Synthesis and Carcinolytic Activity of Some Diaryliodonium Salts[1]

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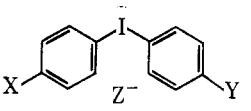
A number of diaryliodonium salts, with substituents chosen in order to vary chemical properties in a systematic way, has been prepared for study as potential carcinolytic agents. Observed biological activity, as well as some aspects of the chemistry of these substances, is reported and discussed.

It is generally believed that nitrogen mustards act by virtue of their ability to form ethylenimmonium ions, which alkylate biologically important nucleophiles.[2] The primary site of alkylation in the cell appears to be DNA,[3] the N-7 position of guanine being most susceptible.[4] It has been found in the aromatic nitrogen mustard series that alkylating ability is generally enhanced by the presence of electron-donating aryl substituents,[5,6] and further that SN1 reactivity in the series parallels antitumor activity.[5]

The successful use of alkylating agents in cancer chemotherapy suggested that arylating agents might find similar application. The arylating agent of choice for use against cancer would be one reactive enough to achieve arylation of a wide variety of nucleophiles under relatively mild conditions, but sufficiently selective to ensure distribution of the substance in the body. Of the arylating agents known, diaryliodonium salts (I) best meet these demands.



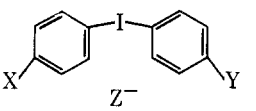
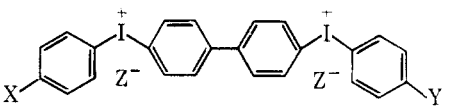
The arylating ability of diaryliodonium salts has been amply demonstrated. It has been shown, for example, that diaryliodonium halides (I, Z = Cl, Br, or I) are capable of arylating bases of such diverse reactivity as halide ions,[7] sulfhydryl groups,[8] arylamines,[9] and alkoxides.[10] The ease with which most of these arylations occur prompted Beringer to investigate the synthetic potential of diaryliodonium salts, with the result that arylation of anions of activated esters[11,12] and ketones[13] has been achieved, often in significant yield.

Beringer further demonstrated that the nature of aryl substituents greatly affects the rate at which iodonium halides undergo decomposition in inert solvents, electronegative substituents facilitating such decomposition, and conversely.[14] Taking this to be a possible criterion for assessing the reactivity of these compounds toward cellular constituents, synthesis of a series of substituted diaryliodonium salts was begun.

Chemistry.—Compounds selected for biological evaluation are listed in Table I; their synthesis was effected for the most part by known methods.[15] In order to assess the possible effect of chemical reactivity on biological activity, a series of simple monofunctional salts (Table I, Ia–j) was prepared. Since in the nitrogen mustard series very high activity is associated with compounds such as chlorambucil and sarcolysin, which bear a carboxylic and amino acid side chain, respectively, it was felt that activity in the iodonium salts might be enhanced by the presence of such

TABLE I

DIARYLIODONIUM COMPOUNDS

Compd[a]	X	Y	Z	Method of prepn[b]
	 I			
Ia	NO_2	H	Br	26
Ib	NO_2	H	NO_3	...[c]
Ic	NO_2	$NHCOCH_3$	Br	26
Id	NO_2	OCH_3	Br	26, 15D
Ie	H	H	Br	26, 15B
If	H	H	NO_3	...[c]
Ig	OCH_3	H	Br	15D
Ih	OCH_3	H	NO_3	...[c]
Ii	OCH_3	OCH_3	Br	15A
Ij	OCH_3	OCH_3	NO_3	...[c]
Ik	CH_2CH_2COOH	H	I	15D
Il	$CH_2CHCOOH$ | $NHCOCF_3$	H	I	15D
	 II			
IIa	H	H	I	10A
IIb	H	H	Br	10A

[a] Ia, IIa, and IIb were prepared by methods not previously employed in their synthesis. Ic, Id, Ih, Ij, Ik, and Il have not been reported previously. [b] Numerals refer to references, letters to methods cited therein. [c] Nitrates prepared by metathesis of the corresponding halides. See Experimental Section.

