386. *Phthalanthranilic Acid, its Structure and Reaction in Friedel–Crafts Syntheses*

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The generally accepted structure (I; R = CO_2H) for phthalanthranilic acid has been shown to be incorrect. Similarly, it has been shown that its chloro-compound, formed on treatment with phosphorus pentachloride, is not an acid chloride as is generally believed and as reactions seemed to indicate. Both from chemical evidence and from *X*-ray crystallographic studies new structures (XVI) and (XVII) are suggested for phthalanthranilic acid and its chloro-compound, respectively. The structures of the products formed on reaction of the chloro-compound with various substituted benzenes in Friedel–Crafts syntheses, as determined by chemical and *X*-ray studies, are given and mechanisms to explain the reactions are suggested.

Gabriel [1] considered the fusion product of anthranilic acid and phthalic anhydride to be *o*-phthalimidobenzoic acid (I; R = CO_2H); it is commonly called phthalanthranilic acid. This suggested structure can be justified by analogy with the formation of phthalanil (I; R = H), which is produced by heat on a mixture of aniline and phthalic anhydride. Gabriel [2] has also shown that phosphorus pentachloride replaces an hydroxyl group in phthalanthranilic acid by a chlorine atom, and he assigned the acid-chloride structure (I; R = COCl) to this chloro-compound, since it reacts with the sodium derivative of diethylmalonate to produce the diester [I; R = $CO{\cdot}CH(CO_2Et)_2$], which on hydrolysis with boiling hydriodic acid gives phthalic acid and *o*-aminoacetophenone. These reactions are all in agreement with the structure (I; R = CO_2H) for phthalanthranilic acid, and the correctness of this structure has never, to our knowledge, been questioned.

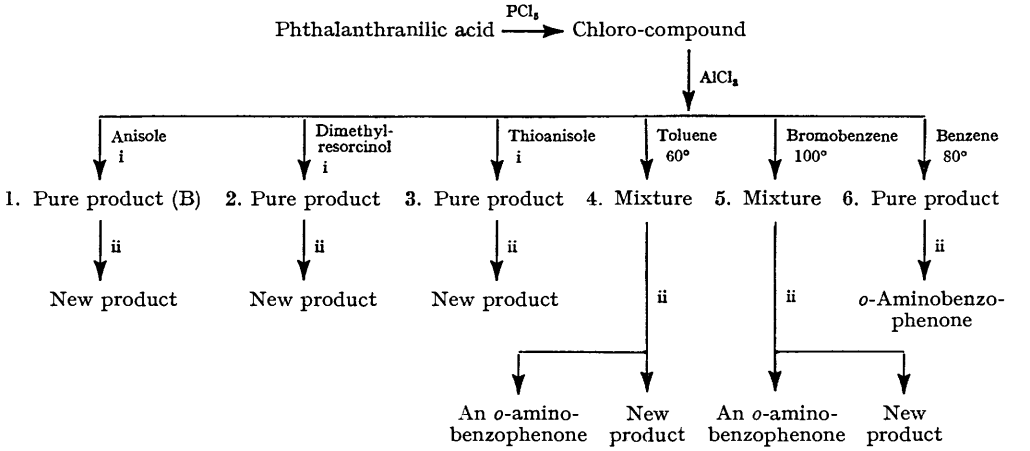
Since certain *N*-toluene-*p*-sulphonylaminobenzophenones were extremely difficult to hydrolyse without side-reactions, Engels, Lamchen, and Wicken [3] prepared *o*-aminobenzophenones from phthalanthranilic acid. The acid was converted into the chloro-compound with phosphorus pentachloride or thionyl chloride (as was done by Gabriel) and used in typical Friedel–Crafts reactions with benzene, and a variety of substituted benzenes, to produce compounds which, after analysis, were considered to be 2-phthalimidobenzophenones (II). The yields and conditions required for condensation varied according to the substituents on the benzene nucleus: (*a*) when strongly electron-repelling substituents

[1] Gabriel, *Ber.*, 1878, **11**, 2261.
[2] Gabriel, *Ber.*, 1918, **51**, 1493.
[3] Engels, Lamchen, and Wicken, *J.*, 1959, 2694.

were present, condensations occurred at room temperature and yields were excellent; (*b*) when substituents were only weakly electron-repelling, heating was necessary and yields were low; (*c*) with benzene itself long heating was required and yields were very poor.

Refluxing solutions of these products in alcohol with hydrazine gave rise (see Table) to two types of reaction: (i) with the product obtained from benzene as in (*c*) above, the compound was split into *o*-aminobenzophenone and phthalhydrazide (Ing and Manske reaction); (ii) with the products obtained as in (*a*), the phthaloyl group was not split off, but reaction with hydrazine occurred readily to form a new type of compound to which the triazepine structure (III) has been assigned (now shown to be incorrect). With products obtained as in (*b*), a mixture of the *o*-aminobenzophenone, phthalhydrazide, and the new type of product was obtained.

