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[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH LABORATORIES, LEPETIT S.P.A., MILAN]

Synthesis of Derivatives of a New Heterocyclic Ring. 1,3-Dihydro-2,3,5-benzothiadiazepine 2,2-Dioxide

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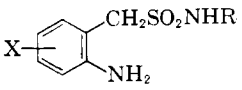
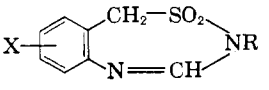
The Ladenburg reaction, when extended to 2-aminobenzylsulfonamide (Ia), leads to 1,3-dihydro-2,3,5-benzothiadiazepine 2,2-dioxide (IIa), a new heterocyclic ring. 2-Amino-5-bromobenzylsulfonamide (Ib) gives the cyclic 8-bromo derivative IIb, thus showing that the reaction may run also with ring substituted 2-aminobenzylsulfonamides. On the contrary, 2-aminobenzylsulfonylmethylamine (Ic) and 2-amino-benzylsulfonanilide (Id) give N,N'-bis-(2-methylaminosulfonylmethylphenyl)-formamidine (IVa) and N,N'-bis-(2-anilinosulfonylmethylphenyl)-formamidine (IVb), thus showing that no ring closure occurs when the sulfonamide nitrogen is substituted by alkyl or phenyl.

The Ladenburg reaction, originally used for the preparation of benzimidazoles,[1-3] has been applied to various α-diamino compounds for synthesizing pyrimidine[4,5] and quinazoline derivatives[6] and to 2-aminosulfonamides for synthesizing 1,4-dihydro-1,2,4-benzothiadiazines,[7-9] even substituted at C-3 when ethyl orthoformate was used as the condensing agent.[10]

It seemed of interest to ascertain whether the Ladenburg reaction could be extended also to 2-aminobenzylsulfonamides of formula I where



Ia, R = X = H
Ib, R = H, X = Br
Ic, R = CH_3, X = H
Id, R = C_6H_5, X = H



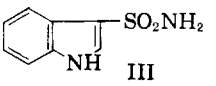
IIa, R = X = H
IIb, R = H, X = Br

the two amino groups are the extremes of a 6-member chain. In this way it would be possible to obtain seven-membered heterocyclic rings, such as the hitherto unknown 1,3-dihydro-2,3,5-benzothiadiazepine 2,2-dioxides (II).

The 4,1,2-, 1,3,4- and 3,1,5-benzothiadiazepines are recorded in the literature.[11] Recently Katz and co-workers[12] described a product, $C_8H_8N_2O_3S$, obtained by treating *o*-mercaptobenzhydrazide with formaldehyde which, in the authors' opinion, could be a 5,3,2-benzothiadiazepinone. The starting 2-aminobenzylsulfonamides, also unknown, were prepared by treating a 2-nitrobenzyl chloride with thiourea according to Johnson and Sprague,[13,14] converting the 2-nitrobenzyl sulfonylchloride so obtained by ammonia or monosubstituted amines into the corresponding 2-nitrobenzylsulfonamides and finally reducing the nitro group with hydrogen over a palladium catalyst.

For the subsequent Ladenburg reaction we selected ethyl orthoformate as the condensing agent because of its smooth reactivity both with unsubstituted and monosubstituted sulfonamides.[10] The reaction was carried out in propylene glycol at 120–130° for 4 to 7 hours with an excess of ethyl orthoformate (4:1).

When unsubstituted 2-aminobenzylsulfonamide (Ia) is treated with ethyl orthoformate a compound, $C_8H_8N_2O_2S$, melting at 234° is obtained. Two different structures can be suggested for this product: the benzothiadiazepine structure IIa resulting from the reaction of ethyl orthoformate with both amino groups of 2-aminobenzylsulfonamide and the 3-indolesulfonamide structure III resulting from the reaction of ethyl orthoformate with the amino and the methylene groups, this latter activated by the sulfonamide group and the benzene ring.



III

The substance of m.p. 234° is acidic in nature. The pK value, determined spectrophotometrically, is 10.0.

