4. Shun'ichi Yamada, Ichiro Chibata, and Ryoya Tsurui: Application of Ion Exchangers in Organic Reactions. I. Application to the Fischer Indole Synthesis.

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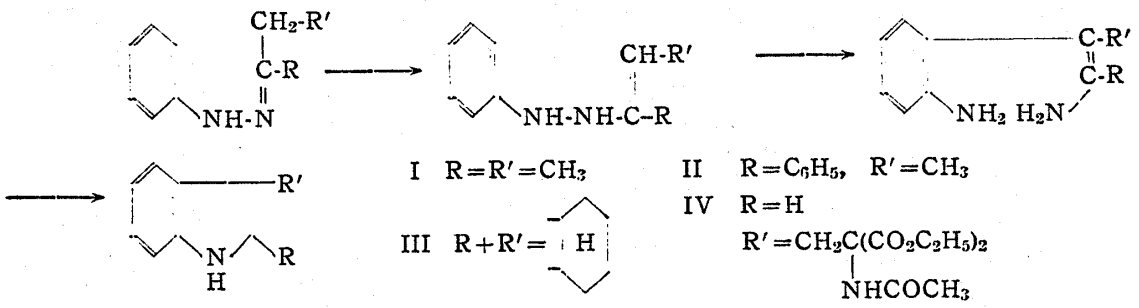
In the course of our studies on the application of ion exchangers to organic reactions, several interesting results were obtained, a part of which has been already published.[1]

Since the discovery of synthetic organic ion exchange resins, a rapid progress in their utilization has been made and they have become quite popular tools in various fields. An interesting application is the use of ion exchangers as catalysts for organic reactions. During the war years, German chemists discovered the usefulness of cation exchangers as a catalyst for esterification. Later, Sussman[2] and others extended the application to acetal synthesis, hydrolysis, sucrose inversion, etc. This paper presents the results of the application of ion exchangers as condensing agent for the Fischer indole synthesis.

Mechanism of the Fischer indole synthesis, cyclization of phenylhydrazone of carbonyl compounds into indole derivatives, is considered to proceed through hydrazo compound, *o*-benzidine type rearrangement, and release of ammonia as follows:



As condensing agents for this ring-closure, metallic chlorides, alcoholic hydrogen chloride, sulfuric acid, and recently, boron trifluoride have been employed. Instead of these conventional catalysts, the use of ion exchangers for the reaction gave quite satisfactory results so far as our experiments were concerned. That is, when the phenylhydrazones of methyl ethyl ketone, propiophenone, cyclohexanone, and *r*-acetamido-*r*,*r*-dicarbethoxy-butyraldehyde were respectively heated in the presence of a cation exchanger, conversion into 2,3-dimethylindole, 2-phenyl-3-methylindole, 1,2,3,4-tetrahydrocarbazole, and ethyl α-acetamido-α-carbethoxy-β-(3-indole)-propionate, respectively, readily took place and in a good yield. The only exception was acetone phenylhydrazone, whose conversion into 2-methylindole was not successful by this method.

The cation exchangers used for the present investigation were nuclear sulfonic acid resin (Amberlite IR-120) and phenolic sulfonic acid resin (Diaion K), the latter having given poor yield. All resins were converted to the hydrogen form before use by regeneration with 5% sulfuric acid and were then rinsed free of acid with deionized water. Excess water was removed by suction. The used resins could be re-used for successive runs after regeneration. In the present work, water and aqueous alcohol were used as solvents and satisfactory results were obtained. Toluene was less satisfactory for this reaction. The

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1) The 72nd Annual Meeting of the Pharmaceutical Society of Japan, at Osaka, May 1, 1952.

