Stereochemistry and Product Distribution in the Thiono-Thiolo Rearrangement of Phosphorothioic Esters. 4.[1] Role of Leaving-Group Solvation

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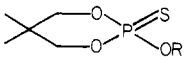
The thiono-thiolo rearrangement of 1-3 in different protic acids was studied. On the basis of the product distribution and stereochemistry of the resulting phosphorothiolates, an ion-pair mechanism is postulated. Depending on the acidity of the reaction medium and the substrate concentration, internal ion-pair recombination and/or attack of the unprotonated substrate molecule on the dissociated ion pair have been taken into consideration in this postulate.

In previous work reported from this Laboratory[1,2] we demonstrated that the thiono-thiolo rearrangement of benzyl and secondary esters of phosphorothioic acid in protic solvents is accompanied by solvolysis. The extent to which solvolysis participates in the overall process depends mainly on the procationoid character of the alkyl group R and the concentration of phosphorothionate 1 in the acidic medium, HA. We have also reported that the stereochemistry of rearrangement-solvolysis of these esters is strongly influenced by the acidity of the reaction medium.[2] Trifluoroacetic acid (TFA) or a mixture of TFA-CH_2Cl_2 causes the thiono-thiolo rearrangement to occur with net inversion of configuration at the carbon atom of the migrating R group, while in acetic acid the rearrangement of the same substrate occurs with predominant retention. "Retention" of the allyl moiety was also observed in the rearrangement of *O*-(3,3-dideuterioallyl) and *O*-(3-phenylallyl) dimethyl phosphinothionates to their *S*-allyl isomers.[3] In this work we present the behavior of 2-[(α-methylbenzyl)oxy]- (1), 2-[(2-buten-1-yl)oxy]- (2), and 2-[(3-buten-2-yl)oxy]-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinanes (3) in media of varying acidity.



1, R = $CH(CH_3)C_6H_5$
2, R = $CH_2CH{=}CHCH_3$
3, R = $CH(CH_3)CH{=}CH_2$
4, R = $CH(CH_3)C_2H_5$
5, R = $CHDC_6H_5$

Results

Influence of Reaction Medium Acidity on the Stereochemistry of the Rearrangement of 2-[(α-Methylbenzyl)oxy]-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (1). It has been shown that the rearrangement of 2-(2-butoxy)- (4), 2-[(α-deuteriobenzyl)oxy]- (5), and 2-[(α-methylbenzyl)oxy]-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (1) in TFA-CH_2Cl_2 (1:1 v/v) occurs with net inversion of configuration at the migrating carbon atom.[1,2] In the case of 1 nearly fully racemized 2-[(α-methylbenzyl)thio]-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (6) was isolated.[2] In CH_3COOH medium the rearrangement 1 → 6 also occurs, but this isomerization process takes place with retention of configuration.[2] Because the numerous parameters like the acidity of the reaction mixture, the different dielectric constants of TFA, CH_3COOH, and hexafluoroisopropyl alcohol, and others which determine the polarity of reaction mixture can in principle be responsible for the stereodifferentiated course of rearrangement, in our former work we were unable to offer an exact rationale of the observed phenomena. In this work we describe the results of our studies on the stereochemistry of the rearrangement 1 → 6 in media of differing acidity.[4] Limitation of our studies to the substrate 1 only results from the low rearrangement rates of compounds 4 and 5 in acids of lower acidity than TFA. The results are summarized in Table I. Inspection of Table I demonstrates that the lowest stereospecificity accompanies the rearrangement 1 → 6 in TFA-CH_2Cl_2 (only 1.5% of inversion). Decreasing medium acidity (TFA → CH_3COOH) causes a change of the steric course of rearrangement with a gradual increase of its stereospecificity. In the light of our former findings that O→S rearrangement is accompanied by an elimination-addition process,[1] the stereochemical results included in Table I need special comment.

It is known that the rearrangement 1 → 6 in TFA solution occurs without elimination of styrene, because the use of TFA-*d* as the reaction medium produces no incorporation of deuterium in 6.[1] Rearrangement of 1, when performed in CCl_3COOH/CH_2Cl_2 medium, was not accompanied by the appearance of a signal characteristic of 2-hydroxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (7) in the ^{31}P NMR spectrum.

Dichloroacetic and chloroacetic acids in the reaction media bring about solvolysis and elimination, since some amounts of the corresponding acetates 7 and styrene were observed. We assume that addition of 7 to styrene leading to 6, indistinguishable from that resulting from rearrangement, does not occur. This assumption is based on the fact that solutions of products resulting from rearrangement, solvolysis, and elimination when stored at room temperature for months have shown constant composition. Thus, addition of 7 to styrene, if it proceeds at all, must be very slow under these circumstances.

Mueller and Oswald[5] have shown that addition of diethyl phosphorothioic acid to styrene leads to the corresponding *S*-α-methylbenzyl *O,O*-diethyl phosphorothioate, but this process requires higher concentrations and longer times; besides that, the yield of product is only moderate.

(1) Part 3: Bruzik, K.; Stec, W. J. *J. Org. Chem.*, preceding paper in this issue.
(2) Bruzik, K.; Stec, W. J. *J. Org. Chem.* **1979**, *44*, 4488.
(3) Stec, W. J.; Uznański, B.; Bruzik, K.; Michalski, J. *J. Org. Chem.* **1976**, *41*, 1291.
(4) Methylene chloride dilutions were applied for the different acids to maintain the polarity of the reaction media at an approximately constant level.
(5) Mueller, W. H.; Oswald, A. A. *J. Org. Chem.* **1966**, *31*, 1894.

