# INVESTIGATION OF THE CLEAVAGE OF N-ACYLETHYLENEIMINES BY THIOPHOSPHATE IONS

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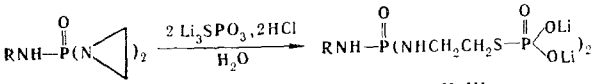
S-[N-Acyl(phosphoryl)-β-aminoethyl]thiophosphates in the form of neutral salts can be obtained only from N-acyl(phosphoryl)ethyleneimines that are sufficiently soluble in water. Cleavage of N-acyl- and N-phosphorylethyleneimines by the monolithiothiophosphate anion occurs with subsequent hydrolysis of the P—S bond of the intermediately formed acidic salts of S-[N-acyl(phosphoryl)-β-aminoethyl]-thiophosphoric acids and is a convenient method for the preparation of N-acyl- and N-phosphoryl-β-mercaptoethylamines.

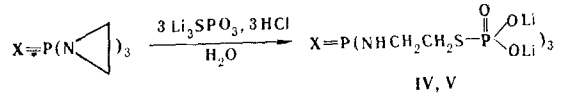
The cleavage of ethyleneimine and N-alkylethyleneimines by monothiophosphate ions [1, 2] leads to S-β-aminoethiophosphates. The very unstable N,N',N''-tris(S-disodiophosphoryl-β-mercaptoethyl)triamidophosphate has been obtained by the same method from N,N', N''-triethylenetriamidophosphate (I) and the monothiophosphate ion [3]. Other N-acylethyleneimines have not been studied in this reaction.

In the present research we investigated the reactions of a number of ethyleneimides of N-acylamino acids, and dicarboxylic and phosphoric acids with mono- and dithiophosphate ions, which were generated in aqueous solution or in $H_2O$—dimethylformamide (DMF) from $(LiO)_3PS$ or $(NaO)_3PS$ by the action of HCl.

We found that a necessary condition for the reaction of N-acylethyleneimines with the dithiophosphate ion is homogeneity of the reaction mixture, which can be created only in the case of sufficient solubility of the starting ethyleneimine compounds in water. Thus the ethyleneimine rings of N-phenyl- and N-cyclohexyl-N',N''-diethylenetriamidophosphates, amidophosphate I, and its thio analog are readily cleaved by the dilithiothiophosphate anion to give the corresponding triamidophosphates II-IV and triamidothiophosphate V (Table 1):



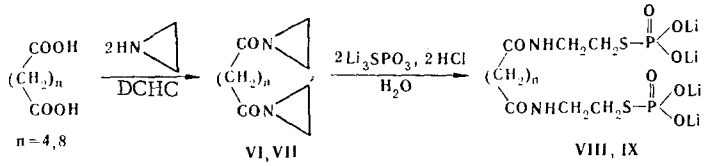
II, III



IV, V

II $R=C_6H_5$; III R= cyclohexyl; IV X=O; V X=S

Diamides VIII and IX (Table 1) were similarly obtained in quantitative yields from adipic and sebacic acid diethyleneimides (VI, VII):



VI, VII

VIII, IX

VI, VIII n=4; VII, IX n=8

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TABLE 1. S-Phosphorylated N-Phosphoryl- and N-Acyl-β-mercaptoethylamines

| Compound | Found, % | | | | Empirical formula | Calc., % | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | C | H | N | P+Li | | C | H | N | P+Li | |
| II | 25,8 | 3,7 | 8,8 | 27,8 | $C_{10}H_{16}Li_4N_3O_7P_3S_2$ | 25,3 | 3,4 | 8,8 | 27,8 | 89 |
| III | 23,4 | 5,3 | 8,0 | 23,2 | $C_{10}H_{22}Li_4N_3O_7P_3S_2 \cdot 2H_2O$ | 23,2 | 5,1 | 8,1 | 23,3 | 91 |
| IV | — | — | 7,4 | — | $C_6H_{15}Li_6N_3O_{10}P_4S_3 \cdot 3H_2O$* | — | — | 7,5 | — | 62 |
| V | 11,9 | 3,4 | — | 25,5 | $C_6H_{15}Li_6N_3O_9P_4S_4 \cdot 3H_2O$ | 11,6 | 3,4 | — | 26,6 | 94 |
| VIII | 26,0 | 4,3 | 6,1 | 44.8 | $C_{10}H_{18}Li_4N_2O_8P_2S_2 \cdot H_2O$ | 25,8 | 4,3 | 6,2 | 45,0 | 97 |
| IX | 33,3 | 5,4 | 5,6 | 38,5 | $C_{14}H_{26}Li_4N_2O_8P_2S_2$ | 33,4 | 5,2 | 5,6 | 38,9 | 94 |

