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The Replacement of Aromatic Hydroxyl by Chlorine

By WALTER T. SMITH, JR. AND LOUIS CAMPANARO

Some phenols, particularly those activated by nitro-, carboxyl, or other *meta*-directing groups in the *ortho* or *para* positions are known to react with phosphorus pentachloride with replacement of the phenolic hydroxyl by chlorine. This transformation has also been accomplished in some cases by treating the phenol with *p*-toluene-sulfonyl chloride in the presence of a tertiary amine such as N,N-dimethylaniline. A notable example of the latter reaction is the conversion of 2,4-dinitro-naphthol to 2,4-dinitro-1-chloronaphthalene (1).

We have studied the replacement of phenolic hydroxyl by chlorine in several different cases. Our results suggest that the nature of the reaction may be influenced both by the activating effect of the other ring substituents and also by the steric effects of the other substituents.

The use of phosphorus pentachloride (or of phosphorus tribromide) for the replacement of the hydroxyl in 2,4-dinitro-1-naphthol is unsuccessful under several conditions. When no solvent is used, a vigorous reaction results which leads to complete charring. When the reaction is modified by using ether as a solvent, no product is formed and the starting material is recovered unchanged.

When the same conditions which result in the satisfactory conversion of 2,4-dinitro-1-naphthol to 2,4-dinitro-1-chloronaphthalene are applied to 2-nitro-1-naphthol the starting material is recovered in nearly quantitative amount. Thus it appears that the nitro group *ortho* to the phenolic hydroxyl is not in itself a sufficient activating influence. It was of interest therefore to try the replacement reaction on a compound in which the reactivity might be somewhat between that of 2,4-dinitro-1-naphthol and 2-nitro-1-naphthol. 2-Nitro-4-acetyl-1-naphthol provides an example of such a compound. When this compound is treated with *p*-toluenesulfonyl chloride and dimethylaniline under the same conditions used to prepare 2,4-dinitro-1-chloro-naphthalene, replacement of hydroxyl took place and the yield of 2-nitro-4-acetyl-1-chloronaphthalene was almost as great as in the case where the hydroxyl was activated by nitro groups in both the *ortho* and *para* positions. This result might be interpreted to mean that the acetyl group has an

activating influence nearly equal to that of a nitro group, although an acetyl group is a much poorer *meta*-directing group than a nitro group.

In order to further study the effect of the acetyl group on the ease of replacement of hydroxyl by chlorine, the naphthol in which the positions of the acetyl and nitro groups are reversed was prepared. When attempts were made to replace the hydroxyl of 2-acetyl-4-nitro-1-naphthol by the same conditions which were successful with the isomeric 2-nitro-4-acetyl-1-naphthol the naphthol was recovered unchanged. It is believed that this indicates that the acetyl group is not as strong an activating group for the replacement reaction as is the nitro group. Such a conclusion would be in accord with the relative *meta*-directive influences of the two groups. It would be expected by analogy with the reactivity of nitrohalobenzenes in the Ullmann reaction that the activating effect of the nitro group would diminish as the group is moved from the 2-position to the more remote 4-position.

The effect of interchanging the acetyl and nitro group can not be interpreted as due only to the weakening of the activating influence without first giving some attention to two other factors which might affect the replacement of hydroxyl in the two compounds under consideration. These factors are steric effects and chelation.

If there is any substantial degree of chelation between the hydroxyl and the carbonyl group in the *ortho* position, such chelation might account for the lack of reactivity of the hydroxyl group. This argument is considerably weakened by the fact that the nitro group *ortho* to the hydroxyl would also chelate. Whether there is more chelation between a hydroxyl group and an *ortho* acetyl group than between a hydroxyl group and an *ortho* nitro group is open to question. A review of the existing literature sheds very little light on this question. Both *o*-nitrophenol and *o*-hydroxyacetophenone show no infra-red absorption due to hydroxyl group when 0.01 *M* solutions are used (2).

