

Summary

1. The substitution of N,N-disubstituted- α -haloamides for α -haloesters in the Reformatsky reaction has been studied and shown to be practical.
2. Sixteen different hydroxyamides prepared by this method are described.
3. Anisaldehyde reacted with two α -halo-

amides to yield the unsaturated relative of the expected hydroxyamide.

4. It was found impossible to isolate the expected product when furfural was one of the reactants.

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Certain N-Alkyl, N-Carboxyalkyl and N-Hydroxyalkyl Derivatives of 4,4'-Diaminodiphenyl Sulfone

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Numerous derivatives of 4,4'-diaminodiphenyl sulfone (I) have been reported¹ since the observation of the antibacterial activity of this sulfone by Buttle, *et al.*,² and by Fournau, *et al.*³ Among the amino substituted derivatives the results of biological studies⁴ indicate the desirability of the presence of one free amino group and suggest the superiority of the alkyl type of substituent. The present paper reports the synthesis of a number of derivatives having an alkyl, carboxyalkyl or hydroxyethyl group substituted in one of the amino groups. Several similar derivatives of 4-amino-4'-nitrodiphenyl sulfone (II) were prepared both for use as intermediates in the synthesis of some of the derivatives of I and also for tests of their antibacterial activity, since compound II is known to show considerable bacteriostatic activity.

Two methods were employed in the preparation of the crystalline derivatives of I shown in the table: (1) direct alkylation or carboxyalkylation of I, an excess of I being used to minimize substitution in the second amino group of the molecule; (2) alkylation or hydroxyethylation of II and subsequent reduction of the nitro group of the product by iron and 1.5% hydrochloric acid in ethanol solution. The first method, the success of which depends on efficient separability of the product from I, was applied to the preparation of compounds IV and X-XIV. As alkylation and carboxyalkylation agents, ethyl iodide was used for the preparation of IV, the appropriate *n*-alkyl bromide for XII-XIV, bromoacetic acid for X and β -bromopropionic acid for XI. In the case of the glycine and β -alanine derivatives, separation

from excess I was effected by removal of the carboxyl compounds as the water-soluble sodium salts. The acids required further purification, which was accomplished readily through the crystalline pyridine salts. The ethyl derivative crystallized from the ethylation solution at the end of the reaction. The difference in solubility of the *n*-butyl, *n*-amyl and *n*-tetradecyl derivatives in 2.5-5% hydrochloric acid as compared with I provides a convenient method of separation. Compounds IV and XIV were prepared also by the second method, which was the way the β -hydroxyethyl (VII) and benzyl (XVII) derivatives were obtained. The yields of amino derivatives in the reduction of the nitro compounds were excellent, 90% in one case.


The hydroxyethylation of II by reaction with 2-bromoethanol proceeds at a slow rate in boiling cellosolve solution to produce compound VI in a yield of 30-35%. Prolonged duration of the reaction results in a secondary reaction involving the hydroxyethyl group of the initial product (VI), as shown by the formation of both the β -hydroxyethyl (VII) and ethyl (IV) derivatives in the reduction of the mixture resulting from the hydroxyethylation reaction under certain conditions. Although the mechanism of the formation of IV in the two-step process has not been established, it seems possible that the compound might result from the reduction of 4-nitro-4'- β -bromoethylaminodiphenyl sulfone, which could be produced by the reaction of VI with the hydrobromic acid accumulated in the hot hydroxyethylation reaction solution. The direct hydroxyethylation of I by the reaction of 2-bromoethanol and I in equimolecular proportions at 100° produced a mixture from which only crystalline 4,4'-bis-(β -hydroxyethylamino)-diphenyl sulfone (VIII) was isolated. During the progress of this investigation Heymann and Heidelberger¹ reported the preparation of VIII, in low yield, through a pressure reaction of ethylene oxide with I followed by isolation of the product as the crystalline N,N'-dinitroso derivative. 2-Bromoethanol possesses advantages over ethylene oxide for the preparation of VIII, since

(1) For references see: Roblin, Williams and Anderson, *THIS JOURNAL*, **63**, 1930 (1941); Heymann and Fieser, *ibid.*, **67**, 1979 (1945); Heymann and Heidelberger, *ibid.*, **67**, 1986 (1945); Jackson, *ibid.*, **68**, 1438 (1946).

(2) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **232**, 1331 (1937).

(3) Fournau, Tréfouël, Nitti, Bovet and Tréfouël, *Compt. rend.*, **204**, 1763 (1937); **205**, 299 (1937).

