[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Dialkylaminoalkyl Phosphonates and Phosphinates

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A number of dialkylaminoalkyl esters of diphenylphosphinic, benzhydrylphosphonic and 9-fluorenylphosphonic acids have been prepared as potential antispasmodics by the reaction of the respective phosphorus acids with dialkylaminoalkyl chlorides. Mechanisms for this reaction, and for the Michaelis–Arbuzov reaction with sterically hindered halides are proposed.

Comparisons of compounds of well-known pharmacologically active types with analogous substances in which carbonyl linkages have been replaced by phosphoryl have been reported on several occasions. For example, alkyl thiazolylphosphonates have been compared with the corresponding esters of nicotinic and thiazolecarboxylic acids,[2] and the biological activities of dialkylanilidophosphates have been contrasted with that of phenylurethan.[3,4] The antimicrobial and anti-cholinesterase properties of substituted para- and meta-aminophenylphosphonic and -phosphinic acids have also been studied.[5,6] Very recently, some dimethylaminoethyl arylphosphonates have been prepared as potential local anesthetics of the aminoalkyl ester type.[7]

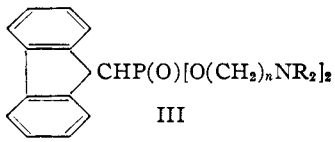
This study is concerned with the synthesis of dialkylaminoalkyl phosphonates and phosphinates of the general formulas (I–III) which were to be compared with ester type antispasmodics such as Trasentine and Pavatrine.

$$(C_6H_5)_2P(O)O(CH_2)_nNR_2$$

I

$$(C_6H_5)_2CHP(O)(OC_2H_5)O(CH_2)_nNR_2 \quad n = 2, 3$$

II



III

The esters of type I, II and III could be prepared readily by a method patterned on the procedure of Horenstein and Pählicke[8] in which carboxylic acids are esterified by treatment with dialkylaminoalkyl chlorides. Diphenylphosphinic acid, 9-fluorenylphosphonic acid and ethyl hydrogen benzhydrylphosphonate reacted smoothly with dialkylaminoethyl and -propyl chlorides in 2-propanol to give oily esters which were characterized as hydrochloride or methiodide salts.

Neither Horenstein and Pählicke[8] nor other authors who have used this reaction with branched carboxylic acids have remarked on the mechanism of this unusual esterification reaction.[9] We have found that in our series the reaction proceeds only if the tertiary amino group and the chlorine atom are separated by two or three carbon atoms; of available significant higher dialkylaminoalkyl halides, 8-diethylaminoöctyl chloride or iodide did not react to give esters of type I or II. It appears likely that dialkylaminoethyl and -propyl chlorides are not reacting by a simple ionic displacement but that they undergo cyclization to intermediate ethyleneimmonium or propyleneimmonium[10] ions, respectively, which then suffer nucleophilic attack by the phosphonic and phosphinic acids. It is probable that a similar mechanism is involved in the esterification of carboxylic acids.[8,9]

The dialkylaminoalkyl esters in our series could not be prepared from the respective phosphonyl and phosphinyl chlorides with dialkylaminoalkanols or their sodium derivatives.

Benzhydrylphosphonic acid had been prepared in 2% yield by the oxidation of diphenylmethane in the presence of phosphorus oxychloride.[11] We found it more profitable to subject benzhydryl bromide to the Michaelis–Arbuzov reaction with triethyl phosphite and obtained diethyl benzhydrylphosphonate in over 85% yield. In a similar manner, diethyl 9-fluorenylphosphonate was synthesized from 9-fluorenyl bromide. Hydrolysis of diethyl benzhydrylphosphonate with concentrated hydrochloric acid could be arrested at the ethyl hydrogen benzhydrylphosphonate stage, while prolonged action of mineral acid led to benzhydrylphosphonic acid. Diethyl 9-fluorenylphosphonate, upon prolonged hydrolysis, gave 9-fluorenylphosphonic acid.

