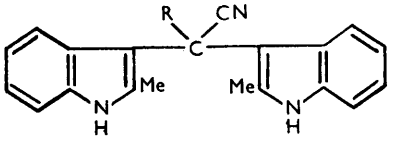
268. *The Action of Acyl Cyanides on 2- and 1 : 2-Substituted Indoles. Part II.* Derivatives of 2-o-Aminophenylindole.*

By A. K. Kiang, F. G. Mann, A. F. Prior, and A. Topham.

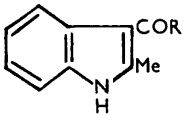
Acetyl cyanide reacts with 2-*o*-aminophenylindole to give the acetamido-indole, 2-methylindolo(3′ : 2′-3 : 4)quinoline, and the isomeric 2-methylindolo-(1′ : 2′-3 : 4)quinazoline under various conditions. Benzoyl cyanide similarly gives the benzamido-indole and the 2-phenylindoloquinoline. The inter-relation of these compounds is discussed.

Acetyl and benzoyl cyanides with 2-*o*-aminophenyl-1-methylindole give the corresponding acylamino-indoles and indoloquinolines.

In Part I,* Kiang and Mann have shown that 2-methylindole in pure chloroform solution reacted with acetyl cyanide to give 1-cyano-1 : 1-di-(2-methyl-3-indolyl)ethane (I; R = Me) and a smaller proportion of 3-acetyl-2-methylindole (II; R = Me) : in chloroform containing a small quantity of hydrogen chloride only the cyano-ethane was formed, whereas in chloroform containing a trace of pyridine the acetyl-indole was the sole product. Benzoyl cyanide reacted similarly with 2-methylindole in chloroform containing hydrogen chloride to give the nitrile (I; R = Ph), and in chloroform with a trace of pyridine to give 3-benzoyl-2-methylindole (II; R = Ph). It is noteworthy that although the action of



(I)



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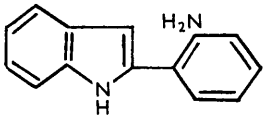


(III)

acetyl and benzoyl cyanide on several other 2- and 1 : 2-substituted indoles was investigated, no other examples of simple acylation in the 3-indole position in neutral or acid solution were encountered, the product being usually a di-indolyl compound analogous to (I) : furthermore, a 2-substituted indole was never attacked in the 1-position.

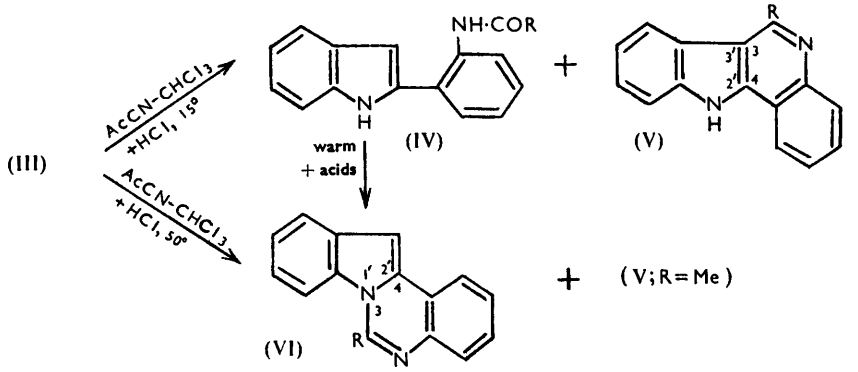
Having thus elucidated the reactions of these simpler indoles, we have now investigated the action of the two acyl cyanides on 2-*o*-aminophenylindole (III) : a greater variety of reactions is now possible, since this indole has three potential points of attack, namely, the amino-group and the 1- and the 3-position in the indole nucleus.

We find that 2-*o*-aminophenylindole (III) and acetyl cyanide (2 equivalents) in chloroform solution interact, slowly at room temperature and readily on boiling, to give 2-*o*-acetamidophenylindole (IV; R = Me). Mildly acidic conditions, *i.e.*, when the above

* Part I, *J.*, 1953, 594.

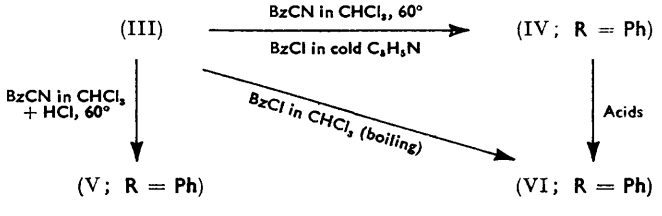
solution is treated at room temperature with chloroform saturated with hydrogen chloride, produce a mixture of the acetamido-compound (IV; R = Me) and the hydrochloride of 2-methylindolo(3′ : 2′-3 : 4)quinoline (V; R = Me), the latter being identical with a sample prepared by the method of Kermack and Smith.[1] More vigorous conditions, *i.e.*, when hydrogen chloride was passed through the above solution at 50°, produce a mixture of the hydrochlorides of the above quinoline (V; R = Me) and of the isomeric 2-methylindolo-(1′ : 2′-3 : 4)quinazoline (VI; R = Me). These conditions are those of the Hoesch reaction, and the addition of stannic or aluminium chloride to the solution had little effect on the products.

Now it is significant that the acetamido-compound (IV; R = Me), which can be prepared by the cautious acetylation of the indole (III), is very sensitive to acids, which readily cyclise it solely to the corresponding salt of the quinazoline (VI; R = Me): this process occurs when the compound (IV; R = Me) is dissolved in cold concentrated hydrochloric acid, or when it is briefly heated with dilute hydrochloric acid, or with acetic acid containing hydrogen chloride, or with ethanol containing a very low concentration of hydrogen chloride. Moreover, the indole (III) with cold acetyl chloride or bromide or warm acetic anhydride gives the quinazoline (VI; R = Me). In none of these experiments could the quinoline (V; R = Me) be detected as a product of the cyclisation of the acetamido-indole (IV; R = Me).



The formamido-compound (IV; R = H) must be particularly sensitive to acids, since all attempts to obtain it by formylation of the indole (III) gave indolo(1′ : 2′-3 : 4)quinazoline (VI; R = H), which was identified by its marked difference from the authentic indolo(3′ : 2′-3 : 4)quinoline (V; R = H) prepared by the method of Clemo and Perkin.[2]

Benzoyl cyanide reacted similarly with the amino-indole (III) with however certain differences, due possibly to the lower reactivity of this cyanide. A solution of the indole and the cyanide (2 equivalents) in chloroform, when heated at 60° for 4 hr. or boiled under reflux for 1 hr., gave 2-*o*-benzamidophenylindole (IV; R = Ph); addition of pyridine to



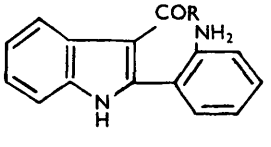
the boiling chloroform solution did not alter the result. The benzamido-derivative could also be obtained by direct benzoylation, for example, by the addition of benzoyl chloride to a pyridine solution of the indole (III). When however a stream of hydrogen chloride

[1] Kermack and Smith, *J.*, 1930, 2000.
[2] Clemo and Perkin, *J.*, 1924, **125**, 1608.

was passed into the original chloroform solution at 60° for 4 hr., only the hydrochloride of 2-phenylindolo(2′ : 3′-4 : 3)quinoline (V; R = Ph) was obtained : this base was identified by an independent synthesis. Under the above conditions, the formation of the isomeric quinazoline (VI; R = Ph) was not observed. The benzamido-compound (IV; R = Ph) is however also very sensitive to acids which readily convert it into the quinazoline : similarly the indole (III) with benzoyl chloride in boiling chloroform gives the quinazoline (VI; R = Ph), undoubtedly *via* the compound (IV; R = Ph).

