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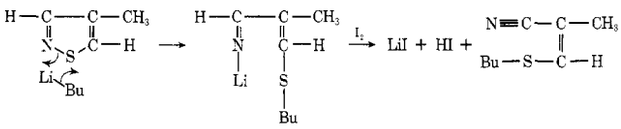

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Reductive Cleavage of Phosphinanilides with Lithium Aluminum Hydride

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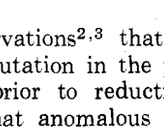
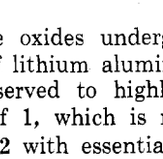
Observations[2,3] that phosphine oxides undergo rapid stereomutation in the presence of lithium aluminum hydride prior to reduction have served to highlight the somewhat anomalous behavior of **1**, which is reported[4] to undergo $LiAlH_4$ reduction to **2** with essentially complete retention of configuration at phosphorus. The behavior of **1** seems even more unusual with our finding that the principal reactions of phosphinanilides **3** and **4** with $LiAlH_4$ produce P–N bond cleavage rather than deoxygenation.



1, X = O
2, X = lone pair



3, R = H
4, R = CH_3

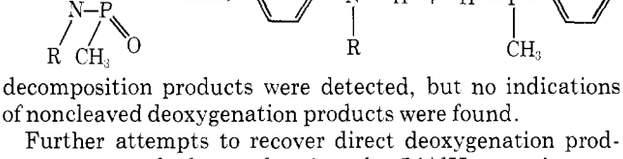
The reduction of optically active **1** to **2** with $LiAlH_4$ afforded the first reported example of a compound whose optical activity could be attributed to a pyramidally stable tervalent phosphorus.[5] Although retention of configuration during the reaction was originally ascribed to the possible formation of an iminophosphorane intermediate which resembles an organophosphorus ylide and might be expected to yield optically active phosphine with retention of configuration,[6] more recent studies[2] have suggested that the lack of stereomutation of **1** probably reflects the presence of barriers to pseudorotation of an intermediately formed phosphorane. Tertiary phosphine oxides are reduced by $LiAlH_4$ with retention of configuration, but yield phosphines of low optical purity owing to the rapid stereomutation of the phosphine oxides. Restraints imposed by the azaphosphorus ring system, the neighboring NH group, or the neighboring nitrogen atom could account for the observed stereochemistry at phosphorus of **1**.

We decided to investigate the reactions of optically active methylphenylphosphinanilide (**3**)[7] and its *N*-methyl derivative (**4**) with $LiAlH_4$, since these compounds provided for a systematic elimination of the alternatives suggested above. Azaphosphorus ring restraints are absent in **3**, and **4** lacks a proton on nitrogen.

The phosphinanilides were synthesized by treating diastereomerically enriched menthyl methylphenylphosphinate[8] with lithium reagents of aniline[9] and *N*-methylaniline, respectively. Both reactions proceeded smoothly, but **4** presented some problems in isolation and purification. It is hygroscopic, crystallizes with some difficulty, and is slightly light sensitive.

Stereomutation probes were performed initially by allowing mixtures of the respective phosphinanilides and $LiAlH_4$ (mole ratios of 2:1) in tetrahydrofuran to stand at room temperature for varying periods of time. Although both **3** and **4** could be recovered[10] without losses in their stereochemical integrities, they differed markedly in their chemical stabilities. Compound **4** is extremely reactive at room temperature, but higher temperatures and increased quantities of $LiAlH_4$ are required to promote a significant reactivity of **3**.

In contrast to expectations based on the reported behavior of **1**, nmr analysis of the reaction mixtures from **3** and **4** demonstrated that the phosphinanilides were undergoing P–N bond cleavage instead of deoxygenation. Aniline and *N*-methylaniline, respectively, could be readily identified and isolated. By comparisons with samples[11] of methylphenylphosphine[12] and methylphenylphosphine oxide,[13] the presence of these organophosphorus cleavage products could be discerned by nmr. They could be isolated in some cases.[14] Small quantities of other unidentified



decomposition products were detected, but no indications of noncleaved deoxygenation products were found.

