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

SCHMIDT REACTION WITH 2,3-DIPHENYLINDONE AND SIMILAR COMPOUNDS

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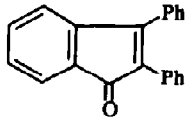
Abstract—The Schmidt reaction with 2,3-diphenylindone, in a mixture of sulphuric and acetic acid, affords 3,4-diphenylcarbostyril (A_1), 3,4-diphenylisocarbostyril (A_2), 5-phenyl-11*H*-indolo[3.2-*c*]-isoquinoline (B_1) and 3-(*o*-aminophenyl)4-phenylisocarbostyril (B_2). The probable mechanism of formation of the four products is discussed. The same reaction, if carried out in sulphuric acid, gives 3-(*p*-sulphophenyl)4-phenylcarbostyril as the only reaction product. The Schmidt reaction with 3-methyl-2-phenylindone and 3-ethyl-2-phenylindone is also described.

IT WAS reported in a preliminary communication[2] that 2,3-diphenylindone (I), when treated with hydrazoic acid in acetic–sulphuric acid solution, affords two neutral products (A_1 and A_2) and two bases (B_1 and B_2). Further work permits now to define the exact course of the reaction and to discuss its possible mechanism.



I

$\longrightarrow$ A_1 + A_2 + B_1 + B_2

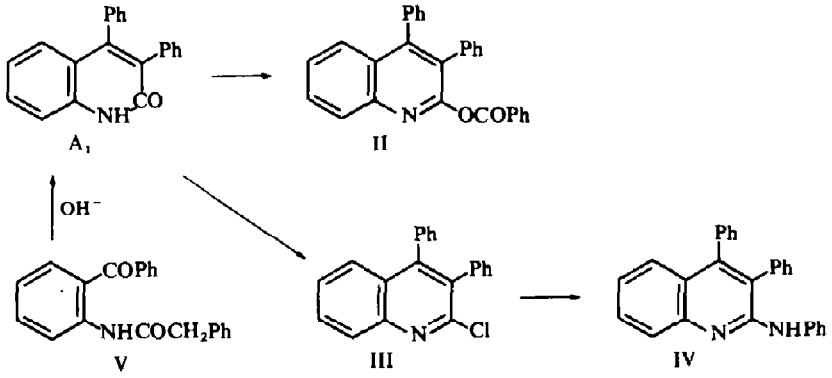
The reaction

A suspension of 2,3-diphenylindone in acetic acid containing sulphuric acid was treated at 70–80° with excess sodium azide. At the end of the reaction, treatment of the mixture with water caused formation of a precipitate consisting of A_1, A_2, B_1 (as a sulphate) and unreacted 2,3-diphenylindone. The base B_2 was obtained on addition of ammonia to the acidic mother liquor from which the previous products had been separated.

Compound A_1. Low solubility in all common solvents, high m.p. and CO stretching absorption at 6·08 μ in the IR spectrum pointed to a carbostyril or isocarbostyril type of structure (in such compounds the NH stretching does not appear when the spectrum is determined on Nujol mulls). The presence of a lactamic structure was proved by easy conversion of the compound into the corresponding O-benzoate (II, λ_{CO} 5·77 μ). Furthermore, treatment of A_1 with phosphorus oxychloride caused transformation of the NH—CO group into N=CCl, thus affording compound III. The facile conversion of the latter compound into the anilino derivative IV, clearly indicated that the Cl atom was in the α position of a pyridine nucleus. Compound

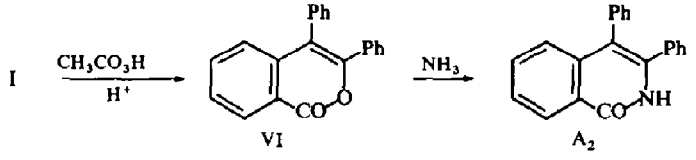
A_1 was definitely identified as 3,4-diphenylcarbostyril through its direct synthesis from 2-(phenylacetamido)benzophenone (V, Scheme 1).

SCHEME 1

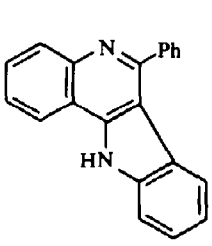


Compound A_2. The IR spectrum of A_2 is very similar to that of A_1. The compound was identified as 3,4-diphenylisocarbostyril[3] by comparison of IR and UV spectra and mixed m.p. with an authentic sample, also prepared by the route indicated in Scheme 2.

