SYNTHESIS OF SOME O,O-DIETHYL S-(β-ACYLAMINOETHYL) DITHIOPHOSPHATES

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The ethyleneimides of N-phthalyl-D,L-valine, N-phthalyl-D,L-glycine, N-phthalyl-D,L-alanine, N-carbobenzoxy-D,L-valine, N-benzoyl-D,L-leucine, and of the γ-methyl ester of N-carbobenzoxy-L-glutamic acid and monomethyl succinate were synthesized. A number of O,O-diethyl S-(β-acrylaminoethyl) dithiophosphates were obtained by opening the ethyleneimine ring in the ethyleneimides of N-acylated amino acids with diethyl dithiophosphoric acid. The β-chloroethylamides of phthalyl-D,L-valine, N-acetyl-D,L-valine, and monomethyl succinate were obtained.

As is well known, O,O-dialkyl dithiophosphates are relatively strong acids ($K_a \approx 10^{-2}$) that are capable of nucleophilic addition. In recent years, the addition of O,O-dialkyl dithiophosphates to olefins has been thoroughly studied. Numerous O,O,S-trialkyl dithiophosphates, which have found broad application as highly active insecticides and acricides of low toxicity to animals and man, have been synthesized [1]. Information is also available regarding the addition of O,O-dialkyl dithiophosphates to ethylene oxide [2] and ethylene sulfide [3]. Ethyleneimine reacts with lower O,O-dialkyl dithiophosphates to form undistillable O,O-dialkyl S-(β-aminoethyl) dithiophosphates, which are characterized as their picrates [4]. Ethyleneimine derivatives, including N-alkyl- and N-acyl-substituted ethyleneimines, have not been studied in this reaction. Because of the high strain of the three-membered ethyleneimine ring, ethyleneimine derivatives are readily opened by various nucleophilic agents, and their reaction with O,O-dialkyl dithiophosphates may serve as a convenient route for the synthesis of substituted O,O-dialkyl S-(β-aminoethyl) dithiophosphates.

In the present research, we have studied the reaction of a number of N-acylated ethyleneimines with O,O-diethyl dithiophosphoric acid. The starting ethyleneimine compounds used were N-phthalyl-D,L-phenylalanine ethyleneimide (I), which we previously synthesized [5], as well as the ethyleneimides of N-phthalyl-D,L-valine (II), -glycine (III), -D,L-alanine (IV), N-carbobenzoxy-D,L-valine (V), the γ-methyl ester of N-carbobenzoxy-L-glutamic acid (VI), and N-benzoyl-D,L-leucine (VII), obtained by the same method used to prepare I – by the action of 1,3-dicyclohexylcarbodiimide on a mixture of the corresponding N-acylated α-amino acid and ethyleneimine. We found that the ethyleneimides of the α-amino acids (I-VII) react comparatively readily with O,O-diethyl dithiophosphoric acid in a polar solvent (usually methanol). In this case, one obtains the corresponding (and apparently difficult-to-obtain by other synthetic methods) O,O-diethyl S-(β-acylaminoethyl) dithiophosphates (VIII-XIV) as stable, crystalline compounds, the structure of which was confirmed by the IR spectra (Table 1). O,O-Diethyl S-(β-aminoethyl) dithiophosphate (XV) was characterized as a water-soluble salt with tartaric acid (XVI). The possibility of the synthesis of O,O-diethyl S-(β-acylaminoethyl) dithiophosphates from β-chloroethylamides of several N-acylated α-amino acids and potassium O,O-diethyl dithiophosphate via the known alkylation of alkaline salts of O,O-dialkyl dithiophosphoric acids with alkyl halides [8] was also investigated. The β-chloroethylamides of N-phthalyl-D,L-valine (XIX), N-acetyl-D,L-

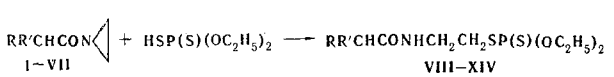

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TABLE 1. O,O-Diethyl S-(β-Acylaminoethyl) Dithiophosphates

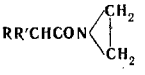
Comp.	R	R′	mp, °C (crystallization solvent)
VIII	Phthalimido	$C_6H_5CH_2$	109—110 (ethyl acetate + petroleum ether)
IX	The same	$(CH_3)_2CH$	107—108 (ethyl acetate)
X	"	H	83—85 (ethyl acetate)
XI	"	CH_3	76—77 (aqueous ethanol)
XII	$C_6H_5CH_2OCONH$	$(CH_3)_2CH$	110—112 (ethanol)
XIII	$C_6H_5CH_2OCONH$	$CH_3OCOCH_2CH_2(L-)$*	64—65 (aqueous ethanol)
XIV	C_6H_5CONH	$(CH_3)_2CH_2CH_2$	104—105 (ethanol)

