# The Condensation Reaction between Sulfamide and Monoketones

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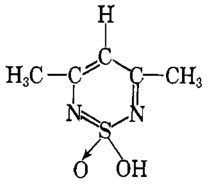
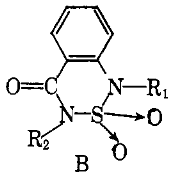
Sulfamide and various monoketones condense in the presence of hydrogen chloride to yield substituted cyclic thiadiazine 1,1-dioxides. Isobutyraldehyde undergoes a comparable reaction. Infrared and proton nuclear magnetic resonance data have been used to establish the existence of the ring system and to suggest the natures of the various substituted groups. The reaction product obtained from 2-butanone has been separated into two geometrical isomers.

The direct reactions between sulfamide and carbonyl groups have received comparatively little attention. Prior to 1940,[1] only the benzal,[2] methylol,[3] and dixanthyl[4] derivatives had been described. More recently, Paquin[5] pointed out analogies between the reaction of formaldehyde with sulfamide and with urea, and Degering and Wilson[6] obtained a cyclic product (A) from the condensation of sulfamide with 2,4-pentanedione. A number of closely related compounds (B) have been obtained from sulfamyl chloride.[7] Other cyclic structures have been obtained from reactions involving crotonaldehyde,[8] malonic acid dichloride,[9] and anthraquinone.[9] The ring system formed with crotonaldehyde probably differs from those described herein (C) only in having hydrogen atoms at the $R_2$, $R_3$, $R_4$, and $R_5$ positions.



A



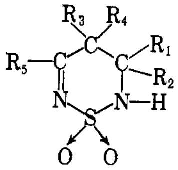
B

Interestingly enough, reactions between sulfamide and monoketones have not been reported, although the formation of cyclic structures as a consequence of the formally analogous reactions of urea with ketones[10] or guanidine with mesityl oxide[11] suggests that they are reasonable. During a study of the interactions of sulfamide with metal ions, a reaction involving copper (II) chloride in acetone was found to yield a white product. This substance proved to be a condensation product of an acid-catalyzed reaction between sulfamide and acetone. Subsequent study has shown that hydrogen chloride is a more effective catalyst both for this reaction and for comparable reactions with 2-butanone, 2-pentanone, 3-pentanone, and acetophenone. On the other hand, self-condensation in the presence of hydrogen chloride prevented similar reactions with 3-methyl-2-butanone and 4-methyl-2-pentanone. Isobutyraldehyde, however, also gave a condensation product.

The compounds obtained are listed in Table I, together with information on their syntheses and properties. All are white crystalline solids that dissolve readily in acetone, pyridine, ethyl acetate, and acetonitrile; they dissolve less readily in chloroform, with difficulty in water, and not at all in petroleum ether. They are best recrystallized from a mixture of ethyl acetate and petroleum ether (b.p. 80–110°).

Unlike the condensation product from sulfamide and 2,4-pentanedione,[6] which is a strong acid in aqueous solution, these compounds (in *ca.* $2 \times 10^{-2}$ *M* solution) are essentially neutral (p$K_a$ *ca.* 9.8 for compound I, Table I). In alkaline solution, each of these compounds reduces the diamminesilver(I) ion to the free metal.

It is not unreasonable to assume, in the light of experimental observation that each condensation requires 2 moles of ketone to 1 mole of sulfamide, that the products have structure C. Such a structure would would permit, *via* geometrical isomerism, the existence of two 2-butanone derivatives as indicated in Table I, but its validity could be better established from physical data.



C, R = H, alkyl, or aryl

The infrared spectra (600–4000 cm.$^{-1}$) of all the compounds are closely similar (Table II), suggesting that the same structural type is characteristic of all of them. The following features are of significance: (1) the N–H stretching frequency at *ca.* 3250 cm.$^{-1}$; (2) the C–H stretching frequency at *ca.* 2900–3000 cm.$^{-1}$; (3) the C=N stretching frequency at *ca.* 1620 cm.$^{-1}$ (although this band appears at a slightly lower frequency than is generally found, this may be a consequence of the presence of this bond in a cyclic structure); (4) the S=O stretching frequencies at 1310–1330 and 1150–1180 cm.$^{-1}$; (5) numerous additional absorptions in the 700–1500-cm.$^{-1}$ region that appear to reflect ring deformation and skeletal vibrations. Each pattern is characteristic, but all are relatively similar. These data indicate, of course, the presence of certain groupings, but are not completely structurally definitive.