It is highly significant therefore that in both the acetyl and the benzoyl series, the acid-catalysed cyclisation of the acylamino-compound (IV) gave solely the quinazoline (VI), and that the quinoline (V) could not be thus prepared : consequently the formation of the latter from the indole (III) must proceed through some intermediate other than the acylamino-compound (IV). The structure of the acylamino-compounds experimentally obtained is therefore of considerable importance, for the acyl derivative (IV) should theoretically be capable of cyclisation to either the quinoline (V) or the quinazoline (VI), whereas the 3-acyl isomer (VII) could give only the quinoline (VI), and the 1-acyl isomer (VIII) only the quinazoline (VI).

The acetamido-compound (IV; R = Me), prepared on many occasions, was always obtained as a highly crystalline compound, m. p. 156—157° : its cold ethanolic solution gave an immediate deep colour with Ehrlich's reagent, indicating strongly that the 1- and the 3-position in the indole were unsubstituted. The benzamido-compound, prepared from the cyanide or by direct benzoylation, was also a crystalline compound, m. p. 176°. On one occasion, a small portion of the indole (III), when benzoylated by the Schotten–Baumann method, gave an isomeric benzamido-derivative, m. p. 167°, depressed to 142—147° on admixture with the former compound. Although the preparation of the product,



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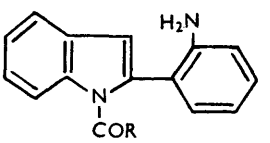
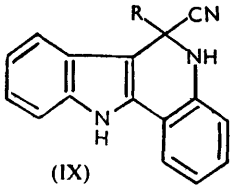


(VIII)



(IX)

m. p. 167°, was once repeated independently by another worker, further attempted repetitions, using the same sample of the indole (III) and many other samples, and a wide variety of conditions, always gave the original product, m. p. 176°.* It is almost certain that the latter has the structure (IV; R = Ph), for its cold ethanolic solution rapidly gave a deep colour with Ehrlich's reagent, whereas that of the isomer, m. p. 167°, gave no colour. Neither compound in ethanolic solution gave a precipitate with 2 : 4-dinitrophenylhydrazine, and it is probable therefore that the isomer, m. p. 167°, has the structure (VIII; R = Ph), a conclusion supported by the cyclisation of the minute quantity available (p. 1325).

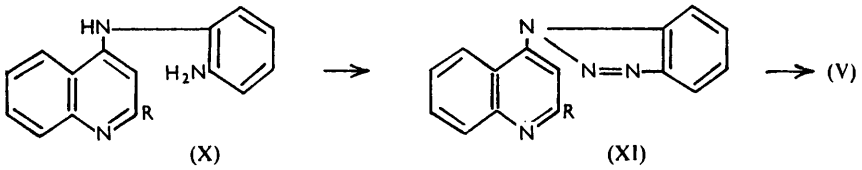
The precursor of the indoloquinolines (V) remains uncertain. Since the latter were formed in the most acidic medium, it is possible that the amino-group in the indole (III) was inactivated by hydrochloride formation, and the acyl cyanide then gave the 3-acyl derivative (VII), with subsequent cyclisation to the quinoline (V). This is unlikely, however, because acyl cyanides react with simpler indoles to give 3-acyl derivatives in good yield only in basic media (cf. Part I). The precursor may be the compound (IX), which

* This failure to repeat the preparation of an acylated indole is not without precedent. The preparation of 3 : 6-dibenzoylcarbazole from 9-benzoylcarbazole by Plant and Tomlinson [3] could not be repeated by Plant, Rogers, and Williams,[4] who state " These discordant observations have not been traced to any obvious variations in conditions and are probably due to very minor changes in the quality of the materials used." The conversion of 2 : 3-diphenylindole into its 1-benzoyl derivative by Fennell and Plant [5] could not be subsequently repeated (personal communication from the late Dr. S. G. P. Plant).

[3] Plant and Tomlinson, *J.*, 1932, 2188.
[4] Plant, Rogers, and Williams, *J.*, 1935, 742.
[5] Fennell and Plant, *J.*, 1932, 2872.

could be formed in a reaction the speed of which is dependent on the acidity of the medium, which would therefore determine the relative proportions of the compound (IX) and the acylamino-compound (IV); this precursor under the influence of the hydrogen chloride could readily undergo aromatisation by loss of hydrogen cyanide, giving the stable hydrochloride of the indoloquinoline (V).

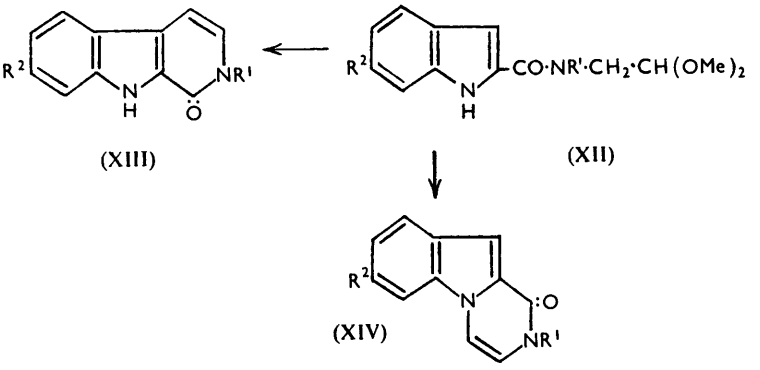
The indoloquinazolines (VI; R = H, Me, and Ph) represent a new heterocyclic system, the structure of which follows from their non-identity with the isomeric indoloquinolines (V; R = H, Me, and Ph). The first two of the latter compounds had previously been synthesised, and the third (V; R = Ph) has now been prepared by a method based essentially on the work of Robinson and Thorneley [6] (cf. also Holt and Petrow [7]). 4-Chloro-2-phenylquinoline was condensed with *o*-phenylenediamine to give 4-*o*-aminoanilino-2-phenylquinoline (X; R = Ph) which with nitrous acid furnished 4-1′-benzotri-



azolyl-2-phenylquinoline (XI; R = Ph). This compound, when heated with phosphoric acid, lost nitrogen with cyclisation to the required 2-phenylindolo(2′ : 3′-4 : 3)quinoline (V; R = Ph). The 2-benzyl analogue (V; R = CH_2Ph) has been similarly synthesised to distinguish it from the 2-benzylindoloquinazoline (VI; R = CH_2Ph) obtained by cyclisation of the phenylacetamido-indole (IV; R = CH_2Ph).

It is noteworthy that salts of these indoloquinolines (V) are colourless, whilst those of the indoloquinazolines (VI) are bright yellow.

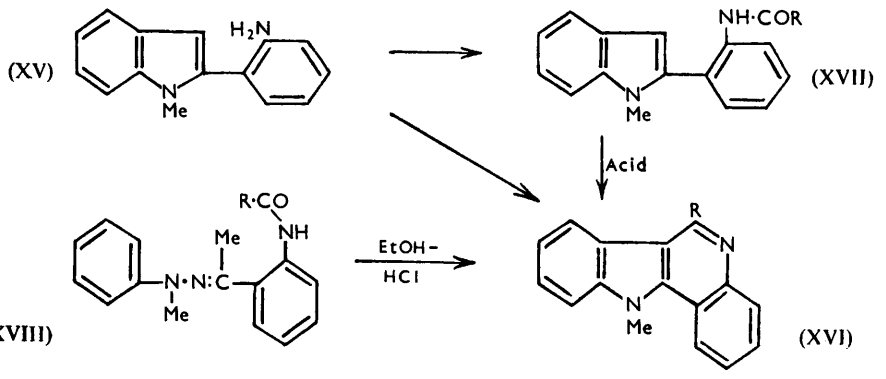
Cyclisation of a 2-substituted indole to the 3- and the 1-position has been previously recorded. In particular, Kermack, Perkin, and Robinson [8] have shown that compounds of type (XII) cyclise in ethanolic hydrogen chloride to either the dihydroindolopyridine derivative (XIII) or the isomeric dihydroindolopyrazine derivative (XIV) or a mixture of both, the nature of the products depending on the substituents R^1 and R^2.



