Reaction of Carbodiimides with Phosphorothioic, Phosphorodithioic, and Phosphoroselenoic Acids: Products, Intermediates, and Steps[1,2]

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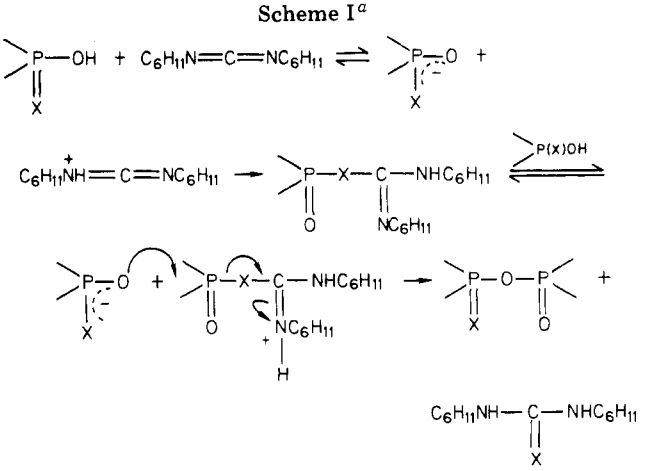
The reaction of the title acids with dicyclohexylcarbodiimide (DCC) used in a 2:1 ratio was found to give a complex mixture of products consisting of thio(seleno)pyrophosphates, thiolo(selenolo)phosphates, thiono(selenono)phosphates, dicyclohexylthiourea (DCTU), and a polymeric alkyl metaphosphate. When both reaction components are mixed in a 1:1 ratio, *N*-phosphoryl-*N,N'*-dicyclohexylthio(seleno)ureas (B) were formed. The formation of equimolar adducts (B) was also observed with other dialkyl- and diarylcarbodiimides. The spectral properties (especially the value of $^3J_{P-H}$) and reactivity of these adducts are strongly dependent on their conformation. The distinct conformational differences between the adducts B derived from DCC and diisopropylcarbodiimide (DiPC) and those obtained from dibenzylcarbodiimide (DBC) and diarylcarbodiimides were revealed by X-ray analysis of the selected *N*-phosphorylthioureas. By means of low-temperature FT ^{31}P NMR spectra it was demonstrated that the adducts (B) arise from the first formed unstable *S(Se)*-phosphorylisothio(seleno)ureas (A) as a result of S(Se)→N phosphoryl migration. The differences in ability of the phosphoryl group to undergo S(Se)→N and O→N 1,3-shifts are briefly described. *N*-Phosphorylthio(seleno)ureas (B) obtained from DCC and DiPC, in contrast to those prepared from DBC and diarylcarbodiimides, reacted with a second thio(seleno)acid molecule. Crossover experiments and the use of *O,O*-diethyl phosphorothioate containing ^{35}S-labeled sulfur showed that the adducts (B) are in equilibrium with their unstable isomers (A), the latter being active phosphorylating agents. The formation of the final reaction products was rationalized in terms of the three-directional attack of the thioacid anion at the phosphorus, alkoxy carbon, and central carbon atoms of the protonated adduct (A).

Introduction

Carbodiimides have found a wide application in nucleic acid chemistry as effective condensing agents.[3,4] Therefore, the mechanism of their reaction with various types of phosphorus acids attracted considerable attention. The reaction of dialkyl phosphates with dicyclohexylcarbodiimide (DCC) has been known since 1953 when they were shown by Khorana and Todd[5] to give tetraalkyl pyrophosphates and dicyclohexylurea (DCU). The formation of products was explained by Khorana and Todd by assuming the two-step mechanism involving *O*-phosphorylisourea as an intermediate. Similar reaction between DCC and monothiophosphonic and monothiophosphinic acids was found[6] to give dicyclohexylthiourea (DCTU) and the unsymmetrical monothiopyrophosphonates and monothiopyrophosphinates, respectively. In this case the addition of thioacid to DCC has been assumed to take place by attack of the sulfur atom leading to *S*-phosphorylisothiourea which reacts further with the second molecule of thioacid to give directly the unsymmetrical form of monothioanhydride (see Scheme I). Experiments with chiral *O*-ethyl ethanephosphonothioic acid were in agreement with the proposed reaction course.[6]

The limited literature data on the reaction of *O,O*-dialkyl phosphorothioates and phosphorodithioates with carbodiimides indicated that it proceeds much slower and in a complex way.[7,8,9]

Scheme I[a]



[a] X = O, S.

The differences in the reactivity of various types of phosphorus thioacids towards carbodiimides encouraged us to carry out more detailed studies of this reaction. It appeared that a careful examination of the reaction products, intermediates, and steps might provide some insight to the causes of this problem.

In a preliminary communication[10] we reported the first, direct detection by ^{31}P NMR spectroscopy of *S(Se)*-phosphorylisothio(seleno)ureas and their rearrangement to *N*-phosphorylthio(seleno)ureas. Herein we report the full results of our investigations on the mechanism of the reaction between carbodiimides and a wide range of

(1) We dedicate this work to Professor F. Cramer on the occasion of his 60th birthday.
(2) These results constitute a part of the Ph.D. Dissertation of P.K., Center of Molecular and Macromolecular Studies, Lodz, 1977.
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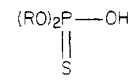
0022-3263/84/1949-0899$01.50/0

Table I. Yields and Proportions of the Products Formed in the Reaction of DCC with Phosphorothioic, $(RO)_2P(S)OH$ (1), Phosphorodithioic, $(RO)_2P(S)SH$ (2), and Phosphoroselenoic, $(RO)_2P(Se)OH$ (3), Acids

					proportions of phosphorus products, %			
entry	acid	R_1	solvent[a]	yield of thio-(seleno)-urea, %	thio-(seleno)-pyro-phosphate, >P(S)OP(O)<	thiolo-(selenolo)-ester, >P(O)SR	thiono-(selenono)-ester, >P(S)OR	yield of pyrophosphate after purification, %
1	1a	Me	PE	35[b]	0	80	20	
2	1a	Me	EE	40[b]	10	90	traces	
3	1a	Me	AN	75	70	30		
4	1b	Et	EE	77	97	3	traces	45
5	1b	Et	AN	86	98	2	traces	
6	1c	*i*-Pr	PE	48	100			30
7	1c	*i*-Pr	AN	83.5	100			
8	1g	Ph	EE	92	100			89
9	1h	$Me_2C(CH_2)_2$	AN	90	100			100
10	2b	Et	PE		25	75		
11	2b	Et	EE	92[c]	33	67		
12	2b	Et	AN	83	41	59		
13	3a	Et	EE	90	70	30	traces	
14	3a	Et	BZN	92	70	30	traces	
15	3a	Et	CHL	62	83	17	traces	
16	3b	*i*-Pr	EE	64	100			70
17	3b	*i*-Pr	AN	80	100			

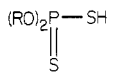
[a] PE, petroleum ether; EE, diethyl ether; AN, acetonitrile; BZN, benzene; CHL, chloroform. [b] Oily polymeric methyl metaphosphate separated, which contained partly dissolved dicyclohexylthiourea. [c] The ^{31}P NMR signals from 64 to 67 and 52 to 57 ppm were ascribed to the polymeric form of ethyl thiometaphosphate formed in this reaction.

phosphorothioic, phosphorodithioic, and phosphoroselenoic acids **1**, **2**, and **3**. Special attention was paid to the



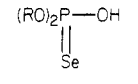
1

a, R = Me
b, R = Et
c, R = *i*-Pr
d, R = *t*-$BuCH_2$
e, R = *n*-Bu
f, R = *t*-Bu
g, R = Ph
h, R + R = $Me_2C(CH_2)_2$



2

a, R = Me
b, R = Et
c, R = *i*-Pr
d, R = *t*-$BuCH_2$
e, R = Ph



3

a, R = Et
b, R = *i*-Pr
c, R = *t*-$BuCH_2$

mechanism of phosphorylations involving *N*-phosphorylthio(seleno)ureas.

