Experimental

Ethylmagnesium Bromide and Trimethylacetonitrile.—To a titrated ether solution of 0.91 mole of ethylmagnesium bromide was added 55 g. (0.67 mole) of trimethylacetonitrile (b.p. 104–105°).[6] The reaction mixture was refluxed under a nitrogen atmosphere for ten hours, and allowed to stand for 12 hours after which time the Gilman test for Grignard reagent was still positive. Large translucent crystals had separated from the reaction mixture. The crystals and ether solution were hydrolyzed with ammonium chloride solution in the cold. The ether was removed from the resulting dried ether layer and ether extract by distilling through a twenty-plate packed column and the residue fractioned through a thirty-plate column to give the following: cuts 1–6 ether; cuts 7–9, b.p. 70–73°, $n^{20}D$ 1.3747–1.3823, 2.1 g., may be impure trimethylacetaldehyde; cuts 10–13, b.p. 75–80.5°, 4.0 g., ethanol, presumably formed from the Grignard reagent; cuts 15–18, b.p. 100.5–106°, 3.0 g., $n^{20}D$ 1.3780–1.3782, recovered trimethylacetonitrile; cuts 21–30, b.p. 123–125°, $n^{20}D$ 1.4049–1.4052, 60.8 g., ethyl *t*-butyl ketone; residue 6.9 g.

Isopropylmagnesium Chloride and Trimethylacetonitrile.—The isopropylmagnesium chloride from 0.6 mole of the halide was treated with 0.5 mole of trimethylacetonitrile under nitrogen for six hours in refluxing ether. After standing 60 hours, it was worked up as indicated above and fractionated through a thirty-plate column to give a 64.2% yield of recovered nitrile, b.p. 104–105°, $n^{20}D$ 1.3780–1.3783; 10.8% of crude isopropyl *t*-butyl ketone, b.p. 134–137°, $n^{20}D$ 1.4064–1.4168, oxime, m.p. 138–140°, mixed m.p. with authentic sample, m.p. 139–141°, and 1.9% of trimethylacetaldehyde, b.p. 70–80°, $n^{20}D$ 1.3740–1.3802. This latter material gave a positive Schiff test, a semicarbazone, m.p. 187–188.5°, and a 2,4-dinitrophenylhydrazone, m.p. 205–207°; melting point when mixed with authentic sample,[8] 205–207°.

In a second experiment the reaction mixture from 0.5 mole of trimethylacetonitrile was prepared as above. Diisoamyl ether, 600 ml., was added and the diethyl ether removed through a Vigreux column attached to the reaction flask. The reaction mixture was then maintained with stirring at 100–110° for eight hours. After hydrolysis with ammonium chloride solution it was worked up as above; a 5.5% yield of trimethylacetonitrile, a 6.3% yield of trimethylacetaldehyde and a 46.3% yield of crude isopropyl *t*-butyl ketone were isolated. This latter material was not homogeneous; it boiled over a range, 135–144°, and seemed to be composed of two components, one boiling at 135°, $n^{20}D$ 1.4038, and the second boiling at 143°, $n^{20}D$ 1.4180. Both cuts gave good yields of the oxime of *t*-butyl isopropyl ketone (m.p. 139–141° and 140–141°, respectively) but the higher boiling cut contained 0.5% nitrogen which possibly may be due to the presence of isopropyl *t*-butyl ketimine. Immediately before the diisoamyl ether solvent began to distil, a small amount, 1.8 g., of a white solid which is yet unidentified, collected on the condenser. This may be the trimer of trimethylacetaldehyde.

***t*-Butylmagnesium Chloride and Trimethylacetonitrile.**—To 0.45 mole of a titrated *t*-butylmagnesium chloride solution was added 33.3 g. (0.40 mole) of trimethylacetonitrile. The ether solvent was replaced with 500 ml. of diisoamyl ether and the reaction temperature maintained at 100–110° with stirring for eight hours. An olive-colored precipitate was formed in the mixture. After hydrolysis with ammonium chloride solution and working up as above, 11.3 g. (39.4%) of trimethylacetonitrile, 5.0 g. (14.5%) of *t*-butyl alcohol and 4.5 g. (6.1%) of trimethylacetonitrile were isolated.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Curare Substitutes from Stilbazoline Quaternary Ammonium Salts

BY ARTHUR P. PHILLIPS AND JULIO C. CASTILLO

In a continuing search for curare-like activity in varied series of synthetic organic compounds active products have again been found in a relatively simple type, stilbazoline quaternary ammonium salts.

While examining the relationship between chemical structure and curare-like activity in a series of simple polymethylene-α,ω-bis quaternary ammonium salts Barlow and Ing[1] and Paton and Zaimis[2] found a maximum activity in the decamethylene-1,10-bis-trimethylammonium iodide.