No mechanism consistent with the well-established electronic effects of the substituents fitted the results obtained in the reactions with hydrazine but, as seen in the Table, no compounds with electron-attracting substituents were included. Such compounds could not be prepared by the method outlined in the Table as Friedel–Crafts condensations do not occur with electrophilic hydrocarbons. It was expected, however, that the reaction of hydrazine with such compounds would throw some light on the mechanism, and alternative routes for the preparation of substituted benzophenones were investigated.



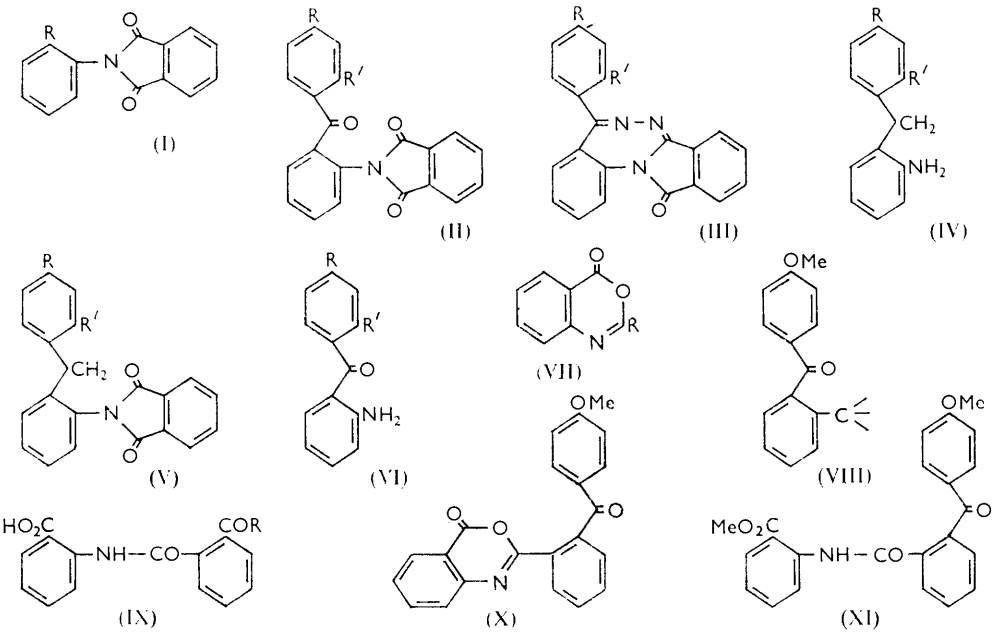
i At room temperature. ii Hydrazine.

Fusion of 2-amino-4′-methoxydiphenylmethane (IV; R = OMe, R′ = H) with phthalic anhydride yielded the phthalimido-compound (V; R = OMe, R′ = H), which on oxidation with chromic acid in glacial acetic acid gave a phthalimidobenzophenone (A), m. p. 197—199°. Hydrazine in boiling ethanol decomposed (A) to 2-amino-4′-methoxybenzophenone (VI; R = OMe, R′ = H) and this in conjunction with its preparation indicated that (A) had the structure (II; R = OMe, R′ = H). The condensation product (B) prepared as in the Table from anisole *via* a Friedel–Crafts reaction with the chloro-compound of phthalanthranilic acid, should be the same phthalimido-compound (II; R = OMe, R′ = H), but this product (B) had m. p. 205—206°, much depressed when the compound was mixed with (A). Hydrazine in boiling ethanol condensed with (B) to form a new product and no aminobenzophenone was obtained. The infrared spectra of (A) and (B) were different. Though (A) gave a strong benzophenone carbonyl absorption at 1648 cm.$^{-1}$, product (B) gave none.

To establish the structure of (A), 2-amino-4′-methoxybenzophenone was synthesised by two routes: (*a*) hydrolysis of the Friedel–Crafts condensation product of *N*-toluene-*p*-sulphonylanthranilic acid chloride and anisole;[4] (*b*) reaction of the Grignard reagent

[4] Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1946, 646.

of *p*-methoxybromobenzene with acetanthranil (VII; R = Me) and acid hydrolysis of the product according to the method of Lothrup and Goodwin.[5] The aminobenzophenones were identical (m. p., mixed m. p., and infrared spectra), and fusion with phthalic anhydride



