The Conversion of Saligenin Cyclic Methyl Phosphorothionate into the Thiolate Analogs and a New Rearrangement Reaction

Sasaki, Mitsuru
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Ohkawa, Hideo
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Eto, Morifusa
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

https://doi.org/10.5109/22828

出版情報：九州大学大学院農学研究院紀要. 17 (2), pp.173-180, 1973-03. Kyushu University
バージョン：
権利関係：

J. Fac. Agr., Kyushu Univ., 17, 173-180 (1973)

The Conversion of Saligenin Cyclic Methyl Phosphorothionate into the Thiolate Analogs and a New Rearrangement Reaction

Mitsuru Sasaki,* Hideo Ohkawa* and Morifusa Eto

Laboratory of Pesticide Chemistry, Faculty of Agriculture,
Kyushu University, Fukuoka

(Received July 2, 1972)

Saligenin cyclic methyl phosphorothionate was smoothly converted into the S-methyl thiolate isomer by the action of methyl iodide in the presence of dimethylformamide and certain salts. Other alkyl iodides also reacted similarly with the cyclic methyl phosphorothionate to give corresponding cyclic S-alkyl phosphorothiolates. The isomerized S-methyl thiolate reacted with ethanol to give phosphate diester. In the course of this phosphorylation reaction a new rearrangement reaction was found ; benzyl group transfered from 0 to S in the phosphorothiolate molecule.

The S-alkyl thiolate analogs of saligenin cyclic methyl phosphorothionate (2-methoxy-4H-1, 3, 2-benzodioxaphosphorin-2-sulfide) (I) are highly reactive and have a fungicidal activity (Eto et al., 1968a ; Kobayashi et al., 1969). They have been prepared by the condensation of saligenin and S-alkyl phosphorodichloridothiolates (Kobayashi et ***al.,*** 1969). As the synthesis of the latter was relatively difficult, some attmpts have been made to prepare the cyclic phosphorothiolates from their isomeric phosphorothionates, particularly from the methyl ester, an insecticide Salithion (I), which is now available in a great quantity. The isomerization reaction of phosphorothionates to phoshorothiolates with heat (Metcalf and March, 1953) or with dimethylformamide (Eto ***et al.,*** 1968b) was applied to the cyclic esters without success (Kobayashi ***et al.,*** 1969).

This report describes the conversion of saligenin cyclic methyl phosphorothionate (I) into thiolate analogs (II) by the action of alkyl iodides, and also a new rearrangement reaction which took place in the course of the reaction of the S-methyl thiolate (II') with alcohol. A preliminary short report on a part of this investigations has appeared (Eto ***et al.,*** 1971).

Pistschimuka undertook first in 1912 an investigation on the reaction of simple alkyl phosphorothionates with alkyl halides and got S-alkyl phosphorothiolates (reviewed by Teichmann and Hilgetag, 1967). The Pistschimuka reaction required generally rather vigorous conditions as heating for many hours at 100 to 150°C and its preparative value was limited by poor yields and by side reactions. However, these disadvantages seemed to be overcome by the use of strongly

* Present address: Research Institute, Pesticide Division, Sumitomo Chemical Co., Takarazuka

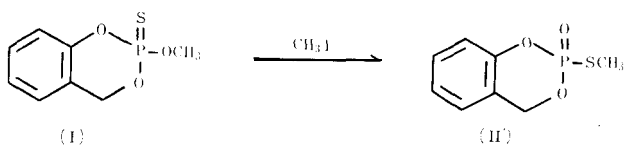
polar solvents (Burn and Cadogan, 1961). Thus, we applied the Pistschimuka reaction to the cyclic phosphorothionate, Salithion (I), for the preparation of its thiolate analogs (II).

