yield of the L-form, m.p. 116–118°, $[\alpha]^{24}D$ −12.3° (*c* 2, ethanol). Recrystallization from alcohol–water gave m.p. 117–118°, $[\alpha]^{24}D$ −12.3° (*c* 2, ethanol). *Anal.* Calcd. for $C_{25}H_{27}N_3O_6$: C, 62.6; H, 6.2; N, 9.5. Found: C, 62.6; H, 6.2; N, 9.7.

Ethyl Carbobenzoxyglycyl-DL-phenylalaninate.—In addition to the examples in Table I, a number of experiments were done. It was found that use of 0.010-mole quantities of carbobenzoxyglycine, ethyl DL-phenylalaninate hydrochloride and tetraethyl pyrophosphite in 7 cc. of diethyl phosphite gave a 69% yield of the peptide derivative after 15 minutes heating on a steam-bath and 65% after 30 minutes heating. Use of 10% excess pyrophosphite gave 66% on heating 25 minutes, 28% when reacting at room temperature for 18 hours and 26% when reacting at room temperature for 120 hours. When a 50% excess of the pyrophosphite was used and the reaction mixture heated for 20 minutes, the yield was 85%. Thus, results with the amine hydrochloride are not quite as good as with the free base. The use of 0.010 mole of the free base with 0.010 mole quantities of the acid and the pyrophosphite, and heating 30 minutes in 7 cc. of diethyl phosphite, gave a yield of 91%. A similar reaction by the "amide" procedure wherein the DL-phenylalanine ester was heated to 90° with the pyrophosphite in diethyl phosphite, then the carbobenzoxyglycine added and all heated 30 minutes, yielded 81%. A reaction by the "anhydride" procedure, wherein the carbobenzoxyglycine and the pyrophosphite were heated in diethyl phosphite to 90°, then the phenylalanine ester added and all heated 30 minutes, yielded 79% of the dipeptide derivative. Reaction of 0.010-mole quantities of the acid, the amine and the pyrophosphite in 15 cc. of refluxing benzene for 30 minutes gave a 90% yield; a similar reaction without any solvent by heating on a steam-bath for 20 minutes yielded 91% of the dipeptide derivative.

Ethyl Carbobenzoxyglycyl-L-tyrosinate.—A number of reactions were run, comparable to those with ethyl DL-phenylalaninate. Heating for 15 minutes gave about the same yield as 60 minutes heating (see Table I). Use of 25% excess of tetraethyl pyrophosphite and 15 minutes heating gave a 71% yield. The "amide" procedure, wherein the ethyl L-tyrosinate was heated with a 10% excess of the pyrophosphite in 7 cc. of diethyl phosphite for 5 minutes on a steam-bath before the carbobenzoxyglycine was added and heated 15 minutes, yielded 63%, and a similar "anhydride" procedure gave 67%.

Ethyl Carbobenzoxy-L-tyrosylglycylglycinate.—Several attempts to improve the yield were made. Use of 150% excess of the pyrophosphite and 20 minutes heating increased the yield 5% over the standard procedure (see Table I). Other variations, such as longer heating with 50 to 150% excess of the pyrophosphite, or use of a 50% excess of either the acid or the amine with a 100% excess of the pyrophosphite, gave crude yields in the 50–65% range. Perhaps significant is that the "amide" procedure with a 10% excess of the pyrophosphite gave a 61% crude yield, m.p. 155–160°, and a comparable "anhydride" procedure yielded 41%, m.p. 155–160°. Acidification of the bicarbonate wash from the "amide" procedure yielded 20% of crude carbobenzoxy-L-tyrosine (presumed) as an oil; a similar oil in 41% recovery was obtained from the "anhydride" reaction. A repetition of the "amide" procedure with a 50% excess of the pyrophosphite gave 63% of the crude peptide derivative and a 29% recovery of the crude acid.

