cholesterylmalonic acid and *i*-cholesterylacetic acid were slightly turbid at *p*H 7.6, but no precipitation occurred. Two other steroid acids, the 3-cholesterylacetic acid and the Δ^4-cholestene-6-acetic acid precipitated when the *p*H of their solutions was lowered to *p*H 7.6 and, therefore, were not used in the inhibition studies.

One ml. of a trypsin solution containing 0.1 mg. of crystalline trypsin and one ml. of the steroid acid solutions were mixed. Five ml. of the hemoglobin substrate solution[10] was added and the mixture digested. The volume of the digestion mixture was 1 ml. larger than the volumes used by Anson.[10] The volume of the blanks, also, was increased by one ml. The intensity of the color developed with the phenol reagent was read on a Coleman spectrophotometer at 650 mμ. The galvanometer readings of the blanks were not changed when the inhibitor acids were omitted.

A solution of 0.0008 milliequivalent of tyrosine was used as a reference standard. The color values of digestion products were calculated and the $10^4 \times (\mathrm{TU})^{\mathrm{HEM}}$ read from the standard curve.[10] The difference between the units found in crystalline trypsin and the units found in crystalline trypsin-inhibitor mixture was the inhibited trypsin units. The percentage of inhibition was calculated from the inhibited trypsin units and the units found in crystalline trypsin.

The following series of determinations were made:

FIG. 1.—The concentrations of crystalline trypsin and hemoglobin were kept constant and the concentration of the inhibitor acids varied.

TABLE I.—The concentration of the hemoglobin solution was varied, the trypsin and inhibitor concentrations were kept constant.[9]

TABLE II.—The concentration of trypsin was varied and the concentration of hemoglobin and inhibitor was kept constant.

TABLE III.—The trypsin activity of a mixture of 0.1 mg. of crystalline trypsin with 1 mg. of 3-cholesterylmalonic acid, respectively, with 1 mg. of *i*-cholesterylmalonic acid or with 1 mg. of *i*-cholesterylacetic acid, was determined. Then 1 mg. of calcium acetate was added to these mixtures and the trypsin activity assayed again.

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Association Phenomena in Some Organophosphorus Compounds

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The recent investigations of dialkyl phosphites, $(RO)_2POH$, by means of the parachor[1] and the Raman spectra,[2] appear to indicate that these substances exist in the form of dimers, or possibly larger aggregates, which are held together probably by hydrogen bonds which involve the singular oxygen atom of each molecule. Since the structure of the POH portion of the molecule in these esters is common among the organophosphorus compounds with the phosphorus atom in a lower oxidation state, including such compounds as phosphinous acids, R_2POH, phosphonous acids, RPO_2H_2, and the mono-esters of the latter class, it was of interest to attempt a verification of such aggregation by other means. Among the most direct methods is the determination of molecular weights by cryoscopic means.

Determination of molecular weights, in benzene solution, of typical dialkyl phosphite and monoalkyl phosphonite failed to show any significant departure from the strictly monomolecular structure. However, the molecular weight of a typical phosphonous acid, namely, benzenephosphonous acid, was shown to be, within the experimental error limits, that of a trimeric aggregate. It appears that the presence of a true hydroxyl is essential for the display of such aggregation among the phosphorus derivatives and that the frequently postulated tautomerically formed POH in substances analogous to the dialkyl phosphites is, apparently, devoid of hydrogen bonding capacity, at least in solution in benzene. The trimeric aggregation of the phosphonous acid indicates the possibility of a cyclic trimer, which may be used to explain the long-known thermal disproportionation of these acids into phosphines and phosphonic acids, *via* the over-all scheme

$$3RPO_2H_2 \longrightarrow RPH_2 + 2RP(O)(OH)_2$$

This reaction therefore may proceed by the way of rearrangement of the protons and of the oxygen atoms within the trimeric cycle, in such a way as to produce the maximum concentration of oxygen atoms at two of the three phosphorus atoms. This phenomenon is rather common in this class of substances, for many of its classical reactions, such as the Arbuzov–Michaelis isomerization, involve the approximation to the highest possible number of semi-polarly linked oxygen atoms at the central phosphorus atom.

