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CONVERSION OF INDONES TO QUINOLINE AND ISOQUINOLINE DERIVATIVES—IV[1]

SCHMIDT REACTION WITH 2-(*o*-CARBOXYPHENYL)3-PHENYL-INDONE AND WITH 2-(*o*-CARBOMETHOXYPHENYL)-3-PHENYLINDONE

A. MARSILI, M. F. SAETTONE and V. SCARTONI

Istituto di Chimica Farmaceutica e Tossicologica dell'Università. 56100 Pisp, Italy

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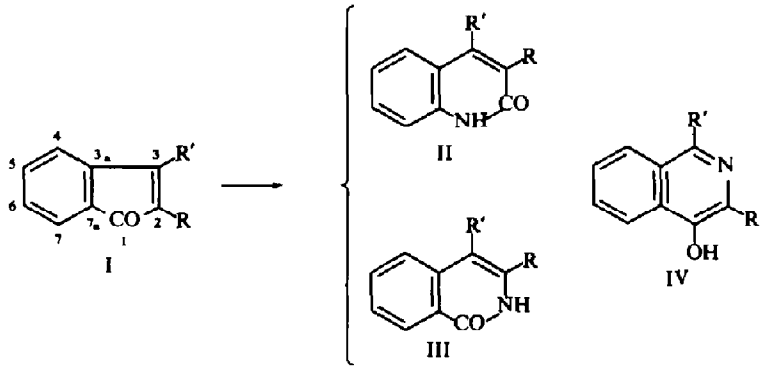
Abstract—The Schmidt reaction with 2-(*o*-carboxyphenyl)3-phenylindone (V) in a mixture of sulphuric and acetic acid affords 12-phenyl-5*H*-[2]benzopyrano[3.4-*b*]quinoline-5-one (VII) as the main product. The methyl ester of V, which is almost unreactive towards hydrazoic acid in acetic-sulphuric acid solution, is converted mainly into 2-phenyl-3-(*o*-carbomethoxyphenyl)4--hydroxyquinoline (XVI) when the reaction is carried out in concentrated sulphuric acid solution.

PREVIOUS work[1-3] has shown that indones (I) can be converted into quinoline and isoquinoline derivatives by the Schmidt reaction. Insertion of the N atom may occur between C atoms 1–7a (I → II), 1–2 (I → III) or 2–3 (I → IV), depending upon the acid strength of the reaction medium and the nature of the substituent R.



