[CONTRIBUTION FROM THE SCIENTIFIC DEPARTMENT, ISRAELI MINISTRY OF DEFENCE]

# The Structure of Isatyde, Sulfisatyde and Some Other Indole Derivatives

BY ERNST D. BERGMANN

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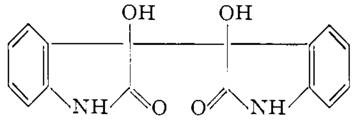
On the basis of the infrared spectrum, isatyde is the 3,3'-pinacol of isatin (I); sulfisatyde is bis-(oxindolyl-3) disulfide (V). The chemical properties of the two substances are in accord with these structures. The C=S absorption in xanthione, thioxanthione and N-methylthioacridone lies at 1320, 1315 and 1360 cm.$^{-1}$, respectively. The infrared spectra of a number of other indole derivatives have been determined; an attempt at their interpretation has been made.

More than 100 years ago, Laurent[1,2] and Erdmann[3] observed the formation of isatyde and sulfisatyde[4,5] by dimerizing reduction of isatin with ammonium hydrosulfide under different conditions

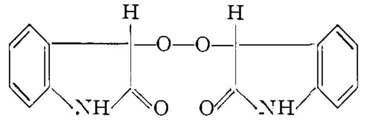
$$2C_8H_5O_2N + H_2S \longrightarrow C_{16}H_{12}O_4N_2 + S \qquad (1)$$

$$2C_8H_5O_2N + 3H_2S \longrightarrow C_{16}H_{12}O_2N_2S_2 + S + 2H_2O \qquad (2)$$

The structure of these two substances, especially that of isatyde, has been the subject of a long controversy; for isatyde, formulas I, II and III, and for sulfisatyde, IV and V have been suggested. It seemed worthwhile to attempt a decision on the basis of the infrared spectra of the substances.



I



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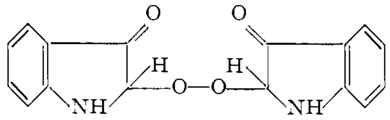
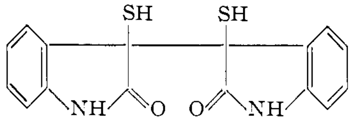
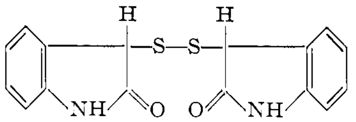


III



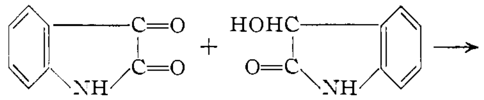
IV



V

For isatyde, formula I proved correct because of the absence of the peroxide band (880 cm.$^{-1}$)[6-8]; moreover, formula II is ruled out by the fact that the infrared spectrum shows hydroxyl absorption (at 3400 cm.$^{-1}$) which persists into the C–H bond region, thus indicating both free and hydrogen-bonded hydroxyl groups. Other bands were observed in the spectrum of I at 914 cm.$^{-1}$ (C–N or N–H stretching frequency), 966 cm.$^{-1}$ (*o*-disubstituted benzene ring), and in the double bond region at 1616 and 1690 cm.$^{-1}$. It may be assumed that the latter corresponds to the absorption of acetanilide (1665 cm.$^{-1}$),[9] the former to the aromatic double bond as in aniline.[10]

Formula I is, indeed, also in accordance with the fact that the compound forms a tetraacetyl derivative[11] and that one can prepare isatyde by piperidine-catalyzed condensation of isatin and dioxindole[5,12,13]; in the latter, the C–H bond of the secondary alcohol group is activated by the neighboring carbonyl:



Isatyde is thus analogous to hydrindantine, the reduction product of triketohydrindene[14] (which, incidentally, for some time also has been ascribed an asymmetric formula of the type of VII) and to alloxantine, the reduction product of alloxan (VI). Also for this substance for which formula VII had been suggested by Nightingale[15] and Winslow,[16] the formula VIII[17] seems to be preferable, as the compound dissociates into alloxan (VI) and dialuric acid (IX).[18] In this case, the infrared spectrum did not appear to afford conclusive evidence as to the structure of the compound.[19]