When methyl iodide was used, the isomerization of Salithion (I) to the S-methyl thiolate (II') proceeded smoothly in dimethylacetamide or dimethylformamide at about 50°C as shown in Table 1. The reaction was accelerated by the addition of certain salt such as potassium bromide or carbonate. Under these conditions, no product other than the cyclic S-methyl phosphorothiolate (II') was observed on thin-layer chromatography visualized with diazotized sulfanilic acid after hydrolysis and the formation of the thiolate isomer reached more than 90 % within 2 hours. The thiolate isomer was actually obtained in 72 % yield after distillation in the presence of dimethylformamide.

Table 1. Isomerization of saligenin cyclic methyl phosphorothionate (I) under a variety of conditions.*'

Methylating agent	Solvent	Salt	% Isomerized
CH_3I	Acetone		35 -- 20
CH_3I	Acetone	K_2CO_3	50 -- 60
CH_3I	Acetone	KC1	10 — 35
CH_3I	Ethanol	K_2CO_3	30 — 35
CH_3I	Nitromethane	K_2CO_3	12 -- 37
CH_3I	DMF*2		55 – 65
CH_3I	DMF	K_2CO_3	68 — 76
CH_3I	DMF	KCl	87 — 92
CH_3I	DMA*3		60 -- 65
CH_3I	DMA	K_2CO_3	90 — 95
CH_3I	DMA	KC1	72 — 78
CH_3I	DMA	KBr	90 — 98
$(CH_3O)_2SO_2$	DMSO""	K_2CO_3	trace
$(CH_3O)_2SO_2$	Acetone	K_2CO_3	trace

*1. A reaction mixture consisting of I (4.6 mmole), methylating agent (6.9 mmole), and solvent (10 ml) was kept at 50 to 60° for 3 hrs in the presence or absence of salt (4.6 mmole).
*2. N, N-dimethylformamide.
*3. N, N-dimethylacetnmide.
*4. dimethylsulfoxide.



(I) (II')

The isomerized product obtained was identical with the preparation synthesized by the condensation procedure from saligenin and S-methyl phosphorodichloridothiolate (Kobayashi et al., 1969). Its infrared spectrum is shown in Fig. 1.

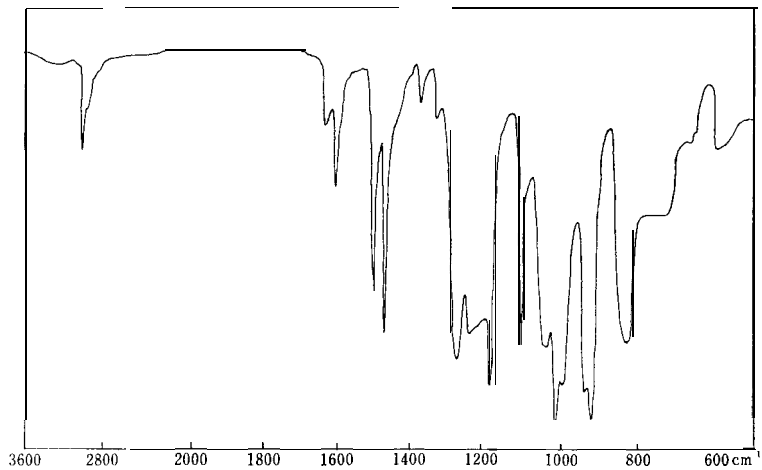


Fig. 1. Infrared spectrum of 2-methylthio-4H-1,3,2-benzodioxaphosphorin-2-oxide (II') obtained by the isomerization of Salithion. ($CHCl_3$).

The use of dimethyl sulfate in place of methyl iodide was ineffective for the isomerzation. Ethanol and nitromethane were poor as the solvent for the isomerization reaction. Acetone was moderate in effectiveness as the solvent, if potassium carbonate was coexistent. In this condition, the actual yield of the thiolate isomer was 43 % after distillation. When ethanol was used as solvent, an additional phenolic substance besides the thiolate and unreacted Salithion was detected from the reaction mixture on thin-layer chromatography. That was characterized as o-(a-methylthio) cresol as will be discussed later.

