# SYNTHESIS OF INDOLES FROM PYRIDINIUM COMPOUNDS

# 10.* INFLUENCE OF SOLVENTS ON PROCESS OF INDOLIZATION OF 3-INTROPYRIDINIUM CATIONS BY THE ACTION OF THE N-METHYLIMINE OF METHYL ETHYL KETONE

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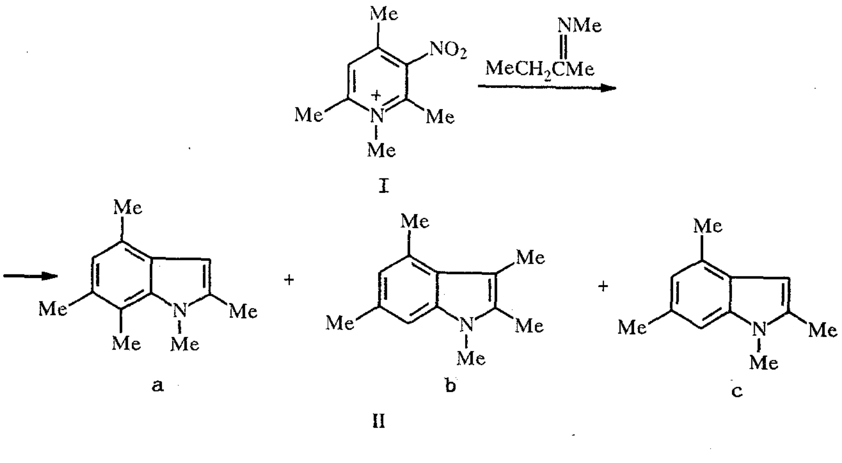
*A study has been made of the influence of solvents on the process of indolization of the methiodide of sym-3-nitrocollidine by the action of the N-methylimine of methyl ethyl ketone. An inversely proportional relationship has been found between the content of the 3,7-unsubstituted indole in the indole fractions and the donor strength of the solvent.*

We had reported previously that the indolization of 1-alkyl-3-nitropyridinium salts by the action of N-alkylimines of asymmetric ketones leads to the formation of a mixture of three compounds of the indole series IIa-c; these indoles are not formed in commensurate quantities, and the content of the 3,7-unsubstituted indole IIc is quite often no greater than 0.1%, depending on the structure of the cation of the original salt [1, 2].

In a previous communication [1] we analyzed the influence of the structure of 3-nitropyridinium cations on the course of the process of indolization by the action of the methylimine of methyl ethyl ketone. This conversion may also be influenced by another factor of no small importance, namely the reaction conditions, in particular the nature of the solvent.

In order to evaluate this influence, we selected as a model the sym-3-nitrocollidine salt (I), since it had been established that for this cation, the formation of all three indoles IIa-c takes place in appreciable quantities.



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*For Communication 9, see [1].

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Since it had been established that N-alkylimines of ketones enter into this reaction in the enamine form and that the position of the imine ⇄ enamine equilibrium depends considerably on the nature of the solvent, the course of the process must be influence greatly by the nature of the solvent. We had previously reported that the best solvents for this reaction are bipolar aprotic solvents such as DMF, DMSO, and HMPA. When the reaction is carried out in these solvents, the conversion time is considerably shorter, the yield of indoles is higher, and the method of separating the indoles is simpler [3].

In nonpolar solvents such as benzene, the reaction is much slower: Commensurate yields are obtained in DMF in 2 days (at room temperature) and only in 10 days in benzene (with refluxing).

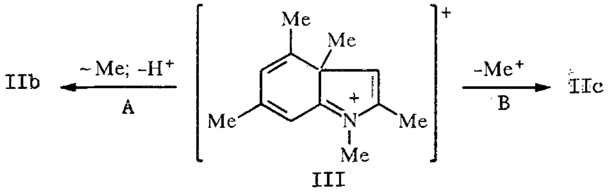
In polar protic solvents such as methanol, ethanol, or 2-propanol, and even in solvents that have very little acidity (formamide, $pK_a \sim 17.2$), the reaction is so slow that only traces of indoles can be detected in 15-20 days, with insignificant conversion of the original salt.

The relationship that we found between the reaction rate and the character of the solvent correlates with the equilibrium content of the enamine form of N-alkylketimines in these solvents. In [4], by means of PMR, contents of the enamine forms of N-alkylimines of cyclopentanone and cyclohexanone were determined, as influenced by the solvent. The maximum content of the enamine form was found in bipolar aprotic solvents (DMSO, DMF, pyridine, ~50%); minimum contents were found in polar protic solvents (alcohols, ~10%); intermediate contents were found in nonpolar solvents ($CCl_4$, benzene, ~35%).

Because of the complexity of the process, apparently, there are a number of other factors influencing the course of the reaction. Even though information reported in the literature indicates that the equilibrium content of enamine forms is approximately the same in benzene and in acetonitrile, the reaction is much faster in acetonitrile, and the yields are higher (Table 1). The apparent reason for this difference is that in benzene, in contrast to acetonitrile, the reaction proceeds in a heterogeneous medium.

