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Some Reactions of 5-Benzyl-2,3,5-trichloro-4,4-dimethoxycyclopent-2-en-1-one and Its Derivatives

F. A. Gimalova, V. A. Egorov, 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

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Abstract—5-Benzyl-2,3,5-trichloro-4,4-dimethoxycyclopent-2-en-1-one and 2-benzyl-2,4,5-trichlorocyclopent-4-ene-1,3-dione were subjected to dehydrochlorination by the action of 1,4-diazabicyclo[2.2.2]octane, selective dechlorination at C^5 by the action of $CrCl_2$, and Ad_NE replacement of the chlorine atom at C^3 by the action of secondary amines. The reduction of 2-benzyl-2,4-dichloro-5-morpholinocyclopent-4-ene-1,3-dione with sodium tetrahydridoborate in methanol and ethanol gave different products.

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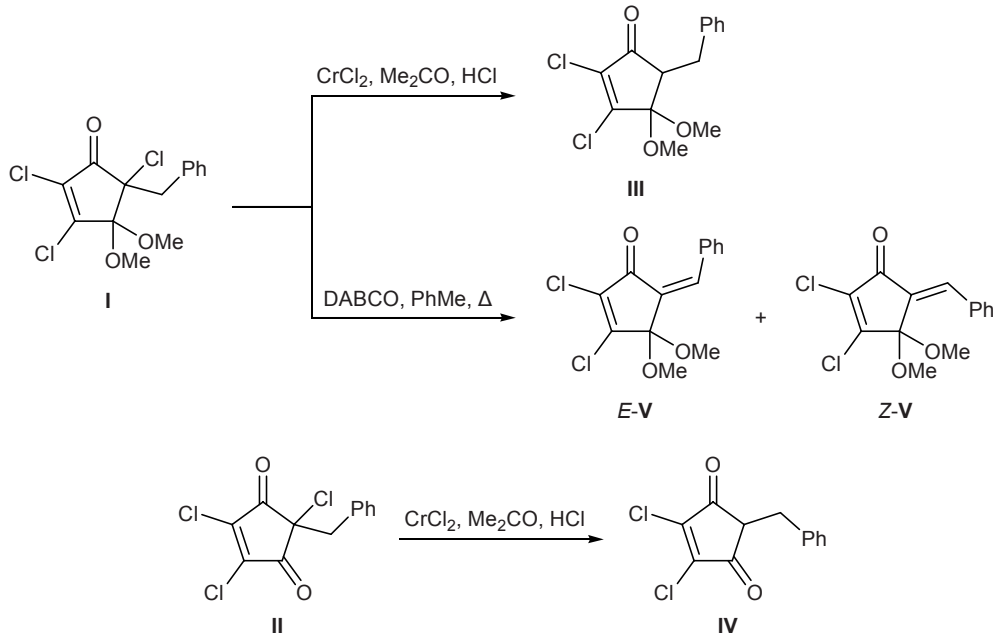
In the preceding communication [1] we described a novel iodine-catalyzed carbonyl–arene-like intramolecular carbocyclization of 2-benzyl-2,4,5-trichlorocyclopent-4-ene-1,3-dione (**II**) obtained from dimethoxy ketone **I**. In the present article we report on some reactions of these compound with a view to obtain products interesting from the viewpoint of pharmacology.

Selective dechlorination of trichloro ketones **I** and **II** at C^5 (C^2) using $CrCl_2$ under standard conditions [2] gave dichlorocyclopentenone derivatives **III** and **IV**, respectively (Scheme 1). Dimethoxytrichlorocyclopentenone **I** was subjected to dehydrochlorination by the action of 1,4-diazabicyclo[2.2.2]octane (DABCO). Although compound **I** is less activated than **II**, it is more stable under the severe dehydrochlorination conditions (heating in boiling toluene). The reaction occurred at a low rate and gave highly electrophilic cross-conjugated styrene derivative **V** as a mixture of *E* and *Z*

