740. *Vibrational Frequency Correlations in Heterocyclic Molecules. Part II.*[1] *Infrared Spectra and Structure of Oxindole and Related Compounds.*

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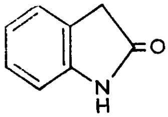
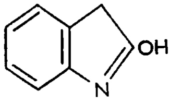
Infrared spectra of oxindole, phthalimidine, phthalimide, and related molecules in chloroform strongly support fully ketonic formulæ for all these compounds. Intermolecular hydrogen bonding is also present provided the NH group remains unsubstituted. The carbonyl stretching frequencies of oxindole vary with the substituents in the benzene ring, probably being dependent on their σ-values. The effect of these substituents is transmitted through the NH group to the carbonyl group. Other features of the spectra of these compounds are discussed in relation to the spectra of substituted isatins.

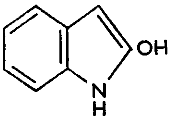
Structures containing NH and CO groups in five-membered rings are often present in naturally occurring compounds and vibrational spectra have frequently been used in their investigation. However, reference data are still sketchy and to supplement previous work on substituted isatins,[1] and provide further basic information, infrared spectra of some oxindoles and related compounds have been obtained. Vibrational spectra have been used in investigating the spiro-structures that arise in degradation products of certain alkaloids which are structurally related to oxindole.[2]



(I)



(II)



(III)

There are three possible formulæ for oxindole. Chemical evidence was assumed by Julian, Pikl, and Wantz [3] to favour the predominance of the lactam form (I), but (II) and (III) were also considered to be present in solution. Bergmann [4] thought that the infrared spectrum of oxindole in Nujol mull supported this view. However, the sole spectral evidence for the existence of an enolic structure, the presence of absorption at 1165—1135 cm.$^{-1}$, can be given alternative interpretations. Ultraviolet spectra of oxindole and its 1-methyl and 1 : 3 : 3-trimethyl derivatives are very similar,[5] suggesting that all these compounds exist in a ketonic form. However, early controversy on the ultraviolet spectrum of isatin [6] shows that this evidence is equivocal. From their chemical behaviour, phthalimidine and phthalimide have always been assigned fully ketonic structures although lactam–lactim tautomerism is possible in both cases.

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[1] The paper by O'Sullivan and Sadler, *J.*, 1956, 2202, is regarded as Part I.

[2] Loudon, " Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," *Chem. Soc. Special Publ.*, 1955, No. 3, p. 12; Stevens, *ibid.*, p. 19; Markees and Burger, *J. Amer. Chem. Soc.*, 1949, **71**, 2031; Kates and Marion, *ibid.*, 1950, **72**, 2308.

[3] Julian, Pikl, and Wantz, *ibid.*, 1935, **57**, 2026.

[4] Bergmann, *ibid.*, 1955, **77**, 1549.

[5] Ramart-Lucas and Biquard, *Bull. Soc. chim. France*, 1935, **2**, 1383.

[6] Morton and Rogers, *J.*, 1925, 2698; Dabrowski and Marchlewski, *Bull. Soc. chim. France*, 1933, **53**, 946; Ault, Hurst, and Morton, *J.*, 1935, 1653.

