253. *Reactions of Carboxylic Acid–Phosphorus Trihalide Systems. Part II.*[1] *Salicylic Acid.*

By J. A. Cade and W. Gerrard.

In the presence of tertiary base, the bicyclic phosphorochloridite (I; R = Cl), formed by interaction of salicylic acid and phosphorus trichloride, gives with acids, such as acetic, anhydride and the hydrogen phosphite (II), but with benzoic acid a benzoyloxy-derivative is obtained.

With hydrogen chloride, the chloridite (I; R = Cl) gives salicylic acid and phosphorus trichloride; the hydrogen phosphite (II) behaves similarly. The butoxy-compound (I; R = OBu) gives, remarkably, the acid and butyl phosphorodichloridite.

Interaction of salicylic acid and a tervalent phosphorus halide appears to involve preliminary attack on the phenolic hydroxyl group, even in the presence of base.

With a tervalent phosphorus compound containing one or more P–Cl links, aliphatic acids such as acetic acid in the presence of pyridine gave acyl chloride (subsequently rapidly converted into anhydride) in the primary step, whereas aromatic acids such as benzoic acid gave compounds containing one or more aroyloxy-groups attached to phosphorus.[1] Hence, the structure of the bicyclic phosphorochloridite (I; R = Cl) formed by interaction of salicylic acid and phosphorus trichloride in the absence or presence of pyridine was elucidated, and likewise that of its butoxy-derivative [2] (I; R = OBu^n). Similarities with the bromides have also been observed.

On account of its ease of preparation and high stability [compared with that of dibutyl phosphorochloridite $(BuO)_2PCl$], we investigated the use of the chloridite (I; R = Cl) as a general reagent to extend our studies on the behaviour of carboxylic acids towards a single active chlorine atom attached to tervalent phosphorus. This substance behaves

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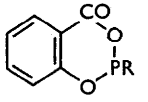
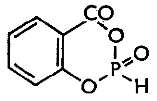
[1] The paper entitled " Interaction of Carboxylic Acids with Phosphorus Trichloride, or Butyl Phosphorodichloridite, or the Chloridite in the Absence and in the Presence of Pyridine," *J.*, 1954, 2030, is regarded as Part I.

[2] Cade and Gerrard, *Chem. and Ind.*, 1954, 402.

superficially like a dialkyl phosphorochloridite, but is not such a good substitute as had been hoped, chiefly because of the nature of the cyclic hydrogen phosphite (II) formed in reactions with acids of normal reactivity, but partly also because of the intractability and sensitivity of the aroyloxy-derivatives (mixed anhydrides) formed with acids such as benzoic.

(I)





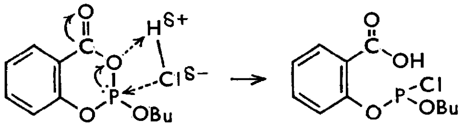
(II)

With acetic acid (1 mol.) in the absence of base, the chloridite (I; R = Cl) gave hydrogen chloride as well as the phosphite (II) and acetyl chloride. With pyridine (1 mol.) and the acid (2 mols.) it gave pyridinium chloride, the hydrogen phosphite (II), and acetic anhydride, but not cleanly as in the corresponding experiment with dialkyl phosphorochloridites, for some acid was recovered. Other aliphatic acids of ordinary reactivity behaved similarly, yields of alkanoic anhydride decreasing with increase in molecular weight.

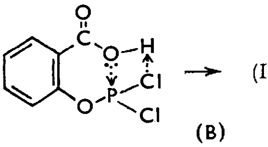
Probably on account of ease of dehydration, the cyclic compound (II) was not obtained pure despite many attempts at recrystallisation from a variety of solvents; ultimately salicylic acid was always formed. It was evident that the anhydride bridge was retained, since a freshly prepared sample reacted readily with one equivalent of aniline, to give a compound which on treatment with cold water gave salicylanilide in high yield.

Equimolar quantities of benzoic acid, base, and chloridite (I; R = Cl) in a solvent gave the hydrochloride of the base and the benzoyloxy-derivative (I; R = OBz).