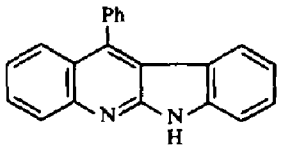
SCHEME 2



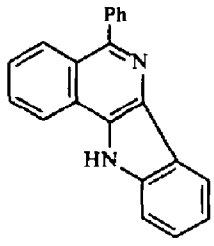
Compound B_1. This compound affords yellow, water-insoluble salts with strong acids. The free base is light yellow and crystallizes from methanol with one mole of solvent, which is lost at 120–140°. Elemental analysis pointed to the formula $C_{21}H_{14}N_2$, which can be derived as follows: $C_{21}H_{14}O$ (indone) + 2(NH) − (H_2O). The IR spectrum in solution shows a band at 2·88 μ, typical of indole derivatives,[4] the band is shifted to 3·89 μ on treatment of the solution with deuterium oxide; a strong band at 6·18 μ may be due to C=N or C=C stretching. The NMR spectrum allows formulation of the following deductions: the molecule contains an active H atom; indeed, deuterium exchange causes disappearance of a broad resonance, near 1 τ, associated with the active hydrogen. The very complex phenyl resonance (in contrast to the corresponding regions in the spectra of I, A_1 and A_2, which are much simpler) points to conjugation of one or both Ph groups with some polar part of the molecule; alternatively, a Ph group may either be disubstituted or involved in the formation of a new ring. The UV spectrum, if compared with that of A_1 (and of A_2)[3] shows the presence in B_1 of a more extended conjugation. The compound could easily be mono-brominated, thus indicating activation of one benzene ring towards electrophilic substitution. On the basis of the aforementioned considerations, structures VII, VIII and IX are possible for B_1. All three can result from the reaction



VII



VIII



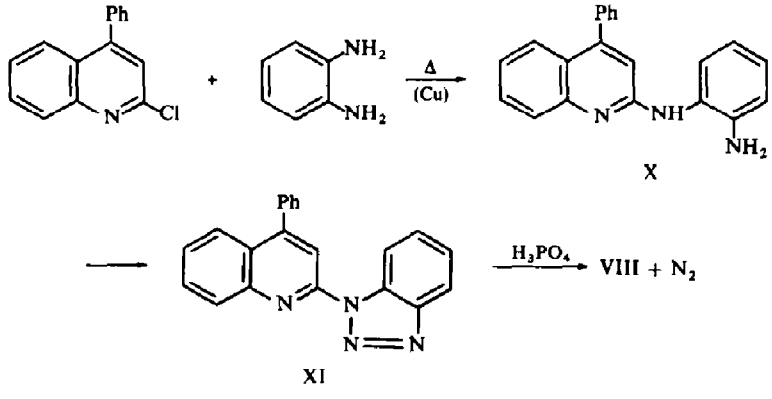
IX

of 2,3-diphenylindone with HN_3 involving: (a) enlargement of the 5-membered ring; (b) amination of the 2-Ph group at the *ortho* position; (c) elimination of a water molecule between the amino and the CO group. The 2-Ph group in indones is activated towards electrophilic substitution (for instance,[5,6] it can be easily sulphonated or nitrated), whereas the 3-Ph is very inert.[7]

The known[8] structure VII was soon discarded, since its reported physical properties did not correspond with those of B_1.

Structure VIII (11-phenyl-5*H*-indolo[2.3-*b*]quinoline) appeared fairly probable, its formation involving insertion of NH between the indone CO group and the condensed benzene nucleus (normal Schmidt reaction[9,10]). However, when this compound was prepared through a Graebe–Ullmann reaction (Scheme 3), its properties were found to be different from those of B_1.

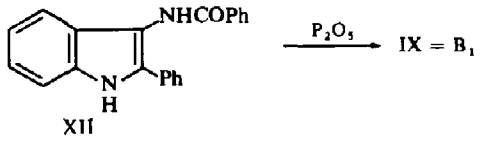
SCHEME 3



It was then decided to synthesize structure IX (5-phenyl-11*H*-indolo[3.2-*c*]-isoquinoline), which could have originated by insertion of NH into the indone double bond (a type of reaction already encountered in the treatment of indones with HN_3[10]), nuclear amination and water elimination.

Robinson and Thornley[11] had failed in the attempt to prepare IX by a Bischler–Napieralski cyclization of 3-benzamido-2-phenylindole with PCl_3. Later, Huang-Hsinmin and Mann[12] obtained 5-methyl-11*H*-indolo[3.2-*c*]isoquinoline on treatment of 3-acetamido-2-phenylindole with phosphoric anhydride in boiling nitrobenzene. We applied this method to 3-benzamido-2-phenylindole (XII, Scheme 4) thus obtaining a low yield of a product identical with B_1. It can be safely assumed

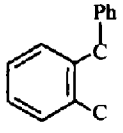
SCHEME 4



XII

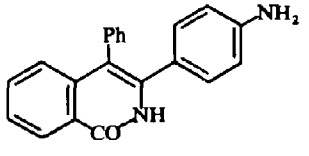
that bromination of B_1 should give the 9- or (more probably) the 8-bromo derivative; indeed, 5- and/or 6-bromo derivatives have been obtained on treatment of indoles with bromine.[13]

Compound B_2. This base affords water-soluble salts, and can be crystallized from methanol. Elemental analysis gave values corresponding to the formula $C_{21}H_{16}N_2O$, which is equal to $C_{21}H_{14}O$ (indone) plus 2(NH). The IR spectrum of the product shows NH (2·9, 3·0, 3·1 μ) and amide CO (6·08 μ) stretching absorption bands. The product was recovered unchanged after protracted reflux with potassium hydroxide in ethylene glycol: such inertness towards alkali is typical of carbostyrils and isocarbostyrils. The NMR spectrum shows two broad resonances (at 1 and 6·35 τ) which disappear after treatment with D_2O, thus supporting the presence of two different types of active hydrogens: these are present in the ratio 1:2. The complex phenyl region indicates that one of the two Ph groups, originally bound to the indone C_2 or C_3 can be disubstituted. Treatment of the product with benzoyl chloride gave a dibenzoate containing a mono substituted amide (λ_{NH} 3·0 μ; λ_{CO} 6·0 μ) and an ester group (λ_{CO} 5·75 μ). Oxidation of B_2 with potassium permanganate afforded 2-benzoylbenzoic acid, thus indicating the partial structure:

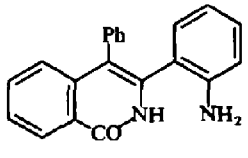


Finally, the UV spectrum of the product (λ_{max} 295, 318 (shoulder) mμ; log ε 4·09, 3·94) is very similar to the spectrum of 3,4-diphenylisocarbostyril.[3]

The previously mentioned observations suggest for B_2 the structure of an amino derivative of 3,4-diphenylisocarbostyril, possibly containing the amino group at the *para* (structure XIII) or at the *ortho* position (structure XIV) of the 3-Ph group.