The isomerization reaction proceeded also at room temperature in the presence of dimethylformamide as shown in Table 2. The effectiveness of dimethylformamide was also demonstrated by the small amounts of its addition to acetone.

Table 2. Isomerization of saligenin cyclic methyl phosphorothionate (I) at room temperature.*1

Solvent	Salt	% Isomerized
Acetone		29
Acetone	K_2CO_3	52
Acetone + DMF*2	K_2CO_3	75
DMF	K_2CO_3	97

*1. A mixture of I(1 g), methyl iodide (0.8 g), potassium carbonate (0.75 g or nothing) and solvent (10 ml) was kept for 24 hrs.

*2. Dimethylformamide (1.2 g) was added to 10 ml of acetone.

Other alkyl iodides also reacted similarly with Salithion to give corresponding S-alkyl phosphorthiolates. Alkyl bromide and chloride were very poor to prepare the phosphorothiolates. The yields are shown in Table 3.

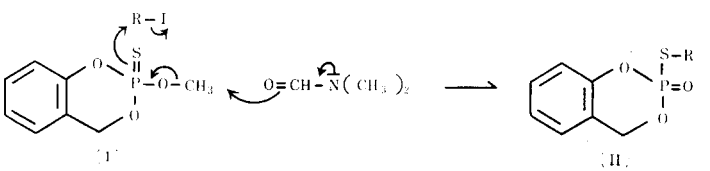
All these results show dimethylformamide is very effective for the Pistschimuka reaction. It has been demonstrated that dimethylformamide reacts with dimethyl

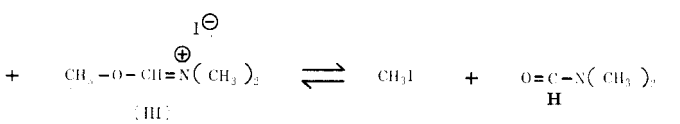
Table 3. Conversion of saligenin cyclic methyl phosphorothionate (I) into S-alkyl thiolate analogs (II).*

Alkyl halide used	Thiolate produced (%)
Ethyl iodide	73 – 75
Isopropyl iodide	63 67
n-Butyl iodide	60 65
Benzyl iodide	40 – 50
Isopropyl bromide	trace
Isopropyl chloride	trace

* A mixture of I (4.6 mmole), potassium carbonate (4.6 mmole), alkyl halide (9.2 mmole) and dimethylformamide (10 ml) was kept at 50–60°C for 4 hrs.

aryl phosphorothionates to form 0-methylated product (III) and accelerates the thiono-thiol isomerization of the phosphorothionates (Eto *et al.*, 1968b). This reaction appears to participate in the Pistschimuka reaction too. There were evidences to indicate the formation of 0-methylated dimethylformamide (N, N-dimethyl methoxymethyleneimmonium salt) (III) ;1) the reaction mixture contained a compound which gave a positive test to Dragendorff's reagent and showed Rf-value of 0.00 on thin-layer chromatography ; 2) the distillate obtained between 40 and 60°C from the reaction mixture gave a positive hydroxamic acid test for carboxylic esters. 0-Methylated dimethylformamide should be hydrolyzed to give dimethylamine and an ester, methyl formate (Eto *et al.*, 196813). Thus the following mechanism can be proposed reasonably for the thiono-thiol conversion of saligenin cyclic methyl phosphorothionate (I).





The reaction of the isomerized Salithion (II') with alcohol was then investigated. As the cyclic methyl thiolate was relatively unstable and its isolation was rather laborious, if dimethylformamide existed, it was used without isolation. This was made possible by the fact that the isomerization reaction proceeded almost quantitatively. By the reaction of the methyl thiolate (II') with ethanol in the presence of a tertiary amine, diethyl phosphate and *o*-(α-methylthio)cresol were unexpectedly obtained.

