[Contribution from the Venable Chemical Laboratory, University of North Carolina]

THE TRUE STRUCTURE OF DIMETHYLAMINOETHYL ESTERS OF AROMATIC PHOSPHONIC ACIDS[1]

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In a recent publication (1), we described the preparation of a number of esters derived from 2-dimethylaminoethanol and aromatic phosphonic acids. The method of preparation of these esters involved the reaction of 2-chloroethyldimethylamine with the silver salts of the phosphonic acids. The products of this reaction were rather high-melting crystalline solids; they were soluble in water and alcohols and insoluble in nonpolar solvents. Although these properties were unlike those of ordinary dialkyl phosphonates, the products contained the correct amounts of nitrogen and phosphorus for an ester composed of two alkyl groups, and it was assumed that the bis(dimethylaminoethyl) phosphonates (I) had been obtained. Another structure which would have the same elemental composition, and indeed which would be more in agreement with the salt-like physical properties of the compounds, is represented by II. This product can be visualized as occurring through an initial dimerization of the 2-chloroethyldimethylamine to 1,1,4,4-tetramethylpiperazinium dichloride (2), followed by formation of silver chloride and the phosphonate of the piperazinium ion. Although no reference to this was made in our previous report, structure II was excluded by the fact that compounds analyzing as the dipicrates of structure I have been obtained by treatment of the esters with picric acid. If structure II were correct, the dipicrate obtained would have been that of tetramethylpiperazinium ion. It was therefore concluded that the products of the 2-chloroethyldimethylamine-silver phosphonate reaction were the desired bis(dimethylaminoethyl) phosphonates (1).

Another structure, (III), also in agreement with the analytical data and the physical properties of the compounds, was recently suggested to us in a private communication from Dr. Frank R. Atherton of Roche Products Ltd. This structure may be considered as a type of betaine; its formation may have occurred either before or after any of the desired bis(dimethylaminoethyl) phosphonate had been formed. This type betaine is not totally unique; the rearrangement of the ester IV to a somewhat similar betaine V has been recently described (3). The betaine V was a water-soluble, high-melting solid, whereas the ester IV was a high-boiling, water-insoluble liquid.

Some experimental work has now been carried out that indicates structure III, rather than I, to be correct for the compounds described in our previous report. This work involved hydrolytic studies of a typical compound, the ester of *p*-nitrobenzenephosphonic acid. In this work, it was assumed that, if structure I

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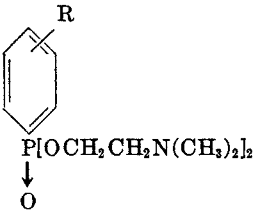
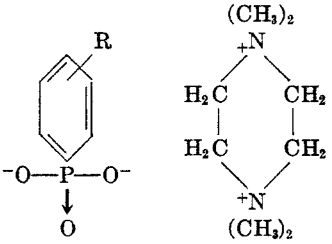
were correct, hydrolysis would form 2-dimethylaminoethanol, whereas if III were correct, the alcohol VI would be formed. Mild temperatures were used in the hydrolysis and product isolation to prevent decomposition of the quaternary salts involved, or other side reactions that would complicate the results. No attempt was made to isolate the free amino alcohol formed; picric acid was used to prepare solid derivatives.

A satisfactory method for the formation of the picrate of 2-dimethylaminoethanol (4), which could be used in the isolation of this compound if present in the hydrolysis mixture, was first developed, as described in the experimental part. The dipicrate of the ester to be hydrolyzed was prepared; its composition agreed with that expected for the dipicrate of structure I or III, but not of II.

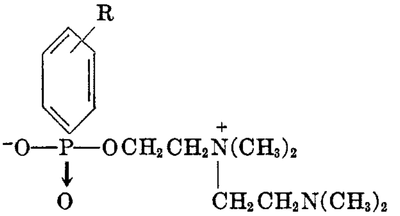
Hydrolysis of the ester with dilute hydrochloric acid was unsuccessfully attempted; hydrolysis of the ester with 10% sodium hydroxide was more effective. A hexane extract of the hydrolysis mixture did not contain any 2-dimethylaminoethanol, as evidenced by the failure of an attempt to form a picrate with this extract. However, a new picrate was prepared from an ethanol extract of a residue obtained by evaporation of the basic hydrolysis solution. A recrystal-



I

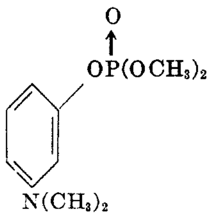


II

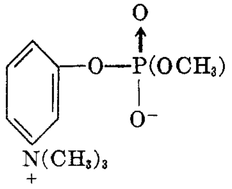


III

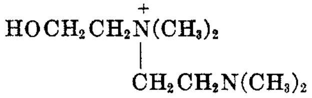
IIIA, R = 4−NO_2
IIIB, R = 4−Cl
IIIC, R = H
IIID, R = 4−CH_3O
IIIE, R = 3,4−OCH_2O^-
IIIF, R = 4−F



IV



V



$$\mathrm{HOCH_2CH_2\overset{+}{N}(CH_3)_2}\atop{\qquad\qquad\mathrm{|}\atop\qquad\qquad\mathrm{CH_2CH_2N(CH_3)_2}}$$

VI

lized portion melted at 195–196°d.; elemental analysis indicated it to be the dipicrate of VI.[3] The yield of crude picrate was 69% from the ester.