We have also investigated the simpler problem of the action of acetyl and benzoyl cyanides on 2-*o*-aminophenyl-1-methylindole (XV), where cyclisation can now give only the indoloquinolines (XVI). In this series also, there are certain differences in the action of the two acyl cyanides. The methylindole (XV) reacts with acetyl cyanide in a basic medium, *i.e.*, in pyridine or in chloroform containing pyridine, to give the acetamido-derivative (XVII; R = Me), but in neutral and acidic media, *i.e.*, in pure chloroform and in chloroform

[6] Robinson and Thorneley, *J.*, 1924, 2169.
[7] Holt and Petrow, *J.*, 1948, 922.
[8] Kermack, Perkin, and Robinson, *J.*, 1922, **121**, 1872.

containing hydrogen chloride respectively, to give the indolo-quinoline (XVI; R = Me), the reaction being most rapid in the acidic medium. The indole (XV) reacts with benzoyl cyanide in both the above basic and neutral media to give the benzamido-derivative (XVII; R = Ph), and in chloroform containing hydrogen chloride to give the quinoline (XVI;



R = Ph). The acylamino-compounds (XVII) are again very sensitive to acids, which readily cyclise them to the indoloquinolines (XVI) : it is noteworthy that in this series the formamido-compound (XVII; R = H) can be isolated, unlike the unmethylated analogue (IV; R = H). The identity of the indoloquinolines (XVI; R = Me and Ph) has been confirmed by their formation by cyclisation of the appropriate *o*-acylaminoacetophenone methylphenylhydrazone (XVIII) : this reaction was originally performed by Kermack and Smith,[1] but the yield and quality of the final product are much improved if ethanolic hydrogen chloride is used as a condensing agent in place of phosphorus oxychloride.

Infrared data for various indoles are given on p. 1330.

Experimental

The indole (III), its acyl derivatives, and the indoloquinazolines obtained by their cyclisation are described first, then (when necessary) the synthesis of the indoloquinolines, so that the members of these three classes are identified before describing their production by the action of acyl cyanides on the indole. The indole (XV) is then similarly treated, although the quinazoline compounds do not occur in this series.

2-o-*Aminophenylindole* (III).—(a) o-*Nitrobenzoyl chloride.* Powdered phosphorus pentachloride (138 g.) was gradually added with shaking to *o*-nitrobenzoic acid (102 g.) in a 1 l. flask fitted with a reflux condenser closed with a calcium chloride tube, and the mixture was heated for 20 min. on a boiling-water bath. Phosphorus oxychloride was removed by distillation (water-pump), and the residual oily *o*-nitrobenzoyl chloride, which cannot always be safely distilled, was then filtered through a sintered glass funnel (yield, 108 g., 95%). It was sufficiently pure for the next stage.

(b) o-*Nitroacetophenone.* Two solutions were prepared : solution A by dissolving sodium wire (27·8 g.) in absolute ethanol (450 c.c.), which was cooled and restored to 440 c.c. with more ethanol, and solution B by dissolving the above chloride (73 c.c., 100 g.) in ether, the solution being then made up to 100 c.c.

Ethyl malonate (103 c.c.) was placed in a 1 l. flask, cooled in ice–salt. Solutions A and B were slowly added through two funnels in the following order so that the temperature of the mixture did not rise above 5° : A 240 c.c., B 50 c.c., A 100 c.c., B 25 c.c., A 50 c.c., B 15 c.c., A 50 c.c., B 10 c.c. After 10 min., the mixture was added to a solution of concentrated sulphuric acid (25 c.c.) in water (500 c.c.). The precipitated oil was extracted with ether, which was then thoroughly shaken with water. The initial solution, combined with the water-washings, was again extracted with ether, which was then washed with water. The united ether extracts were distilled, and traces of solvent removed from the residual ethyl *o*-nitrobenzoylmalonate on a water-bath at 15 mm. until distillation ceased. The residue was mixed with a solution of sulphuric acid (270 c.c.) in water (925 c.c.), boiled under reflux for 4 hr., cooled, and extracted

with ether. The extract was washed in turn with an excess of aqueous 10% sodium hydroxide and with water, and the solvent removed, and the residue, after heating at 100°/15 mm., consisted of almost pure *o*-nitroacetophenone (74 g., 83%). This method is less troublesome and gives higher yields than any of those described by Schofield and Swain.[9]

(c) o-*Aminoacetophenone*. A mixture of *o*-nitroacetophenone (68 g.) and concentrated hydrochloric acid (380 c.c.) was treated at 95° under reflux, with vigorous stirring, with granulated tin (153 g.) during 1 hr., the heating and stirring being then continued for 30 min. Aqueous 30% sodium hydroxide (470 c.c.) was added slowly to the hot stirred mixture, with occasional cooling to prevent boiling. The mixture was distilled in steam, and the distillate (*ca.* 4 l.) extracted with ether. Removal of the ether from the dried (K_2CO_3) extract left almost pure *o*-aminoacetophenone (42 g., 73%).

A mixture of this product (43 g.), ethanol (84 c.c.), phenylhydrazine (35 c.c.), and acetic acid (5 c.c.) was boiled under reflux for 6 hr. and cooled. The crystalline phenylhydrazone (m. p. 104—108°; 63 g., 88%) was collected, washed with ethanol, and dried, a second crop (m. p. 103—108°; 3·5 g.) being obtained by concentration of the filtrate. Auwers and Meyenburg[10] give m. p. 108°: they state inaccurately that the initial crystalline product is the acetate of the hydrazone.

(d) *Cyclisation*. A mixture of the hydrazone (50 g.) and powdered zinc chloride (250 g.) was stirred in an oil-bath at 160—170°. The mixture became pasty as the internal temperature rose to *ca.* 210°. The stirred mixture was kept in the bath at 160° for 10 min., and when removed solidified. Concentrated hydrochloric acid (43 c.c.) in water (615 c.c.) was added, and the stirred mixture heated on the water-bath for *ca.* 1 hr. until the zinc chloride had been extracted. The mixture, after further dilution with water (440 c.c.) and hydrochloric acid (44 c.c.), was heated to boiling to obtain an almost clear solution, to which ammonia (17%; *ca.* 87 c.c.) was slowly added until the mixture was no longer acid to Congo-red. The precipitate was collected, washed with water, and dissolved in boiling water (1060 c.c.) containing hydrochloric acid (88·5 c.c.), and the filtered solution treated with ammonia (*ca.* 126 c.c.) as before. The precipitated indole (III), when washed and dried (38·5 g., 84%), had m. p. 148—150°, increased to 154—156° by recrystallisation from ethanol, and then unchanged by sublimation at 145°/0·001 mm. (Found: C, 80·6; H, 5·9. Calc. for $C_{14}H_{12}N_2$: C, 80·7; H, 5·8%) (lit.,[11] m. p. 154°). The use of a lower proportion of zinc chloride reduced the yield: the use of ethanolic hydrogen chloride as a cyclising agent gave very poor results.