Proton nuclear magnetic resonance spectra of 10% solutions in deuteriochloroform are given in Fig. 1. The letter designations refer to the interpretations summarized in structural formulas I–VII. For compound I, the ratio of areas under the resonance peaks is

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(1) L. F. Audrieth, M. Sveda, H. H. Sisler, and M. J. Butler, *Chem. Rev.*, **26**, 49 (1940).

(2) W. Traube and E. Reubke, *Ber.*, **56**, 1656 (1923).

(3) F. C. Wood and A. E. Battye, *J. Soc. Chem. Ind.*, **52**, 346T (1933).

(4) F. C. Wood, *Nature*, **136**, 837 (1935).

(5) A. M. Paquin, *Angew. Chem.*, **60A**, 316 (1948).

(6) E. F. Degering and J. E. Wilson, *J. Org. Chem.*, **17**, 339 (1952).

(7) E. Cohen and B. Klarberg, *J. Am. Chem. Soc.*, **84**, 1994 (1962).

(8) A. M. Paquin, *Kunstoffe*, **37**, 165 (1947).

(9) I. G. Farbenindustrie, A.-G. (G. Kränzlein and K. Renn, investors), German Patent 673,389 (March 24, 1939); *Chem. Abstr.*, **33**, 4436 (1939).

(10) K. Folkers and T. B. Johnson, *J. Am. Chem. Soc.*, **55**, 3361 (1933).

(11) W. Traube and R. Schwarz, *Ber.*, **32**, 3163 (1899).

TABLE I

PROPERTIES AND ANALYSES OF CONDENSATION PRODUCTS

| Compound[a] | Empirical formula | Carbonyl compound used | Yield, % | M.p.,[b] °C. | Molecular weight[c] Calcd. | Molecular weight[c] Found | Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found | Sulfur Calcd. | Sulfur Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | $C_8H_{12}N_2O_2S$ | Acetone | 66.5 | 142 | 176 | 180 | 40.90 | 41.29 | 6.87 | 6.89 | 15.90 | 15.60 | 18.17 | 17.94 |
| II | $C_{16}H_{16}N_2O_2S$ | Acetophenone | 20.8 | 137 | 300 | 312 | 64.00 | 63.51 | 5.33 | 5.33 | 9.33 | 9.55 | | |
| III | $C_8H_{16}N_2O_2S$ | 2-Butanone | 40.7 | 130 | 204 | 197 | 47.06 | 47.07 | 7.84 | 7.74 | 13.72 | 13.43 | 15.69 | 16.10 |
| IV | $C_8H_{16}N_2O_2S$ | 2-Butanone | ·1.6 | 158 | 204 | 204 | 47.06 | 47.07 | 7.84 | 7.88 | 13.72 | 13.34 | 15.69 | 15.80 |
| V | $C_{10}H_{20}N_2O_2S$ | 3-Pentanone | 24.8 | 117 | 232 | 232 | 51.72 | 52.02 | 8.62 | 8.71 | 12.07 | 11.72 | | |
| VI | $C_{10}H_{20}N_2O_2S$ | 2-Pentanone | 33.1 | 78 | 232 | 238 | 51.72 | 51.88 | 8.62 | 8.68 | 12.07 | 11.80 | | |
| VII | $C_8H_{16}N_2O_2S$ | Isobutyraldehyde | 42.8 | 193 | 204 | | 47.06 | 47.37 | 7.84 | 7.94 | 13.72 | 13.17 | 15.69 | 15.45 |

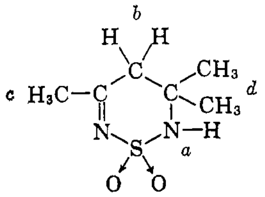
[a] Designation uniform throughout. [b] Uncorrected. [c] In acetone.

