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STEREOCHEMISTRY OF ORGANOPHOSPHORUS CYCLIC COMPOUNDS—III

THE STEREOSPECIFIC SYNTHESIS OF *CIS*- AND *TRANS*-2-N-PHENYLAMINO-2-OXO-4-METHYL-1,3,2-DIOXAPHOSPHORINANS[1]

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Abstract—On the basis of chemical transformations and spectroscopic data the *cis*- and *trans*-geometry was assigned to the previously reported diastereoisomeric 2-N-phenylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (**1**). The addition of phenyl azide to cyclic phosphite (**3**) as well as the reaction of the resulting adduct (**4**) with carbon disulphide or benzoic acid takes place with overall retention of configuration at the P-atom. The conformation of the 1,3,2-dioxaphosphorinanyl ring system in both *cis*- and *trans*-**1** is suggested.

In the stereochemistry of heterocyclic phosphorus compounds, especially 1,3,2-dioxaphosphorinans,[2-4] the majority of investigations report a chair conformation for the dioxaphosphorinan ring systems, and a tendency for the O atom in the phosphoryl group of cyclic phosphates and amidophosphates to occupy the equatorial position has been observed. In an investigation on the application of inner-orbital photoelectron spectroscopy to the differentiation between the geometric isomers of some cyclic organophosphorus compounds,[6] the synthesis of isomeric 2-N-phenylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinans **1** was described. However the spatial positions of functional groups have not been determined and for both diastereoisomers only the conventional formulae have been proposed. In this paper the *cis-trans* geometry is assigned to the above mentioned cyclic N-phenylphosphoramidates **1**.

RESULTS AND DISCUSSION

In the previous paper the synthesis of both isomers of **1** via the reaction of phosphorus oxychloride with butan-1,3-diol followed by treatment of the resulting 2-chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinan **2** with aniline[6] was described. In the light of recent results it is clear that the reaction of butan-1,3-diol with phosphorus oxychloride yields both *cis*- and *trans*-2-chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans **2*** and that the ratio of isomers depends on reaction conditions.[7]

Thus, the reaction of the mixture of isomers of **2** with aniline gave a mixture of the resulting anilides **1** melting at 174–176° (high yield) and 154–156° (low yield). As both *cis*- and *trans*-**2** are formed in the stereospecific chlorination reactions of the corresponding *cis*- and *trans*-2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinans **6** or *trans*- and *cis*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinans **3**, respectively,[7] we decided to examine the stereochemistry of reactions of pure diastereoisomeric **2** with aniline.

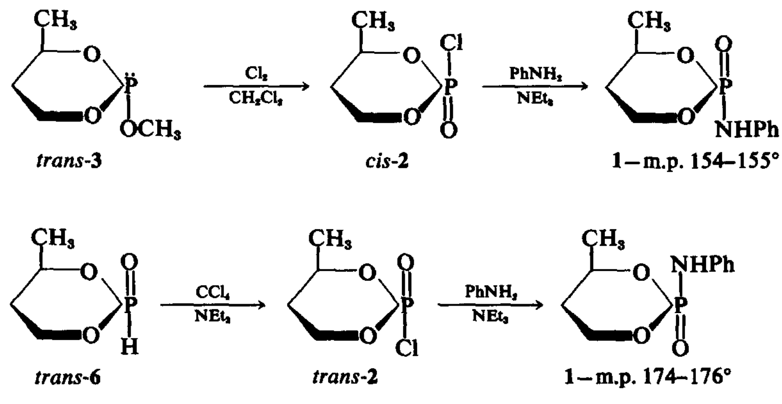
In a series of experiments, *trans*-2-chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinan **2** reacted with aniline in the presence of triethylamine to give isomer **1** m.p. 175–176°. The *cis*-**2** was similarly converted into **1**, m.p. 154–156°. Both isomers gave correct elemental analyses and identical electron-impact behaviour†. The ^{31}P NMR spectra of the crude products showed the full stereospecificity of the investigated reactions.

The isomer melting at 175–176° has $\delta_{^{31}P} = +1\cdot1$ ppm (saturated DMF solution, H_3PO_4 as external standard) and that melting at 154–156°, has $\delta_{^{31}P} = +3\cdot5$ ppm.

