mass from 2.5 l. of hot isopropyl alcohol afforded 7.5 g. (62%) of dianilinium diphenylpyrophosphonate, m.p. 215–217°, identified through a comparison of its infrared spectrum with that of an authentic specimen.

A repetition of this experiment with methyl carbanilate in place of the urea gave similar results.

Dianilinium diphenylpyrophosphonate (I). A mixture of 5 5 g. (0.028 mole) of phenylphosphonic dichloride and 0.76 g. (0.042 mole) of water in 35 ml. of ether was shaken for 45 min., with occasional cooling under a water tap. Most of the volatile material in the resulting heavy oil was removed under water-aspirator pressure. Treatment with 10 ml. of cold water gave a crystalline precipitate which was washed with cold water, slurried with ether, and dried in air to yield without further purification, 2.3 g. (55%) of slightly hygroscopic diphenylpyrophosphonic acid, m.p. 81.5–82.5°[5].

Anal. Calcd. for $C_{12}H_{12}P_2O_5$: C, 48.30; H, 4.06; neut. equiv., 149.1. Found: C, 47.87; H, 4.04; neut. equiv., 150.4.

The dianilinium salt of this acid was prepared by the addition of 3 drops of aniline to a solution of 0.2 g. of the acid in 2 ml. of cold water; the resulting precipitate was recrystallized from hot isopropyl alcohol. The infrared spectrum and properties of this salt are identical in every respect with those of the salt prepared as described above. Aqueous solutions of dianilinium diphenylpyrophosphonate are acidic and fairly stable. Titration with alkali shows a sharp break at *p*H 8.5 with a neutralization equivalent of 241 ± 1 (calcd. 242).

An attempt to prepare this salt by heating a sample of monoanilinium phenylphosphonate (m.p. 210–213° dec.) at 210° failed to show evidence of dehydration. The infrared spectra of this salt and that of dianilinium diphenylpyrophosphonate are quite dissimilar.

Hydrolysis of dianilinium diphenylpyrophosphonate. A mixture of 2 g. of the dianilinium salt and 20 ml. of 10% aqueous sodium hydroxide was heated just to the boiling point, cooled, and extracted with ether to remove aniline (identified as acetanilide, m.p. 113–114°, and benzenesulfonanilide, m.p. 110–111°). Careful treatment of the aqueous alkaline solution with excess concentrated hydrochloric acid caused the precipitation of a crude acid, m.p. 75–77° dec. Recrystallization from *cold* acetone gave material, m.p. 82.5–83°, which was titrated as a strong monobasic acid with a neutralization equivalent of 169 ± 2 (calculated for diphenylpyrophosphonic acid dihydrate, 167). Crystallization of this substance from hot acetone gave material which exhibited a neutralization curve with two unequally spaced breaks. The infrared spectrum of the volatile material obtained by heating a sample of the acid at 100° showed the presence only of water. The spectrum of the residue or of a sample recrystallized from boiling toluene was identical with that of phenylphosphonic acid.

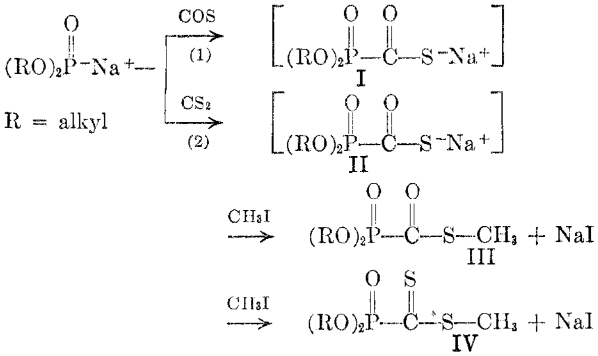
U. S. Naval Research Laboratory
Washington 25, D. C.
Department of Chemistry, University of Maryland
College Park, Md.

The Reactions of Sodium Dialkyl Phosphonates with Carbonyl Sulfide and with Carbon Disulfide

Daniel W. Grisley, Jr.

