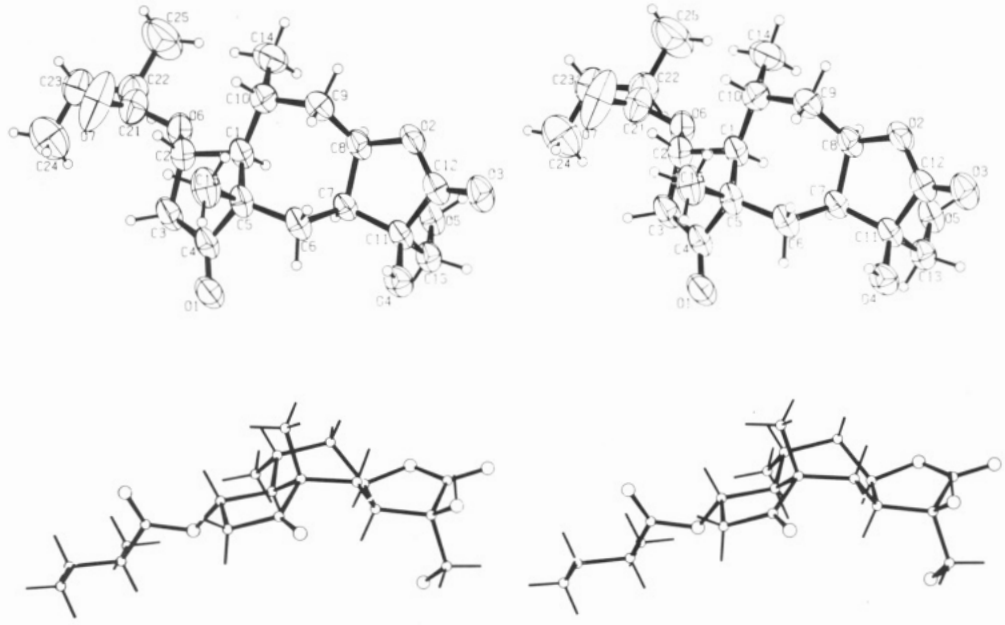

**Figure 1.** Top: stereoscopic view of florigrandin molecule with ellipsoids of thermal motion. Bottom: side view of molecular framework.

Table V. Torsion Angles (in Degrees) in 1 with Standard Deviations in Parentheses

| | |
|---|---|
| C(5)-C(1)-C(2)-C(3) | −39.3 (4) |
| C(1)-C(2)-C(3)-C(4) | 22.9 (5) |
| C(2)-C(3)-C(4)-C(5) | 2.9 (5) |
| C(3)-C(4)-C(5)-C(1) | −26.8 (4) |
| C(4)-C(5)-C(1)-C(2) | 39.7 (4) |
| C(1)-C(5)-C(6)-C(7) | −15.8 (5) |
| C(5)-C(6)-C(7)-C(8) | 66.8 (5) |
| C(6)-C(7)-C(8)-C(9) | −10.2 (6) |
| C(7)-C(8)-C(9)-C(10) | −71.3 (5) |
| C(8)-C(9)-C(10)-C(1) | 44.4 (5) |
| C(9)-C(10)-C(1)-C(5) | 47.6 (5) |
| C(10)-C(1)-C(5)-C(6) | −68.7 (5) |
| C(11)-C(7)-C(8)-O(2) | −15.6 (4) |
| C(7)-C(8)-O(2)-C(12) | 8.5 (5) |
| C(8)-O(2)-C(12)-C(11) | 2.8 (5) |
| O(2)-C(12)-C(11)-C(7) | −12.9 (5) |
| C(12)-C(11)-C(7)-C(8) | 16.9 (4) |

that the absolute configurations of the 2-methylbutyrate ester side chains of florigrandin (**1**) and hymenosignin (**9**),[7] the latter isolated from the closely related *Hymenoxys insignis*, differ.

