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The synthesis of 2-amino-4-chlorophenol-6 sulfonic acid

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THE SYNTHESIS OF 2-AMINO-4-CHLOROPHENOL-6-SULFONIC ACID

by

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INTRODUCTION

THE SYNTHESIS OF 2-AMINO-4-CHLOROPHENOL-6-SULFONIC ACID

INTRODUCTION

A survey of the literature has shown a variety of methods for the synthesis of 2-amino-4-chlorophenol-6-sulfonic acid (V) by the following processes: (A) sulfonation of 2-amino-4-chlorophenol,[1] (B) sulfonation and hydrolysis of 2-acetamino-4-chlorophenol,[2] (C) nitration and reduction of 4-chlorophenol-6-sulfonic acid,[3] and (D) Sandmeyer reaction on, nitration and reduction of 4-aminophenol-6-sulfonic acid.[3] A paper by Kiprianov and Mikhailenko reports a preparation by pressure hydrolysis of 2-nitro-1,4-dichloro-benzene and subsequent sulfonation and reduction of the phenol in good yield.[4] A subsequent Russian paper is rather vague in description.[5] Armstrong and Prevost have studied the reaction of sulfuric and nitric acid on the isomeric monochlorphenols.[6]

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1. Akt.-Ges.f.Anilinf., Ger. Pat. 144618 (1903).

2. Bayer & Co., Ger. Pat. 194955 (1908).

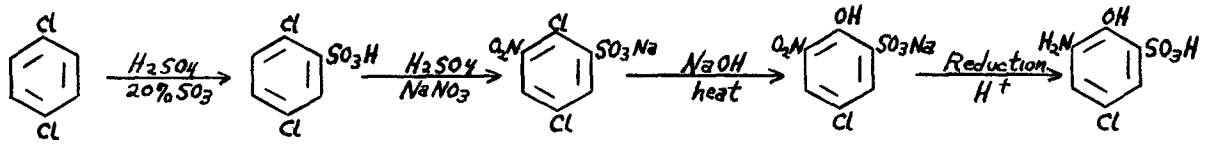
3. Bad. Anilin u.Sodaf., Ger. Pat 132423; Frdl. 6, 118 (1900-1902).

4. Kiprianov & Mikhailenko, Ukrainski Khem. Zhur. 5, Tech. Pt. 225-39 (1930).

5. I. I. Vorontsov, J. Chem. Ind. (U.S.S.R.) 18 No. 23/24, 16-22 (1941).

6. Armstrong and Prevost, Ber., 7, 405 (1874).

However, the course of this investigation was concerned with the following feasible synthetic route essentially described in the French patent:[7]



I II III IV V

German investigators[5] claim a poor yield of the amino sulfonic acid (V) following this method but give no experimental data to support this claim. Our investigation was concerned chiefly with the hydrolysis of the sodium-2-nitro-1,4-dichlore-benzene-6-sulfonate (III) to the sodium-2-nitro-4-chlorophenol-6-sulfonate (IV), and the reduction of the product (IV) to the desired 2-amino-4-chlorophenol-6-sulfonic acid (V) in practicable yield.

It has been found[8] that the preparation of the sodium-2-nitro-1,4-dichlore-benzene-6-sulfonate (III) proceeds in almost quantitative yield (91%) through the sulfonation and nitration steps, using fuming sulfuric acid and sodium nitrate, when the product is "salted out" by the use of sodium chloride. In an alternate procedure the excess sulfuric acid after the nitration may be converted to the calcium salt by the use of calcium

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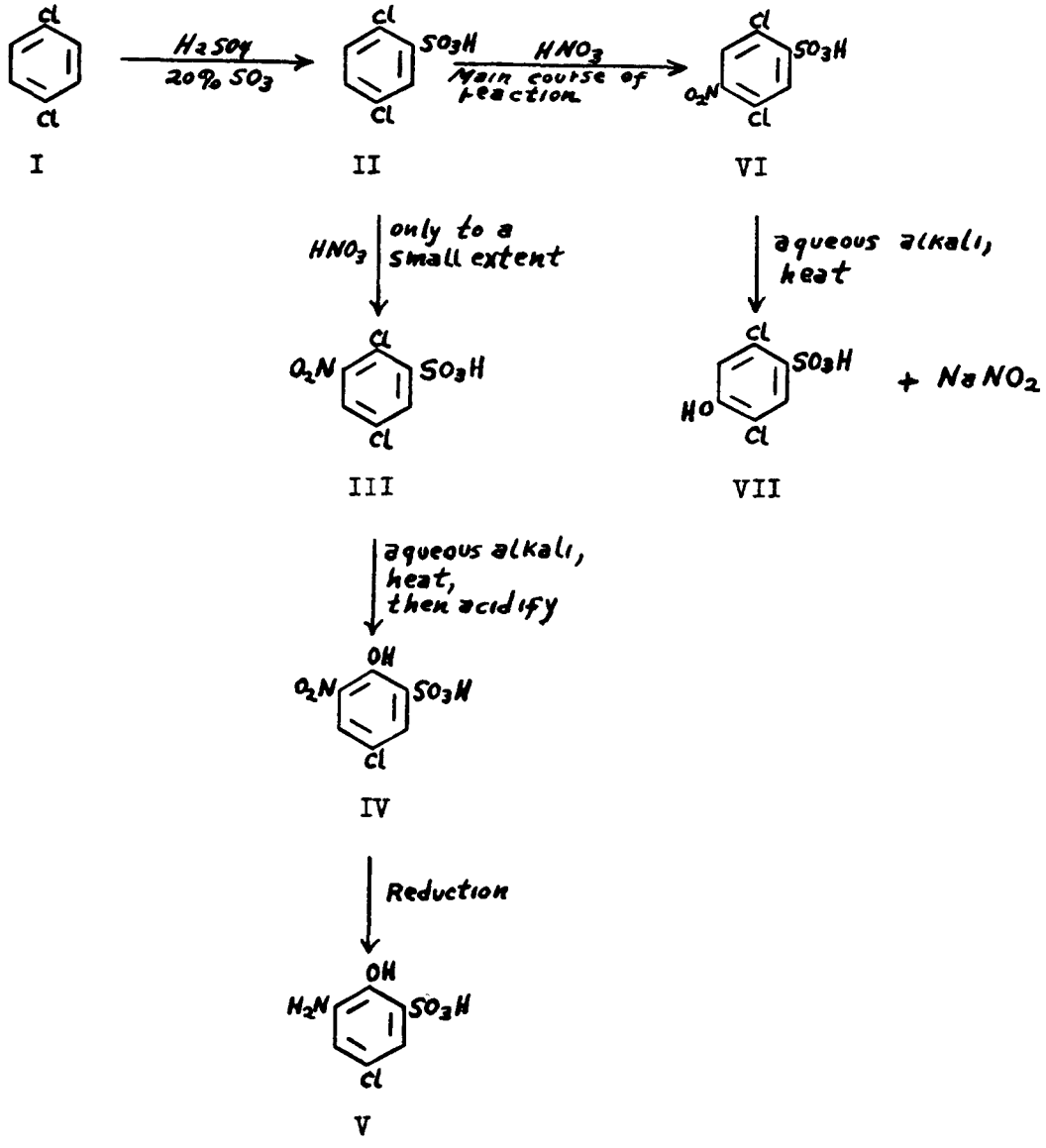
7. French Patent 301530 (1900).

8. This thesis, p. 27.

hydroxide; a process known as "liming out". A yield of only 75.2% of (III) was realizable even after a re-extraction of the insoluble calcium sulfate cake. This could be explained by the formation of a basic salt (which would be insoluble), by inefficient washing, or possibly by an adsorption of the product on the cake, a difficulty which is not encountered in the "salting out" procedure.

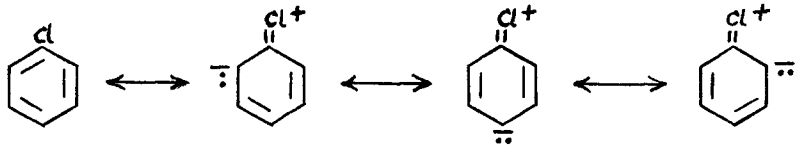
Investigators of the Badische Anilin und Soda-Fabrik in Ludwigshaven reported that a technical preparation of 2-amino-4-chlorophenol-6-sulfonic acid was not realizable following the process described in the French Patent.[3] They stated that when one sulfonated p-dichlorobenzene and nitrated the resulting p-dichlorobenzene sulfonic acid according to the directions of the French Patent, even though the formation of the mono-sulfonic acid (II) proceeded smoothly, nitration of the sulfonic acid, contrary to all expectations, apparently introduced the nitro-group mainly in a position para to the sulfonic acid group and only to a small extent in the desired meta-position. When the nitration products (III, VI) were heated with aqueous alkali, they claimed, only the 2-nitro-1,4-dichloro-benzene-6-sulfonic acid (III) was converted to the corresponding 2-nitro-4-chlorophenol-6-sulfonic acid (IV) which upon reduction produced the 2-amino-4-chlorophenol-6-sulfonic acid (V). The "main product" of the nitration reaction according to this explanation was hydrolysed by loss of the nitro group with the formation of sodium nitrite and apparently formed a dichlorophenol-sulfonic acid (VII) which was of no use in this particular preparation.

The reactions claimed by these investigators are:



In considering the feasability of nitration para to the sulfonic acid group in compound (II) it is necessary to consider the resonance and electrical effects inherent in this type of molecule. The approach to the problem would involve an evaluation of the contributing or opposing effects the substituents have on the benzene ring. This would be best accomplished by examining the electronic structures of chlorobenzene and benzenesulfonic acid in order to rationalize a point of attack on the benzene nucleus during the nitration, considering (II) as a composite structure of the two. Dipole moment data show that chlorine has the highest dipole moment of the halogens and thus attracts electrons strongly from the benzene ring. This induces in the nucleus a condition of low electron density and hence of lowered vulnerability to attack by electron acceptor agents.

Chlorobenzene is regarded as a resonance hybrid of the following structures:[9]



In chlorobenzene, however, two different effects have to be considered separately. The first of these, previously mentioned, results from the fact that the chlorine atom is strongly electronegative and pulls electrons away from the carbon atom to

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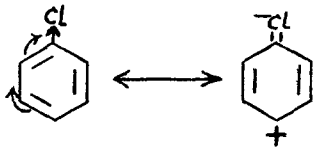
9. Fieser & Fieser, "Organic Chemistry", D.C. Heath and Co., Boston, Mass. 1st Edition, 1944, p. 569.

which it is attached. If this displacement of charge were the only factor to be considered, the orientation should be just as in pyridine or in the trimethylanilinium ion; meta with deactivation for the electrophilic reagents and ortho-para with activation for radical or nucleophilic reagents. The situation could then be represented by the structure in equilibrium with the quinoid type structure,

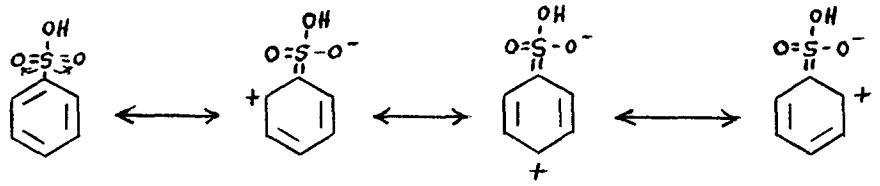


A second effect which must be considered, however, results from the fact that the chlorine atom has an unshared pair of electrons and so can initiate the effect symbolized by the structure

If this displacement of charge were the only factor involved, the orientation would be ortho-para with activation for an electrophilic reagent, indeterminate for a radical reagent, and meta with deactivation for a nucleophilic reagent.

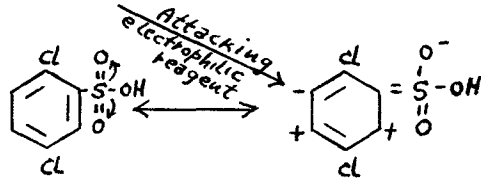
The two effects due respectively to the electro-negativity and to the unshared pair of electrons are largely in conflict with each other. It cannot be predicted with any assurance what the actual orientation will be for any of the different types of reagent. Experimentally it is found that the orientation is ortho-para with deactivation for an electrophilic reagent and ortho-para for a radical reagent.

