

REACTIONS OF PYRIDYL- AND ARYLHYDRAZONES WITH BASES.  
NEW TYPE OF N-N-BOND CLEAVAGE.

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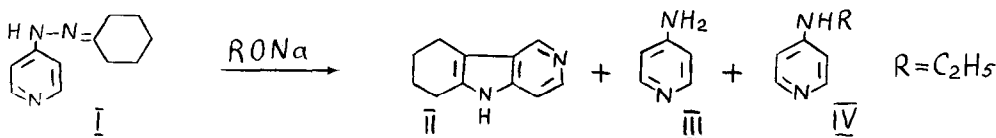
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The Fisher indolization is usually achieved with acid catalysts and this is in a good agreement with the Robinson's mechanism of such reactions. The formation of indole ring in 40% yield by the long (16 hours) heating of acetophenone phenylhydrazone with an ethanolic solution of sodium ethylate is only base catalysed reaction described.<sup>1</sup>

We have investigated at greater length transformations of pyridyl- and arylhydrazones by the action of strong bases and found that the indolization of such compounds with base catalysts seems to be quite general. The reaction of cyclohexanone phenylhydrazone with sodium ethylate at 235°C for 40 min. gives for example 1,2,3,4-tetrahydrocarbazole in 93,6% yield. Cyclohexanone 2,6-dimethylpyridyl-4-hydrazone forms in similar conditions 2,4-dimethyl-5,6,7,8-tetrahydro- $\gamma$ -carboline in 48% yield and cyclohexanone pyridyl-4-hydrazone (at 210°C for 90 min.) gives 5,6,7,8-tetrahydro- $\gamma$ -carboline in 62% yield.

A modification of the reaction conditions by the indolization of aryl(heteryl)hydrazones with base catalysts and an investigation of by-products formed in this process led to the discovery of a new type of N-N-bond cleavage by the interaction of hydrazones with alcoholates.<sup>2</sup>

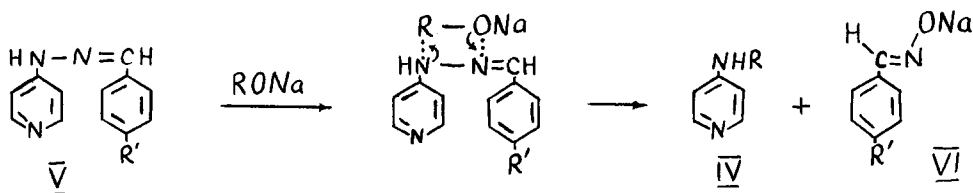
It was found that heating of cyclohexanone pyridyl-4-hydrazone (I) with sodium ethylate at 240°C caused to concomitant formation of the normal indolization product (II) - (42%) and of 4-aminopyridine (III) (5%) together with another compound, which was identified as 4-ethylaminopyridine(IV) [molecular weight 123 (by mass-spectroscopy), IR-spectrum: 3230  $\text{cm}^{-1}$ (NH), 1600  $\text{cm}^{-1}$ (C=C, C=N); UV-spectrum:  $\lambda_{\text{max}}$  -356  $\mu\text{m}$ (lg  $\epsilon$ -4,41); NMR-spectrum: triplet 1,22 ppm (3 p.u.) and quartet 3,14 ppm (2 p.u.) ( $\text{C}_2\text{H}_5$ -N), doublets 6,50 ppm (2 p.u.) and 7,98 ppm (2 p.u.) ( $\beta$ - and  $\alpha$ -protons of pyridine ring). It was independently synthesised in 29% yield from pyridylpyridinium chloride and ethylamine.]



Obviously two main competition reactions occur in the process considered: isomerization of I into enhydrazine with the subsequent transformation into II on the one hand and the N-N-bond cleavage of I with N-alkylation resulting in the formation of IV on the other hand .

Utilization of aromatic aldehydes as carbonyl components of hydrazones let us to exclude the enhydrazine formation and to direct the reaction towards IV . The yields of 4-ethylaminopyridine were 83 and 84% by interactions of benzaldehyde (V, R<sup>1</sup>=H) - and cumic aldehyde [ V, R<sup>1</sup> =CH(CH<sub>3</sub>)<sub>2</sub> ] - pyridyl-4-hydrazones with sodium ethylate .

The formation of various monoalkylaminopyridines in rather high yields by treatment of pyridylhydrazones with sodium derivatives of the corresponding primary or secondary alcohols (methanol, ethanol, iso-propanol, butanol, heptanol) shows that the reaction is general and can be used as preparative method . This method consists in heating of aromatic aldehydes ( for example cumic or benzaldehyde) pyridylhydrazones with sodium (or potassium ) alcoholates at 200-250°C for 10-15 min. and the subsequent extraction of the reaction product by the suitable solvent (for example by chloroform ) .