The failure to isolate any 2-dimethylaminoethanol picrate, and the actual isolation of a picrate presumed to be that of VI, on hydrolysis of a typical dimethylaminoethyl phosphonate, provides chemical proof that the betaine III, and not the dialkyl ester I, represents the correct structure for these products. The physical properties of the products also indicates III to be the preferred structure. It is not to be inferred from this work that compounds of structure I are incapable of existence; in its most restricted interpretation, the work implies that the conditions used here for the 2-chloroethyldimethylamine-silver phosphonate reaction led to the betaine rather than the dialkyl ester. It is possible that other conditions for this reaction, or other synthetic methods, will lead to the preparation of compounds of structure I. In this connection, it is of interest that compounds appearing to be true esters of phosphonic acids and diethylamino alcohols have been described (5) since our previous report. Betaine formation may be more difficult with these more bulky compounds.

Some pharmacological data have been collected on a few of the compounds described in our earlier paper (1). The ester IIIB showed some activity as a blocking agent for reducing hypertension. It was of no value in arresting cardiac fibrillation. Compounds IIIA, C, D, E, and F showed no hypnotic, diuretic, or anticonvulsant activity. Compounds IIIC, D, and E had acute intravenous LD_{50} values of 4.4, 4.8, and 3.5 mg. per Kg., respectively, in mice. Appreciation is expressed to the Wm. S. Merrell Company, Cincinnatti, Ohio, for this evaluation of these compounds.

EXPERIMENTAL[4]

Materials. The dimethylaminoethyl ester of *p*-nitrobenzenephosphonic acid, prepared in connection with previous work (1), was recrystallized from ethyl acetate-ethanol. 2-Dimethylaminoethanol (Eastman) was dried with sodium hydroxide and distilled. Solvents were dried with appropriate agents and distilled.

Dimethylaminoethanol picrate crystallized from ethanol-hexane, m.p. 95–96°; a reported value is 96–97° (4).

Dimethylaminoethyl p-nitrobenzenephosphonate picrate crystallized from methanol in which it is sparingly soluble, m.p. 278° after blackening at 252–258° (metal block).

Anal. Calc'd for $C_{26}H_{30}N_9O_{19}P$: N, 15.69; P, 3.86.

Found: N, 15.37; P, 4.28.

Basic hydrolysis of dimethylaminoethyl ester of p-nitrobenzenephosphonic acid. A solution of 1.2 g. (0.0035 mole) of the dimethylaminoethyl ester of *p*-nitrobenzenephosphonic acid in 50 ml. of 10% sodium hydroxide was held at 50° for three days. The mixture was saturated with sodium chloride and extracted with three 100-ml. portions of hexane. No picrate could be prepared from this extract after it had been concentrated. The basic aqueous solution was then treated with conc'd hydrochloric acid to *p*H 8–9 (test paper). The mixture was evaporated at 30 mm. to near dryness. The residue was extracted with

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[3] Tetramethylpiperazinium ion, although an unlikely product for this reaction, forms a dipicrate of almost the same elemental composition. However, it is reported to decompose without melting at 315° (2).

[4] Melting points are uncorrected.

ethanol and filtered. The filtrate, which should contain any VI formed on hydrolysis, was treated while hot with 1.8 g. (0.0079 mole) of picric acid in 15 ml. of hot ethanol. A bright yellow solid precipitated immediately. It was filtered, washed with ethanol, and dried. The yield was 1.5 g. A portion was recrystallized from ethanol. It had m.p. (capillary) 195–196° (dec.).

Anal. Calc'd. for $C_{20}H_{26}N_8O_{15}$: C, 38.84; H, 4.24; N, 18.12.
Found: C, 38.83: H, 4.27; N, 17.81.

This analysis therefore indicates that the dipicrate of VI had been formed (69% yield), and that the original ester had structure III rather than I.

Analyses. Some of the analyses were performed at the Venereal Disease Experimental Laboratory, School of Public Health, University of North Carolina, through the courtesy of Dr. G. O. Doak. Other analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

SUMMARY

Basic hydrolysis of the dimethylaminoethyl ester of *p*-nitrobenzenephosphonic acid produced the alcohol $HOCH_2CH_2\overset{+}{N}(CH_3)_2CH_2CH_2N(CH_3)_2$ rather than 2-dimethylaminoethanol. This fact, together with the salt-like physical properties of the compound, indicates the correct structure for this, as well as other esters prepared similarly in previous work (1), to be a type of betaine (III) rather than a dialkyl ester (I). Some pharmacological properties of these compounds are reported.

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