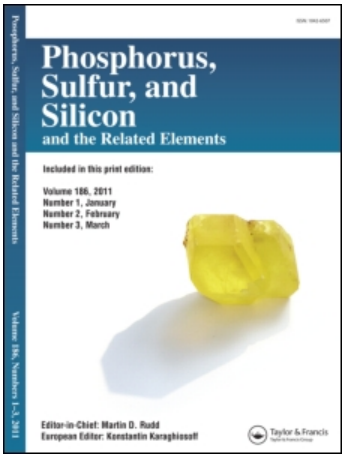

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THE REACTIONS OF N,N-DIMETHYLPHOSPHORAMIDIC DIFLUORIDE WITH TRANS-2-SUBSTITUTED CYCLOALKANOLS

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An interaction between N,N-dimethylphosphoramidic difluoride and cyclic alcohols containing hydroxyl, alkylamine and methylthiol groups in the trans-β position was performed. Trans-1-ethylcyclopentane-1,2-diol and trans-2-(N-alkylamino)cyclopentanols react with N,N-dimethylphosphoramidic difluoride to yield 1-ethyl-6-oxabicyclo(3.1.0)hexane and 6-alkyl-6-azabicyclo(3.1.0)hexane, respectively. In the case of trans-2-(N,N-dialkylamino)cyclopentanols and cyclohexanols, such reaction gives a salt of phosphorodifluoridic acid and the corresponding cyclic N,N,N',N'-tetraalkyl-1,2-diamine whereas trans-2-methylthiocyclopentanol is converted to a salt of phosphorodifluoridic acid and N,N-dimethyl-N-(2-methylthiocyclopentyl)amine.** Some of described reactions appear to be applicable for the synthesis of various organic compounds, e.g. phosphorylated 2-N,N-dialkylaminocyclopentanethiols.

Key words: N,N-dimethylphosphoramidic difluoride, N,N-dimethylphosphoramidothioic difluoride, phosphorodifluoridic acid, phosphorylated dialkylaminocyclopentanethiol, N,N-dialkylaminocycloalkanol, N,N,N',N'-tetraalkyl-1,2-diamine.

INTRODUCTION

During the early 1950s it was shown by G. Schrader, that the interaction of N-methylphosphoramidic difluoride with water[1] and of N,N-dimethylphosphoramidic difluoride (**I**) with alcohols[2] is accompanied by removal of an amide group. Later, this property of I was used for synthesis of cyclic organophosphorus compounds.[3] However, as it was noted, both the direction of reaction and product make-up are dependent on the nature of alcohols involved. In part, the reaction of I with 1,2 or 1,3-cyclic diols is shown to be followed by the formation of compounds belonging to the phospholane or phosphane structural type, which contain a dimethylamide group or a fluorine atom near the P atom, respectively; cholestane-2α, 3α-diol and cholestane-3α, 5α-diol (cis-diols) were used in the above work.

It was of interest to study the behavior of trans-diols (e.g. trans-1-ethylcyclopentane-1,2-diol) in the reaction with I which due to its structural properties is unable to form phospholane structures.[4] The second hydroxyl group, as it was pointed out, would not take part in the formation of cyclic structures incorporating the P atom and is likely to affect otherwise the proceeding reaction, and in our view, an epoxide compound is expected to be produced. Such suggestion is likely to be supported by the fact that cyclic acetal is formed through a reaction involving cis-1,2-cyclohexanediol and N-dimethoxymethyl-N,N-dimethylamine, while the re-

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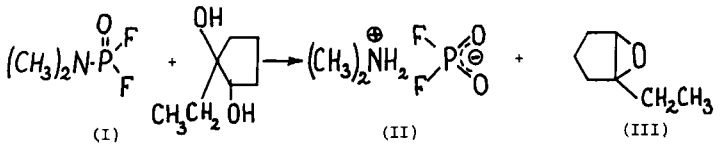
action with trans-1,2-cyclohexanediol is accompanied by cyclohexene oxide formation.[5]

We assumed expedient to study not only trans-1-ethylcyclopentane-1,2-diol involved in reaction with **I**, but also the cyclic alcohols containing other nucleophilic substituents at the trans-β position with respect to the hydroxyl group; trans-2-(N-alkylamino)cyclopentanols, trans-2-(N,N-dialkylamino)cycloalkanols and trans-2-methylthiocyclopentanol were used in this experimental work.

