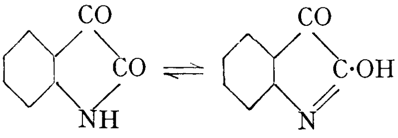
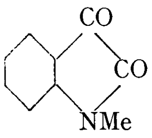
395. *Absorption Spectra in Relation to the Constitution of Derivatives of Isatin and Carbostyril.*

By R. G. AULT, E. L. HIRST, and R. A. MORTON.

CONSIDERABLE importance has been attached to isatin (I) and its *N*- and *O*-methyl derivatives (II and III) as typical examples of the application of absorption-spectrum measurements to structural determination. It is unfortunate, therefore, that uncertainty has arisen concerning the absorption spectrum of the *O*-ether. Hartley and Dobbie (J., 1889, **55**, 640) in their original investigation reported that in alcoholic solution the absorption spectrum of the *O*-ether differed very markedly from those of isatin and its *N*-ether, which were closely similar, and they concluded that isatin had the same structure (lactam) as the *N*-ether. Reinvestigations by Hantzsch (*Ber.*, 1921, **54**, 1221) and by Morton and Rogers (J., 1925, **127**, 2698), who took special precautions in view of the known instability of the *O*-ether, revealed that all three substances possessed similar absorption spectra, and these authors disagreed with the previous workers concerning the absorption spectrum of the *O*-ether. On the other hand, Dabrowski and Marchlewski (*Bull. Soc. chim.*, 1933, **53**, 946) confirm the earliest results and regard Morton and Rogers's results for the *O*-ether as erroneous.


(I.)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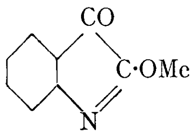

(III).

It was desirable to clear up these discrepancies, and the present work was carried out simultaneously at Birmingham and at Liverpool. Specimens of the *N*- and the *O*-ether, prepared in both laboratories, have been interchanged, and independent series of observations on both sets of materials have been carried out with identical results. There can be no doubt from the chemical properties that the ether of m. p. 102°, used by Hartley and Dobbie (*loc. cit.*), by Morton and Rogers (*loc. cit.*), and in the present experiments, was in fact the true *O*-ether. It is somewhat unstable, particularly in the presence of moisture, but we find that when measurements are made with reasonable speed, its true absorption spectrum is obtainable, even in aqueous alcohol. This spectrum, as stated by Morton and Rogers, closely resembles those of isatin and the *N*-ether (Fig. 1). In any case, all difficulties arising from the presence of moisture in the solvent have been removed by taking advantage of the fact that pure *cyclo*hexane dissolves the *N*- and the *O*-ether sufficiently freely to permit of spectroscopic examination; the absorption spectra of the two solutions are closely alike and show clearly that the general resemblance of the curves for the alcoholic solutions is characteristic of the substances themselves. In *cyclo*hexane, marked resolution of the bands is seen, the effect being most prominent in the case of the middle band of the *O*-ether (Fig. 3). Isatin could not be examined under these conditions.

Hartley and Dobbie's and Dabrowski and Marchlewski's data cannot therefore refer to the *O*-ether, and the discrepancies have arisen because in their experiments the ether had decomposed before the measurements were completed. In confirmation of this explanation, we find that when an aqueous-alcoholic solution of the *O*-ether is kept, the absorption spectrum, which at first resembles that of the *N*-methyl ether, changes its character and is now of the type recorded by those workers and ascribed by them to the *O*-ether. In its main characteristics this spectrum closely resembles that of sodium aminobenzoylformate (see Fig. 2). The solution containing the decomposition products deposits pure isatin on evaporation. The nature of the change in the absorption excludes the formation of isatin as the result of the decomposition in the solution and supports the view that the *O*-ether changes into aminobenzoylformic ester (or acid) which regenerates isatin on evaporation to dryness. We have not encountered "methylisatoid" (Hantzsch, *Ber.*, 1922, **55**, 3180) during the decomposition of the *O*-ether in aqueous alcohol, but on the other hand, when the solid *O*-ether is boiled in benzene, and also when it decomposes slowly in the air, one of the products is "methylisatoid" (absorption band at λ 460 mμ), the identity of which as a bimolecular derivative has been confirmed by *X*-ray methods.

TABLE I.

