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PHOSPHOMETHYLATION OF p-SUBSTITUTED ANILINES

UDC 542.91: 547.1'118

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The phosphomethylation of weakly basic amines proceeds easily in an amine -paraformaldehyde-trialkyl phosphite system [1-3], whereas with dialkyl phosphites the condensation does not always occur, or is complicated by side reactions [1, 4]. The present work is a study of the phosphomethylation of p-aminophenol (I) and p-anisidine (II), for the purpose of synthesizing esters of N-p-hydroxy(or methoxy)phenylaminomethyl-phosphonic and thiophosphonic acids, which are potential complex-formers and rubber stabilizers [5]. The phosphorus components were trialkyl phosphites: triethyl phosphite (IIIa), triisopropyl phosphite (IIIb), tri-butylphosphite (IIIc), diethyl phosphite (IV), and diethyl thiophosphite (V).

The reaction of I, paraformaldehyde, and IIIa or IV, in the absence of a solvent at 70-100°C, is accompanied by resinification of the reaction mixture and the release of ethanol and water as low-boiling products. It was not possible to separate individual products from the resin by precipitation from solvents (alcohol, ethyl acetate, nitromethane, DMFA). However, the condensation of I, paraformaldehyde, and IV in ethyl acetate proceeds with only partial resinification and yields a mixture from which O,O-diethyl- N-p-hydroxyphenylamino-methylphosphonate (VIa) was separated by freezing in 20% yield. In the condensation of I, paraformaldehyde, and IIIa, IIIb, or IIIc, there was practically no resinification. When paraformaldehyde was sprinkled onto a heated mixture of I with IIIa, IIIb, or IIIc, the temperature went up 10-20°C, and within 15 min transparent solutions were formed from which the respective phosphonates (VIa-c) were precipitated in 65-95% yield upon partial removal of the solvent:

O,O-diethyl- N-p-hydroxyphenylaminomethylthiophosphonate could not be synthesized in a three-component system in the presence of diethyl thiophosphite, due to vigorous resinification regardless of reaction con-

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ditions (pH of medium, order of addition and amount of reagents, solvent). Evidently, in the presence of diethyl thiophosphite Schiff bases are formed, which resinify the reaction mixture.

The reaction of p-anisidine (II), paraformaldehyde, and IIIa or IV without a solvent at 70-100°C proceeds with less resinification than with I. The reaction product of II, paraformaldehyde, and IV = 0,0-diethyl-N-pmethoxyphenylaminomethylphosphonate (VIIa) = was separated by high-vacuum distillation in 50% yield; with molecular distillation the yield is increased to 70%. The reaction of II, paraformaldehyde, and IIIa without solvent proceeds with the release of ethanol and water, and after fractional distillation in vacuum yields VIIa in 55% yield, and diethyl phosphite (IV) in 15% yield ($\delta^{31}P 8$ ppm, J_{PH} = 692 Hz; ν P=H 2342 cm⁻¹). To separate the byproducts and increase the yield of the desired product, the reaction was carried out in o-xylene at 110-120°C. By vacuum distillation of the reaction mixture there were separated VIIa in 55% yield, IV in 11% yield, O,O-diethyl α -hydroxymethylphosphonate (VIII) in 16% yield, and a product of mp 131°C (from alcohol). Its IR spectrum did not have an absorption band in the region of NH valence vibrations; by elementary analysis it was a trimer of methylene-p-anisidine (IX), 5.5% yield [6].

The desired products could also undergo various conversions during synthesis. To show that the NH and OH groups could participate in these conversions, the reaction of phosphonate VIa with paraformaldehyde and diethylaminodiethyl phosphite (X) was studied. When VIa and paraformaldehyde, at 2:1 ratio, are heated in butyl acetate, a viscous dark-red resinous product is obtained, the IR spectrum of which contains the follow-ing absorption bands: $\nu P = 0$ 1200-1250, $\nu P(OC)$ 980-1080, νOH 3280 cm⁻¹. Phenolic hydroxyl absorption appears as a broad diffuse band that is probably related to H-bond formation. Elemental analysis corresponded to bis(diethyl-N-p-hydroxyphenylaminomethylphosphonato)methane (XI):