When an alkaline solution of the product is allowed to stand for many hours or is heated for a few minutes no precipitate is formed in acid solution, whereas the diazo reaction both in this solution and in the shortly heated acid suspension is positive.

The instability of the substance in acids and alkalies disagrees with the indolesulfonamide structure in view of the stability of the indole nucleus under the experimental conditions employed. On the other hand, this instability agrees with the behavior of the analog benzothiadiazine 1,1-

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(3) R. von Walther and A. Kessler, *J. prakt. Chem.*, [2] **74**, 188 (1906).
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(8) D. V. Parke and R. T. Williams, *J. Chem. Soc.*, 1761 (1950).
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(12) L. Katz, L. S. Kerger, W. Schröder and M. S. Cohen, *J. Org. Chem.*, **18**, 1380 (1953).
(13) T. B. Johnson and J. M. Sprague, THIS JOURNAL, **58**, 1348 (1936).
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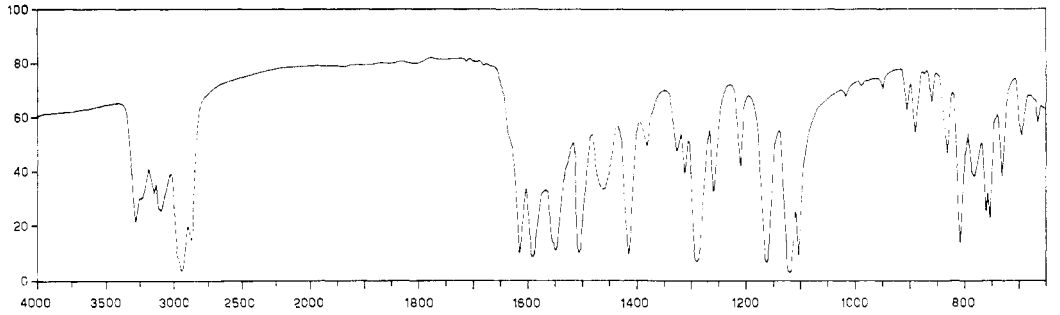


Fig. 1.—Infrared spectrum of 1,3 dihydro-2,3,5-benzothiadiazepine 2,2-dioxide (IIa).

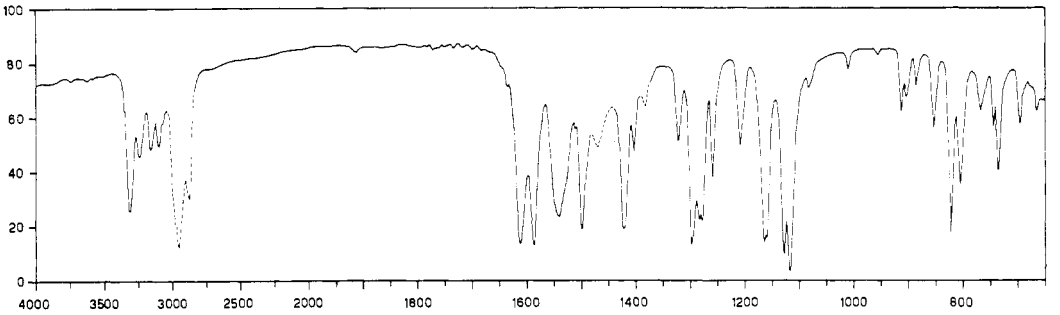


Fig. 2.—Infrared spectrum of 1,3-dihydro-8-bromo-2,3,5-benzothiadiazepine 2,2-dioxide (IIb).

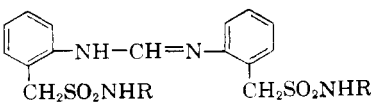
dioxides[10] and therefore with structure IIa. To corroborate our hypothesis we hydrolyzed the product of m.p. 234° with 20% H_3PO_4. The hydrolysate was steam distilled: in the distillate a compound reducing ammoniacal silver nitrate was identified as formic acid; 2-aminobenzylsulfonamide in the form of its phosphate salt was present in the residue. The salt was neutralized: a product was isolated in practically quantitative yield and identified as 2-aminobenzylsulfonamide by its infrared spectrum and its m.p. which were identical with those of an authentic sample. In the Ladenburg reaction of 2-aminobenzylsulfonamide another product melting over 360° was isolated together with the benzothiadiazepine IIa in about the same quantity; the product, possibly a polymer, has not yet been identified.

