Some Observations on Märkl's Cyclic Phosphonium Salt Synthesis. The Synthesis of a Phosphocane

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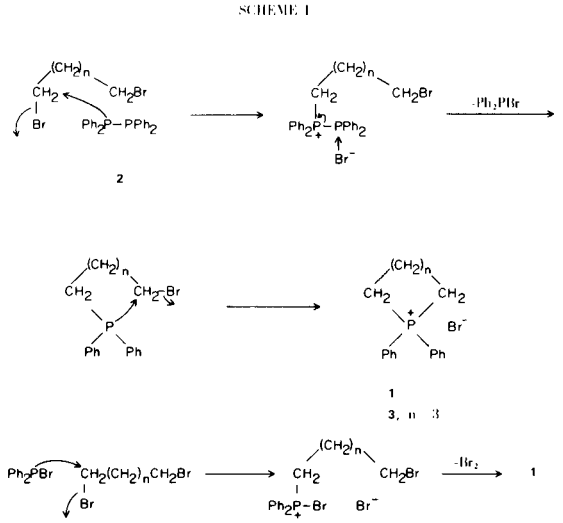
Märkl's cyclic phosphonium salt synthesis was studied and some mechanistic conclusions drawn. The reaction was found to be generally applicable to the synthesis of *C*-methylated five-, six-, seven- and eight-membered ring systems. The first authenticated synthesis of a phosphocane is reported.

The appearance recently of several books and reviews devoted entirely or in part to heterocyclic phosphorus compounds gives some indication of current interest in the synthesis and properties of these substances (1). In connection with our own studies relating to the stereochemical behavior of phosphorus contained in saturated monocyclic ring systems (2,3,4), we have examined Märkl's useful synthesis of this class of heterocycle (Scheme I) (5). We were specifically interested in three aspects of this synthesis, (a) the mechanism as suggested by Märkl (5), (b) the applicability of the synthesis to the preparation of *C*-substituted derivatives of **1** and (c) its potential usefulness for the synthesis of larger ring systems.

SCHEME I



Mechanism.

Märkl has proposed that the diphenylhalophosphine, generated by the reaction of tetraphenyldiphosphine (**2**) with a dihaloalkane, may subsequently react with excess dihalide to produce additional cyclized product as shown in Scheme I. Thus, Märkl's procedure calls for the use of a molar excess of the dihalide to facilitate improved yields. Since some of the dihalides which we have used or anticipate using are expensive or difficult to prepare, we wished to determine the actual improvement in yield, if any, brought about by the utilization of excess dihalide. Two experiments were conducted to provide this information. First, the preparation of 1,1-diphenylphosphorinanium bromide (**3**) was carried out by employing ratios of 1,5-dibromopentane (**4**) and **2** of 2:1 and 1:1 and comparing the isolated yields of **3**. No significant difference in yields was observed after the reactions had been performed under otherwise identical conditions (Table I).

TABLE I

Mole Ratio **4**:**2**	Yield of **3**	M.p., °C
2	71%	259-261
2 (a)	66%	261-262
1	72%	257.5-259

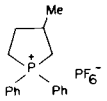
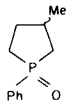
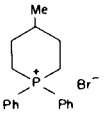
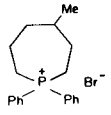
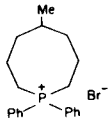
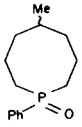
(a) Results taken from reference 5. Berlin and Hellwege (reference 1b, p. 29) point out a discrepancy between this m.p. and a m.p. of 246° reported by Issleib and coworkers (6).

Secondly, when diphenylchlorophosphine was used in place of **2**, no evidence for phosphorinanium salt formation could be found. We thus conclude that the halophosphine at best plays an insignificant role in ring closure.

C-substituted Derivatives of **1**.

The use of Märkl's ring synthesis to prepare *C*-substituted compounds has not been previously explored. We had need for the methylated compounds listed in

TABLE II

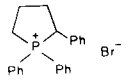
	Compound	Yield %	M.p., °C		C, H Analyses Calcd., %	Found, %	Yield, Non-methyl Compound (5)
5(a)		26	135.5-136.5	C, H,	51.01 5.03	51.08 5.31	72%
6(b)		32	40-60	C, H,	68.02 7.79	68.10 8.04	
7		76	283-284	C, H,	61.90 6.35	62.09 6.36	66%
8		85	212.5-213.5	C,	62.81	62.61	54%
9		40 (c)	oil	C, H,	63.66 6.95	(d) (d)	(e)
10(b)		34	97-103	C, H,	71.14 8.96	70.92 8.89	

(a) Isolated as the hexafluorophosphate since the bromide was a noncrystallizing oil. (b) Mixture of *cis* and *trans* isomers. Yield based on **2**. Obtained by base cleavage of the bromide salt. (c) Estimated yield. (d) Not isolated pure. Converted to **10** and characterized as such. (e) Not prepared.

