tained above were deacetylated by the action of hydrochloric acid on a solution of the compound in methanol. The procedure was essentially the same for all derivatives, except for minor differences in the quantities of methanol used.

A solution of 2.5–4.0 g. of acetamido compound in 25–100 cc. of absolute methanol was treated with 5–15 cc. of concd. hydrochloric acid. This was heated to boiling and concentrated until the insoluble hydrochloride was obtained either as crystals or an oil. In the latter instances, addition of 100–200 cc. of water usually gave crystals. In each case, the hydrochloride was found to have a distinct melting point.

The hydrochloride was converted in the usual manner to the corresponding *p*-(*o*-aminophenyl)-benzenesulfon-N-arylamide which was separated by filtration, washed with water, dried and weighed. The resulting weight was recorded as the yield in Table I. Except for III, which was purified by treating the alkaline solution with Norite, the compounds obtained here were purified by treatment in a dilute methanol solution with Norite and by recrystallization therefrom.

This procedure was used for making compounds III, VI, IX, XII, XV and XVIII.

Method II.—The nitro compounds obtained above were reduced with tin and hydrochloric acid. Except for a slight variation in the quantity of solvent used, the procedure is the same for the different nitro compounds.

To a solution of 3–5 g. in 100–150 cc. of methanol was added 3–4.5 g. of tin and 25 cc. of concd. hydrochloric acid. This was boiled for three and one-half hours and allowed to stand for sixteen hours. The resulting solution was concentrated to a volume of 25 cc. On cooling, the hydrochloride separated either as crystals or as an oil. To the mixture was then added 150 cc. of water. This usually caused the oil to solidify. The hydrochloride was separated by a vacuum filtration, washed free of tin salt with water, and then converted to the corresponding amine in the usual manner. The weight of the resulting *p*-(*o*-aminophenyl)-benzenesulfon-N-arylamide was recorded as the yield in Table I. An ignition of this material showed an ash content of less than 1%, proving that the tin salt can be removed effectively from the hydrochloride by washing with water.

Compounds III, VI, IX, XII, XV and XVIII were prepared by this method. These were shown to be identical, by melting points and mixed melting points, with the corresponding compounds made by deacetylation.

Acknowledgment.—The authors are indebted to the General Printing Ink Corporation for permission to publish this work; to Dr. Milton C. Whitaker of the American Cyanamid Company for making possible the bactericidal tests at the Stamford Laboratory, American Cyanamid Company; to Dr. Richard O. Roblin, Jr., and Dr. W. Harry Feinstone of the Stamford Laboratory for the bactericidal tests.

Summary

Six derivatives of *p*-(*o*-aminophenyl)-benzene sulfonamide, in which a hydrogen of the sulfonamide nitrogen was replaced by an aryl group were prepared from *p*-(*o*-acetamidophenyl)-benzenesulfonyl chloride and from *p*-(*o*-nitrophenyl)-benzenesulfonyl chloride. These and the parent compound were inactive when tested *in vitro* against *E. Coli* and *in vivo* against streptococcal infected mice.

Eighteen new derivatives of biphenyl-4′-sulfonamide have been prepared.

NEW YORK, N. Y. RECEIVED FEBRUARY 12, 1943

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

Reduction Products of 2-Nitrophenyl Esters of Arylsulfonic Acids

BY L. CHAS. RAIFORD AND J. REID SHELTON

When two different acyls derived from carboxylic acids are introduced into 2-aminophenol only one mixed diacyl derivative can generally be obtained, regardless of the order of introduction of these radicals; and in this product the heavier and more acidic of these groups is usually found attached to nitrogen. Migration of acyl from nitrogen to oxygen must occur in one of these reactions.[1] If one of these acyls is derived from a sulfonic acid isomeric mixed diacyl derivatives are obtained and no rearrangement is observed.[2]

Reduction of the 2-nitrophenyl ester of a carboxylic acid gives the related 2-aminophenyl derivative as the first product, but under the ordinary laboratory conditions this rearranges to the isomeric 2-N-acylaminophenol or 2-hydroxyphenylurethan, depending on the starting material. In this case acyl must wander from oxygen to nitrogen.[3] In reduction of 2-nitrophenyl 4-tolylsulfonate Bell[4] obtained a product having an exposed amino radical, indicating that no rearrangement had occurred. Both the above reactions have now been tested in