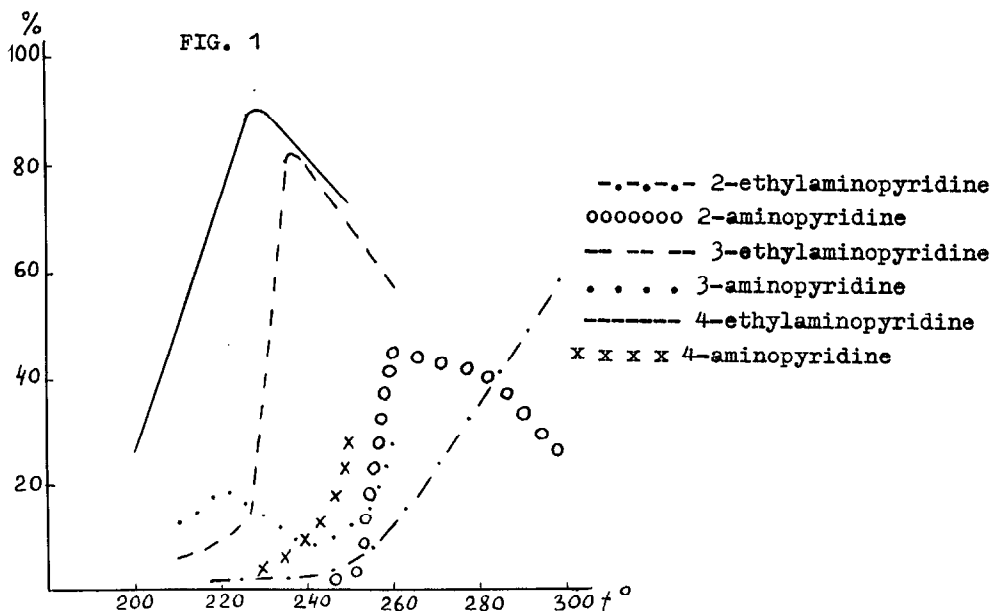


The % yields of 4-monoalkylaminopyridines(IV) from GLC data are ( the yields of the isolated products are given in the parentheses ): for R =CH<sub>3</sub> 72(64); R= C<sub>2</sub>H<sub>5</sub> 90(83); R=i-C<sub>3</sub>H<sub>7</sub> 68(61); R=n-C<sub>4</sub>H<sub>9</sub> 92(83); R=n-C<sub>7</sub>H<sub>15</sub> 83(70) .

4- Aminopyridine(III) is formed as a by-product in between 2 to 17% yield during the synthesis of IV and the amounts of III increase with temperature. It is remarkable that only 4-aminopyridine is obtained in quantitative yield by the interaction of pyridyl-4-hydrazone with sodium alcoholates with no N-alkylated products . Therefore 4-monoalkylaminopyridines(IV) generated by reactions of pyridyl-4-hydrazones with alcoholates are not formed from the unsubstituted 4-aminopyridine(III) by subsequent N-alkylation. The formation of both type of compounds III and IV result from two independent ways of reaction .

Of course, the main route of the process - formation of monoalkylamino - or aminoderivatives - for various aryl(heteryl)hydrazones of aromatic aldehydes depends on the electronic (mesomeric and inductive) effects of both aromatic (or/and heteroaromatic) rings . In contrast to benzaldehyde pyridyl-4-hydrazone, which gives at 240°C for 15 min. mainly 4-ethylamino - pyridine(IV) ; benzaldehyde phenylhydrazone is transformed under the same conditions into aniline in 86% yield ; less than 3% of ethylaniline is

obtained in this case. Aniline in 80% yield is formed starting from p-nitrobenzaldehyde phenylhydrazone (at 240°C for 15 min.) . A mixture of aniline (16%) and ethylaniline (12%) is obtained from the same reaction (at 255°C for 15 min.) starting from p-methoxybenzaldehyde phenylhydrazone. The facility of N-N-bond cleavage for isomeric benzaldehyde pyridyl-2, -3 and -4-hydrazones is different<sup>3</sup>. Most easily the reaction with sodium ethylate occurs in the case of the pyridyl-4-hydrazone ; the 3-isomer is less active and more vigorous conditions have to be used for the 2-substituted pyridine. The dependence of the yields of isomeric ethylaminopyridines and aminopyridines on temperature is shown in fig. 1 (the reaction time is 15 min. for all cases). It is found that the highest yields in these conditions are reached for 4-ethylaminopyridine (90%) at 230°C, for 3-ethylaminopyridine (83%) - at 240°C and for 2-ethylaminopyridine (58%) - at 300°C .



The mechanism of the reaction needs to be investigated in more detail . As a first suggestion the formation of fourmembered cyclic transition state may be presumed , which after redistribution of electron density, is cleaved with the formation of the monoalkylaminopyridine (IV) and the sodium derivative of aromatic aldehyde-syn-oxime (VI) .

Actually the syn-isomer of the cumic aldehyde oxime [VI, R' = CH(CH<sub>3</sub>)<sub>2</sub>] is isolated in yield 60% from the products of reaction of [V, R' = CH(CH<sub>3</sub>)<sub>2</sub>] with sodium ethylate after addition of an ethanolic solution of HCl and precipitation of the resulting salts by ether. The isolated VI [R' = CH(CH<sub>3</sub>)<sub>2</sub>]

is identified by m.p. and IR-spectrum with the sample of the same compound prepared by the independent synthesis .

It should be noted, that the observed N-N-bond cleavage of pyridyl(aryl)hydrazones of the various carbonyl compounds by the action of alcoholates resulting in N-monoalkylaminopyridine (N-monoalkylaniline) formation holds an intermediate place between the Fisher indolization of aryl- or pyridylhydrazones and Kishner-Wolff reductive C=N-bond cleavage at unsubstituted hydrazones .

Further investigation of mechanism and the field of application of this reaction seems to be interesting .

#### References

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