Acyl Derivatives of the Indole (III).—(1) 2-o-*Acetamidophenylindole* (IV; R = Me). When the powdered indole (III) (3 g.) was added to cold acetic anhydride (6 c.c.), heat was evolved, giving a clear solution which when set aside for 1 hr. deposited crystals of the acetamido-derivative (IV; R = Me). After ice-water cooling, the product (2·75 g., 75%) was collected and washed with ethanol: it had m. p. 155—156·5°, increased to 156—157° by crystallisation from ethanol (Found: C, 77·15; H, 6·0; N, 11·3. Calc. for $C_{16}H_{14}ON_2$: C, 76·8; H, 5·6; N, 11·2%). Ruggli and Dinger[12] give m. p. 151—152°. If this preparation is carried out on a larger scale without strong cooling, the higher temperature attained may cause the product to be contaminated with the quinazoline (VI; R = Me).

(2) *Benzamido-derivative* (IV; R = Ph). (*A*) (i) Benzoyl chloride (0·6 c.c., 1·1 mols.) was added to a solution of the indole (1·04 g.) in pyridine (2 c.c.), which was then heated to 50°, set aside for 30 min., and poured into water. The aqueous solution was decanted from the precipitated oil, which when stirred with ethanol solidified (1·1 g., 71%), and on crystallisation from ethanol afforded the *benzamido-compound*, needles, m. p. 175—175·5° (Found: C, 80·5; H, 5·0; N, 9·0. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·15; N, 9·0%).

(ii) In numerous attempts to repeat the preparation of the isomer described below in (*B*), the general conditions were varied widely without effect. The powdered indole, when stirred with cold undiluted chloride, was converted into the hydrochloride of the indoloquinazoline (VI; R = Ph).

(*B*) On two occasions a suspension of the pure powdered indole in an excess of 10% aqueous sodium hydroxide, when shaken with a small excess of benzoyl chloride, rapidly gave a pale brown emulsion which slowly solidified. The solid product, recrystallised from ethanol, gave cream-coloured crystals of the benzamido-compound, m. p. 166°, depressed to 148—160° on admixture with the previous compound (Found: C, 80·5; H, 4·9%).

[9] Schofield and Swain, *J.*, 1948, 384.
[10] Auwers and Meyenburg, *Ber.*, 1891, **24**, 2370.
[11] Kliegl and Haas, *Ber.*, 1911, **44**, 1211.
[12] Ruggli and Dinger, *Helv. Chim. Acta*, 1939, **22**, 908.

(3) *Phenylacetamido-derivative* (IV; R = CH_2Ph). Phenylacetyl chloride (1·32 c.c., 1 mol.), when added dropwise to a solution of the indole (III) (2·0 g.) in pyridine (2 c.c.), caused a vigorous reaction, and the oily product, when set aside for 15 min. and then stirred with *cyclo*hexane, deposited the *phenylacetamido-derivative* (1·2 g., 41%), m. p. 169—170° after crystallisation from ethanol (Found: C, 80·7; H, 5·7. $C_{22}H_{18}ON_2$ requires C, 80·9; H, 5·6%).

Cyclisation to Indolo(1′ : 2′-3 : 4)*quinazolines* (*Ring Index, Indolo*[1 : 2-c]*quinazolines*) (VI).—(1) A solution of the indole (III) (1 g.) in chilled formic acid (10 c.c.) was evaporated at room temperature over sodium hydroxide in a vacuum-desiccator. The dry crystalline residue of *indolo*(1′ : 2′-3 : 4)*quinazoline* (VI; R = H), when washed with cold ethanol and dried, had m. p. 198—200°; recrystallisation from ethanol gave very pale yellow crystals (0·9 g.), m. p. 200—201° (Found: C, 82·7; H, 4·8; N, 12·8. $C_{15}H_{10}N_2$ requires C, 82·6; H, 4·6; N, 12·8%). The same compound was obtained when a solution of the indole (1 g.) in formic acid (5 c.c.) or in formamide (4 c.c.) was boiled for 10 min. and then poured into water. The indole was unaffected when its solution in ethyl formate was boiled.

(2) (*a*) A solution of the indole (III) (2 g.) in acetic anhydride (10 c.c.), when boiled under reflux for 2 hr. and cooled, furnished the crystalline 2-methylindoloquinazoline (VI; R = Me), m. p. 114—116° after crystallisation from ethanol, undepressed by admixture with the product (*b*) below.

When acetyl chloride (0·5 c.c., 1·5 mols.) was slowly added to a solution of the indole (1 g.) in chloroform (20 c.c.) a violent reaction occurred, and the yellow hydrochloride of the indoloquinazoline was deposited. This salt (1·4 g.) was collected and dissolved in hot water (150 c.c.) containing hydrochloric acid (5 c.c.): basification of the solution with ammonia deposited the methylindoloquinazoline (0·84 g.), m. p. 112—114°.

(*b*) A solution of the acetamido-compound (IV; R = Me) (1 g.) in acetic acid (20 c.c.) containing concentrated hydrochloric acid (5 c.c.) was boiled under reflux for 2 hr. and then evaporated to dryness on a water-bath. The residual yellow crystalline hydrochloride, when treated as above, gave the 2-*methylindoloquinazoline* (0·88 g.), pale yellow needles, m. p. 115—116° (from ethanol) (Found: C, 82·2; H, 5·35; N, 12·45. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N, 12·1%).

The acetamido-derivative was also readily converted into the above hydrochloride when its solution in chloroform–hydrogen chloride or in ethanolic hydrogen chloride was gently heated, or when its suspension in an excess of dilute hydrochloric acid was boiled until complete solution was obtained.

(3) (*a*) Solutions of the indole (III) (2·1 g.) and benzoyl chloride (1·15 c.c., 1·1 mols.) each in chloroform (30 c.c. and 10 c.c.) were mixed, boiled under reflux for 3 hr. and evaporated to dryness. The product was extracted with boiling water (500 c.c.) containing 2N-hydrochloric acid (10 c.c.), and the undissolved 2-*phenylindoloquinazoline* (VI; R = Ph) (2·7 g., 92%) had m. p. 194—196°, increased to 197—198° by recrystallisation from ethanol (Found: C, 85·75; H, 4·6; N, 9·7. $C_{21}H_{14}N_2$ requires C, 85·7; H, 4·75; N, 9·5%). Alternatively, when hydrogen chloride was passed through the above mixture at 60° for 3 hr., the product, worked up as before, furnished the indoloquinazoline (1·23 g.), m. p. 197—198°.

(*b*) A solution of the benzamido-derivative (IV; R = Ph), m. p. 175—175·5° (0·1 g.), in chloroform (5 c.c.) containing ethanolic hydrogen chloride (0·1 c.c.) was boiled for 3 hr. and evaporated. The yellow residue of crude hydrochloride (m. p. 140—194°), on recrystallisation as before, underwent dissociation giving the indoloquinazoline, m. p. and mixed m. p. 195—197°.

The isomeric benzamido-compound, m. p. 166—167° (*ca.* 2 mg.), was boiled with ethanolic hydrogen chloride for 10 min., the solution immediately developing a bright yellow colour. Evaporation gave a residue which on basification with ammonia furnished the crudec yclised product, m. p. 188—192°, insufficient in quantity for recrystallisation or mixed m. p. determination. The deep yellow colour of the hydrochloride, and the m. p. of the product, indicate strongly that this product was also the indoloquinazoline (VI; R = Ph) and that this benzamido-compound has therefore the structure (VIII).