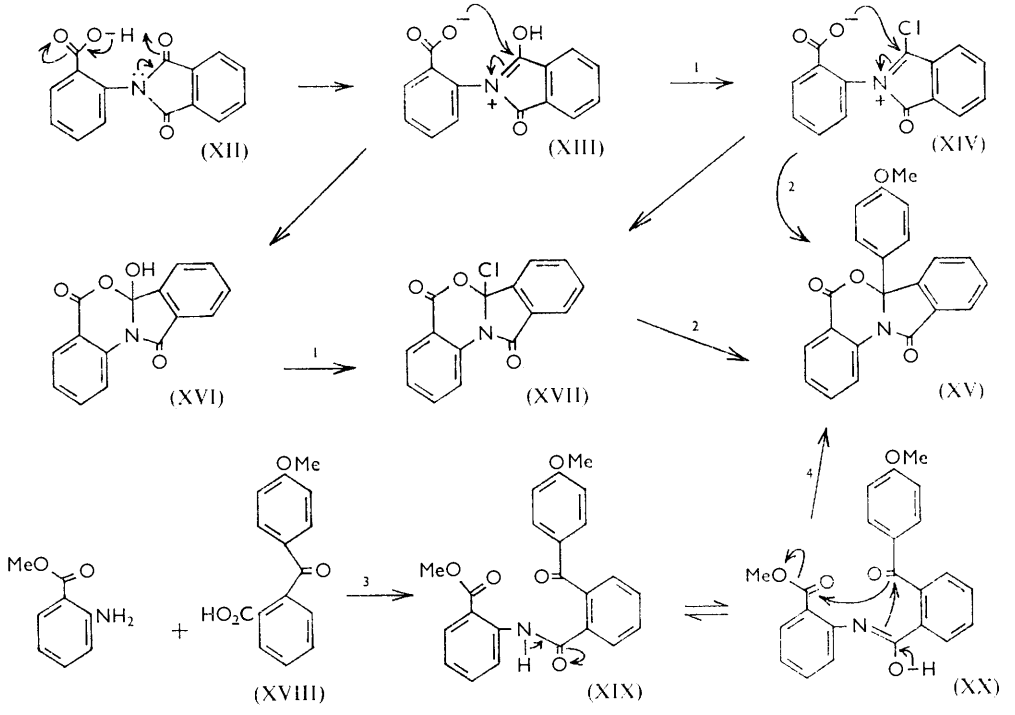
yielded the phthalimidobenzophenone (A). The compound (B) was thus not the expected phthalimidobenzophenone.

Compound (B) slowly dissolved when heated under reflux in sodium hydroxide solution, and on acidification 4-methoxybenzoylbenzoic acid was precipitated. This indicated that the partial structure (VIII) was present in compound (B) and that condensation of phthalanthranilic acid with anisole occurred at a carbonyl group of one of the phthalimido-groups and not of the carboxyl group as would be expected if formula (I; R = CO_2H) was correct. Such a condensation could occur if, during heating with phosphorus pentachloride (or thionyl chloride) or treatment with anhydrous aluminium chloride, the phthalimido-ring opened to produce the compound (IX; R = Cl), which could then condense, with anisole, at the carbonyl group originally of the phthalimido-group. Loss of water could produce the benzoxazinone (X), analogous to the formation of the acetanthranil (VII; R = Me) from *N*-acetylanthranilic acid.[6] However, when phthalanthranilic acid was treated with phosphorus pentachloride and then poured into water, or refluxed with anhydrous aluminium chloride for 2 hr. and then poured into water, only unchanged phthalanthranilic acid was isolated and no 2′-carboxyphthalanilic acid (IX; R = OH) was obtained. On the contrary, the phthalanilic acid (IX; R = OH) prepared by heating a benzene suspension of anthranilic acid and phthalic anhydride, on treatment with phosphorus pentachloride and anhydrous aluminium chloride, gave phthalanthranilic acid. Furthermore, strong heating of methyl anthranilate and phthalic anhydride produced the same ester as was obtained from either phthalanthranilic acid and diazomethane *or* treatment of phthalanthranilic acid in dry benzene with phosphorus pentachloride and then with sodium methoxide. This ester must thus have the structure (I; R = CO_2Me), which

[5] Lothrup and Goodwin, *J. Amer. Chem. Soc.*, 1943, **65**, 363.
[6] Bredt and Hof, *Ber.*, 1900, **33**, 29; Zentmyer and Wagner, *J. Org. Chem.*, 1949, **14**, 967.

supported the structures (I; R = CO_2H) and (I; R = COCl) of Gabriel for phthalanthranilic acid and its chloro-derivative, respectively.

Since the alkaline hydrolysis suggested a structure such as (X) for compound (B), an alternative method for its production was investigated. Thus, condensation of 4′-methoxybenzoylbenzoic acid with methylanthranilate should produce the ester (XI), which on hydrolysis should form the acid (IX; R = *p*-C_6H_4·OMe), and this, like acetanthranil, would be expected to form the benzoxazinone (X). Strong heating of a mixture of 4′-methoxybenzoylbenzoic acid and methylanthranilate, however, produced compound (B) and not the expected ester (XI). Thus, during the heating, not only was an amide formed with the elimination of water, but a molecule of methanol was also lost. Strong heating of benzoic acid and methyl anthranilate produced methyl *N*-benzoylanthranilate and no methyl alcohol was eliminated. When 2-carboxyacetophenone and methyl anthranilate were heated the condensation product (C) again indicated a loss of a molecule of methanol as well as a molecule of water. The loss of methanol was thus associated with the phenone carbonyl group, and in the condensation of the benzoylbenzoic acid with methyl anthranilate a structure such as (X) could not have been formed since this would have been equally possible with methyl *N*-benzoylanthranilate. Similarly, condensation with the loss of a molecule of water as well as a molecule of methanol occurred when methyl anthranilate was heated with *o*-benzoylbenzoic acid, *o*-(4-bromobenzoyl)-benzoic acid, or *o*-(2,4-dimethoxybenzoyl)benzoic acid. The products all have similar infrared spectra and thus all have the same type of structure as (B).



