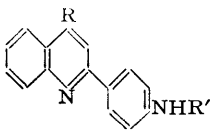
406. *Polyquinolyls.*

By S. G. Waley.

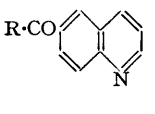
A stepwise synthesis of 2 : 6′-polyquinolyls has been effected. 2-(*p*-Aminophenyl)-quinoline (I; R = R′ = H) has been condensed with β-6-quinolylacraldehyde (V) to give 2 : 6′-triquinolyl (VI), and with *p*-nitrocinnamaldehyde to give 2-[4′-(*p*-nitrocinnamylidene)-aminophenyl]quinoline (VII), or, under more vigorous conditions, 2′-(*p*-nitrophenyl)-2 : 6′-di-quinolyl (IX; R = NO_2). Reduction of the latter gave 2′-(*p*-aminophenyl)-2 : 6′-diquinolyl (IX; R = NH_2) which reacted with the aldehyde (V) to give 2 : 6′-tetraquinolyl (X). 2 : 6′-Diquinolyl-4-carboxylic acid (III; R = CO_2H) has been prepared from 6-acetylquinoline (II; R = Me) and isatin; decarboxylation gave 2 : 6′-diquinolyl (III; R = H).

There are several examples known of a series of short-chain molecules which are rigid in the sense that rotation does not alter the length. Thus, the polyphenyls form such a series (Busch and Weber, *J. pr. Chem.*, 1936, **146**, 1; Bowden, *J.*, 1931, 1111; Müller and Topel, *Ber.*, 1939, **72**, 290; Gillam and Hey, *J.*, 1939, 1170). This series, however, cannot be ascended by stepwise synthesis. The 2 : 6′-polyquinolyl series has now been investigated (the convenient name polyquinolyl has been retained here). The quinoline syntheses used were the Döbner (*Annalen*, 1888, **249**, 98), the Pfitzinger (*J. pr. Chem.*, 1886, **33**, 100), and the Döbner–v. Miller (*Ber.*, 1883, **16**, 1664).

p-Acetamidobenzaldehyde (Beard and Hodgson, *J.*, 1927, 20) was condensed with aniline and pyruvic acid, according to the method of Döbner, to give 2-(p-*acetamidophenyl*)*quinoline*-4-*carboxylic acid* (I; R = CO_2H, R′ = COMe), also prepared by acetylation of the amine (I; R = R′ = H). This amine was prepared by John (*J. pr. Chem.*, 1934, **139**, 17) from isatin and *p*-aminoacetophenone; the latter could conveniently be replaced by the *p*-acetamido-acetophenone obtained from acetanilide (Kunckell, *Ber.*, 1900, **33**, 2641). When, however, *p*-acetamidobenzaldehyde was condensed with 2-(*p*-aminophenyl)quinoline (I; R = R′ = H) and pyruvic acid no pure product could be isolated.



(I.)



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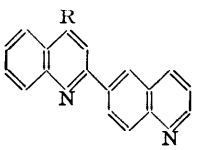

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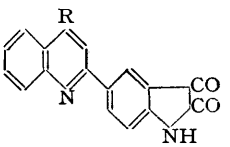
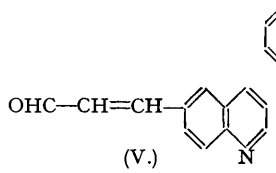


(IV.)

