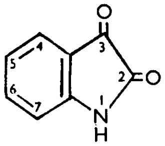
430. *The Structure of Isatin and Substituted Isatins.*

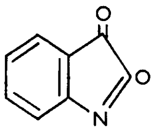
By D. G. O'Sullivan and P. W. Sadler.

The vibrational spectra of isatin and a series of substituted isatins provide no support for the existence of a classical lactim structure in the solid state or in dilute solution in chloroform. Strong intermolecular hydrogen bonding is present in all but three of the compounds examined. Two of these exceptions possess intramolecular hydrogen bonds. Substituents in the benzene ring have only a minor effect on the CO and NH stretching frequencies, but a correlation was found between frequency and chemical reactivity of the β-carbonyl group. The influence of substituents on the character of the ring frequencies is more pronounced.

As the visible-light absorption of isatin resembles that of its *N*-methyl derivative rather than its *O*-methyl ether, Hartley and Dobbie [1] considered that the lactam structure (I) was to be preferred to the lactim structure (II). Subsequent work,[2,3,4] however, indicated that data from this spectral region could not be interpreted unambiguously. The high dipole moment of isatin in dioxan favours the lactam formulation.[5] Cox, Goodwin, and Wagstaff [6] showed, from an *X*-ray study of isatin crystals, that the molecules are arranged in parallel layers with the N and the O atom of one molecule only 2·8 Å distant from the O and the N atom respectively of the adjacent molecule in the same layer. This situation was strongly indicative of intermolecular hydrogen bonding, the presence of which is in accord with the solubility characteristics of isatin in different solvents. For the relevant parts of two adjacent molecules, structures (III) and (V) should contribute to the resonance hybrid. Structure (V) not only strengthens the intermolecular bonding, but also increases the lactam character of the individual molecules. Further *X*-ray investigation by Goldschmidt and Llewellyn [7] led these workers to revise the intermolecular N–O distance to 2·93 Å and to claim that the bonded molecules were not coplanar. The molecular mapping obtained was stated to be consistent with contributions of 62%, 10%, and 10% from (III), (IV), and (V) respectively, a further 10% arising from two structures in which the oxygen atom of the β-carbonyl group carries a negative charge. Total lactam contribution was assessed at 85%. In order to obtain further evidence on this topic, on the existence of the dimer in solution, and on the influence of substituents, infrared absorption data were determined for isatin and for a number of substituted isatins.



(I)



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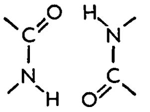

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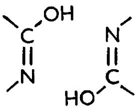

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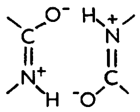

(V)

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[1] Hartley and Dobbie, *J.*, 1899, 640.
[2] Morton and Rogers, *J.*, 1925, 2698.
[3] Dabrowski and Marchlewski, *Bull. Soc. chim. France*, 1933, **53**, 946.
[4] Ault, Hurst, and Morton, *J.*, 1935, 1653.
[5] Cowley and Partington, *J.*, 1936, 47.
[6] Cox, Goodwin, and Wagstaff, *Proc. Roy. Soc.*, 1936, *A*, **157**, 399.
[7] Goldschmidt and Llewellyn, *Acta Cryst.*, 1950, **3**, 294.

RESULTS and DISCUSSIONS

Solid isatin, in a potassium bromide disc, showed maxima at the following wave numbers (cm.$^{-1}$) : 3445 (m), 3215 (m), 2922 (w), 1730 (s), 1620 (s), 1547 (vw), 1469 (m), 1405 (w), 1338 (m), 1295 (w), 1208 (w), 1150 (w), 1101 (m), 951 (w), 890 (w), 774 (w), 740 (w) and 663 (w) (s, m, w, and vw indicate the relative intensities as strong, medium, weak, and very weak respectively). The band at 2922 cm.$^{-1}$ is clearly a CH stretching frequency and the peaks between 1210 and 950 cm.^{1} are characteristic of a 1 : 2-disubstituted benzene ring.[8] The CH deformation frequency of high intensity,[9] which normally appears at 750 cm.$^{-1}$ in 1 : 2-disubstituted benzenes, is split in isatin into two weak maxima at 774 and 740 cm.$^{-1}$ Indubitable assignments cannot be made for the bands at 1547, 1405, 1295, 890, 820, and 663 cm.$^{-1}$. Further data are summarised in Table 1.