The benzothiadiazepine IIa does not absorb hydrogen at room temperature and ordinary pressure in the presence of palladium-on-charcoal. The NH group of IIa cannot be alkylated either with methyl iodide in sodium methoxide or with dimethyl sulfate in sodamide, possibly because of the instability of the benzothiadiazepine ring in alkaline medium.

The Ladenburg reaction has been applied also to a ring substituted 2-aminobenzylsulfonamide. From 2-amino-5-bromobenzylsulfonamide (Ib) we have obtained 1,3-dihydro-8-bromo-2,3,5-benzothiadiazepine 2,2-dioxide (IIb). The infrared spectrum of IIb is recorded in Fig. 2; it shows considerable analogy with the spectrum of compound IIa. Also IIb is acidic in nature; the pK value, determined spectrophotometrically, is 9.3.

The starting compound Ib, not yet described, was prepared by brominating *o*-aminobenzylsulfonamide in glacial acetic acid. To ascertain the position of bromine in the benzene ring, Ib was acetylated and then subjected to permanganate oxidation: a carboxylic acid was recovered and identified as 2-acetamido-5-bromobenzoic acid.[15] When 2-aminobenzylsulfonamides are substituted at the sulfonamide nitrogen the Ladenburg reaction does not occur. The attempted condensation of 2-aminobenzylsulfonylmethyl amine (Ic) and 2-aminobenzylsulfonanilide (Id) with ethyl orthoformate affords products IVa and IVb, respectively: the infrared spectra of both products (Figs. 3 and 4) lack the characteristic bands of compounds IIa and IIb. The ultraviolet spectra of IVa and IVb show in water solution at pH 7.0, respectively, maxima at 278 mμ ($E^{1\%}_{1\,cm.}$ 368) and 284 mμ ($E^{1\%}_{1\,cm.}$ 324), which may be ascribed to a N-substituted anilino group. The above maxima disappear in acid medium. Both compounds are amphoteric in nature. The form IVa preponderates at pH values near 8.0; the pH of the acid dissociation is 11.0; the pH of the basic dissociation is 5.5. The form IVb predominates at pH values near 6.0; the pH of the acid dissociation is 9.0; the pH of the basic dissociation is 3.2. To establish that compounds IVa and IVb give salts with acids the compounds were treated with hydrogen chloride in ether; the expected crystalline hydrochlorides of IVa and IVb were isolated.

On the basis of the above results the structures of N,N'-bis-(2-methylaminosulfonylmethylphenyl)-formamidine and N,N'-bis-(2-anilinosulfonylmethylphenyl)-formamidine have been assigned, respectively, to compounds IVa and IVb. The



reaction pattern in the case of N-substituted 2-aminobenzylsulfonamide can be compared to the

(15) M. T. Bogert and W. J. Hand, THIS JOURNAL, **27**, 1476 (1905).

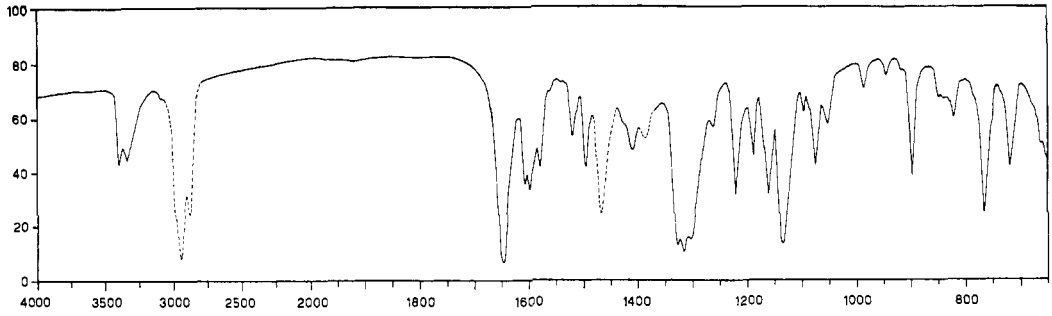


Fig. 3.—Infrared spectrum of N,N'-bis-(2-methylaminosulfonylmethylphenyl)-formamidine (IVa).

