SYNTHESIS OF ESTERS OF p-SUBSTITUTED BENZYLPHOSPHONIC ACIDS

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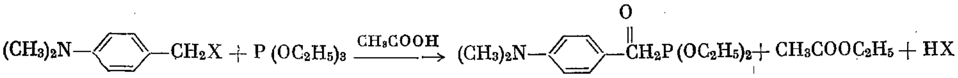
Previously we had shown that bis(dialkylamino)methanes and α-ether amines react with triethyl phosphite in the presence of salt-forming agents [1, 2]. In the present paper we studied the reaction of their phenylogs with triethyl phosphite. It was shown that p-dimethylaminobenzyl ethyl ether (I) and p-dimethylaminobenzyldiethylamine (II) do not react with triethyl phosphite in the absence of a salt-forming agent when heated at 180°, but in the presence of acetic acid the reaction goes at 145-170° with the formation of the diethyl ester of p-dimethylaminobenzylphosphonic acid:



$X=OC_2H_5;\ N(C_2H_5)_2$

From [3, 4] it is known that α-amino derivatives of this type are very reactive. Destroying the conjugation, and also the nature of the p-substituent, both change their reactivity. Actually, we were unable to synthesize the esters of p-substituted benzylphosphonic acids by the reaction of p-methoxybenzyl ethyl ether (III) and p-methoxybenzyl acetate (IV) with triethyl phosphite in the presence of acetic acid. The diethyl ester of p-methoxybenzylphosphonic acid was obtained by the reaction of (III) with diethyl chlorophosphite at 150-160° in a stream of dry nitrogen. The yield was 28%. The hydrochloride of p-dimethylaminobenzyldiethylamine reacts with triethyl phosphite to give diethylphosphorous acid and (II). An analogous result was obtained when the hydrochloride of diethylbenzylamine was reacted with triethyl phosphite. The formation of diethylphosphorous acid and its isolation suggest that if it is capable of reacting with (II), then it is at a much slower rate than triethyl phosphite. This is also corroborated by direct experiments. We were unable to isolate any pure products when (I)-(IV) were reacted directly with diethylphosphorous acid at 180-190°. Here the marked formation of tar was observed, while the reaction failed to go at lower temperatures. p-Dimethylaminobenzyldiethylamine methiodide reacts most easily with triethyl phosphite. The reaction product is the diethyl ester of p-dimethylaminobenzylphosphonic acid. The direct replacement of the amino group in the ammonium form by the phosphono group probably occurs here via the S_N2 mechanism of the Arbuzov rearrangement.

It is interesting to mention that diethylbenzylamine methiodide reacts with triethyl phosphite to give the diethyl ester of benzylphosphonic acid, the constants of which coincide with the literature data [5].

EXPERIMENTAL METHOD

The triethyl phosphite used in the experiments was purified as described in [1]. The low-boiling product, liberated during the course of each reaction, was investigated by GLC using a KhL-3 chromatograph [1].

Reaction of p-Dimethylaminobenzyl Ethyl Ether with Triethyl Phosphite in the Presence of Acetic Acid. To a mixture of 16.6 g of triethyl phosphite and 17.9 g of p-dimethylaminobenzyl ethyl ether, heated to 150°, was slowly added 6 g of glacial acetic acid, after which the reaction mixture was kept at 150-170° for 1.5 h. During the reaction process was distilled off 6.1 g of low-boiling product, which, based on the GLC data, consisted of a mixture of ethyl acetate and ethanol. Fractional distillation of the reaction mixture

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in vacuo gave 12.7 g (47%) of the diethyl ester of p-dimethylaminobenzylphosphonic acid [6] with bp 140-143° (0.01 mm); n_D^{20} 1.5272; d_4^{20} 1.1003. Found: C 57.19; 57.46; N 4.92; 4.95; P 11.20; 11.42%; MR 76.11. $C_{12}H_{22}\cdot NO_3P$. Calculated: C 57.95; N 5.16; P 11.43%; MR 75.64.

The reaction of (II) with triethyl phosphite was run in a similar manner. The diethyl ester of p-dimethylaminobenzylphosphonic acid was isolated, the constants of which coincide with those given above.

Reaction of Diethyl Chlorophosphite with p-Methoxybenzyl Ethyl Ether. A mixture of 16.5 g (excess) of (III) and 11.8 g of diethyl chlorophosphite was heated in a dry nitrogen stream at 150-160° for 6 h. The reaction was accompanied by the evolution of C_2H_5Cl. Fractional distillation of the reaction mixture gave 5.5 g (28.2%) of the diethyl ester of p-methoxybenzylphosphonic acid [7] with bp 159-162° (3 mm); n_D^{20} 1.5032; d_4^{20} 1.13433. Found: C 55.81; 55.97; H 7.17; 7.02; P 11.76; 11.82%; MR 67.08. $C_{12}H_{19}O_4P$. Calculated: C 55.81; H 7.00; P 12.01%, MR 66.52.

Reaction of p-Dimethylaminobenzyldiethylamine Methiodide with Triethyl Phosphite. A mixture of 8.8 g of triethyl phosphite and 17.4 g of the (II) methiodide was heated at 130-150° for 3.5 h. To completely remove the formed precipitate the reaction mixture was treated with 100 ml of ether. The precipitate was separated and recrystallized from alcohol. We isolated 9.2 g (76.6%) of methyltriethylammonium iodide, which fails to decompose when heated to 270°. Found: N 5.39; 5.45%. $C_7H_{18}NI$. Calculated: N 5.76%. The residue from removal of the ether was fractionally distilled. As the result of three fractional distillations we isolated 6.7 g (50.8%) of the diethyl ester of p-dimethylaminobenzylphosphonic acid, the constants of which coincide with those given above.

Reaction of Triethyl Phosphite with N-Diethylbenzylamine Methiodide. A solution of 16.6 g of triethyl phosphite and 30.5 g of N-diethylbenzylamine methiodide in 50 ml of dimethylformamide was heated at 150-170° for 4 h. At the end of reaction a white precipitate, representing 14 g (57.6%) of methyltriethylammonium iodide, deposited from the reaction mixture. After removal of the methyltriethylammonium iodide and solvent, fractional distillation of the residue gave 7 g (30.6%) of the diethyl ester of benzylphosphonic acid with bp 150-152° (10 mm); n_D^{20} 1.5020; d_4^{20} 1.0897. Found: P 12.90; 12.78%; MR 61.7. $C_{11}H_{17}O_3P$. Calculated: P 13.59%. MR 62.5. From [5]: bp 155° (14 mm).

CONCLUSIONS

1. A study was made of the reaction of p-dimethylaminobenzyldiethylamine, p-dimethylaminobenzyl ethyl ether, p-methoxybenzyl ethyl ether and p-methoxybenzyl acetate with triethyl phosphite. The compounds, containing the dimethylamino group in the p-position, react with triethyl phosphite in the presence of acetic acid to give the diethyl ester of p-dimethylaminobenzylphosphonic acid. The other analogs do not react with triethyl phosphite.

2. The methiodides of p-dimethylaminobenzyldiethylamine and diethylbenzylamine react with triethyl phosphite to give respectively the p-dimethylaminobenzyl- and benzylphosphonates.

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