The infrared spectrum of **sulfisatyde** does not show the characteristic absorption bands of the sulfhydryl group (2450–2550 cm.$^{-1}$),[20-22] and has two bands at 489 and 506 cm.$^{-1}$ of which at least one represents the S–S frequency. Trotter and Thompson[20] found in aliphatic disulfides a band characteristic for the disulfide group between 500 and 520,

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(1) A. Laurent, *Ann. chim.*, [3], **3**, 372 (1841).

(2) A. Laurent, *ibid.*, [3], **3**, 469 (1841).

(3) O. L. Erdmann, *ibid.*, [3], **3**, 359 (1841).

(4) A. Wahl and W. Hansen, *Compt. rend.*, **178**, 214 (1924).

(5) W. Hansen, *Ann. chim.*, [10], **1**, 119 (1924).

(6) R. Leadbeater, *Compt. rend.*, **230**, 829 (1949).

(7) O. D. Shreve, *et al.*, *Anal. Chem.*, **23**, 282 (1951).

(8) N. Sheppard, *Discuss. Faraday Soc.*, **9**, 322 (1950).

(9) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 82. Benzanilide absorbs at 1680 cm.$^{-1}$; B. Witkop and J. B. Patrick, THIS JOURNAL, **74**, 3861 (1952).

(10) R. B. Barnes, R. C. Gore, U. Liddel and V. Z. Williams, "Infrared Spectroscopy, No. 241," Reinhold Publishing Corp., New York, N. Y., 1944.

(11) M. Kohn and A. Klein, *Monatsh.*, **33**, 929 (1912); M. Kohn and A. Ostersetzer, *ibid.*, **34**, 789 (1913); **37**, 25 (1916).

(12) G. Heller, *Ber.*, **37**, 943 (1904).

(13) A. Wahl and W. Hansen, *Compt. rend.*, **178**, 393 (1924).

(14) A. Schoenberg and R. Moubasher, *J. Chem. Soc.*, 366 (1944).

(15) D. Nightingale, THIS JOURNAL, **59**, 802 (1937).

(16) N. M. Winslow, *ibid.*, **61**, 2089 (1939).

(17) D. Davidson and E. Epstein, *J. Org. Chem.*, **1**, 305 (1936).

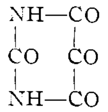
(18) R. Moubasher and A. M. Othman, THIS JOURNAL, **72**, 2666 (1950).

(19) R. S. Tipson and L. H. Cretcher, *J. Org. Chem.*, **16**, 1091 (1951).

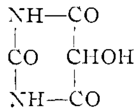
(20) I. F. Trotter and H. W. Thompson, *J. Chem. Soc.*, 481 (1946).

(21) N. B. Colthup, *J. Amer. Opt. Soc.*, **40**, 397 (1950).

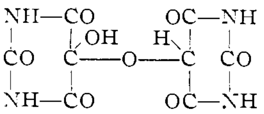
(22) M. St. C. Flett, *J. Chem. Soc.*, 347 (1953).



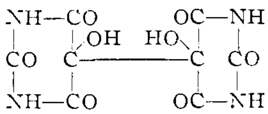
VI



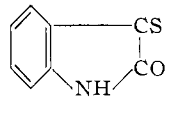
IX



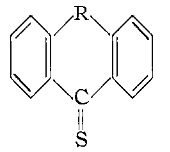
VII



VIII



X



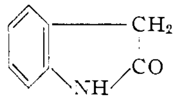
XI (R = O, S, NCH$_3$)

Cymerman and Willis[23] for aromatic disulfides at 480–490 cm.$^{-1}$; the former authors have pointed out that the existence of relatively stable isomers (rotational isomers around the S–S bond) may give rise to more than one frequency.[24,25] Of the numerous other bands in the spectrum of sulfisatyde, the bands between 600 and 700 cm.$^{-1}$ contain those belonging to the C–S frequency,[20] and the band at 1710 cm.$^{-1}$ represents the carbonyl grouping, whilst that at 1620 cm.$^{-1}$ is probably the C=C frequency.

