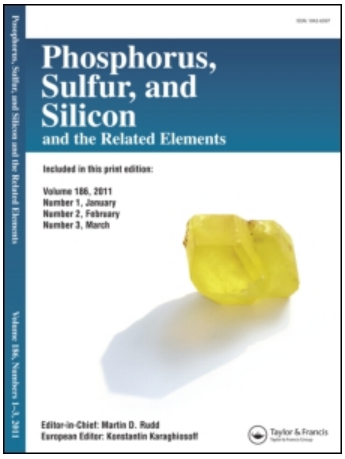

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SYNTHESIS OF 1-METHYL-1-(N-SUBSTITUTED CARBAMOYL- AND THIOCARBAMOYL-AMINO) ALKANEPHOSPHONIC ACIDS-DIETHYL ESTERS

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SYNTHESIS OF 1-METHYL-1-(N-SUBSTITUTED CARBAMOYL- AND THIOCARBAMOYL-AMINO) ALKANEPHOSPHONIC ACIDS-DIETHYL ESTERS

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Diethylesters of 1-methyl-1-(N-substituted carbamoyl- or thiocarbamoyl-amino)-alkane-phosphonic acids are obtained by interaction of O,O-diethyl esters of 1-amino-1-methyl-alkanephosphonic acids and different isocyanates or isothiocyanates at room temperature. Cyclization of 1-methyl-1-(N-butylcarbamoyl-amino)-ethanephosphonic acid diethyl ester to 3-butyl-5,5,-dimethyl-2,4-dioxo-4-hydroxy-1,3,4-diazaphosphole is achieved.

Key words: 1-Methyl-1-(N-substituted carbamoyl- or thiocarbamoyl-amino)-alkanephosphonic acids diethyl esters; 1-aminophosphonates; isocyanates; isothiocyanates; phosphonate esters; cyclization; 3-butyl-5,5-dimethyl-2,4-dioxo-4-hydroxy-1,3,4-diazaphosphole.

INTRODUCTION

It is known that many organophosphorous compounds containing nitrogen and sulphur atoms show physiological activity. In order to synthesize compounds supposed to have a higher biological activity and for studying the relationship between chemical structure and biological activity in new organophosphorous compounds we examined the interaction between 1-aminoalkanephosphonic acid diethyl esters and different isocyanates and isothiocyanates. Interactions between 1-aminophosphonates and phenyliso-, phenylisothio-, 1-naphthyliso- and 1-naphthylisothiocyanates have been reported for the first time by M. I. Kabachnik and T. Medved.[1]

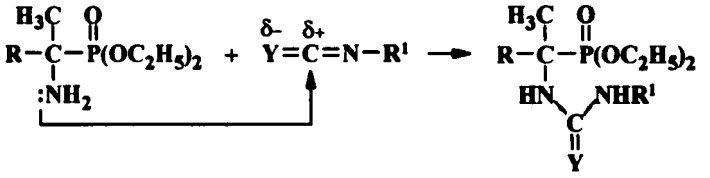
We studied the reaction of O,O-diethyl esters of 1-amino-1-methylethane- and 1-amino-1-methyl-propanephosphonic acids with n-butyl-, phenyl-, 3-chlorophenyl or 4-chlorophenylisocyanates and methyl-, ethyl-, cyclohexyl-, benzyl-, phenyl-, 4-chlorophenyl- and 4-bromophenylisothiocyanates.

RESULTS AND DISCUSSION

1-Methyl-1-(N-substituted carbamoyl- or thiocarbamoylamino)alkane phosphonates were prepared by interactions of 1-amino-alkanephosphonic acids diethyl esters with isocyanates or isothiocyanates in anhydrous aprotic organic solvents such as hexane, diethyl ether, THF or dichloromethane. Ethanol is not a suitable solvent for the reaction because of its partial interaction with isocyanates and isothiocyanates, leading to the formation of ethylcarbamates. This would result in a decrease of the yields. The reactivity of isothiocyanates was less than that of isocyanates. The reactions of diethyl esters of 1-amino-alkanephosphonic acids with isothiocyanates proceeded without any solvent. The solid compounds such as 4-chloro-

phenylisothiocyanate and 4-bromo-phenylisothiocyanate were dissolved in the starting ester.

