started to separate within the first few hours. After 40 hours the crystals were collected, washed with ether and dried; wt. 10.0 g. The trimethyl sulfonium iodide had no definite melting point. A portion was suspended in ethanol and treated with aqueous sodium picrate. A new salt appeared which was filtered and recrystallized from ethanol. The trimethylsulfonium picrate melted at 194–196° (uncor.).[17]

o-Chlorobenzyl Methyl Sulfide from Trimethylsulfonium Iodide and o-Chlorobenzyl Mercaptan.—To a solution of 3.9 g. of *o*-chlorobenzyl mercaptan (0.024 m.) and 0.6 g. (0.027 m.) of sodium in 60 ml. of ethanol there was added 6.9 g. (0.0335 m.) of trimethyl sulfonium iodide. The mixture was refluxed for three hours and was then poured in water. The oil was dissolved in benzene. The solution was dried and distilled to yield 2.6 g. of crude sulfide, b.p. 52–62° (0.1 mm.).

The sulfide was dissolved in 25 ml. of acetic acid and oxidized with 3 ml. of Superoxol at 90°. On pouring the reaction mixture in ice-water a solid was formed which after filtration and recrystallization from ethanol melted at 92–95°. When admixed with an authentic specimen of *o*-chlorobenzyl methyl sulfone there was no melting point depression.

Benzyldimethylsulfonium Picrate.—To a solution of 7.1 g. of dimethyl sulfide in 25 ml. of methanol there was added 19.7 g. of benzyl bromide in 75 ml. of methanol. The whole was allowed to stand for 12 days. Then 5 volumes of ether was added and the supernatant solvent was decanted from the gum. The latter was washed several times with ether and then dissolved in water. The solution was added to a solution of 26.4 g. of picric acid in 350 ml. of water containing 4.6 g. of sodium hydroxide. The yellow solid which separated was crystallized from 300 ml. of ethanol. The total yield of the sulfonium picrate was 23 g. (52%); m.p. 134.4–136° (cor.).[18]

(17) D. Strömholm, *Ber.*, **33**, 827 (1900), reported 193° as the m.p. of trimethyl sulfonium picrate.

(18) J. W. Baker and W. G. Moffett, *J. Chem. Soc.*, 1728 (1930), report m.p. 134°.

Anal. Calcd. for $C_9H_{13}S\cdot O\cdot C_6H_2(NO_2)_3$: S, 8.41. Found: S, 8.52.

Reaction between Benzyldimethylsulfonium Picrate and o-Chlorobenzyl Mercaptan.—To a solution of 1.2 g. of sodium in 100 ml. of absolute alcohol there was added 7.9 g. of *o*-chlorobenzyl mercaptan. Then 19 g. of the sulfonium picrate was added in one portion and the resulting mixture was heated with stirring for one hour. The red solution was poured into ice-water and the oil which separated was collected in benzene. The extract was thoroughly washed with 0.5 *N* sodium hydroxide, water and once with dilute hydrochloric acid. The benzene solution was then dried and distilled. A small forerun was obtained, followed by a fraction, b.p. 77–80° (1.4 mm.); wt. 0.8 g. This was oxidized in acetic acid solution with Superoxol. A crystalline solid, m.p. 78–82° after recrystallization from dilute ethanol, was obtained. A mixed melting point determination with a known specimen of *o*-chlorobenzylmethyl sulfone, m.p. 91–93°, melted at 89–92°.

The residue which weighed 7.8 g. (56%) was dissolved in 70 ml. of glacial acetic acid and oxidized with 15 ml. of Superoxol. Crystals were obtained on pouring the mixture in water. After recrystallization from ethanol the benzyl-2-chlorobenzyl sulfone melted at 121–123° (uncor.) and did not depress the m.p. of an authentic specimen.

Methyl Mesitoate.—A suspension of 5.7 g. of silver mesitoate and 9.3 g. of trimethylsulfonium iodide in 50 ml. of methanol was refluxed for six hours. The mixture was filtered through Filter-cel and the methanol was removed under reduced pressure. A few ml. of dilute ammonia was added to the residue and the whole was steam distilled. The oil that came over was extracted with ether, dried and distilled. The fraction, b.p. 86–87° (2 mm.), weighed 1.4 g. (38%).[19]

(19) M. S. Newman, THIS JOURNAL, **63**, 2434 (1941), reported the b.p. 114.8–115.2° (7–7.5 mm.).

RENSSELAER, N. Y. RECEIVED OCTOBER 14, 1950

[CONTRIBUTION FROM THE LABORATORY OF PATHOLOGY AND PHARMACOLOGY, EXPERIMENTAL BIOLOGY & MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Derivatives of Bis-(4-aminophenyl) Sulfone and Related Compounds

BY HUGO BAUER

Seven different types of substituted diphenyl sulfones were synthesized for evaluation in the chemotherapy of experimental tuberculosis. They included derivatives of sulfamic and amidopyrophosphoric acids, of nicotinic acid and of glycine, methoxysubstituted sulfones, an amidine and an aminoethylamine derivative. These compounds were tested for therapeutic effectiveness upon the chorioallantois of the developing chick embryo or in guinea pigs infected with *Mycobacterium tuberculosis*.

