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Synthesis of Some Quaternary Ammonium Salts Derived from Esters of Dihydromuconic Acid

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Choline esters of dicarboxylic acids, because of their use as short acting neuromuscular blocking agents, have been in the last few years the subject of wide investigations.¹ Bovet and collaborators² have studied the relationship between the chain length of aliphatic dicarboxylic acids and the curariform activity. They found that the activity increases if the length of the chain increases from oxalic to succinic acid, but further lengthening of the chain decreases the paralysing activity. They also claimed that the double bond had no significant influence on the curariform activity.

In a previous paper³ we have described the synthesis of quaternary ammonium salts derived from dimethylaminoethyl- and dimethylaminoisopropyl esters of muconic acid. Since it has been found in our Laboratories that some of the quaternary ammonium salts described in the previous paper show a significant curare-like activity⁴, we considered that it would be of interest to compare the curariform activity of bis-choline esters of adipic, dihydromuconic and muconic acid, and to investigate the influence of the double bonds on the curariform activity.

The esters I and II were purified by high vacuum distillation and were obtained in a yield of 20—25%.

A report on the pharmacological properties of these compounds will be published elsewhere.

EXPERIMENTAL*

Bis(β -dimethylamino ethyl)-dihydromuconate (I)

A solution of 6.3 g (0.08 mole) of dimethylaminoethanol in 50 ml. of dry ether was placed in a three-necked 500 ml. round bottomed flask equipped with a mechanical stirrer, dropping funnel and a condenser. The flask was immersed in an ice-bath and with rapid stirring a solution of 5.4 g. (0.03 mole) of dihydromuconyl dichloride⁵ in 75 ml. of dry ether was added in the course of half an hour. The reaction mixture was then refluxed for additional 2 hours and left overnight at room temperature. The ether was evaporated *in vacuo*, the oily residue dissolved in 20 ml. of water and a solution of 15 g. of potassium carbonate in 15 ml. of water was added. The oily product which separated was extracted with three 50 ml. portions of ether. The ether solution was dried over anhydrous potassium carbonate and evaporated under reduced pressure to give 4.3 g. of a dark viscous oil. The oily product was distilled at a temperature of 175—185° and a pressure of 0.06 mm, to give 2.1 g. (24.5%) of a colourless oil.

Anal. 3.15 mg. subst.: 0.284 ml. N₂ (30°, 752 mm.)
 C₁₄H₂₆O₄N₂ (286.36) calc'd.: N 9.78%
 found: N 10.05%

Dipicrate of the ester I was prepared from a distilled sample with a saturated alcoholic solution of picric acid. The yield was quantitative. The analytical sample (200 mg.) was recrystallized from 25 ml. of ethanol. Melting point 150—152°.

Anal. 11.70 mg. subst.: 17.91 mg. CO₂, 4.37 mg. H₂O
 2.79 mg. subst.: 0.382 ml. N₂ (28°, 751 mm.)
 C₂₆H₃₂O₁₈N₈ (744.58) calc'd.: C 41.94; H 4.33; N 15.05%
 found: C 41.77; H 4.17; N 15.35%

Bis(β -dimethylamino isopropyl)-dihydromuconate (II)

Diisopropyl ester II was prepared in essentially the same way as described for the ethyl ester I. Dihydromuconyl dichloride (2 g., 0.011 mole) was condensed with 2.29 g. (0.022 mole) of β -dimethylaminoisopropanol in 50 ml. of dry ether.

dissolved in 1.8 ml. of water, filtered and crystallized with 9 ml. of absolute isopropanol. After standing overnight in a refrigerator, a crop of 0.4 g. (59%) of white needles was obtained. Melting point 194—195°.

Anal. 12.84 mg. subst.: 15.79 mg. CO₂, 6.18 mg. H₂O
 32.19 mg. subst.: 5.73 ml. 0.02 N AgNO₃
 C₁₆H₃₂N₂O₄I₂ (570.25) calc'd.: C 33.70; H 5.66; I 44.51%
 found: C 33.57; H 5.38; I 44.19%

Bis (β -dimethylethylammonium ethyl)-dihydromuconate diiodide (IV)

Diiodoethylate IV was prepared from 0.21 g. (0.74 mM) of the ester I and 0.65 g. (4.1 mM) of ethyliodide in 3 ml. of acetone. The oily precipitate which separated after one hour, crystallized on scratching. After standing for three days at room temperature, the crystalline product was separated by filtration and washed with 3 ml. of acetone. A crop of 0.35 g. (80%) of yellow crystalline powder was obtained. The product was recrystallized twice from absolute ethanol to a melting point of 129—132°.

Anal. 14.65 mg. subst.: 19.25 mg. CO₂, 8.14 mg. H₂O
 30.82 mg. subst.: 5.11 ml. 0.02 N AgNO₃
 C₁₈H₃₆O₄N₂I₂ (598.30) calc'd.: C 36.15; H 6.03; I 42.42%
 found: C 35.85; H 6.21; I 42.08%

Bis (β -trimethylammonium isopropyl)-dihydromuconate diiodide (V)

Diiodomethylate V was obtained from 0.24 g. (0.76 mM) of an analytically pure ester II and 0.7 g. (4.9 mM) of methyl iodide in 4 ml. of acetone. After standing for two days at room temperature, a quantitative yield of the compound V was obtained; m. p. 204—206°. The product was recrystallized from ethanol to give 0.3 g. (66%) of white needles decomposing at 208—209°.

Anal. 14.22 mg. subst.: 18.70 mg. CO₂, 7.43 mg. H₂O
 20.59 mg. subst.: 3.43 ml. 0.02 N AgNO₃
 C₁₅H₃₆O₄N₂I₂ (598.28) calc'd.: C 36.14; H 6.03; I 42.43%
 found: C 35.88; H 5.84; I 42.28%

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IZVOD

Sinteza nekih kvarternih amonijskih soli, derivata estera dihidromukonske kiseline

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Opisana je sinteza kvarternih amonijskih soli bis (β -dimetilamino etil)-dihidromukonata (I) i bis (β -dimetilamino izopropil)-dihidromukonata (II). Kvarternizacija je provedena u acetonu kod sobne temperature sa suviškom alkil halogenida. Baze I i II priređene su djelovanjem dimetilaminoetanola i 1-dimetilaminopropanola-2 na diklorid dihidromukonske kiseline u eteru kao otapalu.

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