The structure of benzensulfonic acid may also be represented by a resonance hybrid,



Displacement of electrons to the electron-deficient oxygen atom must tend to set up positive centers at the ortho and para position and hence to render these sites particularly unacceptable to electrophilic reagents. The meta carbon, however, is probably quite vulnerable to attack by an electrophilic reagent.

It is now possible to predict what point our electrophilic or cationoid agent will attack in the nitration of p-dichlorobenzenesulfonic acid in view of the foregoing theoretical considerations. The resonating hybrid of p-dichlorobenzenesulfonic acid may be represented as

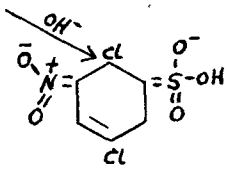


A B

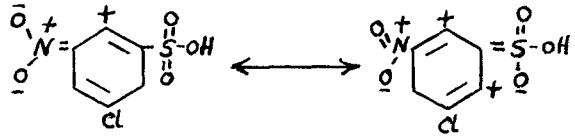
since now the electrical effects of the chlorine atoms in para-position to each other are neutralized by their own influence. We can thus see that in (B) the meta position to the sulfonic acid group is the only one open to attack by the positive cationoid $HO-\overset{+}{N}\leq\overset{O}{O}^{-}$. In the nitration the nitric acid reacts in this form, the hydroxyl taking with it on separation both of the covalency electrons originally binding it to nitrogen and leaving the

positive residue + NO_2 to attach itself to the nucleus at a point where the nitrogen octet may be completed.

The newly formed 2-nitro-1,4-dichloro-benzene-6-sulfonic acid now constitutes a compound where the chlorine atom ortho to both a nitro and a sulfonic acid group should be particularly susceptible to hydrolysis.



This is due to the fact that both the strong sulfonic acid and nitro groups withdraw electrons from the ring making the 1-carbon strongly electropositive and facilitating the ionization of the molecule into chloride and free carbonium ions. The stability of the carbonium ion is enhanced by its ability to achieve a coplanar configuration. The resonating structure of the carbonium ion may be represented as,



Another interesting point which explains the lability of the chlorine atom in the 1-position is the "steric inhibition of resonance". The fact that the 1-chlorine is the one replaced in spite of the steric hindrance of the nitro and sulfonic acid groups is explained on this basis. Position 1 is activated to the full extent for reaction with a nucleophilic reagent because the chloro-

group in position 4 is free to assume the necessary coplanar configuration. Position 4 on the other hand is activated to a much smaller extent probably because the chloro-group in position 1 is effectively held out of the plane of the ring by the bulky nitro and sulfonic acid groups. Several examples of this type are cited in the literature.[10,11,12]

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10. K. Ibbotson and J. Kenner, J. Chem. Soc., 123, 1260 (1923).

11. H. Burton and J. Kenner, J. Chem. Soc., 119, 1047 (1921); J. Kenner and M. Parkin, ibid., 117, 852 (1920).

12. W. C. Spitzer and G. W. Wheland, J. Am. Chem. Soc., 62, 2995 (1940).

Part I

THE HYDROLYSIS OF SODIUM-2-NITRO-1,4-DICHLORO-BENZENE-6-SULFONATE (III) TO SODIUM-2-NITRO-4-CHLOROPHENOL-6-SULFONATE (IV)

To study the hydrolysis of compound (III), the optimum conditions for the hydrolysis of the chlorine atom in the 1 position to produce the phenol (IV) had to be determined. Preliminary experiments were run on the sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate in solution after conversion to the sodium salt in the "liming out" procedure[13] instead of isolating a solid product. The amount of chlorine hydrolyzed was determined by a modified Volhard titration.[14,15] The results are summarized in Table I and Figure I.

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13. This thesis, p. 26.

14. This thesis, p. 55.

15. The percentage of chlorine hydrolyzed was based on 1 gram-atom of hydrolyzable chlorine in the 1-position for every gram mole of (III).

16. "Scott's Standard Methods of Chemical Analysis", D. Van Nostrand Co., Inc., New York, N.Y., 5th Edit., Vol. 1, 1939, p. 271-272.

Table I

Hydrolysis Rates of

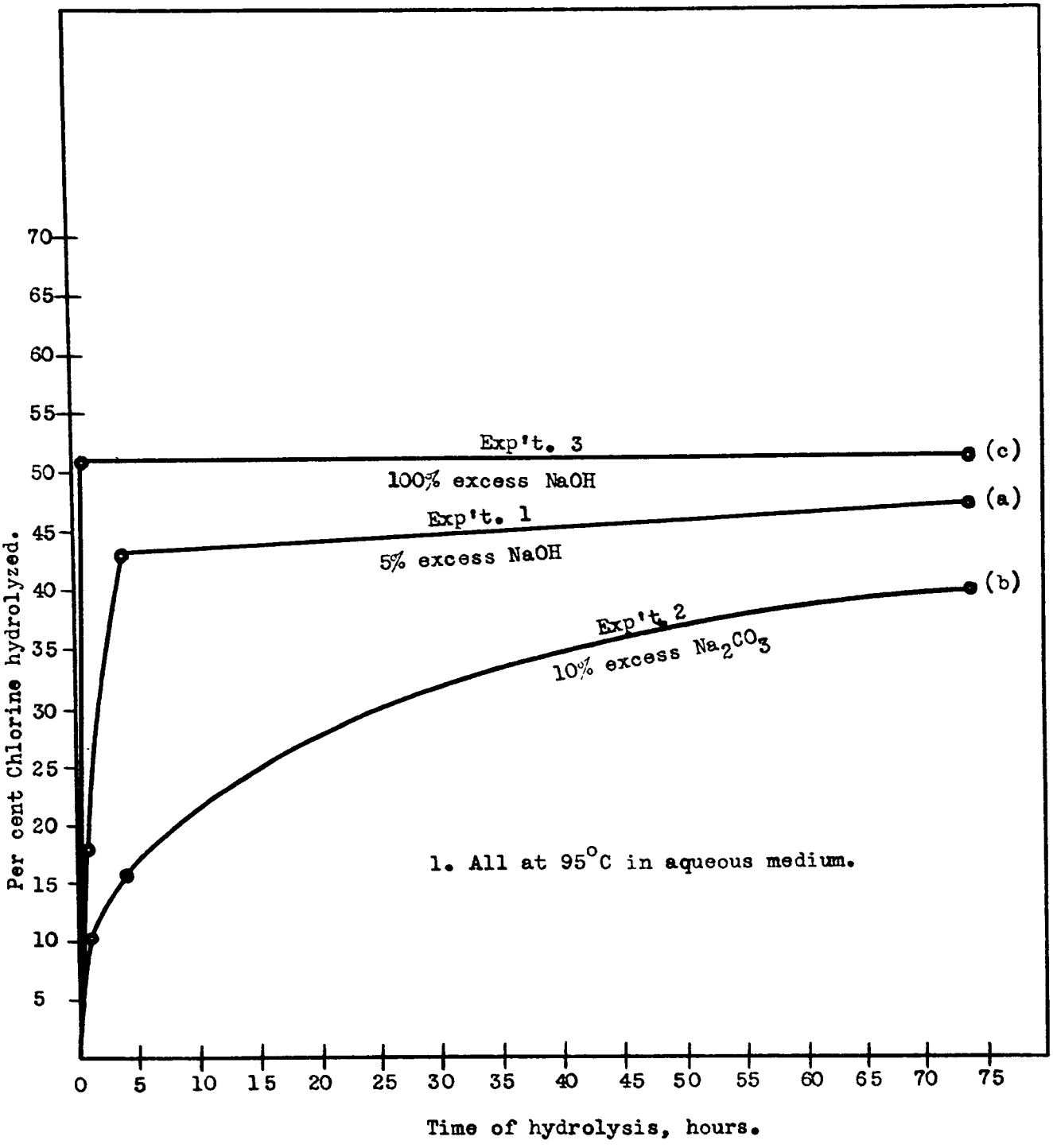
Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate[1]

Moles of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate used	Concentration of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (molarity)	(a) Hydrolyzing agent used (moles) (b) % Molar excess (c) Molar concentration	T°C of hydrolysis	Time of hydrolysis, hours	% Chlorine hydrolyzed	% Maximum yield of Sodium-2-nitro-4-chloro-phenol-6-sulfonate
0.075 Exp't. 1	0.19	(a) NaOH, (0.16) (b) 5.0 (c) 0.4	95	1 4 73	18.2 43.2 47.4	 47.4
0.075 Exp't. 2	0.23	(a) Na_2CO_3, (0.17) (b) 10.0 (c) 0.5	95	1 4 73	10.5 15.8 39.5	 39.5
0.075 Exp't. 3	0.23	(a) NaOH, (0.30) (b) 100.0 (c) 0.5	95	1 4 73	51.0 51.0	 51.0

1. All hydrolyses run in aqueous medium.

Figure I

Hydrolysis Rates of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate[1]



An examination of the rate curves in Figure 1 showed that, under the conditions specified,

(1) A strong base such as sodium hydroxide is more effective than a weak one such as sodium carbonate;

(2) The use of a large excess of a strong base (100%) causes the hydrolysis to reach its limit within approximately 1 hour;

(3) The use of a small excess of strong base (5%) causes the hydrolysis to be completed within approximately 4 hours;

(4) The maximum amount of chlorine hydrolyzed under these conditions was approximately 40 to 50%.

In view of the fact that the chlorine in the 1-position in (III) should be quite labile, it was somewhat suprising at this time to find that a maximum of only 50 percent was hydrolyzed under the influence of such a strong nucleophilic reagent as the hydroxyl ion. There was still, of course, a remote possibility that the undesired 3-nitro isomer (VI) was being formed to some extent. A separation of the 2-and 3-nitro isomers would seem extremely difficult due to the highly polar nature of the compounds. It was deemed worthwhile, however, to attempt a separation by fractional crystallization and to determine the chlorine hydrolyzed from each fraction, the theory being that the 2-nitro isomer (III) would hydrolyze chlorine to a much greater extent than the 3-nitro isomer (VI). The results are summarized in Table II and Figure II.

Table II

Hydrolysis Rates of

Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate[1]

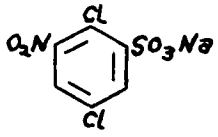
Moles of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate used	Concentration of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (molarity)	(a) Hydrolyzing agent used (moles) (b) %Molar excess (c) Molar concentration	T°C of hydrolysis	Time of hydrolysis, hours	% Chlorine hydrolyzed	Fraction hydrolyzed, % by wt. of total
0.017 Exp't. 4	0.23	(a) NaOH, (0.043) (b) 25.0 (c) 0.568	95	4	54.8	Fract. #1, 57.7
0.010 Exp't. 5	0.23	(a) NaOH, (0.026) (b) 25.0 (c) 0.568	95	4	47.7	Fract. #2, 19.6
0.010 Exp't. 6	0.23	(a) NaOH, (0.026) (b) 25.0 (c) 0.568	95	4	47.7	Fract. #3, 12.5
0.010 Exp't. 7	0.23	(a) NaOH, (0.026) (b) 25.0 (c) 0.568	95	4	29.5	Fract. #4, 10.1
0.010 Exp't. 8[2]	0.23	(a) NaOH, (0.026) (b) 25.0 (c) 0.568	95	4	47.7	

1. Fractionally crystallized.

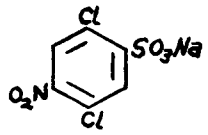
2. This is the product obtained from a second crystallization of Fraction #1, which was then again hydrolyzed.

