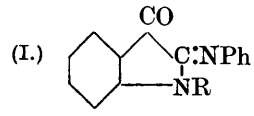
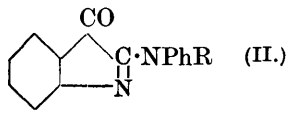
CLVIII.—*Isatin Anils. Part I. The Isomerism of Isatin-2-anil.*

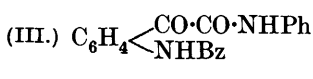
By Robert Kenneth Callow and Edward Hope.

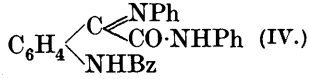
The existence of two tautomeric forms of isatin-2-anil (I and II; R = H) was discovered by Pummerer (*Ber.*, 1911, **44**, 338, 810). The form to which the constitution (I) was assigned, the anil, separated from alcohol in yellowish-brown leaflets, and the anilide (II) formed violet prisms from benzene. Both forms melted at 126°. Confirmation of this isomerism was afforded by the synthesis of the

isomeric methyl derivatives. In the course of an investigation of the acylation of isatin anils we have been able to obtain additional









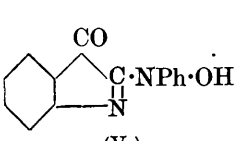
proof of Pummerer's conclusions by preparing directly from isatin-2-anil the isomeric benzoyl derivatives corresponding to the tautomeric forms (I) and (II). N-*Benzoylisatin-2-anil* (I; R = Bz) is readily prepared by heating isatin-2-anil with benzoic anhydride. Its constitution is established by its hydrolysis to *o*-benzamidophenylglyoxylic acid and aniline, and by its ready conversion in boiling alcoholic solution in the presence of a trace of hydrochloric acid into *o-benzamidophenylglyoxylanilide* (III) by opening of the pyrrole ring. The last compound was also obtained by the reaction of the chloride of the acid with aniline. An analogy to the opening of the pyrrole ring of *N*-benzoylisatin-2-anil was found in the transformation of *N*-benzoylisatin under similar conditions to *o*-benzamidophenylglyoxylic acid and its *ethyl* ester. Again, when *N*-benzoylisatin-2-anil was heated with aniline the product was *o-benzamidophenylglyoxylanilideanil* (IV), the water formed in the reaction having evidently brought about immediate opening of the ring.

The action of benzoyl chloride on isatin-2-anil in benzene or nitrobenzene solution at the ordinary temperature yielded *N*-benzoylisatin-2-anil and the hydrochloride of isatin-2-anil. In pyridine solution, however, *isatin-2-benzanilide* (II; R = Bz) was obtained. This compound was very readily decomposed by water with the formation of isatin and benzanilide, and its constitution is, therefore, quite clear.

While this work was in progress, the original assumption of Pummerer regarding the tautomerism of isatin-2-anil was called into question by Rupe and Apotheker (*Helv. Chim. Acta*, 1926, **9**, 1049). These authors obtained by reduction of the product of condensation of isatin and β-phenylhydroxylamine (Rupe and Stöcklin, *ibid.*, 1924, **7**, 557) a substance to which they assigned the constitution of the lactim form of isatin-2-anil (I; R = H). It was obviously different from either of the forms described by Pummerer, which, they concluded, were simply polymorphic forms of the lactam structure. The grounds on which their conclusions were based were, first, the assumption that β-phenylhydroxylamine

condensed with isatin in the 2-position, and, secondly, the non-identity of the product with α-anilinoindoxyl (isatin*leuco*-2-anil) (Pummerer and Göttler, *Ber.*, 1910, **43**, 1376), although the elementary analysis corresponded more closely with the latter substance. It was found necessary to postulate peculiar mechanisms of reaction to explain the formation of the 3-semicarbazone, 3-oxime, and 3-phenylhydrazone from the new " isatin-2-anil " and of the 2-semicarbazone, 2-oxime, and 2-phenylhydrazone from the previously known forms of isatin-2-anil.

Consideration of their arguments convinced us that the first assumption of the constitution of " isatin-β-phenylhydroxylamine " was erroneous. It is certain that the reactive carbonyl group in isatin is that in position 3, and it is *a priori* likely that β-phenylhydroxylamine will react with this. Furthermore, it is not permissible (as Rupe and Stöcklin suppose) to assume that isatin chloride reacts preferentially with its halogen with reagents having the capacity of reacting with a carbonyl group, for we have found that isatin chloride reacts with aniline to yield isatin-3-anil and isatin-dianil. If, then, this substance were not isatin-2-β-phenylhydroxylamine (V) but isatin-3-anil *N'*-oxide (VI), it would yield on reduction 3-anilino-oxindole (isatin*leuco*-3-anil) (VII), already prepared by Pummerer and Göttler (*loc. cit.*). We have now found, by direct comparison, that the product obtained by the method of Rupe and Apotheker is identical with 3-anilino-oxindole, and our suggestion for the actual course of the reaction is therefore confirmed.



