SYNTHESIS OF o-SUBSTITUTED PHOSPHINYLBENZYL AND PHOSPHINYLPHENETHYL ALCOHOLS

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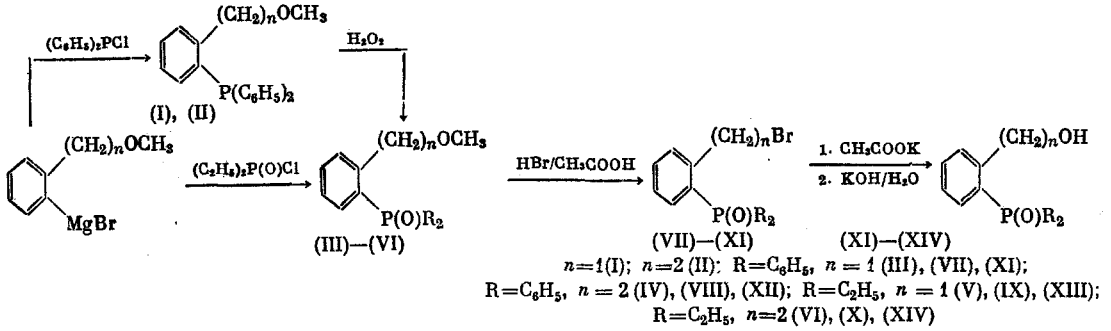
In order to study hydrogen bonding in phosphine oxides containing an OH group, we have synthesized o-diethylphosphinyl- and o-diphenylphosphinylbenzyl and phenethyl alcohols, and also benzyl alcohols containing o-diethylphosphinylmethyl and o-diphenylphosphinylmethyl groups.

The synthesis of the benzyl and phenethyl alcohols containing diethyl- and diphenylphosphinyl groups in the ortho position was performed as follows:

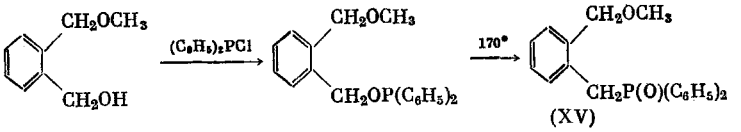


The starting materials were the methyl ethers of o-bromobenzyl and o-bromophenethyl alcohol. In contrast to the method described in [1,2], in which Grignard reagents were prepared from these compounds using EtBr as auxiliary agent, we prepared the organomagnesium compounds using a mixture of the corresponding bromide and dibromoethane in a ratio of 1:1 so that the unavoidable reaction products of ethylmagnesium bromide with the phosphorus acid chlorides would not be formed.

Ethers (III)-(VI) containing a substituted phosphinyl group in the benzene ring were prepared by reacting the Grignard reagents with diphenylchlorophosphine followed by oxidation of phosphines (I) and (II), or with diethylphosphinyl chloride. The products were converted into the bromides (VII)-(X) by reaction with HBr in CH_3COOH. The bromine atom was replaced by OH using the normal method, viz., conversion of the bromides (VII)-(X) into the corresponding acetoxy derivatives followed by alkaline hydrolysis. In this way we prepared benzyl and phenethyl alcohols (XI)-(XIV) containing both ethyl and phenyl radicals attached to the phosphorus atom.

It should be noted that bromides (IX) and (X), which contain a diethylphosphinyl group, hydrolyze on standing in air. This indicates the possibility of direct hydrolysis. Indeed, bromides (IX) and (X) are completely hydrolyzed by a 3% $NaHCO_3$ solution in 10 h at ~20°C.

The methyl ether of o-diphenylphosphinylmethylbenzyl alcohol was prepared using the known [3] thermal rearrangement of benzyl diphenylphosphinites



The o-substituted benzyl ester of diphenylphosphinous acid, prepared by reacting o-methoxymethylbenzyl alcohol with diphenylchlorophosphine in the presence of triethylamine, was rearranged by heating at 170°C for 3 h to give an 18% yield of the corresponding oxide (XV). Oxide (XV) was prepared in good yield by

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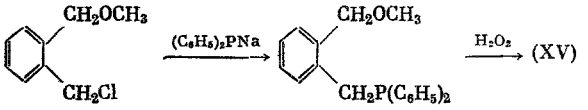
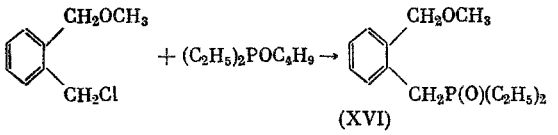
reacting o-methoxymethylbenzyl chloride [4] with sodium diphenylphosphide and oxidizing the resulting phosphine. Diphenyl-o-methoxymethylbenzylphosphine could not be purified by vacuum distillation, possibly due to thermal intramolecular alkylation. This phosphine was separated from the o-xylylene glycol dimethyl ether present in the starting o-substituted benzyl chloride by treatment with HBr acid followed by neutralization of the acidic hydrobromide solution. Oxidation of the phosphine with H_2O_2 gave (XV)