Table 1 (continued)

Comp.	Empirical formula	Found, %			Calc., %			Yield, %
		C	H	P	C	H	P	
VIII	$C_{23}H_{27}N_2O_5S_2P$	54,71	5,16	5,94	54,51	5,37	6,11	86
IX	$C_{19}H_{27}N_2O_5S_2P$	49,33	6,54	6,10	49,75	5,93	7,44	62
X	$C_{16}H_{21}N_2O_5S_2P$	46,58	5,12	7,93	46,15	5,08	7,44	57
XI	$C_{17}H_{23}N_2O_5S_2P$	48,07	6,08	7,79	47,42	5,39	7,19	75
XII	$C_{19}H_{31}N_2O_5S_2P$	49,66	6,92		49,33	6,75		76
XIII	$C_{20}H_{31}N_2O_7S_2P$	47,43	6,57	5,98	47,40	6,27	6,11	80
XIV	$C_{19}H_{31}N_2O_4S_2P$	51,09	7,20	6,54	51,11	7,0	6,93	82

*For XIII, $[\alpha]_{20}^{D} = -7° \pm 2°$ ($CHCl_3$, c 0.5 M).

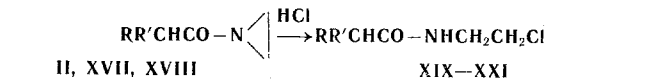
TABLE 2. Ethyleneimides



Comp.	R	R′	mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %		Yield, %
					C	H	C	H	
II	Phthalimido	$(CH_3)_2CH$	97—98 (ethanol)	$C_{15}H_{16}N_2O_3$	66,55	6,35	66,16	5,92	72
III	The same	H*	114 (ethanol)	$C_{12}H_{10}N_2O_3$	—	—	—	—	73
IV	"	CH_3	92—94 (petroleum ether)	$C_{13}H_{12}N_2O_3$	63,75	5,20	63,93	4,95	96
V	$C_6H_5CH_2OCONH$	$(CH_3)_2CH$	Oil	$C_{15}H_{20}N_2O_3$	—	—	—	—	76
VI	$C_6H_5CH_2OCONH$	$CH_3OCOCH_2CH_2$	Oil	$C_{16}H_{20}N_2O_5$	—	—	—	—	80
VII	C_6H_5CONH	$(CH_3)_2CH_2CH_2$	77—78 (petroleum ether)	$C_{15}H_{20}N_2O_2$	69,50	7,88	69,24	7,75	80

*Previously synthesized from the acid chloride of phthalylglycine and ethyleneimine [6].

valine (XX), and of the methyl ester of succinic acid (XXI) were obtained by opening the ethyleneimine ring of the corresponding ethyleneimides of the carboxylic acids (II, XVII, and XVIII) with dry hydrogen chloride. However, the products of the reaction of XIX-XXI with potassium O,O-diethyl dithiophosphate proved to be oils that were difficult to purify.

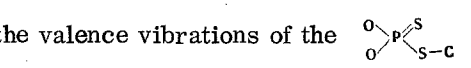


II, XVII, XVIII XIX—XXI

II R = phthalimido R′ = $(CH_3)_2CH$; XVII R = CH_3CONH, R′ = $(CH_3)_2CH$; XVIII R = H, R′ = CH_3OCOCH_2

EXPERIMENTAL

Ethyleneimides II-VII and XVIII were synthesized by the method in [5] by condensation of the corresponding N-acylated amino acids with ethyleneimine in the presence of 1,3-dicyclohexylcarbodiimide in $CHCl_3$ or tetrahydrofuran with cooling to 0° (Table 2). Ethyleneimides V and VI were obtained as oils. The oils could not be purified by chromatography with a column filled with KSK silical gel (65-150 mesh) with elution by benzene. Analysis of the residue after evaporation of the solvent demonstrated the presence of from 5 to 10% of impurities (titration by the thiocyanate method [7]).

General Method for the Synthesis of O,O-Diethyl S-(β-Acylamino) Dithiophosphates (VIII-XIV). A 0.025 mole sample of the ethyleneimide (I-VII) was added slowly with vigorous stirring to a cooled (to −5°) solution of 0.025 mole of diethyl dithiophosphoric acid in 15 ml of absolute methanol while maintaining the temperature no higher than 10°. After stirring at room temperature for 15 min, the reaction mixture was heated slowly and refluxed for 2 h until it gave a negative reaction (with respect to Congo red) to the presence of the starting acid. It was then cooled, and the solvent was vacuum-evaporated to give the O,O-diethyl S-(β-acylaminoethyl) dithiophosphates (VIII-XIV) as solid residues, which were recrystallized from suitable solvents. Intense doublet absorption bands, characteristic for the valence vibrations of the  grouping [9], are present in the IR spectra of VIII-XIV in the 655-660 cm^{-1} region.

