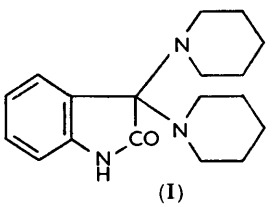
691. *The Structure of Isatin Blue.*

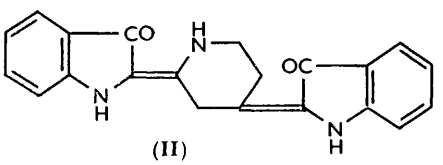
By A. W. Johnson and D. J. McCaldin.

New structures are suggested for isatin blue and the related compounds derived by condensation of isatin with either cyclic secondary bases or cyclic α-imino-carboxylic acids.

Proline [1] and several related compounds [2,3] are frequently characterised by the deep blue colours they give with solutions of isatin. The product from the reaction of proline and isatin can be isolated as deep blue crystals, and is identical with the condensation product from pyrrolidine and isatin in hot acetic anhydride; [4,5] likewise pipecolic acid in aqueous solution, and piperidine in acetic anhydride, both condense with isatin to give the so-called isatin blue which is closely related to the isatin–proline product. Isatin blue is noteworthy for the variety of structural formulæ, all of which are now shown to be incorrect, proposed for it since its discovery in 1891 by Schotten.[6] He prepared the compound by heating 3 : 3-dipiperidino-oxindole (I) ("isatin dipiperidide"; the position of the piperidino-groups was not known at that time) either alone or, better, with acetic anhydride, and he showed that 1·5 mols. of piperidine were eliminated from each mol. of the dipiperidide during the reaction. The correct molecular formula, $C_{21}H_{17}O_2N_3$, was thereby deduced for isatin blue which is thus derived from two mols. of isatin and one of piperidine; but Schotten was unable to suggest a structural formula for the compound.



(I)



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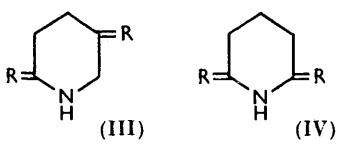

(III) (IV)

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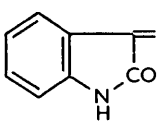
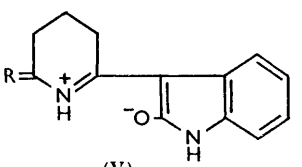




(V)

Isatin blue was next studied by Liebermann and Krauss [7] who showed that it formed a red hydrochloride and that related compounds could be obtained from piperidine and bromo- or chloro-isatin, but not from *N*-substituted piperidines and isatin. On this additional evidence and no doubt influenced by the structure of indigo, they proposed 2 : 4-di-(2-indoxylylidene)piperidine (II) as the structure of isatin blue. Apart from the lack of a convincing mechanism of formation, formula (II) is untenable for several reasons : it does not account for the blue colour; pyrrolidine and morpholine, known to give blue condensation products with isatin, contain no carbon atom equivalent to the 4-C of piperidine; and neither isatin 3-oxime nor 3 : 3-ditolyloxindole condenses with piperidine to give isatin blue.[4] In 1924, Heller [8] reconsidered the earlier work and rejected structure

[1] Acher, Fromageot, and Jutisz, *Biochim. Biophys. Acta*, 1950, **5**, 81.
[2] Zacharius, Thompson, and Steward, *J. Amer. Chem. Soc.*, 1952, **74**, 2949.
[3] Hulme *et al.*, *Nature*, 1952, **170**, 659; 1954, **173**, 588; **174**, 1055.
[4] Grassmann and Arnim, *Annalen*, 1934, **509**, 288.
[5] *Idem, ibid.*, 1935, **519**, 192.
[6] Schotten, *Ber.*, 1891, **24**, 1366, 2604.
[7] Liebermann and Krauss, *ibid.*, 1907, **40**, 2492; see also Liebermann and Häse, *ibid.*, 1905, **38**, 2847.
[8] Heller, *Z. angew. Chem.*, 1924, **37**, 1017; *Chem. Ztg.*, 1930, **54**, 985; 1933, **57**, 74.

