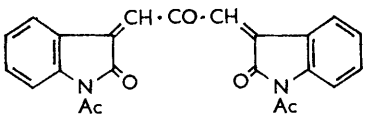
629. *The Reaction of Isatin with Acetic Anhydride and Pyridine.*

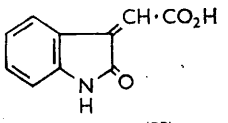
By J. A. Ballantine, A. W. Johnson, and A. S. Katner.

The purple crystalline product formed from the reaction of isatin with acetic anhydride in the presence of pyridine is shown to be a pyridinium salt of structure (VIII). Reactions of the adduct are described and its formation is shown to involve a Diels–Alder addition with an intermediate oxindolylidene derivative acting as the diene component.

In 1936 Grassmann and Arnim [1] described the condensation of isatin with acetic anhydride in the presence of pyridine, from which they obtained a purple compound believed to have the molecular formula $C_{30}H_{25}N_3O_7$. The adduct was shown to contain an equivalent of pyridine and was believed to be a triacetyl derivative, *i.e.*, $C_{19}H_{12}N_2O_4(CO{\cdot}CH_3)_3(C_5H_5N)$; other bases such as tetrahydroisoquinoline could be substituted for pyridine. It was therefore assumed that two equivalents of isatin were involved in the reaction, and a derivative of the structure (I) was suggested for the product. This structure is clearly unsatisfactory in several respects; it does not account satisfactorily for the presence of the pyridine, and such compounds would not be expected to be purple in colour.[2]

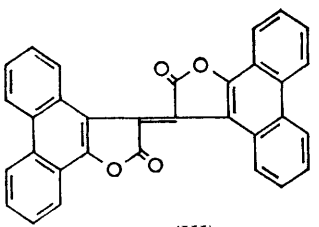


(I)

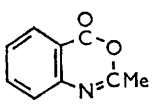


(II)

Apart from a brief reference by Borsche [3] to the nature of oxindolylideneacetic acid (II), believed [1] to be intermediate in the formation of (I), no further reference has been made to the purple condensation product. More recently, Bloom [4] described a study of the nature of a blue condensation product obtained from phenanthraquinone, acetic anhydride, and pyridine.[5] This was formulated as (III), which is a representative of the so-called Pechmann dyes.[6] The nature of the transformation products of (III) was discussed in detail,[4] but although there are clearly superficial similarities between the isatin and phenanthraquinone products, the former is a pyridinium salt, and its properties have therefore been re-examined. We are grateful to Drs. D. J. McCaldin and J. C. Tebby who carried out some preliminary experiments on this topic at Nottingham. The results of our analyses have led us to amend the molecular formula to $C_{29}H_{19}N_3O_7$, or $C_5H_6N^+\ C_{24}H_{13}N_2O_7^-$



(III)



(IV)

when the pyridinium cation is taken into account. The yield of the purple condensation product is about 33%, and similar reactions of isatin and acetic anhydride with β-picoline or isoquinoline have given the appropriate salts, $C_{30}H_{21}N_3O_7$ and $C_{33}H_{21}N_3O_7$, respectively.

[1] Grassmann and Arnim, *Annalen*, 1936, **522**, 66.
[2] Braude and Lindwall, *J. Amer. Chem. Soc.*, 1933, **55**, 325.
[3] Borsche, *Ber.*, 1936, **69**, 1376.
[4] Bloom, *J. Amer. Chem. Soc.*, 1961, **83**, 3808.
[5] Diels and Kassebart, *Annalen*, 1938, **536**, 78; Meyer and Spengler, *Ber.*, 1905, **38**, 440; Scharwin, *ibid.*, p. 1270.
[6] Klingsberg, *Chem. Rev.*, 1954, **54**, 59.

Treatment of isatin with acetic anhydride and sodium acetate gives a purple product, presumably the corresponding sodium salt, with a visible spectrum similar to that of the pyridinium salt, but the product could not be crystallised. The reaction of isatin, acetic anhydride, and copper acetate gave only *N*-acetylisatin.

