p-Benzyloxyphenyl-3-hexanone-4.—Oxidation of the corresponding carbinol to the ketone was effected by stirring with a sulfuric acid solution of chromic acid for two hours at 40–50° and one hour at 60–80°. The product which crystallized on cooling the acid solution was removed by filtration and melted 80–80.5° on recrystallization from dilute ethanol.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.75; H, 7.76.

Anisyl-3-hexanol-4.—The ether extract of the neutral reaction product of anisyl-3-hexanone-4 and potassium hydroxide in ethanol described above was concentrated and distilled *in vacuo*. The product, 15 g. (25%) of a clear, colorless, viscous oil, b. p. 100–105° at 0.2 mm., crystallized on cooling. After recrystallization from dilute ethanol and petroleum ether it melted at 75–76°.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.22; H, 9.84.

A. From Anisyl-3-hexanone-4 by Reduction with Sodium.—To a refluxing mixture of 206 g. of anisyl-3-hexanone-4 and 1 liter of dry isoamyl alcohol was added 100 g. of sodium in small portions. When the evolution of hydrogen was complete the mixture was poured into ice and water, the alcohol layer separated, washed with cold water until free of alkali and finally concentrated and distilled *in vacuo*. The fraction of b. p. 115–125° at 0.5 mm. weighed 180 g. (87.4%). It crystallized on standing and on recrystallization from petroleum ether melted at 75–76°. There was no mixed melting point depression with the anisyl-3-hexanol-4 described above.

B. From α-Anisylbutanal.—To the Grignard reagent from 2.5 g. of magnesium and 16 g. of ethyl iodide was added 18 g. of α-anisylbutanal. After a half hour of refluxing, the reaction mixture was worked up in the usual manner. The product, 16 g. (77%), obtained as a colorless oil, b. p. 90–95° at 0.1 mm., crystallized on cooling and melted at 75–76°. There was no depression on mixed m. p. with either of the samples prepared as described above.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.05; H, 9.54.

3-Anisyl-4-bromohexane.—To a solution of 21 g. of anisyl-3-hexanol-4 in 100 cc. of dry benzene at 10° was added 10 g. of hydrogen bromide. The solution was allowed to warm up to room temperature overnight and was then refluxed for five minutes. After washing with two 25-cc. portions of sulfuric acid, followed by sodium carbonate solution and water, the benzene was distilled and the residue fractionated. The product, 19 g. (70%), was a colorless oil, b. p. 90–95° at 0.1 mm.

Anal. Calcd. for $C_{13}H_{19}OBr$: C, 57.57; H, 7.06. Found: C, 57.77; H, 7.13.

2-Ethyl-3-anisylvaleric Acid.—The Grignard reagent prepared by the entrainment procedure from 13 g. of 3-anisyl-4-bromohexane, 7 g. of ethyl iodide and 2.5 g. of magnesium was carbonated by pouring onto Dry Ice. After decomposition of the addition compound with dilute sulfuric acid the ethereal layer was extracted with 10% sodium hydroxide solution until free of acidic material. Acidification of the alkaline extracts gave an oil which crystallized on standing overnight in the icebox. After 3 recrystallizations from dilute ethanol and 2 from petroleum ether the acid, 1.5 g. (12%) melted at 133.5–134.5°.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.21; H, 8.51.

Concentration and fractionation of the neutral ether solution gave 5 g. (52%) 3-anisylhexane, b. p. 78–80° at 0.5 mm.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.19; H, 10.48. Found: C, 81.46; H, 10.00.

Three grams of a fraction b. p. 155–160° at 0.2 mm. was also obtained. The material analyzed for the dimer of 3-anisylhexane.

Anal. Calcd. for $(C_{13}H_{19}O)_2$: C, 81.63; H, 10.01. Found: C, 81.06; H, 9.76.

Ethylmethoxymethylanisylcarbinol.—The reaction between 103 g. of p-α-dimethoxyacetophenone[13] and the Grignard reagent from 15 g. of magnesium and 110 g. of ethyl iodide gave 96 g. (77%) of carbinol, b. p. 112–113° at 0.5 mm.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 69.07; H, 8.53.

