6. Shun'ichi Yamada and Ichiro Chibata: Application of Ion Exchangers in Organic Reactions. V.[1] Application to the Friedländer Quinoline Synthesis.*

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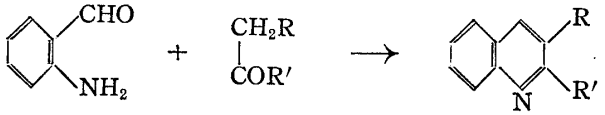
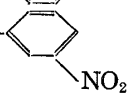
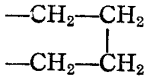
In the previous papers[1] on the application of ion exchangers to organic reactions, it has been shown that the ion exchangers are effective and convenient catalysts for several organic reactions. In this paper the results of the application of anion exchange resins to the Friedländer quinoline synthesis are presented.

The synthesis of quinolines by condensation between *o*-aminobenzaldehyde and a carbonyl compound containing an active methylene group α to the carbonyl group is known as Friedländer's method. The method is of considerable importance for the preparation of quinolines substituted in the pyridine portion, in view of the wide variety of carbonyl compounds that undergo the condensation. Although the reaction is usually carried out in aqueous medium by employing alkali hydroxide as a condensing agent, *o*-aminobenzaldehyde is sparingly soluble in water and in some cases undesirable side reaction of the carbonyl compound occurs by the use of caustic alkali. In order to avoid these disadvantages, the procedure which employs piperidine as a catalyst and alcohol as a solvent was reported by Stark.[2] The use of anion exchangers for the reaction instead of conventional catalysts produced quite satisfactory results. The anion exchangers employed for this study were strong-base anion exchange resins such as Amberlite IRA-400 and Dowex-2. The resins were converted to the hydroxide form before use by regeneration with aqueous sodium hydroxide and were then rinsed free of excess alkali with deionized water and alcohol.

When *o*-aminobenzaldehyde and theoretical or slightly excess amount of carbonyl compound such as ethyl acetoacetate, acetylacetone, acetophenone, *m*-nitroacetophenone, or cyclohexanone were heated with the anion exchangers in alcohol or aqueous alcohol, conversion to the corresponding quinolines readily took place. As the resins are prac-

Table I. Friedländer Quinoline Synthesis



R	R′	Resin	Yield (%)	Other condensing agents	
				Catalyst	Yield†
$-COOC_2H_5$	$-CH_3$	Amberlite IRA-400	89.0	NaOH	85.7
$-COCH_3$	$-CH_3$	Dowex-2	69.3	Piperidine	67.5
—H		Amberlite IRA-400	47.3	NaOH	59.2
—H		Amberlite IRA-400	81.0		
		Amberlite IRA-400	91.8	NaOH	83.2

† Yield based on the results obtained by the authors.

