PHOSPHONOMETHYLATION OF o-AMINOPHENOL AND o-ANISIDINE

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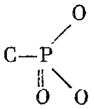
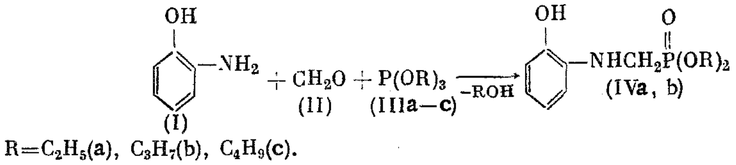
We have previously reported the reaction of trialkyl phosphites with aldehydes in the presence of compounds containing a labile hydrogen atom, which forms esters of phosphonic acids [1-6].

We have sought to prepare polyfunctional organophosphorus compounds with hydroxy, amino, P=O, and other groups of practical interest by condensation in the ternary system trialkyl phosphite—aldehyde—aminophenol (anisidine).

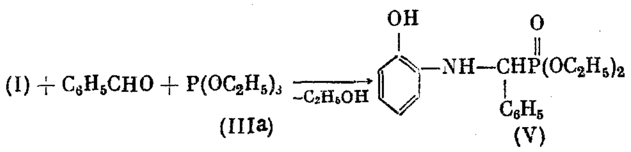
We carried out the reaction of o-aminophenol (I), paraformaldehyde (II), and triethyl phosphite (IIIa) in absolute xylene at 100-110°C. The ^{31}P NMR spectrum of the reaction mixture contained a signal at δ −26 ppm representing the  $C-\overset{\displaystyle O \backslash\!\!/}{\underset{\displaystyle O\ \ O}{P}}$ grouping. Elemental analysis and the IR and ^{31}P NMR spectra indicated that the reaction product was diethyl o-hydroxyanilinomethylphosphonate (IVa). We got the same results when we carried out the reaction in other solvents (absolute benzene, ethyl acetate, butyl acetate).

The reaction of (I) and (II) with tributyl phosphite (IIIc) proceeded in the same way, giving dibutyl o-hydroxyanilinomethylphosphonate (IVc)



The IR spectra of (IVa) and (IVc) showed the characteristic frequencies (cm^{-1}) 1610 (benzene C=C), 1240-1230 (ν P=O), 980 and 1030 (P—O—C alkyl). We assigned the broad, structureless band in the 3400-2400 cm^{-1} region to stretching of associated NH groups involved in hydrogen bonding with the OH and P=O groups.

The reaction of (I) and (IIIa) with benzaldehyde without solvent (100°C) gave the crystalline diethyl α-(o-hydroxyanilino)benzylphosphonate (V)



We also prepared (V) by the published reaction [7] of o-hydroxybenzylideneaniline (VI) with diethyl phosphite (VII) in the presence of C_2H_5ONa. The IR spectrum of (V) had characteristic bands at 3420 cm^{-1} (free HN) and 1230 cm^{-1} (P=O). The absorption at 3200 cm^{-1} indicates a strong intramolecular hydrogen bond, which probably involves the P=O group and the phenolic hydroxyl, since the shape of the spectrum was not altered by dilution of (V) in CCl_4.

o-Anisidine (VIII) reacted with paraformaldehyde and trialkyl phosphites (IIIa)-(IIIc) under more forcing conditions (120-130°C) to form respectively diethyl (IXa), dipropyl (IXb), and dibutyl (IXc) o-methoxyanilinomethylphosphonates in 25-35% yield. Vacuum distillation then gave the byproducts bis(o-anisidino)methane (X) and dialkyl α-hydroxymethylphosphonates

