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Reactions of Quaternary Salts of Gramine with Diethyl and Triethyl Phosphite[1]

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The reactions of gramine and certain of its quaternary salts with triethyl phosphite, diethyl phosphite, and sodium diethyl phosphite have been investigated. Triethyl phosphite and sodium diethyl phosphite react smoothly with gramine methiodide and gramine methosulfate to yield diethyl 3-indolylmethylphosphonate.

Two general procedures for the preparation of esters of alkylphosphonic acids involve the phosphorus alkylation by alkyl halides of trialkyl phosphites (Equation 1, A = Cl; Br; I) and of the sodium salts of dialkyl phosphites (Equation 2, A = Cl; Br; I). These procedures are perhaps best known as the Michaelis-Arbuzov and the Michaelis, Becker-Nylen syntheses, respectively, and have been well reviewed by Kosolapoff.[2,3]

$$\mathrm{RA}\begin{cases}\xrightarrow{\mathrm{P(OR')_3}} \mathrm{RPO(OR')_2 + R'A} & (1)\\[2ex] \xrightarrow{\mathrm{NaPO(OR')_2}} \mathrm{RPO(OR')_2 + NaA} & (2)\end{cases}$$

Classes of compounds other than the alkyl halides may be employed as alkylating agents in these syntheses. Included here, as one type, are reagents bearing a displaceable anionic group other than halogen. For example, Myers, Preis, and Jensen[4] have prepared a series of alkylphosphonates by alkylation of triethyl phosphite and sodium diethyl phosphite with alkyl esters of sulfonic acids (Equations (1) and (2), A = CH_3SO_2O; p-$CH_3C_6H_4SO_2O$).

Ketone Mannich bases and certain of their derivatives have recently been shown to comprise a different class of reagents for alkylation of trivalent phosphorus esters in procedures analogous to (1) and (2).[5] Ketone Mannich base methiodides, for example, react *via* displacement of the nitrogen function to alkylate the phosphorus atom of triethyl phosphite (Equation 3) and of sodium diethyl phosphite (Equation 4) to produce diethyl γ-ketophosphonates.

$$\mathrm{R'COCH_2CH_2\overset{+}{N}R_2Me\overset{-}{I}}\begin{cases}\xrightarrow{\mathrm{P(OEt)_3}} \mathrm{R'COCH_2CH_2PO(OEt)_2 + Et\overset{+}{N}R_2Me\overset{-}{I}} & (3)\\[2ex] \xrightarrow{\mathrm{NaPO(OEt)_2}} \mathrm{R'COCH_2CH_2PO(OEt)_2 + MeNR_2 + NaI} & (4)\end{cases}$$

Reactions of this type, *i.e.*, the phosphorus alkylation of dialkyl and trialkyl phosphites by amines or quaternary ammonium salts, are of potential wide applicability to the synthesis of a variety of phosphonates since in addition to ketone Mannich bases other classes of amines and of quaternary ammonium salts possess alkylating properties[6] and may serve in such reactions as reagents for phosphorus alkylation. Included among these classes are a number of readily obtainable dialkylaminomethyl derivatives of heterocycles of the general type ACH_2NR_2 (A = heterocyclic nucleus) and their quaternary ammonium salts. Gramine (3-dimethylaminomethylindole) and its quaternary derivatives, for example, have found extensive use in the carbon alkylation of a number of species including Grignard reagents, active methylene compounds and cyanide. Similar compounds such as the quaternary salts of 2-dimethylaminomethylpyrrole, 2-dimethylaminomethylfuran and of 2-acetamido-4-methyl-5-dimethylaminomethylthiazole have been employed in the carbon alkylation of active methylene compounds.[7]

To determine the applicability of amines and quaternary salts of this general type as reagents for the phosphorus alkylation of dialkyl and trialkyl phosphites in the synthesis of indolylmethylphosphonates and related compounds [procedures analogous to (3) and (4)], the reactions of gramine, its methiodide, and its methosulfate with triethyl phosphite, diethyl phosphite, and sodium diethyl phosphite were investigated.