When benzyl carbamate is condensed with 5-nitrosalicylaldehyde and with 3-nitrosalicylaldehyde, the former compound gives a very low yield, whereas the latter gives an excellent yield (3). This has been explained on the assumption that in 5-nitrosalicylaldehyde the aldehyde group is tied up in the chelate ring with the *ortho* hydroxyl group and is thus not available for reaction. In the 3-isomer, there is opportunity for chelation of the hydroxyl with either the carbonyl group or the nitro group. It is said in this case that the

chelation of the hydroxyl with nitro is stronger than with carbonyl, and so the aldehyde group is free to take part in the condensation reaction. If this reasoning may be extended to the case of the 2-nitro- and 2-acetyl-1-naphthol, the effect of chelation can not be of any importance since the results predicted on the basis of chelation inactivating the hydroxyl would be just the reverse of those actually observed.

The other possible difference in effect may be steric. An inspection of molecular models indicates that the nitro group would create slightly greater hindrance about the hydroxyl group than would the acetyl group. Such effects are sometimes difficult to determine by an inspection of molecular models and it would be interesting to compare the relative interference effects of nitro and acetyl groups when placed in the ortho position of optically active biphenyls. Unfortunately such data are not available. If it may be assumed that the carboxyl group would have about the same interference effect as an acetyl group, then the existing data on the relative interference effects of nitro and carboxyl groups, as determined by half-life periods of optically active biphenyls, permit the conclusion that the nitro group would cause a greater degree of hindrance than would an acetyl group.

The reaction of 4-chloro-6-nitro-*o*-cresol with *p*-toluenesulfonyl chloride and dimethylaniline illustrates still another reaction which may take place instead of replacement of the phenolic hydroxyl by chlorine. The product isolated from this reaction was the 4-chloro-6-nitro-*o*-cresyl ester of *p*-toluenesulfonic acid. This result may be due to a combination of factors. The single nitro group may be an insufficient activating influence on the hydroxyl group. The reaction in this case may also be hindered by the two ortho groups. The reaction to form the ester would not be affected as much by steric influences as would be the replacement of hydroxyl by chlorine.

SUMMARY

A study of the replacement of phenolic hydroxyl by chlorine by treatment with *p*-toluenesulfonyl chloride and dimethylaniline has been made in order to gain information on the effect of structure of the phenol on the ease of the reaction. The hydroxyl of 2-nitro-4-acetyl-1-naphthol is replaced by chlorine under the same conditions and in about the same yield as is the hydroxyl in 2,4-dinitro-1-naphthol. The hydroxyl group of 4-nitro-2-acetyl-1-naphthol is not easily replaced. 4-Chloro-6-nitro-*o*-cresol is converted to the ester of *p*-toluenesulfonic acid on treatment with *p*-toluenesulfonyl

chloride and dimethylaniline. The structural factors which are involved in these different results are discussed.

ATTEMPTED REPLACEMENT OF HYDROXYL GROUP USING PHOSPHORUS HALIDES

In a 100-ml. flask was placed 50 ml. of dry ether, 5 ml. of phosphorus tribromide, and 1.5 g. of 2,4-dinitro-1-naphthol. The mixture was refluxed for 6 hours. The solution was allowed to stand over night at room temperature. A few drops of water were dropped down the condenser, to decompose the excess phosphorus tribromide, and the contents were then poured into ice water. The solid, 1.5 g., was 2,4-dinitro-1-naphthol.

The reaction was repeated using phosphorus pentachloride and again the starting material was recovered unchanged.

Direct heating of the 2,4-dinitro-1-naphthol with the phosphorus pentachloride gave a charred mass, from which no organic material could be extracted.

ATTEMPTED EXCHANGE OF HYDROXYL GROUP FOR CHLORINE IN 2-NITRO-1-NAPHTHOL

In a 50 ml. flask fitted with a reflux condenser was placed 5 g. (0.027 mole) of 2-nitro-1-naphthol, 12 g. (0.099 mole) of dimethylaniline and 6 g. (0.032 mole) of *p*-toluenesulfonyl chloride. The mixture was heated on a steam bath for 24 hours. The cooled mixture was treated with 10 ml. of dilute hydrochloric acid and filtered. The residue was heated with 5 ml. of alcohol and filtered. The recovery of starting material was almost quantitative.

