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Bifunctional Amines and Ammonium Compounds
I. Preparation of β-Tertiary-Aminoesters and Ammonium Halides of Dibasic Acids

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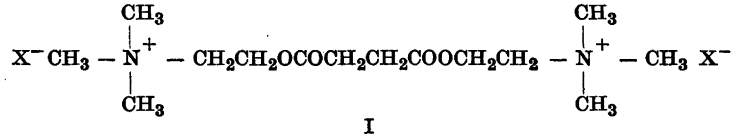
The discovery of synthetic curarizing substances with a potency comparable to or higher than that of *d*-tubocurarine [1–3] has created a great deal of interest in bifunctional 'onium' compounds [4–6]. One of the practical results of this interest has been the introduction into therapy of the bis-methohalides of bis-(β-dimethylamino)ethyl succinate (I) ('succinylcholine' salts) as short acting muscular relaxants for use as adjuvants in anaesthesia [7].

This paper describes a novel method for the preparation of succinylcholine and related substances together with their precursors, the bis-tertiary-amino-esters. The method has proved generally applicable to acids capable of forming cyclic anhydrides, and further makes possible the preparation of 'hybrid' esters, *i.e.* esters containing different groups in the two ends of the molecule.



I

A study of the biological properties of such 'hybrid' compounds should add to our understanding of the pharmacodynamics of agents of this general type.

Another feature of the method is that it enables us the preparation of half-aminoesters and their corresponding ammonium compounds, reported metabolic breakdown products of the bis-quaternary esters [8].

After this work was already completed Rice and coworkers [9] have reported that certain half-aminoesters of dibasic acids have hypotensive properties,

and that one bis-tertiary ester, bis-(β-diethylamino)ethyl cis-Δ^4-tetrahydrophthalate, also was capable of lowering the blood pressure of normotensive dogs.

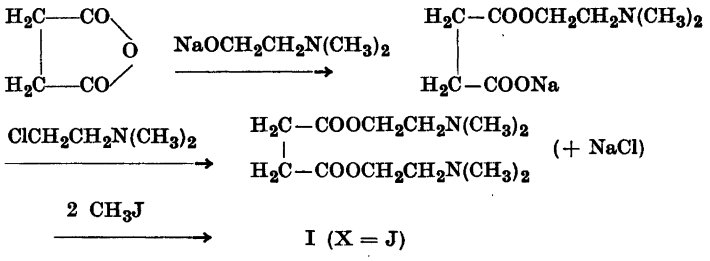
Succinylcholine, which was first reported by Hunt and Taveau [10] in 1911 (no experimental details), and its homologues, has hitherto been prepared by four different routes.

Le Heux [11] prepared it by reacting the chloride of choline with succinoyl chloride. Fusco and coworkers [4] esterified *tert.*-aminoalcohols with succinoyl chloride, isolated the hydrochloride of the bis-ester and quaternized the free ester by heating it in sealed tubes with the proper alkyl halide, while Phillips [12] reported poor to moderate yields of the bis-tertiary aminoester by an ester interchange method. Finally Walker [6] esterified succinic acid with ethylene bromohydrin and subsequently reacted the bis-β-bromoester with trimethylamine.

Phthalylcholine has been reported by Hunt and Taveau [10] while Pyman [13] prepared the corresponding bis-tertiary ester by reaction of phthaloyl chloride with β-diethylaminoethanol.

The half-esters reported by Rice and coworkers [9] were prepared by reacting one mole of β-diethylaminoethanol with one mole of a cyclic anhydride. One of these half-esters was in turn transformed to an acid chloride with oxalyl chloride and then allowed to react with β-diethylaminoethanol to give the desired bis-ester of tetrahydrophthalic acid.

The principle of the method used in the present work will appear from the following diagram (using the preparation of succinylcholine iodide as an example).



The reaction is carried out in an inert solvent such as toluene. The second stage proceeds without isolation of the sodium salt except when a half-ester is desired. In this case the second stage is not carried out. The bis-ester is recovered by distillation and subsequently transformed into the salt of a quaternary ammonium hydroxide by treating it with a reactive alkyl halide.

It has also been found that in production the isolation of the bis-ester is often unnecessary, for instance the bis-methoiodide prepared from the crude

Table 1.

$(R_1)_2NCH_2CH_2OCO(A)COOCH_2CH_2N(R_2)_2$

(A)	R_1	R_2	B.p. °C	Press. mm	Yield %	Empirical formula	Analyses % N calc.	found
succinic	CH_3	CH_3	135—8[a]	1.0—2.0	48	$C_{12}H_{24}O_4N_2$	10.68	10.61
succinic	C_2H_5	C_2H_5	160—5[b]	2.0	62	$C_{16}H_{32}O_4N_2$	8.94	8.96
succinic	CH_3	C_2H_5	147—151[c]	2.0	70	$C_{14}H_{28}O_4N_2$	9.73	9.78
maleïc	CH_3	CH_3	145[d]	1.5	21[e]	$C_{12}H_{22}O_4N_2$	10.85	9.80
phthalic	CH_3	CH_3	178[f]	1.5—2.0	42	$C_{16}H_{24}O_4N_2$	9.19	9.04
phthalic	C_2H_5	C_2H_5	195—200[g]	1.8—2.2	58	$C_{20}H_{32}O_4N_2$	7.70	7.65
d-camphoric	CH_3	CH_3	176—180[h]	2.0—2.2	53	$C_{18}H_{34}O_4N_2$	8.19	7.97
d-camphoric	C_2H_5	C_2H_5	192—8[i]	1.5—2.2	58	$C_{22}H_{42}O_4N_2$	7.04	6.87