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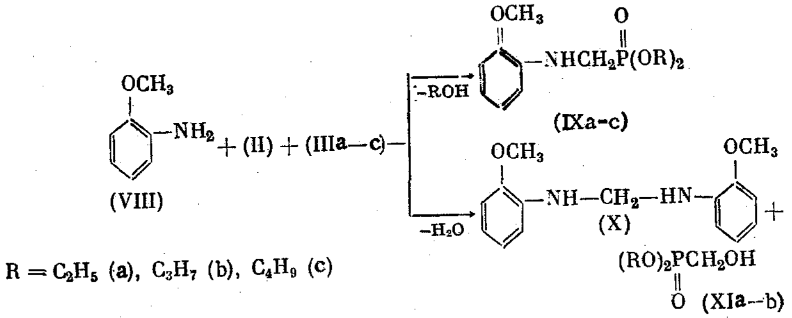
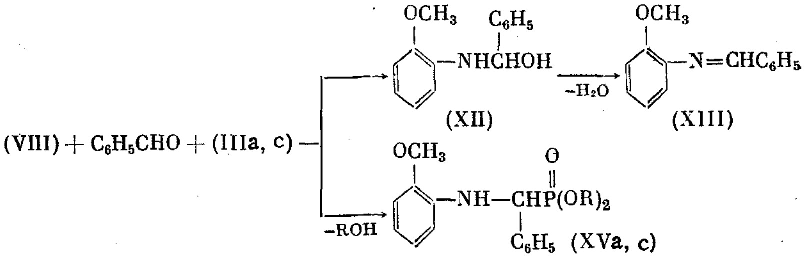
(XIa)-(XIc), which were slightly contaminated with (X) as a result of their close boiling points. Esters (XI) are probably formed by hydrolysis of (III) to the dialkyl phosphites (VII) and their subsequent reaction with (II)



The ^{31}P NMR and IR spectra supported the formation of (XIa)-(XIc) and were the same as those of pure specimens. Partly unreacted (IIIa)-(IIIc) and (VIII) could always be isolated from the reaction mixture.

When benzaldehyde was used in the triple condensation of (VIII) and (III), we isolated α-(o-methoxyanilino)benzyl alcohol (XII) as byproduct after the first fractional distillation when the reaction was carried out under relatively mild conditions (100°C) but the Schiff base (XIII) under more forcing conditions (160-180°C). An attempt to synthesize (XII) and (XIII) from the direct reaction of (VIII) and benzaldehyde by mixing in ethanol gave bis(o-anisidino)phenylmethane (XIV).

The yield of the major phosphonomethylation product, diethyl (XVa) or dibutyl (XVc) α-(o-methoxyanilino)benzylphosphonate, was 25-30% and depended on the order of addition of the components



When (VIII) was added last, the yield of (XV) rose to 40% or more, particularly when added dropwise slowly.

We verified the structures of the products of the interaction of o-anisidine with aldehydes and trialkyl phosphites from their elemental analyses and IR and ^{31}P NMR spectra. Esters (IXa)-(IXc), (XVa), and (XVc) gave a ^{31}P NMR signal at δ -24 ppm and characteristic IR frequencies (cm^{-1}) at 3420 (NH), 1250-1240 (P=O), and 1600 (benzene C=C).

Thus (VIII) is less reactive than (I) in the triple condensation with aldehydes and trialkyl phosphites.

EXPERIMENTAL

The ^{31}P NMR spectra were recorded on a KGU-4 instrument (10.2 MHz) relative to 85% H_3PO_4 (external standard). The low-boiling fractions that distilled off during the reaction were analyzed by GLC on a Khrom-3 instrument with a flame-ionization detector (80°C, helium carrier gas, polymethylsiloxane).

Diethyl o-Hydroxyanilinomethylphosphonate (IVa). 1) Compound (I) (10.9 g, 0.1 mole), (II) (3 g, 0.1 mole), and (IIIa) (16.6 g, 0.1 mole) were heated at 100-110°C for 2 h in absolute xylene (20 ml). The dark, viscous reaction mixture had δ ^{31}P -26 ppm. Removal of the solvent and other highly volatile products under vacuum gave (IVa) (21 g, 81%). Found: C 51.47; H 6.77; N 6.04; P 11.44%. $C_{11}H_{18}NO_4P$. Calculated: C 50.96; H 6.95; N 5.40; P 11.96%.

2) To (I) (10.9 g, 0.1 mole) and (IIIa) (16.6 g, 0.1 mole) in absolute benzene (25 ml) at 70°C was added portionwise (II) (3 g, 0.1 mole). The mixture was refluxed at 85°C for

4 h. The ^{31}P NMR spectrum of the mixture contained a weak signal at —136 ppm and a strong signal at —24 ppm. The mixture was separated from the precipitated paraformaldehyde (1.5 g) by filtration. Removal of the solvent and unreacted (I) under vacuum gave (IVa) (13 g, 50%). Found: P 11.69%. $C_{11}H_{18}NO_4P$. Calculated: P 11.96%.