2) S. Sussman : Ind. Eng. Chem., 38, 1227 (1946).

use of aqueous alcohol permits simplified procedure, namely, after completion of the reaction, cation exchangers are filtered off, and the filtrate gives the cyclized product on cooling. Furthermore, generally pure products are obtained by this mothod. Accordingly, in some cases, procedure of purification can be omitted for practical purposes. Thus, the disadvantages inherent in the hitherto reported methods, *viz.*, the formation of resinous by-products, necessity of troublesome separation of catalysts and purification of the products, are eliminated or minimized by employing ion exchangers as a condensing agent.

The results obtained in this work and the hitherto reported methods are summarized in Table I.

Judging from the results obtained above, the cation exchangers are effective and convenient condensing agent for the Fischer indole synthesis.

The fact that the complicated condensation through intramolecular reaction takes place by the action of ion exchangers is of much interest, and presents the possibility of exploring novel fields of utilization of ion exchangers in organic reactions.

The authors are grateful to Prof. Sugasawa and Mr. Hata, the Director of the Laboratory, for their interests in this work.

TABLE I

Conversion of Phenylhydrazones to Indoles

Phenylhydrazones	Product	Yield	Other Condensing Agents Reagent (solvent)	Yield
Acetone	Methylindole	0	BF_3	0
			$ZnCl_2$	60
			$ZnCl_2$ (m.n.t)†	80
Methyl ethyl ketone	2,3-Dimethylindole	63*	BF_3 (None)	50
			BF_3 (C_2H_5OH)	69
			BF_3 (CH_3CO_2H)	85
			$NiCl_2$	65
Propiophenone	2-Phenyl-3-methylindole	64.7	BF_3 (CH_3CO_2H)	87
			$CuCl_2$	72.5
Cyclohexanone	1,2,3,4-Tetrahydrocarbazole	87	BF_3 (CH_3CO_2H)	93
			H_2SO_4	93
γ-Acetamido-γ,γ-dicarbethoxybutyraldehyde	Ethyl α-acetamido-α-carbethoxy-β-(3-indole)-propionate	73	BF_3	25
			H_2SO_4	73

* Yield based on carbonyl compounds
† methylnaphthalene

Experimental

2,3-Dimethylindole (I) — Phenylhydrazine (2.7 g.) was added to methyl ethyl ketone (1.7 g.), forming the phenylhydrazone, which was boiled with Amberlite IR-120 (30 g.) in 30 cc. of water for 6 hours under vigorous stirring. After cooling the reaction mixture, the resins and the product which separated out were filtered, and extracted with hot alcohol. To the extract some water was added, and after having been decolorized, the extract was allowed to stand in an ice-bath, from which colorless scales of m.p. 103~106° were obtained. Yield, 2.2 g. or 63%. *Anal.* Calcd. for $C_{10}H_{11}N$: C, 82.71; H, 7.64. Found: C, 82.54; H, 7.83.

2-Phenyl-3-methylindole (II)—Propiophenone (1.4 g.) and phenylhydrazine (1.1 g.) were mixed and warmed for a while. The resulting phenylhydrazone and Amberlite IR-120 (8 g.) were heated together with 25 cc. of water for 4.5 hours with vigorous stirring. After the completion of the reaction, the content was treated as above. This gave colorless crystalline precipitate, m.p. 92~93°; yield 1.4 g. or 64.7%. Recrystallization from aqueous alcohol yielded colorless long prisms, m.p. 96~98°. *Anal.* Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found; C, 86.67; H, 6.21; N, 6.57. Picrate: Chocolate brown needles from alcohol, m.p. 136~139°.

1,2,3,4-Tetrahydrocarbazole (III)—A suspension of cyclohexanone phenylhydrazone (3.8 g.) and Amberlite IR-120 (20 g.) in water (20 cc.) was refluxed with stirring. With the advance of the reaction, oily liquefied phenylhydrazone solidified. After completion of the reaction, the resin and crystalline product were filtered, and extracted with hot aqueous alcohol. The extract was decolorized, leaving white fine crystals of m.p. 114~116°. Yield, 3 g. or 87%. *Anal.* Calcd. for $C_{12}H_{15}N$: C, 83.76; H, 8.23; N, 8.09. Found: C, 84.04; H, 7.76; N, 7.78. When this substance

was mixed with 1,2,3,4-tetrahydrocarbazole prepared by the conversion with sulfuric acid according to the method reported by Hoshino and Takiura[3], no melting point depression was observed.