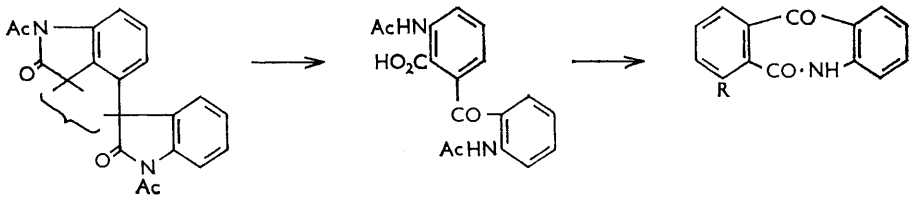
The nuclear magnetic resonance (n.m.r.) spectrum of the purple pyridinium salt also indicated the presence of only two *N*-acetyl groups rather than three, as suggested by the German workers. As the purple product could equally well be formed from *N*-acetylisatin, it appeared that the isatin imino-groups were acetylated and probably played no further part in the reaction. This supposition was borne out by the results of several degradations described below. The infrared (i.r.) spectrum of the purple condensation product showed a strong band at 1811 cm.$^{-1}$ which was indicative of either an anhydride (when considered along with another band at 1752 cm.$^{-1}$, and a strong absorption at 1268 cm.$^{-1}$ corresponding to C–O–C stretching), or a strained five-membered lactone system. In support of the anhydride formulation it was found that the purple compound gave rise to a series of hydrolysis, aminolysis, and alcoholysis products, with liberation of free pyridine and carbon dioxide. The main products from these reactions were monocarboxylic acids or the corresponding esters in every case, *i.e.*, the first-formed dicarboxylic acids or their monoesters suffered very easy decarboxylation. By these means there were obtained a monocarboxylic acid, $C_{19}H_{12}N_2O_4$, its anilide, methyl and ethyl esters, its *NN*-diacetyl derivative, and the corresponding methyl and ethyl esters, all of which were yellow crystalline compounds. In addition, a colourless methanol adduct of the methyl ester of the *NN*-diacetyl carboxylic acid was obtained, suggesting the presence of an activated double bond in the acid itself.

The first insight as to the nature of these adducts came from a study of the permanganate oxidation products. It has long been known [7] that the oxidation of *N*-acetylisatin yields *N*-acetylanthranilic acid, m. p. 185°, and that this on being heated is readily converted into acetylanthranil [8] (IV). Oxidation of the purple pyridinium salt with potassium permanganate gave an acidic product, (methyl ester, m. p. 184·5—186°), which was, however, not *N*-acetylanthranilic acid. Although a trace of acetylanthranil was obtained by sublimation of the crude oxidation product, none was isolated after heating the purified compound, which had the molecular formula $C_{18}H_{16}N_2O_5$, contained two *N*-acetyl groups, and on hydrolysis with hot 2N-hydrochloric acid gave a non-acidic product, $C_{14}H_{10}N_2O_2$, containing only one free amino-group (monoacetyl derivative). Although the two benzene rings of the original *N*-acetylisatin units were still present, the n.m.r. spectrum of the oxidation product showed the presence of only seven aromatic hydrogen atoms, suggesting that one of the aromatic positions had been involved in a further substitution. The structures of these oxidation products were established when it was found that deamination of the above monoamine gave the lactam (V; R = H) of 2-(*o*-aminobenzoyl)benzoic acid, which can also be obtained [9] by a Beckmann rearrangement of anthraquinone monoxime.[10] The course of these degradation experiments can be represented as shown below. The monoamine was also obtained by permanganate oxidation of the monocarboxylic acid obtained by hydrolysis of the blue condensation product.

The monoamine must therefore be formulated as (V; R = NH_2), for the molecule is built up from two anthranilic acid units. The di-*N*-acetyl-carboxylic acid precursor is thus *N*-acetyl-6-(2-acetamidobenzoyl)anthranilic acid (VI), which in turn must be derived from the fragment (VII), which contains two *N*-acetyloxindole units. These are diacylimides and contain a characteristic band in the i.r. spectrum about 1755 cm.$^{-1}$, which is useful in distinguishing these compounds from the *N*-acetylanthranilic derivatives, *e.g.*, (VI). From the structure of (VII) it follows that the 4-position of one isatin unit, a position not

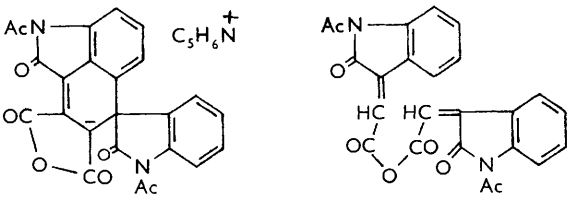
[7] v. Meyer and Bellmann, *J. prakt. Chem.*, 1886, (2), **33**, 31.
[8] Anschütz and Schmidt, *Ber.*, 1902, **35**, 3470.
[9] Beckmann and Liesche, *Ber.*, 1923, **56**, 1.
[10] Julian, Cole, and Diemer, *J. Amer. Chem. Soc.*, 1945, **67**, 1721.

normally reactive, has been involved in the reaction, leading to the ready production of the initial purple pyridinium salt. The molecular formula $C_{20}H_{13}N_2O_4$ of the fragment (VII), together with the pyridinium cation, leaves only C_4O_3, representing the anhydride



(VII) (VI) (V)

fragment, of the initial condensation product. Under the experimental conditions employed, the acetic anhydride will condense with the reactive keto-groups of the *N*-acetylisatin units and thus structure (VIII) is deduced for the purple condensation product.