(4) (a) Smith, Jackson and McClosky, *Am. Rev. Tuberc.*, **53**, 589 (1946); **55**, 366 (1947); (b) Youmans and Doub, *ibid.*, **54**, 287 (1946); Youmans, Feldman and Doub, *ibid.*, **54**, 295 (1946); (c) Smith, McClosky, Jackson and Bauer, *Proc. Soc. Exptl. Biol. Med.*, **64**, 261 (1947); see also Heymann and Fieser, ref. 1.

TABLE I
DERIVATIVES OF DIPHENYL SULFONE R--R'

No.	R	R'	M. p., °C.	Activ- ity ^a	Empirical formula	Analyses, %							
						Calcd.				Found ^b			
						C	H	N	S	C	H	N	S
I	-NH ₂	-NH ₂	++
II	-NO ₂	-NH ₂
III	-NO ₂	-NHCH ₂ CH ₃	223-224	-	C ₁₄ H ₁₁ N ₂ O ₂ S	10.47	10.29
IV	-NH ₂	-NHCH ₂ CH ₃	199-200	++	C ₁₄ H ₁₁ N ₂ O ₂ S	60.84	5.84	10.14	11.60	60.93	5.92	10.28	11.59
V	-NHCOC ₂ H ₅	-NHCH ₂ CH ₃	226-227	-	C ₁₇ H ₁₅ N ₂ O ₃ S	66.30	5.30	7.37	...	66.29	5.44	7.53	...
VI	-NO ₂	-NHCH ₂ CH ₂ OH	210-211	-	C ₁₄ H ₁₁ N ₂ O ₃ S	9.95	9.63
VII	-NH ₂	-NHCH ₂ CH ₂ OH	143.5-144.5 ^c	++	C ₁₄ H ₁₁ N ₂ O ₃ S	57.51	5.52	9.58	10.97	57.80	5.70	9.37	11.12
VIII	-NHCH ₂ CH ₂ OH	-NHCH ₂ CH ₂ OH	187-188	0	C ₁₆ H ₁₃ N ₂ O ₃ S	57.12	5.99	8.33	9.53	56.81	5.92	8.13	9.57
IX	-NO ₂	-NHCH ₂ COOH	231-232	-	C ₁₄ H ₁₁ N ₂ O ₄ S	49.99	3.60	8.33	9.53	49.98	3.66	8.25	9.62
X ^d	-NH ₂	-NHCH ₂ COOH	202-203	++	C ₁₄ H ₁₁ N ₂ O ₄ S	54.89	4.61	9.15	10.47	54.54	4.80	8.87	10.59
XI ^e	-NH ₂	-NH(CH ₂) ₂ COOH	127-128 ^c	++	C ₁₅ H ₁₂ N ₂ O ₄ S	56.23	5.03	8.75	10.01	56.38	5.28	8.79	9.83
XII	-NH ₂	-NH(CH ₂) ₃ CH ₃	192-193	+	C ₁₅ H ₁₃ N ₂ O ₂ S	63.13	6.62	9.21	10.53	63.08	6.55	9.07	10.39
XIII	-NH ₂	-NH(CH ₂) ₄ CH ₃	148-149	+	C ₁₇ H ₁₇ N ₂ O ₂ S	64.12	6.97	8.80	10.07	64.29	7.08	8.51	10.06
XIV	-NH ₂	-NH(CH ₂) ₁₀ CH ₃	174-174.5 ^c	0	C ₂₆ H ₂₀ N ₂ O ₂ S	70.22	9.07	6.30	7.21	70.38	9.02	6.20	7.29
XV	-NO ₂	-NH(CH ₂) ₁₀ CH ₃	98-99	-	C ₂₆ H ₂₀ N ₂ O ₂ S	6.75	6.83
XVI	-NO ₂	-NHCH ₂ C ₆ H ₅	149-150	+	C ₁₉ H ₁₅ N ₂ O ₂ S	8.70	8.79
XVII	-NH ₂	-NHCH ₂ C ₆ H ₅	188.5-189 ^c	++	C ₁₉ H ₁₅ N ₂ O ₂ S	67.43	5.36	8.28	9.47	67.43	5.26	8.29	9.62
XVIII	-NH ₂	-N(CH ₂ C ₆ H ₅) ₂	223-224	-	C ₂₆ H ₂₀ N ₂ O ₂ S	72.87	5.65	6.54	7.48	73.11	5.74	6.36	7.78
XIX	-N(CH ₂ C ₆ H ₅) ₂	-N(CH ₂ C ₆ H ₅) ₂	199-200	0	C ₂₆ H ₂₀ N ₂ O ₂ S	5.27	5.54

