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Phosphonic Acids. II. Synthesis of γ-Ketophosphonic Acids from Methyl Ketones *via* Mannich Bases[1,2]

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Triethyl phosphite reacts smoothly with the methiodide or hydrochloride of the Mannich base, 1-diethylaminobutan-3-one, to yield diethylγ-ketobutylphosphonate. This reaction provides a convenient synthesis of γ-ketophosphonic acids. The reaction of diethyl phosphite and sodium diethyl phosphite with the Mannich base and its derivatives has been investigated.

It is well known that β-dialkylamino ketones, commonly known as Mannich bases and readily prepared by the treatment of ketones with formaldehyde and a secondary amine[3] (equation 1), react with active methylene compounds in the presence of alkaline catalysts[4] to replace the nitrogen function by the active methylene residue.[3,5] The quaternary salts derived from Mannich bases (equation 2) undergo similar reactions, in many cases more readily than the free bases themselves.[3,5] Analogous alkylations by certain quaternary amine salts have been observed with a number of other anionic species including cyanide, sulfide, mercaptide, thiocyanate and bisulfite.[5]

In a search for convenient synthetic routes to γ-ketophosphonic acids,[6] the possibility of alkylation of trivalent phosphorus compounds by Mannich bases or their salts was investigated. This paper describes the reaction of a typical Mannich base, 1-diethylaminobutan-3-one (I, R = CH_3), its hydrochloride and its methiodide with triethyl phosphite, diethyl phosphite and the sodium salt of diethyl phosphite. The results obtained are summarized in Table I. In certain of the reactions, 1-diethylamino-3-phenylpropan-3-one (I, R = C_6H_5) was tried and found to react similarly.

$$\mathrm{RCOCH_3 + HCHO + HNEt_2 \longrightarrow \underset{I}{RCOCH_2CH_2NEt_2}} \quad (1)$$

$$\mathrm{I + CH_3I \longrightarrow \underset{II}{RCOCH_2CH_2\overset{+}{N}Et_2Me\ I^-}} \quad (2)$$

$$\mathrm{II + P(OEt)_3 \longrightarrow \underset{III}{RCOCH_2CH_2PO(OEt)_2} + Et_3\overset{+}{N}Me\ \overset{-}{I}} \quad (3)$$

$$\mathrm{III + H_2O \xrightarrow{HCl} \underset{IV}{RCOCH_2CH_2PO(OH)_2} + 2EtOH} \quad (4)$$

TABLE I

SUMMARY OF THE REACTION OF 1-DIETHYLAMINOBUTAN-3-ONE WITH VARIOUS PHOSPHORUS REAGENTS

Reagent Mannich base as:	Yield[a] of diethyl γ-ketobutylphosphonate, % Methiodide	Hydrochloride	Free base
$P(OEt)_3$	72	61	No reacn.[b]
$P(OEt)_3$ + 1% NaOEt	..	..	Trace[b]
$HPO(OEt)_2$	25	16	Trace[b]
			15
$HPO(OEt)_2$ + 10% $NaPO(OEt)_2$	..	..	35[b]
			9
$NaPO(OEt)_2$	18[b]	..	..

[a] Yield of redistilled product calculated on the Mannich base in methiodide experiments but on the pure salt in hydrochloride experiments. [b] In these reactions equimolar quantities of the Mannich base and phosphorus reagent were employed; in other cases excess phosphorus reagent was used.

Triethyl phosphite was found to react smoothly upon heating with the Mannich base methiodide II to eliminate the nitrogen function and produce the γ-ketophosphonate ester III which, by acid hydrolysis, is converted to the free γ-ketophosphonic acid IV. Thus the sequence of reactions (1–4) provides a convenient and apparently general procedure for the synthesis of γ-ketophosphonic acids.

$$\mathrm{P(OEt)_3 + RCOCH_2CH_2\overset{+}{N}Et_2H\ \overset{-}{Cl} \longrightarrow III + Et_3\overset{+}{N}H\ \overset{-}{Cl}} \quad (5)$$

The hydrochloride of the Mannich base reacts with triethyl phosphite in a manner similar to that of the methiodide to yield the same γ-ketophosphonate (equation 5). Although the yield is slightly higher and the product somewhat cleaner when the methiodide is used, the reaction of the Mannich base hydrochloride with triethyl phosphite is satisfactory and could serve as an alternative synthetic procedure in cases where the use of the methiodide is not convenient. In contrast to the behavior with the quaternary salts, no reaction is observed between triethyl phosphite and the free Mannich base even at 180° unless a catalytic amount of sodium ethoxide is present, in which case diethylamine is evolved, but little γ-ketophosponate is obtained.