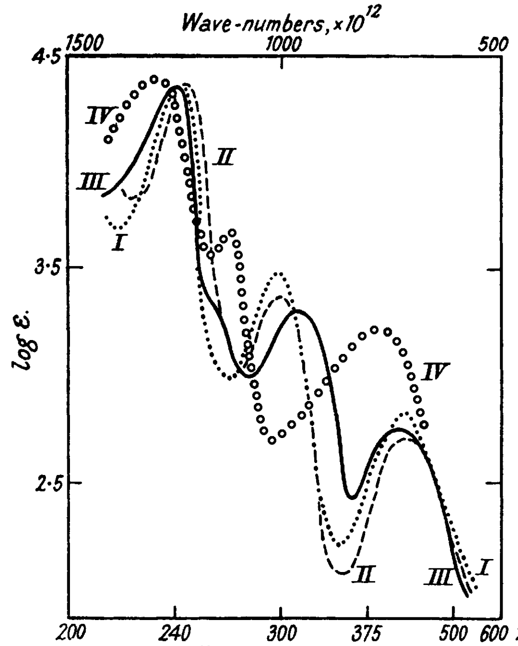
Absorption Spectra in Alcoholic Solution.

	$\lambda_{max.}$	log ε.	$\lambda_{max.}$	log ε.	$\lambda_{max.}$	log ε.
Isatin	413	2·8	296	3·5	243	4·4
N-Methylisatin	420	2·70	293	3·37	245	4·35
O-Methylisatin	415	2·76	310	3·35	240	4·35

Detailed comparisons of the absorption spectra of isatin and the two ethers reveal that the three curves, although similar, are not identical. Isatin shows a closer similarity to its *N*-methyl ether, particularly in the middle region of absorption, than to its *O*-methyl ether (Table I; Fig. 1). This result, so far as it goes, is in agreement with the structural views put forward by Hartley and Dobbie, but all three spectra are so much alike in their general characteristics that no certainty can be attached to conclusions based on this evidence alone. In this instance the structure can be allocated with greater precision by *X*-ray methods, which will be reported by Mr. E. G. Cox. It was of interest to find that a solution of isatin in aqueous alkali undergoes a very rapid change. The purple solution first obtained rapidly gives place to a yellow solution which has an entirely different absorption spectrum (see Fig. 2). The change corresponds to the known chemical transformation by which the ring is opened with formation of sodium *o*-aminobenzoylformate. On the other hand, with sodium ethoxide the purple colour is more stable, and the spectrum now resembles that of isatin, the change in colour being due to a displacement of the 414 mμ

FIG. 1.

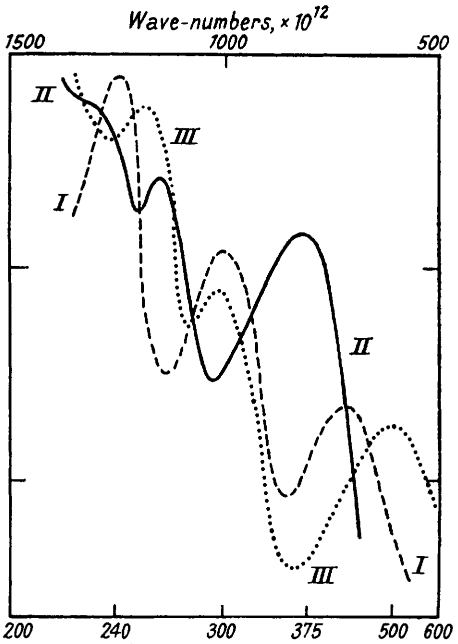
Alcoholic solutions.



I. *Isatin*; II. N-*methylisatin*; III. O-*methylisatin*; IV. O-*methylisatin in aqueous alcohol after completion of transformation.*

FIG. 2.

Isatin.



I. *in water*; II. *in* 5 *per cent.* NaOH; III. *in* NaOEt (2 *equivs.*).

band to about 500 mμ. Such an effect is common in the action of sodium ethoxide on diketonic substances capable of forming chelated enolic metallic derivatives.

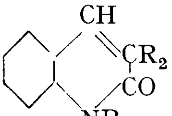
The *N*-ether of isatin is readily obtainable, but difficulty was experienced at first in the preparation of the *O*-ether. When the silver derivative of isatin prepared by Baeyer's method (*Ber.*, 1882, **15**, 2093) was allowed to react with methyl iodide, it almost invariably gave rise to the *N*-ether in place of the expected *O*-derivative, but almost theoretical yields of the latter were consistently obtained when the silver salt prepared by Hantzsch's method (*Ber.*, 1921, **54**, 1221) was similarly treated. Conclusive differentiation between the two ethers is afforded by Zeisel's method for estimating methoxyl groups : the *N*-ether under ordinary conditions gives no methyl iodide, whereas the *O*-ether readily gives the theoretical amount for one methoxyl group.

