provided by the synthesis of VII by an unequivocal route: Arbuzov reaction between 1-bromo-2-butyloctane and triethyl phosphite followed by hydrolysis. A sample of the acid prepared in this manner was identical with VII prepared by the addition of diethyl phosphonate to 2-butyl-1-octene. By analogy structure V is proposed for the acids VI, VIII, and IX.

EXPERIMENTAL

The olefin/phosphorous acid reactions were conducted according to the method previously reported[1]; a 1:1 molar ratio of olefin to phosphorous acid was employed. The 1:1 adducts were isolated by direct crystallization, while the 2:1 adducts were most conveniently isolated by anion exchange chromatography of reaction residues. Reactants and products are listed.

1-Hexene: n-hexylphosphonic acid (23%), m.p. 105–106° (from ligroin) (reported[6] m.p. 104.5–106°); *2-butyloctylphosphonic acid* (VII) (8%), m.p. 99–100° (from 50% ethanol).

1-Decene: n-decylphosphonic acid (18%), m.p. 101.5–103° (from ligroin) (reported[6] m.p. 102–102.5°); *2-octyldodecylphosphonic acid* (VIII) (6%), m.p. 94–95° (from H_2O).

Cyclohexene: cyclohexylphosphonic acid (20%)[1]; *2-cyclohexylcyclohexylphosphonic acid* (IX) (9%), m.p. 98–99.5° (from 50% ethanol).

1-Octene experiments are reported in Part I.

2-Alkyl-1-alkenes were prepared from the appropriate ketones[7] and triphenylphosphine methylene by the modification of a method described in the literature.[8] Products were isolated directly by distillation after removal of triphenylphosphine oxide by filtration.

2-Butyl-1-octene (from undecanone-5)[9] b.p. 83–84°/12 mm. (reported[9] b.p. 88–89°/14 mm.).

2-Octyl-1-dodecene (from nonadecanone-9)[7] b.p. 184–186°/10 mm. (reported[10] b.p. 193–195°/12 mm.).

2-Hexyl-1-decene (from pentadecanone-7)[11] b.p. 165–166°/9 mm.

Anal. Calcd. for $C_{16}H_{32}$: C, 85.63; H, 14.37; mol. wt., 224.4. Found: C, 85.60; H, 14.49; mol. wt. (Rast), 225.9.

1-Cyclohexylcyclohexene was prepared according to the method of Truffault.[12]

Alkylphosphonic acids were prepared from the corresponding olefins and diethyl phosphonate (1:4 molar ratio) in the presence of di-*t*-butyl peroxide according to established procedure.[2] Upon completion of reaction, unchanged diethyl phosphonate was removed by distillation under reduced pressure; the residue was hydrolyzed with concd. hydrochloric acid. Filtration and recrystallization gave the phosphonic acid.

2-Hexyldecylphosphonic acid (VI) m.p. 100.5–101.5° (from ligroin) (reported[1] m.p. 100.5–101.5°).

Anal. Calcd. for $C_{16}H_{35}O_3P$: C, 62.71; H, 11.51; neut. equiv., 153.2. Found: C, 62.84; H, 11.38; neut. equiv., 153.6.

2-Butyloctylphosphonic acid (VII) m.p. 99–100° (from 50% ethanol).

Anal. Calcd. for $C_{12}H_{27}O_3P$: C, 57.57; H, 10.87; neut. equiv., 125.2. Found: C, 57.59; H, 11.01; neut. equiv., 125.9.

2-Octyldodecylphosphonic acid (VIII) m.p. 94–95° (from H_2O).

Anal. Calcd. for $C_{20}H_{43}O_3P$: C, 66.26; H, 11.96; neut. equiv., 181.3. Found: C, 66.30; H, 11.76; neut. equiv., 182.9.

2-Cyclohexylcyclohexylphosphonic acid (IX) m.p. 98–99.5° (from 50% ethanol).

Anal. Calcd. for $C_{12}H_{23}O_3P$: C, 58.50; H, 9.41; neut. equiv., 123.1. Found: C, 58.61; H, 9.43; neut. equiv., 124.2.

