

생합성적 방법을 이용한 천연물의 합성 (제 1 보).

메틸 3-히드록시메틸오르셀리네이트의 합성

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(1978. 8. 3 접수)

Studies on Biogenetic-type Synthesis of Natural Products (I).

Synthesis and Reactions of Methyl 3-Hydroxymethylorsellinate

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(Received Aug. 3, 1978)

요 약. 오르시놀로부터 메틸 3-히드록시메틸오르셀리네이트를 합성하고 이의 아세틸화 반응에 대하여 연구하였다.

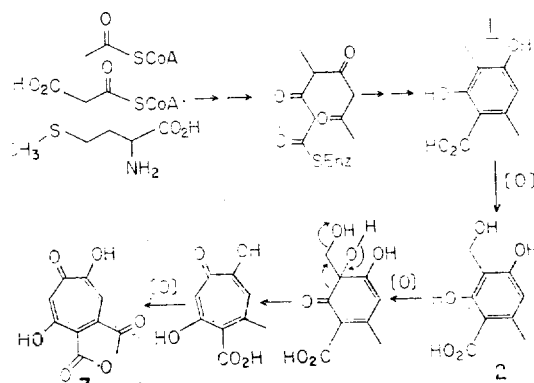
ABSTRACT. Methyl 3-hydroxymethylorsellinate was synthesized from orcinol and various acetylation methods were studied. Two of three possible diacetates were prepared by short-interval acetylation procedure.

INTRODUCTION

It has been recognized for some time that 3-methylorsellinic acid (1) (or some of its derivatives) serves as an intermediate in the biosynthesis of the tropolone system of the *Penicillium stipitatum* metabolites.¹ From the results of the ¹⁸O₂ feeding experiments,² it was further inferred that the action of monooxygenases should precede the crucial ring expanding step and 3-hydroxymethylorsellinic acid (2) may be involved in the biosynthesis of stipitonic acid (3) as shown in Scheme 1.

Demonstrating the existence of such a pathway *in vitro* will further support the proposed biosynthetic scheme. As a first step toward the

ultimate biogenetic-type synthesis of tropolones, methyl ester of 3-hydroxymethylorsellinic acid was prepared and some aspects of its chemistry were investigated, which concerns the interest-



Scheme 1.

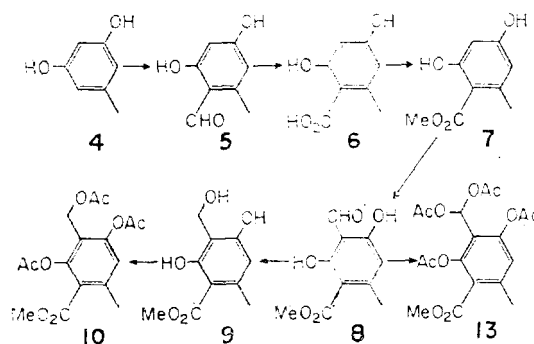
ing moiety of 2-hydroxymethylresorcinol.

RESULTS AND DISCUSSION

Orsellinic acid(6) was prepared from orcinol (4) following known procedures^{3,4} via orcyaldehyde(5). Standard diazomethane treatment converted 6 to methyl orsellinate(7)⁵ from which methyl 3-formylorsellinate(8) was synthesized by the modified Gattermen synthesis as reported⁶ (Scheme 2).

Reduction of 8 was cleanly achieved using sodium cyanoborohydride in buffered methanol at room temperature. Reacting with sodium borohydride in cold ethanol worked as well but a slight delay in work-up produced polar by-products. Disappearance of the aldehyde singlet at δ 10.34 and appearance of a two proton singlet at δ 4.61 and a broad hydroxyl proton signal around δ 4.0 in the nmr spectrum suggested that the product was methyl 3-hydroxymethylorsellinate(9) as expected. The broad infrared absorption band at 1620~1660 cm^{-1} region for aromatic aldehyde and ester with hydrogen bonding in 8 was replaced by a much sharper peak at 1630 cm^{-1} for only the ester functionality confirming the transformation. The compound was stable in crystalline state.

