

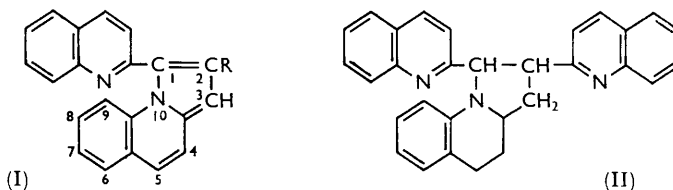
221. The Quinoline Series. Part II.¹ The Reaction between Quinaldine and Sulphuric Acid.

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By reaction between quinaldine and either sulphuric acid or sulphur a pyrroloquinoline (I; R = 2-quinolylyl) has been obtained. Evidence is presented in support of this structure and a possible general synthesis of pyrrolo[1,2-*a*]quinolines by cyclisation of quinolypropanes is described.

The preparation and reactions of intermediates in the synthesis have been re-examined.

In an earlier paper¹ we described the acid-catalysed additions of quinaldine and lepidine to activated olefinic systems. In the addition of quinaldine to ethyl cinnamate with sulphuric acid as catalyst it was evident that other reactions as well as addition were occurring. These have now been shown to involve only the quinaldine and the sulphuric acid. From the reaction mixture, three bases have been isolated. One has been identified as 1,2-di-2'-quinolylethane, and the second is considered to be a pyrroloquinoline (benzo-pyrrocoline) (I; R = 2-quinolylyl), but the nature of the third is unknown.



The identity of the 1,2-di-2'-quinolylethane was confirmed by an independent synthesis from ω -bromoquinaldine and sodium in xylene as described by Hammick *et al.*² Only small amounts of the compound were obtained in this synthesis and it is not considered to be a satisfactory method.

Since sulphur was formed during the quinaldine-sulphuric acid reaction the effect of heating quinaldine with sulphur was examined and the product shown to contain the three bases previously isolated.

von Miller,³ Walker *et al.*,⁴ and Hammick *et al.*,⁵ treating quinaldine with sulphur, isolated 1,2-di-2'-quinolylethane. The nature of the base which we consider to be a pyrroloquinoline has not previously been elucidated although its formation was recorded by Walker *et al.*⁴

The free base, $C_{30}H_{19}N_3$, is pale yellow whereas its quaternary salts are red. It forms a monomethiodide, and a monopicrate. Oxidation with potassium permanganate in pyridine gives 2 mols. of quinaldic acid. Hydrogenation with Raney nickel in ethanol yielded a cream-coloured crystalline compound, $C_{30}H_{25}N_3$, which formed a pale yellow hydrochloride. Structure (II) is proposed for this compound since hydrogenation of benzene and quinoline systems is known to require more vigorous conditions than those employed here.

The ultraviolet absorption spectrum of the free base shows maxima at 270 (strong), 326 (weak), and 352 (weak).

After reaction between 2-picoline and sulphur, Emmert and Groll⁶ isolated a disulphide

¹ Part I, Skidmore and Tidd, *J.*, 1959, 1641.

² Hammick, Brown, and Thewlis, *J.*, 1951, 1145.

³ von Miller, *Ber.*, 1888, **21**, 1828.

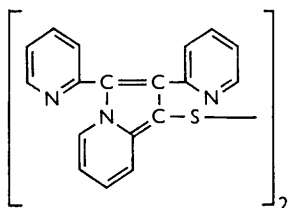
⁴ Walker, Baldwin, Thayer, and Corson, *J. Org. Chem.*, 1951, **16**, 1805.

⁵ Hammick, Lammiman, Morgan, and Roe, *J.*, 1955, 2436.

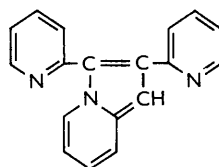
⁶ Emmert and Groll, *Chem. Ber.*, 1953, **86**, 205.

(III) which they reduced to the base (IV). The pyrroloquinoline now isolated from the corresponding reaction of quinaldine appears to be the quinoline analogue of (IV).