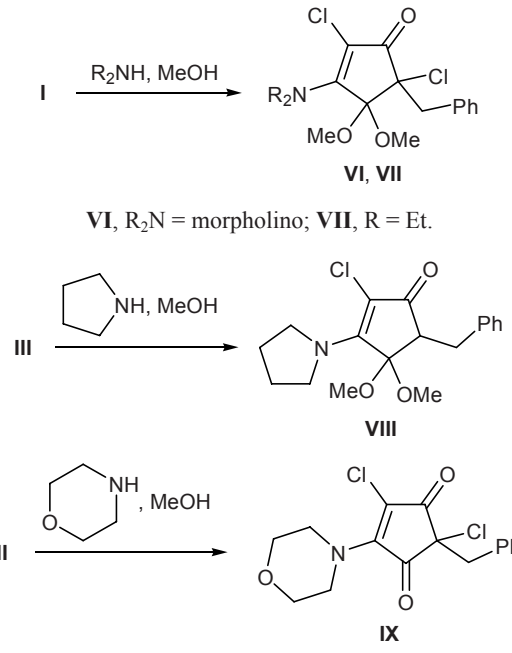
Scheme 1.



isomers in a moderate yield (Scheme 1). According to the spectral data, sterically more favorable *Z* isomer predominated in the product mixture. Isomer *E*-**V** is less favorable because of coplanar arrangement of the carbonyl group and benzene ring at the double bond. The ratio *Z*-**V**:*E*-**V** was estimated at 3:1 on the basis of intensities of signals from the methoxy groups, olefinic proton, and *ortho*-protons in the benzene ring, which appeared separately in the ^{1}H NMR spectrum. For example, the olefinic proton in *E*-**V** resonated at δ 7.75 ppm due to strong deshielding effect of the magnetically anisotropic carbonyl group, while the corresponding signal of *Z*-**V** was located at δ 7.11 ppm.

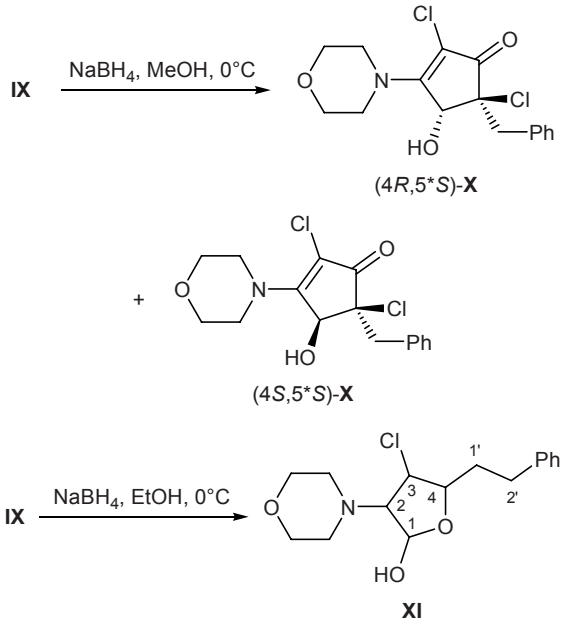
Taking into account that amino derivatives of trichlorocyclopentenones structurally related to compounds **I** and **II** exhibit biological activity [3], cyclopentenones **I**–**III** were brought into reactions with morpholine, diethylamine, and pyrrolidine to obtain new benzyl-substituted vinylogous amides **VI**–**IX** of the cyclopentenone series (Scheme 2).

Scheme 2.



Morpholino-substituted derivative **IX** was reduced with sodium tetrahydridoborate. When the reaction was carried out in methanol at 0°C, a mixture of two diastereoisomeric hydroxycyclopentenones (4*R*,5**S*)-**X** and (4*S*,5**S*)-**X** was obtained, the latter slightly prevailing (Scheme 3). In the ^{13}C NMR spectrum of isomer mixture (4*R*,5**S*)-**X**/(4*S*,5**S*)-**X**, the signal from C^4 was characteristic: δ_C 76.68 and 70.73 ppm for (4*S*,5**S*)-**X** and (4*R*,5**S*)-**X**, respectively. Interestingly,

Scheme 3.



the reduction of **IX** with $NaBH_4$ in ethanol at 0°C gave no expected compounds **X**. We succeeded in isolating (in a poor yield) and identifying 2-hydroxytetrahydrofuran **XI** which was likely to be formed as a result of a tandem transformation. The structure of **XI** and possible paths of formation of this compound will be the subject of a separate publication.

EXPERIMENTAL

The IR spectra were recorded on Specord M-80 and Shimadzu IR Prestige-21 spectrometers from samples prepared as thin films (neat) or dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Thermo Finnigan MAT 95XP mass spectrometer (ion source temperature 200°C, sample injection temperature 5–270°C, temperature ramp 22 deg/min). Thin-layer chromatography was performed using Silufol and Sorbfil plates; spots were detected by calcination or treatment with an alkaline solution of potassium permanganate.