α-Anisylbutanal.—A mixture of 80 g. of ethylmethoxymethylanisylcarbinol and 15 g. of fused potassium bisulfate was heated at 150–170° for one hour, the low boiling reaction products being allowed to distill off during the heating. Fractionation of the residue gave 55 g. (82%) of product, b. p. 95–105° at 0.7 mm.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H 7.92. Found: C, 74.14; H, 8.03.

Summary

Potassium hydroxide in ethanol at 200–220° reduces anisyl-3-hexanone-4 to the corresponding carbinol and its demethylation product.

(13) Pratt and Robinson, *J. Chem. Soc.*, **123**, 748 (1923).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Diaryloxyalkane Derivatives. Diphenoxyethanesulfonamides[1a]

BY JOHN A. KING

In view of the high trypanocidal activity observed[1b] in 4,4′-diamidinostilbene, 4,4′-diamidino-α,γ-diphenoxypropane and 4,4′-diamidino-α,ε-diphenoxypentane, which were prepared by Ashley, Barber, Ewins, Newberry and Self,[2] it seemed desirable to prepare some substances of a similar nature but in which the amidino group was replaced by some other polar functional group. The present paper reports the preparation of a series of α,β-diphenoxyethane-4,4′-disulfonamide derivatives, together with some other closely related substances.

α,β-Diphenoxyethane (I) was found by Huntress and Carten[3] to be converted by chlorosulfonic acid to a disulfonyl chloride (II) (not isolated), from which they prepared the corresponding disulfonamide. It has been found that this disulfonyl chloride can be easily isolated and obtained pure in as high as 97% yield. By reaction of this disulfonyl chloride with the appropriate amines the disulfonamides listed in Table I were prepared.

Because of the low water-solubility of most of

(1a) Presented before the Division of Organic Chemistry at the American Chemical Society meeting in New York, September 14, 1944.

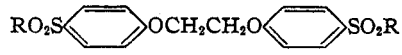
(1b) Laurie and Yorke, *Ann. Trop. Med.*, **33**, 289 (1939).

(2) Ashley, Barber, Ewins, Newberry and Self, *J. Chem. Soc.*, 103 (1942).

(3) Huntress and Carten, THIS JOURNAL, **62**, 603 (1940).

the substances listed in Table I, some other derivatives were made which were water-soluble. These, with intermediates from which they were prepared, are listed in Table II. α,β-Diphenoxyethane-4,4′-disulfonamide was acetylated and the disodium salt of this N,N′-diacetylsulfona-

