Oxidation of Glycocitrine-II. One of the *ortho*-Prenylated Phenolacridone Alkaloids, with *m*-Chloroperbenzoic Acid

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Treatment of glycocitrine-II (1), one of the acridone alkaloids having an *ortho*-prenylphenol moiety isolated from *Citrus* plants, with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane gave a novel oxidation product 2, along with the known cyclization products 3 and 4. The structure of 2 was elucidated by spectrometric and X-ray crystallographic analyses.

Keywords glycocitrine-II; acridone; *m*-chloroperbenzoic acid; crystal structure; oxidation

Many kinds of acridone alkaloids having an *ortho*-prenyl (3,3-dimethylallyl or isopentenyl) phenol moiety in the molecule occur in Rutaceous plants.[1] From a biogenetic viewpoint, the prenylated acridones are considered to be significant precursors of the corresponding dimethylpyrano- or furano-acridone alkaloids that co-occur in Rutaceous plants.[2] This type of oxidative cyclization of the *o*-prenylphenol moiety is considered to occur through a corresponding epoxide intermediate, and is also found in coumarins, flavonoids, chromenes, quinolones, and other some kinds of naturally occurring compounds.[3]

In the laboratory, the transformation based on this biogenetic oxidative cyclization was performed by peracid oxidation of the corresponding *ortho*-prenylated phenols followed by treatment with acid or base[4] to give the corresponding hydroxy-dimethylpyrano and hydroxy-isopropylfurano derivatives.

This time, in the course of structural elucidation of some binary acridone alkaloids[5] isolated from a plant of genus *Glycosmis*, the above peracid oxidation of glycocitrine-II (**1**),[6] one of the acridone alkaloids having an *o*-prenylphenol moiety isolated from *Citrus* plants, was re-examined and found to give a novel oxidation product (**2**) along with the known cyclization products (**3** and **4**).[7]

Structure of the Novel Oxidation Product 2 Treatment of glycocitrine-II (**1**) with *m*-chloroperbenzoic acid (*m*-CPBA) followed by sodium carbonate gave **2** as yellow prisms from chloroform solution in 16% yield along with the known compounds **3** and **4** in 44 and 20% yields, respectively. The molecular formula of **2** was determined as $C_{19}H_{19}NO_4$ from the high-resolution mass spectrum (HR-MS). The ^{1}H- and ^{13}C-NMR spectra of **2** (Table I) showed the presence of hydrogen-bonded hydroxy, *N*-methyl, prenyl, and 9-carbonyl groups besides a non-substituted A-ring in an acridone skeleton, as in **1**. Significant differences in the ^{13}C-NMR spectrum of **2** compared with that of **1** were the observation of an additional carbonyl and a tetrasubstituted sp^3 carbon at δ_C 194.56 and 79.54, instead of an oxygenated C-3 and sp^2 carbon (C-4) bearing a prenyl moiety in **1**, respectively, and a diamagnetic shift (12—16 ppm) of signals due to the methylene (C-11) and 4a angular carbon. In accordance