RESULTS AND DISCUSSION

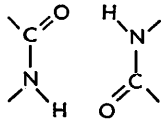
Table 1 shows that all except the *N*-methyl compounds possess a fairly sharp peak at 3478—3444 cm.$^{-1}$ and a broad maximum at 3320—3220 cm.$^{-1}$, and every compound shows intense absorption in the 1772—1680 cm.$^{-1}$ region. Maxima near 3450 cm.$^{-1}$ are usually attributed to stretching vibrations of the NH group and a broad band at 3250 cm.$^{-1}$ to NH groups involved in hydrogen bonding.[7] Absorption at 1772—1680 cm.$^{-1}$, which is at too high a frequency to be associated with C=N or C=C vibrations under normal conditions, must be assigned to the CO stretching mode. This is discussed in more detail below. Only weak absorption occurs with the *N*-methyl compounds at 3500—3400 cm.$^{-1}$ which may be the first carbonyl harmonic.[8] The three bands are present in 3 : 3-dichloro-oxindole in which keto-enol tautomerism is presumably absent, and the 1700 cm.$^{-1}$ band is still present in 3 : 3-dichloro-1-methyloxindole which can only exist in the ketonic form. Of the compounds listed, only *p*-chloroacetamidophenol exhibits an unassociated OH absorption at 3625 cm.$^{-1}$, the solubility of 5-hydroxyoxindole being too low to permit the recording of an OH frequency for this compound. It must be concluded, therefore, that all these substances exist in the fully ketonic form. The hydrogen bonding which occurs when an NH group is present is most likely to be intermolecular bonding, similar to that present in isatin,[1] with (IV) and (V), representing relevant parts of two adjacent molecules, contributing to the structure of the, probably dimeric, hybrid.

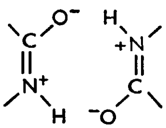
TABLE 1. *Infrared maxima in chloroform.*

	4000—3000 cm.$^{-1}$			1800—1650 cm.$^{-1}$		1650—1290 cm.$^{-1}$						
Oxindole	—	3462m	3220w	1725s	1708s	1627m		—	1472m	—	1356w	1329w
1-Methyloxindole	—	—	—	1700s		1619m		—	1468w	1373w	1354m	1310w
3 : 3-Dichloro-oxindole	—	3448m	3250w	1758s		1624m		—	—	—	1324w	—
3 : 3-Dichloro-1-methyloxindole	—	—	—	1739s		1616m		—	1472w	1370w	1351w	—
p-Chloroacetamidophenol ...	3625w	3420m	3320w	1680s		1609w		1520w	1480w	—	1328w	—
5-Hydroxy-oxindole *	—	—	—	1700m		—		—	—	—	—	—
5-Methyloxindole	—	3460m	3230w	1718s	1700s	1621w	1612w	—	1460w	—	1313w	—
5-Chloro-oxindole	—	3450m	3220w	1731m		1623m		—	1460w	—	—	—
5-Bromo-oxindole	—	3450m	3220w	1733m		1620w		—	1465w	—	1340w	1292w
5-Nitro-oxindole	—	3445m	3270w	1754s	1722s	1630w	1608w	—	1475w	—	1343s	1290w
Phthalimidine ...	—	3478m	3240w	1698s		1621w		—	1458w	—	1333w	1304w
Phthalimide	—	3444m	3230w	1775m	1735s	1608w		—	—	—	1379m	1308m
N-Methylphthalimide	—	—	—	1772m	1712s	1620w	1605w	—	1430w	1387s	—	—
3-Nitrophthalimide	—	3440m	3230w	1778m	1737s	1620w		—	—	—	1350s	—
4-Nitrophthalimide	—	3445m	3230w	1780m	1736s	1622w		—	—	—	1350s	—

* NH frequencies not recorded because of the low solubility of this compound.

(IV)





(V)

Absorption at about 1620 cm.$^{-1}$, present in every case, is produced by CC stretching vibrations of the benzene ring.[9] In isatins [1] this absorption is of similar intensity to that

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[7] (*a*) Richards and Thompson, *J.*, 1947, 1248; (*b*) Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 614; Witkop and Patrick, *ibid.*, 1951, **73**, 1558; Darmon and Sutherland, *Nature*, 1949, **164**, 440.

[8] Jones, Williams, Whalen, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2031.

[9] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.

of the carbonyl groups. Here, however, the strongest absorption is shown by oxindoles unsubstituted in the benzene ring, but even these possess only half the carbonyl intensities. Splitting of the 1620 cm.$^{-1}$ frequency occurs in isatins which possess *meta*- or weakly *para*-directing substituents in the benzene ring and this feature is also present in oxindoles (Table 1) and acetanilides (Table 3).