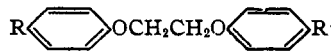
TABLE I



No.	R	M. p., °C.[a]	Yield, %, of pure product	Preparative procedure	Recrystallization solvent	Formula	Analyses, %[b] Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	—NH_2	228–229	89	A	H_2O–EtOH	$C_{14}H_{16}N_2O_6S_2$	[c]					
2	—$NHCH_3$	191–192	69	A	H_2O–HOAc	$C_{16}H_{20}N_2O_6S_2$	48.00	5.00	7.00	48.27	5.10	6.94
3	—$N(CH_3)_2$	198–198.5	79	A	H_2O–HOAc	$C_{18}H_{24}N_2O_6S_2$	50.47	5.60	6.54	51.21	5.69	6.60
4	—NHC_2H_5	170	70	A	H_2O–EtOH	$C_{18}H_{24}N_2O_6S_2$	50.47	5.60	6.54	50.70	5.30	6.79
5	—$N(C_2H_5)_2$	125–125.5	68	B	EtOH	$C_{22}H_{32}N_2O_6S_2$	54.54	6.61	5.78	54.41	6.43	5.73
6	—NHC_3H_7-*n*	177–178	95	C	EtOH	$C_{20}H_{28}N_2O_6S_2$	52.61	6.18	6.13	52.43	5.81	6.08
7	—NHC_3H_7-*i*	190	98	C	BuOH	$C_{20}H_{28}N_2O_6S_2$	52.61	6.18	6.13	52.61	6.44	6.01
8	—$N(C_3H_7$-*n*$)_2$	111	73	C	H_2O–MeOH	$C_{26}H_{40}N_2O_6S_2$	57.77	7.40	5.18	58.23	7.28	5.46
9	—$N(C_4H_9$-*n*$)_2$	82–82.5	78	A	$CHCl_3$–Skellysolve A	$C_{30}H_{48}N_2O_6S_2$	60.40	8.05	4.70	60.11	8.21	4.77
10	—$N(C_8H_{17}$-*n*$)_2$	84	65	D	MeOH	$C_{46}H_{80}N_2O_6S_2$	67.32	9.75	3.41	66.75	10.39	3.68
11	—$N(CH_3)_5$	195	77[d]	C	BuOH	$C_{24}H_{32}N_2O_6S_2$	56.67	6.34	5.51	56.61	6.11	5.41
12	—$NHCH_2CH_2OH$	168.5–169	68	A	H_2O–HOAc	$C_{18}H_{24}N_2O_8S_2$	46.95	5.21	6.08	47.19	5.20	6.05
13	—$N(CH_2CH_2OH)_2$	188–188.5	69	A	H_2O	$C_{22}H_{32}N_2O_{10}S_2$	48.17	5.84	5.11	47.98	5.97	5.20
14	—$N(CH_2CH_2)_2O$	246–246.5	74	A	HOAc	$C_{22}H_{28}N_2O_8S_2$	51.56	5.46	5.46	51.81	5.54	5.45
15	—$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$	93–94	79	D	Bz–Skellysolve B	$C_{32}H_{54}N_4O_6S_2$	58.71	8.26	8.56	58.88	7.53	8.54
16	—$NHCH_2COOC_2H_5$	150–151	98	*e*	H_2O–dioxane	$C_{22}H_{28}N_2O_{10}S_2$	48.53	5.14	5.14	48.41	5.51	5.53
17	—NH—(2-thiazyl)	242–243	79	*e*	H_2O–Py	$C_{20}H_{18}N_4O_6S_4$	44.61	3.34	10.41	45.35	3.77	10.39

[a] See Ref. 8. [b] See Ref. 7. [c] This compound was first prepared by Huntress and Carten.[3] [d] Only 0.13 mole of piperidine was used for 0.06 mole of disulfonyl chloride. [e] See Experimental Part.

TABLE II

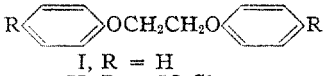


No.	R	R	M. p.,[a] °C.	Yield, %, of pure product
18	—$SO_2NHCOCH_3$	R	190–191	81
19	—$SO_2N(Na)COCH_3$	R	dec.	100
20	—SO_3H	—SO_2NH 	205	50
21	—SO_3Na	—$SO_2N(Na)$ 	dec.	100
22	—SO_2NHCH_2COOH	R	226	100
23	—$SO_2N(Na)CH_2COONa$	R	dec.	100
24	—$SO_2N(Na)$ 	R	dec.	100
25	—$NHSO_2C_2H_5$	R	181–182	54
26	—$N(Na)SO_2C_2H_5$	R	dec.	100
27	—$SO_2NHCH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$	R	dec.	100

No.	Formula	Analyses, %[7] Calcd. C	Calcd. H	Calcd. N	Calcd. Na	Found C	Found H	Found N	Found Na
18	$C_{18}H_{20}N_2O_8S_2 \cdot 2H_2O$	43.90	4.91	5.69		44.11	4.75	5.92	
19	$C_{18}H_{18}N_2O_8S_2Na_2$				9.20				8.94
20	$C_{19}H_{18}N_2O_7S_2$	50.67	4.00	6.22		50.92	3.66	6.28	
21	$C_{19}H_{16}N_2O_7S_2Na_2$				9.31				9.87
22	$C_{18}H_{20}N_2O_{10}S_2$	44.26	4.10	5.73		44.04	3.64	5.64	
23	$C_{18}H_{16}N_2O_{10}S_2Na_4$				15.97				15.95
24	$C_{20}H_{16}N_4O_6S_4Na_2$				7.90				8.58
25	$C_{18}H_{24}N_2O_6S_2$	50.47	5.60	6.54		50.86	6.00	6.77	
26	$C_{18}H_{22}N_2O_6S_2Na_2$				9.74				9.48
27	$C_{32}H_{54}N_4O_6S_2 \cdot 2HCl$		Cl (ionic), 9.76				Cl (ionic), 9.66		

