ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 9, pp. 1278–1281. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © N.A. Ivanova, K.S. Kislitsina, S.A. Torosyan, M.S. Miftakhov, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 9, pp. 1294–1297.

Reactions of 2,3,5-Trichloro-4-hydroxycyclopent-2-en-1-one with Dimethyl- and Diethylamines and Benzenethiol. Some Aspects of Stereochemical Assignments in Cyclopentenone Chlorohydrins

N. A. Ivanova, K. S. Kislitsina, S. A. Torosyan, and M. S. Miftakhov

Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia
e-mail: bioreg@anrb.ru

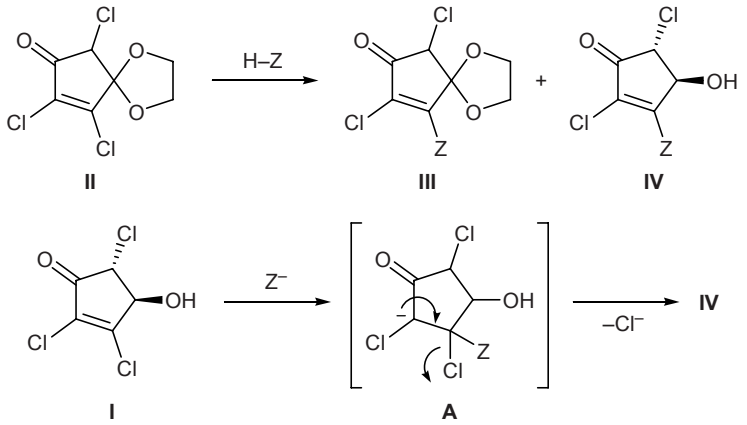
Received July 20, 2007

Abstract—*trans*-2,3,5-Trichloro-4-hydroxycyclopent-2-en-1-one reacted with dimethyl- and diethylamines and sodium benzenethiolate in methanol to give the corresponding products of chlorine replacement at the sp^2-hybridized C^3 atom via Ad_NE mechanism. The reactions were characterized by partial *trans–cis* isomerization. Assignment of configuration of isomeric cyclopentenone chlorohydrins on the basis of the NMR data is discussed.

DOI: 10.1134/S1070428008090054

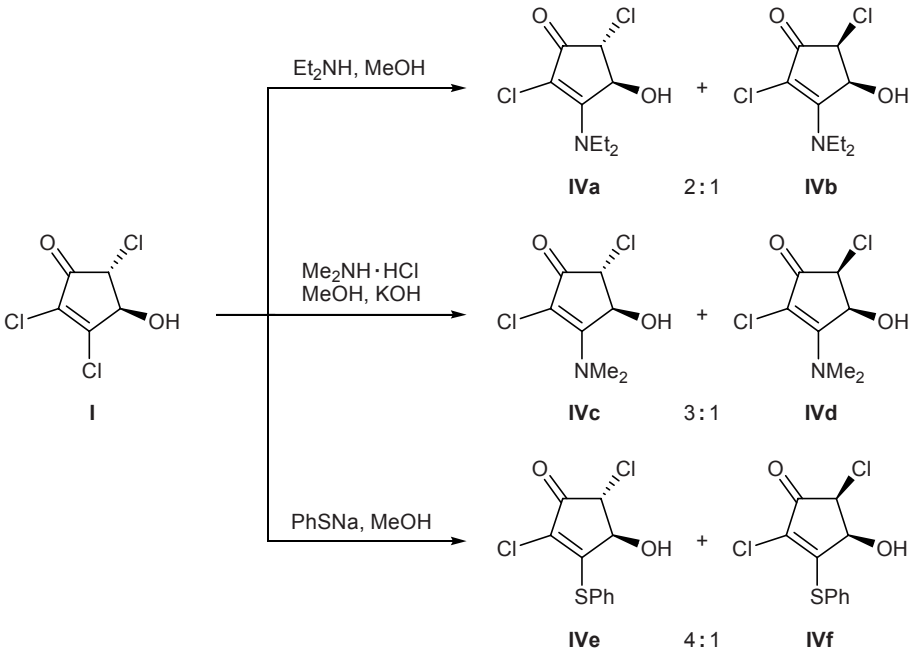
Reactions of prostanoid 4-hydroxycyclopentenones with oxygen- and sulfur-centered nucleophiles are usually nonselective, and they give rise to mixtures of products some of which result from enolate-induced rearrangements of initial hydroxycyclopentenones [1, 2]. In continuation of our studies on the reactivity of 2,3,5-trichloro-4-hydroxycyclopent-2-en-1-one (**I**) [3] toward nucleophiles, in the present work we examined its reactions with dimethylamine, diethylamine, and benzenethiol and discussed specificity of stereochemical assignment of the resulting stereoisomeric amino-substituted cyclopentenone chlorohydrins. 4-Hydroxycyclopentenone **I** smoothly reacted with the above nucleophiles according to the Ad_NE scheme, leading to compounds **IV** via replacement of chlorine at the most activated vinylic C^3 atom. This reaction direction is typical of structurally related systems having a protected oxo group (acetal moiety) instead of hydroxy group on C^4 (Scheme 1; transformation **II**→**III** [4]).

