SYNTHESIS AND PROPERTIES OF TETRAHYDROFURYLACETYLENIC ALCOHOLS

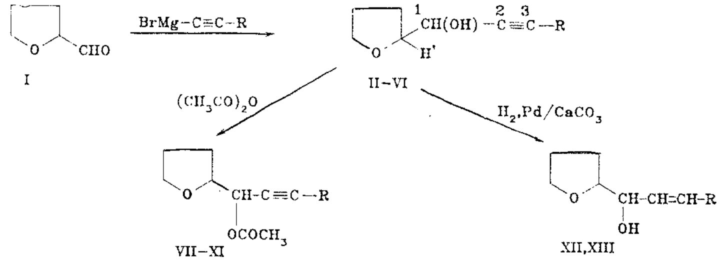
R. A. Karakhanov, M. M. Vartanyan,
T. Yu. Solov'eva, and L. F. Lapuka

UDC 547.722.3'361.362.07:541.63:543.422.25

Previously undescribed tetrahydrofurylacetylenic alcohols were obtained in good yields. These compounds were acetylated and selectively hydrogenated to the corresponding ethylenic derivatives. A PMR spectral study was carried out on the structure of the compounds synthesized.

Acetylenic furan derivatives have high fungistatic activity [1]. On the other hand, biologically active compounds containing a tetrahydrofuran ring are less toxic relative to the furan analogs [2, 3].

We have synthesized previously undescribed compounds containing a tetrahydrofuran ring and fragments such as a triple bond and hydroxyl group. Since the synthesis of such compounds is not possible by the catalytic hydrogenation of acetylenic furan alcohols, the following general scheme was proposed for the preparation of the corresponding tetrahydrofurylacetylenic alcohols from tetrahydrofurfural (I):



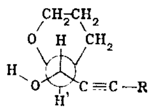
II, VII R=H; III, VIII R=CH_3; IV, IX, XII R=n-C_4H_9; V, X R=n-C_5H_{11}; VI, XI, XIII R=C_6H_5

The action of acetic anhydride on II-VI gave acetates in good yields which were close to quantitative. The hydrogenation of the tetrahydrofurylacetylenic alcohols to the corresponding ethylenic analogs was performed in the presence of Lindlar catalyst [4]. In this case, alcohol VI, in which the triple bond is in conjugation with the phenyl group, is readily hydrogenated with high selectivity at 1 atm and room temperature. Tetrahydrofurylacetylenic alcohol IV with an alkyl substituent at the triple bond could be hydrogenated to the corresponding ethylenic derivative only at 60°C and 100 atm initial hydrogen pressure.

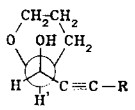
Different stereoisomeric forms are possible for II-XIII. The structure identification was carried out by proton magnetic resonance spectroscopy. Protons bound to a carbon atom bearing a hydroxyl group are deshielded and their signals are found at 3.5-4.5 ppm. The position and shape of the resonance signal depends both on the number and orientation of the adjacent vicinal protons. The large coupling constants between the vicinal protons (8-14 Hz) may be attributed to diaxial orientation of the atoms since smaller couplings (2-6 Hz) are found in the case of gauche interactions. We should also expect that the axial protons at $C_{(1)}$ are at higher field than the equatorial protons in the epimer. The PMR spectra of II-VI indicate that these compounds are a mixture of diastereomers:

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1602-1606, December, 1983. Original article submitted December 27, 1982; revision submitted May 11, 1983.

0009-3122/83/1912-1263$07.50



threo-isomer (T)



erythro-isomer (E)

The proton at $C_{(1)}$ in IIT gives rise to a multiplet at δ 4.17 ppm with coupling constants $J_3 = 6.3$ and $J_4 = 1.9$ Hz. The latter coupling is due to an interaction with the acetylenic proton and is also seen in the splitting of the signal for this proton (at 2.39 ppm). The proton at $C_{(1)}$ in the erythro-isomer IIE gives a doublet of doublets at δ 4.35 ppm with $J_3 = 3.7$ and $J_4 = 2.2$ Hz. The long-range coupling $J_4 = 2.2$ Hz is the result of interaction with the acetylenic proton of this isomer (at 2.37 ppm). Integration of the areas of these multiplets shows that the threo-isomer accounts for 45% of the mixture. In going from II to the phenylacetylenic derivative VI, the content of the threo-isomer increases to 66%. This increase may be the result of substituent stereoelectronic effects. The threo-isomer is stabilized by an intramolecular hydrogen bond between the hydroxyl group proton and the oxygen atom of the tetrahydrofuran ring. Such hydrogen bonding is impossible in the erythro form [7] and the hydroxyl group proton forms a hydrogen bond, apparently, predominantly with the hydroxyl oxygen atom of another molecule. Unsaturated substituents are known to give a negative inductive effect which is enhanced with increasing saturation of the substituent. This factor likely accounts for the increase in the fraction of threo-isomer in VI. On the other hand, the replacement of the acetylenic proton by an alkyl group produces steric hindrance to the formation of an intermolecular hydrogen bond.