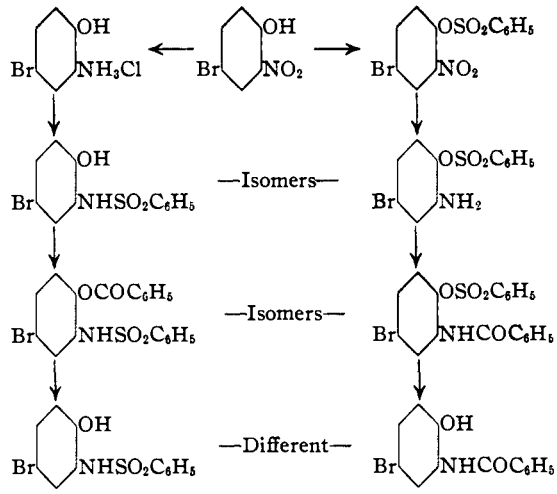
(1) Raiford and Couture, THIS JOURNAL, **46**, 2305 (1924).

(2) Raiford and co-workers, *ibid.*, **47**, 1111 (1925); **53**, 3420 (1931); *J. Org. Chem.*, **4**, 207 (1939); **5**, 300 (1940).

(3) Ransom, *Ber.*, **31**, 1058 (1898); *Am. Chem. J.*, **23**, 43 (1900).

(4) Bell, *J. Chem. Soc.*, 1983 (1930).

many cases and no migration has been observed when a sulfonyl radical was involved.



In trying to account for the difference in behavior noted above, we considered Latimer's[5] theory which states that "if there are a number of possible arrangements of the atoms in a molecule which have the same number of electrons per atom and which satisfy equally well the tendencies of the more electronegative elements to complete their octets of electrons, that form will be the most stable which gives a minimum of repulsion between the atomic kernels." And since he states further that "the great majority of these changes take place with a decrease in the inter-kernel repulsion energy," it was of interest to test our results in terms of that statement. Using the values for kernel charges and distances between atomic centers recorded by Latimer, and calculating the repulsion energies with the help of suggestions from Pauling and Hendricks,[6] and Huggins,[7] it might be expected that 2-aminophenyl benzenesulfonate would rearrange into 2-benzenesulfonylaminophenol. Both are stable under all conditions studied. Data for these and several other related compounds are given below.

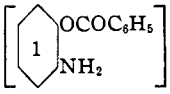
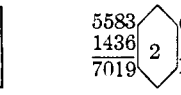
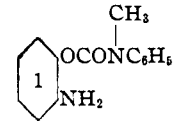
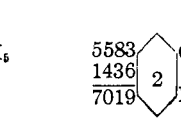
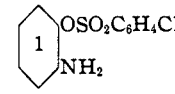
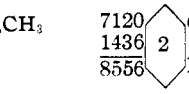
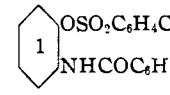
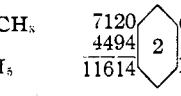
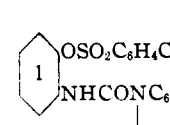
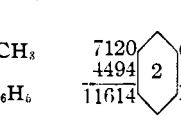
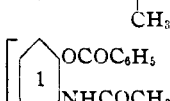
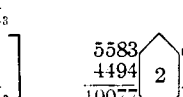
Experimental

Preparation of 2-Nitrophenyl Esters.—Slightly more than one molecular proportion of the necessary arylsulfonyl chloride was slowly added with vigorous shaking to a pyridine solution of the required nitrophenol. When reaction was complete the mixture was acidified with dilute hydrochloric acid, the insoluble material was removed and purified by crystallization from a suitable solvent. Analytical data and other properties for these products are given in Table II.