[a] Literature[4] 131° C/1—2 mm Hg. [b] Literature[4] 152° C/1—2 mm Hg; picrate, m.p. 128° C (from abs. ethanol). [c] Picrate, m.p. 107° (recryst. lowers m.p.). [d] Picrate, m.p. 164—8° (from abs. ethanol). [e] A considerable amount of insoluble polymer is formed in this condensation. After the distillation a colorless precipitate separates from the oil. This precipitate melts at 95—8° and contains only traces of nitrogen. [f] Picrate, m.p. 158—61° (recryst. lowers m.p.). [g] Picrate, m.p. 145—8° (recryst. lowers m.p.); literature[12] 146—7°. [h] Picrate, m.p. 227—9° (from abs. ethanol). [i] Picrate, m.p. 163—5° (from abs. ethanol).

Table 2.

$X^-R_3(R_1)_2\overset{+}{N}CH_2CH_2OCO(A)COOCH_2CH_2\overset{+}{N}(R_2)_2R_3X^-$

(A)	R_1	R_3	R_2	X	M.p. °C	Recryst. from[a]	Yield %[b]	Empirical formula	Analyses % X calc.	found.
succinic	CH_3	CH_3	CH_3	J	255—6[c]	A—W(20:1)	76	$C_{14}H_{30}O_4N_2J_2$	46.60	46.61
—	CH_3	CH_3	C_2H_5	Br	148	A—E(2:5)	90	$C_{16}H_{34}O_4N_2Br_2$	33.44	32.65
—	C_2H_5	C_2H_5	CH_3	J	142—4[d]	A	73	$C_{18}H_{38}O_4N_2J_2$	42.31	42.22
—	C_2H_5	C_2H_5	C_2H_5	Br	185—7	A[e]	64	$C_{20}H_{42}O_4N_2Br_2$	29.90	29.60
—	CH_3	C_2H_5	CH_3	J	180—3	M—Ac(3:2)	83	$C_{16}H_{24}O_4N_2J_2$	44.38	44.36
—	CH_3	C_2H_5	C_2H_5	Br	148	M[e]	79	$C_{18}H_{38}O_4N_2Br_2$	31.57	31.14
maleïc	CH_3	CH_3	CH_3	J	264	M—W(5:1)	57	$C_{14}H_{28}O_4N_2J_2$	46.75	46.25
—	CH_3	CH_3	C_2H_5	Br	206	A	36	$C_{16}H_{32}O_4N_2Br_2$	33.57	33.15
phthalic	CH_3	CH_3	CH_3	J	128	A—M(1:1)	71	$C_{18}H_{30}O_4N_2J_2$	42.85	41.72
—	CH_3	CH_3	C_2H_5	Br	144—7	A	86	$C_{20}H_{34}O_4N_2Br_2$	30.35	29.21
—	C_2H_5	C_2H_5	CH_3	J	177—9	A	72	$C_{22}H_{38}O_4N_2J_2$	39.15	38.85
—	C_2H_5	C_2H_5	C_2H_5	Br	189		60	$C_{24}H_{42}O_4N_2Br_2$	27.44	27.38
d-camphoric	CH_3	CH_3	CH_3	J	229	A—M(2:1)	76	$C_{20}H_{40}O_4N_2J_2$	40.55	40.76
—	CH_3	CH_3	C_2H_5	Br	220	Ac[f]	89	$C_{22}H_{44}O_4N_2Br_2$	28.54	28.36
—	C_2H_5	C_2H_5	CH_3	J	205	A	84	$C_{24}H_{46}O_4N_2J_2$	37.19	36.81
—	C_2H_5	C_2H_5	C_2H_5	Br	205	A[e]	65	$C_{26}H_{52}O_4N_2Br_2$	25.92	25.87

[a] A : ethanol; E : ether; Ac : acetone; M : methanol; W : water [b] after recrystallization [c] with decomposition. Literature[4] 237° C. [d] Literature[4] 142° C. [e] precipitated by addition of ether. [f] Purified by suspension in several portions of boiling acetone.

solution of bis-(β-dimethylamino)-ethyl succinate being generally of 95 per cent purity or better.

In this study the following anhydrides have been subjected to bis-esterification: Succinic, maleïc, phthalic and *d*-camphoric. The alkoxides were prepared from β-dimethylaminoethanol and β-diethylaminoethanol. The halides were β-dimethylaminoethyl chloride and β-diethylaminoethyl chloride. The bis-esters were transformed into the ethobromides and the methoiodides. The esters are summarized in Table 1 and the corresponding quaternary compounds in Table 2. In addition a half-ester of phthalic acid was prepared.