Further attempts to recover direct deoxygenation products were made by performing the $LiAlH_4$ reactions on larger scales using racemic **3** and **4**. However, again only reaction products reflecting P–N bond cleavage could be discerned. In those cases where starting compounds were recovered, it seems highly unlikely that they resulted from a reoxygenation of reduction products during the reaction work-ups. Extreme care was exercised to minimize exposure of the reaction mixtures to air, and the presence of the easily oxidizable methylphenylphosphine could be ascertained. Also, more vigorous reaction conditions led to complete cleavage of the phosphinanilides.

The increased reactivity of **4** compared to **3** is consistent with the well-known cleavage of carboxylic amides with $LiAlH_4$,[15] but is in reverse to the relative rates of alkaline hydrolysis of phosphinamides.[16] This observation suggests

Table I
Reactions of Phosphinanilides with Lithium Aluminum Hydride

Compd	Mmol/mmol $LiAlH_4$	Conditions[a]	Product analysis, % yield[b] 3 or 4	PhNHR	MePhPH	MePhP(O)H
3	5.0/10.0	THF–PhH (50), 4 hr	87	0	0	0
3[c]	2.2/4.4	THF–PhH (25), reflux, 5 hr	62[c]	22	Traces	
3	9.0/18.0	THF–PhH (80), reflux, 15 hr	64	11	1	1
3	10.0/20.0	*n*-Bu_2O–PhH (50), 90°, 5 hr	20	—	Traces[d]	—
3	10.0/20.0	*n*-Bu_2O–PhH (50), 100°, 5 hr	8	—	Traces[d]	—
3	10.0/20.0	*n*-Bu_2O–PhH (50), 90°, 10 hr	0	—	Traces[d]	—
4	2.5/1.25	THF–PhH (25), 15 min	31	54	0	41
4	2.5/2.5	THF–PhH (25), 10 min	1	99	12	57
4	2.5/5.0	THF–PhH (25), 15 min	1	84	23	23
4	5.0/10.0	THF–PhH (50), 4 hr	0	81	21	51
4	5.0/10.0	THF–PhH (50), reflux, 3 hr	0	96	45	0

[a] Reaction medium (tetrahydrofuran, 3:2 THF–benzene, or 2:3 di-*n*-butyl ether–benzene) and quantity (milliliters), temperature (room temperature unless otherwise specified), and time. [b] Approximations based on nmr integration analysis of isolated product mixtures, including unreacted starting materials. [c] Stereomutation probe employing optically active compound in which yield represents actual recovery. [d] Most of the cleavage products were coremoved with the high-boiling di-*n*-butyl ether. Small quantities (5–15%) of methylphenylphosphinic acid were isolated.

an importance of P–N bond strengthening and/or diminution of hydride attack owing to anion formation by the reaction of $LiAlH_4$ with the N–H proton in **3**.

Our results have demonstrated that phosphinanilides are stereochemically stable in the presence of $LiAlH_4$, probably owing to the neighboring nitrogen atom, but, more importantly, we have found that lithium aluminum hydride *should not* be regarded as generally suitable for the deoxygenation of phosphinamides. In light of our bond-cleavage observations, the unusual P–N bond stability of **1** is perhaps due to aromatic stabilization in the azaphosphaphenanthrene ring system.[17]

