[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE PREPARATION OF METHYLENEDIOXY-METHOXYBENZALDEHYDES

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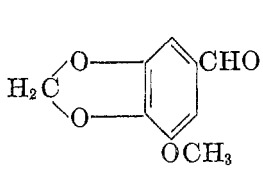
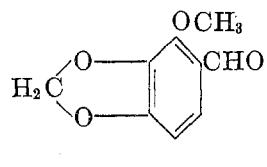
Since many pharamacologically active natural products contain several methoxy and/or methylenedioxy groups attached to one aromatic nucleus, it would be of interest to determine the pharmacological effect of such groups in various types of synthetic drugs. Alles (1) has shown, for example, that the polymethoxy and methylenedioxy phenylaminoethanols have an antifibrillatory action not shown by their unsubstituted analogs. Comparatively few such series have been made, however, because the necessary starting materials are very difficult to obtain.

The object of the present work, therefore, was to investigate methods for the synthesis of the isomeric methylenedioxymethoxybenzaldehydes, with the hope that routes would be found for some or all of them which would make these substances feasible starting materials for further synthetic work.

There are six possible methylenedioxymethoxybenzaldehydes. At the time this work was started two of them, myristicin aldehyde (I) and croweacin aldehyde (II) were known substances, and both of them had been prepared in very low yield. In this paper we are describing new or improved synthetic routes to four of these isomers, including I and II, and III and VI.



I



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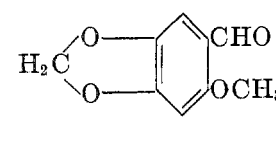

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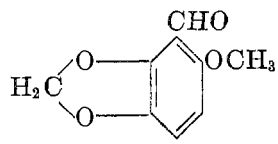

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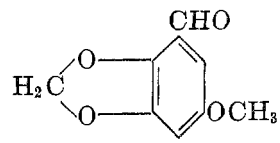

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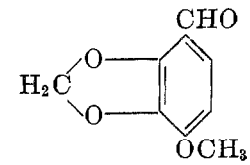


VI

Since piperonal is about the only readily available substance containing the methylenedioxy group, the first step of the present work was an investigation of the methods available for methylenation of *ortho*-dihydroxybenzenes. The literature data on this subject are contradictory and confusing, as some workers claim very high yields (2, 3) while others were able to obtain only very low yields (4, 5).

[1] Miles Laboratories Fellow, University of Notre Dame, 1947–1950. This paper was presented in part at the Cleveland ACS meeting, April, 1951.

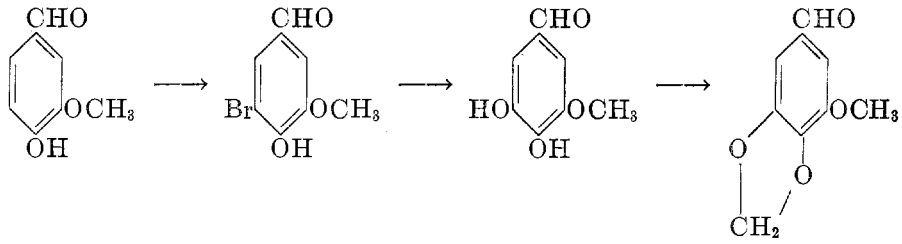
In the present work most of the methods described in the literature were reinvestigated, using catechol as a typical *ortho*-dihydroxybenzene. In general, it was not possible to duplicate the high yields claimed by some workers, even when the reaction was carried out in a reducing atmosphere with every precaution taken to avoid oxidation. The various methylenation agents were also compared; methylene sulfate proved to be disappointing, as the results obtained with it were erratic. Methylene iodide gave the best yields, but as these were only slightly better than those obtained with the bromide, the latter was the reagent of choice. It was found that careful attention to experimental detail was important, and the best results were obtained when catechol was treated with methylene bromide in methanolic potassium hydroxide solution, in the presence of a copper bronze catalyst under pressure. A brief summary of the many runs made is given in Table I.

TABLE I

METHYLENATION OF CATECHOL IN METHANOLIC KOH UNDER PRESSURE
(0.1 mole of catechol, 55 ml. of methanol, 3 g. of catalyst.)

REAGENT	AMOUNT, MOLE	CATALYST	AMOUNT KOH, MOLE	TIME, HOURS	TEMP., °C.	YIELD, %
CH_2Cl_2	0.1	None	0.15	18	100–110	10
CH_2Cl_2	.1	Cu pdr	.15	18	100–110	12
CH_2Cl_2	.1	Bronze	.15	18	100–110	20
CH_2Cl_2	.1	Bronze	.15	20	100–110	21
CH_2Cl_2	.12	Bronze	.15	18	100–110	37
CH_2Cl_2	.12	Bronze	.15	18	110–120	40
CH_2Br_2	.12	Bronze	.15	18	100–110	45
CH_2I_2	.12	Bronze	.15	18	100–110	61
CH_2Cl_2	.12	Bronze	.2	18	100–110	51
CH_2Br_2	.12	Bronze	.2	18	100–110	53
CH_2I_2	.12	Bronze	.2	18	100–110	69
CH_2SO_4	.12	Bronze	.2	18	100–110	12

Preparation of myristicin aldehyde (I). After several other routes were abandoned, myristicin aldehyde was finally prepared in fair over-all yield by a modification of the method of Baker, *et al.* (6), as shown in the following flowsheet.