(VIII) (IX)

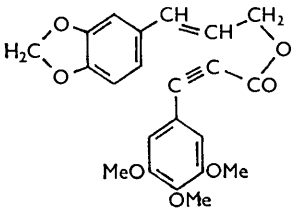
The genesis of this interesting structure probably involves the precursor (IX), which undergoes an internal Diels–Alder reaction with subsequent rearrangement and oxidation. A related reaction (X ⟶ XI) was employed in a recent synthesis of γ-apopicropodophyllin [11] (XI). The product (VIII) may be regarded as a derivative of oxosuccinic anhydride, which is known to be acidic and to form a pyridinium salt.[12] The colour of the anion is readily accounted for by invoking the numerous canonical forms, one of which is illustrated in the partial structure (XII). In contrast to the report of the German authors,[1] the purple pyridinium salt was found to absorb only 1 mole of hydrogen to yield a yellow leuco-derivative which rapidly regenerated the original salt on exposure to air.

Hydrolysis of the anhydride gives the acid (XIII), the intermediate β-keto-acid vinylogue readily losing carbon dioxide. The numerous derivatives of (XIII) and the derived *NN*-diacetyl carboxylic acid obtained by the hydrolysis and alcoholysis reactions of the original adduct have already been described, but the presence of the methylene group, clearly revealed by nuclear magnetic resonance spectra, receives a satisfactory explanation. An alternative 2-quinolone formulation (XIV) rather than (XIII) for the red monocarboxylic acid hydrolysis product was eliminated by comparison of the ultraviolet and visible absorption spectrum of the acid with that of the pale yellow 1,2-dihydro-2-oxoquinoline-4-carboxylic acid.[13]

Confirmation of structure (XIII) was obtained by hydrogenation studies (absorption of 1 mole hydrogen over a platinum catalyst) and by chromic-acid oxidation of the ethanolysis product [*i.e.*, the ethyl ester of the *NN*-diacetyl derivative of (XIII)] of the purple pyridinium salt, when the mono-*N*-acetyl-carboxylic acid (XV; R = H, R′ = Ac) was obtained. Acetylation of (XV; R = H, R′ = Ac) yielded a di-*N*-acetyl-carboxylic acid (XV; R = R′ = Ac), the structure of which was confirmed by the characteristic *NN*-diacetylamino i.r. carbonyl absorption. Hydrolysis of the *N*-acetyloxindole grouping of (XIII) during the oxidation would be expected to occur more readily than the hydrolysis

[11] Klemm and Gopinath, *Tetrahedron Letters*, 1963, 1243.
[12] Wohl *et al.*, *Ber.*, 1901, **34**, 1139; 1907, **40**, 2300.
[13] Julian, Printy, Ketcham, and Doone, *J. Amer. Chem. Soc.*, 1953, **75**, 5305.

of the aromatic *N*-acetamido-group, and it was confirmed by spectral measurements that it was the latter acetyl group that survived. Moreover the characteristic diazotisation and coupling reaction was only shown by (XV; R = H, R′ = Ac) after preliminary hydrolytic removal of the *N*-acetyl group.



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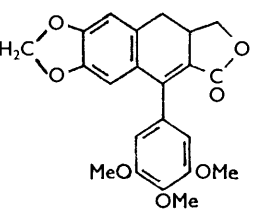

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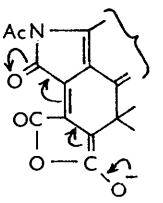

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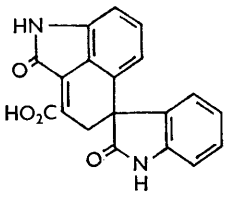

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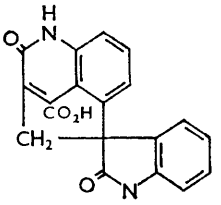

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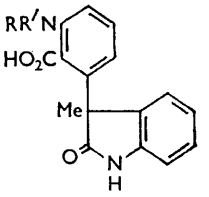

(XV)

Experimental

Ultraviolet absorption spectra were determined on ethanolic solutions and, except where otherwise stated, n.m.r. spectra were determined at 60 Mc./sec. with an A.E.I. (RS2) spectrometer with tetramethylsilane as an internal reference. The numbers of protons were estimated by planimeter measurements.