Table 1 shows that substitution introduces only minor modifications. *N*-Methyl-, 7-trifluoromethyl- and 7-nitro-isatin excluded, the compounds possess a broad band between 3500 and 3200 cm.$^{-1}$ which contains two maxima, a fairly sharp peak at about 3450 cm.$^{-1}$, and a broader maximum near 3230 cm.$^{-1}$. Indole, in chloroform, gives a sharp maximum at 3507 cm.$^{-1}$ (Fuson, Josien, Powell, and Utterback [10] give values between 3491 and 3447 cm.$^{-1}$ for a range of solvents) and only very weak absorption with no definite maximum at 3340 cm.$^{-1}$, the next peak appearing at 1617 cm.$^{-1}$. The broad band is absent also in *N*-methylisation and is replaced by very weak absorption at 3495 cm.$^{-1}$ which may be an overtone frequency. There is no evidence that any of these compounds, even in very dilute solution, possess free OH stretching absorption to be expected at 3650—3550 cm.$^{-1}$ or that they possess resonance-stabilised hydrogen-bonded OH absorption to be expected at 3200—2500 cm.$^{-1}$. It is considered improbable that the 3500—3200 cm.$^{-1}$ band is produced entirely by weak OH–N bonding. These features, if considered in conjunction with previous work on indole derivatives,[11, 12] secondary amides,[13] and thioamides,[14] and

TABLE 1. *Frequencies (cm.$^{-1}$) for isatin and substituted isatins in chloroform.*

Isatin ...	3450 w	3230 w	1755 *	1740 *	—	1621 s	—	—	1326 m
1-Me ...	3495 vw	—	—	1741	—	1615 s	1465 w	1372 m	1332 s
4-I	3440 m	3240 m	1762	1741	—	1608 s	—	1350 w	1307 w
4-Br	3445 m	3250 m	1765	1745	—	1615 s	—	1355 w	1310 w
4-Cl	3450 m	3250 m	1765 sh	1745	—	1615 s	—	1360 w	1310 m
4-Me ...	3460 m	3230 m	1758	1731	1620 s	1608 s	—	—	1315 m
4-CF_3 ...	3450 m	3220 m	1765 sh	1750	1635 m	1613 s	1450 w	—	1320 s
5-F	3458 m	3230 m	1755	1744	—	1630 m	1480 w	—	—
5-MeO ...	3455 m	3250 m	1757	1738	1627 m	1608 m	1492 m	1365 w	1310 w
5-Me ...	3460 m	3250 m	1758	1739	—	1631 s	1480 w	—	1305 w
6-I	3435 m	3250 m	1765	1744	—	1612s	—	1345 w	1325 m
6-Br	3440 m	3230 m	1765 sh	1744	—	1618 s	—	1355 w	1323 m
6-Cl	3450 m	3230 m	1755 sh	1743	—	1618 s	—	1350 w	1322 m
6-F	3450 m	3230 m	1764	1743	—	1624 s	1450 w	—	1322 m
6-MeO ...	3455 m	3250 m	1756	1734	—	1622 s	1458 w	1350 w	1315 m
6-Me ...	3460 m	3240 m	1755 sh	1738	—	1628 s	—	—	1331 m
7-I	3430 m	3230 w	1761	1746	—	1612 s	—	—	1315 m
7-Br	3438 m	3207 w	1763	1748	—	1620 s	—	—	1318 s
7-Cl	3440 m	3205 w	1765	1745	—	1620 s	—	—	1318 m
7-F	3453 s	3210 m	1765	1745	1640 s	1604	1455 vw	1366 vw	1320 s
7-Me ...	3460 m	3240 m	1755 sh	1739	1621 m	1608 m	—	—	1320 m
7-CF_3 ...	3465 m	3240 vw	1768	1750	—	1623 s	—	1348 m	1318 s
7-NO_2 ...	3440 m	—	1772	1751	1631 s	1600 m	1470 vw	1340 m	1320 s

* All absorptions in these two columns are intense.