Inspection of ^{31}P NMR chemical shifts of other *cis-trans* isomeric 4-methyl-1,3,2-dioxaphosphorinans (Table 1) suggests that the order of chemical shifts for the given pair is inconclusive and can lead to erroneous assignment of *cis-trans* geometry. Therefore we decided to correlate the configuration by chemical means. As shown, the reaction of **2** with $MeOH/NEt_3$ or Me_2NH takes place with inversion of configuration at P-atom.[7] However in the light of data presented by Wads-

**trans*—referring to the equatorial—axial relationship between the ring Me group and the P-chlorine or equivalent substituents.

†It is noteworthy that diastereoisomeric *cis*- and *trans*-2-oxo-2-methoxy-4-methyl-1,3,2-dioxaphosphorinans have the same pattern of fragmentation, but relative intensities of major fragments are reversed (unpublished results).

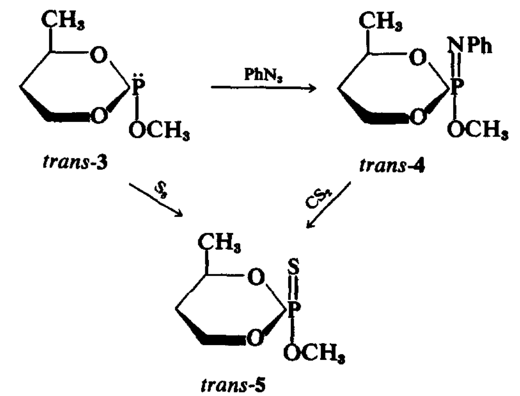


Scheme 1

Table 1. The chemical shift values ^{31}P NMR of some 2-R-2-X-4-methyl-1,3,2-dioxaphosphorinans

R	X	*cis-*	*trans-*
MeO	LP	−126·5[a]	−125·9
H	O	+1·0[7]	−3·1[7]
H	S	−61·2[8]	−54·2[8]
H	Se	−66·0[8]	−67·7[8]
Cl	O	+5·7[7]	+3·7[7]
Br	O	+20·5[7]	+13·7[7]
Cl	S	−55·4[8]	−57·5[8]
MeO	O	+5·1[7]	+6·4[7]
MeO	S	−63·5[a]	−61·5[a]
MeO	Se	−67·3[a]	−65·7[a]
Me_2N	O	−7·5[7]	−4·7[7]
Me_2N	S	−70·7[8,a]	−70·2[8,a]
Me_2N	Se	−70·0[8,a]	−69·0[8,a]
MeO	NPh	+7·5[a]	+9·5[a]

LP = Lone electron pair, a—this work.



Scheme 2

worth and Horton[9] on $S_{N1}P$ type mechanism of nucleophilic substitution at the P atom involved in a dioxaphosphorinanyl ring system, the hypothesis regarding $S_{N2}P$ reaction mechanism of **2** with aniline requires additional proof. Addition of phenyl azide (Staudinger Reaction)[10] to both *cis-* and *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinans **3** in ethyl ether gives the corresponding *cis-* and *trans*-2-methoxy-2-N-phenylamino-4-methyl-1,3,2-dioxaphosphorinans **4**. The stereospecificity of the formation of **4** follows from its subsequent reaction with carbon disulphide.[10,14]

Thus reaction of *trans* **3** with phenyl azide, followed by carbon disulphide yields *trans*-2-methoxy-2-thiono-4-methyl-1,3,2-dioxaphosphorinan **5**.[23]

Compound *cis*-**5** was similarly prepared from *cis*-**3**. Since both *cis-* and *trans*-**5** are available from direct addition of sulphur to **3**, which is known to proceed with retention of configuration at the P-atom[12,13], we concluded that addition of phenyl azide takes place also with retention of configuration. Chart I shows that the treatment of *trans*-**4** with benzoic acid[14] yielded **1**, m.p. 174–175°. Compound *cis*-**4** was similarly transformed into **1** m.p. 153–154°. These reactions are fully stereospecific.

