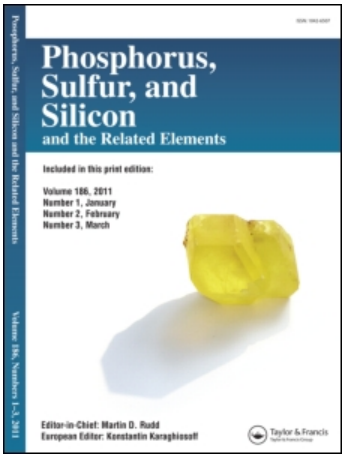

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Biologically Relevant Phosphorus Compounds

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Phosphorus and Sulfur, 1983, Vol. 18 pp. 481-490
0308-664X/83/1801-0481/$18.50/0

SYNTHESIS AND ENZYMATIC ACTIVITY OF NOVEL β,γ-PHOSPHONATE ATP ANALOGUES

By G.M.Blackburn*, Chemistry Department, The University, Sheffield, U.K. &
F.Eckstein, Max-Planck-Institut fur Experimentelle Medizin, Göttingen, BRD.

Syntheses will be described for novel β,γ-substituted analogues of ATP and other nucleotides which incorporate phosphonate analogues of pyrophosphoric acid. Spectroscopic and metal-ion binding studies show that such species are not only isosteric but are also isopolar relatives of ATP.

Compounds of this type act as inhibitors for enzymes such as hexokinase, which catalyse cleavage of the β,γ-phosphate bridge, but they are substrates for enzymes such as RNA polymerase, which effect cleavage of the α,β-phosphate bridge. A comparative study of six nucleotide species shows that enzymes can show different susceptibilities to steric and to polar characteristics as constituent features of nucleotide analogues.

STRUCTURAL AND SPECTROSCOPIC STUDIES OF GUANIDINOPHOSPHONIC ACIDS AND THEIR AMINOPHOSPHONIC PRECURSORS.

G.J.Adetunji, D.G.Cameron, K.Henrick, H.R.Hudson, M.McPartlin and M.Pianka, School of Chemistry, The Polytechnic of North London, Holloway Road, London N7 8DB, U.K.

X-Ray diffraction studies on α-guanidinopropanephosphonic acid and ω-guanidinopropanephosphonic acid have provided the first crystal structure data for these types of compound and confirm the zwitterionic structure in the solid state. Extensive intermolecular hydrogen bonding is present, especially in the α-substituted derivative. The arrangement of atoms around phosphorus is that of a distorted tetrahedron with P-O bond lengths between 1.500(5) and 1.588(5) Å. Spectroscopic identifications of amino- and guanidinophosphonic acids are best made by ^{31}P nmr, ^{13}C nmr, and fast-atom bombardment (FAB) mass spectrometry. ^{31}P chemical shifts for the ω-guanidino acids in D_2O increase with chain length from 14.0 ppm (relative to 85% H_3PO_4) to a limiting value of ca.27 ppm. For the corresponding amino compounds the range is between 11 and 27 ppm. ^1H nmr spectra are usually complex and difficult to employ for the assignment of structures. ^{13}C nmr spectra however, provide a valuable means for the identification of both the amino- and guanidinophosphonic acids either separately or in mixtures, with characteristic phosphorus-carbon coupling constants of $^1J_{PC}$ 133-158, $^2J_{PCC}$ 0-4, $^3J_{PCCC}$ 16-17 and $^3J_{PCNC}$ 4-8 Hz. An additional and important verification of molecular structure is obtained by FAB mass spectrometry which gives a base peak in each case at M+1 together with higher aggregates including one or more molecules of glycerol. A number of significant fragmentations can also be observed.

SYNTHESIS OF BIS (1,2-DIACYL-GLYCERO-3) PHOSPHORIC ACIDS STEREOISOMERS FROM RAC-(1,2-DIACYL)GLYCEROL : ESTIMATION OF THE DIASTEREOSPECIFICITY OF THE PHOSPHORYLATION

DANG, Q.Q.*, ROGALLE, P.*, SALVAYRE, R.*, KLAEBE, A.** and DOUSTE-BLAZY, L.*

*INSERM, U 101, Biochimie des Lipides, C.H.U. Purpan, 31059 TOULOUSE CEDEX

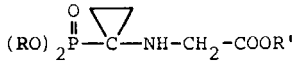
**E.R.A. CNRS 926, Univ. Paul Sabatier, 31620 TOULOUSE CEDEX.

