Anal. Calcd. for $S_2C_2H_{18}O_6Cl_2N_2$: C, 34.21; H, 4.31; N, 6.65. Found: C, 34.2; H, 4.39; N, 6.57.

(L)-Cystine-bis-N-carboxyanhydride (III) was prepared from (II) by heating under reduced pressure at 112° for periods up to 90 minutes; the products decomposed over a wide temperature range (*ca.* 115–150°) and ranged in purity, on the basis of the weight loss from (II), from 93.1 to 97.4%. The purest preparation analyzed 83% cystine by Mecham's modification of the Vassel method[8]; calcd. 82.3%.

Polymerization.—Both II and III polymerized on being heated or treated with moist solvents such as reagent ethyl acetate. The products had no melting points and were insoluble in common neutral organic solvents. They were soluble to varying degrees in solvents having hydrogen bond capacity such as 2-chloroethanol, glycerol dichlorohydrin, 8 *M* aqueous urea and glacial formic acid. The polymeric products were readily soluble in mineral acids, alkalies and in the reducing agent 2-mercaptoethanol. They gave positive biuret tests. X-Ray diffraction photographs[9] indicated that, though amorphous, they showed characteristic peptide chain spacings.

The analyses for carbon, hydrogen and nitrogen deviate considerably from those expected for totally polymerized cystine.

Anal. Calcd. for C_3H_4ONS: C, 35.28; H, 3.95; N, 13.72. Found: C, 34.7–36.8; H, 4.06–4.72; N, 10.1–10.3.

Cystine analyses[8] were low, presumably because of incomplete hydrolysis under the conditions of the determination.

Amino nitrogen values by the manometric Van Slyke procedure[10] ranged from 5.69 to 2.34%, corresponding to polymers of 2.2 to 5.7 cystine units, *i.e.*, molecular weights up to about 1200. On the other hand, ultracentrifuge examination of the polymers dissolved in 2-chloroethanol indicates large molecular-kinetic units, the sedimentation constants of which correspond to minimum molecular weights ranging from 12,000 to 10,000,000. Although the possibility of aggregation of smaller-size units is not excluded, consideration of possible structures of polycystine indicates that high molecular weight polymers are possible which may contain more than two free amino groups per molecule, and this may account for the low values of molecular weights determined from this end-group analysis. This difference between molecular weights determined by physical methods and by end-group analyses, which is probably attributable to aggregation, is also noted in the DL-β-phenylalanine-(L)-leucine copolymer studied by Woodward and Schramm[4] and by Brown, Coleman and Farthing.[6]

That the polymers could be partially fractionated from 2-chloroethanol with ether as precipitant is indicated by the fact that initially precipitated material gives higher sedimentation constants than subsequent fractions. It is significant that reduction of the polycystine with mercaptoethanol gives water-soluble, non-sedimentable products. Moreover, solid polycystine, when treated with small amounts of 2-mercaptoethanol, undergoes plastic flow between parallel plates under high pressure. This seems analogous to the behavior of reduced wool.

Acknowledgments.—We are indebted to Miss G. Secor and Mrs. M. Kilpatrick for the carbon and hydrogen analyses, to Mrs. M. Long for the nitrogen analyses, and to Mr. H. Fujikawa for the cystine analyses.

[8] D. K. Mecham, *J. Biol. Chem.*, **151**, 643 (1943).

[9] K. J. Palmer, unpublished results.

[10] D. D. Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

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The Anhydrides of Dimethyl- and Diethylphosphinic Acids

BY GENNADY M. KOSOLAPOFF AND RICHARD M. WATSON

It was of interest to secure some information about the properties of the two lowest members of the series of aliphatic phosphinic anhydrides, in order to supplement the data obtained for the two higher members.[1]

The desired substances were prepared by the reaction scheme used by us in the synthesis of the higher members. However, the preparation of the dimethyl- and the diethylphosphinic acids, the necessary starting materials, could not be accomplished satisfactorily by the reaction of Grignard reagents with dialkyl phosphites owing to the extreme solubility of the acids in water; this method of synthesis apparently is restricted to the relatively insoluble, higher members of the series. The acids were prepared by the reactions of the respective Grignard reagents with thiophosphoryl chloride, following the procedures given by Kabachnik[2] for the dimethyl derivative and by Strecker and Grossmann[3] for the diethyl derivative.