The effects of the variation of the substituent radicals upon the extent of association in these substances is being studied further.

Experimental

Diethyl phosphite showed no significant deviation from the monomeric molecular weight in benzene solution in cryoscopic method. Calcd. for $(EtO)_2POH$: mol. wt., 138. Found: mol. wt., 141, 141, 143.

Monobutyl benzenephosphonite gave similar results. Calcd. for $C_6H_5P(O)(OC_4H_9)H$: mol. wt., 198. Found: mol. wt., 200, 201, 200.

Benzenephosphonous acid, however, gave consistently trimeric molecular weights. Calcd. for $(C_6H_5PO_2H_2)_3$: mol. wt., 426. Found: mol. wt., 406, 399.

The preparation of this acid deserves some description. Phenyldichlorophosphine yields rather unsatisfactory specimens of this acid upon conventional hydrolysis with water; the product invariably possesses the repulsive odor of phenylphosphine. However, when advantage is taken of the ready cleavage of esters of trivalent phosphorus derivatives by hydrogen halides, a very convenient preparation of the acid may be had. The dichlorophosphine is added, without external cooling, dropwise with stirring into five volumes of absolute ethanol and the hot solution is diluted with two volumes of water, boiled for five to ten minutes, and evaporated under an infrared lamp to incipient crystallization. Addition of two or three volumes of benzene and the removal of the residual water and alcohol by the azeotrope distillation, followed by concentration of the benzene solution to incipient crystallization, yield the pure benzenephosphonous acid in the form of shiny colorless platelets, which melt sharply at 86°, and which possess no detectable odor of the phosphine. Since the product has a higher melting point than the original preparations made many years ago by Michaelis (m. p. 70–71°), which were made by conventional aqueous hy-

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[1] Arbuzov and Vinogradova, *Izvest. Akad. Nauk S. S. S. R., otdel khim. nauk*, No. 6, 617 (1947).

[2] Arbuzov, Batuev and Vinogradova, *Doklady Akad. Nauk S. S. S. R.*, **54**, 603 (1946).

drolysis and crystallization from water, a check of the composition of the product was made by titration, using 0.1 *N* sodium hydroxide with phenolphthalein indicator. The product gave the neutralization equivalent of 142.2, against the theoretical value of 142.1.

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A New Synthesis of Phosphinic Acids

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In the course of the past fifty years a great number of esters of phosphonic acids have been prepared by the reactions of active organic halides either with trialkyl phosphites (equation 1), or with dialkyl sodiophosphites (equation 2).

$$(RO)_3P + R'X \longrightarrow R'P(O)(OR)_2 + RX \quad (1)$$
$$(RO)_2PONa + R'X \longrightarrow R'P(O)(OR)_2 + NaX \quad (2)$$

The rather obvious extension of the first reaction to the dialkyl esters of phosphonous acids, a reaction which yields monoalkyl esters of phosphinic acids, has been used in several instances after the original work of Arbuzov,[1] following equation (3).

$$RP(OR)_2 + R'X \longrightarrow RR'P(O)OR + RX \quad (3)$$

The main drawback of this reaction is the need for preparation of the dialkyl phosphonites, which are substances with rather disagreeable odors and which are subject to hydrolytic decomposition with great ease, thus resembling the trialkyl phosphites to a considerable degree.

The second possible synthesis of phosphinic derivatives *via* the alkali salts of monoalkyl phosphonites has been completely overlooked until this time. Since monoalkyl phosphonites may be expected to have considerable similarity to dialkyl phosphites, which have been very fruitfully employed for the syntheses of various phosphonates, the preliminary investigation of this second mode of synthesis of phosphinates was of appreciable interest. In addition, almost no useful information on the practical synthesis of monoalkyl phosphonites can be found in the literature. The meager mention that oily products obtained by partial hydrolysis of dialkyl phosphonites give analytical results which correspond to the monoesters is hardly a sufficient characterization of the class.[2]

