PYRIDINE CARBOXALDEHYDE-BASED SYNTHESIS OF OXYGEN-CONTAINING HETEROCYCLES

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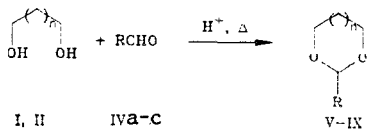
Heterocycles containing one or two atoms of oxygen are synthesized by the condensation of pyridine carboxaldehydes with ethylene glycol, 1,3-propanediol, and 3-methyl-3-buten-1-ol. When the unsaturated alcohol is used, linear acetals are formed along with the cyclic products.

Pyridine and oxygen-containing heterocycles enter into the composition of many natural and synthetic, biologically active substances. Compounds are also known containing both of these fragments in a single molecule, such as derivatives of 5-hydroxy-2-pyridyl-1,3-dioxanes, that possess antimicrobial and antifungal activity [1]. This gives grounds for considering similar polyheterocycles as potentially biologically active substances. In the present work, it is shown possible to obtain pyridine-containing derivatives of dioxolane, dioxane, and dihydropyran by the condensation of ethylene glycol (I), 1,3-propanediol (II), and 3-methyl-3-buten-1-ol (III), respectively, with 2-, 3-, and 4-pyridine carboxaldehyde (IVa-c).

Usually, the acetylation of 1,2- and 1,3-diols with an aldehyde takes place on heating in the presence of catalytic amounts of acidic reagents without any complications [2]. In our case, however, compound IV immediately gives a salt with the catalyst under these conditions, and the reaction does not go. We succeeded in carrying out the condensation of diols I and II with aldehydes IV by using an equimolar amount of p-toluenesulfonic acid. In this case, we obtained the expected 2-pyridyl-1,3-dioxolanes and 1,3-dioxanes (V-IX) (Table 1).



I, II IVa-c V-IX

I $n=0$; II $n=1$; IVa R=2-pyridyl; IVb R=3-pyridyl; IVc R=4-pyridyl; V R=3-pyridyl $n=0$; VI R=4-pyridyl $n=0$; VII R=2-pyridyl, $n=1$; VIII R=3-pyridyl, $n=1$; IX R=4-pyridyl, $n=1$

In the ^{1}H-NMR spectra of 2-alkyldioxolanes and 1,3-dioxanes, the $H(_2)$ protons usually resonate in the 4.2-4.6 ppm region, and the other protons, lying adjacent to the oxygen atoms, in the 3.3-4.0 ppm region [3]. In our case, the signals of the methine protons are shifted downfield (5.2-5.6 ppm) by the effect of the pyridine ring (Table 1).

It is known that the condensation of alcohol III with carbonyl compounds leads to the corresponding 3,6- and 5,6-dihydro-2H- and 4-methylenetetrahydropyrans [4]. It turned out that when aldehydes IVb and c were used, still another compound, linear acetal XIII, was obtained along with the corresponding pyranes, X-XII.

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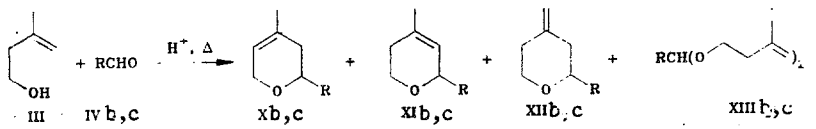
TABLE 1. 2-Pyridyl-1,3-dioxolanes (V, VI) and 1,3-Dioxanes (VII-IX)

