to melt the highest, *viz.*, 320–325°. This material is very insoluble in water but readily soluble in dilute sodium hydroxide solution.

Numerous attempts were made to improve the yield of diphenylbarbituric acid by using stronger sulfuric acid (100% and fuming (20% excess SO_3)) to effect the condensation. Also longer times of reaction were used in some cases. Both of these variations, however, tended to decrease the yields of the barbituric acid and increase the amounts of the associated higher melting material.

Quantitative Hydrolysis of Diphenylbarbituric Acid.—A 1.000-g. sample of diphenylbarbituric acid was boiled for six hours with 40 cc. of 10% potassium hydroxide in a 3-necked flask fitted with an inlet tube for air, a reflux condenser and a dropping funnel. The top of the reflux condenser was attached to another condenser set for downward distillation and which led into a flask containing standard acid. After the six hours of refluxing the water in the reflux condenser was replaced by steam and the ammonia distilled into the standard acid, during which time a slow stream of carbon dioxide- and ammonia-free air was passed through the system. The volume of the hydrolysis solution was maintained by additions of water from the dropping funnel. About 51% of the theoretical amount of ammonia was obtained. The alkaline solution was then refluxed for an additional eight hours and the ammonia distillation repeated. The total amount of ammonia recovered amounted to 0.1147 g. (calcd. 0.1213 g.).

The reaction mixture was then acidified with dilute sulfuric acid from the dropping funnel and the evolved carbon dioxide after drying absorbed in a weighed ascarite bulb. After washing out the system with carbon dioxide-free air the carbon dioxide collected was found to weigh 0.2976 g. (calcd. 0.3144 g.).

The hydrolysis mixture containing the precipitated diphenylacetic acid was treated with solid sodium carbonate until an excess of carbonate was present, filtered to remove the silica formed from the flask by the long alkaline hydrolysis, and the diphenylacetic acid precipitated from the filtrate with sulfuric acid. This precipitate was filtered off, washed with water and dried. The diphenylacetic acid so obtained melted at 145–147° and weighed 0.71 g. (calcd. 0.75 g.).

The author is indebted to Mr. Fred Beyerstedt for the analyses and quantitative hydrolysis of diphenylbarbituric acid.

Pharmacological Properties.—Diphenylbarbituric acid was tested by Mr. E. E. Swanson of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. The tests were made intraperitoneally in rats. It was found that diphenylbarbituric acid is effective only in very large doses (6–8 times the effective dose of luminal) and that such doses invariably caused the death of the animals.

The pharmacological behavior of diphenylbarbituric acid parallels that reported for di-(*p*-hydroxyphenyl)-barbituric acid by Dox and Thomas,[1] and supports their supposition that barbituric acids which are so essentially aromatic in character would not be effective hypnotics in moderate doses.

Summary

Diphenylbarbituric acid has been prepared by the condensation of benzene with alloxan by means of sulfuric acid. It has been found to be ineffective as an hypnotic in sub-lethal doses.

MADISON, WISCONSIN RECEIVED MAY 1, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ALBERTA]

The Reactivity of the Halogen in Some Halogenated Nitrobenzenes. I. Reaction with Piperidine[1]

BY R. B. SANDIN AND M. LISKEAR

It is a well-known fact that a nitro group in para or ortho position to a halogen in the benzene ring activates the halogen. However, comparatively little attention seems to have been paid in the literature to the combined effect of a para nitro group and one or more ortho halogens, on the reactivity of an aryl halide. One contribution is that of Holleman and De Mooy,[2] who have carried out quantitative researches on the replacement of substituents in dichloro, nitrochloro and nitrodichlorobenzenes and have shown that the velocity of replacement of the para halogen in 3,4-dichloronitrobenzene is much greater than in 4-chloronitrobenzene. In this work sodium methylate was used as a reagent for measuring the halogen reactivity.

A very important compound of the above type, *viz.*, 3,4,5-triiodonitrobenzene was used by Harington and Barger[3] in their synthesis of thyroxine. In this case it is the para iodine atom which reacts and it was believed by the authors that the meta iodine atoms had something to do with its activa-

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[1] This work was supported in part by funds from the Carnegie Corporation Research Grant, for which the authors express their thanks.

[2] Holleman and De Mooy, *Rec. trav. chim.*, **35**, 1–66 (1915).

[3] Harington and Barger, *Biochem. J.*, **21**, 169 (1927).

tion. It was the aim, therefore, to determine the reactivity of the para halogen atom in a number of polyhalogenated nitrobenzenes such as 3,4,5-triiodonitrobenzene. This paper reports the results obtained from a study of the reaction of such a series of compounds with piperidine.

