2. Substitution of thiophene and of 3-methyl- and 3-bromothiophenes occurred at positions 2 and 5, of 2-methyl- and 2-chlorothiophenes at position 5, and of N-methylpyrrole at positions 2 and 4.

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ORGANOPHOSPHORUS ANALOGS OF BIOLOGICALLY ACTIVE COMPOUNDS

11.* SYNTHESIS OF ANALOGS OF ACYL PHOSPHATES BASED ON ESTERS OF METHYLENEDIPHOSPHORUS-CONTAINING ACIDS

N. B. Tarusova, Z. S. Novikova,
A. A. Prishchenko, G. M. Yakovleva,
and R. M. Khomutov

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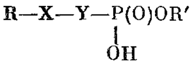
Analogs of acyl phosphates or adenylates (I), which are intermediate compounds in enzymic reactions, have been used successfully in recent years for the investigation of processes of enzymic activation of carboxylic acids. The effectiveness of replacing the anhydride oxygen by a methylene link (II) [2, 3] or the carbonyl group by a phosphonyl (III) [4] has been shown for several enzymes.



$$\text{R—X—}\dot{\text{Y}}\text{—}\underset{\displaystyle\text{OH}}{\underset{|}{\text{P}}}\text{(O)OR}'$$

$X = CO$, $Y = O$, $R' = H$, Ade (I); $X = CO$, $Y = CH_2$, $R' = H$, Ade (II); $X = P(O)OH$, $Y = O$, $R' = $ Ade (III); $X = P(O)OH$, $Y = CH_2$, $R' = H$ (IV); $X = P(O)OH$, $Y = CH_2$, $R' = $ Ade (V)

Hitherto undescribed analogs of aminoacyl phosphates containing the PCH_2 fragment have been obtained in the present work and the possibility of obtaining their adenosine esters (IV) and (V) has been established.

It was shown by us that the available starting acid esters of methylenediphosphorus(III, V)-containing acids (VIa, b) [5] may be added to aldimine (VII) under the action of bases giving compounds (IVa, b) after acidic hydrolysis.

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*For Communication 10 see [1].

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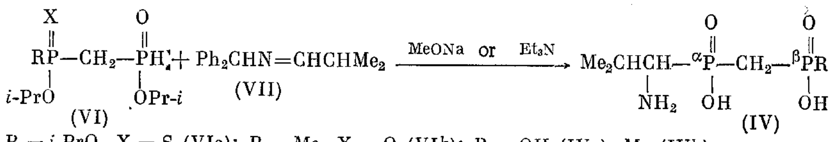
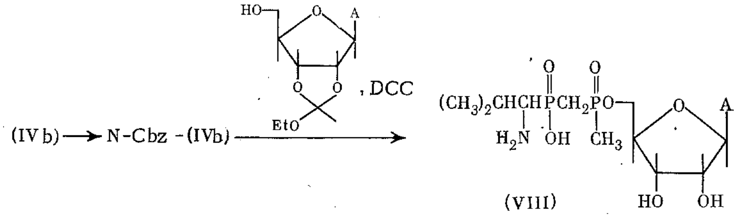


R = *i*-PrO, X = S (VIa); R = Me, X = O (VIb); R = OH (IVa), Me (IVb).



However, the character of the reaction and the yields of (IVa) or (IVb) depended on the structure of the initial (VI). Thus, condensation in the presence of Et_3N proceeded to (IVb) in an adequately high yield, while under analogous conditions the yield of (IVa) did not exceed several percent. Use of MeONa significantly reduced the yield of (IVb), but in the case of (IVa) the yield remained low while the main product of the reaction was 2-amino-3-methylpropylphosphonic acid, i.e., under these conditions fission of the P$-$$CH_2$ bond was observed. Interaction of (VIa), isobutyric aldehyde, and NH_3 under conditions of the synthesis of α-aminophosphonic acids led to only a trace of (IVa).

