Experimental Part

Isolation of the Toxic Material.—About 30 pounds of bark was stripped from freshly cut branches of Rhus Toxicodendron, placed in a 12-liter round-bottomed flask, equipped with a reflux condenser, and boiled with 95% ethyl alcohol for four days. The alcoholic solution was poured off, and concentrated on a steam-bath to about one-tenth of its volume under somewhat reduced pressure (water pump). The concentrate was cooled slowly, finally in ice, to precipitate waxy impurities. Under these conditions the solids formed a compact mass, filterable by the use of a suction pump. The deep red filtrate was saturated with solid sodium chloride and extracted with about three liters of xylene. This solution was dried with calcium chloride or with sodium sulfate and concentrated on the steam-bath under reduced pressure to from 50–100 cc. No air was bubbled through any of the solutions during the concentrations. The xylene concentrate was also cooled in a refrigerator to eliminate more of the waxy material. The liquid portion was decanted from the solids and subjected to vacuum distillation in an atmosphere of nitrogen. A toxic, yellow oil was obtained: b. p. 210° (0.5 mm.). A single run yielded from 5–12 cc. of the oil.

Conclusions

1. The toxic principle of the poison ivy, Rhus Toxicodendron, has been isolated and identified as urushiol, a material previously obtained by another investigator from Rhus Vernicifera.

2. Personal experiments have verified Toyama's conclusion that the hydroxyl groups in urushiol are the chief cause of its well-known violently vesicant action.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, NO. 148]

An Improved Method for the Preparation of Morphenol (3-Hydroxy-4,5-phenanthrylene Oxide) from Morphine[1]

BY ERICH MOSETTIG AND ERICH MEITZNER

In a systematic comparative chemical and pharmacological study of hydroxyphenanthrenes, the preparation of 4,5-phenanthrylene oxide, the inner ether of 4,5-dihydroxyphenanthrene, and its derivatives became desirable. Since at the present time no method of synthesizing this compound is available, we turned our attention toward a satisfactory method for the preparation of morphenol (3-hydroxy-4,5-phenanthrylene oxide) from morphine or codeine,[2] through the methylmorphimethines.

Our attempts to improve the method of Vongerichten[3] led us to a new and surprising observation. β-Methylmorphimethine methohydroxide is stable in aqueous solution even when boiled with alkali. When the aqueous solution is evaporated to dryness in a desiccator, an almost colorless lacquer remains, which on contact with water decomposes spontaneously into amine and methylmorphenol. The mere process of drying must have converted the β-methylmorphimethine methohydroxide into a new compound of yet unknown nature. This intermediate apparently has the side chain still attached, but so loosely that hydrolysis under extremely mild conditions results in complete aromatization.[4,5] It is possible that this intermediate plays a part in the mechanism of the many degradations of opium alkaloids[2] to phenanthrene derivatives.

To avoid the use of expensive methyl iodide and silver oxide in large-scale operations, we converted morphine by treatment with dimethyl sulfate and alkali into codeine methomethyl sulfate, which could be degraded smoothly to α-methylmorphimethine. The rearrangement to β-methylmorphimethine was carried out in the usual fashion. A solution of β-methylmorphimethine methohydroxide was prepared from the corresponding methomethyl sulfate by saponification with 20% sulfuric acid and subsequent removal of the sulfate ion with barium hydroxide.[6] The dried β-methylmorphimethine methohydrox-

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan.

(2) A recent review of the known reactions may be found in the "Chemistry of the Opium Alkaloids," by Small and Lutz, U. S. Government Printing Office, 1932, pp. 268–289.

(3) Vongerichten, *Ber.*, **30**, 2439 (1897); **33**, 358 (1900); **34**, 2722 (1901); **38**, 1853 (1905).

(4) Whether α-methylmorphimethine methohydroxide undergoes an analogous change could not be ascertained because of the instability of its aqueous solution. The tendency to form colloidal solutions containing silver is a further complication.

(5) Vongerichten seems to have noticed the effect of water on the decomposition. He evaporated the solution of β-methylmorphimethine methohydroxide in open dishes on the steam-bath and recommends "gelegentliches Anfeuchten" of the residue during the decomposition. He failed, however, to detect the above intermediate.

(6) This method is described by von Braun and Anton, *Ber.*, **64**, 2865 (1931).

ide was treated with water, resulting in a vigorous evolution of amine and formation of methylmorphenol in yields of 50–60%. This method can be used on a large scale and the yields can probably be improved by careful observation of the drying process. Nevertheless, the filtration of large amounts of barium sulfate[7] is inconvenient, and we therefore began a systematic decomposition of the methyl sulfates with sodium alcoholates.