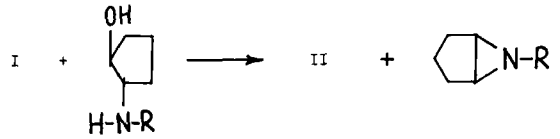
RESULTS

As it was expected, the interaction between **I** and trans-1-ethylcyclopentane-1,2-diol affords 1-ethyl-6-oxabicyclo(3.1.0)hexane (**III**) as shown below:



(I) (II) (III)

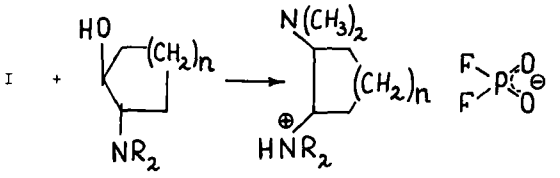
Similarly, compound **I** and trans-2-(N-alkylamino)cyclopentanols react to form 6-alkyl-6-azabicyclo(3.1.0)hexanes (**IV**, **V**), according to the following scheme:



(IV,V)

where R = $CH(CH_3)_2$ (**IV**); R = $C(CH_3)_3$ (**V**).

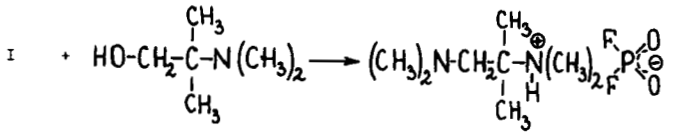
The interaction between product **I** and trans-2-(N,N-dialkylamino)cycloalkanols leads to a salt of the corresponding 1,2-diamine and phosphorodifluoridic acid, as depicted below:



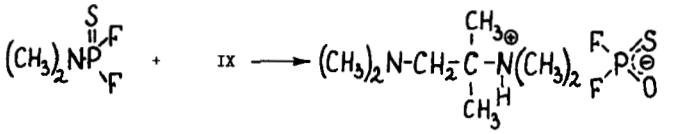
(VIa - VIIIa)

where R = CH_3, n = 1 (**VIa**); R = C_2H_5, n = 1 (**VIIa**); R = CH_3, n = 2 (**VIIIa**).

Product **I** and N,N-dimethylphosphoramidothioic difluoride interact with 2-N,N-dimethylamino-2-methylpropan-2-ol (**IX**) in the same manner, as given:

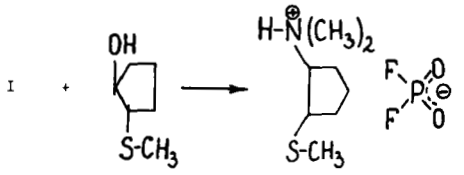


(IX) (Xa)



(XIa)

Trans-2-methylthiocyclopentanol undergoes the reaction with component **I** to form a salt of phosphorodifluoridic acid and N,N-dimethyl-N-(2-methylthiocyclopentyl)amine (**XIIa**) as follows:

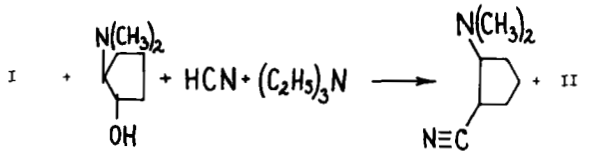


(XIIa)

The compounds **VIa–VIIIa**, **Xa** and **XIIa** were treated with sodium hydride to produce the corresponding free bases **VIb–VIIIb**, **Xb**, **XIIb** (see also Table I).