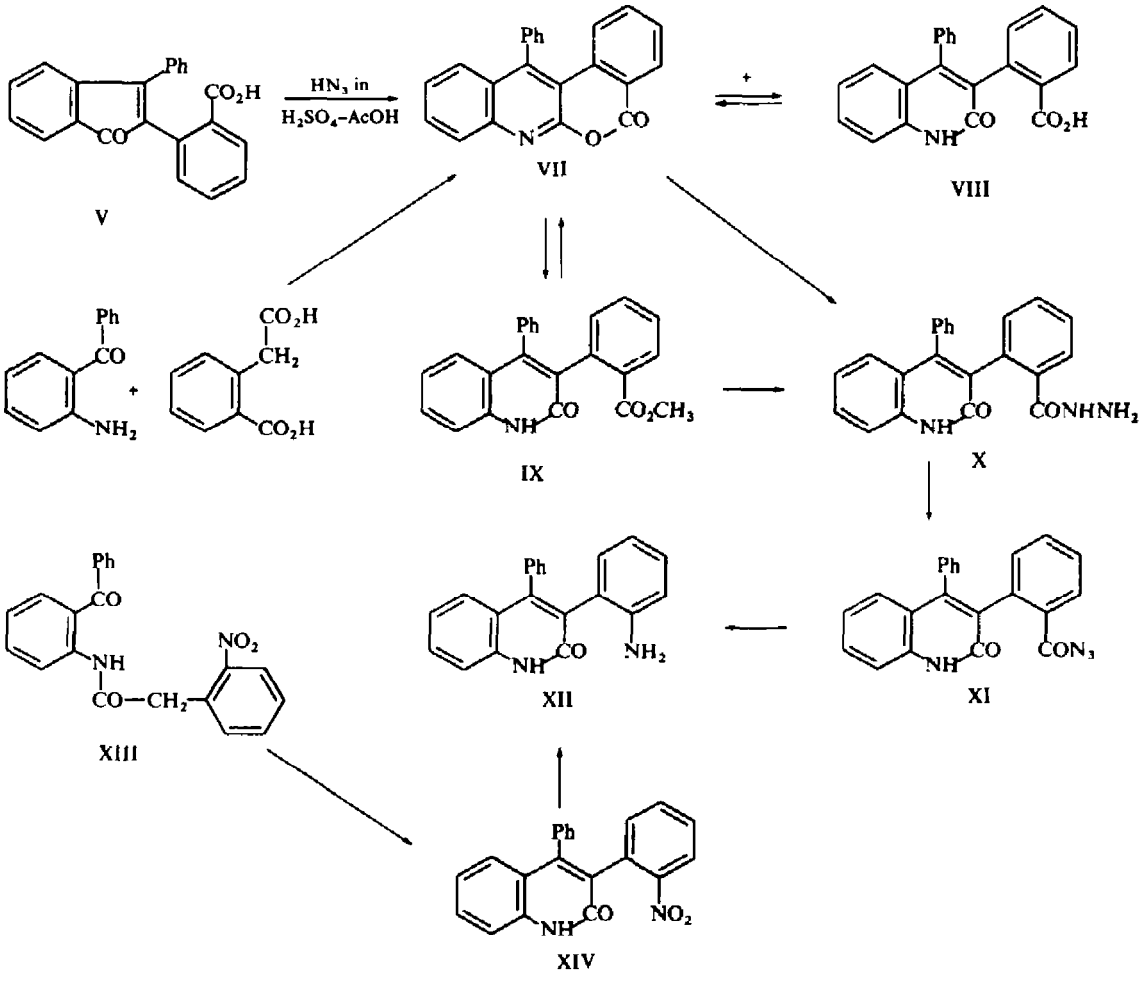
This work is concerned with the application of the Schmidt reaction to 2-(*o*-carboxyphenyl)3-phenylindone (V), and to 2-(*o*-carbomethoxyphenyl)3-phenylindone (VI): the most striking fact observed in the present study is the influence of the free or esterified carboxyl group on the structure of the reaction products.

The indone V reacted with hydrazoic acid in a mixture of acetic and sulphuric acid to give two products, for which analytical and spectral data indicated VII and VIII (Scheme 1) as possible structures. Compound VII, the main reaction product (70%), was a N-containing weakly basic substance, whose IR spectrum showed a single CO absorption band at 5·74 μ. Treatment of this compound with boiling aqueous alkali followed by acidification produced an acid (λ_{CO} 5·99, 6·12 μ), which was identical with the minor product (VIII) isolated in 30% yield from the reaction

mixture. The latter compound could be easily reconverted to VII by sublimation. Treatment of VII with methanol under reflux in the presence of sulphuric acid produced the ester IX (λ_{CO} 5·85, 6·08 μ) which also was reconverted to the starting material by sublimation. The carbomethoxy group of IX was transformed into an amino group by the usual Curtius procedure, through the intermediates X (also directly obtained on treatment of VII with hydrazine) and XI. The end product, 3-(*o*-aminophenyl)4-phenylcarbostyril (XII) was independently prepared from XIII *via* the route indicated in Scheme 1. A further proof for the 12-phenyl-5*H*-[2]benzopyrano-[3.4-*b*]quinoline-5-one structure assigned to VII was given by the direct synthesis of this compound, carried out by condensation of *o*-aminobenzophenone with homophthalic acid.

