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

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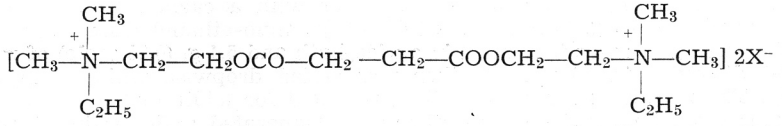
Quaternary ammonium salts of di-(β-dimethylammonium ethyl)-muconate (I) and di-(β-dimethylammonium isopropyl)-muconate (II), were prepared as possible neuromuscular blocking agents.

Characteristic physiological action of curare alkaloids is considered to be due to their onium structure (Brown and Fraser[1]). Later, Hunt and Renshau[2], found that the other onium salts: stibonium, arsonium, phosphonium and sulphonium, also show the curariform activity, but that tetramethylammonium salts, and especially trimethylalkylammonium salts are the most effective. Trimethylbutylammonium salts are almost equivalent to curare in pharmacodynamic tests.

The similarity of trimethylalkylammonium salts to choline has stimulated an intensive study of curare-like activity of various choline derivatives. In search for the therapeutic agents having curariform activity, many structural modifications have been studied. Barlow and Ing[3], working on the assumption that the two ammonium groups in the d-tubocurarin molecule are separated by an optimal distance, investigated curariform activity of a series of polymethylene compounds containing two quaternary ammonium groups. It has been found that the most effective compounds were the salts of decamethonium:

$$[(CH_3)_3\overset{+}{N}\text{-}(CH_2)_{10}\text{-}\overset{+}{N}(CH_3)_3]\ 2X^-$$

Many other compounds, which have the structural resemblance to decamethonium, were intensively studied by a number of workers.[4,5,6] Bis-choline esters of some dicarboxylic acids have been found to be very powerful neuromuscular blocking agents. Bovet et al.[4] applied in 1949 in the therapy di-(β-dimethylethylammonium ethyl)-succinate dichloride under the name of »Tachycuraryl«:

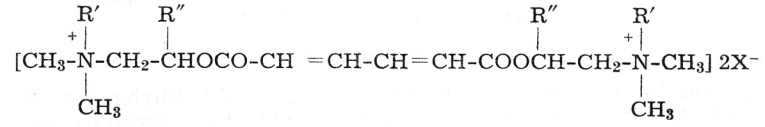


A similar compound, bis-choline succinate, synthesized for the first time by Hunt and Taveau[7] in 1911, is at present produced in many countries as a powerful brief acting neuromuscular blocking agent.

Little information is available concerning the curariform activity of choline esters of unsaturated dicarboxylic acids[8]. In order to find out the influence of conjugated double bonds on the neuromuscular blocking action, we prepared the quaternary ammonium salts of:

di-(β-dimethylamino ethyl)-muconate (I) and
di-(β-dimethylamino isopropyl)-muconate (II).

The following quaternary salts were prepared:



	R'	R''	X		R'	R''	X
III	CH_3	H	I	VII	$C_6H_5CH_2$	H	Br
IV	C_2H_5	H	I	VIII	CH_3	CH_3	I
V	C_2H_5	H	Br	IX	C_2H_5	CH_3	I
VI	n-C_3H_7	H	Br	X	n-C_3H_7	CH_3	Br

The esters I and II were prepared by the condensation of muconyl dichloride with dimethylamino-ethanol, or with 1-dimethylamino-propanol-2 in ether solution at a temperature of 0°. Both compounds were effectively purified by crystallization from a low boiling petroleum ether.

The preparation of quaternary ammonium salts was performed in an acetone solution at room temperature. The ammonium compounds separated as crystalline products, and were purified by crystallization from an appropriate solvent.

The dibromo-n-propylate VI which was partly soluble in acetone was isolated after the acetone was evaporated under reduced pressure, and the residue crystallized from isopropanol. Many difficulties were encountered in the purification of dibromobenzylate VII, and the yield was only 10,2%.

