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Synthesis and Steric Structure of Aroxypropynyl Alcohols of the Tetrahydropyran and Tetrahydrothiopyran Series

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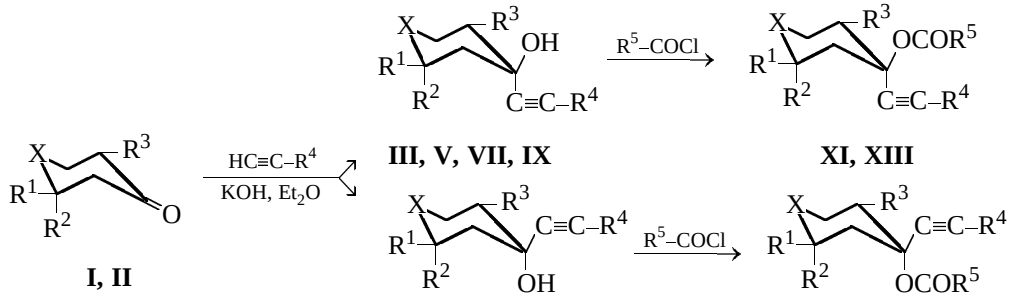
Abstract — Optimal conditions have been developed for the synthesis and isolation of phenoxy- and benzyloxypropynyl alcohols of the tetrahydropyran and tetrahydrothiopyran series. The structures of individual isomers have been established on the basis of the ^1H and ^{13}C NMR spectra. The stereochemical results of the reaction depend on the initial ketone structure.

We previously synthesized phenoxypropynyl alcohols on the basis of isomeric 2,5-dimethyltetrahydrothiopyran-4-one (**I**) and 2,2-dimethyltetrahydropyran-4-one (**II**) [1]. The present communication reports the results of our study aimed at optimizing conditions for preparing tertiary acetylenic alcohols and elucidating stereochemical aspects of nucleophilic addition at the carbonyl group of ketones **I** and **II**. The condensations of 3-phenoxypropyne and benzyloxypropyne with individual stereoisomers of heterocyclic ketones **I** and **II** were carried out at room temperature in the presence of finely powdered potassium hydroxide (technical grade) using dry diethyl ether as solvent; the reaction time was 3–4 h. The products were analyzed by TLC. In each case we obtained mixtures of epimeric tertiary acetylenic alcohols, differing by orientation of the substituents on C^4. The products were epimeric mixtures of 4-hydroxy-2,5-dimethyl-4-(3-phenoxy-1-propynyl)-tetrahydrothiopyran (**III**/**IV**), 4-(3-benzyloxy-1-propynyl)-4-hydroxy-2,5-dimethyltetrahydrothiopyran (**V**/**VI**), 4-hydroxy-2,2-dimethyl-4-(3-phenoxy-1-propynyl)tetrahydropyran (**VII**/**VIII**), and 4-(3-benzyloxy-1-propynyl)-4-hydroxy-2,2-dimethyltetrahydropyran (**IX**/**X**).



I, **III**–**VI**, **XI**–**XVI**, X = S, $R^1 = R^3 = CH_3$, R^2 = H; **II**, **VII**–**X**, **XVII**, **XVIII**, X = O, $R^1 = R^2 = CH_3$, R^3 = H; **III**, **IV**, **VII**, **VIII**, **XI**–**XIV**, **XVII**, $R^4 = CH_2OPh$; **V**, **VI**, **IX**, **X**, **XV**, **XVI**, **XVIII**, $R^4 = CH_2OCH_2Ph$; **XI**, **XII**, **XV**, **XVII**, **XVIII**, $R^5 = CH_3$; **XIII**, **XIV**, **XVI**, $R^5 = C_2H_5$.

The products were isolated from the reaction mixtures and separated into individual isomers by fractional distillation, fractional crystallization, and column chromatography. One stereoisomer always predominated over the other. The resulting alcohols were converted into the corresponding acetates and propionates **XI**–**XVIII**. The structure and purity of the products were confirmed by the data of elemental analysis, thin-layer chromatography, and IR spectroscopy. Table 1 contains their yields and physical properties.

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Table 1. Yields, melting points, R_f values, IR spectra, and elemental analyses of compounds **III**–**VI**, **VIII**, and **X**–**XVIII**