## Experimental Section

Single crystals of florigrandin were prepared by slow crystallization from benzene–ethyl acetate. The crystals were monoclinic, space group $P2_1$, with $a$ = 8.528 (6) Å, $b$ = 10.421 (7) Å, $c$ = 11.530 (7) Å, $\beta$ = 92.76 (6)°, and $d_{calcd}$ = 1.241 g cm$^{-3}$ for $Z$ = 2 ($C_{20}H_{30}O_7$, $M_r$ = 382.45). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K$\alpha$ radiation, $\theta$–$2\theta$ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.04 × 0.5 × 1.0 mm. A total of 1476 independent reflections were measured for $\theta < 57°$, of which 1344 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[11] and was refined by full-matrix least-squares methods. Two reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are $R$ = 0.036 and $R_w$ = 0.041 for the remaining 1342 observed reflections. The final difference map has no peaks greater than ±0.2 e Å$^{-3}$.

**Registry No.** 1, 51292-61-6.

**Supplementary Material Available:** Tables I–IV listing final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for compound 1 (5 pages). Ordering information is given on any current masthead page.

(11) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.

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# (*N*-Alkylthiocarbamoyl)phosphonic Acid Esters. 1. Preparation and Spectral Properties

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(*N*-Alkylthiocarbamoyl)phosphonic acid esters **1** have been prepared and explored only occasionally.[1-3,8] Recently, the increasing interest in the biological effects of $\alpha$-subsituted methyl phosphonate derivatives (carboxy-[4] and carboxamido phosphonate[5] as antiviral agents, aminomethyl phosphonate as substitutes for amino acids,[6] methylene diphosphonate compounds in treating calcium metabolism disorders,[7] and compounds containing the amidinophosphonate group as antihistaminics[8]) led us to

(1) K. A. Petrov and A. A. Nejmysheva, *Zh. Obshch. Khim.*, **29**, 1819 (1959). *N*-Aryl derivatives have been reported by V. V. Alekseev and M. S. Malinovskij, *ibid.*, **30**, 2967 (1960).
(2) E. S. Batyeva, E. N. Ofitserov, and A. N. Pudovik, *Zh. Obshch. Khim.*, **47**, 559 (1977).
(3) M. Sekine, H. Yamagata, and T. Hata, *Tetrahedron Lett.*, 3013 (1979).
(4) E. Helgstrand, B. Eriksson, N. G. Johansson, B. Lannero, A. Larsson, A. Misiorny, J. O. Noren, B. Sjoberg, K. Stenberg, G. Stening, S. Stridh, B. Oberg, S. Alenius, and L. Philipson, *Science*, **201**, 819 (1978).
(5) A. J. E. Helgstrand, K. N. G. Johansson, A. Misiorny, J. O. Noren, and G. B. Stening, European Patent Appl. 3008 (1979); *Chem. Abstr.*, **92**, 76662 (1980).
(6) (a) P. Mastalerz, *Arch. Immunol. Ter. Dosw.*, **7**, 201 (1959); *Chem. Abstr.*, **54**, 6843 (1960). (b) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. W. Lambert, L. J. Nisbet, and P. S. Ringrose, *Nature (London)*, **272**, 56 (1978).
(7) (a) H. Fleisch, F. Straumann, R. Schenk, S. Bisaz, and M. Allgower, *Am. J. Physiol.*, **211**, 821, (1966). (b) G. Krampitz and W. Witt, *Top. Current. Chem.*, **78**, 116 (1979).

