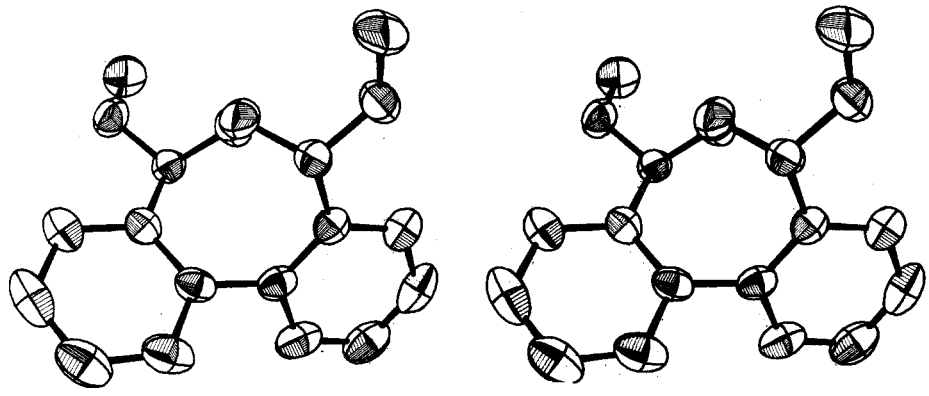
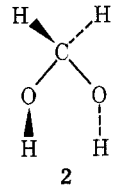


Figure 2.

another, a fact consistent with but not deducible from the spectroscopic studies.[2,5] The peroxide O10–O10′ bond [1.452 (18) Å] is shorter than those reported (1.48 Å) for dimeric and trimeric alkyl ketone peroxides[10–12] accounting, at least in part, for the unusual thermal stability of **1**. The C–O distance in the eight-membered ring is 1.416 (17) Å and is comparable to that observed in trimeric acetone peroxide.[10] The methyl C–O in the methoxy group compares with that observed in other studies,[13] but the Me–O–C angle (110°) is significantly compressed. The C–O–C angles within the eight-membered ring (108.5°) are consistent with those observed in the di- and trimeric alkyl ketone peroxides. The closest intermolecular contact distance is 3.37 Å observed between C3 and O10 in the molecule related by $\frac{1}{2} + x, \frac{1}{2} + y, z$.

The ab initio self-consistent field molecular orbital calculations carried out on methanediol by Radom, Hehre, and Pople[14] provide a useful theoretical framework for understanding the structural details of peroxide **1**.

Pople and co-workers found that of a series of 48 saturated molecules, methanediol possessed the largest "bond separation energy" (15.2 kcal mol^{-1}), or, in other words, the largest positive heat of reaction in its theoretical conversion along with 1 mol of methane to 2 mol of methanol. Therefore, since the bond separation energies evaluate the interactions between various bonds in terms of back-donating n → σ^* electron transfer, the Pople calculations[14] determined that this bond-strengthening interaction is strongest between the two C–O bonds of methanediol. It was further determined that this interaction has its greatest effect when the OCO plane is perpendicular to the COH plane. This leads to a favorable orientation of dipoles for the two OH groups within the preferred double gauche conformation, **2**.[14]



2

Perhaps these same orbital interactions account for the unusual stability of peroxide **1** through strong n → σ^* back-donation of electron density into the peroxide bond from the geminal C–O bonds on the adjacent atoms (C7 and C7′). The double gauche conformation is indeed evident about C7 and C7′. The trends in bond lengths also strengthen the validity of the methanediol theoretical model: n → σ^* back-donation alternately lengthens C9–O8 [1.434 (10) Å], shortens O8–C7 [1.396 (12) Å], lengthens C7–O10 [1.416 (17) Å], and shortens O10–O10′ [1.452 (18) Å].

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Registry No.—**1**, 59645-79-3.

Supplementary Material Available. Tables of temperature and structure factors may be obtained upon request from the authors. The observed fractional coordinates for the unique atoms in the molecule have been retained as supplementary material for the microfilm edition (1 page). Ordering information is given on any current masthead page.