Reaction of Isatin with Acetic Anhydride and Pyridine.[1]—A mixture of isatin (9 g.), pyridine (10 c.c.), and acetic anhydride (40 c.c.) was heated under reflux for 30 min. After cooling, the product, which formed purple plates (VIII) (5·2 g.), m. p. 223—226° (decomp.), was separated and washed with acetic acid, ethanol, and acetone (Found: C, 66·8; H, 3·5; N, 7·7%; *M*(*X*-ray) 515 ± 10. Calc. for $C_{29}H_{19}N_3O_7$: C, 66·8; H, 3·65; N, 8·05%; *M*, 521); $\lambda_{max.}$ (KBr disc) 230, 298, 571, and 602 mμ (ε 2300, 1620, 1550, and 1540, respectively), $\nu_{max.}$ (KBr disc) in the carbonyl region at 1811, 1764 (inflexion), 1752, 1721, 1700, and 1674 cm.$^{-1}$. The n.m.r. spectrum determined on a solution in liquid sulphur dioxide (Perkin-Elmer 40 Mc./sec. instrument with tetramethylsilane as external reference) showed peaks at τ 7·80 and 7·92 (acetyl-methyl groups) as well as absorptions between τ 1·45 and 3·57 (approx. 12 aromatic-type protons).

Reaction of Isatin with Acetic Anhydride and β-Picoline.—The purple condensation product prepared by the above method had m. p. 244—247° (decomp.) (Found: C, 67·5; H, 4·35; N, N, 7·45. $C_{30}H_{21}N_3O_7$ requires C, 67·3; H, 3·95; N, 7·85%); $\lambda_{max.}$ 237, 293, 298, 575, and 610 mμ (ε 4840, 3340, 3350, 4020, and 3700, respectively); $\nu_{max.}$ (KBr disc) in the carbonyl region at 1807, 1765 (inflexion), 1746, 1723, 1696, and 1655 cm.$^{-1}$.

Reaction of Isatin with Acetic Anhydride and Isoquinoline.—Prepared by a method similar to the above, the product had m. p. 248° (decomp.) (Found: C, 69·2; H, 3·9; N, 7·2. $C_{33}H_{21}N_3O_7$ requires C, 69·35; H, 3·7; N, 7·35%); $\lambda_{max.}$ 217, 298, 338, 564, and 600 mμ (ε 27,150, 5580, 4110, 5350, and 4860, respectively); $\nu_{max.}$ (KBr disc) in the carbonyl region at 1810, 1767, 1742br, 1706, and 1671 cm.$^{-1}$.

Pyridine Picrate.—The crystalline purple pyridine salt (1 g.) was dissolved in 2N-sodium hydroxide solution (50 c.c.) with stirring. When solution was complete, the product was distilled in steam and the distillate treated with saturated aqueous picric acid. The yellow crystalline precipitate was separated and crystallised from aqueous methanol, giving yellow prisms, m. p. 166°, identical in all respects with pyridine picrate.

Acid-hydrolysis Product (XI) of the Purple Compound.—A suspension of the purple condensation product (VIII, *i.e.*, the pyridine salt; 10 g.) in 2N-hydrochloric acid (1 l.) was heated

under reflux for 3 hr. The brown precipitate (5·1 g.) was crystallised from aqueous acetone (carbon) to give red plates (4 g.) of the monocarboxylic *acid*, m. p. 278—281°, raised to 283—285° on recrystallisation from aqueous acetone and then methanol (Found: C, 68·5; H, 3·8; N, 8·4. $C_{19}H_{12}N_2O_4$ requires C, 68·65; H, 3·65; N, 8·45%); $\lambda_{max.}$ 205, 258, and 350 mμ (ε 56,000, 17,900, and 5980, respectively), a shoulder at 229 mμ (ε 17,800); $\nu_{max.}$ (KBr disc) 3375 (NH), 1704, 1701, and 1683 (amide and αβ-unsaturated acid carbonyls) cm.$^{-1}$. The n.m.r. spectrum (dimethyl sulphoxide solution) showed max. at τ −2·17 and −1·25 (2 NH groups), a pair of unsplit alkyl protons with τ 6·28 (CH_2) and seven aromatic protons with τ 2·05—3·14. The absorptions associated with the NH groups disappeared after the solution had been treated with sodium deuteroxide.

The acid (XI) was also obtained from the methyl or ethyl esters or the anilide of the corresponding *NN*-diacetyl acid by heating with 10% aqueous sodium hydroxide solution under reflux for 2 hr. The cooled solution was acidified and the precipitate purified as above.