0022-3263/82/1947-3012$01.25/0 

Table I. Methods of Preparation, Yields, and Ultraviolet Data for Compounds 1a-f[a]

| compd | method of prepn | mp, °C | % yield | n → π* absorption in ethanol $\lambda_{max}$, nm | n → π* absorption in ethanol log ε | n → π* absorption in petroleum ether $\lambda_{max}$, nm | n → π* absorption in petroleum ether log ε | π → π* absorption in ethanol[b] $\lambda_{max}$, nm | π → π* absorption in ethanol[b] log ε |
|---|---|---|---|---|---|---|---|---|---|
| 1a | A | 41 | 50 | 390 | 1.30 | | | 283 | 3.90 |
| 1b | A | 52 | 65 | 390 | 1.31 | | | 283 | 3.90 |
| 1c | A | 75 | 80 | 395 | 1.39 | 405 | 1.43 | 288 | 3.94 |
| 1d | B | 85 | 85 | 398 | 1.33 | 411 | 1.56 | 285 | 3.99 |
| 1e | B | 92 | 75 | 409 | 1.58 | 417[c] | 1.60[c] | 288 | 4.05 |
| 1f | C | 142 | 25 | 395 | 1.30 | | | 282 | 3.98 |

[a] Satisfactory analytical values for C, H, N, S, and P were reported for all compounds. [b] The π → π* absorptions in petroleum ether were remarkably similar. [c] The solvent was petroleum ether and carbon tetrachloride (1:1).

investigate the phosphonothioamidates 1 as versatile precursors to different α-substituted methyl phosphonate derivatives.

While the Arbuzov-type reaction of trialkyl phosphite and alkyl isothiocyanate does not usually produce phosphonates of type 1[9] (for exceptions see ref 2 and 3), it was claimed by Petrov and Nejmysheva [1] that the related reaction of dialkyl phosphite with methyl or allyl isothiocyanate gave reasonable yields of a few thiocarbamoyl phosphonates, including **1b** (eq 1).

$$(RO)_2PH(=O) + R'N{=}C{=}S \xrightarrow{\text{base}} (RO)_2P(=O)-C(=S)NHR' \quad (1)$$

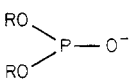
1a, R = $CH_3$; R′ = $CH_3$
b, R = $C_2H_5$; R′ = $CH_3$
c, R = $C_2H_5$; R′ = benzyl
d, R = phenyl; R′ = $CH_3$
e, R = phenyl; R′ = benzyl
f, $(RO)_2$ = $-OCH_2CH_2CH_2O-$; R′ = $CH_3$

As we wanted to widen the scope of the reaction by including other types of phosphites and isothiocyanates and as we found the procedure reported in the literature for the synthesis of **1b** unsatisfactory, we reinvestigated the reaction and also studied in some detail the properties of the products 1 (see Table I).

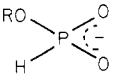
While trying to synthesize **1b** following the literature procedure, we soon found it apparent that the former authors were unaware of the thermal instability of the product. According to them the reaction mixture was heated to 105 °C for 2 h, and the product was isolated by distillation of 133 °C (0.2 mmHg). We found, however, that the long heating period resulted in a low yield of **1b** and that distillation (even of a pure sample of **1b**) caused a substantial degradation. It is thus no wonder that the distillation product is described as being a badly smelling oil, while in practice it is an odorless nicely crystalline compound.

We have found that following the addition of catalytic amount of sodium ethoxide solution to the mixture of the phosphite and the isothiocyanate (as recommended in the original report[1]), the resulting rapid and exothermic reaction was usually completed within a few minutes, as evidenced by the deep yellow color and by TLC. In those cases in which TLC revealed considerable amounts of phosphite, some more base was then added, and the temperature was maintained about 80 °C for another few minutes. However, prolonged heating periods or temperatures higher than about 100 °C led to lower yields of compounds of type 1, as did also the use of a molar amount of the base.

