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Lawrence M. Liggett
Iowa State College

Harvey Diehl
Iowa State College

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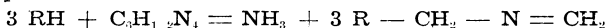
STUDIES ON THE DUFF REACTION FOR THE PREPARATION OF *O*-HYDROXYALDEHYDES

LAWRENCE M. LIGGETT AND HARVEY DIEHL

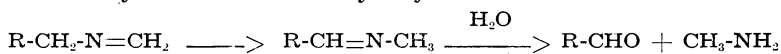
Moderate quantities of a large number of *o*-hydroxyaldehydes were required for certain investigations being conducted in this laboratory. Numerous attempts to modify and improve the classical Reimer-Tiemann reaction were uniformly unsuccessful either in minimizing the undue time required for the synthesis or in sensibly increasing the meager yields obtained. Of the other reactions which were also employed for the synthesis of these aldehydes the method recently described by Duff was found the most fruitful and expedient.

The method of Duff (8) consists in converting a phenol to an *o*-hydroxyaldehyde by causing it to react with hexamethylenetetramine in the presence of anhydrous glycerol and glyceroboric acid at a temperature of 150-160°. The *o*-hydroxyaldehyde in nearly pure form is then obtained by steam distillation of the reaction mixture after treatment with dilute sulfuric acid. No bisulfite extraction is necessary and in most cases no unreacted phenol is recovered. The time required for the complete synthesis is only two to three hours. Duff reported yields of 2 to 8 g. of about a dozen different *o*-hydroxyaldehydes from 25 g. of the requisite phenol, yields considerably better than can usually be obtained by the Reimer-Tiemann reaction.

The mechanism proposed by Duff for the synthesis involves as a first step the reaction



followed by isomerization and hydrolysis



Support for this mechanism was found in the proved presence of methylamine in the residue from the steam distillation and in an analogous simpler reaction reported earlier by Sommelet. That formaldehyde is not directly involved is indicated by the necessity of maintaining anhydrous conditions during the early part of the reaction; at this stage the presence of water, which produces formaldehyde from the hexamethylenetetramine, is decidedly detrimental.

Early experiences in this laboratory with the Duff reaction did not give results comparable with those reported by Duff. In some cases the reaction progressed smoothly and in others a rather violent reaction ensued when the hexamethylenetetramine and phenol were added to the hot glycerol-glyceroboric acid mixture. More perplexing were the erratic results obtained on duplicate preparations carried out simultaneously; sometimes no aldehyde at all was obtained. The difficulty was traced finally to the fact that the hexamethylenetetramine decomposed very rapidly when it was added to the glyceroboric acid medium at a temperature much above 160°. Therefore no aldehyde was formed unless the phenol was added immediately. A

considerable improvement in yield was obtained by mixing the hexamethylenetetramine and phenol intimately prior to the reaction, thus insuring their simultaneous addition to the glyceroboric acid medium in the correct proportions.

In general it was found possible to control the temperature between 150 and 160° merely by removing the reaction vessel from the electric hot plate prior to adding the phenol-hexamethylenetetramine mixture, then heating again if necessary after the initial reaction had subsided. A cooling bath was kept at hand for use in case the reaction became violent. This seldom happened when the glyceroboric acid mixture was cooled to 150° before adding the other reactants. No noticeable improvement in yield was obtained by maintaining the temperature carefully at exactly 160°. From the experience gained in running a large number of these reactions it seems probable that the temperature may vary between 145° and 175° without detriment to the yield.

This method was applied successfully to a number of phenols other than those studied by Duff. The average yield was about 18 per cent. The aldehydes obtained were identified as their phenylhydrazones, oximes, or Schiff's bases with ethylenediamine. A number of them had been prepared previously by others, usually by the Reimer-Tiemann reaction.

Several phenols were encountered on which the Reimer-Tiemann reaction failed to yield an aldehyde but on which the Duff reaction was quite successful, notably *o*-chlorophenol, *o*-bromophenol, 2,4-dichlorophenol, and 2,4-dibromophenol. Several phenols were also dichlorophenol, and 2, 4-dibromophenol. Several phenols were also encountered which did not yield the expected aldehyde, for example 2,4-dinitrophenol, 3,5-dinitro-*o*-cresol, thiophenol, 2-hydroxypyridine, and *o*-hydroxybiphenyl.