Diethyl Phosphite Amide of Ethyl DL-Phenylalaninate.—Tetraethyl pyrophosphite (10.38 g., 0.040 mole) and ethyl DL-phenylalaninate (freshly prepared from the hydrochloride and distilled; 7.72 g., 0.040 mole) were mixed, with no noticeable reaction. Fractionation through a 3-inch Vigreux distilling head yielded 5.30 g. (72%) of diethyl phosphite, b.p. 65–70° (10 mm.), $n^{27}D$ 1.4073[10]; 3.49 g. of an intermediate fraction, b.p. to 140° (1 mm.); and 7.61 g. (61%) of the phosphite amide, b.p. 140–150° (1 mm.), $n^{27}D$ 1.4952; refractionation gave 6.20 g. (50%) of the latter; b.p. 140–150° (1 mm.), $n^{28}D$ 1.4920.[11]

Reaction of Carbobenzoxyglycine with Tetraethyl Pyrophosphite.—Mixture of 0.050-mole quantities yielded a solution which was then distilled at 2 mm. from a water-bath, yielding 4.09 g. (59% yield) of diethyl phosphite, b.p. 50–52°, $n^{29}D$ 1.4042. The residue, presumably the mixed anhydride, was treated with 0.050 mole of aniline for an hour at room temperature. Distillation yielded a liquid with $n^{30}D$ 1.4520, indicating a mixture of diethyl phosphite and aniline. The residue was treated with alcohol–water, then 5% sodium bicarbonate, leaving 9.53 g. (67% of the theoretical) of crude carbobenzoxyglycylanilide, m.p. 135–140°. Recrystallization from alcohol gave 5.18 g. (36%), m.p. 145–146°, which did not depress the m.p. of an authentic sample.[1]

(10) Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 202, lists b.p. 72° (10 mm.), $n^{22}D$ 1.4080.

(11) $n^{25}D$ 1.4917 from a preparation through diethyl chlorophosphite. See paper 1, ref. 1.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Some Alkyl Thiazolephosphonates

BY NORMAN D. DAWSON[1] AND ALFRED BURGER

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The synthesis of ethyl esters of 2-amino-4-methyl- and 4-methylthiazole-5-phosphonic acids from diethyl phosphonate substituted aliphatic bromo carbonyl compounds is described.

The effect of thiazole-5-carboxylic acid and of thiazole-5-sulfonic acid on the multiplication of bacteria has been the subject of numerous investigations.[2–9] We are now reporting the synthesis of two esters of methyl- and amino-substituted thiazole-5-phosphonic acids which have been designed for comparable biological studies.

The routes to these compounds led through diethyl 1-halogeno-2-oxoalkanephosphonates which were cyclized to the substituted diethyl thiazole-5-phosphonates by condensation with thiourea or thioformamide. For the synthesis of diethyl 4-methylthiazole-5-phosphonates, chloroacetone (I) was allowed to react with triethyl phosphite (II) and after completion of the two-stage reaction the resulting diethyl acetylmethanephosphonate (III) was brominated. Treatment of diethyl 1-bromo-2-oxopropanephosphonate (IV) with thioformamide gave diethyl 4-methylthiazole-5-phosphonate (V) while the reaction of the same bromo ketone with thiourea furnished diethyl 2-amino-4-methylthiazole-5-phosphonate (VI).

(1) Virginia-Carolina Chemical Corporation Fellow.

(2) A. Dorfman, S. A. Koser, H. R. Reams, K. F. Swingle and F. Saunders, *J. Infectious Diseases*, **65**, 163 (1939).

(3) S. A. Koser, A. Dorfman and F. Saunders, *Proc. Soc. Exptl. Biol. Med.*, **43**, 391 (1940).

(4) F. C. Schmelkes, *Science*, **90**, 113 (1939).