Figure II

Hydrolysis Rates of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate: An attempt to separate the isomers



III and



VI

The rate curves in Figure II showed that separation of isomers was accomplished by the fractional crystallization. The material that came out first (Fraction 1, Curve d) was the isomer most easily hydrolyzed (the 2-nitro isomer, III), while subsequent fractions were hydrolyzed with increasing difficulty. Thus between fractions 3 and 4 there was a sharp decrease in the ease of hydrolysis, indicating that fraction 4 may be "rich" in the 3-nitro isomer (VI). Fraction 3 may also possibly contain a good deal of the 3-nitro isomer, and since fractions 3 and 4 constitute approximately 23% (by weight) of the total weight of fractions, this correlates fairly well with later experiments where the maximum amount of hydrolyzable chlorine was found to be approximately 73%. In an attempt to further purify fraction 1 by another crystallization, the percentage of chlorine hydrolyzed dropped slightly from 55% to 48% (see Experiment 8, Curve e). The maximum amount of chlorine hydrolyzed again seems to be approximately 50% of the 1 gram atom that is desired.

In an effort to raise the molar percentage of chlorine hydrolyzed above 50%, the following two routes were decided upon:

A. Obtain a pure sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate from the "salting out" procedure, chromatograph the compound by passing it in alcoholic solution over alumina, and run hydrolyses under various conditions on this product.

B. Determine the maximum amount of chlorine hydrolyzable

on a pure sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate under various conditions.

The results of route A are summarized in Table III and Figure III. Those of route B in Table IV and Figure IV.

Table III

Hydrolysis Rates of

Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate[1]

Moles of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate used	Concentration of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (molarity)	(a) Hydrolysing agent used (moles) (b) % Molar excess (c) Molar concentration	T°C of hydrolysis	Time of hydrolysis, hours	% Chlorine hydrolyzed	% Maximum yield of Sodium-2-nitro-4-chloro-phenol-6-sulfonate
0.001 Exp't. 9	0.23	(a) NaOH, (0.003) (b) 25.0 (c) 0.568	95	4	63.7	63.7
0.001 Exp't. 10	0.23	(a) NaOH, (0.004) (b) 100 (c) 0.912	95	4 10	70.1 70.1	70.1
0.001 Exp't. 11[2]	0.23	(a) NaOH, (0.004) (b) 100 (c) 0.912	95	1 4 10	61.5 73.2 73.2	73.2
0.001 Exp't. 12[3]	0.23	(a) NaOH, (0.004) (b) 100 (c) 0.912	80	1 4 10	64.8 64.8 64.8	64.8

1. Crystallised from ethyl alcohol and chromatographed.

2. Chromatographed twice.

3. Chromatographed twice; hydrolysis run in 95% ethyl alcohol.

Figure III

Hydrolysis Rates of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate

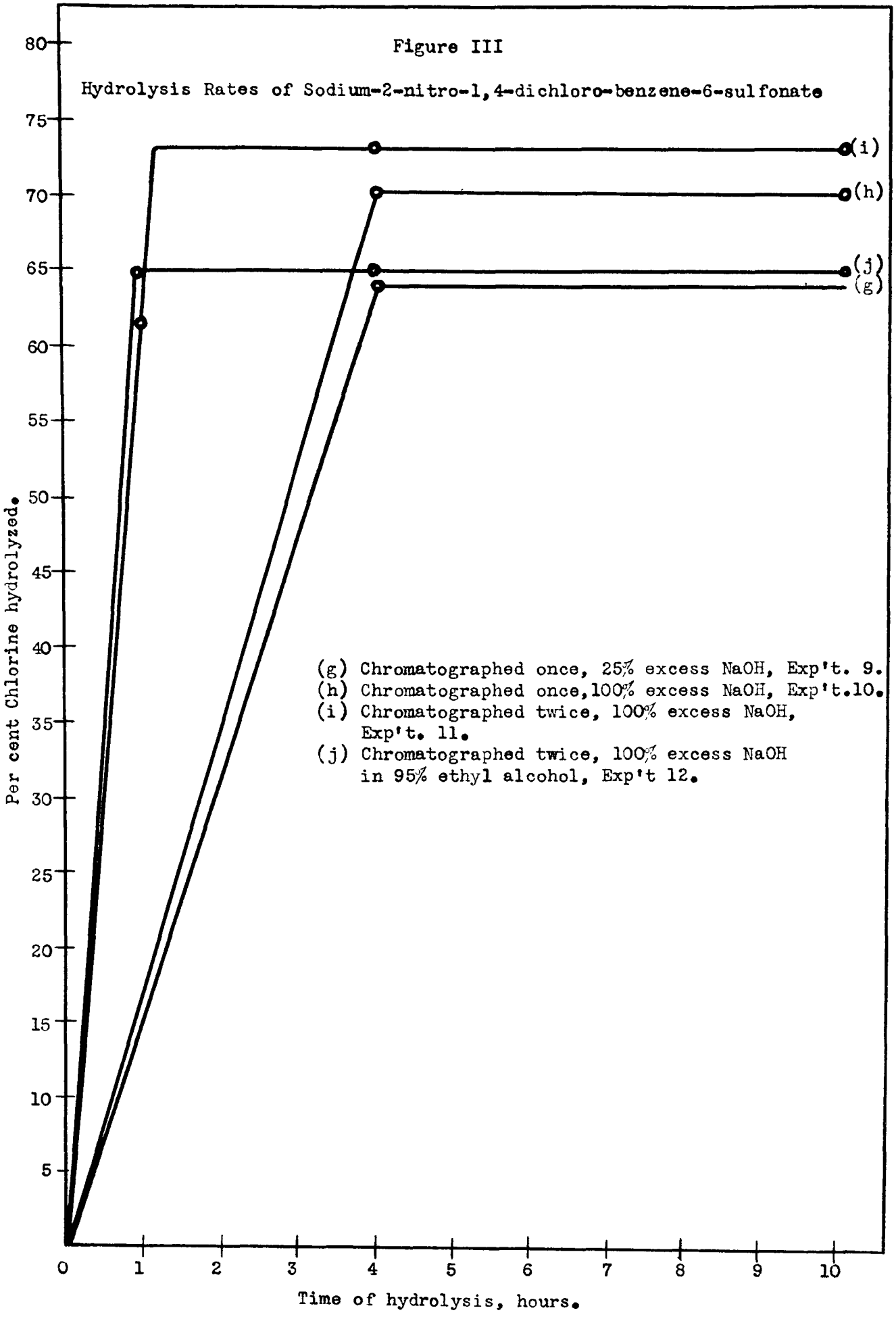


Table IV

Hydrolysis Rates of

Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate

Moles of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate used	Concentration of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (molarity)	(a) Hydrolyzing agent used (moles) (b) % Molar excess (c) Molar concentration	T°C of hydrolysis	Time of hydrolysis, hours	% Chlorine hydrolyzed	% Maximum yield of Sodium-2-nitro-4-chloro-phenol-6-sulfonate
0.010 Exp't. 13[1]	0.23	(a) NaOH, (0.026) (b) 25.0 (c) 0.568	95	4	61.5	61.5
0.001 Exp't. 14[2]	0.23	(a) NaOH, (0.003) (b) 25.0 (c) 0.568	95	4	70.7	70.7
0.001 Exp't. 15[3]	0.23	(a) NaOH, (0.004) (b) 100 (c) 0.912	95	4 10	67.2 67.2	67.2
0.001 Exp't. 16[4]	0.23	(a) NaOH, (0.003) (b) 25.0 (c) 0.568	95	4	61.5	61.5
0.010 Exp't. 17[5]	0.23	(a) NaOH, (0.026) (b) 25.0 (c) 0.568	95	4	40.5	40.5

1. Recrystallized from ethyl alcohol.

2. Recrystallized from n-butyl alcohol, then ethyl alcohol.

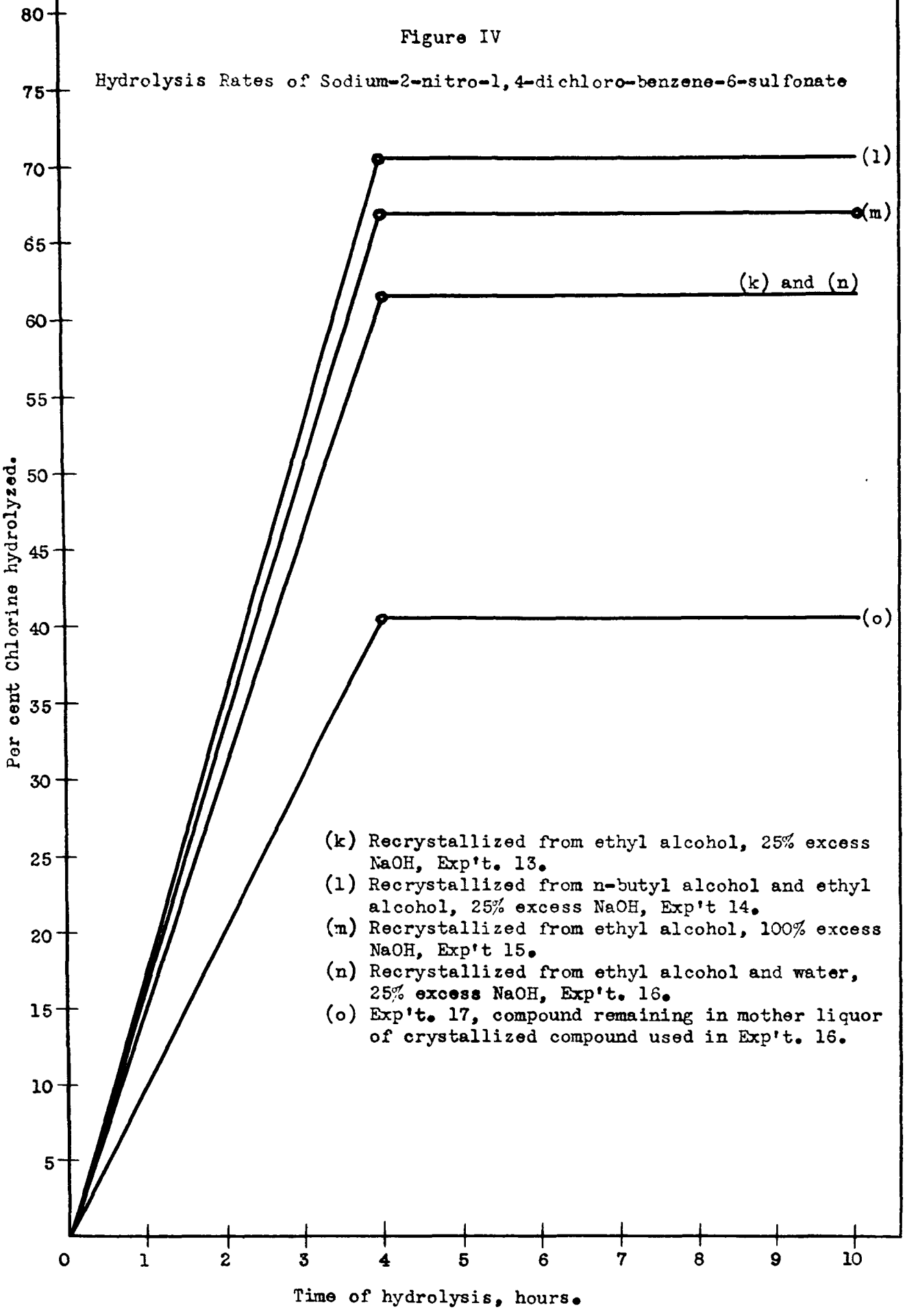
3. Recrystallized from ethyl alcohol.

4. Recrystallized from ethyl alcohol, then from water.

5. Compound remaining in mother liquor of crystallized compound used in Experiment 16.

Figure IV

Hydrolysis Rates of Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate



Discussion of the rate curves in Figure III:

Use of a crystallized and chromatographed pure sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate resulted in an increase of 15 to 25 percent of the chlorine hydrolyzed above the yield obtained when the hydrolysis is run on the crude "limed-out" compound in solution without preliminary isolation (compare Figure 1). Hydrolyses run with 25 percent and 100 percent excess sodium hydroxide in these cases are completed within approximately 4 hours, but the use of 100 percent excess base improves the yield considerably (Curves g and h). When the compound was chromatographed twice, the "chlorine value"[17] increased a negligible amount (Curve i). The use of alcoholic sodium hydroxide as a hydrolyzing medium was of no advantage over the aqueous medium (Curve j).