Scheme 1.



Z = NR_2, SR.

Scheme 2.



Thus, unlike parent chlorine-free analogs [1, 2], the reactions of 4-hydroxycyclopentenone **I** with nucleophiles are regioselective. Presumably, the presence of chloro substituents in the enone system favors effective quenching of primary Michael adducts (enolates **A** generated by addition of nucleophile) via fast elimination of chloride ion (Ad_NE mechanism).

Although the reactions with nucleophiles under standard conditions [4] were performed with stereochemically pure *trans*-chlorohydrin **I**, the substitution products, compounds **IVa**–**IVf** were mixtures of stereoisomeric *cis*- and *trans*-chlorohydrins (Scheme 2).

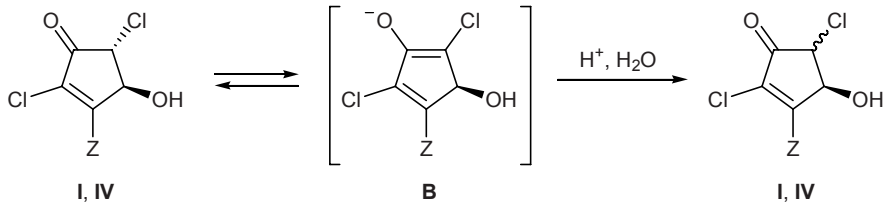
Like initial *trans*- and *cis*-chlorohydroxycyclopentenones **I** [3], stereoisomeric amino- and phenylsulfanyl-substituted derivatives **IVa**–**IVf** characteristically showed in the ^{1}H NMR spectra different coupling constants between the 4-H and 5-H protons (J = 1.4–1.8 Hz for the *trans* isomers and 5.3–5.8 Hz for the *cis* isomers; see table). In addition, the 5-H signal of *trans* isomers **IVa** and **IVc** is located in a stronger field than the corresponding signal of *cis* isomers **IVb** and **IVd** due to shielding effect of the *cis*-oriented vicinal hydroxy group [5]. By contrast, the chlorine atom in *cis* isomers **IVb** and **IVd** exerts deshielding effect on the *cis*-oriented proton in the α-position.

Furthermore, the NMR spectra of **IVa** and **IVb** somewhat differed from the spectra of **IVc** and **IVd**. The 5-H signal of the major *trans* isomer **IVa**, as well as of **IVc**, resonated as a doublet at δ 4.20 ppm with a coupling constant $J_{5,4}$ = 1.4 Hz, whereas the 4-H signal was an almost merged doublet of doublets at δ 5.87 ppm with $J_{4,5}$ = 1.4 and 6.4 Hz. These data indicated that 4-H in **IVa** was coupled with the OH proton, the latter resonating at δ 4.9 ppm ($J_{4,OH}$ = 6.4 Hz). *cis* Isomer **IVb** was characterized by a doublet signal at δ 4.67 ppm ($J_{5,4}$ = 5.8 Hz) from 5-H and a doublet of doublets at δ 5.05 ppm (J = 5.8, 7.6 Hz) from 4-H, while the hydroxy proton signal appeared as

Characteristic chemical shifts and coupling constants in the ^{1}H and ^{13}C NMR spectra of cyclopentenones **IVa**–**IVd**

Compound no.	^{1}H chemical shifts δ, ppm			^{1}H–^{1}H coupling constants, Hz		^{13}C chemical shifts δ_C, ppm	
	4-H	5-H	OH	$J_{4,5}$	$J_{4,OH}$	C^4	C^5
IVa	5.87	4.20	4.90	1.4	6.4	77.23	61.73
IVb	5.05	4.67	5.15	5.8	7.6	67.56	58.89
IVc	5.87	4.20	–	1.4	–	74.48	59.72
IVd	5.06	4.62	–	5.9	–	65.94	57.71

Scheme 3.



Z = Cl, NR_2, PhS.

a doublet at δ 5.15 ppm (J = 7.6 Hz). The C^4 and C^5 signals in the ^{13}C NMR spectra of *cis* and *trans* isomers **IV** were also characteristic. The chemical shifts of C^4 and C^5 in minor *cis* isomers **IVb** and **IVd** were lower due to steric compression.

The formation of considerable amounts of *cis*-adducts **IVb**, **IVd**, and **IVf** in the reactions of 4*r*,5*t*-2,3,5-trichloro-4-hydroxycyclopent-2-en-1-one (**I**) may be rationalized by enolization of the initial compound and vinylogous amides **IV** under basic conditions and by the lack of stereoselectivity in the protonation of enolates **B** (Scheme 3).