Experimental Section

Melting points were determined (uncorrected) with a Thomas-Hoover melting point apparatus. Solvents were dried by distillation from $LiAlH_4$ and stored over sodium ribbons. Optical rotations were measured with a Kern polarimeter. Infrared spectra were obtained with a Perkin-Elmer Model 137 or 457 spectrophotometer; nmr spectra by means of a Varian EM-300 spectrometer using $CDCl_3$ solvent and TMS reference; and glpc analyses by employing a Gow-Mac Model 69-100 gas chromatograph with a commercial column (4 ft, DC-200 on Chromosorb P). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Methylphenylphosphinanilide (3). A. Optically Active. A solution of *n*-butyllithium (20 ml, 2.2 *M*, 44 mmol) in *n*-hexane was added to a cold (ice bath) solution of aniline (4.1 g, 44 mmol) in anhydrous ether (100 ml) in a nitrogen atmosphere. The reaction mixture was stirred in the cold for 1.5 hr, then allowed to warm to room temperature as menthyl methylphenylphosphinate[8] (2.5 g, 8.5 mmol, $[\alpha]D$ −89°) dissolved in dry benzene (100 ml) was added, and finally heated and ether removed until a reflux temperature of 60° was achieved. Heating was continued for 3.5 hr; then the reaction mixture was cooled in an ice bath, decomposed with 50 ml of 5% aqueous HCl, and diluted with 200 ml of CH_2Cl_2. The organic phase was separated, extracted with 5% HCl (3 × 50 ml), and dried over Na_2CO_3. Solvent removal *in vacuo* left a red-brown oil from which menthol was partially distilled by heating under reduced pressure (130° oil bath, 0.6 mm). The oil was dissolved in acetone (10 ml) and recovered as a brown solid by the addition of *n*-hexane. Purification by charcoal treatment (twice) in ether–acetone followed by recrystallization from acetone–hexane gave white needles of **3** (1.35 g, 69%): mp 156–157°; $[\alpha]D$ −24.4° (*c* 1.23, MeOH) [lit.[9] mp 161–163°; $[\alpha]D$ −26.3° (*c* 1.33, MeOH)].

B. Racemic. Methylphenylphosphinyl chloride[8] (17.4 g, 100 mmol) in dry benzene (100 ml) was slowly added to a mixture of aniline (9.3 g, 100 mmol) and triethylamine (10.1 g, 100 mmol) in dry benzene (100 ml). The reaction mixture was heated under slow reflux for 5 hr, then allowed to cool to room temperature as the product and triethylamine hydrochloride coprecipitated. The precipitate was collected and washed with water to remove the amine hydrochloride, leaving the desired product as a hydrate (29 g, mp 90–92°). Removal of the water of hydration by heating the solid under reduced pressure (98°, 0.6 mm, 3.5 hr) and recrystallization of the residue from acetone–hexane gave white crystals of racemic **3** (11.5 g, 50%), mp 125–128°. Nmr spectra for the racemic and optically active samples were superimposable.

***N,P*-Dimethylphenylphosphinanilide (4). A. Optically Active.** In the same manner as described for **3**, menthyl methylphenylphosphinate (5.9 g, 20 mmol, $[\alpha]D$ −94°) was allowed to react with the lithium reagent of *N*-methylaniline prepared from *N*-methylaniline (10.7 g, 100 mmol) and *n*-butyllithium (40 ml, 2.25 *M*, 100 mmol). After the prescribed work-up, the product was isolated by distillation under reduced pressure, bp 155–160° (0.2 mm), and collected as a yellow oil which solidified on cooling. Recrystallization of the solid from *n*-hexane gave hygroscopic white needles of **4** (2.2 g, 45%): mp 86–88° (evacuated capillary); $[\alpha]D$ −40.8° (*c* 0.39, MeOH); ir (neat, oil) 1200 cm^{-1} (P=O); nmr δ 1.5 (d, 3, J = 14 Hz, PCH_3), 2.9 (d, 3, J = 10 Hz, NCH_3), 7.0–8.4 (10, aryl protons for NAr and PAr centered at 7.1 and 7.3, respectively).

Anal. Calcd for $C_{14}H_{16}NOP$: C, 68.56; H, 6.58; N, 5.71; P, 12.63. Found: C, 68.80; H, 6.70; N, 5.58; P, 12.37.

The product is best stored under refrigeration in the absence of light.

B. Racemic. As described for **3**, methylphenylphosphinyl chloride (17.4 g, 100 mmol) and *N*-methylaniline (10.7 g, 100 mmol) were allowed to react in the presence of triethylamine (10.1 g, 100 mmol) in benzene (200 ml). The precipitated triethylamine hydrochloride was removed by filtration, and solvent removal under reduced pressure followed by fractional distillation of the residual oil gave racemic **4** as a yellow oil which solidified on refrigeration (13 g, 53%), bp 155–170° (0.3 mm). Nmr spectra for the racemic and optically active samples were superimposable.

