[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

THE PREPARATION OF 2-ALKYL AND 2-ARYL PYRIDINES AND QUINOLINES BY THE GRIGNARD REACTION[1] (PRELIMINARY)

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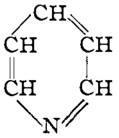
Introduction

Franklin and Strain[2] have pointed out, as a logical result of the known similarities between water and ammonia, that substances containing the grouping —CH=N— may be regarded as aldehydes of an ammonia system, comparable with aldehydes of the water system, which contain the analogous grouping, —CHO. The Schiff bases, of which benzalaniline, $C_6H_5CH{=}NC_6H_5$, is the simplest aromatic representative, are thus found to possess very distinct aldehydic properties.[3]

If the Körner formula of pyridine, , is correct—or potentially so—there is present the same—CH=N—group that occurs in the Schiff bases and is characteristic of aldehydes of the ammonia system. Furthermore, pyridine and all substances containing a pyridine nucleus also partake of the nature of acetals, since one valence of the nitrogen is attached to one side of a closed ring. Hence pyridine, quinoline and isoquinoline can be regarded in a formal sense as cyclic ammono aldehyde acetals.[4] Nevertheless, the aldehydic properties one might expect these substances to show are subordinated because of the remarkable stability of the six-membered ring with alternate double and single bonds.[5] Thus, pyridine is not appreciably oxidized by hot concentrated sulfuric or nitric acid. Quinoline may be oxidized to quinolinic acid by potassium permanganate in alkaline solution with the destruction of the benzene ring.

However, if the stability of the pyridine ring of quinoline be diminished by the destruction of one of the double bonds in this ring, the aldehydic character of the molecule becomes pronounced. The rupture of this

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[1] A portion of the theory was presented by one of us (F. W. B.) at the Swampscott meeting of the American Chemical Society, September, 1928, and at the Pomona meeting of the American Association for the Advancement of Science, June, 1928 (with H. M. Leicester and D. N. Benton).

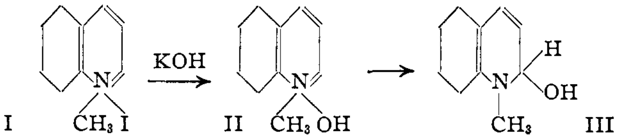
[2] (a) Franklin, THIS JOURNAL, **46**, 2150 (1924); (b) Strain, *ibid.*, **49**, 1558 (1927).

[3] Ref. 2b, p. 1559; Busch, *Ber.*, **37**, 2691 (1904); *ibid.*, **38**, 1761 (1905); Miller and Plöchl, *ibid.*, **25**, 2020 (1892).

[4] A substance which combines in this manner the characteristics of an aldehyde and of an acetal is unknown in the water system, because oxygen is divalent while nitrogen is trivalent.

[5] Compare the difference in properties between the stable and relatively saturated benzene and the typically unsaturated cyclohexadiene.

double bond may be accomplished by adding methyl alcohol to the —CH=N— group of quinoline, in accordance with the equation[6]



Since this process, in so far as the final results are concerned, is clearly analogous to the addition of alcohol to chloral to form chloral alcoholate, we can look upon III, 1-methyl-2-hydroxy-1,2-dihydroquinoline, as an aldehyde alcoholate related at the same time to the water and ammonia systems. The 1-alkyl-2-hydroxy-1,2-dihydroquinolines, like the aldehyde alcoholates, undergo many aldehydic reaction with ease.[6] Because of this it is not unreasonable to believe that several reactions of pyridine, quinoline and isoquinoline themselves may have their counterpart in corresponding reactions of the familiar aquo aldehydes. Thus, Oddo[7] found that 2-phenylquinoline was formed by heating quinoline, or a mixture of quinoline and pyridine with benzene, phenyl bromide and magnesium. Since he was not primarily concerned with the preparation of 2-aryl quinolines, and since his yield of 2-phenylquinoline was undoubtedly low, it was thought worth while to repeat his experiments and to extend them in an attempt to prepare other alkyl pyridines and quinolines. Such an investigation, if successful, would support the view that the —CH=N— group is aldehydic in character, or potentially so, even though it may be present in a stable six-membered ring.

Preliminary Experiments

A number of attempts were made to obtain 2-phenylquinoline by heating quinoline for about two hours with solutions of an excess of phenylmagnesium bromide in boiling diethyl ether, benzene, toluene, xylene or diamyl ether.[8,9] In diethyl ether no reaction occurred other than the formation of the known addition compound,[10] which yields unchanged quinoline on hydrolysis. Large quantities of a viscous tar were formed in the other solvents, together with small amounts of 2-phenylquinoline. Much better results were obtained by autoclaving pyridine, quinoline or isoquinoline with the Grignard reagent in diethyl ether solution at 150–160°.

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[6] (a) Decker, *Ber.*, **25**, 443, 3326 (1892); Decker and Becker, *Ann.*, **395**, 374 (1913); (b) Decker and Kaufmann, *J. prakt. Chem.*, **84**, [N. F.] 241 (1911).

[7] Oddo, *Atti accad. Lincei*, [V] **16**, 538 (1907).