Received October 10, 1960

The nucleophilic characteristics of the alkali metal dialkyl phosphonates, especially toward carbonyl groups,[1] prompted an investigation of their reactivity toward carbonyl sulfide and toward carbon disulfide. It was found that both reagents reacted with sodium dialkyl phosphonates to form a new phosphorus-carbon bond. The salts (I) and (II) were not isolated, but were allowed to react further to produce the corresponding thiolformate (III) and dithioformate (IV) esters. Structure III (R = ethyl) was indicated by a carbonyl absorption in the infrared spectrum at 6.15[2] μ. In addition, the NMR peak of III (R = ethyl) at +4.6 p.p.m., is within the range of the structurally similar acyl phosphonates which have a chemical shift of + 2 ± 1 p.p.m.[3] Finally, *S*-methyl diethoxyphosphinylthiolformate was amidated to yield the known amide (V) in 75% yield.[4] Diethoxyphosphinylformamide had characteristic amide carbonyl (6.0 μ) and N-H (3.0 μ and 3.15 μ) peaks in its infrared spectrum.[5] The NMR spectrum of V had a single peak at +1.4 p.p.m.

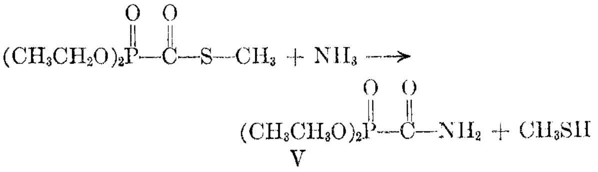


$$(RO)_2\overset{\overset{O}{\|}}{P}{}^-Na^+ \xrightarrow[(1)]{COS} \left[(RO)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}-S^-Na^+\right] \text{ I}$$

$$R = \text{alkyl} \xrightarrow[(2)]{CS_2} \left[(RO)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}-S^-Na^+\right] \text{ II}$$

$$\xrightarrow{CH_3I} (RO)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}-S-CH_3 + NaI \text{ III}$$

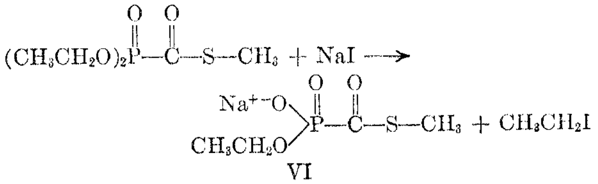
$$\xrightarrow{CH_3I} (RO)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{S}{\|}}{C}-S-CH_3 + NaI \text{ IV}$$



$$(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}-S-CH_3 + NH_3 \longrightarrow (CH_3CH_3O)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}-NH_2 + CH_3SH$$

V

It was found that *S*-methyl diethoxyphosphinylthiolformate was easily dealkylated with sodium iodide to yield *O*-ethyl-*O*-sodium carbomethylthiophosphonate (VI). The NMR peak of VI



$$(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}-S-CH_3 + NaI \longrightarrow \begin{matrix}Na^+{}^-O\\ CH_3CH_2O\end{matrix}\!\!>\!\overset{\overset{O}{\|}}{P}-\overset{\overset{O}{\|}}{C}-S-CH_3 + CH_3CH_2I$$

VI

---

[1] A. N. Pudovik, *Uspekhi Khim.*, **23**, 547 (1954).

[2] It is stated in L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 160, that the carbonyl frequencies of a number of thiol esters occur at 1675 cm.$^{-1}$ (5.96 μ).

[3] J. Van Wazer, C. Callis, J. Shoolery, and R. Jones, *J. Am. Chem. Soc.*, **78**, 5715 (1956).

[4] P. Nylen, *Ber.*, **57**, 1023 (1924).

[5] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Son, Inc., New York, 1954, p. 176 indicates the carbonyl absorption of primary amides at 1650 cm.$^{-1}$ (6.06 μ).

at +3.2 p.p.m. is in agreement with the structure as shown. VI has a carbonyl peak in its infrared spectrum at 6.17 μ with a shoulder at 6.13 μ. Similar dealkylation reactions of phosphonate esters,[6] phosphate esters,[6,7] and pyrophosphates[8] by nucleophiles in general and by inorganic iodides in particular, have been reported.

