

## 197. Hydrogen Bonding in Some Thiosemicarbazones and Thioamides.

By P. W. SADLER.

The infrared spectra of some heterocyclic thioamides and S- and N-methylthiosemicarbazones indicate that intermolecular N-H...N hydrogen bonds may be formed in addition to N-H...S bonds. Both the 2- and 4-imino-groups of thiosemicarbazones may be involved. In  $\alpha$ -diketone monothiosemicarbazones strong intramolecular N-H...O=C bonds predominate; similar six-membered hydrogen-bonded rings occur in hydrazones and phenylhydrazones. No evidence was found, for any of the compounds, of tautomerism of the thione-thiol type, or for  $\sigma$ - $\nu$  correlations in a series of substituted isatin 3-thiosemicarbazones.

MANY studies have been published of the infrared spectra of amides, but few of thioamides or thiosemicarbazones. Davison and Christie<sup>1</sup> recorded the infrared spectra of twenty-four semicarbazones of common ketones and aldehydes, as potassium chloride discs. They assigned characteristic absorptions at 3460 and 3370—2800 cm.<sup>-1</sup> to unbonded and bonded stretching modes. Strong absorptions at 1695 and 1585 cm.<sup>-1</sup> were assigned to the amide I and II bands, and a rather variable absorption at 1665 cm.<sup>-1</sup> was very tentatively assigned to a C=N stretching mode. Bogomolow, Postovskii, and Sheinker<sup>2</sup> reported similar bands for the semicarbazones of acetaldehyde and benzaldehyde and a band at 1516~1533 cm.<sup>-1</sup>, which was found in the spectra of five simple thiosemicarbazones,

TABLE I. Frequencies (cm.<sup>-1</sup>) for thioamides and thiosemicarbazones in potassium bromide discs.

2-Thiopropionylbenzimidazole .....	3230	3040	1613	1472	1456	1380	1280	1242	877			
Indole-5-thiocarbonamide ...	3360	3260	3130	1612	1461	1431	1408	1288	1251	853		
3-Formylindole thiosemicarbazone .....	3200br		1611	1541	1444	1371	1297	1253	878			
Acetaldehyde thiosemicarbazone .....	3360	3250	3140	1596	1512	1460	1433	1366	1271	1250	867	
Benzaldehyde thiosemicarbazone .....	3400	3240	3130	2960	1591	1540	1470	1451	1375	1299	1230	870
Benzaldehyde 4,4'-dimethylthiosemicarbazone .....	3400	3200		1595	1540	1440	1378	1299			876	
Benzaldehyde S-methylthiosemicarbazone .....	3400	3200		1600	1530	1440		1280		868	690	

was assigned to a C=S stretching mode. The C=S vibration had been assigned by Thompson *et al.*<sup>3</sup> and Colthup<sup>4</sup> to the range 1300—1400 cm.<sup>-1</sup>, and to 1410—1550 cm.<sup>-1</sup> by Miller;<sup>5</sup> but for thioamides the assignment has ranged from 1533 to 965 cm.<sup>-1</sup>. Tentative assignments include bands at 1265—1180 cm.<sup>-1</sup> for thiopropionamide and N-butylthioacetamide<sup>6</sup> and 965 and 980 cm.<sup>-1</sup> for thiuram monosulphide and thioacetamide respectively.<sup>7</sup> Other assignments<sup>8,9</sup> for the C=S absorption in thioacetamide and thioformamide have favoured the range 1430—1300 cm.<sup>-1</sup>. Our results (Table I) include strong absorption at 1366—1408 cm.<sup>-1</sup> which is absent from the spectrum of benzaldehyde S-methylthiosemicarbazone, and this is tentatively assigned to a C=S stretching mode. The

<sup>1</sup> Davison and Christie, *J.*, 1955, 3389.

<sup>2</sup> Bogomolov, Postovskii, and Sheinker, *Doklady Akad. Nauk S.S.S.R.*, 1953, **91**, 1111.

<sup>3</sup> Thompson, Nicholson, and Short, *Discuss. Faraday Soc.*, 1950, **9**, 222.

<sup>4</sup> Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.

<sup>5</sup> Miller, "Applications of Infrared and Ultraviolet Spectra to Organic Chemistry," in Gilman's "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, 1953, p. 149.

<sup>6</sup> Marvel, Radzitsky, and Brader, *J. Amer. Chem. Soc.*, 1955, **77**, 5997.

