REACTIONS OF MANNICH BASES WITH TRIETHYL PHOSPHITE COMMUNICATION 1. REACTIONS IN PRESENCE OF ACETIC ACID

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The reactions of triethyl phosphite with methiodides or hydrochlorides of Mannich bases have been described in [1-3]. However, the question of the mechanism of the replacement of the amino group and the sequence of the stages formulated in [2] has remained open.

Our object in the present work was the development of simpler and more convenient methods of conducting this reaction and the determination of the possibilities of this method in synthesis. We have changed the reaction conditions: instead of the hydrochloride or methiodide of the Mannich base, we took an equimolecular mixture of the Mannich base and acetic acid. We supposed that acetic acid would give a salt with the Mannich base and that this would react with triethyl phosphite with formation of diethylamine and an intermediate quasiphosphonium compound, the breakdown of which would give ethyl acetate and the reaction product.

Diethylamine and ethyl acetate formed in the course of the reaction were readily removed from the reaction mixture; they were identified by means of gas chromatography. In a special experiment it was shown that in the case of the reaction of triethyl phosphite with N,N,N',N'-tetraethylmethanediamine in presence of acetic acid the liberation of diethylamine (determined by titration of a sample of the mixture distilled off with 0.5 N H₂SO₄) and ethyl acetate (determined by titration of the excess of alkali remaining after a sample of the condensate had been boiled with alkali) occurred simultaneously in about 1:1 proportions within the limits of experimental error.

We have studied the reactions of triethyl phosphite with a number of ketonic and nonketonic Mannich bases. It was observed that, depending on the structure of the Mannich base used, the temperature at which reaction starts varies. Reaction starts at the lowest temperature with N,N,N',N'-tetraethylmethane-diamine ($\partial 1^\circ$) and 4-(diethylamino)-2-butanone ($\partial 2^\circ$), and it goes exothermically. For other Mannich bases no exothermic effect is observed. Reaction starts at the highest temperature (135°) in the case of 3-(di-ethylamino)propionitrile.

We also studied reactions of triethyl phosphite with amino compounds which are not Mannich bases: N,N-diethylglycine ethyl ester and diethyl [(diethylamino)methyl]phosphonate ethiodide. In the latter case replacement of the amino group did not occur: we isolated diethyl ethylphosphonate and diethyl [(diethylamino)methyl]phosphonate. For reaction to occur a higher temperature (140°) was required. For all the ketonic Mannich bases reaction went with preservation of the carbonyl group, which was confirmed clearly by the IR spectra of the products isolated. Another peculiar feature of the reaction is that it may be conducted not only in an acetic acid medium, but also in phenol or even water. However, the use of these proton donors leads to undesirable by-products which lower the yield of the desired product and makes its isolation in the pure state difficult.

EXPERIMENTAL

Reaction of Triethyl Phosphite with 4-(Diethylamino)-2-butanone in Presence of Acetic Acid. A mixture of 28.6 g of 4-(diethylamino)-2-butanone, 33.2 g of triethyl phosphite

A. E. Arbuzov Institute of Organic and Physical Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1285-1289, June, 1967. Original article submitted March 25, 1966. and 12 g of acetic acid was prepared in a two-necked round-bottomed flask fitted with thermometer and small column with a condenser set for distillation. When the temperature in the oil bath reached 96°, the temperature in the reaction mixture rose to 110° and volatile reaction products began to come off and were collected in a graduated receiver. In the course of 1.5 h the temperature of the reaction mixture was raised to 142°, and 32.8 ml (26.1 g) of volatile products came over. In the fractionation of the reaction mixture we isolated 18.9 g (45.5%) of diethyl (3-oxobutyl)phosphonate; b.p. 140-141° (8 mm); n_D^{2D} 1.4365; d_4^{20} 1.0860. Found: P 14.70, 14.85; C 46.08, 46.18; H 8.15, 8.20%. $C_8H_{17}O_4P$. Calculated: P 14.87; C 46.15; H 8.22%.

<u>Reaction of Triethyl Phosphite with 4-(Diethylamino)-2-butanone in Pres-ence of Water.</u> A mixture of 16.6 g of triethyl phosphite, 14.3 g of 4-(diethylamino)-2-butanone, and 1.8 g of water was heated. At 96° volatile reaction products started to come off. In the course of 1 h the mixture was heated to 130°, and 8.4 g of condensate separated; titration of this with 0.5 N H₂SO₄ gave a content of 4.55 (62%) of diethylamine. In the fractionation of the reaction mixture we obtained 13.3 g (64%) of diethyl (3-oxobutyl) phosphonate; b.p. 147° (15 mm); $n_{\rm D}^{20}$ 1.4379.

