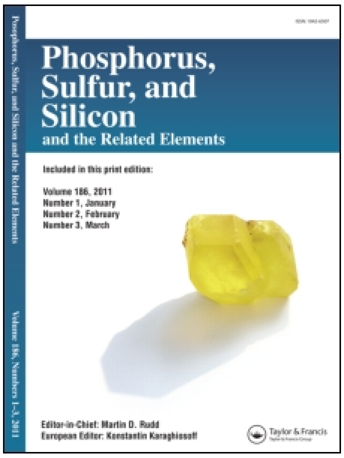

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# IDENTIFICATION OF THE ISOMERIC TRANSFORMATION PRODUCT FROM 2-(DIMETHYLAMINO)ETHYL-(DIMETHYLPHOSPHORAMIDO)FLUORIDATE

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# IDENTIFICATION OF THE ISOMERIC TRANSFORMATION PRODUCT FROM 2-(DIMETHYLAMINO)ETHYL-(DIMETHYLPHOSPHORAMIDO)FLUORIDATE

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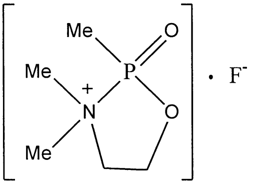
*Using $^{1}H$, $^{13}C$, $^{19}F$, $^{31}P$, and $^{14}N$ NMR spectroscopy, it has been demonstrated that 2-(dimethylamino)ethyl-dimethylphosphoramidofluoridate undergoes spontaneous isomerization to dimethylaziridinium-dimethylamidofluorophosphate.*

*Keywords:* Isomeration; NMR identification; organophosphate

In the end of the 1950s Tammelin described[1,2] two groups of organophosphorus compounds exhibiting high anticholinesterase activity. As a member of one of these groups of fluorophosphorylated cholines, 2-(dimethylamino)ethyl-methylphosphonofluoridate was also studied. This organophosphonate shows low stability, undergoing transformation into a white crystalline substance.[1] Tammelin assumed the formation of an isomeric cyclic product (I); this would explain why the



I

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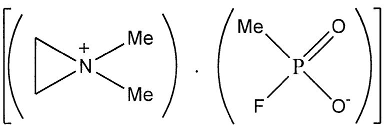
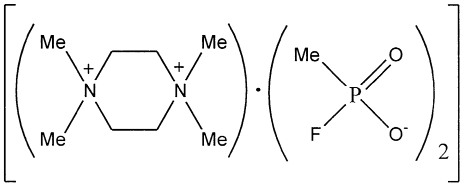
Address correspondence to Zbyněk Kobliha, Department of Chemistry, Military University of the Ground Forces in Vyškov, 68203 Vyškov, Czech Republic. E-mail: kobliha@vvs-pv.cz aminoperoxide test,[1] considered by him a decisive proof of a P-halogen bond, was negative. Also the absence of fluorine in the insoluble precipitate with Reinecke salt was claimed as a proof of the suggested structure (I). On the other hand, Larsson,[3] analogous to Fukuta and Stafford[4] and in accord with the obtained IR spectra, particularly on the basis of the characteristic P-F vibration, assumed formation of dealkylated aziridinium salt (II), or a more stable dimer such as the piperazinium salt (III).



II



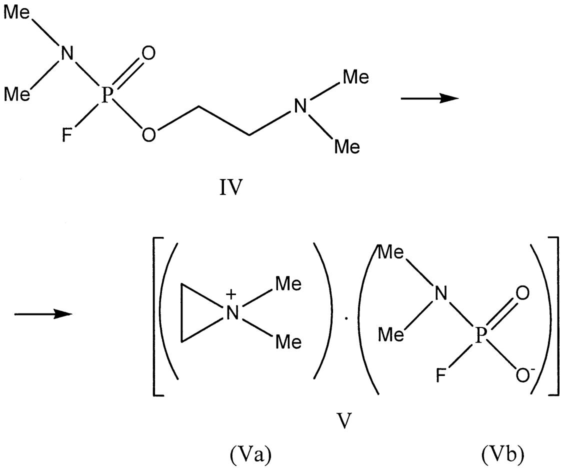
III

On the whole, Larsson favored the piperazinium salt whereas, in accord with other authors,[4–6] he regarded the aziridinium salt as a reactive intermediate.

After a relatively long information vacuum, only in the 1980s, reports on further derivatives with properties and behavior analogous to those of the Tammelin esters began to appear, particularly on organophosphates of the 2-(dialkylamino)ethyl-(dialkylphosphoramido)fluoridate type.[7–9] Compounds in which alkyl was methyl, ethyl, and propyl were studied preferentially.[10–11] In the following period attention was paid particularly to 2-(dimethylamino)ethyl-(dimethylphosphoramido)fluoridate[12] (IV) because of its high cholinergic toxicity ($LD_{50}$ i.m., rat, 17.0 $\mu g\ kg^{-1}$).

Under normal conditions, compound (IV) is not stable,[13] and even in the absence of air, water, or light it turns into a white crystalline substance, the conversion rate depending only on the temperature.

