Reduction of β-(9-Adenyl)-propiophenone

A mixture of the ketone (1 g) and sodium borohydride (0.2 g) in 55 ml of isopropanol containing 5 ml of water was stirred at room temperature over the weekend. After dilution with water the reaction product was extracted with chloroform, the solvent was removed *in vacuo*, and the resin-like residue (0.9 g) was crystallized from ethyl acetate. The analytically pure product (0.66 g, 66%) had a melting point of 139–142°.

Anal. Calcd. for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.62; N, 26.01. Found: C, 62.18; H, 5.86; N, 26.24.

Reduction of β-(9-Adenyl)-α-methylpropiophenone

A mixture of the ketone (4 g) and sodium borohydride (0.3 g) in methanol–isopropanol–water (1:1:0.2, 66 ml) was stirred for 17 h at room temperature. The reaction mixture was worked up as above to give 1.5 g (37%) of pure alcohol, m.p. 229–231° (crystallized from methanol – ethyl acetate).

Anal. Calcd. for $C_{15}H_{17}N_5O$: C, 63.58; H, 6.05; N, 24.72. Found: C, 63.76; H, 6.17; N, 24.56.

ACKNOWLEDGMENT

The skillful technical assistance of Mrs. C. Solomon is gratefully acknowledged.

1. J. C. Craig and M. Moyle. J. Org. Chem. **29**, 410 (1964).
2. C. L. Angell. J. Chem. Soc. 504 (1961).
3. H. J. Schaffer and P. S. Bhargava. Biochemistry, **4**, 71 (1965).
4. H. H. Jaffé and M. Orchin. Theory and applications of ultraviolet spectroscopy. John Wiley & Sons, Inc., New York. 1962.
5. N. J. Leonard and J. H. Deyrup. J. Am. Chem. Soc. **84**, 2148 (1962).
6. H. J. Schaffer and R. Vince. J. Med. Chem. **8**, 710 (1965).
7. P. Brookes and P. D. Lawley. J. Chem. Soc. 539 (1960).

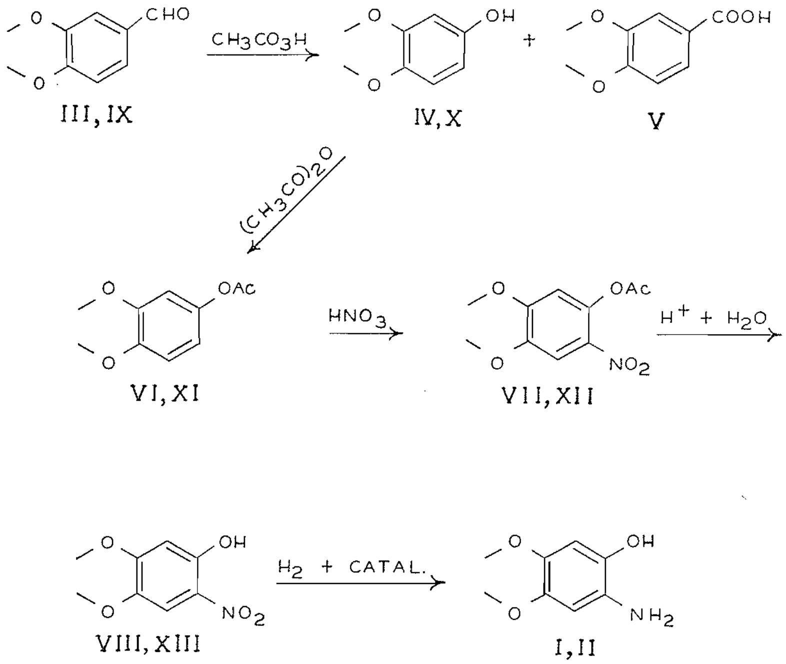
Received September 17, 1965.
Delmar Chemicals Limited,
Lasalle, Quebec.

