AROXYDIHYDROPYRANS

X.* DIENE CONDENSATION OF VINYL ETHERS OF PYRIDYLCARBINOLS WITH ACROLEIN AND SOME TRANSFORMATIONS OF THE ADDUCTS

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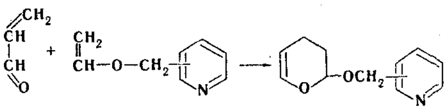
A method was developed for the preparation of 2-pyridylmethoxy-3,4-dihydropyrans on the basis of the thermal interaction of vinyl ethers of 2-, 3-, and 4-pyridylcarbinols and acrolein. The addition of hydrogen, chlorine, and ethanol to the double bond of the dihydropyran ring was studied. The activity of the pyridine nitrogen atom in quaternization and complexing reactions was demonstrated. It was established that both reaction centers participate in the reaction with hydrogen chloride. Nine new compounds were isolated and characterized, and their structures were proved by means of PMR, IR, and UV spectroscopy.

In a previously published series of papers [2], the reaction of acrolein with simple vinyl aryl ethers was reported, and a route to the synthesis of various benzene-ring-substituted 2-aroxy-3,4-dihydropyrans was proposed.

In the present study, vinyl ethers of 2-, 3-, and 4-pyridylcarbinols (VPC) [3] are investigated for the first time as dienophiles in the Diels-Alder reaction. Our previous attempts to introduce acrolein into the diene synthesis with vinyl ethers of aminophenols were unsuccessful. In this connection, a study of the behavior of VPC, the pyridine ring in the molecules of which (which is separated from the vinyloxy group by only one methylene bridge) certainly affects the properties of the vinyloxy group, is of particular interest.

As a result of our investigations, we established that the addition of acrolein to VPC proceeds when the reaction mixture is heated in an autoclave at 130-160° for 4-10 h without the addition of a special catalyst. Adducts with a six-membered oxygen-containing ring are formed in a maximum yield of 40-80%. Under the indicated conditions, the synthesis of 2-pyridylmethoxy-3,4-dihydropyrans (PDP) proceeds via the scheme



While it has been previously noted that the optimum temperature of the diene condensation for vinyl aryl ethers should correspond to or be close to the boiling point of the starting ether [2,4], the reaction of VPC with acrolein requires milder temperature conditions. However, the position of the vinyl group in the ring with respect to the nitrogen atom has an appreciable effect on the rate of the process. The meta isomer of the VPC proved to be the most active in the reaction with acrolein. It gave 2-(-3-pyridylmethoxy)-3,4-dihydropyran in 68% yield after 5 h at 140°. Under the same conditions, the para isomer of VPC reacts more slowly, and we were able to isolate 2-(4-pyridylmethoxy)-3,4-dihydropyran in only 35% yield.

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*See [1] for communication IX.

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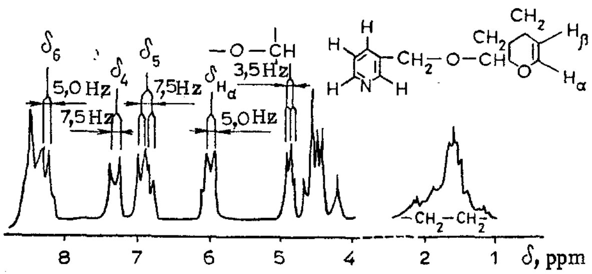


Fig. 1. PMR spectrum of 2-(3-pyridylmethoxy)-3,4-dihydropyran.

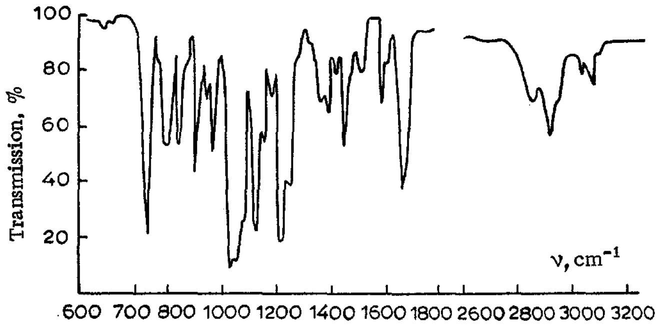


Fig. 2. IR spectrum of 2-(3-pyridylmethoxy)-3,4-dihydropyran.