The use of sodium ethoxide, sodium methoxide, or potassium *tert*-butoxide, added as powders, was more effective than the alcoholic solutions in the production of **1a–c**, but the best results were usually achieved by using sodium hydride. Triethylamine was not effective as a base for the reaction of aliphatic phosphites, probably because it is not basic enough to produce sufficient concentrations of the tricoordinated phosphite anion **2**. Moreover, triethylamine is known to attack the alkoxy moiety of the phosphites, producing the tetracoordinated anion **3**.[10]



**2**



**3**

Purification of the products **1a–e** was achieved by column chromatography using silica gel. It was found that extended contact of the products with silica gel caused a partial breakdown of 1 to the phosphites, and therefore the chromatography had to be performed rather rapidly. In the case of **1a** and **1b** it was essential to obtain the phosphonothioamidates in a high degree of purity, otherwise the presence of some phosphite resulted in difficult recrystallizations and low yields.

In order to achieve a wider variety of the phosphono thioamidates 1, we also prepared compounds **1b** and **1d**, which contain phenyl ester groups, by reacting diphenyl phosphite with the proper alkyl isothiocyanate. This reaction was catalyzed far better by triethylamine than by alkoxides. Here, the phosphite is known to easily undergo transesterification reactions[11] and therefore is attacked by the alkoxides. On the other hand, the phosphite cannot alkylate and quaternize tertiary amines. Also, because of the electron-withdrawing effect of the phenoxy groups, the P–H function is more acidic than in the case of dialkyl phosphites. As a consequence, triethylamine was able to cause a very exothermic and high-yielding reaction, from which the product could be easily purified, while sodium methoxide was barely effective as a catalyst.

In the two following instances the results of the reactions were unsatisfactory: (a) when dibenzyl phosphite was used and (b) when dialkyl phosphite reacted with trimethylsilyl isothiocyanate. In the first instance only small amounts of the required products could be isolated. The reason for this is not well understood, but it cannot be solely due to the low purity of dibenzyl phosphite, as freshly recrystallized samples of di-*p*-xylyl phosphite[12] also gave only very low yields of the appropriate thiocarbamoyl phos-

(8) G. J. Durant, C. R. Young, and Z. Tashma, European Patent Appl. 7326; *Chem. Abstr.*, **93**, 168317 (1980).
(9) T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, **27**, 3651 (1962).
(10) J. Baddily, V. M. Clark, J. J. Michalski, and A. R. Todd, *J. Chem. Soc.*, 815 (1949).
(11) E. N. Walsh, *J. Am. Chem. Soc.*, 81, 3023 (1959).
(12) M. Niyano and S. Funahashi, *J. Am. Chem. Soc.*, **77**, 3522 (1955).