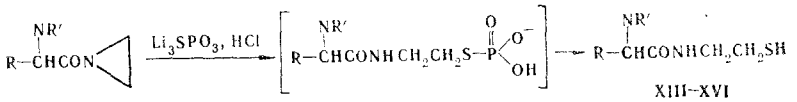
*Found: S 15.8%. Calculated: S 15.9%.

The previously unknown [4] and difficult-to-obtain starting diethyleneimides VI and VII were obtained in high yields by the carbodiimide method.

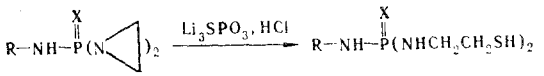
The same N-acyl(phosphoryl)ethyleneimines also react readily with the disodiothiophosphate anion to give the corresponding sodium salts. However, the latter are unstable, and their isolation in pure form is difficult, particularly because of the high solubility in water of their decomposition product, viz., sodium orthophosphate.

The water-insoluble N-acylethyleneimines, as well as N-phenyl-, N-cyclohexyl-, and N-(1-carbethoxy-2-methylpropyl)-N,N'-diethylenetriamidothiophosphates, are virtually unreactive with respect to dithiophosphate ions.

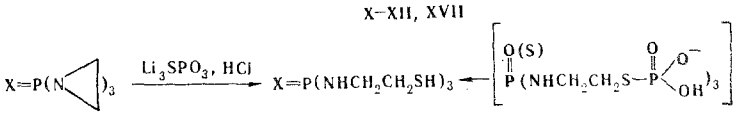
The reaction of N-acyl(phosphoryl)ethyleneimines with the monolithiothiophosphate anion in water leads to N-acyl(phosphoryl)aminoethanethiols X-XX (Table 2), which are formed as a result of hydrolysis of the P—S bond, as in [3], of the intermediate acidic monolithium salts of S-[N-acyl(phosphoryl)-β-aminoethyl]thiophosphoric acids; because of the rapid removal of amino thiols X-XX, which are insoluble in the reaction medium, thiophosphorylation is realized regardless of the solubility of the starting N-acyl(phosphoryl)ethyleneimines in water.



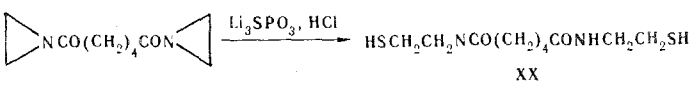
XIII–XVI



X–XII, XVII



XVIII, XIX



XX

X R=$C_6H_5$, X=S; XI R= cyclohexyl, X=S; XII R=*i*-PrCH($COOC_2H_5$), X=S; XIII R= =$CH_3$, R'= phthalyl; XIV R=*i*-Pr, R'= phthalyl; XV R=*i*-Pr, R'=$C_6H_5CH_2OCO$; XVI R= =*i*-Pr, R'=$CH_3CO$; XVII R= cyclohexyl, X=O; XVIII X=O; XIX X=S

The synthesis of N-acyl(phosphoryl)aminoethanethiols by this method is distinguished by the simplicity of isolation of the products and the high yields as compared with their production by cleavage of N-acyl(phosphoryl) ethyleneimines by hydrogen sulfide [3, 5].