In each case the alkylphosphonic acid prepared in this manner was identical with the 2:1 adduct isolated from the olefin/phosphorous acid reactions. Mixture melting points and infrared spectra were employed as criteria of identity.

2-Butyloctylphosphonic acid (VII) was prepared independently by a conventional Arbuzov reaction. 1-Bromo-2-butyloctane was prepared by the action of phosphorus tribromide on the corresponding alcohol in pyridine; after removal of solvent under reduced pressure, the reaction mixture was filtered and dissolved in ether. The ethereal extract was washed with water, dilute hydrochloric acid, and dilute ammonium hydroxide and dried over anhydrous sodium sulfate; removal of ether under reduced pressure gave the crude alkyl bromide. A mixture of the alkyl bromide and a three fold excess of triethyl phosphite was heated at 150° for 30 hr. The reaction mixture was treated as above to isolate the acid. A sample of acid from this preparation was identical with the product of the 2-butyl-1-octene/diethyl phosphonate reaction.

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(6) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **67**, 1180 (1945).

(7) Prepared according to the method of F. L. Breusch and F. Baykut, *Chem. Ber.*, **86**, 684 (1953).

(8) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

(9) J. v. Braun and H. Kroper, *Ber.*, **62B**, 2880 (1929).

(10) J. v. Braun and G. Manz, *Ber.*, **67B**, 1696 (1934).

(11) M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949).

(12) R. Truffault, *Bull. soc. chim. France*, (5), **3**, 442 (1936).

Potential Anticancer Agents.[1] XXX. Analogs of *N,N',P*-Triphenylphosphonothioic Diamide

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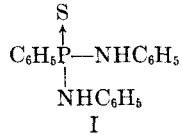
One of the compounds found in the mass screening program of the Cancer Chemotherapy National Service Center to have slight antitumor activity is *N,N',P*-triphenylphosphonothioic diamide (I). This compound showed borderline activity against adenocarcinoma 755. The synthesis of a number of



I

analogs of I for test evaluation was undertaken in this laboratory. The compounds were selected to give the widest possible diversity of structural types (Table I). These compounds were made by interaction of the appropriate phosphorus chloride and amine by one of several methods described in the Experimental.

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TABLE I

No.	R	R′	R″	M.P., °C.	Procedure	Yield,[b] %	Analysis					
							Carbon, %		Hydrogen, %		Nitrogen, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
II	C_6H_5—	*p*-ClC_6H_4NH—[f]	*p*-ClC_6H_4NH—	181–182	A	62[c]	55.0	54.7	3.85	4.30	7.13	7.33
III	C_6H_5—	*o*-ClC_6H_4NH—[f]	*o*-ClC_6H_4NH—	113–114	B[g]	52[c]	55.0	54.8	3.85	4.00	7.13	7.15
IV	C_6H_5—	3,4-$Cl_2C_6H_3NH$—	3,4-$Cl_2C_6H_3NH$—	145	B[g]	47[c]	46.8	46.4	2.83	3.03	6.06	6.08
V	C_6H_5—	3,4-$(CH_3)_2C_6H_3NH$—	3,4-$(CH_3)_2C_6H_3NH$—	132–133	A	70[c]	69.2	69.4	6.62	6.66	7.37	7.22
VI	C_6H_5—	*p*-$CH_3OC_6H_4NH$—	*p*-$CH_3OC_6H_4NH$—	112–114	A	32[c]	62.5	62.6	5.51	5.66	7.29	7.34
VII	C_6H_5—	*p*-$O_2NC_6H_4NH$—	*p*-$O_2NC_6H_4NH$—	198–200	C[h]	30[e]	52.2	52.3	3.65	3.98	13.5	13.3
VIII	C_6H_5—	*p*-$(C_2H_5O_2C)C_6H_4NH$—	*p*-$(C_2H_5O_2C)C_6H_4NH$—	Amorph.	B[g]	87	61.5	61.8	5.38	5.64	5.98	6.11
IX	C_6H_5—	—NH_2	—NH_2	38–40	D	50[c]	41.8	42.2	5.27	5.40	16.3	16.3
X	C_6H_5—	C_2H_5NH—	C_2H_5NH—	80–81[i]	A	79[c]	52.6	52.7	7.50	7.40	12.3	12.2
XI	C_6H_5—			111–112	A	62[c]	53.8	53.9	6.78	6.92	8.97	8.90
XII	C_6H_5—	C_6H_5O—	C_6H_5NH—	93–96[j]	E	53[c]	66.4	66.6	4.96	5.12	4.31	4.67
XIII	C_6H_5NH—	C_6H_5NH—	C_6H_5NH—	150–151	A	43[d]	63.7	64.0	5.35	5.44	12.7	12.7
XIV	C_6H_5O—	C_6H_5NH—	C_6H_5NH—	122–123	E	74[c]	63.5	63.3	5.04	5.15	8.23	8.42
XV	$C_6H_5PO(NHC_6H_5)_2$			207–210[k]	A	61[c]						