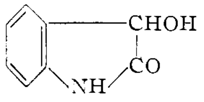
In this case, too, formula V is in accordance with the experience of organic chemistry. One will have to assume that the formation of sulfisatyde from isatin takes place in two stages: formation of the 3-thio analog (X) of isatin and reduction of the latter. Such dimerizing reduction of thioketones leads generally—in contradistinction with the behavior of the analogous ketones—to disulfides and not to dithiopinacols.[26–28] Also the thermal decomposition of sulfisatyde is analogous to that of other disulfides: in the same way, in which dibenzhydryl disulfide decomposes in the presence of copper into tetraphenylethylene and diphenylmethane,[27] sulfisatyde (V) gives oxindole and isoindigo (XV) in the presence of pyridine[29] or cuprous chloride[30] whilst in the presence of alkali a somewhat more complicated reaction takes place, leading to isoindigo and isatin.[31]

In order to exclude conclusively the formula analogous to III for sulfisatyde, the absence of the C=S absorption was proven by comparison of its infrared spectrum with that of xanthione, thioxanthione and N-methylthioacridone (XI, R = O,S, NCH$_3$). In these substances, the C=S group absorbed at 1320, 1315 and 1360 cm.$^{-1}$, respectively[21,32]; no band in this region was observed in the case of sulfisatyde.

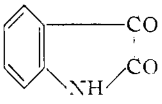
In connection with these experiments the infrared spectrum of a number of other indole derivatives was studied[33]; oxindole (XII), dioxindole (XIII), isatin (XIV) (Fig. 1a), isoindigo (XV) (Fig. 1b), indigo (XVI) (Fig. 1c) and indirubin (XVII) (Fig. 1d).



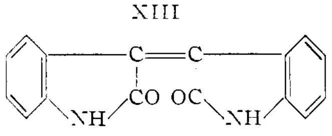
XII



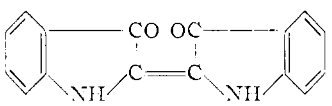
XIII



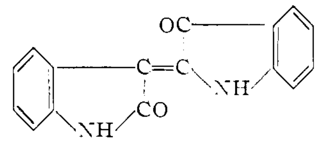
XIV



XV



XVI



XVII

In oxindole (XII), both the lactam form and a form containing a tertiary hydroxyl group XIIa appear to coexist, as already concluded by Julian, Pikl and Wantz[34] from chemical evidence[35]: oxindole shows an absorption characteristic for the CO–NH system at 1710 cm.$^{-1}$ and a band in the region of the absorption of the tertiary hydroxyl (1135–1165 cm.$^{-1}$). Also in the spectrum of dioxindole (XIII), the absorption band at 1710 cm.$^{-1}$ is present; in addition, the secondary hydroxyl group is responsible for the peaks at 1070 and 1265 cm.$^{-1}$. In isatin (XIV) and indirubin (XVII), the CO–NH absorption is shifted to 1730 cm.$^{-1}$, whilst in isoindigo (XV) it appears again at 1710 cm.$^{-1}$. In none of the three "dimeric" compounds, there is definite infrared evidence for the presence of the central double bond, which is often the case in high-molecular and highly symmetric olefin compounds. In indigo (XVI) which is characterized by an unusually large number of bands, the 1710 cm.$^{-1}$ absorp-

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[23] J. Cymerman and J. B. Willis, *J. Chem. Soc.*, 1332 (1951).