A series of derivatives of bis-(4-aminophenyl) sulfone has been prepared for evaluation in the chemotherapy of experimental tuberculosis. This paper deals with the chemical aspects of the problem[1] as related to seven different types of substituted diphenyl sulfones.[2]

Sulfamic and amidopyrophosphoric acid derivatives of bis-(4-aminophenyl) sulfone were prepared by three routes. Reduction of bis-(4-nitrophenyl) sulfone with sodium dithionite (sodium hydrosulfite) gave 4-amino-4′-sulfaminodiphenyl sulfone (I) and its sodium salt (II). The action of chlorosulfonic acid upon 4-nitro-4′-aminodiphenyl sulfone in the presence of pyridine afforded 4-nitro-4′-sulfaminodiphenyl sulfone which was isolated as the pyridine (III) and the mono-(IV) and disodium (V) salts. An attempt to prepare the chloride and the amide of the 4-nitro-4′-sulfaminodiphenyl sulfone gave an unexpected result. By the action of phosphorus pentachloride upon III, the sulfonic acid group was replaced by a phosphorus-containing group. Subsequent treatment with ammonium hydroxide yielded a diamidopyrophosphoric acid derivative which was isolated as a sodium salt (VI).

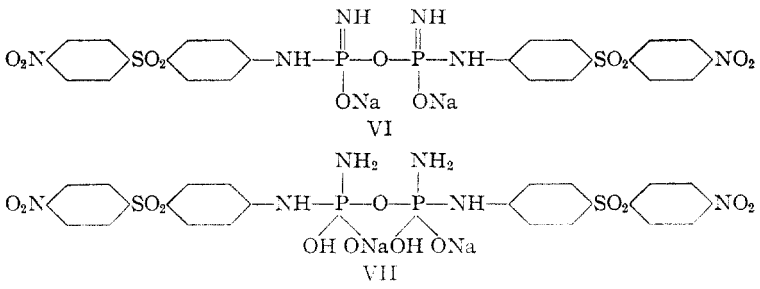
A similar compound (VII) was obtained by the action of phosphorus pentachloride on 4-nitro-4′-aminodiphenyl sulfone and subsequent treatment with ammonium hydroxide and aqueous sodium hydroxide. The following formulas are suggested for the anhydrous compounds.

Two derivatives of nicotinic acid were prepared. Nicotinyl chloride acted upon bis-(4-aminodiphenyl) sulfone with formation of the disubstituted bis-(nicotinyl-4-aminophenyl) sulfone (VIII), previously prepared by E. H. Stuart.[3]

(1) The biological part of this work has been reported in a series of papers from this Laboratory by M. I. Smith and co-workers.

(2) Foregoing papers: THIS JOURNAL, **61**, 617 (1939); **67**, 591 (1945); **70**, 2254 (1948).

(3) E. H. Northey, "The Sulfonamides and Allied Compounds," Reinhold Publishing Corp., New York, N. Y., 1948, p. 355.



VI

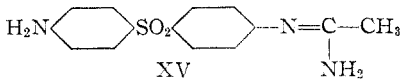
VII

By action of 6-chloropyridine-3-carboxylic acid upon bis-(4-aminophenyl) sulfone, compound IX was prepared, a derivative which preserved one free amino group of the sulfone and the free carboxylic group of the nicotinic acid.

N-*p*-Sulfanilylphenylglycine served as starting material for glycine derivatives. The amide (XIII) was prepared by the usual steps of the preparation of the ethyl ester (XII) and subsequent conversion to the amide by the action of ammonium hydroxide.

4-(4′-Nitrophenylsulfonyl)-N-phenylglycine[4] (X) was synthesized as a possible intermediate for the preparation of the foregoing compounds. It was obtained by the action of bromoacetic acid upon 4-nitro-4′-aminodiphenyl sulfone in the presence of sodium hydrogen carbonate in a dioxane–water mixture. Since the yield was low, the planned procedure was not followed.

4-(4′-Nitrophenylsulfonyl)-phenylacetamidine (XIV) was prepared by converting 4-nitro-4′-acetylaminodiphenyl sulfone to the imidyl chloride[5] and subsequently to the amidine. Catalytic reduction of the nitro group furnished the 4-sulfanilylphenylacetamidine



XV

In preparing N-β-aminoethyl derivatives, substitution with the aminoethyl group was effected by the action of β-bromoethylphthalimide[6] upon 4-nitro-4′-aminodiphenyl sulfone and bis-(4-aminophenyl) sulfone, followed by hydrolysis of the respective products. Condensation was carried out by melting a mixture of the components at 150–160°. An excess of the appropriate sulfone (two moles) was used. The condensation of bis-(4-aminophenyl) sulfone afforded a considerable amount of the disubstituted product XVIII. The phthalic acid residue could be removed either by hydrolysis with concentrated hydrochloric acid or with hydrazine hydrate.[7] Short treatment of the phthalimido compound XVI with sodium hydroxide in alcoholic suspension effected opening of the ring with formation of the phthalylamino compound XIX.

For the preparation of guaiacol derivatives, two routes of preparation were employed, the first consisting in the synthesis of 3-methoxy-4-nitro-4′-aminodiphenyl sulfide (XXVII) and its subsequent oxidation to the sulfone and reduction of the nitro group to yield 3-methoxy-4,4′-diaminodiphenyl sulfone (XXXIV). Conversion of the amino groups of XXIX and XXXIII to hydroxyl groups through the diazotization method could not be accomplished.

The second procedure started from potassium guaiacol-*p*-sulfonate. The acetyl derivative of the sulfonate XXIII was converted into the sulfonyl chloride XXIV and reduced to the acetylated guaiacol-*p*-sulfinic acid (XXV). Attempts to condense this sulfinic acid with *p*-chloro- or *p*-bromonitrobenzene were unsuccessful. Therefore, the guaiacol-*p*-sulfonic acid was reduced to the thiol. Its condensation with *p*-bromonitrobenzene yielded 3-methoxy-4-hydroxy-4′-nitrodiphenyl sulfide (XXXI) which was converted to 3-methoxy-4-hydroxy-4′-aminodiphenyl sulfone (XXXVI).