XIII

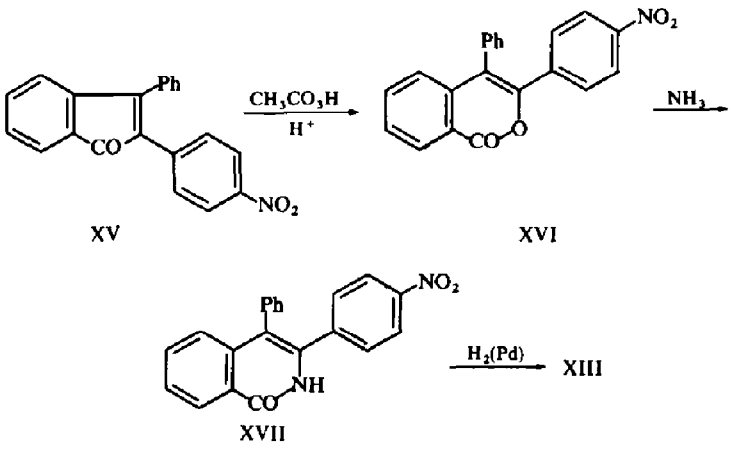


XIV

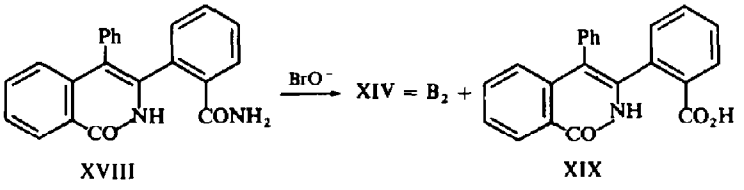
Compound XIII, prepared from 2-(*p*-nitrophenyl)3-phenylindone (XV) by the route indicated in Scheme 5, was different from B_2.

The synthesis of XIV was carried out through Hoffmann degradation of XVIII (Scheme 6), thus obtaining a product identical with B_2.

SCHEME 5



SCHEME 6



DISCUSSION ON THE POSSIBLE REACTION MECHANISM

Several points in the reaction appear unusual: e.g. the formation of relatively large amounts of 3,4-diphenylcarbostyril does not agree with the Smith rule of steric hindrance.[14] The formation of this product could be explained in a speculative way by assuming stabilization of a reaction intermediate in a rigid conformation with the plane of the benzene nucleus, bound to indone C_2, in a nearly normal position with respect to the plane of the indone system, so as to minimize steric interactions.

The formation of B_1 and B_2, which involves amination of the 2-Ph group and, in the case of the former compound, also reaction of a very hindered double bond with hydrazoic acid, appears quite abnormal.

It had been assumed that NH or NH_2^+ are the aminating agents in strongly acid conditions.[15]

Two important factors should, however, be pointed out in the present case: the reaction medium is not strongly acidic, and no *para* aminated products were isolated. The first point is not of fundamental importance, since the reaction with 2,3-diphenylindone is very slow: indeed, some starting product was always recovered even after long reaction times and with a strong excess of HN_3. The relative inertness of the CO group towards hydrazoic acid and the activation of the 2-Ph group towards electrophilic substitution might influence a previous nuclear amination by HN_3 or its decomposition products.

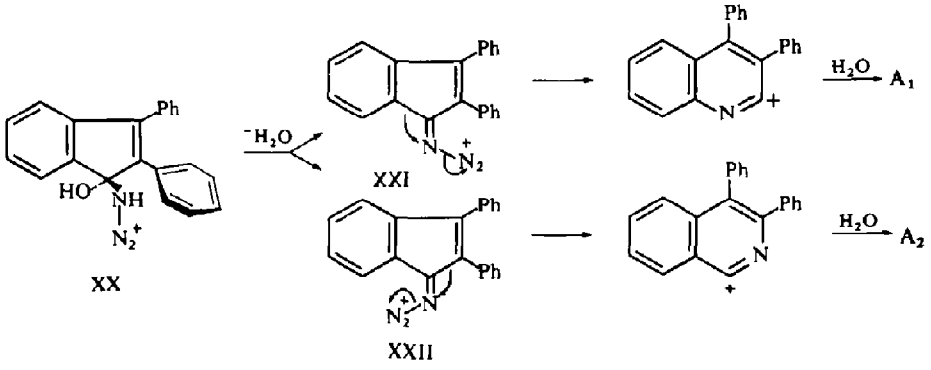
2,3-Diphenylindone is known to yield, on sulphonation or nitration, only the *para* isomers.[5,6] The absence of *para* substituted products in the present case is therefore

in contrast with the postulated amination mechanism by free NH or NH_2^+, in which an attack at the *para* position should be sterically favoured. This may signify that the CO groups plays an important role in directing the nuclear amination, possibly through an electrophilic intermediate formed by interaction with HN_3.