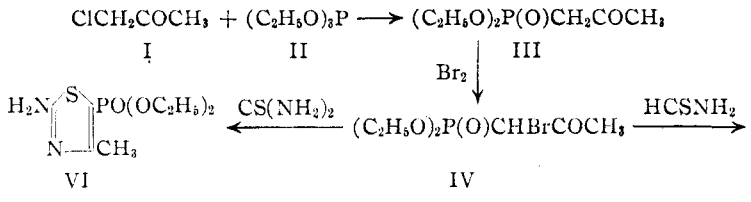
(5) H. Erlenmeyer and W. Würgler, *Helv. Chim. Acta*, **25**, 249 (1942).

(6) H. Erlenmeyer, H. Bloch and H. Kiefer, *ibid.*, **25**, 1066 (1942).

(7) H. Erlenmeyer and H. Kiefer, *ibid.*, **28**, 985 (1945).

(8) E. F. Möller and L. Birkofer, *Ber.*, **75B**, 1118 (1942).

(9) P. Meunier, *Bull. soc. chim.*, **12**, 517 (1945).



The possibility that bromination of III might have occurred at the methyl rather than at the methylene group and that subsequent ring closure might thus have furnished isomeric 4-thiazolylmethylphosphonic acid derivatives cannot be overlooked, but the rapid rate of bromination points to substitution of the active α-methylene group and makes the alternate route appear remote.

Bromoacetal (VII) reacted with triethyl phosphite to give diethyl 2,2-diethoxyethanephosphonate (VIII). This acetal was hydrolyzed readily in dilute acid solution to a colorless oil which was characterized as diethyl formylmethanephosphonate (IX). The reactive α-carbon atom of this aldehyde was brominated, and the resulting diethyl 1-bromo-2-oxoethanephosphonate was allowed to react with thiourea. However, ring closure to a thiazole derivative could not be effected unequivocally.

$$BrCH_2CH(OC_2H_5)_2 \xrightarrow{II} (C_2H_5O)_2P(O)CH_2CH(OC_2H_5)_2 \xrightarrow{H_3O^+} (C_2H_5O)_2P(O)CH_2CHO \xrightarrow{Br_2} (C_2H_5O)_2P(O)CHBrCHO$$

VII → VIII → IX → X

It is interesting that both bromoacetal and chloroacetonitrile react with triethyl phosphite smoothly, the latter furnishing diethyl cyanomethanephosphonate (XI), although in the light of a remark by Atherton[10] "positive halogen" is refractory to this reaction.

$$ClCH_2CN \xrightarrow{II} (C_2H_5O)_2P(O)CH_2CN \quad (XI)$$

The ester (VI) did not inhibit the growth of *Escherichia coli, Streptococcus faecalis R., Lactobacillus casei, L. arabinosus 17-5, Leuconostoc dextranicum 8086,* and *L. mesenteroides 8293* in concentrations up to 1:10,000.[11]

Experimental[12]

Triethyl Formylphosphonoacetate.—To a stirred suspension of 3.08 g. (0.134 g. atom) of sodium powder in 80 ml. of dry ether, cooled in an ice-bath, was added a solution of 30.0 g. (0.134 mole) of triethyl phosphonoacetate[13] and 8.05 g. (0.134 mole) of methyl formate in 6 ml. of absolute methanol at such a rate that gentle refluxing occurred. The cooling bath was removed and the solution was allowed to stand overnight. A white solid precipitated; the mixture was decomposed with 10 ml. of 30% methanol followed by 33 ml. of water. The cooled separated aqueous layer was acidified with 14 ml. of 11 *N* hydrochloric acid and the separated oil was extracted into ether. After drying and removal of the ether, the oily ester distilled at 130–135° (3.2 mm.), or 114° (0.3 mm.) in a yield of 18.3 g. (54%).

The 2,4-dinitrophenylhydrazone melted at 146–148°.

Anal. Calcd. for $C_{15}H_{21}N_4O_9P$: N, 12.98. Found: N, 13.01.

