[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

A SYNTHESIS OF 1-VINYLISOQUINOLINE AND RELATED DERIVATIVES

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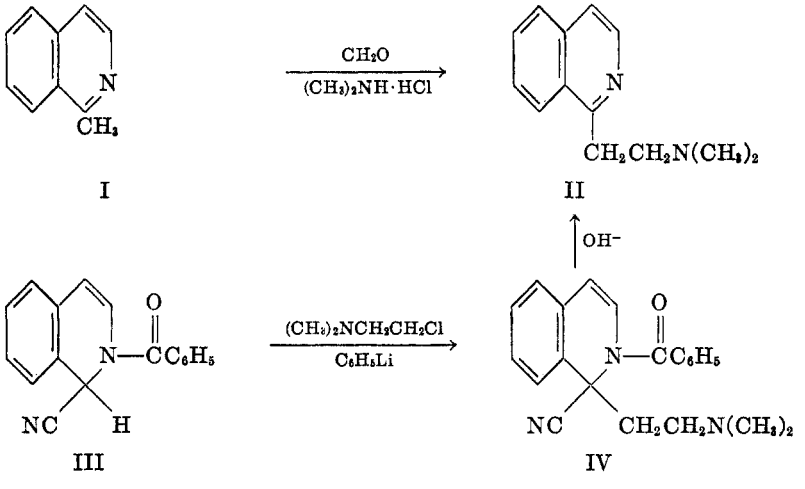
The Michael condensation of 2-vinylpyridine with active methylene compounds has been utilized in previous studies for the preparation of numerous pyridine and quinolizidine derivatives (1–4). In a similar study of the synthesis of quinoline derivatives, the alkylation of active methylene compounds with 2-(β-dimethylaminoethyl)quinoline proved to be a more feasible and practical reaction (5). In the present paper we are reporting the results of an investigation attempting to apply these methods to the synthesis of isoquinoline derivatives. This seemed desirable in view of the possible applications which such syntheses would have in the field of alkaloid chemistry.

In contrast to the situation prevailing in the pyridine and quinoline series, 1-methylisoquinoline is not commercially available nor has 1-vinylisoquinoline been previously prepared. Of the methods which have been reported in the literature for the preparation of 1-methylisoquinoline, the most useful would appear to be the alkylation of Reissert's compound (6). In this way 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (III) has been converted to 1-methylisoquinoline in a 58% over-all yield. Therefore, our first experiments were directed toward the conversion of 1-methylisoquinoline to 1-(β-dimethylaminoethyl)-isoquinoline following the same procedure used previously with quinaldine (5).



When 1-methylisoquinoline (I) was treated with formaldehyde and dimethylamine hydrochloride under the usual conditions of the Mannich reaction, it was readily converted to the corresponding 1-(β-dimethylaminoethyl)isoquino-

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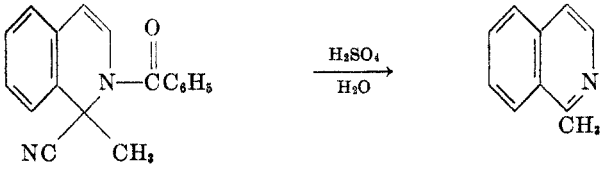
line (II). However, just as was found to be true in the case of quinaldine (5, 7), it was necessary to employ a large excess of 1-methylisoquinoline to obtain a satisfactory yield of II and avoid formation of the di-Mannich base. Since the difficulties of preparing and recovering sizeable quantities of 1-methylisoquinoline made this approach an exceedingly laborious one, alternate methods for the synthesis of 1-(β-dimethylaminoethyl)isoquinoline (II) were investigated.

One obvious alternative approach for the synthesis of II would be to substitute a suitable reagent for methyl iodide in the alkylation of Reissert's compound so that the Mannich base (II) would be produced directly instead of 1-methylisoquinoline. When this was tried, using β-chlorethyldimethylamine as alkylating agent, it was found that Reissert's compound (III) could be converted to 1-(β-dimethylaminoethyl)isoquinoline (II) in an over-all yield of 40%. As is typical of many alkylation reactions with Reissert's compounds (6), the intermediate alkylation product (IV) was obtained as a thick viscous oil and could not be isolated in a pure state. Instead, it was hydrolyzed directly with alkali to give the Mannich base (II). For purposes of characterization the methiodide derivative of the intermediate alkylation product (IV) was prepared.