It was felt that since phosphorus trichloride reacts smoothly with three (or more) moles of an alcohol yielding dialkyl phosphites according to equation (4)

$$PCl_3 + 3ROH \longrightarrow (RO)_2POH + RCl + 2HCl \quad (4)$$

it should be expected that the analogous trivalent halides, *i. e.* $RPCl_2$, should similarly yield the desired monoesters of phosphonous acids, according to equation (5)

$$RPCl_2 + 2ROH \longrightarrow RP(OR)OH + RCl + HCl \quad (5)$$

This expectation was realized without difficulty. It was noted, however, that the ethyl ester of benzenephosphonous acid is a rather unsatisfactory intermediate for these reactions; in the course of distillation this substance develops extremely foul odor of a phosphine, which makes it undesirable for any large scale syntheses. This is analogous to the behavior of diethyl phosphite mentioned earlier.[3] Once again recourse to the butyl ester solved the difficulty and monobutyl benzenephosphonite was obtained in excellent yields as an essentially odorless substance, without recourse to extreme vacuum in the distillations. As expected, the ester reacted smoothly with metallic sodium and the sodio derivative reacted with active organic halides, yielding monoalkyl esters of phosphinic acids according to equation (6).

$$RP(OR)OH + Na \longrightarrow H + RP(OR)ONa \xrightarrow{R'X} RR'P(O)OR + NaX \quad (6)$$

The procedure does not eliminate completely the handling of malodorous substances, since the dichlorophosphines necessary for the preparation of the monoalkyl esters still must be manipulated. However, the handling of the malodorous dialkyl phosphonites is eliminated and the reaction may offer some further advantages over the scheme of reaction (3).

Experimental

Phenyldichlorophosphine was prepared by Dye's useful method[4]; the product boiled at 94° at 12 mm. and was obtained in 60–65% yields by refluxing for two hours a mixture of two moles of benzene with one mole of phosphorus trichloride and one-third of a mole of aluminum chloride. The phosphorus oxychloride variant of Dye's method was used to remove aluminum.

Addition of phenyldichlorophosphine to dry ethanol (two to five moles) with ice-water cooling, followed by vacuum distillation gave monoethyl benzenephosphonite of unsatisfactory quality; the product boiled at 98–99° at 1 mm. but possessed such fearful odor resembling that of phenylphosphine, as to be useless for practical work.

Addition of phenyldichlorophosphine to dry butanol (best mole ratio was found to be three moles of the alcohol per mole of phenyldichlorophosphine) at 5–10° with good stirring, followed by evacuation of the vessel with stirring at room temperature for two or three hours, gave upon distillation of the residual colorless liquid 70–75% yields of monobutyl benzenephosphonite, as a colorless, almost odorless liquid (the odor is reminiscent of that of dibutyl phosphite), which boiled sharply at 149° at 3 mm.; n^{29}_{D} 1.5045, d^{29}_{4} 1.0695; *MR* found, 54.9; calcd., 54.3 (using 4.5 for atomic refractivity of phosphorus, from the average value of this constant in dialkyl phosphites; there are no data on atomic refractivities among the compounds of this series). Calculated for $C_6H_5P(OC_4H_9)OH$: P, 15.65. Found: P, 15.70, 15.75.

The ester (39.0 g.) in 200 ml. of toluene was treated with 4.4 g. of sodium and the mixture was gently warmed with stirring for four hours until hydrogen evolution ceased. The minute residuum of unreacted sodium was removed and the mixture was treated over one hour with 27.0 g. of *n*-butyl bromide. After refluxing with stirring for three hours, filtering the precipitate of sodium bromide and

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(1) Arbuzov, Dissertation, Kazan, 1914; *J. Russ. Phys.-Chem. Soc.*, **42**, 395 (1910), *C. A.*, **5**, 1397 (1911).

(2) Kohler and Michaelis, *Ber.*, **10**, 816 (1877).

(3) Kosolapoff, THIS JOURNAL, **72**, 4291 (1950).

(4) Dye, *ibid.*, **70**, 2595 (1948).