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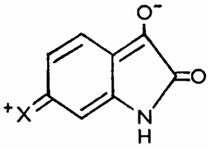
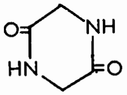
[8] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1954, p. 70.
[9] Ref. 8, p. 66.
[10] Fuson, Josien, Powell, and Utterback, *J. Chem. Phys.*, 1952, **20**, 145.
[11] Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 614.
[12] Witkop and Patrick, *ibid.*, 1951, **73**, 1558.
[13] Darmon and Sutherland, *Nature*, 1949, **164**, 440.
[14] Flett, *J.*, 1953, 347.

with the presence of two intense CO stretching frequencies in all the isatins, lead to the conclusion that the 3450 cm.$^{-1}$ absorption is an NH stretching frequency and that the 3230 cm.$^{-1}$ band exists because of the presence of hydrogen bonds. With increasing dilution, the 3230 cm.$^{-1}$ band diminishes in intensity more rapidly than the 3450 cm.$^{-1}$ band, a result to be expected if the former is produced by hydrogen bonding. Both bands appear in a well-defined form in solid isatin. This effect has frequently been reported for other solids containing the hydrogen-bonded NH group, but no satisfactory explanation has been advanced. It may be that, contrary to expectation, non-bonded NH groups exist in the solid, or perhaps both frequencies may be characteristic of certain completely bonded structures. The accumulated evidence from the spectra of a wide range of solid compounds strongly suggests that both bonds are related to the NH group, but the possibility that one of these frequencies has some completely different origin has not been entirely eliminated. Further investigation of this topic is clearly desirable.

Comparison with the spectra of α-diketones [15, 16] and γ-lactones [16, 17, 18, 19] indicates that the maxima at 1770—1730 cm.$^{-1}$ result from the stretching vibrations of two carbonyl groups. The absorption of lower frequency which we attribute to the β-carbonyl group, is always very sharp and intense, whilst the α-carbonyl absorption is always slightly less intense and, although usually present as a well-defined maximum, is occasionally evident only as a shoulder. In general, the separation of the two carbonyl peaks is less distinct in compounds substituted in the 4- and the 6-position, presumably because the influence of form (VI) and similar structures tends to equalize the character of the two carbonyl groups. These compounds are the least soluble in solvents of low polarity and from the character of the 3230 cm.$^{-1}$ band appear to possess very strong intermolecular links.



(VI)



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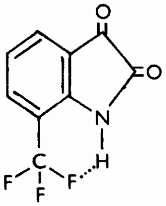

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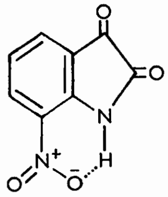

(IX)

Thus infrared data strongly support a lactam structure for isatin and substituted isatins. It is of interest to note that *X*-ray evidence [20] favours a ketonic structure for simple amides, contrary to earlier conclusions from ultraviolet spectra; [21] *X*-ray studies,[22, 23] supported by infrared work,[24] indicate that 2-pyridone possesses a cyclic lactam rather than a hydroxypyridine structure; electron-diffraction methods [25] indicate that dioxopiperazine exists in the form (VII); and infrared investigations [26] indicate that certain pyrimidones also possess a ketonic formula.

Of the compounds that possess no marked absorption at 3230 cm.$^{-1}$, hydrogen bonding is not to be expected with *N*-methylisatin and presumably intramolecular hydrogen bonds will occur in the 7-trifluoromethyl- (VIII) and 7-nitro-compound (IX). The extremely weak, very broad band given by (VIII) at 3240 cm.$^{-1}$ possibly arises from the NH–F link,

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[15] Thompson, *Trans. Faraday Soc.*, 1940, **36**, 988.
[16] Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 956.
[17] Whiffen and Thompson, *J.*, 1946, 1005.
[18] Rasmussen and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1073.
[19] Grove and Willis, *J.*, 1951, 877.
[20] Senti and Harker, *J. Amer. Chem. Soc.*, 1940, **62**, 2008.
[21] Hantzsch, *Ber.*, 1931, **64**, 661.
[22] Penfold, *Acta Cryst.*, 1953, **6**, 591.
[23] *Idem, ibid.*, p. 707.
[24] Gibson, Kynaston, and Lindsey, *J.*, 1955, 4340.
[25] Speakman, *Ann. Reports*, 1954, **51**, 377.
[26] Short and Thompson, *J.*, 1952, 168.

whilst the strong hydrogen bond in 7-nitroisatin may lower the vibrational frequency into the 3000—2500 cm.$^{-1}$ region.