Since the methyl sulfates are practically unaffected by boiling solutions of alkali hydroxides or of alkali methylates or ethylates, we employed the higher-boiling cyclohexanol (160°) in order to attain higher temperatures without being forced to work in closed vessels. It should be noted, however, that the reaction in cyclohexanol is dissimilar to that in aqueous or alcoholic solution. Whereas decomposition of the methomethyl sulfate in water or ethyl alcohol at temperatures from 100 to 160° required several hours and gave yields of methylmorphenol ranging from zero to 10%,[8] with sodium cyclohexanolate in cyclohexanol decomposition of the methyl sulfate even at a temperature of 120° took place almost instantaneously with the formation of methylmorphenol in yields of 65% or more. It is worth mentioning that with sodium amylate in amyl alcohol after four hours of boiling, only a 20% yield of methylmorphenol was obtained. Another advantage of the cyclohexanol process, which we believe to be a new modification of the Hofmann degradation, is that the α-methine can also be thus degraded in favorable yields.

The evidence available does not permit of theoretical conclusions concerning the course of the successful degradation in cyclohexanol. Methylmorphenol is not the primary product of degradation[9] and it is not certain whether the quaternary methylsulfate is degraded as such, or first converted into an alkoxide, which might degrade with unusual ease.[10] Whether the aforementioned intermediate also plays a part in the mechanism of this process is likewise uncertain. The investigations of Ingold[11] and of von Braun[12] on the decomposition of quaternary ammonium salts have established a connection between the course of the reaction on the one hand, and the anion and the solvent on the other, but we have not sufficient data to permit conclusions with respect to our process.

We are greatly indebted to Mr. Ulysse Cormier of this Laboratory for the skillful preparation of materials.

Experimental Part

α-Methylmorphimethine.[13]—Three hundred and three grams of morphine was added to one liter of methyl alcohol, in which 24 g. of sodium had been previously dissolved. Two hundred and fifty-five grams of dimethyl sulfate was then added through a dropping funnel. After addition of one-fourth of the amount, the heat of reaction was apparent, and further addition was regulated in such a way as to keep the solution boiling gently. Refluxing was then continued on a water-bath for three to four hours. After removal of the methyl alcohol in a vacuum, the codeine methomethyl sulfate remained. This could be degraded directly to the methine base by boiling for ten minutes with a solution of 125 g. of sodium hydroxide in 1500 cc. of water. Knorr's directions were followed to isolate and purify the methine base. Recrystallization of the crude material from toluene was also advantageous. The yield was 210 to 225 g., or 67–72% of the theoretical. To isolate the crystalline codeine methomethyl sulfate, 500 cc. of hot water was added to the residue after evaporation of the methanol. The brown mass dissolved and codeine methomethyl sulfate separated in white crystals when the solution was cooled in ice. It was filtered on an ice-cooled funnel, since the salt is rather soluble at room temperature.

Anal. Calcd. for $C_{20}H_{27}O_7NS + 2H_2O$: H_2O, 7.8. Found: H_2O, 6.94. Calcd. for $C_{20}H_{27}O_7NS$: S, 7.52. Found: S, 7.59.

α-Methylmorphimethine methomethyl sulfate failed to crystallize from a variety of solvents, but the addition compound with one molecule of acetone crystallized well. To a suspension of one part of α-methylmorphimethine in three parts of acetone was added the calculated amount of dimethyl sulfate in four portions (caution, vigorous reaction). The oil which separated was crystallized by seeding with crystals which had been previously prepared in a test-tube experiment. It was recrystallized from acetone to which a little alcohol had been added, and lost acetone when heated to about 75°.

Anal. Calcd. for $C_{21}H_{29}O_7NS$: S, 7.29. Found: S, 7.30. Calcd. for $C_{21}H_{29}O_7NS + C_3H_6O$: C_3H_6O, 11.7. Found: C_3H_6O, 11.7.

β-Methylmorphimethine Methomethyl Sulfate.—The rearrangement of α-methylmorphimethine into the β-compound was carried out according to Knorr and Smiles[14] and the crude material purified by crystallization from xylene. The β-methylmorphimethine methomethyl sulfate was obtained by combining equal amounts of the base and

(7) Saponification with sulfuric acid weaker than 20% is too slow to be practical. *Cf.* also the data on the saponification of potassium methyl sulfate by Blaser, *Z. physik. Chem.*, **167A**, 456 (1934).

(8) Chiefly unidentified products of decomposition were obtained.

(9) This primary product would be a hypothetical vinyl derivative of a tetrahydrophenanthrene.

(10) See, however, Ingold and Patel, *J. Chem. Soc.*, 67, 68 (1933).

(11) For a general discussion, see the sixteenth communication, Hughes, Ingold and Patel, *ibid.*, 526 (1933).

(12) Von Braun, seventh communication, *Ber.*, **65**, 1580 (1932). *Cf.* also von Braun, Teuffert and Weissbach, *Ann.*, **472**, 121 (1929).

(13) *Cf.* Knorr, *Ber.*, **27**, 1149 (1894).

(14) Knorr and Smiles, *ibid.*, **35**, 3009 (1902).

dimethyl sulfate in alcohol, in which the salt is only moderately soluble.

Anal. Calcd. for $C_{21}H_{29}O_7NS$: S, 7.29. Found: S, 7.28.

