Chemistry of Natural Compounds, Vol. 37, No. 3, 2001

SELECTIVE FORMATION OF A VICINAL DINITRO DERIVATIVE VIA NITROSOCHLORINATION OF THE SESQUITERPENE LACTONE ACHILLIN

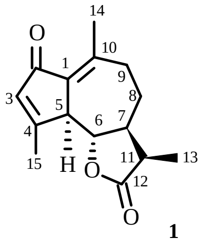
S. M. Adekenov,[1] O. V. Alebastrov,[1] V. A. Raldugin,[2]
I. Yu. Bagryanskaya,[2] Yu. V. Gatilov,[2] M. M. Shakirov,[2]
A. T. Kulyyasov,[1] and G. A. Tolstikov[2]

UDC 547.314+547.737

Bubbling gaseous nitrosylchloride through a chloroform solution of the guaianolide achillin produces very slowly but selectively 1,10-dihydro-1α,10α-dinitroachillin. This product rapidly, quantitatively, and irreversibly isomerizes into the dinitrocarboxylic acid with retention of the guaian carbon skeleton upon dissolution in pyridine. The structures of the new compounds were found by x-ray structural analysis.

Key words: sesquiterpenoids, guaianolides, achillin, nitrosochlorination, nitrocompound, x-ray structure analysis.

We attempted the nitrosochlorination of the guaianolide achillin (**1**) in order to prepare new physiologically active compounds by continuing experiments on the introduction of Cl into sesquiterpene lactones [1, 2]. Passage of gaseous NOCl (produced from $NaNO_2$ and HCl according to the literature [3]) through a $CHCl_3$ solution of **1** forms very slowly a single product (TLC). Complete conversion of the starting material is achieved after 2 d. The product was isolated using known methods [4] for isolating crystalline nitrosochlorides from product mixtures, i.e., adding alcohol with subsequent separation of the resulting crystals.



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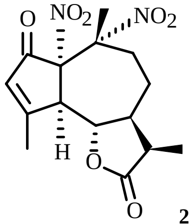

2

As it turned out, the product contains two nitro groups instead of the proposed Cl atom. It has the structure **2** according to x-ray structure analysis (XSA). The seven-membered ring of lactone **2** has the chair conformation (Fig. 1) whereas the lactone ring has the envelope conformation with C7 deviating from the plane of the remaining atoms by 0.499(4) Å. Analogous conformations of these rings were found in the guaianolide tetrahydroleukomisin [5]. The cyclopentenone fragment of **2** is planar within ±0.039(4) Å. The C2–C3 bond length in this fragment is 1.429(4) Å, which is less than the statistical average of 1.464(18) Å [6] for the conjugated fragment C=C–C(=O)–C and agrees with the length of the analogous bond in D-homo-4-norestr-3(5)-en-2,17-dione [7]. The C10–N2 bond [1.562(3) Å] of the equatorial nitro group is elongated compared with the C1–N1 bond [1.537(3) Å]. A similar difference in the lengths of the axial and equatorial C–NO_2 bonds is observed for 2-hydroxy-2,3,4,5,6-pentamethyl-5,6-dinitrocyclohex-3-enone [8].

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1) Institute of Phytochemistry, Ministry of Education and Science, Republic of Kazakhstan, Kazakhstan, 470032, Karaganda, ul. Gazalieva, 4, fax (3212) 43 37 73, e-mail: arglabin@phyto.karaganda.ru; 2) N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences, 630090, Novosibirsk, pr. Akad. Lavrent'eva, 9, fax (3832) 34 47 52, e-mail: raldugin@nioch.nsc.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 197-200, May-June, 2001. Original article submitted June 5, 2001.

TABLE 1. Chemical Shifts (δ, ppm) and Spin—Spin Coupling Constants (J/Hz) in the PMR Spectra of **2** and **3** (0 = TMS)

