DERIVATIVES OF SULFAMIDE

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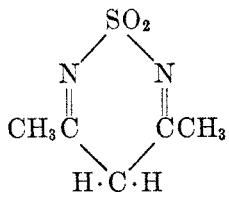
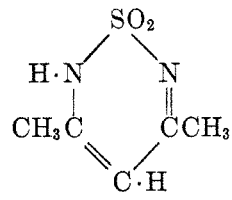
Interest in the derivatives of sulfamide arises from the analogy to urea derivatives which possess remarkable pharmacological value. Recently an approach to the barbituric acid analog has been made in the discovery of cyclic derivatives of sulfamide (4, 6).

The compound 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide, prepared by Glenn and Degering by the condensation of molar equivalents of sulfamide and 2,4-pentanedione in ethanol at 60° for three hours in the presence of a trace of dry hydrogen chloride, was selected for further study because of its ready adaptation in therapeutic work if pharmacological importance is evidenced. This compound is easily prepared, and is stable, readily purified, and water-soluble.

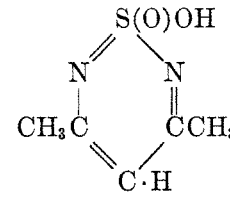
An attempt was made to establish the predominance of formula III over the other two shown below for the structure of the product obtained upon the condensation of sulfamide with 2,4-pentanedione.



I



II



III

Structure III accounts for the strong acidity and the ease of salt formation possessed by 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide. An alkali salt may be obtained by neutralization of the above compound with alkali. Structure II should be soluble only in solvents possessing a basicity comparable to the alkaline hydroxides. Lastly, structure I should not possess acidic properties. Acidic property alone, however, is not sufficient basis for the acceptance of structure III.

Another consideration in favor of structure III is that of conjugation with the resulting possibility of resonance. This may explain both the acidity and the acetylation reaction.

The postulation of structure III for 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide may explain in part the difficulty of replacing its acidic hydrogen by an alkyl group. All attempts to react the sodium salt of this compound with alkyl halides were futile. This behavior is in marked contrast to the behavior of the sulfonamides. With the latter, many N-alkylsulfonamides have been prepared by the action of alkyl halides or sulfates in aqueous or alcoholic alkali upon the sulfonamides that have one or two replaceable hydrogens (7). Since structure II, if it is the correct one, most clearly represents that of a sulfonamide the N-alkylation seems entirely possible.

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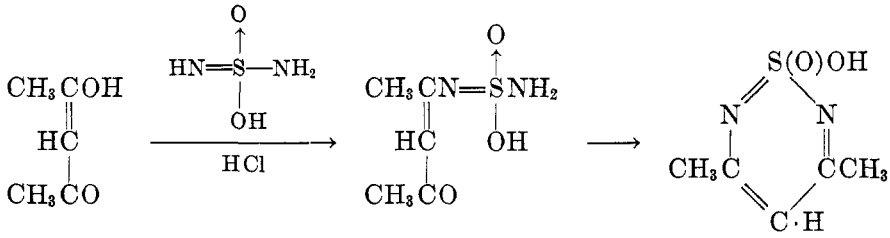
The synthesis of an acetylated derivative that still retains strong acidic properties from 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide is not to be expected if either Formula I or Formula II is correct. It is conceivable that the hydrogen atom attached to the number four carbon atom in the ring of structure II could be replaced with an acetyl group and that the compound would still retain slight acidic properties, but the resulting product can hardly explain the strong acidity actually encountered. The results can be explained more adequately as the replacement of the hydrogen atom attached to the number four carbon atom in the ring of structure III.

Upon review of the chemistry of saccharin (7) perhaps the possibility of preparing an N-alkylated derivative of structure II should not be ruled out entirely. In the case of saccharin, heating the potassium or sodium salt with an alkyl halide results in the alkylation of the nitrogen atom (2, 5). The reaction is slow with ethyl iodide in alcohol solution under reflux but this and less active halides react readily in 2-(β-butoxyethoxy)ethanol-water mixtures. Likewise, the action of an acid chloride upon saccharin or its sodium salt gives only the N-acyl derivative (1, 3). Under the conditions reported in this study, none of these reactions occurred for 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide.