Reagents: 1, PCl_5; 2, *p*-methoxybenzene, $AlCl_3$; 3, Heat, $-H_2O$; 4, —MeOH

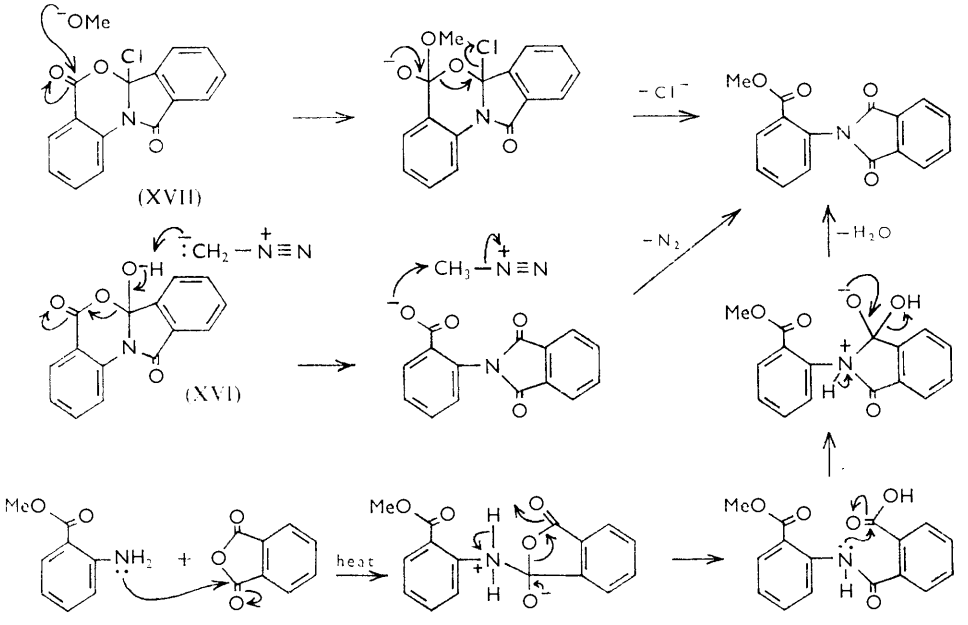
The formation of compound (B) by those two completely different routes can, however, be explained if compound (B) had the structure (XV), and phthalanthranilic acid was either (XIII) or (XVI) or a mixture of the two. This structure could be formed from the Gabriel structure (XII), and the chloro-compound would then have the structure

(XIV) or (XVII) and not the acid-chloride structure (I; R = COCl). The benzoxazinone ring in compound (B) could thus be formed either during the preparation of phthalanthranilic acid, (XII) ⟶ (XIII) ⟶ (XVI), or in the treatment with phosphorus pentachloride, (XIV) ⟶ (XVII), or during the treatment with anhydrous aluminium chloride, (XIV) ⟶ (XV).

Mechanisms whereby a structure such as (XV) would be formed from phthalanthranilic acid are shown in (XIII) ⟶ (XIV) ⟶ (XV), or (XIII) ⟶ (XIV) ⟶ (XVII) ⟶ (XV), or (XIII) ⟶ (XVI) ⟶ (XVII) ⟶ (XV), and one from 4′-methoxybenzoylbenzoic acid is shown in (XVIII) ⟶ (XIX) ⟶ (XX) ⟶ (XV).

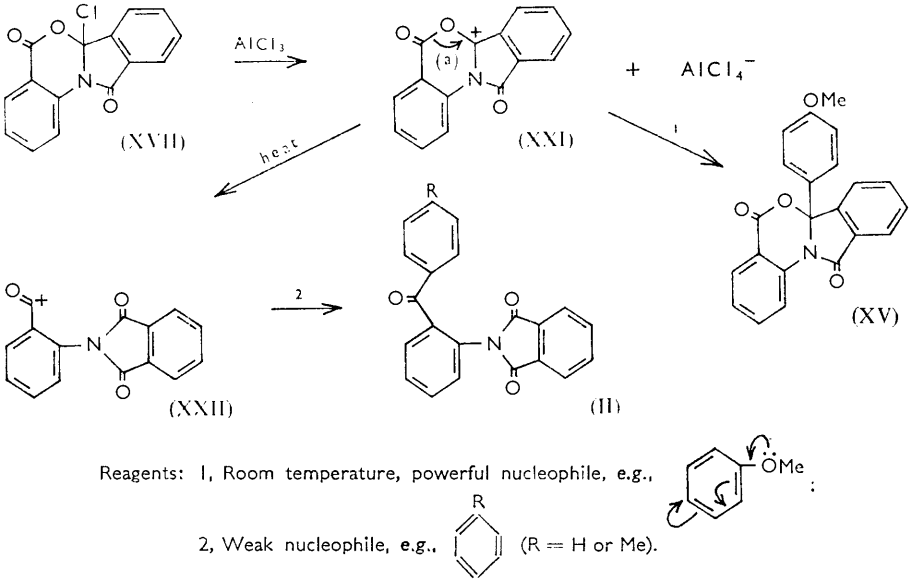
With structure (XVI) for phthalanthranilic acid it is possible to understand why the site of attachment to the molecule is different when the chloro-compound is treated with a nucleophile under Friedel–Crafts conditions from when it is directly treated with a nucleophile. This structure also explains how the same ester (I; R = CO_2Me) could be obtained by reaction of (i) the chloro-compound with sodium methoxide; (ii) the acid with diazomethane, and (iii) phthalanthranilic acid and methylanthranilate on heating (see below). Structure (XIV) must be ruled out for the chloro-compound as it could not give the ester obtained with sodium methoxide.