Two important hypotheses about the mechanism of the Schmidt reaction had been formulated: one by Oliveri-Mandalà[16,*] and another by Smith.[17] Both of them assume initial formation of an azidohydrin derivative, originated by nucleophilic attack of hydrogen azide on the carbonyl group. Whereas in Oliveri-Mandalà's hypothesis the unprotonated azidohydrin is assumed to lose nitrogen before to rearrange, in Smith's mechanism a dehydration of the protonated azidohydrin to a ketiminodiazonium ion is considered to precede the rearrangement.

In the case of 2,3-diphenylindone, whichever mechanism one assumes, the same intermediate could possibly be responsible for the formation of all final products; this intermediate might be the azidohydrin XX (Scheme 7, one enantiomer indicated). Dehydration may afford XXI or XXII (the former in greater amount) which rearrange to give A_1 and A_2, respectively.

SCHEME 7



The intermediate XX could also lose N_2 to give XXIII, which might be the *ortho* aminating agent, responsible for the formation of both B_1 and B_2, as outlined in Scheme 8.

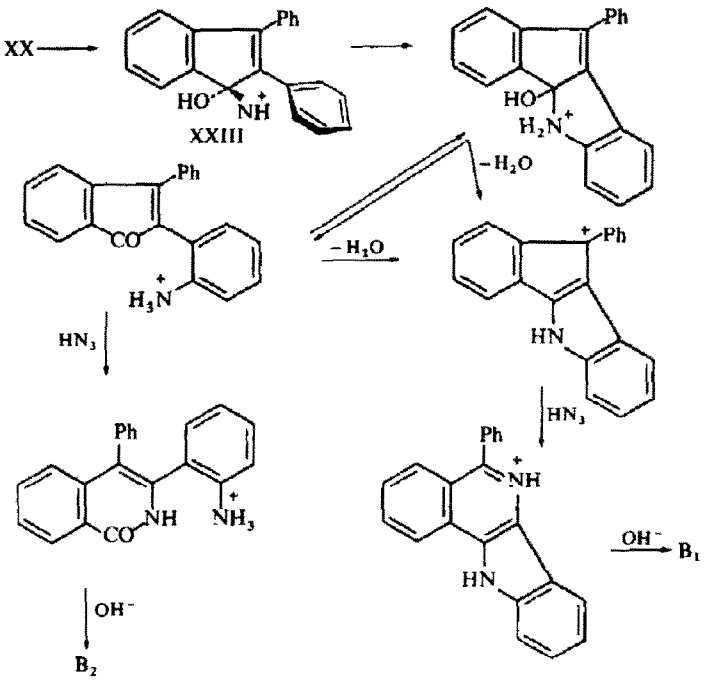
The same intermediate XXIII could also be responsible for the formation of A_1 and A_2, since a dehydration step does not seem strictly necessary, at least in the present case, for the rearrangement.

EXPERIMENTAL

M.ps (Kofler block) are uncorrected. IR spectra on Nujol mulls (Perkin–Elmer Infracord mod. 137). UV spectra (Beckman DU) 95% EtOH solns. NMR spectra, $CDCl_3$ solns, 60 Mc/s, TMS as internal standard (Varian DA-60 spectrometer).

* A modification of Oliveri-Mandalà mechanism has been reported by C. L. Arcus, M. M. Coombs and J. V. Evans [*J. Chem. Soc.* 1498 (1956)]. These authors postulate a mechanism in which electronic, in addition to steric factors, are considered responsible for the migration of substituents in a ketone. This assumption, however, has been criticized by P. A. S. Smith and E. P. Antoniades [*Tetrahedron* 9, 210 (1960)].

SCHEME 8



Schmidt reaction with 2,3-*diphenylindone in* AcOH–H_2SO_4. Finely ground 2,3-diphenylindone[18] (3 g) was suspended in AcOH–96% H_2SO_4 (300 ml, 4:1 v/v). The stirred mixture was heated to 75–80° and NaN_3 (2·5 g) was added during 1 hr; stirring was continued for 1 hr at 75° and at room temp for 2 hr. The homogeneous soln was then treated with ice–water and the ppt was washed with NH_4OH and dried at 100°. Extraction of the solid (2·7 g) with 300 ml boiling Et_2O left a residue, consisting of a mixture of A_1 and A_2 (0·8 g). The ethereal soln was treated with saturated HCl–Et_2O: B_1·HCl precipitated as a yellow–green solid (0·5 g); the soln was evaporated to dryness to give impure unreacted indone (1 g). The aqueous acidic mother liquor from which the previous products were separated, was treated, with cooling, with NH_4OH until basic: a brown ppt (B_2, 0·3 g) was obtained.

Separation of A_1 *from* A_2. The mixture of the two products (3·5 g) was refluxed 1 hr with benzene (70 ml), then allowed to stand 6 hr at room temp. Undissolved A_1 (2·75 g) was collected and crystallized from MeOH to give prisms, m.p. 310–311°, (Found: C, 84·52; H, 5·21; N, 4·82. $C_{21}H_{15}NO$ requires: C, 84·82; H, 5·09; N, 4·71%); UV, λ_{max} 228, 285, 335 mμ, log ε 4·60, 3·94, 3·96. Concentration of the benzene filtrate to 10 ml caused crystallization, after 12 hr, of a mixture of prisms and needles. These were mechanically separated into 0·2 g prisms (A_1) and 0·15 g needles (A_2). Further concentration of the mother liquor gave 0·1 g A_2. Pure A_2, m.p. 250–252°, was obtained after repeated crystallizations from MeOH: IR and UV spectra were identical with those of an authentic sample.[3] (Found: N, 4·78. Calc. for $C_{21}H_{15}NO$: N, 4·71%).