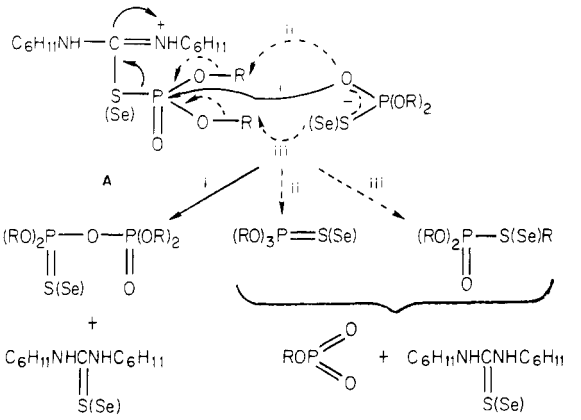
Results and Discussion

Reaction of Phosphorothioic (1), Phosphorodithioic (2), and Phosphoroselenoic (3) Acids with DCC in a Molar Ratio of 2:1. At first we investigated the reaction between DCC and a series of the title acids using 2 mol of the acid per 1 mol of DCC. Such a ratio of reactants is usually applied when acid anhydrides (pyrophosphates) are expected as products. It was found that the reactions of **1**, **2**, and **3** with DCC are very slow and lead to complex mixtures of products. After a fairly long reaction time (several days) the products were isolated and identified. The reaction of *O,O*-dimethyl phosphorothioate (**1a**) and DCC represents a typical example. It was found to give the following reaction products:

$$(MeO)_2P(S)OH + C_6H_{11}NCNC_6H_{11} \rightarrow \underset{\mathbf{1a}}{} (MeO)_2P(S)OP(O)(OMe)_2 + (MeO)_2P(O)SMe + (MeO)_3PS + (MeOPO_2)_n + C_6H_{11}NHC(S)NHC_6H_{11} \quad (1)$$

In addition to the expected unsymmetrical tetramethyl thiopyrophosphate and thiourea (DCTU), *O,O,S*-trimethyl phosphorothioate, *O,O,O*-trimethyl phosphorothioate, and a polymer of methyl metaphosphate were also formed. The latter compound, which is a sticky oil, could be isolated, since it separates from the solution during the reaction. Its ^{31}P NMR spectrum exhibited a series of signals in the region from −11 to −15 and from −28 to −32 ppm. The mass spectrum of this product contained the peaks corresponding to the monomer (*m/e* 94), dimer (*m/e* 188), and trimer (*m/e* 282) of methyl metaphosphate.

Scheme II



The experimental details obtained with this and other thio- and selenoacids are summarized in Table I, which also shows the solvent effect on the product proportions.

The multidirectional course of the reaction under discussion can be satisfactorily explained if one assumes that *S(Se)*-phosphorylisothio(seleno)urea (A) is formed as an intermediate (Scheme II). In the second reaction step another acid anion may react with this protonated intermediate in two ways: it either attacks the phosphorus atom (direction i), which leads to the formation of thio(seleno)pyrophosphate and dicyclohexylthio(seleno)urea, or it attacks the α-carbon atom of the alkoxy group. Attack by the oxygen atom (direction ii) leads to the formation of phosphorothion(selenon)ate and attack by the sulfur(selenium) atom (direction iii) results in phosphorothiol(selenol)ate. Both directions (ii) and (iii) also produce dicyclohexylthio(seleno)urea and very reactive metaphosphate, which under the reaction conditions undergoes cyclization and/or polymerization.

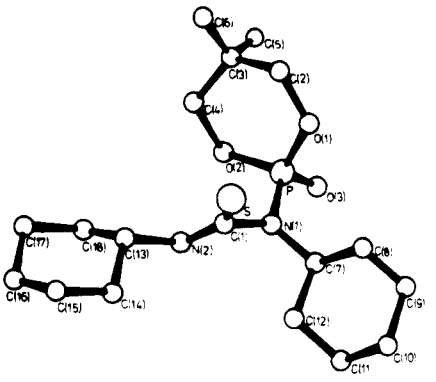


Figure 1. Three-dimensional view of *N,N'*-dicyclohexyl-*N*-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanyl)thiourea (**1h**-DCC-B).

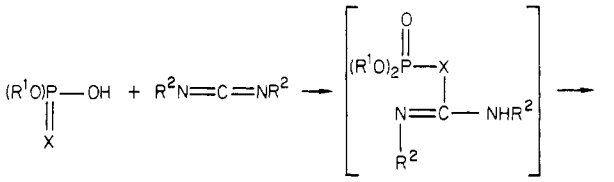
As expected, the relative amounts of thio(seleno)phosphate esters in the reaction products are higher in the case of lower alkyl groups, which are more susceptible to dealkylation. The predominant formation of the thiolo- or selenoloesters is easy to understand in the light of the HSAB concept.[11] Sulfur and selenium, being softer nucleophilic centers than oxygen, react preferentially with the soft sp^3 carbon atom. For the same reason dealkylation is much more pronounced with phosphoroselenoic acid than with phosphorothioic acid, since selenium as a nucleophilic center is softer than sulfur.[12]

An inspection of the results in Table I also reveals that the ratio of products markedly depends on the solvent used with the extent of dealkylation decreasing with increasing polarity of the solvent.

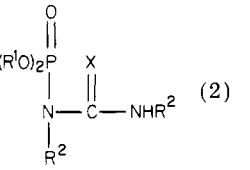
Finally, it should be noted that the reaction of DCC with phosphorus thio- and selenoacids containing alkyl groups which are difficult to dealkylate or cannot be dealkylated at all, gave mainly thio- and selenopyrophosphates (Table I, entry 6–9, 16, 17). However, also in such cases the reaction was occurring very slowly and products were often obtained in low yields. Moreover, the ^{31}P NMR spectra of the reaction mixture always revealed the presence of unreacted starting thio(seleno)acid and other phosphorus-containing compounds.

The observations on the reaction of DCC with the acids **1**, **2**, and **3**, which are in sharp contrast with a clean and smooth reaction of DCC with thiophosphonic and thiophosphinic acids[6] and their selenium analogues,[13] implied that the two reactions may proceed according to different mechanism. This prompted us to attempt isolation of the equimolar adducts of DCC and thio- and selenophosphoric acids having the structure of *S(Se)*-phosphorylisothio(seleno)ureas (A), which were proposed by us to be the key intermediates in these reactions.

Structure and Some Properties of Equimolar Adducts of Carbodiimides and Phosphorothioic (1), Phosphorodithioic (2), and Phosphoroselenoic (3) Acids. In order to obtain the desired 1:1 adducts it was necessary to use equimolar amounts of the reagents and to stop the second reaction step, i.e., to prevent the attack of an acid anion at the phosphoryl center or at the alkoxy carbon atom in the adduct formed. With this in mind in our preliminary experiments we treated DCC in ether at room temperature with an equimolar amount of the sterically hindered acids **1d**, **1f**, and **3c**. In accord with our expectations, the reaction afforded the corresponding 1:1 adducts, as evidenced by elemental analysis and mass spectra. However, spectroscopic study[14] of the adducts isolated revealed that they are not the expected *S(Se)*-phosphoryldicyclohexylisothio(seleno)ureas (A) but they have the isomeric structure of *N*-phosphoryldicyclohexylthio(seleno)ureas (B).[15]



(A)



(2)

(B)

Moreover, it turned out that the formation of *N*-phosphorylthio(seleno)ureas (B) was not limited to the sterically hindered acids, but constituted a general feature of the reaction of thio- and selenoacids **1**, **2**, and **3** with various carbodiimides listed below:

$$R^2\text{–}N{=}C{=}N\text{–}R^2$$

R^2 = *c*-C_6H_{11} (DCC); R^2 = *p*-MeO-C_6H_4 (DMPhC); R^2 = $C_6H_5CH_2$ (DBC); R^2 = *i*-Pr (DiPC); R^2 = *p*-ClC_6H_4 (DCPhC); R^2 = *n*-Bu (DnBC)

The exception was the reaction with di-*tert*-butylcarbodiimide (DtBC), which did not give the corresponding adducts B. It resulted in a slow formation of thio(seleno)pyrophosphates and di-*tert*-butylthio(seleno)urea.

Some physical and spectral properties of the adducts B prepared in the course of this work are collected in Tables II and 2a.[16]

With regard to the spectroscopic data presented in Table II, the coupling constants between phosphorus and protons at C_1 of the thio(seleno)urea moiety ($^3J_{P-H}$) deserve special attention. Thus, for the adducts of thio- and selenoacids with DCC and DiPC the $^3J_{P-H}$ values are extraordinarily high, in the range between 20.5 and 25.4 Hz (Table II entries 1–7, 10, 11, and 26–28), whereas for the adducts with other carbodiimides they remain close to a normal $^3J_{P-H}$ value, i.e., from 9.5 to 10 Hz (entries 12–17, 20, and 21). In the case of the adducts derived from phosphorodithioic acids the above mentioned differences are not so distinct (17.5 and 15.3 Hz, entries 8 and 9, vs. 13.5 and 12.7 Hz, entries 19 and 31).

Since we suspected that the differences observed may be due to steric effect, we performed a comparative X-ray analysis[17] of the adducts obtained from DCC and DBC and

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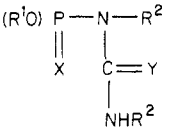
(13) Nuretdinov, A.; Bayandina, E. V.; Sadkova, D. N. *Dokl. Akad. Nauk SSSR.* **1978**, *239*, 1110.
(14) The IR and ^{31}P NMR spectra of the adducts obtained are discussed in detail in our preliminary communication.[10]
(15) For an X-ray analysis of *N*-diphenoxyphosphoryl-*N,N'*-dibenzylthiourea obtained in this way see: Karolak-Wojciechowska, J.; Wieczorek, M.; Mikołajczyk, M.; Kiełbasiński, P.; Struchkov, Y. T.; Antipin, M. Y. *Acta Crystallogr., Sect. B* **1979**, *B-25*, 877.
(16) See paragraph at the end of paper about supplementary material.
(17) For full experimental X-ray data see: Karolak-Wojciechowska, J.; Wieczorek, M. W.; Struchkov, Y. T.; Antipin, M. Y.; Mikołajczyk, M.; Kiełbasiński, P.; Sut, A. *Phosphorus Sulfur*, in press.

