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1,2-Adducts of 5-Allyl-2,3,5-trichloro-4,4-dimethoxy-2-cyclopentenone with Ethyl Acetate Lithium Salt and Their Reactions with Iodine*

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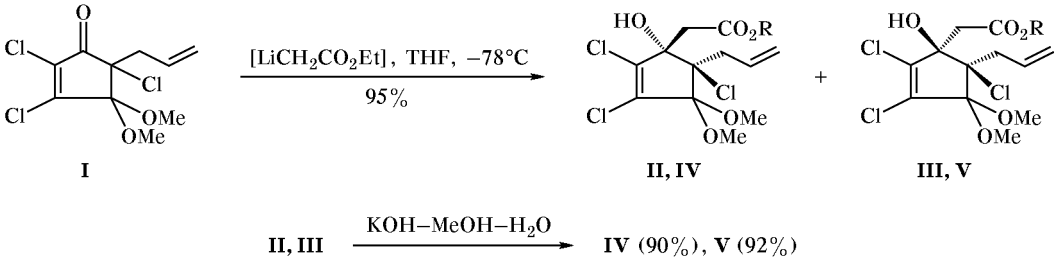
Abstract—The condensation of 5-allyl-2,3,5-trichloro-4,4-dimethoxy-2-cyclopentenone with ethyl acetate lithium salt generated *in situ* in THF at –78°C gave adducts at the carbonyl group, the corresponding *cis*- and *trans*-chlorohydrins. The steric structure of the products was determined by involving them into reaction with iodine. From the *trans*-adduct the expected bicyclic compound was obtained, while the *cis*-chlorohydrin underwent anomalous deacetalization to iodomethoxycyclopentenone. Spectral parameters of the adducts were discussed. Unusual diastereotopicity was observed for the remote methylene groups in the ester moiety.

It was shown previously [1] that the reaction of cyclopentenone **I** with allyl bromide and zinc in DMF [2] is accompanied by exothermic effect, leading to formation of isomeric 1,2-adducts at the carbonyl group (*cis*- and *trans*-chlorohydrins at a ratio of 2 : 3) in a good yield. However, no analogous Reformatsky reaction occurred between ketone **I** and ethyl bromoacetate. Using more nucleophilic lithium derivative of ethyl acetate we succeeded in obtaining isomeric chlorohydrins **II** and **III** at a ratio of 1 : 2 (Scheme 1). The pure isomers were isolated in a good yield by column chromatography on silica gel. Contrary to the expectations, the stereoselectivity was not high despite the conditions of kinetic control. Alkaline hydrolysis of esters **II** and **III** gave the corresponding hydroxy acids **IV** and **V**.

The structure of the diastereoisomers was proved chemically, i.e., by involving them in iodocyclization reaction [3]. It is seen that only *trans*-chlorohydrin **II** is capable of undergoing intramolecular cyclization. In fact, the reaction of **II** with iodine in the presence of sodium carbonate gave the expected bicyclic compound **VI** in 67% yield (Scheme 2). The β-orientation of the iodomethyl group in **VI** follows from the coupling constant $^3J_{4\beta,3}$ = 10.3 Hz in its ^{1}H NMR spectrum [4]. Under analogous conditions, from *cis*-chloro-

Scheme 1.



I **II, IV** **III, V**

II, III $\xrightarrow{KOH–MeOH–H_2O}$ **IV** (90%), **V** (92%)

II, **III**, R = Et; **IV**, **V**, R = H.

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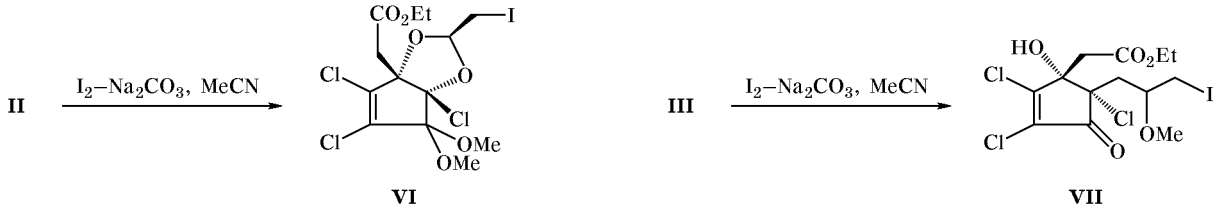
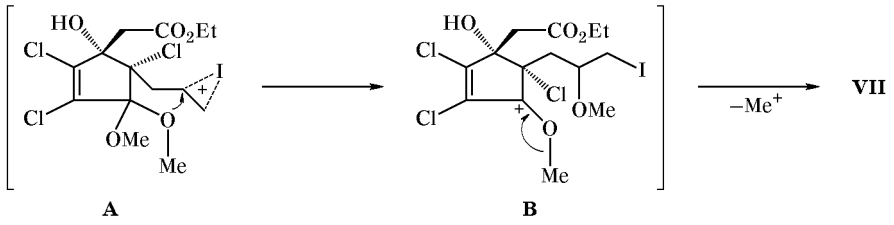
Scheme 2.