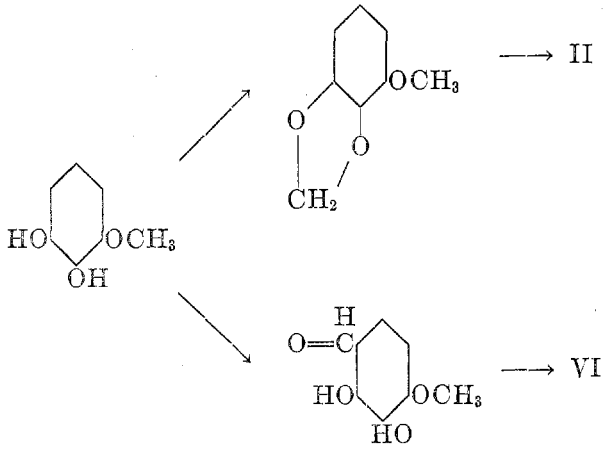


* Yields in parenthesis are those reported by Baker.

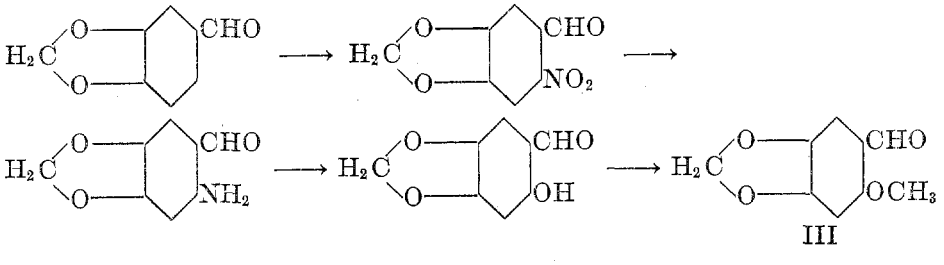
Attempts to prepare myristicin aldehyde from gallic acid by methylenation, methylation, and Rosenmund reduction failed when it was found impossible to methylenate gallic acid by any of the methods investigated. In this connection it is of interest to note that other workers have been unable to methylenate pyrogallol (3, 7), but its 1-methyl ether can be methylenated in high yield. The marked deactivating influence of the third hydroxyl group is somewhat difficult to explain.

Preparation of croweacin aldehyde (II) *and of 2,3-methylenedioxy-4-methoxybenzaldehyde* (VI). It is possible to convert pyrogallol 1-methyl ether into two different methylenedioxymethoxybenzaldehydes with the Gatterman reaction and methylenation, depending on the order with which these reactions are used. If the ether is first methylenated and then the aldehyde group is introduced, it enters *ortho* to the methoxyl, to give croweacin aldehyde (II). The yields in the Gatterman reaction are not very good in this case, since the methylenedioxy group is easily cleaved by Friedel-Crafts type reagents. When attempts were made to apply Adams' butyllithium N-methylformanilide synthesis (8) to methylenedioxymethoxybenzene none of the desired product was obtained.

If, on the other hand, the aldehyde group is introduced before the hydroxy groups are methylenated, then the aldehyde enters *para* to the methoxyl group, and compound VI is formed. In this case, also, the butyllithium N-methylformanilide synthesis failed.



Preparation of 2-methoxy-4,5-methylenedioxybenzaldehyde (III). The fourth isomer prepared was compound III, for which the following synthesis was used:



The synthesis looks straightforward, but unexpected complications were found. Reduction of 6-nitropiperonal to 6-aminopiperonal in satisfactory yield is very difficult to accomplish, as other workers have also found (9–11). Catalytic hydrogenation was totally unsatisfactory, as no conditions could be found which would give absorption of three moles of hydrogen; absorption usually ceased after two moles had been taken up; it is possible that at this stage a condensation occurred between the aldehyde group and the partially reduced nitro group. Reduction with iron or tin and acid was likewise unsatisfactory, and the reaction was best carried out with ferrous sulfate. The quality of the ferrous sulfate was very important, as the reagent grade material gave poor results, but the USP quality was satisfactory; this points to a promoting or catalytic effect of some impurity present in the USP material.

