purified by rapid recrystallization from hot 2*N* HCl; the white, well-crystallized compound decomposes at about 260°, after partial melting around 220°, followed by resolidification. From its solution in warm water, aqueous Na_2CO_3 precipitated the base (VI), m.p. 173° (bath preheated to 160°), alone and in mixture with authentic material. Heating of a sample of the substance with dilute HCl (1:1) in a boiling water bath for 20 min. converted to III, m.p. and mixed m.p. 275° after purification via the perchlorate.

VI forms a crystalline perchlorate of low water-solubility; decomp. 257°.

BETHESDA 14, MD.

[CONTRIBUTION NO. 368 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

4-Aminomethyl-4′-aminodiphenylsulfone and Related Compounds*

WILHELM WENNER

Received May 17, 1957

4-Aminomethyl-4′-aminodiphenylsulfone and a number of its derivatives carrying substituents in the aliphatic amino group have been prepared starting with 4-methyl-4′-nitrodiphenylsulfone. Several related compounds are described.

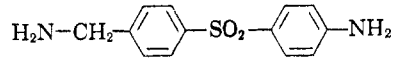
The chemotherapeutic properties of sulfanilamide are changed considerably when the aromatic amino group is replaced by the aminomethyl substituent. Whereas sulfanilamide is more active against aerobic bacteria, 4-aminomethylbenzenesulfonamide[1–4] is superior in its action against anaerobic bacteria.[2,5–8] It appeared worthwhile to prepare compounds containing an aromatic as well as an aliphatic amino group, with the hope of obtaining a sulfa drug exhibiting both types of activity. The simplest compound of this type is 4-aminomethyl-4′-aminodiphenylsulfone I. This sulfone has been described by Klarer[6] and by Dewing,[9] who prepared it from 4-acetylaminomethylbenzenesulfinic acid. In order to obtain in addition to 4-aminomethyl-4′-aminodiphenylsulfone derivatives carrying substituents in the aliphatic amino group, I carried out a different synthesis by which such derivatives are accessible in an unambiguous manner.

The key intermediate in the synthesis is 4-methyl-4′-nitrodiphenylsulfone[10] (II). The compound is prepared in high yields from *p*-thiocresol and *p*-nitrochlorobenzene over 4-methyl-4′-nitrodiphenylsulfide[11] (III), which is oxidized with hydrogen peroxide to II. The alternative procedure of condensing *p*-toluenesulfinic acid with *p*-nitrochlorobenzene gave only low yields.

The sulfone II was brominated to the bromomethyl derivative IV. The method of Genvresse,[12] using elementary bromine at 160°, gave poor yields. However, when benzoyl peroxide was added, the bromination in nitrobenzene proceeded well, resulting in yields of 70% and more of IV.

Reaction of the bromosulfone with a number of secondary amines and with benzylamine gave the amino nitro sulfones listed in Table I. Compound V, unsubstituted in the amino group, was obtained according to Mannich and Hahn[13] by the treatment of IV with hexamethylenetetramine followed by acid cleavage.

Catalytic hydrogenation of the nitro derivatives yielded the desired 4-aminomethyl-4′-aminodiphenylsulfone (I) and its alkyl derivatives, listed in Table III. The compounds lack outstanding chemo-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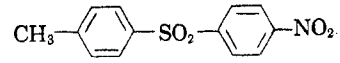
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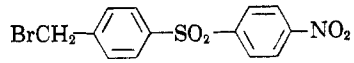
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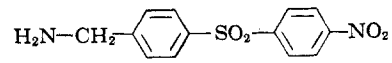
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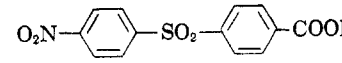
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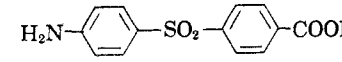
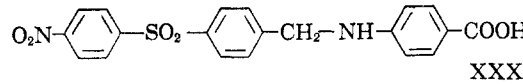

XXXI


XXXVI

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Anonymous, *Nature*, **153**, 707 (1944).

(2) Hamre, Walker, Dunham, van Dyke, and Rake, *Proc. Soc. Exp. Biol. Med.*, **55**, 170 (1944).

(3) Klarer, U. S. Patent **2,288,531**; *Chem. Abstr.*, **37**, 888 (1943); Germ. Pat. **726,386**, *Chem. Zentr.*, **114 I**, 978 (1943).

(4) Klarer, *Angew. Chem.*, **56**, 10 (1943).

(5) Klarer, *Klin. Wochschr.*, **20**, 1250 (1941); *Chem. Abstr.*, **37**, 5704 (1943).