General Procedure.—To determine the reactivity of the para halogen atom, the halogenated nitrobenzene (0.003685 mole) in an all-glass reflux apparatus was allowed to react with piperidine (0.1088 mole) in benzene (20.0 cc.) at the boiling point of the solution, for a period of eight hours. The halide ion was then extracted quantitatively with water and determined gravimetrically. The gravimetric procedure was generally checked by doing a Volhard titration on the filtrate. To determine the amount of meta halogen which might have been displaced the silver halide was treated with chlorine and changed into silver chloride. It is obvious that this method could not be used if all the halogen atoms in the compound were the same. Again in the case of different halogens, if no meta halogen displacement occurred, the gravimetric determination agreed with the volumetric determination.

The above procedure which involves piperidine is somewhat similar to that of Brewin and Turner,[4] who have worked on the comparative reactivities of some chloro, bromo and iodonitrobenzenes. More recently McElvain and co-workers[5] have done important and extensive work on the reaction of organic halides and they have also used piperidine as the reagent for reactive halogen.

Experimental

The piperidine used was obtained from the Eastman Kodak Company and boiled at 105.5–107.5°. The benzene was thiophene free and melted at 5°. The starting material for the preparation of the halogenated nitrobenzenes was *p*-nitroaniline in every case. The di- and trihalogenated compounds were made from the corresponding mono and dihalogenated *p*-nitroanilines, which are weakly basic amines and therefore difficult to diazotize by the ordinary procedure. However little difficulty in diazotizing was experienced if the excellent method of Schoutissen[6] was followed. Recently Hodgson and Walker[7] have also developed a procedure for the diazotization of weakly basic amines, which the authors have found to be very satisfactory. The halogenated compounds were crystallized from benzene or alcohol and sometimes from a mixture of these two solvents, until the melting points were constant.

Since the compounds used are all reported in the literature and their preparation is a standardized one, only the preparation of a typical compound, which involves the diazotization of a weakly basic amine, will be described.

Preparation of 3,5-Dibromo-4-iodonitrobenzene.[8]—2,6-Dibromo-*p*-nitroaniline (50 g.) was dissolved in 200 cc. of concentrated sulfuric acid at room temperature and then cooled to 0°. To this solution was then added with stirring a cold solution of sodium nitrite (10 g.) in 100 cc. of concentrated sulfuric acid. The diazotization was completed by the slow addition of sirupy phosphoric acid (200 cc.) with vigorous stirring and maintaining the temperature at 5 to 10°. The stirring was continued for about one hour longer. The diazonium salt solution was then poured into 2 kg. of a mixture of ice and water, filtered if necessary, and treated with a saturated solution of potassium iodide (35 g.) in water. The mixture was heated and any free iodine was removed wih sodium bisulfite. The yield of crude material was almost the theoretical. It was crystallized from a mixture of benzene and alcohol and melted at 154–155° (corr.).

In Table I are given the data for the percentage removal of halogen. The results are the average of two or more closely agreeing determinations. A typical run is summarized in Table II. By zero replacement of meta halogen is meant that under the experimental conditions no such displacement could be detected. In the case of the 3,4-diiodo- and 3,4,5-triiodonitrobenzenes, the halogen removed is calculated as all para halogen. There un-

TABLE I

PERCENTAGE REMOVAL OF HALOGEN FROM VARIOUS HALOGENATED NITROBENZENES, USING PIPERIDINE

	Substituted nitrobenzenes Substituents	Para halogen displaced, %	Meta halogen displaced, %
(1)	4-Iodo	11.8	
(2)	3,4-Diiodo	55.4	?
(3)	3,4,5-Triiodo	38.6	?
(4)	4-Bromo	37.7	
(5)	3-Iodo-4-bromo	90.8	<0.1
(6)	3,5-Diiodo-4-bromo	66.1	0.3
(7)	4-Chloro	18.5	
(8)	3-Iodo-4-chloro	50.6	0
(9)	3,5-Diiodo-4-chloro	14.3	1.2
(10)	3-Chloro-4-iodo	73.8	0
(11)	3,5-Dichloro-4-iodo	76.7	0
(12)	3-Bromo-4-iodo	77.2	0
(13)	3,5-Dibromo-4-iodo	77.9	0

TABLE II

REMOVAL OF HALOGEN FROM 3,4-DIBROMO-4-IODONITROBENZENE

	Sample I	Sample II
Sample, g.	1.5000	1.5000
Silver halide, g.	0.6734	0.6766
Silver halide as AgCl, g.	0.4114	0.4126
Displacement of iodine, %	77.8	78.1
Displacement of bromine, %	0	0

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[4] Brewin and Turner, *J. Chem. Soc.*, 332 (1928).