(1) Abstracted from the M.S. Thesis of M. A. Salter, University of Kansas, 1965. Supported by the American Cancer Society through its Institutional Grant to the University of Kansas.

(2) C. C. Price, *Ann. N. Y. Acad. Sci.*, **68**, 663 (1958).

(3) G. P. Wheeler, *Cancer Res.*, **22**, 651 (1962).

(4) (a) P. Brookes and P. D. Lawley, *Biochem. J.*, **77**, 478 (1960); (b) P. Brookes and P. D. Lawley, *ibid.*, **80**, 496 (1961).

(5) T. J. Bardos, N. Datta-Gupta, P. Hebborn, and D. Triggle, *J. Med. Chem.*, **8**, 167 (1965).

(6) W. C. J. Ross, *Advan. Cancer Res.*, **1**, 397 (1953).

(7) R. B. Sandin, M. Kulka, and R. McCready, *J. Am. Chem. Soc.*, **59**, 2014 (1937).

(8) R. B. Sandin, R. G. Christiansen, R. K. Brown, and S. Kirkwood, *ibid.*, **69**, 1550 (1947).

(9) L. G. Makarova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 741 (1951); *Chem. Abstr.*, **46**, 7532 (1952).

(10) F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Am. Chem. Soc.*, **75**, 2705 (1953).

(11) F. M. Beringer and P. S. Forgione, *J. Org. Chem.*, **28**, 714 (1963).

(12) F. M. Beringer and S. A. Galton, *ibid.*, **28**, 3417 (1963).

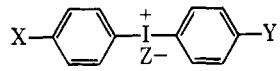
(13) F. M. Beringer, S. A. Galton, and S. J. Huang, *J. Am. Chem. Soc.*, **84**, 2819 (1962).

(14) F. M. Beringer and M. Mausner, *ibid.*, **80**, 4535 (1958).

(15) For a complete list of methods used in preparation of diaryliodonium compounds, see F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausner, and E. Sommer, *ibid.*, **81**, 342 (1959), and ref 10.

TABLE II

ANTITUMOR ACTIVITY[a]



				Whole animal tumors					KB tissue culture	
				Dose,[b]	% T/C[c]				ED_{50},	
No.	X	Y	Z	mg/kg	DA	H1	LE	8P	μg/ml	Slope
Ia	NO_2	H	Br	25			108	84	1.9	−3.6
				12.5	100					
Ib	NO_2	H	NO_3	12.5			120	93	2.1	−0.91
				6.25	120					
Ic	NO_2	$NHCOCH_3$	Br	50			87	73	3.0	−1.9
				25	105					
Id	NO_2	OCH_3	Br	25			113	128	0.68	−2.9
				12.5	105					
				5.0		103				
If	H	H	NO_3	2.5				54	0.54	−0.41
Ih	H	OCH_3	NO_3	2.5				75	0.82	−0.47
Ij	OCH_3	OCH_3	NO_3	2.5			98	73	0.39	−0.55
Ik	H	$(CH_2)_2COOH$	I	100			100	94	36	−0.63
				50	129					
IIa	H	PhI^+-Ph	2I	5.0				66	1.0	<−0.39

[a] CCNSC screening protocols are fully described in *Cancer Chemotherapy Rept.*, **25**, 1 (1962). [b] Toxic doses omitted. [c] % T/C = tumor weight in treated animals/tumor weight in controls × 100. DA = Dunning ascites leukemia, H1 = HS1 human sarcoma (rat, egg), LE = lymphoid leukemia L1210, and 8P = P1798 lymphosarcoma.

moieties. Compounds Ik and Il were prepared to test this approach.