The reaction of diethyl phosphite with Mannich bases and their salts follows a pattern somewhat different from that of triethyl phosphite. Diethyl phosphite reacts with both the methiodide and the hydrochloride, but the yield of γ-ketophosphonate is rather low, and appreciable amounts of higher

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[1] Paper I, THIS JOURNAL, **76**, 4172 (1954).

[2] This investigation was supported in part by a grant from the American Cancer Society as recommended by the Committee on Growth of the National Research Council.

[3] F. F. Blicke in "Organic Reactions," Vol. 2, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

[4] Recently it has been shown that alkylation of ketones, thiols and nitroparaffins by Mannich bases can be effected in the absence of catalysts; N. S. Gill, K. B. James, F. Lions and K. T. Potts, THIS JOURNAL, **74**, 4923 (1952).

[5] J. H. Brewster and E. L. Eliel in "Organic Reactions," Vol. 7, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, p. 99.

[6] Such compounds are of potential biochemical interest as phosphonate analogs of certain phosphorylated intermediates of carbohydrate metabolism, S. Preis, T. C. Myers and E. V. Jensen, to be published.

boiling products are found. Diethyl phosphite appears to catalyze the elimination of diethylamine from the free Mannich base, since the amine is evolved at a temperature (160°) at which no elimination occurs when triethyl phosphite is employed. Under these conditions a low yield of γ-ketophosphonate is obtained provided an excess of diethyl phosphite is employed. If a catalytic amount of sodium diethyl phosphite is added to the reaction of diethyl phosphite with the free Mannich base, diethylamine is evolved at a lower temperature (120°), and a fair yield of the γ-ketophosphonate can be obtained (equation 6). In this case, the presence of excess diethyl phosphite causes a lowering of the yield.

$$\mathrm{HPO(OEt)_2 + RCOCH_2CH_2NEt_2 \xrightarrow{NaPO(OEt)_2} III + Et_2NH} \quad (6)$$

The sodium salt of diethyl phosphite reacts with the Mannich base methiodide in tetrahydrofuran solution to give a low yield of the γ-ketophosphonate. The yield is not improved by carrying out the reaction with sodium dibutyl phosphite in benzene solution.

The mechanism of the reaction of Mannich bases and their salts with diethyl phosphite and with triethyl phosphite bears an interesting relationship to the mechanism or mechanisms of the reaction of Mannich bases with nucleophilic reagents in general. Investigations of this problem are currently in progress and will form the subject of a subsequent paper.

Experimental

Reactants.—Commercial[7] diethyl phosphite and triethyl phosphite were redistilled before use. Sodium diethyl phosphite was prepared by stirring a solution of diethyl phosphite in dry tetrahydrofuran with an excess of metallic sodium for 48 hours with subsequent removal of the undissolved sodium. The Mannich bases were prepared in the usual manner[3] from diethylamine, formaldehyde and acetone or acetophenone, respectively. 1-Diethylaminobutanone was isolated as the free base according to the procedure of Wilds and Shunk.[8] The hydrochloride was prepared by passing dry hydrogen chloride through a shaken solution of the freshly distilled amine in dry ether at 0°. After precipitation was complete, the solid was filtered with suction and washed with dry ether, always keeping the crystals covered with solvent on the filter. The solid was transferred immediately to a vacuum desiccator and allowed to stand several hours over KOH. 3-Ketobutyldiethylammonium chloride thus was obtained in 54% yield, m.p. 77–77.5°, reported[9] 74–77°. 1-Diethylamino-3-phenylpropan-3-one was isolated directly as the hydrochloride, m.p. 108–110°, as described by Blicke and Burckhalter.[10]

The preparation of 3-ketobutyldiethylmethylammonium iodide was carried out by a slight modification of the procedure of Wilds and Shunk.[8] Methyl iodide was added slowly with stirring to an equal weight of 1-diethylaminobutan-3-one held at 0°. Stirring was continued for an hour at 0° and then another hour at room temperature until the methiodide began to crystallize. At this point stirring was discontinued or else the reaction became too violent. The solid methiodide was thoroughly washed with dry benzene three times by decantation, and the diethyl phosphite or triethyl phosphite was added directly.