Discussion of the rate curves in Figure IV:

Again it is indicated that use of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate purified by crystallization results in increases of the chlorine value from approximately 10 to 20 percent over that realized when the crude compound in solution is hydrolyzed without isolation (compare Figure I). Hydrolyses run with 25 percent and 100 percent excess sodium hydroxide are finished within approximately 4 hours, and the yield is several percent better in the latter than when smaller excess concentrations of NaOH are used (Curves k and m). Curves (n) and (k) are identical even though the compound used for the

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17. Hereafter meaning "percentage of labile chlorine hydrolyzed".

rate determination in (n) was crystallized a second time from water. Curve (o) has a low chlorine value (mother liquor of compound used in n), indicating either an impure compound or a partial separation of the unwanted 3-nitro isomer (VI).

It is evident from a consideration of Tables III and IV that a maximum yield of approximately 70 percent to 73 percent of the phenol (IV) is obtainable when using a pure sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate and a large excess concentration of base (100%). The use of chromatography is not warranted on a large scale, since there is no better yield of the phenol (IV) than when using the compound (III) crystallized from ethanol (compare Experiments 10 and 14, Curves h and l). Yields in the chromatography were 83 percent for a pass through one column and 66 percent over two columns. An almost colorless sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate was obtained. The preparation of the pure compound (III) for conversion to the phenol (IV) may be done by crystallization from absolute ethyl alcohol with crystallization yields of approximately 90 percent to 95 percent.

The assumption by the German investigators that the 3-nitro isomer (VI) is formed is based on the claim that during the hydrolysis this isomer splits off the 3-nitro group as sodium nitrite. If this be true, one should be able to determine the nitrite ion quantitatively. A first attempt by potassium permanganate oxidation[18] failed because

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18. U.S.P. XIV, Mack Publishing Co., Easton, Pa., 1950, p. 557.

of the presence of a strong reducing agent, namely the sodium-2-nitro-4-chlorophenol-6-sulfonate formed in the hydrolysis. A method using titration against standard sulfanilamide[19] failed to detect any sodium nitrite. In order to verify this, the nitro group both before and after hydrolysis was reduced with zinc and hydrochloric acid, and the resultant amino group titrated by diazotization with standard sodium nitrite[20]. Results showed no loss of the nitro group during the hydrolysis and indicates that the German theory on this phase of the reaction is invalid.

There was also the possibility that the SO_3Na group was being hydrolyzed concomitantly with the chlorine to form 2,5-dichloro-3-nitro phenol. In this compound both chlorine atoms would be inactive, and this would account for the 73% maximum chlorine value. Such an explanation, however, is unsatisfactory, since analysis showed that the sulfite formed during hydrolysis was only 3.6% of the maximum theoretically possible.[20 (a)]

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19. U.S.P. XIV, Mack Publishing Co., Easton, Pa., 1950, p. 587.

20. Siggia, "Quantitative Organic Analysis via Functional Groups", John Wiley & Sons, New York, N.Y., 1949, p. 70-72.
(a) Determined by microanalytical gravimetric sulfate determination with barium chloride.

Experimental

Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III).-

In a one-liter, 3-neck round-bottom flask equipped with glass stirrer, 250 ml. dropping funnel, thermometer, and reflux condenser vented to a calcium chloride tube there was placed 147 g. (1 mole) of p-dichlorobenzene (Merck), and while agitating the crystals vigorously, there was added 400 g. (215 ml.) of fuming sulfuric acid (Merck Reagent, containing approximately 20 percent SO_3) during 15 minutes. The temperature rose gradually from 22° to 42°, then fell off. The mixture was then heated at 95° for two hours with an electric heating mantle forming a brown colored solution. The solution was allowed to cool slowly and stand at room temperature over night. The solid white crystalline mass which formed upon standing[21] was heated to 45°, and 85 g. (1 mole) of sodium nitrate (Merck Reagent) was added during 45 minutes with vigorous agitation, the temperature rising to 82°. The exothermic reaction at the beginning of the addition period necessitated cooling with an ice bath. The solution was orange in color with frothing at the surface. It was heated at 95° for two hours, forming a clear amber colored solution. The solution was then allowed to cool slowly and stand at room temperature over night. The orange colored thick crystalline mass was poured into approximately 3 liters of ice and water, and gave a yellow somewhat turbid solution. This was extracted with approximately 500 ml. of ethyl ether to remove a small amount of 2-nitro-1,4-dichloro-benzene that formed as a

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21. Contained 2.46% water by Karl Fischer titration.

byproduct of the reaction. The solution was then treated by either of the following procedures.

A. Conversion to Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) by the "liming out" procedure.- To the aqueous solution while agitating vigorously were added 265 g. (3.58 moles) of finely powdered calcium hydroxide (Merck U.S.P.) during 1 hour. The temperature rose steadily to 50° and the color of the solution changed from light yellow to light orange. After stirring an additional hour, the reaction mixture still gave an alkaline test to phenolphthalein indicator. The insoluble calcium sulfate cake was filtered off and extracted with 3.7 liters of boiling water for 30 hours. The filtrate and washings were combined and, while agitating vigorously, 21.6 g. (0.21 moles) of sodium carbonate (as an 18% aqueous solution) were added until a filtered sample of the reaction mixture did not give a precipitate when more sodium carbonate solution was added. The insoluble calcium carbonate was filtered off, and the orange colored filtrate concentrated to a volume of approximately 3 liters in vacuo (steam bath). This solution (3412 g.) contained 221 g. (75.2%) of the sulfonate (III).[22] (III) was not isolated as a solid but hydrolyses were run directly on aliquot portions of the solution. (Experiments 1, 2, and 3, Table I).

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22. Based on organic chlorine analysis of a solid residue aliquot of the solution.

B. Conversion to Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) by the "salting out" procedure.- To the aqueous solution while agitating vigorously was added 450 g. (7.7 moles) of sodium chloride. The product came out shortly as a thick white crystalline mass. It was filtered and dried by suction as completely as possible. The moist product was then dissolved in 2 liters of warm water, neutralized to pH 7 with 60 ml. of 30 percent sodium hydroxide, evaporated to dryness, and dried at 110°. 300 g. of the crude sulfonate (III) were obtained. Recrystallization from 4.6 liters of boiling absolute ethanol gave 109 g. (37.1%) of pure (III). Anal. Calcd. for $C_6H_2O_5Cl_2NSNa$: C, 24.50; H, 0.69; N, 4.76; Cl, 24.11. Found: C, 24.32; H, 1.02; N, 4.43; Cl, 24.34.

If, in the above crystallization, the hot ethanolic solution (4.5 liters) was first concentrated to a small volume and then allowed to slowly crystallize, there were formed 268 g. (91.2%) of pure (III). Anal. Calcd. for $C_6H_2O_5Cl_2NSNa$: N, 4.76; Cl, 24.11. Found: N, 4.66; Cl, 23.65.

The sulfonate (III) gave a sulfonamide, m.p. 144-147° and a p-toluidine salt, m.p. 249-250° (d). (Table VIII).

Hydrolysis procedure.- To a well stirred solution of 2.94 g. (0.01 mole) of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) in 45 ml. of water in a 125 ml. 3-neck round-bottom flask equipped with glass stirrer and reflux condenser there was added 1.6 g. (0.04 moles)[23] of sodium hydroxide

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23. This corresponds to a 100% molar excess.

pellets (Merck Reagent). The solution was heated at 95° for 4 hours by means of an electric mantle.[24] During the first ten minutes of heating the color of the solution changed from orange to deep red and remained that way throughout the hydrolysis. The amount of chlorine hydrolyzed at various time intervals was determined by titration (see Analytical Section, p. 55). Found: 0.258 g. chlorine (73%). This procedure gave the best yield of the phenol sulfonate (IV) and was used in preparing the material for subsequent reduction experiments. The sulfonate (IV) was never isolated as a solid, but its yield was based on the chlorine titration value. The other hydrolyses run are merely modifications of the above and are summarized in Tables I, II, III, and IV.

Fractional crystallization of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III).- Sixty and three-tenths grams of crude sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III)[25] were suspended in 600 ml. of boiling absolute ethyl alcohol and filtered. The orange colored filtrate was allowed to cool slowly, whereupon crystallization took place. It was then allowed to stand over night at 5°. The orange colored crystalline product was filtered off and dried in vacuo at room temperature. The first fraction (57.7% of total wt. of all fractions) weighed 17.0 g.

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24. The time of hydrolysis and percent excess of hydrolyzing agent was varied in many of the experiments.

25. Obtained by concentration of an aliquot of the aqueous solution of (III) in the "liming out" procedure.

Anal. Calcd. for $C_6H_2O_5Cl_2NSNa$: C, 24.50; H, 0.69; N, 4.76; Cl, 24.11. Found: C, 24.25; H, 0.80; N, 4.45; Cl, 24.34. The mother liquor from the first fraction was concentrated in vacuo (steam bath) to approximately three quarters of its original volume and chilled at 5° overnight. The crystalline product was filtered off and dried in vacuo at room temperature, giving 5.78 g. as the second fraction (19.6% of total wt. of all fractions). This procedure was repeated twice more, as above, giving 3.70 g. as the third fraction (12.6% of total wt. of all fractions) and 3.0 g. as the fourth fraction (10.1% of total wt. of all fractions). Fractions 1, 2, 3, and 4 were hydrolyzed as described above, but using a 25% excess of sodium hydroxide (see Table II).

Chromatography of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III).-

A. Five grams (0.017 mole) of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) were dissolved in 300 ml. of absolute ethanol and chromatographed through a 5 cm. O.D. column packed to a height of 4 cm. with Harshaw Alumina. The ethanol fixed the compound on the alumina. This was eluted with 400 ml. of methanol[26], and concentrated and dried in vacuo at room temperature. There was obtained 4.135 g. (82.6%) of an almost white nicely crystalline powder. This was hydrolyzed in the usual manner (Experiments 9 and 10, Table III).

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26. A small yellow band formed on top of the alumina.

B. Ten grams (0.034 mole) of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) was dissolved in 600 ml. of absolute ethanol and chromatographed through a 5 cm. O.D. column packed to a height of 8 cm. with Harshaw Alumina. The ethanol fixed the compound on the alumina. The column was eluted with 800 ml. of methanol[26] and the methanolic eluate chromatographed a second time through an identical column, finally washing the column with a small amount of methanol. The methanolic solution was concentrated in vacuo to dryness and the residue dried in vacuo at approximately 50°. There was obtained 6.6 g. (66%) of an almost white nicely crystalline powder. This was dydrolyzed in the usual manner (Experiments 11 and 12, Table III).

Recrystallization of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) from water.- Five grams (0.017 mole) of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) was dissolved in 20 ml. of boiling water and the clear solution chilled. The product came out heavily in nice crystalline form. This was filtered off and dried in vacuo at 50°. There was obtained 2.02 g. (40.2%) which was hydrolyzed according to standard procedure (Experiment 16, Table IV). The mother liquor of the above crystallization containing 2.98 g. (0.010 mole) of (III) was also hydrolyzed (Experiment 17, Table IV).

Part II

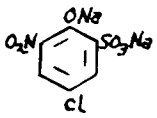
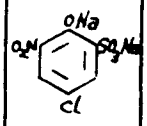
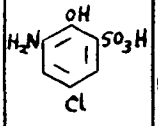
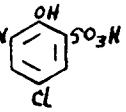
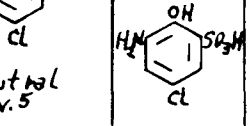
THE REDUCTION OF SODIUM-2-NITRO-4-CHLOROPHENOL-6-SULFONATE (IV) TO 2-AMINO-4-CHLOROPHENOL-6-SULFONIC ACID (V)

The study of the reduction of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV) to 2-amino-4-chlorophenol-6-sulfonic acid (V) was carried out using various reducing agents and conditions. The usual reducing agents sodium sulfide, sodium polysulfide, zinc and hydrochloric acid, and stannous chloride and hydrochloric acid were used in the first experiments. Catalytic hydrogenation was also undertaken since this is usually a clean method of reduction for aromatic nitro compounds. The catalysts palladium oxide, palladium on charcoal, Raney nickel, and platinum oxide were used. Results of the first experiments with inorganic reducing agents are summarized in Table V. Catalytic hydrogenations run on the alkaline side are summarized in Table VI, while those run on the acid side are summarized in Table VII. Hydrogenation rate curves are shown in Figures V, VI, VII, and VIII.

