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SCISSION OF THE METHYLENEDIOXYL GROUP WITH ALUMINUM BROMIDE[1]

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The conversion of methylene ethers into the corresponding dihydroxy derivatives has been for many years a process of considerable importance, because of the frequent occurrence of this grouping in natural products, particularly among the alkaloids. By scission of the methylenedioxyl ring the parent dihydroxy compounds, as well as the monomethyl and dimethyl ethers, are made accessible.

The opening of this ring has for the most part been accomplished through the action of concentrated acid or alkali at elevated temperatures.[2] In recent years, Späth and his co-workers have systematically investigated the method, first devised by Tollens, Weber and Clowes[3] for quantitative estimation of the methylenedioxyl group, which depends upon the immediate destruction of the formaldehyde with phenolic substances. This was elaborated for preparative purposes, and employed with great success in alkaloid chemistry.[4] Phosphorus pentachloride has been employed by Fittig and Remsen,[5] R. Wegscheider,[6] and A. Pauly.[7] Most recently, Parijs[8] has used absolute nitric acid and acetic anhydride to split methylene ethers.

Aluminum halides, especially the chloride, have found much use in the laboratory and in industry in the scission of ethers and have been successfully applied to a number of alkaloids.[9] Aluminum bromide compounds with aromatic ethers were first described by Kohler;[10] they have recently been studied exhaustively by Pfeiffer,[11] who proposed a mechanism for the demethylation process. The splitting of the methylenedioxyl group with aluminum chloride has been attempted only in isolated cases,[12] in which

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[1] This investigation was supported by the Committee on Drug Addiction of the National Research Council.

[2] A complete bibliography on the subject is given in the paper of Späth and Quietensky, *Ber.*, **60**, 1882 (1927).

[3] Tollens, Weber and Clowes, *Ann.*, **299**, 316 (1898); *Ber.*, **32**, 2841 (1899).

[4] Späth and Quietensky, *ibid.*, **58**, 2267 (1925); Späth and Holter, *ibid.*, **60**, 1891 (1927); Späth and Mosettig, *ibid.*, **59**, 1496 (1926).

[5] Fittig and Remsen, *Ann.*, **159**, 144 (1871).

[6] Wegscheider, *Monatsh.*, **14**, 382 (1893).

[7] Pauly, *Ber.*, **40**, 3096 (1907).

[8] Parijs, *Rec. trav. chim.*, **49**, 33 (1930).

[9] Oberlin, *Arch. Pharm.*, **265**, 256–273 (1927).

[10] Kohler, *Am. Chem. J.*, **27**, 249 (1902).

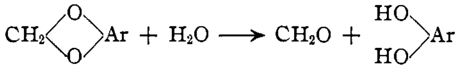
[11] Pfeiffer, *Ann.*, **460**, 156 (1928).

[12] Dreyfus, German Patent 193,958; Thoms and Biltz, *Arch. Pharm.*, **242**, 87 (1904); Mauthner, *J. prakt. Chem.*, [2] **119**, 74 (1928); see also Ref. 9.

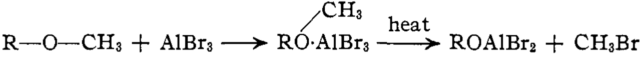
the conditions (especially temperature) are such that the method has a very limited field of application.

The more active and more soluble aluminum bromide would be expected to accomplish the desired result under milder experimental conditions. We have in fact found it possible to carry out the reaction with a number of methylene ethers at room temperature or even at 0°, with very satisfactory yields. The most suitable solvent proved to be nitrobenzene, because of its ability to dissolve the reacting substances and to hold the resulting aluminum bromide double compound in solution.