(4) (*a*) Phenylacetyl chloride (1·33 c.c.) was added to a hot solution of the indole (III) (2·1 g.) in chloroform (40 c.c.), which was boiled under reflux for 75 min. and cooled. The yellow crystals (m. p. *ca.* 254°; 2·4 g.) of the hydrochloride which had separated were collected, and when crystallised from ethanol gave the almost colourless 2-*benzylindoloquinazoline* (VI; R = CH_2Ph), m. p. 194—197° (Found: C, 85·65; H, 5·0; N, 8·95. $C_{22}H_{16}N_2$ requires C, 85·7; H, 5·2; N, 9·1%).

(*b*) A solution of the phenylacetamido-compound (IV; R = CH_2Ph) in chloroform, treated as in 3(*b*), gave the quinazoline, m. p. and mixed m. p. 195—198·5°.

2-*Phenylindolo*(3′ : 2′-3 : 4)*quinoline* (V; R = Ph).—(*a*) 4-Hydroxy-2-phenylquinoline was prepared by the condensation of ethyl anthranilate and acetophenone diethyl acetal [13] and converted into 4-chloro-2-phenylquinoline essentially by the method of Knorr and Fertig.[14] A mixture of the chloro-compound (2·4 g.), *o*-phenylenediamine (1·1 g., 1 mol.), copper powder (0·05 g.), and concentrated hydrochloric acid (0·1 c.c.) was heated at 18 mm. Reaction started when the bath-temperature reached *ca.* 120° and became very vigorous at 130° : the temperature was kept at 130° until the reaction appeared to cease, and was then increased to 140° for 5 min. The cold product was extracted with boiling ethanol (200 c.c.), which was filtered into an excess of dilute ammonia. The greenish precipitate was washed with water, dried (2·85 g.), and extracted with boiling benzene. The filtered extract on cooling deposited a powder, m. p. 178—180°, which, recrystallised from ethanol, gave the hydrated 4-o-*aminoanilino*-2-*phenylquinoline* (X; R = Ph), as very pale yellow crystals, m. p. 179—181° (Found : C, 77·9; H, 6·5; N, 12·8. $C_{21}H_{17}N_3$,0·75H_2O requires C, 77·7; H, 5·7; N, 12·9%).

(*b*) An ethanolic solution of the amino-compound (X; R = Ph) was mixed with N-hydrochloric acid, cooled to 5—10° with stirring, and treated with a slight excess of sodium nitrite. The crystals which separated were collected and recrystallised from methanol, affording colourless 4-1′-*benzotriazolyl*-2-*phenylquinoline* (XI; R = Ph), m. p. 152—153° (Found : C, 78·3; H, 4·5; N, 17·6. $C_{21}H_{14}N_4$ requires C, 78·2; H, 4·4; N, 17·4%). A solution in hot 10% hydrochloric acid on cooling deposited the crystalline *monohydrochloride*, m. p. 185—186° (Found : C, 70·2; H, 4·6; N, 15·8. $C_{21}H_{14}N_4$,HCl requires C, 70·3; H, 4·2; N, 15·6%).

(*c*) The triazole (1 g.) was heated in syrupy phosphoric acid (10 c.c.) at 140—150° until evolution of nitrogen ceased and then at 150° for 1 min. The product was poured into ice-water containing sodium hydroxide (8 g.), and the precipitate washed with water, dried (0·85 g.), and extracted with boiling benzene. The filtered extract was evaporated and the residue, when recrystallised from benzene, afforded 2-*phenylindolo*(3′ : 2′-3 : 4)*quinoline* (V; R = Ph), m. p. 245—246°. This still contained an impurity, for in concentrated sulphuric acid it gave a colourless solution with a blue fluorescence. This impurity could not be removed by absorption on an alumina column : the base was therefore converted into its hydrochloride, which was repeatedly recrystallised from dilute hydrochloric acid, in which the impurity was only slightly soluble. The regenerated base, of unchanged m. p., no longer gave a fluorescent solution (Found : C, 86·0; H, 5·1; N, 9·3. $C_{21}H_{14}N_2$ requires C, 85·7; H, 4·75; N, 9·5%).

A filtered solution of the base (0·5 g.) in hot water (50 c.c.) containing concentrated hydrochloric acid (0·5 c.c.), when allowed to cool, initially formed a gel, which, when drained as far as possible at the pump and then repeatedly recrystallised, gave the *monohydrated monohydrochloride*, m. p. 326—344° (Found : C, 72·0; H, 5·2; N, 8·15; Cl, 10·25. $C_{21}H_{14}N_2$,HCl,H_2O requires C, 72·2; H, 4·9; N, 8·1; Cl, 10·2%).

2-*Benzylindolo*(3′ : 2′-3 : 4)*quinoline* (V; R = CH_2Ph).—(*a*) *Ethyl* α-(*phenylacetyl*)*acetoacetate and* γ-*phenylacetoacetate*. A buffered copper sulphate solution was prepared by mixing aqueous solutions of hydrated copper sulphate (22·8%; 1650 c.c.), sodium formate (40%; 765 c.c.), and formic acid (85%; 81 c.c.).

Ethyl acetoacetate (127 c.c.) was added to a solution of sodium (23 g.) in absolute ethanol (372 c.c.), which was then stirred at 0—5° during the slow addition in turn of (i) phenylacetyl chloride (53 c.c.), (ii) a solution of sodium (9·2 g.) in ethanol (150 c.c.), and (iii) the chloride (32 c.c.). The mixture was added with stirring to concentrated hydrochloric acid (76 c.c.), diluted with water (500 c.c.), then made just alkaline to Congo-red with 30% aqueous sodium hydroxide (*ca.* 12 c.c.). The above copper sulphate solution (600 c.c.) was then added, and after 15 min. the blue copper derivative of ethyl α-(phenylacetyl)acetoacetate was collected, shaken with 95% ethanol (300 c.c.) for 5 min., again collected, washed with ethanol, and dried : the complex (130 g.) had m. p. 177—178° (lit.,[15] m. p. 182—183°).

A mixture of this complex (134 g.), ether (400 c.c.), hydrochloric acid (60 c.c.), and crushed ice was stirred at 0—5° for several hours until a clear solution was obtained. The ethereal layer was washed in turn with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water, and then dried and distilled to remove solvent; final heating under reduced pressure left the residual ester (115·5 g.) as a pale brown oil, pure enough for the next stage.

This ester (107 c.c.) was added to a 0·85N-ethanolic ammonia (832 c.c.), from which next day the excess of ammonia and ethanol were removed at 50°/15 mm. A solution of the residue in

[13] Fuson and Burness, *J. Amer. Chem. Soc.*, 1946, **68**, 1270.
[14] Knorr and Fertig, *Ber.*, 1897, **40**, 938.
[15] Bülow and Hailer, *Ber.*, 1902, **35**, 929.

methanol (1170 c.c.), chilled in ice-water, was treated with a 2·5% solution of copper acetate in 50% aqueous methanol (1760 c.c.). The precipitated copper complex of ethyl γ-phenylacetoacetate (60 g.), when washed with methanol (200 c.c.) and dried, had m. p. 125—125·5°. Zangg [16] gives m. p. 128—129°.

A mixture of the complex (69·5 g.), 2N-hydrochloric acid (175 c.c.), and ether (200 c.c.) was shaken until clear, and the ethereal layer washed in turn with the acid and with water, and dried. Removal of the ether, finally under reduced pressure, gave the residual ethyl γ-phenylacetoacetate as a colourless oil (59·5 g.).

