reflux for 3.5 hr. Most of the ethanol was distilled under reduced pressure, and the dark residue was added to 500 ml. of water. The crude nitrile was extracted with ether, washed with 1:1 hydrochloric acid and water, dried (anhydrous magnesium sulfate), ether removed, and distilled under reduced pressure; b.p. 115–130°/0.5 mm. (reported,[10] b.p. 170°/12 mm.); yield, 71.5 g. (76%). The distillate gradually solidified, and melted at 45–46° after recrystallization from petroleum ether.

*Anal.* Calcd. for $C_8H_5Cl_2N$: Cl, 38.2; N, 7.53. Found: Cl, 37.8; N, 7.34.

*3,4-Dichloro-β-phenethylamine.* To a stirred solution of 16.9 g. of lithium aluminum hydride in 300 ml. of dry absolute ether was added gradually a solution of 37.2 g. of 3,4-dichlorophenylacetonitrile in 100 ml. of dry ether. The reaction mixture was then refluxed for an additional hour, cooled, hydrolyzed cautiously with water, and filtered from inorganic matter. The dried ether solution was treated with dry hydrogen chloride to precipitate 3,4-dichloro-β-phenethylamine hydrochloride, which was recrystallized from methanol-ether; yield, 7.5 g. (17%); m.p. 178–179°.

*Anal.* Calcd. for $C_8H_{10}Cl_3N$: Cl, 47.0; N, 6.18. Found: Cl, 46.9; N, 6.14.

*3,5-Dimethoxy-4-methylbenzoic acid.* To a stirred solution of 40 g. of 3,5-dihydroxy-p-toluic acid in 57 g. of sodium hydroxide and 250 ml. of water were added three 33-ml. portions of methyl sulfate at such a rate that the temperature remained below 30° during addition of the first portion, at 30 to 35° during the second, and at 40 to 45° during the third.[11] The mixture was then boiled under reflux for 2 hr., treated with a solution of 20 g. of sodium hydroxide in 30 ml. of water, and boiled for an additional 2 hr. Acidification with dilute hydrochloric acid precipitated the crude product, which was purified by recrystallization from acetone; yield, 30.5 g. (65%); m.p. 216–217°; (reported[12] m.p., 213–214°).

*ω-Diazo-3,5-dimethoxy-4-methylacetophenone.* A mixture of 30 g. of 3,5-dimethoxy-4-methylbenzoic acid, 30 ml. of dry benzene, and 22 ml. of thionyl chloride was refluxed for 2 hr. After removal of benzene and excess thionyl chloride, the residue was distilled under reduced pressure to yield 21 g. (64%) of 3,5-dimethoxy-4-methylbenzoyl chloride, b.p. 107–110°/0.5 mm. A solution of this acid chloride was added to a cooled (ice bath) and stirred solution of 0.316 mole of diazomethane (generated from *N*-nitroso-*N*-methylurea and 45% potassium hydroxide and assayed against benzoic acid) in 680 ml. of dry ether. After stirring for 20 hr. at room temperature, the diazoketone had separated as a yellow solid. Collection of this solid and concentration of the filtrate by evaporation yielded a total of 19.6 g. (90%) of the pure diazoketone; m.p. 138–139° dec.

*Anal.* Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5. Found: C, 59.7; H, 5.7.

*3,5-Dimethoxy-4-methylphenylacetamide.* To a mixture of 19 g. of ω-diazo-3,5-dimethoxy-4-methylacetophenone and 100 ml. of dioxane was added 200 ml. of concd. ammonium hydroxide and 20 ml. of 10% aqueous silver nitrate. The mixture was heated on a steam bath under a reflux condenser for 16 hr. when evolution of nitrogen, brisk at first, was complete. The hot reaction mixture was treated with Norite, filtered, and concentrated by evaporation whereupon the crude solid amide crystallized on cooling. Recrystallization of the crude product from alcohol-water yielded 10.5 g. (58%) of pure 3,5-dimethoxy-4-methylphenylacetamide, m.p. 166–167°.

*Anal.* Calcd. for $C_{11}H_{15}NO_3$: C, 63.2; H, 7.2. Found: C, 63.2; H, 7.4.