Chemotherapeutic Evaluation

Derivatives containing one free amino group proved to be superior to compounds substituted in both amino groups.[8] The products obtained by combining an acidic group with one of the amino groups showed some activity, but were inferior to alkylated derivatives, *e.g.*, 4-*n*-propylamino-4′-aminodiphenyl sulfone.[9] The sulfonation of one of the amino groups of the bis-(4-aminophenyl) sulfone (see compound II) reduced the tuberculostatic activity to about one-tenth that of the parent compound, as tested on the chorioallantois of the developing chick embryo.[10]

The favorable influence exerted by the glycinamide grouping in the series of the organic arsenic compounds (tryparsamide) could not be produced in the sulfone series. The chemotherapeutic effectiveness of N-*p*-sulfanilylphenylglycine amide (XIII) in guinea pigs infected with *Mycobacterium tuberculosis* was half of that of bis-(4-aminophenyl) sulfone.[8] The amidine derivatives (XIV and XV) showed a moderate activity in experimental tuberculosis.[8] No activity was observed in the N-β-aminoethyl derivative XXI.[11]

The preparation of guaiacol derivatives was undertaken in an attempt to improve the chemotherapeutic index of the 4-hydroxy-4′-aminodiphenyl sulfone[12] which had shown a moderate activity in experimental tuberculosis.[13] By introduction of the methoxy group in ortho position to the phenolic hydroxyl (XXXII, XXXIV and XXXVI), the tolerated dose was increased from 1 g. to 4 g. of kg. of body weight, but no protection, as tested in pneumococcal infections of mice, was observed.[14]

(4) E. L. Jackson, THIS JOURNAL, **70**, 680 (1948).

(5) *Cf.* R. L. Shriner and F. W. Neumann, *Chem. Revs.*, **35**, 362 (1944).

(6) P. L. Salzberg and J. V. Supniewski, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 119.

(7) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2348 (1926).

(8) M. I. Smith, E. L. Jackson and H. Bauer, *Ann. N. Y. Acad. Sci.*, **52**, 704 (1949).

(9) M. I. Smith, W. T. McClosky and E. L. Jackson, *Am. Rev. Tuberc.*, **55**, 366 (1947).

(10) M. I. Smith, *N. Y. State J. Med.*, **45**, 1665 (1945).

(11) Unpublished data by Dr. Y. T. Chang of this Laboratory.

(12) G. W. Raiziss, L. W. Clemence, M. Severac and J. C. Moetsch, THIS JOURNAL, **61**, 2763 (1939).

(13) M. I. Smith, E. W. Emmart and E. F. Stohlman, *Am. Rev. Tuberc.*, **48**, 32 (1943).

(14) Unpublished data by Dr. J. M. Junge of this Laboratory.

Experimental

4-Amino-4'-sulfaminodiphenyl Sulfone (I) and Sodium Salts (IIa, IIb).—To a suspension of 70 g. of bis-(4-nitrophenyl) sulfone in a mixture of 100 cc. of 95% ethanol and 1400 cc. of water, heated at 70–80°, 280 g. of sodium dithionite was added in small portions within an hour. The filtered mixture was acidified with hydrochloric acid and concentrated on a steam-bath until the evolution of sulfur dioxide ceased. Upon alkalization with sodium hydroxide, bis-(4-aminophenyl) sulfone separated and was removed by filtration. The filtrate was evaporated on the steam-bath and the residue was repeatedly extracted with ethanol. Concentration of the extract yielded the sodium salt IIa (16 g.), which was recrystallized from ethanol as colorless needles (11 g.), containing one mole of ethanol of crystallization. The ethanol-free substance took up water from the air to form the monohydrate IIb.

The free acid (I) was precipitated from an aqueous solution of IIb (8.7 g.) by the calculated amount of 2 *N* hydrochloric acid. The compound (7.1 g.) contained one mole of water; one-half mole of water was removed by drying *in vacuo* at 97°. The product softened with darkening at 255° and did not melt up to 290°.

Pyridinium 4-Nitro-4'-sulfaminodiphenyl Sulfone (III).—A solution of 56 g. of 4-nitro-4'-aminodiphenyl sulfone in 200 cc. of pyridine was cooled in a freezing mixture. A solution of 50 cc. of chlorosulfonic acid in 200 cc. of chloroform was added, with vigorous stirring, during 90 minutes. The orange, gelatinous reaction mixture was diluted with water, the yellow precipitate formed was dissolved in dilute aqueous sodium hydroxide and the red solution thus obtained was acidified with acetic acid. Cream-colored crystals (64 g.) of III separated. The crystals dissolved in hot water with acid reaction; the colorless solution turned yellow almost immediately. The compound is easily split by acids with formation of 4-nitro-4'-aminodiphenyl sulfone.

Sodium Salts of 4-Nitro-4'-sulfaminodiphenyl Sulfone (IV and V).—To a solution of 5 g. of III in 10 cc. of 5 *N* sodium hydroxide, 95% ethanol was added until bright orange crystals, probably a disodium salt, began to separate. After the crystallization was complete, the product was filtered and washed with ethanol, changing the orange crystals to the yellow monosodium salt. This was purified by dissolving in hot 50% ethanol and filtering. Upon addition of 95% ethanol to the filtrate cream-colored crystals separated. Fractional crystallization from hot 95% ethanol yielded cream-colored needles (IV) which contained two moles of water of crystallization. The presence of ethanol as solvent of crystallization was excluded by distilling a sample of IV in a test-tube which was narrowed to a capillary. The condensate in the capillary was not inflammable. The anhydrous compound, obtained by heating IV *in vacuo* at 80°, took up one mole of water in the air, yielding compound V.