It seems quite certain that the scission with acids takes place according to the equation



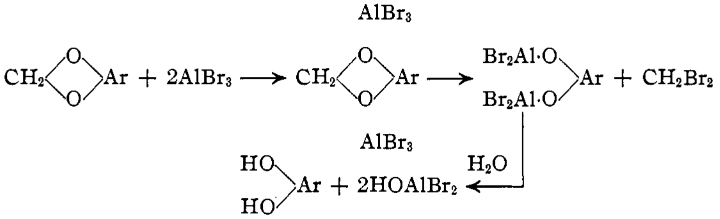
but to our knowledge no mechanism has been proposed for the action of the aluminum halides. According to Pfeiffer,[11] the demethylation process takes the following course



$$R—O—CH_3 + AlBr_3 \longrightarrow \overset{CH_3}{RO}\cdot AlBr_3 \xrightarrow{\text{heat}} ROAlBr_2 + CH_3Br$$

$$ROAlBr_2 + H_2O \longrightarrow ROH + HOAlBr_2$$

and it is not unreasonable to assume that in the case of methylene ethers a similar mechanism is applicable



In support of this assumption, we find that at least two molecules of aluminum bromide must be used for each molecule of methylene ether. With piperonal, for example, the yield of protocatechuic aldehyde was halved when but one molecule of aluminum bromide was used. Similarly, the reaction runs most favorably with acetopiperone in the presence of three molecules of aluminum bromide, in accordance with the Pfeiffer[11] theory that the carbonyl group also adds a molecule of aluminum halide. Since we were interested primarily in the perfection of a preparative method, further quantitative investigations to determine the course of the reaction were not undertaken.

The methylene ethers chosen for investigation were: piperonal, piperonylic acid and its methyl ester, acetopiperone, *m*-nitrocatechol methylene ether, 2,3-methylenedioxy-phenanthrene-9-carboxylic acid, and inactive tetrahydroberberine. It is rather remarkable that, under conditions which give smooth scission of the methylene ether group, the methoxyl group is scarcely affected. In parallel experiments with veratric aldehyde, only traces of alkali-soluble material were obtained; in the case of tetrahydroberberine, the two methoxyl groups remained intact. The ester group in piperonylic acid methyl ester was hydrolyzed only to a small extent.

The method is not applicable to those substances which are extremely sensitive toward aluminum bromide or which may undergo reaction with the methylene bromide assumed to be among the products. It was not possible, for example, with safrole, isosafrole or piperonyl alcohol (even after benzoylation of the alcoholic hydroxyl) to isolate the expected dihydroxy compounds. Instead of these, sparingly soluble, alkali-insoluble amorphous substances were obtained, which probably represented condensation products. The reaction likewise failed with 2,3-methylenedioxyphenanthrene. 2,3-Methylenedioxy-phenanthrene-9-carboxylic acid, on the other hand, was converted in nearly quantitative yield to 2,3-dihydroxy-phenanthrene-9-carboxylic acid, which could then be decarboxylated to the desired 2,3-dihydroxy-phenanthrene.

In contrast to the methylenedioxyl group, the ethylenedioxyl group is exceedingly stable, and even at temperatures up to 130° no ring-opening took place with pyrocatechol ethylene ether, or pyrocatechuic acid ethylene ether.

Experimental Part

The aluminum bromide employed in the following investigations was distilled from aluminum chips before each experiment. The nitrobenzene was dried over calcium chloride. All high-vacuum sublimations were carried out in pyrex bulb-tubes sealed directly onto an efficient mercury-vapor pump.

Preparation of Protocatechuic Aldehyde from Piperonal.—Five grams of piperonal was dissolved in 15 cc. of nitrobenzene and cooled to about 10°. To this was added a cold solution of 18 g. of aluminum bromide (about 2 mols) in 20 cc. of nitrobenzene, giving a deep red solution. After five hours' standing at room temperature, the reaction mixture was poured into 300 cc. of water containing a small amount of hydrochloric acid. The aqueous layer, separated from the nitrobenzene, was extracted with ether. The combined ether extract and nitrobenzene was washed with a little water and the protocatechuic aldehyde extracted with dilute sodium hydroxide. This alkaline solution was extracted with ether to remove traces of nitrobenzene, acidified, saturated with salt and extracted exhaustively with ether. The ether solution, dried with sodium sulfate, yielded on distillation an oil which soon crystallized. After recrystallization from 500 cc. of boiling toluene, the substance melted at 151–153°. Sublimation in high vacuum yielded long white needles of m. p. 154–155.5°. It was readily soluble in alkali and its aqueous solution gave with ferric chloride the characteristic green color of protocatechuic aldehyde. The yield was 3.8 g., 82% of the calculated.

