Coclauril, a Nonglucosidic 2-Cyclohexen-1-ylideneacetonitrile, from *Cocculus lauriforius* DC.

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Coclauril (1), a nonglucosidic 2-cyclohexen-1-ylideneacetonitrile, was isolated from the leaves of *Cocculus lauriforius* DC. (Menispermaceae) collected at Ishigaki Island (Okinawa, Japan), and the structure was elucidated by spectroscopic means. Two known bicyclic butenolides, menisdaurilide (8) and aquilegiolide (9), were also characterized.

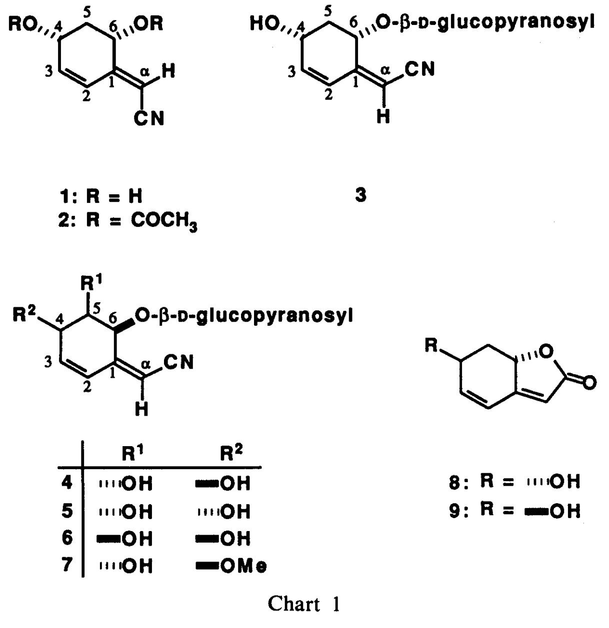
Keywords *Cocculus lauriforius*; Menispermaceae; coclauril; nitrile; menisdaurilide; aquilegiolide; butenolide

Cocculus lauriforius DC. (Menispermaceae), an evergreen shrub, is a rich source of a variety of alkaloids1) such as erythrinans, 1-benzyltetrahydroisoquinolines, aporphines, and dibenz[*d,f*]azonines, and extensive investigations on its alkaloidal constituents have been carried out.

We have examined the constituents of the leaves of this plant collected at Ishigaki Island (Okinawa, Japan) and isolated a novel nonalkaloidal component, named coclauril (**1**). Its structure was assigned as a geometrical isomer of the aglycone of menisdaurin (**3**),2) a cyanoglucoside isolated from *Menispermum dauricum* DC. (Menispermaceae). In addition, two known bicyclic butenolides, menisdaurilide (**8**)2,3) and aquilegiolide (**9**),3) were shown to co-occur with coclauril (**1**) and were characterized. However, no alkaloidal component could be detected.

