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ALOENIN, A NEW BITTER GLUCOSIDE FROM *ALOE* SPECIES

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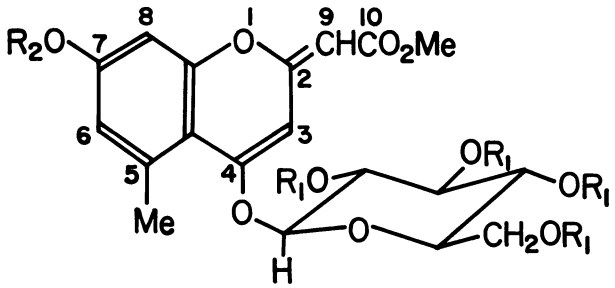
A new bitter glucoside, named aloenin, isolated from *Aloe* species has been established to be 2-(carbomethoxymethyliden)-4-(β-D-glucopyranosyloxy)-7-hydroxy-5-methylchromene (1). This is an unique example of naturally occurring chromene having the carbomethoxymethylidene group on C-2.

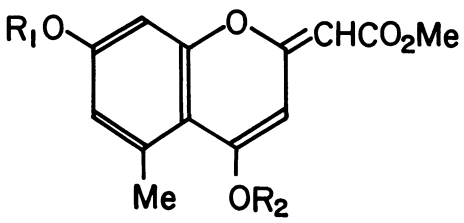
Aloe species has been widely used for a medicinal plant and its constituents have been studied by many groups of workers.[1-4] In connection with biochemical examinations of the plant, we isolated a new bitter glucoside, named aloenin, to elucidate its structure. We now wish to describe evidences leading to structure 1 for aloenin.

Aloenin (1) was isolated from the leaf juice of *Aloe* species (*Kidachi-rokai* in Japanese) grown in Japan by means of column chromatography on silica gel with a mixture of methanol and chloroform, as white needles: mp 145-147°C (monohydrate) and 204-205°C (anhydrous), $C_{19}H_{22}O_{10}\cdot H_2O$ (reguires: C 53,27; H 5,65. found: C 53,02; H 5,76%),[5] $[\alpha]_D^{25}$ -26.79° (c 2.2, MeOH). The melting points and the presence of water of crystallization were determined by a combination of the differential thermal and the thermal gravity analyses. The IR spectrum showed absorption bands due to the hydroxyl group and the ester group conjugated with an unsaturation ($\nu_{max}^{dioxane}$ 1714, 1642, and 1608 cm^{-1}). The UV absorptions of the ethanol solution at 307 nm (ε 8,800), 245 (6,450), and 232 (7,490) suggested the presence of a long conjugated system.

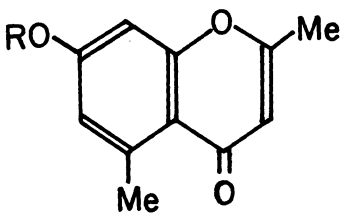
Hydrolysis of aloenin with 3% hydrochloric acid in methanol afforded an aglycone (2) [mp 213-214°C, $C_{13}H_{12}O_5$ (reguires: C 62,90; H 4,87. found: C 62,75; H 4,81%), M^+ 248] and D-glucose [mp 144-145°C, $[\alpha]_D^{25}$ +109° → +49° (c 0.2, H_2O)]. The latter was identified by comparing the IR spectrum and the paper and thin-layer chromatograms with those of the authentic sample. The aglycone (2) was converted into an unknown ketol (3) [mp 235°C(decomp.), $C_{11}H_{10}O_3$ (reguires: C 69,46; H 5,30. found: C 69,24; H 5,23%), M^+ 190] by treating it with 5% hydrochloric acid. The ketol (3) was suggested to be a chromone derivative by its IR and UV spectral data [$\nu_{max}^{dioxane}$ 1663 (C=O), 1651, 1615, and 1585 cm^{-1} (C=C); λ_{max}^{EtOH} 291 nm (ε 12,000), 250 (20,400), and 241 (16,600)]. The presence of two methyl groups in the ketol (3) was indicated by the NMR signals at δ (C_5H_5N) 2.06 (s, 3H) and 2.97 ppm (s, 3H). Methylation of the ketol (3) with diazomethane gave the monomethyl ether (4) [mp 116-117°C, M^+ 204; $\nu_{max}^{CHCl_3}$ 1657 cm^{-1} (C=O)]. Treatment of the ether (4) with 50% potassium hydroxide solution afforded 2-hydroxy-6-methyl-4-methoxyacetophenone (5) [mp 78.0-78.5°C, $C_{10}H_{12}O_3$ (reguires: C 66,65; H 6,71. found: C 66,53; H 6,58%), M^+ 180; ν_{max}^{KBr} 1612 cm^{-1}