5-Benzyl-2,3-dichloro-4,4-dimethoxycyclopent-2-en-1-one (III). Compound **I**, 0.5 g (1.49 mmol), was dissolved in 10 ml of acetone, 15 ml of a freshly prepared aqueous acidic solution of $CrCl_2$ [2] was added under stirring, and the mixture was stirred for ~1 h at room temperature and evaporated. The aqueous layer was treated with chloroform (3×10 ml), the extracts

were combined, washed with a solution of sodium chloride, dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:9) as eluent. Yield 0.4 g (89%), colorless crystals, mp 43–44°C. ^{1}H NMR spectrum, δ, ppm: 2.95 s and 3.55 s (3H each, OCH_3); 3.28 d (2H, CH_2, J = 4.9 Hz); 3.36 t (1H, 5-H, J = 4.8, 4.5 Hz); 7.07 m (1H), 7.22 m (2H), and 7.89 m (2H) (C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 32.40 (CH_2); 52.96 (OCH_3); 57.76 (C^5); 102.68 (C^4); 127.39, 128.67, 129.45, 139.62 (C_{arom}); 135.06 (C^2); 151.58 (C^3); 191.23 (C=O). Found, %: C 55.42; H 5.16; Cl 18.79; N 3.34. $C_{18}H_{21}Cl_2NO_4$. Calculated, %: C 55.97; H 5.48; Cl 18.36; N 3.63.

2-Benzyl-4,5-dichlorocyclopent-4-ene-1,3-dione (IV) was synthesized in a similar way from 0.5 g (1.73 mmol) of compound **II**. The product was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:9) as eluent. Yield 0.18 g (40%), colorless oily substance. ^{1}H NMR spectrum, δ, ppm: 4.01 m (2H, CH_2), 4.62 d (1H, 2-H, J = 4.2 Hz), 7.29 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 41.65 (CH_2); 52.85 (C^2); 127.95, 128.85, 129.24, 138.78 (C_{arom}); 135.03 (C^5); 151.55 (C^4); 191.09 (C^1, C^3).

(*E*,*Z*)-5-Benzylidene-2,3-dichloro-4,4-dimethoxycyclopent-2-en-1-one (V). Compound **I**, 0.3 g (0.89 mmol), was dissolved in 10 ml of toluene, 0.2 g (1.79 mmol) of DABCO was added, and the mixture was heated for 48 h under reflux, cooled to room temperature, washed with a saturated solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:10) as eluent. Yield 0.08 g (30%), oily substance (a mixture of *Z* and *E* isomers at a ratio of ~3:1). IR spectrum, ν, cm^{-1}: 798, 879, 1028, 1097, 1114, 1149, 1190, 1228, 1263, 1452, 1602, 1633, 1712. ^{1}H NMR spectrum, δ, ppm: *E* isomer: 3.19 s (6H, OCH_3), 7.49 d (2H, *o*-H, J = 1.72 Hz), 7.75 s (1H, =CH), 8.03 m (2H, *m*-H), 8.15 m (1H, *p*-H); *Z* isomer: 3.38 s (6H, OCH_3), 7.11 s (1H, =CH), 7.47 d (2H, *o*-H, J = 1.88 Hz), 8.05 d (2H, *m*-H, J = 1.89 Hz), 8.17 d (1H, *p*-H, J = 1.69 Hz). ^{13}C NMR spectrum, δ_C, ppm: *E* isomer: 51.88 (OCH_3); 104.85 (C^4); 125.72 (C^5); 128.82, 131.65, 133.21, 137.92 (C_{arom}); 132.04 (C^2); 138.89 (=CH); 158.82 (C^3); 183.24 (C=O); *Z* isomer: 51.88 (OCH_3); 104.85 (C^4); 125.72 (C^5); 128.04, 129.39, 131.02, 137.92 (C_{arom}); 132.04 (C^2); 138.89 (=CH); 158.82 (C^3); 183.24 (C=O).