The reactivity of benzhydryl and 9-fluorenyl bromide in the Michaelis–Arbuzov reaction contrasts with statements in the literature[12,13] that secondary halides are generally unreactive under these conditions. The mechanism for the reaction of primary alkyl halides with trialkyl phosphites has been explained by the formation of an addition complex, $[R'P(OR)_3]^+X^-$,[13,14] but this course does not seem applicable to the reaction of bulky secondary and tertiary halides where R′ is, for example, benzhydryl, trityl,[15] or (tri-*p*-xenyl)-

(1) Virginia–Carolina Chemical Corporation Fellow.

(2) N. D. Dawson and A. Burger, THIS JOURNAL, **74**, 5312 (1952).

(3) D. Ramaswami, E. R. Kirch and E. H. Jenney, *Science*, **116**, 58 (1952).

(4) D. Ramaswami and E. R. Kirch, THIS JOURNAL, **75**, 1763 (1953).

(5) G. O. Doak and L. D. Freedman, *ibid.*, **75**, 683 (1953).

(6) K. J. M. Andrews, F. R. Atherton, F. Bergel and A. K. Morrison, *J. Chem. Soc.*, 780 (1952).

(7) R. W. Bost, L. D. Quin and A. Roe, *J. Org. Chem.*, **18**, 362 (1953).

(8) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

(9) Compare for example, J. W. Cusic and R. A. Robinson, *J. Org. Chem.*, **16**, 1921 (1951); R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262, 1582 (1943).

(10) R. C. Elderfield and C. Ressler, *ibid.*, **72**, 4059 (1950).

(11) W. L. Jensen and C. R. Noller, *ibid.*, **71**, 2384 (1949).

(12) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 122.

(13) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

(14) W. Gerrard and W. J. Green, *ibid.*, 2550 (1951).

(15) A. E. Arbuzov and B. A. Arbuzov, *J. Russ. Phys.-Chem. Soc.*, **61**, 217 (1929); *C. A.*, **23**, 3921 (1929).

TABLE I

ESTERS OF PHOSPHONIC AND PHOSPHINIC ACIDS

Formula of compound	Yield,[a] %	Solvent of crystallization	M.p., °C. (evac. tube)	Mol. composition	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found
$(C_6H_5)_2P(O)O(CH_2)_2N(CH_3)(C_2H_5)_2\cdot I$	34.4	EtOH–Et_2O	193–194 (dec.)	$C_{19}H_{27}INO_2P$	49.68	49.58	5.93	5.93		
$(C_6H_5)_2P(O)O(CH_2)_2N(CH_3)_3\cdot I$	13.5	EtOH–Et_2O	191–192 (dec.)	$C_{17}H_{23}INO_2P$	47.34	47.10	5.38	5.33		
$(C_6H_5)_2P(O)O(CH_2)_3NH(C_2H_5)_2\cdot Cl$	52	EtOAc–EtOH	133–134	$C_{19}H_{27}ClNO_2P$	62.03	62.01	7.40	7.38		
$(C_6H_5)_2CHP(O)(OC_2H_5)O(CH_2)_2N(CH_3)(C_2H_5)_2\cdot I$	46	EtOH–Et_2O	127–128	$C_{22}H_{33}INO_3P$	51.07	50.88	6.43	6.14		
$(C_6H_5)_2CHP(O)(OC_2H_5)O(CH_2)_2NH(CH_3)_2\cdot Cl$	22.4	EtOAc	125–126	$C_{19}H_{27}ClNO_3P$	59.45	59.04	7.09	7.16		
9-Fluorenyl-P(O)[O$(CH_2)_3NH(C_2H_5)_2]_2\cdot 2Cl$	11	EtOAc–MeOH	153–154	$C_{27}H_{43}Cl_2N_2O_3P$	59.44	59.10	7.95	7.77	13.00	12.74

[a] All yields refer to compounds after at least two recrystallizations.

methyl.[16] Complexes containing such groups appear improbable because of steric hindrance. In order to explain the reaction on an ionic basis, formation of a diethyl phosphite ion and addition of benzhydryl carbonium ion to the latter would have to be assumed.