This conversion practically stops at temperatures in the range of $-20°C$ to $-40°C$. It is accompanied by a change in the physical as well as chemical properties and by a substantial drop of toxicity ($LD_{50}$ i.m., mouse, 2 h, 216.6 $mg\ kg^{-1}$). As shown by toxicological tests, the product of this spontaneous decomposition exhibits low anticholinesterase activity expressed as the inhibition efficiency toward acetylcholinesterase ($I_{50} = 60\,\mu g\ ml^{-1}$), whereas the starting compound (IV) shows an extreme cholinergic activity[14] ($I_{50} = 200$ pg $ml^{-1}$). In our previous article,[15] we described the basic physical properties of the product (V) and suggested its structure. The product (V) melted at 267–272°C and was well-soluble in water, methanol, ethanol, and xylene, whereas it



**SCHEME 1**

was sparingly soluble or insoluble in chloroform, tetrachloromethane, dichloroethane, benzene, toluene, diethyl ether, or acetone. Its elemental analysis corresponded to composition $C_6H_{16}N_2PO_2F$ which is identical with that of the starting compound (IV). The anticipated ionic character of (V) was confirmed by the TLC method.[11] Electron ionization mass spectroscopy[15] proved the presence of the aziridinium part (Va) as the more volatile component, showing a molecular peak, m/z 72, as well as the fragment peaks, m/z 71, 58, 42, and 30. The mass spectrum also comprised a weak peak due to the phosphate ion (Vb) and its fragment peaks, m/z 98 and 99.

It appeared to us that the structure of dimethylaziridinium-dimethylamido-fluorophosphate (V), ascribed to the product of spontaneous decomposition of 2-(dimethylamino)ethyl-(dimethylphosphoramido)fluoridate (IV), requires further confirmation by NMR spectroscopy.

## RESULTS AND DISCUSSION

To study the structure of the product (V) arising by spontaneous decomposition of 2-(dimethylamino)ethyl-dimethylphosphoramidofluoridate, we measured its $^{1}$H, $^{13}$C, $^{19}$F, $^{31}$P, and $^{14}$N NMR spectra.

The $^{1}$H NMR spectrum exhibited the following chemical shifts ($\delta$ scale, ppm): 2.60 and 2.62(2 × 3H, s, $(CH_3)_2N^+$); 3,42 (2 × 3H, s, $(CH_3)_2N\text{-}P$);3.99 (4H, br s, $\text{-}CH_2\text{-}CH_2\text{-}$). Mesurement at 70°C showed only a narrowing of the broad methylene signal at 3.99 ppm.

The $^{13}C$ NMR spectrum exhibited the following signals (ppm): 37.86 ($(CH_3)_2N$-P); 53.25 (broad signal 7–10 ppm, $(CH_3)_2N^+$); 56.69 ($-CH_2-CH_2-$). The signal at 37.86 ppm is ascribed to methyl carbon atoms bonded to amide nitrogen on a phosphorus atom. At 70°C, the signal at 53.25 ppm narrowed to about 0.7 ppm; this corresponds to a three-membered ring bond. The signal at 56.69 ppm corresponds to two methylene carbon atoms bonded to an ammonium nitrogen atom.

The $^{19}F$ NMR spectrum exhibits a doublet (1F, d, $^{l}J_{FP} = 923.4$ Hz) due to an interaction with the phosphorus nucleus. The observed coupling constant is characteristic of a fluorine atom directly bonded to a phosphorus atom.

The same coupling constant was also found in the $^{31}P$ NMR spectrum (8.91 ppm; 1P, d, for $J$ see $^{19}F$ NMR).

The $^{15}N$ NMR spektrum displays a signal at 45.76 ppm $(CH_3)_2\underline{N}$-P) and a narrow signal at 194.48 ppm $(CH_3)_2\underline{N})$, typical for a nitrogen atom in alkylammonium salts.

All the abovementioned data thus confirm that the isomerization product of 2-(dimethylamino)ethyl-(dimethylphosphoramido)fluoridate (IV) is dimethylaziridinium-dimethylamidofluorophosphate (V).

## EXPERIMENTAL

### Chemicals and Apparatus

2-(Dimethylamino)ethyl-(dimethylphosphoramido)fluoridate (IV, CAS 141102-74-1) was synthesized by reaction of (dimethylamido)phosphoryldifluoride with sodium 2-(dimethylamino)ethoxide and purified by distillation in vacuo. Conversion of compound (IV) into the solid product was performed in sealed ampoules in the dark at 21°C for 3 months. The ampoules were then crushed and the product was five times washed with hexane and dissolved in a small amount of methanol. After filtration through a glass frit to remove the broken glass present, the filtrate was concentrated in vacuo over solid KOH. Methanol was added to prepare a saturated solution and the product was precipitated with acetone. It was collected on a glass frit filter, washed three times with acetone and dried in vacuo. Its purity was checked by TLC.[13] The chemicals used were Merck (Germany) products of p.a. purity.

$^{1}H$, $^{13}C$, $^{15}N$, and $^{31}P$ NMR spectra were taken on a Bruker DRY 500 Avance spectrometer, $^{19}F$ NMR spectra were measured on a Varian Mercury Plus 300 BB instrument, at the following frequencies: $^{1}H$-500.13 MHz, $^{13}C$-125.76 MHz, $^{15}N$-50.68 MHz, $^{19}F$-282.29 MHz and $^{31}P$-202.40 MHz. The measurements were performed at 25°C, in the case of $^{1}H$ and $^{13}C$ experiments also at 70°C. Chemical shifts were referenced to the following standards: for $^{1}H$ and $^{13}C$ internal standard DSS [sodium 3-(trimethylsilyl)-1-propanesulfonate], for $^{15}N$ external standard urea, 77.0 ppm referenced to liquid ammonia, for $^{19}F$ external standard $CFCl_3$, and for $^{31}P$ external standard 85% $H_3PO_4$. All experiments with heteronuclei ($^{13}C$, $^{15}N$, $^{19}F$, $^{31}P$) were performed with $^{1}H$ broad band decoupling.

The sample (50 mg) was dissolved in 0.5 ml of $D_2O$ (Aldrich, 99.9% D) without adjusting pH.

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