The methyl ether of o-diethylphosphinylmethylbenzyl alcohol (XVI), prepared by Arbuzov rearrangement of butyl diethylphosphinite with the o-substituted benzyl chloride, was purified by vacuum distillation followed by recrystallization



Ethers (XV) and (XVI) were converted into the alcohols via the corresponding bromides similarly to ethers (III)-(VI). o-Diethylphosphinylmethylbenzyl bromide was hydrolyzed with 3% $NaHCO_3$. The constants of the compounds obtained are given in Table 1.

EXPERIMENTAL

All operations with P(III) compounds were performed in an Ar atmosphere. The PMR spectra were recorded with a Hitachi — Perkin — Elmer R-20 spectrometer using $CHCl_3$ solutions (C = 1.5 moles/liter) with HMDS as internal standard. The spectral parameters of the protons in the phenyl rings and the ethyl groups attached to P are not reported. In determining the boiling points, no corrections were made for the outstanding column of mercury.

Methyl Ether of o-Diphenylphosphinobenzyl Alcohol (I). A Grignard reagent prepared from 5.4 g of Mg in 20 ml of abs. ether and a mixture of 21.0 g dibromoethane and 27.9 g of the methyl ether of o-bromobenzyl alcohol [1] in 30 ml of abs. ether (boiling for 3 h) was treated dropwise at 0°C with 19.7 g of diphenylchlorophosphine in 30 ml of abs. ether. The mixture was boiled for 2 h, decomposed with saturated NH_4Cl solution, the ether layer separated, and the aqueous layer extracted with $CHCl_3$. The combined extract was washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and the solvent distilled off in vacuo to give 19.2 g of (I).

Methyl Ether of 2-(o-Diphenylphosphinophenyl)ethyl Alcohol (II). This was prepared analogously to (I) from the methyl ether of 2-(o-bromophenyl)ethyl alcohol [2] and diphenylchlorophosphine.

Methyl Ether of o-Diphenylphosphinylbenzyl Alcohol (III). A solution of 3.6 g of 30% H_2O_2 in 7 ml acetone was added dropwise to a solution of 9.4 g (I) in 20 ml acetone. The solution was boiled for 30 min, evaporated in vacuo, and the residue dried by azeotropic distillation with benzene and alcohol. The product was dissolved in ether and frozen out to give 9.0 g of (III).

Methyl Ether of 2-(o-Diphenylphosphinylphenyl)ethyl Alcohol (IV). This was prepared analogously to (III) from ether (II).

Methyl Ether of o-Diethylphosphinylbenzyl Alcohol (V). A solution of 19.5 g of diethylphosphinous acid chloride in 20 ml of abs. ether was added dropwise at 0°C to a Grignard reagent prepared from 10.9 g Mg in 50 ml abs. ether and a mixture of 45.4 g of the methyl ether of o-bromobenzyl alcohol and 42.4 g dibromoethane in 75 ml abs. ether (boiling for 2 h). The mixture was boiled for 2 h. After decomposition with 200 ml of dilute HCl (1 : 1), three layers formed. The middle layer* was washed twice with ether and treated with 75 ml $CHCl_3$, 50 ml water, and $NaHCO_3$ until neutral. The organic solution was added to the extract of the aqueous layer, which was worked up as described below. The aqueous layer was neutralized with $NaHCO_3$, evaporated in vacuo, the residue treated with 50 ml $CHCl_3$ and 30 ml acetone, and the precipitate filtered off and washed with 10 ml acetone. The filtrate was combined with the extract of the middle layer, dried with Na_2SO_4, evaporated in vacuo, and the residue distilled to give 17.2 g of (V).

*The methyl ether of benzyl alcohol and the starting methyl ether of o-bromobenzyl alcohol were isolated from the upper layer after washing with saturated $NaHCO_3$ solution.