In our hands the formylmethanephosphonic acid obtained by acid hydrolysis of the ester could not be crystallized and characterized.

Carboxymethanephosphonic Acid.—A mixture of 10 g. (0.1325 mole) of chloroacetonitrile and 22.2 g. (0.1325 mole) of triethyl phosphite was refluxed at 165–170° for seven hours and then distilled. Diethyl cyanomethanephosphonate (17.5 g., 74.5%) was obtained, boiling at 132–135° (1.2 mm.). This ester was hydrolyzed to carboxymethanephosphonic acid, m.p. 139–140°.[14]

Diethyl Formylmethanephosphonate (IX).—A mixture of 70.8 g. (0.474 mole) of triethyl phosphite and 93.5 g. (0.474 mole) of bromoacetal (VII) was refluxed under a Cooper–Fasce still head for 3.5 hours, 29.7 g. (57.7%) of ethyl bromide being collected. Fractionation at 2 mm. yielded 63.7 g. (53%) of diethyl 2,2-diethoxyethanephosphonate (VIII), b.p. 128–130° (2 mm.).

Anal. Calcd. for $C_{10}H_{23}O_5P$: C, 47.23; H, 9.12. Found: C, 45.61; H, 8.86.

Hydrolysis with 3.5 volumes of refluxing 2% hydrochloric acid and extraction with ether for three days gave 75% of oily diethyl formylmethanephosphonate. **Its 2,4-dinitrophenylhydrazone** crystallized from dilute ethanol, m.p. 110–112°.

Anal. Calcd. for $C_{12}H_{17}N_4O_7P$: N, 15.57. Found: N, 15.25.

Bromination of Diethyl 2,2-Diethoxyethanephosphonate.—A stirred mixture of 25.0 g. (0.0985 mole) of tetraethyl acetalphosphonate, 5 g. (0.0492 mole) of calcium carbonate and 70 ml. of dry ether was treated dropwise with 15.7 g. (0.0985 mole) of bromine for about 45 minutes when the colored turbid solution cleared. It was washed with water, dried over sodium sulfate and distilled. A colorless oil weighing 22.8 g. (69.7%), b.p. 150–152° (0.6–0.8 mm.) was obtained; it was too unstable to be analyzed.

Numerous attempts to condense the freshly prepared bromoacetal derivative with thioformamide, or with thiourea under a variety of conditions, failed to give any basic product except in such low yields that identification as thiazole-5-phosphonates could not be carried out.

Diethyl Acetylmethanephosphonate (III).—A mixture of 18.5 g. (0.2 mole) of redistilled chloroacetone and 33.2 g. (0.2 mole) of triethyl phosphite was refluxed at 160–165° for four hours and then fractionated. Diethyl acetylmethanephosphonate (25 g., 64.5%) distilled at 96–98° (1.0 mm.). The yellow **2,4-dinitrophenylhydrazone** crystallized from 50% ethanol, m.p. 124–125.5°.

Anal. Calcd. for $C_{13}H_{19}N_4O_7P$: N, 14.95. Found: N, 14.75.

Diethyl 2-Amino-4-methylthiazole-5-phosphonate.—Diethyl acetylmethanephosphonate (15 g., 0.077 mole) in 150 ml. of dry ether was brominated by the dropwise addition of 12.3 g. (0.077 mole) of bromine. The bromination was rapid and complete in ten minutes. The solution was washed and concentrated on a steam-bath under reduced pressure. The residual red oil, dissolved in 75 ml. of 95% ethanol, was added dropwise over a 20-minute period to a stirred hot solution of 5.9 g. (0.077 mole) of thiourea in 75 ml. of 95% ethanol. After another two hours stirring and refluxing, the solvent was removed under reduced pressure, the residue was made bicarbonate alkaline, filtered and the filtrate was extracted with ether. From the dried ether solution was obtained 6.5 g. (33.6%) of an oil, b.p. 98° (0.25 mm.). The base turned brown in the air and was therefore converted to its **dihydrochloride** in ether solution. This salt crystallized from methanol–ethyl acetate and melted after removal of some solvent of crystallization at 160–162°.