It is possible that unsaturated C=C stretching vibrations of the benzene ring undergo resonance splitting in many of the compounds, producing a weak band at 1450 cm.$^{-1}$ in addition to the very intense band at 1620 cm.$^{-1}$. The 1450 cm.$^{-1}$ band falls in a region in which the chloroform solvent shows strong absorption and it must be noted that the corresponding band (1469 cm.$^{-1}$) for isatin in a solid disc is much more intense. This band could alternatively be an NH deformation frequency or even amide CN absorption,[27] but this is considered to be unlikely in view of the absence of an amide II band in other cyclic lactams.[28] The 1620 cm.$^{-1}$ band is always of comparable intensity to the carbonyl frequencies and in a few cases it is divided into two high peaks with maxima respectively slightly above and slightly below 1620 cm.$^{-1}$. Splitting of the aromatic frequency band does not occur when the substituent has strong *ortho-para*-directing properties and the three peaks are most pronounced when the substituent is *meta*-directing. The frequency of the 1620 cm.$^{-1}$ band for those compounds which are substituted in the 5-, 6-, or 7-position is close to that of isatin, but compounds possessing *ortho-para*-directing substituents in the 4-position show a maximum at a slightly lower frequency in accordance with the usual behaviour of vicinally substituted benzene derivatives.[29]

The isatins, except 5-fluoroisatin, possess a band near 1320 cm.$^{-1}$, and a corresponding band appears just below 1300 cm.$^{-1}$ with the latter compound. A second, less intense band occurs at 1350 cm.$^{-1}$ in those compounds possessing *ortho-para*-directing substituents in the 4- or 6-position or *meta*-directing substituents in the 7-position. By analogy with aromatic secondary amines [30] and with indole, absorption in this region is attributed to stretching vibration of the bond between the benzene ring and the nitrogen atom, but the Ph–CO linkage could also be responsible for these maxima.

Varying over 35 wave numbers, the NH stretching frequencies depend on the nature of the substituent rather than on its position in the benzene ring. Thus 4-, 5-, 6-, and 7-methylisatin all possess maxima at 3460 cm.$^{-1}$, and frequencies increase in the order $I < Br < Cl < F < Me$ in all cases. The behaviour of 4-trifluoromethylisatin is not in accordance with this scheme.

Absorption in the 1750 cm.$^{-1}$ region is outside the reported range of C=N frequencies [31] and can be attributed to the carbonyl groups with little possibility of error. Further interpretation of the carbonyl frequencies is complicated by the existence of two possibilities. Either the α- and the β-carbonyl groups may give rise to one peak each or the two groups in the free state may absorb at the same frequency, the second maximum then arising from vibrations of those α-carbonyl groups that are involved in hydrogen bonding. The second alternative is supported by the following : (*a*) the CO absorptions of monomeric and dimeric aliphatic acids [32,33] differ by about 30 cm.$^{-1}$, (*b*) a few simple amides show two carbonyl frequencies,[34] (*c*) *N*-methylisatin gives a single peak at 1741 cm.$^{-1}$, and (*d*), in general, α-diketones possess a single CO absorption.[16,35,36,37] However, on the basis of the following evidence, the authors consider that the carbonyl groups possess different stretching frequencies : (i) under conditions in which both monomeric and dimeric forms should coexist, γ-lactams show a single CO absorption,[38] (ii) cyclic compounds containing the CO·NH·CO group possess two distinct CO frequencies,[39] (iii) 7-nitroisatin, although containing no hydrogen-bonded carbonyl group, possesses two CO maxima similar in form