A modification of the reaction was tried in which hexamethylenetetramine was replaced by trioxane, $(\text{CH}_2)_3\text{O}_3$. This substance yields formaldehyde on treatment with strong acids. Glyceroboric acid proved too weak an acid to liberate it. Zinc chloride was also too weak. Phosphoric acid and glacial acetic acid were sufficiently strong acids but produced no aldehyde. This lends support to the mechanism proposed by Duff in which formaldehyde plays no part in the reaction.

EXPERIMENTAL WORK

Following are a description of the method used and an outline of the results obtained on applying the Duff reaction to a number of phenols. Two of the phenols reported (*p*-cresol and thymol) were previously used by Duff but are reported here since new data was secured on the derivatives employed for the identification of the aldehydes prepared. When no references are given the aldehydes are new.

General Procedure. A mixture of 300 g. of glycerol and 70 g. of boric acid was heated in a 2-liter beaker with stirring until the tem-

perature reached 165°. About 20 minutes was usually required since a considerable amount of water had to be expelled. An intimate mixture of 50 g. of the phenol and 50 g. of hexamethylenetetramine was prepared by grinding these materials together thoroughly. The mixture was then added with vigorous stirring to the glycerol-glyceroboric acid solution previously cooled to 150°. The reactants were stirred for 20 minutes, during which the temperature was maintained between 150 and 165° as outlined earlier. Finally the reaction mixture was allowed to cool to 115° and was then acidified with a mixture of 50 ml. of concentrated sulfuric acid and 150 ml. of water. When larger amounts of phenol were employed the quantities of the other reactants were increased in proportion.

Two methods were found satisfactory for the isolation of the *o*-hydroxaldehyde from the acidified reaction mixture. Most frequently it was distilled with steam. The fact that the viscous reaction mixture could be heated to about 110-120° while steam was being passed through it was a distinct advantage in removing difficultly volatile aldehydes. The liquid aldehydes were usually insoluble and easily separable from the distillate. The solid aldehydes were filtered off after cooling the steam distillate in an ice bath. When the reaction proceeded in the normal manner, no unreacted phenol was recovered and the aldehyde obtained was relatively pure, the melting point being usually only one or two degrees lower than that of the carefully purified aldehyde. Aldehydes which could not be distilled with steam were extracted directly from the cold, acidified reaction mixture with ether or benzene. When separated in this manner further purification after removal of the solvent was necessary. If any *para*- isomer were formed in the reaction it would also be extracted. Duff was able to obtain a *p*-hydroxaldehyde from the reaction mixture and this has been our experience.

2-Hydroxy-3-bromobenzaldehyde. Starting material: *o*-bromophenol, Eastman Kodak Co. No. 1566, 50 g. Yield 8.5 g., 14.5 per cent. M.p. (without recrystallization) 49°; reported by Müller who reduced nitrosalicylaldehyde and replaced the amino group with bromine) 49° (13). M.p. of Schiff's base with ethylenediamine 174°.

2-Hydroxy-3, 5-dibromobenzaldehyde. Starting material: 2,4-dibromophenol, Eastman Kodak Co. No. 854, 100 g. Yield 7.5 g., 6.8 per cent. M.p. (after recrystallization from alcohol) 75-77°. M.p. of the phenylhydrazone 141-142°, of Schiff's base (with the ethylenediamine from *n*-propyl alcohol) 247°.

2-Hydroxy-5-methylbenzaldehyde. Starting material: *p*-cresol 125 g. Yield 46.3 g., 29 per cent. M.p. 55.8°. M.p. of Schiff's base with ethylenediamine 164°.

Aldehyde from 3-methyl-4-chlorophenol. Starting material: 3-methyl-4-chlorophenol, Eastman Kodak Co., 100 g. Yield 36 g., 30 per cent. M.p. (after recrystallization from alcohol) 99°. M.p. of the phenylhydrazone 205°, of the oxime 131-132° of Schiff's base with ethylenediamine 221°. Apparently the Duff reaction yields only one

of the two possible aldehydes 2-hydroxy-4-methyl-5-chlorobenzaldehyde and 2-hydroxy-6-methyl-5-chlorobenzaldehyde. The former aldehyde, m.p. 68°, was prepared by Walther and Demmelmeyer (14) by the Reimer-Tiemann reaction.