The character of the solvent influences not only the rate of the indolization process, but also the direction of the process.

Since the formation of the indoles IIb and IIc proceeds through the cationic intermediate III, which can be aromatized through two paths, we undertook a study of the influence of solvent type on these processes.



On the one hand, an increase in the donor strength of the solvent might favor aromatization via path B as a result of binding, by the solvent molecules, of the methyl cation that has been split out. On the other hand, solvation of the cationic intermediate III and the formation of a "solvate cage" may prevent the splitting out of the $CH_3^+$ and thus increase the probability of aromatization via path A when a solvent with a higher donor strength is used.

For an experimental evaluation of the influence of solvent donor strength on the direction of aromatization of the cation III, we investigated the content of the 3,7-unsubstituted indole IIe in the indole fraction, as determined from a combination of data obtained by chromatography/mass spectrometry* and GLC (Table 1).

The donor strength of the solvent was characterized by the Gutman donor number, i.e., the heat of solvation of antimony(V) chloride (reference acceptor) by the test solvent in dilute solutions in an inert solvent, measured calorimetrically and expressed in units of kcal/mole. The Gutman donor number reflects the overall magnitude of donor–acceptor interactions in the system under investigation. It includes both ion–dipole and dipole–dipole interactions, and it even reflects certain steric properties of the solvent molecules. Therefore, the donor number of the solvent can be regarded as a semiquantitative measure of solvent–solute interaction [5].

We have been able to establish that with increasing donor strength of the solvent, the fraction of the 3,7-unsubstituted indole IIc that is formed through path B, by elimination of the methyl cation, does decrease (Fig. 1), probably indicating that the cationic intermediate III is solvated to a significant degree and that the subsequent process takes place in a solvate cage.

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*Differences in the mass spectra of the isometric indoles IIa, b were discussed in [1].

TABLE 1. Indolization of 1,2,4,6-Tetramethyl-3-nitropyridinium Iodide by the Action of N-Methylimine of Methyl Ethyl Ketone in Various Sovents*

| Solvent | Reaction time, days | Content, % | | | Total yield, % | DN($SbCl_5$), kcal/mole |
|---|---|---|---|---|---|---|
| | | IIa | IIb | IIc | | |
| Pyridine | 6 | 92,60 | 6,32 | 1,08 | 55 | 33,1 |
| DMSO | 4 | 92,50 | 5,94 | 1,56 | 70 | 29,8 |
| DMF | 4 | 96,00 | 2,50 | 1,50 | 75 | 26,6 |
| Acetonitrile | 8 | 91,00 | 6,70 | 2,30 | 60 | 14,1 |
| Benzene** | 10 | 92,00 | 5,20 | 2,80 | 40 | 0,1 |

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*Reaction conditions: 1.5 mmoles of salt I, 3.8 mmoles of N-methylimine of methyl ethyl ketone; room temperature.

**With refluxing.

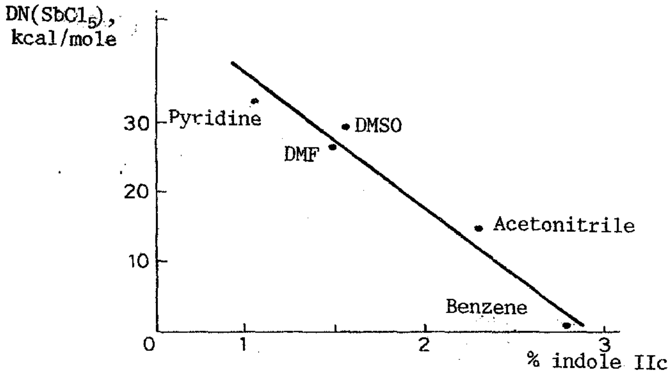

Fig. 1. Content of 3,7-unsubstituted indole IIc in indole fractions (%) as a function of donor strength of solvent.

## EXPERIMENTAL

The indolization of 1,2,4,6-tetramethyl-3-nitropyridinium by the action of the N-methylimine of methyl ethyl ketone was carried out by a procedure that has been described previously [3]. The indole fraction was separated chromatographically in a column with Silpearl support in a 1:1 benzene–hexane system. Also, without separation, the indole fraction was investigated by means of GLC and chromatography/mass spectrometry. The GLC was carried out in a Chrom-5 instrument, quartz capillary column 12.5 m, carrier gas helium, discharge 1:60, flow 1.2 ml/min, $T_{vap}$ 180-200°C, flame ionization detector. The chromatography/mass spectrometry was performed with A Finnigan MAT-112 instrument, ionizing voltage 70 eV, $T_{sep}$ 250°C, $T_{vap}$ 200°C, SPB-5 quartz capillary column 0.25 mm × 30 m, carrier gas helium, temperature programmed from 150° to 260°C at 10°/min.

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