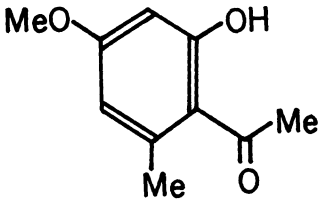
1 : $R_1=R_2=H$
9 : $R_1=H$, $R_2=Me$
11 : $R_1=R_2=Ac$



2 : $R_1=R_2=H$
7 : $R_1=R_2=Me$
10 : $R_1=Me$, $R_2=H$



3 : R = H
4 : R = Me
6 : R = Ac



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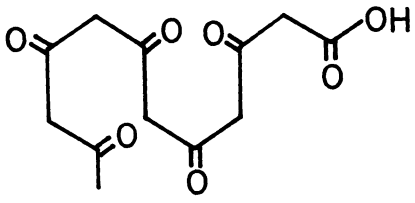

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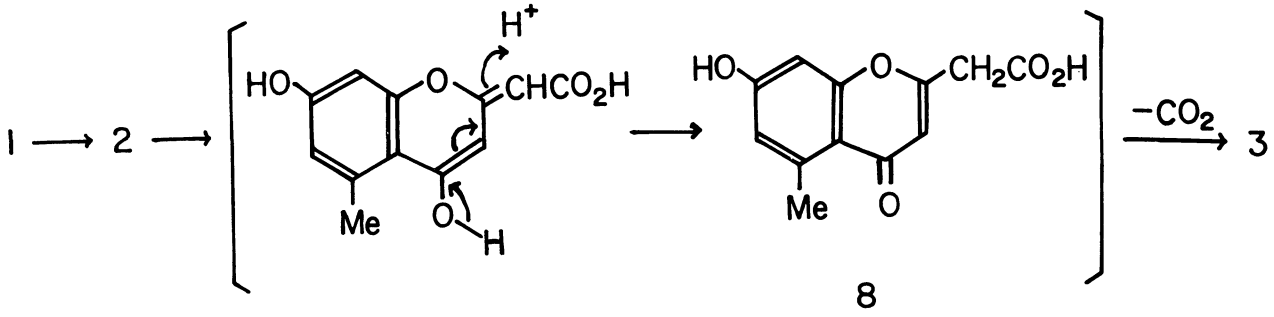
(β-hydroxy-α,β-unsaturated carbonyl); λ_{max}^{EtOH} 279 nm (ε 13,400; the ET band) (calcd.[6] λ_{max} 281 nm); NMR ($CDCl_3$) δ 2.51 (s, phenyl methyl), 2.58 (s, acetyl methyl), 3.77 (s, O-methyl), 6.28 (s, two aromatic protons), and 13.50 ppm (s, phenolic proton)]. These facts show that the ketol (3) is the chromone derivative having a methyl group on C-2 and another methyl and a hydroxyl groups in the benzene ring. The NMR spectrum of the O-methyl derivative (4) in a deuterochloroform solution showed one methoxy proton signal at δ 3.86 ppm, in addition to two methyl proton signals at δ 2.28 and 2.79 ppm, which can be assigned to the C-methyl groups. The signal at 2.79 ppm was assigned to the methyl group at the 5-position of a chromone skeleton, because the group suffers strongly the anisotropic effect owing to the pyrone carbonyl group. The methoxy group of the methyl ether (4) was situated at the 7-position, since the IR spectrum showed bands at 859, 832, and 728 cm^{-1} due to the out-of-plane deformation vibration of the isolated hydrogen atoms remaining in the benzene ring, but did no band for two adjacent aromatic hydrogen atoms. The fact that the two aromatic proton signals of the O-acetyl derivative (6) of the ketol (3) showed meta-coupling