Results and Discussion

Coclauril (**1**) was obtained as colorless plates, mp 121—124 °C, $[\alpha]_D^{26}$ +94.0° (methanol). The molecular formula was established as $C_8H_9NO_2$ by high-resolution mass spectroscopy (MS). The appearance of a broad absorption band at ν_{max} 3375 cm^{-1} in the infrared (IR) spectrum and D_2O-exchangeable proton signals at δ_H 4.90 and 4.45 (each 1H, doublet) in the proton nuclear magnetic resonance (^1H-NMR) spectrum (in acetone-d_6) revealed the presence of two hydroxy groups in **1**. Treatment of **1** with acetic anhydride–pyridine gave a diacetate (**2**). In the ^1H-NMR spectrum of the diacetate (**2**), two 1H signals seen at δ_H 4.53 and 4.41 in the spectrum of **1** were shifted to lower field at δ_H 5.65—5.54 (2H, m). A characteristic sharp and strong absorption band at ν_{max} 2210 cm^{-1} and those at ν_{max} 1630 and 1585 cm^{-1} in the IR spectrum4) together with the ultraviolet (UV) band at λ_{max} 254 nm5) were ascribed to an $\alpha,\beta,\gamma,\delta$-unsaturated nitrile chromophore. Analyses of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum using a single-frequency selective proton-decoupling technique indicated the presence of a cyano carbon (δ_C 117.5),6) a disubstituted sp^2-carbon (δ_C 161.6), and three monosubstituted sp^2-carbons (δ_C 143.9, 123.6, and 91.7), and protons attached to these carbons were observed at δ_H 6.28 (1H, dq, J=10.1, 1.7 Hz), 6.53 (1H, dd, J=10.1, 2.4 Hz), 5.61 (1H, br s), respectively, and were coupled to each other. Further, protons at δ_H 5.61 (H-α) and 6.28 (H-3) were coupled to protons attached to carbons bearing a hydroxy group at δ_H 4.41 (H-6) and 6.28 (H-4), respectively, both also being coupled to the methylene protons at δ_H 2.43 and 1.62. The larger coupling constant values between H-5 and H-4 or H-6 ($J_{4,5_{ax}}$ = 10.1 Hz, $J_{6,5_{ax}}$ = 12.8 Hz) suggested axial orientations of H-4 and H-6. These functionalities taken together with the results of the ^1H–^{13}C long-range coupling correlation 2D (COLOC) spectrum as shown by arrows in Fig. 1 indicated that coclauril had a 2-cyclohexen-1-ylideneacetonitrile system having equatorial hydroxy groups at C-4 and C-6.



	R1	R2
4	''''OH	▬OH
5	''''OH	''''OH
6	▬OH	▬OH
7	''''OH	▬OMe

Chart 1

The *E*-configuration of the cyanomethylene moiety was proposed on the basis of the following ^1H-NMR spectral features. (i) The H-2 signal at δ_H 6.53 in **1** is observed at lower field (*ca.* 0.3 ppm) compared with the signal of the corresponding proton in some cyanoglucosides containing the *Z*-cyanomethylene moiety, such as menisdaurin (**3**),2) lithospermoside (griffonin) (**4**),7) dasycarponin (**5**),7a) compound **6**,8) and bauhinin (**7**).9) (ii) A five-bond long-range coupling10) of 1.7 Hz was observed between H-3 and H-α. (iii) No nuclear Overhauser enhancement (NOE) was observed at any proton signal on irradiation of the olefinic proton at δ_H 5.61 (H-α) in **1**. On the basis of the foregoing

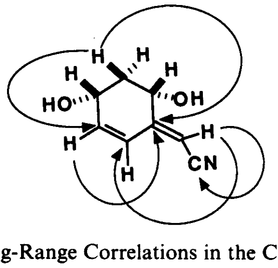


Fig. 1. ^1H–^{13}C Long-Range Correlations in the COLOC Spectrum of **1**

data, coclauril was assigned the structure **1**, except for the absolute stereochemistry.

As other constituents from the same plant, **8** and **9** were characterized as menisdaurilide[2,3] and aquilegiolide,[3] respectively, by comparison of the spectral data (^{1}H-NMR, UV, IR, and MS) with those described in the literature. *p*-Hydroquinone and *p*-hydroxybenzoic acid were also identified by direct comparison with respective authentic samples.

Experimental

All melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM GX-270 spectrometer. ^{13}C-NMR and ^{1}H-^{13}C COLOC spectra were obtained with JEOL JNM FX-100 and JNM GX-400 spectrometers, respectively. Chemical shifts are shown in δ-values (ppm) with tetramethylsilane as an internal reference. MS were measured with a Hitachi M-52 spectrometer having a direct inlet system, and high-resolution MS with a Hitachi M-80 spectrometer. IR spectra were taken with a JASCO IR-810 spectrophotometer, and UV spectra with a JASCO UVIDEC-610 double-beam spectrophotometer.

Extraction and Separation The air-dried leaves of *Cocculus laurifolius* DC. collected at Ishigaki Island (Okinawa, Japan) late in November, 1983, were extracted with acetone at room temperature. The acetone extract was subjected to silica gel column chromatography (CC) eluted successively with hexane, chloroform, isopropyl ether, acetone, and methanol. The acetone eluate was further subjected to silica gel CC to give *p*-hydroquinone (0.0633%). Subsequent preparative thin-layer chromatography (TLC) on silica gel of the mother liquor with chloroform and methanol (40:1—5:1, v/v) afforded *p*-hydroxybenzoic acid (0.0011%), coclauril (**1**) (0.0132%), menisdaurilide (**8**) (0.0019%), and aquilegiolide (**9**) (0.0018%). The latter two compounds showed almost the same *Rf* value on silica gel TLC and were separated by development four times with chloroform–methanol (40:1, v/v).