Dibutyl o-Hydroxyanilinomethylphosphonate (IVc). Compound (I) (5.45 g, 0.05 mole), (II) (1.5 g, 0.05 mole), and (IIIc) (12.5 g, 0.05 mole) were heated at 125°C for 2 h in absolute xylene (26 ml). Removal of the solvent and other highly volatile products under vacuum gave (IVc) (14 g, 89%), as dark crystals, δ ^{31}P —26 ppm. Found: C 57.08; H 8.42; N 4.77; P 10.27%. $C_{15}H_{26}O_4NP$. Calculated: C 57.14; H 8.25; N 4.44; P 9.84%.

Diethyl α-(o-Hydroxyanilino)benzylphosphonate (V). Compound (I) (5.45 g, 0.05 mole), benzaldehyde (5.3 g, 0.05 mole), and (IIIa) (8.3 g, 0.05 mole) were heated at 100-120°C for 1 h to give (V) (7.8 g, 46.5%), as white crystals with mp 139-140°C (from ethanol), δ ^{31}P —24 ppm. Found: C 61.20; H 6.58; N 4.68; P 8.99%. $C_{17}H_{22}NO_4P$. Calculated: C 60.89; H 6.56; N 4.18; P. 9.25%.

o-Hydroxybenzylideneaniline (VI). Compound (I) (5.45 g, 0.05 mole) in ethanol (20 ml) and benzaldehyde (5.3 g, 0.05 mole) gave (VI) (8 g, 80%) with mp 88-89°C (from ethanol). Found: C 79.30; H 5.71; N 7.30%. $C_{13}H_{11}NO$. Calculated: C 79.18; H 5.58; N 7.10%.

Diethyl α-(o-Hydroxyanilino)benzylphosphonate (V). Compound (VI) (10 g, 0.05 mole) and (VII) (6.9 g, 0.05 mole) were heated at 65-70°C for 1 h in absolute ethanol (20 ml) in the presence of C_2H_5ONa to give (V) (7.6 g, 45.3%), as white crystals with mp 138-140°C (from ethanol), δ ^{31}P —24 ppm. Found: C 60.86; H 6.54; N 4.07; P 9.36%. $C_{17}H_{22}NO_4P$. Calculated: C 60.89; H 6.56; N 4.18; P. 9.25%.

Interaction of o-Anisidine (VIII) and Paraformaldehyde (II) with Trialkyl Phosphites (IIIa)-(IIIc). Compound (VIII) (12.3 g, 0.1 mole), (II) (3 g, 0.1 mole), and (IIIa) (16.6 g, 0.1 mole) were heated at 110-120°C for 5 h. Compound (II) was added portionwise over a period of 2 h. The ^{31}P NMR spectrum of the reaction mixture contained two signals at —26 and —140 ppm. Fractional distillation gave: 1) (VIII) (2.46 g, 20%) with bp 99-101°C (8 mm); n_D^{20} 1.5705 [8]; 2) (III) (4.2 g, 25%) with bp 44-46°C (10 mm); n_D^{20} 1.4130; δ ^{31}P —140 ppm [9]; 3) ethanol (1.58 g, 34%) (GLC); 4) (IX) (9.1 g, 33%) with bp 124-127°C (0.03 mm); n_D^{20} 1.5220. Found: C 53.20; H 7.61; N 5.10; P 11.09%. $C_{12}H_{20}O_4NP$. Calculated: C 52.75; H 7.33; N 5.13; P 11.36%; 5) (XI) (5.9 g, 35%) with bp 81-83°C (0.035 mm); n_D^{20} 1.4475; δ ^{31}P —24 ppm. Found: P 17.55%. $C_5H_{13}O_4P$. Calculated: P 18.45%; and 6) (X) (5.5 g, 21%) with mp 79-81°C [10]. Found: C 69.76; H 6.90; N 10.68%. $C_{15}H_{28}O_2N_2$. Calculated: C 69.77; H 6.98; N 10.85%.