The reaction proceeds as a nucleophilic addition to the isocyanates or isothiocyanates according to the following Scheme (I):



(1-19)

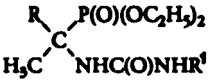
Y=O ; R= CH_3 , CH_2CH_3 ; R^1 = n-C_4H_9 , C_6H_5 , C_6H_4Cl-3 , C_6H_4Cl-4

Y=S ; R= CH_3 , CH_2CH_3 ; R^1 = CH_3 , C_2H_5 , cyclo-C_6H_{11} , $CH_2C_6H_5$, C_6H_5 , C_6H_4Cl-4 , C_6H_4Br-4

SCHEME I

TABLE I

Analytical characterization and yields of



Compd. No.	R	R^1	M.p. (°C)	Formula (M.W.)	Anal. %N found/calc.	Yield (%)
1	CH_3	C_4H_9-n	47.5	$C_{12}H_{27}N_2O_4P$ (294.34)	9.34 / 9.52	85
2	CH_3	C_6H_5	147-148	$C_{14}H_{21}N_2O_4P$ (314.33)	8.66 / 8.91	96
3	CH_3	C_6H_4Cl-3	162-163	$C_{14}H_{22}ClN_2O_4P$ (348.78)	7.89 / 8.03	97
4	CH_3	C_6H_4Cl-4	175-176	$C_{14}H_{22}ClN_2O_4P$ (348.78)	8.25 / 8.03	90
5	CH_2CH_3	C_4H_9-n	~40	$C_{13}H_{29}N_2O_4P$ (308.37)	8.95 / 9.14	87
6	CH_2CH_3	C_6H_5	115-117	$C_{15}H_{25}N_2O_4P$ (328.36)	8.51 / 8.53	96
7	CH_2CH_3	C_6H_4Cl-3	134-135	$C_{15}H_{24}ClN_2O_4P$ (362.81)	7.79 / 7.72	98
8	CH_2CH_3	C_6H_4Cl-4	150-151	$C_{15}H_{24}ClN_2O_4P$ (362.81)	7.83 / 7.72	97

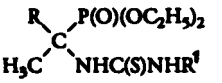
Very pure compounds **1–19** were thus prepared with good yield (85–98%) at room temperature and molar ratio of the starting compounds of 1:1 (Tables I and II). The reaction of isocyanates proceeded faster and with better yields than that of isothiocyanates. The products crystallized easily from polar solvents such as ethanol.

The structures of the compounds **1–19** were proved by elemental analyses and IR-spectra (Tables III and IV).

The reaction proceeds much faster at a molar ratio of the starting diethyl ester of 1-amino alkanephosphonic acid to the corresponding isocyanate of 2:1. For instance, in the case of PhNCO (0.017 mol/dm^3) an almost quantitative yield of the respective product is obtained in a three-fold shorter reaction time since the characteristic band at 2245 cm^{-1} (ν_{NCO}) observed in the IR spectrum disappears completely after 70 min (215 min at the ratio 1:1). At increased PhNCO concentrations, e.g. at a 1-amino-phosphonate to phenylisocyanate molar ratio of 1:2, the reaction rate decreases. The intensity of the band characteristic of the -NCO group decreases within 4 h to the half of its maximum value. Kinetic studies of the interactions of the diethyl esters of 1-amino-alkanephosphonic acids are in progress.

TABLE II

Analytical characterization and yields of



Compd. No.	R	R^1	M.p. (°C)	Formula (M.W.)	Anal. %N found/calc.	Yield (%)
9	CH_3	CH_3	83-84	$C_9H_{21}N_2O_3PS$ (268.32)	10.10/10.44	86
10	CH_3	CH_2CH_3	79-80	$C_{10}H_{23}N_2O_3PS$ (282.35)	9.69 / 9.92	87
11	CH_3	C_6H_{11}	123-124	$C_{14}H_{29}N_2O_3PS$ (336.44)	8.25 / 8.33	89
12	CH_3	$CH_2C_6H_5$	89.5-90	$C_{15}H_{25}N_2O_3PS$ (344.42)	8.02 / 8.13	91
13	CH_3	C_6H_5	105-106	$C_{14}H_{23}N_2O_3PS$ (330.40)	8.62 / 8.48	93
14	CH_3	C_6H_4Cl-4	144-145	$C_{14}H_{22}ClN_2O_3PS$ (364.84)	7.53 / 7.68	94
15	CH_3	C_6H_4Br-4	145-146	$C_{14}H_{22}BrN_2O_3PS$ (409.30)	6.69 / 6.84	95
16	CH_2CH_3	CH_3	113-114	$C_{10}H_{23}N_2O_3PS$ (282.35)	10.13 / 9.92	85
17	CH_2CH_3	C_6H_5	112-112.5	$C_{15}H_{25}N_2O_3PS$ (344.42)	8.24 / 8.13	95
18	CH_2CH_3	C_6H_4Cl-4	86-87	$C_{15}H_{24}ClN_2O_3PS$ (378.87)	7.29 / 7.39	91
19	CH_2CH_3	C_6H_4Br-4	81-82	$C_{15}H_{24}BrN_2O_3PS$ (423.33)	6.42 / 6.62	93