Experimental Part

Dimethylphosphinic Anhydride.—Thiophosphoryl chloride (64.4 g., 0.375 mole) was added slowly to the Grignard reagent prepared from 213 g. (1.5 moles) of methyl iodide and 36.4 g. of magnesium in 500 ml. of dry ether. The addition was done with stirring and ice–salt cooling. After 12 hours the mixture was hydrolyzed with ice and 10% sulfuric acid, and the insoluble dimeric reaction product, $(Me_2PS)_2$, was filtered off and dried. The yield was 17 g., or 48.5%. Repetition of the reaction with the same relative ratio of the reactants but carried out on a larger scale (0.5 mole of thiophosphoryl chloride) gave a 62.5% yield. The material was oxidized to dimethylphosphinic acid with nitric acid according to Kabachnik's directions.[2] The yield of dimethylphosphinic acid was 95% and the product melted at 85–87° (Kabachnik and Shepeleva give m.p. 86.5–88.5°).

Dimethylphosphinic acid (34 g.) and 300 ml. of dry benzene, contained in a flask provided with a reflux condenser, were treated slowly with 75 g. of phosphorus pentachloride and the mixture was refluxed for one hour until the evolution of hydrogen chloride ceased. Distillation gave 30.5 g. (75.5%) of dimethylphosphinyl chloride, a very hygroscopic solid, b.p. 202–204°. Kabachnik and Shepeleva give m.p. 66.8–68.4°.[2]

Dimethylphosphinyl chloride (13 g.) in 200 ml. of dry benzene was treated slowly, with stirring and ice-cooling, with a solution of sodium ethoxide prepared from 2.7 g. of sodium and 50 ml. of absolute ethanol. After 12 hours at room temperature the mixture was filtered and distillation of the filtrate gave 8.7 g. (62%) of ethyl dimethylphosphinate, a colorless liquid; b.p. 88–89° at 15 mm., n^{25}_D 1.4261, d^{25}_4 1.0278.

Anal. Calcd. for $Me_2P(O)OEt$: P, 25.40; *MR*, 30.42. Found: P, 25.22; *MR*, 30.39.

Heating 8 g. of ethyl dimethylphosphinate and 7.4 g. of dimethylphosphinyl chloride for 45 minutes at 145–160° resulted in brisk evolution of ethyl chloride and distillation of the residue yielded 7.5 g. (67%) of dimethylphosphinic anhydride, which boiled at 190–192° at 15 mm., and which showed a considerable tendency to sublime. The substance forms long feathery needles, which melt at 119–121°. The substance is rapidly hydrolyzed by water and titration of the aqueous solution gave the molecular weight of 170.5, against the theoretical value of 170.

Anal. Calcd. for $Me_2P(O)OP(O)Me_2$: P, 36.46. Found: P, 36.31.

Diethylphosphinic Anhydride.—Thiophosphoryl chloride (51 g.), diluted with one volume of absolute ether, was added slowly to ice-cooled solution of the Grignard reagent, prepared from 100 g. of ethyl bromide and 22 g. of magnesium, in 500 ml. of dry ether. The resulting mixture was refluxed for two hours and then was hydrolyzed with 200 g. of ice. Upon acidification with dilute sulfuric acid, the organic layer was separated and the aqueous layer was ex-

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[1] Kosolapoff and Watson, THIS JOURNAL, **73**, 4101 (1951).

[2] Kabachnik and Shepeleva, *Izvest. Akad. Nauk. S. S. S. R., otdel. khim. nauk.*, **No. 1**, 56 (1949).

[3] Strecker and Grossmann, *Ber.*, **49**, 63 (1916).

tracted with two 100-ml. portions of ether. After the evaporation of the solvent from the combined organic layer, the residue (crude diethylthiophosphinic acid) was taken up in 100 ml. of water and was cautiously treated with 30 ml. of 30% hydrogen peroxide. The precipitated sulfur was filtered off and the filtrate was stirred with an excess of freshly precipitated silver oxide, according to Collie's directions.[4]

The filtrate was concentrated to approximately 35 ml. and was mixed with two volumes of 95% ethanol, resulting in precipitation of the previously described silver diethylphosphinate; yield 28.5 g. (41.5%). The silver salt was converted to the free acid by treatment with 1:1 hydrochloric acid, filtration, evaporation to dryness and azeotropic drying with toluene. The free acid was an oil, whose freezing point was in the vicinity of −20°.