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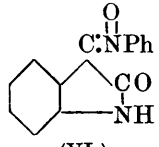
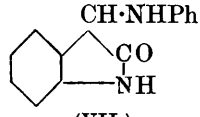


(VI.)



(VII.)

It would appear that the constitutions assigned to certain other derivatives prepared by Rupe and his collaborators should be revised in the light of these results (*locc. cit.* and *Helv. Chim. Acta*, 1927, **10**, 926). The true isatin-2-β-phenylhydroxylamine or 2-phenyliminoindoxyl *N'*-oxide appears to have been prepared by Alessandri (*Gazzetta*, 1927, **57**, 195) by condensation of *o*-nitrophenylacetylene with nitrosobenzene, and the by-product which we obtained in the condensation of indoxyl with nitrosobenzene (see experimental section) is probably identical with it.

In conclusion, we consider, on the basis of this correction of the results of Rupe and Apotheker, and of the additional evidence provided by the preparation of isomeric benzoyl derivatives, that there

is no need to modify the original hypothesis of tautomerism of isatin-2-anil put forward by Pummerer.

EXPERIMENTAL.

Isatin-2-anil.—Attempts made to prepare isatin-2-anil by the condensation of isatin chloride with aniline were unsuccessful, although it is stated by Borsche, Weussmann, and Fritzsche (*Ber.*, 1924, **57**, 1770) that 5-iodoisatin-2-anil is formed from 5-iodoisatin chloride in this way.

(*a*) Isatin chloride (2 g.) and aniline (1·1 g.; 1 mol.) in benzene were heated under reflux for 15 minutes. Isatin-3-anil was the only product which could be isolated.

(*b*) In an experiment in which double the amount of aniline was employed, isatindianil and a substance, m. p. 165—180°, insoluble in light petroleum, were separated. In neither (*a*) nor (*b*) could any trace of isatin-2-anil be recognised.

A small quantity of isatin-2-anil was prepared by the condensation of indoxyl with nitrosobenzene (Pummerer and Göttler, *Ber.*, 1909, **42**, 4269; Pummerer, *Ber.*, 1911, **44**, 338), but this method was rather troublesome. Examination of the red substance obtained as a by-product showed that it was not isatindianil, as suggested by Pummerer and Göttler, but had the composition $C_{14}H_{10}O_2N_2$ (Found: C, 70·8; H, 4·4; N, 11·9; *M*, by Rast's method, 255. Calc.: C, 70·6; H, 4·2; N, 11·8%; *M*, 238). The substance was moderately easily soluble in boiling alcohol, from which it separated in fine, scarlet, flat needles, m. p. 196—197° (corr., decomp.). The m. p. was depressed by mixture with isatin-3-anil *N'*-oxide. Isatin was obtained by decomposition with dilute hydrochloric acid. The decomposition with 10% sulphuric acid, as described by Alessandri (*loc. cit.*) in the case of 2-phenyliminoindoxyl *N'*-oxide [m. p. 195—196° (decomp.)], yielded only a solution which rapidly darkened in the air, and instead of *p*-aminophenol, only a dark material of high melting point could be isolated. The qualitative solubilities of the substance in various solvents agreed completely with those recorded by Alessandri. When the substance was boiled with aqueous permanganate solution, the odour of nitrosobenzene was perceptible. The amount of substance available did not permit further examination.

The most convenient method for the preparation of isatin-2-anil was found to be a modification of the process of Sandmeyer (*Z. Farben- und Textilchemie*, 1903, **2**, 129). The isatin-2-anil obtained by treatment of oxalic diphenylamidine thioamide with sulphuric acid was, however, always accompanied by isatin-3-anil, and it was found better to proceed directly from hydrocyanocarbodiphenyl-

imide * to isatin-2-anil by treatment with aluminium chloride as described in D.R.-P. 277396. The scarlet isatin-2-anil hydrochloride obtained was separated from as much as possible of the water and benzene by filtration and churned with water, and a slight excess of sodium carbonate added. The crude isatin-2-anil was dried on porous plate and crystallised from ether. Yield: 50—60% of the theoretical; m. p. 126° (corr.).