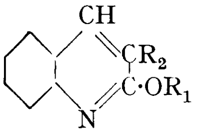
We examined the possibility of preparing these derivatives by the action of diazomethane on isatin. The method is inapplicable, however, and we have confirmed the observations of earlier workers (Heller, *Ber.*, 1919, **52**, 741; Arndt, Eistert, and Ender, *ibid.*, 1929, **62**, 48) that hydroxyquinoline derivatives are the main products. The two crystalline substances obtained, (A), m. p. 260°, and (B), m. p. 191°, are referred to in the literature as 2 : 3-dihydroxyquinoline and its 3-methyl ether, although evidence as to the position of the methyl group is lacking. In view of what follows it is probable that they are respectively 3-hydroxy- and 3-methoxy-quinolone. We now find that (B) is obtainable by direct methylation of (A), and the methyl group must occupy position 3, since (B) is not identical with 3-hydroxy-2-methoxyquinoline (see below). Both (A) and (B) are transformed into *o*-toluidine by distillation with solid sodium hydroxide, confirmation of their ring structure being thereby provided. We have investigated also the action of diazomethane on *N*- and on *O*-methylisatin. In the former case the product is 3-*methoxy*-1-*methyl*-2-*quinolone*, m. p. 142° (IV; $R_1 = CH_3$, $R_2 = OMe$), the constitution of which follows from its mode of preparation and from the fact that it contains one methoxyl group. The *O*-ether similarly gives rise to 3-*hydroxy*-2-*methoxyquinoline*, m. p. 83—84° (V; $R_1 = Me$, $R_2 = OH$). When first isolated this was a syrup with properties similar to those recorded by La Coste and Valeur (*Ber.*, 1887, **20**, 1823) for a substance they had prepared by methylating dihydroxyquinoline. We have now obtained it in the crystalline condition and compared its absorption spectrum with those of other derivatives of carbostyril.

TABLE II.

Substance.	$\lambda_{max.}$	$\epsilon_{max.}$	$\lambda_{max.}$	$\epsilon_{max.}$
*1-Methylquinolone	270·5	6,600	328	6,000
†3-Methoxy-1-methylquinolone	273	6,000	320	9,000
*Carbostyril (quinolone)	269	7,000	327	6,750
†Substance A (3-hydroxyquinolone)	272	6,300	320	12,000
†Substance B (3-methoxyquinolone)	270	7,000	319	11,000
**O*-Methylcarbostyril (2-methoxyquinoline)	308·5	3,700	322	4,500
**O*-Ethylcarbostyril (2-ethoxyquinoline)	308·5	3,700	322·6	4,500
†3-Hydroxy-2-methoxyquinoline	308·5	3,500	322	4,400

* Morton and Rogers, *loc. cit.* † Present work.


(IV.)


(V.)

The main features of the absorption spectra have been collected in Table II, from which it is apparent that the spectra fall sharply into two groups. In the first are those of carbostyril (quinolone) and its 1-methyl- and 3-methoxy-1-methyl-derivatives, together with those of (A) and (B); these are all closely similar, but differ markedly from those of *O*-methyl- and *O*-ethyl-carbostyril and 3-hydroxy-2-methoxyquinoline. Those in the second group are almost identical, and strong evidence is provided of the accuracy of the constitution assigned to the last compound. From the chemical evidence, (A) must be either 2 : 3-dihydroxyquinoline or 3-hydroxyquinolone, and in view of its absorption spectrum it now appears highly probable that it exists in alcoholic solution in the latter form; (B) may therefore be regarded as 3-methoxyquinolone. In this group, the absorption curves of the authentic lactam and lactim derivatives are strongly divergent, and it is possible by the use of absorption spectra to distinguish between hydroxyquinoline and quinolone derivatives.

EXPERIMENTAL.