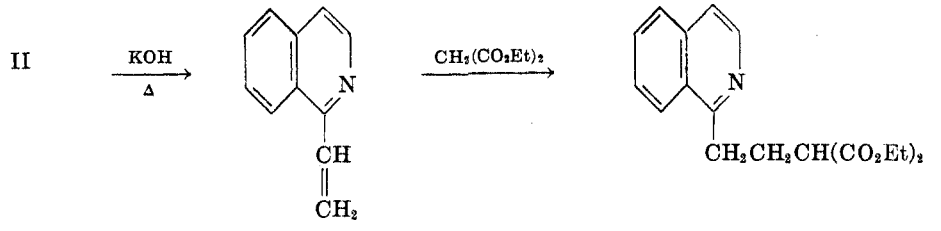
V VI

Since it is well known that Mannich bases are decomposed by heating with alkali, it was of interest to determine whether the hydrolysis of IV might be accomplished in better yield with aqueous acid than with aqueous base. Unfortunately this did not prove to be the case. However, in model studies testing the use of aqueous acid for hydrolyses of this type, it was shown that 2-benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline (V) could be hydrolyzed by 33% aqueous sulfuric acid to give 1-methylisoquinoline (VI) in 93% yield. This result is of interest because it contrasts sharply with the behavior of the unalkylated Reissert's compound. As was originally shown by Reissert (8, 9), the acid hydrolysis of 2-benzoyl-1-cyano-1,2-dihydroisoquinoline gives benzaldehyde and isoquinaldinic acid.[2]

During the distillation of 1-(β-dimethylaminoethyl)isoquinoline, it was observed that some dimethylamine was evolved and a polymeric residue remained in the still-pot. Since this was a good indication that 1-vinylisoquinoline was being formed during the distillation, ways of effecting a more complete conversion were investigated. The most useful method found was the distillation of 1-(β-dimethylaminoethyl)isoquinoline from powdered potassium hydroxide. In this way, 1-vinylisoquinoline was obtained in good yield as a clear mobile

[2] For the probable mechanism of this reaction, see ref. 10.

liquid which, in the absence of inhibitors, polymerized completely within a few hours. The conversion of II to 1-vinylisoquinoline was also accomplished through a Hofmann decomposition, but this was a more laborious procedure. To further identify the 1-vinylisoquinoline, it was hydrogenated to 1-ethylisoquinoline.



VII VIII

Both 1-(β-dimethylaminoethyl)isoquinoline and 1-vinylisoquinoline were investigated as possible alkylating agents for active methylene compounds. Of the two, 1-vinylisoquinoline proved to be the more satisfactory. The Michael addition of diethyl malonate to 1-vinylisoquinoline proceeded readily in the presence of sodium ethoxide to give VIII in 40% yield. Quite probably, this method could be further extended to give a series of 1-substituted isoquinoline derivatives similar to those previously obtained in the pyridine series.

EXPERIMENTAL[3]

1-(β-Dimethylaminoethyl)isoquinoline (II). (*A*) *By the Mannich reaction.* A solution containing 18.5 g. of dimethylamine hydrochloride and 22.0 ml. of formalin was added dropwise with stirring to 65.0 g. of 1-methylisoquinoline (6). After the heterogeneous reaction mixture was heated at 50° for one-half hour, it became homogeneous and was then allowed to cool. The mixture was diluted by the addition of 15 ml. of water and the unreacted 1-methylisoquinoline was removed by extraction with ether. When the aqueous layer was made basic, the oil which separated was taken up in ether and dried. After removal of the ether, the residue was distilled to give 20.0 g. (44%, based on dimethylamine hydrochloride) of a pale yellow oil, b.p. 136–139° at 4 mm.; n_D^{20} 1.5746. In addition there was present an appreciable quantity of higher-boiling material which is probably the di-Mannich base, 1,3-di-(dimethylamino)-2-(1′-isoquinolyl)propane. Due to the fact that dimethylamine was evolved during the distillation of 1-(β-dimethylaminoethyl)isoquinoline in each case, it was not possible to obtain a highly pure sample of the free base.

Anal. Calc'd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05.
Found: C, 76.37; H, 8.61.

The *methiodide* of *1-(β-dimethylaminoethyl)isoquinoline* was obtained after recrystallization from absolute ethanol as white crystals, m.p. 199–200° dec.

Anal. Calc'd for $C_{14}H_{19}IN_2$: C, 49.10; H, 5.65.
Found: C, 48.78; H, 6.00.

The *picrate* of *1-(β-dimethylaminoethyl)isoquinoline* was obtained after recrystallization from ethanol, as yellow crystals, m.p. 175–177°.

Anal. Calc'd for $C_{19}H_{19}N_5O_7$: C, 53.14; H, 4.46.
Found: C, 53.39; H, 4.77.