General Procedure for the Reactions of Phosphinanilides with Lithium Aluminum Hydride. Solutions of the phosphinanilides were added in one portion to equal-volume suspensions of lithium aluminum hydride. The reactions and all subsequent manipulations were performed under nitrogen. After prescribed periods of time, the reaction mixtures were cooled (ice bath), quenched by adding the minimum amounts (2–5 ml) of saturated aqueous NH_4Cl solution required to make the resulting inorganic salts appear granular, and diluted with oxygen-free benzene (15–25 ml). The organic solutions were filtered to remove the insoluble inorganic salts, dried over $MgSO_4$, and concentrated under reduced pressure. The residues were examined by nmr, then rapidly distilled (Kugelrohr) to remove volatile (60–120° or 145°, 0.7 mm) components, and both distillates and residues were reexamined by nmr.[18] In general, aniline or *N*-methylaniline, methylphenylphosphine, and methylphenylphosphine oxide, plus some unidentified decomposition products, were found in the distillates, whereas unreacted starting materials, methylphenylphosphine oxide (distillation <120°), and occasionally methylphenylphosphinic acid remained in the undistilled residues. Pertinent data on the several reactions performed are provided in Table I.

Stereomutation Probes. The general procedure previously outlined was followed except that the unreacted starting materials were carefully recovered.

Optically active **3** could easily be recovered after removal of volatile products, if any, as a white solid. It was dissolved in

methanol, filtered to remove insoluble suspended material, and recovered by evaporation of the methanol under reduced pressure. Three probes with 3 (1.5 mmol, $[\alpha]D$ −22.2°) and $LiAlH_4$ (0.8 mmol) in the following solvents (25 ml) were performed as indicated: THF (5 hr, room temperature), THF (3 hr, reflux), and di-*n*-butyl ether (0.5 hr, 80°). Recovery of 3 was 80, 50, and 85%, respectively, and $[\alpha]D$'s were −22.4, −25.4, and −21.0°. A fourth sample of 3 (2.2 mmol, $[\alpha]D$ −24.4°) was refluxed with $LiAlH_4$ (4.4 mmol) in 25 ml of THF–benzene (3:2) for 5 hr. Recovery of 3 ($[\alpha]D$ −25.4°) was 62%.

Nonstereomutated, optically active 4 could be recovered from its reaction mixtures by dissolving the originally isolated products (no distillation) in benzene, extracting the *N*-methylaniline and organophosphorus cleavage products from the solutions with 0.1 *M* aqueous HCl, and, after drying, evaporating the solvent under reduced pressure. Attempts to distil the reaction mixtures were accompanied by disproportionation of methylphenylphosphine oxide, and complicated efforts to recover unreacted starting material. Three probes gave the following results: (1) 4 (1.8 mmol, $[\alpha]D$ −40.8°) and $LiAlH_4$ (0.9 mmol), 10 min in THF–benzene (3:2, 20 ml) at room temperature with 72% recovery of starting material ($[\alpha]D$ −42.2°); (2) 4 (2.5 mmol, $[\alpha]D$ +12.0°) and $LiAlH_4$ (1.25 mmol), 15 min in THF (20 ml) with 40% recovery ($[\alpha]D$ +12.1°); and (3) 4 (2.4 mmol, $[\alpha]D$ −40.8°) and $LiAlH_4$ (0.5 mmol), 4 hr in THF–benzene (25 ml) with 98% recovery (no reaction observed) of starting material ($[\alpha]D$ −40.7°).

Methylphenylphosphine was prepared in 35% yield from methyl methylphenylphosphinate:[12] bp 67–69° (9 mm); ir (neat) 2280 cm^{-1} (P–H); nmr δ 1.3 (d, 3, J = 3 Hz, PCH_3), 4.3 (s, 1, PH), 6.5–8.0 (broad, 5, aromatic) [lit.[12] bp 62–63° (11 mm)].

Methylphenylphosphine oxide was prepared by the oxidation of methylphenylphosphine:[13] ir (neat) 2320 (P–H), 1190 cm^{-1} (P=O); nmr δ 1.7 (dd, 3, J = 14, 3 Hz), 7.7 (doublet of quartets, 1, J = 462 Hz), 6.2–7.9 (m, 5, aromatic).