Proton	**2***	**2****	**3****
H-3	6.31 dq (J = 2.4; 1.2)	6.20 dq (J = 2.5; 1.2)	6.27 br.s
H-5	3.88 ddk (J = 10.0; 1.4; 1.0)	4.20 dm (J = 10.0)	-
H-6	5.00 t (J = 10.0)	4.94 t (J = 10.0)	6.64 d (J = 4.0)
H-7	3.16 m	3.13 m	3.66 m
H-8A	1.82 m	1.53 qd (J = 14.0; 4.0)	1.80 m
H-8B	3.15 m	1.75 dm (J = 14.0)	1.90 m
H-9A	2.12 m	1.95 dt (J = 14.0; 4.0)	2.10 ddd (J = 14.0; 5.0; 2.0)
H-9B	3.34 td (J = 14.0; 5.0)	3.39 td (J = 14.0; 4.0)	3.60 td (J = 14.0; 8.0)
H-11	2.84 quintet (J = 8.0)	2.75 quintet (J = 8.0)	2.81 dq (J = 5.0; 7.5)
3H-13	1.23 d (J = 8.0)	1.11 (J = 8.0)	1.30 d (J = 7.5)
3H-14	1.59 br.s	1.58 br.s	1.49 br.s
3H-15	2.33 br.s	2.09 br.s	1.94 br.s

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*Solvent: acetone-d_6. **Solvent: Py-d_5.

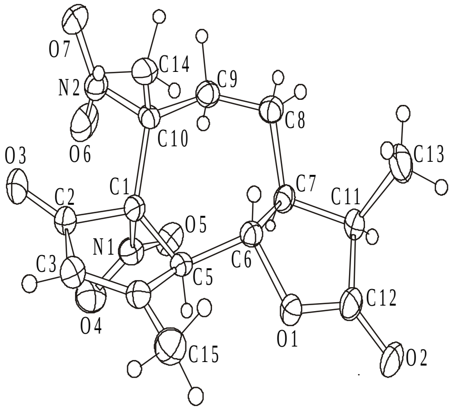

Fig. 1. Structure of dinitrolactone **2**.

It is noteworthy that reaction of NOCl with various types of unsaturated compounds is well known. Numerous examples have been reviewed [9]. α-Enones can give chloroximes [10] or dimers of nitroso compounds [11]. In our instance, nitrosochlorination does not occur. The dinitro compound **2** forms apparently because of traces of N_2O_4 in the gaseous NOCl. It is known that reaction of N_2O_4 with cyclohexene and lower alkenes forms N-containing products, including 1,2-dinitro derivatives [12].

The PMR (Table 1) and ^{13}C NMR (Table 2) spectra of **2** were interpreted using two-dimensional (2D) ^{1}H—^{1}H (COSY) and ^{13}C—^{1}H (COSY, COLOC) spectra. Pyridine-d_5 was used to obtain a more concentrated solution of **2** and accelerate recording of the 2D spectra. However, **2** in this solvent completely and irreversibly transforms into acid **3**, the NMR data of which are listed in Tables 1 and 2. Lactone **2** completely transforms into **3** at 30°C in about 30 min. The PMR spectrum of the mixture of **2** and **3** with a significant (up to 50%) content of **2** could be recorded in the first 10-15 min so that PMR data for **2** could be obtained (Table 1). Subsequent slow evaporation of Py-d_5 produces crystals of **3** that were used for the XSA.

The structure of **3**, which forms a stable crystal solvate with Py-d_5 (Fig. 2), indicates that the seven-membered ring of **3**, like for **2**, has the chair conformation but with a different pseudorotation angle. It is noteworthy that the fragment of **3** that includes C1, C7, C15, and O3 is planar within ±0.137(2) Å. The pyridine solvate contains a CO_2H...N bond between **3** and Py with parameters O2...N1(S) 2.677(3); O2-H 0.82; H...N1(S) 1.86 Å; O2-H...N1(S) 175°.

TABLE 2. Chemical Shifts and Multiplicity of Signals for C Atoms of **2** and **3**

C atom	2*	3**
1	95.40 (s)	93.23 (s)
2	192.89 (s)	191.45 (s)
3	130.95 (d)	130.67 (d)
4	180.08 (s)	171.74 (s)
5	61.08 (d)	136.92 (s)
6	80.92 (d)	138.90 (d)
7	43.03 (d)	39.55 (d)
8	22.46 (t)	27.09 (t)
9	37.62 (t)	38.96 (t)
10	94.00 (s)	89.67 (s)
11	39.47 (d)	44.53 (d)
12	180.10 (s)	177.25 (s)
13	10.61 (q)	13.76 (q)
14	21.39 (q)	20.25 (q)
15	22.63 (q)	14.34 (q)

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*Solvent: acetone-d_6. **Solvent: Py-d_5.

