ride solution when a cross-section was examined under the microscope, indicating tannins.

The hemicellulose, calculated by difference, was considered a dextran, as no other sugar than dextrose was formed when it was subjected to the action of dilute alkalies and acids. This dextran was also proven to be present by subtracting the carbohydrates identified from the total carbohydrates found in the combined filtrates from the crude fiber determination.

The percentage composition is as follows:

	Total carbohydrates.	Pecan kernel.[a]
Sucrose	9.03	1.18
Invert sugars	21.90	2.88
Pentoses	.....	....
Araban	14.82	1.95
Xylan	.....	....
Methylpentosans	1.68	0.22
Cellulose (crude fiber)	14.29	1.76
Mannans	.....	....
Amyloid	4.54	0.59
Starch	.....	....
Tannins	2.57[c]	0.33[c]
Hemicellulose (dextran), etc.[b]	31.17	4.09
	100.00	13.00

[a] Moisture-free basis.

[b] By difference in the nitrogen-free extract plus crude fiber.

[c] Same result by Proctor's modification of Lowenthal's method.

STILLWATER, OKLAHOMA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY.]

THE CONDENSATION OF FORMALDEHYDE WITH ORTHO-NITROPHENOL.[1]

BY JACOB B. FISHMAN.

Received July 9, 1920.

During the last 2 years the attention of pharmacologists has been directed to benzyl alcohol as a local anesthetic. The pharmacological action of this alcohol was first investigated by Macht[2] in 1918. He found it to be a powerful local anesthetic of very low toxicity as compared with cocaine and its substitutes. While it has been found to be active on mucous membranes as well as in subcutaneous injection, nevertheless the compound possesses several objectionable properties which prevent its wide application. Not only does it undergo slow oxidation

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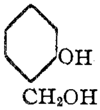
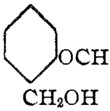
[1] Constructed from a dissertation presented to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy, June 1920 (T. B. Johnson).

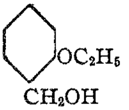
[2] Macht, *J. Pharmacol.*, **13**, 263 (1918); **14**, 323 (1919).

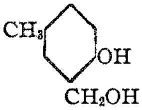
in solution,[1] but it is only sparingly soluble in water and its application produces smarting. Furthermore, its activity has a shorter duration than that of cocaine.

Hirschfelder, Lundhorn and Norrgaard[2] have recently reported that certain phenolic derivatives of benzyl alcohol possess marked anesthetic properties and among the compounds studied by them were saligenin (I), methyl saligenin (II), ethyl saligenin (III) and homosaligenin (IV).


(I).


(II).


(III).


(IV).

Of these different alcohols saligenin I was reported as the most active.

These very desirable properties of benzyl alcohol and its derivatives served as an incentive to search further in this field for new combinations of pharmacological interest. Theoretically a combination of the greatest interest would be that having the constitution of 3,4-dihydroxy-benzyl alcohol on account of its close relationship to adrenaline. Here we have a constitution favorable for both anesthetic and vasoconstrictor action or, in other words, a drug which might be expected to exhibit the combined physiological effects of benzyl alcohol and catechol.[3] The purpose of this investigation was to develop the synthetical aspects of this work. The condensation reaction which we describe in this paper should be of especial interest as affording a convenient method of preparing new benzyl alcohol combinations whose study may contribute still further data of pharmacological interest.

The condensation of formaldehyde with *o*-nitrophenol is productive of combinations which have hitherto received very little attention. Stoermer and Behn[4] first investigated the mutual reactivity of these 2 reagents and found that they interacted in the presence of hydrochloric acid with production of 3-nitro-4-hydroxy-benzyl alcohol (V). Their yield of this compound was, however, very small, and the reaction was always productive of a large amount of other material. Stoermer and Behn separated their alcohol, melting at 97°, by repeated crystallization from hot water, and write that many times they obtained as reaction product material from which they could not isolate the benzyl-alcohol derivative. The structure of their alcohol was established by the fact that it gives a methyl ether (VI), which, on oxidation, is easily converted into nitroanisic acid (VII).[5]

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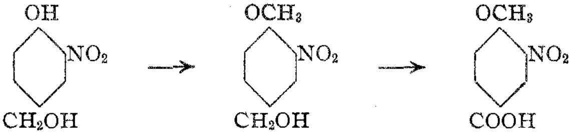
[1] Hjort and Eagan, *J. Pharmacol.*, **14**, 211 (1919).