Table II. Some Physical and Spectral Properties of *N*-Phosphorylthio(seleno)ureas (B)

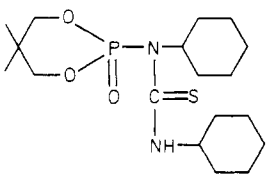


B

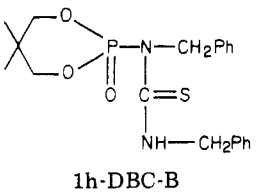
entry	adduct symbol	R^1	R^2	X	Y	mp, °C	^{31}P NMR data: δ ($CDCl_3$, H_3PO_4)	^{31}P NMR data: J_{P-N-CH}, Hz
1	1a-DCC-B	Me	*c*-C_6H_{11}	O	S	87-92	5.5	
2	1b-DCC-B	Et	*c*-C_6H_{11}	O	S	67-70	2.5	22
3	1c-DCC-B	*i*-Pr	*c*-C_6H_{11}	O	S	66-70	0	23
4	1d-DCC-B	neopentyl	*c*-C_6H_{11}	O	S	88-93	3.5	21
5	1f-DCC-B	*t*-Bu	*c*-C_6H_{11}	O	S	oil	−7.6	21
6	1g-DCC-B	Ph	*c*-C_6H_{11}	O	S	88-92	−7.1	25.4
7	1h-DCC-B	$Me_2C(CH_2)_2$	*c*-C_6H_{11}	O	S	128-131	−2.6	
8	2b-DCC-B	Et	*c*-C_6H_{11}	S	S	sticky solid	67.4	17.5
9	2d-DCC-B	neopentyl	*c*-C_6H_{11}	S	S	sticky solid	68.6	15.3
10	3b-DCC-B	*i*-Pr	*c*-C_6H_{11}	O	Se	oil	−2.2	23
11	3c-DCC-B	neopentyl	*c*-C_6H_{11}	O	Se	97-103	1.9	22.9
12	1a-DBC-B	Me	CH_2Ph	O	S	83-84	6.8	9.8[c]
13	1b-DBC-B	Et	CH_2Ph	O	S	30-34	3.6	10
14	1f-DBC-B	*t*-Bu	CH_2Ph	O	S	97-98	−9.5	9[b]
15	1g-DBC-B	Ph	CH_2Ph	O	S	87-89	−8.8	9.5[b]
16	1h-DBC-B	$Me_2C(CH_2)_2$	CH_2Ph	O	S	94-96	1.34	9.8[b]
17	2a-DBC-B	Me	CH_2Ph	S	S	99-103	73	13.3[c]
18	2c-DBC-B	*i*-Pr	CH_2Ph	S	S	oil	66.7	
19	2d-DBC-B	neopentyl	CH_2Ph	S	S	60-62	70	13.5[b]
20	3b-DBC-B	*i*-Pr	CH_2Ph	O	Se	oil	0.2	10
21	3c-DBC-B	neopentyl	CH_2Ph	O	Se	63-68	3.1	9.8
22	1b-DCPhC-B	Et	*p*-Cl-C_6H_4	O	S	75-80	−1	
23	2a-DCPhC-B	Me	*p*-Cl-C_6H_4	S	S	81-83	65	
24	3c-DCPhC-B	neopentyl	*p*-Cl-C_6H_4	O	Se	128-130	1.8	
25	1b-DMPhC-B	Et	*p*-MeO-C_6H_4	O	S		0.2	
26	1b-DiPC-B	Et	*i*-Pr	O	S		2.4[a]	20.5
27	1d-DiPC-B	neopentyl	*i*-Pr	O	S	64-65	2.5[a]	21
28	3c-DiPC-B	neopentyl	*i*-Pr	O	Se		1.3[a]	21.5
29	1b-DnBC-B	Et	*n*-Bu	O	S	sticky solid	4.3	
30	1g-DnBC-B	Ph	*n*-Bu	O	S		−5.5	9.5
31	2e-DnBC-B	Ph	*n*-Bu	S	S		60.6	12.7

[a] In ether. [b] Taken as an average from ^{31}P and ^{1}H NMR spectra. [c] From ^{1}H NMR spectra.

5,5-dimethyl-2-oxo-2-mercapto-1,3,2-dioxaphosphorinane (**1h**).



1h-DCC-B



1h-DBC-B

Three-dimensional views of both adducts are shown in Figures 1 and 2. These diagrams as well as comparison of the structural parameters, indicate that the conformations of the adducts **1h**-DCC-B and **1h**-DBC-B are entirely different in the solid state. The thiourea moiety in **1h**-DBC-B (Figure 2) is planar. The sulfur and phosphorus atoms in this adduct adopt nearly antiperiplanar arrangement around the C(1)–N(1) bond with the torsional angle equal to 159.0 (3) Å. Moreover, the molecule of **1h**-DBC-B is stabilized by an intramolecular N–H···O=P hydrogen bond. On the contrary, in **1h**-DCC-B there are two intermolecular hydrogen bonds (N–H···O=P) which lead to the formation of dimeric crystal structures. This adduct (Figure 1) has a nonplanar thiourea skeleton, the sulfur and phosphorus atoms are closer to each other (the nonbonding distance is equal to 3.73 Å), and in the most favored anticlinal conformation of the *N*-phosphorylthiourea moiety the torsional angle P–N(1)–C(1)–S is 91° (1).

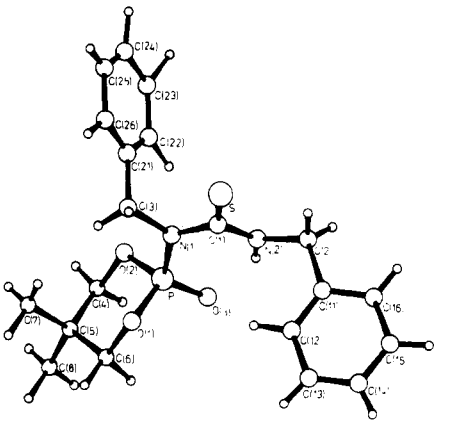


Figure 2. Three-dimensional view of *N*,*N*′-dibenzyl-*N*-(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanyl)thiourea (**1h**-DBC-B).

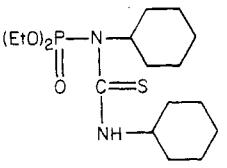
Furthermore, in the adduct derived from DCC the rotation around the C(7)–N(1) bond is restricted by the interaction between H(8) and H(12) and the phosphoryl oxygen atom, and in the most favored conformation the dihedral angle H(7)–C(7)–N(1)–P is 38° (1). Consequently, a high coupling constant $^3J_{PNCH}$ is observed, as predicted by the Karplus equation. In this context, it is interesting to note that in the adduct obtained from DBC there are two dihedral angles, H(5)–C(3)–N(1)–P of 8.7° (3) and H(4)–C(3)–N(1)–P of 125.2° (4), and free rotation around the

Table III. ^{31}P NMR Data of the Unstable Intermediates of the Reaction of Carbodiimides with Some Selected Phosphorus Acids

			salt ^{31}P NMR		isourea (C)/isothio(seleno)urea (A) ^{31}P NMR		
entry	acid	carbodiimide	δ	$J_{^{31}P-^{77}Se}$, Hz	symbol	δ	$J_{^{31}P-^{77}Se}$, Hz
1	1c	DCC	55.3		1c-DCC-A	14.8 (14.2)	
2	1g	DCC	44		1g-DCC-A	9.4 (7)	
3	2b	DCC	110.1		2b-DCC-A	84.8 (79.1)	
4	3b	DCC	48.5	789	3b-DCC-A	10.3 (8.1)	410
5	3c	DCC	49.6	790	3c-DCC-A	12.9 (9.2)	429.7
6	1f	DBC	38.4		1f-DBC-A	8.8	
7	3b	DBC	broad band		3b-DBC-A	13.6	464.8
8	3c	DCPhC			3c-DCPhC-A	17.8	480.4
9	1d	DiPC	56, br		1d-DiPC-A	11.1 (12.3 br)	
10	3c	DiPC	53.3	785	3c-DiPC-A	14.8 (12.2)	420
11	6a	DCC	−2.7		6a-DCC-C	−10.1 (−10.9)	
12	6b	DCC	−12.6		6b-DCC-C	−20.7 (−21.6)	
13	6c	DCC	−3.5		6c-DCC-C	−10.2	

C(3)–N(1) bond can take place.