mide was prepared easily. Several attempts, all unsuccessful, were made to prepare a disodium salt of N,N′-diethyl-α,β-diphenoxyethane-4,4′-disulfonamide. The unsymmetrical pyridine derivative was obtained, by chance, in a reaction intended to produce the N,N′-di-2-pyridyl disulfonamide. It was thought desirable to prepare a diphenoxyethanesulfonamide in which the sulfonic acid was aliphatic and the amine was aromatic, this being the reverse of all the other compounds prepared. 4,4′-Diamino-α,β-diphenoxyethane was converted to the corresponding bisethanesulfonamide and this was made into a disodium salt, thus giving the desired compound.

Although there was no reason to doubt that the orientation of the chlorosulfonyl groups entering α,β-diphenoxyethane was other than 4 and 4′, it was felt that such orientation should be rigorously established. In order to accomplish this N,N,N′,N′ - tetramethyl - α,β - diphenoxyethane-4,4′-disulfonamide (III) was synthesized by an unequivocal method and found to be identical with the amide formed by inter-reaction of dimethylamine and the disulfonyl chloride II prepared from α,β-diphenoxyethane. 4-Acetamidobenzenesulfonyl chloride (IV) on treatment with dimethylamine gave 4-acetamidobenzenesulfondimethylamide (V) in 87% yield. The acetyl group was removed by acid hydrolysis[4] to give 4-aminobenzenesulfondimethylamide (VI) in 80% yield. This amine was converted, through the diazonium sulfate by the procedure of Manske,[5] into the corresponding phenol, 4-hydroxybenzenesulfondimethylamide (VII) in 57% yield. By the procedure of Cope,[6] this phenol was converted, in 18% yield, into the same diphenoxyethane derivative III as had been obtained via the chlorosulfonation method of synthesis.



I, R = H
II, R = SO_2Cl
III, R = $SO_2N(CH_3)_2$

IV, R = $NHCOCH_3$, R′ = SO_2Cl
V, R = $NHCOCH_3$, R′ = $SO_2N(CH_3)_2$
VI, R = NH_2, R′ = $SO_2N(CH_3)_2$
VII, R = OH, R′ = $SO_2N(CH_3)_2$

Preliminary tests carried out with the compounds listed in Tables I and II indicate that these substances are devoid of trypanocidal activity.

Acknowledgment.—The author wishes to thank Drs. C. M. Suter and J. S. Buck for their helpful advice during the course of this work. He also wishes to acknowledge the assistance of Miss Alice Rainey and Mr. Freeman H. McMillan in some of the experimental work.

(4) Walker, *J. Chem. Soc.*, 686 (1940).

(5) Manske, "Organic Syntheses," Coll. Vol. I, second edition, 1941, p. 404.

(6) Cope, THIS JOURNAL, **57**, 572 (1935).

Experimental Part[7,8]

α,β-Diphenoxyethane-4,4′-disulfonyl Chloride (II).—α,β-Diphenoxyethane (I) was prepared by the procedure of Cope.[6]

The ethane derivative was chlorosulfonated by a modification of the procedure of Huntress and Carten.[3] To a vigorously stirred and cooled solution of α,β-diphenoxyethane (42.8 g., 0.20 mole) in chloroform (400 cc.), contained in a 1-liter 3-necked round-bottomed flask holding a thermometer which dipped into the solution, there was added chlorosulfonic acid (200 g., 112 cc., 1.72 moles) at such a rate that the temperature of the reaction mixture never rose above 5°. When the addition was complete the red solution was poured slowly into a vigorously stirred mixture of ice (1.5 kilos) and water (500 cc.). The chloroform layer was separated and the solvent was removed by distillation. The cooled residue was stirred with Skellysolve A (500 cc.) and the white granular solid was removed by filtration. It weighed 79.5 g. (97% yield) and melted at 115–116°. A sample for analysis was recrystallized from Skellysolve B; white needles, m. p. 115–116°.