0022-3263/81/1946-1625$01.25/0

Table I. Stereochemical Course of 1 → 6 Rearrangement in Media of Different Acidities and/or Different Concentrations of 1

no.	reaction conditions[a] [solvent, acid (concn, M), concn of 1, M]	substr 1 config[b]	substr 1 $[\alpha]^{20}_{D}$,[d] deg (% ee)	product 6 config[c]	product 6 $[\alpha]^{20}_{436}$,[d] deg (% ee)	steric course of 1 → 6 rearrangement,[f] %
1	CH_2Cl_2, TFA (1.0), 0.1	R	+33.1 (100)	S	−2.91 (1.5)	1.5 (i)
2	CH_2Cl_2, CCl_3COOH (2.0), 0.2	R	+33.1 (100)	R	+16.2 (8.0)	8.0 (r)
3	$CHCl_2COOH$, 0.1	R	+33.1 (100)	R	+23.9 (11.8)	11.8 (r)
4	CH_2Cl_2, $CHCl_2COOH$ (2.0), 0.2	R	+33.1 (100)	R	+71.5 (35.2)	35.2 (r)
5	CH_2Cl_2, $CHCl_2COOH$ (1.0), 0.1	S	−33.0 (100)	S	−105.2 (52.0)	52.0 (r)
6	CH_2Cl_2, $CH_2ClCOOH$ (1.0), 0.1[e]	S	−15.1 (45.6)	S	−36.5 (18.1)	39.6 (r)
7	CH_2Cl_2, $CH_2ClCOOH$ (1.0), 0.15[e]	S	−15.1 (45.6)	S	−40.6 (20)	43.9 (r)
8	CH_2Cl_2, $CH_2ClCOOH$ (1.0), 0.1[e]	S	−15.1 (45.6)	S	−42.5 (21.0)	46.0 (r)
9	CH_2Cl_2, $CH_2ClCOOH$ (1.0), 0.05[e]	S	−15.1 (45.6)	S	−50.4 (24.9)	54.0 (r)
10	CH_3COOH,[e] 0.1	R	+33.1 (100)	R	+137 (65.6)	65.6 (r)

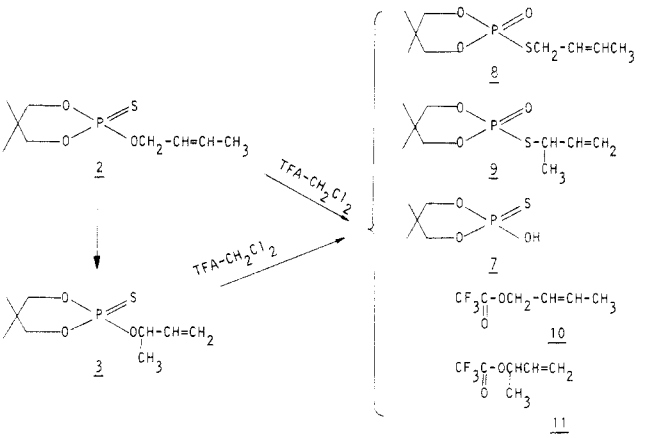
[a] Reactions were performed at 23 °C. It was proved that a small temperature change has no effect on the steric course of rearrangement. Thus, rearrangement 1 → 6 in $CHCl_2COOH/CH_2Cl_2$ medium at 23 and 34 °C proceeds with 52.1% and 51.7% retention, respectively. [b] The configuration and optical purity of phosphorothionate 1 were correlated to that of α-methylbenzyl alcohol.[2] [c] The configuration and optical purity of 6 were correlated to the optical purity and configuration of α-methylbenzyl thiol.[2] [d] Optical rotations were measured in acetone solutions. [e] It was established that under these conditions solvolysis and elimination also occur, but due to the very slow addition of phosphorothioic and acetic acids to styrene, the resulting phosphorothiolate 6 contained negligible amounts of products resulting from the elimination-addition process.[1] [f] Inversion (i) or retention (r) is indicated in parentheses.

All the above arguments hold for experiment no. 10 (Table I), because as shown earlier,[1] addition of CH_3COOD to styrene under the specified reaction conditions does not occur.

Rearrangement and Solvolysis of 2 and 3. Compounds 2 and 3 were obtained in the reaction of 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane with 2-buten-1-ol and 3-buten-2-ol, respectively, in the presence of triethylamine and an excess of elemental sulfur. The structures of 2 and 3 were confirmed by ^1H NMR, ^{31}P NMR, and mass spectrometric analysis. Their solvolytic behavior was studied in TFA–CH_2Cl_2 (10-fold excess of TFA over 2 and 3 at their concentrations 0.2 M) and hexafluoroisopropyl alcohol, and other halogenated acetic acids as CH_2Cl_2 solutions at 23 °C, and the progress of reaction was followed by ^{31}P NMR. In the case of 2 in TFA–CH_2Cl_2 solution the following products were detected: 2-[(2-buten-1-yl)thio]-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (8, 30%), 2-[(3-buten-2-yl)thio]-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (9, 38%), and 2-hydroxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (7, 32%) (Scheme I). Compounds 8 and 9 were isolated by means of preparative GC, and their structures were proved by means of ^1H NMR. The identification of 7 was achieved by observing an increase in intensity of the signal of 7 in the ^{31}P NMR spectrum after addition of genuine sample of 7 to the reaction mixture. In close parallel to the conversion 2 → 7 + 8 + 9, the rearrangement of 2 → 3 occurred. The decrease of concentration of 2 to 27% (73% conversion) was accompanied by the appearance of 3 (12.5% in relation to the concentration of residual 2).[6]

The isomerization of 2 → 3 was proved independently by means of gas chromatography/mass spectrometry. Allyl trifluoroacetates 10 and 11 were detected by the same technique. Under analogous conditions the pure compound 3 was also converted to the mixture of 8 (53%), 9 (26%), and 7 (20%), but the isomerization 3 → 2 was not observed.