(II) in favour of 2 : 5-di-(3-oxindolylylidene)piperidine (III) which is quoted in certain recent reviews of isatin chemistry ; [9] but, like (II), structure (III) contains no chromophoric system capable of accounting for the intense colour of isatin blue and consequently also must be discounted. The most extensive work on these pyrrolidine and piperidine colouring matters is that of Grassmann and Arnim [4, 5] who confirmed the earlier observation that the compounds could not be formed from the *N*-substituted bases and concluded that the pigments were best represented by structures of type (IV).

We were attracted to the problem because the formation of (IV) from (I) would involve a double condensation or rearrangement involving the α-carbon atoms of piperidine, and such condensations are of very limited occurrence.[10] The analogy drawn by the German authors [5] with migrations from nitrogen to carbon in the pyrrole series is clearly invalid. Structure (IV) may be regarded also as the zwitterion (V) which contains an extended conjugated system consistent with the absorption in the visible spectrum. In considering this possibility we showed that analogues (spectra : Table 1) of isatin blue could be produced from a variety of bases including 4-hydroxyproline,[4] morpholine, 2- and 3-methylpiperidine, and *cis*-octahydroindole. The formation of coloured products from 2-substituted piperidines and *cis*-octahydroindole was incompatible with structures (IV) and (V), and in addition the infrared spectrum of the blue product derived from *N*-methylisatin and pyrrolidine showed no bands between 3450 and 2300 cm.$^{-1}$ corresponding to $\rangle$NH or $\rangle\overset{+}{\text{N}}$H.[11] On this evidence, coupled with the observation that the *N*-substituted bases do not give coloured compounds with isatin, it appears that the nitrogen atom of the base is attached directly to one of the isatin fragments in isatin blue, and consequently structures (III), (IV), and (V) must be rejected.

Examination of the spectra of isatin blue and its analogues (Table 1*a*) shows that substitution of pyrrolidine for piperidine rings causes a lowering of the position of the long-wavelength band probably because of steric effects and the introduction of an extra band(s) at *ca.* 330 mμ. Several features of the spectra suggest that substitution at the 3-position of the bases has a more pronounced effect than the corresponding substitution at position 2, *e.g.*, the band at 260 mμ disappears altogether in the spectra of the coloured products derived from 3-methylpiperidine (contrast the 2-methyl isomer), and the introduction of the cyclic oxygen atom (a $C_{(3)}$-substituent) in morpholine has a pronounced hypsochromic effect on the spectrum of the derived pigment. Furthermore the blue compound from 2-methylpiperidine and isatin was obtained without difficulty in high yield (78%), whereas the corresponding product from 3-methylpiperidine could be obtained only in very poor yield (3·5%). These observations, which suggest that it is the 3-positions of the cyclic bases which are involved in the condensation reactions, have led us to propose a resonance hybrid of structures (VI) and (VII) for isatin blue.

The dipiperidide (I) is the first intermediate in the reaction between isatin and piperidine and it can be isolated and converted into isatin blue as observed by Schotten.[6] The experimental conditions are such as to cause the loss of piperidine from this intermediate, to yield the cation (VIII). Activation of the 3-position of the piperidine ring is caused by the electronic shifts shown which give rise to a potential double bond between the nitrogen and $C_{(2)}$ of the piperidine ring. Condensation of the ion (VIII) with a second molecule of the intermediate (I) then gives the hybrid (VI–VII) with elimination of two further molecules of piperidine. The existence of at least one intermediate between (I) and (VI) is substantiated by the formation of transitory green colours during the reaction. Oxidation of isatin blue under various conditions has given isatin, anthranilic acid, and picric acid, but no significant products corresponding to the original base have been isolated.

[9] Sumpter, *Chem. Rev.*, 1944, **34**, 425; "The Chemistry of Heterocyclic Compounds. Indole and Carbazole Systems," Interscience Publ. Inc., 1954, p. 132; Elderfield, "Heterocyclic Compounds," Wiley, 1952, Vol. III, p. 230.

[10] Cf. Huisgen and Rist, *Annalen*, 1955, **594**, 161; Wittig and Ludwig. *ibid.*, 1954, **589**, 58.

[11] Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5597.

Pyrolysis of the colouring matter from isatin and pyrrolidine has yielded oxindole. This degradation, which recalls both the Hofmann degradation and the Wolff–Kishner reduction, provides further evidence in support of a chromophore containing an *N*-substituted piperidine as in (VII).

