(secondary amide carbonyl), 1620 (primary amine NH).

The amine was converted quantitatively to the known (*1*) hydrochloride by dissolving in chloroform, saturating with hydrogen chloride, and adding ether to precipitate the solid. M.p. 170–172° C. (from ethanol-ether). Lit. (*1*), 172° C.

PMR. 1.27 (t, 5.6, J = 7Hz, $COOCH_2CH_3$), 2.12 (S, 3.2, $NCOCH_3$), 3.07, (w.m., 2.1, $=\overline{C}CH_2C$), 3.66 (w.m., 2.5, $NCH_2C=$), 4.27 (q, 3.8, J = 7Hz, $COOCH_2$), 5.78 (w.m., 1.8, $CH=CH$), 7.4 and 8.25 (Broad, NH and CONH).

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Potential Inhibitors of Cholesterol Biosynthesis Phosphonates Derived from Geraniol and Congeners

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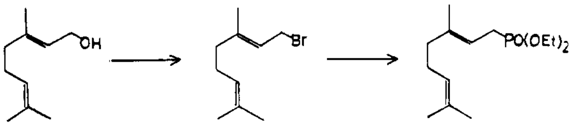
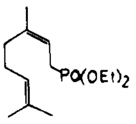
Diethyl (*E*)-3,7-dimethylocta-2,6-diene-1-phosphonate (I), diethyl (Z)-3,7-dimethylocta-2,6-diene-1-phosphonate (II), diethyl 3,7-dimethyloct-6-ene-1-phosphonate (III), and diethyl 3,7-dimethyloctane-1-phosphonate (IV) were prepared from geraniol, nerol, citronellol, and tetrahydrogeraniol, respectively. Under conditions used previously with geraniol, nerol was converted to the corresponding bromide with hydrogen bromide or phosphorus tribromide at low temperatures. Reaction of these allylic bromides with triethyl phosphite gave approximately equal amounts of phosphonates by substitution, and of unsaturated hydrocarbons by elimination. The allylic phosphonates were obtained without cis-trans or allylic rearrangement. The non-allylic phosphonates derived from citronellol and tetrahydrogeraniol were obtained in good yields.

Most of the cholesterol-lowering agents used therapeutically exert their effect after the cyclization of squalene oxide to lanosterol, which often results in the accumulation of undesirable sterols. It seems desirable to develop inhibitors which affect the synthesis earlier in the sequence. This paper describes the synthesis of certain acyclic phosphonates, which might be expected to inhibit the condensation of geranyl pyrophosphate with isopentenyl pyrophosphate mediated by prenyltransferase.

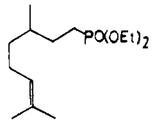
The choice of phosphonates for study was based on the consideration that the nonbonding electrons on the oxygen atoms of geranyl and dimethylallyl pyrophosphates are undoubtedly involved in enzyme-substrate complexes. The external electron distribution in phosphonates, $RPO(OH)_2$, and thus their ability to bind to an enzyme site through magnesium, is similar to that in phosphates. However, the carbon-phosphorus bonds are not expected to cleave in enzymic reactions catalyzed by esterases or prenyltransferase. With regard to the steric requirements of the prenyltransferase surface, citronellyl pyrophosphate and terpene phosphates inhibit the coupling of geranyl pyrophosphate with isopentenyl pyrophosphate in vitro (*4*). The effectiveness of phosphonates as inhibitors of enzymic reactions involving organic phosphates as substrates has been demonstrated recently in a study of the phosphonate analog of pyridoxal phosphate (*1*).



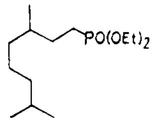
(I)



(II)



(III)



(IV)

The phosphonates of the terpenes were prepared by the Michaelis-Arbuzov reaction: $RBr + P(OEt)_3 \rightarrow RPO(OEt)_2 + EtBr$. The required terpene bromides were obtained from the alcohols either with phosphorus tribromide or hydrogen bromide. In the presence of appropriate amounts of tertiary amine, phosphorus tribromide is known to convert geraniol to its bromide without cis-trans or allylic rearrangement (*6*, *8*). With an insufficient amount of tertiary amine, the reaction is sluggish; with an equivalent amount, the major product is the phosphite, $P(OR)_3$. Hydrogen bromide is, therefore, the preferred reagent with allylic terpene alcohols (*7*). The nonallylic bromides were readily prepared by the phosphorus tribromide method.