The diazotization and replacement of the amino group by hydroxyl was likewise more difficult and more subject to experimental variations than had been anticipated, but a satisfactory procedure was finally developed, so that the overall yield from piperonal to III was adequate.

EXPERIMENTAL[2]

Methylenation of catechol. The most satisfactory results were obtained by the following procedure: A solution of 0.1 mole of catechol in 15 ml. of methanol was placed in a thick-walled Pyrex bomb tube, together with 3 g. of Tobin bronze shavings (Cu 60%, Zn 38%, Sn 1.5%, Fe 0.2%, Pb 0.3%) and 10.2 g. (0.12 mole) of methylene chloride or the equivalent amount of the bromide. Methanol (40 ml.) was then added in such fashion that the minimum amount of mixing occurred. The bomb was clamped vertically in an ice-bath and a cold solution of 11.0 g. (0.2 mole) of potassium hydroxide in 15 ml. of water was added quickly, so that very little mixing occurred. The bomb tube was now about 90% full; it was sealed immediately and heated in a shaking furnace for 18 hours at 105–115°. The product was isolated by steam-distillation and purified by distillation under reduced pressure. The methylenedioxybenzene obtained had b.p. 172–175°/755 mm. Numerous modifications of this method were tried. It was found that unless the bomb tube was carefully charged as described above, and unless it was at least 90% full before sealing, the yields of product were lower, and more oxidative decomposition occurred. It was also found that use of less than the stoichiometric amount of potassium hydroxide (0.2 mole) led to lower yields in contrast to the report of Rao (2). Methylene sulfate gave very poor results by this method; methylene iodide gave the highest yields, but since the pressure in the bomb tubes was much higher when the iodide was used, more of the tubes broke during the heating period, and so this reagent was not used in subsequent work. Methylene chloride and methylene bromide gave comparable results. Some of the results are given in Table I.

Attempts to repeat the procedure of Rao and Seshardi (2) were unsuccessful. This method involves treating the *ortho*-dihydroxybenzene with methylene sulfate in acetone-potassium hydroxide solution at atmospheric pressure, in a stream of illuminating gas, at 60° for several hours. Despite many attempts, no appreciable amount of methylenedioxybenzene could be obtained, and extensive oxidation occurred with the formation of large amounts of tarry by-products.

Attempts to use methylene sulfate under pressure in acetone solution were abandoned because of the highly exothermic reaction which frequently led to destruction of the bomb tube.

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[2] The Microanalyses were done by the Microtech Laboratory, Skokie, Illinois, and by the Clark Analytical Laboratories, Urbana, Illinois.

Preparation of myristicin aldehyde (I). Vanillin was brominated by the method of Dakin (12) and the product, obtained in 97% yield, was converted to 3-methoxy-4,5-dihydroxybenzaldehyde by the procedure of Bradley, Robinson, and Schwerzenbach (13) in 75% yield. The product melted at 130–131°, which is in substantial agreement with the value recorded by Bradley, *et al.*, and by Heilbron (14). Shriner and McCutchan (15) reported this material as the corresponding acid, although Vogl (15b) had found that the acid has a much higher melting point (199–200°). The methylenation of 3-methoxy-4,5-dihydroxybenzaldehyde was carried out with methylene bromide by the procedure described above for catechol, and the myristicin aldehyde was isolated by steam-distillation. The purified product, obtained in 35% yield, had m.p. 131–132°.

Anal. Calc'd for $C_9H_8O_4$: C, 60.00; H, 4.48.

Found: C, 59.84; H, 4.48.

The *p-nitrophenylhydrazone* had m.p. 209–210° after recrystallization from ethanol, and the *semicarbazone* had m.p. 202–204°. Oxidation of myristicin aldehyde with alkaline potassium permanganate gave the corresponding *acid*, m.p. 211–212°. Baker (6) reported the acid as m.p. 209–210°.

Preparation of croweacin aldehyde and of 2,3-methylenedioxy-4-methoxybenzaldehyde (VI). Pyrogallol 1-methyl ether was obtained in 90% yields by the method described in Organic Syntheses (16).

It was converted to 2,3-dihydroxy-4-methoxybenzaldehyde as follows: A solution of 28 g. of pyrogallol 1-methyl ether in 17 ml. of dry benzene was added to a cold (0°) solution of 27.8 g. of aluminum chloride in 20 ml. of benzene, and the temperature was kept at 0° while anhydrous hydrogen cyanide (20 g.) was distilled into the flask. A steady stream of anhydrous hydrogen chloride was then passed in for eight hours. For the first 2–3 hours the temperature was kept at 0–5° and for the remainder of the time at 15–20°. The reaction mixture was allowed to stand overnight, the solvent was decanted, and the thick residue was poured onto ice. The benzene and hydrogen cyanide were removed by steam-distillation, and the residue was extracted with ether. Evaporation of the ether and recrystallization of the residue from boiling water gave a 39% yield of the desired aldehyde, m.p. 117–118°. This was methylenated as described above, using methylene chloride in methanolic potassium hydroxide solution. The yield of 2,3-methylenedioxy-4-methoxybenzaldehyde, m.p. 81–82°, was 20%. This material was insoluble in dilute aqueous alkali and gave no ferric chloride test.