Conversion of (IVb) into the corresponding analog of aminoacyl adenylate (VIII) implied, it seemed, replacement of hydroxyl at the P(α) atom, which would have complicated the synthesis significantly. However, it was shown successfully that condensation of the carbobenzoxy (Cbz) derivative of (IVb) with protected adenosine occurred selectively for P(β) in the presence of dicyclohexylcarbodiimide (DCC) and led to (VIII) in good yield. This compound proved to be an inhibitor of valine tRNA synthetase with K_i 10^{-4} mole/liter. Its biological activity in a series of other analogs has been considered in [6].

EXPERIMENTAL

Plates for TLC were Silufol UV-254 (Czechoslovakia) and cellulose DE-32 (Whatman, England). Systems for TLC were the following: 1) 5% CF_3COONa in a mixture of $MeOH-NH_4OH-H_2O$ (12 : 3 : 5); 2) i-PrOH$-$$NH_4OH-H_2O$ (7 : 1 : 2). Visualization was with ninhydrin and with molybdate reagent. PMR and ^{31}P NMR spectra were taken on a Varian XL-100-15 instrument (100 MHz) in D_2O.

<u>1-Methyl-2-aminopropyl-2-phosphinomethylenephosphonic (IVa) and 1-Methyl-2-aminopropyl-2-phosphinomethylenemethylphosphonic (IVb) Acids.</u> Compound (VI) (3 mmole) was mixed with (VII) (3 mmole), then at 60°C MeONa (0.06 mmole) or Et_3N was added, the mixture heated at 100°C for 1 h, hydrolyzed with conc. HCl (20 ml) for 10 h, extracted with $CHCl_3$, filtered, and the mother liquor evaporated to dryness in vacuum. The residue was purified on a column of Dowex 50 W× 8 (H^- form, 300 ml). Compound (IV) was eluted with water, analyzing fractions by TLC. 2-Amino-3-methylpropylphosphonic acid was eluted with 2% NH_4OH and was identical with a known sample by TLC. Yield of (IVa) was 29 mg (5%), R_f 0.62 (system 1). PMR spectrum (δ, ppm): 1.11 d and 1.16 d (6 H, CH_3, J = 6 Hz), 2.27 d and 2.57 d (2 H, CH_2, J = 6 Hz), 3.33 d and 3.38 d (1 H, CHP, J = 9 Hz). ^{31}P NMR: -20.5 (Pα) and -16.8 (Pβ). Yield of (IVb) was 158 mg (23%) when catalyzed by MeONa and 460 mg (67%) with Et_3N, R_f 0.7 (system 1). PMR spectrum (δ, ppm): 1.13 d and 1.18 d (6 H, CH_3, J = 6 Hz), 1.66 d (3H, CH_3P, J = 16 Hz), 2.44 d and 2.60 d (2 H, CH_2, J = 17 Hz), 3.24 d and 3.30 d (1 H, CHP, J = 9 Hz).

<u>Pβ-Adenosine Ester of 1-Methyl-2-aminopropyl-2-phosphinomethylenemethylphosphinic Acid (VIII).</u> Cbz-Cl (170 mg, 1 mmole) was added to (IVb) (140 mg, 0.6 mmole) in a suspension of $NaHCO_3$, the mixture was extracted with ether, and neutralized with Dowex 50 W × 8 (H^+ form) resin. The N-Cbz derivative was isolated on a column of DE-32 (HCO_3^- form) with a gradient from 0 to 0.2 M NH_4HCO_3. Yield was 135 mg (65%), R_f 0.8 (system 1). Ethoxymethyleneadenosine (117 mg, 0.35 mmole) and DCC (310 mg) were added to the Cbz derivative of (IVb) (275 mg, 0.37 mmole) in its Bu_3N^+ form in abs. pyridine (10 ml) and mixed for 4 days. After filtration, extraction, and removal of pyridine at 15 torr, the residue was treated with 50% AcOH (10 ml) (50 min at 50°C) and evaporated to dryness. Purification was carried out on DE-32 in a similar manner to previously. The adenosine ester was contained in fractions of NH_4HCO_3 concentration 0.11-0.12 M. After evaporation the Cbz protection was removed by hydrogenation over Pd black in 30% AcOH, the catalyst was separated, the filtrate evaporated to dryness, and (VIII) was isolated on DE-32, yield being 95 mg (50%), R_f 0.7 (system 2). PMR spectrum (δ, ppm): 1.13 d and 1.18 d (6 H, CH_3, J = 6 Hz), 1.84 d and 1.89 d (3 H, CH_3P, J = 15 Hz),