The early syntheses of quinoline-6-carboxylic acid (II; R = OH) (Skraup and Brunner, *Monatsh.*, 1881, **2**, 518; Georgievics, *ibid.*, 1891, **12**, 306) were not found satisfactory, but the modified Skraup synthesis of Cohn (*J. Amer. Chem. Soc.*, 1930, **52**, 3685) proceeded smoothly when applied to *p*-aminobenzoic acid. Direct esterification of the crude acid gave a good overall yield of ethyl quinoline-6-carboxylate (II; R = OEt), and this method seems more convenient than that described recently by Seibert, Norton, Benson, and Bergstrom (*ibid.*, 1946, **68**, 2721). Condensation of ethyl quinoline-6-carboxylate with ethyl acetate in the presence of sodium ethoxide gave 6-*acetylquinoline* (II; R = Me), which underwent the Pfitzinger condensation with isatin to give 2 : 6′-*diquinolyl*-4-*carboxylic acid* (III; R = CO_2H)

in good yield. Decarboxylation in the presence of copper carbonate readily gave 2 : 6′-diquinolyl (III; R = H), which had previously been obtained from 2-(*p*-aminophenyl)quinoline (Weidel, *Monatsh.*, 1887, **8**, 140). Attempts to prepare higher polyquinolyls by the Pfitzinger synthesis were unsuccessful, since the quinolylisatins (IV) could not be prepared. Aminophenylquinolinecarboxylic acid (I; R = CO_2H, R′ = H) reacted with chloral and hydroxylamine to give 2-(p-*oximinoacetamidophenyl*)*quinoline-4-carboxylic acid* (I; R = CO_2H, R′ = CO·CH:NOH), but the isatin (IV; R = CO_2H) could not be isolated after treatment with sulphuric acid (cf. Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 234). No pure products could be isolated from the condensation of ethyl mesoxalate with either aminophenylquinoline (I; R = R′ = H) or the acid (I; R = CO_2H, R′ = H).

In view of the apparent difficulty in causing cyclisation of derivatives of 2-(*p*-aminophenyl)-quinoline, the quinoline synthesis of Döbner–v. Miller was investigated, since although the yields are usually low this synthesis very rarely fails. Quinoline-6-aldehyde (Rodinov and Berkengeim, *J. Gen. Chem. Russia*, 1944, **14**, 330) was condensed with acetaldehyde in an alkaline benzene–water emulsion to give β-6-quinolylacraldehyde (V). This aldehyde was heated with aminophenylquinoline (I; R = R′ = H) and hydrochloric acid to give a low yield of the desired 2 : 6′-*triquinolyl* (VI), a high-melting solid which could be sublimed in a vacuum.



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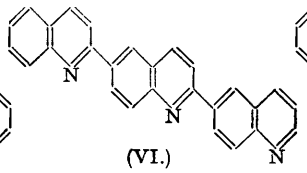
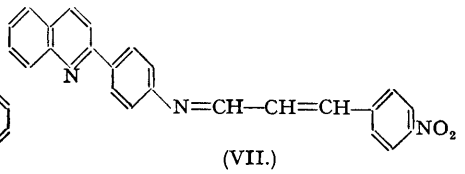
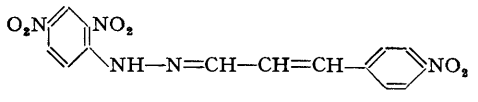


(VI.)

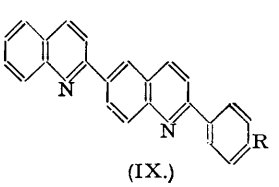


(VII.)

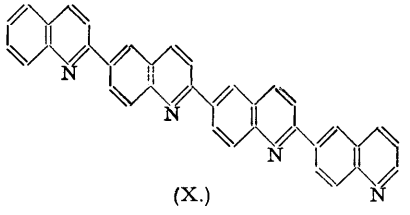
p-Nitrocinnamaldehyde was prepared from *p*-nitrobenzaldehyde (Fecht, *Ber.*, 1907, **40** 3898); details of this preparation are given in the Experimental section because the original description is brief and the conditions were found to be rather critical. When *p*-nitrocinnamaldehyde was heated with the amine (I; R = R′ = H) and hydrochloric acid at 140°, the sole product isolated was 2-[4′-(p-*nitrocinnamylidene*)*aminophenyl*]*quinoline* (VII). This structure was confirmed by fission with dinitrophenylhydrazine in sulphuric acid to the *dinitrophenylhydrazone* of *p*-nitrocinnamaldehyde (VIII), and by the alternative preparation of (VII) from *p*-nitrocinnamaldehyde and the amine (I; R = R′ = H) in ethanol solution. The isolation of the anil (VII) under the conditions used in the Döbner–v. Miller reaction suggests that such anils may be intermediates in the formation of quinolines (cf. Manske, *Chem. Reviews*, 1942, **30**, 113), and also shows how stable such highly conjugated anils are to acids. Cyclisation of the anil (VII) to 2′-(p-*nitrophenyl*)-2 : 6′-*diquinolyl* (IX; R = NO_2) was effected by hydrochloric acid at 175° in a sealed tube or, more conveniently, by prolonged boiling with arsenic pentoxide in 60% sulphuric acid.