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[27] Ref. 8, p. 176.
[28] Lenormant, *Compt. rend.*, 1951, **232**, 2016.
[29] Ref. 8, p. 60.
[30] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.
[31] Ref. 8, p. 226.
[32] Herman and Hofstadter, *J. Chem. Phys.*, 1939, **7**, 460.
[33] Hartwell, Richards, and Thompson, *J.*, 1948, 1436.
[34] Richards and Thompson, *J.*, 1947, 1259.
[35] Rasmussen, Tunnicliff, and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1068.
[36] Barnes and Pinkney, *ibid.*, 1953, **75**, 479.
[37] Leonard and Robinson, *ibid.*, p. 2143.
[38] Ref. 8, p. 183.
[39] Ref. 8, p. 190.

to those shown by the other compounds, and (iv) if one frequency results from a hydrogen-bonded CO group, this should be the lower frequency,[34] but the latter can be correlated with the behaviour of the β-carbonyl group.

The approximately constant separation of the two carbonyl maxima suggests that substituents have a similar effect on both groups, but the higher frequencies cannot be simply correlated with the properties of the β-carbonyl group. Flett,[40] Davison,[41] and Fuson, Josien, and Shelton [42] have shown that relations exist between carbonyl frequencies of substituted aromatic compounds and Hammett's σ constants [43] for the substituents. Table 2 lists σ values and β-carbonyl frequencies for isatins. Included in the Table for comparison purposes are CO frequencies for corresponding benzophenones and acetophenones [42] and α-carbonyl frequencies of the isatins.

The numbers in Table 2, excluding the last column, approximately obey the equation $\nu - \nu_0 = 15\sigma$, where ν_0 possesses the values 1663 (benzophenones), 1690 (acetophenones), and 1740 (isatins). These results further support the contention of Fuson *et al.*[42] that σ values are deducible from infrared measurements.

TABLE 2. *Hammett's σ values and carbonyl frequencies (cm.$^{-1}$).*

Subst.*	σ	Isatins (β-CO)	Benzophenones †	Acetophenones †	Isatins (α-CO)
6-NH_2	—0·660	—	1651	1677	—
6MeO	—0·268	1734	1658	1684	1756
6-Me	—0·170	1738	1661	—	1755
5-Me	—0·069	1739	—	—	1758
7-Me	—0·069	1739	—	—	1755
None	0·0	1740	1664	1692	1755
6-F	0·062	1743	—	—	1764
5-MeO	0·115	1738	—	—	1757
6-Cl	0·227	1743	1666	1692	1755
6-Br	0·232	1744	1665	1693	1765
6-I	0·276	1744	—	—	1765
5-F	0·337	1744	—	—	1755
7-F	0·337	1745	—	—	1765
7-I	0·352	1746	—	—	1761
7-Cl	0·373	1745	—	—	1765
7-Br	0·391	1748	1669	—	1763
7-NO_2	0·710	1751	—	1701	1772
6-NO_2	0·778	—	—	1702	—

* Numbering for substituents refers to isatin; thus, for acetophenones and benzophenones, 6 refers to a *p*-substituent and 5 and 7 to *m*-substituents. Benzophenones are substituted in one ring only.
† Data obtained in carbon tetrachloride.[42]

TABLE 3. *Carbonyl frequencies, rates of oximation, and dehydrogenase activity of isatins.*

	ν (cm.$^{-1}$)	*r*	*t* (min.)	*t′* (min.)
6-MeO	1734	70·9	—	—
6-Me	1738	78·7	72	96
5-Me	1739	98·1	50	—
None	1740	100·0	50	57
5-MeO	1738	106·3	43	—
7-Cl	1745	—	—	31
7-CF_3	1750	—	—	26
7-NO_2	1751	—	—	23

To provide practical demonstrations of this relation, two reactions have been considered. In Table 3, β-carbonyl frequencies of isatins are compared with values given by Giovannini and Portmann [44] for relative rates of oximation *r* at the β-carbonyl group. The reactivity of this group, as assessed by this reaction, is monotonically related to the σ function of the substituent and, except in the case of 5-methoxyisatin, is similarly related to the frequencies.

A brief study has been made of the dehydrogenation of α-amino-acids by isatins.