2-Hydroxy-3,6-dimethylbenzaldehyde. Starting material: 2-hydroxy-1, 4-dimethylbenzene, Eastman Kodak Co. No. 1153, 25 g. Yield 9 g., 29 per cent. M.p. (after recrystallization from alcohol) 61°; reported by Anselmino (1) who prepared it by the Reimer-Tiemann reaction 62°. M.p. of the phenylhydrazone (recrystallized from alcohol) 148.5°; of Schiff's base with ethylenediamine (crystallized as long yellow needles from alcohol) 182°. Upon prolonged steam distillation, a small quantity of a white, crystalline material was obtained, m.p. 155°; this gave a yellow color with an alcoholic solution of ethylenediamine, but did not produce a crystalline Schiff's base; m.p. of its phenylhydrazone was 188-189°. The product was probably a dialdehyde.

2-Hydroxy-3,5-dimethylbenzaldehyde. Starting material: 4-hydroxy-1, 3-dimethylbenzene, Eastman Kodak Co. No. 1150, 25 g. Yield 10 g., 32 per cent of an oily product which crystallized on cooling to 23°; reported by Anselmino (1) who prepared it by the Reimer-Tiemann reaction, m.p. 11°, b.p. 222°. M.p. of the phenylhydrazone was 103°, of the oxime 133° for the latter Bamberger and Weiler (3) reported 138°. M.p. of Schiff's base with ethylenediamine (from alcohol) 142.5°.

Aldehyde from 3,4-dimethylphenol. Starting material: 3,4-dimethylphenol, Eastman Kodak Co. No. 1155, 25 g. Yield 14 g., 45 per cent. M.p. (after recrystallization from alcohol) 69°. Clayton (6) ran the Reimer-Tiemann reaction on this phenol and obtained a mixture of two aldehydes, 2-hydroxy-5, 6-dimethylbenzaldehyde, m.p. 72°, and 2-hydroxy-4,5-dimethylbenzaldehyde, m.p. 71°; the crystals he obtained from petroleum ether were separated by hand. Several attempts made to repeat this separation on the product obtained by the Duff reaction were unsuccessful because different crystalline forms could not be distinguished. Another process was also tried which was analogous to a separation of 2-hydroxy-6-methylbenzaldehyde from 2-hydroxy-4-methylbenzaldehyde in the mixture obtained by the Reimer-Tiemann reaction on *m*-cresol (5), in which the former aldehyde was obtained by steam distillation from a sodium carbonate solution, the latter by continued steam distillation after acidification. Crystalline products were obtained both by alkaline and by acid steam distillation but the m.p. and the mixed m.p. proved that they were identical. M.p. of the phenylhydrazone of each product was 198°. Apparently the Duff reaction yielded only one aldehyde. M.p. of the Schiff's base with ethylenediamine was 212-214°.

Duff (8) reported only one aldehyde from *m*-cresol, the 2-hydroxy-4-methylbenzaldehyde. From this it would seem probable that the aldehyde obtained from 3,4-dimethylphenol is the 2-hydroxy-4,5-dimethylbenzaldehyde.

2-Hydroxy-5-ethylbenzaldehyde. Starting material: *p*-ethylphenol,

Dow Chemical Co., 50 g. Yield 11 g., 18 per cent. Following vacuum distillation, the product crystallized on cooling; m.p. -5° . M.p. of the phenylhydrazone 126° , of the semicarbazone 214° . Auwers (2) reported the m.p. of the product prepared by the Reimer-Tiemann reaction as 208° , the m.p. of its Schiff's base with ethylenediamine as 143° .

2-Hydroxy-3-n-butoxybenzaldehyde. Starting material: 2-n-butoxyphenol, b.p. $150-154^{\circ}/40$ mm., 200 g. Yield 35 g., 15 per cent. M.p. 49° . M.p. of Schiff's base with ethylenediamine 93.5° .