The resonance signals for the $C_{(1)}$ proton in acetates VII-XI are shifted downfield by 1.1 ppm, i.e., to 5.3-5.5 ppm. The acetate group methyl protons give a signal at 2.05-2.12 ppm. The greatest nonequivalence between $CH_3C{=}O$ signals ($\Delta\delta = 0.05$ ppm) was found for the phenylacetylenic derivative XI; the $CH_3C{=}O$ signal of the erythro form is at lower field. The content of the threo-isomer in the mixture increases from 47% in acetate VII to 73% in acetate XI.

The threo-isomer predominates in the mixture of diastereomers of tetrahydrofurylethylenic alcohols XII and XIII. The signal for the $C_{(1)}$ proton of the threo-isomer is seen as a multiplet at higher field (4.15-4.25 ppm) than for the erythro-isomer (4.52-4.65 ppm). The vicinal coupling constants which characterize the interaction of the $C_{(1)}$ proton with the $C_{(2)}$ proton are 3 Hz in the erythro-isomer and 6 Hz in the threo-isomer. The ethylenic protons give two multiplets with chemical shifts characteristic for Z-configuration of the double bond: 5.23 and 5.35 ppm for alcohol XII and 5.66 and 6.65 for XIII [8]. The coupling constant between the protons on the $-C{=}C-$ fragment is 11.5 Hz, which is also characteristic for Z-isomers of disubstituted olefins.

The predominant conformation of the tetrahydrofuran ring was not determined. The tetrahydrofuran molecule is known to exist as a half-chair, in which the oxygen atom, $C_{(2')}$, and $C_{(5')}$ are found in a single plane.

EXPERIMENTAL

The PMR spectra of the compounds synthesized were taken on a Tesla BS-497 spectrometer at 100 MHz and on a Bruker WM-250 spectrometer at 250 MHz in deuterochloroform. HMDS was used as the internal standard. The IR spectra were taken neat on a UR-20 spectrometer between potassium bromide plates. The gas-liquid chromatographic analysis was carried out on a Chrom-4 chromatograph with a flame ionization detector, 5 × 100-mm stainless steel column packed with 4% OV-225 on Chromatone with 300°C injector temperature, and 25 ml/min nitrogen gas carrier flow rate. The column temperature was varied from 130° to 180°C.

1-(Tetrahydrofuryl-2)-propyn-2-ol-1 (II, Tables 1 and 2). A sample of ethylmagnesium bromide prepared from 12 g (0.49 mole) magnesium filings and 56 g (0.51 mole) ethyl bromide in 300 ml dry tetrahydrofuran was added in 4-5 ml portions at a constant acetylene flow rate to 200 ml dry tetrahydrofuran. Then, the flask was placed in an ice bath and 51 g (0.51 mole) tetrahydrofurfural in 50 ml dry tetrahydrofuran was added dropwise with intensive stirring. The complex formed was decomposed with 6% hydrochloric acid. The product was extracted with ether, dried over anhydrous magnesium sulfate, and distilled in vacuum.

TABLE 1. Characteristics of Compounds Synthesized II-XIII

Compound	Bp, °C (pressure, mm)	n_D^{20}	d_4^{20}	IR spectrum, cm^{-1}	Found, %		Chemical formula	Calculated		Yield, %
					C	H		C	H	
II	95—97 (11)	1,4802	1,0819	2118, 3290, 3400	66,7	7,9	$C_7H_{10}O_2$	66,7	8,0	56
III	120—122 (12)	1,4880	1,0634	2230, 3410	68,4	8,6	$C_8H_{12}O_2$	68,5	8,6	61
IV	129—131 (2)	1,4786	1,0213	2230, 3415	72,2	9,9	$C_{11}H_{18}O_2$	72,5	9,9	52
V	139—141 (4)	1,4698	—	2230, 3415	73,3	10,2	$C_{12}H_{20}O_2$	73,4	10,3	60
VI	141—143 (1)	1,5729	1,1205	2235, 3410, 1600	77,1	6,9	$C_{13}H_{14}O_2$	77,2	7,0	62
VII	115—117 (15)	1,4600	1,0765	1740, 2120, 3270	64,0	7,3	$C_9H_{12}O_3$	64,3	7,2	87
VIII	127—128 (10)	1,4689	1,0613	1740, 2235	65,7	7,6	$C_{10}H_{14}O_3$	65,9	7,7	88
IX	106—108 (1)	1,4658	1,0080	1740, 2235	69,5	8,9	$C_{13}H_{20}O_3$	69,6	9,0	87
X	138—140 (3)	1,4649	—	1740, 2235	70,8	9,3	$C_{14}H_{22}O_3$	70,6	9,3	90
XI	137—140 (1)	1,5420	1,1151	1740, 2235, 1600	73,7	6,7	$C_{15}H_{16}O_3$	73,8	6,6	92
XII	89—90 (1)	1,4731	—	978, 1660, 3017, 3440	71,7	10,9	$C_{11}H_{20}O_2$	71,7	10,9	85
XIII	151—153 (3)	1,5584	—	805, 1600, 1648, 3430	76,2	7,8	$C_{13}H_{16}O_2$	76,4	7,9	83