Compound	Tbp (mm Hg), Tmp, °C	n_D^{20}	^{1}H-NMR spectrum, δ, ppm	Yield, %
V	67...68 (1)	1,5209	3,3 (4H, m, $2CH_2$), 5,5 (1H, s, CH), 7,0...8,6 (4H, m, C_5H_4N)	60
VI	72 (2)	1,5197	3,2 (4H, m, $2CH_2$), 5,6 (1H, s, CH), 7,0...8,6 (4H, m, C_5H_4N)	15
VII	40...42	—	1,0...2,4 (2H, m, CH_2), 3,6...4,3 (4H, m, $2CH_2$), 5,3 (1H, s, CH), 6,9...8,5 (4H, m, C_5H_4N)	29
VIII	98...99 (2)	1,5187	1,0...2,3 (2H, m, CH_2), 3,6...4,2 (4H, m, $2CH_2$), 5,3 (1H, s, CH), 7,0...8,6 (4H, m, C_5H_4N)	30
IX	84 (1)	1,5140	1,0...2,4 (2H, m, CH_2), 3,5...4,3 (4H, m, $2CH_2$), 5,2 (1H, s, CH), 7,0...8,8 (4H, m, C_5H_4N)	16

TABLE 2. Mass Spectra of Products of the Reaction of 3-Methyl-3-buten-1-ol with 3-Pyridine Carboxaldehyde

Compound	m/z (relative intensity, %)
Xb	175 (66), 147 (10), 146 (26), 132 (10), 130 (14), 117 (14), 108 (28), 106 (13), 105 (18), 78 (16), 68 (100), 67 (67), 53 (26), 52 (10), 51 (20), 41 (15), 39 (21)
XIb	175 (29), 160 (100), 130 (11), 106 (27), 78 (18), 51 (13), 41 (12)
XIIb	175 (65), 174 (13), 147 (12), 145 (38), 144 (39), 130 (12), 108 (100), 106 (17), 80 (25), 78 (24), 68 (27), 67 (95), 53 (40), 52 (13), 51 (24), 41 (16), 40 (36), 39 (33)

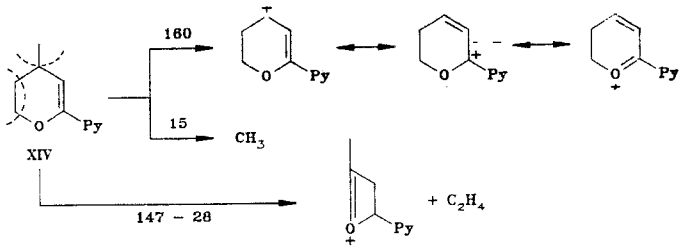
*Shown are peaks of ions having an intensity of not less than 10%.



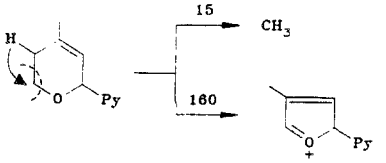
Xb R=3-pyridyl, Xc R=4-pyridyl, XIb R=3-pyridyl, XIc R=4-pyridyl, XIIb R=3-pyridyl, XIIc R=4-pyridyl XIIIb R=3-pyridyl, XIIIc R=4-pyridyl

The composition of the reaction product was studied in detail in the case of the condensation of aldehyde IVb with alcohol III. Isomers Xb, XIb, and XIIb (in a 47:12:41 ratio according to the chromatographic data) are very similar in their physical chemical properties, and it was not possible to separate them preparatively. Definite information on the presence of the heteroatoms and double bonds is given by the ^{1}H-NMR spectrum of a mixture of the isomers, in which there are all of the characteristic signals for cyclic ethers (CCl_4, δ, ppm): 1.65 s (CH_3—C=), 1.8-2.5 m (CH_2 ring), 3.2-4.1 m (CH_2—O—CH), 4.6 s (CH_2=), 5.25-5.42 m (CH=), the pyridine ring is shown by the signals: 6.9-7.2 m (4-CH), 7.3-7.6 m (3-CH), 8.2-8.5 m (2.6-CH). In conjunction with the chromatographic/mass spectral analysis, this allows one to draw a virtually unambiguous conclusion about the structure of each isomer. Compounds X-XIIb are stable under the conditions of electron impact excitation, as shown by the intensity of their molecular ions (m/z 175, Table 2). The presence of the pyridine ring is confirmed by characteristic ions with m/z 78 and m/z 51 (M-HCN) [5].