^a Data supplied by Dr. M. I. Smith and Dr. J. M. Junge on qualitative tests against Type I pneumococcal infections in white mice. The slight activity or inactivity of several of the compounds may be due to poor absorption. Mice tolerate much larger doses of the derivatives than of diaminodiphenyl sulfone. For tests on compounds X and XI in experimental tuberculosis see ref. 4a and Smith, *N. Y. State J. Med.*, **45**, 1665 (1945). In tests by Dr. E. W. Emmart marked inhibition of the growth of tubercle bacilli (human strain A27) was shown by compound VII in Kirchner's medium at a concentration of 4 mg. % and by compound IX in horse meat bouillon at a concentration of 25 mg. %. ^b Micro-combustions and nitrogen analyses by Mr. C. A. Kinser, Mrs. Betty Mount and Mrs. Margaret M. Ledyard. ^c Corrected. Compound XI contained combined solvent. ^d Neut. equiv. calcd., 306; found, 305. ^e Neut. equiv. calcd., 320; found, 325.

the reaction of the former with I is carried out at atmospheric pressure and apparently the product is isolated more readily in crystalline condition.

The reaction of benzyl chloride and II in approximately equimolecular proportions afforded principally the monobenzyl (XVI) derivative and a smaller amount of 4-nitro-4'-dibenzylaminodiphenyl sulfone. The latter compound was not isolated, but its formation is evident since reduction of the benzylation mixture yielded both XVII and XVIII. Mingoia and Berti⁵ obtained 4-nitro-4'-dibenzylaminodiphenyl sulfone through reaction of benzyl chloride with II; the monobenzyl derivative apparently was formed also, but the compound was not isolated in pure condition. Benzyl chloride and I in the molecular proportions of 3.5 to 1.0 yielded the tetrabenzyl (XIX) derivative, which has been described by Buttle, *et al.*⁶

Experimental

4-Nitro-4'-ethylaminodiphenyl Sulfone (III).—A solution of 20 g. of II and 12.3 g. of ethyl iodide in 150 cc. of 95% ethanol was refluxed for twenty-two hours and then cooled to room temperature. After the addition of 25 cc. of water and 7 g. of sodium bicarbonate, which produced crystallization, the refluxing was continued for an additional twenty-nine hours. The yellow crystals were separated from the hot mixture by filtration, washed first with cold 80% ethanol and finally with cold water. The nearly pure III weighed 5.8 g. and melted at 219-220°. The filtrate deposited at room temperature 11.3 g. of crystals melting at 155-160°, and upon concentration yielded more crystals showing a similar melting point.

(5) Mingoia and Berti, *Arquiv. biol. (São Paulo)*, **28**, 84 (1944); *C. A.*, **39**, 2057 (1945).

(6) Buttle, Dewing, Foster, Gray, Smith and Stephenson, *Biochem. J.*, **32**, 1101 (1938).

Additional III was obtained by recrystallization of the lower-melting material from ethanol. The compound is difficultly soluble in absolute ethanol, from which it crystallizes as elongated plates.

4-Amino-4'-ethylaminodiphenyl Sulfone (IV).—To a solution of 4 g. of pure III in 600 cc. of hot 95% ethanol was added 25 cc. of 38% hydrochloric acid. After the addition of 12 g. of 40-mesh, degreased iron filings in several portions to the hot solution, the mixture was refluxed for three hours, then filtered hot to remove excess iron, which was washed with hot ethanol. The hot filtrate was made slightly alkaline by the addition of concentrated aqueous sodium hydroxide solution, the precipitate filtered off and washed thoroughly with hot ethanol. The colorless filtrate, neutralized by hydrochloric acid, was concentrated *in vacuo* to dryness. The residue was extracted with 40 cc. of cold water in two portions to remove sodium chloride. The undissolved crystals were taken up in 70 cc. of hot absolute ethanol, from which a first crop of 2.7 g. of virtually pure IV crystallized. Additional crystals, isolated from the mother liquor, increased the yield to 3.3 g. or 91%. The compound usually crystallized from ethanol as slightly yellow, rod-shaped prisms, but sometimes was observed to crystallize as blades or thick plates. It showed diazotization and coupling according to the Bratton and Marshall⁷ technique.