Bands in the 1480—1430 cm.$^{-1}$ region have the frequency range associated with CH_2 or CH_3 deformation modes [10] and as they are absent in 3 : 3-dichloro-oxindole, phthalimide, and 3- and 4-nitrophthalimide they may reasonably be attributed to these groups. The existence of this absorption in oxindoles and phthalimidine further supports the ketonic structure for these compounds.

It was previously considered [1] that bands in the 1350 cm.$^{-1}$ region might be associated with the Ph–N linkage, but it now becomes apparent that various sources are responsible. The fairly intense peak at 1350—1340 cm.$^{-1}$ in the nitro-compounds owes its presence to the nitro-group.[11] A corresponding band at 1340 cm.$^{-1}$ exists for 7-nitroisatin. Maxima which appear for the *N*-methyl compounds at 1387—1370 cm.$^{-1}$ and the maximum at 1372 cm.$^{-1}$ for *N*-methylisatin are probably N–Me deformation frequencies.[12] Other peaks in the 1350—1300 cm.$^{-1}$ region probably owe their origin to Ph–N or Ph–C vibrations.

The carbonyl maxima of these compounds show features of considerable interest. The phthalimides all show two very sharp and intense peaks, the lower- being about twice the intensity of the higher-frequency absorption. The possibility that one maximum is due to free and the other to hydrogen-bonded carbonyl groups is virtually eliminated as the character of the peaks is unchanged in the *N*-methyl compound. A similar phenomenon occurs with symmetrical acid anhydrides,[13] the two carbonyl peaks sharing an almost constant separation of 60 cm.$^{-1}$, and with symmetrical diacyl peroxides [14] in which these peaks are separated by about 20 cm.$^{-1}$. This feature undoubtedly arises from coupling between identical characteristic vibrations of the two carbonyl groups. The frequency separation with benzoyl peroxides is substantially independent of the nature of substituents. The results in Table 1 suggest that substituents in the benzene ring have little effect on the carbonyl frequencies of phthalimide. Oxindole and some substituted oxindoles, possessing a single carbonyl group, show two peaks in the carbonyl region. Here the higher-frequency maximum is very sharp and intense whilst the lower-frequency absorption is slightly less intense. As the *N*-methyl compounds possess a single peak, partial hydrogen bonding appears an attractive explanation. However, 5-halogeno-substituted compounds, which, from the 3220 cm.$^{-1}$ absorption, are the most extensively hydrogen bonded, show only a single maximum. Differing absorption frequency for free and bonded carbonyl groups does not account for the presence of only a single peak in other cases, *e.g.*, for phthalimidine. It should be noted that aceto-*o*-toluidide, which shows structural similarities to oxindole, also possesses two carbonyl absorptions both in dioxan and in the solid state, the two absorptions being more pronounced in the solid.[7a] Postulating vibrational coupling between the carbonyl groups in the dimer also does not account for all the above features. The possibility that another linkage produces, independently of the carbonyl group, one of these peaks is also unlikely.[15]

Although the number of oxindoles considered is too small for unassailable conclusions to be reached here, certain points deserve comment. A strongly *ortho-para*-directing group in the 5-position gives rise to a unique maximum and the separation of the maxima in other cases increases with the tendency of the substituent to withdraw electrons from the ring. Groups that favour the formation of structures such as (VI) and (VII) produce two maxima. Thus the appearance of a second peak may well be related to the effective

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[10] Thompson and Torkington, *Proc. Roy. Soc.*, 1945, *A*, **184**, 3; *Trans. Faraday Soc.*, 1945, **41**, 246.

[11] (*a*) Barnes, Gore, Liddel, and Williams, " Infra-red Spectroscopy," Reinhold Publ. Corpn., New York, 1944; (*b*) Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 70.