[a] All the compounds contained the proper infrared bands for the type of phenyl substituent as well as P—N bands at 11.0–13.3 μ. Compounds with a P → S bond showed a band at 13.5–14.5 μ. [b] Yields are after at least one recrystallization. [c] Recrystallized from absolute ethanol. [d] Recrystallized from 95% ethanol. [e] Recrystallized from aqueous acetone. [f] The *m*-chloro analog failed to crystallize and the crude product could not be obtained in an analytically pure condition. [g] Procedure A failed to give a crystallizable product or gave a much lower yield. [h] Procedures A and B failed to give any appreciable reaction. [i] Reported[4] m.p. 85.7–86°. [j] Reported[5] m.p. 103°. [k] Reported[6] m.p. 211°.

Although compound I showed activity against adenocarcinoma 755 when tested in these laboratories, none of the analogs showed any appreciable activity against this tumor, sarcoma 180, or leukemia L-1210.[2]

EXPERIMENTAL[3]

Procedure A. To a solution of 1.12 g. (9.2 mmoles) of 3,4-xylidene in 20 ml. of anhydrous ether was added 0.50 g. (2.4 mmoles) of phenylphosphonothioic dichloride dropwise with stirring. The reaction mixture was allowed to stand overnight at room temperature protected from moisture, then the precipitated 3,4-xylidine hydrochloride was removed by filtration. Evaporation of the filtrate to dryness *in vacuo* gave a solid, which was recrystallized from absolute ethanol to give 0.70 g. (77%) of white crystals of V, m.p. 128–130°. Further recrystallizations raised the melting point to 132–133°. The analytical data are recorded in Table I.

Procedure B. A flask containing a mixture of 26.4 g. (0.207 mole) of *o*-chloroaniline and 10.0 g. (0.048 mole) of phenylphosphonothioic dichloride was placed in an oil bath at room temperature and the temperature raised to 165° over 15–20 min., then held at that temperature for 1 hr. The mixture was cooled, then dissolved in 150 ml. of chloroform. Treatment of the chloroform solution with 100 ml. of 1*N* hydrochloric acid caused the precipitation of *o*-chloroaniline hydrochloride. After the removal of the hydrochloride by filtration, the layers were separated and the chloroform layer was washed with two 60-ml. portions of 2*M* aqueous ammonia and 100 ml. of water. The chloroform layer was dried over magnesium sulfate, then concentrated to dryness *in vacuo* to yield 14.8 g. of a white solid. Recrystallization from absolute ethanol gave 9.6 g. (52%) of III as white crystals, m.p. 112–114°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 113–114°. The analytical data are recorded in Table I.

Procedure C. To a mixture of 12.98 g. (0.094 mole) of *p*-nitroaniline and 7.44 g. (0.094 mole) of pyridine in 400 ml. of dry benzene was added 10.0 g. (0.047 mole) of phenylphosphonothioic dichloride dropwise with stirring over a period of about 10 min. After the addition was complete, the reaction was heated at reflux for 7 hr., then cooled and concentrated to dryness *in vacuo*. The residue was dissolved in 200 ml. of ethyl acetate and washed with two 100-ml. portions of 1*N* hydrochloric acid, 150 ml. of 2*M* aqueous ammonia, and finally with two 100-ml. portions of water. The ethyl acetate solution was dried over magnesium sulfate, then evaporated to dryness *in vacuo*. The solid residue was dissolved in 200 ml. of acetone, then water (approximately 50 ml.) was added until the solution became slightly turbid. The solution was cooled to 0° overnight, then filtered to yield 5.95 g. (30%) of pale yellow crystals of VII, m.p. 196–200°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 198–200°. The analytical data are recorded in Table I.