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

EXPERIMENTAL*

Di-(β-dimethylamino ethyl)-muconate (I)

In a 500-ml. round bottomed three necked flask provided with a mercury sealed stirrer, dropping funnel and a condenser with a calcium chloride tube on the top, was placed 6.3 g. (0.08 mole) of dimethylamino-ethanol dissolved in 50 ml. of dry ether. The flask was immersed in an ice-bath and 5.4 g. (0.03 mole) of muconyl dichloride[9] dissolved in 75 ml. of ether was added dropwise while being stirred vigorously. The reaction mixture was then refluxed for additional 2 hours and left overnight at room temperature. The ether was evaporated under reduced pressure, the residue dissolved in 20 ml. of water, and a solution of 15 g. of potassium carbonate in 15 ml. of water was added. The crystalline product which separated

* Melting points are uncorrected

was extracted with four 25 ml. portions of ether. The ether was dried over anhydrous potassium carbonate and evaporated under reduced pressure to give 5.0 g. of a fine crystalline product. Yield 58.5%, m. p. 57—58°. An analytical sample was recrystallized from petroleum ether (b. p. 40—60°) and had a melting point 58—59°

Anal. 9.290 mg. subst.: 20.03 mg. $C0_2$, 7.06 mg. H_2O
$C_{14}H_{24}O_4N_2$ (284.35) calc'd.: C 59.13; H 8.51%
found: C 58.84; H 8.51%.

Dipicrate of the ester I was prepared in a quantitative yield with a saturated alcoholic solution of picric acid. An analytical sample was recrystallized from ethanol. Melting point 191—193° (with decomposition).

Anal. 1.997 mg. subst.: 0.265 ml. N_2 (22°, 754 mm)
$C_{26}H_{30}O_{16}N_6$ (742.56) calc'd.: N 15.09%
found: N 15.21%

Di-(β-dimethylamino isopropyl)-muconate (II)

Diisopropyl ester II was prepared in essentially the same way as described for ethyl ester I. 1.8 g. (0.01 mole) of muconyl dichloride and 2.06 g (0.02 mole) of dimethylamino-isopropanol were condensed in ether to give 2.24 g. of a product melting at 67—74° (yield 71.3%). An analytical sample was recrystallized from petroleum ether to a melting point of 87—88°.

Anal. 16.7 mg. subst.: 37.34 mg. CO_2, 14.05 mg. H_2O
$C_{16}H_{28}O_4N_2$ (312.40) calc'd.: C 61.51; H 9.04%
found: C 61.02; H 9.42%.

Dipicrate of the ester II was prepared in a quantitative yield with a saturated alcoholic solution of picric acid. The crystalline product was filtered off, washed with ethanol, and analysed. Melting point 228—229° (decomposition under prevous darkening at 218°).

Anal. 21.34 mg. subst.: 34.00 mg. CO_2, 8,69 mg. H_2O
$C_{28}H_{34}O_{14}N_8$ (770.62) calc'd.: C 43.64; H 4.45%
found: C 43.48; H 4.55%.

Di-(β-trimethylammonium ethyl)-muconate diiodide (III)

Diiodomethylate III was prepared from 600 mg. of the ester I and 1.32 g. of methyliodide in 8 ml. of acetone. After standing for two days at room temperature, 1.25 g. of a product decomposing at 250° was obtained. The product was crystallized from a mixture of 30 ml. of isopropanol and 15 ml. of water. A yield of 950 mg. (79%) of the pure product was obtained. M. p. 259° (with decomposition).

Anal. 9.14 mg. subst.: 11.32 mg. CO_2, 4.37 mg H_2O
84.16 mg. subst.: 27.59 ml. 0.01*N* H_2SO_4
73.36 mg. subst.: 12.96 ml. 0.02*N* $AgNO_3$
$C_{16}H_{30}O_4N_2I_2$ (568.26) calc'd.: C 33.82; H 5.32; N 4.93; I 44.67%
found.: C 33.79; H 5.35; N 4.59; I 44.84%.