Table II as starting materials for stereochemical studies (2,3,4). These were prepared by the Märkl procedure from the corresponding dihalides. A yield comparison with the non-methylated compounds is made in Table II. It is noteworthy that the methyl substituted five-membered ring compound is obtained in significantly lower yield than its non-methylated analog (reported as the perchlorate by Märkl). Since the bromide salt of **5** would not crystallize, it was isolated as the hexafluorophosphate. The oily bromide salt of **5**, prepared in a separate run, was cleaved by treatment with sodium hydroxide, a reaction reported to take place in high yield (4a), and the ring system recovered as the oxide. Both experiments indicate ring closure to have occurred in low yield. Evidently, the methyl group offers sufficient steric hindrance to ring closure at the already highly shielded phosphorus that polymerization competes successfully with cyclization.

It was also observed that dibromides leading to the six- and seven-membered ring compounds with a methyl substituent in the 4-position gave higher yields than dibromides which yield the non-methylated salts. The higher yields for **7** and **8** may be due to slight procedural differences or possibly to the operation of the Thorpe-Ingold effect (7) on cyclization.

Efforts to prepare 1,1,2-triphenylphospholanium bromide (**11**) from 1-phenyl-1,4-dibromobutane were unsuccessful and provided only intractable oils. Steric hindrance to ring closure afforded by the proximity of the additional phenyl group to phosphorus, and the difference in reactivity between benzylic and alkyl halides toward tetraphenyldiphosphine may be complicating factors in attempted cyclization.



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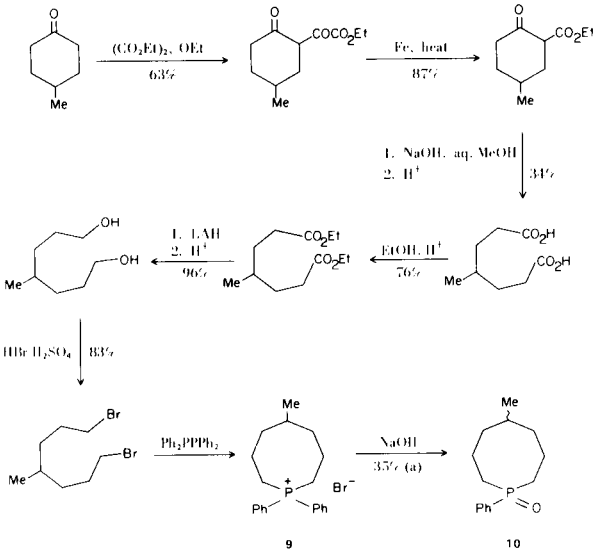
Synthesis of a Phenylphosphocane and Derivatives.

Normally, syntheses of medium-sized rings in homogeneous solutions are difficult to effect (7). However, we have found that when applied to the synthesis of a phosphocane, the Märkl reaction gives a moderate yield of the eight-membered ring compound. The 5-methyl-1,1-diphenylphosphocanium bromide salt (**9**) could not be conveniently obtained as a crystalline material, so it was converted by base cleavage to a mixture of the *cis* and *trans* oxides (**10**), the actual compounds desired from the synthesis. The yield of the phosphonium salt **9** is

SCHEME II



(a) Based on dibromide.

estimated to be about 40% since such cleavage reactions occur in high yields with loss of benzene (4a). Wagner (8) reports in the patent literature the synthesis of 1-phenylphosphocane but gives no analysis, physical properties, yield data or other information to support the structural assignment. Thus our report presents the first authenticated example of the synthesis of a phosphocane. The phosphocane oxide (**10**) was synthesized in an overall yield of 4% by the route shown in Scheme II.

EXPERIMENTAL (9)

General Procedure for Synthesis of **1**.

The cyclization reaction was carried out under an atmosphere of dry nitrogen. To the required volume of a stock solution of 0.555 *M* tetraphenyldiphosphine in dry *o*-dichlorobenzene was added a two-fold molar amount of the dihalide. The resulting solution was added over a three-hour period to boiling *o*-dichlorobenzene of five-times the volume of tetraphenyldiphosphine solution used. When addition was completed, about 80% of the solvent was distilled off and the residue allowed to stand overnight. The crystalline product was removed by filtration, washed with pure dichlorobenzene equal to one-third the volume of tetraphenyldiphosphine solution used, then with two equal-sized portions of benzene and dried *in vacuo* to constant weight. Analytically pure materials were obtained by recrystallization from ethanol-ethyl acetate.