[8] The diamyl ether was presented to us by the Sharples Solvents Corporation.

[9] Gilman, Kirby and Kinney have recently added the Grignard reagent under forced conditions to the —CH=N— group of certain Schiff bases in toluene solution [THIS JOURNAL, **51**, 2252 (1929)]. This addition often takes place without forcing. See Busch, Ref. 3.

[10] Sachs and Sachs, *Ber.*, **37**, 3088 (1904); Oddo, Ref. 7.

The Reaction of Pyridine, Quinoline and Isoquinoline with the Grignard Reagent

The autoclave in which the reactions were carried out was made from a two-foot length of seamless steel tubing, two inches in internal diameter. Into one end was welded a steel plug which took externally the form of an hexagonal nut. The hexagonal screwed top of the autoclave was jacketed and water-cooled for the purpose of keeping the lead gasket in the head cool and thus insuring absolute tightness. The general method of preparing 2-alkyl or 2-aryl pyridines and quinolines may best be illustrated by the preparation of 2-phenylquinoline.

Phenylmagnesium bromide was prepared in the usual manner from 78 g. of phenylbromide, 150 cc. of anhydrous diethyl ether and an excess of magnesium shavings in a pyrex tube fitting snugly into the interior of the autoclave. To this solution was added 52 g. of quinoline in 100 cc. of ether. A white flocculent precipitate of the addition compound of quinoline and phenylmagnesium bromide was formed. The space in the pyrex tube above the ether solution was filled with nitrogen, the tube placed in the autoclave and the head screwed on while the hexagonal nut at the bottom was held in a suitable vise. The autoclave was heated over its full length in an upright electric furnace for three hours at 150–160° (temperature of the furnace). The ethereal solution after heating was a dark red and the reaction vessel contained some ether-insoluble tar. The Grignard addition compound was decomposed with an aqueous solution of ammonium chloride. During this decomposition hydrogen was given off, but in much less than the expected quantity. The ether layer was separated, the water was extracted with an additional quantity of ether and the combined ethereal solutions distilled. The 2-phenylquinoline was contained in the portion boiling between 310 and 330° at atmospheric pressure. The solidified distillate after one crystallization from 70% alcohol weighed 55 g., melted at 78.5° and was therefore crude 2-phenylquinoline, which melts when pure at 83.5°. Light yellow needles having this melting point were obtained after several crystallizations from 70% alcohol. The mixed melting point of this product with known 2-phenylquinoline prepared from cinnamic aldehyde and aniline[10a] was 83.5°; yield of the crude product, 66%.

The yield of 2-phenylquinoline was diminished if too small a quantity of solvent ether was used or if the particles of unused magnesium were allowed to remain in the reaction vessel. In some experiments, therefore, magnesium in a copper basket was suspended in the ethereal solution of the alkyl or aryl halide, the basket being withdrawn together with the unchanged magnesium, after the formation of the Grignard reagent.

In the following experiments a solution of 30–40% excess of the appropriate Grignard reagent in about 150 cc. of anhydrous ether was heated with pyridine or isoquinoline for three hours at 150–160°. A smaller autoclave about one inch in internal diameter served as pressure vessel. The ethereal solutions after heating were colored a dark red or violet and some tar was found in the bottom of the reaction tube. This mixture was hydrolyzed with an aqueous solution of ammonium chloride, the ethereal layer and the ethereal extracts of the aqueous phase were distilled and the fraction of proper boiling point was saved as the product.

2-Phenylpyridine was prepared in 44% yield from 43 g. of phenyl bromide[11] and 16 g. of pyridine; b. p. 270–272° at 760 mm., uncorr.; m. p. of picrate, 169–170°, un-

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[10a] Grimaux, *Compt. rend.*, **96**, 584 (1883).

[11] An excess of magnesium was used in the formation of the Grignard reagent to avoid the presence of free phenyl bromide or ethyl bromide.

corr. (m. p. given in literature, 169–170° uncorr.); nitrogen in the picrate, Dumas, 14.6. Calcd. for $C_{17}H_{12}N_4O_7$: N, 14.5.

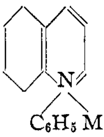
2-Ethylpyridine was prepared in 45% yield from 30 g. of ethyl bromide[11] and 16 g. of pyridine; b. p. 148–150° at 760 mm. The picrate melted at 187–189°, uncorr. Nitrogen in the picrate, Dumas, 16.5. Calcd. for $C_{13}H_{12}N_4O_7$: N, 16.6. Gold chloride double salt, m. p. 120° (m. p. 120°, according to the literature); yield, 45% of the theoretical.