Diamidopyrophosphoric Acid Derivative (VI).—Compound III (10 g.) was suspended in 10 cc. of phosphorus oxychloride and 4 g. of phosphorus pentachloride was added. The mixture became warm with evolution of hydrogen chloride. After being heated to complete solution, the reaction mixture was poured into ice-water. The cream-colored precipitate was filtered, washed with water and immediately worked up. It was mixed with ice and dissolved by addition of 28% ammonium hydroxide. The solution was evaporated to dryness, extracted with water and the extract made strongly alkaline with sodium hydroxide. The cream-colored crystals of VI (5 g.) which separated were recrystallized from ethanol.

Diamidopyrophosphoric Acid Derivative (VII).—To a suspension of 5 g. of 4-nitro-4'-aminodiphenyl sulfone in 5 cc. of phosphorus oxychloride was added 5 g. of phosphorus pentachloride. Upon warming gently the crystals dissolved.

This solution upon cooling to 25° deposited crystals. The mixture was then decomposed by the addition of ice and water, and the crystalline product was filtered and washed with water. To the moist product sufficient 10% ammonium hydroxide was added to dissolve all of it. From this solution the sodium salt VII was precipitated by the addition of 10 *N* sodium hydroxide solution. Recrystallization from ethanol yielded VII as a yellow, crystalline powder (2.7 g.).

Bis-(nicotinyl-4-aminophenyl) Sulfone (VIII).—Freshly prepared nicotinyl chloride (from 10 g. of nicotinic acid)[15] was added to a solution of 9 g. of bis-(4-aminophenyl) sulfone in 50 g. of pyridine. The mixture was warmed to complete solution. The condensation product (10.45 g.), precipitated by the addition of water, was purified by dissolving in 50% acetic acid and adding water.

4-Amino-4'-[2-(5-carboxypyridyl)-amino]-diphenyl Sulfone (IX).—A mixture of 5 g. of 6-chloropyridine-3-carboxylic acid[16] and 10 g. of bis-(4-aminophenyl) sulfone was heated in an oil-bath at 180–190° for 30 minutes. The cooled, pulverized mass was extracted with 250 cc. of cold 2 *N* hydrochloric acid. The extract was alkalinized with sodium hydroxide solution to precipitate the unchanged sulfone. From the filtrate, IX was precipitated with hydrochloric acid and then purified by dissolving in an excess of hydrochloric acid and precipitating with 2 *N* sodium acetate solution. The yield was 4–6 g. Copper powder as a catalyst did not improve this yield.

For further purification, the sodium salt IXa was prepared. This salt was sparingly soluble in 5 *N* sodium hydroxide solution. It was recrystallized from ethanol. The free acid, precipitated from the sodium salt solution with acetic acid, melted at 228°.

4-(4'-Nitrophenylsulfonyl)-N-phenylglycine (X) and Anhydride (XI).—Ten grams of 4-nitro-4'-aminodiphenyl sulfone, 15 g. of bromoacetic acid and 12 g. of sodium hydrogen carbonate were heated in a mixture of 100 cc. of dioxane and 150 cc. of water on the steam-bath for 7 hours. The reaction mixture was diluted with 1000 cc. of water and made basic with ammonium hydroxide. The unchanged nitroaminosulfone was removed and the condensation product was precipitated with hydrochloric acid. The yellow crystals of the anhydride XI (3.6 g.) melted at 220–222°. The m.p. was raised to 229–231° by recrystallization of the crude product from ethanol.

The glycine derivative X was obtained by dissolving the anhydride in dilute sodium hydroxide solution and precipitating by the careful addition of dilute hydrochloric acid. The fine yellow crystals melted at 228° after sintering at 220°.

Ethyl N-*p*-Sulfanilylphenylglycinate (XII).—The pyridine salt of N-*p*-sulfanilylphenylglycine[4] was converted to the ethyl ester by saturating a suspension (20 g.) in absolute ethanol (500 cc.) with hydrogen chloride without cooling. The alcohol solution was concentrated under diminished pressure and poured into ice-water. The ester was precipitated with ammonium hydroxide and recrystallized from ethanol.

N-*p*-Sulfanilylphenylglycine Amide (XIII).—A mixture of 10 g. of XII with 200 cc. of 28% ammonium hydroxide was kept at room temperature for about 70 hours with occasional shaking. The product was recrystallized from 95% ethanol. It was soluble in hot water and in mineral acids.

4-(4'-Nitrophenylsulfonyl)-phenylacetamidine (XIV).—A mixture of 32 g. of 4-nitro-4'-acetylaminodiphenyl sulfone,[17] 25 g. of phosphorus pentachloride and 30 cc. of phosphorus trichloride was allowed to stand for 15 minutes, then was heated at 80–85° for three hours. The imidyl chloride separated in fine crystals upon the addition of petroleum ether. The crystals were added in small portions to an ice-cold saturated solution of ammonia in 130 cc. of absolute ethanol. After 40 hours at room temperature, the impure amidine was freed from a by-product by solution in concentrated hydrochloric acid, followed by the addition of water, neutralization and filtration. The filtrate yielded the amidine as a yellow crystalline precipitate upon the addition of an excess of ammonium hydroxide. It was recrystallized from 95% ethanol as light yellow crystals.

The nitroamidine is not stable in solution and is easily split with the formation of 4-nitro-4'-aminodiphenyl sulfone. This cleavage takes place during preparation and purification of the product.