All the above reactions are rather selective, which is confirmed, in part, by the fact that product **I** and trans-2-N,N-dialkylaminocycloalkanols react to form only the corresponding phosphorodifluoride salts found by ^{31}P, ^{19}F, ^{1}H NMR methods.

It is noteworthy that in the reaction between **I** and trans-2-(N,N-dimethylamino)cyclopentanol in the presence of the HCN-triethylamine complex, 2-N,N-dimethylaminocyclopentanecarbonitrile (**XIII**) was produced, as schematically shown:



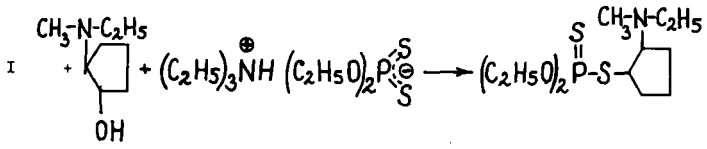
(XIII)

We suggested that the mentioned property of this reaction between **I** and alcohols would be useful for the synthesis of various classes of organic compounds. In part, the interaction of **I** and trans-2-(N-methyl-N-ethylamino)cyclopentanol in the presence of O,O-diethylphosphorodithioate in form of the triethylammonium salt,

TABLE I
Properties of synthesized compounds

Compound	BP °C/mm Hg	n_D^{25}	Yield (%)	pKa values (water, 25°C)	Microanalytical data found/calculated C	H	N	Brutto formulas
III	45/20	1.4387	67	—	75.14 75.00	10.65 10.70	—	$C_7H_{12}O$
IV	128/762	1.4357	55	8.31	77.15 76.80	11.36 12.00	11.42 11.20	$C_8H_{15}N$
V	62/40	1.4416	62	9.22	77.64 77.7	12.03 12.23	10.36 10.07	$C_9H_{17}N$
VIb	45–7/6	1.4576	62	—	70.15 69.23	12.52 12.82	17.26 17.95	$C_9H_{20}N_2$
VIIb	65–6/20	1.4610	72	5.76; 9.91	71.62 71.74	13.56 13.04	15.66 15.22	$C_{11}H_{24}N_2$
VIIIb	71/15	1.4601	38	—	70.72 70.59	12.89 12.94	16.10 16.47	$C_{10}H_{22}N_2$
Xb	57/20	1.4331	60	—	66.60 66.67	13.98 13.89	19.51 19.44	$C_8H_{20}N_2$
XIIb	70–71/7	1.4935	56	8.85	60.12 60.38	10.36 10.69	8.42 8.81	$C_8H_{17}NS$
XIII	103/6	1.4601	31	7.02	69.86 69.57	10.28 10.14	20.22 20.29	$C_8H_{14}N_2$
XIV	120/0.1	1.5170	69	—	46.35 46.30	8.50 8.36	4.41 4.50	$C_{12}H_{26}NPO_2S_2$

was performed to obtain a quantitative yield of S-[2-(N-methyl-*N*-ethylamino)cyclopentyl]-O,O-diethylphosphorothioate (**XIV**), according to:



(XIV)

It is worth noting that no information about phosphorylated 2-N,N-dialkylaminocyclopentanethiol derivatives has been available up to the present time due to difficulties in the production of 2-N,N-dialkylaminocyclopentanethiols. The properties of some synthesized compounds are given in Table I.

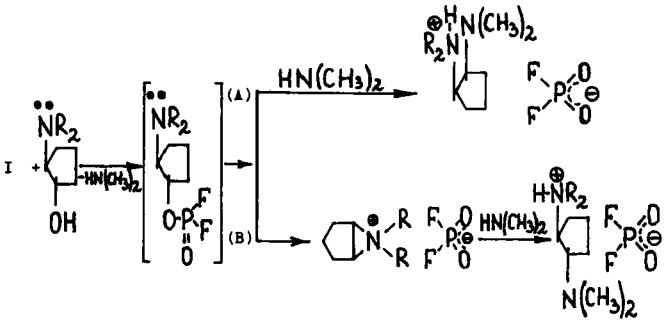
DISCUSSION

It seems convenient to discuss mechanisms of the above reactions on an example of trans-2-(N,N-dialkylamino)cyclopentanols. Amos *et al.* suggested that a reaction between I and alcohols proceeds via phosphorodifluoridate (an intermediate) formed by substitution of a dimethylamino group near the P atom; all products identified by the authors are formed as a result of an interaction between the intermediate and nucleophilic compounds, which occur in a reaction mixture.[3]