Compound IV was prepared also by direct ethylation of I. A mixture of 100 g. of I (2.0 molecular equivalents), 31.4 g. of ethyl iodide (1.0 molecular equivalent), 17 g. of sodium bicarbonate, 500 cc. of 95% ethanol and 100 cc. of water was refluxed for forty-eight hours. The solution deposited at room temperature 16.1 g. of slightly impure IV, which was collected, washed first with 80% ethanol and finally with water. These crystals were purified readily by recrystallization from absolute ethanol. The mother liquor from the crude IV yielded about 80 g. of crystals from which was separated by fractional recrystallization from ethanol about 1 g. of IV. The remainder of the material consisted principally of I.

(7) Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939); *cf.* Roblin and Winnek, *This Journal*, **62**, 1999 (1940).

Benzoylation of IV.—To a solution of 0.4 g. of pure IV in 12 cc. of anhydrous pyridine at 0° was added 0.4 g. of benzoyl chloride. After being kept at room temperature for twenty-two hours, the solution was mixed with ice water which precipitated a sirup that soon crystallized. The crystals were collected and washed with cold water. In order to remove benzoic acid, the substance was extracted with 75 cc. of cold absolute diethyl ether. The undissolved crystals of crude monobenzoyl derivative (V) weighed 0.5 g. It was purified by recrystallization from acetone, from which it crystallized as colorless, rod-shaped prisms melting at 226–227° (uncor.). The compound possesses no free primary amino group, as indicated by its failure to show diazotization and coupling in aqueous acetone solution by the Bratton and Marshall⁷ method.

4-Nitro-4'-(β -hydroxyethylamino)-diphenyl Sulfone (VI).—A solution of 50 g. of II and 23 g. of 2-bromoethanol in a mixture of 250 cc. of 2-ethoxyethanol and 30 cc. of water was refluxed for fifty-eight hours. The filtered solution was neutralized by sodium hydroxide solution and then concentrated *in vacuo*, with the bath at 65–75°, virtually to dryness. The solid residue was mixed thoroughly with 250 cc. of water, then filtered and washed with cold water. It was taken up in hot absolute ethanol, in which it is difficultly soluble, some Norit added and filtered off. The solution deposited yellow, boat-shaped prisms of VI. The mother liquor upon concentration yielded several crops of impure crystals, from which was isolated more VI by fractional recrystallization from ethanol; yield, 17.5 g. or 30%. The analytical sample was obtained by further recrystallization from ethanol.

In a modified experiment evidence was obtained to show that a secondary reaction, involving the hydroxyethyl group, occurs during prolonged refluxing of the reaction solution. A solution similar in composition to that described was refluxed for eighty hours, cooled and stirred with a glass rod to induce crystallization. After twenty-four hours a crop of impure crystalline product was separated. The filtrate, neutralized with sodium hydroxide solution and concentrated *in vacuo* to about one-half the original volume, deposited additional product which was filtered off. The solvent was then removed by distillation *in vacuo*, the residual sirup mixed with water, finally separated and extracted with 70 cc. of hot ethanol. After filtration of the undissolved crystalline product, more material was isolated from the filtrate to make the yield of crystals melting at 200–206° about 46%, calculated as VI. These crystals proved to be a mixture. In an extraction with three parts of hot acetone, about 80% of the crystals melting at 206–209° was undissolved. This material upon reduction by iron and 1.5% hydrochloric acid in hot ethanol solution yielded a mixture consisting principally of VII and about 10% of IV. The two compounds were separated by fractional recrystallization from absolute ethanol. The crystals of IV were identified by the melting point of 199–200° (uncor.) alone or mixed with authentic IV; also by benzoylation according to the previously described procedure to yield the crystalline monobenzoyl derivative melting at 226–227° (uncor.), not depressed by crystals of the authentic compound.