The allylic bromides reacted with triethyl phosphite at relatively low temperatures, but owing to the sluggishness with which the reaction was completed, the reaction was ordinarily run near the boiling point of the reaction mixtures. The yields of allylic phosphonates were low, owing to simultaneous formation of unsaturated C_{10} hydrocarbons by elimination reactions. Attempts to increase the yields of phosphonates by the use of nonpolar solvents or aprotic polar solvents were unsuccessful. This might be predicted, because both the substitution and elimination reactions undoubtedly involve charge separation in the transition state and are favored in polar media.

Geraniol and nerol each yielded single phosphonates which were separable by gas chromatography. Diethyl (*E*)- and (*Z*)-3,7-dimethylocta-2,6-diene-1-phosphonates were obtained without allylic or cis-trans isomerization, as shown by proton magnetic resonance data. Both phosphonates showed two vinylic protons, and the other signals corresponded to unrearranged products. (See data in Experimental section.) Infrared spectra were compatible with the assigned structures.

Dialkyl phosphonates are known to saponify to monoalkyl phosphonates (*5*). The dialkyl terpene phosphonates can be saponified to sodium or potassium salts, although the reaction was sluggish, owing to the large hydrophobic group.

EXPERIMENTAL

Preparation of the Bromides. Geraniol, nerol, and citronellol were commercially available products of 98% purity or higher. Tetrahydrogeraniol (3,7-dimethyloctan-1-ol) was prepared by hydrogenation of geraniol, or geraniol-nerol mixtures, in absolute alcohol over platinum oxide in a Parr stirring reaction vessel at an initial pressure of 25 atm. Tetrahydrogeraniol (b.p. 83–5° C./1.4 mm., n_D^{20} 1.4370) was obtained in 95% yield.

Using Hydrogen Bromide with Allylic Alcohols. Under vigorous stirring, a slow stream of dried hydrogen bromide was passed into a solution of the alcohol in petroleum ether, in which excess anhydrous sodium sulfate was suspended, until the calculated amount of the gas was absorbed. The hydrated sodium sulfate was removed. The filtrate was concentrated below 50° C. at water aspirator pressure, and then at 0.5 mm. at room temperature. The residues were used without further purification. Unreacted geraniol may be removed from geranyl bromide as the calcium chloride complex (*2*).

Using Phosphorus Tribromide. A stirred solution of 0.5 mole of the alcohol containing 1 gram of pyridine was treated dropwise with 0.167 mole of phosphorus tribromide (*8*). With the unsaturated alcohols, the reaction mixture was kept at 0°–5° C. during the addition of the tribromide and then allowed to warm to 15°–20° C. Tetrahydrogeranyl bromide was prepared at room temperature.

Products, RBr, obtained were (R, % yield, b.p./mm., and n_D^{20} listed): geranyl, 69, 87–9° C./0.5, 1.5027; neryl, 67, 73–5° C./0.5, 1.5028; citronellyl, 80, 84–6° C./0.5, 1.4760; tetrahydrogeranyl, 71, 71–3° C./0.1, 1.4552.

Preparation of the Phosphonates. Triethyl phosphite (100% excess) was placed in a flask fitted with a dropping funnel, and arranged for removal of ethyl bromide by distillation as formed and for trapping thereof in an ice-cooled Dean-Stark receiver (*3*). The magnetically stirred phosphite was heated to 155° C., the terpene bromide (0.2 to 0.45 mole) was added dropwise, and the mixture was heated until completion of the reaction, as indicated by the volume of ethyl bromide collected. The mixture was distilled first to remove unreacted triethyl phosphite, diethyl ethanephosphonate, unsaturated hydrocarbons, and other products boiling below 100° C. at 20 mm. The residue was then fractionated at approximately 0.3 mm. to obtain analytically pure phosphonates. Data are given in Table I.