(a) $(C_6H_5)_2CHBr \rightleftharpoons (C_6H_5)_2CH^+ + Br^-$

(b) $Br^- + (C_2H_5O)_3P \longrightarrow C_2H_5Br + [^-OP(OC_2H_5)_2 \leftrightarrow O{=}{}^-P(OC_2H_5)_2]$

$(C_6H_5)_2CHP(O)(OC_2H_5)_2 \xleftarrow{(C_6H_5)_2CH^+}$

Since all the bulky compounds mentioned can exist as relatively stable free radicals, an alternate mechanism might involve a free radical path. Evidence for this possibility lies in the fact that the Michaelis–Arbuzov reaction was run with all these compounds under conditions favorable to free radical formation, and that from the reaction with benzhydryl bromide, some *sym*-tetraphenylethane was isolated.

β - Dimethylaminoethyl diphenylphosphinate methiodide afforded excellent protection against cholinergic spasm in the isolated guinea pig intestinal strip method at a dilution of 1×10^6. Some of the dialkylaminoethyl esters described in Table I inhibited peach brown rot and apple bitter rot at a dilution of 1×10^4.

Acknowledgment.—We are grateful to Virginia–Carolina Chemical Corporation for support of this work and to Smith, Kline and French Laboratories for the pharmacodynamic tests. Details of these tests will be published by E. J. Fellows in the pharmacological literature.

Experimental[17]

Benzhydrylphosphonic Acid.—A mixture of 247 g. (1.0 mole) of benzhydryl bromide and 182.8 g. (1.1 moles) of triethyl phosphite was refluxed at 150° for three hours under a still head until ethyl bromide ceased to distil. The residual viscous yellow oil consisted of a mixture of diethyl benzhydrylphosphonate and *sym*-tetraphenylethane. It was boiled with 300 ml. of 36% hydrochloric acid for 20 hours, cooled, and the liquid was decanted from solid material. The solid was washed with water, treated with 5% sodium carbonate solution, the insoluble tetraphenylethane (identified by melting point and analysis; yield 10%) was filtered and the alkaline filtrate was acidified. Benzhydrylphosphonic acid (204 g., 82%) was obtained by recrystallization of the precipitate from 50% ethanol. It melted at 235–238°. A mixture melting point with a sample kindly furnished by Prof. C. R. Noller of Stanford University (m.p. 234–237°) showed no depression.

Anal. Calcd. for $C_{13}H_{13}O_3P$: C, 62.90; H, 5.28. Found: C, 62.62; H, 5.42.

When the reaction mixture in a similar run was refluxed with only 50.6 g. (0.5 mole) of 36% hydrochloric acid for 1.5 hours, a semi-solid product was formed from which a mixture of benzhydrylphosphonic acid and *ethyl hydrogen benzhydrylphosphonate* could be extracted with 5% sodium carbonate solution, followed by acidification. In contrast to the free phosphonic acid, the monoethyl ester was insoluble in two liters of boiling water and resolidified upon cooling. Recrystallization from carbon tetrachloride–petroleum ether gave 69 g. (25%) of colorless crystals melting at 120–122°.

Anal. Calcd. for $C_{15}H_{17}O_3P$: C, 65.21; H, 6.20. Found: C, 65.44; H, 5.94.

Treatment of benzhydrylphosphonic acid with excess diazomethane yielded 84% of colorless crystals of **dimethyl benzhydrylphosphonate** which after recrystallization from dilute ethanol melted at 96–97°.

Anal. Calcd. for $C_{15}H_{17}O_3P$: C, 65.21; H, 6.20. Found: C, 64.76; H, 6.25.

