

324. *The Quinoline Series. Part I. Addition Reactions of Quinaldine and Lepidine.*

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Quinaldine and lepidine have been added to activated olefinic systems in the presence of organic and inorganic acids as catalysts. The ease of addition is shown to depend upon the temperature of the reaction and the acid strength of the catalyst.

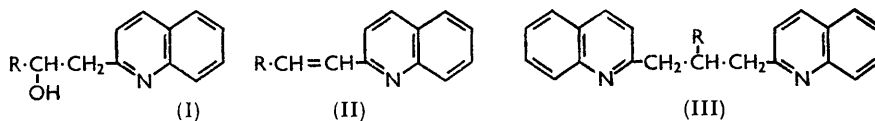
The ultraviolet absorption spectra of some of the addition compounds have been measured, and the formation and hydrolysis of their methiodides examined.

ALDEHYDES react with quinaldine to yield hydroxy-compounds (I), olefins (II), or diquinolylpropanes (III), depending upon the conditions employed.

Koenigs¹ has shown that benzaldehyde and an excess of quinaldine at 150—160° in presence of anhydrous zinc chloride afford mainly the diquinolylpropane (III; R = Ph) which could be formed by condensation of quinaldine with the initially formed hydroxy-compound (I; R = Ph) or by addition of quinaldine to the olefin (II; R = Ph). It has

¹ Koenigs, *Ber.*, 1899, **32**, 3599.

now been found, however, that heating quinaldine with the hydroxy-compound at 100° with anhydrous zinc chloride or benzoic acid yields 2-styrylquinoline by dehydration, but no substituted propane. The alternative mechanism was then considered. Base-catalysed Michael-type additions of quinaldine and lepidine to activated olefinic systems



have been described by Weiss and Hauser² but very little work is recorded on acid-catalysed additions of these bases. Quinaldine or lepidine and 2-styrylquinolines with benzoic acid, a mineral acid, or anhydrous zinc chloride as catalyst, gave good yields of trisubstituted propanes depending upon the catalyst and temperature used (Table 1). No addition occurred at 100°, which would explain the absence of addition product in the attempted reaction between quinaldine and the hydroxy-compound (I; R = Ph). The separation of adducts from unchanged olefin was possible because of the greater solubility of the former in 0.1N-hydrochloric acid.

TABLE 1. *Addition of quinaldine to styrylquinoline.*

Effect of catalyst: 5 hr. at 135°.

Catalyst	BzOH	H ₂ SO ₄	AcOH	<i>o</i> -HO·C ₆ H ₄ ·CO ₂ H	HCl	HCl *
Product (III; R = Ph) (%)	0	82	0	0	82	82

* As hydrochloride of (II; R = Ph).

Effect of temperature: (a) BzOH for 5 hr.

Temp.	135°	140°	145°	150°	155°	166°
Product (III; R = Ph) (%)	0	12	21	67	70	73

(b) H₂SO₄ for 3 hr.

Temp.	100°	110°	120°	125°	130°	135°
Product (III; R = Ph) (%)	0	2	9	42	52	80

The addition reactions were extended to ethyl cinnamate and 4-styrylquinoline. The adduct from quinaldine and ethyl cinnamate gave an acid on hydrolysis which was identical with that isolated by Weiss and Hauser from their base-catalysed reaction. The adduct obtained from quinaldine and 4-styrylquinoline was identical with that obtained from lepidine and 2-styrylquinoline. Attempts to add lepidine to 4-styrylquinoline gave colourless needles which could not be obtained with a sharp melting point and gave an unexpected analysis. Koenigs recorded a similar indistinct melting point for the compound which he isolated from the reaction between lepidine (2 mols.) and benzaldehyde (1 mol.).

Preparation of monomethiodides of the adducts as described by Hamer³ yielded only dimethiodides. Hamer hydrolysed 2-phenyl-1:3-di-2'-quinolypropane dimethiodide by boiling its aqueous solution and obtained 2-styrylquinoline methiodide. When a similar reaction was attempted using 2-phenyl-1:3-di-4'-quinolypropane dimethiodide only unchanged material was recovered. The case of the dimethiodide of 2-phenyl-1-2'-quinoly-3-4'-quinolypropane was of interest since either 2- or 4-styrylquinoline methiodide could be produced. Prolonged hydrolysis of the substance yielded 4-styrylquinoline methiodide.