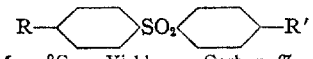
4-Sulfanilylphenylacetamidine (XV).—Compound XIV, in ethanol solution, was reduced with hydrogen in the presence of Raney nickel catalyst at room temperature and ordinary pressure for four hours. The solvent was removed under diminished pressure and the residue dissolved in 2 *N* hydrochloric acid. An impurity present was precipitated by dilution with water and neutralization to congo red

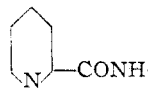
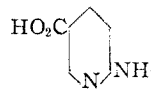
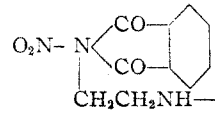
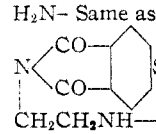
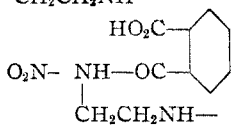
(15) E. Späth and H. Spitzer, *Ber.*, **59**, 1479 (1926).

(16) H. v. Pechmann and W. Welsh, *ibid.*, **17**, 2384 (1884).

(17) Prepared by oxidation of the corresponding sulfide with sodium hypochlorite. *Cf.* F. J. Weijlard, THIS JOURNAL, **67**, 1031 (1945), and ref. 11.

TABLE I



R	R′	M.p., °C. uncor.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
I	H_2N- $-NHSO_3H\cdot{}^1/_2H_2O$							8.30	8.48	19.01	18.71
IIa	H_2N- $-NHSO_3Na\cdot C_2H_5OH$[a]		17	42.72	42.74	3.88	4.06				
IIb	H_2N- $-NHSO_3Na\cdot H_2O$[b]							7.07	6.65	16.18	15.95
III	O_2N- $-NHSO_3H\cdot C_5H_5N$[c]		73					9.61	9.21	14.66	14.77
IV	O_2N- $-NHSO_3Na\cdot 2H_2O$[d]									16.10	15.96
V	O_2N- $-NHSO_3Na\cdot H_2O$[e]										
VI	$C_{24}H_{20}N_6Na_2O_{11}P_2S_2\cdot 2{}^1/_2H_2O$[f]		55					10.70	10.73	8.16	8.19
VII	$C_{24}H_{24}N_6Na_2O_{13}P_2S_2\cdot 3H_2O$[g]		36					10.13	9.65	7.72	7.77
VIII	 Same as R	365	63							6.99	7.04
IX		228	34–51							8.68	8.31
X	O_2N- $-NHCH_2CO_2H$[i]	228		49.99	49.78	3.60	3.79	8.33	8.05		
XI	$[O_2N-$ $-NHCH_2CO]_2O$	229–231	31	51.37	51.42	3.39	3.85			9.80	9.58
XII	H_2N- $-NHCH_2CO_2Et$	178–179	90	57.47	57.45	5.42	5.47	8.38	8.37	9.59	9.72
XIII	H_2N- $-NHCH_2CONH_2$	219	82	55.06	55.13	4.95	5.16	13.76	13.67	10.50	10.61
XIV	O_2N- $-N{=}C(NH_2)-CH_3$	208–209	31–44	52.65	52.51	4.10	4.27	13.16	12.87	10.04	9.82
XV	H_2N- Same as above[k]	185–187	68	58 11	58.30	5.22	5.31	14.52	14.28		
XVI		195	39[l]	58.53	58.75	3.80	4.09			7.10	6.95
XVII	H_2N- Same as above	201–202	50–56	62.69	62.89	4.54	4.80	9.97	9.81		
XVIII	 Same as above	260–261	19	64.63	64.50	4.41	4.64	9.43	9.34	5.39	5.47
XIX		180	91	56.28	56.02	4.08	4.19	8.95	8.83		
XX	O_2N $-NHCH_2CH_2NH_2$	190–191	62	52.32	52.27	4.70	4.74	13.08	12.99		
XXI	H_2N- $-NHCH_2CH_2NH_2$	171	70–80	57.71	57.75	5.88	5.99	14.42	14.65		
XXII	Same as R′ $-NHCH_2CH_2NH_2$	118–120[m]		51.87	51.66	7.07	6.70	15.13	14.81	8.66	8.30

[a] Calcd.: Na, 5.80; C_2H_5OH, 11.61. Found: Na, 5.54; C_2H_5OH, 11.21. [b] Calcd.: H_2O, 4.89. Found: H_2O, 4.80. [c] Pyridine was titrated with 0.1 *N* hydrochloric acid using brom phenol blue as indicator, Calcd.: 18.08. Found: 18.20. [d] Calcd.: H_2O, 8.65. Found: H_2O, 8.35. [e] Calcd.: Na, 5.77; H_2O, 4.52. Found: Na, 5.77; H_2O, 4.57. [f] This is the empirical formula of VI. Amide nitrogen (see appendix): N, 3.57. Found: N, 3.44. Calcd.: Na, 5.85; P, 7.90; H_2O, 5.73. Found: Na, 5.70; P, 7.80; H_2O, 5.62. [g] This is the empirical formula of VII. Amide nitrogen. Calcd.: N, 3.37. Found: N, 3.09. Calcd.: Na, 5.54. P, 7.47; H_2O, 6.51. Found: Na, 5.73; P, 7.42; H_2O, 6.87. [h] The sodium salt (IXa) contained 2 moles of water. Calcd.: Na, 8.43; H_2O, 5.38. Found; Na, 8.50; H_2O, 5.32. [i] See ref. 5. [k] Monohydrochloride: m.p. 265°. Calcd.: Cl, 10.88. Found: Cl, 11.05. Dihydrochloride: m.p. 251–253°. Calcd.: Cl, 19.57. Found: Cl, 19.3. [l] After recrystallization from acetone. [m] After resolidifying, 190–195°.

paper by careful addition of 1% ammonium hydroxide. From the filtrate, the amidine base was precipitated by ammonium hydroxide and recrystallized from dilute ethanol.

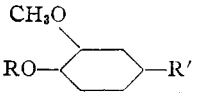
The monohydrochloride crystallized as prisms of m.p. 256° (dec.) and was moderately soluble in water. The dihydrochloride melted at 251–253° and was readily soluble in water.