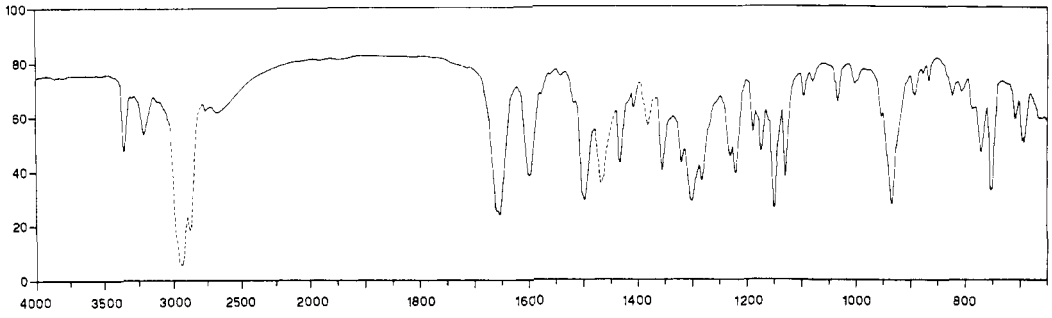


Fig. 4.—Infrared spectrum of N,N'-bis-(2-anilinosulfonylmethylphenyl)-formamidine (IVb).

reaction between aniline or chloroaniline with ethyl orthoformate, which leads to diphenylformamidine[16,17] when carried out with an excess (2:1) of aniline, and to ethylisoformanilide[17,18] when carried out with an excess of ethyl orthoformate. Our experiments never afforded the expected 3-substituted 1,3-dihydro-2,3,5-benzothiadiazepine 1,1-dioxides, even when an excess of ethyl orthoformate was used, possibly because the hydrogen of the group SO_2NHR is not active enough to take part in the intramolecular alcohol elimination leading to the expected cyclic compounds.

Acknowledgments.—The authors gratefully acknowledge the help of Prof. R. Fusco in discussing this work and of Dr. G. G. Gallo who obtained the infrared and ultraviolet spectra.

Experimental

2-Nitrobenzylsulfonyl chloride was prepared from 20 g. of 2-nitrobenzyl chloride and 9 g. of thiourea according to the method of Johnson and Sprague[13,14]; yield 25 g., m.p. 59–61°. The chloride was used for the next step without further purification. On crystallization from ethyl ether the m.p. rose to 61–62°.

Anal. Calcd. for $C_7H_6ClNO_4S$: C, 35.67; H, 2.56; N, 5.94; Cl, 15.04; S, 13.60. Found: C, 35.81; H, 2.60; N, 5.82; Cl, 14.90; S, 13.45.

A sample of the intermediate 2-nitrobenzylthiouronium hydrochloride when crystallized from ethanol appeared as white needles melting at 193–194°.

Anal. Calcd. for $C_8H_9N_3O_2S \cdot HCl$: Cl, 14.31; S, 12.90; N, 16.96. Found: Cl, 14.30; S, 13.20; N, 16.81.

2-Nitrobenzylsulfonamide.—Into a solution of 20 g. of *o*-nitrobenzylsulfonyl chloride in 300 ml. of anhydrous ethyl ether, previously cooled below 5°, a stream of gaseous ammonia was bubbled until a sample of the ether solution failed to give a precipitate by further ammonia addition. The abundant white precipitate was collected by suction and recrystallized from 250 ml. of water; yield 14.5 g. (80%) of white needles, m.p. 139–140°.

Anal. Calcd. for $C_7H_8N_2O_4S$: C, 38.88; H, 3.70; N, 12.95; S, 14.83. Found: C, 39.02; H, 3.78; N, 13.01; S, 14.72.