Gramine methiodide (I, A = I) and gramine methosulfate (I, A = CH_3OSO_2O) were found to react when heated with excess triethyl phosphite to

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[1] Supported by a grant from the Graduate Research Committee, University of Illinois Professional Colleges.

[2] G. M. Kosolapoff, *Organophosphorous Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, Chap. 7.

[3] G. M. Kosolapoff, *Org. Reactions*, **VI**, Chap. 6 (1951).

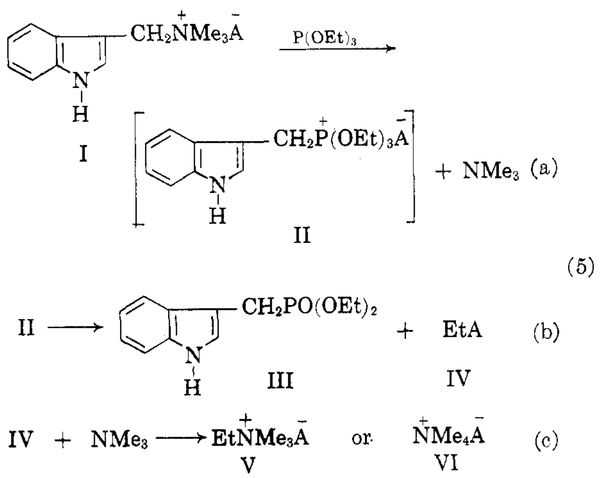
[4] T. C. Myers, S. Preis, and E. V. Jensen, *J. Am. Chem. Soc.*, **76**, 4172 (1954).

[5] T. C. Myers, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, **77**, 3101 (1955).

[6] For an excellent comprehensive review see J. H. Brewster and E. L. Eliel, *Org. Reactions*, **VII**, Chap. 3 (1953).

[7] See 6 for key references.

give diethyl 3-indolylmethylphosphonate (III) in yields approximating 75%. In analogy to the well-established mechanism operating in reactions between alkyl halides and trialkyl phosphites, these reactions may be postulated to occur as shown in Equation 5.

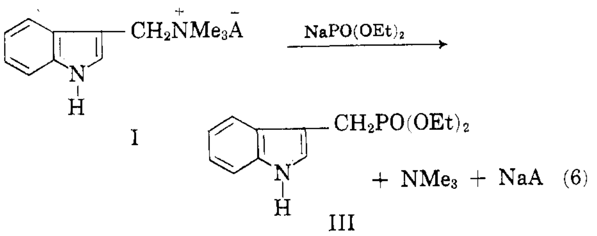


Here is indicated (5,a) the intermediate formation, *via* displacement of trimethylamine, of a quaternary phosphonium salt (II, A = I; $MeOSO_2O$); this salt reacts (5,b) to eliminate a molecule of ethyl iodide (IV, A = I) or of ethyl methyl sulfate (IV, A = CH_3OSO_2O) which in turn (5,c) alkylates the trimethyl amine. A 91% yield of trimethylethylammonium iodide (V, A = I) was isolated from the reaction involving gramine methiodide. A mixture of sulfur-containing salts was obtained from the gramine methosulfate reaction from which was isolated in 50% yield a crystalline salt which gave a sulfur analysis corresponding to trimethylethylammonium methosulfate (V, A = $MeOSO_2O$) or to tetramethylammonium ethosulfate (VI, A = $EtOSO_2O$). While our results tend to substantiate the mechanism as written, there is no direct evidence to indicate that the steps occur in the order indicated above and no evidence relating to the type of mechanism operating in the displacement of trimethylamine from the starting quaternary salts.

