457. *Quinoline Series. Part III.*[1] *Synthesis and Reactions of Quinoline-substituted Ethylenes.*

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A number of quinolylethylenes (V; R = 2-quinolyl, R′ = Ph, 4-pyridyl, 2-quinolyl, or 4-quinolyl) have been made by various routes, and quinaldine and lepidine have been added to some of them. Two of the resulting propanes (VII; R′ = Ph or 2-quinolyl; R = 2-quinolyl, R″ = 4-quinolyl) have been cyclised to pyrroloquinolines (VIII).

Condensation of quinoline or pyridine aldehydes with quinaldine or lepidine in absence of an added basic catalyst [2] has been studied with a view to preparing quinolylethanols (I). Equimolar quantities of quinaldine and quinoline-2-aldehyde in boiling ethanol gave the expected 1,2-diquinolylethanol (I; R = R′ = 2-quinolyl) accompanied by a small quantity of the ethanediol (II) in agreement with a previous observation by Skidmore and Tidd.[1] For confirmation of its structure this compound has now also been prepared by quantitative reduction of the ethylenediol (III; R = R′ = 2-quinolyl) with zinc and formic acid. The ease of this reaction is noteworthy in view of the failure reported by other workers [3] to reduce this ethylene with hydrogen in presence of palladium.

Using an excess of quinaldine raised the yield of ethanol (I; R = R′ = 2-quinolyl) and almost completely suppressed formation of the (II). Similarly, when more than 1 mol. of lepidine was used in the reaction with quinoline-2-aldehyde, formation of the diol (II; R = R′ = 2-quinolyl) by self-condensation of the aldehyde was prevented and the ethanol (I; R = 2-quinolyl, R′ = 4-quinolyl) was the sole product. When an ethanolic solution of equimolar quantities of lepidine and quinoline-2-aldehyde was heated in a sealed tube at 100° lepidine did not participate in product formation since only the diols (II and III; R = R′ = 2-quinolyl) were obtained. Conditions and results of various quinolylethanol preparations are set out in the Table.

Preparation of quinolylethanols (I) in ethanol at 80°.

R in R·CHO (mol.)	R′ in R′·CH_3 (mol.)	Time (hr.)	Products	Yield (%)	Ref.
4-Quinolyl (1)	2-Quinolyl (1)	12	(I)	75	2
,, (1)	,, (2)	10	(I)	90	—
2-Quinolyl (1)	4-Quinolyl (1)	18	(I)	48	2
,, (1)	,, (2)	24	(I)	79	—
,, (1)	,, (3)	24	(I)	86	—
,, (1)	2-Quinolyl (1)	6	(I)	40	2
			(II)	23	3
,, (1)	,, (2)	4	(I)	66	—
			(II)	7	—
,, (1)	1-Isoquinolyl (1)	24	(I) *	71	—
4-Pyridyl (1)	2-Quinolyl (1)	12	(I) †	87	—

* Found: C, 79·7; H, 5·3. $C_{20}H_{16}N_2O$ requires C, 80·0; H, 5·4%. † Found: C, 76·9; H, 5·7. $C_{16}H_{14}N_2O$ requires C, 76·8; H, 5·6%.

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[1] Part II, Skidmore and Tidd, *J.*, 1961, 1098.

[2] Kaplan and Lindwall, *J. Amer. Chem. Soc.*, 1943, **65**, 927

[3] Buehler and Harris, *J. Amer. Chem. Soc.*, 1950, **72**, 5015.

Some quinolylethanols were conveniently made by reduction of quinolyl ketones (IV; *e.g.*, R = R′ = 2-quinolyl; for others see the Experimental section). Goldberg and Levine's method [4] for the synthesis of several quinolyl ketones from methyl picolinates and quinaldine in presence of phenyl-lithium also proved satisfactory in our case. Smooth conversion into secondary alcohols (I) was achieved with zinc dust and aqueous formic acid. The red colour of the reaction mixture indicative of the presence of the ketone was discharged within a few minutes in the cold, and the colour change served as a convenient end-point of the reaction.

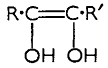
Huang-Minlon conditions for reducing the carbonyl group caused hydrolysis. For instance the ketone (IV; R = R′ = 2-quinolyl) gave mainly quinaldine and quinaldic acid with only a trace of the expected ethane (VI; R = R′ = 2-quinolyl). This is understandable since the ketones were found to be cleaved by hot alkali and also by mineral acid. In this they resemble β-diketones, a similarity which is emphasized by their readiness to give complexes with copper [5] and by our failure to reduce them under Meerwein–Pondorff conditions.[6] Lithium aluminium hydride and Raney nickel at atmospheric pressure also proved ineffective.