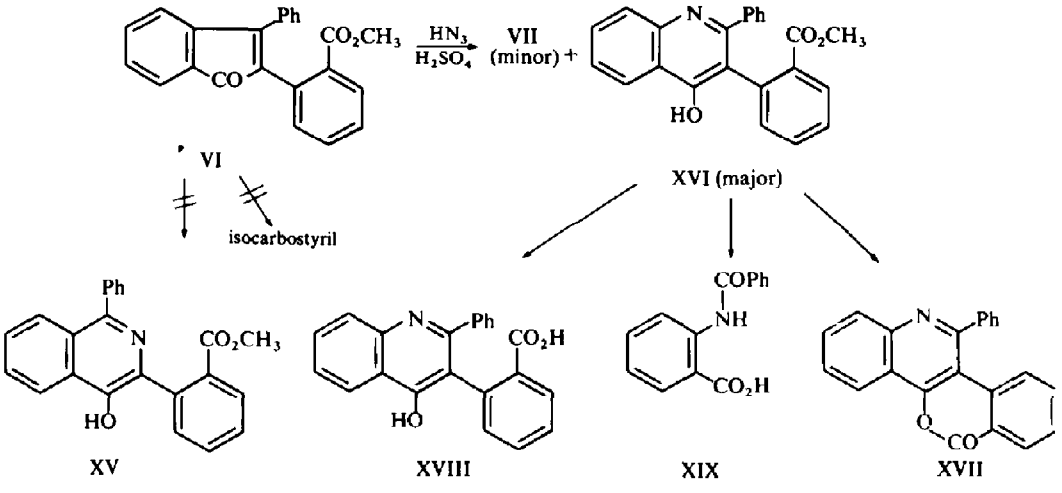
When the Schmidt reaction was carried out on 2-(*o*-carbomethoxyphenyl)3-phenylindone (VI) in acetic-sulphuric acid solution, only small amounts of VII and unreacted material were obtained, even after long reaction times, and in the presence

SCHEME 1



of a large excess of hydrazoic acid. The use of concentrated sulphuric acid as the solvent, led to formation of a weakly basic methyl ester, isomeric with IX, whose IR spectrum showed a single carbonyl absorption band at 5·79 μ. Permanganate oxidation gave no structural evidence for this compound, only benzoic and phthalic acid being formed. Sublimation of the ester afforded a weakly basic compound, λ_{CO} 5·76 μ, isomeric with the lactone VII, while saponification gave an acid, isomeric with VIII, soluble in moderately conc hydrochloric acid. The lack of strong absorption in the 6 μ region of the IR spectra of the ester and the acid, and their easy conversion into a lactone, ruled out the possibility of an isocarbostyril type of structure for these compounds. Structure XV (Scheme 2), formed by insertion of a N atom into the C_2—C_3 bond of the indone nucleus, was also discarded on the consideration that permanganate oxidation of the compound would have led to formation of *o*-benzoylbenzoic and phthalic acids. There was left, as the only alternative, structure XVI, formed by insertion of NH between C_3 and C_{3a}. Therefore the ester was assigned this structure, the lactone and the acid those XVII and XVIII, respectively.

SCHEME 2



Our attempts to transform XVI into known products, or to synthesize it directly, failed. However, evidence supporting structure XVI came from peroxyacetic acid oxidation of the compound, N-benzoylanthranilic acid (XIX) being isolated in the reaction.

The Schmidt reaction in sulphuric acid was also carried out with the indone V, but in this case the results were similar to those obtained in acetic–sulphuric acid solution, only a small amount of the basic lactone XVII being formed.