(10) F. R. Atherton, *Quarterly Revs.*, III, **2**, 146 (1949).

(11) We are grateful to Professor William Shive of the University of Texas for these tests.

(12) All melting points have been corrected. The alkyl phosphites used in this work were obtained from Virginia-Carolina Chemical Corporation.

(13) G. M. Kosolapoff, THIS JOURNAL, **68**, 1103 (1946).

(14) A. E. Arbusov and A. A. Dunin, *Ber.*, **60**, 291 (1927), observed m.p. 139.5°; P. Nylén, *ibid.*, **59**, 1119 (1926), m.p. 142–143°.

Anal. Calcd. for $C_8H_{17}Cl_2N_2O_3PS$: C, 29.73; H, 5.30. Found: C, 29.50; H, 5.25.

The yellow **dipicrate** crystallized from 95% ethanol and melted at 230° (dec.) after sintering at 216–230°.

Anal. Calcd. for $C_{20}H_{21}N_8O_{17}PS$: N, 15.82. Found: N, 16.08.

Diethyl 4-Methylthiazole-5-phosphonate.—A solution of 7.8 g. (0.128 mole) of purified thioformamide[15] in 25 ml. of 95% ethanol was added dropwise to a stirred and refluxing solution of 35 g. of diethyl acetylbromomethanephosphonate in 50 ml. of 95% ethanol which was prepared as described above. After four hours stirring and refluxing another gram of thioformamide was added and refluxing was continued for 30 minutes. The mixture was worked up in a manner analogous to that described in the preceding experiment. The dark oily ester was chromatographed in benzene solution over alumina and purified by extraction into dilute acid and re-basification. Since it decomposed on distillation even under highly reduced pressure, and gave an extremely hygroscopic hydrochloride, it was characterized as the **picrate** which sintered at 173°, m.p. 178–183° (dec.).

Anal. Calcd. for $C_{14}H_{17}N_4O_{10}PS$: C, 36.21; H, 3.69; N, 12.07. Found: C, 36.64; H, 2.28; N, 12.31.

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(15) We are grateful to Dr. Earl Pierson of the Stonewall Plant, Merck and Company, Inc., for the thioformamide used in this study.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF PURDUE UNIVERSITY]

The Reaction of Sodium with Organosilanes at Elevated Temperatures

BY ROBERT A. BENKESER AND DONALD J. FOSTER

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The reaction of sodium with phenylsilanes of the type Ph_xSiCl_{4-x}, Ph_xSiH_{4-x} and $Ph_xMe_ySiH_{4-(x+y)}$ at elevated temperatures was investigated. These compounds appeared to disproportionate into more highly phenylated silanes and dephenylated products. This can be explained by the intermediate formation of phenylsodium arising through a cleavage of phenyl groups from the silane by the alkali metal. The phenylsodium then reacts with more silane to give the highly phenylated compounds. As a consequence of the phenylsodium formation, decalin and heptadecane are to be preferred as solvents for these reactions rather than toluene. The latter is converted to benzylsodium which reacts to form benzylsilanes and thus needlessly complicates the purification of the products. The methylphenylsilanes ($Ph_xMe_ySiH_{4-(x+y)}$) suffer loss of the phenyl groups rather than methyls, indicating the preferential cleavage by sodium of aryl, rather than alkyl groups. However, tribenzylsilane undergoes reaction with sodium despite its aliphatic characteristics. A high speed stirring apparatus was highly advantageous in increasing yields and decreasing the reaction time of these heterogeneous cleavage reactions.