*3,5-Dimethoxy-4-methyl-β-phenethylamine.* To a stirred solution of 6.8 g. of lithium aluminum hydride in 200 ml. of dry absolute ether was added a slurry of 10 g. of 3,5-dimethoxy-4-methylphenylacetamide in 125 ml. of hot dry reagent benzene, using part of the benzene to rinse in the last of the amide. The resulting mixture was stirred and refluxed for 1 hr., cooled in an ice bath, and hydrolyzed by slow and cautious addition of water. The ether solution of the amine obtained after filtration from inorganic matter and drying (anhydrous magnesium sulfate) was treated with dry hydrogen chloride to precipitate the product as its hydrochloride salt; yield, 8.9 g. (80%); m.p. 233–235°. Recrystallization from ethanol-ethyl acetate raised the melting point to 244–245°.

*Anal.* Calcd. for $C_{11}H_{18}ClNO_2$: C, 57.0; H, 7.8; Cl, 15.3. Found: C, 56.2; H, 8.0; Cl, 15.2.

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# Nobiletin from the Peel of the Valencia Orange (*Citrus sinensis* L.)[1]

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During an investigation of the constituents of orange peel, a substance was isolated which was identified as nobiletin by physical and chemical properties, elemental analysis, and degradation products.

Nobiletin was first isolated by Tseng[2] from the Chinese drug chen-pi which, in turn, was made from the peel of a variety of mandarin (*Citrus nobilis*, Lour.). In the original work the isolation was made by a rather tedious process from a cold methanolic extract of the drug but in the present study the juice of fresh orange peel was utilized.

The structural formula for nobiletin was partly elucidated by Tseng[2] and Robinson and Tseng,[3] who isolated veratric acid and acetoveratrone (as the oxime) from the alkaline hydrolysis mixture. On the basis of this and other evidence, Robinson and Tseng came to the conclusion that nobiletin was 3′, 4′, 5, 6, 7, 8-hexamethoxyflavone. This view was supported later by syntheses carried out by Horii,[4] Sreerama Murti and Seshadri,[5]

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[10] C. E. Kwartler and P. Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946) reported this compound as an oil rather than the crystalline solid which we obtained.

[11] See F. Mauthner, *Org. Syntheses*, **Coll. Vol. I**, 537 (1943) for methylation of gallic acid.

[12] K. Yamaguchi, *J. Chem. Pharm. Soc.* (*Japan*), **62**, 491 (1952).

[1] Presented before the Symposium on Chemistry of the Citrus Fruit Industry at the Miami meeting of the American Chemical Society, April, 1957.

[2] K. Tseng, *J. Chem. Soc.*, 1003 (1938).

[3] R. Robinson and K. Tseng, *J. Chem. Soc.*, 1004 (1938).

[4] Z. Horii, *J. Pharm. Soc. Japan*, **60**, 614, Abstracts 246 (1940); *Chem. Abstr.* **35**, 7964 (1941).

[5] V. V. Sreerama Murti and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **27-A**, 217 (1948).

and by Oliverio and Casinovi.[6] Thus there is no doubt about the proposed structural formula.

### EXPERIMENTAL

*Isolation of nobiletin.* Orange peel juice was obtained from the peel oil centrifugals which were operated in connection with a frozen concentrate plant. Peel from the orange juice extractors passed directly through grooved rolls which expressed an emulsion of peel oil and the aqueous peel juice. After screening to remove peel fragments, the emulsion was fed directly to the centrifugals which separated part of the oil.

Juice so obtained was filtered in the laboratory with a diatomaceous filter aid on precoated Büchner funnels. The filtrate was extracted once with petroleum ether (b.p. 60–68°) to remove any remaining peel oil and adjusted to *p*H 8.0 with sodium hydroxide pellets. The alkaline mixture was then extracted batchwise with carbon tetrachloride, using two 50-ml. portions to each 1.5-l. portion of juice. The combined extracts were then concentrated *in vacuo* nearly to dryness and the residue was dissolved in hot methanol. After treatment with a small quantity of decolorizing carbon, the hot solution was filtered and allowed to crystallize. The precipitate was repeatedly recrystallized from methanol to a constant melting point of 137–138° cor. The yield was quite small, 4.7 g. nobiletin being obtained from about 250 l. of peel juice.

The ultraviolet spectrum was determined in 95% ethanol solution. The locations of the maxima and corresponding log $\epsilon$ values were as follows: 210 m$\mu$ (4.627), 248 m$\mu$ (4.341), 271 m$\mu$ (4.283), 333 m$\mu$ (4.449).

*Anal.* Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51; —$OCH_3$, 46.28. Found: C, 62.95, 63.05; H, 5.67, 5.72; —$OCH_3$, 46.34, 46.29. Nobiletin is tasteless in the crystalline form, probably because of its slight solubility. Alcoholic solutions diluted with water are quite bitter.

