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Utility of the Methanesulfonyl Blocking Group. II.[1] Synthesis of Isovanillic Acid and Methanesulfonyl Derivatives of Phenolic Acids[2]

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A procedure for synthesis of isovanillic acid *via* oxidation of mesyl isovanillin is presented. Mesyl[3] derivatives of vanillic, isovanillic, and protocatechuic acids are described. Mesylation of these phenolic acids in pyridine leads to complex products, infrared spectra of which reveal presence of the carboxylic ester function.

The methanesulfonyl blocking group was introduced in 1937 by Helferich and Hiltmann,[4,5] whose initial studies were concentrated in the sugar area. Subsequently, this block was extended to phenolic compounds,[6] including the phenolic aldehyde vanillin,[7] and to amino acids.[8] Helferich and Papalambrous[6] pointed out the acid stable, base labile character of the mesyloxy group in mesyl derivatives of phenolic compounds.

In recent years, studies in this laboratory have demonstrated the remarkable stability of the mesyloxy group under conditions simultaneously strongly acidic and strongly oxidizing,[1] and the utility of the mesyl block in synthesis of mesyloxy acids from *p*-tolyl methanesulfonate[1] and from mesyl blocked phenolic aldehydes.[9,10] It has been demonstrated further that mesyl blocked phenolic acids cannot be prepared by direct mesylation of phenolic acids because of predominant formation of complex products containing polyesters.[11] The present paper describes a synthetic procedure for isovanillic acid based on oxidation of mesyl isovanillin under acidic conditions, preparation of mesyl vanillic acid and dimesyl protocatechuic acid by oxidation of the appropriate mesylated aldehyde, and the formation of complex, ester-type products from mesylation of vanillic, isovanillic, and protocatechuic acids.

The phenolic aldehydes were esterified with methanesulfonyl chloride in pyridine. Mesyl isovanillin was readily prepared and purified. However, dimesyl protocatechualdehyde was obtained in satisfactory yield only under short term mesylation. When a longer reaction period was used, the product was highly colored and difficult to purify.

Oxidation of all mesyl phenolic aldehydes was carried out in acidic dichromate solution. Crude mesyl isovanillin was satisfactory for oxidation. The oxidation product, mesyl isovanillic acid, was isolated and characterized. However, for synthesis of isovanillic acid, isolation of mesyl isovanillic acid was not necessary. The relatively slight solubility of unreacted mesyl isovanillin (in the crude reaction product) in dilute base permitted its ready removal by filtration. Hydrolysis of mesyl isovanillic acid in the alkaline filtrate gave isovanillic acid in 91% yield (corrected for recovered mesyl isovanillin). A 73% quantity of mesyl isovanillin was converted to the acid, and the recovered aldehyde was sufficiently pure for reoxidation without additional purification. Application of this general oxidation procedure to the known mesyl vanillin[7] gave mesyl vanillic acid. In the oxidation of dimesyl protocatechualdehyde, a rather large excess of oxidizing agent was used. Even so, there was an apparent recovery of a considerable quantity of the mesyl aldehyde.

On the basis of earlier studies in this laboratory,[11] mesylation of a phenolic acid in pyridine would not be expected to give the mesyl phenolic acid. Mesylation of the phenolic acids in the present work gave bicarbonate insoluble products, the infrared spectra of which (Table I) indicate the presence of the carboxylic ester function. Spectral data for the authentic mesyl phenolic acids are included in Table I for comparison.

The spectral data of the present study, combined with the data of the previous work,[11] indicate that mesylation products of phenolic acids fall into two classes:

Class I: Mesylation products containing both the carboxylic acid and ester function. The fol-

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[1] Part I: J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **19**, 784 (1954).

[2] This investigation was supported by a research grant (E-1703) from the National Institute of Allergic and Infectious Diseases, Public Health Service.

[3] Mesyl = methanesulfonyl; for a more thorough discussion of nomenclature, see R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 108 (1953).

[4] B. H. Helferich and R. Hiltmann, *Ann.*, **531**, 160 (1937).

[5] Aryl methanesulfonates were described many years ago by C. Schall, *J. prakt. Chem.*, **48**, 241 (1893). However, the preparative procedure employed did not involve a direct introduction of the mesyl block by use of methanesulfonyl chloride.

[6] B. Helferich and P. Papalambrous, *Ann.*, **551**, 235 (1942).

[7] B. Helferich and P. Papalambrous, *Ann.*, **551**, 245 (1942).