(6) Klarer, *Naturforschung und Medizin in Deutschland 1939–1946*, Vol. **43**, Chemotherapie, Wiesbaden, Dietrichsche Verlagsbuchhandlung, 1948, p. 1935.

(7) Lawrence, *J. Bacteriol.*, **49**, 149 (1945).

(8) Mitchell, *Lancet*, **I**, 627. 635 (1944).

(9) Dewing, *J. Chem. Soc.*, 466 (1946).

(10) Louden, *J. Chem. Soc.*, **218**, 220 (1936).

(11) Law and Johnson, *J. Am. Chem. Soc.*, **52**, 3623 (1930).

(12) Genvresse, *Bull. soc. chim. France*, (3) **9**, 707 (1893).

(13) Mannich and Hahn, *Ber.*, **44**, 1542 (1911).

therapeutic properties. Some quaternary derivatives were also prepared. They are listed in Table II.

In addition to these sulfones, two nitro amino sulfides were prepared through the ω-bromo derivative of 4-methyl-4′-nitrodiphenylsulfide (III). The bromination of III in the same manner as described above for the sulfone did not succeed. With *N*-bromosuccinimide and benzoyl peroxide[14] a small amount of the bromomethyl compound XXVI was formed, which was not isolated in pure form. It was allowed to react in the crude state with the appropriate amines to the piperidino (XXVII) and the benzylamino derivative (XXVIII).

The sulfone II was oxidized to the nitro acid XXIX, which was then reduced to the amino acid XXXI. This acid has previously been prepared in a different manner by Roblin and Clapp.[15] Both acids were converted into their methyl esters. The methyl ester of XXXI was converted into the hydrazide XXXIII. None of the acids or their derivatives showed valuable chemotherapeutic properties.

To complete the series of the amino derivatives, the intermediates II and III were catalytically hydrogenated to 4-methyl-4′-aminodiphenylsulfide[11] (XXXIV) and 4-methyl-4′-aminodiphenylsulfone[10] (XXXV). Both compounds showed only moderate antibacterial activity.

When the bromosulfone IV is allowed to react with *p*-aminobenzoic acid, 4-[4-(4-nitrophenylsulfonyl)benzylamino]benzoic acid XXXVI is obtained. Catalytic hydrogenation gave the corresponding amino acid XXXVII.

EXPERIMENTAL

The melting points are uncorrected.

(*1*) *4-Methyl-4′-nitro-diphenylsulfide*[11] (III). To a stirred refluxing solution of 248 g. of *p*-thiocresol and 315 g. of *p*-nitrochlorobenzene in 2000 ml. of abs. ethanol, a solution of 90 g. of sodium hydroxide in 100 ml. of water was slowly added. Heating was continued after complete addition for 3 to 4 hr. After cooling and addition of about 200 ml. of water, 4-methyl-4′-nitrodiphenylsulfide crystallized. Recrystallization from ethanol gave the pure compound which was light yellow and melted at 76–78°. Law and Johnson[11] give m.p. 81.5°. The yield was 450–470 g.

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 64.19; H, 4.41; N, 5.65.

(*2*) *4-Methyl-4′-aminodiphenylsulfide*[11] (XXXIV). 4-Methyl-4′-nitrodiphenylsulfide (15 g.) was hydrogenated in 45 ml. of methanol to which 0.1 ml. of acetic acid had been added, with 2 g. of Raney nickel, at 50–60° and 300 lbs. pressure. The filtered solution was distilled to dryness and the residue was crystallized from abs. ethanol, yielding 10 g. of pure 4-methyl-4′-aminodiphenylsulfide of m.p. 178–179°. Law and Johnson[11] report m.p. 183–184°.

Anal. Calcd. for $C_{13}H_{13}NS$: C, 72.52; H, 6.08; N, 6.51. Found: C, 72.38; H, 5.68; N, 6.53.

(*3*) *4-Methyl-4′-nitrodiphenylsulfone* (II). A. From the sulfide. A solution of 400 g. of 4-methyl-4′-nitrodiphenylsulfide in 2000 ml. of glacial acetic acid was stirred and heated to 80–90°. Over a period of about 1 hr., 600 g. of hydrogen peroxide (30%) were added slowly. The originally dark brown solution turned bright yellow and shortly after the beginning of the oxidation, crystals appeared. Heating was continued for 1 hr. after complete addition of the hydrogen peroxide. After cooling for several hours at 0–10°, the sulfone was filtered. It melted at 169°. The yield was 430–440 g.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.30; H, 4.00; N, 5.05. Found: C, 56.41; H, 3.83; N, 5.01.