Similarly tripropyl phosphite (IIIb) and tributyl phosphite (IIIc) gave the products: 1) (IXb) (28%) with bp 152-154°C (0.08 mm); n_D^{20} 1.5075; δ ^{31}P —24 ppm. Found: C 55.25; H 7.87; N 4.62; P. 10.52%. $C_{14}H_{24}O_4NP$. Calculated: C 55.80; H 7.97; N 4.65; P 10.30%; 2) (IXc) (25%) with bp 143-146°C (0.04 mm); n_D^{20} 1.4940; δ ^{31}P —26 ppm. Found: C 57.83; H 8.50; N 4.04; P 9.68%. $C_{16}H_{28}O_4NP$. Calculated: C 58.36; H 8.51; N 4.25; P 9.42%; and 3) other reactants and by-products, %: (VIIIb) 16, (VIIIc) 13.5, (IIIb) 28, (IIIc) 29, (XIb) 24, (XIc) 34, (Xb) 27, and (Xc) 29.

Diethyl α-(o-Methoxyanilino)benzylphosphonate (XVa). 1) Compound (VIII) (6.15 g, 0.05 mole), benzaldehyde (5.3 g, 0.05 mole), and (IIIa) (4.15 g, 0.025 mole) were heated at 120-125°C for 1.5 h. Fractional distillation under vacuum gave: a) (XVa) (3.6 g, 20%) with bp 165-168°C (0.025 mm); n_D^{20} 1.5620; δ ^{31}P —24 ppm. Found: N 4.28; P 8.48%. $C_{18}H_{24}NO_4P$. Calculated: N 4.01; P 8.88%; and b) (XII) (7.5 g, 65%) with bp 113-115°C (0.02 mm); n_D^{20} 1.6170. Found: N 6.25%. $C_{14}H_{15}NO_2$. Calculated: N 6.11%.

2) To benzaldehyde (5.3 g, 0.05 mole) and (IIIa) (8.3 g, 0.05 mole) was added portionwise at 100°C (VIII) (6.15 g, 0.05 mole). The mixture was heated at 100-120°C for 6 h. Ethanol (2 ml, GLC) was stripped off. The reaction mixture had δ ^{31}P —138 and —24 ppm. Fractional distillation under vacuum gave: a) (XVa) (7 g, 40%), viscous yellow liquid with bp 159-162°C (0.015 mm); n_D^{20} 1.5572. Found: C 61.75; H 6.86; N 3.77; P. 8.60%. $C_{18}H_{24}NO_4P$. Calculated: C 61.89; H 6.88; N 4.01; P 8.88%; and b) (XII) (4.8 g, 42%) with bp 123-125°C (0.04 mm); n_D^{20} 1.6100. Found: N 6.10%. $C_{14}H_{15}NO_2$. Calculated: N 6.11%.

Dibutyl α-(o-Methoxyanilino)benzylphosphonate (XVc). Compound (VIII) (6.15 g, 0.05 mole), benzaldehyde (5.3 g, 0.05 mole), and (IIIc) (12.5 g, 0.05 mole) were heated at 160-185°C for 4 h. Fractional distillation gave: butanol (1.4 g, 38%, GLC); (IIIc) (6.9 g, 55%) with bp 70-73°C (0.1 mm), n_D^{20} 1.4400; (XIII) (5.5 g, 53%) with bp 109-110°C (0.015 mm), n_D^{20} 1.6320. (Found: C 79.25; H 6.46; N 7.04%. $C_{14}H_{13}ON$. Calculated: C 79.62; H 6.16; N 6.65%); and (XVc) (7.5 g, 37%), a viscous yellow liquid with bp 167-170°C (0.015 mm), n_D^{20} 1.5390. (Found: C 65.36; H 7.67; N 3.61; P 7.94%. $C_{22}H_{32}NO_4P$. Calculated: C 65.18; H 7.90; N 3.45; P 7.65%).

Bis(o-anisidino)phenylmethane (XIV). Benzaldehyde (10.6 g, 0.1 mole) and (VIII) (12.3 g, 0.1 mole) in ethanol (20 ml) gave (XIV) (9.5 g, 57%), mp 64-66°C (from alcohol). Found: C 75.30; H 6.64; N 8.57%. $C_{21}H_{22}N_2O_2$. Calculated: C 75.45; H 6.59; N 8.38%.

CONCLUSIONS

1. Condensation in the ternary system o-aminophenol—paraformaldehyde (benzaldehyde)—trialkyl phosphite gives dialkyl o-hydroxyanilinomethyl(benzyl)phosphonates.

2. When o-aminophenol is replaced by o-anisidine in the reaction the dialkyl o-methoxyanilinomethyl(benzyl)phosphonates are accompanied by several by-products, bis(o-anisidino)methane, dialkyl α-hydroxymethylphosphonates, and Schiff bases.

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