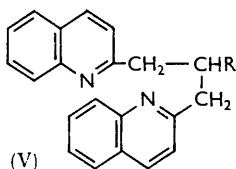
Thayer and Corson⁷ have shown that 1,2-di-4'- and 1,2-di-2'-pyridylethylene are formed by reaction of sulphur with 4- and 2-picoline respectively. Although 1,2-di-2'-quinolyethylene has never been isolated from the quinaldine-sulphur reaction it is likely to be formed by dehydrogenation of the diquinolyethane present. In the presence of acids, addition of quinaldine to the diquinolyethylene could occur and the resulting triquinolypropane (V; R = 2-quinolyl) could undergo dehydrogenation through its tautomeric form (VI). Such a sequence of reactions would account for the absence of a pyrrocoline derivative in the products of reaction of sulphur with 4-picoline or lepidine since a methylene group in the 2-position of the pyridine ring is essential for cyclisation. A synthesis along these lines was successful. 1,2-Di-2'-quinolyethane was obtained from quinaldine and sulphur, and was dehydrogenated with selenium dioxide to the olefin. When quinaldine hydrochloride was used as catalyst, quinaldine was added to the diquinolyethylene to yield 1,2,3-triquinolypropane, and heating this with sulphur gave the pyrroloquinoline (I; R = 2-quinolyl). Similarly 2-phenyl-1,3-di-2'-quinolypropane (V; R = Ph) on dehydrogenation by sulphur gave the pyrroloquinoline (I; R = Ph). Both pyrroloquinolines gave red quaternary salts and they had similar ultraviolet absorption spectra.



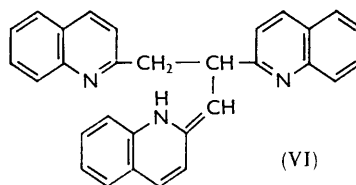
(III)



(IV)



(V)



(VI)

A similar cyclisation was observed by Battersby and Edwards⁸ when they oxidised the bisdihydroisoquinolypropane (VII) with mercuric acetate to the colourless base (VIII) which formed a red hydrobromide. When we used mercuric acetate to oxidise 2-phenyl-1,3-di-2'-quinolypropane the pyrroloquinoline (I; R = Ph) was again obtained, but only in low yield.

During this work problems arose in the preparation of 1,2-di-2'-quinolyl-ethanol and -ethylene. The diquinolyethanol prepared by Kaplan and Lindwall's method⁹ contained 1,2-di-2'-quinolyethane-1,2-diol. In an attempt to prepare quinaldoin from quinoline-2-aldehyde and potassium cyanide, Buehler and Harris¹⁰ reported the formation of a compound they thought to be this diol, on the basis of its formula and formation of a dibenzoate. Their observations have been confirmed and their diol shown to be identical with ours. As further confirmation of its structure, we have oxidised the diol to quinoline-2-aldehyde using periodic acid though the yield was less than 2 mol. per mol. of diol. Heating the

⁷ Thayer and Corson, *J. Amer. Chem. Soc.*, 1948, **70**, 2330.

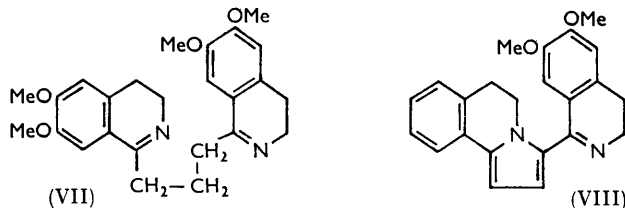
⁸ Battersby and Edwards, *Chem. Soc. Special Publ.* No. 3, 1955, p. 33.

⁹ Kaplan and Lindwall, *J. Amer. Chem. Soc.*, 1943, **65**, 927.

¹⁰ Buehler and Harris, *J. Amer. Chem. Soc.*, 1950, **72**, 5015.

diol with small amounts of acetic or benzoic acid gave a mixture of 1,2-di-2'-quinolyethane and 1,2-di-2'-quinolyethanone. Attempted synthesis of the diol by addition of bromine to 1,2-di-2'-quinolyethylene and hydrolysis of the dibromide gave only 1,2-di-2'-quinolyacetylene.

The preparation of 1,2-di-2'-quinolyethylene has been described by several workers. Thayer and Corson⁷ dehydrated 1,2-di-2'-quinolyethanol with acetic anhydride and



acetic acid and described the product as "yellow-orange" needles. We find that the *trans*-olefin is almost colourless, in agreement with Hammick *et al.*,⁵ and that the orange impurity was 1,2-di-2'-quinolyethanone. Heating the diquinolyethanol with glacial acetic or benzoic acid affords a mixture of approximately equal amounts of the diquinolyethanone and diquinolyethane. The mechanism of this reaction is being further studied.