Ethyl α-Acetamido-α-carbethoxy-β-(3-indole)-propionate (IV)—γ-Acetamido-γ,γ-dicarbethoxybutyraldehyde phenylhydrazone[4] (5 g.) was mixed with Amberlite IR-120 (10 g.) and 30 cc. of water. The reaction mixture was heated to the reflux temperature with vigorous stirring. The phenylhydrazone liquified at first, and after approximately 2 hours the suspended liquid solidified. The refluxing was continued for 4 hours. After cooling, the reaction mixture was treated as in the previous case (III). This gave colorless plates of m.p. 157~158°; yield, 3.4 g. or 73%. *Anal.* Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.44; H, 6.40; N, 8.09. Found: C, 62.21; H, 6.44; N, 8.25.

When the cyclization reaction was carried out in aqueous alcohol, the cyclized product was obtained in approximately the same yield. The use of toluene in this reaction lowered the yield to 35.3%. Cyclization of the phenylhydrazone using the phenolic sulfonic acid resin (Diaion K) as the catalyst gave the cyclized product in a very poor yield. For caution's sake, this compound was also prepared by a reaction between gramine and ethyl acetamidomalonate, as described by Howe, Zambito, Snyder, and Tishler[5]. When resulting substance was mixed with the above-described sample, no melting point depression was observed.

Summary

The authors carried out the Fischer indole synthesis by employing a cation exchanger as the condensing agent. As a result, cation exchangers were found to be an effective and convenient agent for this reaction. 2,3-Dimethylindole, 2-phenyl-3-methylindole, 1,2,3,4-tetrahydrocarbazole, and ethyl α-acetamido-α-carbethoxy-β-(3-indole)-propionate were prepared from corresponding phenylhydrazone by this method.

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5. Takeo Ueda, Kiyoshi Takahashi, Shigeshi Toyoshima, and Seizaburo Kano: Arsenical Chemotherapeutic Drugs. X.* Antibacterial Properties of Arylarsonic Acids and Arylarsonous Acids.

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Arsenical chemotherapeutic drugs have, hitherto, been investigated mainly as to their efficacies against spirochaetosis and trypanosis, but hardly tested as to their activities against pathogenic bacteria. Drugs of the arsphenamine series[1] were studied as to their activities against gonococcus, streptococcus, and staphylococcus, and about 60 compounds belonging to the arylarsonic acid series and a few compounds belonging to the diarylarsinic acid series[2] were tested as to their activities against tuberculosis. However, there still remain systematic studies to be carried out on antibacterial properties of arsenical drugs.

Since arsenical compounds containing poisonous arsenic atom exert more or less toxicity, chemotherapeutic utilization of these compounds should be limited to a short range. Accordingly, it may be noted that arsenical compounds should be non-beneficial in several respects, compared with antibiotics possessing extremely small toxicities. However, it may be expected that arsenical compounds could be clinically utilized, if these compounds would

3) Hoshino, Takiura : Bull. Chem. Soc. Japan, 11, 218 (1936).
4) Moe, Warner : J. Am. Chem. Soc., 70, 2763 (1948).
5) Howe, Zambito, Snyder, Tishler : J. Am. Chem. Soc., 67, 38 (1945).
* Part IX: J. Pharm. Soc. Japan, 72, 1148 (1952).
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1) T. Ueda, S. Toyoshima: Papers read before the Annual Meeting of the Pharmaceutical Society of Japan (1950).
2) M. Matsui, N. Hirano : Saikingaku-zasshi, 567 (1943), (Japan).