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SYNTHESIS OF 2-METHYLTHIO-4H-1,3,2-BENZODIOXAPHOSPHORIN-2-OXIDE BY THIONO-THIOL CONVERSION AND ITS USE AS PHOSPHORYLATING AGENT

Morifusa Eto, Mitsuru Sasaki[1], Masayoshi Iio*, Masayoshi Eto* and Hideo Ohkawa
Department of Agricultural Chemistry and
*Department of Food Science and Technology,
Kyushu University, Fukuoka, Japan

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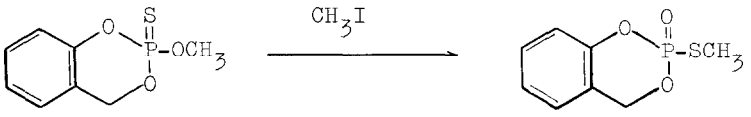
Since the cyclic phosphate esters of saligenin were discovered as the biologically active metabolites of tri-o-tolyl phosphate,[2] many related compounds have been synthesized to study their chemical, biochemical and biological properties.[3] 2-Methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulfide (I) is now commercialized as an insecticide named Salithion.[4] This paper describes that I is easily converted to its thiol isomer (II) and that the latter is useful as a phosphorylating agent.

2-Methylthio-4H-1,3,2-benzodioxaphosphorin-2-oxide (II) is highly active as alkylating agent[5] and has been synthesized by the condensation of saligenin and S-methyl phosphorodichloridothiolate.[6] However, the synthesis of the latter was relatively difficult. Then we tried to prepare II by the isomerization of its thiono analog (I) and found that Pistschimuka reaction[7] was successful. When methyl iodide was used as methylating agent and dimethylformamide or acetamide as solvent and certain salt was added, the conversion accomplished almost quantitatively by 4 hrs at 50°C to afford II, m.p. 44°C, b.p. 125-130°C (0.05 mmHg), IR ($CHCl_3$) 1280 cm^{-1} (P=O). Dimethyl sulfate did not work. Acetone, ethanol and nitromethane were poor as solvent. Potassium bromide or more preferably potassium iodide was very effective for the thiono-thiol conversion. Higher alkyl iodide could be also used to get corresponding alkylthio homologs. Neither alkyl bromide nor chloride was useful.

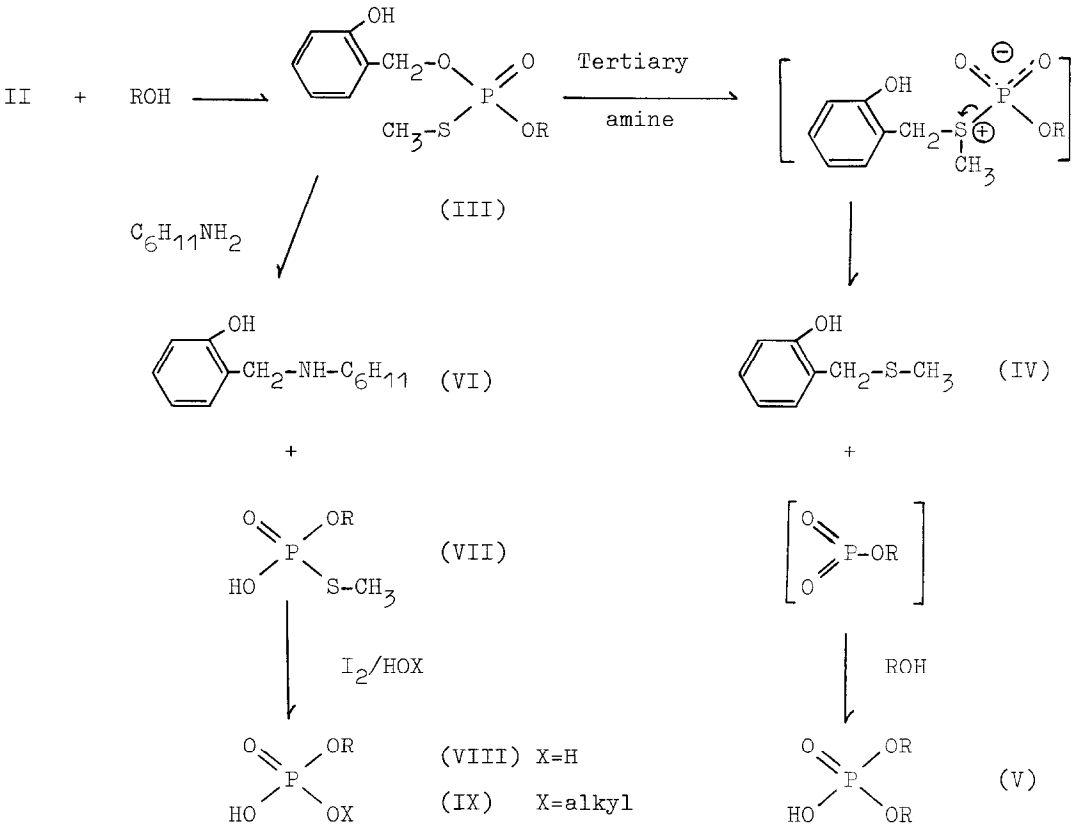


(I) (II)

When the isomerized product (II) was treated with ethanol at 60°C for 4 hrs in the presence of tertiary amine such as triethylamine or pyridine, methyl salicyl sulfide (IV) was unexpectedly produced. From water soluble fraction, diethyl hydrogen phosphate (V) was obtained. A less amount of sulfur-containing ester was also detected on paper electrophoresis. When cyclohexylamine was used instead of tertiary amine, the reaction took place much rapidly. However, neither the sulfide nor the phosphate diester was produced, but N-cyclohexylsalicylamine (VI) and O-ethyl S-methyl phosphorothiolate (VII) were obtained.