It is well known that difunctional mustards are far more active as antitumor agents than the corresponding monofunctional compounds.[5,6] Since the observed low antitumor activity of the latter bear little relation to SN1 reactivity,[5] resolution of the disparity must rest on biological considerations. Brookes and Lawley[4] found alkylated biguanyl as well as monoguanyl residues in hydrolysates of nucleic acids isolated from animals treated with difunctional mustards, which suggests that the antitumor effects of difunctional mustards may be due to the formation of strategic cross-linkages between strands of DNA. It is conceivable that difunctional iodonium salts such as II might likewise be capable of cross-link formation and that antitumor activity might therefore be enhanced. Diphenyl-4,4′-biphenylyldiiodonium diiodide (IIa) was chosen as a prototype difunctional iodonium compound.

Pharmacological Results.—Compounds Ia–d, f, h, j, k, and IIa were submitted for antitumor screening to the Cancer Chemotherapy National Service Center. Both whole animal and cell culture methods were used. The results are shown in Table II. Compounds Ie, g, and i had been submitted by other workers; Il has not been obtained in sufficient yield to allow testing.

The results of testing against whole animal tumors shown in Table II indicate that none of these compounds shows significantly selective antitumor activity when tested in this manner. Since the doses shown are the highest the animals could tolerate, it is clear that toxicity in this series is related to solubility of the substances, since almost without exception the water-soluble nitrates are much more toxic than the relatively insoluble halide salts. This difference, however, is not reflected in antitumor potency, nor does the wide range of chemical reactivity[15] represented in this series appear to be of any consequence. The diiodonium compound IIa is the most active iodide salt we have yet encountered, and soluble salts of this type appear to merit further study.

All compounds tested except Ik showed a reproducibly high order of activity against tumor cells in the KB tissue culture system (Table II). In this test method, compounds are in solution, so that differences in solubility should not be important. Consequently, the nature of the anion should have little effect on observed activity. This is found to be the case. In addition, it is seen that, in general, the highest potency is associated with diaryliodonium salts which are known[14] to be the least reactive toward nucleophiles. That is, it appears that the destabilizing nitro group has a pronounced deleterious effect on antitumor potency in tissue culture, whereas the converse is true of the methoxy group. Further study will be necessary to determine whether this results from too rapid decomposition of the more reactive compounds in water, or whether a biological mechanism other than direct chemical arylation is operative.

Experimental Section

Analytical Procedures. — Microanalyses were performed by Drs. Weiler and Strauss, Oxford, England, and by Huffman Laboratories, Inc., Wheatridge, Colo. Melting points were taken on a calibrated Thomas–Hoover melting point apparatus. Infrared spectra were taken on a Beckman IR-5 or a Beckman IR-8 recording spectrophotometer.

Melting Points of Diaryliodonium Compounds.—Since diaryliodonium salts decompose at or near their melting points, it is necessary to specify at which temperature the sample is inserted and the rate of heating. Samples of compounds prepared in this study were inserted 10–15° below the expected melting point and heated at 4–6°/min.

General Preparation of Diaryliodonium Nitrates.—Preparation of diaryliodonium nitrates was achieved in each case by suspending 4–5 g of the parent halide in methanol (20 ml), to which was added an equimolar quantity of $AgNO_3$ dissolved in a minimum amount of methanol. The mixture was stirred in the dark at room temperature for 1–6 hr and the silver halide was removed by filtration. The solvent was completely evaporated without

application of heat, and the crude nitrate was recrystallized from methanol or methanol–ether. Conversions of diaryliodonium halides to the corresponding nitrates were accomplished in 86–100% yield.