Di-(β-dimethylethylammonium ethyl)-muconate diiodide (IV)

Diiodoethylate IV was prepared from 300 mg. of the ester I and 965 mg. of ethyliodide in 4 ml. of acetone. After standing for two days at room temperature, the crystalline product was separated by filtration and washed with 5 ml. of acetone. 550 mg. (87%) of a product melting at 200° (decomposition) was obtained. The product was dissolved in 11 ml. of methanol and crystallized with 22 ml. of ether. Pale yellow needles; m. p. 209—210° (with decomposition)

Anal. 11.062 mg. subst.: 14.83 mg. CO_2, 5.90 mg. H_2O
81.46 mg. subst.: 27.58 ml. 0.01*N* H_2SO_4
76.30 mg. subst.: 12.76 ml. 0.02*N* $AgNO_3$
$C_{18}H_{34}O_4N_2I_2$ (596.31) calc'd.: C 36.25; H 5.75; N 4.70; I 42.57%
found: C 36.51; H 5.97; N 4.74; I 42.46%

Di-(β-dimethylethylammonium ethyl)-muconate dibromide (V)

Dibromoethylate V was prepared from 300 mg. of the ester I and 652 mg. of ethylbromide in 4 ml. of acetone. After standing for two days at room temperature, a crop of 250 mg. of a crystalline product was obtained. M. p. 206—209° (decomposition), yield 47.2%. The product was dissolved in 5 ml. of methanol and crystallized with 5 ml. of ether. The product crystallized in fine needles. M. p. 225—226 (decomposition, under previous softening and darkening at 206°).

Anal. 72.70 mg. subst.: 28.33 ml. 0.01*N* H_2SO_4
119.9 mg. subst.: 23.37 ml. 0.02*N* $AgNO_3$
$C_{18}H_{34}O_4N_2Br_2$ (502.30) calc'd.: N 5.59; Br 31.82%
found: N 5.46; Br 31.16%.

Di-(β-dimethyl-n-propylammonium ethyl)-muconate dibromide (VI)

Dibromo-n-propylate VI was prepared from 300 mg. of the ester I and 600 mg. of n-propylbromide in 4 ml. of acetone. The reaction mixture was left at room temperature for two days, acetone evaporated under reduced pressure, and the residue crystallized from a methanol-ether mixture (1 : 1). 300 mg (53.5%) of fine needles decomposing at 197° were obtained. An analytical sample recrystallized from isopropanol melted at 197—198° (with decomposition).

Anal. 64.00 mg. subst.: 12.00 ml. 0.02*N* HCl
48.22 mg. subst.: 8.85 ml. 0.02*N* $AgNO_3$
$C_{20}H_{38}O_4N_2Br_2$ (530.35) calc'd.: N 5.28; Br 30.14%
found: N 5.25; Br 29.32%.

Di-(β-dimethylbenzylammonium ethyl)-muconate dibromide (VII)

Dibromobenzylate VII was prepared from 1 g. of the ester I and 4 g. of benzylbromide in 15 ml. of acetone. 225 mg. of a crystalline product separated after standing for two days at room temperature. Yield 10.2%, m. p. 222—223° (decomposition). Three crystallizations from a 90% isopropanol were required to obtain a product which decomposed constantly at 235—236°. The product crystallized in needles. No attempt has been made to purify the mother liquor.

Anal. 5.977 mg. subst.: 0.235 ml. N_2 (22°, 748 mm)
73.15 mg. subst.: 11.65 ml. 0.02*N* $AgNO_3$
$C_{28}H_{38}O_4N_2Br_2$ (626.43) calc'd.: N 4.47; Br 25.57%
found: N 4.48; Br 25.46%.

Di-(β-trimethylammonium isopropyl)-muconate diiodide (VIII)

Diiodomethylate VIII was prepared from 290 mg. of the ester II* and 900 mg. of methyliodide in 4 ml. of acetone. After standing for two days at room temperature 550 mg. (99%) were obtained. The product melted under decomposition at 231—232°. After two crystallizations from a water-dioxan mixture, 300 mg of yellow needles decomposing at 242-243° were obtained.