EXPERIMENTAL

Action of Sulphuric Acid on Quinaldine.—Quinaldine (28 g., 3 mol.) and concentrated sulphuric acid (6.6 g., 1 mol.) were refluxed together during 5 hr. The product, a dark red viscous liquid, was treated with an excess of 15% sodium hydroxide solution and steam-distilled to remove unchanged quinaldine (15.2 g.). The residue (9.3 g.) was dissolved in benzene (200 ml.) and extracted with 0.1N-hydrochloric acid (4 × 100 ml.), and the extracts were basified with sodium hydroxide solution. The oily base which was precipitated became granular when shaken. Trituration with cold acetone (10 ml.) and crystallisation of the residual solid from aqueous ethanol yielded 1,2-di-2'-quinolyethane (1.3 g.) as colourless needles, m. p. 163° (Found: C, 83.7; H, 5.7; N, 10.0. Calc. for C₂₀H₁₆N₂: C, 84.5; H, 5.7; N, 9.9%). Its picrate crystallised from ethanol as orange needles, m. p. 267° (decomp.). Concentration of the acetone solution yielded a dark brown viscous product (2.7 g.). The original benzene solution was washed with alkali, dried, and evaporated. Trituration of the residue with cold acetone (10 ml.) gave 1,2-di-2'-quinolyethylpyrrolo[1,2-a]quinoline which crystallised from ethyl acetate–light petroleum as pale yellow needles (0.5 g.), m. p. 197° (Found: C, 85.1; H, 4.6; N, 10.0%; M, 440. C₃₀H₁₉N₃ requires C, 85.5; H, 4.5; N, 10.0%; M, 421). Its picrate, crystallised from ethanol, had m. p. 265° (Found: C, 66.2; H, 3.5; N, 12.5. C₃₆H₂₂N₆O₇ requires C, 66.5; H, 3.4; N, 12.9%). The methiodide crystallised as red needles (from ethanol), m. p. 219° (Found: I, 21.0. C₃₁H₂₂IN₃ requires I, 22.5%). Evaporation of the acetone solution yielded a dark brown viscous residue (2.6 g.).

Action of Sulphur on Quinaldine.—Quinaldine (29 g.) and sulphur (3.2 g.) were heated at the b. p. during 4 hr. Hydrogen sulphide was evolved. The dark brown solution was steam-distilled, and the residue dissolved in 5N-hydrochloric acid (100 ml.) and filtered. The filtrate was basified and the precipitated bases were extracted with benzene. Washing the benzene solution with 0.1N-hydrochloric acid (6 × 100 ml.) and basification of the extracts yielded initially an oil but finally a granular solid (3.1 g.). Crystallisation from ethyl acetate–light petroleum gave diquinolyethane, m. p. 164°, as needles. Evaporation of the benzene solution yielded a viscous oil which deposited a pale brown base (1.86 g.) on trituration with a little acetone. The base (I; R = 2-quinolyl), gave yellow needles, m. p. 197° (from ethyl acetate–light petroleum).

Oxidation of 1,2-Di-2'-quinolyethylpyrrolo[1,2-a]quinoline.—A solution of the base (0.5 g.) in pyridine (20 ml.) and water (20 ml.) was added to potassium permanganate (2 g.) in water (10 ml.), and the mixture refluxed during 2 hr. The precipitated manganese dioxide was filtered off and washed with hot water, and the filtrate and washings were made just acid with dilute sulphuric acid. Addition of an excess of concentrated copper sulphate solution afforded

a precipitate (0.48 g.) which was suspended in boiling water (150 ml.). Hydrogen sulphide was passed into it for 1 hr. Removal of the precipitated copper sulphide and evaporation of the filtrate left a grey crystalline residue which deposited quinaldic acid (m. p. and mixed m. p. 153°) from light petroleum (b. p. 100—120°).

Hydrogenation of 1,2-Di-2'-quinolylpyrrolo[1,2-a]quinoline.—A solution of the base (0.078 g.) in ethanol (20 ml.) was shaken with hydrogen and Raney nickel (1 ml. settled suspension) in ethanol (40 ml.) for 2 hr. Filtration of the almost colourless solution (Filtercel) and removal of the ethanol under reduced pressure afforded a pale brown solid. Extraction of this with light petroleum removed material (0.069 g.) which, recrystallised from aqueous ethanol (charcoal), gave cream-coloured 1,2,3a,4,5-hexahydro-1,2-di-2'-quinolylpyrrolo[1,2-a]quinoline, m. p. 187° (Found: C, 84.2; H, 5.96; N, 9.8. $C_{30}H_{26}N_3$ requires C, 84.3; H, 5.90; N, 9.8%). The base gave a pale yellow hydrochloride.