2-*Benzoyloxy*-3,4-*diphenylquinoline* (II). A soln of A_1 (0·5 g) and benzoyl chloride (0·5 ml) in pyridine (5 ml) was refluxed for 0·5 hr. Dilution of the mixture with water gave an oily ppt which, on treatment with hot MeOH, afforded blades (0·5 g), m.p. 178–180°. (Found: N, 3·56. $C_{28}H_{19}NO_2$ requires: N, 3·49%).

2-*Chloro*-3,4-*diphenylquinoline* (III). A mixture of A_1 (1 g) and $POCl_3$ (2 ml) was heated on a steam bath for 1 hr. Water was added and the ppt, after solidification, was crystallized from hexane to afford needles (1 g), m.p. 169–171°. (Found: N, 4·51. $C_{21}H_{14}ClN$ requires: N, 4·43%).

2-*Anilino*-3,4-*diphenylquinoline* (IV). A mixture of III (0·5 g), Cu bronze (0·05 g), K_2CO_3 (0·1 g) and aniline (3 ml) was boiled under reflux for 1·5 hr, then poured into 2N HCl (30 ml). The solid (0·35 g) was crystallized from benzene–hexane to give blades, m.p. 207–209°. (Found: N, 7·45. $C_{27}H_{20}N_2$ requires: N, 7·52%).

3,4-*Diphenylcarbostyril* (A_1). To a stirred soln of *o*-aminobenzophenone[19] (0·8 g) in benzene (8 ml) was

added phenylacetyl chloride (0·8 ml). The mixture was refluxed for 1 hr, then poured into water. The separated organic layer was washed successively with 2N H_2SO_4 and 2N Na_2CO_3, then was dried ($MgSO_4$) and evaporated to afford 1·2 g oily residue. This was refluxed for 1 hr with a mixture of KOH (0·4 g), water (24 ml) and EtOH (8 ml). The solid ppt was crystallized from MeOH to give prisms (0·6 g), m.p. 310–311°. The product showed an IR spectrum superimposable on that of A_1.

3,4-*Diphenylisocarbostyril* (A_2). 2,3-Diphenylindone (3 g) was dissolved at 60° in AcOH–96% H_2SO_4 (100 ml, 5:1 v/v); to the soln 33% H_2O_2 aq (12 ml) was slowly added. When the colour of the soln had faded from deep brown to pink rose (~30 min) water was added and the ppt (2·5 g) was crystallized from MeOH to give VI as blades, m.p. 167–169° (lit.[20] 168–171°). A mixture of VI (1 g), conc NH_4OH (3 ml) and EtOH (3 ml) was heated at 100° for 20 hr in a scaled tube. After cooling to room temp the undissolved solid (0·9 g) was crystallized from MeOH to give needles, m.p. 249–252°. The product showed an IR spectrum superimposable on that of A_2.

Purification of B_1. From a soln containing $B_1 \cdot HCl$ (0·5 g) in the minimum amount boiling MeOH, the base was precipitated by adding excess conc NH_4OH. Recrystallization of the product from MeOH gave needles or prisms (0·35 g) m.p. 120–125° with gas evolution, resolidification and new melting at 235–236°. [Found (product dried *in vacuo* at room temp): C, 80·85; H, 5·24; N, 8·83. $C_{21}H_{14}N_2 \cdot CH_3OH$ requires: C, 80·95; H, 5·56; N, 8·58%]. Heating *in vacuo* over boiling xylene caused the substance to lose 9·91% of its weight ($C_{21}H_{14}N_2 \cdot CH_3OH$ requires: 9·82%). [Found (product hot-dried): C, 85·58; H, 4·89; N, 9·85. $C_{21}H_{14}N_2$ requires: C, 85·69; H, 4·79; N, 9·52%]; main IR bands: large absorption in the CH stretching region, 6·16, 6·63, 7·28, 7·42, 7·94, 8·14, 8·64, 9·70, 10·33, 10·92, 12·88, 13·12, 13·45, 14·20, 14·90 μ. The IR spectrum in soln ($CDCl_3$, saturated, cell path 1 mm, Perkin–Elmer model 257 grating spectrophotometer) shows a band at 3470 cm^{-1} which is shifted to 2570 cm^{-1} on treatment of the soln with D_2O; UV, λ_{max} 236, 288, 307, 372 mμ; log ε 4·60, 4·55, 4·20, 4·09.

Bromination of B_1. A soln containing B_1 (0·4 g) in $CHCl_3$ (15 ml) was treated with 10% Br_2–$CHCl_3$ (6 ml). The mixture was refluxed for 2 min. and the yellow–green ppt was collected after addition of hexane (15 ml). The solid was triturated with MeOH containing conc NH_4OH and crystallized from MeOH to give prisms, m.p. 150° with gas evolution, resolidification and new melting at 252–254°. [Found (product dried at room temp): N, 7·16. $C_{21}H_{13}BrN_2 \cdot CH_3OH$ requires: N, 6·89%]. [Found (product hot-dried): N, 7·64. $C_{21}H_{13}BrN_2$ requires: N. 7·51%].