Exploiting this discovery the corresponding bis-quaternary bromide[3]

$$(CH_3)_3\overset{+}{N}-(CH_2)_{10}-\overset{+}{N}(CH_3)_3$$
$$\qquad\qquad Br^- \qquad\qquad Br^-$$

and bis-quaternary ammonium salts from a series of bis-β-dimethylaminoethyl esters of dicarboxylic acids[4,5] were prepared. In this latter group maximum activity, of the same order of potency as *d*-tubocurarine chloride, was encountered in the succinyl choline derivative

$$(CH_3)_3\overset{+}{N}CH_2CH_2OC(=O)-CH_2CH_2C(=O)-OCH_2CH_2\overset{+}{N}(CH_3)_3$$
$$\qquad\qquad\qquad\qquad I^- \qquad\qquad\qquad\qquad I^-$$

in which the quaternary ammonium nitrogens are separated by a chain of ten atoms analogous to the model mentioned above.

There is evidence, however, that, in spite of recent views[6,7,8] the mere existence of such a long chain of atoms, separating two (or more) quaternary ammonium groups by some optimum distance of about 12–14 Å., is in itself neither a *necessary* nor a *sufficient* condition for producing very powerful curariform activity in a molecule. Thus Marsh and Herring[9] report a *mono*-quaternary ammonium chloride from Calabash curarine I to be about six times as active as *d*-tubocurarine chlorine (possessing *two* quaternary nitrogens and the ultimate model from which the decamethylene series was derived) in producing head drop in rabbits. That possession of the optimal long chain bis-quaternary ammonium salt structure was not sufficient to produce invariably strong curare-like effects has been shown by the almost complete lack of such effects in a series of bis-β-tertiaryaminoalkyl amides of dicarboxylic acids and their bis-quaternary ammo-

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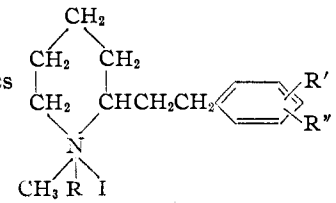
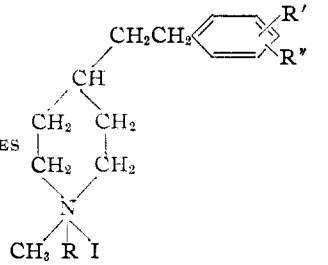
TABLE I

A. QUATERNARY AMMONIUM SALTS FROM 2-STILBAZOLINES



Compound	R', R''	R	M.p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I	None	CH_3	147–148	52.1	52.1	7.0	6.9
II	None	C_2H_5	123–124	53.4	53.3	7.3	7.3
III	None	n-C_3H_7	114–115	54.7	54.7	7.6	7.5
IV	2-HO	CH_3	174–175	49.8	50.1	6.7	6.7
V	4-HO	CH_3	115–120	49.8	49.9	6.7	6.7
VI	2-CH_3O	CH_3	167–168	51.2	51.3	7.0	6.9
VII	4-CH_3O	CH_3	171–172	51.2	51.5	7.0	7.0
VIII	4-CH_3O	C_2H_5	145–150	52.4	52.5	7.2	7.2
			Softens 121–122				
IX	3,4-CH_2O_2	CH_3	182–183	49.3	49.5	6.2	6.2
X	3,4-CH_2O_2	C_2H_5	209–210	50.6	50.9	6.5	6.5
XI	3,4-CH_2O_2	n-C_4H_9	141–142	52.9	53.2	7.0	7.0
XII	2,5-$(CH_3O)_2$	CH_3	142–143	50.4	50.4	7.0	6.8
XIII	2,5-$(CH_3O)_2$	C_2H_5	148–150	51.5	51.7	7.2	7.0
XIV	3,4-$(CH_3O)_2$	CH_3	147–148	50.3	50.3	7.0	6.9
XV	3-Br-4-$(CH_3)_2N$	CH_3	157–158	43.7	43.9	6.0	6.0
XVI	4-$(CH_3)_3N$-I	CH_3	200–201	40.7	41.0	6.1	5.9

B. QUATERNARY AMMONIUM SALTS FROM 4-STILBAZOLINES



XVII	None	CH_3	172–173	52.1	52.3	7.0	7.0
XVIII	None	C_2H_5	146–147	53.5	53.7	7.3	7.4
			Softens 130–145				
XIX	2-Cl	CH_3	180	47.4	47.0	6.1	5.7
			Softens 153		46.9		6.2
XX	4-HO	CH_3	234–235	49.8	49.9	6.7	6.5
XXI	4-HO	C_2H_5	200 sinters	51.2	51.3	7.0	7.0
XXII	2-CH_3O	CH_3	144–145	51.2	51.5	7.0	6.7
				I 33.8	I 33.8		
XXIII	4-CH_3O	CH_3	180–181	51.2	51.0	7.0	7.0
XXIV	4-CH_3O	C_2H_5	135	52.4	52.8	7.3	7.3
			Softens 120–123				
XXV	3,4-CH_2O_2	CH_3	156–157	49.3	49.4	6.2	6.3
XXVI	2,5-$(CH_3O)_2$	CH_3	166–167	50.4	50.5	7.0	6.6
XXVII	2,5-$(CH_3O)_2$	C_2H_5	146–147	51.5	51.8	7.2	7.3
XXVIII	3,4-$(CH_3O)_2$	CH_3	197–198	50.4	50.6	7.0	7.0
XXIX	3,4-$(CH_3O)_2$	C_2H_5	185–190	51.5	51.7	7.2	7.2
			Sinters 165–185				
XXX	3,4-$(CH_3O)_2$	n-C_3H_7	200–205	52.6	52.8	7.5	7.5
			Sinters 183–185				
XXXI	4-$(CH_3)_3N$-I	CH_3	183–185	40.7	40.4	6.1	6.1
				I 47.9	I 47.9		

nium salts,[10,11] although these amides do possess the valuable attribute of greatly prolonging the duration of the block of neuromuscular transmission induced by the analogous bis-aminoester salts.