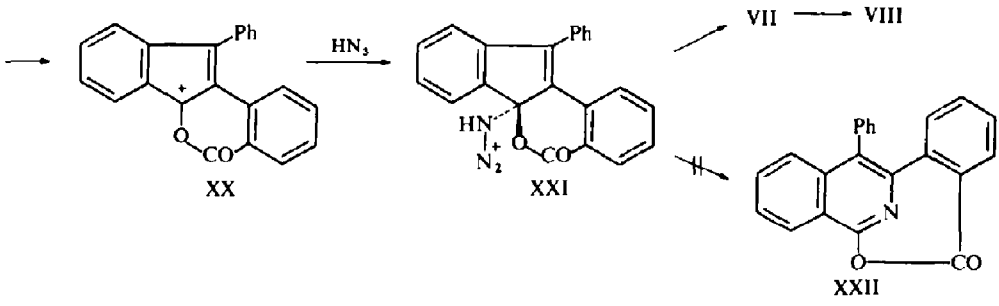
The hydroxylic rather than the tautomeric keto-lactamic structure was chosen for XVI on the basis of its IR spectrum (no carbonyl absorption besides the ester band), and of the coloured reaction with iron (III) chloride.

DISCUSSION

It is known, from previous work,[1] that 2-phenylindones do not follow the Smith

rule[4] of steric hindrance. The formation of the lactone VII from the indone V as the main reaction product can be explained by assuming participation of the *ortho* carboxyl group in the reaction. This group might undergo condensation with the protonated indone carbonyl to give intermediate XX (Scheme 3). Addition of hydrazoic acid to XX might give XXI, and this adduct would rearrange *only* in the direction of formation of VII, and not of a highly strained isoquinoline derivative such as XXII. 2,3-Diphenylindone is known[1] to afford also isocarbostyril derivatives in the Schmidt reaction.

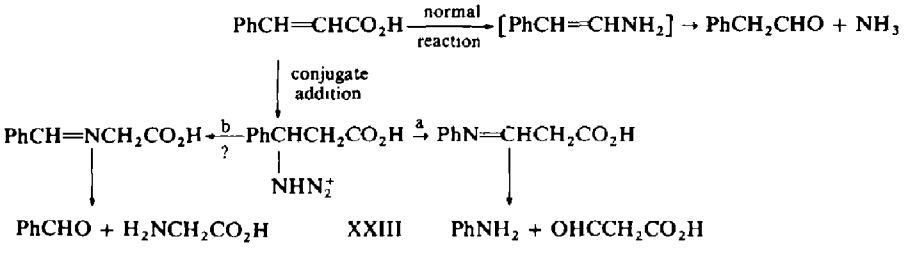
SCHEME 3



The conversion of the indone VI to XVI appears indeed quite unusual, and formulation of a pertinent reaction mechanism offers some difficulties. In our opinion, the hypothesis of a conjugate addition of hydrazoic acid to C_3 of VI is to be held as most likely. Indeed, in many cases insertion of nitrogen into the C_2—C_3 bond of indones occurs under Schmidt conditions,[1,3] and such insertion can only be explained in terms of the rearrangement of an intermediate originated from a conjugate addition of the reagent.

An analogy with the present case is to be found in the reported[5] formation of aniline as an important by-product in the Schmidt reaction with cinnamic acid, phenylacetaldehyde being the main product, originating from normal reaction. Here, aniline might be formed from rearrangement (path a, Scheme 4) of an adduct (XXIII) originated by conjugate addition of hydrazoic to cinnamic acid.*