2-(1-*Benzotriazolyl*)4-*phenylquinoline* (XI). A mixture of 2-chloro-4-phenylquinoline[9] (1·2 g), *o*-phenylenediamine (0·6 g) and Cu bronze (0·05 g) was heated at 150°/20 mm for 20 min. The cooled residue was triturated with a mixture of EtOH (10 ml) and 36% HCl aq (12 ml) and the filtered liquid was slowly poured into 10% $NaNO_2$ aq (20 ml), while stirring and cooling at 0°. The ppt was crystallized from MeOH to afford needles (0·8 g), m.p. 148–150°. (Found: N, 17·35. $C_{21}H_{14}N_4$ requires: N, 17·38%).

11-*Phenyl*-6H-*indolo*[2.3-b]*quinoline* (VIII). A mixture of XI (0·5 g) and polyphosphoric acid (10 ml) was heated to 150° until evolution of N_2 ceased. Addition of water caused formation of a yellow ppt which was crystallized from MeOH to afford needles (50 mg) m.p. 269–271°. (Found: C, 85·40; H, 4·88; N, 9·43. $C_{21}H_{14}N_2$ requires: C, 85·69; H, 4·79; N, 9·52%).

6-*Phenyl*-11H-*indolo*[3.2-*c*]*isoquinoline* (IX = B_1). A mixture of 3-benzamido-2-phenylindole[11] (1·5 g), P_2O_5 (5 g) and nitrobenzene (10 ml) was refluxed in a metal bath for 2 hr. After cooling, the liquid phase was discarded and the black residue was washed with benzene, Et_2O, and boiling 36% HCl aq. It was then collected, washed with water, triturated with conc NH_4OH and extracted several times with boiling Et_2O. The combined ethereal extracts yielded on evaporation a brown oily residue which solidified on trituration with hexane. Sublimation of this material at 300°/20 mm followed by crystallization of the sublimate (30 mg) from MeOH–H_2O and from benzene–hexane afforded a product whose m.p., UV and IR spectra were identical with those of B_1.

Purification of B_2. The product was crystallized from MeOH to afford light yellow needles, m.p. 235–237°. (Found: C, 80·89; H, 5·24; N, 8·77. $C_{21}H_{16}N_2O$ requires: C, 80·75; H, 5·16; N, 8·97%); main IR bands: 2·91, 3·00, 3·11, 6·09, 6·18, 6·24, 6·72, 6·86, 6·91, 7·30, 7·50, 7·65, 8·09, 8·70, 9·74, 10·32, 11·68, 12·76, 13·00, 13·22, 13·80, 14·03 μ. UV, λ_{max} 295, 318 (sh) mμ, log ε 4·09. 3·94.

Oxidation. A mixture of B_2 (0·1 g), $KMnO_4$ (0·15 g) and 0·25N NaOH (10 ml) was refluxed for 1 hr. The excess $KMnO_4$ was destroyed by addition of MeOH, the MnO_2 was filtered off and the filtrate, after acidification with 2N H_2SO_4 was extracted with EtO_2. The oily residue obtained on evaporation of the ethereal extract was dissolved in boiling benzene. Addition of hexane caused formation of a ppt which was crystallized from water to afford 10 mg of *o*-benzoylbenzoic acid monohydrate, m.p. 90–93°. The product was identified by comparison of IR spectra and mixed m.p. with an authentic sample.

Treatment of B_2 *with benzoyl chloride.* A mixture of B_2 (0·1 g), benzoyl chloride (0·3 ml) and pyridine (3 ml) was refluxed for 1 hr. Dilution with water caused separation of an oily product, which solidified on treatment with MeOH. This material (B_2 dibenzoate, 0·1 g) was crystallized from benzene–hexane to afford needles, m.p. 244–247°. (Found: N, 5·28. $C_{35}H_{24}N_2O_3$ requires: N, 5·38%).

3-(p-*Nitrophenyl*)4-*phenylisocoumarin* (XVI). Finely ground 2-(*p*-nitrophenyl)3-phenylindone[18] (1 g) was dissolved at 60–70° in AcOH–H_2SO_4 (100 ml, 3:1 v/v); to the soln 33% H_2O_2 aq (4 ml) was slowly added. Working up of the mixture after 20 min as described for the synthesis of A_2, and crystallization of the ppt from MeOH afforded yellow prisms (0·7 g), m.p. 173–175°. (Found: C, 73·69; H, 4·01; N, 4·04. $C_{21}H_{13}NO_4$ requires: C, 73·46; H, 3·82; N, 4·08%).

3-(p-*Nitrophenyl*)4-*phenylisocarbostyril* (XVII). A mixture of XVI (0·25 g), EtOH (2·5 ml) and conc NH_4OH (2·5 ml) was heated at 100° for 15 hr in a sealed tube. From the cooled reaction mixture separated a product (0·2 g) which was crystallized from benzene to afford yellow prisms, m.p. 295–298°. (Found: N, 8·44. $C_{21}H_{14}N_2O_3$ requires: N, 8·18%).

