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FORMATION OF AN UNUSUAL GUAIANE KETOPENTAENOLIDE FROM DEHYDROISOLEUCOMISIN BY THE ACTION OF ANHYDROUS DMF AND HCl

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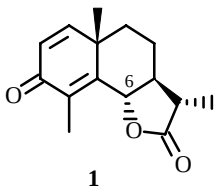
Dehydroisoleucomisin (anhydroaustricin) was converted in good yield to guai-1(10),3,5,7(11),8-pentaen-2-on-12,8-olide by the action of anhydrous HCl in dry DMF. The chemical structure of the product was established using spectral data. The probable formation scheme of this lactone was proposed to include a series of prototopic transformations and ionic dehydrogenation of intermediates.

Key words: dehydroisoleucomisin (anhydroaustricin), DMF, HCl, guai-1(10),3,5,7(11),8-pentaen-2-on-12,8-olide, NMR spectra.

Acid-catalyzed epimerization at C-6 of the natural ketolactone α-santonin (**1**) is known to produce 6-episantonin in 60% yield. This selective process occurs in DMF solution in the presence of HCl at 85°C [1]. In order to modify the structures of available guaianolides, we carried out an analogous reaction with dehydroisoleucomisin (anhydroaustricin) (**2**) [2-5], counting on the possible production of its C-7 epimer, a new guaianolide with *cis*-fusion of the lactone and seven-membered rings.



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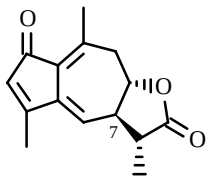

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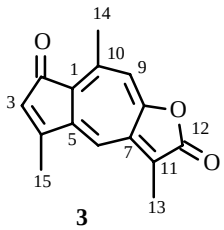

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However, the expected 7-epimer of **2** was not formed under analogous conditions. A new compound of formula $C_{15}H_{12}O_3$ (high-resolution mass spectrum) was isolated in almost the same yield (64%). Nine of its H atoms are found in three methyls. The three remaining ones belong to different double bonds (PMR spectrum). Its IR spectrum contains absorption bands for γ-lactone and α-enone groups. The UV spectrum is consistent with the presence of a complex chromophore (λ_{max} 218, 270, 431 nm), which is also evident from the bright yellow color of the compound.

Structure **3** is proposed for the product. It was derived based on ^{13}C and ^{1}H NMR and two-dimensional ^{13}C—^{1}H COLOC NMR. Table 1 gives the data.

The observation of intramolecular nuclear Overhauser effects is important. The relative integrated intensity of the signals for H-3 and H-6 increase with double resonance and suppression of the signal for 3H-15. Those of the signals for H-6 and H-9 increase with suppression of the signals for 3H-14 and 3H-13, respectively. This is in complete agreement with structure **3**.

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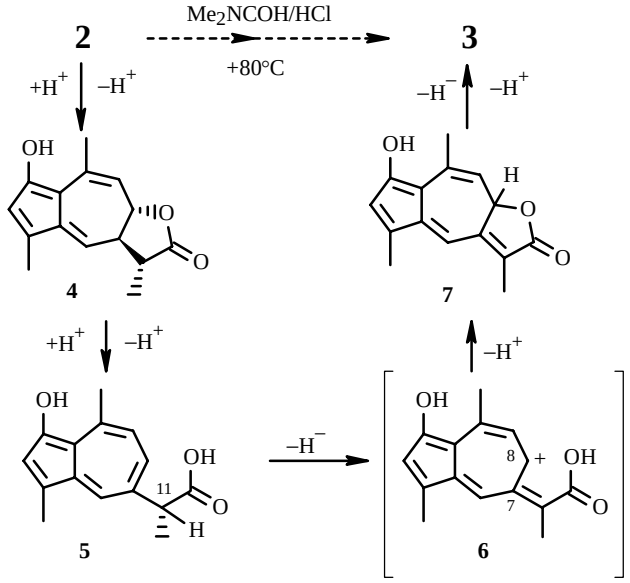
TABLE 1. ^{13}C and ^{1}H NMR Data for **3** ($CDCl_3$, δ, ppm, 0 = TMS)