Like trialkyl phosphites, acyl alkyl phosphites [1] react rapidly with anhydrous hydrogen chloride, deacylation giving acyl halide and preceding dealkylation in mixed acyl alkyl phosphites.[3] However, the chloridite (I; R = Cl) with hydrogen chloride gave unexpectedly salicylic acid and phosphorus trichloride. Similarly, the phosphite (II) gave the same acid and a substance, presumably initially $Cl_2P(O)H$, which quickly degraded. More remarkably, the butoxy-derivative (I; R = OBu^n) with hydrogen chloride gave salicylic acid and butyl phosphorodichloridite with no indication of butyl chloride. This observation, together with the discrepancy between the observed and the calculated values of the molar refraction, indicates considerable delocalisation of the electron pair on the phosphorus, favouring preferential protonation of the oxygen atom of the anhydride bridge, the further decrease in electron density on the phosphorus then hindering dealkylation, just as it does in a dialkyl phosphorochloridite [4] (cf. A).



(A)



(B)

Tribenzoyl phosphite with hydrogen chloride gives phosphorus trichloride, benzoic acid, and a small amount of benzoyl chloride, but we believe the latter to be produced indirectly by back-reaction of trichloride and acid produced in the primary process, the latter behaving in the absence of base as an acid of " ordinary " reactivity.

Without base, reactions of carboxylic acids with phosphorus halides are slower than those of alcohols and phosphorus halides. Even without base, salicylic acid forms aroyl phosphite whereas benzoic acid does not, so from these two facts we believe that initial attack on salicylic acid by phosphorus trichloride occurs at the phenolic hydroxy-group.

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[3] Cade, Thesis, London, 1955.

[4] Gerrard, Isaacs, Machell, Smith, and Wyvill, *J.*, **1953**, 1920.

Then, in terms of the " four-centre " transition state which we envisage for the systems,[1] the proximity of the resulting aroyl phosphorodichloridite group to the carboxyl group must constrain the system into an orientation of the reactive centres favouring ring closure (cf. B). In the presence of base, reactions in both alcohol and acid are very rapid, and stronger bonding of the base with the carboxyl group than with the hydroxyl group is likely. Therefore, with base, the carboxyl group could be the site of initial attack by the trichloride.

We tested this by interaction of the chloridite (I; R = Cl) with salicylic acid and pyridine in ether, using two equivalents of the base so that competition for it by the carboxyl group would not be the decisive factor. The product was expected to be either the salicyloyloxy-derivative (I; R = *o*-$HO{\cdot}C_6H_4{\cdot}CO$) or the *o*-carboxyphenoxy-derivative (I; R = *o*-$HO_2C{\cdot}C_6H_4{\cdot}O$). Methylation of the product, followed by mild hydrolysis, gave methyl salicylate with no indication of *o*-methoxybenzoic acid, showing that the latter product had been formed. Thus even in the presence of base, the hydroxyl group appears to undergo initial attack.

EXPERIMENTAL

After completion of the initial reactions, all operations were conducted at a temperature and in a manner designed to minimise subsequent secondary reactions.

Materials.—Solvents were dried over P_2O_5 and distilled, and reagents were purified.

Analysis.—Chlorine was determined by the Volhard method which was complicated by formation of a violet colour from salicylic acid with the ferric alum indicator. This could be suppressed without affecting the titre either by saturating the solution to be titrated with sulphur dioxide or by conducting titrations in concentrated nitric acid.

Interaction of Salicylic Acid and Phosphorus Trihalides.—(*a*) [5] The acid (13·8 g.), toluene (15 c.c.), and phosphorus trichloride (15·0 g., 1·1 mol.) were heated under reflux until evolution of hydrogen chloride practically ceased (3 hr.). Distillation gave a forerun and 2-chloro-4-oxo-1,3-dioxa-2-phosphanaphthalene (I; R = Cl) (14·0 g., 69%), b. p. 129—132°/14 mm. (Found: Cl, 17·5; P, 15·7. Calc. for $C_7H_4O_3ClP$: Cl, 17·55; P,15·4%), which formed large yellow rhombohedra.

Similarly from the acid (13·8 g.) and phosphorus tribromide (30 g., 1·1 mol.) in toluene (15 c.c.), 2-*bromo*-4-*oxo*-1,3-*dioxa*-2-*phosphanaphthalene* (I; R = Br) (8·45 g., 34·2%), b. p. 143°/9 mm. (Found: P, 12·95; Br, 33·6. $C_7H_4O_3PBr$ requires P, 12·55; Br, 32·4%), was obtained.