3-(p-*Aminophenyl*)4-*phenylisocarbostyril* (XIII). A soln of XVII (0·15 g) in AcOH (15 ml) was stirred in an atmosphere of H_2 in the presence of 5% Pd–Al_2O_3 (0·1 g) until absorption ceased (5 hr). The mixture was heated on a steam bath in order to dissolve a white ppt, the catalyst was filtered off and the filtrate was diluted with an equal volume H_2O. A brown ppt (20 mg) which separated was filtered off. Neutralization of the filtrate with conc NH_4OH caused formation of a ppt (0·1 g) which was crystallized from MeOH to give blades, m.p. 298–300°. (Found: C, 80·42; H, 5·19; N, 8·82. $C_{21}H_{16}N_2O$ requires: C, 80·75; H, 5·16; N, 8·97%).

3-(o-*Aminophenyl*)4-*phenylisocarbostyril* (XIV = B_2). A suspension of XVIII[21] (0·35 g) in 2N NaOH (5 ml) was poured into a stirred soln of NaOBr (prepared at 0° from 0·15 g NaOH and 0·05 ml Br_2 in 10 ml H_2O). After 15 min at room temp the mixture was treated with EtOH (0·5 ml), boiled for 10 min, then heated 1 hr on a steam bath. The product which separated (30 mg), collected and crystallized from MeOH, resulted identical (m.p., UV and IR) with B_2. Further heating (1 hr) of the mother liquor led to separation of more impure B_2 (20 mg). Acidification of the filtrate with AcOH afforded the acid XIX (0·15 g) m.p. 230–235° (dec). (Found: N, 4·33. $C_{22}H_{15}NO_3$ requires: N, 4·10%).

Schmidt reaction with 2,3-*diphenylindone in conc* H_2SO_4. A stirred soln of 2,3-diphenylindone (1 g) in 96% H_2SO_4 (30 ml) was treated at 35–40° with NaN_3 (0·8 g). Stirring of the soln, which changed its colour from deep green to red–brown, was continued for 1 hr at 35–40° and for 1·5 hr at room temp. The reaction mixture was poured into ice: from the resulting clear soln, on addition of excess conc NH_4OH, fine blades separated out (XXIV, 0·5 g). Crystallization from MeOH afforded prisms, m.p. 360° (dec). (Found: N, 7·20. $C_{21}H_{18}N_2O_4S$ requires: N, 7·09%); main IR bands: 2·90, 3·02, 6·10, 6·30, 6·44, 6·88, 6·94, 7·06, 7·29, 7·42, 8·20–8·50 (large), 8·90, 9·05, 9·32, 9·60, 9·69, 9·81, 9·93, 11·53, 12·03, 13·15, 13·30, 13·71, 14·19, 14·82 μ.

Sulphonation of 3,4-*diphenylcarbostyril.* A soln of 3,4-diphenylcarbostyril (0·1 g) in 96% H_2SO_4 (15 ml) was kept at 40–50° for 2 hr. Addition of ice and excess NH_4OH led to separation of a ppt (50 mg) identical (m.p. and IR) with XXIV.

Schmidt reaction with the sodium salt of 2-(p-*sulphophenyl*)3-*phenylindone.* A soln of 2-(*p*-sulphophenyl)-3-phenylindone-Na-salt[5,18] (0·5 g) in 96% H_2SO_4 (15 ml) was treated at 35–40° with NaN_3 (0·3 g). Working up of the reaction mixture in the usual way led to isolation of a product (0·25 g) identical (m.p. and IR) with XXIV.

Schmidt reaction with 3-*methyl*-2-*phenylindone.* A soln of 3-methyl-2-phenylindone[22] (0·5 g) in AcOH–96% H_2SO_4 (30 ml, 4:1 v/v) was treated at 60–70° with NaN_3 (0·5 g). After 1 hr the soln was diluted with ice–water and extracted with Et_2O. The ethereal extract, washed successively with H_2O, 2N Na_2CO_3 and H_2O, afforded on evaporation a residue, which was crystallized from MeOH to give needles (XXIX, 90 mg), m.p. 264–266°. (Found: N, 5·97. $C_{16}H_{13}NO$ requires: N, 5·95%). The acidic mother liquors were treated with excess conc NH_4OH and again extracted with Et_2O. The solid (XXVII, 30 mg) obtained after evaporation of the ethereal extract, was crystallized from MeOH to give a product, m.p. 243–245°, which resulted identical with an authentic sample of 6-methyl-11*H*-indolo[3.2-*c*]isoquinoline;[7] main IR bands: 6·17, 6·62, 6·88, 7·34, 7·85, 8·05, 9·30, 9·75, 10·92, 13·35 μ; NMR: signals at 1 (1H, large: NH), 2–3 (complex, 8H: aromatic), and 6·9 τ (3H, singlet: CH_3).

4-*Methyl*-3-*phenylcarbostyril* (XXIX). A soln of *o*-aminoacetophenone·HCl[8] (1 g) and phenylacetyl chloride (1 ml) in pyridine (5 ml) was heated on a steam bath for 1 hr. The cooled reaction mixture was poured into H_2O and extracted with Et_2O. The organic layer was washed with 2N H_2SO_4, 2N Na_2CO_3, H_2O, then was evaporated to afford an oily residue (0·85 g) which was refluxed for 30 min in a mixture of NaOH (0·6 g), H_2O (20 ml) and EtOH (10 ml). After cooling to room temp a product (0·5 g) was obtained,

which was identical (m.p. and IR) with the neutral substance (XXIX) isolated in the Schmidt reaction with 3-methyl-2-phenylindone.