[8] B. Helferich and H. Grünert, *Ann.*, **545**, 178 (1940).

[9] J. H. Looker and C. H. Hayes, *J. Am. Chem. Soc.*, **79**, 745 (1957).

[10] For a very recent, interesting example of the applicability of the mesyl block to syntheses of *m*-hydroxyphenyl methyl sulfoxide, see F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **79**, 717 (1957).

[11] J. H. Looker, C. H. Hayes, and D. N. Thatcher, *J. Am. Chem. Soc.*, **79**, 741 (1957).

TABLE I

Infrared Spectral Data[a,b] for Phenolic Acid Mesyl Derivatives and Mesylation Products

Compound	M.P. or Range, °C.	Infrared Maxima, cm.$^{-1}$		
		Acid[c] CO	Acid[c] OH	Ester[c] CO
Mesyl derivative of:				
Vanillic acid	167–169	1687	2680, 2650	—
Isovanillic acid	226–227	1685 (1672?)	2650, 2608	—
Protocatechuic acid	208–210	1693	2710, 2650	—
Mesylation product of:				
Vanillic acid	155–177 (dec.)	1692	2650	1733
Isovanillic acid	125–151	1690, 1685	2610	1732
Protocatechuic acid	120–165	—	—	1750

[a] Spectra of Nujol mulls were determined with a Perkin-Elmer Model 21 recording spectrophotometer. [b] All bands are medium or strong, except OH bands. [c] Band-structure correlations are in accordance with L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 5–9.

lowing acids give this type of product: *m*- and *p*-hydroxybenzoic, 3,5-diiodo-4-hydroxybenzoic, vanillic, and isovanillic acids.

Class II: Mesylation products containing the carboxylic ester function, but not the carboxylic acid group. Salicylic, gallic, and protocatechuic acids give this type of mesylation product.

Class I mesylation products very probably are closely related to depsides in structure.[11] Class II mesylation products, while of less certain constitution, may contain cyclic structures or cross-linked polymers. As previously demonstrated,[11] the mesylation product of salicylic acid contains the cyclic ester, trisalicylide.

EXPERIMENTAL[12]

Mesyl isovanillin (3-methanesulfonyloxy-4-methoxybenzaldehyde). A 150 g. quantity of isovanillin was dissolved in 600 ml. of reagent grade pyridine and cooled in ice. To this solution was added 90 ml. of methanesulfonyl chloride. The reaction mixture stood in an ice bath 4 hr., then at room temperature overnight. The mixture then was poured into 2 l. of ice water to which 600 ml. of concentrated hydrochloric acid previously had been added. The precipitated crude product was collected by filtration, washed with cold water, and air-dried; yield, 218 g. (96%), m.p. 80–89°. This product could be recrystallized with 85% efficiency from dilute methanol to give the aldehyde, m.p. 86–89°. Additional crystallization from dilute methanol and methanol gave analytically pure, colorless mesyl isovanillin, m.p. 87–89°.

Anal. Calcd. for $C_9H_{10}O_5S$: C, 46.87; H, 4.38; S, 13.84. Found: C, 47.00; H, 4.57; S, 14.00.

Dimesyl protocatechualdehyde [3,4-bis(methanesulfonyloxy)-benzaldehyde]. A 2.00 g. quantity of protocatechualdehyde (buff-colored, m.p. 150–154°) was dissolved in 20 ml. of reagent grade pyridine. The resulting mixture was cooled in ice to 0–5°, and a 4.4 ml. quantity of methanesulfonyl chloride was added. The reaction mixture stood in an ice bath for 2 hr. A 0.6 ml. quantity of water was added cautiously to the cold solution, and the resulting mixture permitted to stand in an ice bath for 10 min. The reaction mixture then was poured into 200 ml. of cold water containing 20 ml. concentrated hydrochloric acid. The crude cream-colored product precipitated immediately, and was collected by filtration, washed with water, air-dried 24 hr., and then dried *in vacuo* over phosphorus pentoxide and concentrated sulfuric acid for 48 hr.; yield, 3.82 g. (89.7%), m.p. 110–114.5°. This material was of purity suitable for oxidation. Recrystallization of the total crude from 20–22 ml. of chloroform led to a 74.7% recovery of virtually colorless product, m.p. 110–114°. Crystallization also was possible from acetone or dilute methanol.

