SYNTHESIS OF QUINOLINE VINYL DERIVATIVES BY THE MANNICH REACTION

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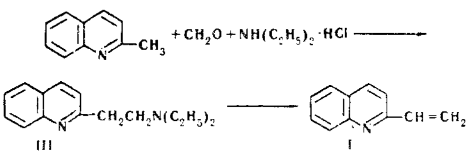
Aminomethylation of quinaldine and lepidine is investigated. Decomposition of quaternary salts of Mannich bases gives 2- and 4-vinylquinoline.

The usual method of synthesizing 2-vinylquinoline (I) is dehydration of 2-(β-hydroxyethyl)quinoline, prepared by hydroxymethylation of quinaldine [1–3]. Dehydration takes place under drastic conditions, at 140° C in the presence of sodium hydroxide. The yield does not, in general, exceed 30% [2, 4, 5]. 4-Vinylquinoline (II) is not accessible by that method, for under those conditions it polymerizes, and a multistage synthesis is used to prepare it [6]. In addition, many quinaldine derivatives do not react with formaldehyde [2].

The present paper shows the possibility of basing synthesis of quinoline vinyl derivatives, in the cases of I and II, on the Mannich reaction.

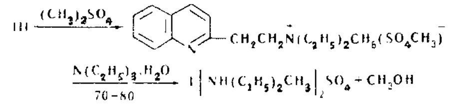


A number of papers [9–13] describe aminomethylation of quinaldine and lepidine, but often the authors give contradictory information regarding properties and yields of the resultant dialkylaminoquinolines. We have now found that the Mannich reaction with quinaldine and lepidine is very sensitive to solution pH; the best yields of 2- and 4-(β-diethylaminoethyl)-quinoline (III and IV) are obtained at pH 7.5–8. Running the reaction in strongly alkaline solution leads to rapid formation of bis(diethylamino)methylene, which in this particular case is not an aminomethylating agent [14].

The nature of the secondary amine has a great effect on the nature of the products of aminomethylation of quinaldine and lepidine. Diethylamine hydrochloride gives mainly a Mannich monobase. Use of considerable amounts of dimethylamine or piperidine hydrochloride gives a Mannich dibase. For example, in the synthesis of 2-(β-dimethylaminoethyl)quinoline, about 40% 1,3-di(dimethylamino)-2-(2'-quinolyl)propane is formed. Lepidine is less reactive in the Mannich reaction, but 1,3-dipiperidino-2-(4'-quinolyl)-propane is a side reaction product in the synthesis of 4-(α-piperidinoethyl)quinoline. The literature states [13] that the sole product of aminomethylation of lepidine is a Mannich monobase. Obviously, aminomethylation of quinaldine and lepidine in alkaline solution involves S_N2 nucleophilic substitution, postulated for the analogous reaction involving aldehydes or cyclohexanone [15, 16], and catalyzed by hydroxyl ions.

2-Methyl-5-ethylpyridine and its N-oxide do not undergo the Mannich reaction even on prolonged heating at 100° C, and at different pHs. The higher reactivities of quinaldine and lepidine are due to intermediate carbanion stabilization by a longer conjugated chain [17–19].

The possibility of converting III to I by thermal decomposition in the presence of potassium hydroxide [20], or by decomposition III N-oxide [21] was investigated, but in both cases the yield of I was under 2%. 60–64% yields of quinoline vinyl derivatives were obtained when the Mannich bases were decomposed thus:



I resulted by decomposing the quaternary salt of III by heating in aqueous solution at 70°–80° C, but decomposition was faster in alkaline solution, in the presence of triethylamine. Similarly II was obtained from IV, and 4-(β-piperidinoethyl)quinoline and 3-dimethylamino-2-(2'-quinolyl)prop-1-ene from 1,3-di(dimethylamino)-(2'-quinolyl)propane. The ease with which Hofmann degradation takes place there can be ascribed to the high acidity of the hydrogen at the α-carbon atom, activated by the electron-accepting actions of the ring nitrogen and the nitrogen of the trialkylammonium group.

EXPERIMENTAL

2-(β-Diethylaminoethyl)quinoline (III). A solution of 42.9 g (0.3 mole) quinaldine, 23.6 g 38% formaldehyde (0.3 mole), 40 ml EtOH, and 1 ml Et_3N at 60° C was brought to pH 7.5–8.0 by adding dropwise, over a period of 1.5–2 hr, a solution of 33 g (0.3 mole) diethylamine hydrochloride and 2 ml Et_3N in 15 ml EtOH + 15 ml H_2O. The mixture was heated for 2 hr, the pH being kept at 7.0–7.5, cooled, the solvent vacuum distilled off, water added to bring the volume to 250 ml, and the unreacted quinaldine (14 g) extracted with ether. The aqueous solution was treated with 70 ml 20% aqueous NaOH, and extracted with ether, the extracts dried over Na_2SO_4, and the ether taken off, to give 43 g III (81% on the quinaldine reacted), n_D^{20} 1.5700. The crude material was vacuum fractionated through a short column, to give 1.5 g quinaldine, bp 100°–105° C (2–3 mm), n_D^{20} 1.6120, and 33 g III, bp 150°–157° C (2–3 mm), n_D^{20} 1.5670, the intermediate cut and residue in the flask amounting to 4 g yield of 67% of purified III, on the reacted quinaldine. The diethylamine hydrochloride unused in the main reaction recovered.