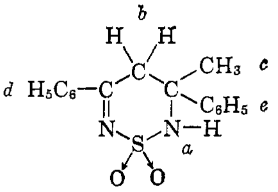
TABLE II

INFRARED SPECTRA OF CONDENSATION PRODUCTS

| Compound | N-H | C-H | C=N | S=O | Others[a] |
|---|---|---|---|---|---|
| I | 3200 | 2950 | 1628 | 1333<br>1175, 1163 | 1465, 1427, 1412, 1370<br>1270, 1210<br>988, 957, 915, 880, 814, 788, 710 |
| II | 3250 | 3080<br>3000 | 1605<br>1598<br>1568 | 1330<br>1170, 1155 | 1450, 1423, 1410, 1380, 1360<br>1258<br>1095, 1025, 950, 910, 850, 798, 760, 695 |
| III | 3260 | 2960 | 1620 | 1320<br>1170 | 1460, 1412, 1385, 1372<br>1220, 1197<br>1090, 1078, 990, 950, 900, 818, 795, 763, 675 |
| IV | 3260 | 2960 | 1620 | 1320<br>1170 | 1460, 1412, 1385, 1370<br>1220, 1195<br>1090, 1080, 990, 948, 895, 820, 798, 762, 675 |
| V | 3280 | 2990 | 1620 | 1325<br>1150 | 1462, 1418, 1360<br>1215, 1180<br>1098, 1090, 980, 960, 890, 805, 787, 748, 667 |
| VI | 3210 | 2960<br>2880 | 1623 | 1322<br>1165 | 1460, 1425, 1405, 1388, 1360<br>1260<br>1090, 1038, 985, 965, 935, 890, 795, 748, 715 |
| VII | 3280 | 2980 | 1615 | 1350<br>1180 | 1470, 1430, 1395, 1380<br>1305, 1290, 1135<br>1035, 1015, 1000, 950, 933, 905, 795, 740,695 |

[a] Major peaks only.


I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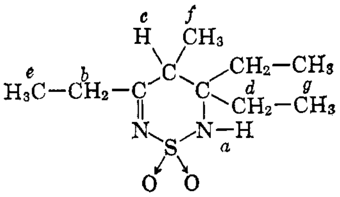
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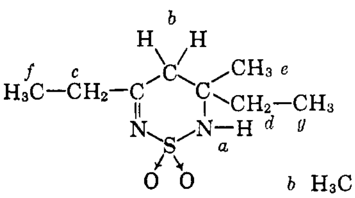
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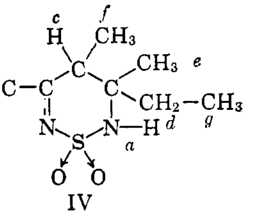
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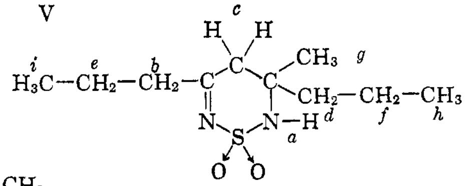
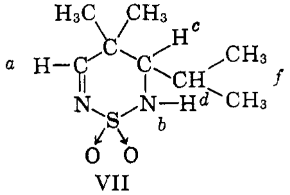

VI


VII

*a*:*b*:*c*:*d* = 1:2:3:6. The assigned structure (I) is thus a reasonable one, insofar as the types of protons present are concerned. Correspondingly, the ratio of the areas for compound II is *a*:*b*:*c* = 1:2:3, in agreement with the assignments indicated for the nonphenyl protons in structure II. In addition, two broad peaks appear in the *ca.* 1.8–2.9-p.p.m. region. These represent, reasonably, proton resonances associated with the two phenyl groups (*d* and *e*). Inasmuch as resonance *a* (compounds I–VI inclusive) disappears both when a pyridine solution is used and when an acetonitrile solution of a compound is treated with a drop of deuterium oxide, the validity of associating it with an N–H proton is supported.

Assignment of structures III and IV to the isomeric products resulting from reaction with 2-butanone has been effected in the same general fashion. Structures

V and VI for the 3- and 2-pentanone products, respectively, are again reasonable interpretations of the nuclear magnetic resonance spectra.

The spectrum of compound VII differs significantly from the other spectra, particularly in the presence of a new peak at *ca.* 2.38 p.p.m. This peak is believed to indicate the presence of *a*-type protons (structure VII). That peak *b* is a consequence of the presence of N–H protons is suggested by its disappearance, as a consequence of H–D exchange, upon addition of deuterium oxide. The area under peak *f* is less than the theoretical value, and peak *e* is split into two components. Ring or side-chain interactions may be the cause of these departures. Hydrolytic decomposition of the compound in aqueous or ethanolic solution containing hydrogen chloride yielded ammonium sulfate (40% yield, determined as barium sulfate) and mesityl oxide (20% yield, determined as 1-(4-nitro-phenyl)-3,5,5-trimethylpyrazoline[12]).

