with alcohols. Regardless of the complete mechanism, however, the difluoromethylene group was again indicated as the primary point of attack.

Experimental

Reaction of Polyfluoroalkyl Tertiary Amines with Alcohols.—1-(2-Chloro-1,1,2-trifluoroethyl)-piperidine (59.0 g.) was added in small portions to 98% isopropyl alcohol (41.6 g.) in a polyethylene bottle. The mixture was shaken after each addition and cooled in a water-bath during the entire time (45 min.). After standing overnight, the mixture was heated at 95° while a stream of dry nitrogen was bubbled through under anhydrous conditions. The effluent gases were passed through a sodium hydroxide solution to remove hydrogen fluoride and thence to a trap chilled in Dry Ice–acetone slush. A portion of the isopropyl ether collected in the trap was lost through accident, but a small amount (6 ml.) was retained. Additional ether (11 ml.) was obtained by distillation of the mixture remaining in the bottle. The main fraction (39.0 g.) distilled at 74° and 0.5 mm. This corresponds to 74% theoretical yield of 1-(chlorofluoroacetyl)-piperidine, which melted at 34–35° after recrystallization from acetone.

Anal. Calcd. for $C_7H_{11}ClFNO$: C, 46.80; H, 6.17; N, 7.80. Found: C, 46.79; H, 6.52; N, 6.99.

N-(2-Chloro-1,1,2-trifluoroethyl)-diethylamine (118.7 g.) was added in small portions to absolute ethanol (53 g.) with agitation and cooling as in the previous reaction. Distillation of the reaction mixture gave low-boiling fractions containing hydrogen fluoride, diethyl ether, and ethanol. A larger fraction (66.2 g.), distilling at 47° and 0.7 mm., was later identified as N,N-diethyl-α-chloro-α-fluoroacetamide. This is equivalent to a 63% theoretical yield.

Reaction of Polyfluoroalkyl Tertiary Amines with Thiols.—1-(2-Chloro-1,1,2-trifluoroethyl)-piperidine (27.8 g.) reacted smoothly with ethane thiol (18.5 g.) when the mixture was held at about 30°. The two liquid layers formed (after 2 hr.) were both heavier than water. After washing the lower layer with water, distillation gave a small amount of ethyl chlorofluorothiolacetate (2.6 g.), b.p. 38° at 2 mm., $n^{25}D$ 1.4680, d^{25}_4 1.2587.

Anal. Calcd. for C_4H_6ClFOS: C, 30.70; H, 3.83. Found: C, 30.75; H, 4.03.

A limited examination of both layers failed to establish the presence of diethyl sulfide as might have been expected by analogy to the reaction with alcohols.

1-(2-Chloro-1,1,2-trifluoroethyl)-piperidine (80.8 g.) and butane thiol (72.0 g.) reacted under the same conditions as when ethane thiol was used. Distillation of the washed lower layer gave butyl chlorofluorothiolacetate (7.0 g.), b.p. 43° at 0.3 mm., $n^{25}D$ 1.4668, d^{25}_4 1.175. Heating this compound with aniline formed butane thiol and the solid derivative, N-phenyl-α-chloro-α-fluoroacetamide, m.p. 81–82°.

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[CONTRIBUTION FROM VENEREAL DISEASE EXPERIMENTAL LABORATORY, U. S. PUBLIC HEALTH SERVICE, SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF NORTH CAROLINA]

Synthesis of Phosphanilic Acid and Related Compounds[1]

BY G. O. DOAK AND LEON D. FREEDMAN

The *m*- and *p*-isomers of both nitrobenzenephosphonic acid and bis-(nitrophenyl)-phosphinic acid are readily reduced to the corresponding amino derivatives by means of Raney nickel and hydrogen at 40 lb. pressure. The corresponding hydroxy derivatives, none of which have been previously described, are obtained from the amino compounds by diazotization with ethyl nitrite and subsequent decomposition of the diazonium salts. *o*-Aminobenzene-phosphonic acid was prepared by the action of aqueous ammonia on *o*-bromobenzenephosphonic acid in the presence of cuprous oxide.

There is evidence that phosphanilic acid and certain of its derivatives have considerable bactericidal activity.[2] Research on these compounds has been hindered by a lack of convenient synthetic methods. With none of the procedures has it been found possible to prepare a wide variety of phosphonic acids.

A recent communication[3] from this Laboratory has described a new synthesis of arylphosphonic and diarylphosphinic acids by the reaction between diazonium fluoborates and phosphorus trichloride in organic solvents. This method makes readily available a wide variety of organophosphorus compounds which hitherto have been difficult if not impossible to prepare.