B. *From 4-toluene sulfinic acid* (13). The sodium salt of 4-toluenesulfinic acid[16] (6 g.), 8 g. of 4-nitrochlorobenzene and 20 ml. of abs. ethanol were heated to 170° for 3 hr. in a bomb tube.[17] The resulting dark material was digested with hot water and, after cooling, the undissolved portion was extracted with ether. The remaining crystals were recrystallized from acetic acid, yielding 1.3 g. of 4-methyl-4′-nitrodiphenylsulfone of m.p. 166–168°.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.30; H, 4.00; N, 5.05. Found: C, 56.36; H, 3.74; N, 4.95.

The yield could not be improved by adding copper powder, or by using the copper salt of 4-toluenesulfinic acid, or by using other solvents (ethyleneglycol, "carbitol").

(*4*) *4-Methyl-4′-aminodiphenylsulfone*[10] (XXXV). 4-Methyl-4′-nitrodiphenylsulfone (II), (20 g.), was suspended in 30 ml. of methanol. The mixture was hydrogenated with about 2 g. of Raney nickel at 50–60° and 500 lbs. Part of the product had crystallized. It was brought into solution by addition of about 50–70 ml. of methanol and refluxing. The catalyst was removed by filtration of the hot mixture. The filtrate was concentrated to a small volume and was allowed to cool. The crude crystals were recrystallized from 50% acetic acid, yielding 15 g. of pure 4-methyl-4′-aminodiphenylsulfone of m.p. 180–182°.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.68. Found: N, 5.95.

(*5*) *4-Bromomethyl-4′-nitrodiphenylsulfone* (IV). A mixture of 72 g. of 4-methyl-4′-nitrodiphenylsulfone and 80 ml. of nitrobenzene was stirred and heated to 155–160°. After addition of 1 g. of benzoyl peroxide, 16 ml. of bromine were added through a dropping funnel below the surface of the reaction mixture. The addition was regulated so that no bromine escaped. This required about 4 hr. After cooling, the crystals were filtered and washed thoroughly with benzene. The crude bromo compound weighed about 60–65 g. and melted at 145–150°. It contained some unchanged starting material but was pure enough for further reactions.

The pure bromo derivative was obtained by two crystallizations from 4 vol. of dioxane. It melted at 177–178°.

Anal. Calcd. for $C_{13}H_{10}BrNO_4S$: C, 43.83; H, 2.83. Found: C, 44.16; H, 2.80.

Other methods of bromination (without benzoyl peroxide, in other solvents, with *N*-bromosuccinimide) were unsatisfactory.

(*6*) *4-Aminomethyl-4′-nitrodiphenylsulfone* (V). A mixture of 72 g. of crude 4-bromomethyl-4′-nitro-diphenylsulfone and 30 g. of hexamethylene tetramine in 400 ml. of chloroform was refluxed for 8 hr. The crystals were filtered, washed with chloroform, suspended in 400 ml. of methanolic hydrochloric acid (18% HCl) and stirred for 5 hr., with exclusion of moisture. A precipitate appeared slowly and was filtered after standing overnight. The crystals were refluxed with 800 ml. of fresh methanolic hydrochloric acid (18% HCl) for 5 hr. After cooling, the crystals were filtered, washed with abs. ethanol, and dried in a desiccator. The yield was 34 g. Recrystallization from glacial acetic acid yielded pure 4-aminomethyl-4′-nitrodiphenylsulfone monohydrochloride (V) of m.p. 273–274°.

Anal. Calcd. for $C_{13}H_{12}N_2O_4S \cdot HCl$: C, 47.49; H, 3.99, N, 8.52. Found: C, 47.19; H, 4.04; N, 8.13.

(14) Karrer and Schmid, *Helv. Chim. Acta*, **29**, 573 (1946).

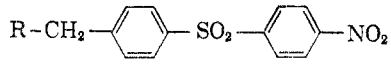
(15) Roblin and Clapp, Brit. Pat. **568,157**; *Chem. Abstr.*, **41**, 3817 (1947).

(16) Whitmore and Hamilton, *Org. Syn.*, **Coll. Vol. I.**, Sec. Ed., 1941, p. 492.

(17) Compare: Ferry, Buck, and Baltzly, *Org. Syn.*, **Coll. Vol. 3**, 1955, p. 239.

