# Reactions of Phosphorus Compounds. VIII. Preparation of Pyrrolizidine Compounds from Vinyltriphenylphosphonium Bromide

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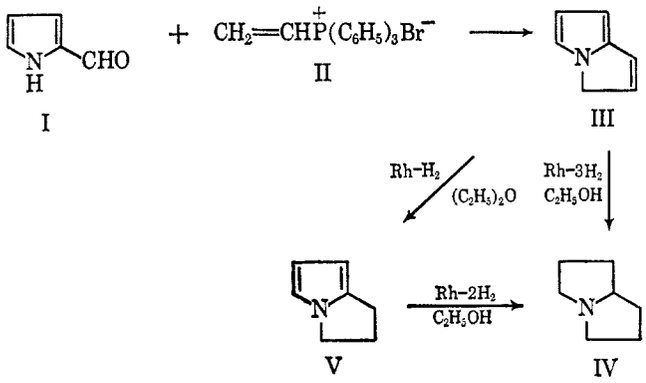
The preparation of 3H-pyrrolizine (III), 1-methyl-3H-pyrrolizine (VIII), and 3H-pyrrolo[1,2-*a*]indole (XI) and their reduction products is reported.

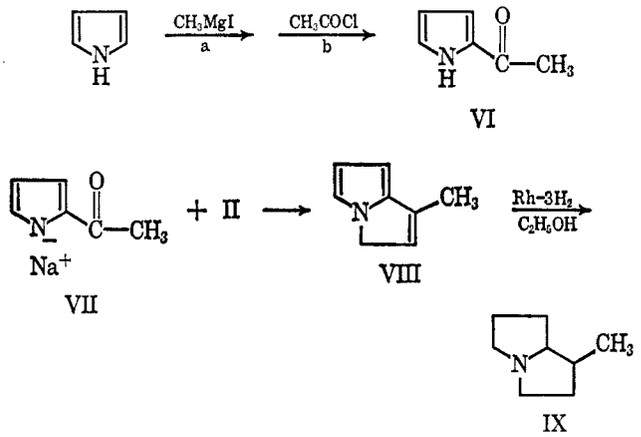
In a previous paper in this series[1] we reported the synthesis of 3H-pyrrolizine (III), 1,2-dihydro-3H-pyrrolizine (V), and pyrrolizidine (IV) by means of the new general ring synthesis developed in these laboratories using vinyltriphenylphosphonium bromide (II).[2] These types of compounds are of interest because of the occurrence of this saturated or partially saturated fused ring system in alkaloids such as those of the *Senecio* group, for example riddelline.[3]

We have more recently prepared several related compounds of this type, namely, 1-methyl-3H-pyrrolizine (VIII), 3H-pyrrolo[1,2-*a*]indole (XI), and dihydro-3H-pyrrolo[1,2-*a*] indole (XII), using the vinyl salt II and suitable carbonyl compounds. Compounds with structure such as XI are of interest because of the antibacterial activity of related compounds such as those reported by Allen.[4]

When pyrrole-2-aldehyde (I) was allowed to react with the vinyl salt II in the presence of sodium hydride in ether suspension, an 87% yield of 3H-pyrrolizine (III) was obtained. Reduction of III with hydrogen using a rhodium-on-carbon catalyst in ethanol solution gave pyrrolizidine (IV), which can be isolated either in the free state or as the picrate. Hydrogenation of III under similar conditions except in ether solution gave only partial reduction to dihydro-3H-pyrrolizine (V). Hydrogenation of V in ethanol gave complete reduction to IV.

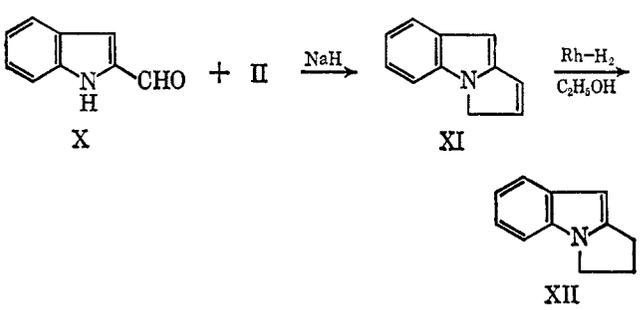



A 43% yield of 2-acetylpyrrole (VI) was obtained by allowing pyrrole to react with methylmagnesium iodide followed by acetyl chloride. When 2-acetylpyrrole (VI) was allowed to react with the vinyl salt II in the presence of sodium hydride in ether solution, 1-methyl-3H-pyrrolizine (VIII) was obtained in 26% yield. It was found that the yield in this case could be improved (43%) if the sodium salt of the 2-acetylpyrrole (VII) was first isolated and dried, the two salts (II and VII) were ground together, and the mixture was fused at 60 to 100°.