Iodoso Compounds.—Preparation of iodosobenzene is described by Lucas, *et al.*[16] 4-Iodosonitrobenzene was prepared by a similar method.[17] Phenyliodoso diacetate was prepared according to the procedure of Pausacker.[18]

Chlorination of a solution of 4,4′-diiodobiphenyl in cold, dry chloroform[19] gave 4,4′-diiodosobiphenyl tetrachloride[20] which was washed with cold $CHCl_3$ (20 ml) and dried. To this (30.7 g, 46 mmoles) was added 5 *N* NaOH (80 ml). After thorough trituration the mixture was allowed to stand (with occasional trituration) for 3 days, at which time the mixture was filtered, washed with water until the washings were no longer basic, and dried. The dried material was washed with chloroform (100 ml) and dried to give crude amorphous 4,4′-diiodosobiphenyl (XI, 18.7 g, 42 mmoles, 76%), mp 176–80°, lit.[20] "about 198°."[21]

Iodoxy Compounds.—Preparation of iodoxybenzene is described by Lucas and Kennedy.[22] 4,4′-Diiodoxybiphenyl[20] was prepared by a similar method.

Diphenyliodonium bromide (Ie) was prepared as described[10] and also from benzene and KIO_3 in the presence of H_2SO_4 as described by Beringer for the corresponding chloride salt.[23]

Diphenyliodonium nitrate (If)[24] was prepared by metathesis of IIIe with $AgNO_3$ as described above.

4,4′-Dimethoxydiphenyliodonium bromide (IIIf) was synthesized by the procedure described by Plati.[25]

4,4′-Dimethoxydiphenyliodonium nitrate (Ij) was prepared from Ii by metathesis with $AgNO_3$. Recrystallization from methanol–ether gave colorless needles, mp 191.5–192.5° dec, inserted at 180°, 6°/min.

Anal. Calcd for $C_{14}H_{14}INO_5$: C, 41.74; H, 3.50; I, 31.48. Found: C, 41.76; H, 3.18; I, 31.40.

4-Nitrodiphenyliodonium bromide (Ia) was obtained by a modification of the persulfate oxidation method of Beringer and Lillien[26]; yield 59%, mp 149–50° dec, inserted at 140°, 4.5°/min; lit.[16] mp 149° dec.

Anal. Calcd for $C_{12}H_9BrINO_2$: C, 35.48; H, 2.22; N, 3.44. Found: C, 35.85; H, 2.08; N, 3.40.

4-Nitrodiphenyliodonium nitrate (Ib)[15] was prepared from Ia by metathesis with $AgNO_3$ as previously described.

4-Acetamido-4′-nitrodiphenyliodonium bromide (Ic) was obtained from the procedure which gave the corresonding iodide.[26] The over-all reaction afforded a 45% yield of Ic, mp 165–167.5° dec, inserted at 150°, 6°/min.

Anal. Calcd for $C_{14}H_{12}BrIN_2O_3$: C, 36.31; H, 2.59. Found: C, 36.97; H, 2.69.

4-Methoxy-4′-nitrodiphenyliodonium Bromide (Id).—To a stirred solution of 4-iodonitrobenzene (10.0 g, 40.2 mmoles) in 100 ml of concentrated H_2SO_4 at 15° was added portionwise $K_2S_2O_8$ (12.0 g, 40.2 mmoles). The mixture was stirred for 2 hr. The reaction flask was maintained at −20° during the addition of anisole (39.6 g, 0.36 mole) and for 1 hr afterward. The temperature was allowed to increase gradually to 0° and was maintained at this level for 1 hr. Stirring was continued at 15° for 2 hr more. The mixture was then poured onto ice (200 g), the solid was removed, and the filtrate was extracted three times with 50 ml of ether to remove unreacted anisole. To the solution was added NaBr (4.55 g, 40.2 mmoles) dissolved in 10 ml of water. The resulting precipitate was quickly removed, washed with water (100 ml) and methanol (50 ml), and dried to give the product (4.95 g, 33%), mp 151–154° dec, inserted at 150°, 8°/min. Washing the compound with water and a number of organic solvents raised the melting point to 155–158° dec, inserted at 150°, 5°/min. However, the extreme insolubility of this substance, together with its pronounced tendency to decompose when heated, made it impossible to procure a sample sufficiently pure to yield a correct microanalysis. In order to characterize the material, a detailed study of its infrared spectrum was made; the spectrum was found to be consistent in every respect with that to be expected. Thus the following bands were observed: 1520 and 1348 (NO_2), 1250 ($ArOCH_3$), 870 and 845 cm^{-1} (1,4-disubstituted aromatic). In addition, bands were observed at 1000 and 728 cm^{-1} which, in our experience, are characteristic of iodonium salts, not being found in any precursors used. The 1000-cm^{-1} band has been previously referred to in this connection.[27] No spurious bands characteristic of other structural features were observed. In order further to secure the structural assignment, the compound was thermally decomposed in refluxing benzene,[14] and the decomposition products were identified by gas–liquid partition chromatography. The major decomposition products were 4-iodonitrobenzene, 4-bromonitrobenzene, 4-iodoanisole, and 4-bromoanisole. Small amounts of anisole and nitrobenzene, but no evidence of any other materials, were also found. This is exactly what would have been expected from 4-nitro-4′-methoxydiphenyliodonium bromide and appears to confirm the structure.