4-Amino-4'-(β -hydroxyethylamino)-diphenyl Sulfone (VII).—Recrystallized VI (8.9 g.), melting at 207–210°, was reduced by iron (27 g.) and 1.5% hydrochloric acid in hot ethanol solution (555 cc.) according to the procedure described for the preparation of IV. The crude product (VII), after being washed with cold water, was recrystallized from absolute ethanol as thick, virtually colorless plates; yield, 6.1 g. or 76%. It is readily soluble in acetone, soluble in ethanol and dioxane, also soluble in cold 1% hydrochloric acid, somewhat soluble in hot water, and only slightly soluble in cold water. The presence of a primary amino group in the molecule was demonstrated by diazotization.⁷

4,4'-bis-(β -Hydroxyethylamino)-diphenyl Sulfone (VIII).—Seventy-five grams of I (1.0 molecular equivalent) and 37.8 g. of 2-bromoethanol (1.0 molecular equivalent) were mixed thoroughly while being heated on the

steam-bath. The mixture was kept at 100° under a reflux condenser for thirteen hours and then dissolved, apparently as the hydrobromides, in 200 cc. of warm water. The addition of 30 g. of sodium bicarbonate precipitated a sirup, which changed to a gum upon being cooled in ice water. The gum, after separation from the aqueous layer by decantation, was taken up in 50 cc. of methanol. The solution, upon being left for several days in an open flask at room temperature with occasional stirring, deposited 9.4 g. of somewhat impure crystals of VIII. The mother liquor, kept in an open beaker with occasional addition of methanol and stirring, yielded 7.7 g. of crystalline VIII. The remainder of the material was a sirup, which probably consisted of a mixture of I, VII and VIII. The crude VIII was purified by recrystallization from methanol as virtually colorless, rod-shaped prisms.

N-[p-(p-Nitrophenylsulfonyl)-phenyl]-glycine (IX).—A mixture of 50 g. of II, 23.9 g. of monobromoacetic acid, 16.7 g. of sodium bicarbonate and 280 cc. of water was shaken until effervescence ceased. After the addition of 420 cc. of 2-ethoxyethanol, the mixture was kept at 100° under a reflux condenser for thirty hours. The red solution was neutralized by sodium bicarbonate, the solvent removed by distillation *in vacuo* with the bath at 50°, some water added and evaporated *in vacuo*. The sodium salt of IX was separated from water-insoluble material by extraction of the residue with 900 cc. of cold water in several portions, the final portion showing no precipitate upon addition of hydrochloric acid. The undissolved solid weighed 39.1 g. and melted at 148–151°. The addition of hydrochloric acid to the sodium salt solution precipitated IX as a sirup which crystallized overnight. To an efficiently stirred suspension of the crude acid in water was added sodium hydroxide solution until the mixture was neutral to phenolphthalein. After filtration to remove some undissolved solid, the acid was precipitated by the addition of hydrochloric acid; air-dried; yield of virtually pure IX, 11.8 g. The analytical sample was obtained by recrystallization of the compound as yellow, spear-shaped prisms from a mixture of acetone and water.

N-[p-(p-Aminophenylsulfonyl)-phenyl]-glycine (X).—A solution of 100 g. of I (2.0 molecular equivalents), 28 g. of monobromoacetic acid (1.0 molecular equivalent) and 19 g. of sodium bicarbonate in a mixture of 500 cc. of water and 250 cc. of 2-ethoxyethanol was kept at 100° under a reflux condenser for thirty-two hours. The crude solid was isolated and preliminary purification accomplished by a procedure similar to that described for IX; air-dried; yield, 39 g. melting at 185–193°. About 62 g. of impure I was recovered. Although the acid could be recrystallized from methanol, its purification is facilitated by the preparation of the pyridine salt.

A solution of 37 g. of the acid in about 175 cc. of hot pyridine, upon being filtered and kept overnight at room temperature, deposited elongated, well-formed prisms of the pyridine salt which were filtered, washed first with cold pyridine and finally with methanol. Crystals obtained from the mother liquor, after concentration *in vacuo*, increased the yield to 38 g., most of which was nearly pure. After being recrystallized to constant melting point from pyridine and dried in an evacuated desiccator over calcium chloride, the pure salt melted at 167–168° (uncor.).

To a suspension of 10 g. of pure pyridine salt in 100 cc. of water was added 27.3 cc. of *N* sodium hydroxide solution. In order to remove pyridine, the filtered solution was concentrated to dryness *in vacuo* with the bath at 55–60°, the residual sirup taken up in water and the concentration repeated. After some absolute ethanol had been added and distilled off *in vacuo*, the sodium salt was dissolved in 35 cc. of water, the solution filtered and the acid precipitated by the addition of 27.3 cc. of *N* hydrochloric acid. The virtually colorless pure X was filtered off, washed with cold water and dried in the air at room temperature; yield, 7.5 g. The presence of a primary amino group in the molecule was demonstrated by a test with *p*-dimethylaminobenzaldehyde, also by diazotization and coupling.⁷