1-Ethylisoquinoline.—B. p. 250°, uncorr., at 760 mm.; light yellow oil of pleasant odor, insoluble in water, but soluble in ether and alcohol; heavier than water; m. p. of picrate, 207–210°, uncorr.; m. p. of $PtCl_4$ double salt, 199–200°, uncorr.; m. p. of gold chloride double salt, 168–172°, uncorr. Calcd. for $C_{11}H_{11}N \cdot HCl \cdot AuCl_3$: Au, 36.6. Found: Au, 40.0. 0.1801 g. of the free base gave 14.2 cc. of nitrogen at 21.5° and 765 mm.; 0.2008 g. gave 16.9 cc. of nitrogen at 25.5° and 765 mm. (Dumas). Nitrogen: 9.0, 9.4. Calcd. for $C_{11}H_{11}N$: N, 9.0. Since the melting point of 3-ethylisoquinoline picrate is 171–173°, of 3-ethylisoquinoline gold chloride is 115–117°, and since 4-ethylisoquinoline is a solid melting at 62°, the present preparation must be 1-ethylisoquinoline; yield, 66% of the theoretical [from 32 g. of ethyl bromide[11] and 28 g. of isoquinoline].

Other Reactions.—Ethylmagnesium bromide reacts with nicotine and cinchonine in diethyl ether at 150°. The products of the reaction with cinchonine are a trifle tarry and have not as yet been identified. Nicotine appears to be converted in some measure to an ethylnicotine, but there is a simultaneous reduction to a base having a piperidine-like odor. 2-Picoline and quinaldine also react with ethylmagnesium bromide under the same conditions, but the products have not been definitely identified. The product of the reaction of 4,4'-dipyridyl, a dicyclic ammono dialdehyde-acetal, and ethylmagnesium bromide in diamyl ether solution at 160° is largely a tar. 2-Phenyl pyridine and 2-ethyl pyridine were formed in poor yield in diamyl ether solution at 150°.

Discussion

In all of the reactions described in this paper, the Grignard reagent first forms with pyridine, quinoline or isoquinoline a precipitate of an addition compound that is only sparingly soluble in ether. These addition compounds[10] are supposed to have the structure of a substituted ammonium salt I. Under the influence of heat, the phenyl group of I migrates to the adjacent carbon atom to give II. As a net result the Grignard reagent has been added to the potentially aldehydic —CH=N— group in the expected manner, that is, with the —MgBr group seeking the nitrogen just as it seeks the oxygen of an aquo aldehyde. The conversion of II into 2-phenylquinoline probably takes the course



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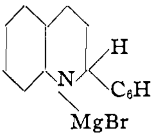
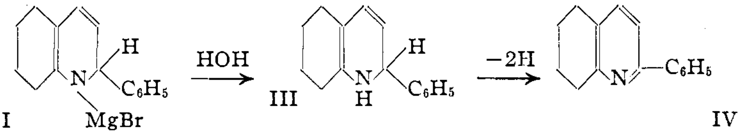


II



The loss of hydrogen from compound III finds its counterpart in the loss of hydrogen from the dihydroquinolines that probably appear as intermediate products in the Döbner–Miller quinaldine synthesis.[12] The dihydropyri-

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[12] Döbner and Miller, *Ber.*, **16**, 2465 (1883).

dines resulting from the action of ammonia on aldehydes likewise lose hydrogen and pass into the corresponding pyridines.[13] The hydrogen resulting from the conversion of III into IV above always fell considerably below the amount theoretically expected. Perhaps some of this hydrogen was utilized in forming reduction products, and some of the dihydro bases (III) may have been polymerized to a tar, without loss of hydrogen.

β- and γ-substituted pyridines and quinolines were not isolated in the present work, although it is posible that they are formed in small quantity. The migration of the alkyl or aryl group of formula I from nitrogen to the 2-carbon then does not strictly follow the migration of an alkyl group from nitrogen to the 2 and 4 carbons in the Ladenburg synthesis of alkyl pyridines and quinolines.[14]

Summary

1. Pyridine, quinoline and isoquinoline react with the Grignard reagent in diethyl ether solution at 150–160° to form α-alkyl or aryl pyridines, quinolines or isoquinolines in yields varying between 44 and 66% of the theoretical.

2. The following compounds have been prepared: 2-ethylpyridine, 2-phenylpyridine, 2-phenylquinoline and 1-ethylisoquinoline. 1-Ethylisoquinoline has been prepared for the first time.

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CELLULOSE SULFONIC ACID ESTER

BY E. GEBAUER-FUELNEGG AND OTTO DINGLER

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In a preliminary report[1] the formation of a trisulfonic acid ester derived from cellulose was reported. This compound was obtained by the action of chlorosulfonic acid in an excess of pyridine on cellulose (pure filter paper or cotton). Data were given as to its formation, general properties and analysis.[2] It was found that films and threads can be formed from this ester and its salts.

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[13] Chichibabin, *J. prakt. Chem.*, **107**, [N. F.] 122 (1924).

[14] Ladenburg, *Ber.*, **32**, 42 (1899); **16**, 1410, 2059 (1883).

[1] Gebauer-Fuelnegg, Stevens and Dingler, *ibid.*, **61**, 2000 (1928).

[2] In the first report the statement has been made that a second treatment of cellulose-trisulfonic acid ester with the pyridine chlorosulfonic acid reagent will give a purer substance and complete the triesterification. We were unable to repeat the results of the respective preliminary experiments, from which the figures have been taken. On the contrary, it was found that under certain circumstances one SO_3H group is eliminated by this procedure. We will report on this reaction later.