TABLE 1. *Spectra of isatin blue and related compounds.*

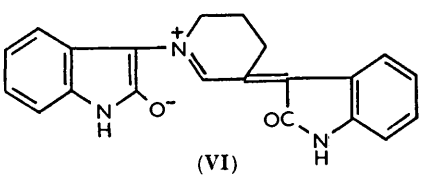
(a) *In* NN-*dimethylformamide.*

Pigment	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε
Piperidine–isatin (or pipecolic acid–isatin)	260	4·09	295	4·12		—	472	3·74	635	4·60
2-Methylpiperidine–isatin ...	260	4·05	294	4·15		—	476	3·71	635	4·57
Morpholine–isatin	261	4·03	287	4·16		—	458	3·87	600	4·64
3-Methylpiperidine–isatin ...		—	294	4·11		—	473	3·74	635	4·63
Pipecolic acid–acenaphthenequinone		—	290	4·22		—	405 489	3·69 3·77	650	4·64
Pyrrolidine–isatin (or proline–isatin)	263	3·99	283	3·96	325	3·79	440	3·77	596	4·68
Octahydroindole–isatin		—	287	3·96	327 340	3·70 3·68	452	3·77	615	4·63
β-Hydroxyproline–isatin [5]	260	3·95	285	3·93	330	3·65	455	3·72	610	4·55
Pyrrolidine–*N*-methylisatin	261	4·00		—	325 338	3·73 3·73	459	3·87	592	4·69
Proline–acenaphthenequinone [5]		—	299	4·14		—	385 490	3·63 3·62	615	4·53
*iso*Indoline–isatin	260	4·20		—	337	3·85	423 445 534	3·90 3·90 4·20	660 830	3·90 3·44

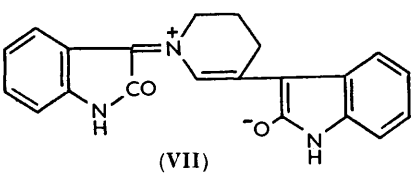
(b) *In* 5N-*hydrochloric acid.*

Piperidine–isatin	207	4·56	263	4·36	371	4·28	488	3·41		
2-Methylpiperidine–isatin	211	4·51	260	4·31	370	4·28	500	3·38		
Morpholine–isatin	209	4·49	262 298	4·29 3·90	412	4·13	510	3·00		
3-Methylpiperidine–isatin	210	4·45	263	4·26	385	4·26	496	3·34		
Pipecolic acid–acenaphthenequinone (in 11N-HCl)	219 238	4·88 4·66	331	4·56		—	477	3·76		
Pyrrolidine–isatin	211	4·51	262	4·28	382	4·28	484	3·46		
Octahydroindole–isatin	211	4·51	261	4·21	384	4·21	498	3·42		
Pyrrolidine–*N*-methylisatin	210	4·57	270	4·25	380	4·28	482 495	3·22 3·23		

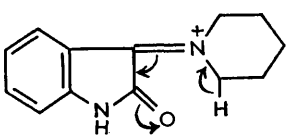
Some of the observations of Grassmann and Arnim[4,5] are not in accord with a general structure of type (VI) (or VII) for the isatin blue series and, in particular, certain cyclic bases containing both β- and β′-substituents were claimed to give coloured products related



(VI)



(VII)



(VIII)

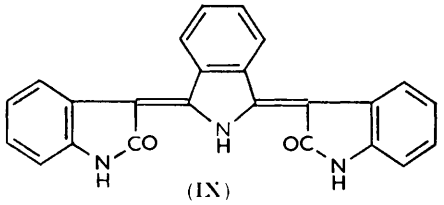
to isatin blue. These included 4-ethyl-3-methylpyrrolidine (prepared by hydrogenation of opsopyrrole; no details given), but as no pure product was isolated from the condensation no great emphasis can be placed on the observation, especially as isatin is known to give other series of coloured products with heterocyclic bases.[12] *iso*Indoline condensed with

[12] Grassmann and Arnim, *Annalen*, 1936, **522**, 66.

isatin to give a coloured product, which was claimed [5] to have the structure (IX) by analogy with isatin blue. This preparation has been repeated and the product, obtained in poor yield, shown to have properties quite different from those of isatin blue, especially the absorption spectrum (Table 1) and the blue solution given in concentrated sulphuric acid (isatin blue gives a red solution which changes to blue after neutralisation). The true nature of the product has not been determined but as it does not belong to the isatin blue series, it no longer presents an anomaly.