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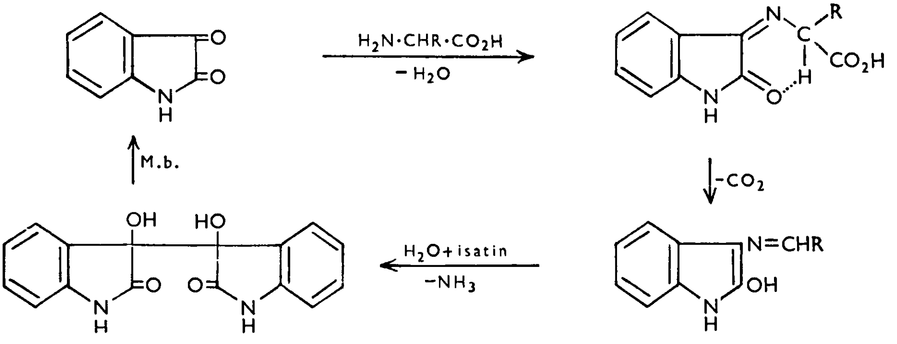
[40] Flett, *Trans. Faraday Soc.*, 1948, **44**, 767.
[41] Davison, *J.*, 1951, 2456.
[42] Fuson, Josien, and Shelton, *J. Amer. Chem. Soc.*, 1954, **76**, 2532.
[43] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 188.
[44] Giovannini and Portmann, *Helv. Chim. Acta*, 1948, **31**, 1373.

Schönberg, Moubasher, and Mostafa[45] have postulated the annexed mechanism for this model-enzyme system :



M.b. = methylene-blue.

Table 3 lists times, t, required for the decolorization of methylene-blue in the oxidation of alanine, as determined by Giovannini and Portmann.[44] These, and similar results by other workers, were obtained with pyridine solutions at room temperature. In view of the biological importance of this reaction, it was decided that further measurements should be performed under more physiological conditions. Results t' (Table 3), obtained with similar concentrations of reactants, but in aqueous solution at 40°, are clearly comparable with the reaction times t. Thus ν, σ, r, and the dehydrogenase activity of substituted isatins increase in the same order. Both carbonyl groups are undoubtedly involved in the dehydrogenation and their individual effects cannot be separated. Hence the general parallelism between reaction rate and stretching frequency suggests that the initial condensation is usually the rate-controlling stage. Amongst the compounds tested, only 6-fluoroisatin ($t' = 111$) behaved exceptionally.

EXPERIMENTAL

Infrared Absorption Spectra.—Spectra were determined by using a Perkin-Elmer 21 double-beam recording spectrometer fitted with a rock-salt prism. Results for the 4000—3000 cm.$^{-1}$ region were determined, if possible, for 10^{-2}M-solutions; otherwise with saturated solutions. For results at lower frequencies, 10^{-2}M-solutions were subjected to three-fold dilution.

Materials.—Substituted isatins were prepared from the corresponding substituted anilines, by the Sandmeyer synthesis.[46, 47] The method used to separate the mixtures of isomeric isatins has been described.[47] Final purification was achieved by crystallization from ethanol or acetic acid. 5-*Fluoroisatin*, obtained as orange-red needles from acetic acid, had m. p. 223° (Found : C, 58·0; H, 2·6; N, 8·8. $C_8H_4O_2NF$ requires C, 58·2; H, 2·4; N, 8·5%). 7-*Fluoroisatin* crystallized as orange needles from ethanol and had m. p. 194° (Found : C, 58·4; H, 2·4; N, 8·7%). Details of the synthetic studies are to be published later.

Dehydrogenase Activity of Substituted Isatins.—A 10^{-2}M-aqueous solution of the isatin (4 ml.), M-DL-alanine (1 ml.), and 1% methylene-blue solution (1 ml.) were rapidly mixed, diluted to 10 ml., and incubated at 40°. The incubation time necessary for the green-blue solution to become suddenly pale yellow was measured for each sample.

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[45] Schönberg, Moubasher, and Mostafa, *J.*, 1948, 176.
[46] Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 234.
[47] Sadler, *J. Org. Chem.*, 1956, **21**, 169.