Table V

Reduction of Sodium-2-nitro-4-chlorophenol-6-sulfonate

with Inorganic Reducing Agents[1]

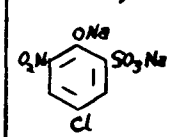
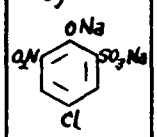
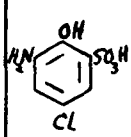
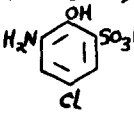
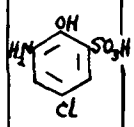
Moles of  used	Concentration of  (molarity)	(a) Reducing agent used (moles) (b) % Molar excess[6] (c) Molar concentration	T°C of Reduction	Time of reduction, hours	% yield[2] of 	Purity of  (a) Neutral equiv.[5] (b) Titration against NaOH (c) Diazotization	% Overall yield[3] of 
0.011 Exp't. 18	0.164	(a) $Na_2S.9H_2O$ (0.038) (b) 70.0 (c) 0.42	100	6	Unable to isolate product[4]		
0.006 Exp't. 19	0.140	(a) Na_2S_2 (0.011) (b) 75 (c) 0.24	100	6	17.4	(a) 217 (b) 100 (c) 99.2	10
0.007 Exp't. 20	0.081	(a) Zinc (0.032)[7] HCl (0.47) (b) Zinc, 43; HCl, 970 (c) Zinc (0.350) HCl (5.20)	5-10	1	57.3	(a) 220 (b) 100 (c) 94	38.2
0.007 Exp't. 21	0.121	(a) Zinc (0.045)[7] HCl (012) (b) Zinc, 104; HCl, 172 (c) Zinc (0.742) HCl (1.99)	0-10	36	36.8	(a) 216 (b) 100 (c) 100	24.6
0.007 Exp't. 22	0.067	(a) $SnCl_2.2H_2O$ (0.060) HCl (0.070) (b) $SnCl_2.2H_2O$, 173 HCl, 1480 (c) $SnCl_2.2H_2O$ (0.545) HCl (6.33)	0-10	48	80.7	(a) 210 (b) 100 (c) 92	53.8

1. All reductions run in aqueous medium.
2. Based on sodium-2-nitro-4-chlorophenol-6-sulfonate(IV). The yield of (IV) was 73% in all the Expt's cited in Tables V,VI,VII, except in Exp't. 19, Table V, where the yield of (IV) was 63%.
3. Based on p-dichlorobenzene.
4. Extraction of the crude reduction product with $NaHCO_3$ and attempted precipitation of the acid with concentrated HCl or HCl gas resulted only in the formation of NaCl; extraction of the crude reduction product with boiling methyl alcohol extracted mostly sulfur.
5. Theory is 223.6.
6. Based on stoichiometric equation.
7. Here expressed as gram-atoms.

Table VI

Reduction of Sodium-2-nitro-4-chlorophenol-6-sulfonate

by Catalytic Hydrogenation in Alkaline Medium[1]

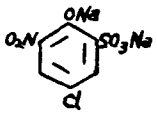
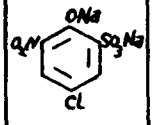
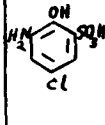
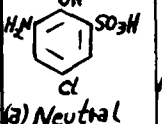
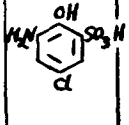
Moles of  used	Concentration of  (molarity)	Catalyst used	Ratio: wt. of catalyst / wt. of cmpd.	Time of reduction, hours	Moles of hydrogen uptake[6]	pH	% Yield[2] of 	Purity of  (a) Neutral equiv.[5] (b) Titration against NaOH (c) Diazotization	% Overall yield[3] of 
0.007 Exp't. 23	0.163	Palladium oxide	0.136	5.5	2.30	10 to 12	Isolated product of unknown structure[4]		
0.007 Exp't. 24	0.163	Raney nickel	0.136	5	2.00	10 to 12	37.7	(a) 220 (b) 100 (c) 100	25.2
0.007 Exp't. 25	0.163	5% Palladium on charcoal	0.136	6.5	2.64	10 to 12	76.8	(a) 222 (b) 100 (c) 99.5	51.2
0.007 Exp't. 26	0.163	Platinum oxide	0.136	6.8	1.73	10 to 12	80.0	(a) 223 (b) 100 (c) 100	53.3
0.099 Exp't. 27	0.168	5% Palladium on charcoal	0.139	5.5	2.36	10 to 12	80.3	(a) 222 (b) 100 (c) 99.8	53.5

1. All reductions run in aqueous medium at room temperature (25°C).
2. Based on sodium-2-nitro-4-chlorophenol-6-sulfonate(IV).
3. Based on p-dichlorobenzene.
4. The product dissolved readily in dilute $NaHCO_3$ solution, but could not be re-precipitated with dilute HCl; qualitative test for elements indicated Nitrogen, Sulfur, and Chlorine present; the compound had a neutral equivalent of 845.
5. Theory is 223.6.
6. Corrected for blank.

Table VII

Reduction of Sodium-2-nitro-4-chlorophenol-6-sulfonate

by Catalytic Hydrogenation in Acid Medium[1]

Moles of  used	Concentration of  (molality)	Catalyst used	Ratio: wt. of catalyst / wt. of cmpd.	Moles of HCl used	Time of reduction, hours	Moles of hydrogen uptake[5]	pH	% yield[2] of 	Purity of  (a) Neutral equiv.[3] (b) Titration against NaOH (c) Diazotization	% Overall yield[4] of 
0.007 Exp't. 28	0.153	5% Palladium on charcoal	0.136	0.035	7	1.9	3.0	83.0	(a) 212 (b) 100 (c) 100	55.2
0.007 Exp't. 29	0.133	Palladium oxide	0.136	0.116	27	1.5	1.0	70.6	(a) 224 (b) 99.5 (c) 100	47.1
0.007 Exp't. 30	0.113	5% Palladium on charcoal	0.136	0.232	48	0.382	1.0	unable to isolate product		
0.007 Exp't. 31	0.153	Platinum oxide	0.136	0.035	7	2.57	3.5	49.1	(a) 222 (b) 100 (c) 100	32.8

1. All reductions run in aqueous medium at room temperature (25°C).
2. Based on sodium-2-nitro-4-chlorophenol-6-sulfonate(IV).
3. Theory is 223.6.
4. Based on p-dichlorobenzene.
5. Corrected for blank.