[5] (a) Semb and McElvain, THIS JOURNAL, **53**, 690 (1931); (b) Howk and McElvain, *ibid.*, **54**, 282 (1932); (c) Drake and McElvain, *ibid.*, **55**, 1155 (1933); (d) **56**, 697 (1934); (e) **56**, 1810 (1934).

[6] Schoutissen, *ibid.*, **55**, 4532 (1933).

[7] Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

[8] Körner and Contardi, *Atti accad. Lincei*, **22**, I, 823–836 (1913).

doubtedly is some meta displacement but it is believed that this is relatively small and would not seriously change the value recorded.

Discussion of Experimental Results

From the data which are now available it may be safely concluded that a halogen meta to the nitro group does increase the mobility of the halogen in the para position. Also when piperidine is used as the reagent for reactive halogen, a steric effect seems to be of importance. Drake and McElvain[5d,e] have shown that with piperidine a rate determining factor in the halogen replacement reaction is the ability of the reagent to approach the carbon carrying the halogen. In the authors' work this is very noticeable from Table I, if the compounds are examined from the standpoint of groups 1, 2 and 3; 4, 5 and 6; 7, 8 and 9. In these three groups it is the dihalogenated compound which is the most reactive, and it would appear that the iodine atom has both an activating and steric effect. The decided decreased activity of the trihalogenated compounds is undoubtedly due to the steric factors associated with the structure of the compounds.

Regarding the last four compounds it is difficult to say whether it is the increased activating effect, or the decreased steric effect of the chlorine or bromine atoms, which is responsible for the slightly increased halogen displacement of the trihalogenated compounds.

Concerning the steric factor it might be supposed that this would be less noticeable if a reagent such as a phenolate instead of piperidine were used. Preliminary work which has been done using phenol in methyl ethyl ketone and potassium carbonate indicates the plausibility of this supposition. In the compounds 4, 5 and 6 it has been found that expressing the reactivity of compound 4, the least reactive, by unity, the reactivities of 5 and 6 are represented by 16 and 42.

Summary

A quantitative study of the removal of the para halogen using piperidine, from thirteen halogenated nitrobenzenes has been made. The results indicate that meta halogen increases the mobility of the para halogen. There is also a steric factor to be considered. This work is being continued.

EDMONTON, ALBERTA RECEIVED MAY 3, 1935

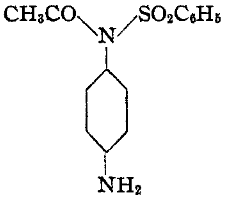
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Anomalous Mutarotation of Amine Salts of *d*-Camphor-10-sulfonic Acid. Attempted Resolution of Tri-substituted Nitrogen Compounds

BY R. S. SCHREIBER AND R. L. SHRINER

The concept of a tetrahedral nitrogen atom predicts the existence of optical isomers of compounds of the type RR'R''N. However, the actual isolation of the *d*- and *l*-forms depends on their stability and the failure to resolve such compounds may be due to very rapid racemization. If the configuration of such a molecule could be fixed by some means, then resolution should be possible. It seemed plausible that heavy negative groups, such as acyl or sulfonyl, would be less mobile than alkyl or aryl groups which were attached to the nitrogen atom in compounds whose resolution has been attempted.[1] Kipping and Salway[2] studied the resolution of a compound with one acyl radical, but no studies have been made on the resolution of imides.

Accordingly, the following unsymmetrically substituted *p*-phenylenediamine derivatives were prepared, then treated with *d*-camphor-10-sulfonic



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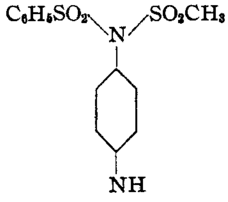

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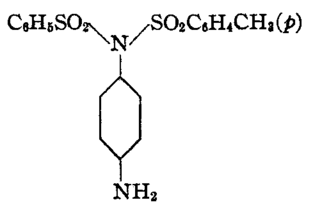

III

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[1] For references, see the recent books on "Stereochemie" by Freudenberg (1933); Goldschmidt (1933); Wittig (1930).

[2] Kipping and Salway, *J. Chem. Soc.*, **85**, 446 (1904).