The proton magnetic resonance spectra of the phosphonates were determined with a Varian A60A spectrometer. The following assignments were made from the integrated spectra [proton type and center of the signal in δ units relative to tetramethylsilane for I, II, III, and IV, respectively (number of protons)]: OCH_2CH_3 (triplet), 1.26 (6), 1.26 (6), 1.25 (6), 1.25 (?); chain CH_3, 1.59 and 1.67 (singlets) (9), 1.61 and 1.67 (singlets) (9), 0.87 (doublet, 3-methyl) (3), 0.87 (doublet) (9); chain CH_2, 2.04 (4), 2.04 (4), .., ..; CH_2P (quartet), 2.51 (2), 2.48 (2), 1.96 (2), ..; OCH_2 (multiplet), 4.1 (4), 4.0 (4), 4.0 (4), 4.1 (4); $=CH$, 5.0 (2), 5.1 (2), 5.0 (1), .. (0). All protons in I and II were assigned. The unassigned methyl, methylene, and methine protons in III and IV were not well separated.

Hydrocarbon By-products. To remove phosphorus esters from the products boiling below 100° C. at 20 mm. in the preparation of diethyl (*E*)-3,7-dimethylocta-2,6-diene-1-phosphonate, the mixture was saponified. The water-insoluble products were dried and fractionated in a spinning-band column. Five fractions boiling between 55° and 65° C. at 10 mm. were collected. The refractive indexes of the fractions rose steadily from 1.4750 to 1.4818 (n_D^{20}). Nuclear magnetic resonance analysis of the fractions showed 3.5 to 4.0 olefinic protons per mole-

Table I. Properties and Analytical Data for Terpene Phosphonates, $RPO(OEt)_2$

Compound No.	R	Reaction Temp., ° C.	% Yield	Boiling Range, ° C. (Mm.)	Refractive Index, n_D^{20}	Molecular Formula	Calcd. C	Calcd. H	Calcd. P	Found C	Found H	Found P
I	(*E*)-3,7-Dimethylocta-2,6-dien-1-yl	155–200	57	131–133 (0.25)	1.4675	$C_{14}H_{27}PO_3$	61.29	9.92	11.29	61.33	9.70	11.08
II	(*Z*)-3,7-Dimethylocta-2,6-dien-1-yl	155–177	37	125–127 (0.1)	1.4648	$C_{14}H_{27}PO_3$	61.29	9.92	11.29	61.04	10.06	11.48
III	3,7-Dimethyloct-6-en-1-yl	155–187	89	123–125 (0.3)	1.4507	$C_{14}H_{29}PO_3$	60.85	10.58	11.21	60.55	10.47	11.34
IV	3,7-Dimethyloct-1-yl	155–195	86	125–126 (0.3)	1.4373	$C_{14}H_{31}PO_3$	60.41	11.23	11.12	60.67	10.79	11.19

cule in all fractions. The low-boiling fraction from the preparation of diethyl (*Z*)-3,7-dimethylocta-2,6-diene-1-phosphonate gave nearly identical results, except that a small amount of a lower-boiling hydrocarbon with a smaller refractive index was obtained.

Saponification of Diethyl (*E*)-3,7-dimethylocta-2,6-diene-1-phosphonate. A mixture of 20.1 grams of I and 10 grams of sodium hydroxide in 100 ml. of water was refluxed 3 1/4 hours. The resultant solution was extracted thoroughly with ether and the aqueous layer was acidified to Congo red with hydrochloric acid. The precipitated acid was extracted with ether and the extractate was evaporated. The residue of crude ethyl hydrogen (*E*)-3,7-dimethylocta-2,6-diene-1-phosphonate (13.2 grams) was dissolved in methanol, filtered, charcoaled, and neutralized with methanolic sodium hydroxide. The methanol was evaporated to give sodium ethyl (*E*)-3,7-dimethylocta-2,6-diene-1-phosphonate. Colorless analytical samples were prepared by recrystallizing the salt from ethyl acetate and drying under vacuum at 70° C.