Anal. 13.31 mg. subst.: 17.62 mg CO_2, 6.96 mg. H_2O
$C_{18}H_{34}O_4N_2I_2$ (596.31) calc'd.: C 36.25; H 5.75%
found: C 36.13; H 5.85%.

Di-(β-dimethylethylammonium isopropyl)-muconate diiodide (IX)

Diiodoethylate IX was prepared from 290 mg. of the ester II and 870 mg. of ethyliodide in 4 ml. of acetone. The crystalline product (550 mg, 95%) which separated after standing for two days at room temperature, was filtered off and washed with 5 ml. of acetone. M. p. 194° (under previous darkening and softening at 175°). An analytical sample (300 mg.) was recrystallized from 12 ml. of isopropanol, and finally from a mixture of methanol and water. M. p. 196° (with decomposition).

Anal. 13.72 mg. subst.: 19.18 mg. CO_2, 7.09 mg. H_2O
$C_{20}H_{38}O_4N_2I_2$ (624.36) calc'd.: C 38.47; H 6.14%
found: C 38.15; H 5.78%.

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* The crude ester (m. p. 67—74°) was used in all preparations.

Di-(β-dimethyl-n-propylammonium isopropyl)-muconate dibromide (X)

Dibromo-n-propylate X was prepared from 208 mg. of the ester II and 492 mg. of n-propylbromide in 3 ml. of acetone. After standing for three days at room temperature, a crop of 100 mg. (26.9%) of a crystalline product separated. M. p. 177 (decomposition). An analytical sample was recrystalized from isopropanol to a decomposition point 183—184°.

Anal. 11.66 mg. subst.: 20.13 mg. CO_2, 7.83 mg. H_2O
$C_{22}H_{42}O_4N_2Br_2$ (558.40) calc'd.: C 47.32; H 7.58%
found: C 47.11; H 7.52%.

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REFERENCES

1. Brown and Fraser, *Trans. Roy. Soc. Edinburgh* **25** (1868—9) 151; *Proc. Roy. Soc.* **6** (1869) 556; **7** (1872) 663. cf. e. g. A. Burger, *Medicinal Chemistry*, Vol. I. Interscience Publishers 1951, p. 390.
2. R. Hunt and R. R. Renshau, *J. Pharmacol. Exptl. Therap.*, **25** (1925) 315; cit. from *Chem. Zentr.* **1925**, II, 1466.
3. R. B. Barlow and H. R. Ing, *Nature* **161** (1948) 718; *Brit. J. Pharmacol.*, **3** (1948) 298.
4. D. Bovet, F. Bovet-Nitti, S. Guarino, V. G. Longo and M. Marotta, *Rend. ist. super. sanità*, **12** (1949) 106.
5. O. Hromatka and C. Skopalik, *Monatsh.*, **84** (1953) 349.
6. A. P. Phillips, *J. Am. Chem. Soc.* **71** (1949) 3264; **73** (1951) 5822.
7. P. Hunt and R. Taveau, *Publ. Health and Marine Hosp. Service Washington Bull.* **1911**, 73; cit. from ref. 5.
8. R. Fusco, G. Palazzo, S. Chiavarelli and D. Bovet, *Gazz. chim. ital.* **79** (1949) 129.
9. P. S. Bailey and J. S. Ross, *J. Am. Chem. Soc.* **71** (1949) 2370.

IZVOD

Sinteza nekih kvarternih amonijskih soli, derivata estera mukonske kiseline

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Opisana je sinteza kvarternih amonijskih soli: di-(β-dimetilamino etil)-mukonata (I) i di-(β-dimetilamino izopropil)-mukonata (II). Kvarternizacija je provedena kod sobne temperature u acetonu, sa suviškom pripadnih alkil halogenida.

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