The synthesized adducts are stable on storage and dissolve in most organic solvents. The purity of the PDP was confirmed by thin-layer chromatography (TLC) on activity II aluminum oxide. The structures of the adducts were proved by means of chemical methods, for example, hydrogenation of the adducts to the corresponding 2-pyridylmethoxytetrahydropyrans, and by PMR and IR spectroscopy.

In the PMR spectrum of 2-(3-pyridylmethoxy)-3,4-dihydropyran (Fig. 1), the protons of the pyridine ring are responsible for the appearance of the following signals: a singlet (2-H), two doublets (6-H and 4-H), and a doublet (5-H); (δ_2 8.40, δ_6 8.33, δ_4 7.48, δ_5 7.08 ppm; $J_{4,5}$ = 7.5, $J_{5,6}$ = 5.0 Hz). The following resonate at strong field: the α-olefinic proton (doublet, δ_6 6.11 ppm; $J_{CH=CH}$ = 5.0 Hz) and the proton of the O−CH group (triplet, δ 4.93 ppm, J_{CH-CH_2} = 3.5 Hz). The signals of the remaining two methylene groups, which form a multiplet, are found at strong field.

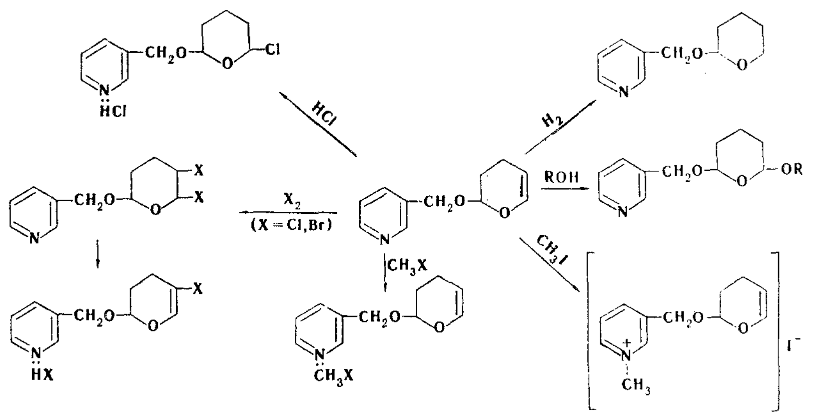
The IR spectrum of 2-(3-pyridylmethoxy)-3,4-dihydropyran is presented in Fig. 2. The spectrum shows the absence of aldehyde groups, while the strong bands that are characteristic for the vibrations of the C−O−C grouping in the pyran ring appear at 1114 cm^{-1}. The band at 1225 cm^{-1} is related to the vibrations of the C−O−C ether group (the oxygen between the rings). The intense absorption band at 1654 cm^{-1} attests to the existence of a carbon−carbon double bond in the pyran ring. The stretching vibrations of the CH_2 groups of the pyran ring are characterized by bands at 2855 and 2935 cm^{-1}. The oxygen atom that links the pyridine and dihydropyran rings forms an acetal grouping with the ring oxygen, and the vibrations of this acetal grouping appear in the spectrum as a broad band at 1025, 1040, and 1060 cm^{-1}. The vibrational frequencies at 1580, 1590, and 1430 cm^{-1} are characteristic for the pyridine ring.

In the case of 3-PDP, several reactions that make it possible to evaluate compounds of a new type were investigated. (See scheme on following page.)

One should note a number of peculiarities in the structures of the PDP molecules that have a substantial effect on the reactivities of these substances. The PDP have several very strong nucleophilic reaction centers − the nitrogen and oxygen atoms and one double bond in the six-membered oxygen-containing ring.

The possible transmission of the effect of the pyridine ring on the reactivity of the isolated double bond of the pyran ring through the double oxygen bridge with alternating methylene groupings cannot be disregarded.