The present paper describes the preparation of several amino and hydroxy substituted arylphosphonic and phosphinic acids. The amino acids were readily prepared, following the procedure of Arnold and Hamilton,[4] by catalytic reduction of the corresponding nitro acids. We have been unable to obtain *o*-nitrobenzenephosphonic acid by our general procedure. Accordingly, the desired *o*-amino compound was prepared from *o*-bromobenzenephosphonic acid by the procedure described by Limaye and Bhide[5] for the corresponding para isomer. Because of the properties of the ortho compound it was found necessary to modify the isolation procedure. The hydroxy acids were obtained from the corresponding amino acids by diazotization with ethyl nitrite and subsequent decomposition of the resulting diazonium salts. The compounds prepared together with their analyses, yields and m.p.'s are listed in Table I.

Experimental

***p*-Aminobenzenephosphonic Acid (Phosphanilic Acid).**—Either *p*-nitrobenzenephosphonic acid or the corresponding hemi-potassium salt[6] was suspended in water and sufficient 10% potassium hydroxide added to give a clear solution. The *p*H of this solution should be approximately 6.7; if the *p*H was above 8, the reduction was slow and incomplete. Raney nickel was added and the compound reduced at 40 pounds pressure. The addition of a few drops of 10% chloroplatinic acid materially increased the rate of reduction of all nitro phosphonic and phosphinic acids. The catalyst was removed and the solution acidified with acetic acid whereupon crystalline phosphanilic acid separated from

(1) Presented before the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., September, 1951.

(2) H. Bauer and S. M. Rosenthal, *U. S. Public Health Rep.*, **54**, 2093 (1939); M. I. Smith, E. W. Emmart and B. B. Westfall, *J. Pharmacol. Exp. Therap.*, **74**, 163 (1942); U. K. Kanitkar and B. V. Bhide, *Current Sci., (India)*, **16**, 223 (1947); G. S. Pendse and B. V. Bhide, *ibid.*, **17**, 125 (1948).

(3) G. O. Doak and L. D. Freedman, THIS JOURNAL, **73**, 5658 (1951).

(4) G. B. Arnold and C. S. Hamilton, *ibid.*, **63**, 2637 (1941).

(5) M. S. Limaye and B. V. Bhide, *J. Indian Chem. Soc.*, **25**, 251 (1948).

(6) This salt, admixed with potassium chloride, is obtained in the procedure for isolating the free acid, as previously described.[3] The use of this salt for reduction avoids the isolation of the soluble acid.

TABLE I

$RC_6H_4PO_3H_2$ R =	Yield, %	M.p.,[a] °C.	Formula	P analyses, % Calcd.	Found	Neutral equivalent[b] Calcd.	Found
o-NH_2[c]	40	199–200	$C_6H_8NO_3P$	17.90	17.44	86.6	87.7
m-NH_2[d,e]	82[f]	>300	$C_6H_8NO_3P$	17.90	17.44	86.6	86.6
p-NH_2[g,h]	82[f]	245[i]	$C_6H_8NO_3P$	17.90	17.41	86.6	86.6
m-OH	29	149–151	$C_6H_7O_4P$	17.79	17.44	87.0	86.6
p-OH	47	177	$C_6H_7O_4P$	17.79	17.28	87.0	[j]
o-Br	41	199–201	$C_6H_6BrO_3P$	13.07	13.23	118.5	118.7
$(RC_6H_4)_2PO_2H$ R =							
m-NH_2[k,l]	70[f]	287–289 dec.	$C_{12}H_{13}N_2O_2P$	12.48	12.07	248.2	246.1
p-NH_2[m,n]	95[f]	Softens 270	$C_{12}H_{13}N_2O_2P$	12.48	12.12	248.2	250.6
m-OH	31	226–229	$C_{12}H_{11}O_4P$	12.38	12.01	250.2	250.9
p-OH	5	213–215	$C_{12}H_{11}O_4P$	12.38	12.03	250.2	252.6[o]
o-Br	12	268.5–269.5	$C_{12}H_9Br_2O_2P$	8.24	8.10	376.0	369.7

[a] Melting points were taken as previously described; *cf.* ref. 3. [b] The indicator used for the primary acids was thymolphthalein; the indicator used for the secondary acid was phenolpthalein. [c] Calcd.: N, 8.09. Found: N, 8.06. [d] Previously prepared by A. Michaelis and E. Benzinger, *Ann.*, **188**, 275 (1877), and other workers. Highest previously reported m.p., dec. 290°. [e] Calcd.: N, 8.09. Found: N, 8.09. [f] Based on the nitro acid. [g] Previously reported by H. Bauer, ref. 7, and other workers. [h] Calcd.: N, 8.09. Found: N, 8.03. [i] The dark blue liquid reported by Bauer was not observed. [j] A sharp end-point could not be obtained with thymolphthalein. [k] Previously prepared by C. Dörken, *Ber.*, 21, 1505 (1888); m.p., dec. 276°. [l] Calcd.: N, 11.29. Found: N, 11.24. [m] Previously prepared by G. M. Kosolapoff, THIS JOURNAL, **70**, 3465 (1948), and other workers. Highest previously reported m.p., 242–243°. [n] Calcd.: N, 11.29. Found: N, 11.33. [o] This result was obtained by using the mixed indicator of T. Ma and G. Zuazaga, *Ind. Eng. Chem., Anal. Ed.*, **14**, 280 (1942).

