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A Note on the Reaction of 4,5-Dichloro-1,3-benzenedisulfonamide with Hydrazine and Amines

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The reaction of 4,5-dichloro-1,3-benzenedisulfonamide (I) (Diclofenamide, Daramide®) with hydrazine is reported [1] to result in 6-chloro-3,5-disulfamyl-phenylhydrazine (II) since after removal of the hydrazino-group with alkaline hypochlorite by the method of Chattaway [2] a chlorobenzene-disulfonamide with m.p. 214—215° * was isolated and suggested to be III. The chlorine atom in *o*-, *p*-position to the sulfonamide groups was thought to be sterically hindered.[3]

In connection with studies on benzenesulfonamide-diuretics we have reinvestigated the above sequence of reactions. The obtained chloro-benzenedisulfonamide had m.p. 223—224° * and was identified as 5-chloro-1,3-benzenedisulfonamide (IV) by means of its NMR spectrum (Table 1) indicating the originally formed phenylhydrazine to be V.

The previously suggested structure II of the chloro-disulfamylphenylhydrazine IV has served as a model for the reaction products of I with several amines.[3,5] For this reason we have reinvestigated *N*-carbethoxypiperazino-chlorobenzenedisulfonamide, prepared [5] from I and dechlorinated to 4-(*N*-carbethoxypiperazino)-1,3-benzenedisulfonamide (VI) by hydrogenation. The structure of VI is proved by its NMR spectrum (Table 1).

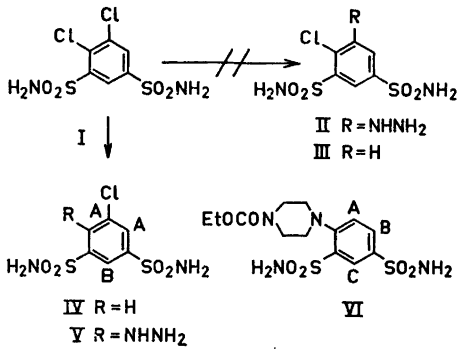

Table 1. NMR data[a] (δ) of IV and VI.

IV[b]		
A	8.09	(d, $J_{A,B}$ = 1.5 cps)
B	8.33	(t, $J_{A,B}$ = 1.5 cps)
VI[c]		
A	8.15	(d, $J_{A,B}$ = 8.6 cps)
B	8.54	(d, $J_{A,B}$ = 8.6 cps; d, $J_{B,C}$ = 2.0 cps)
C	8.91	(d, $J_{B,C}$ = 2.0 cps)

[a] Varian A 60 A (60 MHz);
[b] 10 % in methanol;
[c] 10 % in CF_3COOD, arom. protons recorded only.

The results indicate that the "activated" chlorine atom in the 4-position of I reacts normally with hydrazine and amines and that the earlier reported structure of the reaction products has to be revised in this way.

Experimental. Technical assistance by T. Parbst; Analyses by G. Cornali and W. Egger; NMR spectra by Karin Dehn.

5-Chloro-4-(N-carbethoxypiperazino)-1,3-benzenedisulfonamide. The compound was prepared from 4,5-dichloro-1,3-benzenedisulfonamide and *N*-carbethoxypiperazine as described [5] and purified by several recrystallizations from aqueous ethanol; m.p. 286° (decomp.). (Found: C 36.51; H 4.60; N 12.96. Calc. for $C_{13}H_{19}ClN_4O_6S_2$ (426.89): C 36.57; H 4.49; N 13.12).

4-(N-Carbethoxypiperazino)-1,3-benzenedisulfonamide (VI). To a solution of 1 g of 5-chloro-4-(*N*-carbethoxypiperazino)-1,3-benzenedisulfonamide in 2.7 ml of 2.6 N NaOH and

* 4-Chloro-1,3-benzenedisulfonamide, Lit.[4] m.p. 217—219°; 5-chloro-1,3-benzenedisulfonamide, Lit.[4] m.p. 223—224°.

15 ml of water 0.15 g of 10 % Pd on carbon catalyst was added and the reaction mixture was hydrogenated at room temperature until the hydrogen uptake became negligible. The catalyst was removed by filtration, and VI precipitated by addition of acetic acid to the filtrate to pH 6.5. Yield: 0.8 g; m.p. 248.5°. Several recrystallization from aqueous ethanol raised the m.p. to 250°. NMR spectrum, *cf.* Table 1. (Found: C 39.81; H 5.20; N 14.06. Calc. for $C_{13}H_{20}N_4O_6S_2$ (392.44): C 39.79; H 5.13; N 14.28).

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Preparation of Average Sample Solution of Heterogeneous Organic Materials for Determination of Microquantities of Mercury Using Purified Sodium Hydroxide

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Mercury is often very unevenly distributed in organic materials. Small samples taken out from different parts of, *e.g.* a fish body do not give exactly the same mercury value. Other, more heterogeneous materials require a number of analyses to obtain the right average value.

A fast and simple way to prepare a representative average sample for mercury determination with the direct combustion-photometric method developed by Lidums and Ulfvarson [1] is to heat the material with sodium hydroxide. Since commercial sodium hydroxide (analytical grade) contains relatively large amounts of mercury, it is impossible to use it for this purpose. A sodium hydroxide solution giving low enough mercury blanks is prepared as follows.

Sodium carbonate or preferably sodium hydrogen carbonate is heated in an electric furnace att 700°C for 1—2 days. Calcium carbonate is heated at 1000—1100°C for about 5 h. 170 g of the obtained calcium oxide are transferred to a 2 liter flask and 60 ml of water are added carefully in small portions (double-distilled water is used exclusively). Then 260 g of the sodium carbonate and 800 ml of water are added. The contents of the flask are heated to boiling and the flask is swirled from time to time until all the sodium carbonate is dissolved. After rapid cooling the mixture is transferred to a polyethylene bottle and calcium carbonate is allowed to settle. The clear solution, containing 20—25 % sodium hydroxide, is then decanted.

For the average sample solution a desired amount of the material is weighed and transferred to a Kjeldahl flask of suitable size. The sodium hydroxide solution is added taking 5 ml for each gram of the sample material. The flask is then heated gently until a homogeneous solution is obtained (for fish it takes only a few minutes). The solution is transferred to a weighed polyethylene bottle with as little water as possible. The total amount of the final solution is determined by weighing. A suitable part of the average sample is weighed in a porcelain boat and analysed according to the procedure described by Lidums and Ulfvarson.[1] The mercury blank of the reagents and vessels is determined by carrying out all the operation steps with the same quantity of the sodium hydroxide solution as used for preparation of the average sample.

The method has been tested using a fish, previously analysed by various laboratories. The average mercury content, calculated from 39 single determinations, was found to be 841 ng Hg per gram. A sample solution was prepared taking specimens from different parts of this fish — together 4 g. Three single samples were taken out from the average solution and the analysis of them gave the following values: 830—815—830 ng Hg per g.

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