TABLE III

IR-spectral data (ν cm^{-1}) of the compounds 1–8

Compd. No.	$\nu_{P=O}$	ν_{P-O-C}	ν_{N-C} δ_{N-H}	$\nu_{C=O}$	$\nu_{C_6H_5}$	ν_{NH}
1	1229	1020-1040	1554	1689	—	3345
2	1210-1230	1020-1040	1540	1710	1500, 1600	3340
3	1240	1020-1040	1550	1695	1500, 1600	3280
4	1210-1240	1020-1050	1560	1720	1500, 1610	3280
5	1210-1235	1020-1040	1560	1700	—	3260-3280
6	1210	1010-1030	1545	1700	1500, 1600	3340
7	1200-1230	1020-1050	1555	1720	1500, 1600	3280
8	1220	1020-1040	1535	1700	1500, 1600	3320

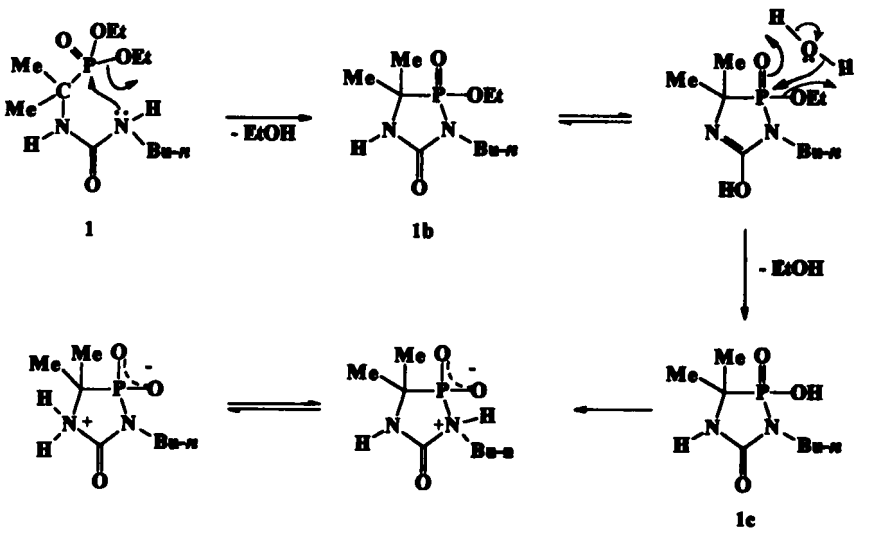
TABLE IV

IR-spectral data (ν cm^{-1}) of the compounds 9–19

Compd. No.	$\nu_{P=O}$	ν_{P-O-C}	$\nu_{C=S}$	$\nu_{S=C-N}$	$\nu_{C_6H_5}$	ν_{NH}
9	1230	1020-1050	1270	1530-1570	—	3280
10	1235	1010-1040	1300	1540	—	3290
11	1235	1020-1040	1276-1300	1530-1575	—	3280
12	1235	1020-1050	1300	1530-1580	1500; 1600	3245
13	1230	1010-1040	1280-1300	1520-1580	1500; 1600	3260
14	1230	1020-1045	1280-1300	1520-1570	1500; 1605	3260
15	1230	1010-1040	1285	1520-1560	1500; 1605	3240
16	1210	1010-1040	1260	1530-1575	—	3280
17	1230	1030-1050	1270	1520-1580	1500; 1600	3240
18	1220	1020-1040	1270	1520-1570	1500; 1600	3255
19	1220	1020-1035	1270	1520-1560	1500; 1600	3240

One of the purposes of the present work is to study the cyclization processes occurring in compounds of the type **1–19**.