Coclauril (1) Colorless plates from acetone–hexane, mp 121—124 °C, $[\alpha]_D^{26}$ +94.0° ($c=0.235$, MeOH). High-resolution MS *m/z*: Calcd for $C_8H_9NO_2$: 151.0632. Found: 151.0619. IR ν_{max}^{film} cm^{-1}: 3375 (br), 2210, 1630, 1585. UV λ_{max}^{MeOH} nm (log ε): 254 (4.36). ^{1}H-NMR (acetone-d_6) δ: 6.53 (1H, dd, $J_{2,3}=10.1$, $J_{2,4}=2.4$ Hz, H-2), 6.28 (1H, dq, $J_{3,2}=10.1$, $J_{3,4}=J_{3,5_{eq}}=J_{3,\alpha}=1.7$ Hz, H-3), 5.61 (1H, br s, H-α), 4.90 (1H, d, $J_{OH-6,6}=6.1$ Hz, OH-6, exchangeable with D_2O), 4.53 (1H, br m, H-4), 4.45 (1H, d, $J_{OH-4,4}=6.1$ Hz, OH-4, exchangeable with D_2O), 4.41 (1H, br m, H-6), 2.43 (1H, dtd, $J_{5_{eq},5_{ax}}=11.4$, $J_{5_{eq},6}=J_{5_{eq},4}=4.9$, $J_{5_{eq},3}=1.7$ Hz, H-5_{eq}), 1.62 (1H, ddd, $J_{5_{ax},6}=12.8$, $J_{5_{ax},5_{eq}}=11.4$, $J_{5_{ax},4}=10.1$ Hz, H-5_{ax}). ^{1}H-NMR (MeOH-d_4) δ: 6.57 (1H, dd, $J_{2,3}=10.1$, $J_{2,4}=2.4$ Hz, H-2), 6.23 (1H, br dd, $J_{3,2}=10.1$, $J_{3,4}=1.7$ Hz, H-3), 5.57 (1H, br s, H-α), 4.48 (1H, br m, H-4), 4.32 (1H, ddd, $J_{6,5_{ax}}=12.8$, $J_{6,5_{eq}}=4.9$, $J_{6,\alpha}=2.0$ Hz, H-6), 2.39 (1H, dtd, $J_{5_{eq},5_{ax}}=11.4$, $J_{5_{eq},4}=J_{5_{eq},6}=4.9$, $J_{5_{eq},3}=1.7$ Hz, H-$5_{eq.}$), 1.59 (1H, ddd, $J_{5_{ax},6}=12.8$, $J_{5_{ax},5_{eq}}=11.4$, $J_{5_{ax},4}=10.4$ Hz, H-5_{ax}). ^{13}C-NMR (acetone-d_6) δ: 161.6 (s, C-1), 143.9 (d, C-3), 123.6 (d, C-2), 117.5 (s, CN), 91.7 (d, C-α), 68.0 (d, C-6), 67.3 (d, C-4), 43.2 (t, C-5). MS *m/z* (%): 152 ($M^+ + \cdot H$, 5), 151 (M^+, 3), 133 ($M^+ - H_2O$, 65), 105 ($M^+ - H_2O - CO$, 100), 104 ($M^+ - H_2O - CO - \cdot H$, 31).