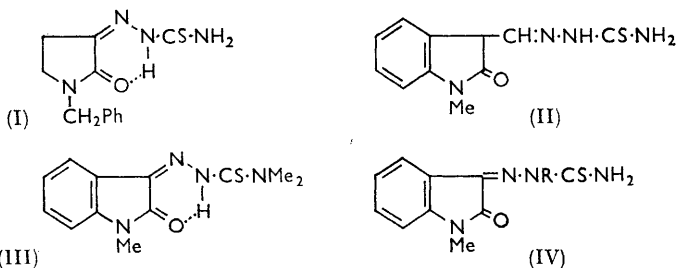
<sup>7</sup> Bellamy, *J.*, 1960, 2218.

<sup>8</sup> Mecke and Speisecke, *Chem. Ber.*, 1956, **89**, 1110.

<sup>9</sup> Davies and Jones, *J.*, 1958, 955.

methyl derivative also has a strong band at  $690\text{ cm.}^{-1}$  which is within the range  $685\text{--}705\text{ cm.}^{-1}$  reported for an  $\text{S-CH}_3$  stretching vibration.<sup>10</sup>

The  $1512\text{--}1540\text{ cm.}^{-1}$  band could be assigned to an N-H bending mode, in which case the 2'-imino-group must be mainly involved as neither the position nor the intensity of this band varies in benzaldehyde thiosemicarbazone and 4,4'-dimethylthiosemicarbazone. Strong absorption at  $1590\text{--}1610\text{ cm.}^{-1}$  is usually associated with a ring vibration, but the C=N group could also be responsible for it as conjugated systems containing both C=N and C=C linkages often exhibit one or more moderately strong bands between  $1700$  and  $1500\text{ cm.}^{-1}$ . It is usually not possible to identify such bands with particular C=C or C=N linkages, but in this instance it appears to be primarily associated with the C=N group as the acetaldehyde derivative also shows a strong band at  $1596\text{ cm.}^{-1}$ ; this is about  $30\text{ cm.}^{-1}$  lower than the usual range quoted, but no other strong absorption is observed in this region. Somewhat similar results have been observed for a series of aliphatic aldehyde dimethylhydrazones, all of which show a peak in the  $1610\text{ cm.}^{-1}$  region attributable to the C=N stretching vibration. For dimethylhydrazones of aromatic and heterocyclic aldehydes interaction with the C=C group obscures this band, and two characteristic absorption bands, at  $1613\text{--}1587$  and  $1580\text{--}1555\text{ cm.}^{-1}$ , result.<sup>11</sup> The two bands centred on  $1280$  and  $1230\text{ cm.}^{-1}$  (Table 1) may fairly confidently be assigned to C-N stretching vibration.



The thiol group in a tautomer should display the thiol band at  $2500\text{ cm.}^{-1}$ , but no bands are present in the  $2500\text{--}2650\text{ cm.}^{-1}$  region, so tautomerism of the thione-thiol type does not occur in these derivatives. This is in agreement with the observation by Hadži that each compound in a series of 4-arylthiosemicarbazones of  $\alpha$ -keto-acids and the derived 2,3,4,5-tetrahydro-5-oxo-3-thiono-1,2,4-triazines exists in the thiono-form.<sup>12</sup>

Characteristic strong hydrogen bonds of the type normally encountered in amides are indicated for these compounds by the solid-state spectra in Table 1. Three strong N-H stretching frequencies are at  $3400\text{--}3360$ ,  $3250\text{--}3200$ , and  $3140\text{--}3040\text{ cm.}^{-1}$ ; in most instances the C-H stretching frequency is merged with the lower N-H stretching frequency. Either the 2'- or the 4'-imino-hydrogen atom may be involved as benzaldehyde 4,4'-dimethylthiosemicarbazone and S-methylthiosemicarbazone have similar bonded N-H stretching frequencies. Amide-hydrogen bonding is usually of the intermolecular  $\text{N-H}\cdots\text{O}=\text{C}$  type, with dimer or trimer formation, and similar structures may exist in thioamides. An accurate determination of the crystal structure of thioacetamide has shown that it consists of planar molecules which are probably held by  $\text{N-H}\cdots\text{S}$  hydrogen bonds.<sup>13</sup> However, for the thiosemicarbazones listed in Table 2, several types of hydrogen bonding are possible owing to the presence of a carbonyl group adjacent to the C=N linkage; and as  $\text{N-H}\cdots\text{O}=\text{C}$  bonds are stronger than  $\text{N-H}\cdots\text{N}$  or  $\text{N-H}\cdots\text{S}$ , the first type is likely to predominate. 1-Benzylpyrrolidine-2,3-dione 3-thiosemicarbazone (I) shows typical bonded N-H frequencies at  $3360$ ,  $3240$ , and  $3140\text{ cm.}^{-1}$  due to the strong

