SYNTHETIC CURARE SUBSTITUTES FROM ALIPHATIC DICARBOXYLIC ACID AMINOETHYL ESTERS

Sir:

The recent publication by Bovet and coworkers[1] of extensive work on synthetic curare substitutes derived from aliphatic dicarboxylic acid aminoethyl esters leads us to record briefly at this time results obtained in these laboratories simultaneously and independently.

Stimulated by the work of Barlow and Ing,[2] and of Paton and Zaimis[3] in discovering powerful curare-like activity in a series of straight-chain polymethylene bis-quaternary ammonium salts we sought to produce compounds of similar activity by duplicating the favorable chain length, found by them to be ten atoms, between the quaternary nitrogens. We did this first by making a series of bis-(β-dimethylaminoethyl) esters of aliphatic dicarboxylic acids, the bis-amino esters then being converted to bis-quaternary salts by reaction with the appropriate alkyl iodide.

The amino esters were obtained in poor or moderate yields by ester exchange reactions of the corresponding methyl or ethyl esters with a small excess of β-dimethylaminoethanol in the presence of a trace of dissolved sodium. The quaternary salts were best made in an inert solvent such as ether or acetone, as use of an alcohol solvent gave poor yields usually, probably because of reversal of the ester exchange process under these conditions.

bis-Dimethylaminoethyl succinate (b. p. 130–135° at 1 mm.); its bis-methiodide (m. p. 254–255°; calcd.: C, 30.87; H, 5.55. Found: C, 30.82; H, 5.45); bis-ethiodide (m. p. 203–204°; calcd.: C, 33.55; H, 5.99. Found: C, 33.56; H, 6.00); bis-*n*-propiodide (m. p. 132–133°; calcd.: C, 35.98; H, 6.38. Found: C, 36.47; H, 6.40); bis-dimethylaminoethyl glutarate (b. p. 145–150° at 1 mm.); its bis-methiodide (m. p. 214–217°; calcd.: C, 32.24; H, 5.79. Found: C, 32.52; H, 5.85); bis-ethiodide (m. p. 151–153°; calcd.: C, 34.79; H, 6.19. Found: C, 35.07; H, 6.10); and bis-dimethylaminoethyl adipate (b. p. 153–158° at 1 mm.) and its bis-methiodide (m. p. 138–139°; calcd.: I, 44.35. Found: I, 42.50) were prepared in this way.

The first compound made, the bis-dimethylaminoethyl succinate bis-methiodide, has ten atoms interposed between the quaternary salt groups, and showed a curariform activity equal in intensity to that of *d*-tubocurarine chloride as determined by its ability to block neuro-muscular transmission in the cat, but the effect was of much shorter duration than that produced by *d*-tubocurarine. This shorter duration of action was tentatively attributed to the action of choline esterases based on the similarity between this substance and two molecules of acetylcholine coupled at the α-carbon. Independent investigations by the pharmacological group of our laboratories confirm the findings of Bovet and co-workers[1] and further work is being carried on with the most active members of this series.

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[1] Bovet, *et al.*, *Rend. Ist. Super. Sanità*, **12**, 1 (1949).

[2] Barlow and Ing, *Nature*, **161**, 718 (1948).

[3] Paton and Zaimis, *ibid.*, **161**, 718 (1948).

THE TETRAMETHYLPLATINUM-BENZENE COMPLEX

Sir:

Tetramethylplatinum forms a crystalline benzene complex.[1] Since Pt(IV) has six low energy orbitals and forms six interatomic links even in tetramethylplatinum,[1] it seemed possible that benzene was acting as a Lewis base, bonded to platinum, perhaps in the manner suggested by Winstein and Lucas for the silver perchlorate–benzene complex.[2] The nature of such a linkage has not been demonstrated, but is currently interesting due to speculation on π-bonding in organic reaction mechanisms, particularly by Dewar.[3]

Crystals of the benzene complex have the composition $(CH_3)_4Pt\cdot{}^1/_2C_6H_6$, as determined by loss of weight in going to the unsolvated form. A composition $(CH_3)_4Pt\cdot 2C_6H_6$ would be expected if benzene satisfied all platinum orbitals. Evidence, outlined below, indicates that the complex contains the tetramer, $(CH_3)_{16}Pt_4$, with molecular configuration unaltered.[1] There are then two benzene molecules per tetramer.

The tetramer configuration permits only methyl–benzene contacts, suggesting that the complex is held together by van der Waals forces, probably augmented by good crystal packing of these highly polarizable molecules.

Molecular Weight in Benzene.—The cryoscopically determined molecular weight in benzene is 1070 ± 100, *versus* 1021 expected for the tetramer. If benzene were bonded to platinum it would be expected that the methyl bridges of the tetramer would be broken, leading to a lower molecular weight.

Ultraviolet Absorption in Benzene and Cyclohexane.—The ultraviolet absorption of tetramethylplatinum in benzene and cyclohexane solutions, determined with a Beckmann spectrophotometer, are identical. Presumably the absorption would be considerably altered by any significant interaction of benzene with platinum.

Crystal Structure.—The benzene complex is orthorhombic, $a_0 = 16.83$, $b_0 = 21.08$, $c_0 = 8.92$ kX. ρ (obsd.) = 2.4, 16 $(CH_3)_4Pt$ and 8 benzenes per unit, with space group, as determined by Weissenberg and procession diagrams, C_{2v}^{9}–Pn2a or D_{2h}^{16}–Pnma. If the higher space group, Pnma,

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[1] R. Rundle and J. H. Sturdivant, THIS JOURNAL, **69**, 1561 (1947).