Analytically pure material was obtained by dissolving a fraction of crude aldehyde, m.p. *ca.* 110–1125°, (possibly contaminated with dimesyl protocatechuic acid formed by air oxidation) in ethyl acetate, extracting with two 50-ml. portions of sodium bicarbonate, back extracting the latter with ethyl acetate, and combining the ethyl acetate extracts. The latter were washed with water and dried over anhydrous sodium sulfate. Solvent removal at room temperature *in vacuo* gave a crystalline residue, m.p. 110–115°. The residue was washed with 2*N* sodium hydroxide, then with water, and dried in a vacuum desiccator over phosphorus pentoxide. A final crystallization from chloroform, with cooling of the chloroform solution in ice, gave analytically pure, colorless, dimesyl protocatechualdehyde, m.p. 112.5–114.5°.

Anal. Calcd. for $C_9H_{10}O_7S_2$: C, 36.73; H, 3.42; S, 21.79. Found: C, 36.55; H, 3.39; S, 21.57.

Mesyl vanillic acid (3-methoxy-4-methanesulfonyloxybenzoic acid). A 34.5 g. quantity of crude mesyl vanillin[7] (prepared from vanillin and methanesulfonyl chloride in pyridine) was suspended in a solution prepared by dissolving 15.0 g. of potassium dichromate in a sulfuric acid solution (prepared from 48 ml. concentrated sulfuric acid added to 198 ml. of water). Upon heating the reaction mixture to 65° with constant stirring, an exothermic reaction commenced. The reaction vessel was removed from the heat source as the temperature rose to 78°. After the initial heat of reaction subsided, the heterogeneous mixture was heated as necessary to maintain the temperature between 70–75° for 45 min. The reaction mixture was cooled in ice, diluted with 150 ml. of water, and again cooled in ice. The crude product was collected by filtration, washed with water, and air-dried; yield 37 g., melting 95–140°. The total crude product was washed with 2 l. of 5% sodium bicarbonate. The extract upon acidification gave 6.3 g. of mesyl vanillic acid, m.p. 164–168°. Recrystallization from dilute ethanol and then from ethyl acetate gave the analytically pure, colorless acid, m.p. 167–169°.

Anal. Calcd. for $C_9H_{10}O_6S$: C, 43.90; H, 4.09; S, 13.02. Found: C, 44.03; H, 4.23; S, 13.04.

Mesyl isovanillic acid (3-methanesulfonyloxy-4-methoxybenzoic acid). An 11.5 g. quantity of mesyl isovanillin, m.p. 86–89°, was suspended in a solution prepared by dissolving 5.0 g. of potassium dichromate in 78 ml. of 30% sulfuric acid. The resulting heterogeneous mixture was heated with constant stirring at 60–70° for 1 hr. After the reaction mixture had cooled to room temperature, the crude product was collected by filtration and washed free of chromium salts with

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(12) Melting points are uncorrected. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

water. Exhaustive extraction with 5% sodium bicarbonate gave 2.2 g. of unreacted mesyl isovanillin, m.p. 84–88°, which was removed by filtration. Acidification of the bicarbonate filtrate with concentrated hydrochloric acid gave 8.0 g. of mesyl isovanillic acid, m.p. 217–226°. Analytically pure acid, m.p. 226–227°, was obtained by crystallization from 300 ml. of boiling ethyl acetate, and then two additional recrystallizations from the same solvent. Recrystallization also was possible from 95% ethanol, in which the acid was appreciably more soluble.

Anal. Calcd. for $C_9H_{10}O_6S$: C, 43.90; H, 4.09; S, 13.02. Found: C, 44.08; H, 4.13; S, 12.88.