2-Aminobenzylsulfonamide (Ia).—A solution of 6.5 g. of *o*-nitrobenzylsulfonamide in 150 ml. of anhydrous ethanol was hydrogenated at room temperature and under atmospheric pressure in the presence of 1.5 g. of 10% palladium-on-charcoal. The reduction was complete after about 45–50 minutes. The catalyst was filtered off and the solution evaporated to dryness *in vacuo;* the residual oil (5.1 g.) became solid after standing for some minutes and showed m.p. 89–90°. Recrystallization from 20 ml. of isopropyl alcohol gave 4.2 g. (75%) of pure product, m.p. 95–96°.

Anal. Calcd. for $C_7H_{10}O_2S$: C, 45.14; H, 5.41; N, 15.04; S, 17.21. Found: C, 45.29; H, 5.60; N, 15.10; S, 17.09.

The reduction was carried out also with iron in dilute acetic acid. Although the yield was fairly good (about 70%), the recovery of the reaction product was somewhat troublesome.

1,3-Dihydro-2,3,5-benzothiadiazepine 2,2-Dioxide (IIa).—In a 50-ml. flask provided with a thermometer and a distilling apparatus a mixture of 3.7 g. of 2-aminobenzylsulfonamide and 10 ml. of propylene glycol was warmed slightly until solution occurred, then 13 ml. of ethyl orthoformate (excess 4:1) was added. The mixture was heated for 6 hours on an oil-bath maintained at a temperature of 120°. The ethanol formed in the reaction distilled off while a solid amorphous product gradually formed in the solution. On cooling to room temperature, 1,3-dihydro-2,3,5-benzothiadiazepine 2,2-dioxide, which is soluble in hot propylene glycol, precipitated in the form of crystals. The solids were collected by suction and extracted with 100 ml. of hot methanol, in which the amorphous product was totally insoluble. On cooling the methanol extract, IIa precipitated in the form of small white crystals; yield 1.7 g. (43.5%). m.p. 234–235°.

Anal. Calcd. for $C_8H_8N_2O_2S$: C, 48.96; H, 4.10; N, 14.27; S, 16.34. Found: C, 49.00; H, 3.94; N, 14.34; S, 16.61.

The solid insoluble in hot methanol (1.7 g.) is perhaps a polymer. It melts above 360° and is totally insoluble in organic solvents, water and acids. It dissolves in dilute sodium hydroxide from which it can be reprecipitated by acidification.

The product IIa is soluble, although with some difficulty, in hot methanol; it is insoluble or very slightly soluble in the other organic solvents. It is slightly acidic in nature. From a survey of the ultraviolet spectrum at different *p*H

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values it was found to have pK_a 10. The benzodiazepine dissolves in dilute alkalies; from the alkaline solution it can be reprecipitated by the addition of mineral acids. It does not dissolve in dilute HCl. When allowed to stand for some hours in alkaline solution it was hydrolyzed to 2-aminobenzylsulfonamide (Ia).

Hydrolysis of 1,3-Dihydro-2,3,5-benzothiadiazepine 2,2-Dioxide (IIa) to 2-Aminobenzylsulfonamide (Ia) and Formic Acid.—One gram of IIa was refluxed for 30 minutes with 10 ml. of 20% phosphoric acid. The mixture then was steam distilled and the formic acid formed in the reaction was collected and identified by reaction with an ammoniacal silver nitrate. The residue from the distillation was adjusted to *p*H 6.0 with dilute sodium hydroxide and the separated oil was extracted with ethyl acetate. The solvent was removed by distillation and the pasty residue (0.7 g.) was recrystallized from isopropyl alcohol giving a product with m.p. 95–96°. From the mixed m.p. with an authentic sample and from the infrared spectrum this product was found to be identical with 2-aminobenzylsulfonamide.