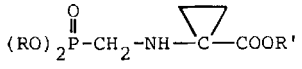
Rac. di (1-^{14}C) palmitoyl-glycerol (I) is prepared from tri (1-^{14}C) palmitoyl-glycerol by hydrolysis with lipase from Rhizopus Arrhizus. (SEMERIVA et al., 1967). Phosphorylation of (I) (2 moles) by phenylphosphoryl dichloride (1 mole) in anhydrous pyridine followed by hydrogenolysis according to a modified procedure of BAER (DANG, Q.Q. et al., 1982), gives a mixture of bis(1,2-diacyl-sn-glycero-3)phosphoric acid (III) and (1,2-diacyl-sn-glycero-3)phosphoryl (2',3'-diacyl-sn-glyceryl-1') (IV) or bis-phosphatidic acids 3-P-3', 1-P-1' and 3-P-1'. Enzymatic hydrolysis of this mixture by phospholipase A_2 from pig pancreas which only deacylates at position 2 of 1,2-diacyl-sn-3-glycerophosphates (VAN DEENEN and DE HAAS, 1963) gives a mixture of bis phosphatidic acid 1-P-1' (II'), lyso bis phosphatidic acid 3-P-3' (III') and semi lyso bis phosphatidic acid 3-P-1', well separated by TLC. From the radioactivity measurements, it is shown that the phosphorylation reaction displays some diastereospecificity, giving 66 % molar for the couple of enantiomers II (33 %) and III (33 %), and 34 % molar for IV (meso form).

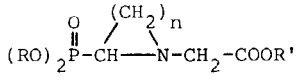
GLYCINO-N-METHYL PHOSPHONIC ACID DERIVATIVES

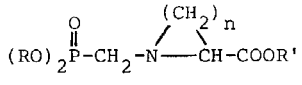
Peter J. Diel and Ludwig Maier, Agricultural Division, CIBA-GEIGY Ltd., Basel, Switzerland.

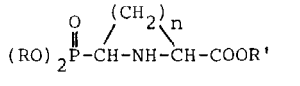
The preparation and the chemical, physical and spectral data of glycino-N-methyl phosphonic acid derivatives of the following type shall be presented.











R = alkyl, H

R'= alkyl, H

PHOSPHOLIPIDE ANALOGUE STRUCTURAL D'UN MEDIATEUR NATUREL DE L'ALLERGIE

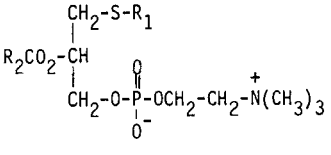
B. GARRIGUES*, G. BERTRAND** et J.P. MAFFRAND***

* E.R.A. 926, Université Paul Sabatier, 31 062 Toulouse Cédex

** E.R.A. 829, Université Paul Sabatier, 31 062 Toulouse Cédex

*** Sanofi Recherche, 195 Route d'Espagne,31024 Toulouse Cédex

Nous décrivons une synthèse originale de l'(acyloxy-2 Alkylthio-1 propyl) phosphorylcholine (I). Ce phospholipide est l'analogue soufré du "Platelet Activating Factor" (PAF) (II) qui est un produit endogène responsable de l'agrégation des plaquettes sanguines. Le PAF joue un rôle dans les processus de thromboses et d'allergies. Nous avons tenté en introduisant une fonction thioether de synthétiser un antagoniste.



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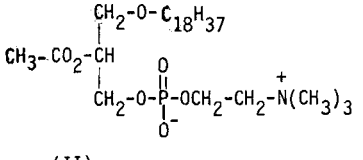


(II)

SYNTHESIS OF α-FLUORINATED PHOSPHONOACETATES. Charles E. McKenna and Leslie A. Khawli, Department of Chemistry, University of Southern California, Los Angeles, CA 90089-1062, USA

We previously reported the synthesis of fluorinated methanediphosphonates ((1): X = H or F, Y = F, R = alkyl or H) from the precursor ester carbanions ((1): X = Y = H, R = alkyl) and perchloryl fluoride (C.E. McKenna and P.D. Shen, J. Org. Chem. 46, 4573 (1981)).