It was shown previously that the position of the double bond in unsaturated cyclic ethers can be established exactly from the type of fragmentation. For 3,6-dihydro-2H-pyrans, a diallylic retrodiene decomposition (RDD) is predicted. This leads to a fragment with m/z 68 with the greatest intensity. The second in intensity, a fragment with m/z 67, is also the result of the RDD, but with the prior 1,2-shift of the proton to the heteroatom [6]. The spectrum of compound Xb fully corresponds to a fragmentation of such nature. In the case of 5,6-dihydro-2H-pyrans, substituents usually split off from the second position on the ring with the formation of oxonium ions [6, 7]. However, the expected fragment with m/z 97 is missing from the spectrum of compound XIb, and the intensity of the fragment with m/z 78 (2-R) is small (18%). The most conspicuous ions is one with m/z 160 (M-CH_3). The splitting off of CH_3 from a vinyl group is unlikely. In the case, however, of vinyl ether XIV, the elimination of CH_3 would, in fact, lead to a stable fragment with m/z 6 160.



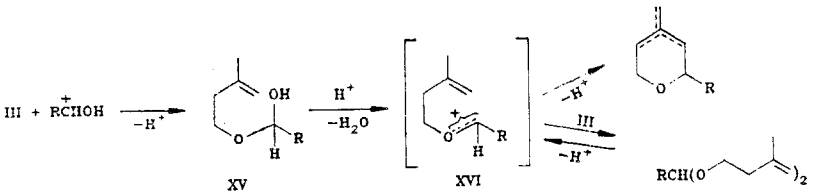
However, such a structure would also have to undergo a characteristic, diallylic scission with the elimination of ethylene and formation of a very stable fragment with m/z 147 that is not in the spectrum (Table 2), Moreover, the ^{1}H-NMR spectrum lacks the 4-CH_3 doublet in the 0.9 ppm region. It is known [8] that, in a number of cases, CH_3 is observed to split off from cyclic ethers that do not have this group, the CH_3 coming from a ring CH_2 group and a 1,2-shift of H. Here, oxonium ions are formed. If such a fragmentation is proposed for structure XIb, then one would in fact have to obtain the very stable oxonium ion conjugated to a pyridine ring with m/z 160.



The spectrum of isomer XIIb is typically complicated, showing the elimination of CH_2O (m/z 145), pyridine ion (m/z 78), deprotonated aldehyde (m/z 108), RDD (m/z 68), RDD with proton transfer (m/z 67), etc. Such a spectrum is characteristic for compounds of this type [6].

Acetal XIIIb was isolated from the reaction mixture by vacuum distillation. Its structure was shown by ^{1}H- and ^{13}C-NMR and elemental analysis.

Pyran compounds are known to be formed by the cyclization of semiacetals, XV, via intermediate XVI according to the scheme [9]



It is obvious that the linear actal is also obtained from it by reaction with alcohol III. The formation of the acetal from intermediate XVI is an intermolecular, reversible reaction [10], and that of compounds such as X-XII an intramolecular, irreversible one because of the stability of six-membered, cyclic ethers. When 3-pyridine carboxaldehyde is used, the cyclic ether is formed predominantly (37 and 5%), while in the case of 4-pyridine carboxaldehyde, the reaction goes poorly and the reaction mixture is dominated by the linear acetal (9 and 1.4%). The key intermediate, XVI, is best stabilized by conjugation with the heteroaromatic ring and this is most effective when R = 4-pyridyl. Consequently, such stabilization hinders the intramolecular reaction to the greatest extent.