Reference should also be made to bases which might have been expected to yield coloured condensation products of the isatin blue type with isatin but in fact did not. These included 2 : 6-dimethylpiperidine and *trans*-decahydroquinoline (neither of which gave a 3 : 3-diamino-oxindole derivative probably for steric reasons), and various partly reduced pyridines, *e.g.*, tetrahydroquinoline and indoline which gave substituted 3 : 3-diamino-oxindoles that were stable to heat, tetrahydro*iso*quinoline which gave a coloured product,[5] not in the isatin blue series, and baikiain,[13] 1 : 2 : 3 : 6-tetrahydropicolinic acid, which gave no recognisable product.

In the ready reaction of proline and other cyclic α-imino-acids with isatin, the decarboxylation is visualised as occurring with the intermediate (X) which is a " vinylogue " of a β-keto-acid and thus readily loses carbon dioxide.



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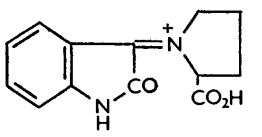
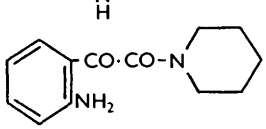


(X)



(XI)

In the course of the work, a variety of 3 : 3-diamino-oxindoles (*e.g.*, I) (spectra : Table 2) were prepared from isatins and cyclic secondary amines, preferably by an azeotropic distillation method [14] or alternatively from the isatin β-anils. We have shown that the equimolecular condensation products from isatin and amines are isatamides (*e.g.*, XI) (spectra : Table 3) and are not concerned in the formation of the isatin blue colouring matters, in agreement with the suggestions of earlier workers.[6, 7]

TABLE 2. *Spectra of the substituted* 3 : 3-*diamino-oxindoles* (e.g., I) (*isatin* + 2 *mols. of base*) *in methanolic solution.*

Base	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε
Piperidine	209	4·15	250	3·82	292	3·28
Morpholine	209	4·43	252	3·78	292	3·23
Tetrahydroquinoline	211	4·90	261	4·38	—	
Tetrahydro*iso*quinoline	207	4·65	254	4·02	289	3·49
Pyrrolidine	211	4·39	{ 244 { 248	{ 4·30 { 4·31	298	3·56
Indoline	208	4·74	263	4·44	—	

It seems probable that cyclic secondary amines and the corresponding α-carboxylic acids will condense with a variety of cyclic α-diketones and *o*-quinones to give coloured products related to isatin blue. We have confirmed the observation by Grassmann and Arnim [5] that a crystalline coloured product can be obtained from acenaphthenequinone and proline and unlike the German workers we have been able to obtain the analogous

[13] King, King, and Warwick, *J.*, 1950, 3590.
[14] Herr and Heyl, *J. Amer. Chem. Soc.*, 1953, **75**, 1918.

compound from pipecolic acid. The similar reactions with ninhydrin have an obvious bearing on the blue colours derived from α-amino-acids and are under investigation.

TABLE 3. *Spectra of substituted isatamides* (e.g., XI) (*isatin* + 1 *mol. of base*) *in methanolic solution.*

	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε	λ (mμ)	log ε
5-Bromoisatin–piperidine	203	4·32	239	4·40	264	3·89	392	3·82
5-Bromoisatin–morpholine	—		231	4·39	264	3·87	395	3·80
5-Bromoisatin–hexamethyleneimine	—		230	4·38	264	3·88	393	3·80
N-*Acetyl derivatives* :								
Isatin–piperidine	202	4·30	235	4·44	267	4·04	339	3·76
Isatin–morpholine	201	4·41	239	4·53	266	3·76	352	3·70
5-Bromoisatin–piperidine	—		240	4·45	266	4·03	355	3·64
5-Bromoisatin–morpholine	—		240	4·48	266	4·04	355	3·63
5-Bromoisatin–hexamethyleneimine	—		240	4·48	265	4·07	353	3·70