Scheme I



A control test has shown that the rearrangement 8 → 9 doesn't occur under the same conditions. The isolated 8 and 9 were diluted with a TFA–CH_2Cl_2 mixture, and their behavior was studied by means of ^{31}P NMR. Even after 2 months of storage, samples of 8 and 9 in TFA–CH_2Cl_2 (sealed NMR tubes) showed no change in composition. The results of product analysis of rearrangement–solvolysis of 2 and 3 in media of differing acidity are collected in Table II. It should be pointed out that solvolysis accompanying the thiono–thiolo rearrangement of 2 and 3 has been observed in the TFA-containing media only.

Discussion

Retention of configuration at the migrating carbon atom is commonly observed in the rearrangement of benzylic

(6) A decrease of the concentration of 2 to 11% was accompanied by a relative increase of concentration of 3 of up to 28%, as calculated for unreacted 2.

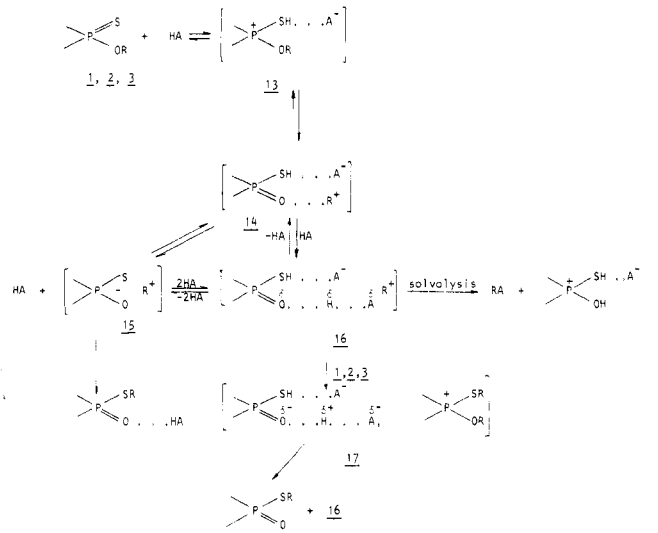
Table II. Product Distribution Analysis in the Rearrangement of Phosphorothionates 2 and 3 in Various Solvents at 23 °C

no.	substr	reaction conditions [solvent, acid (concn, M), concn of 2 or 3, M]	product ratio[a]	extent of rearrangement–solvolysis, %
1	2	CH_2Cl_2, TFA (2.0), 0.2	1.25:1[b]	89
2	2	CH_2Cl_2, TFA (0.2), 0.2	3.2:1[e,f]	23
3	2	CH_2Cl_2, $Cl_2CHCOOH$ (2.0), 0.2	7.7:1	80
4	3	CH_2Cl_2, TFA (2.0), 0.2	2.0:1[c]	90
5	3	CH_2Cl_2, $Cl_2CHCOOH$ (2.0), 0.2	22:1	85
6	2	TFA, 0.75	1.2:1[c]	100
7	2	CH_3COOH, 0.2	17.0:1[e]	35
8	2	$(CF_3)_2CHOH$, 0.2	2.7:1[e]	90
9	3	TFA, 0.25	2.2:1[d]	98
10	3	CH_3COOH, 0.2	>50:1[e]	64

[a] Ratio of the molar concentration of the isomer with an inverted allyl chain to that with a retained one. [b] Extent of trifluoroacetolysis 32%. [c] Extent of trifluoroacetolysis 20%. [d] 46% of trifluoroacetolysis. [e] Solvolysis was not detected. [f] Product ratio is dependent on the progress of the reaction.

derivatives containing bidentate leaving groups[7] such as thiocyanates[8,9] and sulfinates.[7] Under solvolytic conditions these rearrangements are very often accompanied by solvolyses,[10] and the racemic products of solvolyses are obtained.[7,10] Such stereochemical results are best explained in terms of ion-pair mechanisms. Recombination of internal ion pairs leads to products with retained configuration,[11] while an attack of solvent at the solvated external ion pairs results in formation of racemic solvolysis products.[7] In cases where the anionic constituent of an ion pair possesses ambident character, the return at the "subcenter" reconstitutes the substrate (internal ion-pair return or "hidden" return) while recombination with the cationic constituent at the "procenter" gives the isomeric product. A similar interpretation could be applied to rearrangement and solvolysis reactions of secondary alkyl and allyl esters of phosphorothioic acid. The ambident character of phosphorothioate anions and predominant attack of "soft" electrophilic species at the sulfur atom of phosphorothioate anion (procenter) are well documented.[12] Thus, if protonation of the substrate occurs,[13] the species **13** (see Scheme II) may be ionized with formation of ion pair **14**, where strong interactions between anion A^- and the proton located at the sulfur atom and between cationoid R^+ and the oxygen atom of phosphorothioate still