$(RO)_2P(O)CXYP(O)(OR)_2$ (1) $\qquad$ $RO_2CCXYP(O)(OR')_2$ (2)

The fluorinated methanediphosphonic acids are interesting analogs of pyrophosphate and make possible synthesis of related nucleotide fluorophosphonate analogs (N.D. Leswara, P.D. Shen and C.E. McKenna, Fed. Proc. 41, 3453 (1982)). We now have applied this method to prepare α-mono- and α,γ-difluorophosphonoacetates ((2): X = H or F, Y = F, R = R' = Et). Trimethylsilyl bromide (BTMS) selectively silyldealkylates the phosphonate alkyl ester groups, giving the CO-ethyl PO-(bis)trimethylsilyl esters ((2): R = Et, R' = TMS). The compounds hydrolyze to the corresponding triacids ((2): R = R' = H) when treated with H_2O, or can be converted to the CO-ethyl phosphonic acid ((2): R = Et, R' = H) by reaction with wet EtOH. The products (2) were characterized by ^1H, ^{31}P, ^{19}F and ^{13}C nmr spectra. These fluorinated compounds may be of biological interest in view of the anti-viral activity exhibited by phosphonoacetate and some CO-alkyl phosphonoacetates.

PHOSPHORUS CONTAINING INHIBITORS. Stephan G. Kleemann* and James F. Riordan, Harvard Medical School, Seeley G. Mudd Bldg., 250 Longwood Ave., Boston MA 02115 U.S.A.

A series of active-site directed inhibitors of zinc proteases (angiotensin-converting enzyme, carboxypeptidase A, and thermolysin) have been synthesized and their properties investigated. Their general structures are $(HO)_2P(O)$-X-CO-Y , where the phosphonate group serves as metal ligand and Y refers to an amino acid designed to interact with substrate recognition sites. Variation of X = alkyl resulted in a significant change in K_i. Groups shorter or longer than X = $(CH_2)_2$ led to less active inhibitors, presumably due to nonoptimal interaction of the side chain with the S_1 subsite. These inhibitors can be extremely potent; thus 3-phosphonoacetyl-L-proline, for example is a competitive inhibitor of angiotensin-converting enzyme with a K_i of 4.8×10^{-7} M at pH 7.5 and a K_i of 1.1×10^{-7} M at pH 6.8. The mode of inhibition as well as the pH profile of these inhibitors will be discussed in detail.

OPTICALLY ACTIVE 1-AMINOALKANEPHOSPHONIC ACIDS

Barbara LEJCZAK , Lidia KUPCZYK-SUBOTKOWSKA , Paweł KAFARSKI
Przemysław MASTALERZ

Institute of Organic and Physical Chemistry,Technical University of Wrocław,50-370 Wrocław,POLAND

Jerzy SZEWCZYK

Department of Organic Chemistry,Technical University of Gdańsk, 80-952 Gdańsk,POLAND

Two independent methods for the preparation of optically active 1-aminoalkanephosphonic acids are described.Thus,enantiomeric phosphonic analogues of alanine,valine,leucine,phenylglycine and phenylalanine were obtained from the corresponding racemic diphenyl 1-aminoalkane-phosphonates using dibenzoyl-L-tartaric acid anhydride as an resolving agent.The second method consists in separation of unblocked and totally blocked phosphonodipeptides by means of column chromatography followed by acid hydrolysis of the obtained diastereoisomeric dipeptides. In this manner phosphonic analogues of alanine,leucine,phenylalanine, methionine,serine and glutamic acid were obtained.

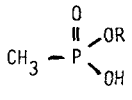
INTERACTIONS OF CHOLINESTERASES WITH ORGANOPHOSPHINATES. C. N. Lieske, J. H. Clark, H. G. Meyer, M. D. Green, P. S. Hammond, and J. R. Lowe, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md. 21010, and P. Blumbergs and M. A. Priest, Ash Stevens Inc., Detroit, Michigan 48202.

