Chemistry of Natural Compounds, Vol. 43, No. 5, 2007

PREPARATION AND STRUCTURE ELUCIDATION OF TWO MINOR PRODUCTS FROM REACTION OF ARGLABIN WITH CHLOROFORM IN THE PRESENCE OF A CROWN ETHER

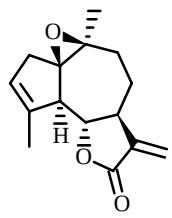
R. I. Jalmakhanbetova,[1] G. A. Atazhanova,[1] V. A. Raldugin,[2] I. Yu. Bagryanskaya,[2] Yu. V. Gatilov,[2] M. M. Shakirov,[2] and S. M. Adekenov[1]

UDC 547.314+547.323

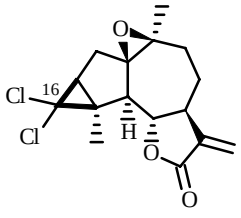
A pentachloro derivative, the structure of which was proved by x-ray structure analysis, in addition to a new dichlorocarbene derivative were obtained for the first time by dichlorocyclopropanation of arglabin guaianolide. The stereochemistry of the principal reaction product was established.

Key words: guaianolide, arglabin, chloroform, dichlorocarbene, NMR, XSA.

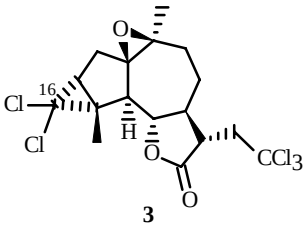
We have previously described [1] the principal product from addition of dichlorocarbene to arglabin guaianolide (**1**) via the action on it of base and $CHCl_3$ under phase-transfer catalysis conditions. Herein we continue the investigation of the products from this reaction.



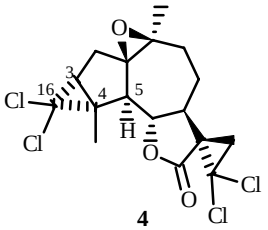
1



2



3



4

Minor products **2** and **3** from this reaction were isolated in 5 and 3% yields, respectively. According to PMR and ^{13}C NMR spectra, less polar product **2** was formed via addition of dichlorocarbene to the triply substituted double bond because resonances of the exo-methylene group did not chagne in the NMR spectrum and resonances of a cyclopropane ring appeared instead of those for the HC(4)=C(5)–CH_3 group (Table 1).

The structure of **3** was estalished by an x-ray structure analysis (XSA) (Fig. 1). This product was apparently formed via addition of trichloromethyl anion (CCl_3^-) and a proton, which were formed from $CHCl_3$ [2], to the exomethylene group of **1**. Table 1 lists the PMR and ^{13}C NMR spectra of the isolated new product **3**.

According to the XSA, the asymmetric unit in the crystal of **3** contains two molecules with the same geometric and conformational parameters within experimental uncertainty. Bond lengths in the molecules are normal [3]. The seven-membered ring has the chair conformation. The five-membered and lactone rings have the envelope conformation with deviations from the corresponding planes of C1 [by 0.49(2) and 0.49(2) Å] and C7 [by 0.62(1) and 0.61(2) Å] (Fig. 1). The Cambridge Structural Database [4] contains one compound isoepoxy estafiatin [5] with the same configuration of the three-membered rings. We note the same conformation of the rings in **3** and isoepoxyestafiatin and the small difference in the conformation of the lactone ring (twist in the latter). The molecular packing in **3** has the following shortened contacts: Cl1...O2A, 3.18(1) Å (sum of van der Waals radii 3.44 Å); Cl2...Cl5, 3.478(6) Å, and Cl2A...Cl4A, 3.449(5) Å (sum of van der Waals radii 3.52 Å [6]).

1) Scientific Research Center Fitokhimiya, Ministry of Education and Science, Republic of Kazakhstan, 100009, Republic of Kazakhstan, Karaganda, fax 8-(3212) 43 37 73, e-mail: arglabin@phyto.kz; 2) N. N. Vorozhtsov Novosibirsk Institute of Organic Cemistry, Siberian Division, Russian Academy of Sciences, 630090, Novosibirsk, fax: (3832) 34 47 52, e-mail: raldugin@nioch.nsc.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 450-452, September-October, 2007. Original article submitted May 23, 2007.