N-[*p*-(*p*-Aminophenylsulfonyl)-phenyl]- β -alanine (XI).—A mixture of 163 g. of I, 50 g. of β -bromopropionic acid, 30 g. of sodium bicarbonate, 500 cc. of water and 250 cc. of 2-ethoxyethanol was kept at 100° under a reflux condenser for forty-six hours. The solution, after being neutralized by sodium bicarbonate, deposited at room temperature 102 g. of I melting at 168–172°. Crude XI was isolated as a sirup in a similar way as described for IX. A solution of the sirup in a mixture of 65 cc. of methanol and 85 cc. of pyridine deposited at 5° crystals of the pyridine salt of XI. After the crystals had been filtered and washed with diethyl ether, the filtrate was concentrated *in vacuo* to a thin sirup which, upon being mixed with 15 cc. of pyridine, gave at 5° a second crop of crystals to make the yield 63 g. The pyridine salt is readily soluble in cold pyridine and in cold methanol, soluble in ethanol and only slightly soluble in diethyl ether. It crystallizes from a mixture of pyridine and absolute ethanol as colorless needles or elongated plates. After being dried in an evacuated desiccator over calcium chloride, the pure salt melts at 134–135° (cor.).

The acid was prepared as a nearly colorless sirup from 33 g. of the pyridine salt as described for X, 84 cc. of *N* sodium hydroxide solution and 84 cc. of *N* hydrochloric acid being used in the operation. The sirupy acid was separated from the aqueous layer at 0–5° by decantation and washed with a little water. The acid crystallized from a solution of the sirup in 23 cc. of methanol saturated with benzene; air-dried; weight, 24 g.; m. p. 119–120°. After being recrystallized further as spear-shaped prisms from a mixture of methanol and benzene and dried in an evacuated desiccator over calcium chloride, the virtually colorless pure XI melted at 127–128° (cor.). These crystals lost no weight at 65° *in vacuo*. Calcd. for $C_{16}H_{18}N_2O_4S + 0.5 C_6H_6$: C, 60.1; H, 5.3. Found: C, 60.1; H, 5.5. The solvent-free analytical sample was obtained by evaporation of a solution of the crystals in acetone followed by drying the residual sirup at 100° *in vacuo*. The compound reacts with *p*-dimethylaminobenzaldehyde and shows diazotization and coupling,⁷ results which demonstrate the presence of a primary amino group in the molecule.

4-Amino-4'-*n*-butylaminodiphenyl Sulfone (XII).—A solution of 85 g. of I (2.5 molecular equivalents) and 18.7 g. of *n*-butyl bromide (1.0 molecular equivalent) in a mixture of 495 cc. of 95% ethanol and 26 cc. of water was refluxed for twenty-five hours. The solution deposited at room temperature 19.3 g. of somewhat impure XII. The mother liquor was neutralized by sodium hydroxide solution, then treated hot with Norit and freed from solvent. The solid residue was extracted thoroughly with cold 2.5% hydrochloric acid. Neutralization of the hydrochloric acid solution by sodium hydroxide precipitated 50 g. of nearly pure I melting at 172–173°. The solid, which was undissolved by the hydrochloric acid, was washed with water and recrystallized from ethanol, yielding colorless plates of XII. The total yield was 27.5 g. or 66%. The compound showed diazotization and coupling.⁷

4-Amino-4'-*n*-amylaminodiphenyl Sulfone (XIII).—A yield of 72 g. or 70% of XIII was obtained from 200 g. of I and 49 g. of *n*-amyl bromide by a procedure similar to that described under XII. The compound crystallized from ethanol as almost colorless, spear-shaped prisms, which are readily soluble in acetone and virtually insoluble in water. It showed diazotization and coupling.⁷

4-Amino-4'-*n*-tetradecylaminodiphenyl Sulfone (XIV).—A solution of 10 g. of I and 4.5 g. of myristyl bromide in a mixture of 55 cc. of ethanol and 6 cc. of water was refluxed for thirty hours. The product was isolated and purified in a similar way as described for XII. It crystallized from absolute ethanol as colorless, thin blades; m. p. 174–174.5° (cor.).

Compound XIV was prepared also by the reaction of I and myristyl bromide in the molecular proportions of 1.25 to 1.00.