Studies on cholinesterase/phosphinate interactions are at an embryonic stage compared to such investigations with organophosphonates and organophosphates. Previous reports from our laboratory have described the inhibition, spontaneous reactivation, and oxime-induced reactivation of several cholinesterases acted upon by a number of esters of diaryl, aryl/alkyl, and dialkylphosphinic acids. More recently we have examined the effect on cholinesterase kinetics of the substitution of chlorine for hydrogen in esters of aryl/alkyl phosphinic acids. For example, the progressive substitution of chlorine for hydrogen in the methyl group of 4-nitrophenyl methyl(phenyl)phosphinate resulted in the following order for the inhibition constants of eel acetylcholinesterase: monochloro > unsubstituted > dichloro > trichloro. We propose a three-centered hydrogen bonding inhibition mechanism to account for the order observed. As a frame of reference, the k_i for the monochloro compound is 75 times larger than the value we obtained for the inhibition of eel acetylcholinesterase by the commercial insecticide paraoxon. Induced reactivation studies using the oxime TMB-4 showed 100% recovery in two hours for enzyme inhibited by the unsubstituted and monochloro compounds. In spontaneous reactivation studies monochloromethyl(phenyl)phosphinylated eel acetylcholinesterase was the most responsive, with 100% recovery of enzymatic activity in 24 hours at pH 7.60. The kinetic pathways observed for the alkaline hydrolysis of the trichloro compound make this phosphinate ester a potentially valuable model for future enzymatic studies on the aging phenomenon.

DEGRADATION PRODUCTS OF NERVE AGENTS IN BLOOD AND URINE. DERIVATIZATION AND GC-MS ANALYSIS.

S-A. Fredriksson, G. Lindberg and B. Olofsson.
National Defence Research Institute, FOA 4, S-901 82 UMEA, Sweden

The O-alkyl methylphosphonic acids (1) necessary for this investigation were synthesized from methylphosphonic anhydride and the appropiate alcohols. Benzylation of the phosphonic acids (1) was performed with the triazene alkylating agents (2). The benzyl esters (3) were analyzed by chromatography on packed and capillary colums.



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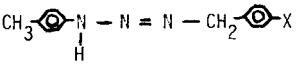

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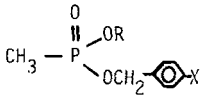


3

R = - H, - CH_2CH_3, - $CH(CH_3)_2$, - $CH(CH_3)C(CH_3)_3$

X = - H, - NO_2, - Cl

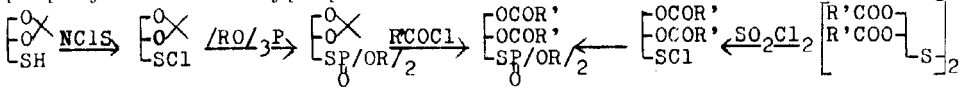
ETUDE PAR RMN du ^{31}P DE L'INTERACTION ENTRE SITES PHOSPHATES DE BIOMOLECULES ET RADIOPROTECTEURS SOUFRES - MALLET Georges et VASILESCU Dane - Laboratoire de Biophysique - Université de NICE - Parc VALROSE - U.E.R. I.P.M. - 06034 NICE Cedex - FRANCE.

La radioprotection chimique consiste en l'administration de molécules à un animal ou à une culture cellulaire, avant irradiation, de manière à réduire la proportion des radiolésions du matériel nucléaire. A ce jour, la classe des radioprotecteurs soufrés du type cystéamine ou WR 2721 et son métabolite le WR 1065 est la plus intéressante. A cet égard, des recherches expérimentales et théoriques menées "in vitro" en notre laboratoire ont mis en évidence une forte interaction électrostatique entre ces radioprotecteurs et les sites phosphates du DNA ou de la tête polaire d'un lipide.

Nous présentons ici une étude par spectroscopie R.M.N. du ^{31}P relative à l'effet des rayons γ (source de ^{60}Co) sur l'environnement électronique des noyaux de ^{31}P de certaines biomolécules. Outre l'effet cumulatif de la dose de rayonnement sur les différents sites phosphates, nous avons suivi l'effet de radioprotecteurs soufrés (WR 1061 par exemple). Une discussion des résultats obtenus avec les molécules de 5' AMP, 5' ATP et Poly A est faite.

THIOLO ISOMERS OF THIOPHOSPHATIDIC ACID. Anna Markowska and Barbara Mlotkowska Institute of Organic Chemistry, Technical University in Lodz, Poland.