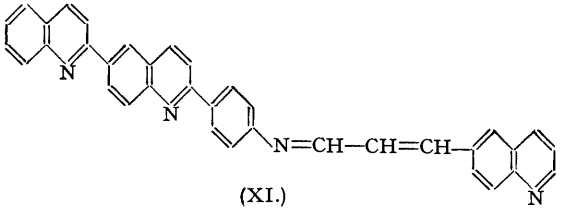
(VIII.)



(IX.)



(X.)



(XI.)

The low solubility and basic properties of the nitro-compound (IX; R = NO_2) rendered its reduction awkward since under ordinary conditions stannous chloride gave a mixture of insoluble stannichlorides whose decomposition yielded a difficultly separable mixture of bases. 2′-(p-*Aminophenyl*)-2 : 6′-*diquinolyl* (IX; R = NH_2) was, however, prepared in good yield by continuous extraction of the nitro-compound (IX; R = NO_2) with a solution of stannous

chloride in 20% hydrochloric acid. Condensation of the amine (IX; R = NH_2) with the quinolylacraldehyde (V) in hydrochloric acid at 150° gave 2 : 6′-*tetraquinolyl* (X), a colourless solid fairly soluble in hot quinoline. When this condensation was effected in dioxan, 2′-[4″-(6‴-*quinolyl*-β-*acrylidene*)*aminophenyl*]-2 : 6′-*diquinolyl* (XI) was isolated.

Experimental.

2-(p-*Acetamidophenyl*)*quinoline*-4-*carboxylic Acid* (I; R = CO_2H, R′ = COMe).—*p*-Acetamidobenzaldehyde (8 g.), freshly-distilled pyruvic acid (3·46 c.c.), and aniline (4·5 c.c.) were refluxed in ethanol (100 c.c.) for 2 hours and kept overnight. The *quinoline* (5·4 g.) separated as a dihydrate which crystallised from ethanol in yellow prisms, m. p. 278—279° (decomp.) (Found : C, 63·2; H, 5·1; N, 8·25. $C_{18}H_{14}O_3N_2,2H_2O$ requires C, 63·1; H, 5·3; N, 8·2%).

The amine (I; R = CO_2H, R′ = H) was prepared in 92% yield by the condensation of *p*-acetamidoacetophenone (14·3 g.) with isatin (11·9 g.) in 50% aqueous potassium hydroxide (36 c.c.); acetylation with acetic anhydride in acetic acid gave the acetamido-compound (I; R = CO_2H, R′ = COMe) identical with that prepared above.

Decarboxylation of the amino-acid (I; R = CO_2H, R′ = H) gave the amine (I; R = R′ = H) (John, *loc. cit.*), from which a *benzylidene* derivative was prepared, crystallising from propanol in colourless leaflets, m. p. 156° (Found : C, 85·3; H, 5·2; N, 9·7. $C_{22}H_{16}N_2$ requires C, 85·7; H, 5·2; N, 9·1%).