(*b*) The acid (13·8 g.) and pyridine (15·8 g., 2 mols.) in ether (50 c.c.) were added to the trichloride (13·8 g., 1 mol.) in ether (100 c.c.) at −10°. Precipitated pyridine hydrochloride (23·5 g.) was separated, washed with ether, and dried (Found: Cl, 0·194 g.-ion; C_5H_5N, 0·198 g.-mol.). The filtrate gave, on removal of solvent at 20°/15 mm., a residue (19·0 g.) from which the chloridite (I; R = Cl) (11·5 g. from 13·5 g., 85%) was obtained by distillation (Found: Cl, 17·4; P, 15·6%).

Preparation of 2-*Butoxy*-4-*oxo*-1,3-*dioxa*-2-*phosphanaphthalene* (I; R = BuO).—(*a*) Butan-1-ol (3·7 g.) and pyridine (3·95 g.) in ether (50 c.c.) were added to the chloridite (10·1 g.) in ether (50 c.c.) at −10° with stirring, and left for 1 hr. The *product* (11·1 g., 93%), b. p. 99—100°/0·03 mm., n_D^{20} 1·5250, d_4^{20} 1·191 (Found: $[R_L]_D$, 61·80; C, 55·0; H, 5·9; P, 13·15%. $C_{11}H_{13}O_4P$ requires $[R_L]_D$, 60·52; C, 55·0; H, 5·4; P, 12·9%), and base hydrochloride (5·65 g., 98%) (Found: Cl, 30·35; C_5H_5N, 67·8%) were obtained as in the preparation of the chloridite. Reversing the order of addition did not significantly affect the yield.

The same ester was obtained when an equivalent amount of the bromidite was used in place of the chloridite.

(*b*) *n*-Butyl phosphorodichloridite (8·8 g., 1 mol.), added in ether (50 c.c.) to salicylic acid (6·9 g., 1 mol.) and pyridine (7·9 g., 2 mol.) in ether (100 c.c.) at −10°, gave the ester (I; R = OBu^n) (86%), b. p. 97—99°/0·02—0·03 mm., n_D^{20} 1·5250 (Found: C, 55·15; H, 5·75; P, 12·95%), and base hydrochloride.

This substance (2·5 g.) with ice-cold water afforded white crystals after 30 min. The mixture

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[5] Cf. Young, *J. Amer. Chem. Soc.*, 1952, **74**, 1672.

was treated with sodium hydrogen carbonate solution and ether (25 c.c.) at 0°. Acidification of the aqueous layer gave salicylic acid (1·2 g., 84%), m. p. 158—159°. The dried ether solution gave an oil (0·6 g.) on evaporation at 10 mm. (Found: P, 11·9%).

Interaction of the Chloridite (I; R = Cl) *and Acetic Acid.*—The acid (7·25 g., 1 mol.) was added rapidly to the molten (50°) chloridite (24·9 g., 1 mol.) and the whole was shaken. No heat was developed. The outlet of the vessel was connected through a cold trap (—80°) to absorption tubes containing potassium hydroxide. White crystals separated (20 min.) and the mixture eventually solidified. Volatile matter was removed at 20°/15 mm., then at 20°/0·1 mm., through the cold trap and absorption tubes. Distillation (with a following absorption tube) of the contents of the trap gave acetyl chloride (5·5 g., 58%), b. p. 50—52° (Found: Cl, 46·1. Calc. for C_2H_3OCl: Cl 45·2%), impure acetic acid (1·0 g., 13·8%), b. p. 112—117° (Found: equiv., 59·1; Cl, 1·2%), and a residue (0·3 g.). The absorption tubes contained together 0·0062 g.-ion of Cl^- (5·1% of total). The primary residue (24·0 g.) was an off-white solid, m. p. 92—124°, smelling of acetic acid (Found: P, 16·2; Cl, 1·1%). A portion (10 g.) was dissolved in chloroform (20 c.c.), and heptane (20 c.c.) was added. Crystals of salicylic acid (2·2 g.), m. p. 158—159°, separated overnight.