[2] Hirschfelder, Lundhorn and Norrgaard, *ibid.*, **15**, 261 (1920).

[3] Fränkel, "Die Arzneimittel-Synthese," p. 428.

[4] Stoermer and Behn, *Ber.*, **34**, 2459 (1901).

[5] Cahours and Salkowski, *Ann.*, **41**, 71 (1842); **163**, 6 (1872).

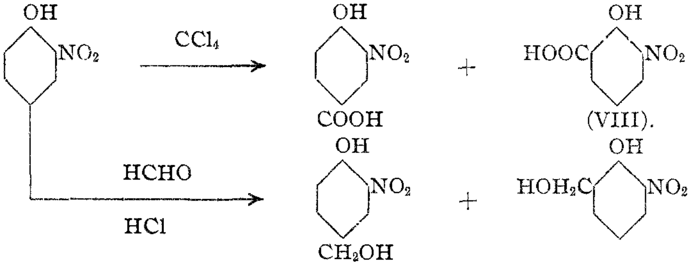


(V). (VI). (VII).

Another method for the preparation of this same alcohol was patented by Bayer and Co.[1] This is based upon the observation that 3-nitro-4-hydroxy-benzyl chloride is converted into the corresponding alcohol by hydrolysis with boiling water. Their method of synthesis is essentially an application of Stoermer and Behn's condensation reaction in the presence of very strong hydrochloric acid when the chloride is formed instead of its alcohol. Neither Stoermer and Behn nor the patentees make any references in their publications to the yields of pure alcohol obtained or the nature of the different by-products formed in the reaction.

We have now subjected their condensation reaction to a very careful study and have established the conditions favorable for the production of a maximum yield of the alcohol. The important factors governing the course of the reaction are concentration of hydrochloric acid, molecular proportion of formaldehyde and the time of heating. A full report of this phase of our research is given in the experimental part of this paper.

We now find that formaldehyde interacts with *o*-nitrophenol to form 2 isomeric alcohols, namely: The compound first identified by Stoermer and Behn, 3-nitro-4-hydroxy-benzyl alcohol (V), melting at 97° and a hitherto unknown isomeric compound having the structure of 3-nitro-2-hydroxy-benzyl alcohol (X). The latter melts at 75°. In other words, formaldehyde attacks the *o*-nitrophenol molecule in the same nuclear positions as carbon tetrachloride when the latter reagent condenses with this phenol.[2] These structural relationships are expressed by the following formulas:



(V). (X).

The structure of the new alcohol represented by Formula X was established by the fact that it underwent oxidation with potassium permanganate giving nitro-salicylic acid (VIII), the same as that obtained

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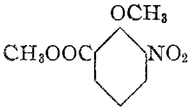
[1] Bayer and Co., *D. R. P.* 136,680 (1902); *D. R. P.* 132,475 (1902).

[2] Hasse, *Ber.*, **10,** 2187 (1877).

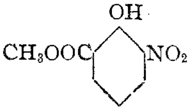
by Deninger[1] by direct nitration of salicylic acid. By alkylation with methyl iodide in alkaline solution, the alcohol X is converted smoothly into its corresponding methyl ether XI. When this compound was subjected to oxidation with potassium permanganate the primary alcohol group was destroyed and the corresponding acid XII, melting at 191°, was formed.

$$\underset{\text{(XI).}}{(NO_2)^3(OCH_3)^2.C_6H_3.CH_2OH} \xrightarrow{O_2} \underset{\text{(XII).}}{(NO_2)^3(OCH_3)^2.C_6H_3.COOH.}$$

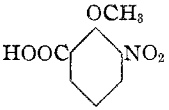
An aromatic acid having this same constitution has already been described by Keller.[2] He investigated the action of dimethyl sulfate on the potassium salt of nitrosalicylic acid, and states that the reaction is productive of 3 compounds melting at 110°, 125° and 220°, respectively. The substance melting at 220° was formed in very small amount and was not further investigated. Since his analyses and melting-points excluded from consideration the methyl ester of nitrosalicylic acid (XIV) and its corresponding methyl ether (XIII), Keller concluded that both of his compounds melting at 110° and 125°, respectively, must be methyl ethers of nitrosalicylic acid, corresponding to Formula XII. Obviously 2 ethers of this constitution are not possible. Furthermore, Keller states that his compound melting at 125° was unstable and was decomposed by heating in aqueous solution giving nitrosalicylic acid. It seems evident from Keller's description of his reaction products that he was dealing with a mixture of 2 or more compounds and did not succeed in isolating pure 3-nitro-2-methoxy-benzoic acid (XII).