Table II. NMR Data for Compounds 1a-f

| compd | solvent | P(OR)$_2$ protons | NR protons[a] |
|---|---|---|---|
| 1a | $CDCl_3$ | 3.90 (d, 6 H, $CH_3O$, $J_{POCH}$ = 12 Hz) | 3.24 (dd, 3 H, $NCH_3$, $J_{PCNCH}$ = 1.7 Hz, $J_{HNCH}$ = 5.1 Hz) |
| 1b | $CDCl_3$ | 4.24 (m, 4 H, $CH_2O$, 1.35 (t, 6 H, $CH_3C$, $J_{HCCH}$ = 7.0 Hz) | 3.21 (dd, 3 H, $NCH_3$, $J_{PCNCH}$ = 1.8 Hz, $J_{HNCH}$ = 5.2 Hz) |
| 1b | $C_6D_6$ | 4.05 (m, 4 H, $CH_2O$), 1.01 (t, 6 H, $CH_3C$, $J_{HCCH}$ = 6.5 Hz) | 2.93 (dd, 3 H, $NCH_3$, $J_{PCNCH}$ = 1.9 Hz, $J_{HNCH}$ = 4.9 Hz) |
| 1c | $CDCl_3$ | 4.21 (m, 4 H, $CH_2O$), 1.31 (t, 6 H, $CH_3C$, $J_{HCCH}$ = 6.9 Hz) | 7.30 (s, 5 H, aromatic), 4.80 (dd, 2 H, $NCH_2$, $J_{PCNCH}$ = 2.2 Hz, $J_{HNCH}$ = 5.5 Hz) |
| 1c | $C_6D_6$ | 3.99 (m, 4 H, $CH_2O$), 0.97 (t, 6 H, $CH_3C$, $J_{HCCH}$ = 7.0 Hz) | 7.09 (s, 5 H, aromatic), 4.89 (br d,[b] 2 H, $NCH_2$, $J_{HNCH}$ = 5.5 Hz) |
| 1d | $CDCl_3$ | 7.36-7.21 (m, 10 H, aromatic) | 3.15 (dd, 3 H, $NCH_3$, $J_{PCNCH}$ = 1.8 Hz, $J_{HNCH}$ = 5.3 Hz) |
| 1d | $C_6D_6$ | 7.35 (d, 4 H, aromatic, ortho), 6.92 (m, 4 H, aromatic, meta), 6.77 (t, 2 H, aromatic, para) | 2.38 (dd, 3 H, $NCH_3$, $J_{PCNCH}$ = 1.8 Hz, $J_{HNCH}$ = 4.9 Hz) |
| 1e | $CDCl_3$ | 7.36-7.09 (m, 15 H, aromatic), 4.80 (dd, 2 H, $NCH_2$, $J_{PCNCH}$ = 2.1 Hz, $J_{HNCH}$ = 5.7 Hz) | |
| 1e | $C_6D_6$ | 7.34-6.79 (m, 15 H, aromatic), 4.45 (d,[b] 2 H, $NCH_2$, $J_{HNCH}$ = 5.8 Hz) | |
| 1f | $CDCl_3$ | 5.25 (m, 2 H) and 4.55 (m 2 H) ($CH_2O$) 2.48 (m, 1 H) and 1.98 (m, 1 H) (C-$CH_2$-C) | 3,21 (dd, 3 H, $NCH_3$, $J_{PCNCH}$ = 1.8 Hz, $J_{HNCH}$ = 5.1 Hz) |

[a] NH proton appears at ca. 10 ppm. [b] An unresolved doublet of doublets.

phonate 1. In the second case the unreactivity is probably due to the electron-donating trimethylsiyl group which reduces the electrophilicity of the isothiocyanato group.

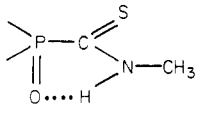
## Spectral Properties of (Thiocarbamoyl)phosphonates 1

The UV–visible spectra of the compounds measured in ethanol contain two separate peaks: a high-frequency, high-intensity peak ($\lambda_{max}$ ~285 nm, log $\epsilon$ ~4), and a low intensity peak at a longer wavelength ($\lambda_{max}$ ~395 nm, log $\epsilon$ ~2) which is responsible for the yellow color of the compounds. The same pattern is characteristic of thioamides in general, the peaks being attributed respectively to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions.[13] However, the $n \rightarrow \pi^*$ bands of **1a–f** are bathochromically shifted relative to *N*-methyl thioacetamide ($\lambda_{max}$ 321 nm in ethanol, 360 nm in petroleum ether[26]) as expected for a system in which the conjugation of the thioamide function is further extended to include the phosphoryl double bond. This shift is consistent with the bathochromic shift reported[14] for $C_2H_5OC(O)C(S)NHCH_3$.[15]

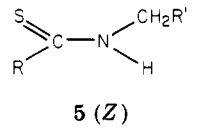
A change of the solvent from ethanol to petroleum ether always resulted in a shift of the $n \rightarrow \pi^*$ band to a higher wavelength.[16] Though the same phenomenon occured in the spectra of our phosphonothioamidates, the shifts observed were rather small (ca. 10 nm compared to 43 nm found for $C_2H_5OC(O)C(S)NHCH_3$.[14] It is not yet clear whether hydrogen bonding (either intenal as in **4** or otherwise) exists, at least in nonpolar solvents, thus partially compensating for the lack of the external hydrogen bonding.