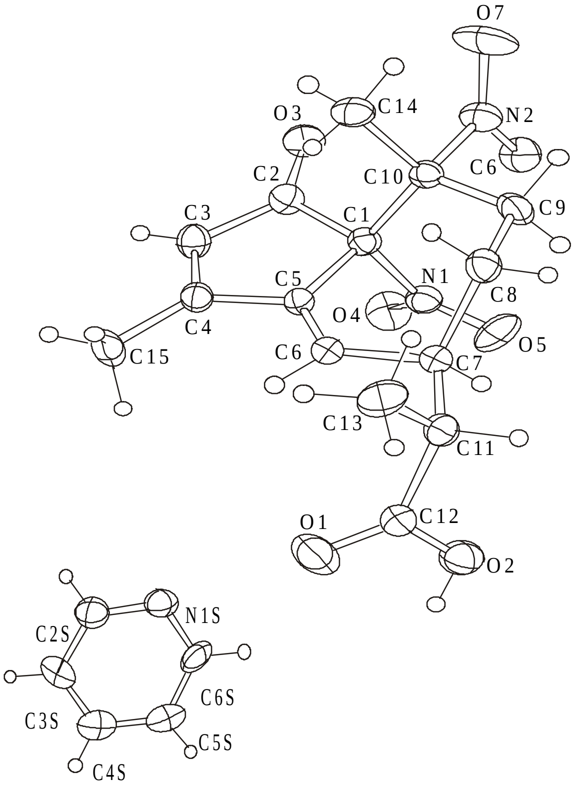
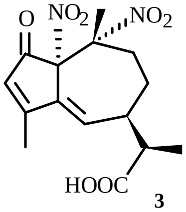


Fig. 2. Strucutre of dinitro acid **3**.

TABLE 3. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Parameters (Å^2 $\times 10^3$) of Nonhydrogen Atoms in **2**

Atom	*x*	*y*	*z*	*U(eq)*
C1	1817 (3)	4738 (1)	1177 (1)	35 (1)
C2	1479 (4)	4464 (2)	2137 (1)	45 (1)
C3	363 (4)	5155 (2)	2541 (1)	50 (1)
C4	-105 (3)	5807 (1)	2000 (1)	40 (1)
C5	910 (3)	5698 (1)	1137 (1)	33 (1)
C6	-320 (3)	5974 (1)	362 (1)	33 (1)
C7	574 (3)	5759 (1)	-515 (1)	36 (1)
C8	42 (4)	4825 (2)	-829 (1)	44 (1)
C9	1223 (4)	4082 (1)	-399 (1)	43 (1)
C10	963 (3)	3997 (1)	583 (1)	36 (1)
C11	-129 (4)	6550 (2)	-1063 (2)	44 (1)
C12	-282 (3)	7289 (1)	-412 (2)	42 (1)
C13	-2117 (6)	6438 (2)	-1505 (2)	69 (1)
C14	-1189 (4)	3829 (2)	823 (2)	43 (1)
C15	-1412 (5)	6582 (2)	2186 (2)	58 (1)
O1	-389 (2)	6947 (1)	391 (1)	41 (1)
O2	-350 (3)	8080 (1)	-526 (1)	58 (1)
O3	1989 (4)	3752 (1)	2427 (1)	63 (1)
O4	5002 (3)	4996 (2)	1714 (2)	70 (1)
O5	4704 (3)	4976 (1)	342 (1)	57 (1)
O6	3913 (3)	3165 (1)	832 (2)	71 (1)
O7	1221 (4)	2430 (1)	822 (1)	64 (1)
N1	4045 (3)	4894 (1)	1060 (1)	46 (1)
N2	2134 (3)	3124 (1)	787 (1)	49 (1)

Lactone **2** transforms into acid **3** owing to the electron accepting group on C1 because **1** itself is inert to Py. On the other hand, this transformation occurs only for the Py solution. It does not occur in acetone or $CHCl_3$ solutions. The dichloro derivative **4** [1] hydrolyzes more slowly in Py-d_5 solution if used as a model compound. Thus, storing the test solution in an NMR tube at room temperature produces no noticeable change in the PMR spectrum during the first hour. A product mixture in which acid **5** predominates forms after 2 d. This conclusion is based on the following signals: δ_H 1.30 (3H, d, J = 7.0 Hz, Me-11), 6.14 (1H, br.s, H-3), 6.51 (1H, br.d, $J_{6,7}$ = 4.5 Hz, H-6) ppm, which are analogous to those observed in the spectrum of **3** (Table 1).