Treatment of the diethylphosphinic acid, in benzene, with the theoretical amount of phosphorus pentachloride (see the dimethyl analog, above) gave 47.5% (based on the silver salt) of diethylphosphinyl chloride, a colorless liquid, b.p. 102–104° at 15 mm. Plets[5] gives b.p. 79–81° at 15 mm., which appears to be much too low.

Treatment of diethylphosphinyl chloride (8.5 g.) with sodium ethoxide, prepared from 1.3 g. of sodium and 40 ml. of absolute ethanol, in benzene, as described above, gave 6 g. (67%) of ethyl diethylphosphinate, a colorless liquid, b.p. 93–95° at 14 mm., d^{25}_{4} 1.0022, n^{25}_{D} 1.4375.

Anal. Calcd. for $\mathrm{Et_2P(O)OEt}$: P, 20.63; *MR*, 39.6. Found: P, 20.49; *MR*, 39.3.

Heating 5 g. of diethylphosphinyl chloride with 5.35 g. of ethyl diethylphosphinate for 45 minutes to 145–160° gave 5.6 g. (69%) of diethylphosphinic anhydride, a viscous liquid, b.p. 186–188° at 14 mm., d^{23}_{4} 1.1053, n^{23}_{D} 1.4720; found, *MR* 57.2; calcd. *MR*, 57.0. The product hydrolyzed rapidly in water and titration of such a solution gave the molecular weight of 227.0, against the theoretical value of 226.2. Calcd. for $\mathrm{Et_2P(O)OP(O)Et_2}$: P, 27.31. Found: P, 27.23. Like the dimethyl analog, the anhydride reacts rapidly with alcohols at moderately elevated temperatures.

Attempted Preparation of Dimethyl-di-*n*-butylphosphinic Anhydride.—When 13 g. of ethyl di-*n*-butylphosphinate and 7.1 g. of dimethylphosphinyl chloride were heated for 45 minutes to 145–160°, normal evolution of ethyl chloride took place. Application of reduced pressure to the liquid residuum led to rapid crystallization of the material and on distillation two fractions were obtained, which corresponded to the two symmetric anhydrides: dimethylphosphinic anhydride and di-*n*-butylphosphinic anhydride, respectively. The sublimation of the former made a sharp separation of the fractions impossible, but no evidence for the unsymmetric anhydride could be detected in the boiling points or the physical constants of the products. Apparently, the unsymmetric anhydride disproportionates into the two symmetric forms very readily.

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[4] Collie, *J. Chem. Soc.*, **127**, 964 (1925).

[5] Plets, Dissertation, Kazan, 1938.

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Dimethyl N-(Phenyl-, 2-Pyridyl-, and 3-Phenylpropyl)-aminoacetals

BY IRVING ALLAN KAYE

The method previously described[1] could not be used for the preparation of compounds of structure, $\mathrm{R'RNCH_2CH(OCH_3)_2}$ (I), where R is phenyl or 2-pyridyl and R′ is hydrogen.

Though a vigorous reaction developed when dimethyl chloroacetal was heated to reflux with two equivalents of aniline in the absence of a solvent, only a tarry mass could be isolated. When repeated in toluene, or in cumene in the presence of potassium carbonate,[2] there was no evidence that any reaction had occurred.

Diethyl N-phenylaminoacetal has been prepared[3] in good yield from aniline and diethyl chloroacetal in the presence of sodium amide. Using a similar procedure, but substituting lithium amide for sodium amide and toluene for ether, both dimethyl N-phenylaminoacetal and dimethyl N-(2-pyridyl)-aminoacetal, were readily prepared.