So far we succeeded to perform a ready cyclization of 1-methyl-1-(N-n-butyl-carbamoyl-amino)ethanephosphonic acid diethyl ester **1** upon storage in the crystalline state (m.p. 47.5°C) or in the liquid state to 3-butyl-5,5-dimethyl-2,4-dioxo-4-hydroxy-1,3,4-diazaphosphole (**1c**) according to the following probable scheme of a two-stage process (Scheme II):



SCHEME II

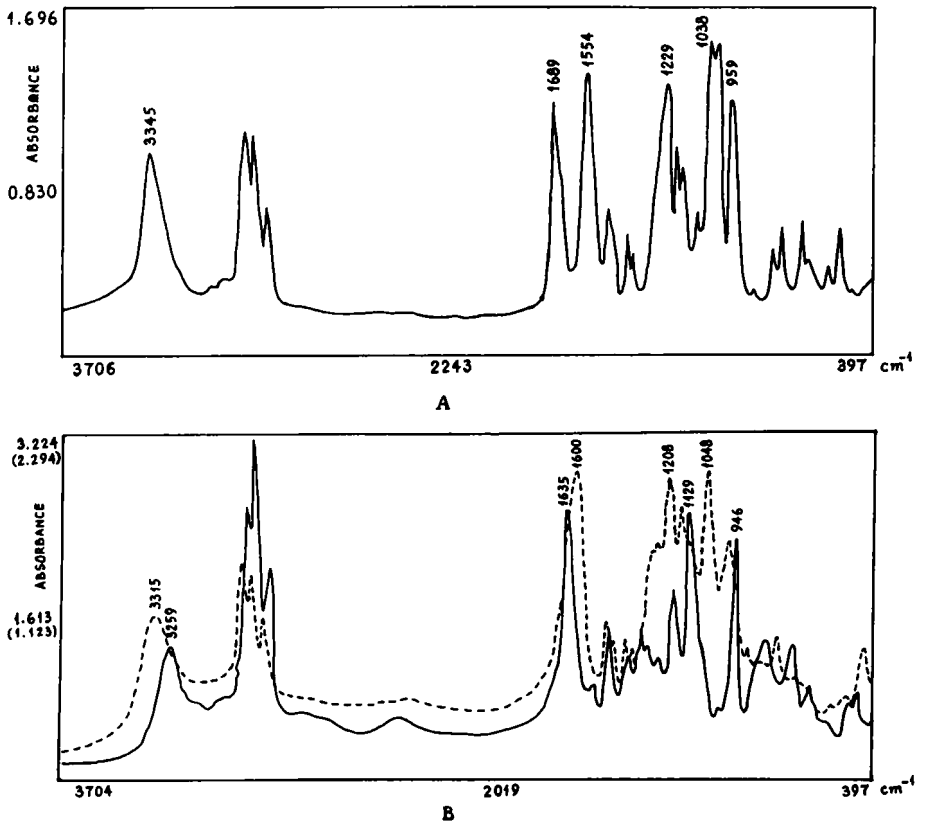


FIGURE 1 IR spectra in nujol of: (A) compound **1**, (B) middle cyclic product **1b** (- - -) and cyclic product **1c** (——).

This scheme was confirmed by equilibrium vapour phase chromatography determination of ethanol evolved during days. Retention time 0.94 min, corresponding to standard ethanol. Gas chromatograph Perkin-Elmer Sigma 3B was used with microprocessor station Sigma 10 and HS-6 adapter (column GTS; adapter and column at 50°C; injector and detector at 120°C).

The IR spectrum of compound **1** (Figure 1A) shows significant changes after storage (Figure 1B). The bands at 3345 cm^{-1} (ν_{NH}), 1689 cm^{-1} ($\nu_{C=O}$, amid I), 1554 cm^{-1} (amid II), 1229 cm^{-1} ($\nu_{P=O}$) and 1040–1020 cm^{-1} (ν_{P-O-C}) of **1** disappear while intensive bands are observed at 1048 cm^{-1} (ν_{O-Et}) and 1208 cm^{-1} ($\nu_{P=O}$), 1600 cm^{-1} ($\nu_{O=C(NH)(NH)}$), 3315 cm^{-1} (ν_{NH}) of middle product **1b** (Figure 1B) and at 946 and 1129 cm^{-1} (antisymmetrical and symmetrical vibrations of