Comp. no.	Yield, %	mp, °C	R_f	IR spectrum, ν, cm^{-1}		Found, %			Formula	Calculated, %		
				OH	C=O	C	H	S		C	H	S
III	55	53–54	0.36	3328	–	69.66	7.35	11.52	$C_{16}H_{20}O_2S$	69.57	7.25	11.59
IV	22	71–72	0.41	3552	–	69.85	7.31	11.48	$C_{16}H_{20}O_2S$	69.57	7.25	11.59
V	36	[a]	0.35	3594	–	70.36	7.79	11.09	$C_{17}H_{22}O_2S$	70.34	7.59	11.03
VI	18	[a]	0.43	3590	–	70.41	7.57	11.03	$C_{17}H_{22}O_2S$	70.34	7.59	11.03
VIII	67	[a]	0.50	3298	–	73.47	7.47	–	$C_{16}H_{20}O_3$	73.85	7.69	–
X	59	[a]	0.40	3585	–	74.40	8.14	–	$C_{17}H_{22}O_3$	74.45	8.03	–
XI	92	64–65	0.51	–	1735	68.01	7.35	9.94	$C_{18}H_{22}O_3S$	67.92	6.92	10.06
XII	89	47–48	0.56	–	1740	67.79	7.54	9.79	$C_{18}H_{22}O_3S$	67.92	6.92	10.06
XIII	87	[a]	0.59	–	1744	68.71	7.29	9.35	$C_{19}H_{24}O_3S$	68.67	7.23	9.64
XIV	83	[a]	0.61	–	1736	68.71	7.40	9.64	$C_{19}H_{24}O_3S$	68.67	7.23	9.64
XV	84	42–43	0.52	–	1748	68.47	7.19	9.45	$C_{19}H_{24}O_3S$	68.67	7.23	9.64
XVI	81	[a]	0.60	–	1725	69.58	7.55	9.11	$C_{20}H_{26}O_3S$	69.36	7.51	9.25
XVII	61	[a]	0.54	–	1748	71.30	7.47	–	$C_{18}H_{22}O_4$	71.52	7.28	–
XVIII	56	[a]	0.49	–	1744	72.02	7.74	–	$C_{19}H_{24}O_4$	72.15	7.59	–

[a] Oily substance.

The steric structure of the products was established on the basis of the ^1H and ^{13}C NMR spectral data (Tables 2 and 3). In the ^1H NMR spectra (Table 2) of the major epimers (**III** and **V**) the signal from the hydroxy proton appears in a weaker field relative to that of the weaker epimer (**IV** and **VI**): $\Delta\delta$ = 0.4–0.55 ppm. This difference may be used to distinguish orientation of substituents on C^4 in epimeric pairs of tertiary alcohols. Judging by the chemical shifts of the OH proton, we concluded that the 4-hydroxy group in compounds **III** and **V** is equatorial. Correspondingly, the hydroxy group in epimers **IV** and **VI** occupies the axial position. It should be noted that in the spectra of equatorial epimers **III** and **V** and acetoxy derivative **XI** the signals from 3-H_a and 5-H_a are displaced upfield by 0.1–0.16 ppm relative the respective signals of **IV**, **VI**, and **XII**. Equatorial OH and OAc groups in **III** and **V** appear in a *synclinal* position with respect to 3-H_a and 5-H_a, so that the oxygen atom exerts a shielding effect on the latter. The axial OH and OAc groups in **IV**, **VI**, and **XII** have no shielding effect, for they occupy a *transoid* position with respect to these protons. Like axial epimers **IV** and **VI**, the 3-H_a and 5-H_a protons in alcohol **VIII** appear in a weaker field due to their *transoid* position with respect to the hydroxy group. The 3-H_e and 5-H_e signals are displaced upfield by 0.1–0.2 ppm relative to the 3-H_a and 5-H_a signals owing to shielding by the axial hydroxy group. Only traces of equatorial epimers **VII** and **IX** were detected by TLC in the product mixtures.

The data of ^{13}C NMR spectroscopy (Table 3) confirm the steric structure of compounds **III**–**VI** and **XI**–**XII**. The C^4 signal of **III**, **V**, and **XI** is observed in a weaker field (by 3.31–3.57 ppm) than the respective signal of **IV**, **VI**, and **XII**, in keeping with the effect of the 4-hydroxy group [2]. The position of the C^3 signal is poorly related with the increments $A_i(C_i)$. Compounds **III**, **V**, and **XI** give more downfield ($\Delta\delta_C$ ~1 ppm) signals from C^3. The methyl group on C^5 is more sensitive to orientation of substituents on C^4. Shielding of the C^5 nuclei is likely to be determined by the increments of the hydroxy group and acetylenic moiety which are arranged *gauche* with respect to the 5-methyl group. The downfield shift of the C^5 signal in the spectra of **III** and **V** by 2.20–2.30 ppm relative to the corresponding signal of **IV** and **VI** is consistent with published data [2]. This pattern is not typical of acetoxy derivatives **XI** and **XII**, presumably due to the different functionality, size, and polarity of the substituent on C^4. The C^2 and C^6 signals of **IV** and **VI** appear in a stronger field, as compared to **III** and **V** ($\Delta\delta_C$ 3.37–4.74 ppm), owing to the γ shielding by the axial hydroxy group.