Secondary alcohols of the general structure (I; R = aryl, R′ = quinolyl) are known to undergo dehydration in the presence of mineral or organic acids. For instance, even a trace of acid converted the ethanols [7] (I; R = *o*-, *m*-, or *p*-$NO_2{\cdot}C_6H_4$, R′ = 2-quinolyl) into the corresponding styrylquinolines (V). On the other hand, attempted dehydration of the diquinolylethanol [1] (I; R = R′ = 2-quinolyl) with acetic or benzoic acid led to disproportionation, producing nearly equal amounts of the corresponding ethane (VI) and ketone (IV).

We observed a similar result in the preparation of the ethanol (I; R = 2-quinolyl, R′ = 1-isoquinolyl) from 1-methylisoquinoline and quinoline-2-aldehyde. Here the presence of the ketone (IV) among the products was caused by traces of quinaldic acid in the aldehyde. The behaviour of a quinolylethanol towards organic acids is bound up with its structural features. A concerted oxidation–reduction takes place only when the hydroxyl group is neighbour to a quinoline nucleus, in all other cases ethylene formation is the preferred course.

$R{\cdot}CH(OH){\cdot}CH_2R'$ (I)

$R{\cdot}CH(OH){\cdot}CH(OH){\cdot}R'$ (II)



$$\underset{OH}{R{\cdot}C}{=}\underset{OH}{C{\cdot}R'}$$

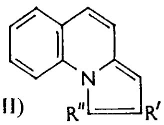
(III)

$R{\cdot}CO{\cdot}CH_2{\cdot}R'$ (IV)

$R{\cdot}CH{:}CH{\cdot}R'$ (V)

$R{\cdot}CH_2{\cdot}CH_2{\cdot}R'$ (VI)

$R{\cdot}CH_2{\cdot}CHR'{\cdot}CH_2{\cdot}R''$ (VII)



(VIII)

In another approach to quinolylethylenes (V) the corresponding ethanes (VI) were of interest. A few symmetrical ethanes with heterocyclic substituents have been recently prepared [8,9] from organolithium compounds. By an analogous method we obtained di-2′-quinolylethane (VI; R = R′ = 2-quinolyl) from quinaldinyl-lithium and bromine albeit in moderate yield which was not improved by treating α-bromoquinaldine with quinaldinyl-lithium. This technique failed to produce unsymmetrically substituted ethanes even when we used an excess of the lithium compound which is said to favour condensation between picolinyl-lithium and alkyl halides.[10] For instance, from α-bromoquinaldine and 2-picolinyl-lithium the symmetrical quinolylethane (VI; R = R′ = 2-quinolyl) was

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[4] Goldberg and Levine, *J. Amer. Chem. Soc.*, 1952, **74**, 5217.

[5] Goldberg, Barkley, and Levine, *J. Amer. Chem. Soc.*, 1951, **73**, 4301.

[6] Lund, *Ber.*, 1937, **70**, 1520.

[7] Tipson, Walton, and Cretcher, *J. Amer. Chem. Soc.*, 1945, **67**, 1501.

[8] Bockelheide and Sieg, *J. Amer. Chem. Soc.*, 1955, **77**, 3128.

[9] Campbell and Teague, *J. Amer. Chem. Soc.*, 1954, **76**, 1371.

[10] Osuch and Levine, *J. Amer. Chem. Soc.*, 1956, **78**, 1723.

invariably obtained. This result can be ascribed to the strongly ionic character of α-bromoquinaldine which engenders a partial halogen–metal exchange between the reactants and so produces the more reactive quinaldinyl-lithium. Dehydrogenation with selenium dioxide in dioxan converted the ethanes (VI) into ethylenes (V).