TABLE 2. N-Acyl- and N-Phosphoryl-β-aminoethanethiols

| Compound | mp, °C | Yield, % | Compound | mp, °C | Yield, % |
|---|---|---|---|---|---|
| X* | 77—78 | 88 | XVI† | 151—153 | 88 |
| XI* | 52—53 | 89 | XVII* | Oil | 91 |
| XII* | Oil | 95 | XVIII | Oil | 92 |
| XIII† | 124—125 | 90 | XIX | Semicrystalline mass | 94 |
| XIV† | 122—123 | 91 | | | |
| XV† | 152—153 | 89 | XX | 142—143 | 86 |

*We described the synthesis of these compounds in [3].
†We previously obtained these compounds in lower yields [5].

## EXPERIMENTAL

The starting compounds were obtained by known methods: N-phenyl-N',N''-diethylenetriamidophosphate by the method in [6], its thio analog by the method in [7], N-cyclohexyl-N',N''-diethylenetriamidophosphate and -thiophosphate by the method in [8], I by the method in [9], its thio analog by the method in [10], N-p-carbethoxyphenyl- and N-(1-carbethoxy-2-methylpropyl)-N',N''-diethylenetriamidothiophosphates by the method in [3], the ethyleneimides of N-phthalyl-substituted glycine, alanine, valine, and N-carbobenzoxyvaline by the method in [5], and the ethyleneimide of N-acetylvaline by the method in [11].

Adipic Acid Diethyleneimide (VI). A solution of 12.36 g (60 mmole) of 1,3-dicyclohexylcarbodiimide in 15 ml of $CHCl_3$ was added with stirring at −5°C to a solution of 2.58 g (60 mmole) of ethyleneimine in 15 ml of dry $CHCl_3$, after which a solution of 4.38 g (30 mmole) of adipic acid in 30 ml of the same solvent was added in portions while preventing the reaction mixture from heating up to above +5°C. The mixture was allowed to stand for 12 h, after which the precipitated 1,3-dicyclohexylurea (13.4 g) was separated, and the filtrate was concentrated *in vacuo* at room temperature. The residual colorless oil crystallized upon cooling to give 5.37 g (91%) of the imide with mp 32-34°C. Three recrystallizations from benzene—cyclohexane gave a product with mp 39-40°C [5].

Sebacic Acid Diethyleneimide (VII). This compound was similarly obtained in 84% yield and had mp 58-59.5°C (from cyclohexane) [5].

N-Phenyl-N',N''-bis(S-dilithiophosphoryl-β-mercaptoethyl)triamidophosphate (II). A 1.12-g (5 mmole) sample of N-phenyl-N',N''-diethylenetriamidophosphate and 2.0 ml of DMF were added to a suspension of 2.31 g (10 mmole) of $Li_3SPO_3 \cdot 5.5H_2O$ in 10 ml of water, after which 1.0 ml (10 mmole) of concentrated hydrochloric acid was added slowly dropwise while preventing the reaction mixture from heating up to above 30°C. The mixture was stirred at room temperature for 20 min (the end of the reaction was monitored from the absence of $SPO_3^{3-}$), after which the mixture was filtered, and the filtrate was poured into 100 ml of alcohol. The precipitate was removed by filtration and dissolved in 5 ml of water and precipitated by the addition of alcohol. The precipitate was separated, washed with alcohol and ether, and air dried to give 2.0 g (89%) of lithium salt II.

A 0.2-g sample of salt I was heated at 60°C for 1 h with 30 ml of 10% hydrochloric acid, after which the mixture was cooled, treated with 12 ml of a 5% solution of KI, and titrated with 0.1 N $KIO_3$ solution. According to the results of titration, the purity of I was 98%.

Compounds III-V, VIII, and IX were similarly obtained.