EXCHANGE OF HYDROXYL GROUP FOR CHLORINE IN 2-NITRO-4- ACETYL-1-NAPHTHOL: 1-CHLORO-2-NITRO-4-ACETYLNAPHTHALENE

A mixture of 5 g. (0.022 mole) of 4-acetyl-2-nitro-1-naphthol, 6 g. (0.049 mole) of dimethylaniline and 5 g. (0.026 mole) of *p*-toluenesulfonylchloride was heated on a steam bath for 24 hours. The mixture was cooled and treated with 10 ml. of dilute hydrochloric acid, filtered and dried. The dry solid was heated gently on the steam bath with 10 ml. of alcohol and filtered. The residue was recrystallized from alcohol and gave 2.9 g. of a product with a melting point of 104-107°. This product was recrystallized from 50 ml. of alcohol and gave 2.6 g. (48 per cent of the theoretical) of a product with a melting point of 107-108°. A sodium fusion was carried out and established the presence of chlorine and nitrogen.

Anal. Calcd. for $C_{12}H_8O_3NCl$; C, 57.73; H, 3.23.

Found: C, 57.75; H, 3.40.

ATTEMPTED EXCHANGE OF HYDROXYL GROUP FOR CHLORINE IN
2-ACETYL-4-NITRO-1-NAPHTHOL

In a 50 ml. flask fitted with a reflux condenser was placed 5 g. (0.022 moles) of 2-acetyl-4-nitro-1-naphthol, 5.24 g. (0.043 moles) of freshly distilled dimethylaniline and 4.15 g. (0.022 moles) of *p*-toluenesulfonyl chloride. The mixture was heated on a steam bath for two hours. The partially crystallized, dark brown mixture was heated slightly with dilute hydrochloric acid and filtered. The residue was heated with a dilute solution of ammonium hydroxide and filtered. The solid was recrystallized from ether and gave a product melting at 161-162°. A mixed melting point with the starting material gave no lowering.

The above experiment was repeated using 10 g. of 2-acetyl-4-nitro-1-naphthol and 24 g. of dimethylaniline. The time of reflux was increased to 4 hours. The final residue was recrystallized from alcohol and gave a product with a melting point of 161-162°.

The above procedure was again repeated using 5 g. of the nitro compound, 6 g. of dimethylaniline and 4.5 g. of *p*-toluenesulfonyl chloride. The mixture was heated in a water bath for 5 hours. The semi-solid was heated on a steam bath with 25 ml. of dilute hydrochloric acid, filtered, dried and then heated lightly with 50 ml. of dilute ammonium hydroxide and filtered. The starting material was again recovered.

The experiment was repeated again using 10 g. of nitro compound, 14 g. of dimethyl aniline, and 9 g. of *p*-toluenesulfonyl chloride. The time of reflux was increased to 24 hours. The 2-acetyl-4-nitro-1-naphthol was recovered unchanged.

p-TOLUENESULFONATE OF 4-CHLORO-6-NITRO-*o*-CRESOL

In a 100 ml. flask fitted with a reflux condenser was placed 10 g. (0.043 mole) of 3-nitro-5-chloro-2-hydroxytoluene, 12 g. (0.099 mole) of dimethylaniline, and 10 g. (0.053) of *p*-toluenesulfonyl chloride. The mixture was heated on the steam bath for 24 hours. The partially crystallized, hardened mixture was heated slightly with 10 ml. of dilute hydrochloric acid and filtered. The dried residue was heated with 20 ml. of alcohol and filtered. The precipitate was recrystallized from glacial acetic acid and the 9 g. (61.5 per cent of the theoretical) of *p*-toluenesulfonate of 4-chloro-6-nitro-*o*-cresol melted at 136-137°.

Anal. Calcd, for $C_{14}H_{12}O_5NCIS$: C, 49.19; H, 3.54.

Found: C, 49.15; H, 3.65.

The above reaction was repeated using both pyridine and diethylaniline. Both reactions gave the same product. The mixed melting points of the three products gave no depression. Mixed melting point with *p*-toluenesulfonamide gave a depression (117-119°).

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