# CHEMISTRY

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1957

SovietRxiv

## Abstract

## Full Text

*CHEMISTRY*

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# NEW TRANSFORMATIONS OF PYRIDINIUM SALTS AND THE SYNTHESIS OF -AMINO-SUBSTITUTED PYRIDINES

*(Presented by Academician A. N. Nesmeyanov, 19 VI 1957)*

Earlier we attempted to open the pyridine ring in $\gamma$-alkoxy-, phenoxy-, and methylmercapto-substituted pyridines by the action of aromatic amines on chloro-(2,4-dinitrophenylate) pyridinium bases (I) ($^1$). It turned out that under these conditions the pyridine ring is not cleaved; instead, the alkoxy (methylmercapto-, phenoxy-) group is replaced by the residue of the aromatic amine, with formation of chloro-(2,4-dinitrophenylates) of $\gamma$-arylaminopyridines (II) ($^1$):

$$\text{I} \xrightarrow[-RH]{+NH_2Ar} \text{II} \qquad \text{V}$$

$$R = \text{AlkO}-,\ CH_3S-,\ C_6H_5O-$$

Subsequently we succeeded in effecting cleavage of the pyridine ring in $\gamma$-alkoxy(methylmercapto-, phenoxy)pyridines by the action of cyanogen bromide and aromatic amines on these compounds ($^2$). In this way, dianil salts of $\beta$-alkoxy(methylmercapto-, phenoxy)-substituted glutaconic aldehydes (III) were obtained.

$$ArNH - CH = CH - C(R) = CH - CH = NHAr^+\ Br^-$$

$$(\beta) \quad (\alpha)$$

$$\text{III}$$

$$R = -OAlk,\ -SCH_3,\ -OC_6H_5$$

Of these compounds, the $\beta$-alkoxy-substituted ones (III; $R = AlkO-$) are distinguished by great instability even in the crystalline state*. Their alcoholic solutions are especially unstable and rapidly become decolorized on heating. During storage of the preparations, especially in the summer months, they gradually turn into pale-yellow crystalline substances impregnated with liquid. Dianil $\beta$-phenoxyglutaconic aldehyde bromide hydrate is somewhat more stable. However, on prolonged storage or on heating it also decomposes.

Investigation of the crystalline products obtained as a result of the transformation of dianil salts (III; $Ar = C_6H_5-$, $R = -OAlk,\ -OC_6H_5$), showed that all of them are one and the same substance—$\gamma$-phenylaminopyridine bromophenylate IV (light-yellow hygroscopic needles). M.p. 192–193°.

$$\text{Found}^{*}\%:\ \text{N } 8.52;\ 8.39;\ \text{Br } 24.45;\ 24.68$$

$$\mathrm{C_{17}H_{15}N_2Br}.\ \text{Calculated}\%:\ \text{N } 8.57;\qquad \text{Br } 24.44$$

The formation of compound IV proceeds according to the general scheme:

[reaction scheme: $\gamma$-alkoxy(phenoxy)-*N*-phenylpyridinium bromide $\longrightarrow$ intermediate pyridinium bromide +N

$$R = \mathrm{CH_3} -\ \ldots\ \text{iso-}\mathrm{C_3H_7} - \mathrm{C_6H_5} -\ \text{etc.}$$

In the case of the $\beta$-phenoxy derivative III, phenol was detected among the transformation products. Thus, the cyclization reaction of salts of dianils of glutaconic aldehyde into *N*-arylpyridinium salts, discovered by Zincke, which proceeds under comparatively severe conditions (melting, heating with concentrated hydrochloric acid, etc.) ($^4$), in the present case takes place with unusual ease.

The transformations studied may be regarded as a special case of the general reaction of replacement of $\gamma$-alkoxy(phenoxy) groups by residues of aromatic amines in pyridinium salts containing electronegative radicals ($\mathrm{C_6H_3(NO_2)_2}-$, $\mathrm{C_6H_5}-$) at the cyclic nitrogen (cf. ($^1$)). Undoubtedly, what is manifested here is conjugation of the *p*-electrons of the oxygen atom in the group $-\mathrm{OAlk}(-\mathrm{OC_6H_5})$ with the remaining part of the pyridinium-salt molecule (see, for example, V), which imparts to these compounds the character of oxonium salts (cf. ($^5$)).

The bromohydrate of the dianil of $\beta$-methylmercaptoglutaconic aldehyde (III; $\mathrm{Ar} = \mathrm{C_6H_5}-$, $R = -\mathrm{SCH_3}$) has a great tendency toward cyclization. In this case, however, the reaction stops at the stage of formation of the bromophenylate of $\gamma$-methylmercaptopyridine. Such a course of the reaction becomes understandable if one takes into account that the sulfur atom in the bromophenylate of $\gamma$-methylmercaptopyridine is partly in the onium state (cf. V), and that sulfonium salts are characterized by lower reactivity in comparison with oxonium salts.

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* This circumstance apparently was the reason for Ebert' s unsuccessful experiments on the cleavage of $\gamma$-methoxypyridine by cyanogen bromide and aniline. He was unable to isolate dianil $\beta$-methoxyglutaconic aldehyde bromide hydrate ($^3$).