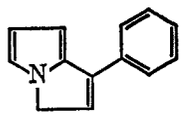

Compound VIII could be hydrogenated at low pressure on rhodium to give perhydro-1-methylpyrrolizine (IX), which was isolated as the picrate. Compound IX is *dl*-heliotridane, one of the degradation products of alkaloids in the *Senecio*, *Heliotropium*, *Crutalaria*, *Erechtites*, and *Trichodesma* genera.[5]

When indole-2-carboxaldehyde (X)[6] was allowed to react with the salt II in the presence of sodium hydride, a 58% yield of 3H-pyrrolo[1,2-*a*] indole (XI) was obtained. Hydrogenation of the pyrroloindole XI over rhodium in ethanol gave only partial reduction, yielding dihydro-3H-pyrrolo[1,2-*a*]indole (XII).




Attempted preparations of 1-phenyl-3H-pyrrolizine (XIII) from 2-benzoylpyrrole by the same methods as described gave only tars which could not be characterized.

(1) See E. E. Schweizer and K. K. Light, *J. Am. Chem. Soc.*, **86**, 2963 (1964), for a preliminary account of this work.
(2) E. E. Schweizer, *ibid.*, **86**, 2744 (1964).
(3) R. Adams, *Angew. Chem.*, **69**, 5 (1957).
(4) G. R. Allen, Jr., J. F. Polletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3877 (1964).
(5) N. J. Leonard and D. L. Felly, *ibid.*, **72**, 2537 (1950).
(6) J. Harley-Mason and E. Pavri, *J. Chem. Soc.*, 2655 (1963).



XIII

Several attempts were made to prepare the dibromo derivatives of the pyrrolizine compounds III, VIII, and XI, but in each case the only product was a rapidly formed, hard, black material. No crystalline material was obtained from this product by sublimation or by attempted recrystallization from a wide range of solvents. Attempts to brominate the allylic position in these compounds with N-bromosuccinimide also gave a similar brittle material. The materials all had melting points greater than 300°. Further studies on the reactions of these compounds are being done.

Research is now being done on similar types of reactions involving allyl and substituted allyl phosphonium salts. Results of these studies will be reported in a future publication.

## Experimental Section[7]

**3H-Pyrrolizine (III).**—To a suspension of 4.20 g of sodium hydride (0.183 mole, 8.0 g of a 52.6% dispersion in mineral oil) in 200 ml of anhydrous ether was added 20.0 g (0.210 mole) of pyrrole-2-aldehyde.[8] When the reaction was complete, 79.5 g (0.215 mole) of the vinyl salt II was added. The mixture was stirred and refluxed for 24 hr, after which the salts were removed by filtration and the ether was distilled. Distillation of the pot residue gave 16.6 g of 3H-pyrrolizine (III, 87% yield), bp 68–70° (15 mm), which showed only one peak on a Carbowax 20 M gas chromatograph column (190°). Redistillation gave an analytical sample, bp 65° (7.5 mm), $n^{27}D$ 1.5745. The analytical sample darkened rapidly on standing. The nmr spectrum (neat, TMS standard) showed a quartet, weight 2, centered at 3.82 ppm; a multiplet, weight 2, centered at 5.80 ppm; and a multiplet, weight 3, centered at 6.4 ppm. The ultraviolet spectrum (ethanol) showed $\lambda_{max}$ 218 mμ (ε 2500) and 290 mμ (ε 6100).

*Anal.* Calcd for $C_7H_7N$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.85; H, 6.60; N, 13.29.

**1,2-Dihydro-3H-pyrrolizine (V).**—To a solution of 4.10 g of 3H-pyrrolizine (0.035 mole) in 50 ml of anhydrous ether was added 0.5 g of 5% rhodium-on-carbon catalyst. Hydrogenation at atmospheric pressure showed an uptake of 1 mole of hydrogen/mole of III. Distillation of the reaction mixture gave 3.04 g (81%) of 1,2-dihydro-3H-pyrrolizine (V), bp 70° (20 mm), $n^{25}D$ 1.5267 [lit.[9] bp 63° (10 mm), $n^{25}D$ 1.5264].