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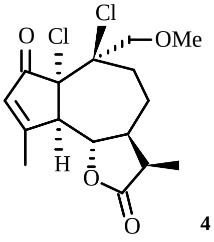

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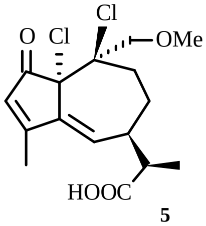

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TABLE 4. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Parameters (Å^2 $\times 10^3$) of Nonhydrogen Atoms in **3**

Atom	*x*	*y*	*z*	*U(eq)*
C1	4483 (4)	13082 (2)	1516 (1)	35 (1)
C2	4576 (4)	14243 (2)	1357 (1)	45 (1)
C3	3663 (5)	14343 (2)	806 (1)	49 (1)
C4	2820 (4)	13468 (2)	638 (1)	40 (1)
C5	3179 (4)	12635 (2)	1047 (1)	33 (1)
C6	2481 (4)	11693 (2)	1008 (1)	36 (1)
C7	2809 (4)	10812 (2)	1411 (1)	38 (1)
C8	2217 (5)	11082 (2)	2024 (1)	45 (1)
C9	3628 (5)	11798 (2)	2333 (1)	45 (1)
C10	3670 (4)	12906 (2)	2118 (1)	37 (1)
C11	1747 (5)	9833 (2)	1210 (1)	43 (1)
C12	2449 (5)	9561 (2)	619 (1)	46 (1)
C13	-521 (5)	9860 (2)	1231 (1)	58 (1)
C14	1640 (4)	13409 (2)	2167 (1)	50 (1)
C15	1597 (5)	13326 (2)	115 (1)	54 (1)
N1	6603 (4)	12690 (2)	1407 (1)	45 (1)
N2	5105 (4)	13455 (2)	2538 (1)	48 (1)
O1	1430 (5)	9616 (2)	206 (1)	92 (1)
O2	4303 (3)	9257 (2)	604 (1)	63 (1)
O3	5231 (4)	14891 (2)	1667 (1)	65 (1)
O4	7708 (3)	13242 (2)	1140 (1)	71 (1)
O5	7052 (3)	11849 (2)	1564 (1)	69 (1)
O6	6877 (3)	13342 (2)	2476 (1)	61 (1)
O7	4387 (4)	13923 (2)	2926 (1)	95 (1)
N1 (S)	5305 (5)	8682 (2)	-449 (1)	64 (1)
C2 (S)	4278 (6)	9121 (3)	-867 (1)	67 (1)
C3 (S)	4765 (6)	9026 (3)	-1429 (2)	75 (1)
C4 (S)	6372 (7)	8441 (3)	-1569 (2)	79 (1)
C5 (S)	7447 (7)	7979 (2)	-1155 (2)	79 (1)
C6 (S)	6854 (6)	8117 (2)	-593 (2)	72 (1)

EXPERIMENTAL

Melting points were determined on a Boetius instrument. IR spectra were obtained on a Vector 22 instrument in KBr; UV spectra (for EtOH solutions), on a Specord UV-VIS instrument. NMR spectra were recorded on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C, and 36.13 MHz for ^{14}N, δ scale) using the standard Bruker programs to record 2D COSY and COLOC (7 Hz) spectra. Mass spectra (EI, 70 eV) were measured in a Finnigan MAT 8200 instrument. Optical rotation was measured (at 580 nm) on a Polamat A polarimeter.

TLC used Silufol plates with visualization by spraying with vanillin (1%) in H_2SO_4 and aqueous $KMnO_4$ (1%).

Starting achillin (**1**), mp 145.5-146.5°C, was isolated by the literature method [2] from the aerial part of *Achillea micrantha* Willd.

Gaseous NOCl was purified by passage successively through three columns packed with $NaNO_2$ and moistened KCl and $CaCl_2$, respectively [4].