The corresponding *ethyl ester* was obtained: (i) by deacetylation of the *NN*-diacetyl ethyl ester (below; 1·335 g.) by heating a solution in ethanol (150 c.c.) containing concentrated hydrochloric acid (5 c.c.) under reflux for 2 hr., all the solid had then dissolved. The solution was evaporated (to 25 c.c.) and on cooling the yellow prisms of the ethyl ester (700 mg.) were separated, washed with ethanol and dried; it had m. p. 244—245°, after crystallisation from aqueous acetone and then ethanol. When methanol was used as solvent for crystallisation, ester interchange occurred (Found: N, 8·15. $C_{21}H_{16}N_2O_4$ requires N, 7·8%); $\nu_{max.}$ (KBr disc) 3330 (NH), 1725, 1710 (ester and amide carbonyls), and 1701 cm.$^{-1}$. The n.m.r. spectrum (dimethyl sulphoxide solution) showed max. at τ −0·40 and −0·32 (NH groups), 2·72 to 3·91 (7 aromatic protons), an unsplit singlet at 6·58 (alkyl CH_2), a quadruplet at 5·74 and a triplet at 8·70 (J = 6·5 c./sec.) corresponding to the ester ethyl group.

(ii) The ester was also obtained from the corresponding *NN*-diacetyl acid (224 mg.) by esterification with a dry 5% ethanolic solution of hydrogen chloride (250 c.c.) by heating under reflux for 2 hr., the *N*-acetyl groups being then removed. The solvent was evaporated (to 15 c.c.) and the residue poured into water (100 c.c.). The yellow solid was separated and purified as above to yield yellow needles (136 mg.), identical with the previous product.

(iii) The purple pyridinium salt (VIII; 7 g.) was suspended in a solution of concentrated hydrochloric acid (30 c.c.) in ethanol (200 c.c.), and the mixture was heated under reflux for 4 hr. The dark solution thus obtained was cooled and poured into water (1 l.), and the precipitate separated, dried in air, and crystallised from ethanol (charcoal), then aqueous acetone and finally ethanol, whereupon it formed orange-yellow prisms (3·6 g.), m. p. 244—245°, identical with the products obtained from the previous experiments.

The *methyl ester* was obtained by deacetylation of the *NN*-diacetyl methyl ester (below) and formed orange-yellow prisms, m. p. 260—262° (decomp.) (methanol) (Found: C, 69·4; H, 4·3; N, 7·9. $C_{20}H_{14}N_2O_4$ requires C, 69·4; H, 4·1; N, 8·1%); $\lambda_{max.}$ 206, 256, and 331 mμ (ε 48,490, 16,210, and 5230, respectively, with inflexions at 227 and 271 mμ (ε 17,730 and 13,500, respectively); $\nu_{max.}$ (KBr disc) 3340 (broad; NH), 1729, 1710, and 1700 (ester and amide carbonyls) cm.$^{-1}$.

The *anilide* was obtained directly from the purple condensation product (VIII; 4 g.) by stirring a suspension in aniline (30 c.c.) for 20 hr. at room temperature. The yellow crystalline product (3·3 g.) was separated, washed with a little acetone, and dried in air. Crystallisation from acetone gave the anilide as yellow prisms, m. p. 279—280° (decomp.) (Found: C, 73·7; H, 4·45; N, 10·35. $C_{25}H_{17}N_3O_3$ requires C, 73·7; H, 4·2; N, 10·3%); $\nu_{max.}$ (KBr disc) in the carbonyl region at 1710 and 1694 cm.$^{-1}$, as well as other prominent bands at 1647, 3215, and 3278 cm.$^{-1}$.

— *NN-Diacetyl Derivative of the Acid-hydrolysis Product.*—The acid-hydrolysis product (XI; 279 mg.) was dissolved in hot acetic anhydride (10 c.c.). The solution was cooled, treated with 60% perchloric acid (1 drop), and kept at room temperature for 2 hr. The product was poured into water (50 c.c.), and the precipitate washed and dried. It was purified by chromatography of a chloroform solution on silica gel, the first brown band being collected. After removal of most of the solvent from the eluate, light petroleum (b. p. 60—80°) was added to initiate crystallisation. The *acid* (72 mg.) was thus obtained as yellow needles, m. p. 243° (decomp.) [Found: C, 65·9; H, 4·2; N, 6·65%; *M*(Rast), 416. $C_{23}H_{16}N_2O_6$ requires C, 66·35; H, 3·9; N, 6·75%; *M*, 416]; $\lambda_{max.}$ (in $CHCl_3$) 364 mμ (ε 5370), $\lambda_{infl.}$ 270 mμ (ε 7700); $\nu_{max.}$ (in $CHCl_3$) 1754, 1731, and 1715—1700br cm.$^{-1}$ in the carbonyl region. The n.m.r. spectrum (in CH_2Cl_2) showed max.

at τ 7·17 and 7·32 (two acetyl groups), 6·30 and 6·43 (CH_2 doublet; J = 3 c./sec.), and 1·72 to 3·66, corresponding to 7 aromatic protons.