Scheme II



exist. These interactions are responsible for the lack of recombination of A^- and R^+ within this ion pair (**14**) assisted by dialkyl hydrogen phosphorothioate. If A^- is basic enough for attraction of the proton, phosphorothioate-assisted ion pair **14** converts to **15**. It is assumed that proton transfer is much faster than migration of the alkyl group. Recombination of phosphorothioate ion with R^+ within **15** leads to formation of the partially racemized phosphorothiolate **6** but net retention of configuration is observed. This seems to be the case for rearrangements of **1–3** in media of lower acidity than TFA[14] and/or TFA–CH_2Cl_2. However, in TFA solution, intervention of another TFA molecule into the ion pair **14** may occur through the protonation of the oxygen atom (vide infra), and species like **16** may undergo either solvolysis, with formation of corresponding alkyl acetate and **7**, or recombination with unprotonated **1** (**2** or **3**). This last process should lead to the transient formation of a phosphonium salt[15] accompanied by the conjugated acid of **7** and two A^- counterparts (**17**). Release of phosphorothiolate **6**, **8**, or **9** from **17** formally reconstitutes **16**, and the overall process can be repeated. Due to the relatively high freedom of the cationoid counterpart R^+ in **16**, highly racemized phosphorothiolates are formed, but due to external attack of nucleophilic substrate **1**, **2**, or **3** on **16**, inversion of configuration still predominates. Such a model allows an explanation also of the influence of concentration of the substrate on the stereochemical course of rearrangement (Table I, entries 6–9). A higher concentration of nucleophilic substrate increases the bimolecular character (with respect to substrate) of the rearrangement, while at lower concentrations the probability of external attack of nucleophile is lower, and rearrangement occurs by collapse of the ion pair **15**. Thus, at the 0.05 M concentration level of **1**, inversion of configuration is less emphasized than in the case where a fourfold higher concentration of starting **1** has been applied. The mechanistic picture represented in Scheme II offers an explanation for the rearrangement

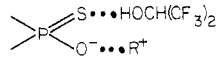
(7) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In "Ions and Ion Pairs in Organic Reactions"; Szwarc, M., Ed.; Wiley-Interscience: New York, 1974; p 311.
(8) Tonellato, U.; Rossetto, O.; Fava, A. *J. Org. Chem.* **1969**, *34*, 4032.
(9) Fava, A.; Tonellato, U.; Congiu, L. *Tetrahedron Lett.* **1965**, 1657.
(10) Hendrickson, J. B.; Skipper, P. L. *Tetrahedron* **1976**, *32*, 1627. Bravermann, S.; Duar, Y. *Tetrahedron Lett.* **1975**, 343. Darwish, D.; McLaren, R. *Ibid.* **1962**, 1231. Barroeta, N.; Macoll, A.; Cavazza, M.; Congiu, L.; Fava, A. *Gazz. Chim. Ital.* **1972**, *102*, 467.
(11) Moss, R. A. *Acc. Chem. Res.* **1974**, *7*, 421.
(12) Mastryukova, T. A.; Orlov, M.; Butorina, L. S.; Matrosov, E. I.; Shcherbina, T. M.; Kabachnik, M. I. *Zh. Obshch. Khim.* **1974**, *44*, 1001 and ref 2–8 cited therein. Mastryukova, T. A.; Orlov, M.; Eremich, D.; Kabachnik, M. I. *Ibid.* **1974**, *44*, 2403.
(13) Olah, G. A.; McFarland, C. W. *J. Org. Chem.* **1975**, *40*, 2582. Borovikov, Y. Y.; Yegorov, Y. P.; Semeni, B. Y. *Zh. Obshch. Khim.* **1976**, *47*, 2608. Shagidullin, R. R.; Lipatova, I. P.; Vachugova, L. I.; Samartseva, S. A. *Dokl. Akad. Nauk SSSR.* **1972**, *203*, 617. Skvortsov, N. K.; Tereshchenko, G. F.; Yonin, B. I.; Petrov, A. A. *Zh. Obshch. Khim.* **1975**, *46*, 521.
(14) For a review of the acidity of the carboxylic acids in inert solvents see: (a) Popov, A. I. In "Chemistry of Nonaqueous Solvents"; Lagovski, J. J., Ed.; Academic Press: New York 1970; Vol. 3, p 366. (b) Milne, J. B. *Ibid.*, Vol. 5B, p 1. (c) Joesten, M. D., Schaad, L. J. "Hydrogen Bonding"; Marcel Dekker: New York, 1974.
(15) Transient formation of phosphonium species during thiono–thiolo rearrangement of *O*-alkyl phosphylthioates in the presence of Lewis or protic acids is strongly evidenced: Teichmann, H.; Hilgetag, G. *Chem. Ber.* **1963**, *96*, 1454; *Ibid.* **1963**, *96*, 1446; *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 914; Bruzik, K.; Stec, W. J., to be submitted for publication.

Table III. Solvent Dependence of the Chemical Shift of 2-Hydroxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane in CH_2Cl_2 Solutions of Protic Acids[a,c]

	CH_2Cl_2-TFA[b]	CH_2Cl_2-CCl_3COOH[b]	CH_2Cl_2-$CHCl_2COOH$[b]	CH_2Cl_2-$CH_2ClCOOH$[b]	AcOH	CH_2Cl_2
$\delta^{31}P$ downfield from H_3PO_4	31.5	40.1	50.1	57-58	59.15	57.8

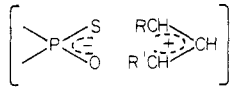
[a] Concentration of 7 is 0.05 M. [b] Concentration of the acid is 0.5 M. [c] All measurements were performed at 27 °C.