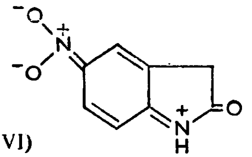
[12] Ref. 11*b*, p. 221.

[13] Randall, Fowler, Fuson, and Dangl, " Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949.

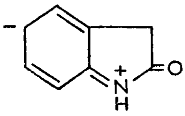
[14] Davison, *J.*, 1951, 2456.

[15] Yates, Ardao, and Fieser, *J. Amer. Chem. Soc.*, 1956, **78**, 650.

conjugation and to the acquirement of positive charge by the nitrogen atom of the NH group. The latter performs some essential function as this splitting does not occur in phthalimidine or in aromatic ketones.[1,16] Its presence in oxindoles also considerably enhances the effect of substituents on the magnitude of the carbonyl frequencies. Two carbonyl peaks are present in benzoyl chloride and have been considered by Rasmussen and Brattain[17] to be caused by either partial association or interaction with a low thermally excited vibration. It seems possible, however, that an increase in quinonoid character of the ring may have some influence in this case also.



(VI)



(VII)

In Table 2, carbonyl frequencies of oxindoles are compared with Hammett's σ-values[18] for the substituents in relation to their position with respect to the NH group. The higher-frequency maxima very accurately obey the equation $\nu - \nu_0 = 37{\cdot}5\sigma$, where $\nu_0 = 1725$. Unfortunately oxindoles substituted in other positions were not available to verify fully this linear dependence.

In a previous discussion of the two carbonyl peaks of substituted isatins,[1] it was shown that the lower-frequency maxima could be correlated with the σ-values of the substituents with reference to the β-carbonyl group. The assignment of these frequencies is further confirmed, and the above argument for oxindole strengthened, by the observation that the higher-frequency maxima of isatins are approximately linearly related to the σ-values of substituents with reference to the NH group. Slight departures from the straight line exist for low σ-values. The α-carbonyl frequency of 6-chloroisatin was previously quoted[1] as 1755 cm.$^{-1}$, where a shoulder is present. However, a second shoulder also occurs at 1765 cm.$^{-1}$ and it now appears likely that the latter is the α-carbonyl frequency and the former is possibly a hydrogen-bonded carbonyl frequency. Very indistinct shoulders are present on some other bands in both the isatin and the oxindole series and may arise from this cause. The influence of substituents on the higher "free" CO frequency is much more marked with oxindoles than with isatins. The lower frequency, which we suggest arises in some way owing to conjugation involving the carbonyl group, does not appear to be linearly related to the σ-constants.

TABLE 2. *Hammett's σ values, with reference to the* NH *group, and α*-CO *frequencies of isatins and oxindoles.*

a, Substituent	5-MeO	5-Me	4-Me	6-Me	None	5-F	6-MeO	5-Cl	5-Br	6-F	4-I	6-I	4-Cl	6-Cl	4-Br	6-Br	5-NO$_2$
b, σ	−0·268	−0·170	−0·069	−0·069	0	0·062	0·115	0·227	0·232	0·337	0·352	0·352	0·373	0·373	0·391	0·391	0·778
c, α-CO frequency (isatins)	1757	1758	1758	1755	1755	1755	1756	—	—	1764	1762	1765	1765	1765	1765	1765	—
d, "Free" CO frequency (oxindoles)	—	1718	—	—	1725	—	—	1731	1733	—	—	—	—	—	—	—	1754
e, "Conjugated" frequency (oxindoles)	—	1700	—	—	1708	—	—	—	—	—	—	—	—	—	—	—	1722

Certain supplementary data are collected in Table 3. The insertion of a nitro-group in the ring has little effect on the carbonyl maximum of phenylacetamide, confirming that the transmission of the effect of substituents occurs through the NH group in oxindoles. From Table 3 it is also seen that the shifts in carbonyl frequency produced by substituents in acetanilide are much smaller than the corresponding shifts in oxindoles. Also,

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[16] Fuson, Josien, and Shelton, *J. Amer. Chem. Soc.*, 1954, **76**, 2532.