TABLE 2. PMR Spectra of Tetrahydrofurylacetylenic Alcohols II-VI

Compound	R	Chemical shifts, ppm, multiplicity, coupling constants, Hz						Fraction of threo-isomer in the mixture, %
		R	—OH	1-H (threo)	1-H (erythro)	tetrahydrofuran ring		
						2'- ı 5'-H	3'- - 4'-H	
II	H	2,39, d, threo $J_4=1,9$; 2,37, d, threo po, $J_4=2,2$	3,40, s	4,17, d. d, $J_3=6,3$, $J_4=1,9$	4,35, d.d, $J_3=3,7$, $J_4=2,2$	3,70—4,05, m	1,70—2,05, m	45
III	CH_3	1,73, d, $J_{(5)}=1,7$	2,78, s	4,23, m	4,48, m	3,60—3,90, m	1,70—2,10, m	49
IV	n-C_4H_9	0,90, t, $J=7,0$; 1,35—1,50, m 2,20, m	3,60, m	4,24, m	4,43, m	3,75—4,15, m	1,80—2,10, m	54
V	n-C_5H_{11}	0,85, t, $J=6,9$; 1,30—1,45, m 2,25, m	3,65, s	4,28, m	4,44, m	3,70—4,10, m	1,75—2,05, m	59
VI	C_6H_5	7,25—7,40, m	3,17, s	4,48, d, $J_3=7,1$	4,69, d, $J_3=4,2$	3,80—4,23, m	1,80—2,15, m	66

1-(2-Tetrahydrofuryl)-2-butyn-1-ol (III, Tables 1 and 2). An ethereal solution of ethylmagnesium bromide prepared from 24 g (0.98 mole) magnesium filings and 109 g (1 mole) ethyl bromide in 500 ml absolute ether was bubbled with dry nitrogen and then, methylacetylene was passed at 5°C for 6 h. A sample of 100 g (1 mole) tetrahydrofurfural in 100 ml absolute ether was added and the reaction mixture was treated as described above.

1-(2-Tetrahydrofuryl)-2-heptyn-1-ol (IV, Tables 1 and 2). A sample of 90 g (1.1 mole) 1-hexyne obtained according to a standard procedure [5] in an equal volume of absolute ether and 100 g (1 mole) I were added dropwise with strong stirring and the use of a reflux condenser to an ehtereal solution of ethylmagnesium bromide obtained from 24 g (0.98 mole) magnesium filings and 115 g (1.06 mole) ethyl bromide with strong stirring and the use of a reflux condenser. The complex formed was treated according to the above procedure.

Samples of 1-(2-tetrahydrofuryl)-2-octyn-1-ol (V) and 1-(2-tetrahydrofuryl)-3-(1-phenyl)-propyn-2-ol (VI) were prepared by analogy (Tables 1 and 2).

The Synthesis of Acetates of Tetrahydrofurylacetylenic Alcohols VII-X. A sample of 20 g tetrahydrofurylacetylenic alcohol II-VI and 45 ml freshly distilled acetic anhydride was heated at reflux for 4 h in a nitrogen atmosphere. Excess acetic anhydride and acetic acid were removed and the residue was distilled in vacuum (Tables 1 and 3).