of 2 and 3 as well. In strong acid, due to the facility of proton transfer from HA to sulfur and oxygen, the formation of ion pair 15 is not privileged. Due to the strong shielding of the sulfur atom in 16 and the reversibility of its formation, return to the thionoester with an "inverted" allyl chain (2 → 3) or a "preserved" allyl chain (3 → 3, hidden return) occurs. "Random" recombination of this ion pair with a neutral substrate molecule leads to 17 and further to nearly equal amounts of thiolates with an "inverted" and "retained" allyl chain. In the case of hexafluoroisopropyl alcohol (HFIP; Table II, entry 8), the hydrogen bonding to sulfur[16] of 2 and 3 activates the substrate molecule and, due to the high ionizing power of the medium, ionization to 18 occurs. Solvolysis was not



18

observed in this medium because, due to weak proton donating properties, solvation of phosphorothioate anion is not so effective, and formation of 16 is negligible. However, due to the high dielectric constant of this solvent, a large fraction of the product can be formed from free carbenium ions, which is indeed the case for rearrangement of 1 in HFIP.[2] This results in a low ratio of "inverted"/"retained" product of rearrangement. It must also be noted that, independently of solvent, the product with the allyl chain inverted predominates in every case over the product with the allyl group retained. It can be concluded that even in trifluoroacetic acid a fraction of the product can arise from ion pair 15a present at low concentration.



15a, R = H or CH_3; R' = CH_3 or H

Lowering the acidity of the medium increases the fraction of product formed from 15a, and this is responsible for the almost exclusive formation of the isomer with the inverted butenyl group in CH_3COOH solution.

The considerations discussed above which lead to the conclusion that the reaction medium has considerable influence on the equilibrium between ion pairs 14–16 is based on the assumption that proton transfer is much faster than recombination of ion pairs or backside nucleophilic attack. It also includes the assumption of a strong interaction of dialkyl phosphorothioate anion and 7 with protic acids. Although literature data on the influence of strong proton donors like halogenated acetic acids on the nucleophilic reactivity of anionic nucleophiles are not available, our assumption seems to be valid because phosphorothioic acids in nonaqueous media are not very strong proton donors,[17] and their conjugate bases are of moderate strength. Also the tendency of phosphorus acids to self-

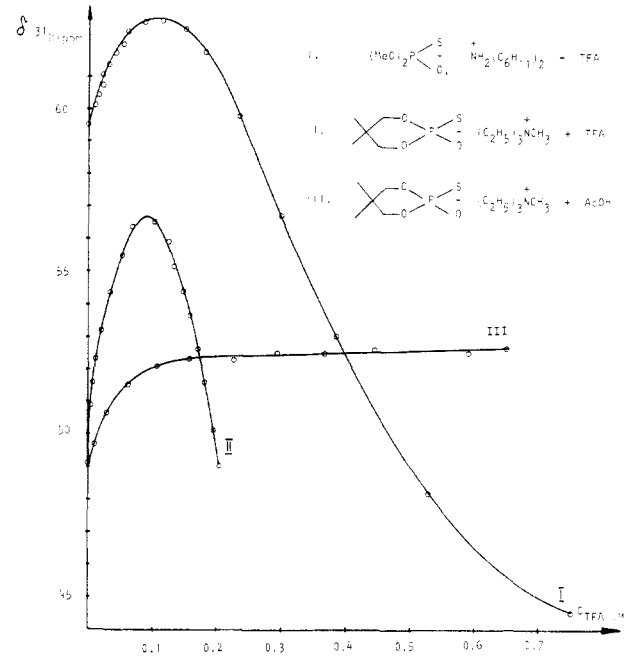
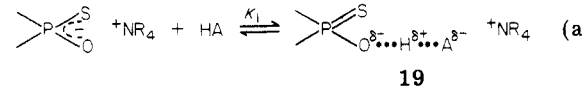


Figure 1. Dependence of the chemical shifts of ammonium dialkyl phosphorothioates upon the concentration of TFA in CH_2Cl_2 solution.

association and formation of heterodimers with other acids is known.[18]

These interactions are well demonstrated in the ^{31}P NMR spectra of 7 recorded in different media (Table III). Increasing the medium acidity in going from CH_2Cl_2 to TFA causes stronger protonation of the sulfur in 7 and a gradual shift toward the "phosphorothiolate" region.[19] The change in chemical shift of 7 can be ascribed to the covalency change of the phosphorus–sulfur bond in the phosphorothioate moiety. Investigation of the acid–base equilibria between the ammonium salt of dialkyl phosphorothioic acid and TFA or acetic acid demonstrates the coexistence of at least two equilibria, K_1 and K_2 (Figure 1). Curves I and II can be divided into regions a and b.



(a)

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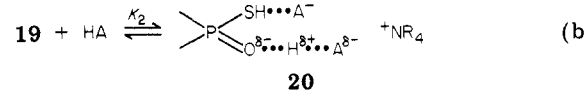

(b)

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Addition of TFA to the ammonium salt of dialkyl phosphorothioic acid causes the formation of salt 19 with a

(16) Sherry, A. D.; Purcell, K. F. *J. Am. Chem. Soc.* **1972**, *94*, 1848.
(17) Mastryukova, T. A.; Kabachnik, M. I. *Russ. Chem. Rev. (Engl. Transl.)* **1969**, *38*, 795. Ovchinnikov, V. V.; Galkin, V. I.; Cherkasov, R. A.; Pudovik, A. N. *Zh. Obshch. Khim.* **1976**, *47*, 290.
(18) Pogorelyi, V. K.; Kuhtenko, I. I.; Butorina, L. C.; Mastryukova, T. A. *Dokl. Akad. Nauk SSSR.* **1974**, *214*, 385. Shagidullin, R. R.; Lipatova, I. P.; Vachugova, L. I.; Cherkasov, R. A.; Khairutdinova, F. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1972**, 847. Shagidullin, R. R.; Lipatova, I. P.; Raevsky, O. A.; Vachugova, L. I.; Cherkasov, R. A.; Khalitov, F. G.; Samartseva, S. A., *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, 541. See also ref 14a, p 39.
(19) Mark, V.; Dungan, C. H.; Crutchefield, M. M.; van Wazer, J. R. *Top. Phosphorus Chem.* **1968**, *5*, 227.

heteroconjugated anion in which the oxygen of the phosphorothioate residue is protonated. Also the "thiono" character of the sulfur is exalted in **19**, a fact which is reflected in the downfield chemical shift parameter (region a). Further addition of TFA causes protonation of the heterodimer **19**, most probably at the sulfur, with formation of the heterotrimer **20**. This causes the change of chemical shift toward the phosphorothiolate region.