Ethyl Quinoline-6-*carboxylate* (II; R = OEt).—*p*-Amir obenzoic acid (55 g.), *p*-nitrobenzoic acid (42·6 g.), ferrous sulphate (14 g.), boric acid (24 g.), glycerol (188 g.), and concentrated sulphuric acid (70 c.c.) were refluxed for 20 hours. The mixture was diluted with water, basified with 5N-sodium hydroxide, filtered, and the filtrate acidified with acetic acid and kept at 0°. The crude, acetone-washed acid (90 g.) was refluxed with ethanol (650 c.c.) and concentrated sulphuric acid (110 c.c.) for 5 hours and the solution concentrated; after dilution with water and basification, the ester was isolated with chloroform and distilled, b. p. 130—150°/2 mm., m. p. 56°, yield 78 g., 60% (Found : N, 7·2. Calc. for $C_{12}H_{11}O_2N$: N, 7·0%).

6-*Acetylquinoline* (II; R = Me).—Ethyl acetate (7·2 c.c.) and ethyl quinoline-6-carboxylate (10 g.) were added to sodium ethoxide (5·07 g.) in benzene (8 c.c.); the mixture was refluxed for 18 hours, and poured on N-sodium hydroxide (10 c.c.), ice (10 g.), and ether (10 c.c.). The yellow solid was collected, and the aqueous layer of the filtrate acidified with carbon dioxide and extracted with ether. The residue after distillation of the ether was added to the yellow solid and heated with 17% hydrochloric acid at 100° for 1½ hours. After basifying with aqueous potassium carbonate, the *ketone* was isolated with ether and distilled, b. p. 145°/2 mm., yield 4·4 g., 52%; it crystallised from light petroleum in colourless rhombs, m. p. 77° (Found : C, 77·2; H, 5·2; N, 8·5. $C_{11}H_9ON$ requires C, 76·9; H, 5·3; N, 8·2%).

2 : 6′-*Diquinolyl*-4-*carboxylic Acid* (III; R = CO_2H).—6-Acetylquinoline (3·4 g.), isatin (2·9 g.), and potassium hydroxide (4·5 g.) in water (12 c.c.) and ethanol (20 c.c.) were boiled under reflux for 6 hours, the ethanol distilled off, and the solution diluted and acidified with acetic acid; the *acid* separated (yield 4·9 g., 82%) and crystallised from quinoline in colourless rhombs, m. p. 334° (decomp.) (Found : C, 76·5; H, 4·3; N, 9·7. $C_{19}H_{12}O_2N_2$ requires C, 76·0; H, 4·0; N, 9·3%).

2 : 6′-*Diquinolyl* (III; R = H).—2 : 6′-Diquinolyl-4-carboxylic acid (4·9 g.) was powdered with copper carbonate (0·5 g.) and the mixture heated till the effervescence ceased. The product was distilled, b. p. 210—250°/3 mm., and the diquinolyl solidified (yield 3·4 g., 81%), m. p. 144° (Weidel, *loc. cit.*, gives m. p. 144°) (Found : C, 84·4; H, 4·7; N, 11·3. Calc. for $C_{18}H_{12}N_2$: C, 84·3; H, 4·7; N, 10·9%).

2-(p-*Oximinoacetamidophenyl*)*quinoline*-4-*carboxylic Acid* (I; R = CO_2H, R′ = CO·CH:NOH).—2-(*p*-Aminophenyl)quinoline-4-carboxylic acid (8·8 g.) in concentrated hydrochloric acid (3·4 c.c.) and water (40 c.c.) was added to chloral hydrate (6 g.) in water (60 c.c.) and ethanol (60 c.c.); hydroxylamine hydrochloride (7·2 g.) was then added and the mixture boiled gently for 35 minutes and vigorously for 5 minutes, cooled, and neutralised with aqueous sodium hydroxide. The *product* separated and crystallised from pyridine–ethanol in yellow needles, m. p. 257—258° (decomp.) (yield 4·6 g., 38%) (Found : C, 64·3; H, 4·0; N, 12·7. $C_{18}H_{13}O_4N_3$ requires C, 64·5; H, 3·9; N, 12·5%).