9-Fluorenylphosphonic Acid.—A mixture of 15.2 g. (0.062 mole) of 9-fluorenyl bromide in 10.3 g. (0.062 mole) of triethyl phosphite was refluxed at 160° for six hours with removal of ethyl bromide as it was formed. Unchanged triethyl phosphite was distilled at 80° (15 mm.) and the yellow oil was boiled with 100 ml. of 36% hydrochloric acid for 20 hours. The resulting solid was reprecipitated from sodium carbonate solution, and extracted into one liter of hot ether. After removal of the solvent, the yellow oily residue was extracted with benzene until a colorless solid was left behind. It was recrystallized from acetone–petroleum ether and decomposed at 256° (evac. tube). The yield was 4.7 g. (31%).

Anal. Calcd. for $C_{13}H_{11}O_3P$: C, 63.41; H, 4.50. Found: C, 63.19; H, 4.58.

Dimethyl 9-fluorenylphosphonate was obtained in 82% yield from the acid and diazomethane. The colorless ester was recrystallized from hot dilute methanol, m.p. 109–110.5°.

Anal. Calcd. for $C_{15}H_{15}O_3P$: C, 65.69; H, 5.51. Found: C, 65.65; H, 5.49.

Diphenylphosphinic acid was prepared in analogy to the directions of Kosolapoff[18] for the synthesis of bis-*p*-tolylphosphinic acid using diethylphosphoramic dichloride.

Dialkylaminoalkyl Phosphinates and Phosphonates.—In a typical preparation, a solution of 9.35 g. (0.069 mole) of N,N-diethylaminoethyl chloride in 60 ml. of 2-propanol was added dropwise to a refluxing solution of 15.06 g. (0.069 mole) of diphenylphosphinic acid in 100 ml. of dry 2-propanol with stirring. The mixture was refluxed for six hours. A small amount of white precipitate that formed was filtered and the remaining solution evaporated to dryness, leaving a yellowish oil. This was treated with 5% sodium carbonate solution and extracted three times with 50-ml. portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The remaining light-colored oil was treated dropwise with ethereal hydrogen chloride. As a rule, the first portion of the resulting precipitate remained oily, and when the product began to appear as a solid, the

(16) A. E. Arbuzov and K. V. Nikonorov, *J. Gen. Chem.* (*U.S.S.R.*) **17**, 2139 (1947); *C. A.*, **42**, 4546*b* (1948).

(17) All melting points are corrected. The microanalyses were performed by Miss Patricia Paynter.

(18) G. M. Kosolapoff, THIS JOURNAL, **71**, 369 (1949).

ether solution was decanted and the oil washed several times with 10-ml. portions of absolute ether. The combined ether solutions were made acid to congo red paper with ethereal hydrogen chloride. In many cases, the colorless hydrochlorides were extremely hygroscopic and could only be recrystallized to analytical purity with difficulty. When this was not possible, the base was liberated with sodium carbonate solution, extracted into ether and converted to the methiodide by warming with methyl iodide.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Synthesis of Pteroic and Pteroylglutamic Acids.[1] II.

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A new synthesis of pteroylglutamic acid is described in which diethyl N-tosyl-*p*-aminobenzoyl-L-glutamate is alkylated with 2,3-oxidopropionaldehyde diethyl acetal, the product oxidized and condensed with 2,4,5-triamino-6-hydroxypyrimidine. Detosylation of this product with hydrogen bromide in acetic acid in the presence of phenol gives the final product in good yield.

In the preceding paper of this series,[2] a synthesis of pteroic acid and pteroylglutamic acid was reported. The general scheme was to alkylate ethyl N-tosyl-*p*-aminobenzoate (I) or diethyl N-[N'-tosyl-*p*-aminobenzoyl]-L-glutamate (II), with a three carbon compound to give a N-substituted sulfonamide. The compound thus formed contained a three-carbon side chain with functional groups either directly or by suitable modifications capable of condensing with 2,4,5-triamino-6-hydroxypyrimidine to form the N^{10}-tosyl-substituted pteroic or pteroylglutamic acids. Although a variety of compounds was prepared and condensed to form pteroic or pteroylglutamic acids, in most cases the yields were low.