From the shape of curve III it is clear that in acetic acid solutions only the ammonium salts of **7** and **19** are present. However, curve III does not reach the region of low-field chemical shift which is observed in the case of TFA-containing solutions (curves I and II). Observed changes of chemical shift in the a region are much smaller for acetic acid solution than for TFA solution. This is due to the different character of the hydrogen-bonded complex **19** in both cases. In solutions containing trifluoroacetic acid, proton transfer rather than hydrogen bonding occurs between phosphorothioate anion and TFA. In acetic acid the complex is much more symmetrical and possesses a hydrogen-bonded nature. This, of course, implies differences in nucleophilicity of the sulfur in both types of complexes. It is also expected that the ammonium salts of **7**, **19**, and **20** possess different nucleophilic reactivity. On the basis of these facts the equilibria **14** $\rightleftharpoons$ **15** and **14** $\rightleftharpoons$ **16** are postulated (Scheme II). In the weaker acids like CH_3COOH the equilibrium **14** $\rightleftharpoons$ **15** is more favorable, which results both in retention of configuration in the rearrangement of **1** and in inversion of the allyl chain. TFA shifts the equilibria toward **16** and renders a more extensive separation of the ion pair constituents which is reflected in "backside" attack on the nucleophile on **16**.

Experimental Section

Melting points are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use. Methylene chloride, trifluoroacetic acid, hexafluoroisopropyl alcohol, and acetic acid were rigorously purified as described previously.[2] Trichloro-, dichloro-, and chloroacetic acids were dried over phosphorus pentoxide, distilled, and stored in sealed ampules under vacuum. ^1H NMR spectra were recorded at 60 MHz with a Perkin-Elmer R12B spectrometer or with a JEOL FX-60 spectrometer. ^{31}P NMR spectra were obtained on a JEOL FX-60 spectrometer operating at 24.3 MHz with external H_3PO_4 as the reference. Positive chemical shifts are assigned for compounds absorbing at lower field than H_3PO_4. GC analyses were performed on a Varian Aerograph 1520 chromatograph. Product purities were also checked by TLC (silica gel F_{254}, standard glass plates). Optical activity measurements were made with a Perkin-Elmer 241 MC photopolarimeter.

Starting Materials. 2-[(α-Methylbenzyl)oxy]-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (**1**), 2-[(2-buten-1-yl)oxy]-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (**2**), and 2-[(3-buten-2-yl)oxy]-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane (**3**) were prepared as described previously.[1,2]

For **2**: mp 50–52 °C; ^{31}P NMR δ 61.7 (C_6H_6); ^1H NMR ($CDCl_3$) δ 0.94 (s, 3, CH_3), 1.22 (s, 3, CH_3), 1.72 (d, 3, CH_3, $^3J_{HCCH}$ = 4.7 Hz), 3.6–4.3 (m, 4, CH_2), 4.55 (dd, 2, CH_2, $^3J_{POCH_2}$ = 10.7 Hz); mass spectrum, *m/e* (relative intensity) 236 (20, $M^{+\cdot}$), 182 (47), 115 (42), 68 (100).

For **3**: mp 57–62 °C; ^{31}P NMR δ 60.4 (C_6H_6); ^1H NMR ($CDCl_3$) δ 1.36 (d, 3, CH_3, $^3J_{HCCH}$ = 6.0 Hz), 1.11 (s, 3, CH_3), 0.86 (s, 3, CH_3); mass spectrum, *m/e* (relative intensity) 236 (22%, $M^{+\cdot}$) 182 (50), 115 (42), 68 (100).

Dicyclohexylammonium Salt of *O,O*-Dimethyl Phosphorothioic Acid. This was obtained by the addition of elemental sulfur to dimethyl phosphonate in the presence of an equimolar amount of dicyclohexylamine in benzene solution. The crude salt was recrystallized twice from benzene–hexane: mp 182 °C; ^{31}P NMR δ 58.6 (CH_2Cl_2).

Methyltriethylammonium Salt of 2-Hydroxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane. This was obtained by demethylation of 2-methoxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane[1] with triethylamine in benzene at 80 °C. Crystallization from benzene–hexane gave the pure compound: mp 74.5–75 °C; ^{31}P NMR δ 49.9 (CH_2Cl_2); the ^1H NMR spectrum was consistent with the structure. Anal. Calcd for $C_{12}H_{28}O_3PSN$: C, 48.46; H, 9.49; N, 4.70; P, 10.41; S, 10.76. Found: C, 48.50; H, 9.8; N, 4.96; P, 10.35; S, 10.54.

