392. *Synthesis of Local Anæsthetics from Cytisine.*

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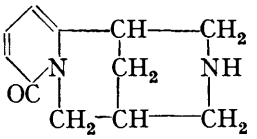
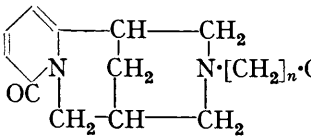
The alkaloid cytisine (I) contains a bridged-ring system reminiscent of tropine and since it is a secondary base it appeared probable that the introduction of an ω-hydroxyalkyl group on nitrogen and subsequent esterification with suitable aromatic acids would lead to substances of type (II) possessing local anæsthetic properties.

(I.) 

 (II.)

Cytisine and ethylene oxide readily combine to form N-β-*hydroxyethylcytisine*, of which the benzoic and the cinnamic ester were prepared and isolated as their *hydrobromides*. The *benzoate*, *cinnamate*, *phenyl-* and *α-naphthyl-carbamates* and p-*aminobenzoate* of *N-γ*-hydroxypropylcytisine were prepared by condensing the corresponding γ-chloropropyl esters with cytisine. Only *γ-cytisinopropyl α-naphthylcarbamate* was obtained crystalline, the other esters being isolated as their *hydrobromides*.

The pharmacological investigation of these compounds will be reported elsewhere. All of them, except the *p*-aminobenzoate, have pronounced local anæsthetic activities and, except the phenylcarbamate, they are less toxic than cocaine. The introduction of an alkyl ester group into cytisine appears to remove entirely the characteristic pharmacological properties of this alkaloid.

Experimental.

N-β-*Hydroxyethylcytisine*.—Cytisine (16 g.) in chloroform (40 c.c.) was heated with ethylene oxide (4 g.) and a trace of water in a pressure bottle at 45° for 5 hours. Evaporation of the solvent left a red oil, which crystallised slowly when rubbed with a few drops of water. The solid was extracted with ether (Soxhlet), from which it crystallised in pale yellow prisms, m. p. 73—74°, containing one molecule of water of crystallisation, which is lost at 105°. The anhydrous *alcohol* did not crystallise (Found: C, 61·8; H, 8·1; H_2O, 7·05. $C_{13}H_{18}O_2N_2,H_2O$ requires C, 61·9; H, 7·9; H_2O, 7·1%).

β-*Cytisinoethyl benzoate*. Anhydrous β-hydroxyethylcytisine (5 g.) in benzene was refluxed with benzoyl chloride (1·2 c.c.) for 3 hours. The benzene solution was filtered and evaporated, and the residual oil washed with ether and stirred with a slight excess of hydrobromic acid (12%); a thick mass of crystals separated. After recrystallisation from alcohol, β-*cytisinoethyl*

benzoate hydrobromide had m. p. 247—248° (decomp.) (Found : N, 6·75. $C_{20}H_{22}O_3N_2$,HBr requires N, 6·7%).

β-Cytisinoethyl cinnamate was prepared in a similar manner except that the free base was neutralised with hydrogen bromide in methyl alcohol. The *hydrobromide*, which crystallised from this solution on concentration, was washed with acetone and recrystallised from alcohol; m. p. 246—247° (decomp.) (Found : N, 6·5. $C_{22}H_{24}O_3N_2$,HBr requires N, 6·4%).

γ-Cytisinopropyl Benzoate Hydrobromide.—γ-Chloropropyl benzoate (2·5 g.) and sodium iodide (3 g.) were refluxed in dry acetone for ½ hour, cytisine (5 g.) then added, and heating continued for 4 hours. The filtered solution was evaporated, the residue dissolved in chloroform, and this solution washed with water to remove cytisine salts and evaporated. The residue was neutralised with *N*-hydrochloric acid, traces of oil removed with ether, and the solution saturated with potassium bromide. A thick oil separated, which solidified slowly. The solid was drained and crystallised from butyl alcohol. *γ-Cytisinopropyl benzoate hydrobromide* melts at 232—233° (decomp.) (Found : C, 58·1; H, 5·8. $C_{21}H_{24}O_3N_2$,HBr requires C, 58·2; H, 5·8%).

The following hydrobromides were prepared in an exactly similar manner from the appropriate γ-chloropropyl ester, but in methyl ethyl ketone solution : *γ-cytisinopropyl cinnamate hydrobromide*, crystallised from ethyl alcohol, m. p. 224—225° (decomp.) (Found : N, 6·05. $C_{23}H_{26}O_3N_2$,HBr requires N, 6·1%); *γ-cytisinopropyl phenylcarbamate hydrobromide*, crystallised from ethyl alcohol, m. p. 225—226° (decomp.) (Found : N, 9·6. $C_{21}H_{25}O_3N_3$,HBr requires N, 9·6%).

γ-Cytisinopropyl α-naphthylcarbamate was prepared similarly, but the free base crystallised when rubbed with methyl alcohol. It crystallised from ethyl acetate in pink plates, m. p. 159° (Found : N, 9·85. $C_{25}H_{27}O_3N_3$ requires N, 10·1%). The *hydrobromide*, crystallised from alcohol, had m. p. 237—238° (Found : N, 8·6. $C_{25}H_{27}O_3N_3$,HBr requires N, 8·4%).

γ-Cytisinopropyl p-*nitrobenzoate hydrobromide*, crystallised from methyl alcohol, had m. p. 255—256° (Found : N, 8·8. $C_{21}H_{23}O_5N_3$,HBr requires N, 8·8%).

γ-Cytisinopropyl p-*aminobenzoate hydrobromide* was prepared by reduction of the above hydrobromide in aqueous solution with hydrogen in the presence of palladised charcoal. The solution was filtered and evaporated at 45—50°. The residual hydrobromide, crystallised from methyl alcohol, had m. p. 236—237° (decomp.) (Found : N, 9·2, 9·15. $C_{21}N_{25}O_3N_3$,HBr requires N, 9·4%).

β-*Cytisinoethyl* p-*nitrobenzoate* was prepared from cytisine and β-chloroethyl *p*-nitrobenzoate in methyl ethyl ketone. The free base crystallised on treatment with ether and was recrystallised by continuous extraction with dry ether; m. p. 103—104° (Found : N, 11·4. $C_{20}H_{21}O_5N_3$ requires N, 11·0%). The *hydrobromide*, crystallised from methyl alcohol, had m. p. 232—233° (Found : N, 8·9. $C_{20}H_{21}O_5N_3$,HBr requires N, 9·05%).

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