TABLE 1. Yields, Constants, and Analytical Data of Products

Compound	Formula	Yield, %	bp, °C (p, mm Hg) mp, °C	Found, %				Empirical formula	Calculated, %			
				C	H	P	Br		C	H	P	Br
(I)	o-$(C_6H_5)_2PC_6H_4CH_2OCH_3$; cf. [5]	70	95,5–96,5 (Alcohol)	78,5	6,2	10,2		$C_{20}H_{19}OP$	78,4	6,2	10,1	
(II)	o-$(C_6H_5)_2PC_6H_4CH_2CH_2OCH_3$	76	63,5–65 (Isopropanol)	78,7	6,6	9,7		$C_{21}H_{21}OP$	78,7	6,6	9,7	
(III)	o-$(C_6H_5)_2P(O)C_6H_4CH_2OCH_3$	90	72–73 (Ether)	74,5	5,9	9,6		$C_{20}H_{19}O_2P$	74,5	5,9	9,6	
(IV)	o-$(C_6H_5)_2P(O)C_6H_4CH_2CH_2OCH_3$	96	84–85,5 (Ether)	75,0	6,4	9,3		$C_{21}H_{21}O_2P$	75,0	6,3	9,2	
(V)	o-$(C_2H_5)_2P(O)C_6H_4CH_2OCH_3$	54	146–147 (1) *	63,6	8,5	13,5		$C_{17}H_{19}O_2P$	63,7	8,5	13,7	
(VI)	o-$(C_2H_5)_2P(O)C_6H_4CH_2CH_2OCH_3$	68	175–177 (2) †	64,9	8,8	12,7		$C_{18}H_{21}O_2P$	65,0	8,8	12,9	
(VII)	o-$(C_6H_5)_2P(O)C_6H_4CH_2Br$	78	115–116 (Cyclohexane–benzene)	61,6	4,5	8,3	21,5	$C_{19}H_{16}BrOP$	61,5	4,3	8,3	21,5
(VIII)	o-$(C_6H_5)_2P(O)C_6H_4CH_2CH_2Br$	85	130–131 (CCl_4-hexane)	62,4	4,9	8,2	20,8	$C_{20}H_{18}BrOP$	62,4	4,7	8,0	20,7
(IX)	o-$(C_2H_5)_2P(O)C_6H_4CH_2Br$	86	162–163 (1) 110–112 (CH_3CN)	48,4	5,9	11,3	29,0	$C_{14}H_{16}BrOP$	48,0	5,9	11,3	29,0
(X)	o-$(C_2H_5)_2P(O)C_6H_4CH_2CH_2Br$	52	132–133 (MEK) ‡	49,8	6,3	10,8	27,6	$C_{12}H_{16}BrOP$	49,8	6,3	10,7	27,6
(XI)	o-$(C_6H_5)_2P(O)C_6H_4CH_2OH$	86	158,5–159,5 (Cyclohexane–acetone)	74,0	5,6	10,0		$C_{19}H_{17}O_2P$	74,0	5,6	10,0	
(XII)	o-$(C_6H_5)_2P(O)C_6H_4CH_2CH_2OH$	70	168–169 (MEK)	74,4	6,0	9,8		$C_{20}H_{19}O_2P$	74,5	5,9	9,6	
(XIII)	o-$(C_2H_5)_2P(O)C_6H_4CH_2OH$	94	168–170 (3) 88,5–89,5 (CCl_4)	62,2	8,0	14,5		$C_{14}H_{17}O_2P$	62,2	8,1	14,6	
(XIV)	o-$(C_2H_5)_2P(O)C_6H_4CH_2CH_2OH$	70	32–33 (Ether–MEK)	63,5	8,4	13,8		$C_{12}H_{19}O_2P$	63,7	8,5	13,7	
(XV)	o-$(C_6H_5)_2P(O)CH_2C_6H_4CH_2OCH_3$	80	137–138 (MEK–hexane)	75,0	6,3	9,5		$C_{21}H_{21}O_2P$	75,0	6,3	9,2	
(XVI)	o-$(C_2H_5)_2P(O)CH_2C_6H_4CH_2OCH_3$	70	167–168 (2) 34–36 (Ether)	64,9	8,8	12,7		$C_{13}H_{21}O_2P$	65,0	8,8	12,9	
(XVII)	o-$(C_6H_5)_2P(O)CH_2C_6H_4CH_2Br$	74	206–207 (MEK)	62,4	4,9	8,2	20,7	$C_{20}H_{18}BrOP$	62,4	4,7	8,0	20,7
(XVIII)	o-$(C_2H_5)_2P(O)CH_2C_6H_4CH_2Br$	66	99,5–100,5 (Cyclohexane)	49,8	6,3	10,7	27,8	$C_{12}H_{18}BrOP$	49,8	6,3	10,7	27,6
(XIX)	o-$(C_6H_5)_2P(O)CH_2C_6H_4CH_2OH$	70	137–138 (Ethylacetate)	74,5	5,9	9,6		$C_{20}H_{19}O_2P$	74,5	5,9	9,6	
(XX)	o-$(C_2H_5)_2P(O)CH_2C_6H_4CH_2OH$	86	69,5–70,5 (CCl_4)	63,8	8,5	13,7		$C_{13}H_{19}O_2P$	63,7	8,5	13,7	

* n_D^{20} 1,5362; d_4^{20} 1,0850.