Spectra.—The ultraviolet absorption spectra of several substituted propanes described above have been determined (see Table 2). The general form of the curves can be interpreted as a result of the combination of the spectra of quinoline and a substituted toluene. The latter behaves as an insulated chromophore since no conjugation can occur between the benzene and quinoline nuclei.

² Weiss and Hauser, *J. Amer. Chem. Soc.*, 1949, **71**, 2023.

³ Hamer, *J.*, 1923, **123**, 246.

TABLE 2. Absorption spectra (λ in $m\mu$) of 2-R-1 : 3-di-2'-quinolylpropane (III).

R = Ph		R = <i>p</i> -C ₆ H ₄ Me		R = <i>m</i> -NO ₂ ·C ₆ H ₄		R = <i>p</i> -NO ₂ ·C ₆ H ₄	
λ_{\max} .	log ϵ	λ_{\max} .	log ϵ	λ_{\max} .	log ϵ	λ_{\max} .	log ϵ
267	3.89	269	3.89	265	4.11	261—275	4.14
290	3.70	291	3.69	~290	3.83		
297	3.67	297	3.66	297	3.78		
304	3.81	304	3.79	304	3.85	304	3.95
309	3.72	309	3.72	309	3.74	309	3.82
317	3.93	317	3.93	317	3.93	317	3.96

EXPERIMENTAL

1-Phenyl-2-2'-quinolylethanol.—Benzaldehyde (500 g.), a small amount of benzoic acid, and quinaldine (750 g.) were shaken together and set aside at room temperature. Precipitation occurred during several weeks and the precipitate was filtered off at 7 day intervals. The product was washed with light petroleum (b. p. 60—80°) and crystallised once from ethanol to give colourless needles (407 g., 34%), m. p. 127° (Benrath⁴ gives m. p. 131°).

2-Styrylquinoline.—(a) 1-Phenyl-2-2'-quinolylethanol (100 g.) was dehydrated with acetic anhydride as described by Benrath, to give cream-coloured needles of 2-styrylquinoline (91.4 g., 98.5%), m. p. 100°.

(b) The method described by Jacobsen and Reimer,⁵ starting from quinaldine and benzaldehyde, was used except that the catalyst was acetic anhydride and the reactants were kept at 125° during 2 hr. (68%).

Nitrostyrylquinolines.—Quinaldine (4.0 g.), *m*- or *p*-nitrobenzaldehyde (4.22 g.), and acetic anhydride (2.85 g.) were heated together in a sealed tube at 125° during 1 hr. The product was steam-distilled to remove unchanged quinaldine and aldehyde, the residue of nitrostyrylquinoline dissolved in the minimum quantity of hot ethanol, and the solution poured into water (250 ml.) with stirring. The precipitated base was removed and dried.

(a) 2-3'-Nitrostyrylquinoline (6.85 g., 89%), m. p. 149—151°, crystallised twice from benzene and once from ethanol to give pale yellow needles, m. p. 156° (Walton, Tipson, and Cretcher⁶ give m. p. 157—158°).

(b) 2-4'-Nitrostyrylquinoline (7.04 g., 91%) formed needles (from ethanol), m. p. 169° (Walton *et al.* give m. p. 171—172°).

2-4'-Methylstyrylquinoline.—Quinaldine (4 g.), *p*-tolualdehyde (3.36 g.), and acetic anhydride (2.85 g.) were treated as described for nitrostyrylquinolines. The crude base crystallised from ethanol as pale yellow needles, m. p. 140° (1.49 g., 22%) (Found: C, 88.0; H, 6.2; N, 5.8. Calc. for C₁₈H₁₅N: C, 88.2; H, 6.1; N, 5.7%). von Grabski⁷ described the preparation of this compound and its hydrochloride but did not record the m. p. of the free base.

4-Styryl-lepidine.—A procedure modified from that described by Kaslow and Stayner⁸ was used. Lepidine (13.7 g.), benzaldehyde (18 g.), and anhydrous zinc chloride (1.6 g.) were heated together at 170° during 3 hr. The product was treated with 20% sodium hydroxide solution (30 ml.), and the viscous oil produced was washed with water by decantation. After 15 min. the oil solidified and was then filtered off and treated with concentrated hydrochloric acid (25 ml.). The yellow base hydrochloride which was precipitated was dissolved in hot water (1 l.), and the solution basified, cooled, and extracted with benzene (250 ml.). Filtering the benzene solution and shaking it with 2N-hydrochloric acid (200 ml.) precipitated a yellow hydrochloride, which was washed with 2N-hydrochloric acid, dissolved in warm water, and basified. The precipitated base was dried and crystallised from light petroleum (b. p. 80—100°), forming pale cream-coloured crystals (15.4 g., 70%), m. p. 88°.

