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# REACTION OF 1-ACETYL-2-PHENYL-5-HYDROXY-PYRAZOLIDINES WITH ALCOHOLS ON THE SURFACE OF ADSORBENTS

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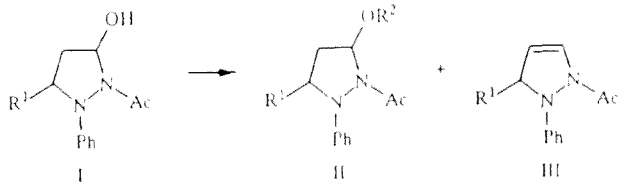
*A novel method for synthesis of 5-alkoxypyrazolidines on the surface of an adsorbent allows us to obtain derivatives of allyl, tertiary, and chiral alcohols.*

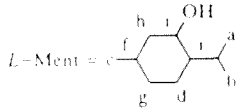
In the literature, we have described a unique method for synthesis of 1-acetyl-2-phenyl-5-alkoxypyrazolidines [1] from the corresponding hydroxypyrazolidine and alcohol using solid-phase catalysis by the ion-exchange resin KU-2 in the $H^+$ form. But the method has serious limitations, since in the case of alcohols of a complex structure the reaction either does not proceed or leads to a large amount of reaction byproducts (products of isomerization, racemization, dehydration). The major byproducts are 1-acetyl-2-phenyl-$\Delta^3$-pyrazoline (III). Since 5-alkoxypyrazolidines can serve as important synthetic precursors of different pyrazolidine derivatives, we set ourselves the goal of developing a preparative synthesis method, eliminating formation of a large amount of byproducts. Earlier we showed that in the azolidine series, carrying out the reaction on the surface of solid adsorbents often proves to be very useful [2, 3].

For the example of the reaction of methyl, allyl, and propargyl alcohols with 5-hydroxypyrazolidine Ia, we developed a method for synthesis of 5-alkoxy derivatives on a sorbent without a solvent. We found that of the large set of adsorbents ($Al_2O_3$, silica gel, diethylaminoethylcellulose, MgO, activated carbon, Florisil, Chromaton, ....), the best was an aluminosilicate catalyst containing 9.7% $Na_2O$.



I a $R^1$ = H, b $R^1$ = Me; II a $R^1$ = H, $R^2$ = Me, b $R^1$ = H, $R^2$ = $CH_2CH{=}CH_2$, c $R^1$ = H, $R^2$ = $CH_2C{\equiv}CH$, d $R^1$ = H, $R^2$ = $C(CH_3)_3$, e $R^1$ = H, $R^2$ = L-Ment, f $R^1$ = Me, $R^2$ = $CH_2CH{=}CHCH_3$, g $R^1$ = Me, $R^2$ = $C(CH_3)_3$, h $R^1$ = Me, $R^2$ = L-Ment*, III $R^1$ = H

* Numbering of atoms in L-menthol.



We should note that while for allyl and propargyl derivatives IIb, IIc the yield approaches 50%, for the methoxy derivative IIa the yield is 19% but for the reaction in solution it is 70% [1]; thus this method is justified mainly for reactions with complex alcohols. According to the PMR spectra, the compound IIc obtained has a cyclic structure [1] and contains signals from the propargyloxy group (4.4, 2.4 ppm). Similarly, in the PMR spectrum of the allyloxy derivative IIb obtained, we see all the necessary signals from the ring and the allyl radical (see Table 1). According to the NMR spectra (see Tables 1 and 2), an allyl rearrangement is not observed in the reaction with crotyl alcohol.

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TABLE 1. Chemical Shifts (d, ppm) in Spectrum of Alkoxypyrazolidines IIb-h in $CDCl_3$

| Compound* | Ac | 3-H | 4-H | 5-H | 3-Me | R' |
|---|---|---|---|---|---|---|
| IIb | 2,21 | 3,69 | 2,28 | 5,91 | — | 4,20 ($CH_2$), 5,32 ($CH_2$=), 5,81 (CH) |
| IIc | 2,20 | 3,61 | 2,30 | 5,89 | — | 2,40 (CH), 4,40 ($CH_2$) |
| IId | 2,02 | 3,60 | 2,11 | 5,9 | — | 1,29 (*t*-Bu) |
| IIe | 2,05, 2,1 | 3,42, 3,76 | 2,2...2,4 | 5,85, 5,95 | — | 0,70...2,25 (Ment., 18H), 3,72 (OCH) |
| IIf | 2,02 | 4,1 | 1,9...2,2 | 5,85 | 1,21 | 1,61 (Me), 4,0...4,20 (CH=), 5,40, 5,60 ($OCH_2$) |
| IIg | 2,05 | 4,11 | 1,88...2,21 | 6,11 | 1,35 | 1,25 (*t*-Bu) |
| IIh | 2,05 | 4,05...4,09 | 2,22...2,33 | 5,85, 6,00 | 1,25 | 0,70...2,2 (Ment., 18H), 3,72, 3,73 (OCH) |