The chloro-compound reacted with sodium methoxide by an S_N2 mechanism, but under Friedel–Crafts conditions an S_N1 mechanism will be operative. Structure (XVII) also offers an explanation for the anomalous results obtained under Friedel–Crafts conditions, when powerful nucleophiles, *e.g.*, anisole, dimethylresorcinol, and thionisole, gave pure products of the structural type (XV) (products **1**, **2**, and **3** in the Table), whereas very weak nucleophiles, *e.g.*, benzene, gave the pure benzophenone (product **6**). The carbonium ion (XXI), resonance-stabilised by sharing of its positive charge with the adjacent oxygen and nitrogen atoms, would be a weak electrophile, capable of reacting only with powerful nucleophiles, and would give products with structures of the type (XV). In the absence



of powerful nucleophiles no reaction will take place until sufficient energy has been supplied to effect the electronic shift (*a*) which will produce the carbonium ion (XXII) not stabilised to the same degree (and so more reactive) and reaction with weak nucleophiles will take place to form products with structure of type (II). With weak nucleophiles like toluene no

reaction would occur at room temperature, but at elevated temperatures, when shift (*a*) is possible, and both carbonium ions (XXI) and (XXII) are present, the $+T$ effect will make the nucleophile strong enough to react not only with the reactive ion (XXII) but also with the weak ion (XXI), to produce a mixture of compounds with structures of types (XV)



and (II). The observation that bromobenzene at 100° also gave this type of mixture (product 5 in the Table) was unexpected. It showed, however, that whereas benzene only reacted with the reactive ion (XXII), bromobenzene could, at 100°, also react with the ion (XXI). This indicates that the forces operative under Friedel–Crafts conditions are somewhat different from those controlling nitration, and that in the experiment described the $+T$ effect was stronger than the $-I$ effect.

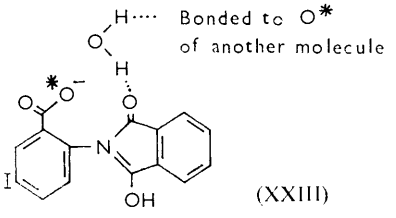
In order to test the accuracy of these ideas, 5-bromoanthranilic acid [7] and 5-iodoanthranilic acid [8] were prepared, and fused with phthalic anhydride to produce the corresponding bromo- and iodo-phthalanthranilic acids. These in turn were treated with phosphorus pentachloride and anisole in Friedel–Crafts reactions to yield condensation products similar to (B) in behaviour; their infrared spectra showed that they had the same structure as (B).

The acids were recrystallised from aqueous ethanol and then slowly from an aqueous ethanol solution, to produce crystals suitable for *X*-ray study. The Friedel–Crafts condensation products were allowed to crystallise slowly from glacial acetic acid and also gave crystals suitable for *X*-ray study.

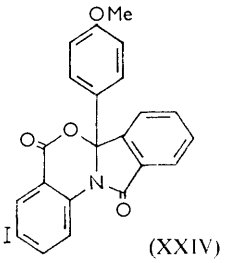
In this way Mayer and Pratt [9] showed that recrystallised 5-iodophthalanthranilic acid was the hydrated product of the structure (XIII), as represented in (XXIII). Structure (XIII) for phthalanthranilic acid is, however, not supported by infrared data, since it showed no strong absorption of carboxylate ion in the region 1610—1550 cm.$^{-1}$. On the other hand, the infrared data are consistent with structure (XVI). The reactions of the chloro-compound with various nucleophiles under differing conditions have already been shown to suggest the structure (XVII), which is to be expected if the acid had structure (XVI). It must thus be assumed that recystallisation from aqueous ethanol opened the

[7] Wheeler and Oates, *J. Amer. Chem. Soc.*, 1909, **31**, 586.
[8] Wallingford and Kreuger, *Org. Synth.*, 1939, **19**, 52.
[9] Mayer and Pratt, *Acta Cryst.*, 1963, **16**, 1086.

benzoxazine ring of the planar structure (XVI) to form the dipolar non-planar structure (XIII), which is stabilised by hydration. Recrystallising phthalanthranilic acid from a non-polar solvent like dry benzene gave a crystalline product, m. p. 213—215° undepressed by admixture with the product recrystallised from aqueous ethanol, m. p. 218—219°. The infrared spectra of the products recrystallised from benzene and aqueous ethanol were



(XXIII)



(XXIV)

different especially in the 1500—1800 cm.$^{-1}$ region, and the product from aqueous ethanol, unlike that from benzene, showed a strong band at 1405 cm.$^{-1}$. The product from aqueous ethanol could be recrystallised again from benzene or glacial acetic acid without changing its infrared spectrum, but if it was melted and allowed to crystallise, the spectrum was identical with the product from benzene.