A crude preparation of gramine methiodide containing bis(3-indolylmethyl)dimethylammonium iodide was found to react smoothly with triethyl phosphite to give III in an over-all yield of 30% based on gramine as compared to a yield of 41% when the pure methiodide was used. Thus the rather laborious procedures for the final purification of the methiodide were of little advantage.

Reactions between gramine methiodide or gramine methosulfate with diethyl hydrogen phosphite under conditions similar to those used with triethyl phosphite produced only high boiling resins from which no diethyl 3-indolylmethylphosphonate could be isolated. Similar results were obtained in a reaction between free gramine and triethyl phosphite.

The reaction in alcohol solution between the sodium salt of diethyl phosphite and the crude preparation of gramine methiodide (I, A = I) just described followed the expected course (Equation 6) to produce diethyl 3-indolylmethylphosphonate (III) in yields from gramine, of 20%. The analogous reaction with gramine methosulfate (I, A = $MeOSO_2O$) produced III in 75% yield (40% based on starting gramine).



Diethyl 3-indolylmethylphosphonate (III) was obtained in each of the above described successful procedures as a crystalline solid of m.p. 61–62°. Its structure was established by elementary analysis and by consideration of its infrared spectrum which showed absorption bands corresponding to the indole nucleus and to the diethylphosphonate grouping.

Attempts to hydrolyze the ester in acid medium were unsuccessful, and resulted in extensive decomposition of the molecule. Hydrolysis by aqueous sodium hydroxide produced the half ester, ethyl hydrogen 3-indolylmethylphosphonate (m.p. 136–137°) in 62% yield.

Diethyl 3-indolylmethylphosphonate and ethyl hydrogen 3-indolylmethylphosphonate are of biological interest as phosphonate analogs of natural metabolites such as tryptophan or heteroauxin (3-indolylmethylacetic acid) which contain the indole nucleus with an acid bearing side chain in the 3-position. They may be of special interest in the latter case since the sulfonic acid analog of heteroauxin (3-indolylmethylsulfonic acid) has been shown to be an inhibitor of heteroauxin.[8] Studies relating to the biological properties of these compounds are in progress.

EXPERIMENTAL[9]

Reactants. Diethyl phosphite and triethyl phosphite, obtained from commercial sources,[10] were redistilled before use.

Gramine was prepared according to the procedure of Snyder, Smith, and Stewart from dimethylamine, formaldehyde, and indole.[11] The preparation of gramine methiodide

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(8) T. Wieland, F. Fischer, and F. Moewus, *Ann.*, **561**, 47 (1948).

(9) Analyses were conducted by G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England. All melting points are uncorrected.

(10) The authors are grateful to the Victor Chemical Works and to the Virginia-Carolina Chemical Corp., for generous samples of diethyl and triethyl phosphites.

(11) H. R. Snyder, C. Smith, and J. H. Stewart, *J. Am. Chem. Soc.*, **66**, 200 (1944).

was carried out by the method of Geissman and Armen by treatment of gramine with a large excess of methyl iodide.[12] A crude product of m.p. 154–158° described by these authors was obtained (1.8 g. from 1 g. of gramine) directly from the reaction mixture by trituration with benzene. This product, the "crude gramine methiodide," used directly in some of the reactions described in the following, contained appreciable amounts of bis(3-indolylmethyl)dimethylammonium iodide and tetramethylammonium iodide. A series of recrystallizations of this material from methanol-benzene gave pure gramine methiodide, m.p. 168–169° in 40% (reported 55%) from gramine.

Gramine methosulfate was prepared by the method of Schöpf and Thesing[13]; yield 63%; m.p. 144–145°.

Reaction of triethyl phosphite with gramine methiodide. A stirred solution of 524 mg. (1.6 mmoles) of pure gramine methiodide in 1.5 g. (8 mmoles) of triethyl phosphite was heated in an oil bath with careful protection from moisture. At a bath temperature of 130° the methiodide dissolved, and the yellow solution was refluxed at a bath temperature of 160° for 30 min., during which time a clean white precipitate was formed. After cooling, the solid was removed by filtration and washed with dry benzene and then with ethanol. Thus was obtained 310 mg. (91%) of trimethylethylammonium iodide, m.p. 290°.