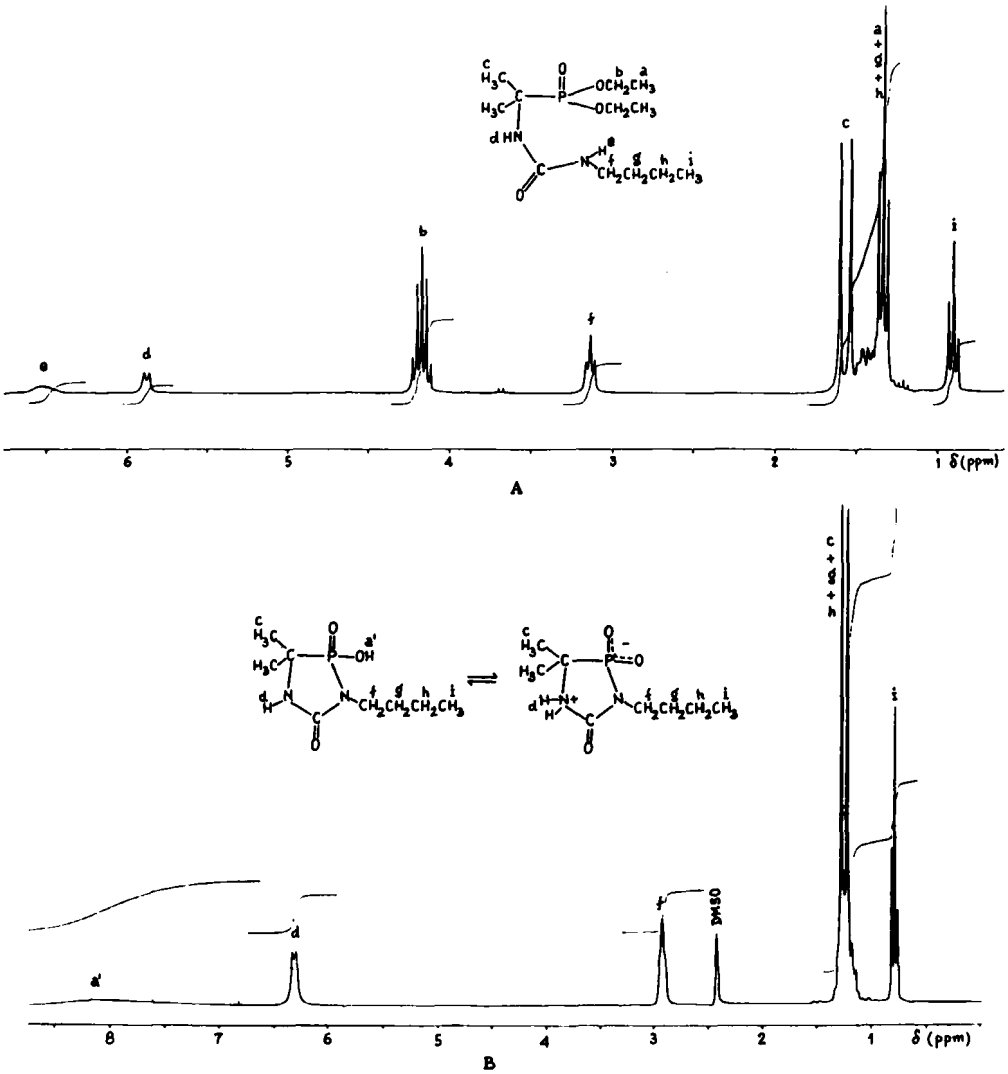


FIGURE 2 ^{1}NMR spectra of: (A) compound **1** ($CHCl_3$) and (B) cyclic product **1c** (DMSO-d_6).

PO_2^-) together with a relatively broad band at 1635 cm^{-1} (for the group O=C—N≡)[2] and a multiplet in the 3260–2200 cm^{-1} spectral region (for ≡N— and P—O—H····O=P—O) of **1c** (Figure 1B). These changes in the IR spectra result from the deethoxylation of the $—P(O)(OC_2H_5)_2$ group. This is confirmed also by the comparison of the ^{1}H-NMR spectra of compound **1** prior to and after its cyclization (Figure 2A).