As the solid state and solution conformations may be different, we determined the value of $^3J_{P-H}$ in the adduct **1b**-DCC-B in various solvents. It was found to be practically constant and solvent independent. This observation strongly suggests that the most stable solid state and solution conformations are the same.

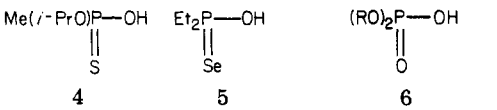


1b-DCC-B

$^3J_{PH}$ = 22.0 (ether), 21.7 (benzene), 22.0 (nitromethane), 21.7 Hz (acetonitrile)

The Low-Temperature ^{31}P NMR Study of the Reaction of Phosphorothioic (1), Phosphorodithioic (2), and Phosphoroselenoic (3) Acids with Carbodiimides. The most reasonable hypothesis that *N*-phosphorylthio(seleno)ureas (B) result from the initially formed, unstable *S*-phosphorylisothio(seleno)ureas (A) by the migration of the phosphoryl group from sulfur or selenium to nitrogen was confirmed by the low-temperature ^{31}P NMR study. The course and ^{31}P NMR spectra of the reaction of *O,O*-diisopropyl phosphoroselenonate (**3b**) with DCC were discussed in detail in our preliminary communication.[10] This reaction was shown to involve the formation of the salt of **3b** with DCC and then *Se*-(diisopropylphosphoryl)-*N,N'*-dicyclohexylisoselenourea (**3b**-DCC-A) as unstable reaction intermediates. Under similar conditions the unstable intermediates were observed using other thio- and selenoacids and carbodiimides.[18] Their spectral properties are given in Table III. It should be pointed out that in some cases small peaks (given in Table III in parantheses) are seen at low temperature in the region characteristic of the adducts A which may be taken as evidence for the *E–Z* isomerism around the C=N— bond in A.

The successful ^{31}P NMR detection of the primary intermediate adducts A formed by the acids **1**, **2**, and **3** with carbodiimides[19] prompted us to extend these studies to *O*-isopropyl methanephosphonothioate (**4**), diethylphosphinoselenoic acid (**5**), and dialkyl phosphates (**6**).

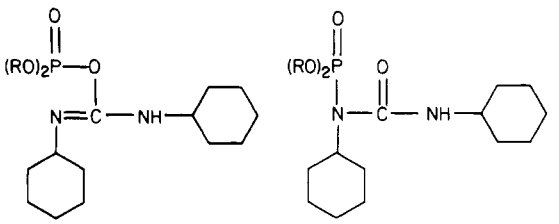


4 5 6

a, R = Et
b, R = Ph
c, R = *t*-BuCH$_2$

In the case of acids **4** and **5** with DCC we were not able to observe in the ^{31}P NMR spectra the formation of the 1:1 adducts of structure A. Immediately after mixing both reaction components in a 1:1 ratio at −78 °C the spectra showed the signals of the final reaction products only, i.e., *O,O*-diisopropyl methylthiopyrophosphonate and tetraethylselenopyrophosphinate, respectively.

The ^{31}P NMR spectra of the mixtures of phosphoric acids (**6**) and DCC, however, clearly revealed in each case the formation at −78 °C of the two species. The first was the salt of **6** with DCC and the second the expected *O*-phosphorylisourea (C). However, in contrast to *S*-phosphorylisothioureas (A), the *O*-phosphorylisoureas (C) obtained from **6** did not rearrange in our hands to the corresponding *N*-phosphorylureas (D) but reacted further to form pyrophosphates. With regard to the question of the O→N phosphoryl migration in C, it should be noted that in some instances *N*-phosphorylureas (D) were obtained[19,20] in this way when sterically hindered phosphoric acids were used and the formation of pyrophosphates was difficult or impossible.



C D

The results presented above showed that there is a distinct difference in reactivity toward carbodiimides between the thio- and selenoacids of phosphorus containing

(18) The ^{31}P NMR investigation of the reaction between *O,O*-dineopentylphosphoroselenoic acid (**3c**) and di-(*p*-chlorophenyl)carbodiimide (DCPhC) was particularly interesting since it revealed that the intermediate *Se*-(dineopentylphosphoryl)-*N,N'*-di-(*p*-chlorophenyl)isoselenourea (**3c**-DCPhC-A), which appeared in the ^{31}P NMR spectrum at 17.5 ppm ($^1J_{^{31}P-^{77}Se}$ = 480.4 Hz), is relatively stable. Its rearrangement to the corresponding *N*-phosphorylselenourea **3c**-DCPhC-B was observed to start at 0 °C and was complete at room temperature after ca. 1.5 h.

(19) Recently Perie et al. succeeded in the isolation of *S*-(thiophosphoryl)-*N,N'*-dicyclohexylisothiourea HBF_4 salt: Blonski, C.; Gasc, M-B., Klaebe, A.; Perie, J-J.; Roques, R.; Declercq, J. P.; Germain, G. *J. Chem. Soc. Perkin Trans. 2* **1982**, 7.

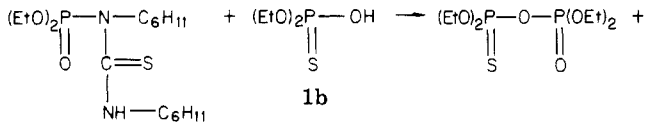
(20) Zarytova, V. F.; Ivanova, E. M.; Lebedev, A. V. *Bioorgan. Khim.* **1976**, *2*, 189.

one or two C–P bonds on the one hand and dialkyl phosphates and their sulfur and selenium analogues on the other.

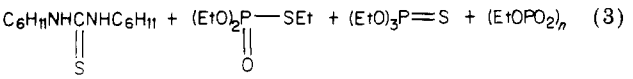
The failure to observe in the ^{31}P NMR spectra the primary adducts **4**-DCC-A and **5**-DCC-A (and their isomers **4**-DCC-B and **5**-DCC-B) strongly supports the view that they are formed in a rate-determining step of the reaction and react very rapidly with a second molecule of **4** or **5** present in the reaction mixture. At least two factors may be considered to be responsible for a high rate of the second reaction step. One is a higher electrophilicity of the phosphonyl or phosphinyl center as compared with a phosphoryl one.[21] Secondly, the migration of the phosphonyl or phosphinyl group from sulfur to nitrogen seems to be much slower than that of the phosphoryl group.[22,23] In consequence, neither *S*(*Se*)-phosphonyl(phosphinyl)-isothio(seleno)ureas can be observed nor N-phosphonyl-(phosphinyl)thio(seleno)ureas formed.

It is also difficult to explain precisely the lack or a very weak tendency of *O*-phosphorylisoureas (C) to undergo the 1,3-shift to *N*-phosphorylureas (D), which is in a sharp contrast with the behavior of the closely related *S*-phosphorylisothioureas (A). In our opinion, these differences may be rationalized if one takes into account the energy of the bonds which should be broken and formed in the course of the rearrangement. Since the bond energy order is[24] P–O ≥ P–N > P–S, the migration of the phosphoryl group from sulfur to nitrogen in A is energetically favorable whereas in C there is no such a driving force for the O→N phosphoryl shift.

The Mechanism of Phosphorylation by means of *N*-Phosphorylthio(seleno)ureas (B). The isolation of *N*-phosphorylthio(seleno)ureas (B) from the mixtures of equimolar amounts of carbodiimides and acids **1**, **2**, and **3** poses the question of their participation in the formation of the final reaction products, i.e., thio(seleno)pyrophosphates, thio(seleno)phosphoric acid esters, and thio(seleno)ureas. With this in mind we carried out the reaction between *N*-(diethoxyphosphoryl)-*N*,*N*′-dicyclohexylthiourea (**1b**-DCC-B) and diethyl phosphorothionate (**1b**) and found that it gave the same products as obtained from the reaction of DCC and thioacid **1b** used in a molar ratio 1:2 (see Table I, entry 4 and 5). Moreover, the fact



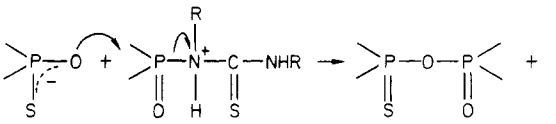
1b-DCC-B



(3)

that the adduct **1b**-DCC-B was formed immediately and then gradually disappeared (^{31}P NMR assay) during the latter reaction demonstrates unequivocally that it is the key reaction intermediate. Similar results were obtained when thio(seleno)acids were reacted with *N*-phosphoryl-*N*,*N*′-diisopropylthio(seleno)ureas. However, we have found that *N*-phosphorylthio(seleno)ureas prepared from *N*,*N*′-dibenzylcarbodiimide (DBC) and *N*,*N*′-diarylcarbodiimides (DCPhC, DMPhC) do not react with the corresponding thio- or selenoacid. These observations prompted us to elucidate more exactly the mechanism of phosphorylation of the thio(seleno)acids **1**, **2**, and **3** by means of *N*-phosphorylthio(seleno)ureas (B) derived from DCC and DiPC.