PREPARATION OF 3,4-METHYLENEDIOXY- AND 3,4-DIMETHOXY-6-AMINOPHENOL

D. G. Orphanos and A. Taurins

The work on the synthesis of 6,7-dialkoxy-1,4-benzoxazin-2-ones (1) required the preparation of 3,4-methylenedioxy- (I) and 3,4-dimethoxy-6-aminophenol (II), which had not been described in the literature. These aminophenols proved to be very sensitive to air oxidation, and could not be isolated from solutions in a pure state. Therefore, their solutions were brought directly into reactions with other components in a nitrogen atmosphere. 3,4-Methylenedioxy- and 3,4-dimethoxy-6-aminophenol were characterized as their acetanilides, which were prepared by reductive acetylation (2) of the corresponding nitro compounds. Most of the intermediates used in the preparation of I and II have been described previously; however, in the present work they were synthesized either by a modification of the known method, or by a new procedure.

3,4-Methylenedioxy-6-aminophenol (I) was prepared from piperonal (3,4-methylenedioxybenzaldehyde) (III) in five steps (Reaction Scheme 1): (*a*) oxidation of piperonal (III) with peracetic acid to give 3,4-methylenedioxyphenol (IV) (sesamol), (*b*) acetylation of sesamol, (*c*) nitration of the acetyl derivative (VI) to obtain 3,4-methylenedioxy-6-nitrophenyl acetate (VII), (*d*) hydrolysis of the latter compound to produce a free nitrophenol (VIII), and (*e*) catalytic hydrogenation of the nitro compound to obtain I. The aminophenol I was characterized as its *N*-acetyl derivative, prepared by reductive acetylation (2) of the nitro compound (VIII).



Reaction Scheme 1.

3,4-Dimethoxy-6-aminophenol (II) (5, 6) was similarly synthesized from veratraldehyde (3,4-dimethoxybenzaldehyde).

The oxidation of piperonal with peracetic acid was reinvestigated because the experimental observations did not agree with the literature data (3, 9). According to previous views, peracetic acid oxidation of piperonal gave sesamol acetate (3), or sesamol acetate and formate (9); therefore, the oxidation product was subjected to alkaline hydrolysis to obtain a uniform substance.

In the present work, neither sesamol acetate nor formate was found to be present. Instead, the oxidation product consisted of sesamol and unreacted piperonal in a ratio of 4:1, and a small amount of piperonylic acid (3,4-methylenedioxybenzoic acid) (V). This mixture could not be separated even by fractional distillation with a spinning-band column. The oxidation of piperonal was studied under a variety of experimental conditions, and it was observed that the reaction never goes to completion. If a greater amount of peracetic acid was used than that established as an optimum, the yields of the product were noticeably lower and more resinous by-products were formed. Freshly prepared peracetic acid was decidedly most efficient, and the best yields of sesamol (45–49%) were obtained when the reaction temperature was between 32 and 38°.

3,4-Methylenedioxy- (VI) and 3,4-dimethoxy-phenyl acetate (XI) were prepared by an adaptation of a method involving the treatment of the sodium salts of phenolic substances with acetic anhydride (8). The yields of VI and XI were 92% and 88%, respectively.

Nitration of 3,4-methylenedioxyphenyl acetate (VI) was carried out by an improved method in which the mixture of nitric and acetic acids was added to the solution of VI in glacial acetic acid at 30–45°. This procedure gave a yield of 88% of pure 3,4-methylenedioxy-6-nitrophenyl acetate (VII), compared with a yield of 67% obtained by a previous method (9). 3,4-Dimethoxy-6-nitrophenyl acetate (XII), a new compound, was prepared by a method analogous to that used for preparing VII.

Both VII and XII were hydrolyzed to give free phenols by reaction with 20% sulfuric acid for 40 min, instead of by the previous method (9) in which VII was refluxed for 20 h with ethanolic sodium hydroxide solution. Acidic hydrolysis of VII and XII produced quantitative yields of VIII and XIII as pure crystalline products.