4-Nitro-4′-phthalimidoethylaminodiphenyl Sulfone (XVI).—Attempted condensation of 4-nitro-4′-aminodiphenyl sulfone with β-bromoethylphthalimide in a solution of diethylene glycol monoethyl ether was unsuccessful, even in the presence of pyridine. A mixture of 5 g. of 4-nitro-4′-aminodiphenyl sulfone and of 5 g. of β-bromoethylphthalimide was heated in an oil-bath at 150–160°. The mixture melted and became crystalline. The heating was continued for 90 minutes. The product was pulverized and extracted with 250 cc. of hot 4 *N* hydrochloric acid in order to remove unchanged sulfone. The substance was washed with hot 4 *N* hydrochloric acid, then with 2 *N* hydrochloric acid and finally with water. Yellow crystals were obtained after recrystallization of the crude product (5.4–5.6 g.) from acetone (charcoal). The substance was not soluble in hot 4 *N* hydrochloric acid, readily soluble in acetone, ethyl acetate and dioxane, and sparingly soluble in hot ethanol.

4-Amino-4′-phthalimidoethylaminodiphenyl Sulfone (XVII) and Bis-(4-phthalimidoethylaminophenyl) Sulfone (XVIII).—A mixture of 20 g. of bis-(4-aminophenyl) sulfone and 10 g. of β-bromoethylphthalimide was melted with occasional stirring at 160–165° in an oil-bath for one hour. Two batches were combined, pulverized, and boiled with 3 l. of 2 *N* hydrochloric acid. Compound XVIII (about 9 g.) remained undissolved. From the hot filtrate, XVII separated in flakes, which were recrystallized from 50% acetic acid. Repeated recrystallizations of XVIII from glacial acetic acid and from dioxane were necessary to obtain it in a nearly pure state.

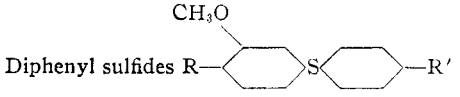
TABLE II

INTERMEDIATES



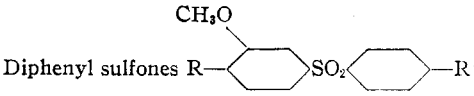
	R	R′	Formula	M.p., °C. uncor.	Yield, %	Analyses, % Sulfur Calcd.	Found
XXIII	CH_3CO-	$-SO_3K$	$C_9H_9KO_6S\cdot H_2O$[a]	290 (dec.)	97	10.60	10.73
XXIV	CH_3CO-	$-SO_2Cl$	$C_9H_9ClO_5S$[b]	85–86	94	12.11	12.21
XXV	CH_3CO-	$-SO_2H$	$C_9H_{10}O_5S\cdot{}^1/_2H_2O$[c]	125–130	50	13.40	13.60
XXVI			$C_{14}H_{14}O_4S_2$[d]	123–125		20.66	20.79

Diphenyl sulfides



XXVII	$-NO_2$	$-NH_2$	$C_{13}H_{12}N_2O_3S$	148–150	67–81	11.60	11.89
XXVIII	$-NO_2$	-NHAc	$C_{15}H_{14}N_2O_4S$[e]	136–138	92	10.07	10.28
XXIX	$-NH_2$	-NHAc	$C_{15}H_{16}N_2O_2S$	105	80–90	11.12	11.25
XXX	$-NH_2$	$-NH_2$	$C_{13}H_{14}N_2OS$[f]	49		13.02	13.17
XXXI	-OH	$-NO_2$	$C_{13}H_{11}NO_4S$	91–92	51	11.56	11.45

Diphenyl sulfones



XXXII	$-NO_2$	-NHAc	$C_{15}H_{14}N_2O_6S$	201	100	9.15	9.28
XXXIII	$-NH_2$	-NHAc	$C_{15}H_{16}N_2O_4S$	211–213	81	10.01	10.26
XXXIV	$-NH_2$	$-NH_2$	$C_{13}H_{14}N_2O_3S$	203	80	11.52	11.44
XXXV	-OH	$-NO_2$	$C_{13}H_{11}NO_6S$	199.5–200	93	10.37	10.24
XXXVI	-OH	$-NH_2$	$C_{13}H_{13}NO_4S$[g]	187–187.5	55	11.48	11.51

[a] Calcd.: K, 12.93; H_2O, 5.96. Found: K, 12.91; H_2O, 5.94. [b] Calcd.: Cl, 13.40. Found: Cl, 13.33. [c] Calcd.: H_2O, 3.77. Found: H_2O, 3.75. [d] Calcd.: C, 54.17; H, 4.55. Found: C, 54.26; H, 4.63. [e] Monohydrate. Calcd.: H_2O, 5.36. Found: H_2O, 5.37. [f] Dihydrochloride. Calcd.: Cl, 22.21; S, 10.04. Found: Cl, 22.10; S, 9.96. [g] Calcd.: C, 55.90; H, 4.96. Found: C, 56.11; HH, 4.86.

4-Nitro-4′-phthalylaminoethylaminodiphenyl Sulfone (XIX).—To a suspension of 1 g. of XVI in 50 cc. of 95% ethanol, 0.5 cc. of 10 *N* potassium hydroxide was added. With gentle warming an orange solution was formed, which upon addition of 0.5 *N* hydrochloric acid yielded a fine yellow, crystalline powder of XIX. This compound when heated *in vacuo* at 102° was transformed to XVI with ring closure.