The *ethyl ester* was obtained directly from a suspension of the purple condensation product (VII; 2 g.) in ethanol (200 c.c.) by heating under reflux for 20 hr. After cooling the brown solution deposited a greenish-brown crystalline solid, which was separated, dried, and dissolved in chloroform (15 c.c.), and the solution chromatographed on a column (20 × 2·5 cm.) of neutral silica gel. The chromatogram was eluted with chloroform and the single brown band collected and concentrated (to *ca.* 20 c.c.). Light petroleum (b. p. 60—80°) was then added gradually to the hot chloroform solution until crystallisation commenced. The ester (1·2 g.) was obtained as yellow-green hexagonal prisms, m. p. 181—183° (decomp.) raised to 183—184° (decomp.) by further crystallisation from chloroform–light petroleum and then ethanol [Found: C, 67·5; H, 4·5; N, 6·05%; M(*X*-ray), 437 ± 13. $C_{25}H_{20}N_2O_6$ requires C, 67·55; H, 4·55; N, 6·3%; M, 444]; $\lambda_{max.}$ 204, 215, and 336 mμ (ε 53,500, 62,460, and 5500, respectively); $\nu_{max.}$ (in CCl_4) 1767, 1727, and 1724 (ester and amide carbonyl) cm.$^{-1}$. The n.m.r. spectrum (CH_2Cl_2) showed absorptions at τ 1·76—3·56 (7 aromatic protons), 7·27 and 7·40 (2 methyls of the acetyl groups), 6·58 (CH_2 grouping), quadruplet at about 5·59, and triplet at about 8·58 (J = 7·5 c./sec.) (ethyl group of ester).

In another experiment the carbon dioxide obtained from the purple condensation product (10 g.) was estimated (as barium carbonate; 2·66 g.); it corresponded to 0·72 mol.

The same ester was also obtained by a similar method from the β-picolinium purple condensation product and by acetylation of the ethyl ester (56 mg.) of the acid-hydrolysis product (XI) with acetic anhydride containing one drop of 60% perchloric acid. The product was purified as above when it (37 mg.) had m. p. 182—184°, identical in all respects with the previous preparation.

The *methyl ester* was obtained similarly by methanolysis of the purple condensation product (21 g.). A stirred suspension in methanol (1500 c.c.) was heated under reflux for 15 hr., concentrated to 1000 c.c., filtered and cooled. The methyl ester (7·5 g.) was thus obtained as yellow plates, m. p. 185—187° (decomp.) [Found: C, 66·5; H, 4·3; N, 6·6%; M(ebull.), 434. $C_{24}H_{18}N_2O_6$ requires C, 66·95; H, 4·2; N, 6·5%; M, 430]; $\lambda_{max.}$ 205, 214, and 339 mμ (ε 48,800 54,000, and 4490, respectively); $\nu_{max.}$ (in CCl_4) 1764 and 1723 (CO) cm.$^{-1}$. Concentration of the mother-liquors to 500 c.c. and cooling gave mixed crystals (3 g.). The filtrate was evaporated to dryness under reduced pressure and the residue dissolved in chloroform and washed with a little dilute hydrochloric acid. The chloroform solution was dried and the solvent removed to yield a gum which was triturated with a little methanol to induce crystallisation. After several crystallisations from ethyl acetate, the *methanol addition-product* of the methyl ester (4 g.) formed prisms, m. p. 215° (Found: C, 64·9; H, 4·85; N, 6·0. $C_{25}H_{22}N_2O_7$ requires C, 64·9; H, 4·8; N, 6·0%); $\lambda_{max.}$ 297 mμ (ε 10,400) with a shoulder at 225 mμ (ε 24,350); $\nu_{max.}$ in the carbonyl region at 1754 and 1723br cm.$^{-1}$.

The *anilide* was obtained from a stirred suspension of the purple condensation product (2 g.) in acetone (20 c.c.) by the addition of aniline (40 c.c.). A mustard-yellow crystalline solid separated; this was stirred for a further hour, and the mixture was kept overnight. The product (1·42 g.; 76%) was separated, washed with ether, and dried, and then crystallised from acetone (soxhlet), giving yellow prisms, m. p. 265° (Found: C, 70·8; H, 4·4; N, 8·4; Ac, 17·9. $C_{29}H_{21}N_3O_5$ requires C, 70·9; H, 4·3; N, 8·6; 2Ac, 17·4%); $\nu_{max.}$ (KBr disc) in the carbonyl region at 1762, 1714, and 1665 cm.$^{-1}$. By a similar method, the same anilide was obtained from the isoquinoline salt of the blue condensation product (Found: C, 70·9; H, 4·3; N, 8·4; Ac, 18·0%).