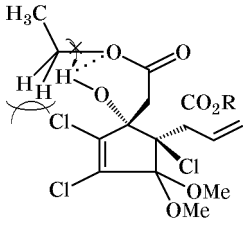
Scheme 3.



hydrin **III** we obtained only the deacetalization product, cyclopentenone **VII**, in 51% yield. According to the spectral data, compound **VII** is an individual stereoisomer in which the configuration of the $C^{2'}$ chiral center was not determined.

The transformation **III** → **VII** can formally be regarded as iodine-initiated deacetalization with migration of methoxy group to the side chain. Its possible mechanism is shown in Scheme 3. It includes intramolecular abstraction of methoxy group in intermediate **A** by iodonium cation and subsequent expulsion of methyl cation from ion **B**.

The ^{1}H NMR spectra of adducts **II** and **III** are characterized by diastereotopic signals from the methylene protons of the ethoxy group, which appear as two quartets. However, it is difficult to reliably determine the geminal coupling constants for the minor components. Compounds **II** and **III** show different signals from the CH_2CO_2 protons: the corresponding signal in the spectrum of *trans*-chlorohydrin **II** is a singlet at δ 2.80 ppm, while *cis*-isomer **III** gives rise to doublets at δ 2.60 and 3.00 ppm. These findings may be explained by formation of intramolecular hydrogen bond in **II** and **III**. As follows from the molecular models, intramolecular H-bonding in



C

II fixes spiro structure **C** with *s-trans* orientation of the ethyl group and carbonyl oxygen atom in the ethoxycarbonyl fragment; here, the rotation about the CH_3CH_2-O bond is restricted by the presence of bulky substituents in positions *2* and *5* (2 chlorine atoms and allyl group; $C^5-Cl-OCH_2$ interaction).

Obviously, this is the reason for the observed diastereotopicity of the OCH_2 protons. However, it is difficult to explain clearly defined diastereotopicity of the CH_2CO_2 protons in the ^{1}H NMR spectrum of **III**, as well as the fact that the CH_2 signals are very similar in the ^{13}C NMR spectrum of **II** (δ_C 39.35 and 39.47 ppm) but different in the spectrum of **III** (δ_C 39.13 and 41.78 ppm).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as thin films or dispersions in Nujol. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively; $CDCl_3$ was used as solvent, and TMS, as internal reference. The mass spectra (70 eV) were run on an MKh-1320 instrument with direct sample admission into the ion source heated to 60–90°C. Thin-layer chromatography was performed on Silufol plates.

(±)-5α-Allyl-2,3,5β-trichloro-1β-ethoxycarbonylmethyl-4,4-dimethoxy-2-cyclopenten-1α-ol (II) and (±)-5α-allyl-2,3,5β-trichloro-1α-ethoxycarbonylmethyl-4,4-dimethoxy-2-cyclopenten-1β-ol (III). To a solution of 0.6 g (5.93 mmol) of diisopropylamine in 20 ml of THF (argon, 0°C) we added with stirring 1.55 ml (5.9 mmol) of a 3.8 N solution of *n*-BuLi in

hexane. The mixture was stirred for 15 min at 0°C and cooled to –78°C, and a solution of 0.5 g (5.63 mmol) of ethyl acetate in 10 ml of THF was added over a period of 15 min. The mixture was stirred for 30 min, and a solution of 0.5 g (1.75 mmol) of ketone **I** in 3 ml of THF was added dropwise. The mixture was stirred to 10 min, warmed up to 20°C, and decomposed with a saturated solution of NH_4Cl. Tetrahydrofuran was evaporated under reduced pressure, the aqueous layer was extracted with ethyl acetate (3×30 ml), and the extract was dried over $MgSO_4$ and evaporated to obtain 0.75 g of an oily residue. It was subjected to chromatography on silica gel to isolate 420 mg (64%) of compound **II**, R_f 0.35, and 204 mg (31%) of **III**, R_f 0.57 (hexane–ethyl acetate, 5 : 1).