Close adherence to the above conditions is necessary for the successful preparation of the esters, particularly the latter. The conditions recorded in the literature gave unsatisfactory results.

(*b*) A mixture of the above ester (20·6 g.), aniline (10 c.c.), benzene (25 c.c.), and acetic acid (0·25 c.c.) was heated under reflux at 125° for 4 hr., water being removed meanwhile through a still-head. The benzene was then removed, finally at 95°/15 mm., and the residual ethyl β-anilino-γ-phenylcrotonate, after recrystallisation from methanol, had m. p. 95—95·5° (22·2 g.) (lit.,[17] m. p. 96—98·5°).

(*c*) The crotonate (30 g.) was added during 2 min. to " Dowtherm " (diphenyl ether 74%, diphenyl 26%) (75 c.c.) at 240°. The mixture was then boiled under reflux for 10 min., cooled, and diluted with light petroleum (b. p. 60—80°) (100 c.c.). The precipitated *2-benzyl-4-hydroxyquinoline* (25·5 g.), when collected, washed with petroleum and dried, had m. p. 209—210°, increased to 210° by recrystallisation from butan-1-ol (Found: C, 82·05; H, 5·6; N, 6·3. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%).

A mixture of this quinoline (29·5 g.) and phosphorus oxychloride (59 c.c.) was heated at 100° until clear, and the excess of chloride removed under reduced pressure. The cold residue was treated with ice and an excess of aqueous sodium hydroxide, and then extracted with ether. The extract, when washed with water, dried, and evaporated, gave crystalline *2-benzyl-4-chloroquinoline*, m. p. 49—51° (Found: C, 75·5; H, 4·7. $C_{16}H_{12}NCl$ requires C, 75·7; H, 4·7%).

(*d*) A mixture of the chloroquinoline (5 g.) and *o*-phenylenediamine (5 g.) was heated at 140°/25 mm. for 3 hr. The resulting solid *hydrochloride* of 4-*o*-aminoanilino-2-benzylquinoline (X; R = CH_2Ph) was digested with boiling N-hydrochloric acid (100 c.c.), cooled, collected, washed in turn with water and much ethanol, and dried (5·2 g.). Recrystallised from 50% aqueous acetic acid, it had m. p. *ca.* 350° (Found: C, 72·4; H, 5·65; N, 11·5. $C_{22}H_{19}N_3$,HCl requires C, 73·0; H, 5·5; N, 11·6%).

(*e*) A 25% aqueous sodium nitrite solution (5 c.c.) was slowly added to the hydrochloride (6·5 g.) in 2N-hydrochloric (65 c.c.) and acetic acid (65 c.c.) at 0—5°. The solution, evaporated under reduced pressure, gave a gum which was shaken with chloroform and dilute aqueous sodium hydroxide. The chloroform extract, when washed with water, dried, and evaporated, gave the triazole (XI; R = CH_2Ph) as a gum. This was heated with phosphoric acid (*d* 1·75; 65 c.c.) at 170° for 10 min., cooled, and added with stirring to a mixture of 30% aqueous sodium hydroxide (215 c.c.), water (700 c.c.), and chloroform (100 c.c.); the whole was stirred for 2 hr. and then filtered. The chloroform layer, when washed with water, dried, and evaporated, gave *2-benzylindolo*(3′ : 2′-3 : 4)*quinoline* (V; R = CH_2Ph), m. p. 215—217° after crystallisation from methanol (Found: C, 85·3; H, 5·05; N, 9·25. $C_{22}H_{16}N_2$ requires C, 85·7; H, 5·2; N, 9·1%): 2·6 g.

Action of Acetyl and Benzoyl Cyanides on the Indole (III).—These reagents were freshly prepared and carefully purified before use. Old samples, particularly of benzoyl cyanide, even if carefully redistilled, did not give consistent results.

The following selected experiments typify the results obtained under different conditions. The products were identified by mixed m. p. determinations with compounds prepared as described above.

Acetyl cyanide. (1) (*a*) Acetyl cyanide (0·72 c.c., 2 mols.) was added to a solution of the indole (1 g.) in chloroform (25 c.c.), which was set aside overnight. Evaporation gave an oil, which when stirred with *cyclo*hexane gave the crude acetamido-compound (IV; R = Me) (1 g.), m. p. 146—156°, increased to 154—156° by crystallisation from ethanol.

(*b*) The above mixture was boiled under reflux for 1 hr. and then evaporated. The gummy residue, when stirred with ethanol, gave the acetamido-compound (0·82 g.), m. p. 155—156·5°.

(2) The above mixture was diluted with a saturated solution (20 c.c.) of hydrogen chloride

[16] Zangg, *J. Amer. Chem. Soc.*, 1946, **68**, 2492.
[17] Sonn and Litten, *Ber.*, 1933, **66**, 1512.

in chloroform, and set aside for 48 hr. The crude yellowish crystals of the hydrochloride of the indoloquinoline (V; R = Me), the deposition of which had soon started, were then collected (0·34 g.), washed with chloroform, dried, and dissolved in hot water (70 c.c.) containing dilute hydrochloric acid (0·1 c.c.), and the solution was filtered into an excess of stirred ammonia solution. The precipitated indoloquinoline (0·23 g.) had m. p. 260—268°, increased to 291—293° by recrystallisation from methanol.

The chloroform filtrate was cautiously evaporated, and a solution of the gummy residue in a minimum of ethanol similarly added to ammonia. The precipitated acetamido-compound (0·88 g.), m. p. *ca.* 140°, when recrystallised from ethanol gave the pure product, pale yellow needles, m. p. 153—154·5°.

Two repetitions of this experiment, in which the volume of chloroform–hydrogen chloride added was 10 and 5 c.c. respectively, gave the indoloquinoline (0·16 and 0·08 g.) and the acetamido-compound (1·05 and 1·1 g.). The purity of the precipitated acetamido-compound increased steadily as the above volume decreased.

(3) The above mixture of the indole (1 g.) and the cyanide (0·72 c.c.) in chloroform was heated at 50° whilst a gentle stream of dry hydrogen chloride was passed through the solution for 15 min. Evaporation gave a yellow residue: its solution in hot water (*ca.* 100 c.c.) was added to ammonia as before. The precipitated mixed bases were dried (0·8 g.) and extracted with boiling benzene (8 c.c.), and the latter was filtered. The residue (0·21 g.), m. p. 240—250°, on recrystallisation from methanol gave the indoloquinoline (V; R = Me), needles, m. p. 293—295°. The benzene filtrate on evaporation left a residue which, on recrystallisation from ethanol, gave the indoloquinazoline (VI; R = Me), m. p. 112—113°. These isomers can thus be readily separated, for the former is almost insoluble in boiling benzene, appreciably soluble in cold ethanol, and only moderately so in cold methanol, whereas the latter is readily soluble in hot benzene and only moderately soluble in cold ethanol.

Addition of aluminium chloride or stannic chloride to the above mixture appeared in general to increase the yield of the indoloquinoline. The use of a vigorous stream of hydrogen chloride left the yield of the quinoline unaffected, but gave an impure sample of the quinazoline.

Benzoyl cyanide. (1) Benzoyl cyanide (0·6 g., 2 mols.) was added to a solution of the indole (0·5 g.) in warm chloroform (7·5 c.c.), which was then heated at 60° for 4 hr. and evaporated. The sticky residue when stirred with ethanol solidified, and when then recrystallised from ethanol gave the benzamido-compound (IV; R = Ph), m. p. 173—175°.