[24] Frequencies of the same magnitude have been observed in the Raman spectrum of liquid sulfur and of several disulfides (for the literature, see H. Gerding and R. Westrik, *Rec. trav. chim.*, **61**, 412 (1942), and furthermore, ref. 20, and J. H. Hibben, "The Raman Effect and its Chemical Applications," Reinhold Publishing Corp., New York, N. Y., 1939, p. 256). *Cf.* O. Foss, *Acta Chem. Scand.*, **8**, 469 (1954).

[25] The infrared spectra of dimethyl and dibutyl disulfide, reproduced by Randall, Fuson, Fowler and Dangl,[9] do not extend into the S–S region. The same applies to the spectrum of bis-perfluoropropyl disulfide, measured by M. Hauptschein and A. V. Grosse (THIS JOURNAL, **73**, 5461 (1951)).

[26] E. Bergmann, M. Magat and O. Wagenberg, *Ber.*, **63**, 2576 (1930).

[27] E. Bergmann and S. Fujise, *Ann.*, **483**, 65 (1930).

[28] A. Schoenberg, O. Schuetz, V. Bruckner and J. Peter, *Ber.*, **62**, 2550 (1929).

[29] A. Wahl and T. Faivret, *Ann. chim.*, [10] **5**, 314 (1926).

[30] A. Wahl and J. Lobeck, *ibid.*, [10] **12**, 156 (1929).

[31] A. Wahl and P. Bagard, *Compt. rend.*, **148**, 716 (1909); *Bull. oc. chim. France*, [4] **5**, 1043 (1909); **7**, 1100 (1910).

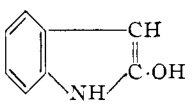
[32] According to E. C. Gregg, THIS JOURNAL, **74**, 3691 (1952), the C=S absorption lies at 1310 cm.$^{-1}$. In carbon disulfide, it has been observed at 1323 cm.$^{-1}$; D. Z. Robinson, *J. Chem. Phys.*, **19**, 881 (1951). *Cf.* A. Kjaer and K. Rubinstein, *Acta Chem. Scand.*, **8**, 598 (1954).

[33] Infrared studies in the indole series: B. Witkop and J. B. Patrick, THIS JOURNAL, **73**, 713 (1951); **74**, 3861 (1952); J. Kebrle, H. Schmid, P. Waser and P. Karrer, *Helv. Chim. Acta*, **36**, 102 (1953); see also *ibid.*, **37**, 553 (1954).

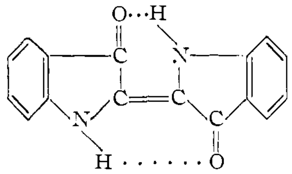
[34] P. Julian, J. Pikl and F. E. Wantz, THIS JOURNAL, **57**, 2026 (1935).

[35] 3,3-Dimethyloxindole has the pure lactam structure: M. Kates and L. Marion, *ibid.*, **72**, 2308 (1950); *Can. J. Chem.*, **29**, 37 (1951).

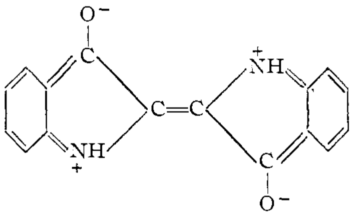
tion is absent. This may be due to the fact—recognized for some time[36]—that indigo has the *trans* structure and, therefore, is likely to form hydrogen-bridged or zwitterionic forms such as XVIa or XVIb, which also are responsible for the band at 3250 cm.$^{-1}$ (NH, participating in a chelate structure).[37]



XIIa



XVIa



XVIb

**Acknowledgment.**—Most of the infrared spectra have been measured by Dr. H. Eisenberg and Dr. S. Pinchas of the Weizmann Institute of Science (Rehovoth); the spectrum of sulfisatyde in the region below 1000 cm.$^{-1}$ we owe to the courtesy of Messrs. S. P. Sadtler and Son, Inc. (Philadelphia, Pa.). Thanks are due to Prof. H. Wahl (Faculté des Sciences, Nancy) for a sample of sulfisatyde.