From the reaction mixture only one product (IV) was detected with palladium chloride reagent. This was the same with the by-product detected in a

small amout in the course of isomerization reaction using ethanol as solvent. The product IV was purified through column chromatography and extraction procedure, and a liquid was obtained in 30 % yield. Qualitative tests showed the compound IV contained neither nitrogen, phosphorus, nor halogen, but sulfur atom. It gave positive tests with diazotized sulfanilic acid, cupric chloride-potassium ferricyanide, and ferric chloride reagents, indicating the existence of free phenolic hydroxy group. It was supported by infrared spectrum, $\nu_{max}^{CHCl_3}$ cm-' : 3300-3340, 3610 (Fig. 2). The elementary analysis indicated the experimental formula of $C_8H_{10}OS$. On the basis of these data, the compound IV was presumed as o-(a-methylthio)cresol. This was synthesized from phenol and dimethylsulfoxide according to Hayashi and Oda (1967). Both preparations were identical in respect with chromatography (Table 4) and infrared spectrum (Fig. 2).

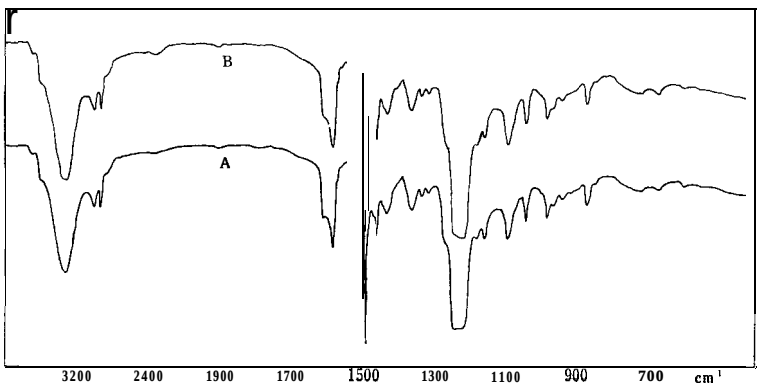


Fig. 2. Infrared spectra of authentic *o*-(*α*-methylthio) cresol (A) and Compound IV (B) obtained by the reaction of isomerized Salithion (II') and ethanol. ($CHCl_3$).

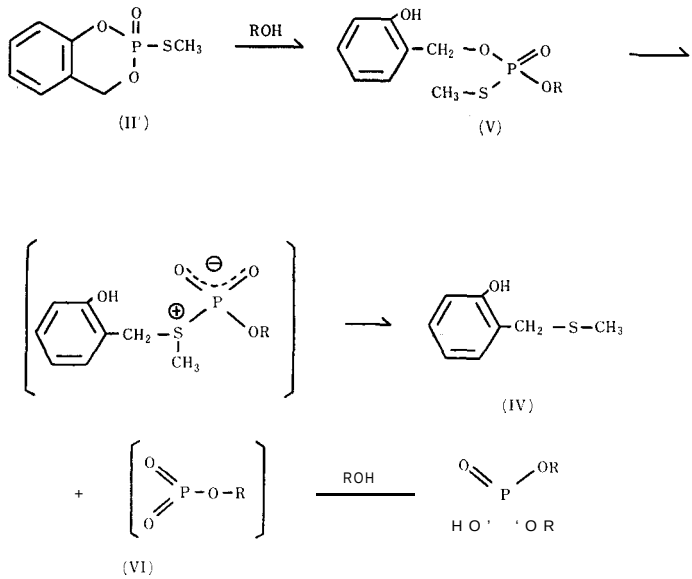
Table 4. Rf-values of Compound IV produced by the reaction of isomerized Salithion (II') and ethanol as compared with related known compounds.