N-Acetyl-6-(2′-acetamidobenzoyl)anthranilic Acid (VI).—The pyridine salt of the purple condensation product (5 g.) was heated under reflux for 1½ hr. with a solution of potassium permanganate (20 g.) in water (200 c.c.). The product was filtered and the filtrate acidified with concentrated hydrochloric acid and thoroughly extracted with chloroform. The combined chloroform extracts were dried, the solvent removed, and the brown residue crystallised from methanol (charcoal). The *product* (0·6 g.) was thus obtained as almost colourless prisms, m. p. 178—182°, raised to 184·5—186° after several further recrystallisations from methanol. The mixed m. p. with *N*-acetylanthranilic acid, m. p. 185°, was 169—172° [Found: C, 63·1; H, 4·85; N, 8·3; Ac, 25·8%; Equiv.(tritration), 353. $C_{18}H_{16}N_2O_5$ requires C, 63·5; H, 4·75; N, 8·25; 2Ac, 25·4%; Equiv., 340]; $\lambda_{max.}$ 225, 230, 257, and 321 mμ (ε 33,600, 34,700, 21,400, and 8600, respectively) $\nu_{max.}$ (KBr disc) 3290 (NH), 1700, 1690 (carboxyl and amide carbonyls),

and 1655 (ketone carbonyl) cm.$^{-1}$. The n.m.r. spectrum (in dimethyl sulphoxide) showed bands at τ −1·13 and −0·43 (NH groups), 1·25 and 2·65 (7 aromatic protons), and 7·75 (methyl groups of acetyls).

Sublimation of the crude oxidation product at 170°/0·1 mm. gave a very low yield of acetylanthranil [8] (IV) as needles, m. p. 81—82°, but none was obtained by sublimation of a purified sample of (VI).

The *methyl ester* of (VI) was obtained by treatment of a solution of the acid (41 mg.) in tetrahydrofuran with excess of ethereal diazomethane at −10° for 3 days. The prisms (39 mg.) which formed were separated, washed with ether, and crystallised from acetone; they then had m. p. 168·5—169° (Found: C, 64·2; H, 5·0; N, 8·15. $C_{19}H_{18}N_2O_5$ requires C, 64·4; H, 5·1; N, 7·9%); $\nu_{max.}$ (KBr disc) 3320, 3298 (NH groups), 1713, 1693 (ester and amide carbonyls), and 1652 (ketone carbonyl) cm.$^{-1}$.

Lactam of 6-(2′-*Aminobenzoyl*)*anthranilic Acid*.—(i) A suspension of the foregoing oxidation product (251 mg.) in 2N-hydrochloric acid (15 c.c.) was heated under reflux for 30 min. The yellow solid (30 mg.) which precipitated on cooling was separated, washed, and dried. It had m. p. 290—297° raised to 298—299° after crystallisation from either aqueous acetone or ethanol when it formed yellow needles [Found: C, 70·4; H, 4·7; N, 12·2%; *M*(Rast), 217. $C_{14}H_{10}N_2O_2$ requires C, 70·5; H, 4·4; N, 11·8%; *M*, 238]; $\lambda_{max.}$ 233 and 374 mμ (ε 17,600 and 4820, respectively), $\lambda_{infl.}$ 267 mμ (ε 12,230); $\nu_{max.}$ (KBr disc) 3405 and 3310 (NH groups), 1660 and 1645 (amide and ketone carbonyls) cm.$^{-1}$. The n.m.r. spectrum (in dimethyl sulphoxide) showed bands at τ −0·90 (NH) and 2·15 to 3·05 (aromatic protons).

When the oxidation product (600 mg.) was heated with ethanol (20 c.c.) containing concentrated hydrochloric acid (3 c.c.) under reflux for 1 hr., the pale yellow plates which separated on cooling proved to be the hydrochloride of the cyclic amide of 6-(2′-aminobenzoyl)anthranilic acid. The salt (550 mg.) was decomposed to the free base by treatment of a hot suspension in acetone (100 c.c.) with water (10 c.c.). The solution was cooled and filtered; yellow needles (320 mg.), m. p. 298—299°, slowly separated and were crystallised from aqueous acetone. The product was identical with that described above.

(ii) The red acid-hydrolysis product (XI; 2 g.) was mixed with a solution of potassium permanganate (8 g.) in water (200 c.c.) and the mixture heated under reflux for 2 hr. The product was worked up as already described and the impure product purified by sublimation at 170°/0·05 mm. to give yellow needles (47 mg.), m. p. 295—298°, identical with the foregoing product.