On basification of the hydrochloric acid mother-liquors, a green oil was obtained which solidified (2.5 g.). Crystallisation from light petroleum (b. p. 100—120°) yielded colourless needles, m. p. 106—110°. The compound gave no colour with hydrochloric acid and was thought to be benzylidenedilepidine.

2-Phenyl-1 : 3-di-2'-quinolylpropane.—Quinaldine (9.3 g.), 2-styrylquinoline (5 g.), and

⁴ Benrath, *J. prakt. Chem.*, 1906, **73**, 383.

⁵ Jacobsen and Reimer, *Ber.*, 1883, **16**, 1082, 2602.

⁶ Walton, Tipson, and Cretcher, *J. Amer. Chem. Soc.*, 1945, **67**, 1501.

⁷ von Grabski, *Ber.*, 1902, **35**, 1957.

⁸ Kaslow and Stayner, *J. Amer. Chem. Soc.*, 1945, **67**, 1716.

anhydrous zinc chloride (1 g.) were heated together in a sealed tube at 150—160° during 5 hr. The product was dissolved in hot *n*-hydrochloric acid (250 ml.) and then basified with aqueous sodium hydroxide. The precipitated bases were extracted with benzene and shaken with 2*N*-hydrochloric acid (200 ml.). Repeated trituration of the precipitated hydrochloride with 0.1*N*-hydrochloric acid and basification of the acid extracts yielded a brown gum (5.1 g., 63%). Crystallised from light petroleum (b. p. 80—100°), the base separated as white rosettes, m. p. 90—92° (Hamer reports 90—94°) (Found: C, 86.5; H, 6.1; N, 7.6. Calc. for C₂₇H₂₂N₂: C, 86.6; H, 5.9; N, 7.5%). The dimethiodide crystallised from ethanol-ether as pale yellow needles, m. p. 179° (Found: C, 52.3; H, 4.4; I, 37.4. Calc. for C₂₉H₂₈N₂I₂: C, 52.9; H, 4.3; I, 38.7%).

With benzoic acid or concentrated sulphuric acid in place of zinc chloride similar results were obtained.

2-m-Nitrophenyl-1:3-di-2'-quinolylpropane.—Quinaldine (8.6 g.), 2-3'-nitrostyrylquinoline (5.5 g.), and concentrated sulphuric acid (1.4 g.) were heated at 135° during 4 hr. The product was dissolved in hot 2*N*-hydrochloric acid, filtered from tar, and basified with aqueous sodium hydroxide. The precipitated bases were extracted with benzene and shaken with 2*N*-hydrochloric acid (200 ml.). The precipitated hydrochloride was dissolved in warm water and basified. The product (7.25 g., 86.6%), crystallised from light petroleum (b. p. 100—120°), gave *2-m-nitrophenyl-1:3-di-2'-quinolylpropane* as colourless rosettes, m. p. 154° (Found: C, 77.6; H, 5.2; N, 9.8. C₂₇H₂₁O₂N₃ requires C, 77.3; H, 5.1; N, 10.0%). The *dimethiodide* had m. p. 202—204° (from ethanol-ether) (Found: C, 49.5; H, 4.1; I, 35.7. C₂₉H₂₇O₂N₃I₂ requires C, 49.5; H, 3.9; I, 36.1%).

2-4'-Nitrostyrylquinoline gave *2-p-nitrophenyl-1:3-di-2'-quinolylpropane* (5.8 g., 69.3%), m. p. 165° [from light petroleum (b. p. 100—120°)] (Found: C, 77.2; H, 5.2; N, 10.3%) [*dimethiodide* (from ethanol), m. p. 201—203° (Found: C, 49.5; H, 3.9%)].

2-4'-Methylstyrylquinoline gave *1:3-di-2'-quinolyl-2-p-tolylpropane* (5.2 g., 66.2%), which crystallised from benzene, light petroleum (b. p. 100—120°), or ethanol as colourless needles, m. p. 121° (Found: C, 86.6; H, 6.4; N, 7.3. C₂₈H₂₄N₂ requires C, 86.6; H, 6.2; N, 7.2%). Its *dimethiodide* had m. p. 201—203° (from ethanol) (Found: C, 54.5; H, 4.7. C₃₀H₃₀N₂I₂ requires C, 53.6; H, 4.5%).