4-Methoxydiphenyliodonium bromide (Ig) was prepared as reported by Beringer.[15]

4-Methoxydiphenyliodonium nitrate (Ih) was obtained from Ig by metathesis with $AgNO_3$ as described above. Two recrystallizations from methanol gave colorless needles, mp 135–136.5° dec, inserted at 125°, 5°/min.

Anal. Calcd for $C_{13}H_{11}INO_4$: C, 41.86; H, 3.48. Found: C, 41.91; H, 3.67.

[*p*-(2-Carboxyethyl)phenyl]phenyliodonium Iodide (Ik).—To a suspension of phenyliodoso diacetate (7.2 g, 22.4 mmoles) in acetic anhydride (20 ml) at 0°, concentrated H_2SO_4 (1.2 ml, 22.4 mmoles) was added dropwise, followed by portionwise addition of hydrocinnamic acid (3.36 g, 22.4 mmoles) in acetic anhydride (30 ml). The mixture was stirred at room temperature for 12 hr, and the solvent was evaporated *in vacuo*. Ice (20 g) was added and the mixture was extracted with two portions of ether (25 ml). To the water fraction solid KI (3.7 g, 22.4 mmoles) was added causing precipitation of a light brown semisolid. The supernatant was decanted and 95% ethanol was added to the flask, producing a yellow solid which was thoroughly triturated, filtered, washed with ethanol (25 ml), and dried to give Ik (3.51 g, 7.31 mmoles, 32.6%). This was washed with water (100 ml) and ethanol (200 ml); mp 159–60° dec, inserted at 150°, 5°/min.

Anal. Calcd for $C_{15}H_{14}I_2O_2$: C, 37.53; H, 2.94. Found: C, 37.73; H, 2.98.

[*p*-(2-Trifluoroacetamido-2-carboxyethyl)phenyl]phenyliodonium Iodide (Il).—To a stirred suspension of phenyliodoso diacetate (3.7 g, 11.5 mmoles) in acetic anhydride (11 ml) at −70° concentrated H_2SO_4 (0.65 ml, 12.1 mmoles) was added dropwise, followed by portionwise addition of *N*-trifluoroacetylphenylalanine (3.2 g, 12.2 mmoles) in acetic anhydride (15 ml). The suspension was stirred at −70° for 3 hr and at room temperature for 2 days. The solvent was evaporated *in vacuo* to one-half the original volume (temperature maintained below 70°). Cold water (100 ml) was added, the mixture was extracted three times with ether (100 ml), and KI (1.91 g, 11.6 mmoles) was added to the water fraction, effecting precipitation of Il (0.43 g, 6.4%). This material was dissolved in about 25 ml of chloroform. Since crystallization could not be induced, the volume was reduced to 7 ml whereupon a dark brown semisolid precipitate was formed. This, when rubbed with ether, became a gold amorphous solid melting at 126–128° dec (sintered at 115°). Although the microanalysis below is somewhat outside usually accepted limits, structural assignment is secured by the infrared spectrum, which is consistent in every detail with the proposed structure.