1,2-Di-2'-quinolyethylene.—1,2-Di-2'-quinolyethane (0.57 g.) and selenium dioxide (0.44 g.) in dioxan (20 ml.) were refluxed together for 2 hr., then filtered, and cooled. The solid which was deposited (0.36 g.) crystallised from methanol to give 1,2-di-2'-quinolyethylene as pale yellow needles, m. p. 189° (Found: C, 84.9; H, 5.0; N, 9.9. Calc. for $C_{20}H_{14}N_2$: C, 85.1; H, 5.0; N, 9.9%). The methiodide crystallised from water as a pale yellow powder, m. p. 212—213°, which became orange on drying (Found: C, 58.6; H, 3.9; I, 31.0. $C_{21}H_{17}IN_2$ requires C, 59.4; H, 4.0; I, 30.0%).

1,2,3-Tri-2'-quinolylpropane.—Quinaldine (0.3 g., 3 mol.) 1,2-di-2'-quinolyethylene (0.2 g., 1 mol.), and quinaldine hydrochloride (0.13 g., 1 mol.) were heated together in a sealed tube at 100° during 3 hr. The product was extracted with benzene and water, and the benzene solution washed with dilute sodium hydroxide solution and concentrated. Extraction of the viscous residue with boiling light petroleum (b. p. 40—60°; 2 × 10 ml.) and concentration of the extract yielded pale yellow crystals (0.11 g.), m. p. 131—133°. Recrystallisation from light petroleum (b. p. 80—100°) gave 1,2,3-tri-2'-quinolylpropane as almost colourless needles, m. p. 136° (Found: C, 84.7; H, 5.5; N, 9.9. $C_{30}H_{27}N_3$ requires C, 84.7; H, 5.5; N, 9.9%). Alternatively, benzoic acid was used as catalyst at 165°.

Reaction between 1,2,3-Tri-2'-quinolylpropane and Sulphur.—The triquinolylpropane (0.5 g.) and sulphur (0.1 g.) were heated at 210° during 1 hr. After cooling, the product was triturated with 0.1N-hydrochloric acid (25 ml.) to remove unchanged triquinolylpropane, and the residue treated with 1.0N-hydrochloric acid (25 ml.). Basification of this red solution gave a cream-coloured solid (0.32 g.) which crystallised from ethyl acetate–light petroleum as yellow needles, m. p. 193°, shown to be the base (I; R = 2-quinolyl) by the m. p. and mixed m. p. of the methiodide.

Dehydrogenation of 2-Phenyl-1,3-di-2'-quinolylpropane by Sulphur.—2-Phenyl-1,3-di-2'-quinolylpropane (1.87 g.) and sulphur (0.32 g.) were heated together at 210° during 1 hr. The dark red product was dissolved in cold benzene (8 ml.) and chromatographed on alumina (Spence's type O). A brown residue remained at the top of the column and a wide orange band was eluted with benzene, yielding a viscous oil which on the addition of ethanol (3 ml.) deposited orange crystals (1.72 g.), m. p. 117—125°. Trituration of the crystals with cold acetone (2 × 3 ml.) yielded a brown solution containing a crystalline suspension. Separation of the suspension by centrifugation, and crystallisation from aqueous acetone, yielded pale yellow 2-phenyl-1,2'-quinolylpyrrolo[1,2-a]quinoline (0.82 g.), m. p. 154—155° (Found: C, 87.7; H, 4.7; N, 7.3. $C_{27}H_{18}N_2$ requires C, 87.6; H, 4.9; N, 7.6%). A further crop (0.13 g.), m. p. 150°, was obtained from the acetone mother-liquor.

Oxidation of 2-Phenyl-1,3-di-2'-quinolylpropane with Mercuric Acetate.—Hot solutions of 2-phenyl-1,3-di-2'-quinolylpropane (1.37 g.) in glacial acetic acid (4 ml.) and of mercuric acetate (3.2 g.) in acetic acid (4 ml.) and water (35 ml.) were mixed together and refluxed during 3 hr. The solution became yellow and mercurous acetate and an oil separated. After cooling, the solution was filtered, the residue was washed with warm acetone, and the washings were added to the filtrate. The filtrate was concentrated to remove the acetone, mercuric acetate (1.6 g.) added, and the solution refluxed for a further hour. On cooling and filtration of the solution, a small amount of mercurous acetate and mercury remained, together with organic material. This residue was extracted with hot acetone (3 × 25 ml.), and the solvent removed from the extract under reduced pressure. Trituration of the solid residue with 0.1N-hydrochloric acid removed any unchanged substituted propane. Extraction of the residue therefrom with a mixture of 1.0N-hydrochloric acid and methanol followed by basification of the deep red solution

obtained yielded a yellow precipitate (0.46 g.) which crystallised from ethanol as yellow needles, m. p. 154°. The original aqueous filtrate containing the mercury salts was heated to the b. p. and hydrogen sulphide passed into it until the solution was cold. The precipitated mercuric sulphide was filtered off (Filtercel) and extracted with hot acetone (3 × 25 ml.). Concentration of the extract gave a green fluorescent solution which slowly deposited a small quantity of yellow needles, m. p. 153°.