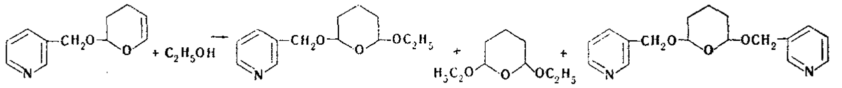
In addition, the PDP molecule can be considered to be a cyclic vinyl ether. In this connection, the reactions characteristic for simple vinyl ethers were mainly carried out in the present research. However, when the reactions were carried out with electrophilic reagents, the reaction with not only the C=C bond of the pyran ring but also with the unshared electron pair of nitrogen was always possible.



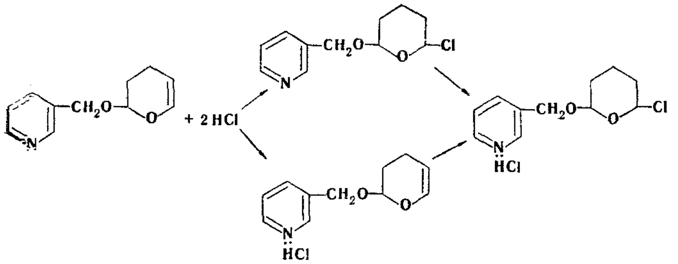
$CH_3 = Sn$

The effect of the presence of a pyridine ring on the properties of the vinyl group has already been well noted in the hydrogenation of PDP. Thus, while 2-alkoxy- and 2-aroxy-3,4-dihydropyrans add hydrogen in the presence of Raney nickel at room temperature and atmospheric pressure, we were able to carry out the hydrogenation of the PDP only on heating them to 50° at elevated hydrogen pressures. This can probably be explained by the suppression of the catalyst activity due to the formation of a stable complex between nickel and the unshared electron pair of the nitrogen atom. The bands at 1654 and 950 cm^{-1} that are characteristic for the double bond of the dihydropyran ring vanish in the IR spectrum of hydrogenated PDP. In this case, the acetal structure of the molecule does not change, and the broad band at 1025 and 1040 cm^{-1} is retained in the spectrum.

It is known that the reaction of 2-aroxy-3,4-dihydropyrans with aliphatic alcohols gives a mixture of cyclic acetals [5]. The reaction of PDP with ethanol also initially proceeds through a step involving the formation of a 2-pyridylmethoxy-6-ethoxytetrahydropyran, which then undergoes disproportionation. We were able to isolate only the previously described 2,6-diethoxytetrahydropyran in the pure state.

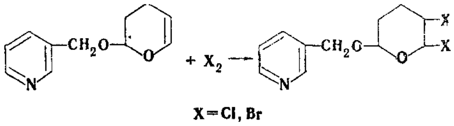


A crystalline water-insoluble product was isolated in 80% yield in the hydrochlorination of PDP. According to the results of elementary analysis, it contains 2 moles of hydrogen chloride per mole of PDP. We suppose that the addition of dry hydrogen chloride in an aprotic solvent proceeds successively or simultaneously at the two reaction centers:



The bands at 950, 1654, 3030, and 3060 cm^{-1}, which are due to the vibrations of the double bond, disappear in the IR spectrum of the hydrochlorinated PDP, and an absorption band that attests to the formation of a carbon–halogen bond appears at 675 cm^{-1}. The bands of the pyridine ring are shifted (1580 → 1563 and 1590 → 1620 cm^{-1}), and their intensities decrease. Bands corresponding to nitrogen-coordinated hydrogen chloride molecules appear at 2500-2800 cm^{-1}.

Considering the information that pyridines catalyze the addition of chlorine to a double bond [6], it can be assumed that addition of halogen to the 5 and 6 positions of the dihydropyran ring will proceed in the first step of the halogenation of PDP. Products containing 26 and 45% halogen, respectively, were obtained on treatment with chlorine or bromine, which attests to the addition of two atoms of halogen to the PDP. The absorption bands of a double bond are present in the IR spectra of the products of halogenation of the



PDP, and a C−X band appears at 670 cm^{-1} together with a number of frequencies due to salt formation at the pyridine nitrogen atom. The β-elimination reaction that is usual for α,β-dihaloalkyl ethers evidently also occurs here. The HX evolved in this case is tied up strongly at the pyridine nitrogen atom. However, we were unable to identify products containing only one halogen atom per PDP molecule. The presence in the PDP of several active centers capable of participating in the reaction complicates the isolation of individual substances.