The mechanistic pathway of the transformation **4**→**1** can be interpreted as the protonation of **4** (which is a moderately strong base)[15] on the N atom and formation of a quasi-phosphonium salt. In the second stage the benzoic acid anion attacks the C atom of the OMe group to give methyl benzoate and the corresponding phosphoramide, with overall retention of configuration at the P-atom.

Since the formation of a pentacovalent intermediate in the reaction of **4** with benzoic acid, or the ligand exchange in the intermediately formed quasi-phosphonium salt has to be considered, we extended our investigation to the acidolysis of *trans* **4** with 0,0-diethylphosphorodithioic acid. The reaction was more vigorous than that with benzoic acid and takes place with retention of configuration yielding **1**, m.p. 174–176° (90%). This result proves that the phosphoryl oxygen in phosphoroamidate **1** originates from the OMe group of the starting **3** and in this diligostatic system[16]

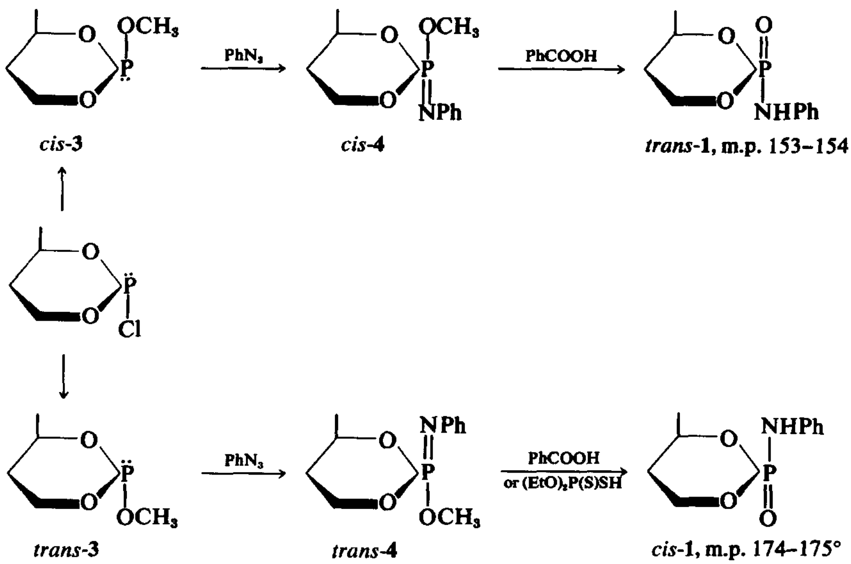


CHART 1

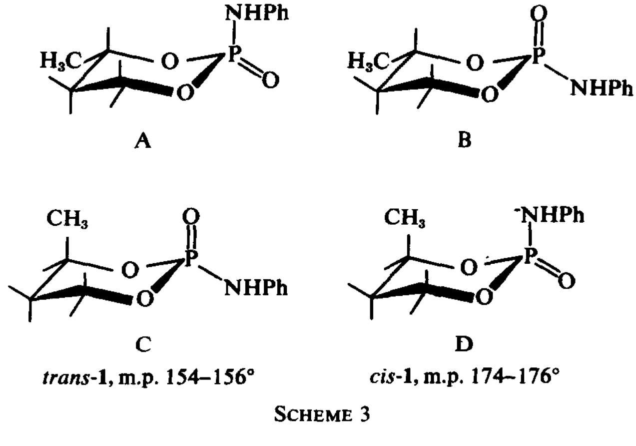
trans-**4** gave *cis*-**1**, m.p. 174–176° and *cis*-**4** yielded *trans*-**1**, m.p. 154–156°.

These results explain not only the *cis*-*trans* geometry in phenyl phosphoramidates **1** but also give additional evidence for the inversion of configuration at the P atom involved in 6-membered rings during the nucleophilic attack by aniline in the presence of triethylamine. Although these chemical facts explain the geometry of phosphoramidates **1**, more information concerning their conformation was obtained from spectral data.