2-Amino-5-bromobenzylsulfonamide (Ib).—2-Aminobenzylsulfonamide (Ia), 5.4 g., was dissolved in 84 ml. of glacial acetic acid. To this solution 1.09 ml. (3.46 g.) of bromine in 80 ml. of acetic acid slowly was added with stirring: the temperature rose to 30–35° and a white crystalline product separated. After the addition was complete, the reaction mixture was stirred for an additional 15 minutes, then filtered and the precipitate washed with ethyl ether to completely eliminate acetic acid. A product (6 g.) was collected melting at 170–173°, which consisted of a mixture of the hydrobromide and the acetyl derivative of Ib. This was heated with 25 ml. of 10% sodium hydroxide for two hours on a boiling water-bath; on cooling and neutralizing with hydrochloric acid the free base Ib precipitated; yield 2.6 g., m.p. 156–157°.

Anal. Calcd. for $C_7H_9BrN_2O_2S$: C, 31.70; H, 3.42; Br, 30.14; N, 10.56; S, 12.09. Found: C, 31.85; H, 3.20; Br, 30.38; N, 10.49; S, 12.20.

2-Acetamido-5-bromobenzylsulfonamide.—To a suspension of 1 g. of Ib in 10 ml. of glacial acetic acid 0.4 g. of acetic anhydride was added. The reaction was exothermic; the starting compound gradually dissolved, then a precipitate was formed. The reaction mixture was heated for 30 minutes on a water-bath to complete the reaction, then cooled and filtered; yield 1 g. of 2-acetamido-5-bromobenzylsulfonamide, m.p. 220–222°.

Anal. Calcd. for $C_9H_{11}BrN_2O_3S$: C, 35.18; H, 3.60; Br, 26.01; N, 9.12; S, 10.43. Found: C, 35.20; H, 3.45; Br, 26.18; N, 9.30; S, 10.75.

To prove that on bromination of 2-aminobenzylsulfonamide the 5-halogenated compound was formed, the latter (0.5 g.) was suspended in 5 ml. of water and heated 3 hours on a boiling water-bath with 0.6 g. of potassium permanganate in the presence of 0.46 g. of magnesium sulfate. After standing 12 hours at room temperature, the mixture was filtered and the filtrate concentrated and acidified with hydrochloric acid; a micro-crystalline precipitate melting at 222–223° was obtained and identified as 2-acetamido-5-bromobenzoic acid.[15] The 2-acetamido-5-bromobenzoic acid was hydrolyzed with sodium hydroxide; the known 2-amino-5-bromobenzoic acid[15] was obtained, m.p. 218°. The latter was converted into its known hydrobromide, m.p. 237–238°.

1,3-Dihydro-8-bromo-2,3,5-benzothiadiazepine 2,2-dioxide (IIb) was prepared in 47% yield according to the process described for 1,3-dihydro-2,3,5-benzothiadiazepine 2,2-dioxide, m. p. 260° dec.

Anal. Calcd. for $C_8H_7BrH_2O_2S$: C, 34.92; H, 2.56; Br, 29.04; N, 10.18; S, 11.65. Found: C, 34.90; H, 2.75; Br, 28.80; N, 10.30; S, 11.75.

Also in this case a methanol-insoluble, amorphous solid was isolated in about the same quantity as IIb. The product, perhaps a polymer, melts above 360°.

2-Nitrobenzylsulfonylmethylamine.—A solution of 10 g. of Ia in 100 ml. of ethyl ether was treated with gaseous methylamine until the solution was saturated. The precipitate formed was collected by suction and crystallized from 250 ml. of water; yield 6.8 g. (70%) of white plates, m.p. 118°.

Anal. Calcd. for $C_8H_{10}N_2O_4S$: C, 41.73; H, 4.37; N, 12.16; S, 13.92. Found: C, 41.75; H, 4.48; N, 12.24; S, 13.87.

2-Aminobenzylsulfonylmethylamine (Ic).—Four and six-tenths grams of 2-nitrobenzylsulfonylmethylamine dissolved in 100 ml. of ethanol was hydrogenated at room temperature and pressure with 1 g. of 10% palladium-on-charcoal as catalyst. After 30 minutes the reaction was complete; the solution was filtered from the catalyst and evaporated to dryness *in vacuo*. The oily residue (3.8 g.) solidified, and on crystallization from isopropyl alcohol 3 g. (75%) was obtained melting at 110–111°.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.97; H, 6.04; N, 13.98; S, 16.01. Found: C, 48.00; H, 5.97; N, 14.16; S, 16.30.