Anal. Calcd. for $C_{14}H_{12}O_6S_2Cl_2$: C, 40.88; H, 2.92. Found: C, 40.69; H, 3.00.

α,β-Diphenoxyethane-4,4′-disulfonamides. Procedure A (Compounds 1, 2, 3, 4, 9, 12, 13 and 14).—To a stirred solution of α,β-diphenoxyethane (21.4 g., 0.10 mole) in chloroform (200 cc.) there was added slowly chlorosulfonic acid (100 g., 56 cc., 0.86 mole) while the temperature of the reaction mixture was maintained at −5 to 5°. As soon as the addition was complete the clear red solution was poured onto ice, the chloroform layer was separated and run into a beaker. To this stirred chloroform solution there was added slowly an aqueous solution of the amine (0.45–0.50 mole), the mixture was stirred until it cooled to room temperature, the product was removed by filtration and recrystallized from an appropriate solvent.

Procedure B (Compound 5).—The chloroform solution of the disulfonyl chloride, prepared as in Procedure A, was stirred with a solution of the amine (0.25 mole) in chloroform (50 cc.) while aqueous potassium hydroxide (500 cc., 10% solution) was dropped in, with external cooling. After an additional hour of stirring at room temperature the chloroform layer was separated and diluted with 3–4 volumes of Skellysolve A; the product was removed by filtration and recrystallized from ethanol.

Procedure C (Compounds 6, 7, 8 and 11).—Into a stirred solution of α,β-diphenoxyethane-4,4′-disulfonyl chloride (30.0 g., 0.073 mole) in dioxane (120 cc.) there was dropped a solution of the amine (0.25 mole) in dioxane (30 cc.). After three hours of stirring at room temperature the mixture was diluted with 2 liters of water, the product was removed by filtration and recrystallized from an appropriate solvent.

Procedure D (Compounds 10 and 15).—A mixture of α,β-diphenoxyethane-4,4′-disulfonyl chloride (20.5 g., 0.05 mole) and the amine (0.20 mole) in chloroform (300 cc.) was stirred with water (200 cc.) at room temperature for two hours. The chloroform layer was separated, the solvent was removed and the residue was crystallized (or recrystallized) from an appropriate solvent.

N,N′-Diacetyl-α,β-diphenoxyethane-4,4′-disulfonamide (Compound 18).—α,β-Diphenoxyethane-4,4′-disulfonamide (25.0 g., 0.0673 mole) was suspended in acetic anhydride (200 cc.), concentrated sulfuric acid (5 drops) was added, and the mixture was refluxed until all the solid dissolved, then fifteen minutes longer. The solution was poured over ice (1 kilo) and allowed to stand overnight. The tan solid (25.0 g., 81% yield) was recrystallized, with charcoaling, from absolute alcohol; m. p. 189–190°. A sample for analysis, after several recrystallizations from aqueous alcohol, melted at 190–191°. See Table II for analysis.

The acetylated sulfonamide (28.9 g., 0.0587 mole) was

(7) Microanalyses are by Misses E. A. Bass, P. Curran and A. Rainey.

(8) All melting points are uncorrected.

dissolved in aqueous sodium hydroxide (252 cc., 0.483 *N*), the solution was evaporated to a thick paste and this was triturated with absolute alcohol (300 cc.) until the solid was granular. The dry disodium salt (Compound 19) weighed 29.3 g. (100% yield). See Table II for analysis.

N-2-Pyridyl-α,β-diphenoxyethane-4-sulfonamide-4'-sulfonic Acid (Compound 20).—A solution of α,β-diphenoxyethane-4,4'-disulfonyl chloride (30.0 g., 0.073 mole) and 2-aminopyridine (18.8 g., 0.20 mole) in dioxane (150 cc.) was stirred three hours at room temperature, then poured into water (2 liters) and acidified with hydrochloric acid. The light tan solid was removed by filtration and recrystallized from propylene glycol; dry weight, 16.5 g. (50% yield); m. p. 205° (dec.). See Table II for analysis.