Anal. Calcd. for $C_5H_{14}NI$: I, 59.0. Found: I, 59.6.

The solvents were evaporated from the filtrate at reduced pressure and the residual oil was distilled *in vacuo*. Crude diethyl 3-indolylmethylphosphonate (III) (320 mg., 72%) was collected at 180–200° (0.3 mm.). The viscous distillate solidified on cooling (m.p. 51–55°) and on recrystallization from 30–60° petroleum ether gave 200 mg. of colorless needles, m.p. 61–62°.

Anal. Calcd. for $C_{13}H_{18}NO_3P$: C, 58.4; H, 6.7; N, 5.2; P, 11.6. Found: C, 58.2; H, 6.8; N, 5.4; P, 11.2.

The infrared spectrum[14] of this product indicated indole peaks at 773, 1627, and 3190 cm.$^{-1}$ as compared to gramine as a reference compound (peaks at 777, 1623, and 3110 cm.$^{-1}$) as well as the usual phosphonate absorption[15] (peaks at 978, 1060, and 1226 cm.$^{-1}$).

When 7 g. of crude gramine methiodide (see Reactants) was heated with 18 g. of triethyl phosphite, a yellow solution was obtained at a bath temperature of 140°, which was refluxed for an additional 45 min. On cooling, 3.6 g. (77%) of trimethylethylammonium iodide was separated. The filtrate was concentrated at reduced pressure and distillation gave 1.8 g. (30% from gramine) of diethyl 3-indolylmethylphosphonate b.p. 180–200° (0.3 mm.); m.p. 61–62° after recrystallization from 30–60° petroleum ether, undepressed when admixed with a previously analyzed sample.

Ethyl hydrogen 3-indolylmethylphosphonate. Diethyl 3-indolylmethylphosphonate (320 mg.) was refluxed with 4 ml. of 5% sodium hydroxide solution for 6 hr. at which time the original two-phase mixture had formed a clear solution. The solution was cooled and neutralized with cold 1:1 hydrochloric acid. The white solid was filtered, washed thoroughly with water, dried and recrystallized from a petroleum ether–acetone mixture to yield 180 mg. (62%) of thread-like colorless crystals, m.p. 136–137°.

Anal. Calcd. for $C_{11}H_{14}NO_3P$: C, 55.22; H, 5.86; N, 5.86; P, 12.97; neut. equiv., 239. Found: C, 55.45; H, 6.13; N, 6.20; P, 12.75; neut. equiv., 236.

All attempts at hydrolysis in acid solution resulted in extensive decomposition and no products could be isolated.

Reaction of triethyl phosphite with gramine methosulfate. A stirred suspension of 1.5 g. (5 mmoles) of gramine methosulfate in 3.0 g. (50 mmoles) of triethyl phosphite was heated in an oil bath with careful exclusion of moisture. After 30 min. of refluxing at a bath temperature of 170° the solid methosulfate was replaced by a liquid phase. Refluxing was continued for an additional 30 min., the reaction mixture was cooled, and the white precipitate which formed on cooling was filtered and washed with dry benzene to give 810 mg. of a hygroscopic solid. Recrystallization from acetone–absolute ethanol gave 498 mg. (50%) of a crystalline solid which analyzed for ethyltrimethylammonium methosulfate or for tetramethylammonium ethosulfate.

Anal. Calcd. for $C_6H_{17}NO_4S$: S, 16.0%. Found: S, 15.9%.

The filtrate and washings were concentrated at reduced pressure and the residual yellow oil was distilled *in vacuo* to give 995 mg. (75%) of diethyl 3-indolylmethylphosphonate; b.p. 200–230° (0.6 mm.); m.p. 55–58°, raised to 61–62° on recrystallization from 30–60° petroleum ether.