*Signals from aromatic protons were observed in the 6.7-7.0 ppm region.

Carrying out the reaction with *tert*-butyl alcohol in solution [1] proved to be unsuccessful: complete dehydration of the alcohol and formation of the pyrazoline III occur. Applying the method of carrying out the reaction on the surface of an adsorbent, we obtained (although in low yield) the corresponding *tert*-butoxy derivatives IId and IIg with small 1-acetyl-2-phenyl-$\Delta^3$-pyrazoline impurity (1-5%). The considerably lower yield in the case of the reaction of *tert*-butyl alcohol with pyrazolidine Ia is probably explained by the high rate of polymerization of the acrolein formed upon cleavage of the pyrazolidine Ia (the polymer is one of the major reaction byproducts).

The relative arrangement of the ring substituents in the molecule of *tert*-butoxypyrazolidine IIg (assignment to a number of *cis* and *trans* isomers) was determined using the proton–proton nuclear Overhauser effect (NOE). According to the NOE data, upon saturation of 5-H the NOE is observed in the signal of the 4-H′ proton, and upon saturation of 3-H it is observed in the signal of the 4-H proton (see Table 3), which suggests a relative *trans* arrangement of the 5-H and 3-H protons. Thus the alkoxy derivative obtained has a *trans* structure, just as does the original hydroxypyrazolidine Ib [4].

As a result of reaction of *L*-menthol with the hydroxypyrazolidine Ia, we obtained compound IIe, which according to NMR spectroscopy data is a mixture of isomers which are diastereomers, since complete racemization of menthol under these conditions is assumed to be difficult. The ratio of the diastereomers was established based on the PMR spectrum and was 3:2. Flash chromatography was able to change the ratio of the diastereomers to 2:1. The ratio of the diastereomers in compound IIh was determined similarly, and also was 3:2. Thus, we have demonstrated the possibility of carrying out the reaction of 5-hydroxypyrazolidines with chiral alcohols without racemization. We could not study the relative arrangement of the substituents on the pyrazolidine ring using NOE, due to the superposition of signals from the menthol moiety of the molecule onto the 3-H and 4-H signals.

## EXPERIMENTAL

The IR spectra were recorded on a Specord IR-50 for films or for solutions in $CH_2Cl_2$. The PMR spectra were recorded on a Tesla BS-467A (60 MHz) and a Varian VXR-400 in $CDCl_3$ solutions, internal standard TMS or HMDS. The $^{13}C$ NMR spectra were measured on a Varian VXR-400 in $CDCl_3$. For the NOE experiments, we used the NOEDIF program [5]. The mass spectra were taken on an MKh-1321A with direct injection of the sample into the ion source, ionization energy 70 eV.

The course of the reaction and the purity of the products obtained were monitored by TLC on Silufol plates in a 1:1 benzene–ethylacetate system, visualization by iodine vapors and an alcoholic solution of iron(III) chloride. Chromatographic purification of the compounds obtained was carried out by flash chromatography on L 40/100 silica gel and Silpearl, and also by flash chromatography on a dry column on L5/40 silica gel [6].

1-Acetyl-2-phenyl-5-hydroxypyrazolidine (Ia) and 1-acetyl-2-phenyl-3-methyl-5-hydroxypyrazolidine (Ib) were synthesized according to the technique in [1].