From the above chemical and spectral data it is concluded that phthalanthranilic acid, as prepared, has the structure (XVI), which is retained on recrystallisation from benzene, and that its ring structure is retained in reactions with phosphorus pentachloride or thionyl chloride, but that it is converted into the structure (XIII) on recrystallisation from aqueous ethanol.

Attempted *X*-ray study of the benzene-crystallised product showed that its crystal structure was different from the product from aqueous ethanol [10] but no structure determination has yet been made owing to twinning of the crystals.

An *X*-ray crystallographic study by K. P. Klein [11] of the Friedel–Crafts condensation product of the chloro-compound of 5-iodophthalanthranilic acid with anisole revealed the benzoxazine ring, and the compound was shown to be 6a,11-dihydro-3-iodo-5,11-dioxo-6a-*p*-methoxyphenyl-5*H*-isoindolo[2,1-*a*][3,1]benzoxazine, (XXIV), as was inferred from the chemical data.

Experimental

Preparation of 4-Methoxy-2′-phthalimidobenzophenone.—(*a*) *By oxidation of 4-methoxy-2′-phthalimidodiphenylmethane.* 4-Methoxy-2′-phthalimidodiphenylmethane (0·2 g.) was dissolved in glacial acetic acid (5 ml.) and refluxed while chromic oxide (0·4 g.) in glacial acetic acid (5 ml.) was slowly added during ½ hr. The solution was further heated (4 hr.) and the resulting green solution was diluted with water until precipitation ceased. Crystallisation of the solid from aqueous ethanol gave *4-methoxy-2′-phthalimidobenzophenone* (0·05 g., 13%), pale yellow crystals, m. p. 197—199° (Found: C, 73·8; H, 4·2; N, 4·6. $C_{22}H_{15}NO_4$ requires C, 73·9; H, 4·2; N, 3·9%); $\nu_{max.}$ (Nujol) 1780sh, 1730vs, 1648s, 1605s, and 1580m cm.$^{-1}$.

(*b*) *From 2-amino-4′-methoxybenzophenone.* 2-Amino-4′-methoxybenzophenone (0·7 g.) and phthalic anhydride (0·45 g.) were mixed and heated to 180—200° for 20 min. After cooling, it was crystallised from aqueous acetic acid to give pale yellow crystals (0·7 g., 63%), identical with the product prepared in (*a*) (m. p., mixed m. p., and infrared spectra).

Preparation of Methyl 2-Phthalimidobenzoate.—(*a*) *From methyl anthranilate.* Methyl anthranilate (1·9 ml.) and phthalic anhydride (2·2 g.) were heated in an oil-bath at 160—170° for 20 min. The mixture was cooled and on addition of ethanol white crystals formed.

[10] Feil, private communication.
[11] Klein, private communication to be submitted to *Acta Cryst.*

Crystallisation from aqueous acetic acid gave methyl 2-phthalimidobenzoate (3·1 g., 74%), m. p. 155—156°.

(*b*) *From phthalanthranilic acid by diazomethane.* To phthalanthranilic acid (5·2 g.) in dry methanol (100 ml.), cooled to 0°, diazomethane solution in ether was added until no more nitrogen was given off and the colour remained pale yellow. A white solid precipitated. The excess of diazomethane, ether, and half the methanol were distilled off. After cooling, the white crystals were filtered off and crystallised from aqueous acetic acid to give the same ester as in (*a*) above (m. p., mixed m. p. and infrared spectra) (4·95 g., 88%).

(*c*) via *The chloro-compound of phthalanthranilic acid.* Phthalanthranilic acid (10 g.) in benzene (50 ml.) and phosphorus pentachloride (8 g.) were refluxed on a water-bath for 2 hr. To this was added dropwise a solution of sodium methoxide obtained by reaction of sodium (2·2 g.) on methanol (20 ml.). After evolution of hydrogen chloride had ceased, the mixture was decomposed with water, the benzene layer was dried and the benzene removed by distillation. The remaining black gum was crystallised from aqueous acetic acid (charcoal) to give the same ester as in (*a*) and (*b*) above (m. p., mixed m. p., and infrared spectra) m. p. 155—156° (lit.,[2] 160—162°).