In the ^{1}H NMR spectra of both isomers, the protons at the C-4 Me group are split by the methine C—H proton and additionally by phosphorus nuclei with $^4J_{PH}$ equal to 2·2 Hz for *cis*- and 2·5 Hz for *trans* **1**. This suggests an equatorial C-4 Me position in view of the lack of other splittings by a C-5 axial methylene proton, which should be observed in the case of an axial C-4 Me.[18] Also the values higher than 1 Hz support this conclusion, since according to Malcolm and Hall,[17] we should expect a much smaller $^4J_{PH}$ value for a C-4 axial Me.

Owing to poor solubility of **1**, in solvents normally used in NMR analyses and some instrumental limitations, we are not able to present the full NMR analysis of the dioxaphosphorinanyl ring in **1**, but the available NMR data indicated that in both isomers the Me group occupies an equatorial position.[18] The IR spectrum of *trans* **1**, m.p. 154–156°, shows a strong absorption at 1250 cm^{-1}, assigned to ν_{PO}. In the spectrum of *cis*-**1**, m.p. 174–176°, ν_{PO} absorption is shifted to lower frequency 1230 cm^{-1}.

Measured values of ν_{PO} indicate an equatorial



SCHEME 3

phosphoryl group in *trans* 1 and an axial one in *cis* 1. This assignment is compatible with the general trend that the axial stretching frequency is lower than the equatorial one.[19] This suggests that the position of the phosphoryl group controls the geometry of the dioxaphosphorinanyl ring in 1.*

On the basis of presented data A and B are chosen as predominant conformers for *trans*- and *cis*-1, respectively.

EXPERIMENTAL

All solvents were reagent grade and were distilled and dried by conventional methods before use.

^{1}H NMR spectra were recorded at 60 MHz with a Jeol C-60 H spectrometer for *ca* 10% (w/v) solutions at room temp. Chemical shifts were measured with respect to internal TMS. Negative values are reported for compounds absorbing at lower field as TMS. ^{31}P NMR spectra were obtained on the same instrument operating at 24·3 MHz observing frequency as neat liquids or saturated solutions with external H_3PO_4 as the reference. Positive values are reported for compounds absorbing at higher field as H_3PO_4.

IR spectra were recorded for KBr discs unless specified otherwise with a Carl Zeiss (Jena) UR-10 spectrometer.

The mass spectra were obtained at 70 eV and 15 eV ionizing energy using LKB-9000 mass spectrometer. The accelerating voltage was 3·5 kV. Samples were introduced via the direct solid probe. M.ps were determined in capillary tubes in a Mel-Temp apparatus and are uncorrected. Phenyl azide,[20] *cis*- and *trans*-3[21] and *cis*- and *trans*-6[22] were prepared according to the methods described in the literature.

1. *Condensation of* cis-2-*chloro*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan with aniline,* trans-2-N-*phenylamino*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan* (1)

(a) To a soln of *trans* 3[21] (8·0 g, 0·053 m) in 20 ml CH_2Cl_2 was added dropwise, with vigorous stirring a soln of Cl_2 (1·9 g, 0·053 m) in 70 ml CH_2Cl_2 at temp $-58 \div -65°$. Stirring was continued for the next 15 min at this temp, the dry-ice/acetone bath was removed and the temp was allowed to reach +10°. Evaporation of the solvent under reduced pressure gave *cis*-2.[7] A soln of this product in 20 ml benzene was dropped into a mixture of triethylamine (5·4 g, 0·053 m) and aniline (5·0 g, 0·053 m) in 50 ml benzene at a temp 20–25°. Stirring at this temp was continued for 15 hr. The solvent was removed under reduced pressure and the solid residue was treated with a mixture of 100 ml CH_2Cl_2 and 20 ml water. The organic layer was separated, washed with 50 ml 5% HCl and dried over $MgSO_4$. The dried soln was filtered, concentrated and the solidified oil was crystallized from EtOAc. Filtration yielded 8·1 g (72%) of white needles, m.p. 154–156°, IR (KBr): 1250 cm^{-1} vs(ν_{PO});† Mass spectrum: *m/e* 227 (58%); 173 (100%); 155 (82%); 93 (22%); 65 (25%); ^{1}H NMR (CD_3SOCD_3): $\delta_{C-CH_3} = -1{\cdot}275$ ppm (3H, quartet), $^3J_{H-CH_3} = 6$Hz, $^4J_{PH} = 2{\cdot}5$ Hz, $\delta_{NH} = -7{\cdot}91$ ppm, (1H, doublet), $^2J_{PH} = 12$ Hz; ^{31}P NMR (MeOH): $\delta = +3{\cdot}5$ ppm after H-decoupling. (Found: C, 52·8; H, 6·4; P, 13·7; N, 6·7. Calc. for $C_{10}H_{14}NO_3P$: C, 52·8; H, 6·2; P, 13·6; N, 6·1%).