In the search for a reactive three-carbon alkylating reagent, the possibility of obtaining a vicinal dicarbonyl or potential vicinal dicarbonyl system was investigated. The oxidation product of ethyl N-tosyl-N-(2-keto-3-hydroxypropyl)-*p*-aminobenzoate[2] with copper acetate in methanol[3] gave an increased yield of pteroic acid over that obtained from the keto-alcohol. This increased yield may be due in part to the fact that in the former case a completely aromatic pteridine nucleus is formed directly whereas in the latter case a dihydropteridine compound is formed which must be oxidized to the completely aromatic compound. This indicated the desirability of using a three carbon alkylating agent which would give directly the desired ethyl N-tosyl-N-(2,3-diketopropyl)-*p*-aminobenzoate. 2,3-Oxidopropionaldehyde diethyl acetal is such an alkylating agent. The use of this compound in the synthesis of pteroic and pteroylglutamic acids is outlined in Fig. 1.

Wohl[4,5] described the preparation of 2,3-oxidopropionaldehyde diethyl acetal by the addition of hypochlorous acid to acrolein diethyl acetal followed by dehydrohalogenation of the halohydrin with solid potassium hydroxide. Acrolein diethyl acetal was prepared[4] by converting acrolein with ethanolic hydrogen chloride to the diethyl acetal of β-chloropropionaldehyde followed by dehydrohalogenation. This is essentially the method later published by Witzemann, *et al.*[6] Acrolein diethyl acetal also has been prepared from acrolein, ethyl orthoformate and ammonium nitrate in boiling ethanol[7] and in a method published by Pingert[8] from acrolein, anhydrous hydrogen chloride, and an excess of ethanol. Since the yields reported by these methods were low or not attainable by us, the following method was developed. In the presence of only 0.002 molar amounts of an acid catalyst, such as *p*-toluenesulfonic acid, acrolein and ethanol were allowed to react to give yields of acrolein diethyl acetal as high as 82%. The water formed by the reaction was removed continuously by codistillation with Skellysolve F. Hypochlorous acid was added to the acrolein acetal by vigorously stirring a solution of the two reagents at low temperature. The 2-chloro-3-hydroxypropionaldehyde diethyl acetal was then extracted and the halohydrin dehydrochlorinated with solid sodium hydroxide to give 2,3-oxidopropionaldehyde diethyl acetal in 60% yield.

The alkylation of ethyl N-tosyl-*p*-aminobenzoate (I)[2] and diethyl N-[N'-tosyl-*p*-aminobenzoyl]-L-glutamate (II)[2] was accomplished by dissolving the solid in 2,3-oxidopropionaldehyde diethyl acetal and stirring the mixture at the desired temperature in the presence of a basic catalyst. Ethyl N-tosyl-N-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoate (III) was obtained in crystalline form, but diethyl N-[N'-tosyl-N'-(2-hydroxy-3,3-diethoxypropyl)-*p*-aminobenzoyl]-L-glutamate (IV), could only be obtained as a heavy sirup. Numerous attempts to crystallize the parent substance or to find a crystalline derivative were unsuccessful. The material could, however, be purified by chromatography over alumina.

In the oxidation of these compounds to the corresponding ketones (V and VI) it was found that a heterogeneous oxidation in the cold employing an aqueous acid solution of sodium dichromate was superior to the chromic acid oxidation in glacial acetic acid previously used.[2] Although neither

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(2) D. I. Weisblat, B. J. Magerlein, A. R. Hanze, D. R. Myers, and S. T. Rolfson, THIS JOURNAL, **75**, 3625 (1953).

(3) H. R. Henze, *Z. physiol. Chem.*, **198**, 82 (1931).

(4) A. Wohl, *Ber.*, **31**, 1796 (1898).

(5) A. Wohl and H. Schweitzer, *ibid.*, **40**, 92 (1907).

(6) E. J. Witzemann, W. L. Evans, H. Hass and E. F. Schroeder, "Org. Syn.," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 17.

(7) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 514 (1935).

(8) F. P. Pingert, *Org. Syn.*, Vol. 25, p. 1, John Wiley and Sons, Inc., New York, N. Y., 1945.