The ^{1}H-NMR spectrum of the new product **1c** (Figure 2B) shows the absence of the two $—OC_2H_5$ groups δ 1.34 ppm (t, CH_3, $J_{PH} \approx 7$ Hz) and δ 4.17 ppm (m, OCH_2, $J_{PH} \approx 7$ Hz) and the appearance of a new doublet at δ 6.32 ppm (d, NH, $J_{PH} \approx 9$ Hz) which is characteristic of the $H_2\overset{+}{N}$=C—P group.

The above mentioned differences in the IR- and ^{1}H-NMR spectra of compound **1** and those of the product of its transformation suggest the occurrence of intramolecular cyclization of compound **1**.

Several prototropic isomeric structures of the cyclic product **1c** are possible.

In the crystalline state the bipolar cyclic structure could be stabilized as a dimer or as a polymer; and this can be achieved by coordinated with water molecules.

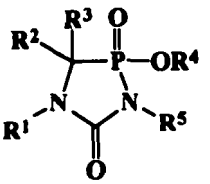
Some physical properties of the new product are in agreement with the proposed structure, e.g. relatively high melting point (140–141°C), solubility in water and insolubility in non-polar solvents or in solvents with medium polarity ($CHCl_3$, etc.) and acidity (pH of about 2).

The data of the elemental analysis correspond to the above described cyclic compound in the hydrate form with 1 mole H_2O.

Anal. for $C_8H_{17}N_2O_3P.H_2O$ (M.W. = 238.23) Calculated %: C 40.33, H 8.03, N 11.76, P 13.00; found %: C 40.77, H 8.35, N 11.66, P 12.35.

A similar cyclization process is reported by R. Merten and C. Weber[3] for the reaction of methylisocyanate and N-(butylamino)-1-methyl-ethanephosphonic acid diethyl ester or its alkyl and aryl N- or C-substituted derivatives carried out by refluxing for 5 hours in dichloromethane, in the presence of 1,4-diaza-bicyclo[2,2,2]octane as catalyst.

However, these authors have not reported the isolation of the intermediate with structure similar to that of compound **1** synthesized by us. Furthermore, their final products:



R^1, R^2, R^3, R^4 - alkyl or phenyl

R^5 - methyl or phenyl

are proved by elemental analysis but the respective IR-spectral data are not correct. ^{1}H-NMR spectral data are also lacking.

The process described here occurs in the absence of the above mentioned catalyst.

The cyclization of compound **1**, which we succeeded to realize at room temperature and in the absence of a catalyst, provides the possibility to study a new type of process and represents a new route to the obtaining of an interesting class of cyclic organophosphorous compounds.

The obtained 1-methyl-1-(N-substituted carbamoyl- or thiocarbamoyl-amino)-ethane or propanephosphonic acids diethyl esters were tested for biological activity—as plant growth regulators.[4]

EXPERIMENTAL

Melting points were determined on a Boetius hotstage microscope and were uncorrected. The IR spectra were recorded on a Specord 75 IR (Carl Zeiss) and Bomem FT-IR spectrophotometers. ^{1}H NMR spectra were recorded on a Bruker WM 250 FT spectrometer with external standard TMS at room temperature. The starting diethyl esters of 1-amino-alkanephosphonic acids were prepared according to literature procedures.[5]

General procedure for the synthesis of compounds **1–19**

Interaction between 1-amino-alkanephosphonic acid diethyl esters and isocyanates or isothiocyanates. The corresponding isocyanate (0.02 mole) dissolved in dry diethyl ether (3 cm^3) was added dropwise to a stirred solution of diethyl ester of 1-amino-alkanephosphonic acid (0.02 mole + 10% excess) in anhydrous diethyl ether or n-hexane (5 cm^3) at room temperature.

After the slightly exothermic interaction was completed, the reaction mixture was allowed to stand at room temperature for about 3 hours, then cooled and the solid product was isolated by filtration in vacuum. When necessary, several cm^3 of a solvent (diethyl ether or n-hexane) were added. The precipitate was washed with ethanol, dried and after two recrystallizations (from ethanol) the product was obtained in high yield (85–98%) and purity.

The physical constants, melting points, results of elemental analyses and yields of the obtained diethyl esters of 1-methyl-1-(N-substituted carbamoyl or thiocarbamoyl)-alkanephosphonic acids are represented in Table I (compds. **1–8**) and Table II (compds. **9–19**). The IR spectral data are given in Tables III and IV, respectively.

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