EXPERIMENTAL

The IR spectra were recorded on UR-20 and Specord M-80 spectrometers from neat substances (films) or suspensions in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer at 300.13 and 75.47 MHz, respectively, from solutions in $CDCl_3$ using the solvent as reference (δ 7.27 ppm, δ_C 77.00 ppm). The progress of reactions was monitored by TLC on Silufol plates using hexane–ethyl acetate as eluent; spots were detected by treatment with an alkaline solution of potassium permanganate [6].

(±)-2,5αβ-Dichloro-3-diethylamino-4β-hydroxycyclopent-2-en-1-one (IVa/IVb, mixture of stereoisomers**).** Diethylamine, 0.21 ml (2.0 mmol), was added under stirring to a solution of 0.2 g (1.0 mmol) of hydroxycyclopentenone **I** in 3 ml of methanol. The mixture was stirred at room temperature until the initial compound disappeared (2 h, TLC), the solvent was distilled off under reduced pressure, a saturated solution of sodium chloride was added to the residue, and the products were extracted into ethyl acetate (3×10 ml). The extracts were combined, washed with a saturated solution of sodium chloride, dried over $MgSO_4$, concentrated, and subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (7:3) as eluent to isolate 0.13 g (54%) of a colorless crystalline substance. According to the ^1H NMR data, the product was a mixture of *trans* and *cis* isomers **IVa** and **IVb** at a ratio of 2:1. IR spectrum, ν, cm^{-1}: 1384, 1464, 1740, 3292. Found, %: C 45.31; H 5.40; Cl 29.69; N 5.80. $C_9H_{13}Cl_2NO_2$. Calculated, %: C 45.40; H 5.50; Cl 29.78; N 5.88.

trans Isomer **IVa.** R_f 0.30 (petroleum ether–ethyl acetate, 1:1). ^1H NMR spectrum (acetone-d_6), δ, ppm: 1.29 t (6H, CH_3, J = 7.0 Hz), 3.60–3.80 br.s (4H, CH_2N), 4.20 d (1H, 5-H, $J_{5,4}$ = 1.4 Hz), 4.90 d (1H, OH, $J_{OH,4}$ = 6.4 Hz), 5.87 d.d (1H, 4-H, $J_{4,5}$ = 1.4, $J_{4,OH}$ = 6.4 Hz). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 14.99 and 15.41 (Me), 45.56 (NCH_2), 61.73 (C^5), 77.23 (C^4), 101.04 (C^2), 166.34 (C^3), 188.36 (C^1).

cis Isomer **IVb**. R_{f-} 0.12 (petroleum ether–ethyl acetate, 1:1). ^1H NMR spectrum (acetone-d_6), δ, ppm: 1.29 t (6H, CH_3, J = 7.0 Hz), 4.85 octet (4H, CH_2N, J = 6.2 Hz), 4.67 d (1H, 5-H, $J_{5,4}$ = 5.8 Hz), 5.05 d.d (1H, 4-H, $J_{4,5}$ = 5.8, $J_{4,OH}$ = 7.6 Hz), 5.15 d (1H, OH, $J_{OH,4}$ = 7.6 Hz). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 14.99 and 15.41 (Me), 45.40 (NCH_2), 58.89 (C^5), 67.56 (C^4), 96.89 (C^2), 163.28 (C^3), 189.92 (C^1).

(±)-2,5αβ-Dichloro-3-dimethylamino-4β-hydroxycyclopent-2-en-1-one (IVc/IVd, mixture of stereoisomers**).** Hydroxycyclopentenone **I**, 0.2 g (1.0 mmol), was dissolved in 3 ml of methanol, 0.16 g (2 mmol) of dimethylamine hydrochloride and 0.1 g (2.0 mmol) of potassium hydroxide were added, and the mixture was stirred at room temperature until the initial compound disappeared completely (2 h, TLC). The solvent was distilled off under reduced pressure, the residue was treated with a saturated solution of sodium chloride, and the products were extracted into ethyl acetate (3×10 ml). The extracts were combined, washed with a saturated solution of sodium chloride, dried over $MgSO_4$, concentrated, and subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (1:1) to isolate 0.09 g (43%) of a colorless crystalline substance. According to the ^1H NMR data, the product was a mixture of isomers

IVc and **IVd** at a ratio of 3:1. IR spectrum, ν, cm^{-1}: 1377, 1422, 1705, 3209. Found, %: C 39.98; H 4.26; Cl 33.72; N 6.53. $C_7H_9Cl_2NO_2$. Calculated, %: C 40.02; H 4.32; Cl 33.76; N 6.67.