 $2 (VIa) + CH_2O \longrightarrow \begin{array}{c} p-HOC_6H_4 - N - CH_2P(O)(OC_2H_5)_2 \\ \downarrow \\ p-HOC_6H_4 - N - CH_2P(O)(OC_2H_5)_2 \\ \downarrow \\ p-HOC_6H_4 - N - CH_2P(O)(OC_2H_5)_2 \\ (XI) \end{array}$

The reaction of VIa with X at 120-150°C yields diethyl (N-p-diethylphosphononmethylamino)phenylphosphate (XII) as a viscous colorless liquid with an amidophosphite odor. The structure of XII was confirmed by elemental analysis and by the IR and ³¹P NMR spectra: δ 128,24 ppm; $\nu P = O$ 1208, 1240; νNH 3335 cm⁻¹. This type of reaction probably also occurs with trialkyl phosphites:

$$(\text{VIa}) + (\text{C}_2\text{H}_5\text{O})_2\text{PN}(\text{C}_2\text{H}_5)_2 \xrightarrow{-\text{HN}(\text{C}_2\text{H}_5)_2} (\text{C}_2\text{H}_5\text{O})_2\text{PO} \xrightarrow{-\text{NHCH}_2\text{P}(\text{O})(\text{OC}_2\text{H}_5)_2} (\text{XII})$$

Thus, the nature of the released materials and the properties of the resulting phosphonates permit the resinification of the reaction mixture to be attributed to Schiff base formation, hydrolysis by the water released, and subsequent conversions of the reaction products.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer (film); ³¹P NMR spectra, on a KGU-4 spectrometer (10.2 MHz); chemical shifts were determined relative to 85% H₃PO₄. Volatile reaction products were studied by GLC on a Chrom-3 apparatus [3].

Diethyl Ester of N-p-Hydroxyphenylaminomethylphosphonic Acid (VIa). A. To a mixture of 66.4 g (0.4 mole) of IIIa and 43.6 g (0.4 mole) of I in 200 ml of ethyl acetate (EA) at 60°C was added 12 g (0.4 mole) of paraformaldehyde in portions with stirring. At 70°C the mixture frothed, and the reaction proceeded with boiling until all the components dissolved (15-20 min). When part of the EA was removed and the mixture was cooled, pale-rose crystals of VIa precipitated, 93.2 g (90%), mp 102-103°C (from EA). Found: C 50.76; H 6.85; N 5.60; P 11.76%. C₁₁H₁₈NO₄P. Calculated: C 50.96; H 6.94; N 5.41; P 11.96%. IR spectrum (ν , cm⁻¹): 1235, 1260 (P = O), 980-1080 P(OC)), 3383 (NH), 3260 (OH). $\delta^{31}P$ 24 ppm.

B. A mixture of 13.8 g (0.1 mole) of IV, 10.9 g (0.1 mole) of I, and 3 g (0.1 mole) of paraformaldehyde was heated with stirring in 50 ml of boiling EA for 6 h. After part of the solvent was removed from the viscous resinous residue, freezing precipitated crystals of VIa, 5.1 g (20%).

<u>Diisopropyl ester of N-p-hydroxyphenylaminomethylpho sphonic acid (VIb)</u> was obtained by a procedure similar to A, 70% yield, mp 86-87°C (from EA). Found: C 54.18; H 7.60; N 4.78; P 10.88%. $C_{13}H_{22}NO_4P$. Calculated: C 54.31; H 7.66; N 4.84; P 10.82%.

<u>Dibutyl ester of N-p-hydroxyphenylaminomethylphosphonic acid (VIc)</u> was obtained similarly in butyl acetate at 100-110°C in 87% yield; it is a viscous liquid that crystallizes on standing, and was purified by repeated washing with ether and vacuum evaporation. Found: P 9.30; N 4.47%. $C_{15}H_{26}NO_4P$. Calculated: P 9.84; N 4.44%.