Reaction of Sodium Diethyl Phosphite with 3-Ketobutyldiethylmethylammonium Iodide.—The methiodide prepared from 14.3 g. (0.1 mole) of 1-diethylaminobutan-3-one was dissolved in 20 ml. of dry tetrahydrofuran and treated with a tetrahydrofuran solution containing 0.1 mole of sodium diethyl phosphite. The mixture was stirred in an atmosphere of dry nitrogen at room temperature for two hours and then on the steam-bath for another hour. After most of the tetrahydrofuran had been removed in a stream of nitrogen, the residue was filtered to remove solid material; the filtrate was evaporated and the product extracted from the viscous residue by trituration with several portions of toluene. The toluene was removed at reduced pressure and the residue distilled. Diethyl γ-ketobutylphosphonate (3.78 g. 18%) was collected at 105–107° (0.3 mm.), $n^{25}\text{D}$ 1.4353.

Anal. Calcd. for $C_8H_{17}O_4P$: C, 46.15; H, 8.23; P, 14.87. Found: C, 46.30; H, 8.50; P, 14.74.

The infrared spectrum of this product indicated a carbonyl peak (1718 cm.$^{-1}$) in addition to the usual phosphonate absorption[11] (peaks at 735, 1030, 1162 and 1245 cm.$^{-1}$). Its identity was confirmed further by hydrolysis to the free phosphonic acid (see below) and by conversion to the 2,4-dinitrophenylhydrazone derivative. For the latter reaction, a solution of 0.42 g. of the γ-ketophosphonate ester, 0.40 g. of 2,4-dinitrophenylhydrazine and 0.3 ml. of concentrated sulfuric acid in 10 ml. of absolute methanol was heated to reflux for 15 minutes and allowed to stand at room temperature overnight. The reaction mixture was then poured through a column of Amberlite IR-4B (OH$^-$) resin which previously had been well washed with ethanol. The eluant from the column was concentrated under reduced pressure and the residual orange oil crystallized from ethanol at 0°. After three recrystallizations from ethanol, the 2,4-dinitrophenylhydrazone melted at 105–107°.

Anal. Calcd. for $C_{14}H_{21}O_7N_4P$: C, 43.30; H, 5.45; N, 14.40; P, 8.16. Found: C, 43.70; H, 5.62; N, 13.90; P, 7.90.

γ-Ketobutylphosphonic Acid.—Diethyl γ-ketobutylphosphonate (980 mg.) was heated under reflux for four hours with 5 ml. of concentrated hydrochloric acid. The mixture was evaporated to dryness *in vacuo*, and the last traces of moisture were removed from the residual oil by distilling off two 10-ml. portions of dry benzene. After evacuation overnight with an oil-pump, the resulting solid was recrystallized from chloroform to yield 500 mg. (70%) of γ-ketobutylphosphonic acid, m.p. 81–82°.

Anal. Calcd. for $C_4H_9O_4P$: C, 31.59; H, 5.96; P, 20.37. Found: C, 31.44; H, 6.34; P, 20.26.

Reaction of Triethyl Phosphite with 3-Ketobutyldiethylmethylammonium Iodide.—The methiodide, prepared by the reaction of 7.15 g. (0.05 mole) of 1-diethylaminobutan-3-one with 7.15 g. of methyl iodide, was treated with 41.5 g. (0.25 mole) of triethyl phosphite, and the mixture was heated at 130° for one hour. After cooling, the white precipitate was removed by filtration and washed on the filter with dry benzene. Thus was obtained 10.6 g. (87%) of triethylmethylammonium iodide, m.p. 283–285°.

Anal. Calcd. for $C_7H_{18}NI$: I, 52.20. Found: I, 52.25.

The benzene was evaporated from the filtrate at reduced pressure and the residual light yellow oil distilled *in vacuo*. Crude diethyl γ-ketobutylphosphonate (8.4 g., 81%) was collected at 89–97° (0.08 mm.) and redistilled to yield the purified product (7.5 g., 72%, b.p. 96–98° (0.14 mm.), $n^{25}\text{D}$ 1.4352) whose infrared spectrum was similar to that of the previously analyzed sample of this ester.

1.0 g. of the product was hydrolyzed in hydrochloric acid as described previously to yield 650 mg. (89%) of γ-ketobutylphosphonic acid, m.p. 80–81°; neut. equiv., calcd. 152.1, found 152.4.

Reaction of Triethyl Phosphite with 3-Ketobutyldiethylammonium Chloride.—6.0 g. (0.034 mole) of the hydrochloride of 1-diethylaminobutan-3-one was treated with 27.7 g. (0.167 mole) of triethyl phosphite and the mixture heated under reflux to 140° whereupon vigorous boiling took place. The reaction was maintained at this temperature for two hours and then at room temperature overnight. A small amount of white solid precipitate was removed by filtration, and the pale yellow reaction mixture was distilled. A product with the odor of diethylamine was collected at

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(7) Generously supplied by the Monsanto Chemical Co. and the Virginia-Carolina Co.