Several different methods were investigated to see whether selective acetylation is possible. Heating 9 under reflux in acetic anhydride with sodium acetate or reaction in pyridine and acetic anhydride at room temperature yielded a single product in high yield. It was shown to be the triacetate(10) as deduced from the nmr spectrum displaying the methylene singlet at δ 4.94 and the three acetate singlets at δ 1.90, 2.22 and 2.26. In the third and new trial acetylation, 9 was dissolved in dimethylformamide and treated with acetic anhydride and catalytic amount of potassium fluoride at room temperature. A clean conversion to the same

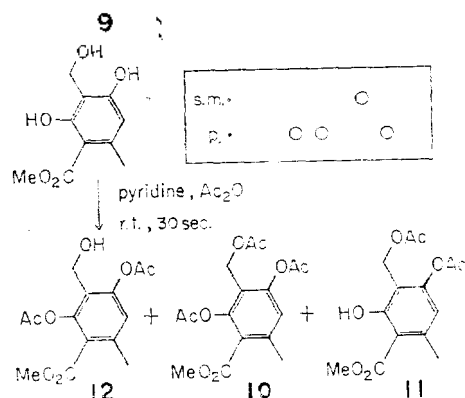


Scheme 2.

triacetate was achieved. Omission of potassium fluoride under the same reaction conditions resulted in full recovery of the starting material. A similar type of phenol activation by fluoride ion hydrogen bonding was reported.⁷ This method of acetylation seems to be of some value in organic synthesis and will be reported elsewhere in detail.

Since the best substrate for further reactions is the diacetate like 11 and selective acetylation of 9 was not possible, acetylation of 8 prior to reduction was explored. Under various conditions of acetylation, a single unstable compound was obtained characterized only by nmr spectrum in the crude state. The four acetate singlets at δ 2.00 (six protons), 2.25, and 2.30, and a methine singlet at δ 7.83 suggested that the product was a tetraacetate (13). This compound reverted to 8 upon standing in solution without apparent formation of isolable intermediates. The same type of acetate was reported in analogous systems.⁸

Selective acetylation was finally realized by a short-interval acetylation procedure (Scheme 3). Thus reaction of 9 with pyridine and acetic anhydride for 30 seconds at room temperature yielded two more products well separated from both the starting material 9 and the usual product 10 on TLC. The products were separ-



Scheme 3.

ated on a silica gel column and the structures were elucidated by nmr spectroscopy. The nmr spectrum of the most polar product showed two acetate singlets at δ 1.92 and 2.20 and no phenolic proton peaks suggesting the structure of methyl 3-hydroxymethylorsellinate diacetate (12). More interestingly, the least polar product gave rise to an nmr spectrum which possessed two acetate singlets at δ 1.91 and 2.24, a phenolic proton singlet at δ 11.71, and no alcoholic proton signal. The structure of methyl 3-acetoxymethylorsellinate 4-acetate (11) was assigned since the remaining phenolic proton signal corresponded to the more deshielded of the two present in 9. Hydrogen bonding with methyl ester group is expected to slow down the rate of the phenolic proton exchange giving rise to a sharper nmr peak, which was observed in 9 and 11. Infrared spectra were also informative in that 11 had a broad band at 2900 cm^{-1} indicating intramolecular hydrogen bonding whereas 12 had a sharper band at $3,300\text{ cm}^{-1}$ assigned to the free hydroxy group.

In 11 and 12, non-hydrogen-bonding 4-hydroxy group is acetylated, but 2-hydroxy group internally hydrogen-bonded with the methyl ester moiety stays intact in 11. It is not surprising to find that intramolecular hydrogen bond

makes 2-hydroxy group less reactive. Both 11 and 12 quickly disappear under mild acetylating conditions to yield 10, which support the structural assignment.

Further transformations of derivatives like 11 are in progress and will be reported in due course.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus, and are corrected. Infrared spectra were obtained with a JASCO IR-G infrared spectrophotometer. Ultraviolet spectra were determined with a Hitachi 124 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Anaspec EM 360 NMR spectrometer at 60 MHz to an internal standard of tetramethylsilane; *s* signifies a singlet. Crude reaction mixture was always checked with the thin layer chromatography. TLC plates were made by dipping microscopic slides in the chloroform slurry of Merck 7749 silica gel 60 PF₂₅₄ and drying in the air. Developing solvents were carbon tetrachloride-chloroform-acetic acid (10 : 9 : 1) and ether-petroleum ether (1 : 1). Spots were viewed under a uv light or by charring after spraying with 2% ceric sulfate solution in 1 *M* sulfuric acid.