Isovanillic acid. A dichromate solution was prepared by dissolving 47.0 g. of potassium dichromate in a sulfuric acid solution (prepared by adding 150 ml. of concentrated sulfuric acid to 620 ml. of water). This dichromate solution first was heated to 60°, and then a 107.5 g. quantity of crude mesyl isovanillin, m.p. 85–89°, was added. Upon heating the reaction mixture to 71° with constant stirring, an exothermic reaction started. The mixture was removed from the heat source until the exothermic reaction subsided (*ca.* 20 min.), and then was heated intermittently to maintain temperature at 72–75° for 40 min. The temperature was increased over a 30-minute period to 90°. The reaction mixture was permitted to cool, and stood at room temperature overnight. The crude product was collected by filtration, washed free of chromium salts on the filter, and then with an additional 1 liter quantity of water; yield, after air drying, 110 g., m.p. 210–218°, with softening at 185°. The total crude product was dissolved as much as possible in approximately $2N$ sodium hydroxide (prepared by dissolving 107 g. of sodium hydroxide in 1330 ml. of water). Unreacted mesyl isovanillin (21.5 g., m.p. 84–88°) was removed by filtration, and retained for subsequent reoxidation. The alkaline filtrate after standing at room temperature for 24 hr. was acidified with concentrated hydrochloric acid. The precipitated acid was collected by filtration, washed well with water, and air-dried for several weeks; yield, 57.5 g. (91%, based on 86 g. of mesyl isovanillin), m.p. 244–249°. Recrystallization was effected by heating the total acid with 1400 ml. of absolute ethanol under reflux for 90 min., filtering, and permitting the filtrate to cool for 2.5 hr., or until the temperature was *ca.* 35°. The crystalline isovanillic acid was collected by filtration of the warm mixture, and air-dried overnight; yield, 32.8 g., m.p. 247–249.5° (lit. m.p.[13] 251°). Additional isovanillic acid was recovered by concentration of the mother liquor. A higher efficiency of crystallization (66%) was realized by permitting crystallization mixtures to cool to room temperature before filtration. However, the acid thus obtained was rather highly colored.

Acetylation of isovanillic acid, m.p. 247–249.5°, by the procedure of Lesser and Gad,[14,15] gave *O*-acetylisovanillic acid, m.p. 211.0–212.5° (lit. m.p.[15] 212–215°).

Dimesyl protocatechuic acid [3,4-bis(methanesulfonyloxy)-benzoic acid]. A 1.47 g. quantity of dimesyl protocatechualdehyde was suspended in a dichromate solution, prepared by dissolving 0.75 g. of potassium dichromate in 12 ml. of 30% sulfuric acid. The reaction mixture was heated at 70–75° for 90 min. under constant stirring, and then the temperature gradually was increased to 95°. The mixture was cooled, permitted to stand at room temperature overnight, and diluted to a volume of 25 ml. The crude product was collected by filtration, washed free of chromium salts on the filter, and air-dried for several days; yield, 1.45 g., m.p. 188–195°, with sintering at 170°. The crude acid was washed with three successive 50-ml. portions of 5% sodium bicarbonate. Bicarbonate insoluble material (Fraction A, 0.73 g., melting 170–187°) was collected by filtration and retained. Acidification of the bicarbonate extracts gave 0.47 g. of crude dimesyl protocatechuic acid, m.p. 195–201°. Additional acid was obtained by extracting an ethyl acetate solution of Fraction A with 5% sodium bicarbonate; acidification gave 0.28 g., m.p. 206–210°. Total yield of colorless dimesyl protocatechuic acid thus was 0.75 g. Analytically pure acid was obtained by recrystallizing total acid thrice from 95% ethanol, and the crystals, after being dried *in vacuo* 6 hr. over boiling water, melted at 208–210°.

Anal. Calcd. for $C_9H_{10}O_8S_2$: C, 34.84; H, 3.25; S, 20.66. Found: C, 35.08; H, 3.39; S, 20.95.

Mesylation of vanillic and isovanillic acids. A 1.36-g. quantity of the acid was dissolved in 7.5 ml. of reagent grade pyridine, cooled to 5°, mixed with 0.7 ml. of methanesulfonyl chloride and allowed to stand for 20 hr. Product isolation as previously described,[11] followed by washing with 50 ml. boiling water and 50 ml. 5% sodium bicarbonate (insoluble material retained), gave 0.88 and 0.78 g. of the mesylation products of vanillic and isovanillic acids, respectively. Products were dried in a vacuum desiccator over phosphorus pentoxide prior to infrared analysis.

Mesylation of protocatechuic acid. A 3.08-g. quantity of protocatechuic acid was dissolved in 30 ml. of reagent pyridine, cooled to 5°, mixed with 3.4 ml. of methanesulfonyl chloride and allowed to stand for 23 hr. Product isolation as previously described,[11] followed by washing with 100 ml. of 5% sodium bicarbonate and then with several hundred ml. of water at room temperature (insoluble material retained), gave 1.58 g. of the mesylation product. The latter was dried in a vacuum desiccator over phosphorus pentoxide before infrared spectral analysis.

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[13] E. Späth and G. Burger, *Ber.*, **59**, 1494 (1926).

[14] R. Lesser and G. Gad, *Ber.*, **59B**, 233 (1926).

[15] The specific procedure employed was that of V. Deulofeu and N. Schopflocher, *Gazz. chim. ital.*, **83**, 449 (1953).