Preparation of 2′-Carboxyphthalanilic Acid [12] (IX; R = OH).—(*a*) A suspension of phthalic anhydride (14·8 g.) in benzene (100 ml.) was mixed with a suspension of anthranilic acid (13·7 g.) in benzene (100 ml.) and heated on a water-bath for 15 min. A yellow solid formed, which, after cooling, was filtered off, and crystallised from aqueous ethanol to give 2′-carboxyphthalanilic acid as fine white needles (23·9 g., 84%), m. p. 171—172°.

(*b*) *Hydrolysis of methyl-2-phthalimidobenzoate.* Methyl 2-phthalimidobenzoate (0·5 g.) was refluxed with sodium hydroxide (10 ml. of 10% soln.) for ½ hr. (all solid was dissolved in 10 min.). The alkaline solution was extracted with ether and then acidified, and the precipitate (0·5 g., 99%) was crystallised from aqueous ethanol and found to be identical with the product prepared in (*a*) (m. p., mixed m. p., and infrared spectra).

Hydrolysis of Friedel–Crafts Condensation Products.—(*a*) *Product from chloro-compound of phthalanthranilic acid and anisole*[3] (*compound B*). The compound (B) (1·0 g.) was heated under reflux with sodium hydroxide (20 ml. of 10% aqueous solution). After 2½ hr. most of the solid was dissolved to give a pale yellow solution. Heating was continued (6 hr.). The solution was cooled and filtered, and the filtrate extracted with ether. The ether extract left no residue on evaporation. The alkaline solution was then acidified with hydrochloric acid and the precipitate was filtered off. Crystallisation from aqueous ethanol yielded *o*-4-methoxybenzoylbenzoic acid (0·5 g.), m. p. 141—142°, identical with the acid made according to the literature [13] (m. p., mixed m. p., and infrared spectra).

(*b*) *Product from chloro-compound of phthalanthranilic acid and* 1,3-*dimethoxybenzene.*[3] The compound (1 g.) was heated with sodium hydroxide (20 ml. of 10% aqueous solution) for 1¾ hr. The clear yellow solution was cooled, treated with ether, and set aside. (Nothing was extracted by the ether.) From the solution white crystals separated out; they were filtered off (0·34 g.) and found to be starting material. The filtrate was acidified with hydrochloric acid, and the yellow solid which formed was twice crystallised from ethanol to yield *o*-(2,4-dimethoxybenzoyl)-benzoic acid, m. p. 158—160°, unchanged on admixture with an authentic sample. Infrared spectra were also identical.

Fusion of Benzoylbenzoic Acid and Derivatives with Methylanthranilate.—(*a*) o-*Benzoylbenzoic acid.* *o*-Benzoylbenzoic acid (5·0 g.) and methyl anthranilate (10 ml.) were heated under reflux for 1 hr. in a wax-bath at 250°. Excess of methyl anthranilate was distilled off under reduced pressure. The remaining brown gum crystallised when heated with ethanol. Crystallisation from aqueous ethanol gave 6a,11-dihydro-5,11-dioxo-6a-phenyl-5*H*-isoindolo-[2,1-*a*][3,1]benzoxazine as white crystals (3·6 g., 50%), m. p. 181—182° (Found: C, 77·4; H, 4·0; N, 4·2. $C_{21}H_{13}NO_3$ requires C, 77·1; H, 4·0; N, 4·3%).

(*b*) o-4-*Methoxybenzoylbenzoic acid.* The acid (2·0 g.) and methyl anthranilate (6 ml.) were heated under reflux for 1 hr. in a wax-bath at 250°. The product was worked up as described under (*a*) and gave 6a,11-*dihydro*-5,11-*dioxo*-6a-*p*-*methoxyphenyl*-5H-*isoindolo*[2,1-a][3,1]-*benzoxazine* (XV) as white crystals, m. p. 205—206° (Found: C, 73·6; H, 4·3; N, 3·9. Calc. for $C_{22}H_{15}NO_4$: C, 73·9; H, 4·2; N, 3·9%); $\nu_{max.}$ (Nujol) 1738s, 1728vs, 1985m, 1601s, and

[12] Furortes and Gaetani, *Proc. XIth Internat. Congr. Pure and Appl. Chem.*, 1947, **2**, 85.
[13] Nourrisson, *Ber.*, 1886, **19**, 2103; Orndorf and Kelly, *J. Amer. Chem. Soc.*, 1922, **44**, 1526.