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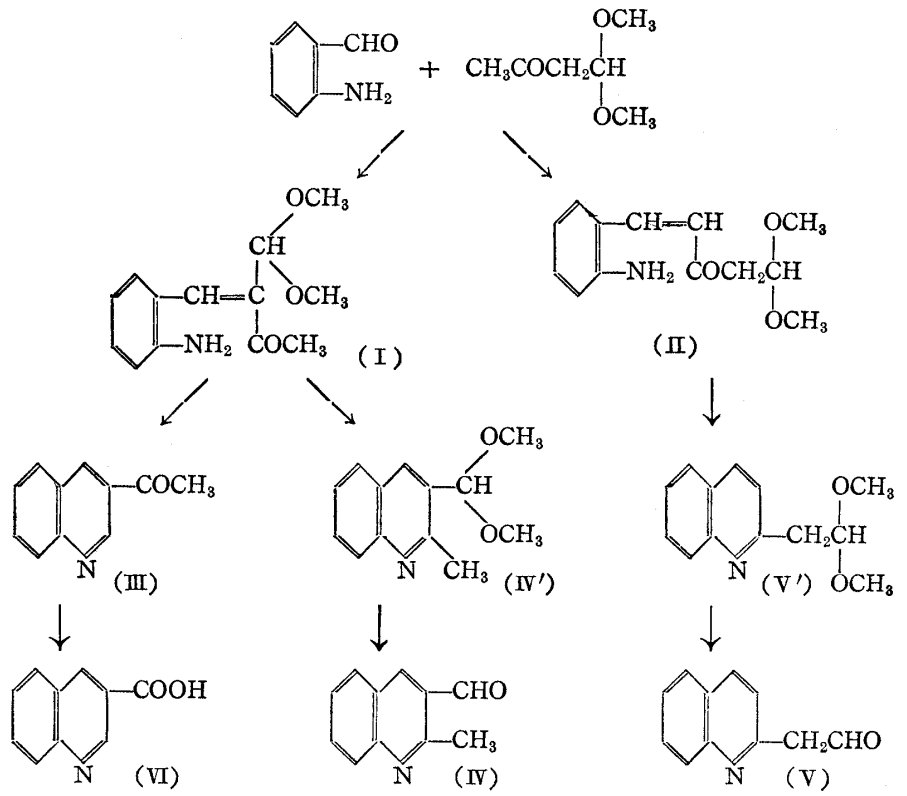
1) S. Yamada, I. Chibata, R. Tsurui: This Bulletin, **2**, 62(1954).
2) O. Stark: Ber., **40**, 3425(1907).

tically insoluble in the solvent and the products, the used resins were recovered by filtration after completion of the reaction and could be used for subsequent run with or without regeneration. The quinoline derivatives were easily obtained in good yields by direct vacuum distillation of the filtrate or by diluting the filtrate with water. The results obtained in this work are summarized in Table I.

Furthermore, this method was extended to the condensation between *o*-aminobenzaldehyde and *β*-keto-acetal such as formylacetone dimethylacetal. The reaction was carried out by the general procedure described above. The concentration of the filtrate of the reaction mixture left no crystalline substance but an orange-colored oily substance. This oil was treated with hydrochloric acid and neutralized. Recrystallization of the resulting precipitate yielded colorless crystals which were considered to be a quinoline derivative. Comparative study of the phenylhydrazones of the oil and crystalline product revealed that the former immediately decolorized the acetone solution of potassium permanganate indicating the presence of a double bond and showed positive diazo reaction for primary aromatic amines, but the latter was negative to these tests. It would appear, therefore, that the structure of the oily intermediate is not a cyclized product such as the acetal of 2-methylquinoline-3-aldehyde (IV′) or of 2-quinolylacetaldehyde (V′) but must be either *β*-(*o*-aminophenyl)-*α*-acetylacralaldehyde dimethylacetal (I) or *o*-aminocinnamoylacetaldehyde dimethylacetal (II).

3-Acetylquinoline (III), 2-methylquinoline-3-aldehyde (IV), and 2-quinolylacetaldehyde (V) are the theoretically possible structures for the quinoline derivative obtained by the condensation, depending on the course of the cyclization, as shown in the schema. Although (III) and (V) are known compounds, and their characteristics and properties



have been reported, there is no recognizable difference between the compounds except the melting points of the semicarbazones. There has been no description in the literatures for 2-methylquinoline-3-aldehyde (IV). In order to determine the structure of the product from these three structures the following studies were carried out. Investigations

on the infrared spectrum of the product, melting point of the semicarbazone prepared from the product, and the detection of a methyl ketone by color reaction supported the belief that the product must be (III). For further identification of this structure, the authors carried out the oxidation of the product with alkaline permanganate solution and were able to isolate quinoline-3-carboxylic acid (VI), which could only have resulted from the oxidation of (III) among the possible three quinoline derivatives. This offers further confirmatory evidence for the structure of the product as (III). Consequently, the structure of the oily intermediate is considered as (I).