trans Isomer **IVc**. R_f 0.48 (petroleum ether–ethyl acetate, 2:3). ^{1}H NMR spectrum (methanol-d_4–acetone-d_6), δ, ppm: 3.38 s and 3.40 s (3H each, NMe), 4.20 d (1H, 5-H, $J_{5,4}$ = 1.4 Hz), 5.87 d (1H, 4-H, $J_{4,5}$ = 1.4 Hz). ^{13}C NMR spectrum (methanol-d_4–acetone-d_6), δ_C, ppm: 40.35 (NMe), 60.94 (C^5), 76.01 (C^4), 98.75 (C^2), 164.48 (C^3), 184.41 (C^1).

cis Isomer **IVd**. R_f 0.31 (petroleum ether–ethyl acetate, 2:3). ^{1}H NMR spectrum (methanol-d_4–acetone-d_6), δ, ppm: 3.10 br.s (OH), 3.39 s and 3.40 s (3H each, NMe), 4.62 d (1H, 5-H, $J_{5,4}$ = 5.9 Hz), 5.06 d (1H, 4-H, $J_{4,5}$ = 5.9 Hz). ^{13}C NMR spectrum (methanol-d_4–acetone-d_6), δ_C, ppm: 40.35 (NMe), 58.86 (C^5), 67.59 (C^4), 98.02 (C^2), 164.48 (C^3), 186.68 (C^1).

(±)-2,5α,β-Dichloro-4β-hydroxy-3-phenylsulfanylcyclopent-2-en-1-one (IVe/IVf, mixture of stereoisomers**).** Hydroxycyclopentenone **I**, 0.2 g (1.0 mmol), was dissolved in 3 ml of anhydrous methanol, a solution of 1.3 mmol of sodium benzenethiolate in 5 ml of methanol was added, and the mixture was stirred at room temperature until the initial compound disappeared (1 h). The mixture was treated with a saturated solution of sodium chloride, the solvent was distilled off under reduced pressure, and the residue was extracted with ethyl acetate (3×10 ml). The extracts were combined, washed with a saturated solution of sodium chloride, dried over $MgSO_4$, concentrated, and subjected to column chromatography on silica gel using petroleum ether–ethyl acetate (8:2) as eluent to isolate 0.26 g (96%) of a yellow oily substance. The product was a mixture of isomers **IVe** and **IVf** at a ratio of 4:1 (according to the ^{1}H NMR data), which could not be separated by chromatography. IR spectrum, ν, cm^{-1}: 1476, 1547, 1717, 3421. Found, %: C 47.91; H 2.86; Cl 25.72; S 11.59. $C_{11}H_8Cl_2O_2S$. Calculated, %: C 48.02; H 2.93; Cl 25.77; S 11.65.

trans Isomer **IVe**. R_f 0.33 (petroleum ether–ethyl acetate, 7:3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.10 br.s (OH), 4.20 d (1H, 5-H, J = 1.8 Hz), 4.60 d (1H, 4-H, J = 1.8 Hz), 7.35–7.70 m (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 60.00 (C^5); 77.42 (C^4); 125.84 (C^i), 129.69, 130.69, 135.05 (C_{arom}); 126.73 (C^2); 169.39 (C^3); 187.12 (C^1).

cis Isomer **IVf**. R_f 0.33 (petroleum ether–ethyl acetate, 7:3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.10 br.s (OH), 4.43 d (1H, 5-H, J = 5.3 Hz), 4.60 d (1H, 4-H, J = 5.3 Hz), 7.35–7.70 m (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 58.35 (C^5); 66.23 (C^4); 125.18 (C^2); 126.01 (C^i), 129.54, 130.77, 135.92 (C_{arom}); 169.83 (C^3), 187.12 (C^1).

REFERENCES

1. Novak, L., Kolonits, P., Szàntay, Cs., Aszodi, J., and Kajtàr, M., *Tetrahedron*, 1982, vol. 38, p. 153.
2. Novak, L., Szàntay, Cs., Meisel, T., Aszodi, J., Szabo, É., and Fekete, J., *Tetrahedron*, 1985, vol. 41, p. 435.
3. Akhmetvaleev, R.R., Imaeva, L.R., and Miftakhov, M.S., *Russ. J. Org. Chem*., 1997, vol. 33, p. 1267.
4. Shavaleeva, G.A., *Cand. Sci. (Chem.) Dissertation*, Ufa, 2003.
5. Donaldson, R.E., Saddler, J.C., Byrn, S., McKenzie, A.T., and Fuchs, P.L., *J. Org. Chem*., 1983, vol. 48, p. 2167.
6. Kirchner, J.G., *Thin-Layer Chromatography*, Perry, E.S., Ed., New York: Wiley, 1978, 2nd ed. Translated under the title *Tonkosloinaya khromatografiya*, Moscow: Mir, 1981, vol. 1, p. 269.