Reaction of 4- (Diethylamino)-3-methyl-2-butanone with Triethyl Phosphite in Presence of Acetic Acid. A mixture of 15.7 g of 4- (diethylamino)-3-methyl-2-butanone, 16.6 g of triethyl phosphite, and 6.0 g of acetic acid started to react at 114°. In the course of the next 65 min the mixture was heated to 141° and 14.1 ml (11.3 g) of condensate was collected. In the fractionation of the reaction mixture we obtained 12.5 g (57%) of diethyl (2-methyl-3-oxobutyl)phosphonate; b.p. 100° (0.03 mm); n_D^{20} 1.4402; d_4^{20} 1.0679. Found: P 13.6, 13.64; C 48.88, 48.76; H 8.51, 8.57%; MR 54.89. $C_3H_{19}O_4P$. Calculated: P 13.95; C 48.65; H 8.55%; MR 54.64.

<u>Reaction of 1- (Diethylamino)-4,4-dimethyl-3-pentanone with Triethyl</u> <u>Phosphite in Presence of Acetic Acid.</u> A mixture of 18.5 g of 1-(diethylamino)-4,4-dimethyl-3-pentanone prepared by the method described in [4] [b.p. 61° (0.03 mm); n_D^{20} 1.4370; d_4^{20} 0.8561; MR found 56.69; calculated 56.95], 16.6 g of triethyl phosphite, and 6 g of acetic acid started to react at 125°. In the course of the next 30 min the mixture was heated to 145°; 13.4 ml (10.6 g) of volatile products came off. In the fractionation of the reaction mixture we isolated 19.7 g (79%) of diethyl (4,4-dimethyl-3-oxopentyl)phosphonate; b.p. 122° (0.1 mm); n_D^{20} 1.4417; d_4^{20} 1.0336. Found: P 11.55; 11.72; C 54.50, 54.33; H 9.19, 9.32%; MR 64.04. $C_{11}H_{23}O_4P$. Calculated: P 12.38; C 54.01; H 9.26%; MR 63.87.

Reaction of 1-(Diethylamino)-4,4-dimethyl-3-pentanone with Triethyl Phosphite in Presence of Acetic Acid. A mixture of 18.5 g of 1-(diethylamino)-4,-dimethyl-3-pentanone prepared by the method described in [4] (b.p. 122° (0.1 mm); n_D^{20} 1.4417; d_4^{20} 1.0336. Found: P 11.55, 11.72; C 54.50, 54.33; H 9.19, 9.32%; MR 64.04. C₁₁H₂₃O₄P. Calculated: P 12.38; C 54.01; H 9.26%; MR 63.87. b.p. 61° (0.03 mm); n_D^{20} 1.4370; d_4^{20} 0.8561; MR found 56.69; calculated 56.95), 16.6 g of triethyl phosphite, and 6 g of acetic acid started ro react at 125°. In the course of the next 30 min the mixture was heated to 145°; 13.4 ml (10.6 g) of volatile products camd off. In the fractionation of the reaction mixture we isolated 19.7 g (79%) of diethyl (4,4-dimethyl-3-oxopentyl)phosphonate;

<u>Preparation of 3-[(Diethylamino)methyl]-2,6-dimethyl-4-heptanone.</u> A mixture of 142 g of 2,6-dimethyl-4-heptanone, 109.5 g of diethylamine hydrochloride, 36 g of paraform, 40 ml of ethanol, and 7 ml of concentrated HCl was prepared in a three-necked flask fitted with stirrer, reflux condenser, and thermometer. With vigorous stirring the reaction mixture was heated for 4 h in such a way that its temperature attained 112-115°. The reaction mixture was cooled, 100 ml of water was added, and the layer of unchanged original ketone which formed was separated (67 g). The aqueous layer was treated with 40% aqueous KOH and extracted with benzene. The benzene solution was washed with water to remove diethylamine, and after it had been dried over anhydrous $MgSO_4$ it was fractionated. We obtained 70 g (59%, based on the ketone which reacted) of 3-[(diethylamino)methyl]-2,6-dimethyl-4-heptanone; b.p. 95° (0.08 mm); n_{D}^{20} 1.4400; d_4^{20} 0.8500; found MR 70.50; calculated MR 70.80.