The conditions affecting acid-catalysed addition of quinaldine and lepidine across 1,2-disubstituted ethylenes have recently been investigated.[11] We could not make an adduct from lepidine and 1,2-di-2′-quinolylethylene with benzoic acid as catalyst, even at 200°. With hydrochloric or sulphuric acid, however, the methyl group became sufficiently activated and most additions proceeded smoothly, yielding a number of trisubstituted propanes (VII; R = R′ = 2-quinolyl, R″ = 4-quinolyl; R = R′ = R″ = 4-quinolyl; R = R″ = 4-quinolyl, R′ = Ph). The reaction between 2-picoline and 1,2-di-2′-quinolylethylene unexpectedly produced the ethane (VI; R = R′ = 2-quinolyl) instead of a propane (VII). Quinaldine gave only one adduct with the unsymmetrical quinolylethylene (V; R = 2-quinolyl, R′ = 4-quinolyl), namely, 1,2-di-2′-quinolyl-3-4′-quinolylpropane; this we also obtained, unambiguously, from lepidine and the symmetrical 1,2-di-2-quinolylethylene. The preferred direction of this addition is not surprising since the anionic part of the addendum (quinaldinyl) becomes attached to the more polarised " quinaldylidene end " of the ethylene.

Two of the propanes (VII; R = 2-quinolyl, R′ = Ph or 2-quinolyl, R″ = 4-quinolyl) were cyclised to the pyrroloquinolines (VIII; R′ and R″ as before) by heating them with an equivalent amount of sulphur.[1] The progress of this reaction was conveniently followed by measuring the hydrogen sulphide evolved, as cadmium sulphide. An excess of sulphur had no effect on yields. Selenium failed to bring about cyclisation at 250°, and at higher temperatures the propanes decomposed. The propane (VII; R = R″ = 4-quinolyl, R′ = Ph) could not be made to cyclise, presumably because addition across the N=C bond to form a pyrrole system is not possible: even on strong heating with sulphur, evolution of hydrogen sulphide was negligible and most of the starting material was recovered. This seems to indicate that cyclisation precedes dehydrogenation.

EXPERIMENTAL

Quinolylethanols.—(*a*) Their preparation from heterocyclic aldehydes and methyl heterocycles is set out in the Table.

(*b*) *By reduction of ketones.* The ketone (0·5 g.), dissolved in 50% aqueous formic acid (50 ml.), was treated with zinc dust (0·5 g.) at room temperature with stirring. When the red colour of the reaction was discharged (*ca.* 5 min.), the excess of zinc was filtered off and the filtrate poured into ice-cold 5N-sodium hydroxide. The quinolylethanol separated and was recrystallised from ethanol. Yields of ethanols (I) from the corresponding ketones were as follows: 1,2-di-2′-quinolyl- 70%; 1,4′-pyridyl-2-2′-quinolyl- 60%; 1-4′-quinolyl-2-2′-quinolyl- 100%; 1-2′-quinolyl-2-1′-isoquinolyl- 40%.

Quinolyl Ketones.—In a typical preparation finely divided lithium (0·7 g.) was added to a solution of bromobenzene (7·9 g.) in sodium-dried ether (50 ml.) under nitrogen and the mixture refluxed and stirred for 1 hr. Quinaldine (7·2 g.) in ether (25 ml.) was then added during 10 min. and stirring continued for a further 15 min. A solution of methyl quinaldate (4·7 g.) in ether (100 ml.) was then introduced at such a rate as to cause the mixture to boil. After 3 hours' refluxing, water (100 ml.) was added and the crude precipitated ketone was filtered off and redissolved in concentrated hydrochloric acid (100 ml.). The ketone (6·5 g., 87%) was reprecipitated with ice-cold aqueous ammonia as yellow needles, m. p. 212—213° [from light petroleum b. p. 100—120°)] (Buehler and Harris[3] report m. p. 221°). Similar conditions were used for the following ketones: 1-4′-*Quinolyl*-2-2′-*quinolylethanone* (30%), m. p. 170° (Found: C, 80·7; H, 4·7. $C_{20}H_{14}N_2O$ requires C, 80·5; H, 4·7%). 2-1′-*Isoquinolyl*-1-2′-*quinolylethanone* (53%), m. p. 169—170° (Found: C, 80·7; H, 4·7. $C_{20}H_{14}N_2O$ requires C, 80·5; H, 4·7%). 1-2′-, m. p. 152° (54%), 1-3′-, m. p. 130° (87%), and 1-4′-Pyridyl-2-2′-quinolylethanone, m. p. 146° (71%), whose m. p.s agree with those reported.[4]

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[11] Skidmore and Tidd, *J.*, 1959, 1641.