Figure V

Hydrogenation Rates of Sodium-2-nitro-4-chlorophenol-6-sulfonate

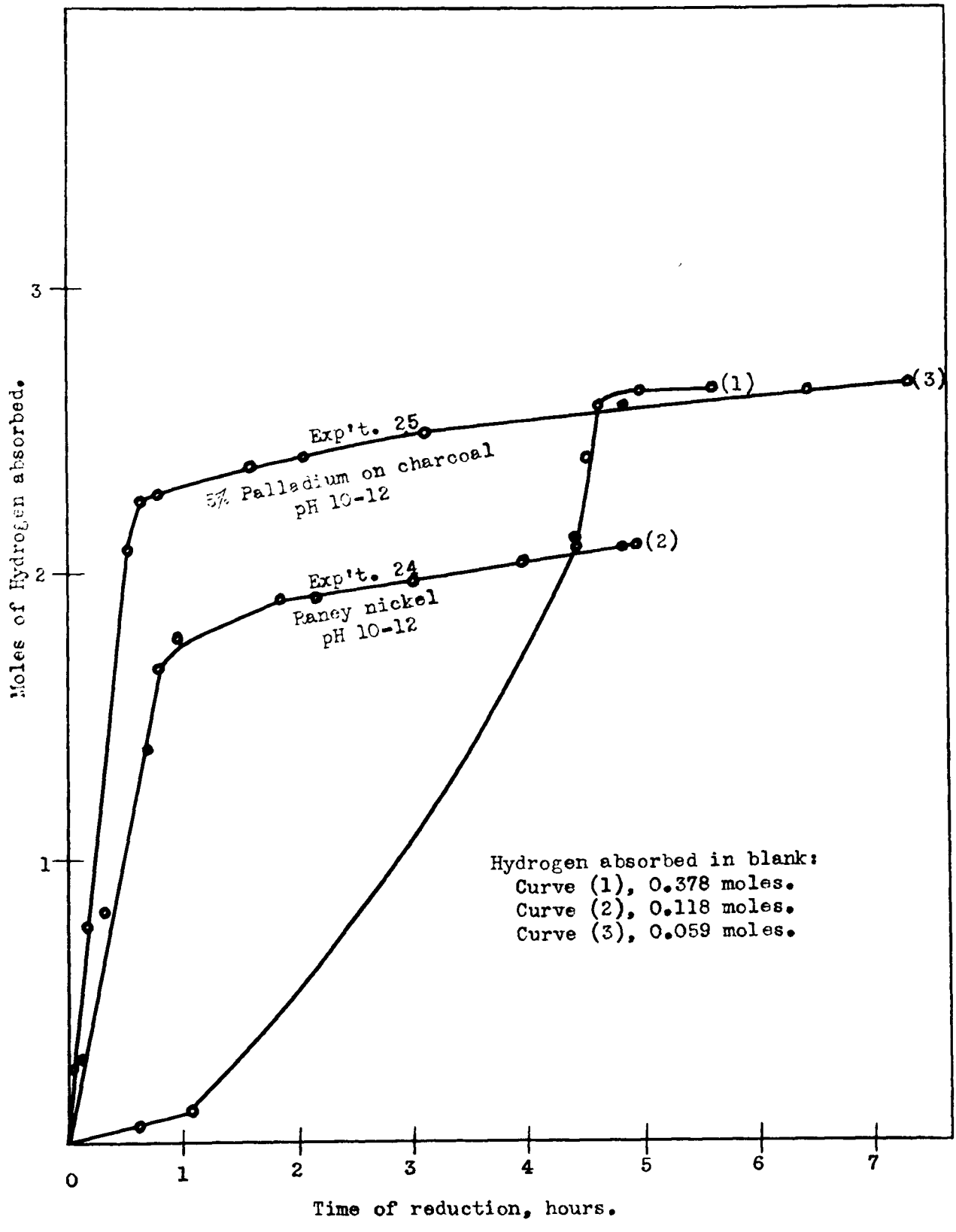


Figure VI

Hydrogenation Rates of Sodium-2-nitro-4-chlorophenol-6-sulfonate

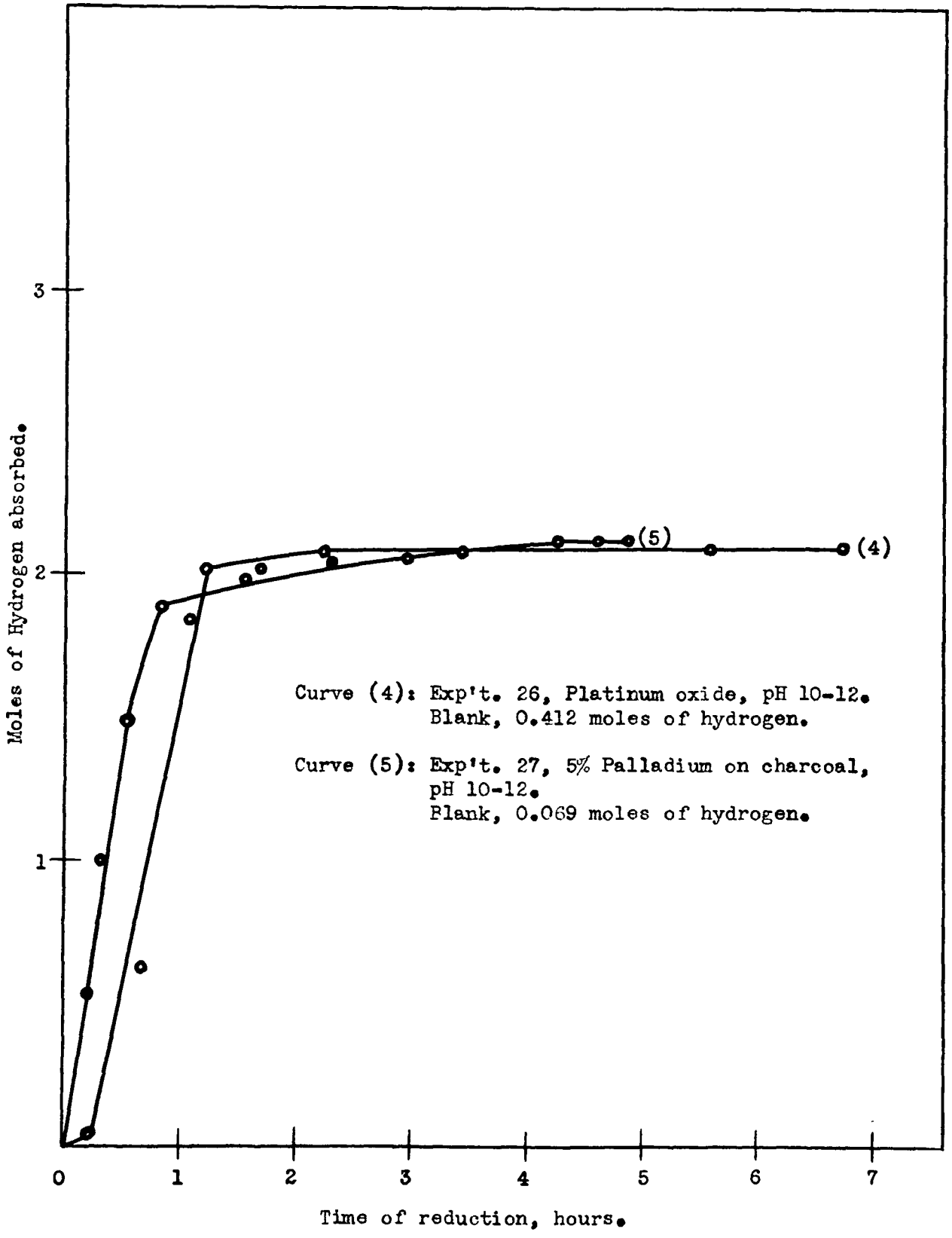


Figure VII

Hydrogenation Rates of Sodium-2-nitro-4-chlorophenol-6-sulfonate

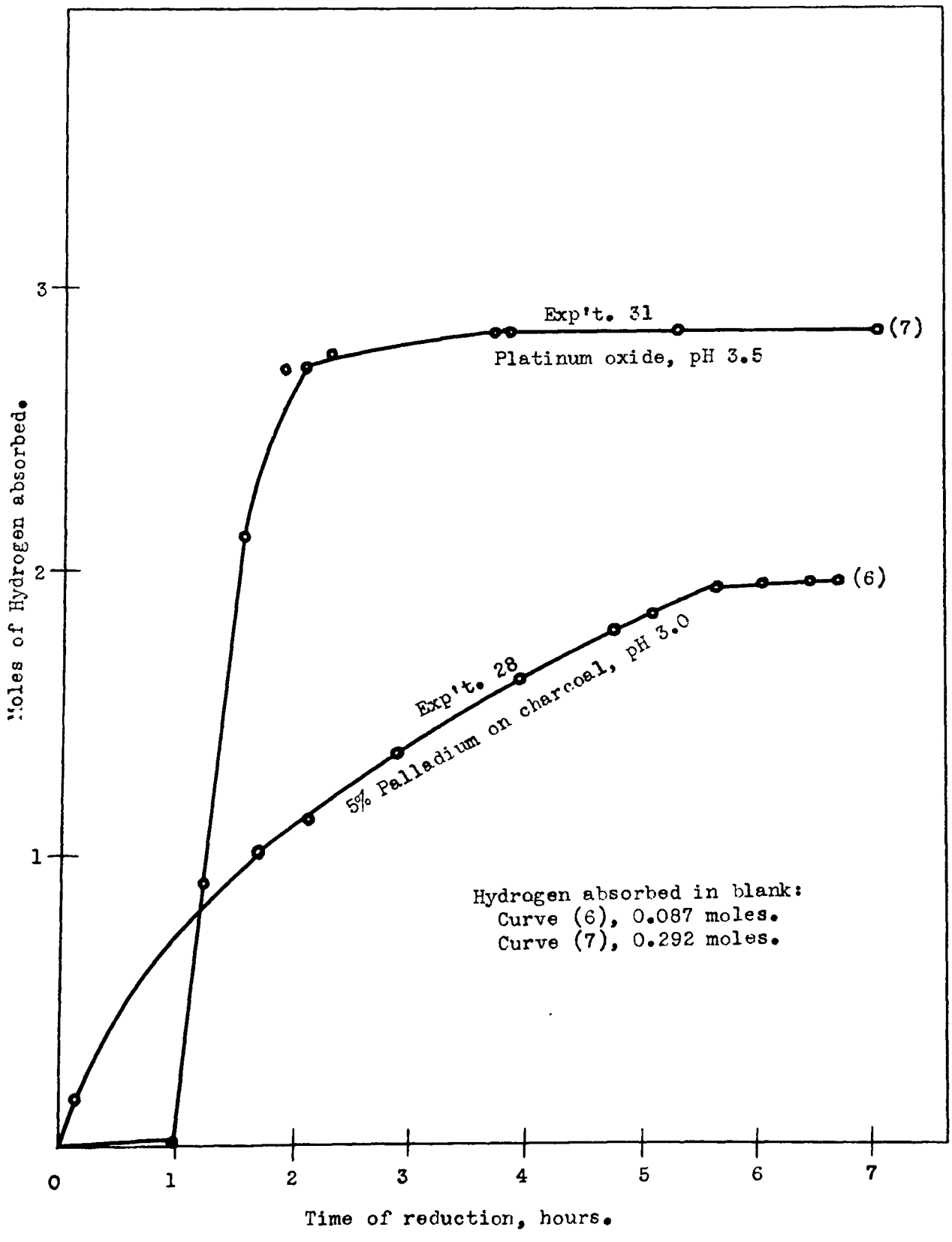
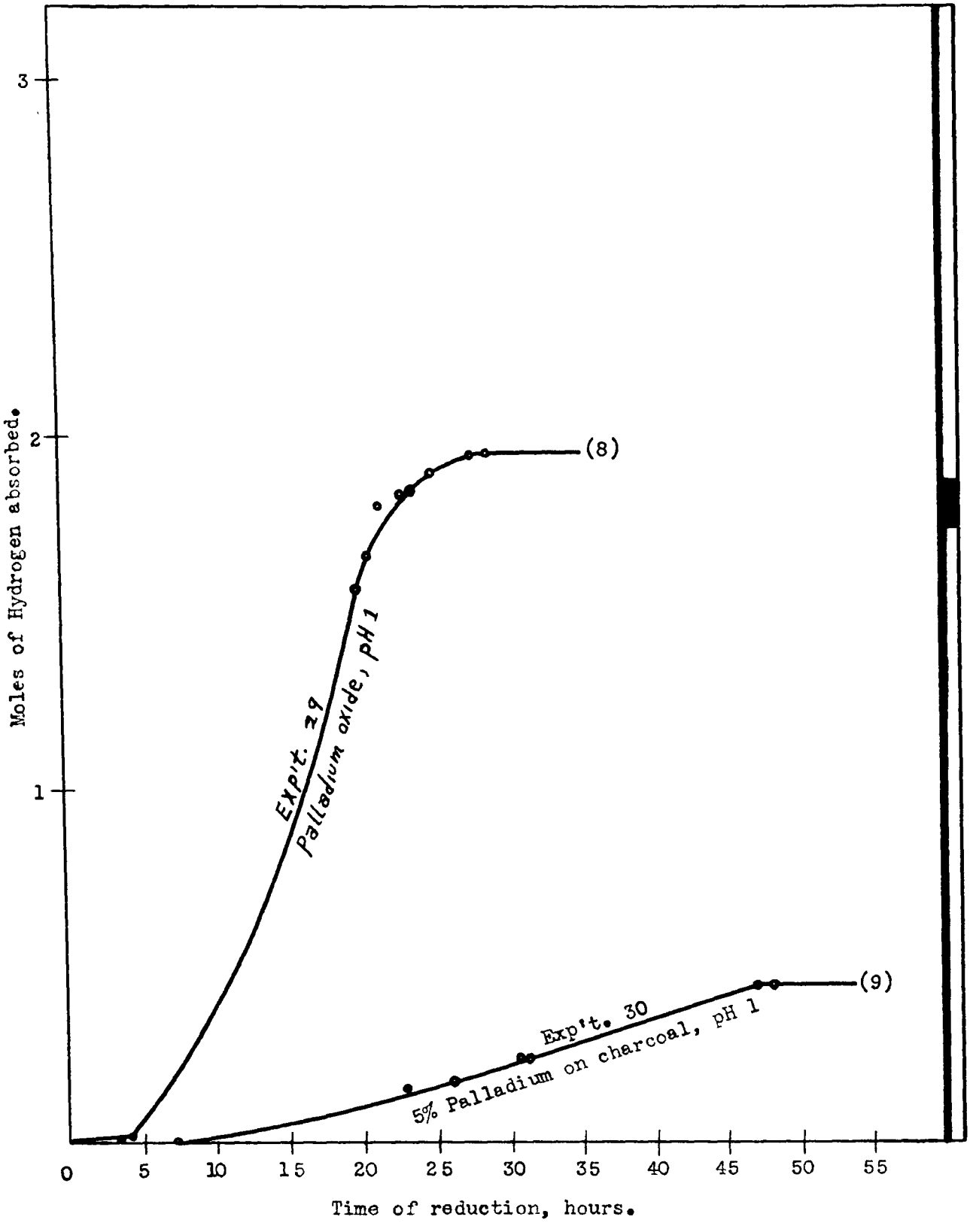


Figure VIII

Hydrogenation Rates of Sodium-2-nitro-4-chlorophenol-6-sulfonate



Of the inorganic reducing agents, stannous chloride and hydrochloric acid when present in large excess over a long reduction period at low temperature produced the highest yield (80.7%) of the amino sulfonic acid (V), while zinc and hydrochloric acid, when present in favorable concentration, give a fair yield (57.3%), (Experiments 20 and 22, Table V). The use of a large molar excess of zinc and a smaller excess of hydrochloric acid than in Experiment 20 resulted in a poor yield (36.8%) of (V) even over a much longer reduction period (Experiment 21, Table V).

High temperatures employing sodium sulfide or sodium polysulfide seemed definitely unfavorable; in the former case resisting efforts to isolate a product, while in the latter case a product was isolated with difficulty and in very poor yield (17.4%), (Experiments 18 and 19, Table V).

Catalytic hydrogenation affords a smooth, though some what more expensive, method of reducing the sodium-2-nitro-4-chlorophenol-6-sulfonate (IV) to the 2-amino-4-chlorophenol-6-sulfonic acid (V). Platinum oxide and 5% palladium on charcoal are excellent catalysts at a highly alkaline pH with yields of 80 percent and 80.2 percent respectively (Experiments 25, 26, 27, Table VI). Hydrogen absorption is rapid within the first hour and is completed in approximately 4 to 5 hours for the palladium on charcoal catalyst, while for the platinum oxide catalyst the limit is reached within approximately 2 hours (Curve 3, Figure V, and Curves 4 and 5, Figure VI). Raney nickel afforded a poor

yield (37.7%) of compound (V), (Experiment 24, Table VI). Hydrogen absorption was rapid within the first hour in this case, reaching its limit in approximately 5 hours (Curve 2, Figure 5). Palladium oxide at a highly alkaline pH is detrimental to the formation of compound (V), since, after the hydrogenation period, when the reduction mixture was exposed to air, immediate deep coloration took place indicating some kind of oxidation, and the isolated product was not the desired one (Experiment 23, Table VI). Hydrogen absorption in this instance was gradual within the first 4½ hours and was completed within approximately 5 hours (Curve 1, Figure V).