If the participation of this intermediate in the form of an appropriate difluorophosphatic ester may be regarded as a working hypothesis, it is necessary to consider two possible pathways for its conversion to 1,2-diamine salts, i.e.:

—the intermolecular attack of dimethylamine released at the first step on the alpha-carbon atom of the alkyldifluorophosphatic ester radical;

—dimethylamine carries out the nucleophilic opening of the corresponding 6,6-dialkyl-6-azoniabicyclo(3.1.0)hexane ring formed through an intramolecular reaction involving the dialkylamine group and the α-carbon atom of the ester radical.



When the reaction proceeds in the direction (A), cis-isomers should be formed while the pathway (B) would lead to trans-isomers, and in our view, from the fact that only either cis- or trans-isomers are produced which is proved by physicochemical methods, including chromatographic ones, it becomes possible to exclude a combined mechanism. We presume that the (B) pathway is more probable, since the fact that **IV** and **V** have been isolated, indicates a possibility to form aziridine derivatives in this process. Moreover, N,N,N′,N′-tetramethyl-2-methylpropan-1,2-diamine (**Xb**) is unlikely to be formed by an intermolecular nucleophilic attack of dimethylamine on O-[2-N,N-dimethylamino)-2-methylpropyl]phosphoro difluoridate, because this attack is difficult due to the protected α-carbon atom of the ester radical.

When other nucleophiles, besides dimethylamine, are available, they react with the intermediates to yield such end products, as compounds **XIII** and **XIV**.

It is reasonable to suppose that N,N-dimethyl-N-(2-dimethylthiocyclopentyl)amine is formed in the same manner. Probably, the reaction mechanism for **III**, **IV** and **V** proceeds via 1-ethyl-6-oxoniabicyclo(3.1.0)hexane and 6-alkyl-6-azoniabicyclo(3.1.0)hexane cations, respectively, which are converted into the end products after deprotonation by dimethylamine. If the above suggestions are correct, the products **VIb–VIIIb**, **XIIb**, **XIII** and **XIV** must be trans-isomers.

Further work is necessary to confirm the formation of phosphorodifluoridate serving as an intermediate during the above mentioned reactions, which, however could proceed via an intermediate of another structural type, e.g. phosphorane type.

EXPERIMENTAL

General. The ^{31}P NMR spectroscopy was performed on a "Varian-HA-100D" spectrometer (40.5 MHz, 85% H_3PO_4 as a standard), ^{19}F NMR spectra were recorded by using a "Varian-EM-390"

spectrometer (84.7 MHz, freon-12 as a standard), ^{1}H NMR spectra were obtained by using a "Varian-EM-390" spectrometer (90 MHz, Me_4Si served as a standard). IR spectroscopy was performed on "Perkin-Elmer" M-580, M-283 spectrophotometers. pKa values were determined by the procedure.[10]

Materials. We synthesized the following starting compounds by using of the corresponding techniques, namely for: N,N-dimethylphosphoramidic difluoride (**I**),[6] dimethylphosphoramidothioic difluoride,[7] trans-2-(N-alkylamino)cyclopentanols and trans-2-(N,N-dialkylamino)cycloalkanols[8] and trans-1-ethyl-cyclo-pentane-1,2-diol.[9] The other starting reagents of various chemical companies were purified before used.