Reaction of N-Phenyl-N',N''-diethylenetriamidothiophosphate with Disodio- or Dilithiothiophosphate Anions. A 1.19-g (5 mmole) sample of N-phenyl-N', N''-diethylenetriamidothiophosphate was added slowly with stirring at room temperature to a suspension of 3.96 g (10 mmole) of $Na_3SPO_3 \cdot 12H_2O$ or 2.31 g (10 mmole) of $Li_3SPO_3 \cdot 5.5H_2O$ in 6-8 ml of water, after which 1 ml (10 mmole) of concentrated hydrochloric acid was added dropwise while preventing the reaction mixture from heating up to above +30°C. The mixture was stirred for ∿50 h, after which 0.5 g of the starting thiophosphate, with mp 96-97°C (from benzene), was separated. Sodium chloride was added to the filtrate, and the precipitated colorless oil, which crystallized slowly, was treated with 5% aqueous NaOH solution, acidified with 5 N HCl, and extracted

with ethyl acetate. The extract was washed with 5% aqueous $NaHCO_3$ solution and dried with magnesium sulfate. Removal of the ethyl acetate gave 0.3 g (20%) of N-phenyl-N',N"-bis-(β-mercaptoethyl)triamidothiophosphate (X) with mp 77-78°C (from a mixture of chloroform with petroleum ether). Found: C 38.8; H 5.7; N 31.1; P 10.0%. $C_{10}H_{18}N_3PS_3$. Calculated: C 39.0; H 5.9; N 31.2; P 10.1%.

Similar results were obtained in the case of N-cyclohexyl- and N-(1-carbethoxy-2-methylpropyl)-N'N"-diethylenetriamidothiophosphates and the ethyleneimides of N-phthalyl-substituted alanine and valine and N-carbobenzoxy- and N-acetylvaline. The corresponding amino thiols XI-XVI (Table 2) were identified by means of TLC. According to iodometric titration, their percentages in the reaction mixtures ranged from 20 to 30%.

Reaction of Ethyleneamidophosphates and Their Thio Analogs with the Monolithiothiophosphate. A 2-ml (20 mmole) sample of concentrated hydrochloric acid was added gradually with stirring to a suspension of 2.31 g (10 mmole) of $Li_3SPO_3 \cdot 5.5H_2O$ in 6-8 ml of water, after which 5 mmole of diethylenetriamidophosphate or 3 mmole of I or its thio analog was added. A 2-3 ml sample of DMF was then added while preventing the reaction mixture from heating up to above 25°C, and the mixture was stirred for 1-8 h (until the test for $SPO_3^{3-}$ was negative). The precipitated lithium orthophosphate was separated, and the filtrate was saturated with NaCl. The emulsion was extracted four to five times with ethyl acetate, the extract was dried with magnesium sulfate, and the ethyl acetate was evaporated *in vacuo*. The difficult-to-crystallize oil was dried *in vacuo* over $P_2O_5$ and recrystallized to give, respectively, X-XII, XVII, and XVIII, which were identical to the compounds described in [3], and N,N',N"-tris(β-mercaptoethyl)triamidothiophosphate (XIX) in the form of a semicrystalline mass. Found: P 10.5%. $C_6H_{18}N_4PS_4$. Calculated: P 10.6%.

Reaction of Ethyleneimides with the Monolithiophosphate Anion. A 10-mmole sample of the N-acylamino acid ethyleneimide or 5 mmole of diethyleneimide VI was added slowly with stirring at room temperature to a suspension of 2.31 g (10 mmole) of $Li_3SPO_3 \cdot 5.5H_2O$ in 6-8 ml of water, after which ∿2 ml (20 mmole) of concentrated hydrochloric acid (to pH 6.5-7) and 5 ml of DMF were added slowly dropwise without allowing the reaction mixture to heat up. The mixture was stirred until it gave a negative test for $SPO_3^{3-}$. The precipitated crystals were removed by filtration and recrystallized to give XIII-XVI, which were identical to the compounds described in [5], and adipic acid N,N'-bis(β-mercaptoethyl)diamide (XX), with mp 142-143°C (from aqueous methanol), in 86% yield. Found: C 45.2; H 7.5; S 23.5%. $C_{10}H_{20}N_2O_2S_2$. Calculated: C 45.5; H 7.6; S 24.0%.

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