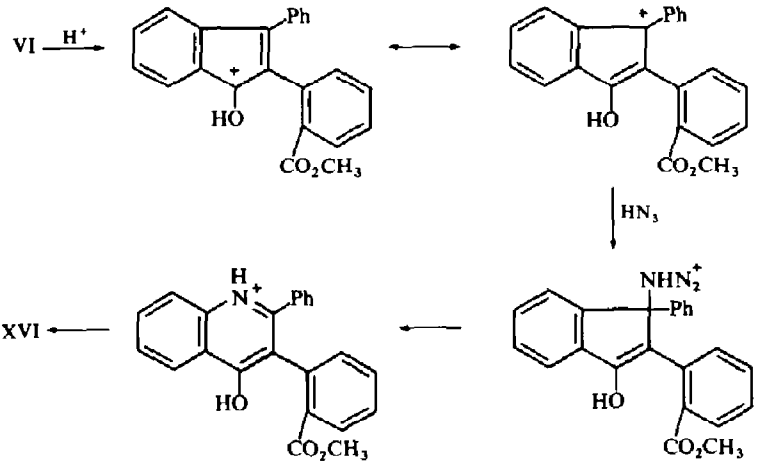
SCHEME 4



* This reaction needs, in our opinion, further investigation, since a rearrangement of the adduct XXIII from the side of the —CH_2CO_2H group (path b) to give benzaldehyde as an end-product should be also probable, but no benzaldehyde was reportedly found among the reaction products.

The observed inertness of VI towards hydrazoic acid under moderately acid conditions is probably due to difficulty of protonation of the carbonyl group, perhaps because of steric hindrance in its environments, caused by the *o*-carbomethoxy group, and of the impossibility of the latter to participate intramolecularly to the reaction. Under strongly acid conditions, protonation of the CO group takes place, but the approach of hydrazoic acid to C_1 would still be hindered, thus leaving C_3 as the only position available for attack by the reagent (conjugate addition, Scheme 5). The rearrangement of the adduct, then takes place on the less hindered side to give XVI. Alternative pathways, such as an attack to C_{3a}, seem very unlikely.

SCHEME 5



EXPERIMENTAL

M.ps (Kofler block) are uncorrected. IR spectra (Perkin–Elmer Infracord mod. 137 spectrophotometer) were taken on Nujol mulls.

2-(*o-Carboxyphenyl*)3-*phenylindone* (V). A soln of VI[6] (0·5 g) in 10% KOH–EtOH (10 ml) was refluxed for 15 min, diluted with H_2O and acidified with conc HCl aq. The yellow ppt (0·44 g) was recrystallized from MeOH to give red prisms, m.p. 247–249° (lit.[7] 251–252°).

Schmidt reaction with 2-(*o-carboxyphenyl*)3-*phenylindone in* H_2SO_4–AcOH. A suspension of finely ground V (2 g) in H_2SO_4–AcOH (160 ml, 1:4 v/v) was heated to 75–80° and treated under stirring with NaN_3 (2·5 g), in 0·5 g portions at 10 min interval. The mixture was stirred at 80° for one additional hr, and diluted with H_2O. The collected brown ppt was washed with H_2O until neutral; then it was heated on a steam bath for 5 min with 3% $NaHCO_3$ aq (90 ml). The insoluble material (1·05 g), on crystallization from diglyme-H_2O, afforded VII as white needles, m.p. 256–258°. (Found: C, 81·67; H, 4·15. $C_{22}H_{13}NO_2$ requires: C, 81·72; H, 4·05%). The $NaHCO_3$ soln gave on acidification 0·45 g VIII. An analytical sample, crystallized from Me_2CO–hexane, melted with decomposition between 270 and 300°. (Found: N, 4·23. $C_{22}H_{15}NO_3$ requires: N, 4·10%). This product was converted to VII on heating at 300° for 10 min.

3-(*o-Carbomethoxyphenyl*)4-*phenylcarbostyril* (IX). A sample of VII (1·5 g) was refluxed with MeOH (250 ml) and H_2SO_4 (0·1 ml) until a clear soln was obtained (5 hr). After concentration to a small volume, 1·2 g IX separated as prisms, m.p. 256–258° dec. (Found: C, 77·75; H, 5·10; N, 4·03. $C_{23}H_{17}NO_3$ requires: C, 77·73; H, 4·82; N, 3·94%).

Hydrazide X

(a) *From* IX. A suspension of IX (0·6 g) in EtOH (10 ml) and $N_2H_4 \cdot H_2O$ (1 ml) was heated on a steam bath for 30 hr. The product did not dissolve but changed from prisms to flat needles of practically pure X, m.p. 296–299°. (Found: N, 11·90. $C_{22}H_{17}N_3O_2$ requires: N, 11·84%).