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—(−)-3, 50682-94-5; (±)-3, 51703-89-0; (−)-4, 51593-48-7; (±)-4, 51593-49-8; aniline, 62-53-3; menthyl methylphenylphosphinate, 39837-64-4; methylphenylphosphinyl chloride, 5761-97-7; *N*-methylaniline, 100-61-8; methylphenylphosphine, 6372-48-1; methylphenylphosphine oxide, 19315-13-0.

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(18) Quantitative nmr analyses were made before (when possible) and after distillation for comparisons. Glpc analyses of several distillates indicated the presence of aniline or *N*-methylaniline, methylphenylphosphine, and small quantities of other more volatile products. However, disproportionation of methylphenylphosphine oxide prevented quantitative glpc analyses.

Sterochemistry of the Reduction of Diastereomeric α-Bromo-α-methylbenzyl α-Methylbenzyl Sulfones[1]

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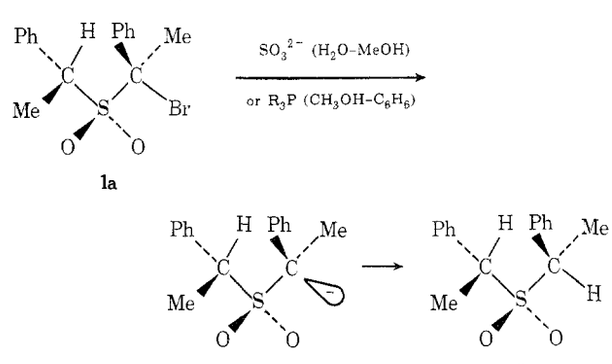
There are numerous reports in the literature of the reduction of α-halo sulfones by removal of a "positive" halogen atom in the presence of a proton donor. Electron donors such as alkoxide ions,[2-4] phenylmagnesium bromide,[3] mercaptide ions,[3] thiophenoxide ion,[4] piperidine,[4] sulfite ion,[1] and triphenylphosphine,[1,5] have been used. The mechanism of these reductions has been assumed in recent years to involve slow generation of an α-sulfonyl carbanion intermediate and rapid subsequent protonation.[4] A recent detailed study of the mechanism of the reduction of $ArCHXSO_2PH$ sulfones with triphenylphosphine in aqueous DMF provides strong evidence for the formation of an α-sulfonyl carbanion intermediate.[6]

Generation of asymmetric α-sulfonyl carbanions has been accomplished by deprotonation (or dedeuteration), decarboxylation, or a reverse aldol reaction.[7] A high degree of stereospecificity has been observed for the overall generation and protonation of the 2-octylphenylsulfonyl carbanion $[PhSO_2C(Me)(C_6H_{11})]^-$, by each of these methods. Base-catalyzed deprotonation and deuteration occurs with retention of configuration, and the same stereochemistry has been assumed for the other two reactions.[7,8] Generation of an asymmetric α-sulfonyl carbanion by a reverse aldol in such a manner as to produce a carbanion in which the orbital containing the electron pair is anti to the sulfonyl oxygen atoms results in overall inversion of configuration.[11] Inversion also appears to be the usual result when the carbanion, generated either by deprotonation[12] or dehalogenation,[5] reacts with an electrophilic site within the molecule to effect a 1,3-elimination reaction. The present paper is concerned with the stereochemistry of the reduction of an α-bromo sulfone (**1**) by generation of the corresponding α-sulfonyl carbanion (**2**) in the presence of a proton donor.[1]

Results and Discussion

The *dl*-erythro structure for the higher melting isomer (**1a**) of the diastereomeric α-bromo-α-methylbenzyl α-methylbenzyl sulfones $C_6H_5C(Br)(Me)SO_2CH(Me)C_6H_5$ (**1a** and **1b**) has been assigned by X-ray crystallographic analysis.[1] Structure assignments to the reduction products of **1a** and **1b**, *dl*- and *meso*-bis(α-methylbenzyl) sulfones (**3a** and **3b**), have been made by nmr spectroscopy.[13]



Most of the reduction experiments were carried out with the more readily isolable erythro isomer **1a**. Reduction of