(XIII).



(XIV).



(XII).

Experimental Part.

The Preparation of *o*-Nitrophenol.—All of the reagent used in this research was prepared by direct nitration of phenol according to the method outlined by Hart.[3] Operating with a unit of phenol corresponding to 1000 g., the following proportions of necessary reagents were used to accomplish the reaction. 1600 g. of sodium nitrate, 2000 g. of conc. sulfuric acid, 4000 g. of water and 100 g. of 95% alcohol. The method of operating was as follows: The sulfuric acid was added slowly with stirring and cooling to the aqueous solution of the sodium nitrate and into this acid mixture, which was kept at room temperature, the alcoholic solution of the phenol was dropped in slowly with constant and vigorous

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[1] Deninger, *J. prakt. Chem.*, [2] **42**, 551 (1890).

[2] Keller, *Arch. Pharm.*, **246**, 1 (1908).

[3] Hart, THIS JOURNAL, **32**, 1105 (1910),

stirring. After 4 hours the reaction mixture was poured into twice its volume of ice water, when the crude phenol separated and was purified by steam distillation. Our best yield was equivalent to 51% of the weight of phenol used for nitration.

The Interaction of Formaldehyde with *o*-Nitrophenol. 3-Nitro-4-hydroxy-benzyl Alcohol, $(NO_2)^3.(OH)^4.C_6H_3.CH_2OH$.—In order to obtain this aromatic alcohol the method described by Stoermer and Behn was first employed. Fifty g. of *o*-nitrophenol mixed with 125 g. of formaldehyde solution (39%) and 250 g. of hydrochloric acid (35.4%) were digested on a sand-bath for 6 hours. The reaction mixture was then cooled, the supernatent liquor poured off and the residual oily product distilled with steam to remove unchanged nitrophenol. The recovered *o*-nitrophenol weighed 12 g. The undistilled oily residue, which solidified on cooling, was filtered off, and after drying weighed 32 g. In order to purify this material it was extracted with boiling water until no more oil dissolved, and the aqueous solution allowed to cool, when golden-yellow crystals were obtained. These were further purified by crystallizing them several times from hot water, when pure prismatic crystals of 3-nitro-4-hydroxy-benzyl alcohol melting at 97° were obtained. Upon concentrating the aqueous filtrates, crystalline material varying in appearance and of indefinite melting-point was always obtained, but it was extremely difficult to purify it by crystallization. The material insoluble in water was amorphous and constituted more than $^1/_2$ of the weight of crude reaction product.

From the results of this preliminary experiment it was very apparent that the reaction was incomplete under the conditions employed, since unchanged nitrophenol was recovered, and furthermore, other products besides the desired alcohol were also formed by condensation with formaldehyde. In fact, the reaction was more complicated than we anticipated. In order to gain a better knowledge of the changes involved our work resolved itself into 2 definite phases: first, the investigation of the best conditions for controlling the reaction; and second, the purification and identification of the different products formed.

In order to determine the best conditions for bringing about a more complete condensation between the *o*-nitrophenol and formaldehyde, several series of experiments were conducted in each of which the effect of varying one of the following factors was studied, *viz.*, molecular concentration of hydrochloric acid, quantity of formaldehyde, length of time of heating, and use of condensing agents other than hydrochloric acid. It was found that the quantity of *o*-nitrophenol, which will interact with formaldehyde, varies according to the proportions of hydrochloric acid used as condensing agent, the yield of condensation product is increased and the quantity of unaltered nitrophenol is reduced by using a liberal excess of hydrochloric acid. When using 125 g. of formaldehyde the maximum yield of alcohol was obtained by condensing 50 g. of nitrophenol with the formaldehyde in the presence of 275 g. of conc. hydrochloric acid. Dilution of the hydrochloric acid leads to a poorer yield of the condensation product and consequently to an increase in the amount of nitrophenol which can be recovered.