 0009-3130/07/4305-0548

TABLE 1. PMR and ^{13}C NMR Spectra of **2** and **3** (500 MHz, $CDCl_3$, δ, ppm, J/Hz)

C atom	**2**		**3**	
	δ_H	δ_C	δ_H	δ_C
1	-	69.38 s	-	74.50 s
2a	2.01 (d, 16.0)		2.01 (dd, 16.0; 8.0)	35.47 t
2b	2.64 (dd, 6.0; 16.0)	35.73 t	2.20 (dd, 16.0; 3.0)	
3	1.71 (d, 6.0)	39.56 d	1.83 (dd, 8.0; 3.0)	38.28 d
4	-	41.35 s	-	40.60 s
5	2.85 (d, 10.0)	51.81 d	2.61 (d, 11.0)	49.90 d
6	4.33 (t, 10.0)	79.83 d	4.16 (dd, 11.0, 10.0)	80.73 d
7	2.13 m	54.79 d	1.40-1.59 m	51.11 d
8a	1.42 m	20.76 t	1.40-1.59 m	22.39
8b	1.79 m	-	1.85-1.93 m	
9a	2.13 m	32.61 t	2.12 m	33.80 t
9b	1.89 m		1.85-1.93 m	
10	-	61.82 s	-	62.78 s
11	-	138.98 s	2.64 (ddd, 12.0; 5.0; 2.4)	44.35 d
12	-	170.09 s	-	175.72 s
13a	6.10 (d, 3.0)	118.31 t	3.40 (dd, 15.0; 6.0)	52.62 t
13b	5.37 (d, 3.0)		2.72 (dd, 15.0; 3.0)	
14	1.25 s	22.65 q	1.29 s	23.27 q
15	1.63 br.s	21.28 q	1.61 s	16.86 q
16	-	70.10 s	-	78.90 s
17	-	-	-	97.73 s

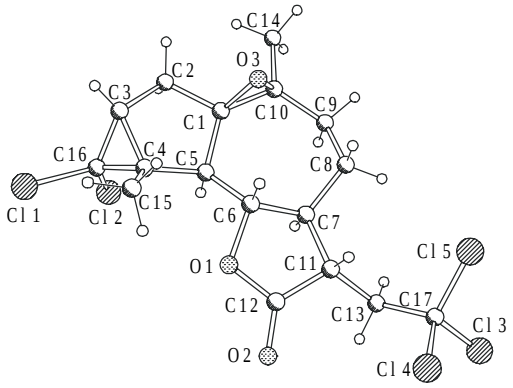


Fig. 1. Molecular structure of **3**.

Unambiguous establishment of the stereochemistry for addition of the cyclopropane ring in **3** enabled this question to be addressed for **2**. Table 1 shows that the resonances for C-16 in the ^{13}C NMR spectra of these two molecules differed sharply (by 8 ppm). This indicated that the environment of C-16 was different in them. In **2**, it was strongly deshielded by the epoxy-ring and its resonance shifted strongly to weak field. Thus, the stereochemistry of addition of the dichlorocyclopropane ring in **2** was opposite that for **3** and is described as 3*β*,4*β*.

Elucidation of the differences in **2** and **3** from the ^{13}C NMR spectra enabled the stereochemistry of the main product from the reaction (**4**) to be examined again. It was proposed as 3*β*,4*β* due to the lack of through-space spin—spin coupling of 3H-15 and H-5 in the PMR spectrum [1]. However, this turned out to be unimportant because this coupling was not observed in the PMR spectrum of **3**, the molecular structure of which we unambiguously proved by XSA in the present work. On the other hand, the chemical shift of C-16 (76.25 ppm) in the ^{13}C NMR spectrum of **4** was similar to that for the 3*α*,4*α*-cyclopropyl derivative **3** (78.90 ppm, Table 1). Thus, the main product from reaction of dichlorocarbene and **1** (**4**) has the same stereochemistry of addtion for the cyclopropane ring to C-3 and C-4 as that for **3**.