(*B*) *By the alkylation of Reissert's compound.* To a solution of 23.0 g. of 2-benzoyl-1-cyano-

[3] We are indebted to Miss Viola Williams for the microanalyses and to Mr. Gerrit Hospers for technical assistance. All melting points are corrected.

1,2-dihydroisoquinoline (9) in 200 ml. of benzene[4] maintained at 5° under an atmosphere of nitrogen, there was added dropwise with stirring 133 ml. of a 0.75 *M* ethereal solution of phenyllithium. To the deep red reaction mixture there was then slowly added 10.8 g. of β-chloroethyldimethylamine (11). After the mixture had slowly warmed to room temperature, it was heated at 70 to 80° for 5 hours. The reaction mixture was then cooled, 100 ml. of water was added and the organic layer was removed by extraction with ether. The ethereal solution was extracted in turn with three 50-ml. portions of 1 *N* hydrochloric acid. When the aqueous layer was made basic, an oil separated which was taken up in ether and dried. Concentration of the ethereal extract gave 20.0 g. of a crude red oil. This oil could not be distilled without decomposition and it did not crystallize, so it was subjected directly to alkaline hydrolysis. For purposes of characterization, the *methiodide* of *2-benzoyl-1-cyano-1-(β-dimethylaminoethyl)-1,2-dihydroisoquinoline* was prepared. This was obtained directly from the crude oil as white crystals, m.p. 224–225°, after recrystallization from absolute ethanol.

Anal. Calc'd for $C_{22}H_{24}IN_3O$: C, 55.96; H, 5.11.
Found: C, 56.26; H, 5.35.

A solution of 20.0 g. of the crude oil from the preceding experiment in 50 ml. of ethanol was added to a solution of 10.0 g. of potassium hydroxide in 100 ml. of water. The mixture was boiled under reflux for 30 minutes, cooled, and extracted three times with ether. The combined ethereal extracts were dried and then concentrated. Distillation of the residue gave 7.1 g. (40% yield based on 2-benzoyl-1-cyano-1,2-dihydroisoquinoline) of a pale yellow oil, b.p. 105° at 1 mm. This material was shown to be identical with the sample of 1-(β-dimethylaminoethyl)isoquinoline prepared in (*A*) by the preparation of the corresponding methiodide (m.p. 199° dec.) and picrate (m.p. 175–177°) derivatives. Also, the two samples of the methiodide derivatives were found to have identical infrared spectra. Attempts to effect this hydrolysis with aqueous acid as was done in the case of 2-benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline (see below) led only to tarry decomposition products.

Acid hydrolysis of 2-benzoyl-1-cyano-1-methyl-1,2-dihydroisoquinoline (V). A solution of 1.2 g. of compound V in 25 ml. of 33% aqueous sulfuric acid was boiled under reflux for 4 hours. During this period an appreciable quantity of benzoic acid sublimed out of the reaction mixture into the condenser. After the reaction mixture had cooled, the precipitated benzoic acid was removed and the filtrate was made basic with sodium carbonate. The yellow oil which separated was extracted with ether, dried, and converted to the corresponding picrate derivative. This gave 1.4 g. (93%) of yellow crystals, m.p. 226–230°. Admixture of an authentic sample of 1-methylisoquinoline picrate (m.p. 229–232°) gave no depression of melting point.

1-Vinylisoquinoline (VII). A 7.0-g. sample of 1-(β-dimethylaminoethyl)isoquinoline was slowly distilled from a mixture of 0.5 g. of powdered potassium hydroxide and a trace of N-phenyl-β-naphthylamine under reduced pressure. Redistillation of the product gave 3.8 g. (70%) of a colorless oil; b.p. 95–97° at 1 mm., n_D^{20} 1.6312.

Anal. Calc'd for $C_{11}H_9N$: C, 85.13; H, 5.84; N, 9.03.
Found: C, 84.89; H, 5.70; N, 9.17.

The *picrate* of *1-vinylisoquinoline* was prepared in ethanol and was obtained, after recrystallization from the same solvent, as yellow crystals, m.p. 154–156°.

Anal. Calc'd for $C_{17}H_{12}N_4O_7$: C, 53.15; H, 3.15.
Found: C, 53.44; H, 3.04.

When a solution of the methiodide of 1-(β-dimethylaminoethyl)isoquinoline in methanol was passed over an ion-exchange column (Amberlite IRA-400, previously treated with aqueous sodium hydroxide), the methanol eluate became warm. Treatment of this with methanolic picric acid gave yellow crystals, m.p. 155°. Admixture of the picrate of 1-vinylisoquinoline from the preceding experiment gave no depression of melting point. In view of the simplicity of the distillation procedure for preparing 1-vinylisoquinoline, the Hofmann decomposition of 1-(β-dimethylaminoethyl)isoquinoline was not further investigated.