In hydrogenations employing an acidic medium the pH seems to have definite influence on the rate and molar absorption of hydrogen. Palladium on charcoal at a pH of 3 affords a good yield (83%) of compound (V) comparable to that on the alkaline side. Hydrogen absorption was gradual within the first 5½ hours and reached its limit in approximately 7 hours (Experiment 28, Table VII, and Curve 6, Figure VII). When the amount of hydrochloric acid was increased approximately 500% and the pH lowered to 1 a product could not be isolated. Hydrogen absorption was not observable before 7 hours and required about 47 hours for completion. The molar uptake of hydrogen was very low (Experiment 30, Table VII, and Curve 9, Figure VIII).

However, a good yield (70.6%) of compound (V) was experienced at a pH of 1 using palladium oxide even though the time of reduction was rather long. Hydrogen absorption started

after 4 hours gradually reaching its limit after approximately 25½ hours (Experiment 29, Table VII, and Curve 8, Figure VIII). It is to be recalled that use of the same catalyst at a highly alkaline pH did not give the desired amino phenolsulfonic acid (V), (compare Experiment 23, Table VI). Platinum oxide at a pH of 3.5 afforded a fair yield (49.1%) of (V). Hydrogen absorption did not start until after the first hour, increased rapidly in the next hour, and finally reached its peak within approximately 4 hours (Experiment 31, Table VII, and Curve 7, Figure VII). Platinum oxide on the alkaline side gave a better yield of (V), (compare Experiment 26, Table VI).

Experimental

Reduction of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV) to 2-amino-4-chlorophenol-6-sulfonic acid (V).-

A. Reduction procedure with inorganic reducing agents.[27]

1. Conversion of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV) to 2-amino-4-chlorophenol-6-sulfonic acid (V) with stannous chloride and hydrochloric acid.- The well stirred cooled solution (10°) after the hydrolysis containing 2.18 g. (0.007 mole) of the sodium-2-nitro-4-chlorophenol-6-sulfonate (IV)[28] was neutralized with 5 ml. of concentrated hydrochloric acid. Then a solution of 13.5 g. (0.060 mole) of stannous chloride.$2H_2O$ (Merck Reagent) in 60 ml. (25.4 g., 0.070 mole) of concentrated hydrochloric acid was added. After stirring for a half hour between 5 and 10° C the compound started to crystallize out. Stirring was continued for another hour. Then the reaction mixture was placed in the refrigerator for approximately 46 hours. The product was filtered off, washed with a small amount of ice cold water, and dried in vacuo at 50°. A yield of 1.315 g. (80.7%) of 2-amino-4-chlorophenol-6-sulfonic acid (V), a buff colored crystalline powder was obtained. Its purity was

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27. To obtain the maximum yield of the phenol sulfonate (IV) the hydrolysis procedure as described in the experimental part (p. 27) was followed throughout. (IV) was never isolated as a solid compound but the reductions were run directly on the hydrolysis mixture.

28. Determined by chloride titration, corresponding to a 73% yield of (IV).

determined by titration against standard sodium hydroxide and against sodium nitrite (see the Analytical Section and Experiment 22, Table V).

2. Conversion of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV) to 2-amino-4-chlorophenol-6-sulfonic acid (V) with zinc and hydrochloric acid.- The well-stirred and cooled solution (10°) after the hydrolysis containing 2.18 g. (0.007 mole) of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV)[28] was neutralized with 5 ml. of concentrated hydrochloric acid. Then there was added 45 ml. (17.2 g., 0.47 mole) of concentrated hydrochloric acid, and to this slowly with vigorous stirring 2.06 g. (0.032 mole) of zinc dust (Merck Reagent). After approximately a half hour the product started to crystallize out. Stirring was continued for an additional half hour until all of the zinc was dissolved. The product was filtered off, washed with a small amount of ice cold water, and dried in vacuo at 40°. The product was 0.840 g. (51.5%) of 2-amino-4-chlorophenol-6-sulfonic acid (V), a tan colored crystalline powder. Upon standing in the refrigerator for some time the mother liquor yielded 0.095 g. more of the same crystalline powder. This brought the total yield to 57.3%. Its purity was determined by titration against standard sodium hydroxide and sodium nitrite (see Analytical Section and Experiment 20, Table V).

A similar experiment in which the molar concentration of the zinc was increased and that of the hydrochloric acid decreased resulted in a lowering of the yield of (V), (Experiment 21, Table V).

3. Conversion of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV) to 2-amino-4-chlorophenol-6-sulfonic acid (V) with sodium polysulfide.- To the solution after the hydrolysis containing 1.87 g. (0.006 mole) of the sodium-2-nitro-4-chlorophenol-6-sulfonate (IV)[29] was added 1.21 g. (0.011 mole) of sodium polysulfide[30] and refluxed for 6 hours at 100° forming a dark green solution. The solution was then cooled to 10° and 20 ml. of concentrated hydrochloric acid added until the solution had a pH of 1. A grayish-yellow solid came out shortly. The stirring was continued for an additional hour, and the material was placed in the refrigerator over night. The precipitate was filtered off and air-dried obtaining 1.08 g. of a green colored product. This solid was extracted with 30 ml. of boiling water, the filtrate decolorized with norite, and chilled. The product came out in beautiful almost white patelets. It was filtered and dried in vacuo at 50°. There was obtained 0.245 g. (17.4%) of 2-amino-4-chlorophenol-6-sulfonic acid (V). The purity was determined by titration against standard sodium hydroxide and against sodium nitrite (see Analytical Section and Experiment 19, Table V).

A similar experiment utilizing sodium sulfide was unsuccessful (Experiment 18, Table V).

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29. A yield of 63% of (IV).

30. Prepared in the usual manner from sodium sulfide and sulfur.

B. Reduction procedure with catalytic hydrogenation.[27]

The apparatus used in all of the following hydrogenations is essentially the same as one designed and employed in the hydrogenation laboratory of Merck & Co., Inc., Rahway, N.J. It consists of a pressure tank filled with hydrogen, connected to a calibrated gauge, and thence to the shaker bottle containing the catalyst and solution which is continually agitated by a motor. The moles of hydrogen taken up are determined from the drop in pressure (lbs.) registered by the gauge. All the hydrogenations were run at room temperature (24-25° C) at an initial pressure of approximately 45 lbs/sq.in. The palladium oxide, palladium on charcoal, Raney nickel, and platinum oxide catalysts were obtained from this laboratory.

1. Catalytic hydrogenation of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV) to 2-amino-4-chlorophenol-6-sulfonic acid (V) with 5% palladium on charcoal at a highly alkaline pH.- To the cooled solution (25°) after the hydrolysis containing 2.18 g. (0.007 mole) of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV)[28] was added 0.297 g. of 5% palladium on charcoal catalyst and hydrogenated to completion using the apparatus described above. The uptake of hydrogen in approximately 6½ hours was 2.64 moles (see Curve 3, Figure V). The catalyst was filtered off from the dark solution and 10 ml. of concentrated hydrochloric acid were added to the filtrate which then turned deep maroon in color (pH1). The filtrate was chilled and the product crystallized out in beautiful prisms. This was placed in the refrigerator for several hours, the product filtered off and washed with a small amount of ice cold water. It was dried in vacuo at 50°

giving 0.800 g. (49.2%) of 2-amino-4-chlorophenol-6-sulfonic acid (V) as beautiful tan colored shining platelets. Concentration of the mother liquor in vacuo (steam bath) to approximately one third volume yielded 0.450 g. more of less crystalline product. This brought the total yield to 76.8%. Its purity was determined by titrations against standard sodium hydroxide and against sodium nitrite (see Analytical Section and Experiment 25, Table VI).

In an experiment as above on a larger scale, a yield of 80.2% of (V) was obtained (Experiment 27, Table VI). Purity of the product was determined by microanalysis:

Anal. Calcd. for $C_6H_6O_4ClNS$: C, 32.22; H, 2.70; N, 6.26; Cl, 15.85. Found: C, 31.98; H, 3.00; N, 6.52; Cl, 15.58.

The 2-amino-4-chlorophenol-6-sulfonic acid (V) gave an acetyl derivative, m.p. 135-137°(d); a benzoyl derivative, m.p. 289-291°; and a p-toluidine salt, m.p. 267-268°(d), (see Table VIII). It also gave a deep red color with ferric chloride, reduced Tollen's reagent at room temperature, and reduced both Fehling's solution and dilute potassium permanganate with warming.

Catalytic hydrogenations with palladium oxide, Raney nickel, and platinum oxide were run, using the same procedure as described above. Results are summarized in Table VI.

2. Catalytic hydrogenation of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV) to 2-amino-4-chlorophenol-6-sulfonic acid (V) with 5% palladium on charcoal in acidic medium.- To the cooled solution (25°) after the hydrolysis containing 2.18 g. (0.007 mole) of sodium-2-nitro-4-chlorophenol-6-sulfonate (IV)[28] was added 3 ml. (1.27 g., 0.035 mole) of concentrated hydrochloric acid to pH 3 and 0.297 g. of 5% palladium on charcoal catalyst. The hydrogenation was run to completion, using the apparatus described above. The uptake of hydrogen in approximately 7 hours was 1.9 moles (Curve 6, Figure VII). To the hydrogenation mixture (yellow supernatant liquor) was then added 50 ml. of 5% sodium bicarbonate solution to pH 7. The solution turned quite dark. It was filtered from the catalyst and 10 ml. of concentrated hydrochloric acid were added to the filtrate until a pH of 1 was reached, at which time the solution turned deep amber. The solution was chilled, and the product crystallized out shortly as long needles. It was placed in the refrigerator over night, and the product filtered off and washed with a small amount of ice cold water and dried in vacuo at 50°. The yield was 0.675 g. (41.4%) of 2-amino-4-chlorophenol-6-sulfonic acid (V) as tan colored triclinic needles. Concentration of the mother liquor in vacuo (steam bath) to approximately one third volume yielded 0.423 g. more of a less crystalline product. This brought the total yield to 83%. Its purity was determined by titrations against standard sodium hydroxide and against sodium nitrite (see Analytical Section and Experiment 28, Table VII).

Catalytic hydrogenations with palladium oxide at pH 1, palladium on charcoal at pH 1, and platinum oxide at pH 3.5 were run, using the same procedure as described above, except that the molar quantity of hydrochloric acid in the experiments varied (see Table VII). The final isolation of the product in Experiment 31 (platinum oxide) was unusual in that the catalyst was filtered off at pH 3.5, avoiding the addition of sodium bicarbonate, and the product crystallized by adding the usual amount of concentrated hydrochloric acid.

Part III

THE PREPARATION OF DERIVATIVES OF SODIUM-2-NITRO-1,4-DICHLORO-BENZENE-6-SULFONATE (III) AND 2-AMINO-4-CHLOROPHENOL-6-SULFONIC ACID (V)

Since the purity of the compounds used in the course of this investigation could not be determined by melting point and since the literature does not list any derivatives, it was deemed worthwhile to characterize the intermediate sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) and the final product 2-amino-4-chlorophenol-6-sulfonic acid (V) by preparing solid crystalline derivatives with melting points. The acetyl and benzoyl derivatives and the p-toluidine salt of (V) were prepared, along with the sulfonamide and p-toluidine salt of (III).[31] The results are summarized in Table VIII.

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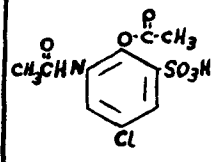
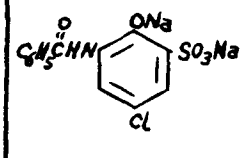
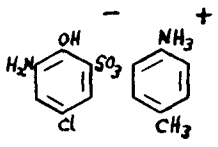
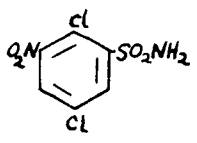
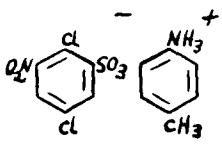
31. Attempts to prepare the sulfonamide, methyl ether, and chloroacetyl derivatives of (V) in the usual manner failed.