Schmidt reaction with 3-ethyl-2-phenylindone.[22] The reaction was carried out as described for the methyl analogue, using the same amounts of reagents. The neutral product (XXX, 70 mg) had m.p. 229–230° (from MeOH). (Found: N, 5·70. $C_{17}H_{15}NO$ requires: N, 5·62%). The basic product (XXVIII, 40 mg) had m.p. 276–278° (from benzene–hexane). (Found: C, 83·01; H, 5·92. $C_{17}H_{14}N_2$ requires: C, 82·90; H, 5·73%); main IR bands: 6·15, 6·62, 6·89, 7·37, 7·76, 7·81, 8·01, 8·14, 8·76, 9·18, 10·46, 10·95, 13·09, 13·41 μ.

4-*Ethyl-3-phenylcarbostyril* (XXX). This preparation was carried out as previously described for the methyl analogue. By using the same amounts of *o*-aminopropiophenone[23] and other reagents, a product was obtained (0·6 g), identical (m.p. and IR) with the neutral substance (XXX) isolated in the Schmidt reaction with 3-ethyl-2-phenylindone.

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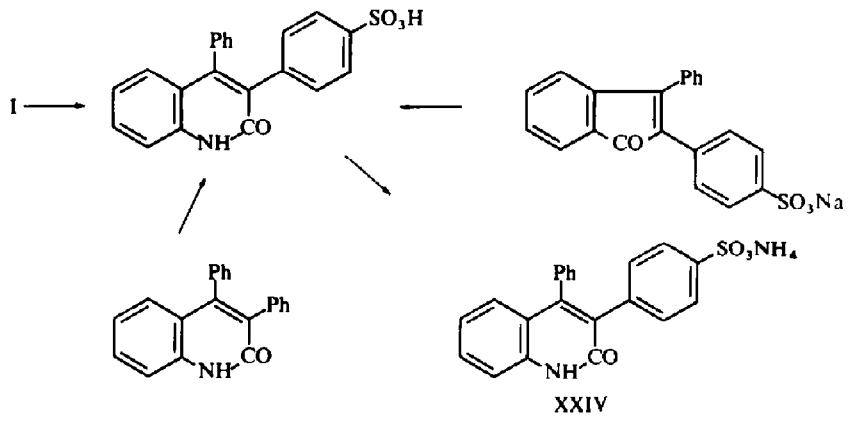
APPENDIX

1. *Schmidt reaction with 2,3-diphenylindone in concentrated sulphuric acid.* The Schmidt reaction was also carried out in concentrated sulphuric acid. In this case, after dilution of the reaction mixture with water, a clear solution was obtained. This solution, on treatment with ammonia, yielded a single product, which was identified as the ammonium sulphonate XXIV (Scheme 9). Indeed, the same product was obtained on sulphonation of 3,4-diphenylcarbostyril, and on treatment of the sodium salt of 2-(*p*-sulphophenyl)3-phenylindone in sulphuric acid with hydrazoic acid.

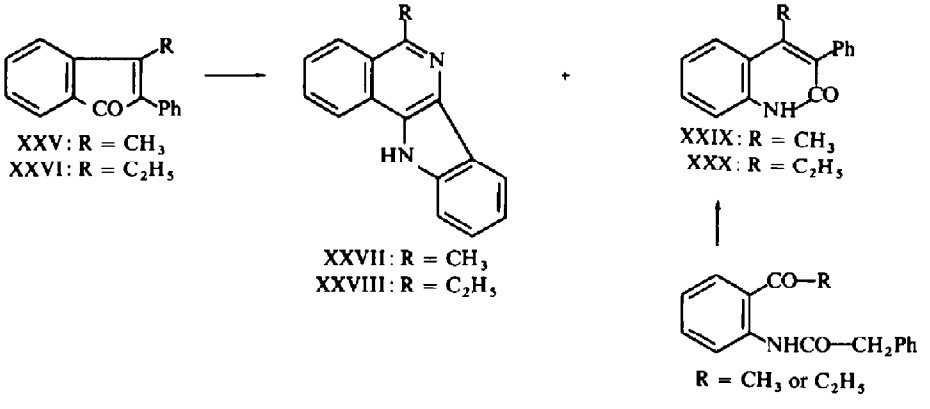
SCHEME 9



XXIV

2. *Schmidt reaction with 3-methyl-2-phenylindone and 3-ethyl-2-phenylindone.* The reaction with these compounds (XXV and XXVI, Scheme 10) was carried out in acetic–sulphuric acid solution as previously described for 2,3-diphenylindone. From both compounds only two products were isolated: the indolo-isoquinoline derivatives XXVII and XXVIII, and the carbostyrils XXIX and XXX. Compound XXVII is known,[12] direct comparison with a sample of 5-methyl-11*H*-indolo[3.2-*c*]isoquinoline, prepared according to Mann's method, proved its identity. We have attributed to XXVIII an analogous structure on the basis of similarity of chemical properties and IR spectra. The structures of products XXIX and XXX were established through direct synthesis.

SCHEME 10



XXV: R = CH_3
XXVI: R = C_2H_5

XXVII: R = CH_3
XXVIII: R = C_2H_5

XXIX: R = CH_3
XXX: R = C_2H_5

R = CH_3 or C_2H_5