solution. The crystals were thoroughly washed with cold water and dried *in vacuo*. The compound, thus obtained, was colorless and gave satisfactory analyses without purification.[7] The yield from the hemipotassium salt was 53%, based on *p*-nitrobenzenediazonium fluoborate.

***m*-Aminobenzenephosphonic Acid.**—The method of reduction and isolation of this compound was similar to that described for the *p*-isomer.

Bis-(*p*-aminophenyl)-phosphinic Acid.—Bis-(*p*-nitrophenyl)-phosphinic acid was dissolved in 10% sodium hydroxide solution and the *p*H adjusted to approximately 5 with acetic acid. The subsequent reduction and isolation of the amino acid was similar to that described for the primary acid.

Bis-(*m*-aminophenyl)-phosphinic acid was obtained in a similar manner.

***o*-Bromobenzenephosphonic Acid and Bis-(*o*-bromophenyl)-phosphinic Acid.**—These compounds were readily obtained from *o*-bromobenzenediazonium fluoborate by the general method described previously.[3] The following slight modification effected a better separation of the two acids. After the reaction mixture was steam distilled, the residual liquid in the flask was filtered hot. The secondary acid remained on the filter and was purified by precipitation from alkaline solution followed by recrystallization from 80% aqueous ethanol. The primary acid was then isolated and purified by Procedure A as previously described.[3]

***o*-Aminobenzenephosphonic Acid.**—*o*-Bromobenzenephosphonic acid (12 g.) and 9 g. of freshly-prepared cuprous oxide[8] was added to 200 ml. of aqueous ammonia (d. 0.90) in a 2-necked flask equipped with a sealed stirrer and a reflux condenser. The mixture was stirred and heated on a water-bath for 18 hours. Hydrogen sulfide was then passed in to precipitate copper sulfide which was removed by filtration. The filtrate was acidified with concentrated hydrochloric acid, evaporated to 5 ml. and cooled. The ammonium chloride, which precipitated, was filtered off; the filtrate was evaporated on a water-bath and finally dried *in vacuo* over sodium hydroxide and calcium chloride. The resulting solid was boiled with 50 ml. of absolute alcohol and the mixture cooled. White crystals of *o*-aminobenzenephosphonic acid were obtained, admixed with a small amount of ammonium chloride. For purification the solid was dissolved in 300 ml. of hot water, and 250 ml. of alcohol was added. On standing colorless crystals of the pure amino acid separated from solution.

o-Aminobenzenephosphonic acid differs materially from the *m*- and *p*-isomers in its properties. It is soluble in water and dilute hydrochloric acid. We have been unable to prepare an acetyl derivative. The amino group can be diazotized and the diazonium salt coupled with β-naphthol to produce a red dye. When treated with bromine water, *o*-aminobenzenephosphonic acid gives a quantitative yield of tribromoaniline. This result was anticipated from the work of Kosolapoff,[9] who obtained tribromoaniline from a mixture which he believed to consist of the *o*- and *m*-isomers.

***p*-Hydroxybenzenephosphonic Acid.**—*p*-Aminobenzenephosphonic acid (12 g.), suspended in 50 ml. of water and 17.5 ml. of concentrated hydrochloric acid, was diazotized at 0° with ethyl nitrite. When a starch–iodide test remained positive for five minutes, the solution was warmed until the evolution of nitrogen was completed. The solution was then concentrated to a small volume when the crude acid separated from solution. It was recrystallized from 6 *N* hydrochloric acid.

***m*-Hydroxybenzenephosphonic Acid, Bis-(*p*-hydroxyphenyl)-phosphinic Acid and Bis-(*m*-hydroxyphenyl)-phosphinic Acid.**—These compounds were obtained by the method used for the preceding compound. In the case of bis-(*p*-hydroxyphenyl)-phosphinic acid, the decomposition of the diazo solution yielded a considerable amount of gummy material, which was removed mechanically.

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(7) *Cf.* H. Bauer, THIS JOURNAL, **63**, 2137 (1941).

(8) C. Weygand, "Organic Preparations," Interscience Publishers, Inc., New York, N. Y., 1945, p. 296.

(9) G. M. Kosolapoff, THIS JOURNAL, **71**, 4021 (1949).