Compound **II**. mp 65–67°C. IR spectrum, ν, cm^{-1}: 1650, 1720, 3400. ^1H NMR spectrum, δ, ppm: 1.28 t (3H, CH_3, J = 6 Hz), 2.80 s (2H, CH_2CO_2), 2.87 d.d.t (1H, J = 15.9, 5.7, 1.3 Hz) and 3.04 d.d.t (1H, J = 15.9, 6.7, 1.3 Hz) (CH_2, allyl), 3.42 s (3H, OCH_3), 3.48 s (3H, OCH_3), 4.15 q and 4.18 q (2H, OCH_2, J = 5.6 Hz), 5.10–5.20 m (2H) and 5.87–6.00 m (1H) ($CH{=}CH_2$). ^{13}C NMR spectrum, δ_C, ppm: 13.97 (CH_3), 39.35 (CH_2), 39.47 (CH_2), 50.86 (OCH_3), 52.13 (OCH_3), 61.47 (OCH_2), 81.43 (C^5), 85.15 (C^1), 103.95 (C^4), 118.36 and 132.59 ($CH{=}CH_2$), 131.02 (C^3), 138.80 (C^2), 170.58 (CO_2). Found, %: C 45.53; H 5.15; Cl 27.53. $C_{14}H_{19}Cl_3O_5$. Calculated, %: C 45.00; H 5.13; Cl 28.46.

Compound **III**. IR spectrum, ν, cm^{-1}: 1650, 1720, 3400. ^1H NMR spectrum, δ, ppm: 1.30 t (3H, CH_3, J = 7 Hz), 2.68 d (1H, J = 16 Hz) and 3.00 d (1H, J = 16 Hz) (CH_2CO_2), 2.75 d.d.t (1H, J = 14.2, 7.1, 1.2 Hz) and 2.90 d.d.t (1H, J = 14.2, 7.0, 1.1 Hz) (CH_2, allyl), 3.40 s (3H, OCH_3), 3.55 s (3H, OCH_3), 4.20 q and 4.21 q (2H, OCH_2, J = 5.6 Hz), 4.97–5.10 m (2H) and 5.68–5.80 m (1H) ($CH{=}CH_2$), 6.20 s (1H, OH). ^{13}C NMR spectrum, δ, ppm: 13.99 (CH_3), 39.13 (CH_2), 41.78 (CH_2), 51.12 (OCH_3), 51.85 (OCH_3), 61.65 (OCH_2), 82.48 (C^5), 83.90 (C^1), 102.40 (C^4), 117.71 and 133.96 ($CH{=}CH_2$), 131.02 (C^3), 138.59 (C^2), 173.68 (CO_2). Found, %: C 43.76; H 4.92; Cl 30.10. $C_{14}H_{19}Cl_3O_5$. Calculated, %: C 45.00; H 5.13; Cl 28.46.

(±)-5α-Allyl-1β-carboxymethyl-2,3,5β-trichloro-4,4-dimethoxy-2-cyclopenten-1α-ol (IV) and (±)-5α-allyl-1α-carboxymethyl-2,3,5β-trichloro-4,4-dimethoxy-2-cyclopenten-1β-ol (V). A solution of 100 mg (0.27 mmol) of ester **II** or **III** and 22.5 mg (0.4 mmol) of KOH in 2 ml of methanol and 2 ml of water was stirred for 2 h at 20°C. Methanol was distilled off, the aqueous phase was adjusted to pH 3, and the product was extracted into ethyl acetate (3×30 ml). The combined extracts were dried over $MgSO_4$ and evaporated.

Compound **IV**. Yield 83 mg (90%). mp 107–109°C. R_f 0.53 (hexane–ethyl acetate, 1 : 1). IR spectrum, ν, cm^{-1}: 1630, 1700, 3400. ^1H NMR spectrum, δ, ppm: 2.72 m (1H) and 3.00 d.d (1H, J = 7.2 and 13.8 Hz) (CH_2), 2.80 br.s (2H, CH_2), 3.40 s (3H, OCH_3), 3.45 s (3H, OCH_3), 5.05–5.15 m (2H) and 5.80–6.00 m (1H) ($CH{=}CH_2$), 7.10–7.60 (COOH, OH). ^{13}C NMR spectrum, δ, ppm: 38.90 (CH_2), 39.38 (CH_2), 50.90 (OCH_3), 52.01 (OCH_3), 81.40 (C^5), 84.81 (C^1), 103.84 (C^4), 118.37 and 132.50 ($CH{=}CH_2$), 131.05 (C^3); 138.70 (C^2), 173.85 (COO).

Compound **V**. Yield 85 mg (92%). Oily substance, R_f 0.6 (hexane–ethyl acetate, 1 : 1). IR spectrum, ν, cm^{-1}: 1620, 1720–1740, 3400. ^1H NMR spectrum, δ, ppm: 2.7–2.95 (2H, CH_2), 2.80 d (1H, J = 6.4 Hz) and 3.10 d (1H, J = 6.4 Hz) (CH_2COO), 3.42 s (3H, OCH_3), 3.57 s (3H, OCH_3), 5.00–5.15 m (2H) and 5.70–5.80 m (1H) ($CH{=}CH_2$). ^{13}C NMR spectrum, δ, ppm: 39.20 (CH_2), 41.67 (CH_2), 51.08 (OCH_3), 51.78 (OCH_3), 82.48 (C^5), 83.65 (C^1), 102.28 (C^4), 117.87 and 133.71 ($CH{=}CH_2$), 131.44 (C^3); 138.02 (C^2), 178.31 (COO).