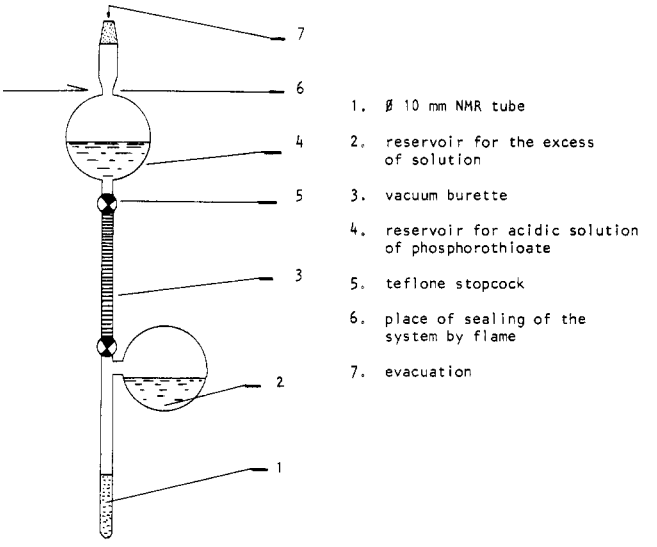

Figure 2. Vacuum-vessel system.

Determination of the Steric Course of 1 → 6 Rearrangement in the Presence of Various Acids. General Procedure. The solution of the acid in CH_2Cl_2 or acid alone was added under vacuum to a known amount of phosphorothionate **1** (286 mg, 10^{-3} mol) placed in a small (10 mL) flask connected with a 10-mm NMR tube. Part (2.5 mL) of the sample was transferred under vacuum before the tube was immersed in liquid nitrogen and sealed with a flame. The progress of the reaction was controlled by means of ^{31}P NMR monitoring. When reaction was completed, the solvent and excess acid were evaporated, and the residue was neutralized with anhydrous, gaseous ammonia. The crude product was purified by column chromatography as described recently.[2] The pure product **6** was analyzed for its optical rotation, and this value compared with $[\alpha]^{20}_{436}$ ±203° (acetone) assigned previously[2] for the pure enantiomer of **6**. The identity of the product was also confirmed by means of TLC and mass spectrometry.

Measurements of Product Distribution in Rearrangement of 2 and 3. The ratio of products of the thiono–thiolo rearrangement of **2** and **3** was estimated by means of ^{31}P NMR and/or GC. All reactions were performed under vacuum-line conditions. The procedure applied in the stereochemical studies (vide supra) was also applied for the preparation of samples.

2-[(2-Buten-1-yl)thio]- (8) and 2-[(3-Buten-2-yl)thio]-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (9). A quantity of **2** (2.38 g, 10 mmol) was dissolved in the mixture (50 mL) of methylene chloride and TFA (11.4 g, 0.1 mol; concentration of **2** = 0.2 M). The solution was left overnight, and the reaction was quenched by evaporation of the acid and solvent, followed by neutralization of the residue with NH_3. The crude mixture of **8** and **9** was purified by means of column chromatography. Both isomers **8** and **9** were separated by preparative gas chromatography [10% SE-30 on Chromosorb WAW (45–60 mesh), 15-m column] as colorless oils. The structures of products were confirmed by ^{31}P NMR, ^1H NMR, and gas chromatography/mass spectrometry.

For **8**: ^{31}P NMR δ 20.9 ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.26 (s, 3, CH_3), 1.67 (d, 3, CH_3, $^3J_{HCCH}$ = 4.9 Hz), 3.47 (dd, 2, SCH_2), 4.0 (m, 4, CH_2), 5.6 (m, 2, CH); mass spectrum, *m/e* (relative intensity) $M^{+\cdot}$ (13%), 182 (29), 115 (22), 68 (base peak).

For **9**: ^{31}P NMR δ 19.3 ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.89 (s, 3, CH_3), 1.30 (s, 3, CH_3), 1.55 (d, 3, CH_3, $^3J_{HCCH}$ 6.8 Hz), 4.0 (m, 5); mass spectrum, *m/e* (relative intensity) $M^{+\cdot}$ (13%), 182 (39), 115 (36), 68 (base peak).

Studies of Acid–Base Equilibria between Phosphorus Bases and Protic Acids in CH_2Cl_2. These were carried out by

means of ^{31}P NMR spectrometry using the special system of vacuum vessels shown in Figure 2. The ammonium salt of phosphorothioic acid (1×10^{-4} mol) was placed in part 1 of Figure 2. The system was connected to a vacuum line and evacuated before methylene chloride (2 mL) was distilled into the NMR tube (part 1 of the system). The tube was closed with a Teflon stopcock (no. 5), and 5×10^{-4} mol of the same base was stored in reservoir 4. This sample was analogously dissolved in the mixture (10 mL) of CH_2Cl_2 and TFA (273.6 mg, 2.4×10^{-3} mol). The vessel (part 4) was immersed in liquid nitrogen and sealed under vacuum with a flame. The system allows for the gradual change of concentration of TFA in tube 1 without affecting of the concentration of phosphorothioate in tube 1. The desired portion of the acidic solution was added from reservoir 4 through buret 3 to the solution in the tube 1 before each measurement of the chemical shift was performed. This operation was sequentially repeated.

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Registry No. (*R*)-**1**, 71719-69-2; (*S*)-**1**, 75716-63-1; **2**, 75716-64-2; **3**, 75716-65-3; (*R*)-**6**, 71719-72-7; (*S*)-**6**, 71719-71-6; **7**, 45734-11-0; **8**, 75716-66-4; **9**, 75716-67-5; *O,O*-dimethyl phosphorothioic acid dicyclohexylammonium salt, 13941-61-2; dimethyl phosphonate, 868-85-9; 2-hydroxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane methyltriethylammonium salt, 75716-68-6; 2-methoxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane, 1005-97-6.