Methyl 3-Hydroxymethylorsellinate (9). To a stirred solution of 400 mg methyl 3-formylorsellinate (nmr in acetone-*d*₆, δ 2.53, 3 H, *s*; 4.00, 3 H, *s*; 6.33, 1 H, *s*; 10.34, 1 H, *s*; 12.36, 1 H, *s*; 12.97, 1 H, *s*) in 40 ml methanol, 200 mg sodium cyanoborohydride in 10 ml methanol was added. The reaction mixture was further treated with 200 mg anhydrous potassium dihydrogen phosphate and 400 mg anhydrous potassium hydrogen phosphate and stirred 20 minutes at room temperature. The suspension was partitioned between excess water and

ether and the aqueous layer was extracted once more with ether. The combined ether extract was washed once with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Filtered ether solution was concentrated to yield 320 mg (80 %) white crystalline product. Alternatively 400 mg methyl 3-formylorsellinate in 40 ml ethanol was treated with 200 mg sodium borohydride in 10 ml ethanol and the reaction mixture was stirred 10 minutes in an ice bath. The same work-up gave the product in similar yield: m.p 126°C; uv (methanol) 302, 266 nm; ir (KBr) 3400~2850, 1630 cm^{-1} ; nmr (acetone- d_6 plus dimethylsulfoxide- d_6) δ 2.37, 3 H, s; 3.85, 3 H, s; 4.0, 1 H, broad s; 4.61, 2 H, s; 6.25, 1 H, s; 10.17, 1 H, s; 11.77, 1 H, s (Fig. 1).

Methyl 3-Acetoxyethylorsellinate diacetate (10). Methyl 3-hydroxymethylorsellinate (100 mg) was added to 10 ml acetic anhydride containing 100 mg sodium acetate and the mixture was heated to reflux for 3 hours. The reaction mixture was boiled briefly with excess water to destroy acetic anhydride and the aqueous solution was extracted twice with ether. The combined ether extract was washed once with water, once with saturated sodium

bicarbonate solution, and once with sodium chloride solution. After drying with anhydrous sodium sulfate, ether was evaporated to yield 140 mg (88 %) of the product, which was recrystallized in ether-petroleum ether. The same product was obtained exclusively by reacting 100 mg of the starting material in 20 ml pyridine with 1 ml acetic anhydride at room temperature for 40 minutes. Same results was obtained when 100 mg methyl 3-hydroxymethylorsellinate was reacted in 20 ml dimethylformamide with 1 ml acetic anhydride and stirred at room temperature for 40 minutes in the presence of 10 mg solid anhydrous potassium fluoride. Addition of dicyclohexyl-18-crown-6 did not change the course of the reaction but the presence of potassium fluoride was required. The triacetate had the following physical characteristics: m.p 72~73°C; uv (methanol) 270, 218 nm; ir (KBr) 1780, 1740, 1625 cm^{-1} ; nmr (acetone- d_6) δ 1.90, 3 H, s; 2.22, 3 H, s; 2.26, 3 H, s; 2.34, 3 H, s; 3.81, 3 H, s; 4.94, 2 H, s; 6.95, 1 H, s; (Fig. 2).

Acetylation of Methyl 3-Formylorsellinate. Methyl 3-formylorsellinate was reacted with acetic anhydride and sodium acetate in the same way as in the case of methyl 3-hydroxy-