β-6-*Quinolylacraldehyde* (V).—Acetaldehyde (1·5 c.c.) in water (20 c.c.) was added to quinoline-6-aldehyde (2·6 g.) in benzene (10 c.c.) and aqueous sodium hydroxide (8 c.c.; 5·7%), and the mixture stirred at 3° for 3 hours. The *aldehyde* separated, was triturated under ethanol, and then recrystallised from ethanol, yield 1 g., 33%, m. p. 162—163° (Found : C, 78·8; H, 5·1; N, 7·9. $C_{12}H_9ON$ requires C, 78·7; H, 5·0; N, 7·6%). Other conditions, such as the use of aqueous alcohol as solvent, for this condensation gave no pure product.

2 : 6′-*Triquinolyl* (VI).—β-6-Quinolylacraldehyde (0·37 g.), 2-(*p*-aminophenyl)quinoline (0·48 g.), and concentrated hydrochloric acid (5 c.c.) were heated together in a sealed tube at 150° for 5 hours. Dilute hydrochloric acid was added, the solution filtered, the filtrate basified, and the brown powder collected. After trituration with ethanol, the residual *triquinolyl* crystallised from quinoline in colourless plates (0·027 g.), m. p. 267—269°; high-vacuum sublimation did not raise the m. p. (Found : C, 84·45; H, 4·6; N, 11·1. $C_{27}H_{17}N_3$ requires C, 84·6; H, 4·5; N, 11·0%).

p-*Nitrocinnamaldehyde*.—Methanolic potassium hydroxide (3·5 c.c.; 25%) was added dropwise to a vigorously-stirred suspension of finely-powdered *p*-nitrobenzaldehyde (75 g.) in freshly-distilled acetaldehyde (185 c.c.); the mixture was kept at 5—7° during the addition. Acetic anhydride (120 c.c.) was added, the solution heated to 120° for 1 hour, poured into water (450 c.c.), and, after the addition of 4·35N-hydrochloric acid (180 c.c.), refluxed for 30 minutes. The next day, the nitrocinnamaldehyde was collected, washed with water, and recrystallised from ethanol (64·7 g., 72%), m. p. 140—141°.

2-[4′-(p-*Nitrocinnamylidene*)*aminophenyl*]*quinoline* (VII).—(*a*) *p*-Nitrocinnamaldehyde (4·2 g.) was added to 2-(*p*-aminophenyl)quinoline (6·3 g.) in concentrated hydrochloric acid (12 c.c.); after the addition of further concentrated hydrochloric acid (5 c.c.) the mixture was refluxed for 5 hours. Extrac-

tion with hot concentrated hydrochloric acid (40 c.c.) left a yellow solid which was added to aqueous sodium hydrogen carbonate, the mixture heated, and the solid collected and washed with hot ethanol (200 c.c.). Recrystallisation from 90% dioxan–water, then twice from amyl acetate gave the *anil* (2·6 g., 29%) as orange plates, m. p. 211—214° (decomp.) (Found : C, 76·1 ; H, 4·3 ; N, 11·2. $C_{24}H_{17}O_2N_3$ requires C, 76·0 ; H, 4·5 ; N, 11·1%). Heating with 2 : 4-dinitrophenylhydrazine in dilute sulphuric acid gave p-*nitrocinnamaldehyde dinitrophenylhydrazone* (VIII), m. p. 267—268° (decomp.), mixed m. p. with a sample prepared directly from the aldehyde, 271° (decomp.). This sample crystallised from nitrobenzene–amyl alcohol in scarlet needles, m. p. 273° (decomp.) (Found : C, 50·6 ; H, 3·2 ; N, 19·7. $C_{15}H_{11}O_6N_5$ requires C, 50·4 ; H, 3·1 ; N, 19·6%).