O,O-Diethyl S-(β-Aminoethyl) Dithiophosphate (XV). A 0.046-mole sample of ethyleneimine was added dropwise with stirring to a cooled (to −5°) solution of 0.042 mole of diethyl dithiophosphoric acid in 20 ml of absolute methanol. At the end of the addition, the reaction mixture was stirred at room temperature for 1 h. The solvent and excess ethyleneimine were vacuum-evaporated to give 8 g (85%) of analytically pure XV with n_D^{20} 1.5280 and d_4^{20} 1.185 (n_D^{20} 1.5287, d_4^{20} 1.17 [4]). The substance was quite soluble in organic solvents and insoluble in water. Found: C 32.4; H 7.2; S 13.5%; MR_D 59.59. $C_6H_{16}NO_2S_2P$. Calculated: C 32.7; H 7.3; S 13.7%; MR_D 59.99.

Tartrate of O,O-Diethyl S-(β-Aminoethyl) Dithiophosphate (XVI). A solution of 0.01 mole of tartaric acid in 2 ml of water was added slowly to 0.02 mole of O,O-diethyl S-(β-aminoethyl) dithiophosphate. The mass warmed up spontaneously and solidified at the end of the addition. It was triturated with ether, filtered, and washed with acetone to give 2 g (52%) of XVI with mp 155-157° (from methanol). Found: C 32.1; H 6.0; P 7.9; S 3.8%. $C_{10}H_{22}NS_2P$. Calculated: C 31.6; H 5.8; P 8.2; S 3.7%.

N-Phthalyl-D,L-valine β-Chloroethylamide (XIX). A total of 20 ml of a cooled (to −5°) absolute ether, saturated at 0° with dry hydrogen chloride, was added with stirring to a cooled (to −5°) solution of 0.0075 mole of N-phthalyl-D,L-valine ethyleneimide (II) in 35 ml of absolute ether. The solution was allowed to stand in a refrigerator to give 2.0 g (84%) of XIX with mp 131-132° (from ether). Found: C 58.2; H 5.5; Cl 11.6%. $C_{15}H_{17}N_2O_3Cl$. Calculated: C 58.4; H 5.6; Cl 11.5%.

N-Acetyl-D,L-valine β-Chloroethylamide (XX). A total of 25 ml of absolute methanol saturated with dry hydrogen chloride was added rapidly with stirring at −5° to a solution of 0.01 mole of N-acetyl-D,L-valine ethyleneimide (XVII) [5] in 10 ml of absolute methanol. The mixture was stirred at −5° for 3 h and at room temperature for 1 h. The solvent was removed in vacuo, and the residual viscous oil began to crystallize on trituration with absolute ether to give 1.5 g (68%) of XVIII with mp 175-177° (from ethanol). Found: C 49.3; H 8.1; Cl 16.1%. $C_9H_{16}N_2O_2Cl$. Calculated: C 49.0; H 7.8; Cl 16.1%.

β-Chloroethylamide of Methyl Succinate (XXI). Dry hydrogen chloride was bubbled for 6 h into a solution of 0.03 mole of the ethyleneimide of monomethyl succinate (XVIII) [10] in 40 ml of benzene at 0°. The mixture was then allowed to stand for several hours at room temperature, the solvent was vacuum-evaporated, and the residue was distilled to give 4.4 g (52%) of XXI with bp 141-142° (1.5 mm), n_D^{20} 1.4854, and d_4^{20} 1.2480. Found: C 43.4; H 6.1; Cl 17.6%; MR_D 44.72. $C_7H_{12}NO_3Cl$. Calculated: C 43.4; H 6.2; Cl 17.8%; MR_D 44.66.

O,O-Diethyl S-[β-(N'-Phthalylvalyl)aminoethyl] Dithiophosphate (IX). A 0.015-mole sample of potassium diethyl dithiophosphate [11] was added in small portions to a solution of 0.0125 mole of the β-chloroethylamide of N-phthalyl-DL-valine (XIX) in 15 ml of acetone, and the mixture was heated at 50-60° for 3 h. The KCl (0.89 g) was removed by filtration, the filtrate was vacuum-evaporated, and the residual oil was purified by chromatography with a column filled with KSK silica gel (65-150 mesh) with benzene–ether–

methanol (8 : 2 : 1) as the eluent. Thin-layer chromatography on plates with a fixed layer of KSK silica gel (200-250 mesh) in the same solvent system (with iodine as the developer) demonstrated that the product was identical to an analytical sample of IX (see Table 1).

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