Reduction of 1.2 g. of the pure nitro derivative (XV) by iron filings (4 g.) and 1.5% hydrochloric acid in ethanol

solution (84 cc.) yielded crystals of XIV. Identity with the crystals prepared from I was established by the melting point of 174–174.5° (cor.), not depressed by crystals prepared from I; also by resemblance in crystal form and solubility. Samples prepared by both methods showed diazotization and coupling.⁷

4-Nitro-4'-*n*-tetradecylaminodiphenyl Sulfone (XV).—A solution of 20 g. of II and 19.9 g. of myristyl bromide in a mixture of 100 cc. of 2-ethoxyethanol and 12 cc. of water was kept at 100° under a reflux condenser for fifty-four hours. The solid material was recovered and neutralized in aqueous suspension. Fractional recrystallization from absolute ethanol afforded a partial separation of XV from unreacted II. Crystals of pure XV were obtained by recrystallization of selected fractions of the mixture from acetone, from which the compound crystallized as yellow blades. The analytical sample was dried at 65° *in vacuo*.

4-Nitro-4'-benzylaminodiphenyl Sulfone (XVI).—A mixture of 200 g. of II, 96 g. of benzyl chloride, 480 cc. of 95% ethanol and 720 cc. of water was refluxed for fifty hours. After the reaction mixture had been kept overnight at 25°, the supernatant liquid was decanted from a sirup, which was washed thrice with cold water and then dissolved in 200 cc. of hot dioxane. The filtered solution deposited at room temperature 168 g. of crystals, the yield of crude product being increased to about 225 g. by the isolation of more crystals from the mother liquor. Purification was completed by recrystallization from dioxane as thick, yellow plates which, in the air-dried condition, retained combined solvent. The analytical sample was dried to constant weight at 100° *in vacuo*; it then melted at 149–150° (uncor.).

Some 4-nitro-4'-dibenzylaminodiphenyl sulfone is formed in the benzylation reaction, as shown below by the isolation of crystals of XVIII from the products of the reduction of some impure XVI.

4-Amino-4'-benzylaminodiphenyl Sulfone (XVII) and 4-Amino-4'-dibenzylaminodiphenyl Sulfone (XVIII).—A solution of 15 g. of XVI, which had been dried at 100° *in vacuo*, in 460 cc. of hot 95% ethanol was treated with 18 cc. of 38% hydrochloric acid and 45 g. of iron filings by the procedure described for the preparation of IV, with the exception that methanol was substituted for ethanol in washing the excess iron and iron compounds. The solution, neutralized by hydrochloric acid, deposited at room temperature 6.7 g. of crystals, melting at 178–180°, which proved to be a mixture of XVII and XVIII. The mother liquor was decolorized with carbon and concentrated virtually to dryness. The residue was stirred with 100 cc. of water, the undissolved crystals collected and washed with water. Extraction of the 6.7 g. of crystals with 100 cc. of hot methanol left undissolved 1.7 g. which, upon recrystallization from a mixture of acetone and methanol, yielded about 1 g. of difficultly soluble, rod-shaped prisms of XVIII. Fractional recrystallization of the remainder of the material from methanol, with the use of decolorizing carbon when necessary, afforded 7.6 g. or 55% of virtually pure, colorless blades of XVII. The crystals of XVII showed diazotization and coupling.⁷ Crystals of pure XVIII in aqueous acetone solution gave a diazotization⁷ value of 28% as compared with I; calculated, 29%.

4,4'-bis-(Dibenzylamino)-diphenyl Sulfone (XIX).—A mixture of 10 g. of I (1.0 molecular equivalent), 17.8 g. of benzyl chloride (3.5 molecular equivalents), 36 cc. of water and 24 cc. of 95% ethanol was refluxed for forty-seven hours. The crude product was isolated as a sirup, which crystallized from a mixture of acetone and ethanol. Purified by recrystallization first from a mixture of acetone and ethanol and finally from acetone, the colorless rod-shaped prisms melted at 199–200° (uncor.). Buttle, *et al.*,⁶ reported a melting point of 200° (cor.).

Summary

A number of new derivatives of 4,4'-diaminodiphenyl sulfone having an alkyl, carboxyalkyl or

hydroxyethyl group substituted in one of the amino groups have been synthesized. Several similar derivatives of 4-amino-4'-nitrodiphenyl sulfone were prepared. The preparation and

the properties of the compounds are described.

The antipneumococcal and antitubercular activities of certain of the compounds are recorded.