Anal. Calcd for $C_{17}H_{14}F_3I_2NO_3$: C, 34.54; H, 2.39; I, 42.94. Found: C, 35.67; H, 2.30; I, 42.15.

Diphenyl-4,4′-biphenylyldiiodinium Diiodide (IIa).—To a flask containing 4,4′-diiodosobiphenyl (13.2 g, 30 mmoles) and iodoxybenzene (14.25 g, 60 mmoles) was added 1 *N* NaOH (120 ml). The mixture was stirred for 3 hr, at which time stirring was discontinued due to the formation of lumps of a yellow solid,

(16) H. J. Lucas, E. R. Kennedy, and M. W. Formo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p 483.

(17) C. Willgerodt, *J. Prakt. Chem.*, **33**, 154 (1886).

(18) K. H. Pausacker, *J. Chem. Soc.*, 107 (1953).

(19) The procedure is essentially the same as that employed in the synthesis of iodosobenzene dichloride. *Cf.* H. J. Lucas and E. R. Kennedy, ref 16, p 482.

(20) C. Willgerodt and G. Hilgenberg, *Ber.*, **42**, 3826 (1909).

(21) Willgerodt[20] noted that XI could not be obtained in pure form. He nevertheless successfully employed crude XI in the synthesis of diaryliodonium compounds.

(22) H. J. Lucas and E. R. Kennedy, ref 16, p 485.

(23) F. M. Beringer, E. J. Geering, I. Kuntz, and M. Mausner, *J. Phys. Chem.*, **60**, 141 (1956).

(24) F. M. Beringer and E. M. Gindler, *J. Am. Chem. Soc.*, **77**, 3203 (1955).

(25) J. T. Plati, U. S. Patent 2,839,583 (July 17, 1958).

(26) F. M. Beringer and I. Lillien, *J. Am. Chem. Soc.*, **82**, 725 (1960).

(27) I. Lillien, *J. Chem. Soc.*, 4498 (1962).

presumably the diiodate IIc which was removed and dried in air. The material was then suspended in ethanol (60 ml), the solid was removed, and the filtrate was retained. The extraction was repeated three times, the filtrates were combined, and the residue was discarded. To the combined filtrates excess NaI was added, precipitating IIa (3.39 g, 4.17 mmoles, 13.8%), mp 145–148° dec. Washing IIa with ethanol raised the melting point to 155–157° dec inserted at 145°, 6°/min; lit.[20] mp 158° dec.

To the solution remaining after IIc had been removed was added excess NaBr, precipitating a white solid which was washed with water until the washings were no longer basic and dried to give Ie (3.5 g, 9.7 mmoles, 32.4%), the infrared spectrum of which was superimposable with that of Ie prepared by another method.

Diphenyl-4,4'-biphenylyldiiodonium Dibromide (IIb).—A suspension of 4,4'-diiodoxybiphenyl (7.89 g, 16.5 mmoles), iodosobenzene (7.3 g, 33 mmoles), and 1 *N* NaOH (62.1 ml) was stirred for 3 hr, and the yellow residue IIc was removed from the reaction mixture and washed with 1.4 l. of water at 60°. To the filtrate was added excess NaBr, precipitating IIb (4.17 g, 36%), mp 183–186° dec. It was washed with water (50 ml) and ethanol (25 ml), raising the melting point to 185–186° dec inserted at 175°, 5°/min; lit.[20] mp 185° dec.

Acknowledgment.—We are grateful to Professor E. C. Jorgensen of the University of California for encouraging us to undertake this work.

