

Synthesis of 2-[4(or 5)- (2-Hydroxyimidazolyl)]ethyl- trimethylammonium Chloride

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In a search for reactivators of phosphorylated acetylcholinesterase for treatment of nerve gas poisoning, 2-[4(or 5)-(2-hydroxyimidazolyl)]ethyltrimethylammonium chloride (V) has been prepared.

The starting material, 4(or 5)-(2-dimethylaminoethyl)imidazole (I), was benzoylated in ethyl ether-water giving II in low yield. However, the yield could be improved by repeating the reaction on the aqueous phase.

The structure of compounds obtained on benzoylation of imidazoles has been discussed.¹⁻³ The structure of II was confirmed by NMR. Signals (in DMSO(d_6)) were obtained at δ 7.50–8.33 (m, 10H, aromatic protons), 6.72 (d, $J=9$ Hz, 1H, =CH), 2.58 (s, same place as DMSO, $-\text{CH}_2\text{CH}_2-$), 2.30 (s, 6H, $\text{N}(\text{CH}_3)_2$), 10.50 (s, 1H, NH) and 10.34 (d, $J=9$ Hz, 1H, NH). When D_2O was added the $-\text{NH}$ signals disappeared and the =CH signal at 6.72 became a one proton singlet. The IR and mass spectra were also in agreement with the proposed structure.

Methylation of II yielded III, which on acid hydrolysis yielded IV. The latter compound was not isolated in a pure state since the equimolar amount of ammonium chloride formed was not removed. Furthermore, electrophoresis showed the presence of trimethylamine indicating some decomposition during the hydrolysis. If desired it is possible to obtain pure IV by ion exchange chromatography on a Dowex 50 W X-8 (200–400 mesh) column with 0.75 M HCl as eluent.

Electrophoresis and TLC indicated that no other impurities were present and the NMR spectrum was in agreement with the proposed structure.

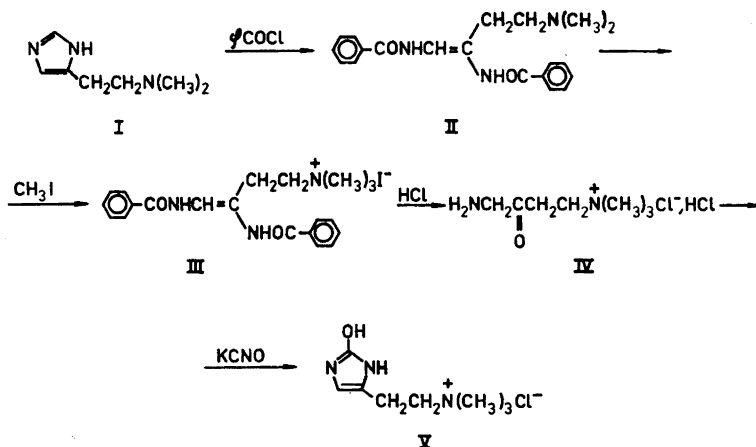
The formation of V from crude IV, by reaction with isocyanate, was performed as described by Åkerfeldt and Dahlén.³ The product contained ammonium, sodium, and potassium chloride, some trimethylamine hydrochloride and one substance (V) able to react with a diazonium salt.

Purification of V via the picrate was not successful, but could be effected by ion exchange chromatography. The IR, NMR, and mass spectra were in agreement with the proposed structure. The ion exchange method used for purification of V was also used for separation of 2-hydroxyhistamine³ from alkali salts and starting material.

Experimental. General methods. All melting points are corrected. NMR spectra were recorded on a Varian A-60A instrument and chemical shifts given in ppm (δ) relative to sodium trimethylsilylpropanesulphonic acid as internal standard. TLC was performed on layers of silica gel (HF₂₅₄, Merck). Thin-layer high voltage electrophoresis was performed on water-cooled cellulose (Macherey Nagel MN 300, 0.3 mm) plates sprayed immediately before use with a buffer pH 2 (35 ml HCOOH and 59 ml HOAc diluted to 1000 ml). The plates (12×16.5 cm) were placed with the longest side in the direction of the electric field. Imidazoles and hydroxyimidazoles were detected by spraying with a 1% solution of Echtblausalz B (Merck) and then with M NaOH. Solutions were concentrated under reduced pressure at a temperature not exceeding 50°.