This substance was converted to its disodium salt (Compound 21) in the same way as the above-described diacetyl derivative. See Table II for analysis.

N,N'-Dicarbethoxymethyl-α,β-diphenoxyethane-4,4'-disulfonamide (Compound 16).—To a stirred solution of α,β-diphenoxyethane-4,4'-disulfonyl chloride (41.1 g., 0.10 mole) in ethylene dichloride (250 cc.) there was slowly added a solution of ethyl aminoacetate hydrochloride[9] (40.0 g., 0.286 mole) and potassium carbonate (55.3 g., 0.40 mole) in water (200 cc.). The mixture was stirred for three hours at room temperature, diluted with Skellysolve A (500 cc.) and filtered. The material, m. p. 149–150°, was recrystallized from aqueous dioxane to give the pure ester (53.3 g., 98% yield), m. p. 150–151°. See Table I for analysis.

N,N'-Dicarboxymethyl-α,β-diphenoxyethane-4,4'-disulfonamide (Compound 22).—The ester was hydrolyzed to the acid by refluxing it with 5% hydrochloric acid until the solution was clear and then chilling the solution to obtain the acid in practically quantitative yield. This was recrystallized from 1% hydrochloric acid to give the pure acid, m. p. 226°. All attempts to prepare this compound from the disulfonyl chloride and glycine itself were unsuccessful; four different sets of experimental conditions were used, none of which gave any of the desired compound. See Table II for analysis.

The di-acid was converted to the tetrasodium salt (Compound 23) by recrystallization from aqueous sodium hydroxide and ethanol. See Table II for analysis.

N,N'-Di-2-thiazyl-α,β-diphenoxyethane-4,4'-disulfonamide (Compound 17).—A mixture of α,β-diphenoxyethane-4,4'-disulfonyl chloride (20.6 g., 0.05 mole) and 2-aminothiazole (12.0 g., 0.12 mole) suspended in pyridine (100 cc.) was warmed to 90° on a steam-bath, stirred until everything was in solution, and then allowed to cool overnight. The solution was diluted with Skellysolve A (6 volumes) and thoroughly stirred; the Skellysolve was decanted and the process was repeated. The residual heavy oil was triturated with ethanol (400 cc.) until it became solid, then it was removed by filtration and dried; wt., 20.5 g. (79% yield), m. p. 235–245° (dec.). A sample for analysis was recrystallized from aqueous pyridine and then melted at 242–243° (dec.). See Table I for analysis.

The disodium salt (Compound 24) was prepared by adding the theoretical amount of aqueous sodium hydroxide to an aqueous suspension of the sulfonamide. The clear solution was evaporated to a thick sirup which was triturated with ethanol until it was solid. See Table II for analysis.

4,4'-Bis-(ethanesulfonamido)-α,β-diphenoxyethane (Compound 25).—According to the procedure of Weddige[10] ethylene bromide (188 g., 1.0 mole), potassium *p*-nitrophenoxide (354 g., 2.0 moles) and ethanol (75 cc.) were heated ten hours at 140° in an autoclave to give 189 g. (63% yield) of 4,4'-dinitro-α,β-diphenoxyethane; after recrystallization from acetic acid it had a m. p. of 145–146°.

To a vigorously stirred and refluxing suspension of iron filings (300 g., 5.35 moles) in ethanol (900 cc.) and water (900 cc.) and acetic acid (10 cc.) there was added during the course of one hour the above-described dinitro compound (50.0 g., 0.165 mole). The mixture was refluxed three hours after the addition was complete, then made alkaline with solid carbonate and filtered hot. By concentration and chilling of the filtrate there was obtained 4,4'-diamino-α,β-diphenoxyethane (40.2 g., 75% yield), m. p. 174–176° (dec.); Wagner[11] reported the m. p. as 168–172° and Kinzel[12] reported it as 176°.

Diethyl disulfide was prepared from ethyl bromide and sodium thiosulfate by the procedure of Price and Twiss[13] and Stutz and Shriner[14] in 50% yield; colorless liquid, b. p. 151–153° (760 mm.).