Quinolylethylenes.—(*a*) *Dehydration of ethanols.* The quinolylethanol was refluxed with ten times its volume of acetic anhydride for 0·5 hr. The crude ethylene separated on cooling or was obtained by pouring the mixture into 5N-aqueous ammonia. Recrystallisation was from light petroleum (b. p. 80—100°). The following ethylenes were thus obtained: 1,2-di-2′-quinolyl[1] (71%), m. p. 190°, from 1,2-di-2′-quinolylethanol; 1,2-di-4′-quinolyl-[2] (58%), m. p. 205°, by heating quinoline-4-aldehyde (2 g.), lepidine (2 g.), acetic acid (4 ml.), and a few drops of acetic anhydride in a sealed tube at 110° for 6 hr.; 1-2′-*quinolyl*-2-4′-*quinolyl*- (61%), m. p. 116° (Found: C, 85·1; H, 4·8. $C_{20}H_{14}N_2$ requires C, 85·1; H, 5·0%), from 1-4′-quinolyl-2-2′-quinolylethanol or 1-2′-quinolyl-2-4′-quinolylethanol, in 35% yield [*dibromo-derivative*, made in carbon tetrachloride, m. p. 174° (Found: C, 53·8; H, 3·2. $C_{20}H_{14}Br_2N_2$ requires C, 54·3; H, 3·2%)], and 1-4′-*pyridyl*-2-2′-*quinolyl*- (86%), m. p. 124° (Found: C, 82·8; H, 5·1. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2%), from 1-4′-pyridyl-2-2′-quinolylethanol.

(*b*) *Dehydrogenation of ethanes.* The 1,2-diquinolylethane (0·5 g.) was heated with selenium dioxide (0·4 g.) in dioxan (20 ml.) for 2 hr. The residue was filtered off and the filtrate gave 1,2-di-2′-quinolylethylene (0·3 g.) on evaporation. 1,2-Di-4′-quinolylethane similarly gave 1,2-di-4′-quinolylethylene (53%).

Quinolylethanes.—(*a*) 1,2-*Di*-2′-*quinolylethane.* To a solution of phenyl-lithium prepared from lithium (0·7 g.) and bromobenzene (7·9 g.) as described for quinolyl ketones, quinaldine (7·15 g.) in ether (25 ml.) was added during 10 min. α-Monobromoquinaldine (11·1 g.) in ether (50 ml.) was then introduced and the mixture refluxed for 2 hr. Addition of water (100 ml.) removed lithium salts. The ethereal solution was extracted with N/20-hydrochloric acid (3 × 100 ml.), followed by 0·1N-hydrochloric acid (3 × 100 ml.). On basification of the latter acid solution and extraction of the pale yellow solid with hot light petroleum (b. p. 80—100°) 1,2-di-2′-quinolylethane was produced as white plates (4·2 g., 28%), m. p. 159—160° (lit.,[12] 162·5—163°).

In another experiment a solution of quinaldinyl-lithium, prepared as above, was cooled to −50° and to it bromine (5·1 g.) in ether (50 ml.) was added slowly. The mixture was kept at −50° for 1 hr. and then slowly allowed to reach room temperature. Addition of water precipitated a solid which was discarded. On evaporation the ether layer gave an oil from which quinaldine was removed by steam-distillation. The residue was then extracted with light petroleum (b. p. 100—120°) from which 1,2-di-2′-quinolylethane (40%) crystallised on cooling.

(*b*) *Attempts to prepare* 1-2′-*pyridyl*-2-2′-*quinolylethane.* To a solution of phenyl-lithium prepared as in (*a*), 2-picoline (4·65 g.) in ether (25 ml.) was slowly added. The mixture was stirred for 15 min. and then a solution of α-bromoquinaldine (11·1 g.) in ether (50 ml.) was added during 10 min. After 2 hours' refluxing lithium salts were removed with water (100 ml.), and the solvent was driven off. Fractional distillation of the residue gave 2-picoline (2·5 g.), quinaldine, and 1,2-di-2′-quinolylethane. The preparation also failed when two equivalents of 2-picoline and one equivalent of α-bromoquinaldine and of phenyl-lithium were used.