Reduction of the Esters.—This was accomplished by treatment of the hot alcoholic solution of the nitro compound with a 20% excess of stannous chloride dissolved in

TABLE I

RELATION OF INTER-KERNEL REPULSION ENERGIES TO CERTAIN MOLECULAR REARRANGEMENTS

Isomers and repulsion energies calculated in terms of kilocal.			Changes suggested by Latimer's theory	Observed facts	Number of pairs tested
	5583 + 1436 = 7019	 1887 + 4494 = 6381	1 → 2	Rearranged	3
	5583 + 1436 = 7019	 1887 + 4494 = 6381	1 → 2	No change	3
	7120 + 1436 = 8556	 1887 + 5762 = 7649	1 → 2	No change	20
	7120 + 4494 = 11614	 5583 + 5762 = 11345	1 → 2	No change	5
	7120 + 4494 = 11614	 5583 + 5762 = 11345	1 → 2	No change	3
	5583 + 4494 = 10077	 5583 + 4494 = 10077	No change	Rearranged 1 → 2	50+

(5) Latimer, THIS JOURNAL, **51**, 3190 (1929).

(6) Pauling and Hendricks, THIS JOURNAL, **48**, 641 (1926).

(7) Huggins, *Phys. Rev.*, **28**, 1086 (1926).

TABLE II

2-NITROPHENYL BENZENESULFONATE AND SUBSTITUTION PRODUCTS

Other substituents in nitrophenyl radical	Substituent in aryl sulfonyl radical	Yield, %[a]	Crystal form (col. = colorless, n. = needles)	M. p., °C.	Composition	Analyses, % Halogen Calcd.	Halogen Found	Sulfur Calcd.	Sulfur Found
Unsubst.	Unsubst.	75	Nearly col. n.	64[b]	$C_{12}H_9NO_5S$			11.47	10.80
	4-Methyl-	93	Blunt n.	81[c]	$C_{13}H_{11}NO_5S$			10.92	11.30
	4-Bromo-	71	Blunt n.	98.5	$C_{12}H_8BrNO_5S$	22.34	22.35		
	3-Nitro-	88	Col. n.	88	$C_{12}H_8N_2O_7S$			9.87	9.76
4,6-Dibromo-	Unsubst.	91	Col. n.	131.5	$C_{12}H_7Br_2NO_5S$	36.61	36.70		
	4-Methyl-	85	Col. blocks	141	$C_{13}H_9Br_2NO_5S$	35.47	35.34		
	4-Bromo-	81	Col. prisms	131	$C_{12}H_6Br_3NO_5S$	46.51	45.48[d]		
	3-Nitro-	60	Col. n.	113	$C_{12}H_6Br_2N_2O_7S$	33.19	33.06		
4-Methyl-6-bromo-	Unsubst.	91	Col. n.	155	$C_{13}H_{10}BrNO_5S$	21.50	21.50		
	4-Methyl-	88	Col. prisms	127	$C_{14}H_{12}BrNO_5S$	20.69	20.69		
	4-Bromo-	77	Pale yellow n.	151	$C_{13}H_9Br_2NO_5S$	35.47	35.21		
	3-Nitro-		Yellow n.	98	$C_{13}H_9BrN_2O_7S$	19.18	18.78		
4-Bromo-	Unsubst.	Nearly quant. (crude)	Cream needles	88–89	$C_{12}H_8BrNO_5S$	22.34	22.35		
5-Methyl-		Nearly quant. (crude)	Cream needles	83–84	$C_{13}H_{11}NO_5S$			10.92	10.87
4-Bromo-5-methyl-		98 (crude)	Cream rhomb.	119–120[e]	$C_{13}H_{10}BrNO_5S$	21.50	21.05		
4,6-Dibromo-5-methyl		[f]	Cream rhomb.	124–126	$C_{13}H_9Br_2NO_5S$	35.47	35.26		
4-Bromo-	4-Bromo-	Nearly quant.	Cream needles	101	$C_{12}H_7Br_2NO_5S$	36.61	36.62		
4-Bromo-5-methyl-		[f]	Blunt needles	86–87	$C_{13}H_9Br_2NO_5S$	35.47	35.41		
5-Methyl-		Nearly quant.	Cream flakes	91–92	$C_{13}H_{10}BrNO_5S$	21.50	21.49		