2-Hydroxy-3-iso-propyl-6-methylbenzaldehyde. Starting material: thymol, Eastman Kodak Co. No. 248, 100 g. Yield 19 g., 16 per cent. The crude product was extracted with ether, dried over Drierite, the ether evaporated away, and the residue carefully fractionated. B.p. $100^{\circ}/3.5$ mm., $105^{\circ}/5$ mm., $139^{\circ}/13$ mm., $243^{\circ}/730$ mm. (slight decomp.); reported by Beli and Henry (4) (prepared by the Gattermann reaction) $110^{\circ}/15$ mm. N_{25} 1.551. M.p. of the semicarbazone (from alcohol) 194° ; reported (4) 198° . M.p. of the Schiff's base with ethylenediamine $112-113^{\circ}$. Prolonged steam distillation yielded 1 g. of white, crystalline material which yielded a Schiff's base with ethylenediamine melting above 200° . The Reimer-Tiemann reaction on thymol yields only the *para* aldehyde and some dialdehyde (11).

2-Hydroxy-3-iso-propyl-5-chloro-6-methylbenzaldehyde. Starting material: *p*-chlorothymol, Eastman Kodak Co. No. 2777, 100 g. Yield 12 g., 10 per cent. M.p. (from alcohol) 49° . M.p. of the oxime $150-151^{\circ}$, of the Schiff's base with ethylenediamine 171° .

Aldehyde from 2-hydroxy-4-tert-butylphenol. Starting material: 2-hydroxy-4-*tert*-butylphenol, 100 g. Yield 31 g., 26 per cent. M.p. (yellow crystals from alcohol) 85° . M.p. of the phenylhydrazone $160-161^{\circ}$; of the Schiff's base with ethylenediamine 226° . Of the two aldehydes which might be formed, 2, 3-dihydroxy-5-*tert*-butylbenzaldehyde and 2,3-dihydroxy-6-*tert*-butylbenzaldehyde, apparently only one was produced, to judge from the sharpness of the melting points.

Aldehyde from 3-methyl-4-tert-butylphenol. Starting material: 3-methyl-4-*tert*-butylphenol, Koppers Chemical Co., b.p. $160^{\circ}/100$ mm., $237-238^{\circ}/743$ mm. [reported (12) 238°], 300 g. Yield 50 g., 14 per cent. B.p. after careful fractional distillation $109-110^{\circ}/2$ mm. N_{25} 1.540. M.P. of Schiff's base with ethylenediamine 165° . Constancy of boiling point implied that only one isomer was present of the two aldehydes possible, 2-hydroxy-4-methyl-5-*tert*-butylbenzaldehyde and 2-hydroxy-6-methyl-5-*tert*-butylbenzaldehyde.

2-Hydroxy-3-chloro-5-tert-butylbenzaldehyde. Starting material: 2-chloro-4-*tert*-butylphenol, Eastman Kodak Co. No. P-4871, 100 g. Yield 33 g., 29 per cent. M.p. (pale yellow crystals from alcohol) 72° . M.p. of the phenylhydrazone 146° ; of the Schiff's base with ethylenediamine (from alcohol) 115° .

2-Hydroxy-3-bromo-5-tert-butylbenzaldehyde. Starting material: 2-bromo-4-*tert*-butylphenol, Eastman Kodak Co. No. P-4868, 100 g. Yield 25 g., 22 per cent. M.p. 88° ; reported by Daines and Rothrock (7) $86-87^{\circ}$. M.p. of the phenylhydrazone $143-144^{\circ}$; of the oxime 169° ;

reported (9) 164°. M.p. of Schiff's base with ethylenediamine 120°.

2-Hydroxy-3-tert-amylbenzaldehyde. Starting material: 2-*tert*-amylphenol, Sharples Chemical Co., b.p. 147-148°/45 mm., 150 g. Yield 20 g., 11 per cent. B.p. after careful fractional distillation was 106°/10 mm., m.p. of Schiff's base with ethylenediamine 109.5°.

2-Hydroxy-3-methyl-5-tert-amylbenzaldehyde. Starting material: 2-methyl-4-*tert*-amylphenol, Sharples Chemical Co., b.p. 158-159°/39 mm., 200 g. Yield 45 g., light yellow oil, 19 per cent. B.p. 108-110°/1 mm. M.p. of Schiff's base with ethylenediamine (from alcohol) 90°.

