·9; Cl, 7·9. $C_{23}H_{26}O_6N_2$,HCl requires N, 6·1; Cl, 7·6%).

Ethyl α-Piperidino-β-benzoyloxy-β-p-aminophenylpropionate.—The above nitro-compound (0·5 g.) was reduced with a platinum oxide catalyst (0·05 g.) for 4 hours. After the removal of the solvent, the product was converted by ethereal hydrogen chloride into its *dihydrochloride*, which crystallised from acetone–ether in long needles, m. p. 113° (decomp.) (Found : N, 6·0; Cl, 15·0. $C_{23}H_{28}O_4N_2$,2HCl requires N, 6·0; Cl, 15·1%).

Methyl α-Diethylamino-β-hydroxy-β-phenylpropionate.—Prepared in the same manner as the corresponding piperidino-compound, this substance was purified *via* its *hydrochloride*, which crystallised from ether–methyl alcohol in needles, m. p. 187° (decomp.) (Found : Cl, 12·3. $C_{14}H_{21}O_3N$,HCl requires Cl, 12·3%).

Propyl α-diethylamino-β-hydroxy-β-phenylpropionate hydrochloride, m. p. 147° (Found : N, 4·1; Cl, 11·2. $C_{16}H_{25}O_4N$,HCl requires N, 4·1; Cl, 11·25%), and iso*propyl α-diethylamino-β-hydroxy-β-phenylpropionate hydrochloride*, m. p. 181° (Found : Cl, 11·2. $C_{16}H_{25}O_3N$,HCl requires Cl, 11·25%), were similarly prepared.

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