Anal. Calc'd for $C_9H_8O_4$: C, 60.00; H, 4.48.

Found: C, 60.11; H, 4.55.

This aldehyde formed a *p-nitrophenylhydrazone*, m.p. 223–224°, and a *semicarbazone*, m.p. 219–220°. Oxidation with alkaline potassium permanganate gave an acid, m.p. 255–256°. Baker, Penfold, and Simonsen (17) report m.p. 256–257.6° for 2,3-methylenedioxy-4-methoxybenzoic acid.

When pyrogallol 1-methyl ether was methylenated by the procedure described above, using methylene chloride, a 62% yield of methylenedioxymethoxybenzene, m.p. 41°, was obtained. When this was subjected to the Gatterman reaction, as described above, it gave a 20% yield of croweacin aldehyde, m.p. 104°, which is in agreement with the value reported by Penfold, *et al.* (3). The *p-nitrophenylhydrazone* formed red needles, m.p. 240–242°; the *semicarbazone* had m.p. 235°. The aldehyde was oxidized to the corresponding *acid*, m.p. 152–153°; Penfold (3) reported the melting point of 2-methoxy-3,4-methylenedioxybenzoic acid as 153°.

Preparation of 4,5-methylenedioxy-2-methoxybenzaldehyde (III). Piperonal was nitrated by the procedure of Ekeley and Klemms (18) using nitric acid, *sp. gr.* 1.38; the yield by this method was 75% while the yield by the method of Bogert and Elder (11), in which more concentrated nitric acid (*sp. gr.* 1.42) was used, was only 40–60%. Attempts were made to reduce 6-nitropiperonal catalytically over platinum and Raney nickel, and chemically with sodium hydrosulfite or iron and acetic acid; in none of these cases was an appreciable amount of the aminoaldehyde obtained. A modification of the procedure of Bogert and Elder (11) was most satisfactory: Ten grams of 6-nitropiperonal in 500 ml. of boiling 50% ethanol was added to a boiling solution of 100 g. of USP ferrous sulfate in

500 ml. of water. The solution was boiled for one minute, and then 130 ml. of concentrated ammonium hydroxide was added with rapid stirring in 5–10 ml. portions. An interval of 30–40 seconds was allowed between each addition, and the mixture was kept at the boiling point for 5–10 minutes after addition was complete. It was then centrifuged while hot, and the residue washed with 500 ml. of boiling water. The filtrate and washings were cooled in an ice-bath, and the precipitated 6-aminopiperonal was collected and recrystallized from hot water. The product was obtained in 70–75% yields as yellow needles, m.p. 107–108°.

A suspension of 10.6 g. of 6-aminopiperonal in 300 ml. of water was cooled to 5° and acidified with 10 ml. of concentrated sulfuric acid in 60 ml. of water. The cold mixture was diazotized by the addition of 4.5 g. of sodium nitrite in 50 ml. of water at 0–5°. The diazonium solution was gradually warmed to room temperature, diluted with an equal volume of water, and added slowly to a boiling solution of 125 g. of copper sulfate in 125 ml. of water. The solution was steam-distilled for eight hours, and the product was recovered from the steam-distillate by extraction with ether. The yield of product of m.p. 125–126° was 60%. This product was methylated as follows: To a mixture of 4 g. of 3,4-methylenedioxy-6-hydroxybenzaldehyde, 14 g. of anhydrous potassium carbonate, and 100 ml. of dry benzene there was added 9 g. of methyl sulfate, slowly, with stirring. The mixture was refluxed for 48 hours and filtered while hot. The solvent was removed from the filtrate, and the residue was recrystallized from hot water. The yield of 3,4-methylenedioxy-6-methoxybenzaldehyde was 92–95%, and the material had m.p. 111.5–112°.

Anal. Calc'd for $C_9H_8O_4$: C, 60.00; H, 4.48.

Found: C, 60.13; H, 4.75.

It formed a *p-nitrophenylhydrazone*, m.p. 249–251°, and a *semicarbazone*, m.p. 220.5–222°. Oxidation with alkaline potassium permanganate gave the corresponding *acid*, m.p. 147–147.5°. 3,4-Methylenedioxy-6-methoxybenzoic acid is reported to melt at 148–149° (19).

SUMMARY

An improved procedure has been developed for the methylenation of *ortho*-dihydroxybenzenes.

New or improved syntheses for four of the isomeric methylenedioxymethoxybenzaldehydes have been described.

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