TABLE I

4-SUBSTITUTED 4-AMINOMETHYL-4′-NITRO-DIPHENYLSULFONES



Compound	R	Formula	M.P.	Analysis Calcd. / Found C	H	N
V	$-NH_2$	$C_{13}H_{12}N_2O_4S\cdot HCl$		See Exp. 6		
VII	$-N(CH_3)_2$	$C_{15}H_{16}N_2O_4S$		See Exp. 9		
		$C_{15}H_{16}N_2O_4S\cdot HCl$		See Exp. 9		
VIII	$-N(C_2H_5)_2$	$C_{17}H_{20}N_2O_4S$	76°	58.60 58.73	5.79 5.76	8.02 7.88
		$C_{17}H_{20}N_2O_4S\cdot HCl$	206°	53.08 53.23	5.50 5.65	7.08 7.40
IX	$-N(CH_2CH_2CH_3)_2$	$C_{19}H_{24}N_2O_4S$	77–78°	60.61 60.80	6.43 6.16	7.44 7.23
		$C_{19}H_{24}N_2O_4S\cdot HBr$	180–182°	49.87 50.34	5.51 5.45	6.13 6.05
X	$-N(CH_2CH_2CH_2CH_3)_2$	$C_{21}H_{28}N_2O_4S$	59–60°	62.35 62.13	6.98 6.61	6.93 7.00
		$C_{21}H_{28}N_2O_4S\cdot HBr$	160–161°	51.88 52.01	6.02 6.11	5.77 5.54
XI	$-N(CH_2CH_2)_2CH_2$	$C_{18}H_{20}N_2O_4S$	66–68°	59.98 59.87	5.59 5.17	7.77 7.42
		$C_{18}H_{20}N_2O_4S\cdot HCl$	237–238°	54.47 54.56	5.33 5.34	7.06 6.98
XII	$-N(CH_2CH_2)_2O$	$C_{17}H_{18}N_2O_5S$	170–171°	56.34 56.52	5.01 5.15	7.73 7.67
		$C_{17}H_{18}N_2O_5S\cdot HBr$	218–220°	46.05 45.81	4.32 4.60	6.23 6.06
XIII	$-NH\cdot CH_2C_6H_5$	$C_{20}H_{18}N_2O_4S\cdot HCl$	259–260°	57.33 57.09	4.41 4.32	6.69 6.59

(7) *4-(4-Nitrophenylsulfonyl)benzylurea* (VI). 4-Aminomethyl-4′-nitrodiphenylsulfone hydrochloride (7 g.), (Exp. 6), was dissolved by warming in 200 ml. of dilute methanol (60%). A solution of 2 g. of potassium cyanate in 25 ml. of water was added and the mixture was heated to 70–80° for 4 hr. Crystals separated slowly. They were purified by two crystallizations from 50% acetic acid and one crystallization from *n*-butanol. The yield of pure 4-(4-nitrophenyl-sulfonyl)benzylurea of m.p. 198–200° was 4 g.

Anal. Calcd. for $C_{14}H_{13}N_3O_5S$: C, 50.15; H, 3.91; N, 12.53. Found: C, 50.08; H, 3.47; N, 12.26.

(8) *Substituted 4-aminomethyl-4′-nitrodiphenylsulfones.* The reactions between 1 mole of 4-bromomethyl-4′-nitrodiphenylsulfone and two moles of secondary amines were carried out by warming the components in benzene, toluene, dioxan, or chloroform. The resulting amino derivatives were isolated over the free bases and converted into salts with mineral acids. As an example, the preparation of one compound is described in detail.

(9) *4-Dimethylaminomethyl-4′-nitrodiphenylsulfone* (VII). Crude 4-bromomethyl-4′-nitrodiphenylsulfone (39 g.) was dissolved in 200 ml. of hot dioxan. The solution was added slowly through a dropping funnel to a stirred solution of 18 g. of dimethylamine in 80 ml. of benzene which was cooled to 20–25°. When the addition was finished, the mixture was warmed for 1 hr. to 40–50°. Dimethylamine hydrobromide crystallized and was filtered off. The filtrate was distilled to dryness *in vacuo*. The residue was boiled with about 600 ml. of 10% hydrochloric acid for 1 hr. This converted the 4-methyl-4′-nitrodiphenylsulfone present as by-product in the starting material into an easy filterable form. The hot mixture was filtered and the filtrate was cooled overnight in the refrigerator. The crude 4-dimethylaminomethyl-4′-nitrodiphenylsulfone hydrochloride was filtered. It was dissolved in water in which it is much more soluble than in dil. hydrochloric acid. The solution was charcoaled and filtered and the filtrate was made strongly acid by addition of concd. hydrochloric acid. The pure 4-dimethylaminomethyl-4′-nitrodiphenylsulfone hydrochloride melted at 243–244°, yield 25–30 g.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S\cdot HCl$: C, 50.49; H, 4.80; N, 7.85. Found: C, 50.75; H, 4.67; N, 7.56.