(±)-5α,7,8-Trichloro-1α-ethoxycarbonylmethyl-3β-iodomethyl-6,6-dimethoxy-2-oxabicyclo[3.3.0]-octane (VI) and 2,3,5α-trichloro-4β-ethoxycarbonylmethyl-4α-hydroxy-5-(3-iodo-2-methoxypropyl)-2-cyclopenten-1-one (VII). To 200 mg (0.535 mmol) of compound **II** or **III** in 3 ml of acetonitrile we added 568 mg (5.35 mmol) of Na_2CO_3 and 680 mg (2.68 mmol) of I_2, the mixture was stirred for 24 h in the dark, 5 ml of ethyl acetate was added, and the mixture was treated with a 10% solution of Na_2SO_3. The organic layer was separated, washed with a saturated solution of NaCl, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel.

Compound **VI**. Yield 144 mg (67%). R_f 0.48 (hexane–ethyl acetate, 5 : 1). IR spectrum, ν, cm^{-1}: 1610, 1720. ^1H NMR spectrum [$(CD_3)_2CO$], δ, ppm: 1.23 t (3H, CH_3, J = 7 Hz), 2.50 d.d (1H, 4-H, J = 10.7, 14.3 Hz), 2.68 d.d (1H, 4-H, J = 5.4, 14.3 Hz), 3.34 s (3H, OCH_3), 3.30–3.43 m (2H, CH_2I), 4.05 q (2H, OCH_2, J = 7.0 Hz), 4.42 sext (1H, 3-H, J = 5.4 Hz). ^{13}C NMR spectrum [$(CD_3)_2CO$], δ, ppm: 8.09 (CH_2I), 13.35 (CH_3), 39.23 (CH_2), 46.30 (CH_2), 50.23 (OCH_3), 51.45 (OCH_3), 59.58 (OCH_2), 78.77 (C^3), 82.23 (C^5), 92.92 (C^1), 101.76 (C^6), 129.24 (C^4), 139.07 (C^8), 167.01 (CO_2). Found, %: C 33.48;

H 3.60; Cl 20.37; I 24.52. $C_{14}H_{18}Cl_3IO_5$. Calculated, %: C 33.66; H 3.63; Cl 21.29; I 25.40.

Compound **VII**. Yield 133 mg (51%). R_f 0.45 (hexane–ethyl acetate, 7:3). IR spectrum, ν, cm^{-1}: 1610, 1720, 1760, 3480. ^1H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3, J = 7.1 Hz), 2.10 d.d (1H, J = 8.2, 14.6 Hz) and 2.40 d.d (1H, 1′-H, J = 1.1, 14.6 Hz), 2.89 d (1H, 1″-H, J = 15.6 Hz), 3.08 d (1H, 1″-H, J = 15.6 Hz), 3.15 s (3H, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 7.77 (CH_2I), 14.32 (CH_3), 35.94 (CH_2), 47.04 (CH_2), 56.50 (OCH_3), 62.53 (OCH_2), 75.44 ($C^{2'}$), 77.25 (C^5), 80.41 (C^4), 133.42 (C^2), 156.64 (C^3), 170.87 (COO), 189.26 (C^1). Mass spectrum, *m*/*z*: 484 M^+, 469 $[M-CH_3]^+$, 453 $[M-OCH_3]^+$, 449 $[M-Cl]^+$, 357 $[M-I]^+$, 343 $[M-CH_2I]^+$, 325 $[M-I-CH_3OH]^+$, 289, 275, 257, 243, 185 (base peak), 141 $[CH_2I]^+$, 87 $[ClC{\equiv}CC{=}O]^+$, 71, 59, 58, 43. Found, %: C 32.55; H 3.23; Cl 21.18; I 25.48. $C_{13}H_{16}Cl_3IO_5$. Calculated, %: C 32.16; H 3.32; Cl 21.91; I 26.14.

REFERENCES

1. Akhmetvaleev, R.R., Imaeva, L.R., Belogaeva, T.A., and Miftakhov, M.S., *Russ. J. Org. Chem.*, 1999, vol. 35, no. 2, pp. 238–241.
2. Shomo, L., Ishifine, M., and Kashimura, S., *Chem. Lett.*, 1990, no. 3, pp. 449–452.
3. Cardillo, G. and Orena, M., *Tetrahedron*, 1990, vol. 46, no. 10, pp. 3321–3408.
4. Akbutina, F.A., Torosyan, S.A., Vostrikov, N.S., Spirikhin, L.V., and Miftakhov, M.S., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 1996, no. 12, pp. 2961–2963.