EXPERIMENTAL

The ^{1}H-NMR spectra were taken on a Tesla BS-487 C instrument (80 MHz) in CCl_4; the ^{13}C-NMR spectra on a Bruker SX-90 Q (22.5 MHz) in $(CD_3)_2CO$ with HMDS as an internal standard. The chromatographic/mass spectral analysis was done on a Finningan-4021 instrument with a glass capillary column (50 m × 0.25 mm, BP-1 silicone) in a programmed temperature regime of 50 to 280 °C (5 °C/min) at 70 eV and a scanning rate of 1 spectrum/sec.

Dioxolanes (V, VI). A mixture of 4.5 g (0.04 moles) of aldehyde IVb, c, 1.9 g (0.03 moles) of diol I, 6.0 g (0.03 moles) of p-toluenesulfonic acid, and 45 ml of benzene is boiled with stirring by a Dean—Stark attachment until the evolution of water ceases. The solvent is removed in a rotary evaporator, the residue neutralized to pH 7 with a 20% NaOH

solution, washed with 30 ml of H_2O, dried with $MgSO_4$, and distilled under reduced pressure. The yields and constants of compounds V and VI are given in Table 1.

Dioxanes (VII-IX). Compounds VII-IX are obtained in an analogous manner from 4.5 g (0.04 moles) of aldehydes IVa-c, 2.8 g (0.03 moles) of diol II, and 6.0 g (0.03 moles) of p-toluenesulfonic acid in benzene (45 ml). The yields and constants are given in Table 1.

4-Methyl-2-(3-pyridyl)-3,6- (Xb) and 4-Methyl-2-(3-pyridyl)-5,6-dihydro-2H-pyran (XIb), 4-Methylene-2-(3-pyridyl)tetrahydropyran (XIIb), and Di-3-methyl-3-butenylacetal of 3-Pyridine Carboxaldehyde (XIIIb). In an analogous manner, from 3.6 g (0.04 moles) of alcohol III, 4.5 g (0.04 moles) of aldehyde IVb, and 7.4 g (0.04 moles) of p-toluenesulfonic acid, one obtains 2.7 g (37%) of a fraction with T_{bp} 106-120 °C (1 mm Hg) and n_D^{20} 1.4975, which is a mixture of isomers Xb-XIIb, and 0.4 g (5%) of XIIIb with T_{bp} 155°C (1 mm Hg) and n_D^{20} 1.5010. Compound XIIIb, $C_{15}H_{23}NO_2$. ^{1}H-NMR spectrum (CCl_4): 1.6 (3H, s, CH_3), 2.2 (2H, m, CH_2), 3.4 (2H, m, CH_2), 4.6 (2H, m, CH_2=), 5.4 (1H, m, CHO), 7.0-8.6 (4H, m, C_5H_4N). ^{13}C-NMR spectrum $(CD_3)_2CO$): 23.3 (CH_3), 38.77 (CH_2), 64.95 (CH_2), 100.12 (CH), 112.54 (CH_2=), 143.74 (C=), 124.03 ($C_{(5)}$), 135.12 ($C_{(5)}$), 135.12 ($C_{(4)}$), 135.52 ($C_{(3)}$), 149.62 ($C_{(2)}$), 150.53 ($C_{(6)}$).

In an analogous manner, from 3.6 g (0.04 moles) of alcohol III, 4.5 g (0.04 moles) of aldehyde IVc, and 7.4 g (0.04 moles) of p-toluenesulfonic acid, one obtains 0.1 g (1.4%) of a mixture of isomers Xc-XIIc with T_{bp} 95-100°C (1 mm Hg) and n_D^{20} 1.5160 and 0.9 g (9%) of acetal XIIIc with T_{bp} 105-114 °C (1 mm Hg) and n_D^{20} 1.4960. Compound XIIIc ^{1}H-NMR spectrum (CCl_4): 1.7 (3H, s, CH_3), 2.2 (2H, m, CH_2), 3.5 (2H, m, CH_2), 4.7 (2H, m, CH_2=), 5.4 (1H, s, CHO), 7.2-8.4 (4H, m, C_5H_4N).

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