[δ 6.83 (d, J=2.0 Hz, 1H) and 7.06 ppm (d, J=2.0 Hz, 1H)], but not ortho-coupling, emphasized the above assignment. Thus, the structure of the ketol (3) was determined to be 2,5-dimethyl-7-hydroxychromone.

The NMR spectrum of the aglycone (2) in a pyridine solution suggested the presence of a carbomethoxy (δ 3.61 ppm) and an aromatic methyl groups (δ 2.33 ppm). Methylation of the aglycone (2) with diazomethane afforded the dimethyl ether (7) [mp 124-125°C; ν_{max}^{Nujol} 1725 (C=O) and 1641 and 1613 cm^{-1} (C=C)]. The NMR spectrum of 7 showed signals of one aromatic methyl, one carbomethoxy, two methoxy, and four unsaturated protons at δ 2.23 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 5.49 (d, J=2.0 Hz, 1H), 5.99 (d, J=2.0 Hz, 1H) and,6.34 ppm (s, 2H) respectively. These facts indicate the aglycone to be shown by the structure 2. Thus, the conversion of the aglycone (2) to the ketone (3) on treatment with hydrochloric acid may be explained by the acid-catalyzed reaction via the intermediate (8) as shown below.



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Two alternative structures, the C-4 glucosyloxyl or the C-7 glucosyloxyl derivative of the aglycone (2), may be possible for aloenin. However, the presence of a phenolic proton in aloenin was indicated by the bathochromic shift of the principal bands of the UV absorption in a 0.05N ethanolic potassium hydroxide solution [λ_{max} 353 nm (ε 14,300), 253 (13,800), and 225 (9,600)]. Treatment of the monomethyl ether (9) (mp 117-118°C) with 5% hydrochloric acid in methanol gave the hydrolyzed product (10) (mp 194-195°C), which was derived to the O-methyl derivative (4). This fact shows that the glucose moiety in aloenin is located on the C-4 hydroxyl group of the aglycone (2). The pentaacetate (11) [mp 192-193°C, $C_{29}H_{32}O_{15}$ (reguires: C 56,13; H 5,00. found: C 56,15; H 5,00%)] derived from aloenin revealed signals of all protons assigned for the structure 11 on the NMR spectrum [δ 1.96 (s, 2xOAc), 2.00 (s, OAc), 2.07 (s, OAc), 2.26 (s, C_5-Me), 2.27 (s, phenolic OAc), 3.83 (s, COOMe), 5.49 (d, J=2.5 Hz, C_3-H), 5.94 (d, J=2.5 Hz, C_9-H), 6.70 (s, C_6- and C_8-H), and 4.0-5.3 ppm (7H on the glucose moiety)]. On the other hand, the β-glucopyranosyloxy structure was proved by the hydrolysis of aloenin with β-glucosidase. Consequently, the structure of aloenin has been established to be 2-(carbomethyoxymethyliden)-4-(β-D-glucopyranosyloxy)-7-hydroxy-5-methylchromene (1).

In naturally occurring chromenes, the C-2 carbomethoxymethylidene derivative has not yet been reported. Aloenin (1) is such an unique example of the chromene

derivative, and it awakenes the biochemical and medicinal interests. It is likely that aloenin is biosynthesized by the cyclization of the polyketide, as shown in the formula 12, formed through the acetate-malonate pathway.

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