Low-pressure catalytic hydrogenation of 3,4-methylenedioxy- (VIII) and 3,4-dimethoxy-6-nitrophenol (XIII) produced the desired products, 3,4-methylenedioxy- (I) and 3,4-dimethoxy-6-aminophenol (II), which were characterized and analyzed as their acetanilides (*N*-acetylamino derivatives). I and II were not isolated in a pure state from solutions because of their sensitivity to oxidation, but were used directly in syntheses (1).

EXPERIMENTAL

The melting points were determined in a Thiele–Dennis melting point tube containing Dow Corning silicone fluid No. D.C. 550, and are uncorrected. The analyses were carried out in the laboratory of C. Daessle, Montreal, Quebec. Infrared spectra were determined in potassium bromide, on a Perkin–Elmer model 21 double-beam instrument equipped with a sodium chloride prism.

20% Peracetic Acid Solution

This solution, containing catalytic amounts of *p*-toluenesulfonic acid, and being free of explosive Ac_2O_2, was always freshly prepared according to Böeseken *et al.* (3), and used within 24 h.

3,4-Methylenedioxyphenol (Sesamol) (IV)

To a solution of piperonal (III) (50 g, 0.333 mole) in glacial acetic acid at 32°, 20% peracetic acid solution (145 g, 0.38 mole) was added in portions of 20–30 ml, with occasional shaking. After the addition of the first portion, the temperature rose slowly to about 38°. It was allowed to fall to 32° before the next portion was added. When the addition had been completed, the reaction mixture was left at room temperature for 24 h, and then distilled under reduced pressure to free it from acetic acid. The dark-brown viscous oil was mixed with toluene (250 ml) and stirred for 15 min, during which time most of the resinous by-products separated as a viscous mass. After separation and distillation of the solvent, the residual dark-brown oil was subjected to vacuum distillation, and gave 40.5 g of a yellow oil boiling at 110–114° and 2 mm Hg. At the end of this distillation, the temperature was raised to 130–145° and piperonylic acid was distilled over. This acid, collected and crystallized from methanol, weighed 1.2 g and melted at 229°. The yellow oil obtained from the vacuum distillation was shaken with 150 ml of 10% sodium hydroxide solution and extracted three times with 50 ml portions of diethyl ether. The combined ether extracts, washed with water and dried over potassium sulfate, left 13.1 g of pure unreacted piperonal after removal of the solvent. The alkaline layer, acidified with 20% sulfuric acid solution, was then extracted with diethyl ether (200 ml). The ether extract, washed three times with 50 ml portions of 5% sodium bicarbonate solution and then with water, was dried over potassium sulfate. Removal of the ether gave a colorless to light-yellow oil which, with evolution of heat, rapidly solidified to pure sesamol (22.5 g), m.p. 64–65° (lit. (3) m.p. 65.8°). The yield of pure product, when the recovery of 13.1 g of pure unreacted piperonal was considered, amounted to 67.5%.

3,4-Dimethoxyphenol (X)

Oxidation of 55.5 g (0.333 mole) of veratraldehyde (IX) with peracetic acid was carried out under the conditions described above. Distillation of the reaction product gave 39.8 g of a yellow oil boiling at 118–127° and 2 mm Hg. Purification of the oil gave 25.8 g of crude 3,4-dimethoxyphenol, m.p. 71–76°. Crystallization from carbon tetrachloride raised the melting point to 79–80° (lit. m.p. 78–80° (6), 80–81° (7), 81.5° (5)); 11.5 g of pure unreacted veratraldehyde was isolated.