C atom	^{13}C	^{1}H	Cross-peaks in ^{13}C-^{1}H COLOC (10 Hz) 2D spectrum
1	126.86 s	-	C-1/H-6, H-9, 3H-14
2	194.97 s	-	C-2/H-3
3	132.47 d	6.22 (1H, br.q, $J_{3,15}$ = 1.5)	C-3/3H-15
4	160.53 s	-	C-4/3H-15
5	145.78 s	-	C-5/H-3, 3H-15
6	114.47 d	6.52 (1H, s)	-
7	143.24 s	-	C-7/H-6, 3H-13
8	155.86 s	-	C-8/H-6, H-9
9	116.76 d	6.83 (1H, s)	-
10	144.54 s	-	C-10/3H-14
11	116.75 s	-	C-11/3H-13, 3H-14
12	169.04 s	-	C-12/3H-13
13	8.34 q	2.10 (3H, s)	-
14	22.13 q	2.68 (3H, s)	-
15	14.14 q	2.99 (3H, d, $J_{3,15}$ = 1.5)	-



Scheme 1

The reaction does not occur at room temperature. The reaction mixture must be heated to carry it out. TLC on Silufol indicates that starting lactone **2** converts to **3** after 3 h at 80°C.

Scheme 1 presents hypothetically the formation of **3**. First, starting ketone **2** isomerizes into intermediate hydroxyketone **4** and then into hydroxyacid **5**, which eliminates under the reaction conditions hydride (H^-) from C-11 with subsequent intramolecular neutralization of the positive charge in intermediate **6** by the carboxylic acid in it. This forms neutral hydroxylactone **7**, which eliminates hydride from C-8 and completes this neutralization scheme through reverse enolization that starts with loss of a proton from the C-3 hydroxyl. Research on this transformation is continuing.

EXPERIMENTAL

NMR spectra were recorded on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^{1}H; 125.76 MHz, ^{13}C) using standard Bruker programs for recording the 2D ^{1}H—^{13}C COLOC spectrum. High-resolution mass spectra (EI, 70 eV) were obtained in a Finnigan MAT 8200 instrument.

Column chromatography was carried out over Armsorbsil 160/100 silica gel with ~1:20 ratio of compound to sorbent. TLC used Silufol plates with development by spraying with vanillin (1%) in H_2SO_4 or saturated aqueous $KMnO_4$.

Melting points were determined on a Boetius apparatus.

IR spectra were obtained on a Vector 22 instrument.

Starting lactone **2**, mp 193-195°C, was prepared as before [5].

Guai-1(10),3,5,7(11),8-pentaen-2-on-11,8-olide (3). A stream of dry HCl was passed for 3 min through dry distilled DMF (5 mL). The resulting solution was stirred, treated with **2** (0.1 g, 0.14 mmol), heated at 80°C for 3 h (until the spot of the starting material disappeared on TLC), cooled, diluted with water (20 mL), and extracted with $CHCl_3$ (2×15 mL). The extract was washed successively with saturated aqueous NaCl and $NaHCO_3$ and water. Solvent was removed to afford an oily product, chromatography of which isolated **3** (0.065 g, 64% yield), mp 263-265°C (EtOAc). UV spectrum (EtOH, λ_{max}, nm): 218, 270, 431 (log ε 4.14, 4.38, 4.13).

IR spectrum (KBr, ν, cm^{-1}): 1757 (γ-lactone), 1689 and 1622 (O=C–C=C), 1549, 1376, 1331, 1208, 1149, 1037 (C–O), 913, 747, 706, 686, 614.

Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 240 (100), 211 (52), 184 (29), 183 (16), 169 (18), 155 (11), 141 (21), 115 (21), 46 (16). Found: *m*/*z* 240.07876 $[M]^+$. $C_{15}H_{12}O_3$. Cald: M = 240.07864.

Table 1 lists the ^{13}C and ^{1}H NMR data. The 2D ^{1}H—^{1}H COSY NMR (1 Hz) exhibits cross-peaks 3H-13/H-6, H-9; 3H(14)/H-9; and 3H-15/H-3.

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