The N-*acetyl* derivative was obtained by acetylation of the product with acetic anhydride containing a small quantity of 60% perchloric acid in the usual manner. After crystallisation from acetone it formed needles, m. p. 262—263° [Found: C, 68·7; H, 4·15; N, 9·75%; *M*(Rast), 283. $C_{16}H_{12}N_2O_3$ requires C, 68·6; H, 4·3; N, 10·0%; *M*, 280]; $\lambda_{max.}$ 221, 242, 265, and 314 mμ (ε 25,400, 30,100, 15,200, and 6230, respectively); $\nu_{max.}$ (KBr disc) in the carbonyl region at 1671, 1665, and 1652 cm.$^{-1}$. The n.m.r. spectrum (in dimethyl sulphoxide) showed peaks at τ −1·13 and −0·80 (2 NH groups), 6·44 (methyl of acetyl group), and a diffuse absorption 1·50—2·78 (7 aromatic protons).

Lactam of 2-(2′-*Aminobenzoyl*)*benzoic Acid*.—The foregoing anthranilic acid derivative (100 mg.) was dissolved in concentrated sulphuric acid (3 c.c.) and water (30 c.c.) was added gradually. A white precipitate gradually dissolved as more water was added and the solution warmed. The final solution was cooled to 0° and solid sodium nitrite was added slowly, with shaking, until diazotisation was complete (starch–iodide). Hypophosphorous acid (50%; 2 c.c.) was then added dropwise with stirring and the solution was kept at 5° for 48 hr. The yellow precipitate (75 mg.) was crystallised from acetic acid; it formed yellow needles, m. p. 243—245° alone and mixed with an authentic specimen prepared by the Beckmann rearrangement [9] of anthraquinone monoxime; [10] $\lambda_{max.}$ 231, 245, 267, 298, and 328 mμ (ε 30,150, 20,550, 12,400, 4570, and 2700, respectively); $\nu_{max.}$ (KBr disc) 1654 and 1642 (ketone and amide carbonyls) cm.$^{-1}$.

N-*Acetyl*-3-(3′-*methyl*-3′-*oxindolyl*)*anthranilic Acid* (XV; R = H, R′ = Ac).—The ethanolysis product (2·5 g.; ethyl ester of *NN*-diacetyl derivative of XIII) of the purple pyridinium salt was dissolved in glacial acetic acid (100 c.c.), and a solution of sodium dichromate (10 g.) in glacial acetic acid (150 c.c.) was added dropwise over ½ hr. The solution was then heated to 100° for 3 hr. whereupon a test sample no longer gave a precipitate of starting material on dilution. The product was cooled, poured into water (4 l.), and extracted with chloroform (5 × 100 c.c.). The chloroform extracts were washed with water (3 × 200 c.c.), dried, and

concentrated (to 20 c.c.). The resulting solution was chromatographed on alumina (15 × 2 cm.; Spence type " H ") and eluted with chloroform. The first yellow band was collected, the solvent removed, and the residual yellow gum triturated with a little benzene; a pale yellow solid was obtained and crystallised from benzene giving small colourless needles (0·51 g.), m. p. 178—180° [Found: C, 67·0; H, 4·85; N, 8·6%; *M* (Thermistor drop), 303. $C_{18}H_{16}N_2O_4$ requires C, 66·7; H, 4·95; N, 8·65%; *M*, 324]; $\lambda_{max.}$ 214, 251, and 305 mμ (ε 38,500, 14,120, 12,460, and 6660, respectively), $\lambda_{infl.}$ 224 mμ (ε 31,700); $\nu_{max.}$ 3426 and 3357 (NH groups) and in the carbonyl region at 1747, 1706, and 1686 cm.$^{-1}$. The n.m.r. spectrum (in dimethyl sulphoxide) showed absorptions at τ 0·03 and 0·27 (NH groups, exchangeable with deuterium), 1·60—3·14 (aromatic protons), 7·73 (singlet, CH_3–CO) and 7·84 (singlet, CH_3–C–CO).

The NN-*diacetyl* derivative (acetic anhydride–pyridine, or acetic anhydride alone) formed plates (ethanol), m. p. 189—191° (Found: C, 65·4; H, 4·65; N, 7·75. $C_{20}H_{18}N_2O_5$ requires C, 65·6; H, 4·95; N, 7·65%); $\lambda_{max.}$ 199, 215, 253, 261, and 305 mμ (ε 30,900, 36,700, 11,020, 10,700, and 5660, respectively); $\nu_{max.}$ 3357 (NH), 1749, 1721, and 1711 cm.$^{-1}$. The n.m.r. spectrum showed max. at τ 0·63 (1; NH), 1·52—3·68 (7; aromatic protons), 7·39 and 7·72 (2; *N*-acetyls), and 7·95 (1; C–CH_3).

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