INDOLES

IV. Fischer Synthesis of Indoles on Cation-Exchange Resins in a Continuous System*

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When solutions of arylhydrazones of aldehydes or ketones are passed in aqueous hydroxyl-containing solvents through cation-exchangers in the H^+ form at temperatures of from 70 to 100° C, it is possible to obtain the corresponding indoles in good yields and in a form not requiring further purification.

In Japanese patents [1, 2] some years ago, information was published on the possibility of the occurrence of the Fischer rearrangement when phenylhydrazones are boiled with cation exchangers. We decided to attempt to carry out this reaction in a continuous system, which would make it possible to perform in industry the continuous synthesis of these biologically active systems, which are extremely important for pharmacology. It was found that arylhydrazones of even the most active carbonyl compounds (cyclohexanone) underwent no change on being passed through a column of cation-exchanger (H^+ form) at the ordinary temperature. The reaction begins to take place only at 50° C, and the optimum temperature is 90–100° C. However, it is difficult to achieve such a temperature in aqueous ethanolic solutions without the use of increased pressure, and, in view of this, in the majority of cases we worked at a temperature of 70° C. The use of aqueous ethanolic solutions considerably facilitates the isolation of the indoles obtained, and the use of aqueous solutions of ethylene glycol, although it enabled the temperature to be raised to 100° C, complicated the subsequent isolation of the pure indole.

The best results were obtained on the Russian cation exchanger KU-2-8 (type A); the use of Dowex 50 × 16, 20/50 caused an irreversible darkening of the ion-exchanger because of resin formation. The ion-exchanger evidently also plays the part of an adsorbent, since the indole isolated is directly of analytical purity and the by-products of the reaction formed and the resins are retained in the column. The optimum time of contact of the arylhydrazone with the cation exchanger was 1.5–2 hr, a decrease in this time leading to the partial issue of unchanged hydrazone from the column and an increase to a fall in the yield per unit time, although it caused almost no additional resin formation. The reaction takes place similarly both when a solution of a pure arylhydrazone and when an equimolar mixture of an arylhydrazine and a carbonyl compound previously heated in ethanol to cause condensation with the separation of the water are used.

It is obvious that the optimum conditions for synthesis will be the use of aqueous ethanolic solutions at 100° C with external pressure preventing the solvent from boiling.

We followed the course of the reaction by a spot test with Ehrlich's reagent. The indoles give spots

Reaction Conditions, Constants, and Yields of the Compounds Obtained

Initial hydrazine	Carbonyl compound	Indole	Solvent	Cation-exchanger	Reaction temperature, °C	Yield, %	Mp, °C	R_f[3]
Phenylhydrazine	Cyclohexanone	1,2,3,4-Tetrahydrocarbazole	Water–ethanol (3 : 10)	KU-1	70	80	116—117	0.65
Phenylhydrazine	Cyclohexanone	1,2,3,4-Tetrahydrocarbazole	Water–ethanol (3 : 10)	KU-2	70	85	116—117	0.65
Phenylhydrazine	Methyl ethyl ketone	2,3-Dimethylindole	Water–ethanol (3 : 10)	KU-2	70	60	105—106	0.55
Phenylhydrazine	Methyl ethyl ketone	2,3-Dimethylindole	Water–ethylene glycol (1 : 10)	KU-2	100	91	105—106	0.55
Phenylhydrazine	Propionaldehyde	3-Methylindole	Water–ethanol (3 : 10)	KU-2	70	81	93—95	0.74
o-Tolylhydrazine	Cyclohexanone	8-Methyl-1,2,3,4-tetrahydrocarbazole	Water–ethanol (3 : 10)	KU-2	70	72	96—97	—
α-Methylphenylhydrazine	Cyclohexanone	N-Methyl-1,2,3,4-tetrahydrocarbazole	Water–butanol–ethylene glycol (1 : 1 : 8)	KU-2	100	79	49—50	0.75

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*For part III, see [3].

of different shades of blue, green, and violet, and all the arylhydrazones give orange spots. Where the reaction did not go to completion, the indoles obtained were not contaminated with the initial arylhydrazones since the latter issue from the column considerably later than the indoles produced.

EXPERIMENTAL

The cation-exchanger in the H^+ form, previously covered with aqueous ethanol, was charged into a glass column 300 mm long and 15 mm in internal diameter with a jacket heated via a thermostat. The column was filled with solvent and then, in a current of nitrogen, a solution containing 0.01 mole of the arylhydrazone in 30 ml of solvent (prepared by boiling the starting materials in a suitable solvent for half an hour) (see table) was added dropwise. The rate of passage was 0.4 ml/min, and the time of contact of the solution with the cation-exchanger about 1 hr 30 min. After the addition of the solution, the column was eluted with ethanol at the same rate. The issue of the indole from the column was followed by means of Ehrlich's reagent. The cation-exchanger was used repeatedly. The eluate containing the indole was evaporated in vacuum in a current of nitrogen, and the indole that separated out was filtered off with suction. Where solutions containing ethylene glycol were used, they were diluted with water three- to fourfold, and the indole was extracted with benzene.

The reaction conditions, constants, and yields of the compounds obtained are given in the table.

REFERENCES

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