In order to ascertain the activity of the unshared pair of electrons of the nitrogen atom, we synthesized the quaternary salts of the PDP. Methyl iodide was used as the quaternizing agent. It was found that the reaction proceeds readily at the boiling point of the mixture of components to form a viscous mass that is soluble in water, alcohol, acetone, and dimethylformamide. The structure of the product was proved by means of spectral methods. The bands characteristic for the double bond are retained in the IR spectrum, while the bands of the pyridine ring are shifted from 1432 to 1509 cm^{-1}. A bathochromic shift of the absorption band at 260 nm with a simultaneous significant increase in the extinction is observed when one compares the electronic spectra of PDP and its quaternized product, and, in addition, an extremely intense absorption band appears at 218 nm.

Hydrated stannic chloride reacts with PDP to give a donor-acceptor complex due to the vacant orbital of the metal and the unshared electron pair of the nitrogen atom. A shift in the vibrational frequencies of the pyridine ring and the appearance of new bands at 1500-1550 cm^{-1} are observed in the spectrum of this compound. According to the results of elementary analysis, the complex is a mixture of compounds with PDP to $SnCl_4$ ratios of 2 : 1 and 1 : 1.

Thus the indicated chemical transformations demonstrated that the combination in the molecule of two of the most highly active centers – the unshared electron pair of nitrogen and the double bond of the pyran ring – certainly has an effect on the reactivities of the synthesized PDP. The centers frequently compete in electrophilic addition reactions.

EXPERIMENTAL

The starting vinyl ethers of 2-, 3-, and 4-pyridylcarbinols were obtained from the corresponding hydroxypyridines and acetylene by the method we previously described in [3].

2-(2-Pyridylmethoxy)-3,4-dihydropyran. A 6-g sample of the vinyl ether of 2-pyridylcarbinol [bp 73-74° (7 mm), n_D^{20} 1.5130] and 2 g of acrolein (equimolecular amounts) were placed in a rotary steel autoclave, and the mixture was held at 130° for 10 h. The resulting dark-brown viscous liquid was vacuum distilled to give 4.9 g (58%) of a product with bp 118° (3 mm), n_D^{20} 1.5240, and d_4^{20} 1.1078. Found: C 68.9; H 6.8; N 7.4%; MR_D 52.82. $C_{11}H_{13}NO_2$. Calculated: C 69.1; H 6.8; N 7.3%; MR_D 53.16.

2-(3-Pyridylmethoxy)-3,4-dihydropyran. A viscous product was obtained from 20 g of the vinyl ether of 3-pyridylcarbinol [bp 96-98° (15 mm), n_D^{20} 1.5210] and 8.3 g of acrolein (without hydroquinone) by heating at 160° for 6 h. Vacuum distillation yielded a substance with bp 112° (2 mm), n_D^{20} 1.5288, and d_4^{20} 1.1207. Found: C 68.9; H 6.9; N 7.2%; MR_D 52.56. $C_{11}H_{13}NO_2$. Calculated: C 69.1; H 6.8; N 7.3%; MR_D 53.16. The yield was 23.1 g (82%), and the R_f value [in benzene–ether (1 : 5)] was 0.55.

2-(4-Pyridylmethoxy)-3,4-dihydropyran. A 1.2-g sample of acrolein was added to 3.5 g of the vinyl ether of 4-pyridylcarbinol [bp 85° (7 mm), n_D^{20} 1.5160], and the mixture was heated at 130° in an autoclave for 4 h to give 1.8 g (43%) of 2-(4-pyridylmethoxy)-3,4-dihydropyran with bp 108-110° (6 mm), n_D^{20} 1.5255, and d_4^{20} 1.0963. Found: C 69.0; H 7.0; N 7.1%; MR_D 53.55. $C_{11}H_{13}NO_2$. Calculated: C 69.1; H 6.8; N 7.3%; MR_D 53.16.