In a recent publication[1] from this Laboratory, it was reported that triphenylsilane reacts with sodium–potassium alloy (1:5 by weight) in ether at room temperature to give triphenylsilylpotassium; whereas, under the same conditions, diphenylsilane and phenylsilane form tetraphenylsilane. These reactions can be summarized as

$$(C_6H_5)_3SiH + Na/K \xrightarrow{Et_2O} (C_6H_5)_3SiK + KH$$

$$(C_6H_5)_2SiH_2 + Na/K \xrightarrow[(2)\ H^+,\ H_2O]{(1)\ Et_2O} (C_6H_5)_4Si + \text{silicic material}$$

$$C_6H_5SiH_3 + Na/K \xrightarrow[(2)\ H^+,\ H_2O]{(1)\ Et_2O} (C_6H_5)_4Si + \text{silicic material}$$

The presence of triphenylsilylpotassium has been established by various coupling, reduction and hydrolysis reactions.[1-3] The formation of tetraphenylsilane from diphenylsilane or phenylsilane was visualized as follows: A primary cleavage of the silane by alloy is followed by reaction of the arylmetal compound with unreacted silane.

$$(C_6H_5)_2SiH_2 + Na/K \xrightarrow{Et_2O} C_6H_5SiH_2K + C_6H_5K$$
$$(C_6H_5)_2SiH_2 + 2C_6H_5K \longrightarrow (C_6H_5)_4Si + 2KH$$

and

$$C_6H_5SiH_3 + Na/K \xrightarrow{Et_2O} H_3SiK + C_6H_5K$$
$$C_6H_5SiH_3 + 3C_6H_5K \longrightarrow (C_6H_5)_4Si + 3KH$$

Recently, in an attempt to prepare triphenylsilylsodium from triphenylsilane and sodium, it was found that no reaction occurred until higher temperatures were obtained and then, *only* when traces of potassium were present. When toluene was used as a solvent, the products, after acid hydrolysis, were tetraphenylsilane, triphenylbenzylsilane and a silica-like material. These products can be explained if one assumes the intermediate formation of phenylsodium, resulting from a cleavage of phenyl groups by the alkali metal.

$$(C_6H_5)_3SiH \xrightarrow{Na} (C_6H_5)_2SiHNa + C_6H_5Na \xrightarrow{Na}$$
$$C_6H_5SiHNa_2 + 2C_6H_5Na \xrightarrow{Na} SiHNa_3 + 3C_6H_5Na$$

The phenylsodium thus produced can react with both triphenylsilane[4] to form tetraphenylsilane

$$(C_6H_5)_3SiH + C_6H_5Na \longrightarrow (C_6H_5)_4Si + NaH$$

and also with toluene[5] to form benzylsodium.

$$C_6H_5Na + C_6H_5CH_3 \longrightarrow C_6H_5CH_2Na + C_6H_6$$

The benzylsodium in turn is then capable of reacting with triphenylsilane to form triphenylbenzylsilane.

$$(C_6H_5)_3SiH + C_6H_5CH_2Na \longrightarrow (C_6H_5)_3SiCH_2C_6H_5 + NaH$$

The insoluble, infusible powder obtained in this reaction could have arisen from the hydrolysis of the dephenylated silicon atoms. Undoubtedly, this material was not pure SiO_2 but contained some silicon atoms that carried phenyl groups. How-

(1) R. A. Benkeser and D. J. Foster, THIS JOURNAL, **74**, 4200 (1952).

(2) R. A. Benkeser and R. G. Severson, *ibid.*, **73**, 1424 (1951).

(3) R. A. Benkeser, H. Landesman and D. J. Foster, *ibid.*, **74**, 648 (1952).

(4) Unpublished studies at this Laboratory have shown that compounds of type $(C_6H_5)_xSiH_y$ react with phenylsodium, quantitatively, at temperatures as low as 50°.

(5) V. L. Hansley, *Ind. Eng. Chem.*, **43**, 1759 (1951).