<u>Reaction of 3-[(Diethylamino)methyl]-2,6-dimethyl-4-heptanone with</u> <u>Triethyl Phosphite in Presence of Acetic Acid.</u> A mixture of 22.7 g of 3-[(diethylamino)-methyl]-2,6-dimethyl-4-heptanone, 16.6 g of triethyl phosphite, and 6 g of acetic acid started to react at 123°, and in the course of 1 h the temperature was raised to 168°. 13.6 ml (10.7 g) of volatile products was driven off. In the fractionation of the reaction mixture we obtained 16.2 g (55%) of diethyl (2-iso-propyl-5-methyl-3-oxohexyl)phosphonate; b.p. 117° (0.03 mm); n_D^{20} 1.4452; d_4^{20} 1.0012. Found: P 10.71, 10.50; C 57.49, 57.31; H 9.43, 9.67%; MR 77.75. $C_{14}H_{29}O_4P$. Calculated: P 10.59; C 57.48; H 9.99%; MR 77.73. <u>Reaction of 2-[(Diethylamino)methyl]cyclopentanone with Triethyl Phos-</u> phite in Presence of Acetic Acid. On addition of 6 g of acetic acid to a mixture of 8.5 g of 2-[(diethylamino)methyl]cyclopentanone and 8.3 g of triethyl phosphite an exothermic reaction set in and the temperature of the reaction mixture rose to 102°. In the course of 20 min the mixture was heated to 140°, and 5.4 ml of volatile products was distilled off. In the fractionation of the reaction mixture we obtained 8.6 g (73%) of diethyl [(2-oxocyclopentyl)methyl]phosphonate; b.p. 120-128° (0.05 mm); n_D^{20} 1.4607; d_2^{20} 1.1140. Found: P 12.78, 12.91; C 52.29, 52.18; H 8.17, 8.42; MR 57.69. $C_{10}H_{19}O_4P$. Calculated: P 13.22; C 51.28; H 8.17%. MR 57.05.

<u>Reaction of 2-[(Dimethylamino)methyl]cyclohexanone with Triethyl Phos-phite in Presence of Acetic Acid.</u> A mixture of 23.2 g of 2-[(dimethylamino)methyl]cyclohexanone, 24.9 g of triethyl phosphite, and 9 g of acetic acid started to react at 110°. In the course of the next 60 min the mixture was heated to 152°, and 9 ml of volatile products came off. By the simple fractionation of the reaction mixture we were unable to isolate an analytically pure reaction product. We isolated a fraction with b.p. 125° (0.04 mm); n_D^{20} 1.4709; d_4^{20} 1.0975. Found: P 10.14, 9.92; C 56.62, 56.35; H 8.63, 8.91%; MR 63.22. $C_{11}H_{21}O_4P$. Calculated: P 12.47; C 53.1; H 8.46%. The IR spectrum of this fraction contains an intense carbonyl absorption band (1724 cm⁻¹), and absorption due to an ethylenic bond is absent which excludes the presence of diethyl [(2-extocyclohexyl)methyl]phosphonate contaminated by products of the decomposition of the original Mannich base.

<u>Reaction of 2-[(Dimethylamino)methyl]-6-methylcyclohexanone with Tri-</u> ethyl Phosphite in Presence of Acetic Acid. 6 g of acetic acid was added dropwise to a mixture of 16.9 g of 2-[(dimethylamino)methyl]-6-methylcyclohexanone (prepared by the method described in [4]; n_D^{20} 1.4670; d_4^{20} 0.9381; found MR 50.01; calculated MR 50.13) and 16.6 g of triethyl phosphite heated to 130°. 8.2 ml of volatile products distilled off. The reaction mixture was heated further at this temperature for 0.5 h and then fractionated. Again we were unable to isolate an analytically pure product by simple distillation. We isolated a fraction with b.p. 142° (0.06 mm); n_D^{20} 1.4674; d_4^{20} 1.0773. Found: P 10.28, 10.48; C 57.06, 56.79; H 9.23, 8.96%; MR 67.57. $C_{12}H_{23}O_4P$. Calculated: P 11.81; C 54.95; H 8.83%; MR 66.29. The yield of the crude products was 14.4 g (52%).

Reaction of N, N, N', N'-Tetraethylmethanediamine with Triethyl Phosphite in Presence of Acetic Acid. A mixture of 15.6 g of N, N, N', N'-tetraethylmethanediamine, 16.6 g of triethyl phosphite, and 6 g of acetic acid began to react exothermically when its temperature attained 92°. In the course of the next 50 min the mixture was heated to 134°. 13.6 ml (10.8 g) of volatile products came off. In the fractionation of the reaction mixture we isolated 21.1 g (95%) of diethyl [(diethylamino)methyl]phosphonate; b.p. 118° (12 mm); n_D^{20} 1.4341; d_4^{20} 0.9966. Found: P 13.93, 14.20; N 6.25, 6.38%; MR 58.28. C₉H₂₂NO₃P. Calculated: P 13.91; N 6.28%; MR 58.28.