Hydrogenation of 2-(3-Pyridylmethoxy)-3,4-dihydropyran. A solution of 4 g of PDP in 20 ml of alcohol was placed in a 0.5-liter autoclave, 2 g of Raney nickel was added, and hydrogen was fed into the system under a pressure of 50 atm. The mixture was heated at 50° for 4 h to give 3.4 g (85%) of 2-(3-pyridylmethoxy)tetrahydropyran with bp 118-119° (2 mm), n_D^{20} 1.5157, and d_4^{20} 1.0897. Found: C 68.4; H 7.8; N 7.3%; MR_D 53.52. $C_{11}H_{15}NO_2$. Calculated: C 68.4; H 7.8; N 7.2%; MR_D 53.63.

Reaction of 2-(3-Pyridylmethoxy)-3,4-dihydropyran with Ethanol. Two to three drops of anhydrous dioxane saturated with hydrogen chloride was added with stirring to an equimolecular mixture of 6 g of 2-(3-pyridylmethoxy)-3,4-dihydropyran and 1.4 g of absolute ethanol. The reaction mass was heated at 80° for 1 h, 0.9 ml of alcohol was removed by distillation at atmospheric pressure, and 0.3 g of 2,6-diethoxytetrahydropyran [bp 47° (2 mm), n_D^{20} 1.4323] was isolated by vacuum distillation (bp 82° (13 mm), n_D^{20} 1.4290 [7]).

Hydrochlorination of 2-(3-Pyridylmethoxy)-3,4-dihydropyran. Saturation of a solution of 1.1 g of the pyran in 40 ml of carbon tetrachloride at 20° with dry hydrogen chloride gave 1.2 g of a powder with mp 93-95°. Found: Cl 26.9%. $C_{11}H_{15}NO_2Cl_2$. Calculated: Cl 26.8%.

Chlorination of 2-(3-Pyridylmethoxy)-3,4-dihydropyran. A total of 40 ml of chlorine-saturated carbon tetrachloride was added dropwise in the course of 40 min at +5° to a solution of 1 g of PDP in 40 ml of CCl_4. Workup gave 0.5 g of a very viscous product. Found: Cl 25.9%. $C_{11}H_{13}NO_2Cl_2$. Calculated: Cl 27.0%.

The bromination of PDP was carried out similarly to give a product with mp 50-55°. Found: Br 45.6%. $C_{11}H_{13}NO_2Br_2$. Calculated: Br 45.5%

Synthesis of the Quaternary Salt of 2-(3-Pyridylmethoxy)-3,4-dihydropyran. A 2-g sample of 2-(3-pyridylmethoxy)-3,4-dihydropyran was added dropwise to 8 g of freshly distilled methyl iodide, during which the reaction mixture became yellowish. The mixture was heated at 51° for 4 h, and the resulting precipitate was washed with 80 ml of absolute diethyl ether to give 3.4 g (97%) of the quaternary salt. Found: I 38.3%. $C_{12}H_{16}NO_2I$. Calculated: I 38.1%.

Complex of PDP with Hydrated Stannic Chloride. A solution of 1 g of PDP in 5 ml of diethyl ether was added dropwise to a solution of 1.83 g of $SnCl_4 \cdot 5H_2O$ in 10 ml of absolute diethyl ether. A copious white precipitate formed immediately upon mixing the solutions. It was separated, washed several times with ether to remove unchanged starting materials, and dried to constant weight to give 2.0 g of a mixture of complexes with mp 108°. Found: Sn 21.7%. $C_{22}H_{26}N_2O_4Cl_4Sn$. Calculated: Sn 18.5%.

The IR spectra were obtained with a UR-20 spectrophotometer at 500-3600 cm^{-1}. Solid samples were prepared by pressing with KBr, while the spectra of the liquid compounds were recorded in microlayers. Carbon tetrachloride was used as the solvent for the recording of the PMR spectra, and hexamethyldisiloxane was used as the internal standard. The chemical shifts in parts per million (ppm) were measured on the δ scale.

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