Table VIII

Derivatives of 2-Amino-4-chlorophenol-6-sulfonic acid

and Sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate

Name of Compound	Structural Formula	Molecular Formula	Molecular Weight	M.p., °C[1]	Carbon, %		Hydrogen, %		Nitrogen, %		Acetyl, %	
					Calcd.	Found	Calcd.	Found	Calcd	Found	Calcd	Found
1-Acetoxy-2-acetamido-4-chloro-benzene-6-sulfonic acid		$C_{10}H_{10}O_6ClNS$	307.72	135/37 (dec.)	39.03	38.87	3.28	3.08			27.98	27.73
Sodium-2-benzamido-4-chloro-phenol-6-sulfonate		$C_{13}H_8O_5ClNSNa_2$	371.74	289/91	42.00	41.76	2.17	2.42	3.77	3.79		
p-toluidine salt of 2-amino-4-chlorophenol-6-sulfonic acid		$C_{13}H_{15}O_4ClN_2S$	330.78	267/68 (dec.)	47.20	46.89	4.57	4.76	8.47	8.22		
2-Nitro-1,4-dichloro-benzene-6-sulfonamide		$C_6H_4O_4Cl_2N_2S$	271.12	144/47	26.58	26.28	1.49	1.48	10.33	10.13		
p-toluidine salt of 2-nitro-1,4-dichloro-benzene-6-sulfonic acid		$C_{13}H_{12}O_5Cl_2N_2S$	379.22	249/50 (dec.)	41.17	41.38	3.19	3.48	7.39	7.13		

1. All melting points were taken with an Anschutz (immersion) thermometer.

Experimental

1-Acetoxy-2-acetamido-4-chloro-benzene-6-sulfonic acid.-[32]

A half gram (0.002 mole) of 2-amino-4-chlorophenol-6-sulfonic acid (V) was suspended in 5 ml. of acetic anhydride (Merck Reagent) and 3 drops of concentrated sulfuric acid added. This mixture was then heated on the steam bath for a few minutes. It gave a clear, slightly yellow, colored solution. The solution was allowed to stand at room temperature over night, then diluted with 10 ml. of water and again allowed to stand for several hours. The solution was then concentrated in vacuo (steam bath) to a thick syrup which gradually crystallized on standing at room temperature. Upon drying in vacuo over night there was obtained 0.556 g. of a crude, somewhat gummy, almost white product; m.p. 131.5-134°(d). This crude product was purified by dissolving in 2 ml. of a 1:1 boiling ethyl acetate-methanol mixture, using norite to clarify, then cooling to room temperature. To the filtered clear solution was then added 40 ml. of ethyl acetate, whereupon the product came out as an oil, but gradually crystallized upon chilling and scratching. It was allowed to crystallize further in the refrigerator for several hours, filtered off, washed well with ethyl ether, and air-dried at room temperature. The yield was 0.2 g. (29.1%) of white crystals, m.p. 135-137°(d). The structure was proven by microanalysis (see Table VIII).

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32. This is a modification of the standard acetylation procedure as described in Fieser, "Experiments in Organic Chemistry", D. C. Heath & Co., New York, N.Y., Second Edition, 1941, p. 165.

Sodium-2-benzamido-4-chlorophenol-6-sulfonate.-[33] One gram (0.005 mole) of the 2-amino-4-chlorophenol-6-sulfonic acid (V) was dissolved in 20 ml. of 10% sodium hydroxide, and 2 ml. of benzoyl chloride were added in portions with vigorous shaking. The reaction mixture warmed up to approximately 50°, and the product separated as fine yellow needles. It was filtered off and recrystallized from 1.5 ml. of boiling absolute ethyl alcohol. There was obtained 0.475 g. (28.6%) of small yellow needles, m.p. 289-291°. The structure was proven by microanalysis (see Table VIII).

p-Toluidine salt of 2-amino-4-chlorophenol-6-sulfonic acid.-[33(a)] Three-tenths of a gram (0.001 mole) of 2-amino-4-chlorophenol-6-sulfonic acid (V) were dissolved in 6 ml. of boiling water. To this solution was then added 0.3 g. (0.003 mole) of p-toluidine and 2 ml. of concentrated hydrochloric acid. The resultant, almost colorless, clear solution was chilled and the product crystallized out. The compound was filtered and recrystallized from a minimum amount of boiling water and gave 0.2 g. (45%) of white crystals, m.p. 267-268°(d). The structure was proven by microanalysis (see Table VIII).

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33. The Schotten-Baumann reaction, Shriner & Fuson, "The Identification of Organic Compounds", John Wiley & Sons, Inc., New York, N.Y., 3rd Edition, 1948, p. 88.
(a) ibid, p. 216; (b) ibid., p. 216; (c) ibid., p. 216.

2-Nitro-1,4-dichloro-benzene-6-sulfonamide.-[33(b)]

One gram (0.004 mole) of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) was intimately mixed with 2.5 g. of phosphorous pentachloride (Merck Reagent) and heated at 150° for 30 minutes. To the cooled mixture was then added 25 ml. benzene. It was boiled for a few minutes, and filtered. The benzene filtrate was cooled, washed with 50 ml. water and dried (drierite). It was concentrated in vacuo (steam bath) to a yellow oil which refused to crystallize. This oil was redissolved in 10 ml. of benzene and added dropwise to a rapidly stirred solution of 20 ml. of concentrated ammonium hydroxide. The aqueous ammoniacal phase was separated from the benzene phase and concentrated in vacuo (steam bath) to dryness. It gave 0.650 g. of crude yellow crystalline product, m.p. 135-145° (containing chloride). This crude compound was purified by continuously extracting it in a Soxhlet extractor with 250 ml. of chloroform for fourteen hours.[34] The chloroform extract was concentrated in vacuo (steam bath) to dryness and finally flushed with ethyl ether. Obtained 0.475 g. (51.5%) of a yellow crystalline powder, m.p. 144-147°. The structure was proven by microanalysis (see Table VIII).

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34. Recrystallization was not possible because of the insolubility of the compound in all organic solvents in which the sodium chloride formed was also insoluble.

p-Toluidine salt of 2-nitro-1,4-dichloro-benzene-6-sulfonic acid.-[33(e)] One gram (0.004 mole) of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) was dissolved in 4 ml. of boiling water. To this solution was then added 0.5 g. (0.005 mole) of p-toluidine and 2 ml. of concentrated hydrochloric acid. A precipitate formed at this time, so 1 ml. more of concentrated hydrochloric acid was added and the volume increased to approximately 50 ml. with boiling water. A clear yellow solution was obtained. The solution was chilled and the product crystallized out. The product was filtered off, yielding 0.995 g. of fine yellow needles, m.p. 244-245°(d). The crude compound was purified from 30 ml. boiling water, giving 0.550 g. (34.2%) of fine yellow needles, m.p. 249-250°(d). The structure was proven by microanalysis, (see Table VIII).

Analytical

1. Determination of chlorine hydrolyzed in the conversion of sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (III) to sodium-2-nitro-4-chlorophenol-6-sulfonate (IV).- The method used was a modified Volhard titration with silver thiocyanate, using ferric alum as an indicator[16] The total weight of the hydrolysis mixture (see p. 28) was first determined, then aliquots (usually 1/100th of this) were taken, either during time intervals or at the end of the hydrolysis. These were cooled to room temperature in a small tared flask, and accurately weighed. The sample was then transferred to a 250 ml. Erlenmeyer flask and diluted to approximately 150 ml. with distilled water. Enough pure nitric acid (Merck Reagent) was added to make the solution acid and about 5 ml. excess. Five ml. of nitro-benzene and approximately 25 ml. of standard tenth normal silver nitrate were then added and the mixture shaken until spongy flakes of silver chloride were obtained. The mixture was then titrated with tenth normal ammonium thiocyanate after adding ferric alum indicator, which gave the sharp characteristic reddish-brown end point of ferric thiocyanate. From this it was possible to calculate the degree of hydrolysis.

2. Determination of the neutral equivalent and purity of 2-amino-4-chlorophenol-6-sulfonic acid (V) by titration with standard sodium hydroxide.-[35] A sample of the acid (about 0.1 g.) was weighed accurately and dissolved in approximately 200 ml. of water (warming if necessary to dissolve all of the compound). This solution was then titrated with standardized tenth normal sodium hydroxide, phenolphthalein being used as the indicator. The neutral equivalent of the acid is calculated according to the formula

$$\text{Neutral equivalent} = \frac{\text{wt. of sample (g)} \times 1000}{\text{volume of alkali (ml.)} \times \text{Norm.}}$$

The purity of the acid is calculated according to the formula

$$\% \text{ purity} = \frac{\text{ml. of alkali} \times \text{Norm.} \times \text{milli equiv. wt. of compound} \times 100}{\text{wt. of sample (g)}}$$

3. Determination of the purity of 2-amino-4-chlorophenol-6-sulfonic acid (V) by titration with standard sodium nitrite.- Siggia's method[20] for the diazotization of amines was used. A sample of the acid (about 0.1 g.) was accurately weighed and dissolved in about 200 ml. of water in a 1 liter beaker. Thirty ml. of concentrated hydrochloric acid and enough chopped ice were then added to bring the volume up to about 500 ml. When the temperature was about 5°, the tip of the burette was placed well below the surface of the solution and tenth-normal standard sodium nitrite solution added

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35. Shriner & Fuson, "The Identification of Organic Compounds", John Wiley & Sons, Inc., New York, N.Y., 3rd Edition, 1948, p. 129.

dropwise while agitating intermittently with a glass rod. The end point was taken as the point at which the blue-black color was produced on the starch-iodide paper when the solution had stood for some time. The purity of the acid is calculated according to the formula

$$\% \text{ purity based on diazotization} = \frac{\text{ml. of nitrite} \times \text{Norm.} \times \text{milli equiv. wt. of compound} \times 100}{\text{wt. of sample (g)}}$$

SUMMARY

Summary

The work described in this thesis was undertaken with the view of exploring a reaction sequence suggested by early French investigators to synthesize 2-amino-4-chlorophenol-6-sulfonic acid especially in reference to the German claim that a low yield of product would result following this preparation. In particular, a successful application of this procedure would afford a relatively direct and inexpensive route to the sulfonic acid which is used as an azo dyestuff intermediate and could possibly find application in medicinal chemistry.

It was found that sulfonation and nitration of p-dichlorobenzene gave a high yield of the sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate (91%) when using the "salting out" procedure. Rate studies on the hydrolysis of this product indicate that high purity of the sulfonate as well as concentration and strength of base are essential for conversion to the sodium-2-nitro-4-chlorophenol-6-sulfonate. Use of a pure starting material afforded a substantial increase in yield (10-20%) over use of crude sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate. Purification may be accomplished by recrystallization from absolute ethanol. A ratio of four moles of sodium hydroxide per mole of the sodium-2-nitro-1,4-dichloro-benzene-6-sulfonate in aqueous medium gave the maximum yield of the sodium-2-nitro-4-chlorophenol-6-sulfonate (73%) during four hours at a temperature of 95°. This was in contrast to the German claim of a preponderance of their undesired

"3-nitro isomer" along with the formation of sodium nitrite which could not be detected by several analytical methods.

The employment of inorganic reducing agents for the conversion of sodium-2-nitro-4-chlorophenol-6-sulfonate to 2-amino-4-chlorophenol-6-sulfonic acid resulted in either failure or poor yields except for stannous chloride and hydrochloric acid which gave a yield of 81% and zinc and hydrochloric acid which gave 57%. Catalytic hydrogenation in either aqueous acid or alkaline media afforded a smooth means of reduction, yields of 70 to 83% being experienced with 5% palladium on charcoal, platinum oxide, and palladium oxide. Raney nickel gave only 38% of product.

By a careful study of reaction conditions it was possible to obtain the 2-amino-4-chlorophenol-6-sulfonic acid in overall yields of 51 to 55%.

Biographical Note

The author was born in Germany, and arrived in the United States of America in 1927. He received his primary and secondary education in Union, New Jersey, and entered Seton Hall University in September, 1941. His course of study was interrupted by service in the Army from 1943 to 1946. After reentering school, the author was awarded a Bachelor of Science degree from Seton Hall University in May, 1947. He then joined the Research and Development Division of Merck and Co., Inc., Rahway, New Jersey, and entered the Newark College of Engineering as an evening graduate student in September, 1947. He completed the requirements for the Master of Science degree in June, 1951.