Although no evidence is available upon which to base the following theory, a proposed mechanism for the reaction discovered by Degering and Glenn of sulfamide with 2,4-pentanedione in the presence of dry HCl or other catalysts is as follows:



EXPERIMENTAL

The 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide used in this experiment was prepared by a modification of the method used by Glenn and Degering (4). Instead of using absolute ethanol as a solvent, an excess of 2,4-pentanedione was used. Upon completion of the reaction, the excess was removed by vacuum distillation and the product purified by rystallization (Norit) from water. The pure compound melted at 147° (corr.) and gave a neutralization equivalent of 162 (corr.).

Preparation of the silver salt of 3,5-dimethyl-1,2,6,4H-thiadiazin-1,1-dioxide. The silver salt may be prepared readily by the addition of a five % aqueous silver nitrate solution to an aqueous solution of 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide and removing the white crystalline precipitate of the silver salt by filtration (m.p. 234°, dec.).

Anal. Calc'd for $C_5H_7AgN_2O_2S$: Ag, 40.5. Found: Ag, 39.1.

Preparation of the sodium salt of 3,5-dimethyl-1,2,6,4H-thiadiazin-1,1-dioxide by the neutralization of 3,5-dimethyl-1,2,6,4H-thiadiazin-1,1-dioxide with sodium hydroxide. The sodium salt may be obtained most conveniently by neutralization of an alcoholic solution of 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide with alcoholic sodium hydroxide using

phenolphthalein as an indicator. The addition of a hot benzene solution and subsequent cooling is sufficient to promote crystallization of the sodium salt (m.p. 314°, dec.).

Anal. Calc'd for $C_5H_7N_2NaO_2S$: Na, 12.6. Found Na, 12.2.

Attempted reaction of the sodium salt of 3,5-dimethyl-1,2,6,4H-thiadiazin-1,1-dioxide with alkyl halides. (a). Attempted reaction with ethyl bromide. In an eight-inch test tube equipped with a reflux condenser was placed 45 ml. of acetone and 0.218 g. (0.00120 mole) of the sodium salt of 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide. The mixture was warmed, but complete solution was not effected even when the temperature was raised to the boiling point of acetone. The addition of ethyl bromide to the hot acetone solution caused no precipitation of sodium bromide. Cooling the mixture in an ice-bath resulted in crystals being formed that possessed the same appearance as the original sodium salt. A test for bromide upon these crystals was negative. A rough melting point determination gave a decomposition point of 330°. In the recovered material the percentage of sodium was found to be 11.2 as compared to a calculated value of 12.6 for $C_5H_7N_2NaO_2S$.

(*b*). *Attempted reaction with n-butyl bromide.* No appearance of sodium bromide occurred when *n*-butyl bromide was added to an alcoholic solution of the sodium salt of 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide. Even warming the solution failed to cause any separation of sodium bromide.

(*c*). *Attempted reaction with benzyl chloride.* The attempted reaction of the sodium salt of 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide was identical to that of the *n*-butyl bromide with the exception that benzyl chloride was used. Reaction assumed to be negative as sodium chloride was not precipitated.

Reaction of the sodium salt of 3,5-dimethyl-1,2,6,4H-thiadiazin-1,1-dioxide with acetyl chloride. In a 25-ml. flask, equipped with a reflux condenser and a drying tube containing Drierite, was placed 0.407 g. (0.00224 mole) of the sodium salt of 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide and 10 ml. of acetyl chloride. A reaction occurred at once with the formation of a white colloidal precipitate. The contents were refluxed for 5 to 10 minutes. The colloidal precipitate remained suspended, but was removed upon repeated filtration, and identified as sodium chloride. Evaporation of the filtrate yielded colorless crystals. An alcoholic solution of the crystals was decolorized with Norit and the alcohol removed by evaporation. Recrystallization from benzene yielded 0.089 g. (m.p. 142–144°) of solid material. A neutralization equivalent performed upon a sample of this crystalline material gave a value of 196. The yield of 4-acetyl-3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide thus produced was 22%.

SUMMARY

A conjugated 6-membered ring is proposed for the structure of 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide as an explanation for its marked acidity and its reasonably high thermal stability.

It is postulated that acetylation of 3,5-dimethyl-1,2,6,4*H*-thiadiazin-1,1-dioxide occurs *para* to the sulfone group.

A reaction mechanism is advanced for the reaction between sulfamide and 2,4-pentanedione.

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