N-Benzoylisatin-2-anil (I; R = Bz).—(a) *Benzoylation with benzoic anhydride.* Isatin-2-anil (10 g.) and benzoic anhydride (27·5 g.; 2 mols.) were mixed and heated at 100° for 2 hours. The mixture was then poured into alcohol (250 c.c.). On scratching, the product separated as needles (9 g., m. p. 169—172°). Recrystallised from 50 parts of boiling alcohol, *N-benzoylisatin-2-anil* was obtained as fine, bright red, prismatic needles, m. p. 172·5—173° (corr.) (Found: C, 77·2; H, 4·3; N, 8·5. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3; N, 8·6%). It was moderately easily soluble in benzene, slightly soluble in ether, and practically insoluble in light petroleum.

The colour of the solution from which the crude *N*-benzoylisatin-2-anil separated changed from dark brown to light red on standing or warming. After removal of alcohol and benzoic ester the residue was separated into isatin, benzoic acid, and benzanilide. In the light of the results described below, it seems likely that isatin-2-benzanilide was formed in the reaction and subsequently decomposed.

(b) *Benzoylation with benzoyl chloride in benzene solution.* Dry isatin-2-anil (4·5 g.) was dissolved in dry benzene (200 c.c.), benzoyl chloride (7 g., freed from hydrogen chloride by distillation under reduced pressure) added, and the mixture kept for 2 days. A light red, crystalline precipitate was formed, which, when removed, washed, and dried, melted at 205° (decomp.) and was identified as isatin-2-anil hydrochloride. The solution was evaporated under reduced pressure, and the pasty residue washed with light petroleum. After two recrystallisations of the solid from benzene and light petroleum, nearly pure *N*-benzoylisatin-2-anil was obtained. The amounts of the hydrochloride (2·6 g.) and of *N*-benzoylisatin-2-anil (2·7 g.) separated were approximately equivalent. Another method of working-up adopted at first and involving treatment with water led to the separation only of isatin, benzanilide, and benzoic acid.

No indigoid substance was formed when *N*-benzoylisatin-2-anil

* The hydrocyanocarbodiphenylimide was always accompanied by a *substance* resembling it in appearance, but differing in solubility in alcohol. It melted at 186—187° (Found: C, 77·65; H, 5·19; N, 17·1%. $C_{21}H_{16}N_4$ requires C, 77·8; H, 4·9; N, 17·3%). This substance has not yet been examined in detail.

was treated with ammonium sulphide in alcoholic solution. The addition of caustic soda solution to the alcoholic solution gave a blue colour which disappeared on acidification. The ethereal extract of the blue solution was red. This reaction is also given by isatin-2-anil and *N*-methylisatin-2-anil, but not by isatin-3-anil. The addition of sodium hyposulphite to the alkaline solution caused the blue colour to disappear, probably because of the formation of the "leuco-anil," but it returned on shaking with air.

Hydrolysis of N-*Benzoylisatin*-2-*anil*.—*N*-Benzoylisatin-2-anil (1 g.) was boiled under reflux with concentrated hydrochloric acid (35 c.c.) for 10 minutes. After cooling, the pale yellow solid was collected and dried. It melted at 192—193·5°, and was identified as *o*-benzamidophenylglyoxylic acid (Schotten, *Ber.*, 1891, **24**, 774) by a mixed melting-point determination with an authentic specimen obtained as described below. Yield : 0·6 g. (75% of the theoretical). Basification of the solution and extraction with ether yielded aniline.

o-*Benzamidophenylglyoxylanilide* (III).—*N*-Benzoylisatin-2-anil (0·5 g.) was boiled under reflux for 20 minutes with 50% aqueous alcohol (100 c.c.), to which one drop of concentrated hydrochloric acid had been added. The *N*-benzoylisatin-2-anil slowly dissolved and the colour of the solution changed to pale yellow. On cooling, pale yellow crystals (0·24 g.) separated. After two recrystallisations from 70% aqueous alcohol, very pale yellow, microscopic needles of o-*benzamidophenylglyoxylanilide*, m. p. 183—184° (corr.), were obtained (Found : C, 73·7; H, 4·8; N, 8·0. $C_{21}H_{16}O_3N_2$ requires C, 73·3; H, 4·6; N, 8·1%).