Thiolo isomers of thiophosphatidic acid are particularly useful in investigations of biological functions of phospholipids[1]. We have obtained the thiolo isomer of thiophosphatidic acid ester **6** starting from the blocked thioglycerol **1** as well as from the related disulphide **2**. Chlorination of **1** and **2** resulted in the formation of sulfenyl chlorides **3** and **4** respectively. The chlorides **3** and **4** were phosphorylated with trimethylphosphite



1 **3** R = Me **5** **6** **4** R' = $C_{17}H_{35}$ **2**

to give the corresponding phosphorothiolates **5** and **6**. The thiolate **5** was transformed into the thiolate **6** on treatment with stearoyl chloride in the presence of $ZnCl_2$. The thiolates **5** and **6** were monodemethylated with tert-butylamine to produce the corresponding tert-butyl-methyl-ammonium salts. The yields of the final products were satisfactory (70%). The structure of all the compounds obtained was confirmed by ^{31}P and ^{1}H nmr spectroscopy and elementary analysis.

1) E.E. Nifant'ev, D.A. Predvoditelev, Bioorg. Khimia 7 (9) 1285 (1981).

^{31}P NMR TITRATION STUDIES OF β,γ-FLUOROMETHYLENE ATP ANALOGS. Charles E. McKenna, Nelly D. Leswara and Inja Yi, Department of Chemistry, University of Southern California, Los Angeles, CA 90089-1062, USA

In earlier work we reported the synthesis of two new pyrophosphate analogs, fluoromethanediphosphonic acid ((1a): X = H, Y = F) and difluoromethanediphosphonic acid ((1b): X = Y = F), as well as the synthesis of the corresponding fluorinated β,γ-methylene adenosine-5'-triphosphate (ATP) derivatives ((2a): X = H, Y = F; (2b): X = Y = F).

$(HO)_2P(O)CXYP(O)(OH)_2$ (1)

AMP-OP(O)(OH)CXYP(O)$(OH)_2$ (2)

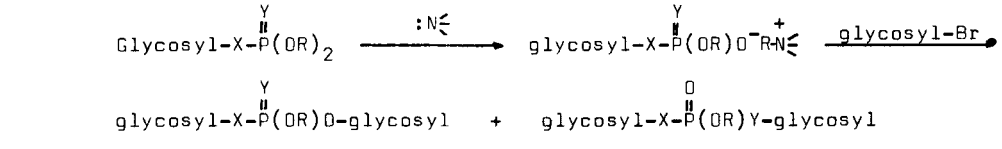
We have now studied the ^{31}P NMR-pH dependence of the four analogs (1a) - (2b) to establish their potential as spectrometric pH probes. Titration of (1a) with OH^- over a pH range from 1 to 11 results in a biphasic plot of $\delta(P^{31})$ from 9.75 to 11.0 ppm (1a), while (1b) gives a monophasic plot from 3.3 to 6.1 ppm. Similar titrations of (2a) and (2b) over a pH range of 6.1 - 8.1 reveal sharply differing pH-$\delta(P^{31})$ dependencies for the three non-equivalent phosphorous nuclei. Analysis of the data yield pKa values that will be compared with pKa values obtained by classical pH-volume titration methods, and with pKa values for pyrophosphate, unfluorinated methanediphosphonic acid, ATP and β,γ-methylene ATP.

DIGLYCOSYL PHOSPHOROTHIOATES AND DITHIOATES

by M.Michalska, P.Lipka and T.Rokita-Trygubowicz

Department of Organic Chemistry, Faculty of Pharmacy, Medical Academy, 90-145 Lodz, Narutowicza 120a, Poland.

O,O-Dimethyl- and O,O-di-t-butyl-S(glycosyl)phosphorothioates and dithioates are selectively dealkylated and the ambident monoanions formed are condensed with glycosyl bromides to give the title compounds. Both O-glycosylated and S-glycosylated products are observed.



X = S; Y = O,S; glycosyl = peracetylated pentose or hexose residue.

Regio- and stereoselectivity of the reaction is discussed.

SYNTHESIS OF NEW DIPHOSPHONATE DERIVATIVES OF PHARMACOLOGICAL INTEREST.