TABLE 2. $^{13}C$ Chemical Shifts ($\delta$, ppm) for Compounds IIa,e,f,h in $CDCl_3$

| Compound | Pyrazolidine | | | | | $R^2$ | Phenyl | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $C_{(3)}$ | 3-Me | $C_{(4)}$ | $C_{(5)}$ | $CH_3CO$ | | *i*-C | *o*-C | *m*-C | *p*-C |
| IIa | 53,52 | – | 33,80 | 88,98 | 21,22, 175,86 | 29,82 | 152,31 | 115,64 | 129,61 | 121,72 |
| IIe | 53,74, 53,45 | – | 33,89, 33,36 | 88,30, 84,22 | 21,14, 21,25, 175,40, 174,87 | 16,03, 15,96 ($C_a$), 21,32, 21,41 ($C_b$), 22,33, 22,39 ($C_c$), 22,83, 22,99 ($C_d$), 25,53, 24,81 ($C_e$), 31,15, 31,61 ($C_f$), 34,35, 34,49 ($C_g$), 42,19, 40,56 ($C_h$), 48,20, 48,95 ($C_j$), 80,34, 80,16 ($C_i$) | 150,44, 150,79 | 115,53, 116,02 | 129,12 | 122,00 |
| IIf | 61,75, 17,60 | 21,14 | 40,39 | 85,74 | 21,14, 175,50 | 21,40 (Me), 53,00 (OC), 129,75, 126,71 (C=C) | 150,64 | 114,84 | 126,77 | 121,40 |
| IIh | 42,20, 40,58 | 20,34, 20,74 | 34,48, 34,35 | 84,12, 84,44 | 21,13, 21,24, 175,09, 175,76 | 15,87, 16,02 ($C_a$), 21,29, 21,39 ($C_b$), 22,34, 22,36 ($C_c$), 22,77, 22,97 ($C_d$), 25,49, 24,85 ($C_e$), 31,14, 31,59 ($C_f$), 34,35, 34,48 ($C_g$), 42,20, 40,58 ($C_h$), 48,21, 48,90 ($C_j$), 76,88, 80,55 ($C_i$) | 150,42, 150,76 | 115,60, 116,12 | 128,74, 128,70 | 121,48 |

*Spectrum in $(CD_3)_2CO$.

TABLE 3. NOE Values ($\eta$, %) for Compound IIg

| Observed protons | Irradiated protons | | | |
|---|---|---|---|---|
| | 5-H | 4-H | 4-H' | 3-H |
| 5-H | — | 1,5 | 5,2 | — |
| 4-H* | 1,51 | — | 19,2 | 3,33 |
| 4-H'* | 3,4 | 19,5 | — | 0,5 |
| 3-H | — | 4,6 | 1,9 | — |

*4-H) downfield proton; 4-H') upfield proton.

TABLE 4 Constants and Yields for Obtained Compounds IIb-h

| Compound | IR spectrum, $\nu$, $cm^{-1}$ | $R_f$ | Empirical formula | M* | $M_{calc}$ | Yield,* % |
|---|---|---|---|---|---|---|
| IIb | 1680 | 0,65 | $C_{14}H_{18}N_2O_2$ | 246 | 246 | 44,7 |
| IIc | 1678, 2140, 3260 | 0,60 | $C_{14}H_{16}N_2O_2$ | 244 | 244 | 61 |
| IId | 1680 | 0,75 | $C_{15}H_{22}N_2O_2$ | 262 | 262 | 13 |
| IIe | 1680 | 0,85 | $C_{22}H_{32}N_2O_2$ | 343 | 343 | 75 |
| IIf | | 0,65 | $C_{16}H_{22}N_2O_2$ | | 274 | 52 |
| IIg ** | 1680 | 0,78 | $C_{16}H_{24}N_2O_2$ | | 276 | 24 |
| IIh | 1680 | 0,88 | $C_{23}H_{34}N_2O_2$ | 357 | 357 | 82 |

*Compounds purified by method: A) IIa,b,d,e,f,g,h; B) IIc.

**Elemental analysis data for compound IIg: found, %: C 67.05, H 8.6, N 9.4; calculated, %: C 69.5, H 8.69, N 10.14.

**1-Acetyl-2-phenyl-5-hydroxypyrazolidines (IIa-h)** (general technique). Dissolve with heating 5-hydroxypyrazolidine and the corresponding alcohol in a minimal amount of benzene and add to a 20-fold excess (with respect to weight) of calcined adsorbent. Shake the adsorbent with the reagents supported on it for 2-3 min. Remove the solvent under vacuum to dryness. Shake the mixture for 20 min and allow it to stand at room temperature away from light, periodically monitoring specially withdrawn samples by TLC. After the reaction has gone to completion, extract the products with chloroform, evaporate the solvent, and chromatograph the residue by flash chromatography (method A) or by chromatography on a dry column (method B). The constants and yields for the compounds obtained are presented in Table 4.

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