Treatment of the compound with concentrated hydrochloric acid yielded a material which did not melt below 330°. Hydrolysis by caustic alkali was, however, simpler. The compound (1 g.) was boiled under reflux with 2*N*-sodium hydroxide solution (25 c.c.) until complete solution took place (½ hour). Extraction of the cold solution with ether gave aniline, and from the remaining liquid, after acidification, isatin and benzoic acid were separated.

The constitution assigned to *o*-benzamidophenylglyoxylanilide was confirmed by synthesis, after two unsuccessful attempts. (1) Mixture of *o*-benzamidophenylglyoxylic acid and aniline in ether gave the *aniline* salt, m. p. 120—121° (corr., decomp.) (Found : N, 7·8. $C_{21}H_{18}O_4N_2$ requires N, 7·7%). After treatment of the aniline salt with phosphorus pentachloride in benzene, the acid alone was recovered. (2) When *o*-benzamidophenylglyoxylic acid was boiled with aniline and a crystal of iodine for a few minutes, and excess of aniline removed by dilute hydrochloric acid, a white precipitate of *o*-benzamidobenzaldehyde (Bischler and Lang, *Ber.*,

1895, **28**, 287) was obtained. It formed fine needles, m. p. 73—74°, from dilute acetic acid (Found: N, 6·0. Calc. for $C_{14}H_{11}O_2N$: N, 6·2%).

Finally the following method was successful. A large excess (20 c.c.) of thionyl chloride was shaken with *o*-benzamidophenylglyoxylic acid (2·5 g.), which dissolved with slight evolution of heat. The liquid was evaporated on the water-bath to 5 c.c., and the remainder of the thionyl chloride removed by two further evaporations to 5 c.c. after dilution with benzene. Attempts to isolate the chloride by adding smaller amounts of thionyl chloride to the acid suspended in benzene, or evaporation of the solution to dryness, yielded a dark, insoluble solid, m. p. 205—207°, which decomposed on keeping. The solution of the chloride was diluted with ether and added, drop by drop, to aniline (0·9 g.) dissolved in ether, in the presence of potassium carbonate. After addition of water, the emulsion was extracted with ether. The ethereal solution, washed with dilute acid and dried, yielded the impure anilide (1·6 g.) when evaporated. After recrystallisation, its identity with the product from *N*-benzoylisatin-2-anil was confirmed by a mixed melting-point determination.

N-*Benzoylisatin*.—Repetition of the preparation by the method of Heller (*Ber.*, 1903, **36**, 2764)—the action of benzoyl chloride upon isatin—led to the isolation of a product which, fractionally crystallised from dilute acetic acid, was separated into *N*-benzoylisatin, m. p. 213—214° (corr.), and an equal amount of *o*-benzamidophenylglyoxylic acid, which was more soluble.

N-Benzoylisatin was more easily prepared by heating isatin (12 g.) with benzoic anhydride (36 g.; 3 mols.) for 1 hour at 150—160°. After cooling, the solid product was ground with a little alcohol, and the insoluble residue of *N*-benzoylisatin (13·5 g.) purified by recrystallisation from glacial acetic acid.

Ring Scission of N-*Benzoylisatin*.—*N*-Benzoylisatin (6 g.), when boiled under reflux for 1 hour with 50% aqueous alcohol (400 c.c.) to which four drops of concentrated hydrochloric acid had been added, gradually dissolved, and, on evaporation to small bulk, oil and solid separated. The solid was dissolved by sodium carbonate solution, and the oil removed. Acidification of the solution precipitated *o*-benzamidophenylglyoxylic acid (3·2 g.). The oil (1·4 g.) solidified on standing, and on recrystallisation from dilute acetic acid gave *ethyl* o-*benzamidophenylglyoxylate* as colourless needles, m. p. 80° (corr.) (Found: N, 4·7. $C_{17}H_{15}O_4N$ requires N, 4·7%). The ester was rapidly hydrolysed to the acid when warmed with 2*N*-sodium hydroxide.

o-Benzamidophenylglyoxylic acid was conveniently prepared by

warming *N*-benzoylisatin (18·8 g.) for several minutes with dilute sodium hydroxide solution (2·6 g. in 170 c.c.). The solution was quickly cooled, filtered, and the acid precipitated by addition of hydrochloric acid. The precipitate was freed from isatin and benzoic acid by washing with hot water. Yield, 17·5 g. After repeated recrystallisation from dilute acetic acid, it had m. p. 196—197° (corr., decomp.) (Schotten, *loc. cit.*, gives 188°).

o-*Benzamidophenylglyoxylanilideanil* (IV).—*N*-Benzoylisatin-2-anil (0·5 g.) was heated on the water-bath for a few minutes with aniline (2 c.c.) and a crystal of iodine. Yellow crystals separated when the mixture was poured into alcohol, and, after recrystallisation from 50 parts of benzene, o-*benzamidophenylglyoxylanilideanil* was obtained as canary-yellow, microscopic needles, m. p. 204—205° (corr., decomp.) (Found: C, 77·6; H, 5·1; N, 10·0. $C_{27}H_{21}O_2N_3$ requires C, 77·3; H, 5·0; N, 10·0%).