**Pyrrolizidine (IV).**—Reduction of 1.41 mmoles of III over 5% rhodium on carbon in ethanol showed rapid absorption of 99% of 3 moles of hydrogen. The pyrrolizidine picrate was obtained directly from solution by addition of picric acid and filtration, mp 258–260° dec (lit.[10] mp 256–258°). A similar reduction of V showed a rapid uptake of 2 moles of hydrogen/mole of V, and the picrate could be obtained in 91% yield directly from the hydrogenation solution, mp 260–262°.

**2-Acetylpyrrole (VI).**—To 12 g (0.5 g-atom) of magnesium turnings in 25 ml of anhydrous ether was added 70 g (0.5 mole) of methyl iodide in 200 ml of anhydrous ether at a rate such that gentle reflux was maintained. Then 33.5 g (0.5 mole) of pyrrole was added slowly. When reaction was complete, 39 g (0.5 mole) of acetyl chloride was added slowly to the solution with cooling. When addition was terminated, 200 ml of water was added dropwise to dissolve the salts. The ether solution was separated and the water was extracted with 100 ml of ether. The combined ether layers were allowed to evaporate, and the resulting solid was purified by two sublimations to give the desired 2-acetylpyrrole (VI, 43.5%), mp 88–90° (lit.[11] mp 90°).

**1-Methyl-3H-pyrrolizine (VIII).**—To a suspension of 2.20 g (0.092 mole, 4.20 g of a 52.6% dispersion in mineral oil) of sodium hydride in 200 ml of anhydrous ether was added 10.0 g of 2-acetylpyrrole (0.092 mole). After reaction was complete, 34.0 g of vinyl triphenylphosphonium bromide (0.092 mole) was added, and the mixture was stirred for 24 hr. After this time, the salts were removed by filtration and the ether was distilled. Distillation of the pot liquor gave 3.90 g (26% yield) of compound VIII with bp 68° (10 mm), which showed only one peak on a Carbowax 20 M gas chromatograph column at 190°.

**1-Methyl-3H-pyrrolizine (Fused Salts) (VIII).**—Ten grams of 2-acetylpyrrole sodium salt (VII, 0.076 mole) was prepared by adding the acetylpyrrole (VI) to a suspension of sodium hydride in ether, filtering the resulting salt, and drying it under vacuum. To the salt VII was added 28 g of the vinyl salt II and the mixture was placed in a 100-ml flask fitted with a distilling head and a condenser. A vacuum (10 mm) was reached on the system and the flask was warmed slowly. At about 60° the solid turned to a red-brown liquid and the product was distilled as the bath temperature was raised slowly to 100°. Heating was continued until no additional material distilled; a yield of 4.0 g (43.5%) of compound VIII (one peak by vpc) was obtained. Redistillation of this material on a spinning-band column gave an analytical sample, bp 72° (8 mm), $n^{25}D$ 1.5554. The pure sample darkened rapidly on standing. The nmr spectrum (neat, TMS standard) showed a quartet, weight 3, centered at 1.90 ppm; a multiplet, weight 2, centered at 3.90 ppm; and four multiplets, each weight 1, centered at 5.50, 5.93, 6.25, and 6.72 ppm. The ultraviolet spectrum (ethanol) showed $\lambda_{max}$ 287 mμ (ε 6150).

*Anal.* Calcd for $C_8H_9N$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.66; H, 7.65; N, 11.76.

**Hydrogenation of 1-Methyl-3H-pyrrolizine (VIII).**—To a solution of 0.1104 g of the pyrrolizine VIII in 5 ml of ethanol was added 0.1 g of a 5% rhodium-on-carbon catalyst. The solution absorbed 93% of the theoretical amount of hydrogen (atmospheric pressure). The catalyst was removed by filtration, and 0.2 g of picric acid in ethanol was added. The resulting picrate was recrystallized from ethanol to give perhydro-1-methyl-3H-pyrrolizine picrate, mp 248–250° (lit.[5] mp 243–244°).

*Anal.* Calcd for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12. Found: C, 47.63; H, 5.19.