(*b*) *p*-Nitrocinnamaldehyde (40·2 g.) in hot ethanol (525 c.c.) was added to 2-(*p*-aminophenyl)-quinoline (50 g.) in hot ethanol (525 c.c.), the solution refluxed for 3½ hours, kept overnight, and the solid collected (78 g.). It had m. p. and mixed m. p. with the product of method (*a*) of 210—212° (decomp.).

2′-(p-*Nitrophenyl*)-2 : 6′-*diquinolyl* (IX ; R = NO_2).—2-[4′-(*p*-Nitrocinnamylidene)aminophenyl]-quinoline (72 g.), arsenic pentoxide (21·6 g.), and 60% sulphuric acid (240 c.c.) were refluxed together for 12 hours, the mixture diluted with an equal volume of water, decanted from tar, cooled, and basified with 5N-sodium hydroxide. The brown solid was collected and extracted with hot amyl acetate (2000 c.c.) ; the *diquinolyl* which separated crystallised from *cyclo*hexanone in buff needles, m. p. 266—268° (decomp.) (yield 4·5 g., 6%) (Found : C, 76·6 ; H, 4·2 ; N, 11·0. $C_{24}H_{15}O_2N_3$ requires C, 76·4 ; H, 4·0 ; N, 11·1%). The yield was lower when more concentrated sulphuric acid was used, and no product could be isolated when the arsenic pentoxide was omitted.

The reaction could also be carried out by heating the anil (6 g.) in concentrated hydrochloric acid (15 c.c.) for 5 hours at 175° in a sealed tube ; the yield was 4% and was not improved by the addition of arsenic pentoxide.

2′-(p-*Aminophenyl*)-2 : 6′-*diquinolyl* (IX ; R = NH_2).—2′-(*p*-Nitrophenyl)-2 : 6′-diquinolyl (2 g.) was extracted in an all-glass Soxhlet apparatus with 20% hydrochloric acid (50 c.c.) containing stannous chloride (4 g.). The red solid was collected and decomposed with hot 5N-sodium hydroxide ; the *amine* crystallised from much 70% dioxan–water in yellow acicular plates, m. p. 234° (yield 1·16 g., 63%) (Found : C, 82·8 ; H, 5·15 ; N, 12·25. $C_{24}H_{17}N_3$ requires C, 83·0 ; H, 4·9 ; N, 12·1%). The solution of the amine in acetic acid was deep red, and dilute solutions in organic solvents showed a blue fluorescence.

2 : 6′-*Tetraquinolyl* (X).—β-6-Quinolylacraldehyde (0·28 g.) was added to 2′-(*p*-aminophenyl)-2 : 6′-diquinolyl (0·54 g.) in concentrated hydrochloric acid (4·3 c.c.) and, after the addition of further concentrated hydrochloric acid (4·3 c.c.), the mixture was heated in a sealed tube at 150° for 5 hours. Dilute hydrochloric acid (4 c.c.) was added, and the red solid collected, washed with 8N-hydrochloric acid, and treated with aqueous ammonia. The yellow material was digested with hot dioxan ; the residual *tetraquinolyl* crystallised from quinoline in colourless leaflets (0·035 g.), m. p. 348—350° (evacuated capillary) (Found : C, 84·5 ; H, 4·3 ; N, 11·1. $C_{36}H_{22}N_4$ requires C, 84·7 ; H, 4·3 ; N, 11·0%).

2′-[4″-(6‴-*Quinolyl*-β-*acrylidene*)*aminophenyl*]-2 : 6′-*diquinolyl* (XI).—β-6-Quinolylacraldehyde (0·13 g.) was added to 2′-(*p*-aminophenyl)-2 : 6′-diquinolyl (0·25 g.) in dioxan (12 c.c.) and acetic acid (1·5 c.c.). After 2 hours' heating, the *anil* separated (0·27 g.), and crystallised from pyridine in yellow prisms, m. p. 248—249° (decomp.) (Found : C, 84·0 ; H, 4·9 ; N, 11·1. $C_{36}H_{24}N_4$ requires C, 84·3 ; H, 4·7 ; N, 10·9%).

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