The condensation of formaldehyde with *o*-nitrophenol is a change of slow velocity, and an extension of the time of digestion in presence of hydrochloric acid is productive of increased yields of reaction products. The yield of crude condensation product is not, however, any criterion of the success of the reaction. Three hours appears to be the most favorable time for heating in order to obtain the maximum yield of the benzyl alcohol. While much unaltered *o*-nitrophenol is recovered under these conditions, on the other hand, the condensation product is much purer. Longer time of digestion leads to the formation of increased quantities of secondary products which are difficult to separate.

Stoermer and Behn[1] recommend using 125 g. of formaldehyde for condensation with 50 g. of *o*-nitrophenol. This is an excess of 350% over the theoretical quantity and much more than is necessary. Fifty g. of formaldehyde is sufficient to produce almost as good a yield of the alcohol. Several experiments were conducted in order to ascertain the best proportions of this reagent to be used, and also the effect of changing the time of digestion when different quantities of the aldehyde were taken. It was found that an increase in the proportion of formaldehyde was favorable for the formation of secondary reaction products. The best yields of nitrobenzyl alcohol are obtained by using 60 g. of formaldehyde and 100 g. of *o*-nitrophenol and digesting with 500 g. of conc. hydrochloric acid for about 6 hours. The yield of crystallized alcohol under these conditions is about 50% of the calculated quantity. For example, a representative experiment gave 94 g. of total reaction product which yielded 54 g. of unaltered nitrophenol and 40 g. of crude condensation product. From the latter were isolated 24 g. of crystalline alcohol. No advantage is gained by extending the time of heating beyond 6 hours and almost as good yields of alcohol are obtained after 4 or 5 hours' digestion. In other words, one molecular proportion of formaldehyde can satisfy theoretically only one position in the *o*-nitrophenol nucleus, and the use of larger quantities leads to the formation of secondary products which contaminate the nitrobenzyl alcohol formed.

We also investigated the effect of different condensation agents on the course of the reaction. Several experiments were conducted in which sulfuric acid, dil. sodium carbonate solution, phosphoric acid and mag-

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[1] *Loc. cit.*

nesium chloride were each substituted for hydrochloric acid, but the results obtained were entirely unsatisfactory.

The following conclusions may be drawn from the results of our experiments: (1) a high concentration of hydrochloric acid is essential for maximum condensation of formaldehyde with *o*-nitrophenol; (2) in order to avoid side reactions leading to secondary products and to obtain the maximum yield of alcohol it is not advisable to use more than a theoretical quantity of formaldehyde for condensation; (3) working with molecular proportions of formaldehyde it is not advisable to continue the heating for a longer period than 6 hours in order to obtain a maximum yield of alcohol. This time should be reduced if an excess of formaldehyde is used in order to avoid formation of by-products.

The Separation of 3-Nitro-4-hydroxy-benzyl Alcohol from 3-Nitro-2-hydroxy-benzyl Alcohol.—Application of a formaldehyde *o*-nitrophenol condensation with 200 g. of formaldehyde solution (40%), 300 g. of *o*-nitrophenol and 1500 g. of conc. hydrochloric acid, by digestion for 6 hours is productive of 144 g. of unchanged *o*-nitrophenol and 63 g. of crystalline material containing the 2 isomeric benzyl alcohols. The remainder of the reaction product is an amorphous substance insoluble in hot water and not distillable with steam.

The yellow crystalline material (63 g.) was a mixture of 2 alcohols. Two distinct crystalline forms were apparent by examination under a microscope and the material melted at about 80°. Repeated fractional crystallizations from hot water enables one to isolate, in a pure condition, Stoermer and Behn's[1] 3-nitro-4-hydroxy-benzyl alcohol melting at 97°, but the yield is poor, and on concentrating the aqueous filtrates a crystalline product is obtained which cannot be purified by crystallization from the ordinary solvents. The separation of the 2 alcohols is, however, easily accomplished by digestion of the mixture in ethyl alcohol with potassium hydroxide. Stoermer and Behn's compound melting at 97° interacts with formation of a soluble potassium salt, while the isomeric alcohol gives a potassium salt which is insoluble in this solvent. Our method of operating was as follows.