Indeed, the dealkylation of *S*-methyl diethoxyphosphinylthiolformate by sodium iodide formed in reaction (1) could have accounted for the low yield of III (R = ethyl), (48%). Moreover, formation of the theoretically[9] less readily dealkylated isopropyl analog (III) in substantially higher yield (70%) under similar conditions supports this idea.

In the reaction of sodium diisopropyl phosphonate with carbon disulfide followed by reaction with methyl iodide (reaction (2)) choice of the structure (IV) (R = isopropyl) was based upon its NMR spectrum. *S*-Methyl diisopropoxyphosphinyldithioformate had a P^{31} chemical shift of +4.2 p.p.m. The similarity of this peak shift to that of the thiol ester (III) (R = isopropyl) (+6.5 p.p.m.) indicates a structure of the type IV. It is interesting that whereas the thiol esters (III) are colorless liquids, the dithio ester (IV) and *S*-*p*-chlorobenzyl diisopropoxyphosphinyldithioformate are by contrast, deeply red colored.

EXPERIMENTAL[10,11]

Materials. Sodium hydride was a 50.9% suspension in mineral oil purchased from Metal Hydrides Co. Tetrahydrofuran used as a reaction mixture solvent was Matheson (b.p. 64–66°). It was distilled from sodium hydride directly into the reaction flask immediately before use. Hexane, used to free the sodium hydride from mineral oil, was distilled. The first 10% of the distillate was discarded and the fraction b.p. 66–67° was collected. Diethyl hydrogen phosphonate (Virginia-Carolina Chemical Co.) was distilled at reduced pressure and a middle cut was taken. Diisopropyl hydrogen phosphonate, b.p. 81–82°/15 mm., $n_{\rm D}^{25}$ 1.4066, was prepared by the reaction of gaseous hydrogen chloride with triisopropyl phosphite purchased from the Virginia-Carolina Chemical Co. Carbonyl sulfide (Matheson) was purified by passing it through a series of three traps each containing approximately 700 ml. of a saturated lead acetate solution in water and then through a Drierite column before admitting the gas to the reaction mixture. Carbon disulfide (Baker and Adamson Reagent) was dried over anhydrous magnesium sulfate. Gaseous ammonia was Matheson. Methyl iodide was Matheson, b.p. 42–44°. Sodium iodide (Baker and Adamson Reagent) was dried *in vacuo* at 100°. *p*-Chlorobenzyl chloride was obtained from Matheson.

The reaction of sodium diethyl phosphonate with carbonyl sulfide followed by reaction with methyl iodide. Diethyl hydrogen phosphate (27.6 g., 0.2 mole) was added dropwise to a stirred slurry of sodium hydride (50.9% dispersion in mineral oil) (9.6 g., 0.2 mole) in tetrahydrofuran (200 ml.) at 25–30° in a dry atmosphere. The reaction was stirred and refluxed until hydrogen evolution ceased. The reaction mixture was cooled to 6°. Carbonyl sulfide gas was passed over the mixture at 2–5° until the mixture had absorbed a total of 13.3 g. (0.22 mole). Methyl iodide (28.4 g., 0.2 mole) was added to the stirred mixture at 3–5° over 10 min. The mixture was poured into 1 l. of ice water; an oil separated. The oil was extracted into ether (200 ml.). The water layer was saturated with salt and then extracted with ether (200 ml.). The ether layers were combined, dried (magnesium sulfate), filtered, and evaporated to yield a colorless oil. The oil was distilled through a 10-in. vacuum jacketed Vigreux column to yield a main fraction, *S*-methyl diethoxyphosphinylthioformate (20.5 g., 0.1 mole, 48%), b.p. 80–81°/0.1 mm. The infrared spectrum[12] (neat) had a peak at 6.15 μ (C=0); it was identical with that of an authentic sample prepared in the same manner. The authentic sample had b.p. 116–118°/1.7 mm., $n_{\rm D}^{25}$ 1.4705.

Anal. Calcd. for $C_6H_{13}O_4PS$: C, 33.96; H, 6.17; P, 14.60; S, 15.11. Found: C, 34.24; H, 5.98; P, 14.92; S, 15.34.