These observations may be explained rationally by the following mechanism. The cyclic structure may be opened at first at the P-O-C aryl bond by the nucleophilic attack of alcohol to give O-alkyl O-salicyl S-methyl phosphorothiolate (III). The electron-releasing hydroxyl group at the ortho position of the benzyl ester may promote the formation of a carbonium ion. This benzyl cation may transfer to the nitrogen atom of cyclohexylamine to give VI and VII or, in the presence of tertiary amine, rearrange mainly to the thiolate sulfur atom giving the sulfide (IV) and consequently metaphosphate, which is active enough to phosphorylate another molecule of alcohol. In the latter case, the transfer of salicyl group to the nitrogen atom to result in the formation of quaternary ammonium ion should be unfavorable in the non-aqueous conditions.

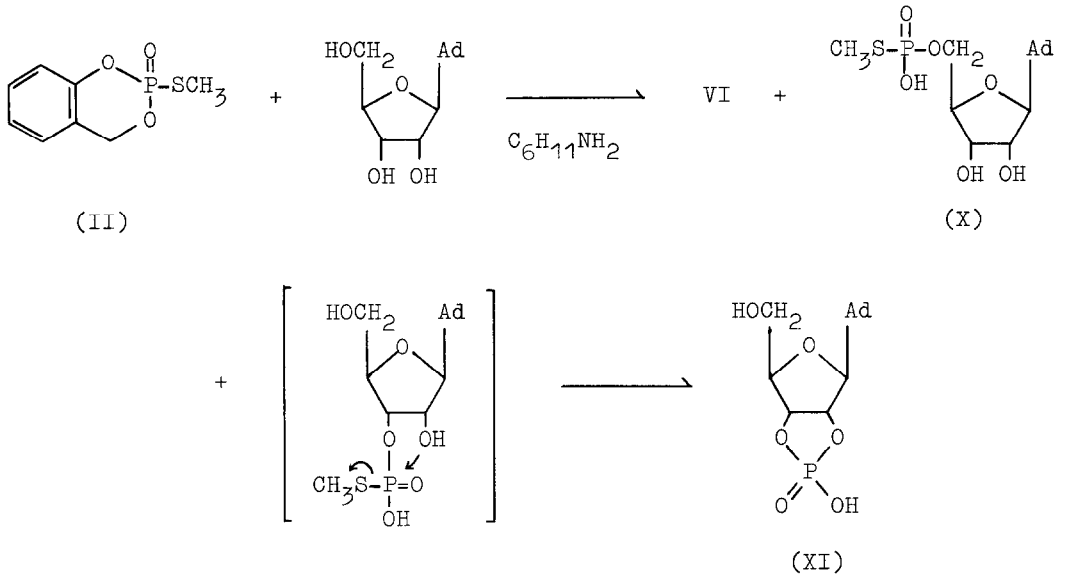
The methylthio group of phosphorothiolate ester (VII) is readily removable by iodine oxidation.[8] When it was carried out in an aqueous condition or in an anhydrous alcohol solution, phosphate monoester (VIII) or corresponding diester (IX) was produced respectively.



These reactions were then applied for the synthesis of nucleotides. When adenosine dissolved in dimethylformamide was treated with the isomerized Salithion(II) in the presence of cyclohexylamine at 100°C for 6 hrs, adenosine-2':3'-cyclic phosphate (XI) and adenosine-5'-S-methyl phosphorothiolate (X) were produced. The major product, XI, was characterized by electrophoresis, paper chromatography, UV spectrum, NMR spectrum and degradation with barium hydroxide giving adenosine-2'-phosphate and 3'-phosphate. The minor product, X, was characterized by iodine oxidation giving adenosine-5'-phosphate. When 5'-O-acetyladenosine was used as a starting material, the cyclic nucleotide (XI) was obtained in more than 50% yield after the hydrolysis of the reaction product with dilute ammonium hydroxide. In spite of the presence of cyclohexylamine in both cases, the methylthio group was removed spontaneously by

the participation of neighboring hydroxyl group to give cyclic ester.

After the isomerization of Salithion, II could be used as phosphorylating agent without isolation. The presence or formation of two different types of readily removable substituents such as o-hydroxybenzyl and methylthio group is the characteristic of this reagent.



References

1. Present address: Research Department, Sumitomo Chemical Co., Osaka
2. J.E. Casida, M. Eto and R. L. Baron, Nature, 191, 1396 (1961); M. Eto, J. E. Casida and T. Eto, Biochem. Pharmacol., 11, 337 (1962).
3. M. Eto, Residue Reviews, 25, 187 (1969).
4. M. Eto, Y. Kinoshita, T. Kato and Y. Oshima, Nature, 200, 171 (1963).
5. M. Eto, H. Ohkawa, K. Kobayashi and T. Hosoi, Agr. Biol. Chem., 32, 1056 (1968); H. Ohkawa and M. Eto, Agr. Biol. Chem., 33, 443 (1969).
6. K. Kobayashi, M. Eto, Y. Oshima, T. Hirano, T. Hosoi and S. Wakamori, Botyu-Kagaku, 34, 165 (1969).
7. A. J. Burn and J. I. G. Gadogan, J. Chem. Soc., 1961, 5532.
8. A. F. Cook, M. J. Holman and A. L. Nussbaum, J. Am. Chem. Soc., 91, 1522 (1969).