**3H-Pyrrolo[1,2-*a*]indole (XI).**—To an ether suspension of 0.69 g of sodium hydride dispersion in mineral oil (52.6% NaH, 0.36 g, 0.0159 mole) was added slowly 3.2 g (0.0169 mole) of indole-2-carboxaldehyde, prepared according to Mason and Pavri,[6] dissolved in 150 ml of anhydrous ether. The solution turned yellow-green. After addition was complete, 5.9 g of the vinyl salt II (0.016 mole) was added. The solution was stirred under reflux overnight, and the salts were removed by filtration. The ether was allowed to evaporate, resulting in a yellow crystalline mass. Sublimation of the crystalline mass at 60° (0.3 mm) gave 1.90 g of white crystals (58% yield). The melting point was not sharp (85–90°). Chromatography of the product on silica gel with benzene eluent gave a pure product, mp 92–93°. The nmr spectrum of XI (in $CCl_4$, TMS standard) showed a singlet, weight 2, at 3.75 ppm; a multiplet, weight 1, at 5.95 ppm; a triplet, weight 1, at 6.22 ppm; and a multiplet, weight 5, at 6.96 ppm. The ultraviolet spectrum (ethanol) showed $\lambda_{max}$ at 215 mμ (ε 11,100) and 265 mμ (ε 17,770).

*Anal.* Calcd for $C_{11}H_9N$: C, 85.12; H, 5.85; N, 9.09. Found: C, 84.95; H, 5.64; N, 9.08.

**Dihydro-3H-pyrrolo[1,2-*a*]indole (XII).**—To 5 ml of an ethanol solution containing 0.1 g of 3H-pyrrolo[1,2-*a*]indole (XI) was added 0.1 g of 5% rhodium-on-carbon catalyst. The mixture was stirred under hydrogen at atmospheric pressure. After uptake of hydrogen ceased (1 mole), the catalyst was removed by filtration and the ethanol was evaporated. The resulting white crystals were sublimed to give compound XII, mp 78–79°. The nmr spectrum of XII (in $DCCl_3$, TMS standard) showed a multiplet, weight 4, at 2.06 ppm; a triplet, weight 2, at 3.90 ppm; a singlet, weight 1, at 6.10 ppm; and a multiplet, weight 4, at 7.25 ppm. The ultraviolet spectrum showed $\lambda_{max}$ 229 mμ (ε 16,900) and 283 mμ (ε 6500).

(7) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Analyses were done by Micro Analysis, Wilmington, Del. Nmr spectra were taken on a Varian A-60A spectrometer.

(8) Obtained from Eastman Kodak.

(9) J. M. Patterson, J. Brasch, and P. Drenchko, *J. Org. Chem.*, **27**, 1652 (1962).

(10) N. J. Leonard and W. E. Goode, *J. Am. Chem Soc.*, **72**, 5404 (1950).

(11) R. Schiff, *Ber.*, **10**, 1500 (1877).

*Anal.* Calcd for $C_{11}H_{11}N$: C, 84.03; H, 7.05; N, 8.91. Found: C, 83.90; H, 7.15; N, 8.84.

**Attempted Preparation of 1-Phenyl-3H-pyrrolizine (XIII).**—To a suspension of 0.46 g of sodium hydride (0.0199 mole, 0.89 g of a 52.6% dispersion in mineral oil) in 250 ml of anhydrous ether was added 3.6 g of 2-benzoylpyrrole (prepared by the method of Oddo[12]). The mixture was stirred for several hours to ensure complete conversion to the salt. To the suspended salt was added 7.2 g (0.0199 mole) of the vinyl salt II while the mixture was cooled in an ice bath. The slurry was stirred with continued cooling for 4 hr. The salts were removed by filtration and the ether was distilled. The pot residue consisted of a brown tar, which was found to contain triphenylphosphine oxide by thin layer chromatography. No crystalline material could be obtained from the mass by sublimation or recrystallization from a wide range of solvents. Column chromatography on silica gel with benzene eluent gave only a dark oil which could not be characterized. The nmr spectra of the oil did not agree with compound XIII.

(12) B. Oddo, *Ber.*, **43**, 1012 (1910).

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# Trialkyl Phosphates. I. Halogenation of Trialkyl Phosphites in the Presence of Alcohols

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Trialkyl phosphates can be prepared in high yield and purity by the halogenation of trialkyl phosphites in the presence of the corresponding alcohols. The principal side reactions, which can all be suppressed, are isomerization of the phosphite and cleavage of the phosphite and phosphate by hydrogen halide. Competition of the alcohol for the halogen was observed in only one case. A mechanism involving the direct alcoholysis of a quasi-phosphonium intermediate, $(RO)_3PX_2$, is proposed. Phosphonous esters, phosphinous esters, and tertiary phosphines can also be oxidized in this manner.