The NMR spectrum[13] had a P^{31} chemical shift of +4.6 p.p.m.

The reaction of sodium diisopropyl phosphonate with carbonyl sulfide followed by reaction with methyl iodide. The reaction conditions and work-up procedure used were the same as those used for sodium diethyl phosphonate. The amounts used were diisopropyl hydrogen phosphonate (33.2 g., 0.2 mole), sodium hydride (50.9% dispersion in mineral oil) (9.6 g., 0.2 mole), carbonyl sulfide (25.1 g., 0.43 mole), methyl iodide (28.4 g., 0.2 mole), and tetrahydrofuran (200 ml.). There was obtained *S*-methyl diisopropoxyphosphinylthiolformate (33.8 g., 0.14 moles, 70%), b.p. 100–101°/0.5 mm., $n_{\rm D}^{25}$ 1.4634. The infrared spectrum (neat) was identical with that of an authentic sample prepared in the same manner. The NMR spectrum had a P^{31} chemical shift of +6.5 p.p.m. The authentic sample had b.p. 76–77°/0.1 mm. and $n_{\rm D}^{25}$ 1.4630.

Anal. Calcd. for $C_8H_{17}O_4PS$: C, 39.98; H, 7.13, P, 12.89; S, 13.34. Found: C, 40.10; H, 7.16; P, 12.97; S, 13.32.

The reaction of S-methyl diethoxyphosphinylthiolformate with ammonia. Ammonia was bubbled into a solution of *S*-methyl diethoxyphosphinylthiolformate (4.24 g., 20 mmoles) in tetrahydrofuran (30 ml.) at room temperature for 3 hr. The white crystals were filtered; the filtrate was concentrated *in vacuo* to yield solid. The crystalline solids were combined, washed with ether, filtered, and dried at 70°/20 mm. to yield diethoxyphosphinylformamide (2.80 g., 15 mmoles, 75%), m.p. 138–139° (lit.[4] m.p. 134–135°). A small sample was recrystallized from hot ethyl acetate and was dried at room temperature *in vacuo*, to yield crystals, m.p. 138–139°.

Anal. Calcd. for $C_5H_{12}NO_4P$: C, 33.16; H, 6.68; N, 7.74; P, 17.10. Found: C, 33.03; H, 6.73; N, 7.84; P, 17.19.

The infrared spectrum (potassium bromide) had peaks at 3.0 μ and 3.15 μ (N—H), and a peak at 6.0 μ (C=O). The nuclear magnetic resonance spectrum had a P^{31} chemical shift at +1.4 p.p.m. (15.9% solution in acetone).

The reaction of S-methyl diisopropoxyphosphinylthiolformate with ammonia. The procedure was essentially the same as that used for *S*-methyl diethoxyphosphinylthiolformate. *S*-Methyl diisopropoxyphosphinylthiolformate (4.9 g., 21 mmoles) was amidated to yield a white solid, diisopropoxyphosphinylformamide (3.3 g., 16 mmoles, 76%), m.p. 94–96°. A small sample was recrystallized from hot ethyl acetate to yield colorless needles, m.p. 95–97°.

Anal. Calcd. for $C_7H_{16}NO_4P$: C, 40.19; H, 7.71; P, 14.81; N, 6.70. Found: C, 40.09; H, 7.51; P, 14.72; N, 6.73.

---

(6) R. Cremlyn, G. Kenner, J. Mather, and A. Todd, *J. Chem. Soc.*, 528 (1958).

(7) L. Zervas and I. Dilaris, *J. Am. Chem. Soc.*, **77**, 5354 (1955).

(8) L. Zervas and I. Dilaris, *Ber.*, **89**, 925 (1956).

(9) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 586 (1956).

(10) All melting and boiling points are uncorrected.

(11) Elemental analyses were performed by the Galbraith Laboratories, P. O. Box 4187, Knoxville, Tenn.

(12) Infrared spectra were run on a Baird Infra-Red Recording Spectrophotometer Model B.

(13) All measurements were performed with a Varian Dual-Purpose Nuclear Magnetic Resonance Spectrometer. 9400 gauss. 16.2 mc. Ref. 85% phosphoric acid.