EXPERIMENTAL

Preparation of 3 : 3-*Diamino-oxindoles.*—3 : 3-*Dipiperidino-oxindole.* (*a*) Isatin and piperidine were caused to react in warm alcoholic solution (method A) or under anhydrous conditions (method B; Herr and Heyl [14]). Isatin (10 g.) was suspended in dry benzene (250 c.c.) and heated under reflux in a Dean and Stark apparatus until all water had been removed. Dry piperidine (22 g.) was then added and the heating continued for 10 min., a further 0·9 c.c. of water (theor. for 1 mol., 1·2 c.c.) being collected. On cooling, the product crystallised as colourless plates, and was separated, washed with benzene and ethanol, and dried (9·3 g., 45%) (Found : C, 71·7; H, 8·25. Calc. for $C_{18}H_{25}ON_3$: C, 72·2; H, 8·4%). Above 100°, the product was converted into isatin blue.

(*b*) (Method C) : Isatin β-*p*-nitroanil [15] (500 mg.) and piperidine (1·5 c.c.) were shaken in ethanol (5 c.c.) and xylene (45 c.c.) at room temperature for 3 hr. The ethanol was removed under reduced pressure and the remaining solution cooled; the product crystallised and was separated as before (350 mg., 64%).

3 : 3-*Dipyrrolidino-oxindole.* This was best prepared by method C from isatin β-anil (1 g.) and pyrrolidine (5 g.) in methanol (2 c.c.) and xylene (48 c.c.). The colourless crystalline *product* (985 mg., 82%) so obtained liberated pyrrolidine and became bright blue at about 100° (Found : C, 70·6; H, 7·6; N, 15·3. $C_{16}H_{21}ON_3$ requires C, 70·8; H, 7·8; N, 15·5%).

3 : 3-*Dimorpholino-oxindole.* Prepared by method C from isatin β-anil (500 mg.) and morpholine (1·5 c.c.) as above, the colourless *product* (400 mg., 61%) was washed, dried, and crystallised from methanol and was rather more stable than the piperidino- or pyrrolidino-analogues (Found : C, 63·1; H, 7·0; N, 13·4. $C_{16}H_{21}O_3N_3$ requires C, 63·35; H, 7·0; N, 13·8%). Above 120° the product decomposed with formation of the corresponding blue product.

3 : 3-*Di*-(1 : 2 : 3 : 4-*tetrahydro*-1-*quinolinyl*)*oxindole.* Prepared by method A, the *product* (44%) formed colourless prisms, m. p. 296—298°, on crystallisation from methanol (Found : C, 78·6; H, 6·3; N, 10·5. $C_{26}H_{25}ON_3$ requires C, 78·95; H, 6·4; N, 10·6%).

3 : 3-*Di*-(1 : 2 : 3 : 4-*tetrahydro*-2-iso*quinolinyl*)*oxindole.* Prepared by method A, the *product* (19%) formed colourless prisms (from ethanol) which darkened above 200° and had m. p. 268—270° (decomp.) (Found : N, 10·5. $C_{26}H_{25}ON_3$ requires N, 10·6%). Solutions in hot methanol were purple but became colourless on cooling.

3 : 3-*Di-indolino-oxindole.* Prepared from isatin (0·5 g.) and indoline [16] (1·1 g.) by method A, the *product* (0·2 g.) formed colourless prisms, m. p. 204—206° (from methanol) (Found : N, 11·2. $C_{24}H_{21}ON_3$ requires N, 11·4%).

Isatin Blue.—(i) *From* 3 : 3-*dipiperidino-oxindole.* The product was prepared according to Schotten [6] by the action of acetic anhydride on 3 : 3-dipiperidino-oxindole at 60°. The reaction mixture was cooled, and the isatin blue separated and then crystallised slowly from methanol by a hot-extraction method (48 hr. for 500 mg.). The product was thus obtained as blue prisms with a green metallic sheen which had m. p. 230° (decomp.) (Found : C, 73·4; H, 5·05; N, 12·1. Calc. for $C_{21}H_{17}O_2N_3$: C, 73·45; H, 5·0; N, 12·2%).

[15] Angyal, Bullock, Hanger, Howell, and Johnson, *J.*, 1957, 1592.
[16] King, Barltrop, and Walley, *J.*, 1945, 277.