N-*Methyl Ether of Isatin.*—Prepared by the method of Hartley and Dobbie (*loc. cit.*), this formed long, red needles (a), m. p. 131—132°, from water (Found : C, 67·3; H, 4·4; OMe, nil. Calc. for $C_9H_7O_2N$: C, 67·1; H, 4·4%). After slow recrystallisation from benzene–ether, the substance was obtained as red plates, m. p. 131° (Found : C, 67·2; H, 4·6%; OMe, nil). The absorption spectra of the two varieties were identical. Yet a third form [red needles different from (a), m. p. 131°; no depression of m. p. on admixture with either of the other forms] was obtained on several occasions when attempts were made to prepare the *O*-ether by Baeyer's method (*loc. cit.*). Separation from the other variety of needles could be effected only by hand picking under the microscope.

The absorption spectrum of *N*-methylisatin in alcoholic solution was identical with that recorded by previous investigators. In *cyclo*hexane resolution of the principal bands was observed. The main features are given in the accompanying table and in Fig. 3.

$\lambda_{max.}$, mμ ...	243	247	253	274*	283*	294	305*	413	445*	460*
log ε	4·42	4·45	4·42	3·1	3·2	3·3	3·13	2·87	2·70	2·55

* Inflexion.

O-*Methyl Ether of Isatin.*—This was prepared by Hantzsch's method (*loc. cit.*), and formed clusters of blood-red prisms from benzene, m. p. 102° (Found : C, 67·0; H, 4·3; OMe, 18·7. Calc. for $C_9H_7O_2N$: C, 67·1; H, 4·4; OMe, 19·2%). The main features of the absorption spectrum in alcoholic solution are given on p. 1654. Resolution of the bands occurred in *cyclo*hexane solution (Fig. 3) :

$\lambda_{max.}$, mμ	241	247	298*	307	318	332	415
log ε	4·5	4·5	3·3	3·45	3·45	3·22	2·9

* Inflexion.

The absorption spectrum in aqueous alcohol (10% water) is shown in Fig. 1 together with that of the same solution after 2 days. No further change was observed when the solution was kept for long periods, and on evaporation to dryness the solution gave pure isatin, recognised by m. p. and mixed m. p. (201°), crystallographic data, and *X*-ray analysis. When *O*-methylisatin was kept for some days in moist air or for a short time in air containing a trace of acid vapour, a yellow powder was obtained. On recrystallisation this gave a yellow solid, m. p. 236° (decomp.), possessing the properties of "methylisatoid." The *M.W.* (306) determined by *X*-ray methods confirmed the bimolecular formula. The same compound (identity confirmed by crystallographic and *X*-ray examination) was produced by decomposition in hot benzene solution.

Hydroxyquinoline Derivatives from Isatin.—The following is a simplified method for the preparation of 3-hydroxyquinolone and its 3-methyl ether. Isatin (2·0 g.) in dry acetone (500 c.c.) was kept at 0° for 12 hours with a slight excess of diazomethane. The solution was concentrated at 30°, giving a crystalline mass. Extraction with alcohol left 3-hydroxyquinolone (A), which crystallised from a large volume of boiling alcohol as colourless needles, m. p. 260°, subliming when heated (Found : C, 67·0; H, 4·6; N, 8·6; OMe, nil. Calc. for $C_9H_7O_2N$: C, 67·1; H, 4·4; N, 8·7%). The substance gave a purple colour with ferric chloride and yielded *o*-toluidine (identified as acetyl derivative, m. p. 110°) on fusion with solid sodium hydroxide.

The alcoholic extract gave on evaporation 3-methoxyquinolone (B), light yellow needles, m. p. 191°, from ether–ethyl alcohol (Found : C, 68·6; H, 5·4; N, 8·1; OMe, 18·0. Calc. for $C_{10}H_9O_2N$: C, 68·6; H, 5·2; N, 8·0; OMe, 17·7%). It sublimed readily when heated, and gave *o*-toluidine (identified as before) when fused as above. The same methyl ether, m. p. 191°, was obtained when a methyl-alcoholic solution of 3-hydroxyquinolone was treated with an excess of diazomethane for 24 hours at 0°. (Prolonged treatment gave no trace of dimethoxyquinoline.) When freshly prepared, the substance gives no colour with ferric chloride solution, but after being kept for several months in a desiccator it undergoes partial decomposition, as shown by a fall in m. p. (191° ⟶ 170°) and by the formation of a greenish colour with ferric chloride solution.