## Experimental

Isatyde (I) was prepared according to Laurent,[1] dioxindole (XIII) (from amyl alcohol, m.p. 168°) according to Kalb[38] and oxindole (XII) (from cyclohexane, m.p. 124°) according to Marschalk.[39] For the synthesis of isoindigo (XV), the condensation of oxindole and isatin, for that of indirubin (XVII) the reaction of 3,3-dichlorooöxindole[40] with oxindole was employed.[31] XV was purified by sublimation *in vacuo*, XVII by recrystallization from aniline. Isatin and indigo were commercial preparations which were recrystallized from glacial acetic acid (m.p. 200–201°) and aniline. Xanthione (from benzene, m.p. 156°) and thioxanthione (from xylene, m.p. 168°) were prepared according to Schoenberg, *et al.*,[41] and N-methylthioacridone (from xylene, m.p. 263°) according to Gleu and Schaarschmidt.[42]

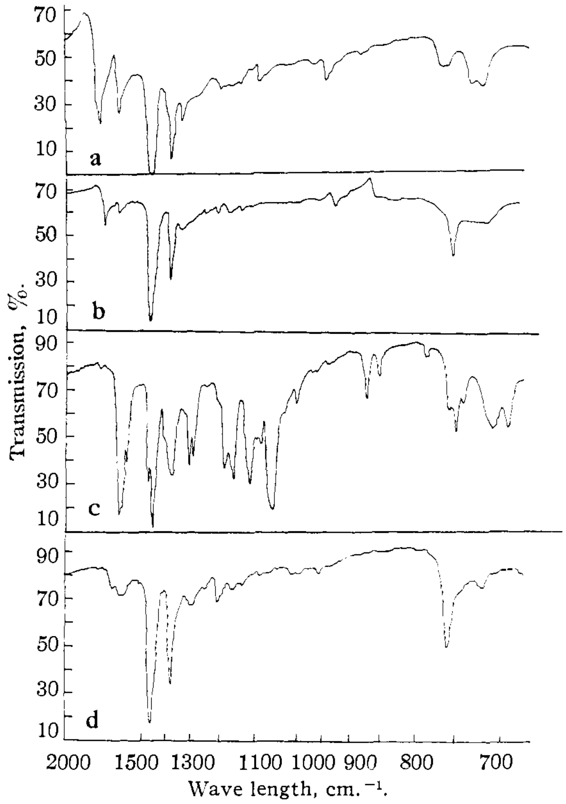


Fig. 1.—Infrared spectrum of Nujol suspensions of: a, isatin (XIV); b, *iso*-indigo (XV); c, indigo (XVI); d, indirubin (XVII).

The infrared spectra of the indole derivatives were measured on the suspensions of the compounds in liquid paraffin; for the three thioketones XI, the solutions in chloroform (1 ml.) were employed (XI, R = O: 13.0 mg.; XI, R = S: 12.5 mg.; XI, R = NCH$_3$: 11.0 mg.).

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[36] For a discussion of this question, see R. C. Elderfield, "Heterocyclic Compounds," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 262 ff. *Cf.* H. von Eller, *Compt. rend.*, **239**, 975 (1954).

[37] The measurements are in good accord with the infrared spectrum of indigo reported recently by W. R. Brode, E. G. Pearson and G. M. Wyman, THIS JOURNAL, **76**, 1034 (1954).

[38] L. Kalb, *Ber.*, **44**, 1455 (1911).

[39] Ch. Marschalk, *ibid.*, **45**, 582 (1912).

[40] A. v. Baeyer, *ibid.*, **12**, 456 (1879).

[41] A. Schoenberg, O. Schuetz and S. Nickel, *ibid.*, **61**, 1375 (1928).

[42] K. Gleu and R. Schaarschmidt, *ibid.*, **72**, 1246 (1939).