white powder was further extracted with three 20-ml. portions of carbon disulfide, dried and sublimed three times at 140° and 1 mm. pressure, yield, 1.6 g. (89%), m.p. of the colorless acicular crystals 224–225°.

Anal. Calcd.: C, 33.40; H, 5.00. Found: C, 33.56; H, 5.18.

Mol. wt. Calcd.: 180. Found: 174.

1-Methyl-4-arsa-3,5,8-trioxabicyclo[2.2.2]octane. The preparation of this compound involved arsenic trichloride and was analogous to that of the -4-phospha- compound. The first sublimation of the crude syrup, however, was carried out at room temperature. The solid sublimate, contaminated with a small amount of oily material, was dissolved in ether, in which the oily substance was insoluble. The ether solution was decanted and evaporated to dryness. The residual white solid was sublimed three times at room temperature and 1 mm. pressure, yield, 38%, m.p. of the colorless prismatic crystals 41–42°.

Anal. Calcd.: C, 31.25; H, 4.68. Found: C, 31.15; H, 4.68.

Mol. wt. Calcd.: 192. Found: 185.

Infrared Spectra. Spectra were taken in chloroform and carbon disulfide solutions as well as in nujol mulls on a Perkin-Elmer Model 21 Spectrophotometer.

Acknowledgment. The authors gratefully acknowledge the help of Prof. E. G. Rochow in making possible the execution of this work.

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Phosphonic Acid and Esters. II. Formation of Telomers in Olefin/Phosphorous Acid Reactions

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Received August 31, 1959

In Part I it was shown that alkylphosphonic acids (I) could be formed by the addition of phosphorous acid to olefins in the presence of peroxides or ultraviolet irradiation (steps 1–2).[1] The low

$$RCH{=}CH_2 + \underset{II}{\cdot P(O)(OH)_2} \longrightarrow \underset{III}{RCHCH_2P(O)(OH)_2} \quad (1)$$

$$III + HP(O)(OH)_2 \longrightarrow \underset{I}{RCH_2CH_2P(O)(OH)_2} + II \quad (2)$$

yields of products obtained were attributed to the occurrence of polymerization, inhibition by allylic abstraction and telomerization (steps 3–4). Specific evidence for the occurrence of telomerization was provided by the isolation of a telomeric 2:1 adduct,

$$III + RCH{=}CH_2 \longrightarrow \underset{IV}{RCHCH_2CHRCH_2P(O)(OH)_2} \quad (3)$$

$$IV + HP(O)(OH)_2 \longrightarrow \underset{V}{RCH_2CH_2CHRCH_2P(O)(OH)_2} + II \quad (4)$$

2-hexyldecylphosphonic acid (VI; V, R = *n*-hexyl), as well as the primary reaction product (*n*-octylphosphonic acid) from the reaction of 1-octene and phosphorous acid. Similar telomers have been shown to arise in the peroxide initiated addition of dialkyl phosphonates to olefins.[2] In order to determine the extent of telomer formation, the previous investigation[1] has now been extended to a study of the reactions of 1-hexene, 1-decene, and cyclohexene.

1-Hexene was treated with phosphorous acid in the presence of dibenzoyl peroxide at reflux temperature; fractionation of the products led to the isolation of *n*-hexylphosphonic acid (23%) and the 2:1 adduct, 2-butyloctylphosphonic acid (VII; V, R = *n*-butyl). Reaction with 1-decene gave *n*-decylphosphonic acid (18%) and 2-octyldodecylphosphonic acid (VIII: V, R = *n*-octyl). A reinvestigation of the cyclohexene/phosphorous acid reaction led to the isolation of 2-cyclohexylcyclohexylphosphonic acid (IX) and the primary reaction product, cyclohexylphosphonic acid. Thus, telomerization appears to be generally characteristic of the olefin/phosphorous acid reactions and additional evidence for the low transfer constant of phosphorous acid is provided.

The structures proposed for the telomeric acids (V) are those which would arise from telomerization of conventional (head to tail) orientation, i.e., attack of the radical (III) at the terminal olefinic carbon.[3] The identity of the acids (V) was confirmed by comparison with samples prepared by an independent route: peroxide initiated addition of diethyl phosphonate to the appropriate olefin and acidic hydrolysis of the resulting diethyl alkylphosphonate. The requisite olefins, including

$$RCH_2CH_2CR{=}CH_2 + HP(O)(OC_2H_5)_2 \longrightarrow V$$

the previously unreported 2-hexyl-1-decene, were conveniently prepared from the corresponding ketones by means of the Wittig reaction. In each case the acid prepared independently was identical with the 2:1 adduct isolated from the olefin/phosphorous acid reactions.

The independent route employed above is, however, capable of yielding two produts: V by attack of the phosphonate radical at the terminal olefinic carbon and the isomeric 2-methyl alkylphosphonic acid $RCH_2CH_2CR(CH_3)P(O)(OH)_2$ by attack at carbon two. On the basis of the known chemistry and orientation of this and similar free radical addition reactions, terminal attack is most probable.[2,4,5] A conclusive demonstration was

(1) C. E. Griffin and H. J. Wells, *J. Org. Chem.*, **24**, 2049 (1959).

(2) A. R. Stiles, W. E. Vaughan, and F. F. Rust, *J. Am. Chem. Soc.*, **80**, 714 (1958).

(3) Alternatively, the attack of III at carbon two of the olefin would yield a primary radical (less stable than the secondary radical IV) and, ultimately, the isomeric acid $RCH(CH_3)CHRCH_2P(O)(OH)_2$.

(4) P. C. Crofts, *Quarterly Revs.*, **12**, 363 (1958).

(5) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, Inc., New York, 1957, pp. 239–89.

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

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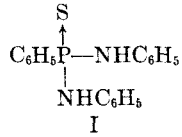
Received September 21, 1959

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



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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.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, in press.