For the synthesis of **10** and one run of **3** an amount of dihalide equimolar to that of tetraphenyl diphosphine was used.

When no crystalline product was obtained, as was the case for the bromide salt of **5** and **9**, all of the volatiles were removed by vacuum distillation until a viscous oil remained. The residue was boiled with a two mole excess of 1 *N* sodium hydroxide for 24 hours, the cooled aqueous solution extracted with four portions of chloroform totaling half the volume of sodium hydroxide solution used, the solvent evaporated off and the residue distilled *in vacuo* to give the oxide **6** (b.p. 113-126°/0.05 mm.) or **10** (b.p. 173°/0.1 mm.).

The hexafluorophosphate salt (**5**) was prepared by dissolving the oily residue in water, titrating to neutrality with sodium bicarbonate, extracting with ether and then continuously extracting the water layer with chloroform. Chloroform was removed from the extract and a saturated solution of potassium hexafluorophosphate (10) was added. Recrystallization of the precipitate from absolute ethanol afforded the pure crystalline hexafluorophosphate salt of **5**.

Attempted Synthesis of **3** with Diphenylchlorophosphine.

The above procedure for the synthesis of **3** was followed except that diphenylchlorophosphine was substituted for tetraphenyldiphosphine. Since no crystals separated, the volatiles were removed *in vacuo* leaving an oily residue. This was treated with sodium hydroxide and worked up as described above. No oxide could be obtained by distillation.

1,4-Dibromo-2-methylbutane.

This compound was prepared in 79% yield by treatment of 2-methyl-1,4-butanediol (Aldrich Chemical Co.) with hydrogen bromide in the customary manner (11); b.p. 100°/24 mm. [lit. (12) 90-92°/18 mm.].

1,5-Dibromo-3-methylpentane.

Diethyl 3-methylglutarate (J. T. Baker Chemical Co.) was reduced with lithium aluminum hydride (13) to the diol, b.p. 104°/6 mm. [lit. (14) 134°/9 mm.], and the diol converted to the dibromide with hydrogen bromide (11); b.p. 79°/2 mm. [lit. (15) 114°/16 mm.].

1,6-Dibromo-3-methylhexane.

3-Methylhexanedioic acid (J. T. Baker Chemical Co.) was reduced with lithium aluminum hydride (16) to the diol, b.p. 101-103°/0.5 mm. [lit. (17) 135°/3 mm.], which was treated with hydrogen bromide (11) to give the dibromide; b.p. 83°/14 mm.

Anal. Calcd. for $C_7H_{14}Br_2$: Br, 61.95. Found: Br, 61.95.

1,7-Dibromo-4-methylheptane.

Ethyl 5-methyl-2-oxocyclohexaneglyoxylate was prepared from 4-methylcyclohexanone following the general procedure of Snyder (18); b.p. 115°/20 mm. with some decarbonylation (19). The glyoxalate ester was decarbonylated (18) to 2-carbethoxy-4-methylcyclohexanone, b.p. 90-137°/40 mm. [lit. (20) 112°/10 mm.], which was cleaved (18) to 4-methylpimelic acid, an oil [lit. (15) m.p. 50-51.5°; incorrectly named as "3-methylpimelic acid" in this reference]. The oil was esterified with the aid of Linde 3A molecular sieves (21) to the diester, b.p. 145°/9 mm. [lit. (15) 139-140°/7 mm.; incorrectly named as diethyl "3-methylpimelate" in this reference] which was in turn reduced with lithium aluminum hydride to the diol, b.p. 155°/10 mm. [lit. (15) 136-137°/4 mm.]. The diol was treated with hydrogen bromide and sulfuric acid (15) to yield the dibromide, b.p. 138°/13 mm. [lit. (15) 125-127°/7 mm.].

5-Methyl-1-phenylphosphocane and 1-Benzyl-5-methyl-1-phenylphosphocanium Bromide.

1-Phenylphosphocane 1-oxide (**10**) (3.96 g.), a mixture of *cis* and *trans* isomers [nmr (deuteriochloroform), δ from TMS: δ 1.0 (d, 3H, J = 6 Hz, CH_3), δ 1.0-3.0 (m, 13H, ring H), δ 7.2-7.8 (m, 5H, C_6H_5)] was heated with 1.21 g. of phenylsilane under nitrogen. After effervescence subsided, 2.60 g. of the phosphine, b.p. 130-132° (0.3 mm.), was obtained by distillation. The phosphine was converted to 3.53 g. of the phosphonium salt by addition to 2.20 g. benzyl bromide dissolved in 25 ml. benzene; m.p. 187.5-189°.

Anal. Calcd. for $C_{21}H_{28}BrP$: C, 64.45; H, 7.21. Found: C, 64.63; H, 7.14.

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