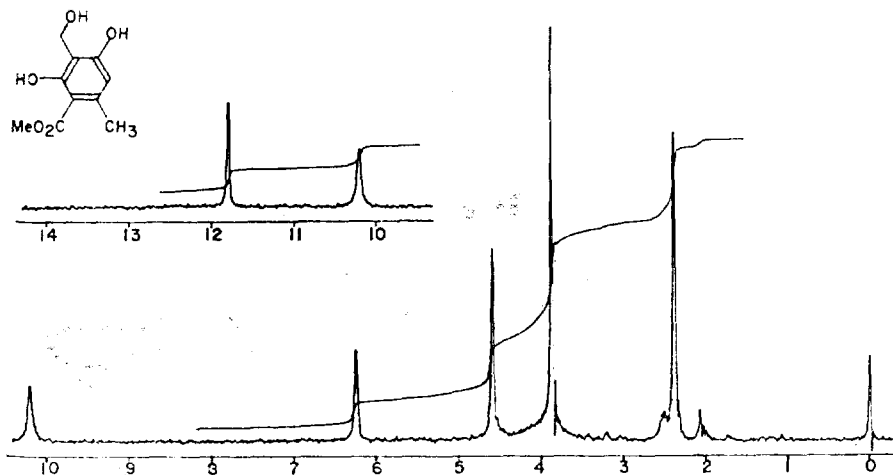


Fig. 1.

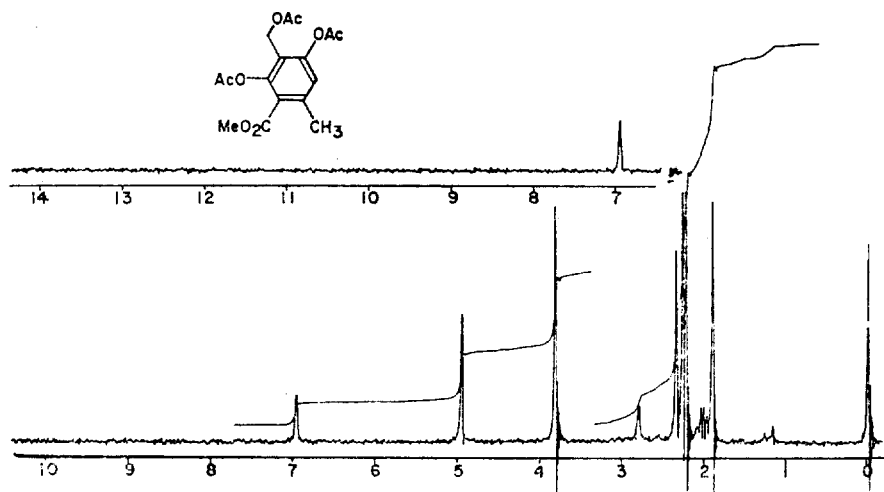


Fig. 2.

methylorsellinate to yield a single product which was slowly converted back to the starting material upon standing. Reaction in pyridine with excess acetic anhydride or with acetyl chloride at room temperature for 1 hour, and reaction in acetic anhydride with catalytic amount of concentrated sulfuric acid at room temperature for 1 hour yielded the same product. The product could not be fully characterized due to instability but was assigned to be the tetraacetate(13) from the nmr data (acetone- d_6 plus dimethylsulfoxide- d_6) δ 2.00, 6 H, s; 2.25, 3 H, s; 2.30, 3 H, s; 2.36, 3 H, s; 3.82, 3 H, s; 7.00, 1 H, s; 7.83, 1 H, s. **Methyl 3-hydroxymethylorselinate Diacetate (12) and Methyl 3-Acetoxyethylorselinate 4-acetate (11)**. To a stirred solution of 100 mg methyl 3-hydroxymethylorselinate in 100 ml dry pyridine, 5 ml acetic anhydride was added in one batch. After stirring 30 seconds at room temperature the clear mixture was poured into 1 l of water and the resulting suspension was extracted three times with ether. The ether extract was washed several times with cupric sulfate solution to remove pyridine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was

checked with TLC using ether-petroleum ether (1 : 1) (Scheme 3). The crude product mixture which was obtained upon evaporation of ether was separated on a silica gel column (50 g Merck 7734 silica gel 60). The least polar product was eluted in 200 ml ether-petroleum ether (1 : 1). The triacetate (10) and the most polar product were separated with 200 ml hexane-acetone (1 : 1). The fractions were collected and evaporated to produce roughly equal yield (30 %) of each product which were separately recrystallized in ether-petroleum ether. The product ratio changes quickly with time and 10 is about the only product after 5 minute acetylation at room temperature. The least polar product was assigned as methyl 3-acetoxyethylorselinate 4-acetate(11): m. p 97~98°C; uv (methanol) 305, 245, 221 nm; ir (KBr) 2900, 1750, 1710, 1630 cm^{-1} ; nmr (acetone- d_6) δ 1.91, 3 H, s; 2.24, 3 H, s; 2.48, 3 H, s; 3.94, 3H, s; 5.03, 2 H, s; 6.51, 1 H, s; 11.71, 1 H, s (Fig. 3). The most polar product was proved to be methyl 3-hydroxymethylorselinate diacetate(12): m. p 112~113°C; uv (methanol) 252, 227 nm; ir (KBr) 3300, 1742, 1690, 1590 cm^{-1} ; nmr (acetone- d_6) δ 1.92, 3 H,