<sup>10</sup> Sheppard, *Trans. Faraday Soc.*, 1950, **46**, 429.

<sup>11</sup> Wiley, Slaymaker, and Krauss, *J. Org. Chem.*, 1957, **22**, 204.

<sup>12</sup> Tišher and Urbaški, *J. Org. Chem.*, 1960, **25**, 770.

<sup>13</sup> Truter, *J.*, 1960, 997

intramolecular bond. 3-Formyl-1-methyloxindole thiosemicarbazone (II) shows similar N-H stretching frequencies, which probably result from intermolecular bonds (insolubility excludes solution spectra). The position of the carbonyl absorption in this compound is of particular interest. 1-Methyloxindole gives a single strong peak at 1700  $\text{cm}^{-1}$  in chloroform, whereas for 3-formyl-1-methyloxindole the carbonyl peak is lowered to 1680  $\text{cm}^{-1}$  owing to formation of a very strong intramolecular hydrogen bond, as indicated by a bonded O-H absorption appearing as a broad band between 2600 and 2400  $\text{cm}^{-1}$ . Therefore, the strong absorption at 1665  $\text{cm}^{-1}$  in (II) represents the formation of much stronger hydrogen bonds than those in either 3-formyl-1-methyloxindole or its oxime, in which the carbonyl frequency lies at 1696  $\text{cm}^{-1}$ .

The 3-hydrazone, 3-phenylhydrazone, 3-thiosemicarbazone, and 3-4'-phenylthiosemicarbazone of 1-methylisatin all show bonded N-H frequencies at 3400 and 3200  $\text{cm}^{-1}$  (Table 3). The broad band at 3400—3200  $\text{cm}^{-1}$  shown by 1-methylisatin 3-4',4'-dimethylthiosemicarbazone favours the intramolecular structure (III), which is supported by the data for the 2'-methyl and the 2'-phenyl derivative (IV; R = Me, Ph). Although these compounds in the solid state show bonded N-H frequencies the carbonyl stretching frequency of the 2'-phenyl derivative is raised to 1712  $\text{cm}^{-1}$ , and a similar peak appears as a shoulder at 1710  $\text{cm}^{-1}$  in the 2'-methyl derivative. Compounds of type (IV) are unlikely to possess intramolecular hydrogen bonds and the intermolecular bonding

TABLE 2. *Frequencies ( $\text{cm}^{-1}$ ) for thiosemicarbazones and hydrazones of heterocyclic  $\alpha$ -diketones in potassium bromide discs.*

1-Benzylpyrrolidine-2,3-dione 3-thiosemicarbazone .....	3360	3240	3140	1689	1611	1488	—	1359	—	1107	1076
3-Formyl-1-methyloxindole thiosemicarbazone .....	3340	3240	3160	1665	1607	1492	1470	1370	1347	1121	1098
1-Methylisatin 3-4'-phenylthiosemicarbazone .....	—	3200br	—	1677	1609	1493	1470	1368	1335	1158	1090
1-Methylisatin 3-hydrazone .....	3360	3200	—	1680	—	1493	1472	1376	1332	1115	1098
1-Methylisatin 3-phenylhydrazone ...	3400	3200	3160	1680	—	1510	1476	1376	1340	1120	1100
1-Methylisatin 3-2'-phenylthiosemicarbazone .....	3400	3200	2900	1712	1610	1489	1468	1374	1340	1152	1092
1-Methylisatin 3-2'-methylthiosemicarbazone .....	3400	3300	1710sh	1680	1610	1490	1470	1365	1320	1125	1100
1-Methylisatin 3-4',4'-dimethylthiosemicarbazone .....	3400	3200	2960	1690	1615	—	1475	1375	1340	1120	1100