(*c*) 1,2-*Di*-4′-*quinolylethane.* Lepidine (10 g.) and sulphur (2·2 g.) were heated together under reflux for 5 hr. To the cold mixture were added 50 ml. of carbon tetrachloride, and insoluble material was filtered off. The filtrate was then poured into light petroleum (b. p. 40—60°; 300 ml.). A brown solid (2·3 g.) was removed and the filtrate evaporated. Recrystallisation of the residue from light petroleum (b. p. 100—120°) yielded the ethane (0·85 g.) as needles, m. p. 178° (lit.,[13] 182°) (Found: C, 84·2; H, 5·6; N, 10·3. Calc. for $C_{20}H_{16}N_2$: C, 84·5; H, 5·6; N, 9·9%).

1,2-*Di*-2′-*quinolyl*-3-4′-*quinolylpropane.*—(*a*) Lepidine (0·86 g.), 1,2-di-2′-quinolylethylene (0·29 g.), and its dihydrochloride (0·35 g.) were heated in a sealed tube at 150° for 3 hr. The mixture was then dissolved in hot N-hydrochloric acid (10 ml.), made alkaline with aqueous 2N-sodium hydroxide, and steam-distilled to remove lepidine. From the residue which was taken up in benzene and dried ($MgSO_4$) the *propane* (0·29 g.) was obtained on evaporation. From ethyl acetate–light petroleum (b. p. 100—120°) it formed prisms (0·2 g., 24%), m. p. 134° (Found: C, 84·5; H, 5·5. $C_{30}H_{23}N_3$ requires C, 84·7; H, 5·5%). The same compound was obtained by heating quinaldine (0·86 g.), 1-2′-quinolyl-2-4′-quinolylethylene (0·28 g.), and its dihydrochloride (0·35 g.) at 150° for 3 hr. Its *tripicrate*, obtained from acetic acid, had m. p. 233—235° (Found: C, 51·2; H, 2·7. $C_{48}H_{36}N_{12}O_{21}$ requires C, 51·8; H, 2·9%).

[12] Hammick, Lammiman, Morgan, and Roe, *J.*, 1955, 2436.
[13] Brown, Hammick, and Thewlis, *J.*, 1951, 1145.

1,2,3-*Tri-4′-quinolylpropane.*—Lepidine (0·86 g.) and 1,2-di-4′-quinolylethylene dihydrochloride (0·71 g.) gave, as above, 1,2,3-*tri-4′-quinolylpropane* (37%), m. p. 174—175° (Found: C, 84·8; H, 5·3%).

Dehydrogenation of Propanes.—2-Phenyl-1-2′-quinolyl-3-4′-quinolylpropane[11] (0·94 g.) was heated with sulphur (0·16 g.) at 220° for 1 hr. Hydrogen sulphide evolved was passed into aqueous cadmium chloride containing acetic acid and sodium acetate, and was estimated as cadmium sulphide. Chromatography (alumina) of a benzene extract of the mixture, followed by elution with benzene, gave a red solid. Crystallisation from light petroleum (b. p. 100—120°) produced 2-*phenyl*-1-4′-*quinolylpyrrolo*[1,2-a]*quinoline* as yellow needles, m. p. 229—230° (Found: C, 87·6; H, 4·9. $C_{27}H_{18}N_2$ requires C, 87·6; H, 4·9%) [*picrate*, red needles, m. p. 235° (Found: C, 65·6; H, 3·4. $C_{33}H_{21}N_5O_7$ requires C, 66·1; H, 3·5%); *methiodide*, red, m. p. 180° (Found: C, 65·0; H, 4·2. $C_{28}H_{21}IN_2$ requires C, 65·6; H, 4·1%)].

Similarly 1,2-di-2′-quinolyl-3-4′-quinolylpropane (1·0 g.) and sulphur (0·16 g.) at 230° (1 hr.) gave 1-4′-*quinolyl*-2-2′-*quinolylpyrrolo*[1,2-a]*quinoline*, yellow needles, m. p. 182° (Found: C, 85·9; H, 4·8. $C_{30}H_{19}N_3$ requires C, 85·5; H, 4·5%) [*tripicrate*, red, m. p. 218° (Found: C, 52·3; H, 2·3. $C_{48}H_{28}N_{12}O_{21}$ requires C, 52·0; H, 2·5%)].

1,2-*Di-2′-quinolylethane*-1,2-*diol.*—A solution of 1,2-di-2′-quinolylethylene-1,2-diol[3] (0·5 g.) in formic acid (26 ml.) was reduced with zinc dust (0·5 g.) as described for the quinolyl ketones. A quantitative yield of the ethanediol, m. p. 210—212°, was obtained.

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