† n_D^{20} 1,5325; d_4^{20} 1,0704.

‡ MEK = methyl ethyl ketone.

Methyl Ether of 2-(o-Diethylphosphinylphenyl)ethyl Alcohol (VI). This was prepared analogously to (I) from the methyl ether of 2-(o-bromophenyl)ethyl alcohol [2] and diethylphosphinous acid chloride.

o-Diphenylphosphinylbenzyl Bromide (VII). Method A. A mixture of 3.0 g (III) and 6.8 g of 43% HBr solution in CH_3COOH was boiled for 6 h, diluted with 50 ml water, and extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and evaporated in vacuo. The residue was crystallized by trituration with ether to give 2.2 g of (VII).

Method B. A solution of 5.3 g of 30% H_2O_2 in 10 ml acetone was added dropwise to a solution of 14.5 g of (I) in 50 ml acetone. The solution was boiled for 2 h, evaporated in vacuo, and the residue dissolved in $CHCl_3$. The solution was washed with aqueous $FeSO_4$ and then with water, dried with Na_2SO_4, and evaporated in vacuo. The residue was treated with 88.6 g of 43% HBr in CH_3COOH. The solution was boiled for 4 h, diluted with 200 ml water, and extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and evaporated in vacuo. The residue was crystallized by trituration with ether to give 13.6 g of (VII).

2-(o-Diphenylphosphinylphenyl)ethyl Bromide (VIII), o-Diethylphosphinylbenzyl Bromide (IX), and 2-(o-Diethylphosphinylphenyl)ethyl Bromide (X). These were prepared analogously to (VII) (method A) from the corresponding ethers (IV), (V) and (VI). Bromides (IX) and (X) hydrolyze in air.

o-Diphenylphosphinylbenzyl Alcohol (XI). A mixture of 3.5 g (VII) and 1.8 g of CH_3COOK was wetted with a few drops of anhydrous DMF and heated at 150°C (bath temperature) for 2 h. The mixture was treated with 1.1 g of KOH in 5 ml water and 1 ml DMF. The solution was boiled for 30 min, diluted with 50 ml water, and extracted with $CHCl_3$. The extract was dried with Na_2SO_4 and evaporated in vacuo to give 2.5 g of (XI). PMR spectrum (δ, ppm): 4.7 s (CH_2O), 6.2 s (OH).

2-(o-Diphenylphosphinylphenyl)ethyl Alcohol (XII). This was prepared analogously to (XI) from bromide (VIII). PMR spectrum (δ, ppm): 3.1 t ($CH_2C_6H_4$), 3.8 t (CH_2O, $J_{CH_2-CH_2}$ = 6.0 Hz), 6.9 s (OH).

O-Diethylphosphinylbenzyl Alcohols (XIII). Method A. Alcohol (XIII) was prepared analogously to (XI) from bromide (IX). PMR spectrum (δ, ppm): 4.8 s (CH_2O), 6.2 s (OH).

Method B. A solution of 3.3 g (IX) in 60 ml of a 3% $NaHCO_3$ solution was kept at 20°C for 10 h, and then evaporated in vacuo down to ~5 ml and extracted with $CHCl_3$. The extract was dried with Na_2SO_4 and the solvent removed to give 2.1 g of (XIII).

2-(o-Diethylphosphinylphenyl)ethyl Alcohol (XIV). A solution of 3.9 g CH_3COOK in 20 ml water was treated with 5.8 g of (X) and then, after 3 h (20°C), with 2.2 g KOH. After 1 h (20°C), the mixture was extracted with $CHCl_3$. The extract was dried with Na_2SO_4 and evaporated in vacuo. The residue crystallized on standing for 2 weeks to give 3.0 g of (XIV). PMR spectrum (δ, ppm): 3.3 t ($CH_2C_6H_4$), 3.9 t (CH_2O, $J_{CH_2-CH_2}$ = 6.0 Hz), 6.6 s (OH).