(b) *From* VII. By refluxing VII (2·15 g) with EtOH (100 ml) and $N_2H_4 \cdot H_2O$ (5 ml) for 27 hr, 2·10 g X were obtained.

Azide XI. A mixture of X (1 g), 36% HCl aq (28 ml) and crushed ice (14 g) was treated at 0°, under stirring, with 2·8% $NaNO_2$ aq (7 ml). After 0·5 hr at room temp, the insoluble material (0·9 g) was collected and thoroughly washed with H_2O. The product, which was not further purified, consisted mainly of XI, as evidenced by a strong IR band at 4·66 μ.

3-(o-*Nitrophenyl*)4-*phenylcarbostyril* (XIV). A soln of *o*-nitrophenylacetic acid (1·8 g) in anhyd Et_2O (50 ml) was treated with powdered PCl_5 (2·1 g) and refluxed 30 min. The soln was then washed with H_2O (2 × 30 ml), 3% $NaHCO_3$ (2 × 30 ml) and the Et_2O was removed at room temp under reduced press. To the residue, dissolved in anhyd benzene (25 ml) were successively added, with stirring and cooling (0–5°), *o*-aminobenzophenone (1·6 g) and pyridine (5 ml). The mixture was refluxed on a steam bath for 30 min and diluted with Et_2O (100 ml). An insoluble material was filtered off and the filtrate was washed with 2N H_2SO_4, 2N Na_2CO_3, H_2O, dried ($MgSO_4$) and evaporated. The residue (crude XIII, 2·8 g) was refluxed for 15 min with a soln of NaOH (1·5 g) in H_2O (30 ml) and EtOH (15 ml). The crystalline ppt (1·3 g) which separated out, was purified by crystallization from AcOH–H_2O. From the alkaline mother liquor, after dilution with H_2O, a further 0·5 g of the same product was obtained. An analytical sample (yellow prisms) had m.p. 311–313°. (Found: C, 73·35; H, 4·32; N, 8·22. $C_{21}H_{14}N_2O_3$ requires: C, 73·67; H, 4·12; N, 8·18%).

3-(o-*Aminophenyl*)4-*phenylcarbostyril* (XII)

(a) *Curtius rearrangement of* XI. A mixture of XI (0·5 g) and 36% HCl aq (20 ml) was refluxed for 30 min and rapidly filtered. The insoluble material (0·25 g) was identified as VIII. The acid soln was made alkaline by means of NH_4OH and 0·15 g XII precipitated. An analytical sample (yellow blades from MeOH) had m.p. 313–316°. (Found: C, 80·50; H, 5·31; N, 8·82. $C_{21}H_{16}N_2O$ requires: C, 80·75; H, 5·16; N, 8·97%).

(b) *Catalytic hydrogenation of* XIV. A soln of XIV (0·5 g) in AcOH (50 ml) was stirred at room temp and press in an atmosphere of H_2 in the presence of 5% Pd–Al_2O_3 (0·25 g), until absorption ceased (6 hr). The catalyst was filtered off and the solvent was removed at 100° reduced press. The residue (0·35 g), after crystallization from MeOH, had identical m.p. and IR spectrum with the product obtained as described under (a).

11-*Phenyl*-6H-*indolo*[2.3-b]*quinoline*. A sample of XII (100 mg) was heated at 300° for 5 min, then sublimed at 20 mm, 300°. The sublimate (60 mg) was crystallized from MeOH to afford yellow needles, m.p. 269–271°. (Found: N, 9·43. Calc. for $C_{21}H_{14}N_2$: N, 9·52%). The IR spectrum of the product was identical with the spectrum of an authentic sample.[1]

12-*Phenyl*-5H-[2]*benzopyrano*[3.4-b]*quinoline*-5-*one*[8]. A mixture of *o*-aminobenzophenone (0·6 g), homophthalic acid (0·6 g), $ZnCl_2$ (0·1 g), AcONa (0·2 g) and Ac_2O (10 ml) was refluxed for 4 hr. The excess Ac_2O was hydrolyzed by addition of H_2O and the insoluble material was collected, washed with MeOH and crystallized from diglyme–H_2O to afford a product (0·4 g), whose m.p. and IR spectrum were identical with those of VII.