[a] Unless otherwise indicated all products were crystallized from ethanol and figures refer to purified materials. [b] Georgesco [*Buletinul Societatii de Scinte*, 8, 668 (1900), *Abstr. Centralbl.*, 71, 543 (1900)] recorded 75°. Our product was repeatedly crystallized from alcohol until a constant melting point was obtained. [c] This is the melting point found by Ullmann and Nadai [*Ber.*, 41, 1872 (1908)] who recorded no analysis. [d] Though analysis for bromine gave a low value, the product obtained by reduction seemed to be pure. [e] Crystallized from ether. [f] Esterification was incomplete, and separation of unchanged phenol caused some loss of ester.

TABLE III

2-AMINOPHENYL BENZENESULFONATE AND SUBSTITUTION PRODUCTS

Other substituent in aminophenyl	Substituent in aryl-sulfonyl	Yield, %[a]	Crystal form	M. p., °C.	Composition	Analyses, % Halogen Calcd.	Halogen Found	Nitrogen Calcd.	Nitrogen Found
Unsubst.	Unsubst.	74	Col. flakes	86	$C_{12}H_{11}NO_3S$			5.62	5.61
	4-Methyl-	72	Pink flakes	98.5[b]	$C_{13}H_{13}NO_3S$			5.32	5.33
	4-Bromo-	68	Brown powder	111–112	$C_{12}H_{10}BrNO_3S$	24.39	23.95	4.26	4.22
	3-Amino-	70	Brown prisms	125–126	$C_{12}H_{12}N_2O_3S$			10.60	10.31
4-Bromo-5-methyl-	Unsubst.		Tan needles	100[c]	$C_{13}H_{12}BrNO_3S$[d]	23.39	23.36		
4,6-Dibromo-	4-Methyl-	53	Tan flakes	129–130	$C_{13}H_{11}Br_2NO_3S$	37.97	38.25	3.32	3.32
	4-Bromo-	73	Nearly col. n.	128	$C_{12}H_8Br_2NO_3S$	49.38	49.37	2.88	2.89
4-Methyl-6-bromo-	Unsubst.	70	Pale brown masses	95	$C_{13}H_{14}BrNO_3S$	23.39	23.42		
	4-Methyl-	46	Tan scales	88	$C_{14}H_{14}BrNO_3S$	22.47	22.59	3.93	3.92
	4-Bromo-	25[e]	Dark granules	112–113	$C_{13}H_{11}Br_2NO_3S$	38.00	37.84	3.32	3.32

[a] Unless otherwise indicated all products were crystallized from ethanol, and figures for yields represent purified materials. [b] Bell [*J. Chem. Soc.*, 1983 (1930)] recorded 102° but did not analyze his product. [c] This represents the ether-soluble portion. Almost one-third of the crude product was insoluble and was not studied further. [d] Composition was checked by freezing point determination in dioxane. Calcd. for $C_{13}H_{12}BrNO_3S$: mol. wt., 342. Found: mol. wt., 332. [e] Low yield was due to incomplete reduction.

concentrated hydrochloric acid. The mixture was usually boiled under reflux until the action was complete. The cooled mixture was made alkaline, it was extracted with ether, the solvent was distilled off and the residue was purified by crystallization from a suitable solvent. Data for these compounds are given in Table III.

Summary

1. 2-Nitrophenyl benzenesulfonate and a number of its substitution products have been reduced to the corresponding 2-aminophenyl derivatives. Under the conditions of our experiments these products showed no tendency to rearrange.

2. Latimer's theory does not seem to us to account for the remarkable differences in behavior of the acyl derivatives of *o*-aminophenol obtained from carboxylic and sulfonic acids, respectively.