The IR spectra of compounds 1 contain the three bands generally attributed to secondary thioamides,[17] 1570–1500, 1400–1300, and 1150–950 cm$^{-1}$, and also the ~1250-cm$^{-1}$ absorption, characteristic of the P=O strech.

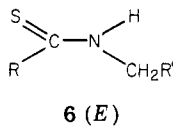
Proton NMR spectra of amides and thioamides have been used extensively to investigate geometrical isomerism around the amidic C–N bond (such as **5** and **6**), taking advantage of the different magnetic environment of the methylene group adjacent to the nitrogen atom.[18] In the case of simple secondary aliphatic thioamides, the **5** (*z*) isomer is much more stable, and except for the case of thioformamide (**5** and **6**, R = H) it is usually difficult to show the existence of the other isomer.[19,20]




4




5 (*Z*)




6 (*E*)

As can be seen in Table II the $NCH_3$ and the $NCH_2Ar$ protons of the phosphonothioamidates 1 always appear as closely spaced equal-intensity doublet of doublets. The pattern simplifies to a doublet upon addition of $D_2O$. To find out whether geometrical isomerism is indeed responsible for the remaining splitting, we recorded the spectra of **1b, d, e** at 60 and at 300 MHz. The distance (in hertz) between the peaks remained unchanged, indicating that the splitting must be due to a long-range P—C–N—CH coupling and not to the existence of a second geometrical isomer. An additional proof was provided by studying the changes that occurred in the spectra on replacing deuterated chloroform by hexadeuterated benzene as a medium. It is well-known that benzene exerts magnetic shielding on the methyl or methylene protons adjacent to the nitrogen atom of amides and thioamides, the effect being much greater for the protons located trans to the sulfur atom such as in the *E* compound.[21,23] Thus,

(13) (a) H. Hosoya, J. Tanaka, and S. Nagakura, *Bull. Chem. Soc. Jpn.*, **33**, 850 (1960); (b) M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **79**, 464 (1960); (c) W. Walter and J. Voss in "The Chemistry of Amides", E. Jabicky, Ed., Interscience, London, New York, Sydney, and Toronto, 1970, p 400.

(14) B. Persson and J. Sandstrom, *Acta Chem. Scand.*, **18**, 1059 (1964).

(15) The frequencies of the $n \rightarrow \pi^*$ bands of thioamides in nonpolar solvents may be obtained from empirically determined increments by using a formula developed by J. Fabian, H. Viola, and R. Mayer, *Tetrahedron*, **23**, 4323 (1967). Using their method, we calculated an absorption increment value of –3.2 for the $(C_6H_5O)_2PO$ group. This value is lower than Fabian's value for the $C_2H_5OCO$ group (–5.30), and this might reflect a weaker conjugation of the phosphoryl double bond with the thioamide moiety.

(16) Reference 13c, pp 401–402.

(17) K. A. Jansen and P. H. Nielsen, *Acta Chem. Scand.*, **20**, 597 (1966).

(18) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).

(19) (a) J. Sandstrom and B. Uppstrom, *Acta Chem. Scand.*, **21**, 2254 (1967); (b) Reference 13c, p 390; (c) Reference 18, p 520.

(20) O. Dahl and S. A. Laursen, *Org. Magn. Reson.*, **8**, 1, (1976).

(21) R. C. Neuman, Jr., and L. Brewster Young, *J. Phys. Chem.*, **69**, 1777 (1965).

(22) (a) T. H. Siddall, III, and W. E. Stewart, *Spectrochim. Acta, Part A*, **24A** 81 (1968); (b) T. H. Siddall, III, and C. A. Prohaska, *Appl. Spectrosc.*, **21**, 9 (1967).

the distance between the signals of the two isomers should change considerably upon changing the solvent, but in none of the compounds tested (**1b–d**) could any meaningful change in the distance between the lines be found, indicating the existence of only one isomeric form. As secondary amides, thioamides, and phosphonothioamides[20] always exist preferentially in the **5** (*z*) form, we assume that compounds **1a–f** are also of the same geometry.