Isatin-2-benzanilide (II; R = Bz).—Benzoyl chloride (7·2 g.) was added to isatin-2-anil (10 g.) dissolved in dry pyridine (18 c.c.). After 5 hours the mixture was poured into water (400 c.c.), and the precipitate collected and dried in a vacuum without delay. The yield was practically theoretical. The crude product was dissolved in 4 parts of boiling dry toluene, and twice the volume of dry light petroleum (b. p. 100—110°) added; *isatin-2-benzanilide* then crystallised in crimson prisms, m. p. 131° (corr.) (Found: C, 77·6, 77·0; H, 4·5, 4·3; N, 8·7, 8·3. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3; N, 8·6%). It was moderately easily soluble in boiling light petroleum (b. p. 100—110°) and readily soluble in benzene or toluene. It was essential to use carefully dried pyridine in the benzoylation and dried solvents for recrystallisation, otherwise mixtures of isatin and benzanilide were obtained. If the crystals were allowed to remain in the air, they acquired a superficial coating of colourless plates of benzanilide. When isatin-2-benzanilide (0·5 g.) was boiled under reflux for 1 hour with water (50 c.c.), it became tarry, and crystals of benzanilide (0·25 g.) were then deposited. Filtered hot and allowed to cool, the solution deposited isatin (0·16 g.). Decomposition into these products took place immediately in dilute hydrochloric acid and rapidly in aqueous alcohol.

Isatin-3-anil N'-Oxide (VI).—The condensation of isatin and β-phenylhydroxylamine in boiling alcohol, as described by Rupe and Stöcklin, gave isatin-3-anil *N'*-oxide in 60% of the theoretical yield. Recrystallised from alcohol, it formed scarlet, flat needles, m. p. 217·5—219° (corr., decomp.) (Rupe and Stöcklin give 216°).

3-*Anilino-oxindole* (VII).—(*a*) A solution of isatin-3-anil *N'*-oxide (10 g.) in a mixture of glacial acetic acid (150 c.c.) and water (15 c.c.)

was raised to boiling, and zinc dust (about 10 g.) added in small portions until the colour of the solution had faded to pale gold. The solution was then rapidly filtered into a vessel filled with coal-gas; hot, air-free water (100 c.c.) was added, and the mixture allowed to cool. The white solid which separated (4·7 g.) was twice recrystallised from alcohol. It was found to be most important to protect the product from oxidation during recrystallisation, otherwise the product, presumably contaminated with the products of oxidation, separated as a caseous mass which was difficult to filter rapidly and preserve from oxidation. 3-Anilino-oxindole separated as colourless plates, m. p. 192·5° (corr., decomp.) in an evacuated capillary tube (Rupe and Apotheker, *loc. cit.*, give m. p. 176° in an open tube) (Found : C, 75·1; H, 5·5. Calc. for $C_{14}H_{12}ON_2$: C, 75·0; H, 5·4%. Calc. for $C_{14}H_{10}ON_2$: C, 75·7; H, 4·5%).

(*b*) Isatin-3-anil, prepared as described by Knoevenagel (*J. pr. Chem.*, 1914, **89**, 46), was reduced by zinc dust in aqueous acetic acid in the same way as isatin-3-anil *N'*-oxide, the same precautions being employed against oxidation. 3-Anilino-oxindole separated in colourless plates from alcohol, indistinguishable under the microscope from the product of reduction of isatin-3-anil *N'*-oxide. The substance had m. p. 192° (corr., decomp.) in an evacuated capillary tube, and this was unchanged by mixture with the product from isatin-3-anil *N'*-oxide. The solubilities of both products in light petroleum, ether, chloroform, and acetone were as described by Pummerer and Göttler (*loc. cit.*).

One of us (R. K. C.) wishes to thank the Department of Scientific and Industrial Research for a maintenance grant during part of the time he was engaged in this work.

THE DYSON PERRINS LABORATORY,
OXFORD. [*Received, April 12th,* 1929.]