*Hydrolysis of nobiletin.* A 2.0-g. portion of nobiletin was refluxed with a mixture of 100 ml. of ethanol and 100 ml. of 20% aqueous potassium hydroxide for 6 hr. The mixture was concentrated at atmospheric pressure to half its volume and 100 ml. of water were added. Carbon dioxide was bubbled into the mixture until it was saturated. An ether extraction of the neutral products of hydrolysis was then made and reserved for the isolation of acetoveratrone. The aqueous residue was also retained for the isolation of the acidic hydrolysis products.

*Isolation of acetoveratrone oxime.* The ethereal extract of the neutral hydrolysis products was evaporated nearly to dryness. To this was added a mixture containing 0.5 g. of hydroxylamine hydrochloride and 4 ml. of 5% sodium hydroxide and enough ethanol to give a clear solution. After heating for 10 min. in a hot water bath, the mixture was cooled and placed in a cold room at 4°. A yield of 0.23 g. of crystals melting at 141° cor. was obtained which agrees with that reported by Robinson and Tseng[3] for acetoveratrone oxime.

*Anal.* Calcd. for $C_{10}H_{13}O_3N$: C, 61.55; H, 6.66; —$OCH_3$, 31.80; N, 7.18. Found: C, 61.98, 61.74; H, 6.65, 6.72; —$OCH_3$, 31.24, 31.09; N, 6.76, 6.80.

*Acidic hydrolysis products. Veratric acid.* The aqueous residue remaining after the extraction of the neutral hydrolysis products was acidified with dilute sulfuric acid and extracted again with ether. The ether was removed by evaporation and the residue weighing 1.4 g. was twice crystallized from about 70 ml. water. After drying, the melting point was found to be 182° cor. A mixture with anisic acid gave a melting-point depression of 30°, thus excluding this as a possibility. Analysis and a neutral equivalent determination were in agreement with those of veratric acid. The yield was 0.4 g. The amide melted at 164–166°, which is in agreement with the values given in the literature for veratric acid.

*Anal.* Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53; —$OCH_3$, 34.07; Neut. equiv., 182.2. Found: C, 59.56, 59.67; H, 5.70, 5.68; —$OCH_3$, 34.26, 34.34; Neut. equiv., 185.1.

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[6] A. Oliverio and C. Casinovi, *Gazz. Ital.*, **80**, 798 (1950); *Chem. Abstr.* **46**, 977 (1952).

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## Reaction of Cyclic Sulfites of 1,3-Glycols with Sodium Iodide

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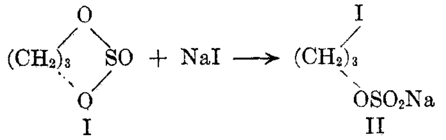
Alkyl sulfites have not been studied extensively as alkylating agents because of the ease of preparation and reactivity of the corresponding sulfates and sulfonates.

Cyclic sulfites of 1,3-glycols which are much more readily available than the cyclic sulfates have not been studied in this respect. Their behavior as alkylating agents would offer a convenient route to 3-monosubstituted derivatives of 1-propanol.

In this work the reaction of sodium iodide with the sulfites of trimethylene glycol, 3,3-bishydroxymethyloxetane, pentaerythritol, 3,3-dimethyl-1,3-propanediol, and 3-methyl-3-hydroxymethyl-1,3-propanediol has been studied and found to proceed normally with the first three compounds; 3-iodo-1-propanol, 3-hydroxymethyl-3-iodomethyloxetane, and 2,2-bisiodomethyl-1,3-propanediol were obtained, respectively.

The reaction was carried out in methyl ethyl ketone and found to proceed in a similar fashion to that found by others[2] for the reaction of sodium iodide with alkyl sulfites in acetone. Simultaneous condensation of methyl ethyl ketone apparently occurs with the liberation of water and subsequent hydrolysis of the intermediate sulfite. The methyl ethyl ketone bisulfite addition compound in contrast to the findings of Foster, *et al.*[2] coprecipitated



$$(CH_2)_3(O)_2SO + NaI \longrightarrow I(CH_2)_3OSO_2Na$$

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[1] Abstracted in part from the Ph.D. thesis of J. T. Loft, August 1959.

[2] A. B. Foster, E. B. Hancock, W. G. Overend, and J. C. Robb, *J. Chem. Soc.*, 2589 (1956).