The shielding effect of benzene on the $CH_3$ groups of **1b** and **1d** varied considerably in magnitude, from 0.28 to 0.77 ppm, respectively. As the typical value reported for *N*-alkyl thioamides (*Z* form) is about 0.4 ppm,[21] the high value found for **1d** probably reflects a different arrangement of the benzene solvation layer, which results from complexing of the benzene molecules with the phenoxy groups. Indeed, the aromatic signals of **1d** are also shifted upfield by the solvent, and their different protons become completely resolved, indicating that the phenoxy groups are strongly coordinated by the benzene.

Somewhat surprisingly, benzene added as a solvent had no effect on the location of the benzylic N–$CH_2$ protons of **1c**. It seems that the aromatic ring of the benzyl substituent (which probably lies out of the thioamide's plane) hinders the arrangement needed[23] between the benzene and the thioamide moiety. In accordance with this phenomenon, the aromatic signals of the benzyl group of **1c** are also very weakly affected by the benzene.

A phosphonothioamidate, **1**, that bears both *N*-benzyl and phenoxy ester groups should show a compromise between the conflicting influences of these groups, and indeed the shielding caused by benzene as a solvent on the N–$CH_2$ protons of **1e** (0.35 ppm) is intermediate between the values found for **1c** and **1d**.

The electron-impact mass spectrometry of compounds **1** always revealed the molecular peak, the typical olefinic and alkoxy cleavages of the phosphonate esterifying groups,[24] and two fragmentation routes of the thioamide function: an N–R cleavage resulting in *m/e* values of M − 15 and M − 91 and, more significantly, a loss of 33 mass units to probably produce the nitrilium ion $(RO)_2(P{=}O){-}C{\equiv}NR'^{+}$. Another type of fragmentation, typical of **1**, leads to the corresponding phosphite from which the compound was synthesized, and is probably due to the thermal reversibility of reaction (1).

## Some Chemical Properties of (Thiocarbamoyl)phosphonates 1

Compounds **1** are considerably less reactive than simple thioamides toward oxidizing agents such as hydrogen peroxide.[27] We found that while *N*-methylthioacetamide was destroyed instantly when added to an excess of a 1:1 mixture of glacial acetic acid and perhydrol at 0 °C, as indicated by the bleaching of the yellow color and by TLC, compound **1b** could be traced by TLC as long as 20 min after the beginning of the reaction.[28]

Because of the presence of the strongly electron-withdrawing phosponate group, compounds **1** are hardly attacked by potent electrophiles. Thus **1b–d,f** were almost quantitatively recovered after being reacted for 6 h with dimethyl sulfate (at 50 °C) or with ethyl chloroformate[29] (at reflux temperature). An exception to this generality, is the efficient reaction of **1a–c** with methyl iodide which will be discussed in a later paper.

Compounds **1a** and **1b** deteriorate slowly when kept for a few months at room conditions, as evidenced by the decrease of their melting points and by the appearance of a dialkyl phosphite spot on TLC. The other compounds, especially **1d** and **1f**, seem to be much more stable.

## Experimental Section

UV spectra were recorded on a Varian Technotron 635 UV–vis spectrophotometer and infrared spectra on a Perkin-Elmer 457 spectrophotometer. NMR spectra were measured on Bruker WP and on Bruker WH 300 instruments with $Me_4Si$ as an internal standard. Low-resolution mass spectra were obtained on Varian CH5DF instrument.

**Materials.** The phosphites, isothiocyanates, and bases were purchased from Aldrich Chemical Co. unless otherwise stated. The phosphites and the isothiocyanates were redistilled prior to use. Careful cleaning of these reagents is of special importance in the synthesis of **1a** and **1b**. Sodium methoxide and potassium *tert*-butoxide were used from recently opened packings but without further purification. Sodium hydride was used in the form of an 80% dispersion in oil without prior removal of the oil.