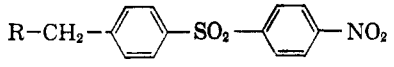
The compound is practically insoluble in acetone and little soluble in alcohol.

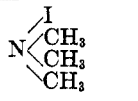
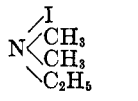
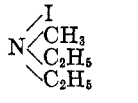
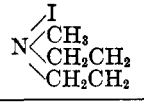
The free base was obtained by dissolving the hydrochloride in water, adding ammonia, and extracting with ether. The ether solution was dried over potassium carbonate and concentrated to a small volume. On cooling, 4-dimethylaminomethyl-4′-nitrodiphenylsulfone of m.p. 106–107° crystallized.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.23; H, 5.03; N, 8.75. Found: C, 56.33; H, 4.99; N, 8.75.

In Table I are listed the amino derivatives prepared essentially in the above manner. The solubility in water of the

TABLE II



Compounds	R	Formula	M.P.	Analysis Calcd. / Found C	H	N
XIV		$C_{16}H_{19}IN_2O_4S$	226–227°	See Exp. 10A		
XV		$C_{17}H_{21}IN_2O_4S$	215°	42.86 / 42.87	4.44 / 4.32	5.88 / 6.22
XVI		$C_{18}H_{23}IN_2O_4S$	138–139°	44.09 / 44.40	4.73 / 4.55	
XVII		$C_{19}H_{23}IN_2O_4S$	200–201°	45.42 / 45.49	4.61 / 4.48	

salts of these substituted compounds with mineral acids decreases with increasing molecular weight.

(*10*) *Quaternary derivatives of 4-aminomethyl-4′-nitrodiphenylsulfones.* Some of the nitrocompounds were reacted with methyl iodide to the quaternary bases. As an example, the preparation of the methiodide of VII is described.

A. 4-Dimethylaminomethyl-4′-nitrodiphenylsulfone methiodide (XIV). 4-Dimethylaminomethyl-4′-nitrodiphenyl sulfone (9 g.) was dissolved in 100 ml. of acetone and 5 g. of methyliodide were added. Within 10 min. crystals of the methiodide started to separate. After standing overnight, the dark orange-colored methiodide was filtered and recrystallized from methanol and ether. The yield was 16 g. of m.p. 226–227°.

Anal. Calcd. for $C_{16}H_{19}IN_2O_4S$: C, 41.57; H, 4.14; N, 6.06. Found: C, 41.50; H, 4.34; N, 6.15.

B. *4-Dimethylaminomethyl-4′-nitrodiphenylsulfone methochloride* (XVIII). 4-Dimethylaminomethyl-4′-nitro-diphenylsulfone methiodide (16 g.) was shaken for 24 hr. in 500 ml. of methanol with freshly prepared silver chloride from 10 g. of silver nitrate. The solution was filtered and the silver chloride residue was extracted repeatedly with fresh methanol. The combined methanol solutions were evaporated. The crystalline residue was recrystallized from a little methanol, yielding 8 g. of 4-dimethylaminomethyl-4′-nitrodiphenylsulfone methochloride of m.p. 271°, containing one mole of water of crystallization.

Anal. Calcd. for $C_{16}H_{19}ClN_2O_4S \cdot H_2O$: C, 49.41; H, 5.44; N, 7.21. Found: C, 49.65; H, 5.92; N, 6.94.

C. A few of the other sulfones were also converted into their methiodides. They are listed in Table II.

(*11*) *Reduction of 4-aminomethyl-4′-nitrodiphenylsulfones.* The nitro derivatives described above were reduced catalytically to the corresponding amines. The hydrogenations were carried out mostly by dissolving or suspending the hydrochlorides of the 4-aminomethyl-4′-nitrodiphenylsulfones in water and using Raney nickel as catalyst. The reductions can be carried out also with palladium charcoal in acetic acid.

A. *4-Aminomethyl-4′-aminodiphenylsulfone* (I). 4-Aminomethyl-4′-nitrodiphenylsulfone (10 g.) was suspended in 50 ml. of water and hydrogenated with 2 g. of Raney nickel at 40° and 400 lbs. pressure. When the absorption of hydrogen had stopped, the solution was filtered and distilled to dryness. The crystalline residue was recrystallized from ethanol, yielding 6 g. of pure 4-aminomethyl-4′-aminodiphenylsulfone monohydrochloride of m.p. 195°. The compound contained one mole of water of crystallization. It is very soluble in water.

Anal. Calcd. for $C_{13}H_{14}N_2O_2 \cdot HCl \cdot H_2O$: C, 49.28; H, 5.41; N, 8.84. Found: C, 49.27; H, 5.31; N, 8.87.