Solvent*	a	b	c
Compound IV	0.63	0.44	0.09
o-(a-methylthio)cresol	0.63	0.44	0.09
Salithion (I)	0.96	—	—
Thiolate isomer (II')	0.51		—

* Silica gel thin-layer chromatography ;
Solvent a : chloroform-ether (9 : 1 v/v), b : chloroform, c : benzene

For the formation of the sulfide IV, o-hydroxybenzyl group should rearrange to the sulfur atom of phosphorothiolate (V). This suggests the production of diethyl phosphate via metaphosphate. Actually diethyl phosphate was isolated as barium salt from the water-soluble fraction of the reaction mixture. Thus, a reasonable reaction mechanism is proposed as follows : The cyclic structure of II' may be opened at first at the P-O (aryl) bond by the nucleophilic attack of

alcohol to give O-ethyl S-methyl 0-salicyl phosphorothiolate (V). The presence of an electron-releasing hydroxy group at the ortho position of the benzyl ester may promote the formation of a carbonium ion, which may rearrange to the phosphorothiolate sulfur atom giving the sulfide (IV) and consequently metaphosphate (VI) which is active enough to phosphorylate another molecule of alcohol. Similar rearrangement reaction has been known (Hilgetag and Teichmann, 1965).



Because the easiness to prepare and the high reactivity with alcohols, 2-methylthio-4H-1, 3, 2-benzodioxaphorin-2-oxide (II') appears to be useful as a phosphorylating agent. The application to the syntheses of mixed phosphate diesters and cyclic nucleotides will be reported elsewhere.

MATERIALS AND METHODS

2-Methoxy-4H-1, 3, 2-benzodioxaphosphorin-2-sulfide (I). An insecticide Salithion, technical grade, was obtained from Sumitomo Chemical Co., Osaka, and was purified by recrystallization from methanol. M. p. 55°C.

2-Methylthio-4H-1, 3, 2-benzodioxaphosphorin-2-oxide (II'). A mixture of I (10 g), methyl iodide (7.2 g) and potassium carbonate (7.5 g) in acetone (60 ml) was refluxed for 2.5 hrs. After removal of acetone and methyl iodide by evaporation, the residue was extracted with 50 ml of chloroform and insoluble materials were filtered off. The solvent was evaporated under reduced pressure and the residue was distilled in vacuo at 125-130°C (0.05 mmHg) to yield 4.3 g (43 %). The distillate solidified slowly into colorless crystals whose melting point was 44°C.

A reaction mixture which additionally contained 12 g of dimethylformamide was heated at 55°C for 4 hrs and processed similarly as mentioned above, but

the solvents were removed in vacuo and chloroform extract was washed with water and dried before distillation. Yield was 72 %.

Isomerization of I under the variety of conditions. A mixture of I, methyl iodide (or dimethyl sulfate) in an appropriate solvent in the presence or absence of potassium salt was heated on a water-bath at 50 to 60°C for 2 hrs. In another series of experiments, the reaction mixture was kept at room temperature for 24 hrs. The reaction mixture was then submitted to a silica gel thin-layer chromatography (TLC).

The TLC was developed with a mixture of chloroform and ether (9: 1 v/v) and visualized by spraying diazotized sulfanilic acid after treatment with alcoholic potassium hydroxide solution. Semiquantitative determination was carried out with a densitometer (Atago Densitomaster Type 8) at 440 mp.

Conversion of I into S-alkyl thiolate analogs by the action of alkyl halides. A mixture of I (4.6 mmole), potassium carbonate (4.6 mmole), alkyl halide (9.2 mmole) and dimethylformamide **(10** ml) was kept at 50 to 60°C for 4 hrs and submitted to TLC.

Reaction of isomerized Salithion (II') with ethanol. A mixture of I (3 g), methyl iodide (2.1 g), potassium carbonate (2.5 g), dimethylformamide (2 g). and acetone (20 ml) was heated on a water-bath at 50 to 60°C. After the isomerization was completed (4 hrs; confirmed by TLC), potassium carbonate was filtered off. Acetone and methyl iodide were evaporated under reduced pressure. To a residual solution containing II' (ca. 3 g) and dimethylformamide (2 g), 1.2 g of ethanol and 10 ml of triethylamine or pyridine were added and the mixture was kept at 50 to 60°C for 4 hrs.