Ethanesulfonyl chloride was prepared by chlorination of diethyl disulfide in aqueous acetic acid, according to the procedure of Lee and Dougherty[15]; pale yellow fuming liquid, b. p. 172–178° (760 mm.).

To a finely divided suspension of 4,4'-diamino-α,β-diphenoxyethane (12.5 g., 0.051 mole) in a mixture of dry benzene (250 cc.) and dry pyridine (25 cc.) there was slowly added a solution of ethanesulfonyl chloride (12.8 g., 0.10 mole) in dry benzene (50 cc.). The suspension turned a brilliant red color; it was then refluxed until the solvent was colorless and only the suspended solid was red; this required three hours. The cooled reaction mixture was filtered and the solid residue was stirred with hydrochloric acid (500 cc., 5% acid) for fifteen minutes. The remaining solid was removed by filtration and recrystallized, with charcoaling, from absolute alcohol to give fine white crystals, m. p. 180–181°; wt., 11.5 g. (54% yield). A sample for analysis, after a second recrystallization, had a m. p. of 181–182°. See Table II for analysis.

For its conversion to the disodium salt (Compound 26) an aqueous suspension of the free sulfonamide was titrated into solution with dilute sodium hydroxide solution. The resultant clear solution was evaporated to a thick sirup on the steam cone and then allowed to stand overnight, during which the sirup changed to a solid mass. This solid was ground with successive portions of anhydrous ether (it was soluble in absolute alcohol) until it was powdery; five portions of ether were required. See Table II for analysis.

N,N'-Di-1-methyl-4-diethylaminobutyl-α,β-diphenoxyethane-4,4'-disulfonamide Dihydrochloride (Compound 27).—Dry hydrogen chloride was passed into a dry chloroform solution of the free sulfonamide until no more oil was precipitated. On repeated trituration with many successive portions of Skellysolve A this oil gradually changed to a granular solid and then to a powder. See Table II for analysis.

4-Hydroxybenzenesulfondimethylamide (VII).—4-Acetaminobenzenesulfonyl chloride (IV) (100 g. of technical paste; assay: 55% water, 45% acid chloride, 0.1% free acidity; 0.193 mole) was converted, in chloroform–acetone solution, to the corresponding dimethylamide V (40.5 g., 87% yield), m. p. 144°; Walker[4] reported the m. p. as 145–146°.

The acetyl compound V (35.0 g., 0.145 mole) was converted to the free amine by acid hydrolysis. The dry white 4-aminobenzenesulfondimethylamide (VI) weighed 23.0 g. (80% yield) and melted at 170–170.5°; Walker[4] reported the m. p. as 169–170°.

The amine VI (4.0 g., 0.02 mole) was diazotized and the diazonium sulfate was decomposed in hot sulfuric acid by the procedure of Manske.[5] The cooled sulfuric acid reaction solution was extracted three times with ether, the combined ethereal extract was extracted with 10% aqueous potassium hydroxide, the alkaline extract was acidified and chilled. A heavy oil precipitated and crystallized on standing a few minutes. It weighed 4.16 g. and melted at 63–66°. The material was purified by decolorization in hot aqueous solution, extraction with ether and crystallization from Skellysolve A; it then weighed 2.30 g. (57% yield)

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(14) Stutz and Shriner, THIS JOURNAL, **55**, 1242 (1933).

(15) Lee and Dougherty, *J. Org. Chem.*, **5**, 81 (1940).

and melted at 90–91°. The pure amide VII, after repeated recrystallization from benzene, melted at 95°.

Anal. Calcd. for $C_5H_{11}NO_3S$: C, 47.75; H, 5.50; N, 6.96. Found: C, 48.25; H, 5.70; N, 6.79.

N,N,N',N'-Tetramethyl-α,β-diphenoxyethane-4,4'-disulfonamide (III).—4-Hydroxybenzenesulfondimethylamide (VII) (1.00 g., 0.005 mole) and potassium hydroxide (0.30 g., 0.00535 mole) were dissolved in ethanol (25 cc.). Ethylene dibromide (0.47 g., 0.0025 mole) was added and the mixture was refluxed three hours, diluted to 200 cc. with water and filtered. The product (0.193 g., 18% yield) melted at 192–196°. When it was mixed with a sample of the same material, m. p. 198–198.5°, prepared by Procedure A (above), the mixture melted at 195–197°.