The Friedländer ring closure involves two distinct reactions: (1) Schiff base formation between amino group of the *o*-aminobenzaldehyde and the carbonyl group of another reagent, and (2) an internal condensation between the aryl aldehyde group and the active methylene group of the carbonyl compound. In practice, however, quinoline is obtained directly from the reaction mixture without the isolation of the intermediate product of the initial reaction. It is of interest that in the Friedländer condensation between *o*-aminobenzaldehyde and *β*-keto-acetal such as formylacetone dimethylacetal, the reaction does not proceed to the quinoline derivative in the presence of a basic catalyst but stays at the formation of the intermediate (I). The ring closure, conversion into 3-acetylquinoline, is accomplished by the subsequent acid treatment of the above intermediate.

Judging from results obtained, the use of anion exchangers as a condensing agent for the Friedländer quinoline synthesis is practical, convenient, and simplifies the procedures.

The authors are grateful to Prof. Sugasawa and Dr. Fujisawa, Director of the Laboratory, for their helpful advices and encouragements during the course of this work.

Experimental

Ethyl 2-Methylquinoline-3-carboxylate—To a solution of *o*-aminobenzaldehyde (0.5 g.) and ethyl acetoacetate (1.5 g.) in EtOH (10 cc.) was added Amberlite IRA-400 (0.5 cc.). The reaction mixture was heated with stirring for 2 hrs. at 40~50°, and further refluxed for 30 mins. to complete the reaction. The resin was filtered off and washed with EtOH. To the hot combined solution of the filtrate and washings, water was added, cooled, and the separated crystals were collected; yield, 0.95 g. (89.0%), m.p. 68~71°. Recrystallization from aq. EtOH gave colorless pillars, m.p. 71~72°. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.16; H, 6.40; N, 6.35.

2-Methyl-3-acetylquinoline—A mixture of *o*-aminobenzaldehyde (0.44 g.), acetylacetone (0.40 g.), Dowex-2 (0.5 cc.), and EtOH (8 cc.) was refluxed under stirring for 4 hrs. After removing the resin by filtration, the filtrate was poured into ice water and the separated needles were collected; yield, 0.51 g. (69.3%). After recrystallization from ligroine it melted at 79~80°. *Anal.* Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.12; H, 6.16; N, 7.71.

Semicarbazone: Colorless needles from aq. EtOH, m.p. 208~210°.

2-Phenylquinoline—Amberlite IRA-400 (0.5 cc.) was added to a solution of *o*-aminobenzaldehyde (0.5 g.) and acetophenone (0.7 g.) in EtOH (5 cc.). The mixture was refluxed while stirring for 3.5 hrs., and was filtered to remove the resin. Addition of water and chilling gave pale yellow needles, m.p. 82~83.5°. Yield, 0.4 g. (47.3%).

Picrate: Yellow prisms from EtOH, m.p. 191~192°. *Anal.* Calcd. for $C_{21}H_{14}O_7N_4$: C, 58.07; H, 3.25; N, 12.90. Found: C, 58.56; H, 3.25; N, 12.50.

2-(3-Nitorophenyl)quinoline—A solution of *o*-aminobenzaldehyde (0.48 g.) and *m*-nitroacetophenone (0.78 g.) in EtOH (10 cc.) was refluxed for 5 hrs. under vigorous stirring in the presence of a small amount of Amberlite IRA-400. The resin was removed by filtration after completion of the reaction. The filtrate was decolorized, treated with water, and cooled. The resulting crystals, m.p. 122~124°, were collected; yield, 0.8 g. (81.0%). Crystallization from EtOH gave colorless needles which melted at 124°. *Anal.* Calcd. for $C_{15}H_{10}O_2N_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 72.51; H, 4.19; N, 11.12.

Picrate: Yellow prisms from EtOH, m.p. 182°, with previous softening.

1,2,3,4-Tetrahydroacridine—A mixture of *o*-aminobenzaldehyde (1.8 g.), cyclohexanone (2.0 g.), EtOH (15 cc.), and Amberlite IRA-400 (0.5 cc.) was refluxed with stirring for 4 hrs. The reaction mixture was filtered to remove the resin, and EtOH was removed from the filtrate. On fractional distillation of the residue, after little amount of a forerunner, the main fraction came over at 180~

180.5°(15~15.5 mm. Hg), 2.5 g. (91.8%), which readily crystallized on standing, m.p. 54°.