Preparation of **III**. Trans-1-ethylcyclopentane-1,2-diol (6.5 g, 0.05 mol) was added to 30 ml of a diethyl ether solution containing 7.7 g (0.06 mol) of **I**. After 24 h of storing, the residue **II** was filtered off and mixed with 10% aqueous sodium carbonate solution for 4 hours. After separation, the organic layer was dried over $MgSO_4$. **III** was produced after removing of diethyl ether by distillation. The properties are given in Table I. MS: M/z (%) 112 (36), $[M]^+$; 97 (5); 84 (100); 83 (36); 69 (20); 68 (43); 56 (83); 55 (57); 42 (31); 41 (64); 39 (22); ^{1}H NMR, δ: 0.5, tr, 3H, J = 5 Hz, (CH_3); 1.4, m, 6H((CH_2)$_3$); 1.6, m, 2H(CH_2); 2.7, s, 1H(OCH).

Preparation of **IV**. Trans-(2-N-isopropylamino)cyclopentanol (18.6 g, 0.13 mol) in 50 ml of diethyl ether was added to 50 ml of a diethyl ether solution containing 19.35 g (0.15 mol) of **I**. After a short-term induction, warming of the reaction mass up to 30–35°C was observed which caused slow boiling of the solution. After 24 h the dimethylammonium difluorophosphate precipitate was filtered and then treated in the same manner as for **III**. **IV** was isolated as a liquid (see Table I). MS: M/z (%): 125 (50), $[M]^+$; 124 (21); 110 (20); 83 (100); 55 (75); ^{1}H NMR, δ: 0.9, d, 6H, J = 5 Hz, ($C(CH_3)_2$); 1.3, m, 6H, ((CH_2)$_3$); 1.7, s, 2H,(CHNCH); 2.1, k, 1H, J = 5 Hz, (NCH).

Product **V** was prepared as described above (see Table I); ^{1}H NMR, δ: 0.9, s, 9H ($C(CH_3)_3$); 1.4, m, 6H((CH_2)$_3$); 2.0, s, 2H(CHNCH).

Preparation of **Xa**. To 14.2 g (0.11 mol) of **I** dissolved in benzene (50 ml) was added 11.1 g (0.1 mol) of product **IX** in 50 ml of benzene. After a short-term induction, the reaction mass was heated up to 60°C, then the lower layer was separated and evaporated by using a vacuum pump for 2 h at 50–60°C to produce 28.3 g of **Xa**. This product is a viscous liquid at ambient temperature. ^{31}P NMR, δ, −15, t, $J_{(P-F)}$ = 960 Hz, ^{19}F NMR, δ: 80, d, $J_{(P-F)}$ = 960 Hz; ^{1}H NMR, δ: 1.2, s, 6H($N(CH_3)_2$); 2.4, s, 6H($N(CH_3)_2$); 2.6, s, 2H(CH_2); 2.7, s, 6H($N(CH_3)_2$); 9.4, s, 1H(H^+). Compounds **VIa–VIIIa**, **XIIa** were produced in the same manner as for **Xa** with a yield of about 100%, and their ^{31}P, ^{19}F NMR characteristics were shown to be similar to that of **Xa**.

Preparation of **Xb**. To an intensively stirred mixture of 16.8 g (0.07 mol) of **Xa** and benzene (50 ml), was added NaH (1.7 g, 0.08 mol). After H_2 output, the mixture was filtered and on removal of the solvent, distillation gave the product **Xb** (see Table I). ^{1}H NMR spectrum δ: 0.8, s, 6H($C(CH_3)_2$); 1.1, s, 2H(CH_2); 2.0, s, 6H($N(CH_3)_2$); 2.1, s, 6H($N(CH_3)_2$). Products **VIb–VIIIb**, **XIIb** were synthesized in the same manner (see Table I), ^{1}H NMR, **VIb**, δ: 1.6, m, 6H((CH_2)$_3$); 2.3, s, 12H(($N(CH_3)_2$)$_2$); 2.6, m, 2H(CHN); for **VIIb**: δ: 0.9, t, 6H, J = 6 Hz ((CCH_3)$_2$); 1.7, m, 6H((CH_2)$_3$); 2.4, s, 6H($N(CH_3)_2$); 2.7, m, 4H($N(CH_2)_2$); 2.75, m, 2H(NCH); for **VIIIb**: δ: 1.0, m, 4H(($N(CH_3)_2$)$_2$); 1.6, m, 4H((CH_2)$_2$); 2.1, s, 12H(($N(CH_3)_2$)$_2$); 2.2, m, 2H(NCH); for **XIIb**: δ: 1.6, m, 6H((CH_2)$_3$); 2.0, s, 3H(SCH_3); 2.2, s, 6H($N(CH_3)_2$); 2.4, m, 1H(SCH); 2.9, m, 1H(NCH).