The pharmacological properties of the compounds described in this paper are being studied by Dr. J. G. A. Pedersen of this laboratory. Dr. Pedersen will report his results elsewhere.

EXPERIMENTAL *

Bis-(β-dialkylamino)ethyl esters. The compounds listed in Table 1 were prepared by essentially the procedure described for *bis-(β-dimethylamino)ethyl succinate.* To a solution of 217 g of freshly distilled β-dimethylaminoethanol (2.44 mole) in 1 830 ml of dry toluene in a 10 l three necked flask equipped with stirrer, reflux condenser, drying tube, and dropping funnel is added 56.1 g of sodium (2.44 atom) at once. After the spontaneous reaction has subsided the mixture is refluxed for 12 hours and cooled to room temperature. At this point 244 g of succinanhydride (2.44 mole) is added in small portions while stirring. The reaction is exothermic. When addition is complete the mixture is left standing overnight and later refluxed for 2 hours. In the meantime 422 g of β-dimethylaminoethylchloride hydrochloride (2.44 mole plus an excess of 20 %) moistened with 300 ml of toluene is treated with a solution of 146 g of sodium hydroxide dissolved in 1 250 ml of water while kept under the water tap. The two layers are separated (if there is emulsion formation addition of potassium carbonate will hasten separation into two layers) the aqueous layer is extracted with two extra portions of 300 ml each of toluene. The toluene extracts of the free amine are united and dried over potassium carbonate (100 g). The dry extract is added to the supension of the half-ester sodium salt in toluene from the dropping funnel while the mixture is stirred and kept gently refluxing. The precipitate soon changes appearance (sodium chloride). When addition is finished the reaction mixture is refluxed for further 4 hours.

Sodium chloride is removed by filtration, toluene by evaporation through a 60 cm Widmer column, and the residue distilled in vacuum. After a small amount of lower-boiling material the main fraction, consisting of bis-(β-dimethylamino)ethyl succinate distils at 135—142° C at 1 to 2 mm Hg. Redistillation gives 325 g (48 % yield) of a light yellow oil which turns dark upon standing, b. p. 135—139° C at 1 mm Hg.

The bis-methoiodides of the bis-(β-dialkylamino)ethyl esters listed in Table 2 were prepared essentially according to the method used for the preparation of *bis-methoiodide*

* All boiling points and melting points are uncorrected. Analyses are macro determinations by Mrs. E. Ifversen and Mrs. G. Speggers of this laboratory.

of bis-(-dimethylamino)ethyl succinate (I, X = J) (succinylcholine iodide). In a three-necked flask equipped with stirrer, reflux condenser, and dropping funnel 200 g of bis-(β-dimethylamino)ethyl succinate (0.77 mole) is dissolved in 1 500 ml of dry acetone. The flask is placed in a crushed ice bath and during stirring 144 ml (2.31 mole) of methyl iodide (freshly distilled) is added from the dropping funnel during one hour. The mixture is then allowed to stand at room temperature overnight. The precipitate is filtered and dried. Recrystallized from 2 000 ml of ethanol and 100 ml of water it melts at 256°. Yield 318 g (76 %).

The bis-ethobromides of bis-(β-dialkylamino)ethyl esters listed in Table 2 were prepared essentially as described for the preparation of *bis-ethobromide of bis-(β-dimethylamino) ethyl succinate.* Fifty-two grams of bis-(β-dimethylamino)ethyl succinate (0.2 mole) is dissolved in 500 ml of dry acetone, 55 g of ethyl bromide added, the mixture placed in a steel pressure-tank of 750 ml volume and heated at the steam bath for 36 hours. The tank is cooled and the contents removed (sometimes it is necessary to dissolve the crystalline cake out with dilute ethanol and later recover the products from this solution). Recrystallized from ethanol-ether (2 : 5) there is obtained 86.0 g (90 %) of white hygroscopic plates, m. p. 148°.

For the preparation of smaller portions it is more convenient to use sealed glass tubes for the preparation of ethobromides.

Diethylaminoethyl phthalate. This compound was prepared from 23.4 g of diethylaminoethanol (0.2 mole), 4.6 g (0.2 atom) of sodium, and 29.6 g of phthalic anhydride (0.2 mole) in 200 ml of toluene essentially as described earlier with the exception that the mixture is only refluxed for 6 hours after addition of anhydride. The precipitate is then removed by filtration and dried in vacuo. This sodium salt is hygroscopic and has no definite melting point. It was dissolved in ethanol and dry hydrogen chloride was added until 0.2 mole had been absorbed. The precipitated salt was removed by filtration and the solution evaporated to one third of its original volume. Addition of dry ether precipitates diethylaminoethyl phthalate, but only after several days. The precipitate was removed, recrystallized from acetone. Yield 12 g (22.8 %). M. p. 114° C (Rice *et al.*[9] reports a m. p. of 119—20° C).

SUMMARY

A new synthesis of bis-(β-dialkylamino)alkyl esters of dibasic acids is described.

Using this method eight esters have been prepared and transformed into sixteen corresponding methoiodides and ethobromides.

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