Dimethyl N-benzyl-N-(2-pyridyl)-aminoacetal was synthesized by the aralkylation of dimethyl N-(2-pyridyl)-aminoacetal with benzyl chloride, using lithium amide as a condensing agent. An attempt to prepare the tertiary amine from 2-bromopyridine and dimethyl N-benzylaminoacetal in pyridine gave only tars; in toluene, in the presence of potassium carbonate,[2] no reaction was observed. From a reaction mixture of 2-benzylaminopyridine, dimethyl chloroacetal, lithium amide and toluene, there were obtained only unreacted starting materials.

Molar equivalents of dimethyl chloroacetal and 3-phenylpropylamine[4] in tri-*n*-propylamine gave only a 25% yield of dimethyl-N-(3-phenylpropyl)-aminoacetal; in the absence of solvent and using two moles of amine to one of acetal there was obtained a 43% yield. The hydrochloride of the product shows powerful, though transient, topical anesthetic properties. The other three acetals (I; R′ is H and R is phenyl or 2-pyridyl; R′ is 2-pyridyl and R is benzyl) were inactive in retarding the growth of sarcoma 180.[5]

Experimental[6]

Dimethyl N-Phenylaminoacetal.—To a stirred suspension of 64 g. of lithium amide in one liter of dry toluene there was added slowly 232.5 g. (2.5 moles) of aniline. When addition was complete, the reaction mixture was refluxed for 3.5 hours. During this time, the suspension changed into a purple-colored solution which soon deposited a tan solid with the simultaneous evolution of ammonia. Without interrupting the refluxing, 311.3 g. (2.5 moles) of dimethyl

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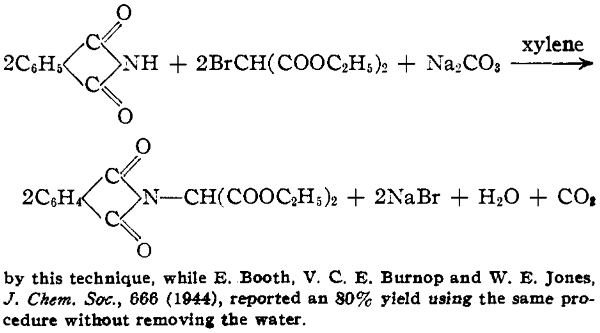
[1] I. A. Kaye and I. Minsky, THIS JOURNAL, **71**, 2272 (1949).

[2] A moisture trap was included in the set-up and the progress of the reaction was conveniently observed by noting the amount of water collected in this trap. When carbonates are used in reactions where acids are formed as by-products, yields are usually improved somewhat when the water which has formed in the reaction is removed from the reaction mixture in this fashion. For example, the yield of ethyl phthalimidomalonate, prepared by the following method, was 86% by this technique, while E. Booth, V. C. E. Burnop and W. E. Jones, *J. Chem. Soc.*, 666 (1944), reported an 80% yield using the same procedure without removing the water.



$$2\mathrm{C_6H_5}\!\left\langle\begin{matrix}\mathrm{C{=}O}\\ \\ \mathrm{C{=}O}\end{matrix}\right\rangle\!\mathrm{NH} + 2\mathrm{BrCH(COOC_2H_5)_2} + \mathrm{Na_2CO_3} \xrightarrow{\text{xylene}}$$

$$2\mathrm{C_6H_4}\!\left\langle\begin{matrix}\mathrm{C{=}O}\\ \\ \mathrm{C{=}O}\end{matrix}\right\rangle\!\mathrm{N{-}CH(COOC_2H_5)_2} + 2\mathrm{NaBr} + \mathrm{H_2O} + \mathrm{CO_2}$$

[3] A. Wohl and M. Lange, *Ber.*, **40**, 4727 (1907). The same compound and diethyl N-(2-pyridyl)-aminoacetal were described by R. G. Jones, E. C. Kornfeld, K. C. McLaughlin and R. C. Anderson, THIS JOURNAL, **71**, 4000 (1949), but there is some ambiguity as to which method of preparation they employed.

[4] A sample generously donated by Sharples Chemicals, Inc.

[5] These compounds were tested at The Sloan-Kettering Institute for Cancer Research, under the supervision of Dr. C. Chester Stock.

[6] All melting points are corrected; boiling points are not.