The most simple mechanism which can account for the thioanhydride formation, is shown below. However, such



$(RNH)_2CS$ (4)

a possibility was ruled out by the crossover experiments in which *N*-phosphoryl-*N*,*N*′-dicyclohexylthioureas (B) were treated with phosphorothioic acids having different substituents at phosphorus. Thus, when equimolar amounts of *N*-(diisopropoxyphosphoryl)-*N*,*N*′-dicyclohexylthiourea (**1c**-DCC-B) and *O*,*O*-diethyl phosphorothioic acid (**1b**) were mixed in ether at room temperature, the ^{31}P NMR spectrum revealed, apart from the substrates, the presence of *O*,*O*-diisopropyl phosphorothionate (**1c**), *N*-diethoxyphosphoryl-*N*,*N*′-dicyclohexylthiourea (**1c**-DCC-B), and a mixture of thiopyrophosphates (for the sake of simplicity we shall neglect in our further discussion the other products formed in this reaction). An almost identical mixture of products was formed when the adduct **1b**-DCC-B was reacted with the thioacid **1c**. The presence of the two acids **1b** and **1c** as well as two adducts **1b**-DCC-B and **1c**-DCC-B in the reaction mixture should lead to the formation of four possible thiopyrophosphates. This was proved indeed by GLC of the reaction mixture which was kept at room temperature for 27 days.

Basically the same, but somewhat different results were obtained from another set of the crossover reactions in which *N*-(diphenoxyphosphoryl)-*N*,*N*′-dicyclohexylthiourea (**1g**-DCC-B) was treated with *O*,*O*-diethyl phosphorothionate (**1b**) and *N*-(diethoxyphosphoryl)-*N*,*N*′-dicyclohexylthiourea (**1b**-DCC-B) was reacted with *O*,*O*-diphenyl phosphorothionate (**1g**). In both cases *O*,*O*-diphenyl phosphorothionate (**1g**) was detected in the reaction mixture in a much larger amount than *O*,*O*-diethyl phosphorothionate (**1b**). As a consequence, the thiopyrophosphate containing the diphenoxythiophosphoryl and diethoxyphosphoryl groups was formed (direction a in Scheme III) as a predominant product. The formation of other possible thiopyrophosphates (directions b, c, and d in Scheme III) was observed to occur to small extent. Additionally, *N*-(diphenoxyphosphoryl)-*N*,*N*′-dicyclohexylthiourea (**1g**-DCC-B) was subjected to the reaction with *O*,*O*-diethyl phosphorothionate (**1b**) containing sulfur labeled with ^{35}S isotope. After 14 days the precipitated dicyclohexylthiourea (DCTU) was isolated and it was found to contain 91% of the labeled sulfur used in the experiment.

The results of the crossover experiments discussed above indicate that an equilibrium must exist between the adducts B and thioacids. The most reasonable mechanistic interpretation of this process is based upon the assumption that the rearrangement of *S*-phosphoryl-*N*,*N*′-dicyclohexylisothioureas (A) to *N*-phosphoryl-*N*,*N*′-dicyclo-

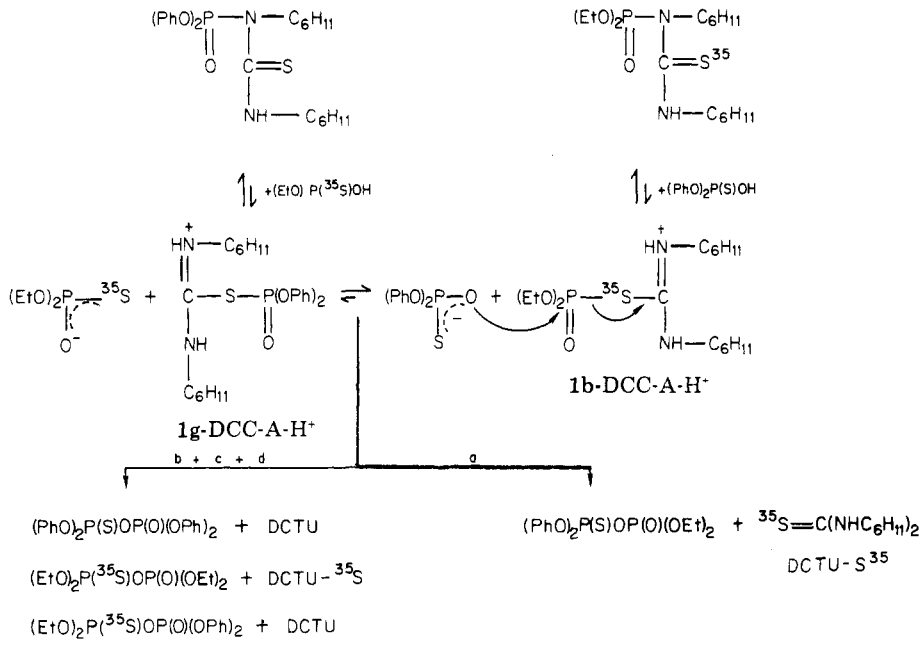
(21) Cox, J. R.; Ramsay, O. B. *Chem. Rev.* **1964**, *64*, 325.

(22) Chupp and Leschinsky have investigated a similar rearrangement taking place during the reaction of phosphorus thioacids with isonitriles and have found that *S*-phosphoryl adducts rearrange to N-phosphoryl isomers faster than *S*-phosphonyl analogues, while S-phosphinyl adducts do not rearrange to *N*-phosphinyl isomers even at elevated temperature.[23] The results of our studies on the stereochemistry and mechanism of the S→N phosphoryl group migration in *S*-phosphorylisothioureas (**A**) will be published elsewhere. For a preliminary account see: Kiełbasiński, P.; Sut, A.; Mikołajczyk, M. 9th International Symposium on Organic Sulfur Chemistry, Riga, 1980; Abstract A 144, p 182. Karolak-Wojciechowska, J.; Wieczorek, M. W.; Mikołajczyk, M.; Sut, A.; Kiełbasiński, P.; Struchkov, Y. T.; Antipin, M. Y. *Acta Crystallogr., Sect. C* **1983**, *C39*, 587.

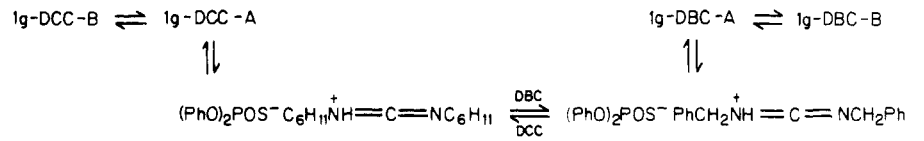
(23) Chupp, J. P.; Leschinsky, K. L. *J. Org. Chem.* **1975**, *40*, 66.

(24) Hudson, R. F. "Structure and Mechanism in Organo-phosphorus Chemistry"; Academic Press: London and New York, 1965.

Scheme III



Scheme IV



hexylthioureas (B) is a reversible reaction and that the exchange of the phosphoryl group is realized via the exchange of the whole thioacid anion in the adducts A. The fact that there is no spectral evidence for the presence of *S*-phosphoryl isomers A in the isolated *N*-phosphoryl adducts B suggests that either the equilibrium A⇌B is shifted very strongly to the right or the reverse reaction only takes place in the presence of an acidic catalyst.

By making these assumptions the results of the crossover experiments become more comprehensible and a satisfactory explanation for the rather curious transfer of the radioactive sulfur from **1b** to DCTU is depicted in Scheme III and briefly interpreted below.

It is believed that the protonated *N*-phosphoryl adduct **1g**-DCC-B is converted at first into its isomeric *S*-phosphoryl form **1g**-DCC-A. Then, the nucleophilic attack of the anion of *O,O*-diethyl phosphorothionate-S^{35} (**1b**) at the central carbon atom of **1g**-DCC-A leads to the anion of *O,O*-diphenyl phosphorothionate (**1g**) and *S*-phosphoryl adduct **1b**-DCC-A containing radioactive sulfur. The latter adduct (or its stable *N*-phosphoryl isomer **1b**-DCC-B) may react with the liberated anion of the thioacid **1g** giving the corresponding nonradioactive thiopyrophosphate and dicyclohexylthiourea, DCTU, containing the labeled sulfur (direction a). Since this reaction pathway is prevailing and the other three directions b, c, and d have a small contribution to the total reaction, the high content of ^{35}S in the isolated DCTU is obvious. Moreover, the fact that the labeled sulfur is present in DCTU proves unambigously that the whole thioacid anion is exchanged during the reaction.