Methylmorphenol by Decomposition of β-Methylmorphimethine Methohydroxide.—Sixty-six grams of β-methylmorphimethine methomethyl sulfate was saponified by refluxing with 130 cc. of 20% sulfuric acid for one and a half hours. The solution was diluted and the sulfate ion was precipitated with approximately 120 g. of barium hydroxide (slight excess). The filtrate from the barium sulfate was evaporated under diminished pressure (15–20 mm.) and the residue dried at 100–105° for four hours at 15 mm. When treated with 150 cc. of water, the mass became warm, amine escaped, and the methylmorphenol separated as an oil. This was taken up in ether, washed with dilute hydrochloric acid and with sodium bicarbonate. The residue crystallized when methyl alcohol was added: yield, 21 g. or 65% of the theoretical.

Methylmorphenol by Decomposition of the Methyl Sulfates.—The degradation was carried out in a 2-liter 3-necked flask fitted with a mercury-sealed stirrer, a thermometer, and a delivery tube through which the gases passed into dilute hydrochloric acid. Twenty-eight grams of sodium was added slowly with stirring to 800–850 cc. of cyclohexanol at 110°. The temperature must be raised to 140° to keep the sodium cyclohexanolate from separating, but should be maintained at 120° during the addition of the salt. When the sodium was dissolved, 220 g. of the β-methylmorphimethine methomethyl sulfate (or 250 g. of the α-salt) was added in portions over a period of thirty minutes. Stirring was then continued for fifteen minutes.

The cyclohexanol was distilled off with steam and the residue extracted with ether. The extraction was hindered by the formation of emulsions. The ether extract was washed with dilute hydrochloric acid and sodium bicarbonate. After evaporation of the ether, the methylmorphenol remained as an oil, which was crystallized by addition of 100 cc. of methyl alcohol. The product was purified by crystallization from methyl alcohol or distillation at 1 mm.

The average yield from twenty runs with β-methomethyl sulfate was 65–70% of pure material (m. p. 64–65°). The mother liquors were treated with picric acid, and yielded a crude picrate which gave after decomposition a mixture of about 50% methylmorphenol and a white crystalline compound, m. p. 116–116.5° (nitrogen-free), which has not yet been investigated.

Because of the difficulty in obtaining crystalline α-methylmorphimethine methomethyl sulfate, most of the degradations were carried out with the β-compound. Later we obtained a crystalline α-salt (with acetone) which could be degraded in yields of 60–65%. The conversion of α- into β-methylmorphimethine is thus rendered unnecessary.

Morphenol.—A mixture of 25 g. of methylmorphenol, 50 cc. of 48% hydrobromic acid and 175 cc. of acetic acid was heated under reflux in a sand-bath. A homogeneous solution was obtained after a few minutes of refluxing. After eight hours, the mass was poured into 600 cc. of water. The morphenol, which is thus precipitated in almost quantitative yield, melted at 140–143°, after one recrystallization from benzene at 145°.

Summary

A method for the large-scale preparation of methylmorphenol (3-methoxy-4,5-phenanthrylene oxide) from β- (and α-) methylmorphimethine by a modified Hofmann degradation is described.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL CHEMISTRY, COLUMBIA UNIVERSITY]

Identification of Alkyl Halides: N-Alkyl-*p*-bromobenzenesulfon-*p*-anisidides

BY H. B. GILLESPIE

The reaction between alkyl halides and a selected arylsulfonanilide should yield derivatives whose melting points would be useful constants to aid in the identification of the halides. In order to obtain solid products *p*-bromobenzenesulfon-*p*-anisidide[1] was selected as the reagent for study. This amide dissolves readily in 5% potassium hydroxide and the alcoholic solution of the potassium salts reacts smoothly with alkyl halides to yield the corresponding N-alkyl derivatives. The procedure is simpler than are those which have been used to give alkyl phthalimides.[2]

(1) Marvel and Smith, THIS JOURNAL, **45**, 2696 (1923).

(2) Sah and Ma, *Ber.*, **65**, 1630 (1932); Allen and Nichols, THIS JOURNAL, **56**, 1409 (1934).

Experimental Part

***p*-Bromobenzenesulfon-*p*-anisidide.**—To a solution of 14.8 g. (0.12 mole) of *p*-anisidine and 7.9 g. (0.1 mole) of pyridine in 150 cc. of ether, there was added at room temperature with mechanical stirring during the course of one hour a solution of 25.6 g. (0.1 mole) of *p*-bromobenzenesulfonchloride in 150 cc. of ether. When the addition was complete, the reaction mixture was heated on the steam-bath under reflux for thirty minutes. After distilling the ether, the red colored residue was washed with dilute hydrochloric acid (1:1), then with water and filtered on a Büchner funnel. After two recrystallizations from 150 cc. of alcohol, 23.7 g. (69.3%) of *p*-bromobenzenesulfon-*p*-anisidide, melting at 142° (uncorr.), was obtained.

Small amounts of this compound can be prepared as described by Marvel and Smith.[1]