N,N'-Bis-(2-methylaminosulfonylmethylphenyl)-formamidine (IVa).—A solution of 3 g. of IIc in 10 ml. of propylene glycol was treated with 10 ml. of ethyl orthoformate. The mixture was heated at 130–140° for 7 hours, then allowed to cool to room temperature and diluted with 5 ml. of water. The separated oily product was extracted with 100 ml. of chloroform. The chloroform solution was dried over anhydrous sodium sulfate and concentrated to one-half its volume, a microcrystalline product separated. After cooling in ice, the precipitate was collected by suction and recrystallized from methanol; yield 1.3 g. of white small crystals, m.p. 184–185°.

Anal. Calcd. for $C_{17}H_{22}N_4O_4S_2$: C, 49.73; H, 5.40; N, 13.64; S, 15.62. Found: C, 49.87; H, 5.60; N, 13.40; S, 15.85.

Compound IVa is a base with pK 8.38; it is slightly soluble in alkali. The alkaline solutions undergo hydrolysis on standing, giving some *o*-aminobenzylsulfonamide. In dilute hydrochloric acid compound IVa yields a slightly soluble product which was crystallized from ethyl ether–ethanol and identified as formamidine hydrochloride (m.p. 198–199°). The above hydrochloride also was obtained by treating with hydrogen chloride an ether solution of formamidine.

Anal. Calcd. for $C_{17}H_{22}N_4O_4S_2 \cdot HCl$: N, 12.53; Cl, 7.93. Found: N, 12.71; Cl, 8.12.

2-Nitrobenzylsulfonanilide.—A solution of 15 g. of aniline in 50 ml. of ethyl ether was treated with 15 g. of 2-nitrobenzylsulfonyl chloride added in portions during 30 minutes while stirring. A voluminous precipitate separated which was slurried with 50 ml. of ethyl ether and stirred for 15 minutes. The ether was distilled off and the residue treated with 50 ml. of 10% hydrochloric acid and 50 ml. of water in order to dissolve aniline hydrochloride. The insoluble 2-nitrobenzylsulfonanilide was collected by suction and crystallized from ethanol; yield 16 g. (80.5%), m.p. 132°.

Anal. Calcd. for $C_{13}H_{12}N_2O_4S$: C, 53.41; H, 4.13; N, 9.58; S, 10.96. Found: C, 53.25; H, 3.98; N, 9.59; S, 11.00.

2-Aminobenzylsulfonanilide (Id).—A solution of 15 g. of 2-nitrobenzylsulfonanilide in 300 ml. of acetic acid was hydrogenated at room temperature and ordinary pressure in the presence of 2.5 g. of 10% palladium-on-charcoal. The reduction was complete after 2 hours. The mixture was filtered from the catalyst, the filtrate concentrated *in vacuo* to one-third of its volume and poured into 400 ml. of water. After neutralization with sodium bicarbonate, the mixture was extracted with two 100-ml. portions of ethyl ether. The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue crystallized when dissolved in 50 ml. of isopropyl alcohol and treated with petroleum ether until cloudy. After standing in the ice-box overnight large crystals were collected; yield 7 g., m.p. 81–82°. A further crop of 2.5 g. (m.p. 81–82°) was obtained by adding petroleum ether to the mother liquor of the crystallization; over-all yield 9.5 g. (71%).

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.56; H, 5.38; N, 10.72; S, 12.23. Found: C, 59.70; H, 5.31; N, 10.60; S, 12.35.

N,N'-Bis-(2-anilinosulfonylmethylphenyl)-formamidine (IVb) was prepared in 40% yield according to the procedure described for compound IVa. The m.p. of compound IVb when crystallized from chloroform was not very sharp (about 170°); after drying in the oven at 100° or recrystallizing from ethanol the pure product melting at 176–178° was obtained.