The PMR spectra of **4** were recorded in acetone-d_6; of **2** and **3**, in $CDCl_3$. However, chemical shifts of resonances in ^{13}C NMR spectra, as is well known [7], are almost independent of the solvent used.

In conclusion, we note that formation of the trichloromethyl derivative of the sesquiterpene lactone during the studied reaction was unexpected.

EXPERIMENTAL

The course of reaction and purity of products were monitored by TLC. TLC used Silufol plates with development by spraying with aqueous $KMnO_4$ solution (2%); column chromatography, Armsorb silica gel. Dicyclohexyl-18-crown-6 was used as received. Melting points were determined on a Boetius instrument. IR spectra were obtained on an Avatar 360 ESP instrument in KBr. NMR spectra were recorded on a Bruker DRX-500 spectrometer (operating frequency 500.13 MHz for ^1H; 125.76 MHz, ^{13}C; δ-scale) using standard Bruker programs to record two-dimensional $^1H—^1H$ and $^{13}C—^1H$ COSY spectra. Mass spectra (EI, 70 eV) were obtained in a Finnigan MAT 8200 instrument. Optical rotation was measured (at 580 nm) on an Atago Polax-21 polarimeter. Starting lactone **1** was isolated from the aerial part of *Artemisia glabella* Kar. et Kir. [8].

Reaction of 1 and Dichlorocarbene. Dicyclohexyl-18-crown-6 (30 mg) and aqueous NaOH (2 mL, 50%) were added to $CHCl_3$ (3 mL). The mixture was stirred, treated after 15 min with **1** (100 mg, 0.4 mmol), stirred vigorously at room temperature (15.5°C) for 4 h, treated with water (2 mL), and extracted with $CHCl_3$ (3 × 3 mL). The organic layer was dried over Na_2SO_4 and filtered. Solvent was removed. The solid (220 mg) was chromatographed over a column with elution by petroleum ether and EtOAc to isolate **4** (100 mg, 61%), **2** (7 mg, 5%), and **3** (6 mg, 3%), respectively.

1,10β-Epoxy-3,4β-dichloromethano-5,7α,6β(H)-guai-11,13-en-12,6-olide (2). Colorless crystals, mp 154-156°C, R_f 0.32 (EtOAc:petrol. ether, 2:4), $C_{16}H_{18}O_3Cl_2$.

IR spectrum (KBr, ν_{max}, cm^{-1}): 3023, 2993, 2975, 2928, 2898, 2883, 1769 (γ-lactone C=O); 1670 (C=C); 1436, 1409, 1383, 1337, 1307, 1296, 1251, 1231, 1219, 1194, 1179, 1156 (epoxy); 1138, 1126, 1104, 1066, 1030, 1004, 974, 958, 941, 922, 884, 873, 849, 836, 816, 711, 669 (C–Cl); 646, 629, 509, 487, 447, 433.

Table 1 lists the PMR and ^{13}C NMR spectra.

1,10β-Epoxy-3,4α-dichloromethano-13-trichloromethyl-5,7α(H),6,11β(H)-guai-12,6-olide (3). Colorless crystals, mp 160-163°C, R_f 0.81 (EtOAc:petrol. ether, 2:4).

IR spectrum (KBr, ν, cm^{-1}): 2996, 2926, 1782 (γ-lactone C=O); 1459, 1449, 1430, 1416, 1381, 1315, 1277, 1238, 1204, 1177 (epoxy); 1155, 1125, 1100, 1051, 1026, 1000, 982, 970, 930, 873, 845, 819, 798, 785, 772, 729, 700 (C–Cl); 678, 652, 626, 602, 572, 552, 500, 483, 422.

Table 1 lists the PMR and ^{13}C NMR spectra.