(ii) *From* L-*pipecolic acid.* The acid (150 mg.) and isatin (300 mg.) were heated in ethanol (15 c.c.) under reflux for 30 min. The green mixture was cooled and the crystalline product (80 mg., 23%) separated and was washed with ethanol and ether. It crystallised from hot methanol as before (Found : C, 73·2; H, 4·8; N, 12·2%).

An attempted condensation of isatin and L-pipecolic acid according to the method of Grassmann and Arnim [5] gave *N*-acetylisatin as the main product.

Analogues of Isatin Blue.—(i) *From pyrrolidine.* Isatin (440 mg.) and pyrrolidine (100 mg.) were warmed with 2N-acetic acid (25 c.c.) on the steam-bath for ½ hr. After cooling, the resulting solution deposited the product as glistening green crystals (304 mg., 66%) which were separated, washed, and crystallised from methanol by the hot-extraction method (Found : C, 72·8; H, 4·7; N, 12·8. Calc. for $C_{20}H_{15}O_2N_3$: C, 72·9; H, 4·6; N, 12·8%).

(ii) *From* L-*proline.* Isatin (650 mg.) and L-proline (255 mg.) were suspended in phosphate buffer solution (50 c.c. at pH 7) and the mixture boiled for 15 min. The insoluble product (181 mg.) was separated from the solution, washed with hot water, ethanol, and ether, and crystallised from methanol as before; it formed glistening green crystals (80 mg., 23%) which showed an ultraviolet and visible spectrum identical with that of the product obtained from pyrrolidine.

(iii) *From morpholine.* 3 : 3-Dimorpholino-oxindole (2·5 g.) was suspended in a mixture of xylene (25 c.c.) and acetic anhydride and heated under reflux for 30 min. The green product was cooled and the precipitated coloured *compound* separated and washed with xylene, ethanol, and ether. It was then crystallised from methanol by the hot-extraction method to yield blue prisms (600 mg., 43%) with a green metallic lustre (Found : C, 69·6; H, 4·6; N, 12·1. $C_{20}H_{15}O_3N_3$ requires C, 69·6; H, 4·4; N, 12·2%).

(iv) *From 2-methylpiperidine.* Isatin (500 mg.) was suspended in a mixture of xylene (10 c.c.) and 2-methylpiperidine (500 mg.; b. p. 118—121°, prepared by hydrogenation of purified 2-picoline over Raney nickel at 200°/150 atm.) and heated under reflux for 4 hr. The blue *pigment* (460 mg., 78%) was isolated and purified by crystallisation from hot methanol, as blue prisms (Found : C, 73·6; H, 5·35; N, 11·6. $C_{22}H_{19}O_2N_3$ requires C, 73·9; H, 5·35; N, 11·75%). An *X*-ray crystallographic determination of the molecular weight (kindly carried out by Mr. D. Daniels) gave a value of 348 (theor. 355).

(v) *From 3-methylpiperidine.* Isatin (1·8 g.) and 3-methylpiperidine (600 mg.; b. p. 122—126°, prepared by hydrogenation of purified 3-picoline as in the previous experiment), in xylene (25 c.c.), were heated under reflux for 90 min. The blue *product* (90 mg., 3·5%) was purified and recrystallised in the usual way (Found, on a sample dried at room temperature/14 mm. for 1 hr. : C, 70·2; H, 6·0. $C_{22}H_{19}O_2N_3,CH_3{\cdot}OH$ requires C, 70·9; H, 5·95%). Longer heating of the reactants gave a brown tar.

(vi) *From* cis-*octahydroindole.* Isatin (400 mg.) and *cis*-octahydroindole [16] (200 mg.) in xylene (5 c.c.) were heated under reflux for 2 hr. The solid *product* (170 mg.) was separated and crystallised from hot methanol in the usual manner (Found, on a sample dried at 100°/0·1 mm. for 4 hr. : C, 72·1; H, 6·0; N, 10·3. $C_{24}H_{21}O_2N_3,CH_3{\cdot}OH$ requires C, 72·3; H, 6·1; N, 10·1%).