The infrared spectrum (Nujol slurry) had peaks at 3.05 μ and 3.15 μ (N—H), and a peak at 6.05 μ (C=O). The NMR spectrum had a P^{31} chemical shift of +2.7 p.p.m. and a minor resonance at +5.1 p.p.m. (15.9% solution in acetone).

The reaction of S-methyl diethoxyphosphinylthiolformate with sodium iodide. A solution of *S*-methyl diethoxyphosphinylthiolformate (10.61 g., 50 mmoles) and sodium iodide (7.49 g., 50 mmoles) in tetrahydrofuran (100 ml.) was stirred in a dry atmosphere at 25° for 9.5 hr. The reaction mixture contained solid. The mixture was cooled to 0°. The solid was filtered, was washed with ether, and was dried at 60°/20 mm. for 1 hr. to yield *O*-ethyl *O*-sodium carbomethylthiophosphonate (9.50 g., 46 mmoles, 92%), m.p. 205°-210°. The hydroscopic product was recrystallized twice from hot acetone to yield white crystals, 7.17 g., m. p. 205-207°.

Anal. Calcd. for $C_4H_8NaO_4PS$: C, 23.31; H, 3.91; P, 15.03; S, 15.56. Found: C, 23.19; H, 3.61; P, 15.29; S, 15.74.

The infrared spectrum (potassium bromide) had a peak at 6.17 μ with a shoulder at 6.13 μ (C=O). The NMR spectrum had a P^{31} chemical shift of +3.2 p.p.m.

The reaction of sodium diisopropylphosphonate with carbon disulfide followed by reaction with methyl iodide. Sodium diisopropyl phosphonate was prepared in the usual manner. A solution of sodium diisopropylphosphonate (0.2 mole) in tetrahydrofuran (200 ml.) was added to well stirred carbon disulfide (76 g., 1 mole) at 2-8° over 15 min. The solution became deep red colored. Methyl iodide (30 g., 0.21 mole) was added to the stirred solution at 5° during 5 min. The reaction mixture was stirred for an additional 5 min. at 5°. The homogeneous dark-red mixture was poured into ice water (750 ml.). The organic phase was extracted into ether (300 ml.). The ether phase was washed with water (4 × 500 ml.). The organic phase was dried, (magnesium sulfate), filtered, and evaporated to yield an oil. The oil was distilled through a 10-in. vacuum jacketed Vigreux column to yield a main fraction, a dark red-colored liquid, *S*-methyl diisopropoxyphosphinyldithioformate (30.8 g., 0.12 mole, 60%), b.p. 116-117°/0.4 mm., n_D^{25} 1.5168.

Anal. Calcd. for $C_8H_{17}O_3PS_2$: C, 37.49; H, 6.69; P, 12.09; S, 25.02. Found: C, 37.75; H, 7.07; P, 11.88; S, 24.72.

The NMR spectrum had a P^{31} chemical shift of +4.2 p.p.m.

The reaction of sodium diisopropyl phosphonate with carbon disulfide followed by reaction with p-chlorobenzyl chloride. In this experiment the sodium hydride (50.9% dispersion in mineral oil) (4.8 g., 0.1 mole) was freed of mineral oil by washing with hexane (3 × 300 ml.). The supernatant liquor was removed by means of nitrogen pressure by filtering through a dip tube having a frittered glass tip. The sodium diisopropyl phosphonate (0.1 mole) was prepared in tetrahydrofuran (100 ml.) in the usual manner. The tetrahydrofuran solution of the sodium diisopropyl phosphonate was added to carbon disulfide (38 g., 0.5 mole) as before. A solution of *p*-chlorobenzyl chloride (14.5 g., 0.09 mole) in tetrahydrofuran (100 ml.) was added to the reaction mixture at 1-3° over 5 min. The reaction mixture was stirred in a nitrogen atmosphere at room temperature for 19 hr. The mixture was then refluxed for 1 hr. Ether was added to the mixture. The mixture was washed with water (3 × 500 ml.). The organic phase was dried, (magnesium sulfate), filtered and evaporated *in vacuo* at 80° to yield a dark red oil. The oil was evacuated at 80°/0.1 mm. for 1 hr. and then at room temperature at 0.1 mm. for 20 hr. to yield a deep red oil, *S-p*-chlorophenyl diisopropoxyphosphinyldithioformate (27.4 g., 0.075 mole, 83%).