The free base may be obtained by neutralizing an aqueous solution of the hydrochloride. It is, however, not very stable and discolors soon in the air, even in the dry state.

B. *Substituted 4-amino-methyl-4′-aminodiphenylsulfones.* The catalytic hydrogenation of the nitro compounds listed in Table I was carried out essentially in the same manner as described in Experiment 11A. The resulting diamines are listed in Table III. In contrast to the compound I the substituted compounds are considerably more stable as free bases. They are best purified by crystallization as free bases. Their salts with mineral acids are generally quite soluble in water.

(*12*) *4-Dimethylaminomethyl-4′-aminodiphenylsulfone methochloride.* 4-Dimethylamino-methyl-4′-nitrodiphenylsulfone methochloride (4 g.) was dissolved in about 50 ml. of water. After addition of 5 ml. of acetic acid the solution was hydrogenated at 25–30° and 50 lbs. pressure. The resulting solution was distilled to dryness. The residue was dissolved in about 5 ml. of water. Acetone was added until a slight turbidity developed. On standing, 2 g. of 4-dimethylaminomethyl-4′-aminodiphenylsulfone methochloride of m.p. 194–195° crystallized. The compound contained one molecule of water of crystallization, which was not lost at 120° *in vacuo*.

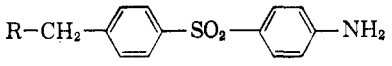
Anal. Calcd for $C_{16}H_{21}ClN_2O_2S \cdot H_2O$: C, 53.54; H, 6.46; N, 7.81. Found: C, 53.61; H, 5.71; N, 7.70.

(*13*) *4-Bromometoyl-4′-nitrodiphenylsulfide* (XXVI). The bromination of 4-methyl-4′-nitrodiphenylsulfide, according to the procedure described above (Exp. 5) for bromination of the corresponding sulfone was not successful, probably because the free bromine oxidizes the sulfur. With bromosuccinimide in the presence of benzoyl peroxide, bromination occurred, but the yields were low. The reaction product, 4-bromomethyl-4′-nitrodiphenylsulfide, is not very stable and is difficult to purify. It was therefore used in the crude state as obtained by simple evaporation of the solution in carbon tetrachloride for the following experiments.

(*14*) *4-(N-Piperidinomethyl)-4′-nitrodiphenylsulfide* (XXVII). 4-Methyl-4′-nitrodiphenylsulfide (25 g.), 18 g. of *N*-bromosuccinimide, and 2 g. of benzoyl peroxide were refluxed in 100 ml. of carbon tetrachloride. Almost immediately after refluxing started, bromine vapors appeared. After 8

TABLE III

4-SUBSTITUTED AMINOMETHYL-4′-AMINO-DIPHENYLSULFONES



Compound	R	Formula	M.P.	Analysis Calcd. / Found C	H	W
I	NH_2	$C_{13}H_{14}N_2O_2S\cdot HCl$	195°	See Exp. 11A		
XIX	$N(CH_3)_2$	$C_{15}H_{18}N_2O_2S$	163–165°	62.04 / 62.18	6.25 / 6.52	9.65 / 9.21
		$C_{15}H_{18}N_2O_2S\cdot HCl\cdot{}^1/_2H_2O$	284–285°	53.64 / 53.52	6.00 / 5.72	8.34 / 8.59
XX	$N(C_2H_5)_2$	$C_{17}H_{22}N_2O_2S$	167–168°	64.12 / 64.43	6.97 / 6.15	8.50 / 8.39
		$C_{17}H_{22}N_2O_2S\cdot HCl\cdot{}^1/_2H_2O$	206°	56.11 / 56.05	6.65 / 6.27	7.70 / 7.47
XII	$N(CH_2CH_2CH_3)_2$	$N_{19}H_{26}N_2O_2S\cdot{}^1/_2H_2O$	108–110°	64.19 / 63.99	7.66 / 7.32	7.88 / 7.56
XXII	$N(CH_2CH_2CH_2CH_3)_2$	$C_{21}H_{30}N_2O_2S$	92–93°	67.34 / 67.55	8.07 / 7.66	7.88 / 7.42
XXIII	$N(CH_2CH_2)_2CH_2$	$C_{18}N_{22}N_2O_2S$	223–224°	65.42 / 65.41	6.71 / 5.82	8.48 / 8.34
		$C_{18}H_{22}N_2O_2S\cdot HCl$	304°	58.92 / 58.41	6.32 / 5.88	7.64 / 7.54
XXIV	$N(CH_2CH_2)_2O$	$C_{17}H_{20}N_2O_3S$	218–220°	61.42 / 60.88	6.07 / 5.36	8.43 / 8.47
		$C_{17}H_{20}H_2O_3S\cdot HCl$	308–310°	55.35 / 55.05	5.74 / 5.62	
XXV	$NH—CH_2C_6H_5$	$C_{20}H_{20}N_2O_2S\cdot HCl\cdot{}^1/_2H_2O$	260–261°	60.31 / 60.15	5.57 / 5.37	