2.44 d and 2.59 d (2 H, CH_2, J=17 Hz), 3.12 d and 3.18 d (1 H, CHP, J=9 Hz), 6.24 d (1 H, H^1, J=5 Hz), 8.18 s (1H, 2-H), 8.26 s (1 H, 8-H).

SUMMARY

1. The possibility has been shown of synthesizing aminoalkylphosphinomethylenephosphonic and phosphinic acids from esters of methylenediphosphorus-containing acids.

2. The obtained analogs of acyl phosphates may be selectively esterified with adenosine.

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SYNTHESIS AND PROPERTIES OF DERIVATIVES OF HEPTAMETHYLCYCLOTETRASILOXANOMETHYLPHOSPHONIC ACID

N. N. Godovikov, L. A. Polyakova,
E. G. Kireeva, and M. I. Kabachnik

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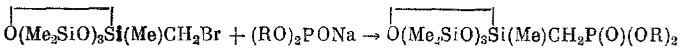
Derivatives of phosphonic acids containing a cyclosiloxane group at the P atom have only been studied to a small extent. Of the compounds of this type, only the O,O-diethylheptamethylcyclotetrasiloxanomethylphosphonate has been previously prepared by the Arbuzov reaction, i.e., by the prolonged heating of chloromethylheptamethylcyclotetrasiloxane with triethyl phosphite [1]. It was of interest to synthesize a number of derivatives of this type and to study their properties.

With this aim esters of heptamethylcyclotetrasiloxanomethylphosphonic acid (I) (Table 1) were prepared by the Michaelis–Becker reaction, i.e., by the interaction between sodium dialkylphosphite and bromomethylheptamethyltetrasiloxane.

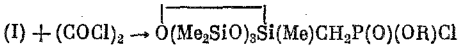


$$\overline{O(Me_2SiO)_3Si}(Me)CH_2Br + (RO)_2PONa \rightarrow \overline{O(Me_2SiO)_3Si}(Me)CH_2P(O)(OR)_2$$

(I)

R = Et, *i*-Pr, *n*-Pr, *n*-Bu.

Attempts to convert the esters which had been prepared into chloroanhydrides by the action of PCl_5 or $SOCl_2$ turned out to be unsuccessful. This was probably due to cleavage of the cyclotetrasiloxane ring [2]. It was only when O,O-dialkylheptamethylcyclotetrasiloxanomethylphosphonates were treated with oxalyl chloride under mild conditions that the chloroanhydrides of the monoesters (II) (Table 2) were successfully prepared with yields of 80–90%.



$$(I) + (COCl)_2 \rightarrow \overline{O(Me_2SiO)_3Si}(Me)CH_2P(O)(OR)Cl$$

(II)

R = Et, *i*-Pr, *n*-Pr, *n*-Bu.

The reaction of the chloroanhydride of the ethyl ester (II) with sodium p-nitrophenolate in toluene yielded O-ethyl-O-(p-nitrophenyl)heptamethylcyclotetrasiloxanomethylphosphonate (III) with a yield of 23%. The presence of traces of alcohol sharply decreases the yield of the product, which is apparently associated with the cleavage of the cyclotetrasiloxane ring under the action of a sodium alcoholate [2].

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow.
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