Summary

1. A series of seventeen N-substituted α,β-diphenoxyethane-4,4'-disulfonamides has been prepared.

2. A series of ten other derivatives of α,β-diphenoxyethane has been prepared; six of these are water-soluble.

3. The orientation of the groups entering α,β-diphenoxyethane on treatment with chlorosulfonic acid has been established as 4 and 4'.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

Some Bromination Products of the Fluorophenols[1]

BY L. CHAS. RAIFORD AND ARTHUR L. LEROSEN[2]

We have studied the bromination of the three isomeric fluorophenols under various conditions and have prepared the following new derivatives: 2-fluoro-4,6-dibromophenol, 2,4,5,6-tetrabromo-3-fluorophenol, and 2,4,6-tribromo-3-fluorophenol bromide. We have repeated the preparation of some others already reported by Hodgson and Nixon.[3]

The 2,4,6-tribromo-3-fluorophenol bromide was of special interest, and consequently was studied in more detail than the other compounds.

The isomeric fluorophenols differed considerably from each other in their reactions with bromine as shown below.

When a glacial acetic acid solution of *o*-fluorophenol was treated with slightly more than two moles of bromine, 2-fluoro-4,6-dibromophenol was obtained. This structure was assumed from the fact that the hydroxyl group directs much more strongly[4] to the 4 and 6 positions than the fluorine atom does to the 3 and 5 positions. With a large excess of bromine an unidentified oil was obtained.

p-Fluorophenol was brominated according to the directions given by Hodgson and Nixon[3] to yield 2,6-dibromo-4-fluorophenol. An excess of bromine in glacial acetic acid oxidized *p*-fluorophenol to tetrabromoquinone.[5]

The bromination products of *m*-fluorophenol depended to some extent on the solvent. In water solution both the tribrominated phenol and the phenol bromide were formed. Bromination in glacial acetic acid produced the same compounds, even under the conditions that caused oxidation or decomposition of *p*- and *o*-fluorophenol. In carbon tetrachloride the highest brominated derivative was a dibromo compound, *viz.*, 3-fluoro-4,6-dibromophenol; however, if solid sodium bicarbonate was added to the reaction mixture, the phenol bromide was formed. Tribromophenol bromide[6,7] could also be prepared by this method.

When 2,4,6-tribromo-3-fluorophenol bromide was heated in concentrated sulfuric acid, it rearranged to give 2,4,5,6-tetrabromo-3-fluorophenol. Benedict[6] observed an analogous behavior of tribromophenol bromide.

Reduction with zinc and hydrochloric acid, or treatment with phenylhydrazine converted 3-fluorotribromophenol bromide into 2,4,6-tribromo-3-fluorophenol.

Since there has been considerable discussion concerning the relative merits of the quinoid and hypobromite structures for the phenol bromides,[8,9,10] an attempt was made to replace some of the bromine in 3-fluorotribromophenol bromide by fluorine through the use of silver fluoride. When this reaction was carried out in acetone at room temperature it was possible to isolate a small amount of bright yellow crystals, m. p. 169°. Analysis for fluorine indicated the composition $(C_6HOBr_3F)_2$. A second treatment at the boiling point of acetone gave some 2,4,6-tribromo-3-fluorophenol as the only product isolated.

Thiele and Eichwede treated tribromophenol bromide with lead acetate in glacial acetic acid and obtained 2,6-dibromobenzoquinone. When 3-fluorotribromophenol bromide was treated in the same way, a white granular solid, practically insoluble in all solvents, appeared (m. p. 162°). This substance possessed the formula $(C_6HOBr_3F)_2$ on the basis of its bromine content, it readily

(1) From a thesis submitted by Arthur L. LeRosen in partial fulfillment of the requirements for the degree of Doctor of Philosophy, to the Graduate College of the State University of Iowa, June, 1940.

(2) This paper was prepared after the death of Dr. Raiford.

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