Anal.: Calcd. for $C_{12}H_{22}PO_3Na$: C, 53.72; H, 8.25; Na, 8.50.

Found: C, 54.16 (assuming Na converted to Na_2CO_3); H, 7.93; Na, 8.67.

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New Data Compilations

DASA 1971-3. Thermal Radiation Phenomena, Volume 3. Tables of Radiative Properties of Air. AROESTE, H., MAGEE, J. L. Lockheed Missiles and Space Co., Palo Alto Research Laboratories, Palo Alto, Calif., May 1967. 633 pp. Available from CFSTI, AD 654773.

This volume presents tables of the equilibrium radiative properties of air and its constituents for a wide range of temperatures and densities. The work is divided into five parts: Part A is a summary section designed to give an overview of the field. Some of the data are presented in semi-schematic form and should not be used for quantitative work. Part B gives basic data and references used in the preparation of the subsequent parts. Finally, parts C, D, and E contain the absorption coefficients in the range 1000° to 24,000° K. (Part C), 1 to 20 eV (Part D), and above 20 eV (Part E).

Thermodynamic Properties of Neon from 25° to 300° K. between 0.1 and 200 Atmospheres. MCCARTY, R. D., STEWART, R. B. in "Advances in Thermophysical Properties at Extreme Temperatures and Pressures," Serge Gratch, Ed., pp. 84–97, American Society of Mechanical Engineers, New York, 1965. Available from CFSTI.

Selected P-ρ-T data for liquid and gaseous neon have been fitted to an analytical function. The selected data are the available experimental data, supplemented in regions of pressure and temperature where experimental data are not available by values calculated from the theory of corresponding states and a generalized equation of state. Deviation plots are given which indicate the accuracy with which the analytical function represents the experimental data. The uncertainty of the tabulated properties is also estimated. The equation of state and the zero pressure specific heat were used to calculate tables of density, entropy, and enthalpy for selected temperatures and pressures. These properties are also illustrated in temperature-entropy diagrams.

Physical Properties of Some Plutonium Ceramic Compounds: A Data Manual. B. J. SEDDON, ED. TRG Report **1601,** 54 pages, United Kingdom Atomic Energy Authority, Reactor Group, Risley, England, December 1967. Available from the Clearinghouse for Federal Scientific and Technical Information, $3.00.

This report is a compilation of the best available data on the physical properties of some of the plutonium compounds which are, or may be, of interest as fuel materials. These are the dioxide, monocarbide, mononitride, monosulphide, and monophosphide of plutonium, uranium-plutonium dioxide, uranium-plutonium monocarbide, uranium-plutonium mononitride, and the plutonium silicides.

Cesium Data Sheets, ORNL-4186, 27 pages; **Curium Data Sheets,** ORNL-4187, 52 pages; **Strontium Data Sheets,** ORNL-4188, 45 pages. S. J. RIMSHAW, E. E. KETCHEN. Oak Ridge National Laboratory, Oak Ridge, Tenn., December 1967. Available from the Clearinghouse for Federal Scientific and Technical Information.

Data on ^{137}Cs are tabulated. Properties of the fuel forms CsCl, Cs_2SO_4, and cesium borosilicate glass are given.

Data on the fuel forms of ^{244}Cm are presented. Properties of ^{244}Cm metal, Cm_2O_3, Cm_2O_2S, CmF_3, ^{242}Cm, and $^{242}Cm_2O_3$ cermet are tabulated.

Data are given on composition, specific power, radiation, critical mass, container compatibility, thermophysical properties, mechanical properties, chemical properties, biological tolerance, and shielding for strontium-90 metal, titanate ($SrTiO_3$), oxide (SrO_3), fluoride (SrF_2), and orthotitanate (Sr_2TiO_4).

Each set of data sheets contains references.

These documents have been reviewed by the Editorial Board of the National Bureau of Standards.