Procedure D. To 40 ml. of concentrated ammonium hydroxide was added 2.0 g. (9.5 mmoles) of phenylphosphonothioic dichloride dropwise with stirring. An oily layer separated which slowly crystallized on standing. The reaction was heated on a steam bath for 0.5 hr., then concentrated to dryness *in vacuo* and the residue was taken up in 20 ml. of water. The aqueous layer was extracted with two 10-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, then evaporated to dryness *in vacuo* to yield 0.91 g. (57%) of an oil. Crystallization from absolute ethanol gave 0.80 g. (50%) of IX as white crystals, m.p. 30–35°. Recrystallization from absolute ethanol raised the melting point to 38–40°. The analytical data are recorded in Table I.

Procedure E. A solution of 7.3 g. (0.078 mole) of phenol and 6.2 g. (0.078 mole) of pyridine in 20 ml. of anhydrous ether was added dropwise with stirring to a solution of 13.2 g. (0.078 mole) of thiophosphoryl chloride in 20 ml. of anhydrous ether over a period of about 10 min. The reaction mixture was heated at reflux for 1 hr., then cooled to 0° and the precipitated pyridine hydrochloride was removed by filtration. The filtrate was concentrated to dryness *in vacuo* to yield 15.6 g. (88%) of crude *o*-phenylphosphorothioic dichloride as an oil.

To a cold (5–10°) solution of 15.6 g. of this dichloride in 10 ml. of dry benzene was added 28.1 g. (0.30 mole) of aniline in 30 ml. of benzene dropwise with stirring. The reaction mixture was stirred for 2 hr. in an ice bath, then filtered to remove aniline hydrochloride. The filtrate was concentrated to dryness *in vacuo* to yield a solid, which was recrystallized from absolute ethanol to give 17.4 g. (74%) of XIV as white crystals, m.p. 118–120°. An analytical sample was prepared from a similar run and recrystallized to constant melting point, 122–123°. The analytical data are recorded in Table I.

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(2) These tests were performed at Stanford Research Institute by Dr. Joseph Greenberg and staff under a contract with the Cancer Chemotherapy National Service Center.

(3) Melting points were taken on a Fisher-Johns block and are uncorrected.

(4) E. J. Kohn, U. E. Hanninen, and R. B. Fox, Naval Research Laboratory *Rept.* **C-3180,** 1947.

(5) M. F. Hersman and L. F. Audrieth, *J. Org. Chem.*, **23,** 1889 (1958).

(6) A. Michaelis, *Ann.*, **293,** 215 (1896).

Selective Oxidation of Alkyl Groups

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Previous workers[2] have shown that the oxidation of *p*-dialkylbenzenes with nitric acid will yield alkylbenzoic acids, but no generalization has been expressed concerning the relative ease of oxidation of the alkyl groups. Cullis[3] reported the relative rates of oxidation of some monoalkylbenzenes by permanganate. However, other than with *t*-butyl groups, the literature reveals that permanganate oxidizes dialkylbenzenes to benzene dicarboxylic acids. It would be useful sometimes in organic synthesis to be able to oxidize selectively only one alkyl group of dialkylbenzenes. For this reason,

(1) Taken from the M.S. Thesis of Andrew I. Wims, Howard University, 1959. Present position: Teaching Assistant, Pennsylvania State University.

(2) *Cf.* W. F. Tuley and C. S. Marvel, *Org. Syntheses*, **Coll. Vol. III.** Wiley and Sons, N. Y., 1955, p. 822; G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, **12,** 1102 (1952).

(3) C. F. Cullis and J. W. Ladbury, *J. Chem. Soc.*, 555 4186 (1955).