(2) When a solution of the indole (0·5 g.) and the cyanide (0·89 g., 2·5 mols.) in chloroform (20 c.c.) containing pyridine (0·2 c.c.) was boiled under reflux for 2 hr., the compound (IV; R = Ph), m. p. 174—175°, was similarly isolated.

(3) The cyanide (1·3 g.) was added to a solution of the indole (1·04 g.) in chloroform (20 c.c.), which was then heated at 60° whilst a steady stream of hydrogen chloride was passed through for 4 hr. The pale yellow precipitate (1·55 g.) was collected from the cold mixture, dissolved in hot water (160 c.c.) containing concentrated hydrochloric acid (0·2 c.c.), and filtered into aqueous ammonia. The precipitate, when collected, washed with water, dried, and repeatedly recrystallised from benzene (charcoal), gave the indoloquinoline (V; R = Ph) (0·75 g.), pale yellow crystals, m. p. 245—246°. This compound may be dimorphic, for the first samples prepared by this method and recrystallised from toluene had m. p. 202—203° (Found: C, 85·25; H, 4·9; N, 9·4%), whereas later samples prepared by this and by the former method (p. 1326) and recrystallised from benzene had the higher m. p. The low-melting material readily sublimed when heated at 240°/0·005 mm., giving cream-coloured crystals, m. p. 243—244°, and a trace of black residue.

2-o-*Aminophenyl*-1-*methylindole* (XV).—(*a*) Potassium (0·4 g.) in *tert.*-butanol (10 c.c.) and methyl benzenesulphonate (1·72 g.) were added in turn to a solution of the indole (III) (2·1 g.) also in *tert.*-butanol (40 c.c.), which was boiled under reflux for 10 min. and the butanol then removed with steam. The reddish tarry residue recrystallised from ethanol: when set aside overnight at 0° it solidified, and then readily sublimed at 150°/0·003 mm., affording the colourless *indole* (XV) (*ca.* 90% yield), m. p. 129° after crystallisation from ethanol (Found: C, 81·0; H, 6·45; N, 12·4. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·35; N, 12·6%). The use of methyl toluene-*p*-sulphonate (1·87 g.) also gave excellent results. The solubility of this indole in chloroform is markedly greater than that of the indole (III).

(*b*) *o*-Aminoacetophenone (5 g.), *N*-methyl-*N*-phenylhydrazine (4·85 c.c.), ethanol (10 c.c.), and acetic acid (0·6 c.c.) were boiled together under reflux for 6 hr., then evaporated under reduced pressure to give an oil which solidified and when recrystallised from light petroleum (b. p. 60—80°) afforded the *methylphenylhydrazone*, bright yellow needles, m. p. 76·5—77°

(Found : C, 74·8; H, 7·1; N, 17·5. $C_{15}H_{17}N_3$ requires C, 75·2; H, 7·1; H, 17·6%). The Fischer cyclisation, using zinc chloride essentially as previously described (p. 1324), then gave the indole (XV), m. p. 132—133°, but the yield was very low : when ethanolic hydrogen chloride was used, the indole was not obtained.

Acyl Derivatives of the Indole (XV).—(1) A solution of the indole (1 g.) in formic acid (8 c.c.) at 0° was evaporated to dryness in a vacuum-desiccator. The residue, m. p. 92—95°, when recrystallised from benzene, gave the 2-o-*formamido-compound* (XVII; R = H), m. p. 99—100° (Found : C, 76·7; H, 5·5; N, 11·5. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%). It sublimed unchanged when heated at 0·001 mm. : on exposure to air it slowly became sticky.

(2) The indole (0·4 g.) was dissolved in acetic anhydride (1 c.c.) with cooling, and the solution after 1 hr. was shaken with water (10 c.c.). The residual oil was thoroughly washed in turn with 10% aqueous potassium hydrogen carbonate and water, and dried; it solidified. Careful recrystallisation from 50% aqueous ethanol afforded the 2-o-*acetamido-compound* (XVII; R = Me), colourless crystals, m. p. 96—97° (Found : C, 77·0; H, 6·2; N, 10·9. $C_{17}H_{16}ON_2$ requires C, 77·2; H, 6·05; N, 10·6%). The crystallisation of this compound initially gave considerable trouble : the crude material, unless thoroughly washed, may undergo cyclisation during attempted recrystallisation.

(3) A suspension of the indole (XV) in 10% aqueous sodium hydroxide, when shaken with benzoyl chloride, gave the 2-o-*benzamido-compound* (XVII; R = Ph), m. p. 133—134° after crystallisation from ethanol containing 20% of water (Found : C, 80·85; H, 5·75; N, 8·7. $C_{22}H_{18}ON_2$ requires C, 80·9; H, 5·5; N, 8·6%).

Ethanolic solutions of the acylamino-compounds (XVII; R = H, Me, and Ph) gave no precipitate with cold ethanolic 2 : 4-dinitrophenylhydrazine containing hydrochloric acid : warming the solutions readily caused the following cyclisation.

Cyclisation to 1′-*Methylindolo*(3′ : 2′-3 : 4)*quinolines* (XVI).—(1) A solution of the indole (XV) (0·5 g.) in 85% formic acid (3 c.c.) was boiled under reflux for 2 hr., cooled, and poured into water, which when basified with ammonia deposited the colourless *indoloquinoline* (XVI; R = H). This compound was readily soluble in many solvents, and was purified by sublimation at 150°/0·001 mm., which afforded crystals, m. p. 146° (Found : C, 82·6; H, 5·3; N, 12·4. $C_{16}H_{12}N_2$ requires C, 82·6; H, 5·2; N, 12·1%). Similar treatment of the formamido-derivative (XVII; R = H) in formic acid also gave (XVI; R = H), m. p. 144° after sublimation at 150°/0·002 mm., undepressed by admixture with the above sample. When an ethanolic solution of the derivative (XVII; R = H) containing a trace of hydrogen chloride was boiled for 15 min., hydrolysis occurred, and the indole (XV) was recovered, m. p. 122—125°, increased by sublimation at 135°/0·001 mm. to 127—128° (mixed and alone).

(2) A solution of the 2-*o*-acetamido-compound (XVII; R = Me) in acetic acid containing *ca.* 5% of hydrochloric acid was boiled for a few minutes, and when cooled deposited the colourless hydrochloride of the 1′ : 2-dimethylindoloquinoline (XVI; R = Me). An aqueous solution of this salt, basified with ammonia, gave the base, colourless needles, m. p. 179—180° after crystallisation from ethyl acetate (Found : C, 82·5; H, 5·8; N, 11·4. Calc. for $C_{17}H_{14}N_2$: C, 82·9; H, 5·7; N, 11·4%). Kermack and Smith [1] describe this compound as " characteristic yellow sharp-pointed petal-like crystals, m. p. 173—174° : " their analytical figures indicate an impure product.

(3) A solution of the 2-*o*-benzamido-compound (XVII; R = Ph) in ethanolic hydrogen chloride was boiled under reflux for 10 min. : working up in the usual way gave the colourless 1′-*methyl*-2-*phenylindolo*(3′ : 2′-3 : 4)*quinoline* (XVI; R = Ph), m. p. 188° (from ethyl acetate) (Found : N, 8·8. $C_{22}H_{16}N_2$ requires N, 9·1%).