TABLE 3. PMR Spectra of Acetates of Tetrahydrofurylacetylenic Alcohols VII-XI

Compound	R	Chemical shifts, ppm, multiplicity, coupling constants, Hz							(Content of threo-isomer in mixture, %
		R	CH_3—C=O (threo)	CH_3—C=O (erythro)	1-H (threo)	1-H (erythro)	tetrahydrofuran ring		
							2'-and 5'-H	3'and 4'-H	
VII	H	2,51, d, threo J_4=2,2; 2,52, d, threo po, J_4=2,1	2,15, s	2,15, s	5,30, d. d, J_3=7,2, J_4=2,2	5,41, d. d, J_3=3,7, J_4=2,1	3,80—4,20, m	1,80—2,15, m	47
VIII	CH_3	1,82, d, J_5=2,1	2,06, s	2,07, s	5,25, d. q, J_3=7,0, J_5=2,2	5,35 d. q, J_3=3,6, J_5=2,0	3,70—4,10, m	1.85—2,10, m	67
IX	n-C_4H_9	0,91, t, J=7,2; 1,30—1,56, m 2,22, m	2,11, s	2,12, s	5,30, d. t, J_3=7,2, J_5=1,8	5,43, d. t, J_3=3,9, J_5=1,7	3,80—4,15, m	1,80—2,10, m	69
X	n-C_5H_{11}	0,83, t, J=6,9; 1,20—1,50, m 2,14, m	1,98, s	2,01, s	5,28, d. t, J_3=7,1, J_5=1,7	5,45, d. t, J_3=3,9, J_5=1,7	3,74—4,15, m	1,70—2,10, m	71
XI	C_6H_5	7,25—7,50, m	2,13, s	2,18, s	5,55, d., J_3=7,5	5,69, d, J_3=3,2	3,80—4,30, m	1,85—2,10, m	73

1-(Tetrahydrofuryl-2)-hepten-2-ol (XII, Table 1). A sample of 5 g IV, 0.5 g 5% Pd/$CaCO_3$ modified with lead acetate, 0.2 ml quinoline, and 20 ml absolute ethanol was placed in a glass ampul. The ampul was placed in a rotating metal autoclave. The hydrogenation was carried out at 60°C for 4 h with 100 atm initial hydrogen pressure. After filtration and distillation of the ethanol, the product was washed with 6% hydrochloric acid and then water, extracted with ether, dried over anhydrous magnesium sulfate, and distilled in vacuum. PMR spectrum: 0.80 (t, 3H, J = 7.2 Hz), 1.25 (m, 4H), 1.78 (m, 4H), 1.98 (m 2H), 2.65 (s, 1H), 3.50-3.90 (m, 3H), 4.15 (m, 1H-threo), 4.52 (m, 1H-erythro), 5.23 (m, 1H), 5.35 (m, 1H).

1-(2-Tetrahydrofuryl)-3-(1-phenyl)-2-propen-1-ol XIII, Table 1). A sample of 5 g VI, 0.5 g 5% Pd/$CaCO_3$ modified with lead acetate, 0.~~2 g~~ quinoline, and 20 ml absolute ethanol was added in an argon atmosphere to a glass long-necked hydrogenation flask attached to a mechanical stirrer. The hydrogenation was carried out for 4 h at room temperature and atmospheric pressure. After filtration and distillation of the ethanol, the product was washed with 6% hydrochloric acid and then water, extracted with ether, dried over anhydrous magnesium sulfate, and distilled in vacuum. PMR spectrum: 1.70-1.90 (m, 4H), 2.85 (s, 1H), 3.70-4.00 (m, 3H), 4.33 (m, H-threo), 4.70 (m, H-erythro), 5.65 (m, 1H), 6.65 (m, 1H) 7.10-7.40 (m, 5H).

LITERATURE CITED

1. S. Giller, M. Alberta, Z. Zile, L. Vereshchagin, K. Venter, and S. Korshunov, Izv. Akad. Nauk Latv. SSR, No. 2, 63 (1966).
2. S. A. Giller, R. A. Zhuk, and M. Yu. Lidak, Dokl. Akad. Nauk SSSR, 176, 332 (1967).
3. O. M. Ramazonov, "The synthesis and properties of tetrahydrofurfural and some of its derivatives," Candidate's Dissertation, Ufa (1982).
4. H. Z. Lindlar, Helv. Chim. Acta, 35, 446 (1952).
5. Organic Synthesis [Russian translation], Vol. 4, Izd. Inostr. Lit., Moscow (1953), p. 111.
6. N. Bhacca and D. Williams, Applications of NMR Spectroscopy in Organic Chemistry, Holden-Day (1964).
7. W. E. Truce and T. C. Klingler, J. Org. Chem., 35, 1834 (1970).
8. A. Gordon and R. Ford, Chemist's Companion, Wiley (1973).
9. E. Eliel, N. Allinger, S. Angyal, and G. Morrison, Conformational Analysis, Wiley (1965).