Another experiment carried out under the same conditions was interrupted at the end of fifteen minutes and worked up as described. Even after this short reaction period, the yield amounted to 56% of the theoretical.

If piperonal and aluminum bromide are allowed to react in equimolecular amounts for eleven hours, a yield of 41% of protocatechuic aldehyde is obtained, and about 40% of the piperonal used can be regained with sodium bisulfite.

To compare the action of aluminum bromide on the methoxyl group, veratric aldehyde was treated with aluminum bromide under the conditions described above. Alkali-soluble substances were obtained only in traces; judging from odor, these may have been vanillin or isovanillin. No protocatechuic aldehyde was formed (negative ferric chloride test).

Preparation of Protocatechuic Acid from Piperonylic Acid.—Nine grams of finely powdered piperonylic acid suspended in 180 cc. of nitrobenzene was treated with a solution of 3 g. of aluminum bromide in 70 cc. of nitrobenzene, whereby the piperonylic acid went into solution. The red solution stood for four hours at room temperature and was then poured into 400 cc. of acidified ice water. The nitrobenzene was distilled off with steam and the aqueous solution concentrated to 200 cc. Most of the protocatechuic acid separated crystalline at this point. The remainder was obtained by ether extraction of the mother liquors from the crystallization. After treatment with animal charcoal in 30 cc. of boiling water, the acid was obtained nearly pure in a yield of 7.7 g., 92% of the theoretical. Purified by high-vacuum sublimation, it had the m. p. 200–202°.

Protocatechuic Acid Methyl Ester from Piperonylic Acid Methyl Ester.—Piperonylic acid methyl ester was prepared by heating 2 g. of piperonylic acid in 80 cc. of methyl alcohol with 2 g. of concd. sulfuric acid. After neutralization of the sulfuric acid the alcohol was distilled off in a strong current of carbon dioxide and the residue dissolved in ether, which was now washed with dilute soda solution and dried over sodium sulfate. The oily residue from distillation of the ether was distilled in a vacuum (12 mm.). The highly refracting distillate solidified on cooling, m. p. 49.5–50.5°, yield 2 g.

A solution of 2.6 g. of the methyl ester in 52 cc. of nitrobenzene was cooled in ice and treated with a cold solution of 8 g. of aluminum bromide in 35 cc. of nitrobenzene. After three and one-half hours at room temperature the mixture was poured into ice water, acidified, extracted with ether and the ether–nitrobenzene solution extracted as rapidly as possible with very dilute ice-cold sodium hydroxide. The alkaline solution was made weakly acid immediately, saturated with salt, and extracted exhaustively with ether; 0.2 g. of protocatechuic acid was removed from the ether by shaking with dilute sodium bicarbonate. Distillation of the ether yielded an oily product, which solidified to faintly colored crystals on standing in a vacuum desiccator overnight. The melting point was 130–133°, unsharp; the yield, 1.43 g. or 58% of the theoretical amount. After high-vacuum sublimation it was obtained in radiated clusters of crystals, m. p. 134.5–135°.[13]

3,4-Dihydroxyacetophenone from Acetopiperone.—One gram of acetopiperone[14] dissolved in 10 cc. of nitrobenzene was treated with a solution of 5.3 g. (somewhat more than 3 mols) of aluminum bromide in 40 cc. of nitrobenzene. After two and one-half hours' reaction at room temperature, the mixture was poured into acidified ice water, the nitrobenzene layer diluted with ether, separated, and the phenolic product shaken into 0.5 *N* potassium hydroxide. This was acidified and exhaustively extracted with ether. The product, which separated nearly pure, was further purified by cautious precipitation from its xylene solution with petroleum ether, or by high-vacuum sublimation. The pure substance melted at 117–118°;[15] yield, 0.45 g., 48% of the theoretical amount.