Synthesis and Conformational Properties of *N,N*-Dialkyl-6,7-dihydro-5*H*-dibenzo[*b,g*][1,5]thiazocinium Salts[1]

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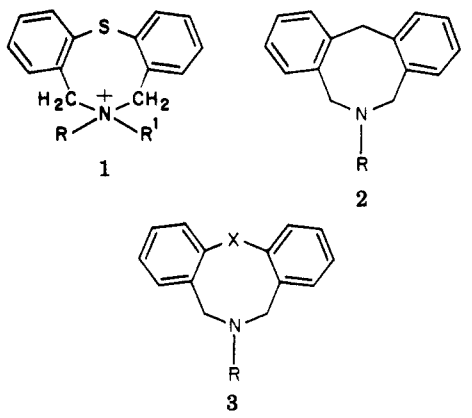
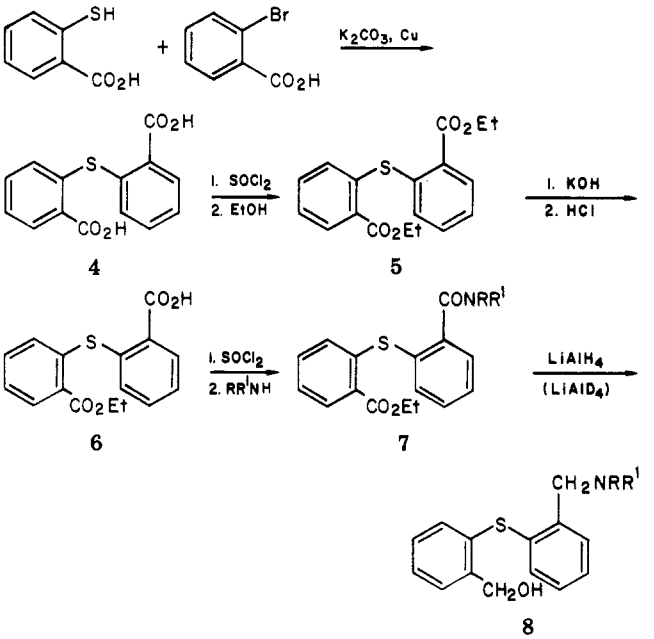
N,N-Dialkyl-6,7-dihydro-5*H*-dibenzo[*b,g*][1,5]thiazocinium salts have been prepared from their corresponding amino alcohols by using *p*-toluenesulfonyl chloride in acetonitrile. The conformational changes of these quaternary salts were studied by NMR and assigned as either TB (twist–boat) or BC (boat–chair). To simplify the assignment of the tetradeuterio derivative 6-benzyl-6,7-dihydro-6-methyl-5*H*-dibenzo[*b,g*][1,5]thiazocinium bromide was prepared. Temperature dependence and concentration/salt effects are discussed.

This paper describes the synthesis and some conformational properties of some *N,N*-dialkyl-6,7-dihydro-5*H*-dibenzo[*b,g*][1,5]thiazocinium salts (**1**). The conformational properties of systems similar to **1** have been described by Renaud and co-workers,[3] who have studied *N*-alkyl-6,7-dihydro-5*H*,12*H*-dibenzo[*c,f*]azocine (**2**) and similar systems by NMR. Also Tanaka and co-workers[4] have studied *N*-alkyl-6,7-dihydro-5*H*-dibenzo[*b,g*][1,5]oxazocines and thiazocines (**3**; X = O, S).



Scheme I[a]



[a] **a**, R = H, R¹ = Me; **b**, R = R¹ = Me; **c**, R,R¹ = -$(CH_2)_4$-; **d**, R,R¹ = -$(CH_2)_5$-; **e**, R = Me, R¹ = $CH_2C_6H_5$; **f**, 5,5,7,7-D_4, R = Me, R¹ = $CH_2C_6H_5$; **g**, 5,5,7,7-D_4, R = CH_3, R¹ = H.

Synthesis

Our previous work[5] has demonstrated the use of *p*-toluenesulfonyl chloride with triethylamine in achieving ring closure of amino alcohols. Scheme I outlines the synthetic route used to prepare the amino alcohols dis-

(1) Brieaddy, L. E. Presented in part at the 6th Northeast Regional Meeting of the American Chemical Society, Burlington, VT, Aug 18–21, 1974.

(2) (a) Department of Organic Chemistry. (b) Spectroscopy Laboratory.

(3) (a) Renaud, R. N.; Bovenkamp, J. W.; Fraser, R. R.; Roustan, J. A. *Can. J. Chem.* **1977**, *55*, 3456. (b) Renaud, R. N.; Bovenkamp, J. W. *Ibid.* **1977**, *55*, 650. (c) Fraser, R. R.; Rand, M. A.; Renaud, R. N.; Layton, R. B. *Ibid.* **1975**, *53*, 167. (d) Renaud, R. N.; Layton, R. B.; Fraser, R. R. *Ibid.* **1973**, *51*, 3380.

(4) (a) Tanaka, S.; Hashimoto, K.; Watanabe, H.; Sakaguchi, K. *Chem. Pharm. Bull.* **1973**, *21*, 1683. (b) Tanaka, S.; Hashimoto, K. *Yakugaku Zasshi* **1973**, *93*, 982.

(5) (a) Mehta, N. B.; Brooks, R. E. *J. Org. Chem.* **1962**, *27*, 1266. (b) Mehta, N. B.; Brooks, R. E.; Strelitz, J. Z.; Horodniak, J. W. *Ibid.* **1963**, *28*, 2843.

0022-3263/81/1946-1630$01.25/0