(8) A. L. Wilds and C. H. Shunk, THIS JOURNAL, **65**, 469 (1943).

(9) K. Tsuda, S. Hukushima and A. Oguri, *J. Pharm. Soc. Japan*, **61**, 71 (1941).

(10) F. F. Blicke and J. H. Burckhalter, THIS JOURNAL, **64**, 451 (1942).

(11) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 853 (1951).

39–52°; then the excess triethyl phosphite was removed under reduced pressure and the residue distilled *in vacuo*. Crude diethyl γ-ketobutylphosphonate (5.2 g., 73%) was collected at 95–107° (0.4 mm.) which, on redistillation, yielded the purified product (4.3 g., 61%, b.p. 95–107° (0.08 mm.)), n^{25}D 1.4356. Hydrolysis of this product in concentrated hydrochloric acid gave an 86% yield of γ-ketobutylphosphonic acid, m.p., 78–80.5°.

Reaction of Triethyl Phosphite with 1-Diethylaminobutan-3-one.—No visible change was observed when a mixture of 5.6 g. (0.039 mole) of the free Mannich base and 6.4 g. (0.039 mole) of triethyl phosphite was heated to 180°. With the addition of a trace of sodium ethoxide there was an immediate darkening of the reaction mixture, and the theoretical amount of diethylamine was evolved within 30 minutes. After two distillations of the reaction mixture there was obtained 1.5 g. of a material boiling at 98° (0.15 mm.) whose refractive index (n^{25}D 1.4375) and infrared spectrum indicated that it was probably diethyl γ-ketobutylphosphonate.

Reaction of Diethyl Phosphite with 3-Ketobutyldiethylmethylammonium Iodide.—The methiodide prepared from 7.15 g. (0.05 mole) of 1-diethylaminobutan-3-one was treated with 34.5 g. (0.25 mole) of diethyl phosphite and the mixture heated to 135° whereupon refluxing took place. After two hours at this temperature the reaction mixture was cooled and allowed to stand overnight. The precipitate of triethylmethylammonium iodide (3.9 g., 32%) was removed by filtration and the pale yellow filtrate distilled at reduced pressure. After removal of the excess diethyl phosphite, the fraction boiling at 112–150° (0.6 mm.) collected and redistilled to yield diethyl γ-ketobutylphosphonate (2.6 g., 25%, b.p. 97–100° (0.3 mm.), n^{25}D 1.4357). There remained a high boiling residue which on strong heating *in vacuo* decomposed without darkening to yield volatile products, the nature of which has not been established as yet.

Hydrolysis of the diethyl γ-ketobutylphosphonate in hydrochloric acid gave a 64% yield of γ-ketobutylphosphonic acid, m.p. 81–82°.

Reaction of Diethyl Phosphite with 3-Ketobutyldiethylammonium Chloride.—12.5 g. (0.07 mole) of the Mannich base hydrochloride was treated with 48.2 g. (0.35 mole) of diethyl phosphite, and the mixture heated to 140–150° for 2 hours. The reaction mixture gradually darkened and ethyl chloride was evolved (mol. wt. calcd. for C_2H_5Cl, 64.5; found by vapor density, 64.4). The excess diethyl phosphite was removed under reduced pressure and the dark viscous residue distilled *in vacuo*. The fraction boiling at 60–98° (0.15 mm.) was collected and redistilled to yield slightly impure diethyl γ-ketobutylphosphonate (2.3 g., 16%, b.p. 89–96° (0.01 mm.), n^{25}D 1.4365).

Hydrolysis of a portion of this product in concentrated hydrochloric acid gave a 16.5% yield of γ-ketobutylphosphonic acid, m.p. 79–81°.

Reaction of Diethyl Phosphite with 1-Diethylaminobutan-3-one.—When the free Mannich base (14.3 g., 0.1 mole) was heated with an equimolar amount of diethyl phosphite (13.8 g., 0.1 mole), evolution of diethylamine (6.9 g., 0.09 mole, identified as the hydrochloride, m.p. 223–224°) took place at 160°. On distillation of the red viscous residue only a small amount of material which appeared to be diethyl γ-ketobutylphosphonate was obtained.