Isolation and characterization of o-(a-methylthio) cresol (IV). For this purpose the above mentioned reaction mixture of II' and ethanol which contained triethylamine was used. Triethylamine was removed under reduced pressure. The residue was dissolved in a small portion of chloroform and submitted to a silica gel column (4.5 x 45 cm) and eluted with a mixture of chloroform and ether (9: 1 v/v). Fractions giving a positive test withpalladiumchloride reagent were collected and concentrated. The residue was dissolved in ether and extracted with 2 % sodium hydroxide. The aqueous layer was acidified with hydrochloric acid and reextracted with ether. The ethereal solution was washed with water and dried over anhydrous sodium sulfate. The ether was evaporated and the oily residue was dried in a vacuum desiccator over phosphorus pentoxide. The yield was 0.62 g (30 %). ***Anal.*** Found: C, 62.14; H, 6.60 %. Calcd. for $C_8H_{10}OS$; C, 62.33 ; H, 6.49 %. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3320, 1210-1240 (phenolic OH) ; 1610, 1585, 1490 (aromatic ring).

An authentic o-(a-methylthio)cresol was prepared from phenol and dimethylsulfoxide according to Hayashi and Oda (1967). It was distilled at 90-95°C (1.0 mmHg) and purified through column chromatography. The infrared spectra of the both preparations are completely identical as shown in Fig. 2.

Isolation of diethyl phosphate. After removal of triethylamine, 30 ml of water was added to the reaction mixture of II' and ethanol. Anion exchange resin, Dowex I-x8 (OH form) (30 g) was added to the aqueous solution and stirred at

room temperature for 1 hr after adjusted the solution pH 7. The resin was then filtered, washed with water, and then suspended in water acidified to pH 1 with N hydrochloric acid. After stirring for 1 hr, the resin was filtered. The filtrate was adjusted to pH 7.5 with saturated barium hydroxide. After centrifugation, three volumes of ethanol were added to the supernatant. The precipitate was collected, washed with acetone and ether, and dried. Yield 120 mg. Anal. Found; P, 11.46 %. Calcd. for $C_8H_{20}O_6P_2Ba.6H_2O$; P, 11.25 %.

This was identical with an authentic diethyl phosphate on the basis of paper chromatography.

REFERENCES

Burn, A. J. and J. I. G. Cadogan 1961 The reactivity of organophosphorus compounds. Part IX. The reaction of thionates with alkyl iodides. *J. Chem. Soc.*, 5532

Eto, M., H. Ohkawa, K. Kobayashi and T. Hosoi 1968a Saligenin cyclic phosphorus esters as biological alkylating agents and fungicides. *Agr. Biol. Chem., 32 : 1056*

Eto, M., L. C. Tan, Y. Oshima, and K. Takehara, 1968b The isomerization of alkyl phosphorothionates induced by carboxylic acid amides. *Agr. Biol. Chem., 32: 656.*

Eto, M., M. Sasaki, M. Iio, M. Eto, and H. Ohkawa 1971 Synthesis of 2-methylthio-4H-1, 3,2-benzodioxaphosphorin-2-oxide by thiono-thiol conversion and its use as phosphorylating agent. *Tetrahedron Letters, No. 45, 4263*

Hilgetag, G. and H. Teichmann 1965 The alkylating properties of alkyl thiophosphates. *Angew. Chem. Internat. Edit., 4* : 914

Kobayashi, K., M. Eto, Y. Oshima, T. Hirano. T. Hosoi, and S. Wakamori 1969 Synthesis and biological activities as insecticides and fungicides of saligenin cyclic phosphorothiolates. *Botyu-Kagaku, 34 : 165*

Metcalf, R. L. and R. B. March 1953 The isomerization of organic thionophosphate insecticides. *J. Econ. Entomol., 46: 288*

Teichmann, H. and G. Hilgetag 1967 Nucleophilic reactivity of the thiophosphoryl group. *Angew. Chem. Znternat. Edit., 6: 1013*