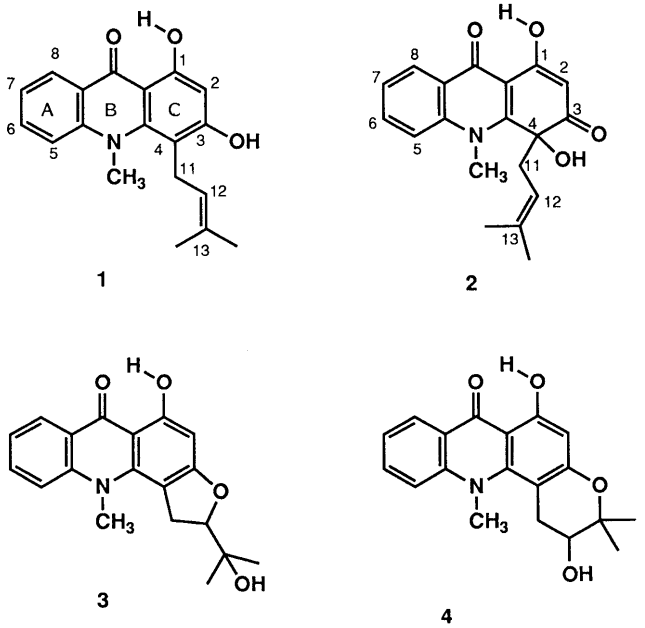

Chart 1

TABLE I. ^{1}H- and ^{13}C-NMR Data for **2** and **1**

No.	**2**		Glycocitrine-II (**1**)	
	δ_H	δ_C	δ_H	δ_C
1	—	175.75	—	162.33
1-OH	16.34 (s)	—	14.78 (s)	—
2	5.52 (s)	95.52	6.33 (s)	96.57
3	—	194.56	—	164.29
4	—	79.54	—	104.92
4 or 3-OH	5.25 (s)	—	10.71 (br s)	—
4a	—	158.87	—	146.82
5	7.81 (d, 8.5)	116.77	7.55 (d, 8.5)	116.99
6	7.88 (t, 8.5)	134.40	7.73 (t, 8.5)	133.81
7	7.60 (t, 8.5)	126.25	7.26 (t, 8.5)	121.23
8	8.48 (d, 8.5)	126.31	8.17 (d, 8.5)	124.93
8a	—	125.01	—	120.46
9	—	178.07	—	180.34
9a	—	106.50	—	105.82
N-CH_3	4.44 (3H, s)	39.48	3.77 (3H, s)	43.28
10a	—	141.09	—	145.26
11	2.74 (2H, d, 7.3)	42.66	3.37 (2H, br d, 4.4)	26.50
12	5.01 (br t, 7.3)	115.52	5.33 (br s)	124.74
13	—	137.85	—	130.62
13-CH_3	1.40 (3H, s)	17.62	1.73 (3H, s)	17.83
	1.65 (3H, s)	25.90	1.75 (3H, s)	25.39

Spectra of **2** and **1** were measured in $CDCl_3$ and DMSO-d_6, respectively. Values are in ppm (δ_H and δ_C). Each proton signals corresponds to 1H, unless otherwise stated. Figures in parentheses are coupling constant (*J*) in hertz. Assignments of ^{13}C signals were determined by H–C COSY and HMBC spectrometries.

with these structural changes, significant shifts of the δ-values of signals due to H-2 and H-11 were also observed (see Table I). Further information on the structure of **2** was obtained from the results of H–C two- and three-bond long-range correlations, as shown by arrows in Fig. 1, in the ^{1}H detected heteronuclear multiple bond connectivity (HMBC) spectrum. Appearance of three-bond correlation between the carbonyl carbon (C-3) at δ_C 194.56 and both hydroxy and methylene protons at δ_H 5.25 and 2.74, respectively, and between a strongly hydrogen-bonded hydroxyl proton at δ_H 16.34 and carbon (C-2, δ_C 95.52) having a singlet proton (H-2) at δ_H 5.52, which also correlated with sp^3-carbon (C-4) at δ_C 79.54, suggested the partial structure of the right side of the molecule of **2**. On the basis of these spectral data together with other H–C long-range correlations shown by arrows in Fig. 1, we proposed the structure **2** for the new oxidation product. A single-crystal X-ray analysis defined the complete structure of **2** as shown in Fig. 2.

