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N-ALKYL THIOCARBAMOYL PHOSPHONIC ACID ESTERS—2[1]

ALKYLATION BY METHYL IODIDE ACCOMPANIED BY PHOSPHONATE DEALKYLATION

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Abstract—Thiocarbamoyl phosphonates **1** did not react with alkylating agents to give the S-alkyl derivatives **2**, but gave zwitterions **3a–c** in which the phosphonate ester moiety was dealkylated. In some cases starting material could be recovered. A mechanism is suggested in order to explain the relationship between the alkylation and the dealkylation steps of the reaction.

Thioamides are known to be alkylated easily by a variety of alkylation agents, such as alkyl iodides and dimethyl sulphate, to give S-alkyl thioimidate cations.[2]

In the course of our study of the chemistry of the thiocarbamoyl phosphonates **1**, it was noticed that their reaction with alkylating agents differs from that of simple thioamides. Compounds **1a–e** did not yield any methylation product after standing in solution in dimethyl sulfate for over two months. Moreover, even at elevated temperatures (reflux in toluene) there was no evidence for the production of any of the expected cations **2**, but rather for a slow decomposition manifested by weakening of the TLC spots of **1**, and by the appearance of a brown colouration. A similar pattern of decomposition was obtained from the reaction of **1b** with methyl fluorosulfonate in toluene at room temperature.

Somewhat surprisingly, methyl iodide, a weaker electrophile, does react with **1a–1c** within a few hours at room temperature, but instead of the expected products **2**, dealkylated zwitterions, **3**, are obtained, along with the appropriate alkyl iodides.

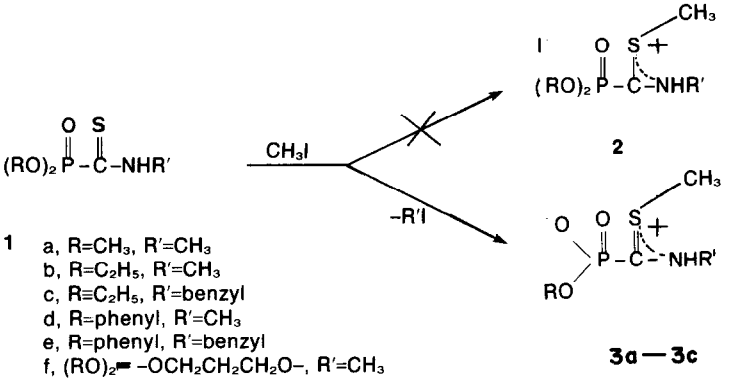
Related alkyl iodides are much less reactive in this reaction. Thus, refluxing **1b** in ethyl iodide for 4 hours (at 72°) resulted in some crude S-ethyl analogue of **3b**,[3] but ethyl bromide solution of **1b** was unchanged even after several weeks, and benzyl chloride (in refluxing benzene) was also unreactive.

The reactivity of methyl iodide is rather selective, being dependent upon the nature of the phosphonate esterifying groups. Thus, unlike the neat conversion of **1a–c** to the corresponding zwitterions **3a–c**, compounds **1d** and **1e**, in which the esterifying groups are phenols, were quantitatively recovered after being dissolved in methyl iodide for many weeks, including 48 hours of reflux. Nearly as stable to methyl iodide is the cyclic aliphatic compound **1f**, about 80% of which was recovered after 48 hours of reflux.

It is thus clear that the behaviour of the thioamide function is profoundly influenced by the adjacent phosphonate ester group, and indeed, when these groups are separated by a methylene moiety, as in $(EtO)_2PO–CH_2–CSNH_2$, the methylation product is the expected cation $(EtO)_2PO–CH_2C(SCH_3)=NH_2^+$ which is analogous to **2**.[4]

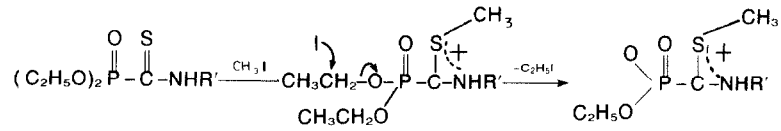
Our first assumption regarding the mechanism of the reaction was that there were two discrete steps, as in Scheme B: (a) usual S-methylation to produce a cation **2**. As the positively charged thioimidate moiety exerts a strong electron-withdrawing effect on the phosphonate group, it facilitates the second stage of the reaction; (b) nucleophilic attack by the iodide on the α-carbon atom, expelling the zwitterionic product **3** as a leaving group.

Indeed, a multi-stage reaction was investigated by Birum[5] in connection with the synthesis of tetramethyl amidinophosphophosphonic anhydride **6**. In that case even



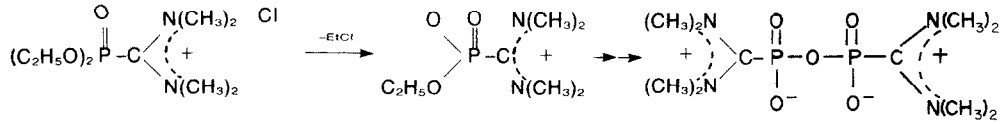
1 a, R=CH_3, R'=CH_3
b, R=C_2H_5, R'=CH_3
c, R≡C_2H_5, R'=benzyl
d, R=phenyl, R'=CH_3
e, R=phenyl, R'=benzyl
f, $(RO)_2$= $-OCH_2CH_2CH_2O-$, R'=CH_3

Scheme A.