4-Nitropyrocatechol from 4-Nitropyrocatechol Methylene Ether.—The methylene ether used was obtained as a secondary product from the nitration of piperonal by the

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[13] Matsmoto, *Ber.*, **11**, 129 (1878), gives the m. p. 134.5°.

[14] Prepared by the method of Mosettig and Jovanovič, *Monatsh.*, **53** and **54**, 427 (1929).

[15] Mauthner, *J. prakt. Chem.*, [2] **119**, 74 (1928); Dzierzgowski, *Ber.*, **27**, 1988 (1894), give the m. p. 116°.

method of Ekeley and Klemme.[16] Five grams of 4-nitropyrocatechol methylene ether in 70 cc. of nitrobenzene was treated with a cold solution of 18 g. of aluminum bromide in 60 cc. of nitrobenzene with good cooling and allowed to react for one and one-half hours at 0°. At the end of this time the double compound had precipitated in part from the solution. The mixture was decomposed with ice-cold dilute hydrochloric acid and the phenolic products extracted from the nitrobenzene layer with alkali. When the purple alkaline solution was acidified, a nearly insoluble substance precipitated and was filtered off. This material was not further investigated. The filtrate was concentrated and the 4-nitropyrocatechol extracted with ether. Crystallization from water gave 3 g. of pure substance, corresponding to 65% yield. It sublimed readily in a vacuum, m. p. 174–175°, agreeing with the melting point given in the literature.[17]

Scission of the Methylene Ether Group of Inactive Tetrahydroberberine.[18]—Five grams of tetrahydroberberine in 150 cc. of nitrobenzene was cooled to a point just above that where the nitrobenzene started to crystallize and a cold solution of 8.5 g. of aluminum bromide in 85 cc. of nitrobenzene added slowly, cooling in a freezing mixture. After standing for one-half hour at this temperature with frequent shaking, the reaction mixture was poured into 500 cc. of ice water containing 20 cc. of hydrobromic acid. A heavy precipitate of hydrobromides separated, which was filtered out and washed with ether. The filtrate was freed from nitrobenzene by extracting with ether and the bases remaining in it were thrown out as hydriodides with a large excess of potassium iodide. These salts were dissolved in water together and the solution made alkaline. By shaking out with ether, about 30% of the tetrahydroberberine employed was regained. The red alkaline solution was acidified, again made alkaline with sodium bicarbonate, and the dihydroxy base extracted into a large amount of ether. Concentration of the ether to about 100 cc. yielded the base in colorless micro crystals; 3 g. of product was obtained, melting in a vacuum at 260–261°. The substance agreed also in its other properties with the base described by Späth and Mosettig.[4]

Anal. Subs., 6.573 mg.: AgI, 9.118 mg. (Zeisel–Pregl). Calcd. for $C_{17}H_{13}(OH)_2(OCH_3)_2N$: OCH_3, 18.97. Found: OCH_3, 18.33.

For further confirmation, our dihydroxy base was methylated with diazomethane[4] and racemic tetrahydropalmatine (m. p. 147–148°) obtained.

Synthesis of 2,3-Dihydroxy-phenanthrene.—This preparation was carried out according to the Pschorr method for the synthesis of phenanthrene derivatives.

The 6-nitropiperonal was prepared and purified by the method of Ekeley and Klemme.[16]

α-Phenyl-2-nitro-4,5-methylenedioxy-cinnamic Acid.—Twenty grams of 6-nitropiperonal was heated with 15.2 g. of anhydrous sodium phenylacetate and 1 g. of anhydrous zinc chloride in 85 cc. of acetic anhydride for four and one-half hours in an oil-bath at 110–120°. The reaction mixture was poured into 500 cc. of water and, after the initial cloudiness had settled, the clear solution was decanted from the brown resinous products. These resins were brought into solution by boiling with 3 liters of water, with addition of concd. ammonia, and filtered through a layer of paper pulp. The filtrate was acidified and the pale yellow precipitate of acid filtered out. It was dried and recrystallized from about 60 parts of boiling benzene. The yield was 17.3 g., 54% of the theoretical. It consisted of pale yellow crystals, m. p. 193–195°.