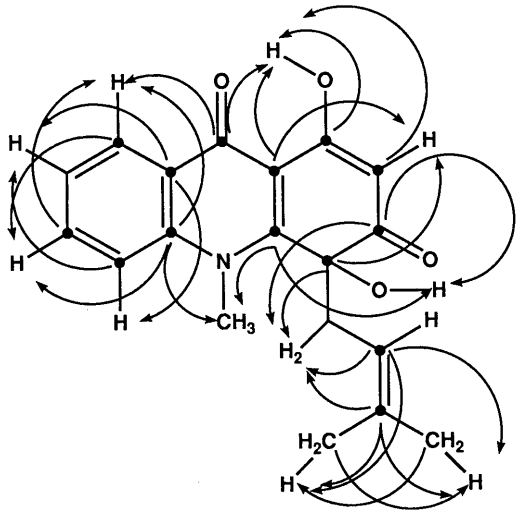

Fig. 1. C–H Long-Range Correlations in the HMBC Spectrum of **2**

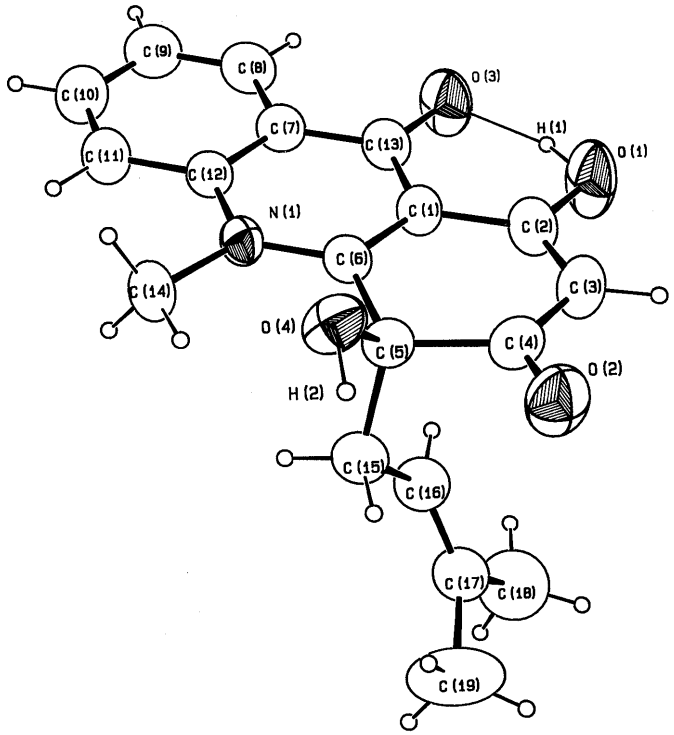

Fig. 2. Perspective View of **2** with Atomic Labels and Thermal Ellipsoids at 50% Probability for Non-hydrogen Atom

Hydrogens are shown as arbitrary circles. Octant shaded ellipsoids are heteroatoms.

Description of Molecular Structure of 2[8] A molecule of **2** in an asymmetric unit is illustrated in Fig. 2 with the atomic labels. This compound has a chiral center [C(5)], so a racemic pair exists in a unit cell (only the *S* enantiomer is displayed in Fig. 2). No unusual bond parameters were found in the molecule. A somewhat shortened bond length of C(2)–O(1), 1.329(5) Å, from the ideal single C–OH bond was found, indicating electronic conjugation with a slightly elongated C(2)=C(3) double bond [1.349(6)] Å and a hydrogen-bonding chelate ring. The chelate ring is an intramolecular six-membered ring including the H(1) hydrogen, and is almost planar. The bond parameters around H(1) are as follows: O(3)–H(1), 1.54 Å; O(1)–H(1), 0.96 Å; O(1)–H(1)–O(3); 152°. The N(1) nitrogen is in a planar bond system (*i.e.*, sp^2-character) with three carbons, although the repulsion of the C(14) methyl carbon and the bulky prenyl substituent at C(5) seems to open the C(6)–N(1)–C(14) angle slightly, 124.0(3)°. The hydroxy group at C(5) makes an intermolecular hydrogen bond with the carbonyl oxygen [O′(2): translation, $-x$, $-y$, $2-z$], so two molecules related mutually by the center of symmetry form a dimer bridged by two hydrogen bonds, O(4)–O′(2) and O(2)–O′(4), with the atomic distance of 2.73 Å.

Experimental

Melting point was measured on a micromelting point hot-stage apparatus (Yanagimoto). ^{1}H- and ^{13}C-NMR spectra were recorded on GX-270 (JEOL) and GX-400 (JEOL) spectrometers, respectively, in $CDCl_3$. Chemical shifts are shown in δ values (ppm) with tetramethylsilane as an internal reference. The HMBC spectrum was measured at $J=8$ Hz on the GX-400. All mass spectra were measured under electron impact (EI) conditions, using an M-80 (Hitachi) or a JMS-HX-110 (JEOL) spectrometer having a direct inlet system. UV spectra were recorded on a UVIDEC-610C double-beam spectrophotometer (JASCO) in methanol and IR spectra on an IR-810 (JASCO) in $CHCl_3$. Preparative TLC was done on Kieselgel 60 F_{254} (Merck).

Oxidation of Glycocitrine-II (1) with *m*-CPBA[7] A mixture of glycocitrine-II[6] (**1**) (5.8 mg, 0.019 mmol) and *m*-CPBA (4.9 mg, 0.028 mmol) in CH_2Cl_2 was left at room temperature under N_2 gas for 4 d. The solution was washed with saturated aqueous Na_2CO_3 solution, dried with anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was subjected to silica gel preparative TLC (CH_2Cl_2: AcOEt = 25 : 2) to obtain **2** (1.0 mg), **3** (2.7 mg), and **4** (1.2 mg), along with the starting material (**1**) (1.1 mg).