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A Novel Route to 1-Aminoalkylphosphonic Acids

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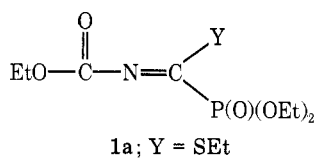
In view of the increasing interest in the biological[1] and chelating[2] properties of 1-aminoalkylphosphonic acids and 1-aminoalkylphosphine oxides we wish to report a convenient new route for the synthesis of these important classes of compounds. Recently we described a simple synthesis of *O,O*-diethyl 1-[*N*-ethoxycarbonylimino]-1-thioethyl methylphosphonate (**1a**) and its reaction with sulfuryl chloride to give **1b**.[3]

Table I. Spectral and Physical Characteristics of 1-Aminoalkylphosphonic Acids and 1-Aminoalkylphosphonoxides

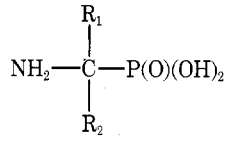
Ex.	Compd	Mp, °C	^{31}P NMR, δ, ppm	^{1}H NMR, δ	Yield, %	Lit. mp, °C
1	**2a**[a]	256–257	−16.8 (2 N KOH)	(2 N KOH/D_2O) 1.5 (6, d, J_{P-H} = 12 Hz)	45[b]	274–275[7] 258 (monohydrate)[8]
2	**2b**	272–273	−15.3 (H_2O)	(D_2O) 1.8 (3, pair of d, J_{H-H} = 7, J_{P-H} = 15 Hz), 3.8 (1, m)	58[b]	272–274[9]
3	**2c**	267–269	−14.5 (H_2O)	(D_2O) 1.4 (3, t, J_{H-H} = 7 Hz), 2.0–2.4 (2, m), 3.3–3.7 (1, m)	50[b]	264–266[9] 285–286[7]
4	**2d**	262–263	−22.2 2 N KOH)	(2 N KOH/D_2O) 1.5 (6, t, J_{H-H} = 6 Hz), 2.3–2.7 [1, m, C**H**$(CH_3)_2$], 2.9 (1, pair of d, CHP)	46[b]	274[10]
5	**2e**	268–270	−21.2 (2 N KOH)	(2 N KOH/D_2O) 2.7–3.7 (3, m, $CHCH_2$), 7.8 (5, s, aromatic protons)	41[b]	226[8] 276–277[11]
6	**8**	108–109	−34.5 ($CHCl_3$)	($CDCl_3$) 1.3 (3, pair of d, J_{H-H} = 7, J_{P-H} = 15 Hz), 3.4–3.9 (1, m), 7.3–8.1 (10, m, aromatic protons)	55[c]	

[a] Isolated as a monohydrate. [b] Yield calculated on the basis of starting **1a**. [c] Yield calculated for the conversion **7** → **8**.

Because of the presence of the >P(O)C=N– unit in such compounds it was expected that they could be employed in a convenient synthesis of the important 1-aminoalkylphosphonic acids **2**.[4]



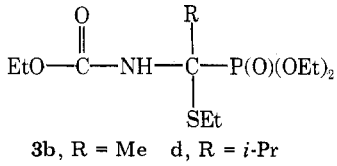
1a; Y = SEt
1b; Y = Cl



2a, R_1 = R_2 = Me
b, R_1 = H; R_2 = Me
c, R_1 = H; R_2 = Et
d, R_1 = H; R_2 = *i*-Pr
e, R_1 = H; R_2 = CH_2Ph

As expected, treatment of chloride **1b** with methylmagnesium iodide and subsequent hydrolysis by means of concentrated HBr gave 1-amino-1-methylethylphosphonic acid (**2a**).

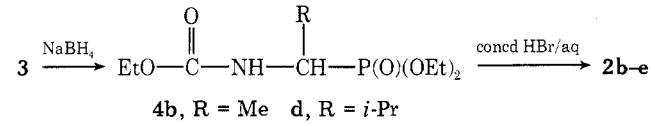
The dimethyl derivative **2a** was formed exclusively without regard to the molar ratio of methylmagnesium iodide used relative to chloride **1b**. However, its reaction with excess of isopropylmagnesium iodide gave only **2d** in 44% yield. On the other hand, reaction of **1a** with methylmagnesium iodide gave the thioethyl derivative *O,O*-diethyl 1-[*N*-ethoxycarbonylamino]-1-thioethylmethylphosphonate (**3b**). Other Grignard reagents (RMgX, R = Et, *i*-Pr, $PhCH_2$; X = I, Br) reacted similarly with **1a** to give the corresponding *O,O*-diethyl 1-[*N*-ethoxycarbonylamino]-1-thioethylalkylphosphonates (**3c–e**).



3b, R = Me **d**, R = *i*-Pr
c, R = Et **e**, R = CH_2Ph

Since distillation of the thioethylalkylphosphonates **3** caused partial decomposition, the compounds were identified by means of mass spectrometry and ^{1}H NMR spectroscopy without isolation.