Anal. Subs., 7.185 mg.: N, 0.305 cc. (25°, 740 mm.). Calcd. for $C_{16}H_{11}O_6N$: N, 4.47. Found: N, 4.73.

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[16] Ekeley and Klemme, THIS JOURNAL, **50**, 2711 (1928).

[17] Kempf, *J. prakt. Chem.*, [2] **78**, 257 (1908); Dakin, *Am. Chem. J.*, **42**, 490 (1909).

[18] Späth and Mosettig (Ref. 4) accomplished this with phloroglucinol and sulfuric acid at 100°.

α-Phenyl-2-amino-4,5-methylenedioxy-cinnamic Acid.—Five grams of the nitro acid was dissolved in 30 cc. of water and 10 cc. of 25% ammonia, heated to boiling and poured into a suspension of ferrous hydroxide, prepared from 35 g. of hydrated ferrous sulfate in 105 cc. of water with 20 cc. of 25% ammonia. This was heated for one-half hour on the steam-bath with frequent shaking and filtered through paper pulp. The pulp filter and residue was boiled out three times with dilute ammonia and the combined ammoniacal liquors acidified with acetic acid. The amino acid, which separated in yellow crystals, was filtered out and dried at 100°. The yield was 2.8 g., 62% of the theoretical. After recrystallizing from boiling toluene it melted at 201–203° (decomp.).

If the ammoniacal solution is acidified with hydrochloric instead of acetic acid, the amino acid separates in pale pink crystals, which become yellow on drying at 100°. The acid apparently exists in two modifications, as other authors[19] have shown with analogous compounds.

Anal. Subs., 7.050 mg.: N, 0.328 cc. (27°, 747 mm.). Calcd. for $C_{16}H_{13}O_4N$: N, 4.95. Found: N, 5.20.

2,3-Methylenedioxy-phenanthrene-9-carboxylic Acid.—Ten grams of the amino acid, suspended in 200 cc. of water, was neutralized with a solution of 2.8 g. of sodium carbonate and mixed with 44 cc. of normal sodium nitrite solution. The mixture was now added dropwise with mechanical stirring to 140 cc. of ice-cold 5 *N* sulfuric acid keeping the temperature below 2°. At the end of the reaction, the solution was filtered, molecular copper[20] added and the suspension stirred for one hour at 75°. After cooling the precipitate of copper and phenanthrene-carboxylic acid was filtered off, the acid dissolved out by hot ammonia and reprecipitated with hydrochloric acid. Recrystallized from boiling xylene, it melted at 259–260°. It consists of colorless crystals, which sublime in high vacuum.

Anal. Subs., 0.0980: CO_2, 0.2595; H_2O, 0.0359. Calcd. for $C_{16}H_{10}O_4$: C, 72.16; H, 3.80. Found: C, 72.22; H, 4.10.

The methyl ester was prepared by refluxing a suspension of the acid in absolute methyl alcohol containing 5% of concd. sulfuric acid. The organic acid dissolved completely after about forty-five minutes and the reaction was stopped at the end of four hours. The sulfuric acid was neutralized with potassium hydroxide and the mixture poured into ten times its volume of water. The amorphous precipitate soon crystallized and was filtered off and washed with dilute sodium carbonate. Recrystallization from methyl alcohol gave white needles in a yield of 76%; m. p. 151–151.5°.

Anal. Subs., 0.1370: CO_2, 0.3666; H_2O, 0.0562. Calcd. for $C_{17}H_{12}O_4$: C, 72.83; H, 4.32. Found: C, 72.98; H, 4.59.