(b) The condensation of *cis*-2-chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (prepared by chlorinolysis of *cis*-2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinan[22] with sulphuryl chloride) with aniline in the presence of NEt_3 gave the same result.

2. *Condensation of* trans-2-*chloro*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan with aniline,* cis-2-N-*phenylamino*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan* (1)

Into a soln of *trans* 6 (1·4 g, 0·01 m) in 40 ml CCl_4, a mixture of NEt_3 (1·1 g, 0·01 m) and aniline (0·95 g, 0·01 m) was added, and the reaction was carried out at room temp for 12 hr. The ppt was filtered off, dried under vacuum to remove the solvent and finally washed twice with water (2 × 20 ml). The residual crystals were dried and crystallized from EtOAc yielding 2·1 g (92%) of pure *cis* 1, m.p. 174–176°; IR(KBr): 1230 cm^{-1} vs ($\nu_{P=O}$); Mass spectrum the same as *trans*-1; ^{1}H NMR (CD_3SOCD_3): $\delta_{C-CH_3} = -1{\cdot}30$ ppm (3H, quartet), $^3J_{HCH_3} = 6$ Hz, $^4J_{PH} = 2{\cdot}1$ Hz, $\delta_{NH} = -8{\cdot}16$ ppm (1H, doublet), $^2J_{PH} = 9$ Hz; ^{31}P NMR (DMSO): $\delta = +1{\cdot}1$ ppm after the H-decoupling. (Found: C, 53·0; H, 6·2; P, 13·5; N, 6·2; Calc. for $C_{10}H_{14}NO_3P$: C, 52·8; H, 6·2; P, 13·6; N, 6·1%).

The ^{31}P NMR spectrum of the crude product did not show the presence of *trans*-1.

3. *Reaction of phenyl azide with* cis-2-*methoxy*-4-*methyl*-1,3,2-*dioxaphosphorinan* (3)

A soln of phenyl azide (6 g, 0·05 m) in ethyl ether (10 ml) was added dropwise to a magnetically stirred soln of *cis* 3 (7 g, 0·046 m) at 20–30°. As the reaction was very exothermic, the temp was controlled by the rate of addition of phenyl azide; N_2 was evolved. Stirring at 35° (reflux) was continued for the next hr, then the solvent was removed under reduced pressure and the residual undistillable pale-yellow oil was identified as *cis* 4, $n^{20} = 1{\cdot}5445$; 11·1 g (99%); IR (film): 1280 cm^{-1} s/br ($\nu_{P=N}$); ^{1}H NMR (CCl_4): $\delta_{H-CH_3} = -1{\cdot}15$ ppm (3H, quartet), $^3J_{H-CH_3} = 6$ Hz, $^4J_{P-H} = 1{\cdot}6$ Hz, $\delta_{OCH_3} = -3{\cdot}75$ ppm (3H, doublet), $^3J_{P-H} = 12$ Hz, ^{31}P NMR (neat) $\delta = +7{\cdot}5$ ppm.

4. *Reaction of* cis 4 *with carbon disulphide*

Compound 4 (18·1 g, 0·075 m), prepared as described in section 3 $n_D^{20} = 1{\cdot}5447$, was dissolved in 25 ml CS_2 and the resulting soln was heated under reflux for 10 hr. The mixture was left overnight at room temp, CS_2 was removed by distillation and the residue was fractionated under reduced pressure to give (a) b.p. 42–47°/0·6 mm Hg, $n_D^{20} = 1{\cdot}6477$, 7·7 g (76%), identified as phenyl isothiocyanate (IR spectrum identical with that of authentic sample); (b) b.p. 57–60°/0·02 mm Hg, $n_D^{20} = 1{\cdot}4988$, 10 g (73%) identified as *cis* 5[12] (elemental analysis, GLPC, IR, ^{1}H NMR, ^{31}P NMR (neat) $\delta = -63{\cdot}5$ ppm).