Schmidt reaction with 2-(o-*carbomethoxyphenyl*)3-*phenylindone in conc* H_2SO_4. To the green coloured soln of VI (5 g) in 96% H_2SO_4 (100 ml), NaN_3 (3·2 g) was added portionwise (45 min) with stirring, keeping the reaction temp at 35–40°. The brown soln was then poured into ice-water (500 ml) and the ppt (VII, 0·4 g, after purification) was filtered off. Neutralization of the filtrate with NH_3 aq caused formation of a ppt (XVI, 3·6 g) which was crystallized from MeOH to afford white needles, m.p. 242–244°. (Found: C, 77·92; H, 4·73; N, 4·15. $C_{23}H_{17}NO_3$ requires: C, 77·73; H, 4·82; N, 3·94%). The product gives a red-brown colour when treated with $FeCl_3$ in EtOH soln. When this ester (0·5 g) was heated to 300° until evolution of gas ceased (10 min) and the residue was crystallized from diglyme-H_2O, the lactone XVII (11-phenyl-6*H*-[2]benzopyrano[4.3-*c*]quinoline-6-one, 0·35 g) was obtained as white needles, m.p. 207–209°. (Found: C, 81·80; H, 4·15; N, 4·47. $C_{22}H_{13}NO_2$ requires: C, 81·72; H, 4·05; N, 4·33%). The acid XVIII was obtained by refluxing the ester XVI (0·7 g) with 10% NaOH aq until the product dissolved completely. Acidification of the soln with AcOH caused formation of a ppt (0·6 g) which was crystallized from MeOH to give white needles, m.p. 270–275° dec. (Found: N, 3·94. $C_{22}H_{15}NO_3$ requires: N, 4·10%). This compound also gives a deep brown colour with $FeCl_3$ in EtOH soln.

Schmidt reaction with 2-(o-*carboxyphenyl*)3-*phenylindone in conc* H_2SO_4). The reaction was carried out as described for VI, using V (4·6 g), 96% H_2SO_4 (90 ml) and NaN_3 (3 g). When the reaction mixture was poured into ice-water (400 ml), 3 g of a ppt was obtained. This was stirred with 2N Na_2CO_3 (50 ml) and the insoluble part was filtered off. Crystallization of this material from diglyme–H_2O afforded VII (1·2 g).

Acidification with AcOH of the alkaline filtrate caused precipitation of VIII (0·9 g). The acid filtrate from which VII and VIII were separated was neutralized with NH_4OH and the ppt (0·7 g) was identified as the lactone XVII, m.p. 207–209°.

Oxidation of XVI *with* $KMnO_4$. A mixture of XVI (0·3 g), $KMnO_4$ (1·5 g) and 0·2N NaOH (50 ml) was refluxed for 3 hr. The excess $KMnO_4$ was destroyed by addition of MeOH, the MnO_2 was removed by filtration and the filtrate, after addition of 5N H_2SO_4 was extracted with Et_2O (5 × 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give 0·2 g solid residue. Boiling hexane extracted 100 mg benzoic acid and left 70 mg phthalic acid undissolved.

Oxidation of XVI *with peroxyacetic acid.* A soln of XVI (0·2 g) and 30% H_2O_2 aq (0·5 ml) in AcOH (10 ml) was heated on a steam bath for 1 hr. The mixture was then diluted with H_2O, extracted with Et_2O and the ethereal extract was evaporated. The residue was triturated with 1N Na_2CO_3 (15 ml) and the filtered soln was acidified with 2N HCl to give 35 mg of a product, m.p. 178–181°, which was identified by mixed m.p. and comparison of IR spectra, as N-benzoylanthranilic acid (XIX).[9]

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