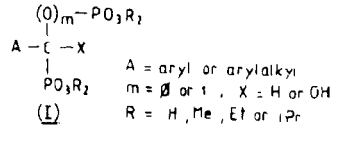
Lân M. Nguyen, Eric Niesor & Craig L. Bentzen, Symphar S.A., 6 ch. des Carpières
1219 LE LIGNON/GENEVA-SWITZERLAND

A series of novel *gem*-diphosphono compounds (I) has been prepared and shown to possess interesting plasma lipid altering activities in rats.

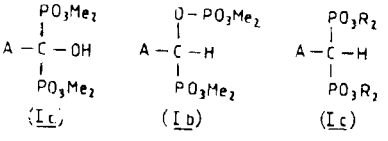
Tetramethyl hydroxydiphosphonates Ia or phosphonate-phosphates Ib were obtained by the addition of dimethyl phosphite to the corresponding ketophosphonates, depending on the reaction conditions used. Compounds Ia and Ib displayed TLC and HPLC behaviors consistent with their structural differences and were identified by ^1H NMR.

Reaction of tetraalkyl methylenediphosphonate with an arylalkyl halide yielded tetraalkyl *gem*-diphosphonates (Ic), (R=Et or iPr). The tetramethyl derivatives Ic (R=Me) were prepared by esterification of the corresponding diphosphonic acids Ic (R=H) with trimethylorthoformate.

Some data on the biological activity of compounds type Ia, Ib and Ic in rats will be presented.



(I)



(Ia) (Ib) (Ic)

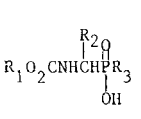
LES NOUVELLES DONNEES SUR LA CHIMIE DES OSES CYCLOPHOSPHORYLES.

E.E. Nifant'ev, M.P. Korotéev, S.A. Roumiantseva. Institut pédagogique d'Etat de Moscou, 119882, Malaya Pirogovskaya, I, Moscou, U.R.S.S..

Pour la première fois ont été obtenus les 1,2-cycloamidophosphites des oses à l'aide de phosphorylation par $P(NR_2)_3$ des hydroxyles alcooliques et glycosidiques des pentoses et hexoses partiellement substitués. La phosphorylation de 3-methylglucopyranose et des systèmes parents a été effectuée pour donner des 1,2,4-bicyclophosphites de pyranoses. Les 3,5,6-bicyclothio- et amidophosphites ont été obtenus à l'aide de la cyclisation des 3,5-cyclothio- et amidophosphites des 6-tosyl-1,2-alkoylidenglucofuranoses. Comme les autres phosphites les cyclophosphites des oses forment des complexes avec les sels de Ca, Co, Pt, Pd, Cu. Les derniers sont des catalyseurs d'hydrogénation et d'hydrosilylation. Les complexes des 1,2-cycloamidophosphites sont des agents de glucolisation. Les bicyclophosphites des oses réagissent difficilement sur les électrophiles et au contraire très facilement sur les réactifs homolytiques. Par exemple, ils se transforment en cyclophosphates halogénés par action des halogènes et par action des hydrohalogénures en cyclophosphites acidiques. En présence de peroxyde d'hydrogène on obtient des cyclophosphates acidiques, avec des peroxydes organiques on obtient des phosphates non acidiques.

PREPARATION OF N-PROTECTED 1-AMINOALKYL PHOSPHINIC ACIDS AND THEIR CONVERSION TO NOVEL INHIBITORS OF ANGIOTENSIN-CONVERTING ENZYME. Edward W. Petrillo, Jr., Donald S. Karanewsky, Ervin R. Spitzmiller, and Mark E. Duggan, Squibb Institute for Medical Research, P.O. Box 4000, Princeton, New Jersey 08540, U.S.A.

Aldehydes, carbamates, and alkyldichlorophosphines react with 2 equiv. trimethylacetic acid at room temperature to yield 1-alkoxycarbonylaminoalkyl phosphinic acids I. The method is compatible with the presence of other functional groups in the reactants, and acylation of the products by the carboxylic acid coreactant does not occur. The method is especially suited to the synthesis of complex targets such as the novel angiotensin-converting enzyme inhibitors II and III.



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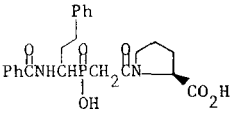
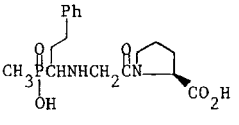


II



III

NEW METHODS IN THE SYNTHESIS OF PHOSPHOLIPIDS AND THEIR ANALOGS ON THE BASIS OF GLYCEROPHOSPHITES AND -AMIDOPHOSPHITES. D.A.Predvoditelev, E.E.Nifant'yev. V.I.Lenin State Pedagogical Institute, Moscow. USSR, 1199882, Malaya Pirogovskaya, 1.