[4] Benzene was employed as solvent rather than dioxane, since β-chloroethyldimethylamine was stable in benzene but rapidly polymerized when it was dissolved in dioxane.

Hydrogenation of 1-vinylisoquinoline. A solution of 4.5 g. of 1-vinylisoquinoline (VII) in 20 ml. of absolute ethanol was subjected to hydrogenation in the presence of Adams catalyst at room temperature and 3 atm. pressure of hydrogen. When hydrogen absorption was complete, the catalyst and solvent were removed, and the residual oil was distilled. This gave 4.2 g. (90%) of a light yellow oil; b.p. 105° at 1.2 mm., n_D^{20} 1.6002. Evidence that the product was 1-ethylisoquinoline was obtained through the preparation of the corresponding picrate derivative which, after recrystallization from ethanol, was obtained as yellow crystals, m.p. 208–210° [Bergstrom and McAllister (12) give 207–210° as the m.p. for the picrate derivative of 1-ethylisoquinoline].

Diethyl β-(1-isoquinolyl)ethylmalonate (VIII). To a boiling mixture of 15.5 g. of diethyl malonate and 0.5 g. of sodium ethoxide in 10 ml. of absolute ethanol there was added dropwise a solution of 3.8 g. of 1-vinylisoquinoline in 10 ml. of absolute ethanol. After the mixture had boiled under reflux for 2 hours, it was concentrated under reduced pressure, taken up in ether, and extracted with dilute hydrochloric acid. The aqueous layer was separated, made basic with aqueous sodium hydroxide, and extracted with ether. After the ethereal extract had been dried, it was concentrated and the residual oil was distilled. This gave 2.6 g. (40%) of a pale yellow oil; b.p. 140° at 1.5 mm., n_D^{20} 1.5390.

Anal. Calc'd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71.

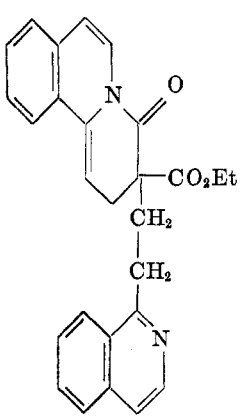
Found: C, 68.31; H, 6.75.

The picrate of diethyl β-(1-isoquinolyl)ethylmalonate was obtained from ethanol as yellow crystals, m.p. 188–190°.

Anal. Calc'd for $C_{24}H_{24}N_4O_{11}$: C, 52.94; H, 4.46.

Found: C, 52.78; H, 4.70.

Attempted alkylation of diethyl malonate with 1-(β-dimethylaminoethyl)isoquinoline methiodide. The procedure followed was essentially that described by Snyder and Smith (13) for the alkylation of ethyl acetaminomalonate with gramine methiodide. A mixture of 0.17 g. of powdered sodium and 1.25 g. of diethyl malonate in 100 ml. of dry dioxane was heated at 95° until formation of the sodium salt appeared complete (11 hours). To the resulting light yellow suspension there was added 2.42 g. of the methiodide of 1-(β-dimethylaminoethyl)isoquinoline (II), and the mixture was heated at 120° for 19 hours with stirring. Finally, the reaction mixture was heated at 130° for another 3 hours. After removal of the inorganic precipitate, the dioxane solution was concentrated under reduced pressure to give a dark red oil. Trituration of this oil with ethyl acetate yielded 0.55 g. (33%) of a light yellow solid, m.p. 206–209°. When this was converted to the corresponding picrate derivative for purification, it became apparent that this was not the desired product (II). The composition and molecular weight of the picrate derivative strongly suggest that this product has structure IX (See below). However, no further work was done to confirm this in view of the successful alkylation of diethyl malonate using 1-vinylisoquinoline.



IX

The *picrate* of IX(?) was obtained from ethanol as glistening yellow crystals, m.p. 200–202°.

Anal. Calc'd for $C_{33}H_{27}N_5O_{10}$: C, 60.64; H, 4.16; Mol. wt., 653.6.
Found: C, 60.30; H, 3.86; Mol. wt. [by the spectrophotometric method (14)]: 655.8.

SUMMARY

The synthesis of 1-(β-dimethylaminoethyl)isoquinoline has been accomplished both through the Mannich reaction with 1-methylisoquinoline and by the alkylation of Reissert's compound. 1-Vinylisoquinoline has been prepared from this intermediate and has been shown to be a useful reagent for condensations of the Michael type.

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