Reaction of 3-(Diethylamino)propionitrile with Triethyl Phosphite in Presence of Acetic Acid. 12 g of acetic acid was added dropwise to a mixture of 25.2 g of 3-(diethylamino)propionitrile [5] and 33.2 g of triethyl phosphite heated to 180°; 10.6 ml of volatile products distilled off. The reaction mixture was heated for 3 h at 190-200° and then fractionated. We isolated 14.9 g (39%) of diethyl (2-cyanoethyl)phosphonate; b.p. 159° (9 mm); n_D^{20} 1.4380; d_4^{20} 1.1067. Found: C 44.35, 44.15; H 7.50, 7.49; P 16.53, 16.30%; MR 44.91. C₇H₁₄O₃NP. Calculated: C 43.88; H 7.33; P 16.23%; MR 45.21.

A mixture of 12.6 g of 3-(diethylamino)propionitrile, 16.6 g of triethyl phosphite, and 6 g of acetic acid started to react at 135°. In the course of 40 min the mixture was heated to 151°; 9.2 g of volatile products was driven off. In the fractionation of the reaction mixture we obtained 9.5 g (50%) of diethyl (2-cyanoethyl)phosphonate.

Reaction of Ethyl 3-(Diethylamino)propionate with Triethyl Phosphite in Presence of Acetic Acid. 6 g of acetic acid was added dropwise to a mixture of 16.5 g of ethyl 3-(diethylamino)propionate and 16.6 g of triethyl phosphite heated to 170°; 15 ml of volatile products distilled off. The reaction mixture was heated for 3 h at 200° and fractionated. We isolated 13.5 g (57.6%) of 3-phosphonopropionic acid triethyl ester; b.p. 147° (8 mm); n_D^{20} 1.4310; d_4^{20} 1.0969. Found: C 45.00, 45.17; H 8.02, 8.22; P 12.12, 12.19%; MR 56.16. CgH₁₉O₅P. Calculated: C 45.37; H 7.98; P 13.02%; MR 56.20.

<u>Reaction of N, N-Diethylglycine Ethyl Ester with Triethyl Phosphite in</u> <u>Presence of Acetic Acid.</u> 6g of acetic acid was added dropwise to a mixture of 15.9g of N,N-diethylglycine ethyl ester and 16.6 g of triethyl phosphite heated to 170° ; 7.1 ml of volatile products distilled off. The reaction mixture was heated further at this temperature for 3 h. In the fractionation of the reaction mixture we isolated 6 g (27%) of phosphonoacetic acid triethyl ester; b.p. 130-132° (0.03 mm); n_{20}^{20} 1.4330; d_{40}^{20} 1.1330. Found: P 14.20%; MR 51.35. $C_8H_{17}O_5P$. Calculated: P 13.8%; MR 52.67.

<u>Reaction of Triethyl Phosphite with Diethyl [(Diethylamino)methyl]phos-</u> <u>phonate Ethiodide.</u> A mixture of 27.5 g of diethyl [(diethylaminomethyl]phosphonate ethiodide {prepared by mixing ethyl iodide and diethyl [(diethylamino)methyl]phosphonate, leaving the mixture for 3 days, filtering, and washing the product with dry ether; m.p. 75-80°; for $C_{11}H_{27}INO_3P$, found P 7.9%; calculated 8.17%} and 18 g of triethyl phosphite was heated with stirring for 6 h at 140°. A viscous resin, soluble in water and alcohol, was formed; it was extracted with benzene four times, and the combined extract was fractionally distilled. We obtained 10 g (81.2%) of diethyl ethylphosphonate; b.p. 88° (10 mm); n_D^{20} 1.4160. [6] gives: b.p. 86-88° (9 mm); n_D^{20} 1.4163.

CONCLUSIONS

1. A study was made of the reactions of triethyl phosphite with Mannich bases from acetone, butanone, 3-pentanone, 2,6-dimethyl-4-heptanone, 3,3-dimethyl-2-butanone, cyclohexanone, 2-methylcyclohexanone, and cyclopentanone, with N,N,N',N'-tetraethylmethanediamine, with 3-(diethylamino)propionitrile with ethyl 3-(diethylamino)propionate, with N,N-diethylglycine ethyl ester, and with diethyl [(diethylamino)methyl]phosphonate ethiodide.

2. For these reactions to take place it is necessary for an equimolecular amount of acetic acid or water to be present as a salt-forming agent.

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