4-Nitro-4′-aminoethylaminodiphenyl Sulfone (XX).—Refluxing of XVI with concentrated hydrochloric acid for nine hours yielded only 10% of XX. A better result was obtained by refluxing 0.9 g. of XVI with 4 cc. of molar hydrazine hydrate solution in 20 cc. of 95% ethanol. After 75 minutes of refluxing, solution was complete. Refluxing was continued for three hours. The yellow crystals, which separated on cooling, were boiled with 4 *N* hydrochloric acid and the solution filtered hot. Colorless crystals of a hydrochloride separated on cooling. The base was freed with ammonium hydroxide. Yellow crystals of XX were obtained.

4-Amino-4′-aminoethylaminodiphenyl Sulfone (XXI).—Compound XVII (36 g.) was refluxed with concentrated hydrochloric acid (360 cc.) for seven hours. The reaction product, after cooling, consisted of a crystalline mixture of the dihydrochloride of XXI and phthalic acid. It was extracted with cold water and mixed with 10% ammonium hydroxide. The monohydrochloride of XXI separated, but was not isolated. An excess of ammonia yielded XXI which was recrystallized from dilute ethanol. From boiling water, colorless needles were obtained. The solubility in boiling water was approximately 0.8%, in water at 28° about 0.13%. The picrate was sparingly soluble in water. Removal of the phthalic acid residue with hydrazine hydrate was completed within one hour and gave a 70% yield of XXI.

Bis-(4-β-aminoethylaminophenyl) Sulfone (XXII).—This compound was obtained by refluxing XVIII with an excess of hydrazine hydrate in ethanol for four hours. The base was crystallized from ethanol.

3-Methoxy-4-nitro-4′-aminodiphenyl Sulfide (XXVII).—A mixture of 240 g. of crystalline sodium sulfide, 64 g. of *p*-chloronitrobenzene and 1000 cc. of water was refluxed for seven hours. After the addition of 76 g. of 1-chloro-3-methoxy-4-nitrobenzene[18] to the hot solution, refluxing was continued for 16 hours. The orange oil, produced in the reaction, solidified upon cooling. The product was washed with water and recrystallized from ethanol as yellow crystals.

3-Methoxy-4-nitro-4′-acetylaminodiphenyl Sulfide (XXVIII).—The acetyl derivative of XXVII was prepared in the usual way with a mixture of glacial acetic acid and acetic anhydride.

3-Methoxy-4-amino-4′-acetylaminodiphenyl Sulfide (XXIX).—Compound XXVIII was reduced with stannous chloride in a suspension of glacial acetic acid, the tin being removed with sodium hydroxide. The product crystallized as colorless needles from 50% ethanol. Attempts to replace the 4-amino group by a hydroxyl group through diazotization and heating with sulfuric acid[12] were unsuccessful.

3-Methoxy-4,4′-diaminodiphenyl Sulfide (XXX).—Compound XXIX was deacetylated by boiling with 5 *N* hydrochloric acid for 50 minutes. From the cooled solution, colorless needles of a dihydrochloride separated. The free base was obtained as an oil which could be crystallized from benzene by the addition of petroleum ether.

3-Methoxy-4-nitro-4′-acetylaminodiphenyl Sulfone (XXXII).—Compound XXVII was acetylated and oxidized with acetic anhydride and 30% hydrogen peroxide at 70–85°. The product crystallized as fine colorless needles from ethanol.

3-Methoxy-4-amino-4′-acetylaminodiphenyl Sulfone (XXXIII).—Compound XXXII was reduced as described for the preparation of XXIX. The product crystallized as fine needles from 50% ethanol. Attempts to replace the 4-amino group by a hydroxyl group were unsuccessful.

3-Methoxy-4,4′-diaminodiphenyl Sulfone (XXXIV).—Compound XXXIII was deacetylated by boiling with 5 *N* hydrochloric acid for 30 minutes, and the base liberated by the addition of ammonium hydroxide. The product crystallized as colorless needles from 50% ethanol.

Potassium 3-Methoxy-4′-hydroxybenzenesulfonate.—The procedure used was essentially that described.[19] From

(18) J. J. Blanksma, *Rec. trav. chim.*, **21**, 321 (1902).

(19) German Patent 188,506; Chem. Fabrik v. Heyden, in P. Friedlaender, *Fortschr. d. Teerfarbenfabrikation*, **8**, 936; *cf.* F. A. Rising, *Ber.*, **39**, 3685 (1906).

124 g. of guaiacol, 108 g. of large crystals of potassium 3-methoxy-4-hydroxybenzenesulfonate were obtained. The product gave a blue color reaction with ferric chloride.

Potassium 3-Methoxy-4-acetoxybenzenesulfonate (XXIII).—A mixture of 100 g. of the foregoing potassium salt with 200 cc. of acetic anhydride was heated to boiling with stirring for ten minutes. The reaction mixture was cooled and washed with ethyl acetate. Colorless needles, containing one mole of water, crystallized from ethanol.

3-Methoxy-4-acetoxybenzenesulfonyl Chloride (XXIV).—A mixture of equal weights of XXIII and of phosphorus pentachloride was gently warmed and poured into ice-water. The white, powdery sulfonyl chloride was crystallized from ligroin.

3-Methoxy-4-acetoxybenzenesulfinic acid (XXV) was prepared by the reduction of XXIV with sodium sulfite.