Picrate : Yellow plates, m.p. 217~218°(decomp., with previous browning). *Anal.* Calcd. for $C_{19}H_{16}O_7N_4$: C, 53.34; H, 3.91; N, 13.59. Found : C, 55.60; H, 4.10; N, 13.18.

3-Acetylquinoline—Amberlite IRA-400 (1 cc.) was added to a solution of formylacetone dimethylacetal (6.3 g.) and *o*-aminobenzaldehyde (4.8 g.) in MeOH (30 cc.). The reaction mixture was refluxed with stirring for 4 hrs. and filtered to remove the ion exchanger. Evaporation of a portion of the filtrate at reduced pressure gave an orange colored oil. Attempts to crystallize the oily substance were unsuccessful. A portion of the filtrate was treated with phenylhydrazine in the presence of AcOH and formed crystals considered to be β-(*o*-aminophenyl)-α-acetylacralaldehyde phenylhydrazone. Several crystallizations from MeOH produced pale yellow plates, m.p. 225~226°. *Anal.* Calcd. for $C_{23}H_{23}N_3$: C, 74.77; H, 6.28; N, 18.96. Found : C, 74.26; H, 6.24; N, 19.31. The phenylhydrazone gives positive diazo reaction and decolorizes an acetone solution of $KMnO_4$.

The remaining filtered reaction mixture was heated on a steam bath with 10% HCl (10 cc.) for 20 mins. During the reaction, the color of the solution turned from orange to red. It was cooled and made slightly alkaline with $NaHCO_3$ solution. The separated reddish brown solid was collected, recrystallized from aq. MeOH, and yielded colorless needles which proved to be 3-acetylquinoline, m.p. 97~101°; yield 51.2%. The analytical sample melted at 101~103°. *Anal.* Calcd. for $C_{11}H_9ON$: C, 77.17; H, 5.30; N, 8.18. Found : C, 77.00; H, 5.45; N, 8.07. Several derivatives of the product were prepared for characterization.

Phenylhydrazone : Yellow prisms from EtOH, m.p. 195~197°. Mixed m.p. with the phenylhydrazone of the intermediate depressed to around 180°. *Anal.* Calcd. for $C_{17}H_5N_3$: C, 78.13; H, 5.79; N, 16.08. Found : C, 77.52; H, 5.78; N, 16.34.

Semicarbazone : White silky needles from EtOH, m.p. 236~236.5°. *Anal.* Calcd. for $C_{12}H_{12}ON_4$: C, 63.14; H, 5.30; N, 24.55. Found : C, 63.44; H, 5.20; N, 24.72.

Picrate : Yellow leaflets from dioxane, m.p. 215~215.5°(decomp.). *Anal* Calcd. for $C_{17}H_{12}O_8N_4$: C, 51.00; H, 3.02; N, 14.00. Found : C, 51.29; H, 2.83; N, 14.16.

Oxidation of the product was also carried out by employing $KMnO_4$ in aq. alkaline medium. After the removal of MnO_2 from the reaction mixture, neutralization of the filtrate and concentration gave white minute crystals of quinoline-3-carboxylic acid, m.p. 274~275°(decomp.) after crystallization from EtOH. *Anal.* Calcd. for $C_{10}H_7O_2N$: C, 69.36; H, 4.07; N, 8.09. Found : C, 69.64; H, 4.09; N, 8.31.

Picrate : Yellow needles from EtOH, m.p. 214~216°(decomp., with previous softening).

Summary

The Friedländer quinoline synthesis was carried out by employing anion exchange resins as a condensation agent. As a result, anion exchangers were found to be an effective and convenient catalyst for this reaction. The method was also extended to the condensation between formylacetone dimethylacetal and *o*-aminobenzaldehyde, and the product was identified as 3-acetylquinoline.

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