hr. of refluxing, the solution was filtered and the filtrate was distilled to dryness *in vacuo* at 50°. The crystalline residue was dissolved in 100 ml. of benzene and 20 ml. of piperidine were added. After standing for 2 days, the mixture was filtered. The filtrate was distilled to dryness. The residue was dissolved in abs. ethanol and ethanolic hydrobromic acid was added in excess; on standing, crystals separated slowly. They were filtered after 2 days and were recrystallized repeatedly, first from abs. ethanol, then from water, yielding 6 g. of 4-(*N*-piperidylmethyl)-phenyl-4′-nitrophenyl-sulfide hydrobromide of m.p. 222–223°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2S\cdot HBr$: C, 52.81; H, 5.17; N, 6.84. Found: C, 52.92; H, 5.12; N, 6.61.

(*15*) *4-Benzylaminomethyl-4′-nitrodiphenylsulfide* (XXVIII). Crude 4-bromomethyl-4′-nitrodiphenylsulfide, prepared as described in Experiment 13, was allowed to react with excess benzylamine. After standing for 2 days at room temperature, the solution was filtered. The filtrate was shaken with 10% hydrochloric acid. A crystalline precipitate appeared immediately. It was filtered and recrystallized repeatedly from acetic acid, yielding 3 g. of 4-benzylaminomethyl-4′-nitro-diphenylsulfide hydrochloride of m.p. 241–242°.

Anal. Calcd. for $C_{20}H_{18}N_2O_2S\cdot HCl$; C, 62.09; H, 4.95; N, 7.24. Found: C, 62.18; H, 5.03; N, 7.35.

The remaining benzene solution on evaporation left 24 g. of unchanged 4-methyl-4′-nitro-diphenylsulfide.

(*16*) *4-(4-Nitrophenylsulfonyl)benzoic acid* (XXIX). 4-Methyl-4′-nitrodiphenylsulfone (27 g.) was dissolved in 300 ml. of acetic acid. With stirring and warming to 80°, 30 g. of chromium trioxide were slowly added. After 8 hr. the solution was allowed to cool. After standing overnight, the crude 4-(4-nitrophenylsulfonyl)benzoic acid was filtered off and washed with acetic acid. It was dissolved in boiling 10% sodium hydroxide. The solution was filtered hot from some undissolved starting material. The filtrate was concentrated to a small volume. On cooling, the sodium salt of the acid crystallized. It was filtered and washed with some ice cold water. The yield was 27 g. The sodium salt was dissolved in hot water and the colorless solution was acidified with 10% hydrochloric acid. The free acid separated immediately. It was recrystallized from acetic acid and melted at 305–306°. No melting point is given by Roblin and Clapp.[15]

Anal. Calcd. for $C_{13}H_9NO_6S$: C, 50.82; H, 2.95; N, 4.56. Found: C, 51.18; H, 2.98; N, 4.52.

(*17*) *4-(4-Nitrophenylsulfonyl)benzoic acid methylester* (XXX). 4-(4-Nitrophenylsulfonyl)benzoic acid (16 g.) was stirred and refluxed with a solution of 20 ml. of concd. sulfuric acid in 300 ml. of methanol for 5 hr. After cooling, the crystals

were filtered and washed with a little methanol. They were stirred for 1 hr. with 10% sodium carbonate solution to remove some unreacted acid and were then crystallized from methanol. The yield of pure methylester of m.p. 155–156° was 13 g.

Anal. Calcd. for $C_{14}H_{11}NO_6S$: C, 52.33; H, 3.45; N, 4.36. Found: C, 52.31; H, 3.27; N, 4.52.

(*18*) *4-(4-Aminophenylsulfonyl)benzoic acid* (XXXI). A. *By catalytic reduction.* 4-(4-Nitrophenylsulfonyl)benzoic acid (10 g.) was suspended in 10 ml. of water and sodium hydroxide was added dropwise to dissolve the acid. The solution was hydrogenated with Raney nickel at 50° and 300 lbs. pressure. The catalyst was filtered and the solution was acidified with acetic acid. The crude amino acid was filtered and recrystallized from 80% acetic acid, yielding 6 g. of pure 4-(4-aminophenylsulfonyl)benzoic acid of m.p. 253–254°. Roblin and Clapp[15] do not report the melting point of the acid.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.30; H, 4.00; N, 5.05. Found: C, 56.14; H, 4.02; N, 5.00.