3-Methoxy-4-hydroxybenzene Thiol and Bis-(3-methoxy-4-hydroxyphenyl) Disulfide (XXVI).—The thiol was prepared using the procedure described for the preparation of thiophenol.[20] Compound XXIV (82 g.) was added to a stirred mixture of 173 cc. of concentrated sulfuric acid and 970 g. of ice at a temperature of −5°. Then 162 g. of zinc dust was added within ten minutes. The temperature was kept below 0° for two hours, then the reaction mixture was slowly heated until a reaction with evolution of heat took place. The mixture was cooled and the temperature kept at about 60° until the reaction subsided. The temperature was raised to 110° with constant stirring until the zinc dust had dissolved. The oily reaction product was separated from the mother liquor, dissolved in ether and dried with calcium chloride. The ether was distilled off; the remaining crude thiophenol (57 g.) was slightly yellow colored and was used for the following condensation with nitrobromobenzene. A sample of the crude thiophenol was distilled under diminished pressure; the boiling point was 150–152° at 20 mm. From the crude thiophenol, the corresponding disulfide (XXVI) could be isolated by dissolving a sample of 5 g. in little benzene and adding petroleum ether until the mixture became turbid. Crystals separated (1.9 g.) which were recrystallized from 36% acetic acid (charcoal). Colorless needles (1.2 g.) of m.p. 123–125° were obtained. Analysis agreed with the formula of XXVI.

3-Methoxy-4-hydroxy-4′-nitrodiphenyl Sulfide (XXXI).—The foregoing crude thiol (20 g.) was dissolved in a solution of 20 g. of potassium hydroxide in 200 cc. of methanol. To the mixture, 25 g. of *p*-bromonitrobenzene was added; a violent reaction occurred. The mixture was refluxed for six hours, then poured into water. The sticky mass was converted to the orange sodium salt by the addition of an excess of aqueous sodium hydroxide. The free acid, crystallized from 36% acetic acid, formed light yellow needles.

3-Methoxy-4-hydroxy-4′-nitrodiphenyl Sulfone (XXXV).—Compound XXXI (11.2 g.) was added to a mixture of 110 cc. of acetic anhydride and 55 cc. of 30% hydrogen peroxide. The temperature was kept at about 60° by cooling with water. The sulfide went rapidly into solution; from the reaction mixture pale yellow crystals separated. Water was added to complete precipitation. The crystals were collected, washed with water and dried in the desiccator (11.7 g.). From 36% acetic acid, pale yellow needles were obtained. A crystalline orange sodium salt was obtained by dissolving XXXV in dilute sodium hydroxide solution and adding an excess of 5 *N* sodium hydroxide.

3-Methoxy-4-hydroxy-4′-aminodiphenyl Sulfone (XXXVI).—Reduction of XXXV was performed with stannous chloride in glacial acetic acid, the tin being removed by hydrogen sulfide. From hot water, feathery needles were obtained.

(20) R. Adams and C. S. Marvel, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 504.

Appendix

Sodium Estimation in the Presence of Phosphorus.—If sodium and phosphorus are present in the molecular ratio of 1:1, the estimation can be carried out by destroying the organic compound in a crucible with sulfuric and nitric acids and igniting. The residue then consists of sodium metaphosphate. In this way, sodium and phosphorus can be determined in one procedure.

Determination of Nitrogen Bound to Phosphorus (Amide Nitrogen).—About 1.5 g. of substance was boiled in a Kjeldahl flask with 5 cc. of hydrochloric acid of sp. gr. 1.12 for 30 minutes, in order to hydrolyze the amide. The flask was then connected with the distilling apparatus, the contents were alkalized with 22 cc. of 10 *N* sodium hydroxide solution, and distilled.

Acknowledgment.—I am indebted to Mr. E. A. Garlock, Mr. W. C. Alford, Mrs. M. M. Ledyard and Mrs. E. G. Peake for carrying out the microanalyses.

BETHESDA, MARYLAND RECEIVED AUGUST 10, 1950

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

The Action of Ammonia and Amines on 1,4-Dichloro-2-butene[1]

BY LAWRENCE H. AMUNDSEN, ROWLAND H. MAYER, LEONARD S. PITTS AND LENA A. MALENTACCHI

The vapor phase reaction between approximately equimolecular amounts of chlorine and butadiene is more satisfactory than liquid phase reactions for the preparation of 1,4-dichloro-2-butene. The product obtained from the vapor phase reaction appears to differ from *cis*-1,4-dichloro-2-butene prepared from *cis*-2-butene-1,4-diol, and is presumably *trans*.

Secondary amines react with 1,4-dichloro-2-butene to give fair yields of the corresponding diamine, whereas primary amines or ammonia under the conditions tried give largely polycondensation products. 1,4-Dichloro-2-butene has been converted to N,N,N′,N′-tetramethyl-, tetraethyl-, tetra-*n*-propyl- and tetra-*n*-butyl-2-butene-1,4-diamine and also to N,N-diethyl-2-butene-1,4-diamine, N,N′-dibutyl-2-butene-1,4-diamine and 2-butene-1,4-diamine.

Now that 1,3-butadiene is one of the cheap industrial chemicals there are many interesting possibilities for the synthesis of other compounds from it. It has been the purpose of this investigation to study the possibility of the synthesis of diamines by adding chlorine to 1,3-butadiene and treating the 1,4-dichloro-2-butene resulting therefrom with ammonia and with amines.

It was found that the addition of chlorine to butadiene was best accomplished by vapor phase reaction using equimolecular amounts of the gases. The reaction between the resulting 1,4-dichloro-2-butene and secondary amines gave fair yields of N,N,N′,N′-tetraalkyl diamines, but similar reactions with primary amines and with ammonia gave little diamine, the major products being condensation polymers.

After experimenting with certain modifications of the previously reported methods of carrying out the reaction between chlorine and butadiene,[2,3,4] we came to the conclusion that the reaction is best carried out between equal molecular quantities of the reactants in the vapor phase.

(1) Reported in part at the 109th Meeting of the American Chemical Society, April 10, 1946.

(2) Muskat and Northrup, THIS JOURNAL, **53**, 4043 (1930).

(3) Schmidt, German Patent 709,942 (1941).

(4) Hearne and LaFrance, U. S. Patent 2,299,477 (1942).