Fifty g. of impure crystalline product melting at about 80° was dissolved in 30 cc. of 95% alcohol, and 18 g. of potassium hydroxide then dissolved in the solution by warming it on the steam-bath. A red precipitate was formed at once, and after boiling the mixture for about 20 minutes it was then cooled and the solution filtered by suction. The precipitate was washed with a little alcohol and saved. The filtrate, which contained the potassium salt of 3-nitro-4-hydroxy-benzyl alcohol, was heated in an open dish to remove alcohol, the potassium salt then dissolved in water and the solution acidified with hydrochloric acid. An

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[1] *Loc. cit.*

oil separated which dissolved in boiling water. Upon cooling this solution, yellow prisms of Stoermer and Behn's alcohol deposited, which melted sharply at 97°.

The potassium salt which separated from the alcohol was dissolved in water and the solution acidified with hydrochloric acid, when an oil separated at once. This dissolved in hot water and on cooling separated in the form of yellow needles. This substance melted at 75° and was not altered by further crystallization from hot water. Apparently it was a definite substance and its separation from Stoermer and Behn's alcohol was practically quantitative. From 50 g. of the condensation product about 35 g. of 3-nitro-4-hydroxy-benzyl alcohol and 12 g. of the isomeric compound melting at 75° was obtained. The proportion of these 2 compounds formed in the interaction of *o*-nitrophenol with formaldehyde is thus about 75% of the alcohol melting at 97° and 25% of the compound melting at 75°.

3-Nitro-2-hydroxy-benzyl Alcohol, $(NO_2)^3.(OH)^2.C_6H_3CH_2OH$.—This new alcohol formed as a secondary product in the condensation of *o*-nitrophenol with formaldehyde, crystallizes in the form of yellow needles melting at 75°. It is easily soluble in alcohol, ether and benzene and more easily soluble in cold water than its isomer, 3-nitro-4-hydroxy-benzyl alcohol. It forms a bright red potassium salt which is very difficultly soluble in alcohol. It may be further distinguished from its isomer by its behavior towards cold strong sulfuric acid. This acid dissolves it readily with a deep red color, while its isomer is only sparingly soluble.

Calc. for $C_7H_7O_4N$: N, 8.28.
Found: 8.09, 7.98 (Kjeldahl).

In order to establish the structure of this compound it was subjected to oxidation with potassium permanganate in alkaline solution. Five g. of the alcohol and 4 g. of potassium hydroxide were dissolved in about 100 cc. of water. The solution was then heated on the steam-bath while 5 g. of potassium permanganate was added in small portions, while the solution was shaken. After warming the mixture for about one hour, the manganese dioxide was filtered off and the clear red filtrate acidified with hydrochloric acid. A crystalline substance separated immediately. This was filtered off and purified by crystallization from hot water, when small yellow needles were obtained on cooling. This substance was an acid melting at 144° and was characterized by its easy solubility in alcohol and in boiling water and its property of forming red colored salts with alkalies. It also interacted to give a blood-red coloration with ferric chloride. Analysis, the melting point and properties of the compound established its identity with the known 3-nitrosalicylic acid, which has been prepared by Deninger[1] by the direct nitration of salicylic acid.

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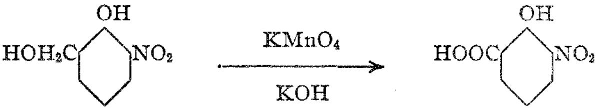
[1] *Loc. cit.*

Calc. for $C_7H_5O_5N$: N, 7.65. Found: 7.61, 7.44.

The constitution of 3-nitro-2-hydroxy-benzyl alcohol is, therefore, definitely established by its behavior on oxidation as is expressed by the following reaction.