5-Benzyl-2,5-dichloro-4,4-dimethoxy-3-morpholinocyclopent-2-en-1-one (VI). A solution of 0.1 ml (1.16 mmol) of morpholine in 5 ml of methanol was added dropwise under stirring to a solution of 0.20 g (0.60 mmol) of compound **I** in 8 ml of methanol, and the mixture was stirred for 3 h at room temperature (until the initial compound disappeared according to the TLC data). The solvent was removed, the residue was treated with 10 ml of cold water and extracted with chloroform (4×20 ml), and the combined extracts were washed with a saturated aqueous solution of sodium chloride, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:4) as eluent. Yield 0.22 g (96%), colorless crystals, mp 153–155°C (from Et_2O). ^{1}H NMR spectrum, δ, ppm: 3.20 s and 3.71 s (3H each, OCH_3), 3.33 m and 3.53 m (2H each, CH_2N), 3.38 d (2H, CH_2, J = 2.7 Hz), 7.17–7.22 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 46.13 (CH_2); 48.94 (CH_2N); 51.16 and 53.13 (OCH_3); 66.57 (CH_2O); 77.27 (C^5); 104.26 (C^4); 107.51 (C^2); 126.93, 127.60, 130.53, 135.34 (C_{arom}); 158.53 (C^3); 186.48 (C=O).

5-Benzyl-2,5-dichloro-3-diethylamino-4,4-dimethoxycyclopent-2-en-1-one (VII) was synthesized in a similar way from 0.1 g (0.297 mmol) of compound **I** and 0.1 ml (0.90 mmol) of diethylamine. Yield 0.08 g (72%), colorless crystals, mp 109–110.5°C (from EtOAc–petroleum ether, 1:5). ^{1}H NMR spectrum, δ, ppm: 1.01 m (6H, CH_3); 3.14 s and 3.72 s (3H each, OCH_3), 3.39 s (2H, CH_2), 7.17 br.s (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 13.66 (CH_3); 44.91 (CH_2N); 46.15 (CH_2); 50.89 and 53.06 (OCH_3); 77.19 (C^5); 102.76 (C^4); 104.38 (C^2); 126.91, 127.61, 130.61, 135.40 (C_{arom}); 158.49 (C^3); 186.15 (C=O). Found, %: C 58.42; H 6.41; Cl 18.49; N 3.47. $C_{18}H_{23}Cl_2NO_3$. Calculated, %: C 58.07; H 6.23; Cl 19.05; N 3.76.

5-Benzyl-2-chloro-4,4-dimethoxy-3-(pyrrolidin-1-yl)cyclopent-2-en-1-one (VIII) was synthesized in a similar way from 0.21 g (0.73 mmol) of compound **III** and 0.12 ml (1.46 mmol) of pyrrolidine. Yield 0.16 g (49%), mp 65–67°C. ^{1}H NMR spectrum, δ, ppm: 1.88 m (4H, CH_2); 2.77 d.d (1H, PhC**H**$_2$, J = 6.4, 14.35 Hz); 2.91 d.d (1H, PhC**H**$_2$, J = 6.4, 5.2 Hz); 3.09 s and 3.23 s (3H each, OCH_3); 3.47 s (1H, 5-H); 3.87 m (4H, CH_2N); 7.19 t (1H, J = 7.2 Hz), 7.29 m (2H), and 7.37 d (2H, J = 7.34 Hz) (C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 24.98 (**C**H_2CH_2N); 32.60 (Ph**C**H_2); 50.26 (CH_2N); 52.16 and 52.43 (OCH_3); 53.11 (C^5); 102.28 (C^4); 106.23 (C^2); 126.51, 128.15, 129.11, 136.45 (C_{arom}); 158.37 (C^3); 189.62 (C^1).

2-Benzyl-2,4-dichloro-5-morpholinocyclopent-4-ene-1,3-dione (IX) was synthesized in a similar way

from 0.22 g (0.76 mmol) of compound **II** and 0.13 ml (1.48 mmol) of morpholine. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1:5) as eluent. Yield 0.18 g (70%), colorless powder, mp 95–96°C. ^{1}H NMR spectrum, δ, ppm: 3.30 d (1H, PhC**H**$_2$, *J* = 12.9 Hz), 3.48 d (1H, PhC**H**$_2$, *J* = 12.9 Hz), 3.54 t (4H, CH_2N, *J* = 4.75, 4.30 Hz), 3.77 m (4H, CH_2O); 6.93 m (2H) and 7.17 m (3H) (Ph).