Reaction of triethyl phosphite with free gramine. No change was observed when a mixture of gramine and a 5 molar excess of triethyl phosphite was stirred at room temperature. On heating to 110° the gramine dissolved and the yellow solution was refluxed for an additional 3 hr. at a bath temperature of 150°. The excess triethyl phosphite was removed under reduced pressure and distillation of the residual resin was attempted. A small amount of a very viscous distillate was collected at 230–250° (0.3 mm.) with the aid of a free flame. No crystalline product could be isolated from this material.

Reaction of sodium diethyl phosphite with gramine methiodide. A solution of sodium diethyl phosphite was prepared by addition at room temperature of 1.04 g. (7.5 mmoles) of diethyl phosphite to sodium ethoxide from 170 mg. (7.5 mmoles) of sodium in 21 ml. of absolute ethanol. To this solution there was added 2.6 g. of crude gramine methiodide (from 1.4 g., 7.5 mmoles, of gramine; see Reactants) and the resulting solution was stirred at room temperature. An odor characteristic of trimethylamine was detectable within a few minutes and sodium iodide began to separate after about 1 hr. After 6 hr. the solution was filtered from sodium iodide and concentrated under reduced pressure to a viscous oil. This material was exhaustively extracted with ether, the ether extracts concentrated, and the residual oil distilled *in vacuo* to yield diethyl 3-indolylmethylphosphonate (430 mg., 20% from gramine); b.p. 200–250° (0.6 mm.); m.p. 55–58°, raised to 61–62° after recrystallization from 30–60° petroleum ether, undepressed when admixed with previously described samples.

Reaction of sodium diethyl phosphite with gramine methosulfate. Gramine methosulfate, 1.5 g. (5 mmoles), was added to a solution of sodium diethyl phosphite prepared from 695 mg. (5 mmoles) of diethyl phosphite and sodium ethoxide from 11.5 mg. (5 mmoles) of sodium in 12 ml. of absolute ethanol. The mixture warmed spontaneously to about 50° and the resulting solution was stirred at room temperature for 6 hr. The odor of trimethylamine was detectable within a few minutes; no precipitate was formed during the reaction. The solution was concentrated at reduced pressure and the residual oily solid was extracted exhaustively with ether. After evaporation of the ether the product was distilled *in vacuo* to yield 550 mg. (40% from gramine) of diethyl 3-indolylmethylphosphonate; b.p. 180–200° (0.3 mm.); m.p. 57–60°, raised to 61–62° on recrystallization from petroleum ether.

Reaction of diethyl phosphite with gramine methiodide. A mixture of gramine methiodide and a 5 molar excess of diethyl phosphite was stirred at room temperature for 4 hr. The slightly cloudy solution was concentrated under reduced pressure to a brown viscous residue. On attempted distillation at 0.3 mm. this material produced a small amount of viscous oil which did not solidify on seeding.

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(12) T. A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952).

(13) C. Schöpf and J. Thesing, *Angew. Chem.*, **63**, 377 (1951).

(14) The authors are grateful to Dr. James Brader of the Department of Chemistry, University of Illinois, Urbana, for the spectrum analyses and for his interpretations of the different peaks of the product as compared to those of gramine which was the reference compound.

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

The bulk of the material carbonized in the flask when heated over 200°.

When gramine methiodide was heated for several hours at 100° with excess diethyl phosphite the reaction mixture colored and turned resinous, and carbonization occurred on attempted distillation.

Reaction of diethyl phosphite with gramine methosulfate. A suspension of gramine methosulfate in a 5 molar excess of diethyl phosphite was stirred at room temperature for 3 hr. during which time no change was observed. The temperature was raised to 110° to produce a pale yellow solution which was refluxed for 3 hr. On cooling about 60% of the gramine methosulfate reprecipitated and was recovered by filtration. Attempted distillation of the filtrate produced a resinous material which carbonized when heated to 200°.

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