Attempted Preparation of 2-Hydroxy-3,5-dinitrobenzaldehyde. Starting material: 2,4-dinitrophenol, Eastman Kodak Co. No. T-102, 25 g. No aldehyde was obtained and unlike the usual Duff reaction about 50 per cent of the original phenol was recovered. 2-Hydroxy-3,5-dinitrobenzaldehyde has been prepared by the nitration of salicylaldehyde (10). 2,4-Dinitrophenol is a strong enough acid to form a stable salt with ethylenediamine, m.p. 190°, which may easily be mistaken for a Schiff's base.

Attempted Preparation of 2-Hydroxy-3-methyl-4,6-dinitrobenzaldehyde. Starting material: 3,5-dinitro-*o*-cresol, Eastman Kodak Co. No. 1344, 25 g. No aldehyde was obtained and about 50 per cent of the unreacted phenol was recovered.

Attempted Preparation of Thiosalicylaldehyde. Starting material: thiophenol, Eastman Kodak Co., 50 g. About 1 g. of a crystalline material was obtained, m.p. of product recrystallized from alcohol 60°. The product would not form a phenylhydrazone or Schiff's base. Thiosalicylaldehyde was prepared by Friedlander and Lenk (9) by the diazotization of *o*-aminobenzaldehyde, followed by reaction of the diazonium compound with potassium xanthate in alkaline solution. The product was reported to be a yellow liquid and to form a phenylhydrazone, m.p. 127-129°.

Attempted Preparation of 2-Hydroxy-3-aldehydopyridine. Starting material: 2-hydroxypyridine, Reilly Chemical Co., 50 g. Because of the basic character of the expected product, the solution was made neutral to litmus with sodium bicarbonate and extracted with ether. A small amount of liquid obtained after removal of the ether failed to give reactions characteristic of an aldehyde.

Attempted Preparation of 2-Hydroxy-3-phenylbenzaldehyde. Starting material: *o*-hydroxybiphenyl, Dow Chemical Co., 25 g. The reaction following the addition of the hexamethylenetetramine-phenol mixture was vigorous but no aldehyde was produced. A considerable portion of the original phenol was recovered. Several modifications, principally alterations of the temperature of the reaction, were also unsuccessful. As reported by Duff (8), the application of the reaction to *p*-hydroxybiphenyl was found to give a good yield of 2-hydroxy-5-phenylbenzaldehyde.

SUMMARY

The method of Duff for the synthesis of *o*-hydroxyaldehydes has

now been applied to a sufficiently large number of phenols to warrant the conclusion that it is as general a reaction as the Reimer-Tiemann reaction. The Duff method is the shorter and gives better yields. It has been successfully applied to several phenols on which the Reimer-Tiemann method fails. It is not applicable to the preparation of aldehydes from nitrophenol, dinitrophenol, thiophenol, or 2-hydroxypyridine.

DEPARTMENT OF CHEMISTRY,
IOWA STATE COLLEGE

LITERATURE CITED

- (1) Anselmino, *Ber.*, *35*, 4108 (1902).
- (2) Auwers, *Ber.*, *39*, 3764 (1906).
- (3) Bamberger and Weiler, *J. prakt. Chem.*, [*2*], *58*, 352 (1898).
- (4) Bell and Henry, *J. Chem. Soc.*, *1928*, 2215.
- (5) Chuit and Bolsing, *Bull. soc. chim.*, *35*, 130 (1906).
- (6) Clayton, *J. Chem. Soc.*, *97*, 1404 (1910).
- (7) Daines and Rothrock, *Amer. Chem. J.*, *16*, 644 (1894).
- (8) Duff, *J. Chem. Soc.*, *1941*, 547.
- (9) Friedlander and Lenk, *Ber.*, *45*, 2086 (1912).
- (10) Hill and Robinson, *J. Chem. Soc.*, *1933*, 486.
- (11) Kobek, *Ber.*, *16*, 2104 (1883).
- (12) Meyer and Bernhauer, *Monatsh.*, *53*, 721 (1929).
- (13) Muller, *Ber.*, *42*, 3700 (1909).
- (14) Walther and Demmelmeyer, *J. prakt. Chem.*, [*2*], *92*, 121 (1925).