1 2 3

Scheme B.



4 5 6

Scheme C.

the less nucleophilic chloride anion dealkylated rapidly the cation **4** at room temperature (Scheme C).

However, while this mechanism explains the tendency of the reaction to proceed to the zwitterion **3**, it cannot explain why there is no reaction between compound **1** and dimethyl sulphate or between methyl iodide and the phenyl esters **1d** and **1e**. In these cases it is obviously difficult to perform the second, dealkylation, stage of the reaction, but threre seems to be no reason as to why the preceding methylation step fails to take place either.[6]

A mechanism which best fits the results is outlined in Scheme D.

We assume that even though the thioamide moiety of **1** is not sufficiently nucleophilic to dispel the iodide and form a full cation, it is still nucleophilic enough to form **7** reversibly, which is probably best depicted as a tightly held ion-pair. In some cases (e.g. the phenyl esters **1d–e**) the reaction cannot proceed any further, and starting material can be almost fully recovered. When the aliphatic compounds **1a–c**, however, react with methyl iodide, the negatively charged iodine atom which is present in **7** is properly positioned for attacking an α-carbon atom. The negative charge that developes on the phosphonate group strongly reduces its electron-withdrawing ability[7] and therefore stabilizes the zwitterion **3**.

The inertness of the cyclic aliphatic compound **1f** is probably a result of its restricted conformation. The cyclic structure holds the α-carbon and the sulfur atoms apart so that bridging the gap between them by a molecule of methyl iodide is difficult, and thus the necessary cyclic arrangement of the reactants is prevented.

EXPERIMENTAL

The thiocarbamoyl phosphonates mentioned were previously described,[1] as were also the zwitterionic products **3a** and **3b**.[8] A typical procedure for the synthesis of these zwitterions is demonstrated in the following synthesis of **3b** and **3c**.

S,N-Dimethyl thioimidoyl phosphonic acid monoethyl ester, inner salt (**3b**)

2.11 g (0.01 mole) **1b** was dissolved in 10 ml methyl iodide. The yellow solution was left overnight at ambient temperature (or refluxed for 2 h). Crude **3b** separated as hygroscopic clusters of crystals in nearly quantitative yield. Recrystallization from dry acetonitrile resulted in 60% yield of nice crystals of m.p. 144–147° (dec); NMR($CDCl_3$, 3.90(2H, m, CH_2C), 3.24(3H, d, CH_3N), 3.06(3H, s, CH_3S) and 1.22(3H, t, CH_3C). The microanalytical and mass spectral results also confirmed the structure. The development of ethyl iodide as a by-product was confirmed by GLC using a 6 ft × $\frac{1}{4}$ in. column of 10% Carbowax 20M on 60/80 Chromosorb W, at 45°.

S-Methyl-N-benzylthioimidoyl phosphonic acid monoethyl ester, inner salt (**3c**)

This was produced in a similar way, except that a 1:1 mixture of methyl iodide and petroleum ether had to be used because of the solubility of **3c** in pure methyl iodide. Recrystallization from chloroform and hexane resulted in 50% yields of **3c**, m.p. 148–151° (dec); NMR, $CDCl_3$, 7.37(5H, broad s, aromatic), 4.87(2H, broad s, CH_2N), 3.85(2H, m, CH_2O), 3.09(3H, s, CH_3) and 1.20(3H, t, CH_3C). The structure was confirmed by the microanalytical and mass spectral results.

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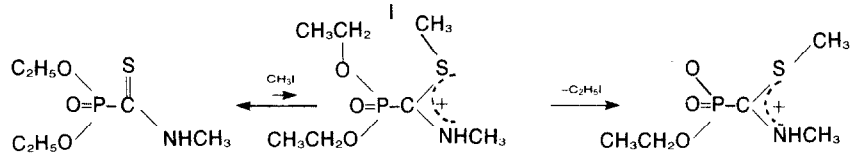

1 7 3

Scheme D.

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[3]NMR of the crude product: 3.90, 2H, m; 3.30, 3H, broad s; 2.70, 2H, m; 1.45, 3H, t; and 1.28, 3H, t, contaminated by some **1b** and unidentified by-products.

[4]C. J. Wharton and R. Wriggleworth, *J. Chem. Soc. Perkin I* 433 (1981).

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[6]An alternative two-stage mechanism in which dealkylation by traces of iodide precedes the S-methylation was disproved by showing that **1b** was quite stable to dealkylation by iodides at room temperature.

[7]The σ_m value of the $-P{=}O(OH)O^-$ group is 0.2 {D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958)} compared to the σ_m value of 0.55 reported for the $-P{=}O(OEt)_2$ group {L. D. Freedman and H. H. Jaffe, *J. Am. Chem. Soc.* **77**, 920 (1955)}. The difference in the electron-withdrawing power is reflected also in the different pKa values of phosphoric acid and derivatives.

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