1,10-Dihydro-1*α*,10*α*-dinitroachillin (2). Gaseous NOCl [4] was bubbled through a cooled (from 0 to -10°C) solution of **1** (0.20 g, 0.8 mmole) in $CHCl_3$ (10 mL, freshly distilled) at 10 mL/min until the starting material completely disappeared (2 d, TLC). The $CHCl_3$ was removed by evaporation in vacua at room temperature. The solid was treated with EtOH (5 mL), stirred, and left for 0.5 h. The small rhombic crystals that formed were filtered off and recrystallized from CH_3CN. Yield 0.19 g (69.1%) of **2**, mp 220°C (dec.), $[\alpha]^{20}_{580}$ +94.4° (*c* 1.80, acetone), R_f 0.54 (eluent: petroleum ether—ethylacetate, 2:1). UV spectrum (λ_{max}, nm): 233 (sh, log ε 4.07). IR spectrum (ν, cm^{-1}): 1783 (*γ*-lactone), 1724 (C=O), 1626 (C=C), 1556 and 1230

(C–NO_2), 1150, 1043, 995, 850. Mass spectrum, *m/z* [I_{rel} (%)]: 292 [M - NO_2]$^+$ (1), 246 [M - $2NO_2$]$^+$ (100), 217 (13), 173 (22), 172 (12), 105 (12), 91 (19). Tables 1 and 2 contain data for ^{1}H and ^{13}C NMR spectra. ^{14}N NMR spectrum (acetone-d_6, formamide external standard at 112.4 ppm): 383.0, 390.8 (broad signals with approximately identical integrated intensities).

(1*R*,7*R*,10*S*,11*S*)-1,10-Dinitro-2-oxoguai-3,4;5,6-dien-12-oic acid (3). Lactone **2** (0.03 g) was dissolved in Py-d_5 (0.4 mL). ^{1}H NMR spectra were recorded every 10-15 min, observing the rapid weakening of the signals for the starting compound and the appearance and growth of the signals for **3**. Only the signals of **3** were observed after 30 min. The solution was poured from the NMR tube into an open flask from which Py-d_5 was freely evaporated overnight to produce crystals with mp 103-106°C (dec.) that were used for the XSA. Recrystallization from acetone—hexane isolated crystals with mp 139-142°C (dec.), $[\alpha]^{22}_{580}$ +52.5° (*c* 0.99, $CHCl_3$). UV spectrum (λ_{max}, nm): 284 (log ε 3.65). IR spectrum (ν, cm^{-1}): 1720 (C=O), 1556 and 1234 (C–NO_2), 1387, 1339, 1308, 1194, 883, 868, 808, 640. Mass spectrum, *m/z* [I_{rel} (%)]: 245 [M - $2NO_2$]$^+$ (14), 189 (10), 173 (14), 161 (16), 105 (12), 84 (100). Tables 1 and 2 list the ^{13}C and ^{1}H NMR spectra.

XSA of **2** and **3** were performed on a Bruker P4 diffractometer (graphite monochromatized Mo Kα-radiation, 2θ/θ-scanning for 2θ < 55 and 50°). Crystals of dimensions 0.32×0.48×0.84 mm^3 (**2**) and 0.40×0.46×0.70 mm^3 (**3**) were selected. The structures were solved by direct methods using the SHELXS-97 programs. Positions of H atoms were calculated geometrically. Final structure factors over all F^2 were refined by anisotropic (isotropic for H atoms) full-matrix least-squares methods using the SHELXL-97 program.

Crystals of **2** are rhombic: $a = 6.7727(3)$, $b = 14.9825(11)$, $c = 15.5849(8)$ Å, $V = 1581.4(2)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $C_{15}H_{18}N_2O_7$, $d_{calc} = 1.421$ g/cm^3, $\mu = 0.114$ mm^{-1}. A total of 2096 independent reflections were measured. The final factors were $wR_2 = 0.0951$, $S = 1.056$, 290 parameters ($R = 0.0339$ for 1897 $F > 4\sigma$).

Crystals of **3** are rhombic: $a = 6.7042(4)$, $b = 13.1091(10)$, $c = 23.554(2)$ Å, $V = 2070.0(3)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $C_{15}H_{18}N_2O_7 + C_5H_5N$, $d_{calc} = 1.339$ g/cm^3, $\mu = 0.103$ mm^{-1}. A total of 2022 independent reflections were measured. The final factors were $wR_2 = 0.1028$, $S = 1.044$, 273 parameters ($R = 0.0366$ for 1846 $F > 4\sigma$).

Tables 3 and 4 contain atomic coordinates and equivalent thermal factors of nonhydrogen atoms for **2** and **3**.

ACKNOWLEDGMENT

We thank the Ministry of Science and Higher Education of the Republic of Kazakhstan for support through the Basic Research Program (No. F0092) and the Russian Foundation for Basic Research (Project 96-07-89187) for assistance in licensing the Cambridge Structure Database.

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