2-Phenyl-1:3-di-4'-quinolylpropane.—(a) *Addition of lepidine to 2-styrylquinoline*. Lepidine (7.2 g.) and 2-styrylquinoline hydrochloride (5.4 g.) were heated together at 135° during 5 hr. The product solidified. Treatment with 5*N*-hydrochloric acid yielded a red-brown solution which on cooling in ice gave no precipitate, indicating the absence of unchanged 2-styrylquinoline. Pouring the solution into an excess of ice-cold (15%) sodium hydroxide solution gave a green viscous base which was washed several times by decantation, then redissolved in 2*N*-hydrochloric acid, and 2*N*-sodium hydroxide was added until the solution remained faintly acid. A pale green, granular, precipitate became sticky after separation (5.1 g., 58.4%). Dissolving the base in ether and setting the solution aside yielded a granular *product* which crystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 107—108° (Found: C, 85.9; H, 6.1; N, 7.6. C₂₇H₂₂N₂ requires C, 86.6; H, 5.9; N, 7.5%). The *dimethiodide*, crystallised from ethanol, had m. p. 175—176° (Found: I, 38.8; N, 4.4. C₂₉H₂₈N₂I₂ requires I, 38.7; N, 4.3%).

(b) *Addition of quinaldine to 4-styrylquinoline*. Quinaldine (1.86 g.), 4-styrylquinoline (1.0 g.), and concentrated sulphuric acid (0.28 g.) were heated together at 135—140° during 3 hr. The mixture was dissolved in 2*N*-hydrochloric acid (20 ml.), basified with aqueous sodium hydroxide, and freed from quinaldine by steam-distillation. The residue was dissolved in 2*N*-hydrochloric acid (20 ml.), cooled in ice-water, and set aside for 1 hr. The yellowish-brown deposit was filtered off, dissolved in water, and basified. The base was extracted with ether, and the ethereal solution dried (Na₂SO₄) and concentrated. The resulting viscous oil solidified overnight and crystallised from light petroleum (b. p. 60—80°) as needles (1.05 g., 65%), m. p. 107—108°, alone or mixed with the product from (a).

2-Phenyl-1:3-di-4'-quinolylpropane.—Lepidine (1.86 g.), 4-styrylquinoline (1.0 g.), and concentrated sulphuric acid (0.28 g.) were heated together at 135—140° during 3 hr. Working up as in the preceding case gave a solid base (1.32 g.) which on attempted crystallisation from light petroleum (b. p. 100—120°) yielded an oil. Shaking it with ether (10 ml.), however, afforded a white powder (0.5 g.) which gave no colour with *n*-hydrochloric acid and crystallised from light petroleum (b. p. 80—100°) as needles, m. p. 109—124° (Koenigs¹ gives 110—127°)

(Found: C, 82.4; H, 6.3; N, 6.7. Calc. for $C_{27}H_{22}N_2, H_2O$: C, 82.6; H, 6.2; N, 7.1%). The *dimethiodide*, crystallised from methanol, had m. p. 234—235° (Found: C, 52.8; H, 4.3; I, 38.4. $C_{29}H_{28}N_2I_2$ requires C, 52.9; H, 4.3; I, 38.7%).

β-Phenyl-γ-2-quinolylbutyric Acid.—Quinaldine (14.3 g.), quinaldine hydrochloride (2 g.), and ethyl cinnamate were heated at 250° during 5 hr. The product was cooled, then treated with an excess of 2N-hydrochloric acid, and unchanged ethyl cinnamate extracted with ether. The aqueous solution was basified with 2N-ammonia, and the resulting reddish-brown oil extracted with ether. After drying of the extract (Na_2SO_4) and removal of the ether an oil was obtained which on distillation at 2 mm. gave fraction (1), quinaldine (10.3 g., b. p. 100°), (2) a viscous red oil (2.82 g., b. p. 190—205°). The latter was refluxed for 3 hr. with alcoholic 10% potassium hydroxide solution (50 ml.), the solvent was distilled off, and the residue treated with a little water. Acidification of the solution with 10% acetic acid yielded a white product which crystallised from aqueous ethanol as colourless leaflets, m. p. 193°.

Ultraviolet Absorption Spectra.—The spectra were determined for 2 : 2 : 4-trimethylpentane solutions with a Unicam S.P. 500 spectrophotometer and 1 cm. quartz cells.

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