Anal. Calcd. for $C_{14}H_{20}ClO_3PS_2$: C, 45.83; H, 5.49; P, 8.44; S, 17.48. Found: C, 45.98; H, 5.75; P, 8.14; S, 17.77.

The NMR spectrum (neat) had P^{31} chemical shifts of +4.2 p.p.m., 0.0 p.p.m. and −16.1 p.p.m. The peak at +4.2 p.p.m. accounted for >95% of the combined areas under the peaks.

Acknowledgment. The author wishes to thank Mr. John Pustinger and Dr. Gail Birum for their valuable assistance in this work. He wishes to thank Mr. John W. Cooper for the infrared spectra and Messrs. William S. Coakley, Robert E. Dorsett and John E. Strobel for the NMR data.

CHEMICAL RESEARCH DEPARTMENT
RESEARCH AND ENGINEERING DIVISION
MONSANTO CHEMICAL CO.
DAYTON 7, OHIO

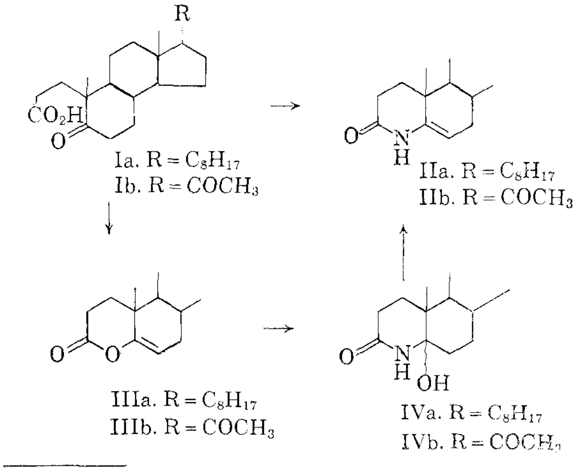
Steroids. II. 4-Aza-5-cholesten-3-one and 4-Aza-5-pregnene-3,20-dione[1,2]

NORMAN J. DOORENBOS, CHIEN LI HUANG,[3] C. RICHARD TAMORRIA,[4] AND MU TSU WU

Received September 28, 1960

The synthesis of 4-aza-5-cholesten-3-one (IIa), m.p. 252-253°, from 3,5-seco-4-norcholestan-5-on-3-oic acid (Ia) by reaction with ammonia at 140° has been reported by our laboratory.[5] Wildi[6] described a similar preparation for this compound. Recently the synthesis of IIa with a much lower melting point, m.p. 189°, by the reaction of ammonia with 4-oxa-5-cholesten-3-one (IIIa) at 25° was announced.[7] The reported spectra of these compounds were similar and it was thought that they might be different crystalline forms.

The procedure of Uskoković and Gut[7] was



Ia. R = C_8H_{17}
Ib. R = $COCH_3$

IIa. R = C_8H_{17}
IIb. R = $COCH_3$

IIIa. R = C_8H_{17}
IIIb. R = $COCH_3$

IVa. R = C_8H_{17}
IVb. R = $COCH_3$

---

(1) For paper I in this series see R. E. Havranek and N. J. Doorenbos, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 328 (1960).

(2) This work was supported by Research Grant CY-4132 from the National Cancer Institute, National Institutes of Health.

(3) Sterling-Winthrop Research Fellow, 1958-59.

(4) H. A. B. Dunning Research Fellow, 1959-60.

(5) N. J. Doorenbos and C. L. Huang, Abstract, 136th National A.C.S. Meeting, 30-O, Atlantic City, September 1959.

(6) R. S. Wildi, U. S. Patent **2,897,202**, July 28, 1959.

(7) M. Uskoković and M. Gut, *Helv. Chim. Acta*, **42**, 2258 (1959).