2,3-Dihydroxy-phenanthrene-9-carboxylic Acid.—Two grams of finely powdered methylenedioxy-phenanthrene-carboxylic acid was suspended in 20 cc. of nitrobenzene and treated with 3.5 g. of aluminum bromide in 30 cc. of nitrobenzene. The acid went into solution with deep red color. After three hours at room temperature it was poured into ice-cold diluted sulfuric acid. The larger part of the dihydroxy product separated and was filtered off and pressed dry. A little more was obtained from extraction of the nitrobenzene layer with sodium hydroxide. The acid was purified by dissolving in sodium hydroxide, filtering and precipitating with acids. The crude product was obtained in a yield of about 97%. The acid starts to decompose at about 280°; its solution in dilute alcohol gives a deep blue color with ferric chloride. Since no suitable solvent could be found for recrystallizing the acid, the crude substance was used for decarboxylation.

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[19] Pschorr, *Ber.*, **39**, 3110 (1906); **29**, 499 (1896); Mayer and Balle, *Ann.*, **403**, 194 (1914).

[20] Gattermann, *Ber.*, **23**, 1219 (1890).

2,3-Dihydroxy-phenanthrene.—One gram of crude dihydroxy-phenanthrene-carboxylic acid was distilled at 25–30 mm. pressure in a hard-glass bulb-tube. The distillate was dissolved in ether and washed with dilute sodium bicarbonate to remove unchanged acid. The dihydroxy-phenanthrene was extracted from the ether with dilute alkali, precipitated with acid and again brought into ether. Distillation of the ether gave a fairly pure, crystalline product in 46% yield. The substance is quite soluble in most organic solvents, excepting benzene, insoluble in water or petroleum ether. The best purification method is high-vacuum distillation or sublimation and recrystallization from benzene; m. p. 158.5–159°.

Anal. Subs., 0.1005: CO_2, 0.2942; H_2O, 0.0446. Calcd. for $C_{14}H_{10}O_2$: C, 79.97; H, 4.80. Found: C, 79.84; H, 4.97.

The dihydroxy-phenanthrene was converted to its dimethyl ether, previously prepared by Pschorr in another way: 0.3 g. of dihydroxy-phenanthrene was dissolved in 1 cc. of absolute methyl alcohol and the ethereal diazomethane solution from 1 cc. of nitrosomethylurethan added. After ten hours the mixture was washed with dilute alkali and the ether distilled off. The residue was recrystallized from methyl alcohol and sublimed in high vacuum; m. p. 130.5–132° (Pschorr, m. p. 131°). The picrate showed the melting point 126.5–127.5°, given by Pschorr.[21]

2,3-Methylenedioxy-phenanthrene.—One gram of 2,3-methylenedioxy-phenanthrene-carboxylic acid was distilled slowly at 250 mm. pressure. The distillate was taken up in ether and washed with dilute potassium hydroxide. The residue obtained from distillation of the ether, recrystallized from methyl alcohol, had the m. p. 93–94°. The yield varies from 45 to 50%.

Anal. Subs., 0.0973: CO_2, 0.2899; H_2O, 0.0404. Calcd. for $C_{15}H_{10}O_2$: C, 81.05; H, 4.54. Found: C, 81.26; H, 4.65.

The brick-red picrate, recrystallized from methyl alcohol, melts at 151–152°.

Anal. Subs., 5.764 mg.: N, 0.481 cc. (25°, 740 mm.). Calcd. for $C_{21}H_{13}O_9N_3$: N, 9.32. Found: N, 9.31.

The ring-opening of methylenedioxy-phenanthrene was unsuccessful. We obtained only amorphous, brown-colored substances, sparingly soluble in water or ether, soluble with difficulty in alkali.

Summary

A new method of converting methylene ethers to the corresponding dihydroxy compounds is described. The reaction offers special advantages in operating at temperatures from 0 to 20°, and leaving methoxyl or ester groupings practically intact.

It has been employed successfully with the methylene ethers of a variety of aromatic compounds, and with one alkaloid.

The preparation of 2,3-dihydroxy-phenanthrene and its methylene ether is described.

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[21] Pschorr, *Ber.*, **33**, 1829 (1900).