(*b*) The acid (6·0 g.) and the chloridite (20·25 g.) in benzene (100 c.c.) gave during 3 days large white crystals (8·5 g.) which were separated, washed by decantation, and dried at 20°/0·1 mm.; they had m. p. 120—135° (Found: P, 17·6%). This solid (1·85 g.) in ether (30 c.c.) was treated with aniline (0·9 g.) and after 2 hr. ether was removed and cold dilute sodium carbonate solution was added. Salicylanilide (1·5 g., 70%) was filtered off, washed with water, and dried (m. p. and mixed m. p. 135°). Another sample of the solid (1·8 g.) gave, with cold water, salicylic acid (1·2 g., 88%), m. p. 159°. Volatile products of the primary reaction included hydrogen chloride, acetyl chloride, and acetic acid.

Interaction of the Chloridite (I; R = Cl) *with Carboxylic Acids and Pyridine.*—The chloridite (20·25 g., 1 mol.) in ether (50 c.c.), added dropwise to propionic acid (14·8 g., 2 mol.) and pyridine (7·9 g., 1 mol.) in ether (100 c.c.) at —10°, gave pyridinium chloride (9·8 g., 85%) (Found: Cl, 30·5; C_5H_5N, 67·4%). The filtrates, after evaporation of solvent at 20°/15 mm. and separation of volatile matter at 30°/0·05 mm., gave a residue (18 g.). Attempted distillation gave a fraction (0·9 g.), b. p. 120°/0·05 mm., and an undistillable viscous residue which crystallised (12·8 g., 85%). This was 4-*oxo*-1,3-*dioxa*-2-*phosphanaphthalene* 2-*oxide* (II) (Found: P, 16·1. $C_7H_5O_4P$ requires P, 16·85%). A portion recrystallised from benzene had m. p. 97—100° (Found: P, 17·5%). The contents of the cold trap afforded, on repeated distillation, propionic anhydride (10·7 g., 81%), b. p. 62—65°/15 mm. (Found: equiv., 65·2. Calc.: equiv., 65·0), and a mixture of acid and anhydride.

Acetic, butyric, and trimethylacetic acid gave by the same procedure the respective anhydrides (71, 60, and 40·4% yields) and recovered acid, together with the hydrogen phosphite (II) of variable purity. Attempts, including low-temperature recrystallisation, failed to provide the pure compound.

The products obtained in the same way from crotonic acid (8·6 g.), pyridine (3·95 g.), and the chloridite (10·13 g.) were base hydrochloride (5·55 g., 96%), recovered acid (1·15 g., 13·4%), m. p. 70—72° (Found: equiv., 85·7. Calc.: equiv., 86·0), impure anhydride (3·15 g., 41%), b. p. 50—72°/0·005 mm. (Found: equiv., 78·2. Calc.: equiv., 77·1), and an unidentified compound [not (II)] (4·4 g.), m. p. 154—157° (Found: P, 13·95%). In another experiment this compound (3·3 g.) had m. p. 157—158° (Found: P, 14·5%); on recrystallisation from acetic anhydride (1·1 g. from 1·7 g.) it had m. p. 158—159° (Found: P, 14·6%).

Benzoic acid (6·1 g., 1 mol.), pyridine (3·95 g.), and the chloridite (10·15 g., 1 mol.) gave by a similar procedure 2-*benzoyloxy*-4-*oxo*-1,3-*dioxa*-2-*phosphanaphthalene* (I; R = OBz), m. p. 107—110° (Found: P, 10·85. $C_{14}H_9O_5P$ requires P, 10·8%), but the yield (6·8 g., 47·2%) was reduced by co-precipitation with the base hydrochloride from ether. With benzene as solvent, a nearly quantitative yield of this compound was obtained, but of inferior quality. The product was very sensitive to heat and moisture, and was not improved by recrystallisation. Sublimation at 120°/0·02 mm. gave phenyl salicylate, contaminated with a phosphorus compound.

Interaction of Hydrogen Chloride and Phosphorus Esters.—(*a*) The dried gas was passed into the chloridite (I; R = Cl) (20·25 g.) in ether (50 c.c.) at 0° in a flask, the outlet of which was connected to a cold trap (—80°). Crystals separated (10 min.) and after 1 hr. the trap contained a few droplets. Volatile matter from the trap and from the reaction mixture was removed at 20°/15 mm. *via* an absorption tower containing moist glass rods and potassium hydroxide pellets (Found: P, 0·0205 g.-atom). Salicylic acid (6·1 g., 44·2%) was filtered off (m. p. and mixed m. p. 157—159°) (Found: equiv., 136·9). On attempted distillation the filtrate decomposed with evolution of hydrogen chloride.