Anal. Calcd. for $C_{27}H_{26}N_4O_4S_2$: C, 60.65; H, 4.90; N, 10.48; S, 11.99. Found: C, 60.69; H, 5.00; N, 10.28; S, 11.45.

The physical and chemical properties of compound IVb are quite similar to those of compound IVa. The hydrochloride of compound IVb was obtained by suspending the base in ethyl ether with 10% methanol and passing through the suspension a stream of hydrogen chloride; IVb hydrochloride separated as a white crystalline powder melting at 187–188°.

Anal. Calcd. for $C_{27}H_{26}N_4O_4S_2 \cdot HCl$: N, 9.81; Cl, 6.20. Found: N, 9.78; Cl, 5.95.

MILANO, ITALY

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Thioethers. III. Preparation of Aromatic Di- and Tri-mercapto Compounds by Dealkylation of Aryl Alkyl Thioethers

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Aromatic di- and tri-mercaptans have been synthesized by dealkylation of the corresponding aryl alkyl thioethers with sodium in liquid ammonia.

The synthesis of aromatic di- and tri-alkylmercapto compounds from the corresponding di- and tri-bromo compounds and cuprous alkylmercaptides has been described in previous papers.[2] Since these thioethers are readily accessible, their possible uses as intermediates in a synthetic approach to aromatic di- and tri-mercapto compounds has been explored.

The dealkylation of 1,2- and 1,4-diethylmercaptobenzenes was first investigated with each of the three reagents, sodium in liquid ammonia, lithium in monomethylamine, and sodium in pyridine. The first two reagents proved to be equally satisfactory and better than the third one. Sodium in liquid ammonia was selected as the method of choice for subsequent studies. From the appropriate diethylmercapto derivatives by this means 1,2- and 1,4-dimercaptobenzenes, 4,4′-dimercaptobiphenyl, 4,4′-dimercaptobibenzyl, 2,5-dimercaptotoluene, 1,3,5-trimercaptobenzene and 2,4,6-trimercaptomesitylene were synthesized in 70–99% yields.

The use of sodium in liquid ammonia has been extensively and successfully applied to the debenzylation of alkyl benzyl sulfides[3] and for hydrogenolysis of alkyl sulfides,[4] and in a single instance for hydrogenolysis of an aryl alkyl sulfide, namely, thioanisole.[5] Aryl alkyl sulfides are reported to be cleaved in excellent yields into thiophenol and alkanes with lithium in monomethylamine.[6]

Di- and tri-mercapto aromatic compounds have usually been prepared by reduction of the corresponding sulfonyl chlorides.[7–18] A second method, applicable when the required disulfonic acids cannot be formed by direct sulfonation,[7,8,15] involves the use of an aminosulfonic acid. The amino group is diazotized and allowed to react with potassium ethyl xanthate. Upon hydrolysis of the product, the resulting mercapto sulfonic acid is transformed into the dimercaptan in one of two ways: oxidation with potassium permanganate converts the product to a disulfonic acid which is reduced, through the acid chloride, to the dimercaptan. Mild oxidation may be used to convert the mercapto group to a disulfide; this is followed by formation of the sulfonyl chloride from the sulfonic acid group, and finally reduction of both the sulfonyl chloride and disulfide groups to the di- or tri-mercaptan.

The new method described in this Communication is definitely superior to those previously used whenever the corresponding bromo compounds are more readily available than the corresponding sulfonic acids or sulfonyl chlorides. Thus, 1,2- and 1,4-dimercaptobenzenes are synthesized preferably from the 1,2- and 1,4-dibromobenzenes rather than from the 1,2- and 1,4-benzenedisulfonic acids.

It is reported that an inactive halogen atom in aromatic halogen compounds will react with potassium hydrogen sulfide in presence of copper sulfate as catalyst to give a mercaptan, but a temperature of 250° is required for completion of the reaction.[19] This procedure has not been applied to dihalogen compounds. The vigorous conditions required would normally lead to a preference of the pathway through the alkylmer-

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