3-Nitro-2-Methoxy-benzyl Alcohol, $(NO_2)^3(OCH_3)^2.C_6H_3.CH_2OH$.—Five g. of 3-nitro-2-hydroxy-benzyl alcohol was alkylated by digestion in 30 cc. of 60% methyl alcohol with 1.5 g. of sodium hydroxide and 6 g. of methyl iodide. To complete the reaction the solution was heated on the water-bath for 10 hours. The alcohol was then distilled and the oily reaction product extracted with ether. The ethereal solution, after having been washed several times with dil. sodium hydroxide solution to remove any unchanged nitro-hydroxy-benzyl alcohol, was dried over sodium sulfate and the ether removed by distillation, when the above alcohol was obtained. It crystallized from a mixture of petroleum ether and ordinary ether in colorless needles melting at 42°. The alcohol is sparingly soluble in hot water but extremely soluble in ether, benzene, alcohol, chloroform and acetic acid. The yield of the methoxy alcohol was about 60%.

Calc. for $C_8H_9O_4N$: N, 7.65. Found: 7.64, 7.38.

3-Nitro-2-methoxy-benzoic Acid, $(NO_2)^3(OCH_3)^2.C_6H_3.COOH$.—This acid was obtained by the oxidation of the nitro-alcohol described above. Potassium permanganate was used for this purpose and the operation was carried out in a manner similar to that used in the oxidation of 3-nitro-2-hydroxy-benzyl alcohol. The corresponding benzoic acid derivative was obtained in the form of colorless needles which were easily purified by crystallization from alcohol, and melted at 191–2°. This acid is moderately soluble in alcohol but difficultly soluble in water.

Calc. for $C_8H_7O_5N$: N, 7.11. Found: (Kjeldahl), 7.20, 7.00.

Keller[1] claims to have obtained an acid of this same constitution by the alkylation of 3-nitrosalicylic acid. He assigned a melting-point of 110° to his compound.

Summary.

1. A careful study has been made of the conditions governing the formation of 3-nitro-4-hydroxy-benzyl alcohol by the condensation of *o*-nitrophenol with formaldehyde in aqueous solution. The best results are obtained by applying the reaction in the presence of hydrochloric acid as a catalyst.

2. It has been found that formaldehyde can react with *o*-nitrophenol

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[1] Keller, *Arch. Pharm.*, **246**, 1–50 (1908).

to form 3-nitro-2-hydroxy-benzyl alcohol. This compound has been isolated and its constitution established.

3. The methoxy derivative of 3-nitro-2-hydroxy-benzyl alcohol has been prepared. Oxidation of this alcohol leads to the formation of 3-nitro-2-methoxy-benzoic acid. This is a new method of synthesizing this aromatic acid and its constitution is definitely established by the method of formation.

New Haven, Conn.

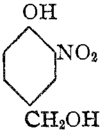
[Contribution from the Department of Chemistry, Yale University.]

SOME DERIVATIVES OF 3-NITRO-4-HYDROXY-BENZYL ALCOHOL.[1]

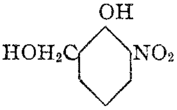
By Jacob B. Fishman.

Received July 15, 1920.

In the preceding paper the writer has described the behavior of *o*-nitrophenol when heated with formaldehyde in the presence of hydrochloric acid. It was shown that this reaction is productive of the 2 isomeric alcohols (I) and (II), which result theoretically by addition of the aldehyde to the nitrophenol in Positions 4 and 6 of the benzene nucleus, respectively.



(I).



(II).

The isomer presented by Formula I is formed in the larger proportion in this reaction, and, since it accumulated in large amount as a result of our investigation, it seemed of especial interest to utilize the material for the preparation and study of new derivatives. The structure of the compound is favorable not only for the synthesis of new and important derivatives of benzyl alcohol possessing possible therapeutic interest, but also for the formation by oxidation of 3-nitro-4-hydroxy-benzaldehyde and the corresponding 3-nitro-4-hydroxy-benzoic acid which are products of pharmaceutical and biochemical interest.

Oxidation of the alcohol (I) with the required proportion of potassium permanganate resulted in the smooth formation of the corresponding aldehyde, $C_6H_3\overset{1}{(CHO)}\overset{3}{(NO_2)}\overset{4}{(OH)}$, which has already been described by Paal.[2] If an excess of permanganate is used for oxidation, the aldehyde is converted into 3-nitro-4-hydroxy-benzoic acid almost quantita-

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[1] Constructed from a dissertation presented to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy, June 1920. (T. B. Johnson).

[2] Paal, *Ber.*, 28, 2413 (1895).