Preparation of **XIa**. Reagent **IX** (11.1 g, 0.1 mol) dissolved in benzene (50 ml) was added to a 50 ml benzene solution containing dimethylphosphoramidothioic difluoride (16.0 g, 0.11 mol). After a short-term induction, the reaction mass was heated and let stand; two layers were formed, the lower one was separated and dried in the vacuum for 2 h at 50–60°C. We obtained 25.5 g of **XIa** (a viscous liquid at ambient temperature), ^{31}P NMR, δ: 49, t, $J_{(P-F)}$ = 1072 Hz, ^{19}F NMR, δ: 35, d, $J_{(P-F)}$ = 1072 Hz; ^{1}H NMR, δ: 1.2, s, 6H($C(CH_3)_2$); 2.4, s, 6H($N(CH_3)_2$); 2.6, s, 2H(CH_2); 2.7, s, 6H($N(CH_3)_2$); 9.4, s, 1H(H^+).

Preparation of **XIII**. To a cooled (10°C) mixture composed of trans-2-dimethylaminocyclopentanol (12.9 g, 0.1 mol), HCN (7.5 g, 0.3 mol), triethylamine (30.3 g, 0.3 mol) and benzene (70 ml) was added the reagent **I** (12.9 g, 0.1 mol) dissolved in 30 ml of benzene. The reaction mass was stirred for 10 h at ambient temperature and dried. Hexane was added to the reaction mass and the formed precipitate was filtered off. Distillation gave the product **XIII** (see Table I), ^{1}H NMR, δ: 1.7, m, 6H((CH_2)$_3$); 2.2, s, 6H($N(CH_3)_2$); 2.4, m, 1H(NCH); 2.7, m, 1H(N≡CCH). IR spectrum: 2230 cm^{-1} (C≡N).

Preparation of **XIV**. To 100 ml of a benzene solution of O,O-diethylphosphorodithioate triethylammonium salt (14.4 g, 0.05 mol) and trans-2-(N-methyl-N-ethylamino)cyclopentanol was added the reagent **I** (6.5 g, 0.05 mol). After 24 h of storing, the reaction mixture was washed by two 100 ml portions of water and two 100 ml parts of sodium carbonate solution. After separation, the organic layer was dried over $MgSO_4$, the solvent was removed by distillation and the residue distilled (see Table I). ^{31}P NMR, δ: 94, s; ^1H NMR, δ: 1.1, t, 3H, J = 6 Hz, ($NCCH_3$); 1.4, t, 6H, J = 6 Hz, ($(OCCH_3)_2$); 1.75, m, 6H($(CH_2)_3$); 2.3, s, 3H(NCH_3); 2.6, q, 2H, J = 5 Hz, (NCH_2); 3.0, m, 1H(NCH); 3.5, m, 1H(PSCH); 4.2, m, 4H($(POCH_2)_2$); IR spectrum, cm^{-1}: 2791 (NC—H); 1019 (PO—C); 661 (P═S); 540 (P—S).

The data of the elementary analysis for the synthesized compounds are in accord with calculated values (see Table I). The infrared absorption spectra of the compounds, except **III**, **V**, presented in the Table I show the Bohlmann band in the range 2776–2824 cm^{-1}.

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