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 448 (5) $[M]^+$, 413 (7), 411 (5), 377 (6), 375 (6), 331 (5), 311 (7), 309 (5), 283 (7) 281 (8), 259 (6), 258 (6), 256 (9), 255 (6), 253 (6), 241 (7), 233 (7), 223 (5), 207 (10), 205 (15), 203 (7), 193 (7), 191 (6), 189 (7), 187 (7), 181 (6), 179 (19), 178 (6), 177 (22), 175 (5), 171 (7), 169 (8), 165 (16), 163 (10), 161 (7), 157 (7), 155 (6), 153 (7), 151 (6), 149 (6), 145 (7), 143 (15), 141 (12), 139 (10), 137 (12), 135 (10), 131 (6), 129 (9), 128 (6), 127 (10), 125 (11), 123 (9), 119 (7), 117 (9), 115 (11), 113 (8), 111 (10), 109 (14), 107 (7), 105 (9), 103 (6), 101 (7), 99 (9), 97 (12), 93 (5), 91 (23), 89 (11), 87 (5), 83 (5), 82 (7), 81 (13), 79 (15), 77 (20), 75 (10), 71 (15), 69 (16), 68 (8), 67 (7), 65 (11), 55 (35), 53 (11), 43 (100), 41 (28), 39 (11), 27 (6).

The XSA of **3** was performed on a Bruker P4 diffractometer (Mo Kα-radiation, graphite monochromator) by θ/2θ-scanning for $2\theta < 48°$. A total of 3471 reflections was measured, of which 3152 were independent ($R_{int} = 0.0281$). Absorption corrections were applied by integrating over the crystal faces (transmission 0.880-0.905). The structure was solved by direct methods using SHELXS-97 programs and was refined by anisotropic full-matrix least-squares methods using the SHELXL-97 program over all reflections. Positions of H atoms were fixed geometrically and refined by the standard "rider" model. Crystallographic data: monoclinic system, space group $P2_1$, $a = 6.343(2)$, $b = 19.985(5)$, $c = 15.809(4)$ Å, $\beta = 91.31(2)°$, $V = 2003.5(10)$ $Å^3$, $C_{17}H_{19}Cl_5O_3$, $Z = 4$, $\rho_{calc} = 1.487$ g/cm^3, $\mu = 0.738$ mm^{-1}, size 0.16 × 0.25 × 0.8 mm. Final R-factors were $wR_2 = 0.1802$, $R = 0.0938$, $S = 1.014$ for all reflections, $R = 0.0671$ for 2079 reflections with $F > 4\sigma(F)$. The absolute structure parameter (Flack parameter) was 0.03(13). Crystallographic data for **3** were deposited in the Cambridge Structural Database under number CCDC 609346.

ACKNOWLEDGMENT

The work was supported financially by the Ministry of Education and Science of the Republic of Kazakhstan (Basic Research Program F.0286, Search for New Biologically Active Plant Substances and Development Based on Them of Practically Valuable Preparations, Theme 01.01.01, New Sesquiterpene Lactones from Plants, Their Chemical Modification and Biological Activity, state registration number No. 0103RK00176).

REFERENCES

1. R. I. Jalmakhanbetova, V. A. Raldugin, I. Yu. Bagryanskaya, Yu. V. Gatilov, M. M. Shakirov, A. T. Kulyyasov, and S. M. Adekenov, *Khim. Prir. Soedin.*, 451 (2005).
2. J. Hine, *J. Am. Chem. Soc.*, **72**, 2438 (1950).
3. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc. Perkin Trans. 2*, S1 (1987).
4. *Cambridge Structural Database*, University of Cambridge, UK, Version 5.27.
5. D. L. Ponomarev, K. M. Turdybekov, G. K. Buketova, A. Zh. Turmukhambetov, and S. M. Adekenov, *Khim. Prir. Soedin.*, 66 (1997).
6. R. S Rowland and R. Taylor, *J. Phys. Chem.*, **100**, 7384 (1996).
7. H.-O. Kalinovski, S. Berger, and S. Braun, *^{13}C NMR Spectroskopie*, G. Thieme Verlag, Stuttgart-New York (1984), p. 73.
8. S. M. Adekenov, M. N. Mukhametzhanov, A. N. Kupriyanov, and A. D. Kagarlitskii, *Khim. Prir. Soedin.*, 655 (1982).