5. *Reaction of* 4 *with benzoic acid*

Into a soln of 4 (11 g, 0·045 m) in 20 ml benzene, a soln of benzoic acid (5·6 g, 0·045 m) in 40 ml of the same solvent was added in 3 equal portions with vigorous stirring. After addition, the temp rose from 25° to 60°.

*However, the general trend that the axial stretching frequency is lower than the equatorial one is not compatible with our observations of $\nu_{P=N}$ absorption frequencies in 4. In *cis* 4 axial phosphorus–phenylimino-group has the higher frequency band (1280 cm^{-1}) than in *trans* (1270 cm^{-1}).[11]

†Abbreviations used: s-strong, vs-very strong, br-broad.

The resulting mixture was refluxed for 1·5 hr, 50 ml of petroleum ether (50–60°) was added and the mixture was cooled to room temp.

The ppt was filtered off and crystallized from EtOAc, m.p. 154–155° (needles), 6·7 g (81%) identified as *trans* 1. The product was identical with that described in section 1 (elemental analysis, m.m.p., IR, ^{1}H NMR, ^{31}P NMR).

6. *Reaction of phenyl azide with* trans-*2-methoxy-4-methyl-1,3,2-dioxaphosphorinan* (3)

Into a soln of *trans*-3 (7·5 g, 0·05 m) in 30 ml ethyl ether, phenyl azide (6·7 g, 0·06 m) was added in one portion and the resulting mixture was refluxed with vigorous stirring for 3 hr. The mixture was kept overnight at room temp, the solvent and excess phenyl azide were removed under reduced pressure, and the residual undistillable pale-yellow oil was identified as *trans*-4, $n_D^{20} = 1·5410$, 12·0 g (100%); IR (film): 1270 cm^{-1} s ($\nu_{P=N}$); ^{1}H NMR (CCl_4): $\delta_{C-CJ_3} = -1·15$ ppm (3H, quartet), $^3J_{H-CH_3} = 6$ Hz, $^4J_{P-H} = 2·25$ Hz, $\delta_{OCH_3} = -3·75$ ppm (3H, doublet), $^3J_{P-H} = 12$ Hz; ^{31}P NMR (neat): $\delta = +9·5$ ppm.

7. *Reaction of* trans 4 *with carbon disulphide*

Phenyl isothiocyanate (64·2%) and *trans* 5 (61%), $\delta_{^{31}P} = -61·5$ ppm, were obtained by the method described in section 4 above.

8. *Reaction of* trans 4 *with benzoic acid*

A mixture of *trans* 4 (12 g, 0·05 m), benzoic acid (6·1 g, 0·05 m) and benzene (70 ml) was refluxed for 4 hr. Further work-up (described in section 5) yielded 8·9 g (79%) of *cis* 1, m.p. 175–176° (from EtOAc) identical with the product obtained in section 2 above, (m.m.p., elemental analysis, IR, ^{1}H NMR, ^{31}P NMR).

9. *Reaction of* trans 4 *with diethyl phosphorodithioic acid*

Into a soln of *trans* 4 in 50 ml light petroleum (40–50°) was added dropwise with stirring an equimolar amount of diethyl phosphorodithioic acid at 40–50°. The exothermic reaction was accompanied by precipitation of crystals. Refluxing was continued for 10 min, the crystals were filtered off and recrystallized from EtOAc, m.p. 172–173°, 5·9 g (85%), identified as *cis* 1.

Evaporation of the solvent from the filtrate and vacuum distillation of residue gave O,O-diethyl-S-methyl phosphorodithioate,[13] b.p. 44–46°/0·01 mm Hg, $n_D^{20} = 1·5094$, ^{31}P NMR (neat): $\delta = -95$ ppm, identical with an authentic sample (^{1}H NMR, GLPC) prepared in the reaction of ammonium diethylphosphorodithioate with MeI.

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