**Method A. Diethyl (*N*-Methylthiocarbamoyl)-phosphonate (1b).** To a magnetically stirred mixture of 13.8 g (0.1 mol) of redistilled diethyl phosphite and 7.7 g (0.105 mol) of redistilled methyl isothiocyanate was added about 200 mg of sodium hydride in three portions within about 2 min. The solution turned strongly yellow, and the temperature rose to about 80 °C. The temperature was kept by external heating for another 5 min. If a considerable amount of the phosphite was still present (as evidenced by TLC) another ca. 70 mg of the base was added and the reaction mixture warmed to 80 °C for another 10 min. After the mixture cooled to room temperature, 50 mL of salt water was added, and the product was extracted with chloroform (3 × 50 mL). The combined organic phase was washed once with water, dried over sodium sulfate, and evaporated to give a yellow viscous oil. The product was purified by a silica gel column chromatography (ethyl acetate eluent). The chromatography had to be performed rather quickly, and usually only the first half of the product was pure enough to crystallize. Once pure enough to start crystallizing, it can be conveniently recrystallized from petroleum ether.

**Method B. Diphenyl (*N*-methylthiocarbamoyl)-phosphonate (1d).** To a stirred mixture of 23.4 g (0.1 mol) of diphenyl phosphite and 7.3 g (0.1 mol) of methyl isothiocyanate was added triethylamine dropwise. After the addition of about 1 ml of $Et_3N$, a strongly exothermic reaction took place, and the mixture turned deep yellow. The product was purified by silica gel column chromatography (ethyl acetate eluent).

**Method C. 1,3-Dioxa-2-(*N*-methylthiocarbamoyl)-2-oxophosphorinane (1f).** In this case, potassium *tert*-butoxide in *tert*-butyl alcohol was found to be superior to sodium hydride. Trimethylene phosphite[25] (1.22 g, 0.01 mol) and 1.10 g (0.015 mol) of methyl isothiocyanate were dissolved in 10 mL of absolute *tert*-butyl alcohol. About 0.5 mL of saturated potassium *tert*-butoxide solution in absolute *tert*-butyl alcohol was then added, causing some warming and development of yellow coloration. After 5 min of reflux, 50 mL of water was added, and the product was extracted with chloroform (4 × 50 mL), which was dried over sodium sulfate and removed under reduced pressure. The crude product crystallized and was contaminated with methyl isothiocyanate. In order to purify it, the solid was washed three times with 10-mL quantities of anhydrous ether, a process which reduced the yield considerably. The remaining fine light yellow crystals were recrystallized from benzene.

**Registry No. 1a**, 73992-63-9; **1b**, 70385-36-3; **1c**, 81940-06-9; **1d**, 81940-07-0; **1e**, 81940-08-1; **1f**, 81940-09-2; diethyl phosphite, 762-04-9; methyl isothiocyanate, 556-61-6; diphenyl phosphite, 4712-55-4; trimethylene phosphite, 16352-21-9; dimethyl phosphite, 868-85-9; benzyl isothiocyanate, 622-78-6.

(23) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **5**, 139 (1962); **3**, 253 (1960).
(24) (a) T. Nishiwaki, *Tetrahedron*, **22**, 1383 (1966); (b) Z. Tashma, J. Katzhendler, and J. Deutch, *Org. Mass Spectrom.*, **7**, 955 (1973).
(25) A. A. Oswald, *Can. J. Chem.*, **37**, 1498 (1959).
(26) M. J. Janssen, *Recl. Trav. Chim. Pays-Bas* **79**, 454 (1960).
(27) W. Walter, *Justus Liebigs Ann. Chem.*, **633**, 35 (1960).
(28) At least three products could be spotted by TLC, but so far they have not been identified.
(29) F. H. Suydam, W. E. Greth, and N. R. Langerman, *J. Org. Chem.*, **34**, 292 (1969).