Diethyl Ester of N-p-Methoxyphenylaminomethylpho sphonic Acid (VIIa). A. Compound II, 24.6 g (0.2 mole), and 33.2 g (0.2 mole) of IIIa in 85 ml of o-xylene were heated to 95°C, and 6 g (0.2 mole) of paraform-aldehyde was added in portions over 1 h. The mixture was heated another hour at 120 h, and 6.5 ml of ethanol distilled off. The solvent was removed in vacuum (50 torr), and the residue was distilled at high vacuum. Separated: 1) VIIa, 30 g (55%), bp 130-133°C (0.025 mm), nD²⁰ 1.5160. Found: C 53.21; H 7.62; N 5.97; P 10.89%. $C_{12}H_{20}NO_4P$. Calculated: C 52.74; H 7.33; N 5.12; P 11.36%. IR (ν , cm⁻¹): 1242, 1254 (P = O), 980-1080 P(OC)), 3340 (NH). $\delta^{31}P$ 24 ppm. 2) VIII, O,O-diethyl α -hydroxymethylphosphonate, 2.8 g (16%), bp 90-96°C (0.015 mm), nD²⁰ 1.5160. Found: P 17.52%. $C_5H_{11}O_4P$. Calculated: P 18.45%. $\delta^{31}P$ 24 ppm (see [3]); 3) fraction with bp 82-95°C (0.015 mm); after crystallization and recrystallization from ethanol, mp 131-133°C, trimer of methylene-p-anisidine (IX), 2.2 g (5.5%). Found: C 68.73; H 6.8; N 10.85%. $C_{24}H_{27}O_3N_3$. Calculated: C 69.13; H 6.66; N10.41% (see [6]); 4) diethyl phosphite (IV), 1.5 g (11%). $\delta^{31}P$ 8 ppm, JPH = 692 Hz.

B. Compound II, 6.15 g (0.05 mole), 1.5 g (0.05 mole) of paraformaldehyde, and 6.9 g (0.05 mole) of IV were heated together to 110°C. The mixture effervesced and warmed up to 125°C. It was heated for 2 h at 125-130°C until all water had been removed. Molecular distillation at a heater temperature of 110°C (0.015 mm) from an Arbuzov flask yielded 9.5 g (70%) of VIIa.

Dibutyl Ester of N-p-Methoxyphenylaminomethylphosphonic Acid (VIIc). To a mixture of 25 g (0.01 mole) of IIIc and 12.3 g (0.01 mole) of II, heated to 100°C, was added 3 g (0.01 mole) of paraformaldehyde in portions cautiously. The reaction was carried out at 115-125°C until butanol separation was finished. During distillation 24.4 g (73.2%) of VIIc was separated, bp 151-155°C (0.025 mm), n_D^{20} 1.5071. Found: C 59.04; H 8.80; N 4.46; P 9.12%. C₁₆H₂₆NO₄P. Calculated: C 58.40; H 8.85; N 4.25; P 9.42%.

Diethyl (N-p-Diethylphosphonomethylamino)phenylphosphite (XII). A mixture of 7.77 g (0.03 mole) of VIa and 4.83 g (0.03 mole) of diethylamidodiethylphosphite was heated in an Arbuzov flask. At 75°C all the components dissolved, the mixture heated up to 118°C, and diethylamine and traces of ethanol came off. Heating was continued for 4 h at 130-150°C. The reaction mixture was washed several times with ether. After the ether was removed, vacuum distillation of the residue yielded XII as a viscous liquid with an amidophosphite odor. Found: C 48.74; H 7.08; N 4.04; P 15.60%. $C_{15}H_{27}NO_6P_2$. Calculated: C 47.5; H 7.12; N 3.69; P 16.35%. Yield 10.1 g (95%).

Bis (diethyl N-p-hydroxyphenylaminomethylphosphonato)methane (XI). A mixture of 6.47 g (0.025 mole) of VIa and 0.35 g (0.0125 mole) of paraformaldehyde was boiled in butyl acetate for 3 h. Removal of the solvent yielded a dark-red resinous liquid that was dissolved in ethanol and reprecipitated ether. Removal of the solvent and vacuum distillation yielded XI. Found: C 51.34; H 6.97; N 5.62; P 11.06%. $C_{23}H_{36}N_2O_3P_2$. Calculated: C 52.07; H 6.47; N 5.28; P 11.69%.

CONCLUSIONS

The phosphomethylation of p-substituted anilines in three-component systems (amine-paraformalde-hyde-trialkyl phosphite, diethyl phosphite, or diethyl thiophosphite) proceeds best with trialkyl phosphites, and the yields are 55-95%.

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