When the free Mannich base (14.3 g., 0.1 mole) was heated with excess diethyl phosphite (69.1 g., 0.5 mole), diethylamine was evolved at 170°. After two hours at this temperature the excess diethyl phosphite was removed at reduced pressure after which the crude product (8.2 g., b.p. 80–104° (0.09 mm.)) was collected. The residue was a clear red glass. On redistillation of the crude product there was obtained diethyl γ-ketobutylphosphonate (3.2 g., 15%, b.p. 76–108° (0.35 mm.), n^{25}D 1.4356). A portion of this product was hydrolyzed to γ-ketobutylphosphonic acid, m.p. 81–83°, in 34% yield.

When the free Mannich base (14.3 g., 0.1 mole) was mixed with an equimolar amount (13.8 g., 0.1 mole) of diethyl phosphite in the presence of 10 mole per cent. of sodium diethyl phosphite (prepared by dissolving 0.01 mole of sodium in 0.11 mole of diethyl phosphite) spontaneous warming was observed. The reaction mixture was heated to 120° whereupon evolution of diethylamine commenced. After 20 minutes at this temperature followed by 40 minutes at 175°, 5.5 g. (74%) of diethylamine had been collected. Distillation of the dark reaction mixture yielded crude diethyl γ-ketobutylphosphonate (8.5 g., b.p. 40–108° (0.4 mm.)) which, on redistillation, gave the purified product (7.2 g., 35%, b.p. 84–91° (0.01 mm.), n^{25}D 1.4358) whose identity was confirmed by hydrolysis in 60% yield to γ-ketobutylphosphonic acid, m.p. 80–81°.

When the free Mannich base was heated in an inert atmosphere with a fivefold excess of diethyl phosphite in the presence of 10 mole per cent. sodium diethyl phosphite, evolution of diethylamine took place at 140°, but there was no darkening of the reaction mixture. However, only a 9% yield of diethyl γ-ketobutylphosphonate could be isolated accompanied by a considerable amount of a higher boiling product (b.p. 160–161° (0.35 mm.), n^{25}D 1.4500).

Reaction of Triethyl Phosphite with 2-Benzoylethyldiethylammonium Chloride.—12.1 g. (0.05 mole) of the hydrochloride of 1-diethylamino-3-phenylbutan-3-one was treated with 41.6 g. (0.25 mole) of triethyl phosphite and the mixture heated while stirring at 140° for two hours. Volatile products (amines) and excess triethyl phosphite were removed under reduced pressure, and the residual oil was distilled *in vacuo*. Crude diethyl 2-benzoylethylphosphonate (9.8 g., 73%) was collected at 172–181° (0.08 mm.) and redistilled to yield the purified product (6.4 g., 47%, b.p. 163–167° (0.008 mm.), n^{25}D 1.5050). The infrared spectrum of this substance indicated a conjugated carbonyl peak (1685 cm.$^{-1}$) in addition to the phosphonate absorption (736, 1030, 1162 and 1242 cm.$^{-1}$).

Anal. Calcd. for $C_{13}H_{19}O_4P$: C, 57.8; H, 7.09; P, 11.46. Found: C, 56.5[12]; H, 7.19; P, 11.37, 11.56.

540 mg. of this product in 1 ml. of absolute ethanol was treated with a solution of 400 mg. of 2,4-dinitrophenylhydrazine and 0.2 ml. of concentrated sulfuric acid in 5 ml. of absolute ethanol, and the mixture was refluxed for 15 minutes. On cooling, reddish crystals separated which were removed by filtration, washed with cold absolute ethanol and dried *in vacuo* to yield 690 mg. (76%) of a 2,4-dinitrophenylhydrazone which, after recrystallization from absolute ethanol, melted at 138–139°.

Anal. Calcd. for $C_{19}H_{23}N_4O_7P$: C, 50.66; H, 5.15; N, 12.44; P, 6.88. Found: C, 49.00[12]; H, 5.43; N, 12.00; P, 6.68.

2-Benzoylethylphosphonic Acid.—500 mg. of diethyl 2-benzoylethylphosphonate was hydrolyzed with concentrated hydrochloric acid in the manner previously described for diethyl 3-ketobutylphosphonate. Two recrystallizations from chloroform gave 300 mg. (75%) of 2-benzoylethylphosphonic acid, m.p. 123–124°.

Anal. Calcd. for $C_9H_{11}O_4P$: C, 50.47; H, 5.18; P, 14.47; neut. equiv., 214.2. Found: C, 49.36[12]; H, 5.45; P, 14.29; neut. equiv., 215.8.

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[12] It is noteworthy that the carbon analyses were consistently low in this phosphonic acid and its derivatives.