2: Yellow prisms from $CHCl_3$ mp 158—161 °C. UV λ_{max} nm: 207, 230, 286, 340, 384 (sh). IR ν_{max} cm^{-1}: 3350, 1630, 1580, 1520, 1480. ^{1}H- and ^{13}C-NMR: see Table I. FAB-MS *m/z*: 326 [M$^+$+H]. EI-MS *m/z* (%): 325 (M$^+$, 14), 323 (13), 308 (15), 292 (10), 269 (26), 257 (100), 242 (87), 228 (54), 214 (90). HR-MS Calcd for $C_{19}H_{19}NO_4$: 325.1312. Found: 325.1315. Differential nuclear Overhauser effect (NOE): irradiation of the N–CH_3 protons at δ_H 4.44—4 and 5% enhancements of H-5 (δ_H 7.81) and H-11 (δ_H 2.74), respectively.

3: An amorphous powder. UV λ_{max} nm: 204, 213, 227, 250, 264 (sh), 273, 300, 332, 400. IR ν_{max} cm^{-1}: 3670, 1630, 1600. ^{1}H-NMR δ_H: 15.20 (1H, s), 8.42 (1H, dd, $J=8.4$, 1.5 Hz), 7.71 (1H, t, $J=7.1$ Hz), 7.41 (1H, d, $J=8.4$ Hz), 7.28 (1H, overlapped with a solvent), 6.27 (1H, s), 4.65 (1H, t, $J=9.0$ Hz), 3.99 (3H, s), 3.62 (1H, d, $J=9.0$ Hz), 3.61 (1H, d, $J=9.0$ Hz), 1.39 (3H, s), 1.28 (3H, s). EI-MS *m/z* (%): 325 (M$^+$, 72), 292 (24), 266 (55), 254 (20), 241 (24), 225 (27). HR-MS Calcd for $C_{19}H_{19}NO_4$: 325.1312. Found: 325.1310.

4: An amorphous powder. UV λ_{max} nm: 204, 216, 226, 252, 265 (sh), 275, 300, 331, 396. IR ν_{max} cm^{-1}: 3650, 1640, 1590. ^{1}H-NMR δ_H: 14.29

TABLE II. Summary of Crystal Data and Intensity Collection Parameters for **2**

Compound	**2**
Formula	$C_{19}H_{19}NO_4$
F.W., amu	325.4
Crystal dimensions (mm^3)	$0.21 \times 0.21 \times 0.06$
Space group	$P\bar{1}$
Temperature	293 K
a, Å	7.892 (1)
b, Å	9.076 (2)
c, Å	12.329 (1)
α, °	83.09 (1)
β, °	88.53 (1)
γ, °	65.11 (1)
V, Å^3	795 (3)
Z	2
Calcd density (D_c)	1.359 g/cm^3
Radiation	Graphite monochromated MoK_α
2θ range	3—50°
Scan technique	$\omega - 2\theta$
Scan range (ω, °)	$0.7 + 0.35 \tan\theta$
No. of data measured	2935
Criterion for observation	$F_O > 3\sigma(F_O)$
Unique obsd data	1816
R	0.049
R_w	0.044
No. of variables	218