It must be stressed, however, that although the anion exchange may be considered to proceed as shown in Scheme III, there is another possibility to achieve this. This possibility is connected with the fact that the formation of *S*-phosphorylisothiourea (A) from dicyclohexylcarbodiimide and thioacid is a reversible step.[25] The latter conclusion is based on the following experimental observation. When *N*-(diphenylphosphoryl)-*N,N'*-dicyclohexylthiourea (**1g**-DCC-B) was mixed in ether with dibenzylcarbodiimide (DBC) in a 1:1 ratio, *N*-(diphenylphosphoryl)-*N,N'*-dibenzylthiourea (**1g**-DBC-B) was exclusively formed after several days as evidenced by ^{31}P NMR. It was also isolated from the reaction mixture.

This result indicates that an equilibrium should exist not only between *N*-phosphoryl-*N,N'*-dicyclohexylthiourea (B) and *S*-phosphoryl-*N,N'*-dicyclohexylisothiourea (A) (even in the absence of acid) but also between *S*-phosphoryl-*N,N'*-dicyclohexylisothiourea and the salt of DCC with a thioacid, which makes the exchange of both the thioacid anion and carbodiimide in the adduct A possible. Furthermore, the exclusive formation of the adduct **1g**-DBC-B strongly suggests that the rearrangement of *S*-phosphoryl-*N,N'*-dibenzylisothiourea (**1g**-DBC-A) to *N*-phosphoryl-*N,N'*-dibenzylthiourea (**1g**-DBC-B) is, under the reaction conditions applied, an irreversible process. Scheme IV shows in detail how the conversion of **1g**-DCC-B into **1g**-DBC-B may occur.

In this context, we would like to note that the different chemical properties of *N*-phosphoryl-*N,N'*-dicyclohexyl- and *N*-phosphoryl-*N,N'*-dibenzylthioureas mentioned above are due to their different conformations which are shown in Figures 1 and 2. In our opinion, an anticlinal conformation of the *N*-phosphorylthiourea moiety in *N*-phosphoryl-*N,N'*-dicyclohexylthioureas with a short nonbonding S···P distance (comparable with the sum of the van der Waals radii for P and S, 3.75 Å) can be responsible for their very easy reverse rearrangement to *S*-phosphoryl-*N,N'*-dicyclohexylisothioureas which function,

(25) Chupp and Leschinsky observed a similar reversibility at the stage of formation of S-phosphoryl adducts from an isonitrile and a thioacid.[23]

in fact, as active phosphorylating agents.[26] In the case of *N*-phosphoryl-*N,N'*-dibenzylthioureas, which adopt antiperiplanar conformation, there are no proper spatial conditions for the rearrangement to *S*-phosphoryl isomers and, therefore, they are unreactive towards thio- and selenoacids.

However, there are some experimental observations which indicate that the equilibrium A⇌B is not the only factor responsible for the thioanhydride formation. Thus, for example the reaction of di-(*p*-chlorophenyl)carbodiimide (DCPhC) with 2 mol of *O,O*-dineopentyl phosphoroselenoate (**3c**) does not afford the corresponding selenopyrophosphate, though *Se*-phosphorylisoselenourea **3c**-DCPhC-A undergoes very slow isomerization to *N*-phosphoryl isomer **3c**-DCPhC-B and is present in the reaction mixture at room temperature together with an excess of the free acid **3b**. One can assume that in this case the nitrogen atoms of the adduct **3c**-DCPhC-A are too weakly basic to be protonated which is a prerequisite of the thio(seleno)pyrophosphate formation (see Scheme II and III). In conclusion, *N*-phosphorylthio(seleno)ureas can react with phosphorothio(seleno)ic acids at a reasonable rate to form the corresponding thiopyrophosphates when two conditions are simultaneously fulfilled: (a) The nitrogen atoms should bear bulky substituents which force a special geometry of the adducts facilitating their reverse rearrangement to *S*-phosphorylisothio(seleno)ureas. (b) The nitrogen atoms must be sufficiently basic to be protonated by phosphorothio(seleno)ic acid which allows the final phosphorylation reaction to proceed.

Conclusions

The results presented above allow the formulation of the mechanistic details of the reaction under discussion. This mechanism consists of the following principal steps. In the first step the thio(seleno)acid anion attacks the protonated carbodiimide molecule producing an adduct (A) having the structure of *S(Se)*-phosphorylisothio(seleno)-urea. The latter undergoes isomerization (S(Se)→N phosphoryl 1,3-shift) to the stable and isolable *N*-phosphorylthio(seleno)urea (B). In the case of DCC and DiPC all the above-mentioned three-step reactions are reversible. The formation of adducts (B) is most probably irreversible when diarylcarbodiimides and DBC are used for the reaction.

S(Se)-Phosphorylisothio(seleno)ureas (A) derived from DCC and DiPC are active phosphorylating agents which are able to react with the second molecule of the thio-(seleno)acid. Thus, the reaction of the protonated adduct (A) with the thio(seleno)acid anion leading to the final reaction products may occur in two ways as shown in Scheme II: Nucleophilic O attack of the thio(seleno)acid anion at phosphorus leads to the formation of thio(seleno)pyrophosphate and thio(seleno)urea; on the other hand, nucleophilic S(Se) and/or O attack of the thio(seleno)acid anion at the carbon atom of the alkoxy group results in a mixture of isomeric thio(seleno)phosphates, thiourea, and alkoxymetaphosphate. Additionally, the nucleophilic S attack of the thio(seleno)acid anion at the central carbon atom of the protonated adduct (A) causes the anion exchange, which can be experimentally observed when the adduct (A) and thio(seleno)acid have different substituents at phosphorus. In such a case one observes the fast formation of two adducts (A) and two thio(seleno)acids and consequently the formation of four different thiopyrophosphates.

The phosphorylating properties of *S(Se)*-phosphoryl-isothio(seleno)ureas strongly depend on their conformation and to some extent on the basicity of the nitrogen atom.

Experimental Section

^{1}H NMR spectra were measured with a Perkin-Elmer R-12 and ^{31}P NMR spectra with a FT Jeol FX-60 instrument. Mass spectra were recorded with a LKB 2091 mass spectrometer. Melting and boiling points are uncorrected.

Phosphorothioic acids (**1a–h**) and phosphoroselenoic acids (**3b,c**) were synthesized from the corresponding dialkyl(aryl) phosphites and sulfur or selenium, respectively, according to general methods.[27] Phosphorodithioic acids (**2a–c,e**) were obtained from P_4S_{10} and the corresponding alcohols.[27] *O,O*-dineopentyl phosphorothioic acid (**1d**) was synthesized according to the method of Michalski et al.[28]

***O,O*-Dineopentyl Phosphorodithioate (2d).** To a stirred solution of *O,O*-dineopentyl thiophosphite (6 g, 0.026 mol) in benzene (25 mL was added sulfur (1 g, 0.031 mol). Then, triethylamine (2.6 g, 0.026 mol) was added dropwise at room temperature. After 2 h benzene was evaporated and the residue was crystallized from hexane to give a triethylammonium salt of the acid **2d** (8.5 g, 92.5%): mp 108–110 °C. Anal. Calcd for $C_{16}H_{38}NO_2PS_2$: C, 51.75; H, 10.24; P, 8.36; N, 3.77. Found: C, 52.20; H, 10.39; P, 8.50; N, 3.66. This salt was dissolved in water and acidified with a diluted solution of HCl. The free acid was extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness to give pure **2d** as a low melting solid in a quantitative yield: ^{31}P NMR δ ($CHCl_3$, H_3PO_4) 85 ppm. Anal. Calcd for $C_{10}H_{23}O_2PS_2$: C, 44.44; H, 8.52; P, 11.48. Found: C, 44.69; H, 8.60; P, 11.82.

***O,O*-Dineopentyl Phosphoroselenonate (3c).** Dineopentyl phosphite[28] (9.3 g, 0.042 mol), selenium (3.9 g, 0.049 mol), and triethylamine (4.45 g, 0.044 mol) were stirred in benzene (40 mL) at room temperature for three days. The unreacted selenium was filtered off and benzene was evaporated. The residue was crystallized from petroleum ether to yield 12.2 g (68%) of a triethylammonium salt of the acid **3c**: mp 98–102 °C. Anal. Calcd for $C_{16}H_{38}NO_3PSe$: C, 47.76; H, 9.45; N, 3.48; P, 7.71. Found: C, 48.14; H, 9.56; N, 3.51; P, 7.93.

The salt was dissolved in water and acidified with a diluted solution of HCl. The free acid was extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness to give pure **3d** in a quantitative yield: mp 65–67 °C; ^{31}P NMR δ (CCl_4, H_3PO_4) 61, $J_{^{31}P-^{77}Se}$ = 910 Hz. Anal. Calcd for $C_{10}H_{23}O_3PSe$: C, 39.87; H, 7.64; P, 10.30. Found: C, 40.25; H, 7.68; P, 10.60.