1,2-Dibenzamido-1-dimethylamino-1-butene (II). A mixture of 4(or 5)-(2-dimethylaminoethyl)imidazole^{4,5} (15 g) in water (400 ml) and ethyl ether (200 ml) was stirred and cooled externally with ice. Benzoyl chloride (69.5 g) was added in one portion, followed by sodium hydroxide (42.5 g) in 8 portions during 8 h. After 22 h, when all the benzoyl chloride had reacted (TLC), the phases were separated and the aqueous phase extracted with ether (2×150 ml). Concentration of the combined and dried ether solutions yielded crude II (4.8 g). TLC (propanol-conc. ammonia, 8:2) on the ether phase gave one spot $R_F \sim 0.78$ corresponding to II. In the presence of unreacted benzoyl chloride, two further spots $R_F \sim 0.73$ (benzamide) and $R_F \sim 0.45$ (ammonium benzoate) were detected. Since the aqueous phase showed one spot from unchanged I ($R_F \sim 0.62$) it was subjected to new benzoylations using the same conditions as above but with addition of water (75 ml) before each step. The yield of crude II after 5 successive benzoylations was 13.1 g (55%). Recrystallisation from ethanol yielded the pure substance, m.p. 141–142°. (Found: C 70.8; H 7.08; N 12.3. Calc. for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_2$: C 71.2; H 6.87; N 12.5.)

(3,4-Dibenzamido-3-butene-1-yl)trimethylammonium iodide III. A solution of II (7.0 g) and methyl iodide (6.0 g) in ethanol (100 ml) was kept at room temperature. After 18 h,



when no II remained (TLC), the solution was concentrated and the solid residue recrystallized from ethanol yielding pure III (8.1 g, 82 %), m.p. 201–202°. (Found: C 52.9; H 5.65; N 8.78. Calc. for $\text{C}_{21}\text{H}_{28}\text{N}_5\text{O}_2\text{I}$: C 52.6; H 5.47; N 8.77.)

(4-Amino-3-oxobutyl)trimethylammonium chloride (IV). A solution of III (13.5 g) in 3 M methanolic hydrogen chloride (100 ml) was refluxed for 3 h, concentrated to dryness, the residue dissolved in 4 M hydrochloric acid (200 ml) and the solution refluxed for 9 h. The cooled solution was then extracted with ether, to remove benzoic acid, and concentrated, yielding crude IV (8.0 g).

2-[4(or 5)-(2-Hydroxyimidazolyl)]ethyltrimethylammonium chloride (V). Crude IV (8.0 g) was dissolved in water (75 ml) and the pH adjusted to 6.0 with M sodium hydroxide. Potassium isocyanate (2.6 g) was added and the pH readjusted to 6.0 with acetic acid. After 24 h at room temperature, 4 M hydrochloric acid (50 ml) was added and the solution concentrated to dryness. Electrophoresis revealed that the product contained one main component (35 mm migration in 10 min at 1120 V and 18 mA) which gave a positive reaction with Dragendorff's reagent and Echtblausalz. The crude product (11 g) in water (750 ml) was added to the top of a Dowex 50 W X-8 (H^+) column (200–400 mesh, 275 ml). The column was eluted with M hydrochloric acid (4000 ml) giving a mixture (6.5 g) comprised mainly of alkali salts, and

then with 1.5 M hydrochloric acid giving V (3.2 g) as a hygroscopic powder by concentration of the Echtblausalz positive fraction. V was purified by repeated precipitation from propanol with acetone. Part of the purified product was transformed into the Reineckate. (Found: C 28.5; H 4.66; N 24.9. Calc. for $\text{C}_{12}\text{H}_{22}\text{N}_6\text{S}_4\text{O}_6\text{Cr}\cdot\text{H}_2\text{O}$: C 28.5; H 4.77; N 24.9. The water of crystallization content was determined by GLC on a Porapac column of a sample dissolved in DMSO.) Another part of the product was converted to the picrate, m.p. 166° (d).

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