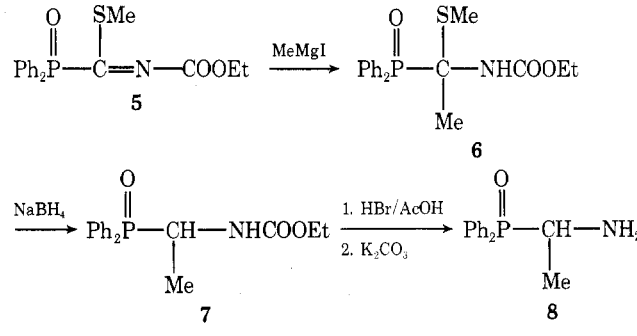
Conversion of the phosphonates **3** to the corresponding



4b, R = Me **d**, R = *i*-Pr
c, R = Et **e**, R = CH_2Ph

phosphonic acids **2** was achieved by reduction of **3** with sodium borohydride,[5] followed by hydrolysis of the desulfurated intermediate **4** by means of aqueous hydrogen bromide. The phosphonic acids were isolated and purified according to the procedure of Isbell.[6] Spectroscopic and physical data characteristic of the compounds obtained are collected in Table I.

The present synthetic method can also be applied to the preparation of 1-aminoalkylphosphine oxides. Treatment of [(ethoxycarbonylimino)(thiomethyl)methyl](diphenyl)-phosphine oxide (**5**)[3] with methylmagnesium iodide gave [1-(ethoxycarbonylamino)-1-(thiomethyl)ethyl](diphenyl)-phosphine oxide (**6**), which was reduced as usual by means of sodium borohydride to give intermediate **7**, which upon hydrolysis with 40% HBr in acetic acid gave 1-aminoethyl(diphenyl)phosphine oxide (**8**).



Experimental Section

Melting points and boiling points are uncorrected. ^{31}P NMR spectra were recorded at 24.3 MHz with H_3PO_4 as reference (negative chemical shift values for compounds absorbing at lower fields than H_3PO_4). ^{1}H NMR spectra were recorded at 80 MHz. Gas chromatography/mass spectrometric analyses were performed on an instrument (LKB 2091-PDP11) operated at 70 eV, ion source temperature 250 °C.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylimino)-1-thioethylmethylphosphonate (1a).** To a solution of ethoxycarbonyl isothiocyanate (13.1 g, 0.1 mol) in tetrahydrofuran (100 ml), triethyl phosphite (17.3 g, 0.11 mol) was dropped at a temperature of 30–40 °C. The reaction mixture was left for 6 h at room temperature, the solvent evaporated, and the residue distilled: bp 115 °C (0.05 mm); n^{20}D 1.4860; yield 18.5 g (62%); $\delta_{^{31}P}$ 1.2 ppm.

Anal. Calcd for $C_{10}H_{20}NO_5PS$: C, 40.40; H, 6.73; P, 10.43. Found: C, 40.71; H, 6.85; P, 10.69.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylimino)-1-chloromethylphosphonate (1b).** Sulfuryl chloride (14.8 g, 0.11 mol) was dropped into a solution of phosphonate **1a** (29.7 g, 0.1 mol) in methylene chloride (140 ml) without cooling. After 1 h at room temperature the solvent was evaporated and residue distilled: bp 102–103 °C (0.1 mm);

n^{20}D 1.4544; yield 19.3 g (71%); δ_{31P} 3.2 ppm. Anal. Calcd for $C_8H_{15}NO_5PCl$: C, 35.40; H, 5.54; P, 11.40. Found: C, 35.11; H, 5.89; P, 11.06.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)-1-methylethylphosphonate (4a).** To a solution of phosphonate **1b** (13.6 g, 0.05 mol) in ethyl ether (300 ml) a solution of MeMgI (0.15 mol) in ether (100 ml) was dropped with vigorous stirring while maintaining the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C after which the mixture was cooled to −5 °C and a saturated solution of ammonium chloride in water (60 ml) was carefully added. The organic layer was separated and the aqueous phase extracted with chloroform (2 × 40 ml). The combined organic layers were dried over anhydrous magnesium sulfate, the solvent evaporated, and the oily residue distilled, bp 93–94 °C (0.05 mm), n^{20}D 1.4505, yield 8.4 g (63%).

Anal. Calcd for $C_{10}H_{22}NO_5P$: C, 44.90; H, 8.25; P, 11.61. Found: C, 45.22; H, 8.05; P, 11.40.