Methyl Ether of o-Diphenylphosphinylmethylbenzyl Alcohol (XV). o-Methoxymethylbenzyl alcohol was prepared as follows. A Grignard reagent prepared from 7.9 g Mg and a mixture of 21.8 g of the methyl ether of o-bromobenzyl alcohol [1] and 23.5 g C_2H_5Br in 100 ml abs. ether was treated with 14.5 g of dry paraformaldehyde and 100 ml of anhydrous dibutyl ether. The mixture was heated at 100°C (bath temperature) for 10 h, and decomposed with 25% H_2SO_4. The organic layer was separated and the aqueous layer was extracted with benzene. The combined extract was washed with saturated $NaHCO_3$ solution and dried with Na_2SO_4. The solvent was distilled off in a column and the residue was distilled in vacuo to give 9.2 g (56%) of product, bp 132-135°C/11 mm (cf. [4]).

Method A. A solution of 13.4 g diphenylchlorophosphine in 15 ml abs. ether was added dropwise at 0°C to a stirred solution of 9.2 g o-methoxymethylbenzyl alcohol and 6.2 g triethylamine in 50 ml abs. ether. The mixture was boiled for 4 h, the precipitate filtered off and washed with abs. benzene, and the filtrate evaporated in vacuo. The residue was heated under vacuum (10 mm) at 150°C (bath temperature) for 3 h and then recrystallized from hexane—benzene to give 3.7 g of (XV).

Method B. A solution of 4.6 g Na in 400 ml dry liquid NH_3 was treated with 18.6 g diphenylphosphine, stirred at −45°C (bath temperature) for 2 h, the NH_3 evaporated off, and the residue diluted with 150 ml abs. benzene and cooled with cold water while treating dropwise with 17.7 g of o-methoxymethylbenzyl chloride.* The mixture was boiled for 1 h, treated with 10 ml alcohol and then 100 ml water, the benzene layer separated,

*This was prepared from o-xylylene glycol dimethyl ether and CH_3COCl in the presence of $ZnCl_2$ [4]. According to GLC data, it contained 25-45% of the starting dimethyl ether, which cannot be removed by distillation. This mixture was used in the reaction.

and the aqueous layer extracted with benzene. The combined benzene solution was extracted with 40% HBr (3 × 50 ml). The acidic solution was neutralized with 20% NaOH (phenolphthalein) and extracted with $CHCl_3$. The extract was evaporated in vacuo at 20°C, the residue dissolved in 75 ml acetone, and the solution treated dropwise with 9.0 g of 30% H_2O_2 in 15 ml acetone while stirring. The solvent was removed in vacuo and the residue dried by azeotropic distillation with benzene and alcohol to give 20.0 g of (XV).

Methyl Ether of o-Diethylphosphinylmethylbenzyl Alcohol (XVI). Butyl diethylphosphinite (5.8 g) was added dropwise while stirring to 6.1 g o-methoxymethylbenzyl chloride at 150°C. The mixture was heated at 150°C for 1 h and distilled in vacuo to give 6.0 g of (XVI). The product was very hygroscopic.

o-Diphenylphosphinylmethylbenzyl Bromide (XVII) and o-Diethylphosphinylmethylbenzyl Bromide (XVIII). These were prepared analogously to (VII) (method A) from the corresponding ethers (XV) and (XVI). Compound (XVIII) hydrolyzes on standing in air.

o-Diphenylphosphinylmethylbenzyl Alcohol (XIX). This was prepared analogously to (XI) from bromide (XVII). PMR spectrum (δ, ppm): 3.8 d (CH_2P, J_{CH_2-P} = 12.8 Hz), 4.7 s (CH_2O), 5.6 s (OH).

o-Diethylphosphinylmethylbenzyl Alcohol (XX). This was prepared analogously to (XIII) (method B) from bromide (XVIII). PMR spectrum (δ, ppm): 3.3 d (CH_2P, J_{CH_2-P} = 12.8 Hz), 4.6 s (CH_2O), 6.9 s (OH).

The authors wish to thank V. A. Svoren' for recording the PMR spectra.

CONCLUSIONS

1. We have synthesized o-phosphorus-substituted benzyl and phenethyl alcohols of formula o-$R_2P(O)$-$C_6H_4(CH_2)_nOH$ and o-$R_2P(O)CH_2C_6H_4CH_2OH$ (R = C_6H_5 or C_2H_5, n = 1 or 2) from their methyl ethers via the corresponding bromides and acetoxy derivatives.

2. Hydrolysis of the substituted bromides containing a diethylphosphinyl group can be effected not only via the corresponding acetoxy derivatives but also by treatment with sodium bicarbonate.

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