3,4-Methylenedioxyphenyl Acetate (VI)

3,4-Methylenedioxyphenol (IV) (13.8 g, 0.1 mole) was dissolved in 10% sodium hydroxide solution (60 ml), and to the cooled solution acetic anhydride (15 g, 0.15 mole) was added, with stirring, over 10 min. The reaction mixture was extracted with carbon tetrachloride. The extract was neutralized with sodium carbonate solution and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue, 3,4-methylenedioxyphenyl acetate, was distilled at 112° and 2.5 mm Hg, yield 16.6 g (92%), n_D^{20} 1.5281 (lit. (4) n_D^{25} 1.5265).

3,4-Dimethoxyphenyl Acetate (XI)

3,4-Dimethoxyphenol (X) (15. g, 0.1 mole) was acetylated by a similar procedure. The crude acetate distilled at 128° and 2 mm, yield 17.8 g (88%). 3,4-Dimethoxyphenyl acetate forms colorless plates when crystallized from dilute ethanol, m.p. 44° (lit. (7) m.p. 44°).

3,4-Methylenedioxy-6-nitrophenyl Acetate (VII)

3,4-Methylenedioxyphenyl acetate (VI) (18 g, 0.1 mole) dissolved in glacial acetic acid (60 ml) was treated at room temperature gradually with a solution of concentrated nitric acid (11 g, 0.12 mole, specific gravity 1.42) in glacial acetic acid (20 ml). The solution was stirred for 3 h and then poured into cold water (400 ml). After 1 h the pale-yellow crystalline precipitate was separated by filtration, washed with water, and dried. 3,4-Methylenedioxy-6-nitrophenyl acetate (VII) was crystallized from ethanol, yield 19.8 g (88%), m.p. 104–105° (lit. (9) m.p. 104–105°).

3,4-Dimethoxy-6-nitrophenyl Acetate (XII)

Nitration of 3,4-dimethoxyphenyl acetate (XI) (19.6 g, 0.1 mole) was carried out by the method used for the preparation of VII. 3,4-Dimethoxy-6-nitrophenyl acetate was crystallized from ethanol as yellow prisms, m.p. 117–118°, yield 20.7 g (85.4%).

Anal. Calcd. for $C_{10}H_{11}NO_6$: C, 49.79; H, 4.59; N, 5.81. Found: C, 49.51; H, 4.47; N, 6.08.

The structure of XII was confirmed by its infrared spectrum and hydrolysis of the acetate to the known XIII.

3,4-Methylenedioxy-6-nitrophenol (VIII)

3,4-Methylenedioxy-6-nitrophenyl acetate (VII) (22.5 g, 0.1 mole), ethanol (220 ml), and 20% (by volume) sulfuric acid solution (125 ml) were heated on a water bath for 40 min. The solution deposited golden-yellow needles when cooled. The product VIII was separated by filtration, washed with cold water, and dried, yield 18.1 g (98.3%), m.p. 95–96° (crystallized from 60% ethanol) (lit. (9) m.p. 93–94°).

3,4-Dimethoxy-6-nitrophenol (XIII)

3,4-Dimethoxy-6-nitrophenyl acetate (XII) (24.1 g, 0.1 mole) was hydrolyzed under conditions similar to those employed for the preparation of VIII. The compound XIII formed yellow crystals, m.p. 145–146° (crystallized from 60% ethanol) (lit. (10) m.p. 143°).

3,4-Methylenedioxy-6-aminophenol (I) (in Ethanol Solution)

3,4-Methylenedioxy-6-nitrophenol (VIII), dissolved in 25 times its weight of 96% ethanol, was reduced at room temperature with either platinum oxide or palladium on charcoal as catalyst, and with hydrogen at 3 atm pressure, until 3 molecular equivalents had been absorbed. The time required was about 10 min. When Raney nickel was used as a catalyst, the hydrogenation was carried out at 80–90°, and the time required was 1 h. Removal of the catalyst by filtration in a nitrogen atmosphere gave a colorless solution. Many efforts to isolate the reduction product I as a solid were unsuccessful. The amino compound I was characterized as its acetanilide and hydrochloride.