[2] S. Winstein and H. J. Lucas, *ibid.*, **60**, 836 (1938).

[3] M. J. S. Dewar, *J. Chem. Soc.*, 777 (1946).

is correct, and if the molecular configuration of the tetramethylplatinum tetramer is unaltered,[1] y-parameters of all platinum positions are determined. Intensities of $(0k0)$ reflections can then be calculated, and are in good agreement with observation (Table I). One could not achieve this agreement if the molecular structure of the tetramer were seriously altered by complexing with benzene.

TABLE I

INTENSITIES OF $(0k0)$ REFLECTIONS

k	Intensity Obsd.	Intensity Calcd.	k	Intensity Obsd.	Intensity Calcd.
2	S	1475	16	M^-	75
4	M^+	641	18	O	0
6	O	0	20	O	12
8	W	173	22	M^-	325
10	S	1178	24	M^+	573
12	VS	1575	26	M^+	630
14	S^+	722			

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HYDROLYSIS OF THE α-1,6-GLUCOSIDIC LINKAGE IN ISOMALTOSE BY CULTURE FILTRATE OF *ASPERGILLUS NIGER* NRRL 330

Sir:

The α-1,6-glucosidic linkage in the amylopectin fraction of starch is resistant to hydrolysis by the action of the more common amylolytic enzymes. Inasmuch as the linkage between the two glucose residues in isomaltose is of the α-1,6 type, it was of interest to test the ability of a culture filtrate of *Aspergillus niger* NRRL 330 to hydrolyze this disaccharide. Isomaltose is now available in crystalline form. The sample of sugar used in these experiments was prepared from starch by the method of Montgomery, Weakley and Hilbert[1] and characterized as 6-(α-D-glucopyranosyl)-α-D-glucose monohydrate, rotating +120° in water (anhydrous). This particular strain of *A. niger* was selected because it elaborates, when grown in submerged culture, an enzyme capable of hydrolyzing maltose in large amounts.

To 20 ml. of 0.06 M isomaltose monohydrate, buffered at pH 4.4 (acetate buffer, 0.3 M), was added 10 ml. of culture filtrate. The reaction mixture was held at 50°. The extent of hydrolysis was measured at two and five hours by the increase in reducing power as determined by the method of Somogyi.[2] The glucose formed in the reaction mixture after five hours was identified biologically by "fermentation" at pH 8.8 with an excess of yeast by the procedure of Somogyi.[3] A collection of some of our experimental data is given in Table I.

TABLE I

		1	2	3
Reaction mixture no.		1	2	3
Culture filtrate diluted		Un-	1:1 50%	1:3 25%
Two hr.	Isomaltose hydr./ml. culture filt., mg.	27.4	19.4	14.3
	Hydrolysis, %	63.4	44.9	33.1
Five hr.	Isomaltose hydr./ml. culture filt., mg.	39.0	35.1	29.0
	Hydrolysis, %	90.2	81.2	67.1
"Fermentable" glucose per ml. cult. filt., mg.		37.5	33.0	25.7

It will be noted that the undiluted culture filtrate hydrolyzed 90.2% or 39.0 mg. of the isomaltose per ml. of culture filtrate in five hours. The amount of fermentable glucose produced, 37.5 mg., per ml. of culture filtrate checks reasonably well with this figure. (The hydrolysis of isomaltose proceeds more slowly than the hydrolysis of maltose as indicated by the fact that 38.2 mg. of maltose is hydrolyzed per ml. of culture filtrate in one hour at 30°). In addition, the sugar formed in a reaction mixture identical to No. 1 in Table I, but incubated for six hours, was isolated as crystalline α-D-glucose monohydrate; $[\alpha]^{25\circ}{}_{D}$ +47.8° (c, 4 in water); m. p., 82.8°[4]; yield, 83.4%.

Further work on characterization of the enzyme system responsible for the hydrolysis of isomaltose is in progress.

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[1] Edna M. Montgomery, F. B. Weakley and G. E. Hilbert, THIS JOURNAL, **71**, 1682 (1949).

[2] M. Somogyi, *J. Biol. Chem.*, **160**, 61 (1945).

[3] M. Somogyi, *ibid.*, **119**, 741 (1937).

[4] *Cf.* Nat. Bur. Stand. Circ. No. C440, p. 728.

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DERIVATIVES OF DIBORINE

Sir:

Although tetrachlorodiborine, B_2Cl_4, first prepared by Stock, Brandt and Fischer (*Ber.*, **58**, 855 (1925)) by striking an arc across zinc electrodes immersed in liquid boron trichloride, is a compound of considerable potential interest, the original preparative method gave such poor yields (about 1%) of material of such low purity (less than 90%) that detailed study of the compound was not feasible.

Much better results have now been obtained by passing gaseous boron trichloride at 1 to 2 mm. through a glow discharge established between mercury electrodes. The mercurous chloride and other non-volatile products remain in the discharge tube; the volatile material is passed through a −78.5° trap, which retains the tetrachlorodiborine and allows the unchanged trichloride to pass. The latter is repeatedly subjected to the action of mercury in the discharge tube, since the amount converted per pass is small. The yield, however, is approximately 50%. There is evidence that other less volatile boron–chlorine compounds are obtained.

Tetrachlorodiborine is completely hydrolyzed by aqueous sodium hydroxide at 70°.

$$B_2Cl_4 + 6NaOH \longrightarrow 2NaBO_2 + 4NaCl + 2H_2O + H_2$$

Determination of the amounts of hydrogen, boron and chlorine in the hydrolysate of an unweighed sample by the usual methods gave the following results: H, 74.64 cc.; B, 0.0727 g.;