In view of the foregoing results it is an interesting coincidence that, of the series of compounds to be described in the current study, although planned

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(11) J. C. Castillo and E. J. de Beer, *Federation Proceedings*, **9**, 262 (1950).

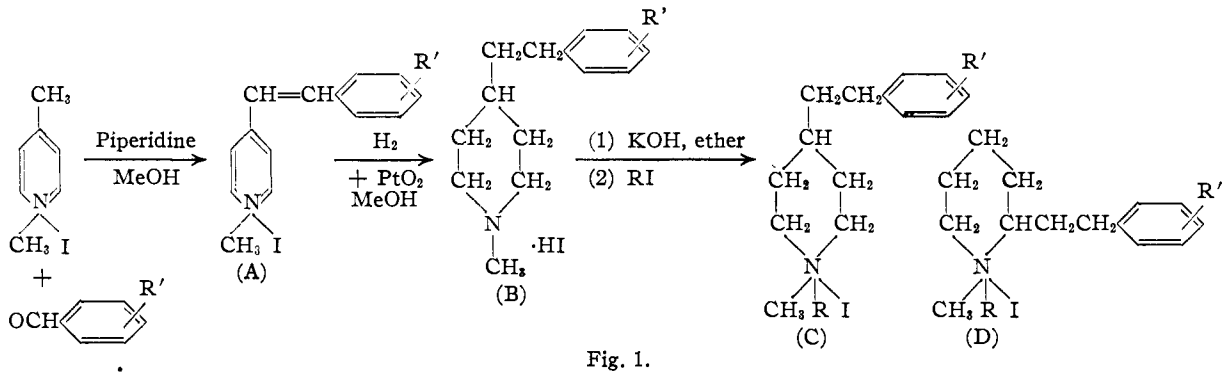

Fig. 1.

and many prepared before the reports of Barlow and Ing[1] and Paton and Zaimis,[2] the most active curare-like compound (XXXI of Table I-(B)) is formally relatable structurally to their model.

The current series of compounds was started some years ago by the condensation of aromatic aldehydes with 2-picoline methiodide[12] and with 4-picoline methiodide.[13] Catalytic hydrogenation transformed these 2- and 4-stilbazole methiodides into 2- and 4-stilbazoline hydroiodides[14] which have now been transformed into their quaternary ammonium salts shown in Table I. The over-all synthetic route is illustrated for the 4-stilbazoline series in Fig. 1.

Numerous representatives from both series of stilbazoline quaternary ammonium salts (parts A and B of Table I; also illustrated by (C) and (D) in Fig. 1) were examined for their ability to block neuromuscular transmission in the cat.

In the 4-stilbazoline series compound XXXI (Table I-(B)), 1-methyl-4-(4′-dimethylaminophenethyl)-piperidine 1,4′-bismethiodide, was found to be by far the most active with a potency approaching that of the decamethylene-1,10-bis-trimethylammonium bromide and about five times that of *d*-tubocurarine chloride.

Examination of the 2-stilbazolines (Table I-(A)) revealed that although they are relatively devoid of curarimimetic action, compound XVI (Table I-(A)), which is the closest analog of compound XXXI, the most active compound of the 4-series, completely reverses the neuromuscular block produced by Compound XXXI.

A detailed pharmacological report on these compounds will be made elsewhere.

An interesting structural analogy can be drawn between the powerful curare-like activity of Compound XXXI and its complete reversal by the shorter chain analog Compound XVI and the strong curare-like effect and reversal reported for the decamethylene-1,10-bis-trimethylammonium iodide and pentamethylene-1,5-bis-trimethylammonium iodide pair by Paton and Zaimis.[2,15] In compound XXXI a nine carbon chain separates the quaternary ammonium nitrogens while in Compound XVI only seven carbons are interposed.

Exploitation of the more significant results is in progress.

Experimental

Preparation of the Quaternary Ammonium Salts.—The base stilbazolines were obtained by treatment of the hydroiodides[14] with aqueous alkali, ether extraction and drying of the ethereal solution over potassium carbonate. After filtration and removal of ether the oily base was dissolved in 10 volumes of methanol and 3–5 mols of the alkyl iodide was added. The reaction mixture was refluxed for periods of from four to 60 hours and then evaporated to dryness. The quaternary alkiodides were purified by recrystallization from mixtures of methyl or ethyl alcohol and ethyl acetate and ether. Yields were virtually quantitative. The details are compiled in Table I.

Acknowledgment.—The authors are indebted to Mr. Samuel W. Blackman for the microanalytical results reported here.

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