IOWA CITY, IOWA RECEIVED MAY 5, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensations. XX. Certain Acetoacetic Ester Condensations Effected by Means of Sodium or Potassium Amide and Isopropylmagnesium Bromide

BY J. C. SHIVERS, B. E. HUDSON, JR., AND CHARLES R. HAUSER

Although ethyl acetate gives only low yields (8–15%) of ethyl acetoacetate with sodium amide,[1] and apparently little if any of the β-keto ester with isopropylmagnesium bromide,[2] certain esters having a relatively reactive α-hydrogen or a relatively unreactive carbonyl carbon undergo the acetoacetic ester condensation very satisfactorily in the presence of these reagents.

Conant and Blatt[3] have shown that, in the presence of isopropylmagnesium bromide, ethyl phenylacetate, in which the α-hydrogen is relatively reactive, gives an excellent yield (93%) of its self-condensation product, ethyl α,γ-diphenylacetoacetate. Ivanov and Spassov[4] found that in the presence of this Grignard reagent, ethyl *p*-chlorophenylacetate similarly undergoes the acetoacetic ester condensation in excellent yield. We have found that the self-condensation of ethyl phenylacetate may be effected very satisfactorily in the presence of potassium amide in ether, and that, in the presence of either isopropylmagnesium bromide or sodium amide in ether, *t*-butyl acetate, in which the carbonyl carbon is relatively unreactive, gives fair to good yields (40–50%) of its self-condensation product, *t*-butyl acetoacetate.

$$2C_6H_5CH_2CO_2C_2H_5 \xrightarrow[(CH_3)_2CHMgBr]{KNH_2\text{ or}} C_6H_5CH_2COCH(C_6H_5)CO_2C_2H_5 + C_2H_5OH$$

$$2CH_3CO_2C(CH_3)_3 \xrightarrow[(CH_3)_2CHMgBr]{NaNH_2\text{ or}} CH_3COCH_2CO_2C(CH_3)_3 + (CH_3)_3COH$$

Similarly, in the presence of these reagents, *t*-butyl isovalerate undergoes self-condensation to form *t*-butyl isovalerylisovalerate, but the yields are lower; with isopropylmagnesium bromide the yield was 29%, while with potassium amide in benzene the yield was only 11%, some of the ester being recovered in each case. Spielman and Schmidt[5] found that ethyl isovalerate is self-condensed by isopropylmagnesium bromide to only a very small extent (1%).

It should be pointed out that, while the activation of the α-hydrogen by the phenyl group or the deactivation of the carbonyl carbon by the *t*-butyl group favors the attack of the amide ion or isopropylmagnesium bromide at the α-hydrogen of the ester, this does not necessarily mean that the acetoacetic ester reaction can be effected. The reaction depends not only upon the primary ionization of the α-hydrogen to form the ester anion (or magnesium enolate) but also upon the condensation of the ester anion with molecules of unchanged ester,[6] and this second step may occur too slowly for the reaction to be realized.

Experimental

Condensation of Ethyl Phenylacetate by Potassium Amide.—Essentially dry commercial ammonia (300 cc.) was placed in a 500-cc. three-necked, round-bottomed flask, equipped with a mercury sealed stirrer, dropping funnel and a drying tube of drierite. Pieces of clean potassium (7.8 g., 0.20 g. atom) and a small strip of rusty iron gauze were placed in the ammonia and the mixture stirred about thirty minutes until the blue solution became

(1) Titherly, *J. Chem. Soc.*, **81**, 1520 (1902); Freund and Speyer, *Ber.*, **35**, 2321 (1902). These workers used a benzene suspension of sodium amide or carried out the reaction without a solvent. We have found that in the presence of potassium amide in liquid ammonia, either with excess ester or excess base, ethyl acetate similarly gives only low yields (5–10%) of ethyl acetoacetate.

(2) With isopropylmagnesium chloride, ethyl acetate gives a 85% yield of the ketol of methyl isopropyl ketone; Ivanov and Spassov, *Bull. soc. chim.*, [5] **2**, 816 (1935).

(3) Conant and Blatt, THIS JOURNAL, **51**, 1227 (1929).

(4) Ivanov and Spassov, *Bull. soc. chim.*, [4] **49**, 375 (1931).

(5) Spielman and Schmidt, THIS JOURNAL, **59**, 2009 (1937).

(6) See Hauser and Hudson in Adams' "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter IX.