1578m cm.$^{-1}$. This compound was identical (m. p., mixed m. p., and infrared spectra) with the compound previously wrongly reported as 4-methoxy-2′-phthalimidobenzophenone.[3]

(*c*) o-(2,4-*Dimethoxybenzoyl*)*benzoic acid*. The acid (5·0 g.) and methyl anthranilate (8 ml.) were heated and worked up as described under (*a*), and gave 6a,11-*dihydro*-5,11-*dioxo*-6a-(2,4-*dimethoxyphenyl*)-5H-*isoindolo*[2,1-a][3,1]*benzoxazine*, as white crystals (3·4 g., 50%), m. p. 231—232° (Found: C, 71·5; H, 4·7; N, 3·6. $C_{23}H_{17}N_5O$ requires C, 71·3; H, 4·4; N, 3·6%); $\nu_{max.}$ 1742s, 1730s, and 1630m cm.$^{-1}$. This compound was identical (m. p., mixed m. p., and infrared spectra) with the compound previously wrongly reported as 2,4-dimethoxy-2′-phthalimidobenzophenone.[3]

(*d*) o-4-*Bromobenzoylbenzoic acid*. The acid (2·0 g.) and methyl anthranilate (4 ml.) were heated and worked up as described in (*a*), but recrystallised from aqueous acetic acid to give 6a-*p*-*bromophenyl*-6a,11-*dihydro*-5,11-*dioxo*-5H-*isoindolo*[2,1-a][3,1]*benzoxazine* as white crystals (0·5 g., 17%), m. p. 223—224° (Found: C, 62·0; H, 3·1; Br, 19·6; N, 3·4. $C_{21}H_{12}BrNO_3$ requires C, 62·1; H, 3·0; Br, 19·7; N, 3·4%); $\nu_{max.}$ (Nujol) 1724s, 1732s, and 1610m cm.$^{-1}$.

Fusion of Phthalic Anhydride with Substituted Anthranilic Acids.—(i) *With* 2-*amino*-5-*bromobenzoic acid*. The acid (2·82 g.) was heated with phthalic anhydride (1·92 g.) to 190—200° for 15 min. A hard crystalline mass formed from the melt after 10 min. The cooled product was crystallised (charcoal) from aqueous ethanol to give 3-*bromo*-6a,11-*dihydro*-6a-*hydroxy*-5,11-*dioxo*-5H-*isoindolo*[2,1-a][3,1]*benzoxazine* as white prisms (3·7 g., 81·5%) (Found: C, 52·1; H, 3·0; Br, 23·3; N, 4·5. $C_{15}H_6BrNO_4$ requires C, 52·0; H, 2·3; Br, 23·1; N, 4·1%).

(ii) *With* 2-*amino*-5-*iodobenzoic acid*. The acid (6·15 g.) and phthalic anhydride (3·46 g.) were fused and worked up as described under (i) to give 6a,11-*dihydro*-6a-*hydroxy*-3-*iodo*-5,11-*dioxo*-5H-*isoindolo*[2,1-a][3,1]*benzoxazine* as white crystals (5·3 g., 58%), m. p. 222—223° (Found: C, 46·5; H, 2·7; I, 31·9; N, 3·6. $C_{15}H_8NIO_4$ requires C, 45·8; H, 2·1; I, 32·3; N, 3·6%).

Friedel–Crafts Condensation Products of Products under (i) *and* (ii) *above with Anisole*.—(*a*) The 3-bromo-compound in (i) above (4·5 g.) and phosphorus pentachloride (2·7 g.) were heated under reflux in anhydrous tetrachloroethane (30 ml.) until no more hydrogen chloride was evolved (1¼ hr.). To the cooled solution excess dry anisole (1·9 g.) was added, and anhydrous aluminium chloride (3·5 g.), finely crushed, was added during ½ hr. A bright red complex formed immediately. After the aluminium chloride was added the mixture was left at room temperature for 20 min., and then heated on a water-bath at 40—50° for 1½ hr., with frequent shaking. The product was decomposed with ice/HCl and the tetrachloroethane and excess anisole were removed by steam-distillation. The yellow oil remaining soon solidified, and on recrystallisation from ethanol gave 3-*bromo*-6a,11-*dihydro*-5,11-*dioxo*-6a-*p*-*methoxyphenyl* 5H-*isoindolo*[2,1-a][3,1]*benzoxazine*, as white crystals (5·0 g., 88%), m. p. 221—223° (Found: C, 60·4; H, 3·6; Br, 18·4; N, 4·0. $C_{22}H_{14}BrNO_4$ requires C, 60·5; H, 3·2; Br, 18·4; N, 3·2%); $\nu_{max.}$ (in Nujol) 1746s, 1733vs, 1685w, 1603m, and 1593sh cm.$^{-1}$.

(*b*) The 5-iodo-compound in (ii) above (5·4 g.), phosphorus pentachloride (2·8 g.), and dry tetrachlorethane (50 ml.) were heated and allowed to react with anisole (1·8 g.) and anhydrous aluminium chloride (3·6 g.) as described under (a) above, and crystallised from acetic acid to give 6a,11-*dihydro*-3-*iodo*-6a-*p*-*methoxyphenyl*-5,11-*dioxo*-5H-*isoindolo*[2,1-a][3,1]*benzoxazine* (XXIV) as shiny white crystals (3·9 g., 60%), m. p. 215—216° (Found: C, 54·7; H, 3·1; I, 26·3. $C_{22}H_{14}NIO_4$ requires C, 54·7; H, 2·9; I, 26·3%); $\nu_{max.}$ (in Nujol) 1742s, 1730vs, 1785sh, 1605m, and 1588m cm.$^{-1}$.

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