Reactions of DCC with Acids 1, 2, and 3 in a Molar Ratio of 1:2. DCC and 1a. To a solution of DCC (4.2 g, 0.0211 mol) in petroleum ether (20 mL) was added a solution of **1a** (6 g, 0.0422 mol) in ether (20 mL) and petroleum ether (20 mL) and the mixture was left for several days at room temperature. DCTU was filtered off (1.8 g, 35%). An insoluble oily polymeric methyl metaphosphate (contaminated with DCTU) was separated from the filtrate and examined by ^{31}P NMR and mass spectroscopy. The filtrate was washed with a 2% solution of $NaHCO_3$, dried, and after evaporation of the solvents, distilled. A fraction boiling at 68–75 °C (3 Torr) was obtained (1.3 g), which was found by

(26) The view that active phosphorylating agent reacting in the final reaction step with the second thio- and seleacid molecule is *S(Se)*-phosphorylisothio(seleno)urea (A) was indirectly supported by comparing the reaction course of equimolar amounts of *O,O*-dimethylphosphorothioic acid (**1a**) with DCC at −80 °C and at room temperature. At low temperature *N*-dimethylphosphoryl-*N,N'*-dicyclohexylthiourea (**1a**-DCC-B) was formed with some amounts of tetramethyl thiopyrophosphate, whereas at room temperature the yield of the adduct **1a**-DCC-B was quantitative. Most probably at low temperature when the isomerization of the primary *S*-phosphorylisothiourea **1a**-DCC-A is slow, it reacts directly with the thioacid **1a** giving the corresponding thiopyrophosphate. At a higher temperature, when the isomerization is very fast, the direct reaction between **1a** and the adduct **1a**-DCC-B does not take place.

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means of ^{31}P NMR and GLC to contain 80% of trimethyl phosphorothiolate and 20% of trimethyl phosphorothionate. The reaction of **1a** with DCC was similarly performed in ether and acetonitrile. The results are collected in Table I.

DCC and 1b. A solution of **1b** (5 g, 0.029 mol) in ether (30 mL) was added to a solution of DCC (3 g, 0.0146 mol) in ether (30 mL) and the mixture was left for ten days. The precipitated DCTU was filtered off (2.7 g, 77%). On the basis of ^{31}P NMR and TLC (benzene–chloroform–acetone 4:2:1) the filtrate was found to contain tetraethyl thiopyrophosphate and traces of triethyl phosphorothionate (R_f 0.64) and triethyl phosphorothiolate (R_f 0.47). Distillation (90 °C, (0.1 Torr)) gave tetraethyl thiopyrophosphate[29] (2.0 g, 45%): n^{26}_D 1.4500; ^{31}P (^1H) NMR δ (CCl_4, H_3PO_4) 55 (d), −20 (d, J_{P-O-P} = 22 Hz). This reaction was similarly performed in acetonitrile.

DCC and 1c. A solution of **1c** (10 g, 0.05 mol) in petroleum ether (50 mL) was added to a solution of DCC (5.15 g, 0.025 mol) in petroleum ether (50 mL) and the mixture was left at room temperature for several days. The precipitated DCTU (2.6 g, 47.5%) was filtered off. A similar reaction was carried out in acetonitrile. The yield of the isolated DCTU was 4.8 g (83.5%). The filtrates from both reactions were evaporated and the residues were combined and distilled. A fraction boiling at 90–100 °C (0.01 Torr) was collected (3.6 g). On the basis of ^{31}P NMR it was found to contain tetraisopropyl thiopyrophosphate[7] and the unreacted acid **1c**.

DCC and 1g. To a solution of DCC (2.06 g, 0.01 mol) in ether (20 mL) was added a solution of **1g** (5.32 g, 0.02 mol) in ether and the mixture was left for several days at room temperature. The precipitated DCTU was filtered off (2.2 g, 92%) and the filtrate was washed with 2% aqueous $NaHCO_3$, dried, and evaporated to dryness to give pure tetraphenyl thiopyrophosphate (4.4 g, 88.5%): n^{24}_D 1.5747; ^{31}P (^1H) NMR (CCl_4, H_3PO_4) δ 42.5 (d), −27.3 (d, J_{P-O-P} = 24.3 Hz). Anal. Calcd for $C_{24}H_{20}O_6P_2S$: C, 57.83; H, 4.02; P, 12.45. Found: C, 57.38; H, 4.36; P, 12.06.

DCC and 1h. To a solution of DCC (0.849 g, 0.00412 mol) in acetonitrile (5 mL) was added a solution of **1h** (1.5 g, 0.00824 mol) in acetonitrile (8 mL) and the mixture was left for several days. The precipitated DCTU was filtered off and the solvent was evaporated. Benzene was added and the next portion of DCTU was filtered off (total yield of DCTU was 0.97 g, 98%). Benzene was evaporated to give 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan-2-yl 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl oxide[30] (1.36 g, 100%): mp 165–166 °C (from benzene); ^{31}P (^1H) NMR δ ($CHCl_3$, H_3PO_4) 44 (d), −21 (d).

DCC and 2b. A solution of **2b** (12 g, 0.0645 mol) in ether (50 mL) was added to a solution of DCC (6.65 g, 0.03225 mol) in ether (50 mL) and the mixture was left for several days at room temperature. The precipitated DCTU was filtered off (7.2 g, 92%). On the basis of ^{31}P NMR the filtrate was found to contain 67% of *O,O,S*-triethyl phosphorodithioate[31], δ_{31_P} ($CHCl_3$, H_3PO_4) 93, and 33% of tetraethyl trithiopyrophosphate,[32] δ_{31_P} ($CHCl_3$, H_3PO_4) 79. Similar reactions were performed in petroleum ether and acetonitrile. The results are collected in Table I.

DCC and 3a. A solution of **3a** (6 g, 0.0277 mol) in ether (40 mL) was added to a solution of DCC (2.86 g, 0.0139 mol) in ether (40 mL) and the mixture was left for two days at room temperature. The precipitated *N,N'*-dicyclohexylselenourea was filtered off (3.6 g, 90%) and the filtrate was found by means of ^{31}P NMR and TLC to contain tetraethyl selenopyrophosphate[33] [$\delta_{^{31}P(^1H)}$ 58.5 (d), −15.5 (d), J_{P-O-P} = 24 Hz, $J_{^{31}P-^{77}Se}$ = 1020 Hz)], triethyl phosphoroselenolate ($\delta_{^{31}P(^1H)}$ 20.5), traces of triethyl phosphoroselenonate (TLC), and unreacted acid **3a**. Similar reactions were performed in benzene and chloroform; the results are shown in Table I.

DCC and 3b. A similar reaction was carried out between **3b** (8 g, 0.0327 mol) and DCC (3.49 g, 0.01635 mol). The precipitated *N,N'*-dicyclohexylselenourea was filtered off [2.7 g (64%) when the reaction was carried out in ether, 3.4 g (80%) when it was carried out in acetonitrile]. Both filtrates were evaporated and the residues were combined and distilled (90–100 °C (0.4 Torr)) to give tetraisopropyl selenopyrophosphate[33] (4.2 g, 70%): n^{26}_D 1.4520; ^{31}P(^1H) NMR (CCl_4, H_3PO_4) δ 54 (d), 17.5 (d), J_{P-O-P} = 24 Hz, $J_{^{31}P-^{77}Se}$ = 1020 Hz.

***N*-Phosphorylthio(seleno)ureas (B). General Procedure.** A solution of the acid **1**, **2**, or **3** (0.01 mol) in ether (10–30 mL) was slowly added dropwise at room temperature to a solution of a carbodiimide (0.01 mol) in ether (10–30 mL). After several minutes ether was evaporated to give the desired adduct B in most cases in a quantitative yield. The oily products were not purified. The crystalline compounds were purified by freezing from the solutions in ether or petroleum ether at −78 °C. The physical and spectral properties of the adducts are collected in Table II.

Reactions of *N*-Phosphorylthio(seleno)ureas (B) with Acids 1, 2, and 3. "Crossover" Experiments. *N*-Phosphorylthio(seleno)ureas (B) were treated with acids (**1**, **2**, and **3**) at room temperature in various solvents. The substrates were mixed in a 1:1 ratio and the resulted mixture was examined by means of ^{31}P NMR, GLC, and TLC. The products were isolated in the same way as in the case of the reaction of DCC with acids in a molar ratio of 1:2.

Reaction of *N*-Diphenylphosphoryl-*N,N'*-dicyclohexylthiourea (1g-DCC-B) with *O,O*-Diethyl Phosphorothioate-^{35}S. To a solution of **1g**-DCC-B (0.47 g, 0.001 mol) in ether (5 mL) was added *O,O*-diethylphosphorothioate-^{35}S[34] (0.17 g, 0.001 mol) and the mixture was left at room temperature for 14 days. The precipitated DCTU was filtered off and crystallized from ethanol. The specific radioactivity of the starting acid and DCTU obtained were measured with a scintillation spectrometer, "Intertechnique-SL-30", using 2,5-diphenylooxazol (PPO) in toluene (4 g/L) as a scintillation solution. The specific radioactivity of the acid **1b**-^{35}S was 54.09 μCi/mmol and of the DCTU obtained was 49.78 μCi/mmol, which means that DCTU contains 91% of the labeled sulfur (^{35}S) used.