When *N*-methylisatin (1·0 g.) in anhydrous ether (50 c.c.) containing about 5 c.c. of methyl alcohol was treated with a slight excess of diazomethane at 0°, effervescence occurred and the red solution became yellow. After 24 hours at 0°, the solvent was removed at 30°, and the solid product was recrystallised from methyl alcohol–ether, giving 3-*methoxy*-1-*methylquinolone* as light blue needles, m. p. 142° (Found: C, 69·95; H, 5·9; N, 7·6; OMe, 14·7. $C_{11}H_{11}O_2N$ requires C, 69·85; H, 5·9; N, 7·4; OMe, 16·4%). This substance gave a reddish-brown coloration with ferric chloride solution and could be distilled at atmospheric pressure without decomposition. After distillation, the crystals were colourless but were otherwise identical with the original substance (m. p. and mixed m. p. 142°; ultra-violet absorption spectra; crystallographic, *X*-ray, and analytical data). The blue colour could not be removed or diminished in intensity by repeated crystallisation from alcohol–ether. Concentrated alcoholic solutions were red. The colour, the origin of which is not understood, disappeared on acidification of an aqueous solution with hydrochloric acid. 3-Methoxy-1-methylquinolone was recovered unchanged, m. p. 142°, after fusion with sodium hydroxide. No hydrolysis of the methoxyl group took place during 10 hours' boiling with 6% aqueous hydrochloric acid, nor was the substance in any way affected. The methoxyl group was readily demethylated by hydriodic acid.

FIG. 3.

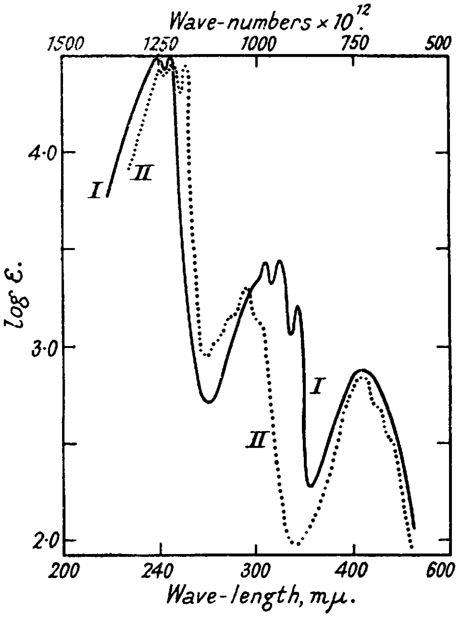


FIG. 4.

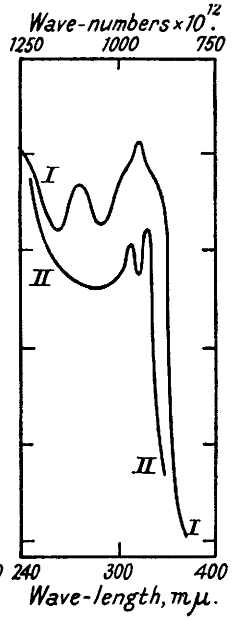


FIG. 3.—I. O-*Methylisatin in* cyclo*hexane*; II. N-*methylisatin in* cyclo*hexane*.

FIG. 4.—I. 3-*Methoxy*-1-*methylquinolone in alcohol* (*curves for* 3-*methoxyquinolone and* 3-*hydroxyquinolone are almost identical with the above*); II. 3-*hydroxy*-2-*methoxyquinoline in alcohol.*

The absorption spectra in ethyl alcohol of 3-hydroxy-, 3-methoxy-, and 3-methoxy-1-methylquinolone were almost identical (see Fig. 4).

Treatment of *O*-methylisatin (m. p. 102°) with a slight excess of diazomethane in ethereal solution gave a viscid yellow oil, which darkened on exposure to the atmosphere. When kept, it slowly crystallised, but after distillation (b. p. 115°/0·02 mm.) it solidified rapidly. After recrystallisation from ether–light petroleum, 3-*hydroxy*-2-*methoxyquinoline* was obtained as clusters of colourless needles, m. p. 83—84° (Found: C, 68·8; H, 5·1; N, 7·9; OMe, 16·5. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·2; N, 8·0; OMe, 17·7%), soluble in alcohol, ether, ethyl acetate, dioxan, and benzene; insoluble in cold water and in light petroleum. In hot water it gave a dark brown colour with ferric chloride. The absorption spectrum is shown in Fig. 4.

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