3,4-Methylenedioxy-6-hydroxyacetanilide

3,4-Methylenedioxy-6-nitrophenol (VIII) (1.83 g, 0.01 mole) was mixed with glacial acetic acid (50 ml) and acetic anhydride (1.1 g, 0.011 mole). The nitro group was reduced and acetylated at room temperature and 3 atm hydrogen pressure with 10% palladium on carbon (0.015 g) as catalyst. The reaction mixture was dissolved in hot ethanol and the catalyst removed by filtration. The solution was concentrated under reduced pressure to a small volume (10 ml), and diluted with water (100 ml); the solid which precipitated was separated by filtration, washed with water, and dried. 3,4-Methylenedioxy-6-hydroxyacetanilide was crystallized from 50% ethanol as cotton-like white crystals, m.p. 209–211°, yield 1.78 g (91%); ν_{max} 3 270, 3 090, 1 648 (sh), 1 635, and 1 565 cm^{-1}.

Anal. Calcd. for $C_9H_9NO_4$: C, 55.39; H, 4.64; N, 7.18. Found: C, 55.17; H, 4.75; N, 7.33.

3,4-Methylenedioxy-6-aminophenol Hydrochloride

A mixture of VIII (0.5 g), 10% palladium on carbon (0.01 g), and anhydrous diethyl ether (250 ml) was shaken with hydrogen under 3 atm pressure at room temperature. The reduction of the nitro group was completed in about 2 h. The catalyst was filtered under a nitrogen atmosphere, and hydrogen chloride gas was introduced into the filtrate. The white crystalline hydrochloride of I was separated by filtration, washed with benzene (5 ml), and dried *in vacuo* (0.45 g yield), m.p. 195–210° (decomp.); ν_{max} 3 540 (sh), 3 450, 3 160, 2 620, 1 595, and 1 298 cm^{-1}.

Anal. Calcd. for $C_7H_7NClO_3$: N, 7.39. Found: N, 7.51.

3,4-Dimethoxy-6-aminophenol (II) (in Methoxyethylene Glycol Solution)

The procedure employed for the reduction of 3,4-dimethoxy-6-nitrophenol (XIII) was similar to that used for the preparation of I, except that methoxyethylene glycol was used as the solvent because of the low solubility of XIII in ethanol. The resulting aminophenol II was characterized as its acetanilide.

3,4-Dimethoxy-6-hydroxyacetanilide

This derivative of II was prepared by reductive acetylation of XII, in a yield of 90%. It was crystallized from benzene as colorless needles, m.p. 137–138°; ν_{max} 3 365, 3 145, 1 648, and 1 630 (sh) cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.08; H, 6.04; N, 6.41.

1. D. G. Orphanos and A. Taurins. Can. J. Chem. This issue.
2. K. Hayes and G. Gever. J. Org. Chem. **16**, 276 (1951).
3. J. Böeseken, W. D. Cohen, and C. J. Kip. Rec. Trav. Chim. **55**, 815 (1936).
4. M. Beroza. J. Agr. Food Chem. **4**, 49 (1956).
5. J. Böeseken and J. Greup. Rec. Trav. Chim. **58**, 528 (1939).
6. R. I. Meltzer and J. Doczi. J. Am. Chem. Soc. **72**, 4986 (1950).
7. W. Baker and C. Evans. J. Chem. Soc. 372 (1938).
8. A. Vogel. Practical organic chemistry. 3rd ed. Longmans, Green & Co., Inc., New York. 1957. p. 669.
9. S. I. Gertler, B. H. Alexander, and M. Beroza. J. Org. Chem. **24**, 327 (1959).
10. A. Oliverio. Gazz. Chim. Ital. **73**, 181 (1943).

RECEIVED FEBRUARY 22, 1966.
DEPARTMENT OF CHEMISTRY,
MCGILL UNIVERSITY,
MONTREAL, QUEBEC.