On the basis of the steric structure of the isolated alcohols we can draw some conclusions on the stereochemistry of nucleophilic addition of aroxypropynes at the carbonyl group of ketones **I** and **II**. The reaction with ketone **I** in which the carbonyl group is not sterically hindered yields mainly alcohols **III** and **V** with equatorial orientation of the hydroxy group.

Table 2. ^{1}H NMR spectra of compounds **III**–**VI**, **VIII**, and **X**–**XVI**

Comp. no.	Chemical shifts δ, ppm												
	2-H	3-H_e	3-H_a	5-H_e	5-H_a	6-H_e	6-H_a	2-CH_3	5-CH_3	CH_2OPh	CH_2Ph	OH	Ph
III	3.02	2.18	1.59	–	1.76	2.31	2.57	1.14	1.02	4.73	–	2.25	6.93–7.31 m
IV	3.13	2.25	1.75	–	1.86	2.18	2.78	1.12	1.05	4.64	–	1.85	6.92–7.30 m
V	3.15	2.24	1.63	–	1.81	2.39	2.70	1.19	1.12	4.58	4.21	2.55	7.32 s
VI	3.15	2.29	1.78	–	1.89	2.22	2.80	1.14	1.13	4.56	4.18	2.00	7.30 s
VIII	–	1.66	1.86	1.70	1.89	3.81	3.65	1.25, 1.21	–	4.70	–	2.49	6.95–7.29 m
X	–	–	–	–	–	–	–	1.30, 1.29	–	4.56	4.19	3.33	7.15–7.43 m
XI	3.08	2.98	1.57	–	2.03	2.24	2.65	1.13	0.95	4.75	–	–	6.94–7.30 m
XII	2.78	3.20	1.65	–	1.87	2.27	2.83	1.12	1.05	4.71	–	–	6.93–7.29 m
XIII	3.08	2.99	1.56	–	2.05	2.25	2.66	1.13	0.95	4.78	–	–	6.94–7.30 m
XIV	2.77	3.21	1.65	–	1.87	2.27	2.84	1.11	1.06	4.72	–	–	6.93–7.29 m
XV	2.83	3.25	1.69	–	1.94	2.32	2.88	1.19	1.14	4.58	4.20	–	7.22–7.29 m
XVI	2.82	3.26	1.70	–	1.95	–	2.89	1.19	1.14	4.58	4.20	–	7.24–7.34 m

Comp. no.	Coupling constants J_{HH}, Hz										
	H^2–CN_3	H^2_a–H^3_a	H^2_a–H^3_e	H^3_a–H^3_e	H^5–CN_3	H^5_a–H^5_e	H^5_a–H^6_a	H^5_a–H^6_e	H^5_e–H^6_a	H^5_e–H^6_e	H^6_a–H^6_e
III	6.9	12.0	2.7	12.3	6.6	–	11.4	3.6	–	–	14.1
IV	6.9	12.5	2.1	13.5	6.6	–	11.4	3.3	–	–	13.5
V	6.6	12.0	2.4	12.6	6.9	–	11.7	3.3	–	–	14.1
VI	6.6	12.0	2.4	13.8	6.9	–	12.0	3.6	–	–	13.8
VIII	–	–	–	13.8	–	13.5	11.6	3.6	3.3	6.3	12.3
XI	6.9	12.0	2.4	12.3	6.3	–	11.7	3.0	–	–	14.1
XII	6.6	12.0	2.4	14.7	6.6	–	11.7	3.6	–	–	13.8
XIII	6.6	11.7	2.7	12.6	6.6	–	11.4	3.3	–	–	14.1
XIV	6.9	12.0	2.7	14.7	6.9	–	11.7	3.6	–	–	14.1
XV	6.9	12.0	2.4	14.3	6.9	–	11.7	3.9	–	–	13.8
XVI	6.9	12.0	2.7	14.1	6.6	–	11.7	3.9	–	–	14.1

According to the NMR data, the equatorial-to-axial isomeric ratio is 68 : 32 for compounds **III**/**IV** and 62 : 38 for **V**/**VI**. In this case predominant nucleophilic attack on the carbonyl group from the axial region is favored by stereoelectronic factors. The addition to sterically hindered ketone **II** is governed by a steric factor: The axial methyl group on C^2 hampers attack on the carbonyl group from the axial region. Therefore, the major products are alcohols **VIII** and **X** with axial orientation of the hydroxy group. Epimeric alcohols **VII** and **IX** are formed in trace amounts (TLC). Thus, our results are consistent with the known stereochemical relations holding in nucleophilic addition of acetylenes at the carbonyl group of heterocyclic ketones.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer; samples were prepared as KBr pellets (c = 0.25%) or thin films. The NMR spectra were obtained on a Varian Mercury-300 instrument at 300 MHz for ^{1}H and 75.457 MHz for ^{13}C. The ^{13}C signals were assigned using the ^{13}C–{^{1}H} monoresonance spectra. The products were separated by column chromatography on Silpearl silica gel using 1 : 4 ethyl acetate–petroleum ether (bp 40–70°C) as eluent. Silufol UV-254 plates were used for TLC in the system acetone–hexane (1 : 3). The melting points were determined on a Boetius device. The yields, melting points, analytical data, and IR spectra of compounds **III**–**VI**, **VIII**, and **X**–**XVIII** are collected in Table 1.