[17] Rasmussen and Brattain, *ibid.*, 1949, **71**, 1078.

[18] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 188.

acetanilides in chloroform give sharp bands and show no evidence of splitting. The difference is probably related to the presence of free rotation at the Ph–N and HN–CO bonds in acetanilide and its absence from the planar oxindole molecule. Much bigger substitution shifts occur with solid acetanilides,[7a] where this rotation is either restricted or absent. Oxindole's 5-membered ring may influence the magnitude of the frequency shifts. A study of analogous 6-membered ring compounds is in progress.

TABLE 3. *Maxima in the* 1800—1550 *cm.*$^{-1}$ *region for amides in chloroform.*

Phenylacetamide	1678	1589	*p*-Chloroacetanilide	1688	1598	
p-Nitrophenylacetamide	1682	1600	*m*-Nitroacetanilide	1696	1618	1598
Acetanilide	1685	1601	*p*-Nitroacetanilide	1698	1605	1595

Correlations of frequencies with σ-values may perhaps be useful for the assignment of certain frequencies in other aromatic compounds.

Comparison of the spectra of isatin, oxindole, 3 : 3-dichloro-oxindole, and phthalimide with the spectra of the *N*-methyl compounds shows that the presence of the methyl group lowers the frequency of the adjacent carbonyl group by about 20 cm.$^{-1}$ in agreement with the behaviour of other amides.[7a] The lower-frequency carbonyl absorption of oxindole is eliminated when this methyl group is introduced. Introducing chlorine substituents into the 3-position produces the usual frequency increment.[19]

EXPERIMENTAL

Spectra were determined by means of a Perkin-Elmer 21 double-beam recording spectrometer fitted with a rock-salt prism. Results for the 4000—3000 cm.$^{-1}$ region were determined, where possible, for 10^{-2}M-solutions. For the lower frequencies, 10^{-2}M-solutions were subjected to three-fold dilution.

Oxindole and 5-methyloxindole were prepared by the Stollé synthesis from ω-chloroacetanilide and ω-chloroaceto-*p*-toluidide respectively.[20] An attempt to make 5-methoxyoxindole by this method at the standard temperature (225°) gave *p*-chloroacetamidophenol, but this was converted [21] into 5-hydroxyoxindole in poor yield by aluminium chloride at 240°. *p*-Chloro-ω-chloroacetanilide was unchanged by aluminium chloride at 225°, but at 250° gave 5-chloro-oxindole [22] in poor yield. 5-Nitro- and 5-bromo-oxindole were prepared by direct nitration [23] and bromination [24] respectively. Treatment of isatin and *N*-methylisatin with phosphorus pentachloride gave 3 : 3-dichloro- and 3 : 3-dichloro-1-methyl-oxindole respectively.[25]

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[19] Hartwell, Richards, and Thompson, *J.*, 1948, 1436; Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; Djerassi and Scholz, *ibid.*, 1948, **70**, 1911; Jones, Humphries, and Dobriner, *ibid.*, 1950, **72**, 956; Jones, Ramsey, Keir, and Dobriner, *ibid.*, 1952, **74**, 80; Jones, Ramsey, Herling, and Dobriner, *ibid.*, p. 2828.

[20] Stollé, *J. prakt. Chem.*, 1930, **128**, 1; Giovannini and Portmann, *Helv. Chim. Acta*, 1948, **31**, 1381.

[21] Beer, Davenport, and Robertson, *J.*, 1953, 1263.

[22] Wahl and Féricéan, *Compt. rend.*, 1928, **186**, 379.

[23] Sumpter, Miller, and Magan, *J. Amer. Chem. Soc.*, 1945, **67**, 499.

[24] Sumpter, Miller, and Hendricks, *ibid.*, p. 1656.

[25] Hantzsch, *Ber.*, 1921, **54**, 1254.