Acetylation of 1 A mixture of **1** (4.5 mg), acetic anhydride (0.5 ml), and pyridine (2 drops) was stirred overnight at room temperature. After the usual work-up, the residue was subjected to preparative TLC on silica gel (solvent: chloroform–hexane, 3:1, v/v) to give a diacetate (**2**) (6.1 mg, 87%) as a colorless, viscous oil. High-resolution MS *m/z*: Calcd for $C_{12}H_{13}NO_4$: 235.0843. Found: 235.0851. ^{1}H-NMR ($CDCl_3$) δ: 6.76 (1H, dd, $J_{2,3}=10.1$, $J_{2,4}=2.0$ Hz, H-2), 6.18 (1H, dq, $J_{3,2}=10.1$, $J_{3,4}=J_{3,5_{eq}}=J_{3,\alpha}=1.2$ Hz, H-3), 5.65—5.54 (2H, m, H-4 and H-6), 5.32 (1H, br s, H-α), 2.51 (1H, dtd, $J_{5_{eq},5_{ax}}=11.8$, $J_{5_{eq},6}=J_{5_{eq},4}=5.1$, $J_{5_{eq},3}=1.2$ Hz, H-5_{eq}), 2.16 and 2.09 (each 3H, each s, $COCH_3 \times 2$), 1.87 (1H, dt, $J_{5_{ax},6}=J_{5_{ax},5_{eq}}=11.8$, $J_{5_{ax},4}=9.7$ Hz, H-5_{ax}).

Menisdaurilide (8)[2,3] Colorless prisms from benzene, mp 117—120 °C, $[\alpha]_D^{26}$ −28.9° ($c=0.130$, MeOH). High-resolution MS *m/z*: Calcd for $C_8H_8O_3$: 152.0473. Found: 152.0477. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1780, 1755, 1650. UV λ_{max}^{MeOH} nm (log ε): 255 (4.32). ^{1}H-NMR ($CDCl_3$) δ: 6.59 (1H, dd, $J_{2,3}=10.1$, $J_{2,4}=2.4$ Hz, H-2), 6.31 (1H, br d, $J_{3,2}=10.1$ Hz, H-3), 5.84 (1H, br s, H-α), 4.88 (1H, ddd, $J_{6,5_{ax}}=13.4$, $J_{6,5_{eq}}=5.2$, $J_{6,\alpha}=1.6$ Hz, H-6), 4.65 (1H, br m, H-4), 2.95 (1H, br dt, $J_{5_{eq},5_{ax}}=10.7$, $J_{5_{eq},4}=J_{5_{eq},6}=5.2$ Hz, H-5_{eq}), 1.95 (1H, br d, $J_{OH-4,4}=6.4$ Hz, OH-4, exchangeable with D_2O), 1.68 (1H, dt, $J_{5_{ax},6}=13.4$, $J_{5_{ax},4}=J_{5_{ax},5_{eq}}=10.7$ Hz, H-5_{ax}). MS *m/z* (%): 152 (M^+, 62), 134 (11), 123 (59), 110 (69), 108 (41), 107 (35), 106 (30), 95 (100).

Aquilegiolide (9)[3] Colorless needles from benzene, mp 77—79 °C, $[\alpha]_D^{26}$ −399.5° ($c=0.105$, MeOH). High-resolution MS *m/z*: Calcd for $C_8H_8O_3$: 152.0473. Found: 152.0457. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1785 (sh), 1750, 1650. UV λ_{max}^{MeOH} nm (log ε): 250 (4.33). ^{1}H-NMR (acetone-d_6) δ: 6.66 (1H, d, $J_{2,3}=9.7$ Hz, H-2), 6.37 (1H, br dd, $J_{3,2}=9.7$, $J_{3,4}=5.0$ Hz, H-3), 5.84 (1H, br s, H-α), 5.26 (1H, ddd, $J_{6,5_{ax}}=12.4$, $J_{6,5_{eq}}=5.0$, $J_{6,\alpha}=1.7$ Hz, H-6), 4.62—4.51 (2H, br m, H-4+OH-4), 2.50 (1H, br dd, $J_{5_{eq},5_{ax}}=12.4$, $J_{5_{eq},6}=5.0$ Hz, H-5_{eq}), 1.74 (1H, td, $J_{5_{ax},6}=J_{5_{ax},5_{eq}}=12.4$, $J_{5_{ax},4}=4.4$ Hz, H-5_{ax}). MS *m/z* (%): 152 (M^+, 57), 134 (14), 123 (56), 110 (76), 108 (43), 107 (43), 106 (41), 95 (100).

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