Enhancement of the electronegative character of the radical attached to the nitrogen atom in $\gamma$-methylmercaptopyridine leads to exchange of the methylmercapto group for an amine residue: chloro-(2,4-dinitrophenylate) of $\gamma$-methylmercaptopyridine reacts with aromatic amines, although somewhat more slowly than the $\gamma$-alkoxy derivatives (cf. ([1])).

We were interested in the question of the mobility of the alkoxy group in haloalkylates of $\gamma$-alkoxypyridines. It turned out that, upon interaction of $\gamma$-methoxypyridine iodomethylate with aniline (in alcoholic solution, with heating on a water bath), methyl iodide is split off and $N$-methyl-$\gamma$-pyridone is formed. Iodomethylate of $\gamma$-phenylaminopyridine was not detected in this case.

Consequently, in order to impart to the alkoxy group the capacity for substitution, it is not sufficient merely to convert the cyclic nitrogen atom into the tetravalent state; in addition, this atom must bear an electronegative radical.

Next, the capacity for substitution by residues of aromatic amines of the phenoxy group in $\gamma$-phenoxypyridine methyl iodide was investigated. Cleavage of the haloid aryl (under the action of an aromatic amine) in this case seemed extremely unlikely. On heating $\gamma$-phenoxypyridine methyl iodide with aniline (115–120°), $\gamma$-phenylaminopyridine methyl iodide was obtained (yield $\sim 88\%$).

It was subsequently found that exchange of the phenoxy group for the residue of an aromatic amine proceeds readily on heating a mixture of the hydrohalide salt of $\gamma$-phenoxypyridine with an aromatic amine, or the salt of an aromatic amine with $\gamma$-phenoxypyridine. Exchange of the phenoxy group does not occur, however, on heating a mixture of salts of $\gamma$-phenoxypyridine and of an aromatic amine.

It follows from this that the reaction involves the $\gamma$-phenoxypyridinium cation and the free amine:

$$[\text{Reaction: } \gamma\text{-phenoxypyridinium cation} + \mathrm{ArNH_2} \rightarrow \gamma\text{-arylaminopyridinium cation} + \mathrm{C_6H_5OH}]$$

$$\mathrm{Ar:}\ \mathrm{C_6H_5}\text{—}(94\text{-}96),\quad (p)\ \mathrm{CH_3C_6H_4}\text{—}(86),\quad (o)\ \mathrm{CH_3C_6H_4}\text{—}(\sim 58),$$

$$(p)\ \mathrm{ClC_6H_4}\text{—}(\sim 73),\quad (p)\ \mathrm{CH_3OC_6H_4}\text{—}(83),\quad \alpha\text{–}\mathrm{C_{10}H_7}\text{—}(42)^*$$

Naturally, the idea arose of carrying out the reaction of $\gamma$-phenoxypyridine with salts of aliphatic amines and with the simplest ammonium salts. It turned out that the phenoxy group can in this way be replaced by an amino group and by residues of primary and secondary aliphatic amines. Thus, on fusion

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* After drying in vacuum at 40–50°.

of $\gamma$-phenoxypyridine with cyclohexylamine hydrobromide (200–210°, 1 hour), $\gamma$-cyclohexylaminopyridine was obtained (yield 72%). Colorless prisms (from ether). M.p. 147-148°.

| | |
|---|---|
| Found, %: | N 15.87; 16.05; |
| $C_{11}H_{16}N_2$. Calculated, %: | N 15.90 |

In an analogous manner, $\gamma$-dimethylaminopyridine was synthesized (190–200°, 1 hour). Yield 82%. Colorless plates with m.p. 112-113°. M.p. of picrate 204-206° (cf. ([6])).

It was further found that on heating $\gamma$-phenoxypyridine with ammonium chloride in an open vessel (300–310°, 1 hour), $\gamma$-aminopyridine is readily formed (yield 90–95%); for extraction of $\gamma$-aminopyridine from the aqueous solution, *n*-butanol was used, which greatly simplifies the isolation of this base.

The preparation of $\gamma$-aminopyridine by this method considerably surpasses, in simplicity and convenience of operations, the known syntheses of Koenigs and Greiner ([7]) and of Hertog and Overhoff ([8]), which, owing to a number of limitations, practically cannot be used for the synthesis of pyridines substituted at the amino group. Meanwhile, the reaction investigated by us can serve as a convenient general method for preparing various $\gamma$-aminosubstituted pyridines.

It should be noted that $\gamma$-phenoxypyridine behaves in the reaction with amine salts analogously to 9-phenoxyacridine ([9]). This analogy, however, was difficult to foresee, since it is known that 9-alkoxyacridines react with amine salts differently from $\gamma$-alkoxy-substituted pyridines and quinolines ([10]).

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[*] The percentages in parentheses indicate the yields of $\gamma$-arylaminopyridines (VI).

When our investigation was nearing completion, an article by Jerchel and coworkers appeared, devoted to reactions of salts of $\gamma$-pyridylpyridinium ([11]). The German investigators, proceeding from different considerations, arrived at the idea of the possibility of synthesizing $\gamma$-aminopyridine by the interaction of $\gamma$-phenoxypyridine with ammonia. In the experimental part of the work, however, a description of these experiments is absent.

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Received
18 VI 1957

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*Note: Figure translations are in progress. See original paper for figures.*

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