B. *By reduction with ferrous sulfate.* A solution of the sodium salt, prepared from 38 g. of 4-(4-nitrophenylsulfonyl)benzoic acid in 500 ml. of water and a small excess of sodium hydroxide, was added with stirring at 25° to a solution of 210 g. of ferrous sulfate ($FeSO_4 \cdot 7H_2O$) in 1000 ml. of water. To this mixture, 400 g. of 25% sodium hydroxide was slowly added. The mixture was stirred for 8 hr. The undissolved material was filtered and the clear filtrate was acidified, yielding 24 g. of 4-(4-aminobenzylsulfonyl)-benzoic acid of m.p. 253–254°.

(*19*) *4-(4-Aminophenylsulfonyl)benzoic acid methylester* (XXXII). A mixture of 5 g. of 4-(4-aminophenylsulfonyl)-benzoic acid, 100 ml. of methanol, and 20 g. of concd. sulfuric acid was refluxed on the steam bath. After about 3 hr., a homogeneous solution had formed. It was filtered and cooled. The crude methyl ester was filtered and recrystallized from about 100 ml. of methanol, yielding 4 g. of pure ester of m.p. 175–176°.

Anal. Calcd. for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.87. Found: C, 58.23; H, 4.38; N, 4.92.

(*20*) *4-(4-Aminophenylsulfonyl)benzoic acid hydrazide* (XXXIII). A mixture of 9 g. of the ester (Experiment 19) and 2.5 ml. of hydrazine hydrate in 60 ml. of methanol was refluxed for 3 hr. On cooling in the refrigerator, 8 g. of 4-(4-aminophenylsulfonyl)benzoic acid hydrazide crystallized. Recrystallization from methanol gave the pure compound of m.p. 199–200°.

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42. Found: C, 53.30; H, 4.35; N, 14.63.

(*21*) *4-[4-(4-Nitrophenylsulfonyl)benzylamino]benzoic acid* (XXXVI). 4-Bromomethyl-4′-nitrodiphenylsulfone (18 g.) and 14 g. of p-aminobenzoic acid were refluxed in 125 ml. of dioxane for 4 hr. The hot solution was filtered from undissolved material and distilled to dryness. The residue was dissolved in 3% sodium hydroxide and the solution was again filtered from undissolved crystals. The clear, yellow filtrate was acidified with acetic acid. After 1 hr. the crystals were filtered and recrystallized from dioxane, yielding 12 g. of 4-[4-(4-nitrophenylsulfonyl)benzylamino]benzoic acid of m.p. 256–258°.

Anal. Calcd. for $C_{20}H_{16}N_2O_6S$: C, 58.24; H, 3.91; N, 6.79. Found: C, 58.07; H, 3.80; N, 6.73.

(*22*) *4-[4-(4-Aminophenylsulfonyl)benzylamino]benzoic acid* (XXXVII). The nitro acid (XXXVI) (5 g.) was hydrogenated catalytically with 2 g. palladium charcoal (3% Pd) in 30 ml. of acetic acid at 40° and 500 lbs. pressure. The resulting mixture contained cyrstals. After addition of 40 ml. of acetic acid, it was refluxed and filtered hot from the catalyst. On cooling, the acid crystallized. Recrystallization from acetic acid yielded 2 g. of pure 4-[4-(4-aminophenylsulfonyl)benzylamino]benzoic acid of m.p. 243–244°.

Anal. Calcd. for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.74; N, 7.34. Found: C, 62.60; H, 5.03; N, 7.14

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Glycosidation with Trimethyl Orthoformate and Boron Trifluoride*

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Methanolic trimethyl orthoformate in the presence of boron trifluoride constitutes a convenient system for glycoside synthesis in the sugar field.

Bergmann[3] applied the Claisen[4] acetalation reaction to the preparation of ethyl 4,6-di-*O*-acetyl-α-D-*erythro*-2-*cis*-hexosenide by heating 4,6-di-*O*-acetyl-D-*erythro*-2-*cis*-hexosene under reflux with ethanolic trimethyl orthoformate in the presence of a small amount of ammonium chloride. This reaction has been repeated by Stacey and co-workers[5] and performed, without ammonium chloride catalysis, with the corresponding D-galactose derivative by Lohaus and Widmaier[6] and with the methyl D-glucose analog by Bergmann and Freudenberg.[7] The corresponding reaction[8] with tetramethyl orthosilicate in the presence of hydrogen chloride was applied by Freudenberg and Jakob[9] to the preparation of

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