Compound I was also synthesized, in almost the same yields (60–65%) as from the acetone–sulfamide reaction, by the hydrogen chloride catalyzed reaction of sulfamide with either mesityl oxide or diacetone alcohol.

## Experimental

**3,3,5-Trimethyl-1,2,6,2H-thiadiazine 1,1-Dioxide.**—Five grams (0.052 mole) of sulfamide[13] and 30 ml. (*ca.* 0.41 mole)[14] of acetone were mixed in a standard-taper, 100-ml., round-bottomed flask and the mixture was treated with a stream of dry hydrogen chloride for 5 min. The mixture was then heated under a reflux condenser for 6 hr. at 70°.[15] The remaining acetone was removed *in vacuo* at 50–60°, and the residue was treated with chloroform. After filtration to remove unchanged sulfamide, the chloroform was removed *in vacuo* at 50–60°, and the product was recrystallized two times from a 1:1 mixture of acetone and petroleum ether (b.p. 80–110°). It was dried at room temperature under reduced pressure.

**Other products** were obtained similarly with the ketone or isobutyraldehyde in at least fourfold excess.[16] Compounds III and IV were separated from each other by crystallization from ethyl acetate, compound IV being much less soluble at lower temperatures. Compounds III–VII were all recrystallized conveniently from ethyl acetate–petroleum ether (b.p. 80–110°) mixtures. These compounds were dried *in vacuo* at room temperature.

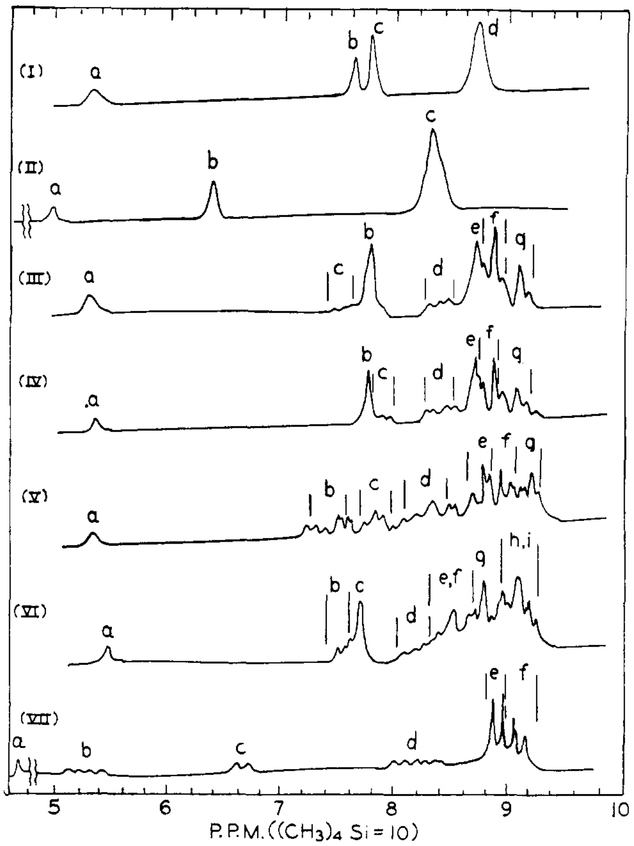


Fig. 1.—Proton nuclear magnetic resonance spectra.

**Spectra.**—Infrared spectra were obtained by the potassium bromide disk procedure with a Perkin-Elmer Model 21 instrument. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 instrument.

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(12) K. von Auwers and A. Kreuder, *Ber.*, **58**, 1974 (1925).

(13) Obtained from Allied Chemical Corp., General Chemical Division, Morristown, N. J. and had m.p. 93°, after recrystallization from ethanol.

(14) A substantial excess of acetone is essential for a good yield.

(15) Higher temperatures, prolonged heating, or insufficient acetone yields a black, oily by-product that is removed only with difficulty by means of activated charcoal. It is better to stop the reaction before the system becomes black and turbid.

(16) Up to one-half of the ketone may be substituted by ethanol without affecting the yield.