

# SYNTHETIC CURARE SUBSTITUTES FROM ALIPHATIC DICARBOXYLIC ACID AMINOETHYL ESTERS

Sir:

The recent publication by Bovet and co-workers<sup>1</sup> 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,<sup>2</sup> and of Paton and Zaimis<sup>3</sup> 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-( $\beta$ -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  $\beta$ -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  $\alpha$ -carbon. Independent investigations by the pharmacological group of our laboratories confirm the findings of Bovet and co-workers<sup>1</sup> and further work is being carried on with the most active members of this series.

THE WELLCOME RESEARCH LABORATORIES

TUCKAHOE 7, NEW YORK

ARTHUR P. PHILLIPS

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# THE TETRAMETHYLPLATINUM-BENZENE COMPLEX

Sir:

Tetramethylplatinum forms a crystalline benzene complex.<sup>1</sup> Since Pt(IV) has six low energy orbitals and forms six interatomic links even in tetramethylplatinum,<sup>1</sup> 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.<sup>2</sup> The nature of such a linkage has not been demonstrated, but is currently interesting due to speculation on  $\pi$ -bonding in organic reaction mechanisms, particularly by Dewar.<sup>3</sup>

Crystals of the benzene complex have the composition  $(\text{CH}_3)_4\text{Pt} \cdot \frac{1}{2}\text{C}_6\text{H}_6$ , as determined by loss of weight in going to the unsolvated form. A composition  $(\text{CH}_3)_4\text{Pt} \cdot 2\text{C}_6\text{H}_6$  would be expected if benzene satisfied all platinum orbitals. Evidence, outlined below, indicates that the complex contains the tetramer,  $(\text{CH}_3)_6\text{Pt}_4$ , with molecular configuration unaltered.<sup>1</sup> 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  $1070 \pm 100$ , 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.  $\rho$  (obsd.) = 2.4, 16  $(\text{CH}_3)_4\text{Pt}$  and 8 benzenes per unit, with space group, as determined by Weissenberg and precession diagrams,  $\text{C}_{2v}^9$ -Pn2a or  $\text{D}_{2h}^{16}$ -Pnma. If the higher space group, Pnma,

(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).

(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).