1′ : 2-*Dimethyl- and* 1′-*Methyl*-2-*phenyl-indolo*(3′ : 2′-3 : 4)*quinoline* (XVI; R = Me and Ph) *by the Fischer Cyclisation.*—(1) *o*-Acetamidoacetophenone *N*-methyl-*N*-phenylhydrazone (XVIII; R = Me) was prepared as the *o*-amino-analogue (p. 1328). The crude product, which crystallised from the initial reaction mixture in 78% yield on cooling, had m. p. 131—132° after crystallisation from aqueous ethanol. Kermack and Smith [1] give m. p. 131°. A solution of this hydrazone (8 g.) in ethanolic hydrogen chloride (50 c.c.) was boiled under reflux for 7 hr., and the deep red solution, when thoroughly cooled in ice-water, deposited the colourless hydrochloride of the base. This salt, when treated with ammonia, gave the 1′ : 2-dimethylindoloquinoline (XVI; R = Me) (1·7 g., 23%), m. p. 178° (after crystallisation from ethyl acetate), unchanged on admixture with the previous sample. Kermack and Smith [1] do not give the yield obtained by their phosphorus oxychloride cyclisation.

The deliquescent hydrated hydrochloride of the base could not readily be obtained pure. An ethanolic solution of the base, treated with hydriodic acid, deposited the colourless *hydriodide*,

m. p. 358—360° (decomp.), which was washed with hot ethanol and dried (Found : C, 54·5; H, 4·3. $C_{17}H_{14}N_2$,HI requires C, 54·5; H, 4·1%); it is insoluble in the usual organic solvents.

(2) o-*Benzamidoacetophenone* N-*methyl*-N-*phenylhydrazone* (XVIII; R = Ph), similarly prepared in 71% yield, formed yellow crystals, m. p. 126°, from ethanol (Found : C, 76·8; H, 6·0; N, 11·8. $C_{22}H_{21}ON_3$ requires C, 77·1; H, 6·1; N, 12·2%). Cyclisation by ethanolic hydrogen chloride afforded the 1'-methyl-2-phenylindoloquinoline (XVI; R = Ph), which, after crystallisation from light petroleum (b. p. 100—120°) and sublimation at 220°/0·001 mm., had m. p., alone and mixed with the earlier sample, 188° (Found : C, 85·2; H, 5·1; N, 9·0. Calc. for $C_{22}H_{16}N_2$: C, 85·65; H, 5·2; N, 9·1%) : yield 27%.

The hydrated hydrochloride of this base crystallised readily from its solution in hydrochloric acid, but attempted dehydration always caused some dissociation of the salt. A solution of the base in chloroform, when treated with hydrogen chloride and evaporated, gave the anhydrous colourless *hydrochloride*, m. p. 288—292° (decomp.; immersed at 275°) (from dimethylformamide) (Found : C, 76·1; H, 5·3; N, 8·3. $C_{22}H_{16}N_2$,HCl requires C, 76·6; H, 4·9; N, 8·1%).

Action of Acyl Cyanides on the Indole (XV).—*Acetyl cyanide.* (1) Basic conditions. The cyanide (0·15 c.c.; 1·1 mol.) was added to a solution of the indole (0·44 g.) in chloroform (5 c.c.) containing pyridine (0·1 c.c.), which was set aside overnight, and then evaporated. A solution of the residual oil in 50% aqueous ethanol deposited the acetamido-compound (XVII; R = Me), m. p. 96—97° after further recrystallisation (Found : N, 10·8%). A repetition of this experiment with solely pyridine as a solvent gave the same product.

(2) Neutral conditions. The above mixture, but without addition of pyridine, when similarly set aside, deposited colourless crystals of the acetate of the indoloquinoline (XVI; R = Me), m. p. 338—340° : this salt, treated with ammonia, gave the base, m. p. 176—177°, after crystallisation from ethyl acetate. The mother-liquor from which the acetate separated furnished no other crystalline compound.

(3) Acidic conditions. Hydrogen chloride was passed for 2—3 min. through the above mixture of cyanide and indole in chloroform, which by next day had deposited the hydrochloride of the indoloquinoline in almost theoretical yield; when worked up as in (2) above, it also furnished the pure base. When hydrogen chloride was passed through the above mixture for 1 hr., the solution became dark red and deposited an intractable tar.

Benzoyl cyanide. (1) Basic conditions. (*a*) Pyridine (0·2 c.c.) was added to a solution of the indole (0·44 g.) and the cyanide (0·8 g., 2·5 mols.) in chloroform, which was boiled under reflux for 2 hr., and evaporated. The residue, recrystallised from ethanol, gave the benzamido-compound (XVII; R = Ph), m. p. 132—134°.

(*b*) A solution of the indole (0·44 g.) and the cyanide (0·3 g., 1·1 mols.) in pyridine (5 c.c.) was boiled for 1 hr. and poured into water (50 c.c.). The precipitated solid, recrystallised as before, gave the benzamido-compound, m. p. 132—133°. Repetition of this experiment, using the cyanide (0·8 g.) with boiling for 2 hr., gave the same result.

(2) Neutral conditions. A solution of the indole (0·44 g.) and the cyanide (0·3 g.) in chloroform (5 c.c.) was set aside for 2 days, and the solvent then removed. The gummy residue, when stirred with ethanol, gave the crystalline benzamido-compound (0·5 g.), m. p. 132—133° after recrystallisation (Found : N, 8·6%). A similar mixture, when boiled for 1 hr., gave the same result.

(3) Acidic conditions. Hydrogen chloride was passed for 5 min. through a solution of the indole (0·6 g.) and the cyanide (0·4 g.) in chloroform (10 c.c.), which was then boiled under reflux for 3 hr., filtered to remove a trace of insoluble matter, and evaporated. The solid residue when stirred with acetone to dissolve a brown, tarry impurity, consisted of the hydrochloride of the indoloquinoline (XVI; R = Ph). Decomposition with ammonia gave the free base (0·5 g.), m. p. 188° after crystallisation from ethyl acetate (Found : N, 9·35%). No other products could be isolated. Repetition of this experiment, in which the mixture was set aside for 48 hr. instead of being boiled, gave the same result.

In all the above experiments it is particularly essential to use freshly prepared benzoyl cyanide to obtain consistent results.

Infrared Data.—The benzamido-compound (IV; R = Ph), m. p. 176°, in a Nujol mull shows strong bands at 5·98 and 2·98 μ due to the :CO and :NH groups respectively, with weaker bands at 6·17 and 6·32 μ assigned to the amide group; in carbon tetrachloride solution, it shows a strong :CO band at 5·90 μ and a weak band at 5·98 μ, and a weak band at 2·88 μ due to the :NH group. These values are closely similar to those of phenylbenzamide, which in the mull shows strong bands at 6·03 and 2·99 μ, and at 6·24 and 6·33 μ, and the tetrachloride solution shows a strong band at 5·91 and 2·90 μ. The isomeric benzamido-compound, m. p. 167°,

probably (VIII; R = Ph), in the mull shows three strong bands at 5·89 and 5·95, and at 2·96 μ, and in the solution a strong and a weak band at 5·89 and 2·93 μ respectively. All the tetrachloride solutions were necessarily very dilute. The 1-methyl-benzamido-compound (XVII; R = Ph) in the mull shows strong bands at 6·00, 6·07, and 3·05 μ, and a weak and a strong band at 6·19 and 6·33 μ: in the tetrachloride solution, it shows strong bands at 5·91 and 2·94 μ, and in hexachlorobutadiene solution, a strong band at 3·05 μ.

It is noteworthy that 3-benzoyl-2-methylindole in the mull shows a weak and a strong band at 6·26 and 6·37 μ, with none in the normal :CO region and only a faint inflection in the normal :NH region; in the tetrachloride solution it shows strong :CO and :NH bands at 6·08 and 2·87 μ. The crystalline indole must therefore show considerable intermolecular hydrogen bonding.

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