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Registry No. **1a**, 1112-38-5; **1a**-DCC-B, 87763-29-9; **1a**-DBC-B, 64643-55-6; **1b**, 2465-65-8; **1b**-DCC-B, 81017-62-1; **1b**-DBC-B, 64643-56-7; **1b**-DCPhC-B, 87763-38-0; **1b**-DMPhC-B, 87763-41-5; **1b**-DiPC-B, 87763-42-6; **1b**-DnBC-B, 87763-45-9; **1c**, 4486-44-6; **1c**-DCC-B, 87763-30-2; **1c**-DCC-A, 87763-48-2; **1d**, 53324-09-7; **1d**-DCC-B, 81017-63-2; **1d**-DiPC-B, 81017-68-7; **1d**-DiPC-A, 87763-44-8; **1f**, 45098-72-4; **1f**-DCC-B, 87763-31-3; **1f**-DBC-B, 64643-59-0; **1f**-DBC-A, 64643-65-8; **1g**, 14156-07-1; **1g**-DCC-B, 81017-64-3; **1g**-DBC-B, 70206-07-4; **1g**-DnBC-B, 87763-46-0; **1g**-DCC-A, 87763-49-3; **1h**, 45734-11-0; **1h**-DCC-B, 87763-32-4; **1h**-DBC-B, 87763-36-8; **2a**, 756-80-9; **2a**-DBC-B, 81017-66-5; **2a**-DCPhC-B, 87763-39-1; **2b**, 298-06-6; **2b**-DCC-B, 87763-33-5; **2b**-DCC-A, 87763-50-6; **2c**, 107-56-2; **2c**-DBC-B, 87763-37-9; **2d**, 74862-73-0; **2d**-DCC-B, 87763-34-6; **2d**-DBC-B, 81017-67-6; **2d** triethylamine salt, 87763-60-8; **2e**, 2253-60-3; **2e**-DnBC-B, 87763-47-1; **3b**, 64643-66-9; **3b**-DCC-B, 87763-35-7; **3b**-DBC-B, 64643-58-9; **3b**-DCC-A, 87763-51-7; **3b**-DBC-A, 64643-64-7; **3c**, 64643-67-0; **3c**-DCC-B, 81017-65-4; **3c**-DBC-B, 64674-21-1; **3c**-DCPhC-B, 87763-40-4; **3c**-DiPC-B, 87763-43-7; **3c**-DCC-A, 87763-52-8; **3c**-DCPhC-A, 8763-53-9; **3c**-DiPC-A, 87763-54-0; **3c** triethylamine salt, 68305-66-8; **6a**, 598-02-7; **6a**-DCC-C, 87763-55-1; **6b**, 838-85-7; **6b**-DCC-C, 87763-56-2; **6c**, 57778-13-9; **6c**-DCC-C, 87763-57-3; DCTU, 1212-29-9; DCC, 538-75-0; DBC, 6721-03-5; DCPhC, 838-98-2; DiPC, 693-13-0; DnBC, 693-64-1; DMPhC, 10076-13-8; $(MeO)_2P(O)SMe$, 152-20-5; $(MeO)_3P(S)$, 152-18-1; $(MeO)_2P(S)OP(O)(OMe)_2$, 18764-12-0; $(EtO_2P(S)OP(O)(OEt)_2$, 645-78-3; $(i\text{-}PrO)_2P(S)OP(O)(OPr\text{-}i)_2$, 22665-50-5; $(PhO)_2P(S)$-$OP(O)(OPh)_2$, 87763-58-4; $Me_2C(CH_2O)_2P(S)OP(O)(OCH_2)_2CMe_2$,

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Supplementary Material Available: Table 2a containing mass spectral data and elemental analysis of *N*-phosphorylthio-(seleno)ureas (B) (5 pages). Ordering information is given on any current masthead page.

Intramolecular Cyclization of 6-Amino-5-[(2-substituted-2-cyanovinyl)amino]-1,3-dimethyluracil: Synthesis of 9-Deazaxanthine Derivatives and 8-(Cyanomethyl)theophylline

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The intramolecular cyclization reactions of **4a** and **4b** have been studied. Hydrolysis of **4a** and **4b** afforded **12a** and **12b**, respectively. Treatment of **12a** with $POCl_3$ in DMF provided hygroscopic gum **16**, a useful intermediate for the synthesis of 9-deazaxanthine derivatives. Compound **16** was converted with alcohols, amines, and water to **19b–e**, **21b,c**, and **19a**, respectively. Oxidative cyclization of **1a**, **1b**, and **4b** with ferric chloride gave **22a**, **22b**, and **26**, respectively. Decarbalkoxylation of **26** gave 8-(cyanomethyl)theophylline (**27**).

Sardesai and Sunthankar[2] reported that *o*-[(2,2-dicyanovinyl)amino]aniline (**1a**) and its ester derivative **1b** were readily converted into benzimidazole (**2**) on heating (Scheme I). When Stahl and co-workers[3] attempted to extend this cyclization reaction to 6-amino-5-[(2,2-dicyanovinyl)amino]-1,3-dimethyluracil (**4a**), they failed to obtain 1,3-dimethylxanthine (**5**) but instead isolated compound **7** after refluxing **4a** in DMF. In contrast to Sardesai and Sunthankar, we obtained 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (**3a**) and its ester derivative **3b**, respectively, in high yield when **1a** and **1b** were heated in the presence of hydrochloric acid.[4] Our attempts to extend this intramolecular cyclization reaction to **4a** and **4b** failed to give the expected products **6a,b** and led to the formation of pyrrolo[3,2-*d*]pyrimidines **12a** and **12b**, respectively. We now report the full details of this work,[5] including a new preparation of 8-(cyanomethyl)-theophylline (**27**) from **4b**.

Results and Discussion

Hydrolytic Cyclization of 4a and 4b. Heating **4a** or **4b** in hydrochloric acid led to the evolution of CO_2 and the formation of 9-substituted-1-methyl-9-deazaxanthines **12a** and **12b** in 69% or 57% yield, respectively. From the filtrate, a trace of 1,3-dimethyl-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (**15**) was recognized. The structural assignment of these products was based on spectroscopic data. In particular, the UV spectrum of **12b** [λ_{max}^{EtOH} nm (log ϵ) 228.5 (4.35), 269 (3.92)] was a very similar to that of its 8-methyl derivative [λ_{max}^{EtOH} nm (log ϵ) 229.5 (4.48), 270 (4.00)] reported by Murata and Ukawa.[6] The structure **12a** was further confirmed by conversion to **12b** as described below. Recently, Senga and co-workers[7] synthesized **12b** by another method, in which the IR spectrum coincided with that of ours. We propose a mechanism involving an initial Dimroth rearrangement[8] for the formation of **12a** and **12b** as shown in Scheme II.

No reaction was found to occur when **4c** was heated in hydrochloric acid. In contrast to the above results, **15** was obtained in 50% yield accompanied with a trace of **12a** when hydrogen chloride gas was passed into a suspension of **4a** in ethanol and the solution then refluxed. We suggest the mechanism in Scheme II involving covalent hydration of the C(5)–C(6) double bond to form **13**, followed by C(4)–C(5) bond fission to form *s*-triazine ring system **14** and fragmentation to **15**.

Synthesis of 3-Methyl-7-substituted-pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (1-Methyl-9-substituted-9-deazaxanthine). Many 9-deazapurine derivatives (including the 9-deazaxanthine ring system) have been synthesized[9] because the ring system is isomeric with that of naturally occurring purines and indoles. We attempted to chlorinate the 2-oxo group of **12a** with $POCl_3$ by the method of Imai;[10] however, no reaction occurred when **12a** was refluxed in $POCl_3$ or $POCl_3$ mixed with another solvent such as acetonitrile, dichloromethane, or dimethyl sulfoxide. This is probably due to the solubility properties of **12a**, which is insoluble in hot $POCl_3$ and only slightly soluble in hot acetonitrile, dichloromethane, and dimethyl sulfoxide. In contrast, **12a** reacted vigorously with the Vilsmeier–Haack reagent to give a brown solution, which was heated on a water bath for 1 h and the solvent then removed in vacuo to give a hygroscopic gum which was assumed to be **16**. Alcoholysis of **16** followed by hydrolysis gave 1-methyl-9-deazaxanthine-9-carboxylates **19b–e**. When ethanol was used, **19c** was obtained, which was identical with **12b**. Similarly, treatment of **16** with amines followed by hydrolysis gave 1-methyl-9-deazaxanthine-9-carboxamide derivatives **21b** and **21c**. On treatment with hydrochloric acid, **16** was converted to carboxylic acid **19a**.

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