The oxidation of trialkyl phosphites to trialkyl phosphates can be accomplished with a variety of oxidizing agents, both organic and inorganic.[2] Direct oxidation with air or oxygen is possible in some cases, but the lower trialkyl phosphites, such as triethyl phosphite, are not appreciably attacked unless a catalyst is employed.[3] An interesting development in recent years has been the emergence of indirect methods of oxidation employing an organic halide in combination with an alcohol. The organic halides which have been employed for this purpose are carbon tetrachloride,[4,5] bromotrichloromethane,[4] carbon tetrabromide,[6] chloroform,[7] monobromocyanoacetamide,[8] and hexachlorocyclopentadiene.[9] In the absence of the alcohols these reactions all follow entirely different paths.

We have investigated the use of the halogens themselves for this purpose and have found the halogenation of a trialkyl phosphite in the presence of the corresponding alcohol to be a useful method for preparing trialkyl phosphates in high yield and purity. In most cases, competition of the alcohol for the halogen is not observed. The stoichiometry of the reaction is given in eq 1.

$$(RO)_3P + X_2 + ROH \longrightarrow (RO)_3PO + RX + HX \quad (1)$$

In the absence of the alcohol, the product of the reaction of a trialkyl phosphite with a halogen is a dialkyl phosphorohalidate.[10,11]

When gaseous chlorine was passed into a dilute solution of trimethyl phosphite in methanol, a product which appeared to be trimethyl phosphate was obtained in 56.5% yield.[12] A gas chromatographic analysis, however, showed that it consisted of trimethyl phosphate (82%), dimethyl methylphosphonate (11%), and other minor impurities (7%). Dimethyl methylphosphonate is the product of self-isomerization of the trimethyl phosphite, catalyzed perhaps by the methyl chloride which is evolved as a by-product (eq 1, R = $CH_3$; X = Cl). The extent of self-isomerization was reflected also in the chlorine consumption, which was 12% less than the theoretical for this reaction.

The need for the excess of methanol is demonstrated in Table I, which shows the effect of reducing the molar

TABLE I

EXTENT OF DEALKYLATION AS A FUNCTION OF THE ALCOHOL TO PHOSPHITE RATIO

| Moles of $CH_3OH$/ mole of $(CH_3O)_3P$ | $(CH_3O)_2PHO$, % |
|---|---|
| 30 | 0.2 |
| 15 | 0.3 |
| 5 | 7.3 |
| 1 | 19.3 |

(1) To whom correspondence should be addressed.

(2) J. I. G. Cadogan, *Quart. Rev.* (London), **16**, 208 (1962).

(3) J. I. G. Cadogan, M. Cameron-Wood, and W. R. Foster, *J. Chem. Soc.*, 2549 (1963); (b) K. Smeykal, H. Baltz, and H. Fischer, *J. Prakt. Chem.*, [4] **22**, 186 (1963); (c) J. B. Plumb and C. E. Griffin, *J. Org. Chem.*, **28**, 2908 (1963); (d) C. F. Baranauckas and J. J. Hodan, U. S. Patent 3,136,805 (June 9, 1964); (e) W. G. Bentrude, *Tetrahedron Letters*, 3543 (1965).

(4) A. J. Burn and J. I. G. Cadogan, *J. Chem. Soc.*, 5788 (1963).

(5) P. C. Crofts and I. M. Downie, *ibid.*, 2559 (1963).

(6) B. Miller, "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., John Wiley and Sons, Inc., New York, N. Y., 1965, p 133.

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(8) T. Mukaiyama, C. Mitsunobu, and T. Obata, *J. Org. Chem.*, **30**, 101 (1965).

(9) H. von Brachel, German Patent 1,103,328 (March 30, 1961); *Chem. Abstr.*, **56**, 7176 (1962).

(10) H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

(11) A notable exception is tris(2,2,2-trichloroethyl) phosphite, which forms a stable adduct with chlorine: H. N. Rydon and B. L. Tonge, *ibid.*, 4682 (1957); see also W. Gerrard, W. J. Green, and R. J. Phillips, *ibid.*, 1148 (1954); W. Gerrard and B. H. Howe, *ibid.*, 505 (1955).

(12) Trimethyl phosphate is extraordinarily sensitive to acid degradation. We discovered later that the yields in many of our earlier experiments could have been improved simply by stripping the acidic methanol solutions at the lowest possible temperature.