Synthesis of Potential Antineoplastic Agents. XXXV. Phosphorus-Containing Structural Analogs of Myleran[1]

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Three classes of phosphorus-containing structural analogs of myleran have been synthesized in which the methanesulfonate group of myleran has been replaced by phosphonate groups (II) and by disubstituted phosphinate (III) and phosphinite groups (IV). Five of the analogs displayed cytotoxic activity at a concentration of 100 μg/ml against Eagle's KB cells. No significant *in vivo* activity was observed.

Among antineoplastic agents of the alkylating agent class, several compounds with chemical alkylating activity weaker than that of the nitrogen mustard type have been synthesized. Myleran (I) is a well-known representative of this type of alkylating agent, and in order to determine whether replacement of sulfur by phosphorus in myleran-type structures would produce compounds with antineoplastic activity, three groups of phosphorus-containing analogs have been synthesized in which the methanesulfonate group of myleran (I) has been replaced by phosphonate groups (II) and by disubstituted phosphinate (III) and phosphinite groups (IV).

$CH_3SO_2O(CH_2)_4OSO_2CH_3$
I

$R(C_2H_5O)P(O)O(CH_2)_4O(O)P(OC_2H_5)R$
IIa, R = CH_3
b, R = C_2H_5
c, R = n-C_4H_9
d, R = C_6H_5

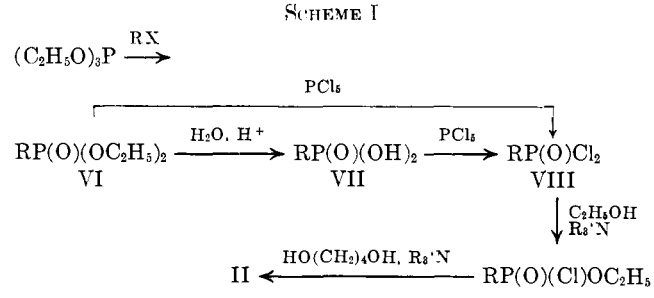
$R_2P(O)O(CH_2)_4O(O)PR_2$
IIIa, R = CH_3
b, R = C_2H_5
c, R = n-C_4H_9
d, R = C_6H_5

$R_2PO(CH_2)_4OPR_2$
IVa, R = n-C_4H_9
b, R = C_6H_5

$RP(O)(Cl)OC_2H_5$
V

The phosphonate (II), phosphinate (III), and phosphinite (IV) analogs were synthesized by reaction of 1,4-butanediol with the appropriate phosphorus acid chloride in the presence of a tertiary amine. The phosphonates (II) were obtained as shown in Scheme I. Alkylphosphonate esters (VI) were converted to phosphonic dichlorides (VIII) with or without prior conversion to phosphonic acids (VII); somewhat

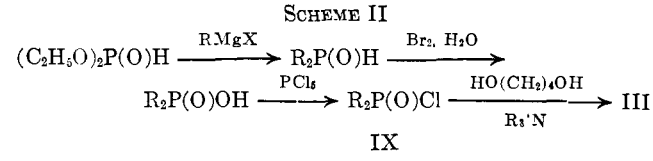
SCHEME I



higher yields of the chlorides (VIII) were generally obtained when the esters were hydrolyzed to the acids before treatment with phosphorus pentachloride.

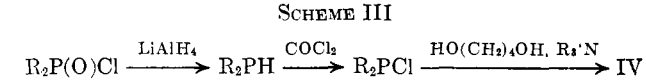
Scheme II outlines the reactions used to prepare the phosphinates (III). Dimethylphosphinic chloride

SCHEME II



(IX, R = CH_3) was prepared by the convenient method of Pollart and Harwood[2] from tetramethyl bi(phosphine sulfide). The phosphinites (IV) were prepared as shown in Scheme III. Diphenylphosphinous chloride (X, R = C_6H_5) was secured from commercial sources.

SCHEME III



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(2) K. A. Pollart and H. J. Harwood, *J. Org. Chem.*, **27**, 4444 (1962).