TABLE III. Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B (Å^2)
O(1)	−0.2812 (4)	0.4936 (3)	0.5976 (2)	6.23 (7)
O(2)	−0.1646 (3)	0.1908 (3)	0.9404 (2)	5.18 (6)
O(3)	−0.1017 (3)	0.3769 (3)	0.4409 (2)	5.37 (6)
O(4)	0.0579 (3)	−0.0740 (2)	0.8460 (2)	3.94 (5)
N(1)	0.2268 (3)	−0.0349 (2)	0.6413 (2)	2.95 (5)
C(1)	−0.0245 (4)	0.2315 (3)	0.6183 (2)	3.24 (6)
C(2)	−0.1797 (4)	0.3617 (4)	0.6657 (3)	4.15 (8)
C(3)	−0.2256 (4)	0.3531 (4)	0.7716 (3)	4.41 (8)
C(4)	−0.1223 (4)	0.2131 (3)	0.8448 (2)	3.74 (7)
C(5)	0.0601 (4)	0.0797 (3)	0.8082 (2)	3.19 (6)
C(6)	0.0871 (3)	0.0895 (3)	0.6848 (2)	2.95 (6)
C(7)	0.1490 (4)	0.1162 (3)	0.4593 (2)	3.29 (6)
C(8)	0.1813 (4)	0.1235 (4)	0.3469 (3)	4.13 (8)
C(9)	0.3188 (4)	−0.0050 (4)	0.3041 (3)	4.55 (8)
C(10)	0.4297 (4)	−0.1442 (4)	0.3737 (3)	4.67 (8)
C(11)	0.4016 (4)	−0.1550 (4)	0.4842 (3)	3.98 (7)
C(12)	0.2596 (3)	−0.0249 (3)	0.5290 (2)	3.10 (6)
C(13)	0.0017 (4)	0.2502 (3)	0.5032 (2)	3.61 (7)
C(14)	0.3530 (4)	−0.1912 (3)	0.7059 (3)	3.93 (7)
C(15)	0.2213 (4)	0.0998 (3)	0.8658 (3)	3.88 (7)
C(16)	0.2160 (4)	0.2677 (3)	0.8444 (3)	3.84 (7)
C(17)	0.2520 (4)	0.3471 (3)	0.9160 (3)	4.06 (7)
C(18)	0.2441 (5)	0.5149 (4)	0.8831 (4)	6.4 (1)
C(19)	0.3045 (7)	0.2839 (5)	1.0337 (3)	8.2 (1)

(1H, s), 8.35 (1H, dd, J=8.1, 1.7 Hz), 7.72 (1H, t, J=8.5 Hz), 7.43 (1H, d, J=8.4 Hz), 7.30 (1H, t, J=7.7 Hz), 6.26 (1H, s), 3.88 (3H, s), 3.81 (1H, br m), 3.15 (1H, dd, J=5.1, 15.5 Hz), 2.93 (1H, dd, J=6.4, 15.5 Hz), 1.48 (3H, s), 1.45 (3H, s). EI-MS m/z (%): 325 (M^+, 23), 254 (17), 241 (23), 225 (34), 185 (12). HR-MS Calcd for $C_{19}H_{19}NO_4$: 325.1312. Found: 325.1306.

Crystal Structure Determination and Refinement of 2[8] Yellow crystals of **2** suitable for X-ray analysis were obtained by slow evaporation of a $CHCl_3$ solution. A preliminary examination of a crystal on an Enraf–Nonius CAD4 diffractometer indicated a triclinic unit cell and the space group $P\bar{1}$, this being confirmed by the subsequent structure determination. A least-squares refinement of the setting angles of 20 reflections, collected in the range of $14° < 2\theta < 26°$, led to the crystal data given in Table II. Diffracted intensities were measured with graphite-monochromated MoK_α radiation (λ=0.7093 Å). The data collection is summarized also in Table II. Net intensities were reduced to a set of relative structure factors by the application of the standard Lorentz and polarization factors. No absorption correction was made. The structure was solved by the direct method and refined by least-squares techniques.[9] Most non-hydrogen atoms of a molecule in an asymmetric unit were found in an initial E-map. Subsequent difference Fourier (DF) syntheses revealed all non-hydrogen atomic positions. The non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms bound to carbon were included in calculated positions as fixed parameters. The two hydrogen atoms bound to oxygen were found in a DF-map, refined partially, and then fixed. Final cycles of full-matrix least-squares refinement[9] were carried to convergence at R=0.049 (R_w=0.044).[10] The final difference Fourier was judged to be essentially featureless. The atomic coordinates for non-hydrogen atoms with the isotropic equivalent thermal factors are given in Table III.[11]

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8) Atomic nomenclature illustrated in Fig. 2 was tentatively used.

9) Progams of the Enraf–Nonius SDP package were used. The package includes modified versions of Main, Hull, Lessinger, Germain, Declerq, and Woolfson's MULTAN82 and Johnson's ORTEP II.

10) The atomic scattering factors were taken from "International Tables for X-ray Crystallography," Vol. IV, Kynoch Press, Birmingham, 1974. $R = \sum||F_O| - |F_C|| / \sum|F_O|$, $R_w = [\sum_w(|F_O| - |F_C|)^2 / \sum_w(F_O)^2]^{1/2}$ with unit weight.

11) Tables of the bond lengths, the bond angles, the anisotropic temperature factors for non-hydrogen atoms, the idealized atomic coordinates for hydrogen atoms, and the observed and calculated structure factors are available from one of the authors (K. H.) on request.