4-(β-Diethylaminoethyl)quinoline (IV). The reaction was run under the same conditions, and using the same mole ratios as above. Heating a mixture of 42.9 g lepidine, 33.6 g 38% formaldehyde, and 33 g diethylamine hydrochloride for 5 hr gave 45 g crude IV, and 14.2 g lepidine was recovered. Fractional distillation of the crude IV gave 1.2 g lepidine, bp 105°-110° C (2-3 mm), n_D^{20} 1.6140, 2 g intermediate cut bp 110°-160° C (2-3 mm), and 31 g IV (72% on the reacted lepidine), bp 165°-172° C (2-3 mm)[12], n_D^{20} 1.5687. Monohydrochloride mp 156° C [13].

4-(β-Piperidinoethyl)quinoline. Prepared similarly to III. 42.9 g lepidine, 23.6 g 38% formaldehyde, and 36.5 g piperidine hydrochloride gave 17.5 g 4-(β-piperidinoethyl)quinoline, bp 200°-210° C, 5 mm), mp 82°-83° C (ex petrol ether) [12]. Also isolated were 22 g unreacted lepidine and 12.5 g 1,3-dipiperidino-2-(4'-quinolyl)propane, bp 235°-237° C (5 mm), a very viscous oil. Found: C 78.1; H 9.3; N 12.6%, calculated for $C_{22}H_{31}N_3$: C 78.3; H 9.3; N 12.4%.

2-Vinylquinoline (I). 12.6 g (0.1 mole) Me_2SO_4 was added to 22.9 g (0.1 mole) III in 30 ml EtOH, with cooling, at such a rate that the temperature of the reaction mixture did not exceed 40° C. The solution was diluted with 150 ml water, 10 ml Et_3N added, and the mixture heated on a steam bath for 1 hr. I formed an upper layer, it was steam distilled off, the distillate extracted with ether, the extracts dried over Na_2SO_4, and after removing the ether the residue distilled to give 9.9 g (64%), bp 100°-101° C (2 mm); 121° C (5-6 mm); d_4^{20} 1.0715; n_D^{20} 1.6490, equiv. wt. 155.0. Found: MR_D 52.76, calculated MR_D 51.14. Picrate mp 172° C [2, 4, 5].

Decomposition of III N-oxide by a known method [21] gave only traces of I.

4-Vinylquinoline (II). Prepared similarly to I. 24 g (0.1 mole) 4-(β-piperidinoethyl)quinoline gave 9.5 g (61%) II, bp 120°-122° C (3 mm); n_D^{20} 1.6457; d_4^{20} 1.0928. Found: MR_D 51.52, calculated MR_D 51.14. Picrate mp 187° C.

22.9 g (0.1 mole) IV was treated similarly to the above. Yield of II 9.3 g (60%), bp 120°-123° C (3 mm); n_D^{20} 1.6450, picrate mp 187° C.

2-(β-Dimethylaminoethyl)quinolyl and 1,3-di(dimethylamino)-2-(2'-quinolyl)propane. An ethanol solution of 85.8 g (0.6 mole) quinaldine, 33.6 g 38% (0.3 mole) formaldehyde, and 24.5 g (0.3 mole) dimethylamine hydrochloride, were heated together for 45 min at 50°. The pH of the solution was held at 7.0-7.5. The mixture of bases was isolated as in the case of III. 30 g mixed bases were obtained, bp 149°-155° C (1-2 mm), and 62 g unreacted quinaldine was recovered. The boiling points of the bases being close to one another, the mixture was difficult to separate. The decomposition of the mixture was established by decomposing it after alkylation with dimethyl sulfate. 20 g mixed bases were dissolved in 20 ml EtOH, and alkylated with Me_2SO_4 as described above. The solution was diluted with water, 12 g Na_2CO_3 added, and the I steam distilled off. Yield of I 6.0 g, bp 101°-102° C (1-2 mm); n_D^{20} 1.6450, picrate mp 172°.

The residue in the flask after steam distilling was extracted with ether, the ether extracts dried over Na_2SO_4, the ether taken off, and the residue distilled to give 3-dimethylamino-2-(2'-quinolyl)prop-1-ene, yield 4 g bp 145°-150° C (1-2 mm), n_D^{20} 1.6060, picrate mp 166° C [10]. Found: C 79.00; H 7.70; N 13.40%, calculated for $C_{14}H_{16}N_2$: C 79.21; H 7.60; N 13.19%.

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