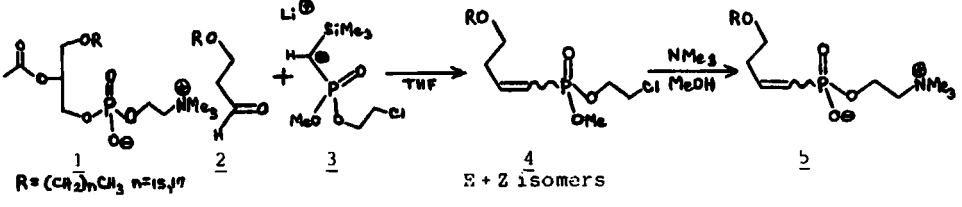
A New possibilities of methods of phosphite chemistry for creating "a phosphoric junction" are described in the present report. By means of oxidation (sulphur- and selenorisation) with the further acylation of triesterphosphites of isopropylidenglycerine the phosphatide acids and their analogues were obtained. The same compounds were also produced on the basis of anilido- and selenorphosphites of glycerine. The amido-phosphite method was also used in the simple synthesis of complex hydro-carbons containing lipids, for instance, phosphatidyl-6-maltose. The cyclis phosphites appeared to be a very convenient intermediate for synthesis of phospholipids and their analogues of various types. The lasts were obtained by alkylation of trimethylamine or sodium iodide or stearate with alkylenphosphates and alkylenthionphosphates of glycerine derivatives obtained from cyclophosphites. During the reaction of thion-phosphates with sodium iodide thion-thiol isomerisation was established. Thanks to this it became possible to obtain the thion- and thiolphospho-lipids.

REACTIONS OF 2-CHLOROETHYL METHYL (LITHIO) (TRIMETHYLSILYL) METHYLPHOSPHONATE. SYNTHESIS OF UNSATURATED CARBON ISOSTERES OF PLATELET ACTIVATING FACTOR. John C. Tomesch and Judit M. Koletar, Preclinical Research, Sandoz, Inc., East Hanover, NJ 07936 U.S.A.

Platelet Activating Factor (PAF; 1-o-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine) (1) is a physiologic mediator of inflammatory reactions, possessing potent platelet aggregating, antihypertensive, and allergic properties. As part of a program directed to finding antagonists of PAF we prepared several unsaturated carbon isosteres 5.

The synthesis of 5 was accomplished by reaction of the novel lithio reagent 3, which contains all of the essential features of the choline side chain, with a 3-alkoxypropanal 2 to form an E-, Z- mixture of 4. Treatment of 4 with trimethylamine in methanol afforded the PAF carbon isosteres 5.

The preparation of reagent 3 will be discussed as well as details of its reaction with various substituted aldehydes.



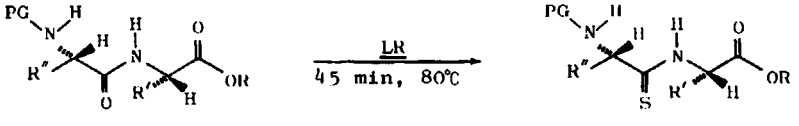
1 2 3 4 5

R = $(CH_2)_nCH_3$ n=15,17

E + Z isomers

THE PREPARATION OF PEPTIDE SURROGATES, ESPECIALLY THIOPEPTIDES, BY USE OF THE THIATION REAGENT 2,4-BIS(4-METHOXYPHENYL)-1,3,2,4-DITHIADIPHOSPHETANE 2,4-DISULFIDE, LR, B.Yde, M.Thorsen, K.Clausen and S.-O. Lawesson, Department of Organic Chemistry, University of Aarhus, 8000 Aarhus C, Denmark

LR, an effective thiation reagent, converts protected peptides into the corresponding thiopeptides. Under suitable conditions Z, Boc and alkoxycarbonyl functions are not thiated. LR is also used as coupling reagent in peptide synthesis.



HPLC analyses of thiopeptides show that no racemization has occurred under the thiation reactions.