Reaction of Phosphonate 1b with Isopropylmagnesium Iodide. To a solution of isopropylmagnesium iodide (0.075 mol) in ethyl ether (150 ml) a solution of phosphonate **1a** (6.8 g, 0.025 mol) in ether (30 ml) was dropped with vigorous stirring while keeping the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C and after cooling to −5 °C the mixture was worked up as described for the case of **4a**. The crude phosphonate was identified as **4d** and was hydrolyzed without purification according to the procedure described by Chambers and Isbell, yielding 1.7 g (44%) of 1-aminoisobutylphosphonic acid **2d**.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)-1-thioethylalkylphosphonates (3b–e).** To a solution of alkylmagnesium iodide (0.05 mol) (MeI, EtI, *i*-PrI, $PhCH_2Cl$) in ethyl ether (200 ml), a solution of phosphonate **1a** (7.5 g, 0.025 mol) in ether (30 ml) was dropped with vigorous stirring while keeping the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C and after cooling to −5 °C the mixture was worked up as described above for the case of **4a** except that the crude product obtained after the evaporation of solvent was used directly in the next step.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)alkylphosphonates (4b–e).** Solutions of the crude phosphonates **3b–e** (prepared from 0.025 mol of **1a**) in THF (70 ml) were refluxed with sodium borohydride (1.5 g, 0.04 mol) for 2 h. After cooling to 20 °C, water (30 ml) was carefully added. The organic layer was separated, the water layer extracted with chloroform (3 × 30 ml), and the combined extracts dried over anhydrous magnesium sulfate. After evaporation of solvent the crude phosphonates **4b–e** were hydrolyzed without purification.

1-Aminoalkylphosphonic Acids (2a–e). Hydrolysis of phosphonates **4a–e** and isolation of the corresponding aminophosphonic acids **2a–e** was carried out according to the procedure described by Chambers and Isbell.[7] For the results see Table I.

1-(*N*-Ethoxycarbonylamino)ethyldiphenylphosphine Oxide (7). A solution of phosphine oxide **6**[3] (7.2 g, 0.02 mol) in THF (70 ml) was refluxed with sodium borohydride (1.5 g, 0.04 mol) for 2 h. After cooling to 20 °C, water (30 ml) was carefully added. The organic layer was separated and the aqueous phase extracted twice with chloroform (2 × 30 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent evaporated. The oily residue crystallized upon adding a small amount of ethyl ether. The product was filtered and recrystallized from benzene–petroleum ether (2:1) to give 5.5 g (87%) of **7**, mp 146–147 °C, δ_{31P} −35.0 ppm. Anal. Calcd for $C_{17}H_{20}NO_3P$: C, 64.30; H, 6.32; P, 9.78. Found: C, 64.37; H, 6.46; P, 9.84.

1-Aminoethyldiphenylphosphine Oxide (8). Phosphine oxide **7** (2.0 g, 0.0063 mol) was dissolved in a solution of HBr in acetic acid (40%, 20 ml). The reaction mixture was let stand at room temperature for 3 days. The crude 1-aminophosphine oxide hydrobromide separated as an oily liquid after addition of ethyl ether (about 100 ml). The oil was dissolved in 10 ml of water and the solution extracted twice with chloroform (2 × 10 ml) in order to remove unchanged **7**. The aqueous solution was neutralized with potassium carbonate and crude **8** extracted with chloroform (10 × 10 ml). The organic layer was dried ($MgSO_4$), the solvent evaporated, and the oily residue crystallized from benzene–petroleum ether (2:1) to give 0.7 g (55%) of pure **8**.

Anal. Calcd for $C_{14}H_{16}NOP$: C, 68.60; H, 6.53; P, 12.66. Found: C, 68.42; H, 6.31; P, 12.91.

Registry No.—**1a**, 60064-40-6; **1b**, 35156-57-1; **2a**, 5035-79-0; **2b**, 6323-97-3; **2c**, 14047-23-5; **2d**, 18108-24-2; **2e**, 6324-00-1; **3b**, 60064-41-7; **3c**, 60064-42-8; **3d**, 60064-43-9; **3e**, 60064-44-0; **4a**, 60064-45-1; **4b**, 60064-46-2; **4c**, 60064-47-3; **4d**, 60064-48-4; **4e**, 60064-49-5; **6**, 59766-64-2; **7**, 60064-50-8; **8**, 60064-51-9; ethoxycarbonyl isothiocyanate, 16182-04-0; triethyl phosphite, 122-52-1; sulfuryl chloride, 7791-25-5; isopropyl iodide, 75-30-9.

References and Notes

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A Convenient Synthesis of 25-Oxo-27-norcholesteryl Acetate

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During an examination of the scope of the Wittig reaction with C-20 steroidal ketones as reported by Piraux and co-