The compound showed no depression of m. p. in admixture with the base obtained by dehydrogenation of 2-phenyl-1,3-di-2'-quinolylpropane with sulphur. The base gave a red *methiodide*, m. p. 228—229° (from ethanol-ether) (Found: C, 65.1; H, 4.2. C₂₃H₂₁IN₂ requires C, 65.6; H, 4.1%).

1,2-Di-2'-quinolyethanol.—Quinaldine (5 g.) and quinoline-2-aldehyde (5 g.) were refluxed in 1:4 v/v aqueous ethanol (25 ml.) during 30 hr., the solution being cooled at intervals of 6 hr. and the precipitates removed (7.2 g.). Extraction of the combined products with hot ethanol yielded a soluble product (6.0 g.) and an insoluble residue (1.2 g.). Crystallisation of the former from ethanol yielded 1,2-di-2'-quinolyethanol as plates (4.1 g.), m. p. 165°. The ethanol-insoluble material crystallised from dimethylformamide to give plates of 1,2-di-2'-quinolyethane-1,2-diol (1.0 g.), m. p. 210° (decomp.).

Oxidation of 1,2-Di-2'-quinolyethane-1,2-diol.—The diol (0.10 g.) and periodic acid (0.5 g.) in water (20 ml.) were kept at 80° during ½ hr. After cooling, the solution was basified and the white precipitate extracted with ether (3 × 20 ml.). The ethereal solution was dried and the solvent removed to leave a residue (0.09 g.), extraction of which with *N*-hydrochloric acid and addition of 2,4-dinitrophenylhydrazine in 2*N*-hydrochloric acid to the extract gave a yellow precipitate. After 2 hr. the precipitate was filtered off, washed, and dried (0.07 g.). Crystallisation from aqueous acetic acid gave yellow needles of quinoline-2-aldehyde 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 247—248°.

Attempted Hydrolysis of 1,2-Dibromo-1,2-di-2'-quinolyethane.—The bromo-compound (0.3 g.) was refluxed with potassium hydroxide (5.0 g.) in water (30 ml.) and dioxan (20 ml.) during 5 hr. When the solution was cooled a white base was precipitated which gave colourless crystals of 1,2-di-2'-quinolylacetylene, m. p. 182°, from dioxan. Under milder conditions there was no reaction.

Action of Benzoic Acid on 1,2-Di-2'-quinolyethanol.—The diquinolyethanol (0.31 g.) and benzoic acid (0.12 g.) were heated together in a sealed tube for 3 hr. at 100°. The product, which smelled of quinaldine, was dissolved in warm *N*-hydrochloric acid and the solution poured into an excess of cold dilute sodium hydroxide solution. The yellow precipitate (0.27 g.) was removed, treated with 0.05*N*-hydrochloric acid (3 × 15 ml.), and then basified to give a pale yellow precipitate (0.13 g.) which crystallised from light petroleum (b. p. 100—120°) as colourless needles of 1,2-di-2'-quinolyethane, m. p. and mixed m. p. 158° [picrate, m. p. 267° (decomp.)]. Treatment of the residue with hot *N*-hydrochloric acid and basification of the deep red solution gave an orange precipitate (0.14 g.) which crystallised from light petroleum (b. p. 100—120°) to give orange needles of 1,2-di-2'-quinolyethanone, m. p. 212° (Found: C, 80.1; H, 4.7; N, 9.4. Calc. for C₂₀H₁₄N₂O: C, 80.5; H, 4.7; N, 9.4%).

Action of Acetic Acid on 1,2-Di-2'-quinolyethane-1,2-diol.—The diol (0.54 g.) and glacial acetic acid (5 ml.) were refluxed together during 15 min., and the deep red solution cooled and poured into an excess of ice-cold dilute sodium hydroxide solution with stirring. The brown precipitate (0.41 g.) was extracted with 0.05*N*-hydrochloric acid (5 × 10 ml.) and the extracts were basified separately. The first two extracts yielded a cream-coloured base (0.07 g.) which crystallised from aqueous ethanol as pale yellow needles, m. p. 165°. Its picrate had m. p. 270° (decomp.) and a mixed m. p. of the base and 1,2-di-2'-quinolyethane showed no depression. Further treatment of the original brown base with hot *N*-hydrochloric acid and filtration and cooling of the filtrate yielded a sparingly soluble dark red hydrochloride; this afforded 1,2-di-2'-quinolyethanone (0.27 g.), m. p. and mixed m. p. 212°.

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