(vii) *From pyrrolidine and* N-*methylisatin.* *N*-Methylisatin (500 mg.) and pyrrolidine (500 mg.) were dissolved in 2N-acetic acid (25 c.c.) and warmed on the steam-bath for 1 hr. The solution was then heated to boiling, next cooled, and the blue solid product (465 mg., 75%) separated and washed with ethanol and ether. It was purified by slow crystallisation from methanol by the hot-extraction method, being obtained as blue glistening needles [5] (Found : N, 11·6. Calc. for $C_{22}H_{15}O_2N_3$: N, 11·9%). The infrared spectrum (in Nujol) showed no medium or strong absorption below 1673 cm.$^{-1}$. Other bands were observed at 1634, 1599, and 1582 cm.$^{-1}$.

Reaction of Isatin and iso*Indoline* (cf. Grassmann and Arnim [5]).—Isatin (1 g.) and *iso*indoline hydrochloride (500 mg.; the base was prepared by the electrolytic reduction of phthalimide according to Rollet, Dinet, and Willemart's directions [18]), in acetic acid (3·5 c.c.), were heated for 10 min. The mixture was cooled and the solid which separated (130 mg.) was removed and washed with alcohol. The spectrum of the product in solution is recorded in Table 1. In concentrated sulphuric acid the compound formed a clear blue solution.

Reaction of Acenaphthenequinone and L-*Pipecolic Acid.*—Acenaphthenequinone (300 mg.) and L-pipecolic acid (150 mg.) in ethanol (30 c.c.) were heated under reflux for 30 min. After cooling,

[17] King, King, and Thompson, *J.*, 1948, 552.
[18] Rollet, Dinet, and Willemart, *Bull. Soc. chim. France*, 1950, 877.

the greenish-brown crystalline *product* was separated, washed with ethanol, dried (179 mg.), and crystallised from methanol (Found : C, 84·0; H, 4·7; N, 3·6. $C_{29}H_{19}O_2N$ requires C, 84·2; H, 4·6; N, 3·4%).

Isatic Acid Piperidide.—Prepared from equimolecular quantities of isatin and piperidine (Liebermann and Krauss [7]), this derivative formed yellow prisms, m. p. 135° (from ethanol), and gave an *acetate*, pale yellow needles, m. p. 135° (from 50% aqueous methanol) (Found : C, 66·3; H, 6·4; N, 10·2. $C_{15}H_{18}O_3N_2$ requires C, 65·9; H, 6·6; N, 10·2%).

5-Bromoisatic Acid Piperidide.—Prepared as above from 5-bromoisatin and piperidine,[6] this piperidide formed yellow prisms, m. p. 206—208° (from ethanol), which sublimed at 140°/0·1 mm. (Found : C, 50·2; H, 5·1. Calc. for $C_{13}H_{15}O_2N_2Br$: C, 50·2; H, 4·8%), and gave a pale yellow *acetate*, m. p. 138—140° (from 50% aqueous methanol) (Found : C, 51·5; H, 4·9; N, 8·3; Br, 22·0. $C_{15}H_{17}O_3N_2Br$ requires C, 51·1; H, 4·8; N, 8·0; Br, 22·7%), and *2 : 4-dinitrophenylhydrazone*, orange-red needles, m. p. 371—373° (from nitrobenzene) (Found : N, 17·2. $C_{19}H_{19}O_5N_6Br$ requires N, 17·1%).

5-Bromoisatic Acid Morpholide.—This *derivative*, prepared as above from 5-bromoisatin and morpholine, formed yellow needles, m. p. 208—210° (decomp.) (from aqueous methanol) (Found : C, 45·7; H, 4·4; N, 8·4; Br, 23·7. $C_{12}H_{13}O_3N_2Br$ requires C, 45·6; H, 4·15; N, 8·95; Br, 25·6%). Its *acetate* formed colourless needles, m. p. 168° (from water) (Found : C, 47·1; H, 4·2. $C_{14}H_{15}O_4N_2Br$ requires C, 47·4; H, 4·2%).

5-Bromo-NN-hexamethyleneisatamide.—5-Bromoisatin (500 mg.) and hexamethyleneimine (400 mg.) were dissolved in warm methanol (2 c.c.). The solution was cooled and crystallisation of the product induced by scratching. The yellow *amide* was separated and recrystallised from methanol, to give yellow prisms (320 mg.), m. p. 165—166° (Found : C, 52·2; H, 5·3; N, 8·3. $C_{14}H_{17}N_2O_2Br$ requires C, 51·8; H, 5·25; N, 8·6%).