In another experiment, after hydrogen chloride had been passed, volatile products were removed at 25°/0·01 mm.) into a trap (90° K) from which phosphorus trichloride (2·2 g., 16%) was obtained by distillation.

(*b*) The solid (3·7 g., 0·02 mol.) obtained by interaction of acetic acid (2·4 g.), pyridine (1·6 g.), and the chloridite (4·04 g.), as described above, was degassed at 50°/0·005 mm. for 2 hr. and dissolved in ether (20 c.c.). Hydrogen chloride was passed into the solution. White needles were precipitated. After 30 min. volatile matter was removed at 20°/10 mm. Treatment of the residue with warm benzene (20 c.c.) dissolved the crystals, leaving a water-soluble, unstable syrup (1 g. after washing with benzene and degassing at 20°/0·1 mm.) (Found: P, 0·0078 mole; Cl, 0·011 g.-ion). The benzene solutions yielded, on evaporation, salicylic acid (2·6 g., 93%), m. p. 158—160° (Found: equiv., 137·0). In absence of a solvent reaction was slower.

(*c*) Hydrogen chloride was passed into the butyl ester (I; R = OBu^n) (26·2 g.) in ether (100 c.c.) at 0° and after 2 hr. volatile matter was removed at 15 mm. and then at *ca.* 50°/0·005 mm. and trapped (90° K) in two lots. The less volatile portion (9·2 g.) gave, on distillation, butyl phosphorodichloridite (*ca.* 5 g., 26%), b. p. 52—54°/16 mm. (Found: Cl, 39·04. Calc. for $C_4H_9OCl_2P$: Cl, 40·55%). This (3·85 g.) was identified by conversion with butanol (3·26 g.) and pyridine (3·48 g.) in ether into tributyl phosphite (5 g., 91%), b. p. 125—127°/14 mm., n_D^{20} 1·432 (Found: P, 12·4. Calc. for $C_{12}H_{27}O_3P$: P, 12·4%), which with acetyl chloride (2 g.) gave, on distillation, dibutyl acetylphosphonate (3·2 g.), b. p. 78—80°/0·08 mm., n_D^{20} 1·435 [2,4-*dinitrophenylhydrazone*, pale yellow, m. p. 80° (Found: P, 10·1; N, 14·0. $C_{16}H_{25}O_7N_4P$ requires P, 7·5; N, 13·5%)]. Examination, by vapour-phase chromatography and spectrophotometry, of the more volatile products, freed from hydrogen chloride by low-temperature distillation from calcium oxide, failed to reveal butyl chloride. The primary residue, when recrystallised from benzene, gave salicylic acid (3·75 g., 25%) and an orange product (0·6 g.) (Found: P, 29%).

Similar results were obtained when no solvent was used.

Interaction of the Chloridite (I; R = Cl) *with Salicylic Acid and Pyridine, and Methylation of the Product.*—The chloridite (10·15 g.) in ether (20 c.c.) was added to the acid (6·9 g., 1 mol.) and pyridine (7·9 g., 2 mol.) in ether (80 c.c.) at −10°. After filtration from the hydrochloride (6·1 g.) which retained some of the other products (Found: Cl, 0·0482 g.-ion; C_5H_5N, 0·0505 g.-mol.), diazomethane in ether was added in a slow stream to the filtrate at 0°. When the initial instantaneous decolorisation ceased, a 10% excess was added. After being kept at room temperature overnight, the bulk of the ether was removed at 20°/15 mm. and the solution was extracted several times with aqueous sodium carbonate, dried, evaporated, and distilled, giving a forerun (3·1 g.), b. p. 35—50°/17 mm. (Found: C_5H_5N, 0·0361 mole), a mixed fraction (0·8 g.), b. p. 50—103°/17 mm., methyl salicylate (6·55 g., 86%), 103—104°/17 mm. (Found: sap. equiv., 150·5. Calc.: sap. equiv., 152·0), and a brown residue (2·35 g.). Acidification of the aqueous extracts gave a precipitate (0·3 g.) from which *o*-methoxybenzoic acid was not obtained.

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