4-Hydroxy-2,5-dimethyl-4-(3-phenoxy-1-propynyl)tetrahydrothiopyran (III/IV) (mixture of epimers). A solution of 0.1 mol of 3-phenoxypropyne in 20 ml of diethyl ether was added dropwise over a period of 0.5 h to a mixture of 150 ml of dry diethyl

Table 3. ^{13}C NMR spectra (δ_C, ppm) of compounds **III**–**VI**, **VIII**, **X**–**XII**, and **XV**

Comp. no.	C^2–CN_3	C^5–CN_3	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}	C^i	C^o	C^m	C^p
III	20.38	15.09	35.30	50.37	72.32	42.88	33.14	86.79	82.48	55.56	–	156.94	129.08	114.86	121.30
IV	20.30	15.84	30.64	49.36	69.01	40.58	29.77	90.51	78.41	55.64	–	157.19	129.08	114.63	121.17
V	20.45	15.32	35.47	50.51	72.32	42.88	33.33	85.88	83.33	56.92	71.35	136.82	128.16	127.76	127.66
VI	20.38	16.01	30.73	49.64	68.96	40.68	29.80	89.89	79.26	56.94	71.27	136.96	128.13	127.74	127.61
VIII	26.45 28.51	–	64.83	47.84	71.47	38.93	55.59	90.83	78.70	57.40	–	157.17	129.11	114.11	121.20
X	26.78 28.33	–	64.83	47.96	71.55	38.99	57.03	90.20	79.59	58.00	71.42	136.88	128.13	127.71	127.61
XI	20.32	15.35	34.53	45.56	79.31	41.47	32.03	84.78	82.90	55.61	–	156.99	129.03	114.96	121.20
XII	20.24	16.03	30.76	44.41	75.74	41.73	30.04	86.25	80.82	55.73	–	157.28	129.00	114.78	121.09
XV	20.28	16.27	30.96	44.57	75.92	41.83	30.05	85.59	81.76	56.90	71.03	137.08	128.08	127.88	127.54

ether and 0.3 mol of finely powdered technical grade potassium hydroxide, stirred at room temperature. The mixture was stirred for 3 h, a solution of 0.1 mol of ketone **I** in 150 ml of diethyl ether was added over a period of 0.5 h, and the mixture was stirred for 1.5 h. It was then treated with 20 ml of water, the organic phase was separated and dried over $MgSO_4$, the solvent was distilled off, and the residue (22.6 g, 82%) was subjected to column chromatography.

4-(3-Benzyloxy-1-propynyl)-4-hydroxy-2,5-dimethyltetrahydrothiopyran (V/VI), 4-hydroxy-2,2-dimethyl-4-(3-phenoxy-1-propynyl)tetrahydropyran (VII/VIII), and 4-(3-benzyloxy-1-propynyl)-4-hydroxy-2,2-dimethyltetrahydropyran (IX/X) were synthesized in a similar way.

4-Acetoxy-2,5-dimethyl-4-(3-phenoxy-1-propynyl)tetrahydrothiopyran (XI/XII). A mixture of 0.40 g of alcohol **III**/**IV** and 10 ml of freshly distilled acetic anhydride was heated for 1 h at 60–65°C. Excess acetic anhydride was distilled off under reduced pressure (water-jet pump), and the residue was recrystallized from acetone–hexane.

4-Acetoxy-4-(3-benzyloxy-1-propynyl)-2,5-dimethyltetrahydrothiopyran (XV), 4-acetoxy-2,2-dimethyl-4-(3-phenoxy-1-propynyl)tetrahydropyran (XVII), and 4-acetoxy-4-(3-benzyloxy-1-propyniyl)-2,2-dimethyltetrahydropyran (XVIII) were synthesized in a similar way. Oily acetates **XVII** and **XVIII** were isolated by column chromatography.

2,5-Dimethyl-4-(3-phenoxy-1-propynyl)-4-propionyloxytetrahydrothiopyran (XIII/XIV). A mixture of 0.40 g of alcohol **III**/**IV** and 10 ml of freshly distilled propionyl chloride was heated for 1 h at 65–70°C. Excess propionyl chloride was distilled off under reduced pressure (water-jet pump), and the residue was purified by column chromatography.

4-(3-Benzyloxy-1-propynyl)-2,5-dimethyl-4-propionyloxytetrahydrothiopyran (XVI) was synthesized in a similar way.

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