TABLE 3. *Frequencies ( $\text{cm}^{-1}$ ) for substituted isatin 3-thiosemicarbazones in potassium bromide discs.*

Subst.															
7-CF <sub>3</sub> .....	3300	3200	1700	1625	1485	1330	1300	1110	1060	888	875	804	750		
7-Br .....	3440	3270	3200	1690	1615	1475	1330	1285	1130	1060	884	852	794	728	
5-F .....	3450	3290	3220	1680	1608	1485	1300	1135	1050	902	860	799	762		
5-CH <sub>2</sub> ·CO <sub>2</sub> Et .....	3420	3300	3200	1690	1620	1487	1270	1125	—	—	854	804	762		
5-CH <sub>2</sub> ·CO <sub>2</sub> H .....	3440	3300	3200	1680	1610	1480	1379	1276	1124	1057	897	863	809	758	
—	3400	3230	3170	1685	1612	1485	1340	1270/80	1130	1055	884	850	788	750	
5-Me .....	3400	3250	—	1680	1600	1480	1288	1127	1058	897	855	788	759		
6-MeO .....	3425br	—	—	1680	1620/1580	1492	1305/1280	1120	—	—	856	756	—		
1-Me .....	3410	3280	—	1685	1600	1485/70	1370	1340	1270	1100	1040	890	788	753	
1-Me-4-CF <sub>3</sub> .....	3450	3270	3190	1675	1600	1475	1360	1340	1300	1110	1065	907	837	780	
1-Me-5-CH <sub>2</sub> ·CO <sub>2</sub> H	3420	3350	—	1675	1620	1475	1360	1339	1279	1101	—	908	852	783	738
1-Me-5-CH <sub>2</sub> ·CO <sub>2</sub> Et	3410	3280	2920	1675	1600	1475	1360	1335	1270	1098	1032	904	842	787	740

appears to be rather weak. This is confirmed by results for dilute solutions in carbon tetrachloride. The compounds are not sufficiently soluble to provide good records in the 3  $\mu$  region, but 1-methylisatin 3-2'-phenyl- and 3-2'-methyl-thiosemicarbazone have peaks at 1722 and 1708  $\text{cm}^{-1}$ , respectively; whereas, 1-methylisatin 3-phenylhydrazone and compound (III) absorb strongly at 1687 and 1683  $\text{cm}^{-1}$ . Again, as in the case of oxindole,

the  $\alpha$ -carbonyl stretching frequency is considerably lower for the 3-thiosemicarbazone than for the parent compound<sup>14</sup> or the 3-oxime.<sup>15</sup> The demonstration that strong intramolecular hydrogen bonds are formed in compounds of type (III) is important in interpreting the antivaccinial<sup>16</sup> and antivariola activities<sup>17</sup> of 1-alkylisatin 3-thiosemicarbazones.

Table 3 contains solid state spectroscopic data for some ring-substituted and *N*-methylated isatin 3-thiosemicarbazones. Correlation exists between  $\sigma$ -values of substituents<sup>18</sup> and both the  $\alpha$ - and  $\beta$ -carbonyl stretching frequencies of substituted isatins,<sup>14</sup> and the latter frequencies are also directly related to the dehydrogenase activities of these compounds.<sup>19</sup> However, reference to Table 3 shows no sign of correlation between  $\sigma$ -values and either the  $\alpha$ -carbonyl or C=N stretching frequency, in accord with the lack of relation of antivaccinial activities to  $\sigma$ -values of substituted isatin 3-thiosemicarbazones.<sup>16</sup>

*Experimental.—Infrared absorption spectra.* Spectra were determined by using a Perkin-Elmer 21 double-beam recording spectrometer fitted with a rock-salt prism. Preparative details for the compounds have already been given.<sup>16</sup>

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THE MIDDLESEX HOSPITAL, LONDON, W.1.

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<sup>14</sup> O'Sullivan and Sadler, *J.*, 1956, 2202.

<sup>15</sup> O'Sullivan and Sadler, *J. Org. Chem.*, 1957, **22**, 283.

<sup>16</sup> Bauer and Sadler, *Brit. J. Pharmacol.*, 1960, **15**, 101.

<sup>17</sup> Bauer and Sadler, *Lancet*, 1960, **1**, 1110.

<sup>18</sup> Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 188.

<sup>19</sup> O'Sullivan and Sadler, *Arch. Biochem. Biophys.*, 1957, **66**, 243.