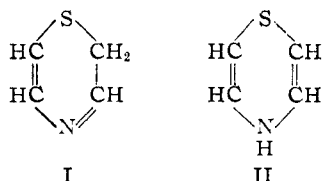
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY]

The Preparation of 1,4-Thiazine

BY CHARLES BARKENBUS AND PHILLIP S. LANDIS¹

Compounds containing the uncondensed heterocyclic 1,4-thiazine ring have never been thoroughly investigated although, condensed with the benzene ring, this heterocyclic structure occurs in the important thiazine dyes. 1,4-Thiazine, which can theoretically exist in two forms (I) and (II), has never been described in the literature.



It has been found possible to synthesize 1,4-thiazine by making the imide of thiodiglycolic acid and reducing this imide with aluminum powder at an elevated temperature.

Thioglycolic acid, the starting point in the synthesis of 1,4-thiazine can be made easily by the usual method of the reaction of monochloroacetic acid with sodium sulfide. By extracting the acid from the reaction mixture with ether yields of 90% can be obtained.

The imide of thiodiglycolic acid was mentioned by Schulze in 1865 but no further reference to this interesting imide could be found. It was found that thiodiglycolimide could be made in excellent yields by heating the dry ammonium salt of thiodiglycolic acid in a partial vacuum.

The reduction of thiodiglycolimide to 1,4-thiazine is comparable to the preparation of pyrrole from succinimide. A literature search easily reveals that the reduction of succinimide, in spite of the large amount of space devoted to it by standard texts, is of very little preparative value and no one recommends this reduction as a means of making pyrrole or pyrrolidine. The most encouraging reduction method appeared to be that of Ray and Dutt,² who heated succinimide at an elevated temperature with aluminum powder instead of the customary zinc dust and obtained a 15% yield of pyrrole. The high temperature recommended, namely, dull red heat, placed some doubt as to whether the sulfur of the ring would survive such treatment. After many modifica-

tions of the original method, however, yields of 13% of 1,4-thiazine were finally obtained.

1,4-Thiazine, the mother substance of this interesting type of ring structure, is a colorless liquid boiling at 76.5–77°, miscible with water in all proportions, and is a weak base, $K = 4.0 \times 10^{-9}$. It has an ammoniacal odor combined with a faint but detectable odor of sauerkraut. It does not form a sulfonamide by the Hinsberg method and appears to be a tertiary amine having the structure corresponding to formula (I).

In investigating the many methods of reduction that have been tried on imides the reduction of chloro substituted imides appeared to offer some possibilities. Succinimide when treated with phosphorus pentachloride can be chlorinated to dichlorosuccinimide³ which on further treatment gives tetrachloropyrrole. Prolonged treatment of thiodiglycolimide with phosphorus pentachloride completely destroyed the imide but careful heating of the imide with small amounts of phosphorus pentachloride gave a white crystalline compound having only one chlorine in the molecule. At first it was thought that this compound, because of the ease of hydrolysis of the chlorine, was an imino-chloride. Mild treatment with alkali, however, did not regenerate the imide but produced instead thioglycolic acid, glyoxalic acid and ammonia. This would indicate that the chlorine had entered the α -position and that on hydrolysis a cyclic hemithioacetal was produced which on further hydrolysis gave the above products.

Experimental

Thiodiglycolic Acid.—Nine hundred and forty-five grams (10 moles) of monochloroacetic acid was placed in a 5 liter round-bottomed flask and dissolved in 1500 ml. of water. To this solution was added slowly with stirring 840 g. (10 moles) of solid sodium bicarbonate until the solution was neutral to litmus. The flask was placed in an ice-bath and 1320 g. (5.1 moles) of hydrated sodium sulfide dissolved in 1850 ml. of water was added slowly with stirring keeping the temperature between 25–30°. The solution was allowed to stand in the ice-bath for one hour and then 750 ml. of concentrated sulfuric acid was added with stirring, keeping the temperature between 25–30°.

The resulting solution was placed in a continuous extractor and ether passed through the solution at the rate of about 6 ml. per minute for twelve hours. At the end of each twelve-hour period fresh ether was placed in the extractor and the extraction continued for a total of thirty-

(1) Taken in part from a thesis presented in partial fulfillment of the requirements for the degree of Master of Science, University of Kentucky, August, 1947.

(2) A. C. Ray and S. B. Dutt, *J. Ind. Chem. Soc.*, **5**, 103 (1928).

(3) R. Anschütz, *Ann.*, **295**, 27 (1897).