(4*RS*,5S*)-5-Benzyl-2,5-dichloro-4-hydroxy-3-morpholinocyclopent-2-en-1-one (X).** A solution of 0.1 g (0.29 mmol) of compound **IX** in 3 ml of methanol was added dropwise under stirring to a suspension of 0.011 g (0.29 mmol) of $NaBH_4$ in 5 ml of methanol, cooled to 0°C. The mixture was stirred at that temperature until the initial diketone disappeared (TLC) and treated with a calculated amount of water (0.03 ml), methanol was distilled off, the residue was dissolved in chloroform, the solution was dried over $MgSO_4$ and evaporated, and the residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (1:4) as eluent to isolate 0.06 g (60%) of a mixture of diastereoisomeric compounds **X** as an oily substance. ^{1}H NMR spectrum, δ, ppm: (4*S*,5**S*) isomer: 3.22 d (1H, PhC**H**$_2$, *J* = 13.03 Hz), 3.39 d (1H, PhC**H**$_2$, *J* = 13.77 Hz), 3.30 m (4H, CH_2N), 3.73 m (4H, CH_2O), 4.50 m (1H, OH), 4.98 s (1H, 4-H), 7.17–7.28 m (5H, Ph); (4*R*,5**S*) isomer: 3.22 d (1H, PhC**H**$_2$, *J* = 13.03 Hz), 3.39 d (1H, PhC**H**$_2$, *J* = 13.77 Hz), 3.30 m (4H, CH_2N), 3.73 m (4H, CH_2O), 4.50 m (1H, OH), 4.71 s (1H, 4-H), 7.13–7.28 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: (4*S*,5**S*) isomer: 40.26 (Ph**C**H_2); 49.08 (CH_2N); 66.65 (CH_2O); 73.14 (C^5); 76.69 (C^4); 98.78 (C^2); 126.92, 128.08, 131.22, 136.19 (C_{arom}); 163.60 (C^3); 188.38 (C=O); (4*R*,5**S*) isomer: 44.79 (Ph**C**H_2); 49.06 (CH_2N); 66.24 (CH_2O); 70.74 (C^4); 73.60 (C^5); 99.48 (C^2); 127.58, 128.56, 130.62, 135.11 (C_{arom}); 163.55 (C^3); 188.82 (C=O).

4-Chloro-3-morpholino-5-(2-phenylethyl)tetrahydrofuran-2-ol (XI). A solution of 0.1 g (0.29 mmol) of compound **IX** in 3 ml of ethanol was added dropwise under stirring to a suspension of 0.022 g (0.58 mmol) of $NaBH_4$ in 5 ml of ethanol, cooled to 0°C. The mixture was stirred at that temperature until the initial diketone disappeared (TLC) and was then treated as described above for the synthesis of compounds **X**. Purification by column chromatography on silica gel using ethyl acetate–petroleum ether (1:4) as eluent gave 0.06 g (60%) of compound **XI** as an oily substance. ^{1}H NMR spectrum, δ, ppm: 2.01 m and 2.39 d.d (1H each, 1′-H, *J* = 13.8, 9.6 Hz), 2.64 m and 2.74 m (2H each, CH_2N), 3.10 t (1H, 3-H, *J* = 11.7 Hz), 3.19 d.d (1H, 2′-H, *J* 13.7, 3.4 Hz), 3.45 t (1H, CHCl, *J* = 10.77, 8.6 Hz), 3.68 m (6H, 5-H, 2′-H, CH_2O), 4.29 m (1H, 2-H), 7.15–7.32 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 34.49 and 35.21 (CH_2); 45.23 (C^3); 47.37 (CH_2N); 62.36 (C^4); 67.01 and 67.56 (CH_2O); 76.91 (C^5); 94.94 (C^2); 126.24, 128.44, 128.99, 138.55 (C_{arom}). Found: $[M]^+$ 311.126. $C_{16}H_{22}ClNO_3$. Calculated: *M* 311.804.

REFERENCES

1. Gimalova, F.A., Egorov, V.A., Galkin, E.G., and Miftakhov, M.S., *Russ. J. Org. Chem*., 2008, vol. 44, p. 1.
2. Rosenkranz, G., Mancera, O., Gatica, J., and Djerassi, C., *J. Am. Chem. Soc*., 1950, vol. 72, p. 4077.
3. Ismailov, S.A., *Doctoral (Chem.) Dissertation*, Ufa, 1992.