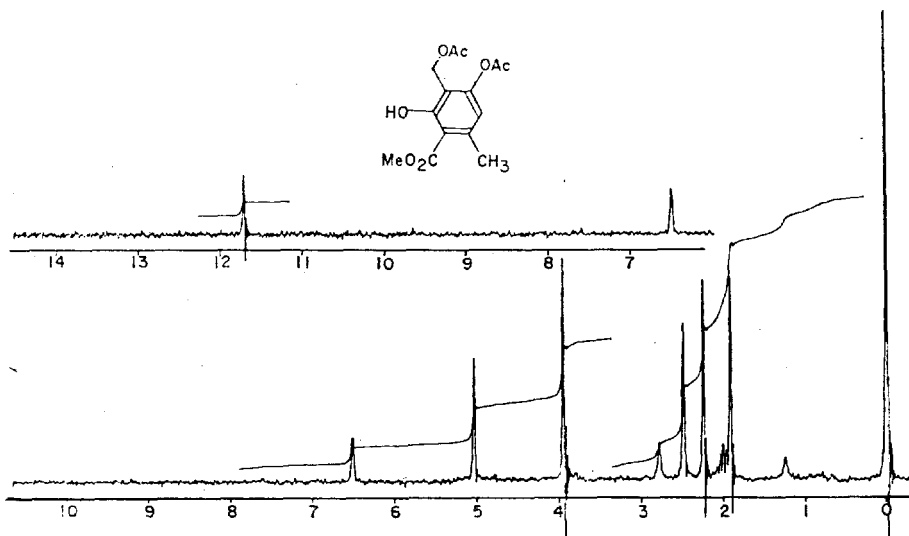


Fig. 3.

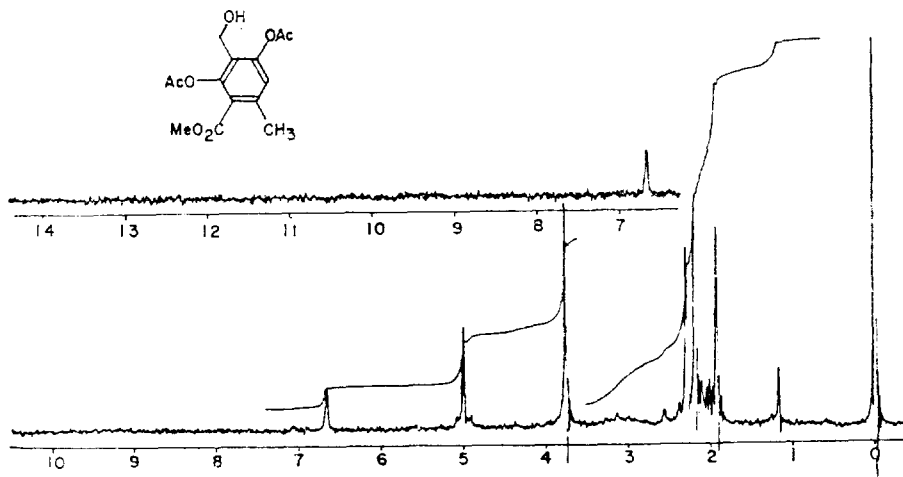


Fig. 4.

δ 2.20, 3 H, s; 2.29, 3 H, s; 3.76, 3 H, s; 4.99, 2 H, s; 6.66, 1 H, s. The signal from the alcoholic proton is thought to be part of the broad peak around δ 3.1 (Fig. 4).

ACKNOWLEDGEMENTS

The authors wish to thank the ministry of Education for support of this work.

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