3 : 4-Benzisatic Acid Pyrrolidide (CO_2H = 1).—Prepared as above from 4 : 5-benzisatin (500 mg.) and pyrrolidine (600 mg.), the *product* (300 mg.) formed yellow prisms (from methanol), m. p. 179—180° (Found : C, 72·0; H, 6·1. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0%).

Oxidation of Isatin Blue.—(i) *With nitric acid.* Isatin blue (2 g.) was treated with concentrated nitric acid (100 c.c.; redistilled) and, when the vigorous reaction had subsided, the resulting solution was warmed for a short while and then evaporated to dryness under reduced pressure. A little water was added and the solution again evaporated to dryness, although during the evaporation a yellow steam-volatile solid (100 mg.) was obtained. The same product was the major constituent of the residue which was sublimed at 100°/0·1 mm., and yielded a further quantity (700 mg.) of the yellow solid, m. p. 118° alone and 118—119° when mixed with picric acid (Found : C, 31·4; H, 1·65. Calc. for $C_6H_3O_7N_3$: C, 31·5; H, 1·3%).

(ii) *With alkaline potassium permanganate.* Isatin blue (2 g.) was suspended in a 1% solution of potassium hydroxide (200 c.c.) at 70° and a solution of potassium permanganate (2·65 g.; theor. for oxidation of two double bonds) was added with frequent shaking during 1 hr. at 70°. The solution became green and then brownish-yellow and after the reaction had ceased the whole was filtered (Supercel) and the filtrate evaporated under reduced pressure to *ca.* 50 c.c. The residual solution was acidified with hydrochloric acid, filtered, and extracted with ether (6 × 30 c.c.) and chloroform (6 × 30 c.c.). The combined yellow ethereal extract was dried ($MgSO_4$) and the solvent removed to yield a red solid (500 mg.) which was crystallised from ethanol and was identified as isatin, m. p. and mixed m. p. 201°. A further quantity (150 mg.) was obtained from the chloroform extract. The residual aqueous layer was extracted with ether continuously for 24 hr. Evaporation of the ether gave a red gum containing some white solid. Sublimation of the residue at 60°/1 mm. gave the solid product which crystallised from ethyl acetate–light petroleum (b. p. 60—80°), to yield oxalic acid, m. p. and mixed m. p. 97—99°.

(iii) *With excess of alkaline potassium permanganate.* The above experiment was repeated with alkaline potassium permanganate (3·33 g.). The product was treated as before and after acidification was extracted with ether (6 × 30 c.c.).

From the ethereal extract, isatin (300 mg.) was obtained. Evaporation of the aqueous solution gave a dark brown resin (1·4 g.) which was extracted with hot ethanol (2 × 50 c.c.), and the solvent removed from the extract to yield a sticky red solid which was sublimed at 76°/0·6 mm. A mixture of a yellow and a white solid sublimate (400 mg.), m. p. 95—130°, was obtained, but by repeated sublimation at 80°/0·5 mm. a compound was obtained which after crystallisation from chloroform had m. p. 140—142°. When mixed with authentic anthranilic acid it had m. p. 142—144°.

(iv) *With chromic acid.* To a suspension of isatin blue (2·2 g.) in glacial acetic acid (30 c.c.), a solution of chromic acid (1·7 g.) in acetic acid (57 c.c.) was added dropwise at room temperature during 1 hr. with shaking. The solvent was removed from the product under reduced pressure and the residue extracted repeatedly with ether. After removal of the ether from the extract isatin (350 mg.) was obtained and identified by comparison with an authentic specimen. No other recognisable products could be isolated.

Pyrolytic Degradation of Isatin Blue.—Isatin blue (700 mg.) was heated at 185°/0·1 mm. for 48 hr. Several products could be discerned in the sublimate but the most volatile product was easily separated from the others. This was repeatedly sublimed at 72°/0·1 mm., being obtained as a pale yellow crystalline compound (8·5 mg.), m. p. 125° (Found : C, 71·7; H, 5·1. Calc. for C_8H_7ON : C, 72·15; H, 5·3%). When mixed with authentic oxindole, it had m. p. 125—127°.

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