CH_3), 7.58 (3/5×2H, s, $COCH_2$), 6.98 (3/5×2H, d, CH_2N), 6.33 (3/5×3H, s, OCH_3), 5.36 (3/5×1H, d, CH=) and 4.5—4.9 (3/5×1H, b-s, NH), signals due to IIIB, 8.96 (2/5×6H, s, di-CH_3), 7.67 (2/5×2H, s, CH_2CO), 6.77 (2/5×2H, s, CH_2N), 6.71 (2/5×2H, s, $COCH_2C{=}N$) and 6.28 (2/5×3H, s, OCH_3).

Treatment of III with 10% acetic acid or 10% hydrogen chloride brought about a ring contraction to give methyl 4,4-dimethyl-2-pyrrolidylideneacetate (V), mp 85° (from water), in 71% or 63% yield; UV λ_{max} (EtOH) mμ: 282 (log ε 4.24). IR ν_{max} ($CHCl_3$) cm^{-1}: 3380 (NH hydrogen-bonded with ester carbonyl), 1660 and 1600 ($N{-}C{=}C{-}CO_2CH_3$). NMR ($CDCl_3$) τ: 8.88 (6H, s, di-CH_3), 7.66 (2H, s, $CH_2C{=}$), 6.76 (2H, s, CH_2N), 6.38 (3H, s, OCH_3), 5.50 (1H, s, CH=) and 2.1—2.3 (1H, b-s, NH).

A similar series of the reactions employed for V converted 3-chloro-2-cyclohexen-1-one to ethyl 2-pyrrolidylideneacetate,[8] mp 63° (lit.[8] 63—63.5°), *via* 2-ethoxy-4,5,6,7-tetrahydr - 1H-azepin-4-one. The ring contraction and hydrolysis of III may be reasonably explained by the mechanism as shown in Chart 2.

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8) Z. Horii, K. Morikawa and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **17**, 2230 (1969).

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UDC 547.982.02.05 : 581.192

A New Trichloro-depsidone from a Lichen of the Genus *Caloplaca*

Very recently, Santesson[1] has reported an extensive phytochemical study on the anthraquinone components in *Caloplaca* spp. (Caloplacaceae), where he has covered 230 species of the genus, while shortly before that Bohman surveyed the anthraquinones in some lichens of the same genus.[2] On the other hand, during the course of the investigations on the lichen phenolic products[3] we have been aware of the rich phenolic components of an orange crustose lichen[4] belonging to the genus *Caloplaca* collected at Settsu-kyō in Osaka prefecture. Since no work has been done on the metabolic products other than anthraquinones of *Caloplaca* spp., we have performed the structural study on the phenolic products of the lichen and reached a conclusion leading the structures I and II to the depsidones as described below.

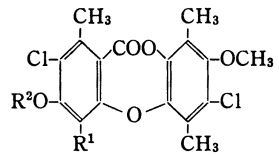
Successive extraction of the lichen using ether and acetone followed by silica gel chromatography (column and thin-layer chromatography (TLC)) furnished four anthraquinone derivatives, *i.e.* parietin (III) (0.80%), fallacinal (IV) (0.15%), fallacinol (V) (trace), and emodin (VI) (trace), in addition to two chlorine-containing depsidones tentatively designated Ca-III (1.78%) and Ca-II (0.45%).

1) J. Santesson, *Phytochemistry*, **9**, 2149 (1970).
2) G. Bohman, *Phytochemistry*, **8**, 1829 (1969); **9**, 461 (1970).
3) *a*) I. Yosioka, H. Yamauchi, K. Morimoto, and I. Kitagawa, *Tetrahedron Letters*, **1968**, 1149; *b*) *Idem*, *ibid.*, **1968**, 3749; *c*) *Idem*, *Journ. Jap. Bot.* (Tokyo), **43**, 343 (1968); *d*) I. Yosioka, T. Nakanishi, S. Izumi, and I. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **16**, 2090 (1968); *e*) I. Yosioka, Y. Morita, and K. Ebihara, *ibid.*, **18**, 2364 (1970).
4) The identification of the lichen is in progress.

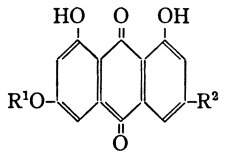
Ca-III (I), $C_{17}H_{13}O_5Cl_3$, mp 260.5° (colorless needles from benzene); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (OH), 1735, 1240 (-COO-), showed a positive Beilstein test. The molecular formula having three chlorine atoms was substantiated by its mass spectrum giving the molecular ions at *m/e* 402, 404, 406, and 408 with the intensity ratio of 27:27:9:1. The same isotope abundance has also been observed in the mass spectra of the acetate (Ia) and methyl ether (Ib).

Acetylation of Ca-III with acetic anhydride and pyridine furnished a monoacetate (Ia), $C_{17}H_{12}O_4Cl_3$ ($OCOCH_3$), mp 230—231.5°: IR ($CHCl_3$): 1785, 1740, 1240, 1180 ($OCOCH_3$, -COO-); NMR ($CDCl_3$, 60 MHz) τ: 7.65, 7.53, 7.43, 7.36 (3H each, all s, aromatic $CH_3\times3$ and phenolic $OCOCH_3\times1$), 6.18 (3H, s, OCH_3), whereas diazomethane treatment of Ca-III gave a monomethyl ether (Ib), $C_{17}H_{12}O_4Cl_3$ (OCH_3), mp 228—228.5°; IR (CCl_4): 1754, 1240 (-COO-); NMR: 7.70, 7.49, 7.38 (3H each, s, arom. $CH_3\times3$), 6.24, 6.09 (3H each, s, $OCH_3\times2$). The accumulated data[5] in addition to the biogenetic presumption on the depsidone skeleton[6] has led us to figure out the plausible structures [A], [B], and I for Ca-III, and the correctness of I has been provided by the following evidence.

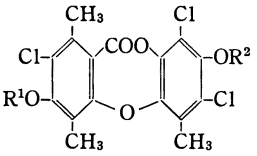
Thus, a monoethyl ether (Ic), $C_{17}H_{12}O_4Cl_3$ (OC_2H_5), mp 217—218°; IR (CCl_4): 1756, 1239 (-COO-); NMR: 8.51 (3H, t, J=7 Hz), 5.84 (2H, q, J=7 Hz) (OCH_2CH_3), 7.69, 7.50,



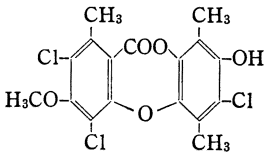
I : R^1=Cl, R^2=H (Ca-III=caloploicin)
Ia : R^1=Cl, R^2=Ac
Ib : R^1=Cl, R^2=CH_3
Ic : R^1=Cl, R^2=C_2H_5
II : R^1=CH_3, R^2=H (Ca-II=vicanicin)
IIa : R^1=CH_3, R^2=Ac
IIb : R^1=CH_3, R^2=CH_3
IIc : R^1=CH_3, R^2=C_2H_5



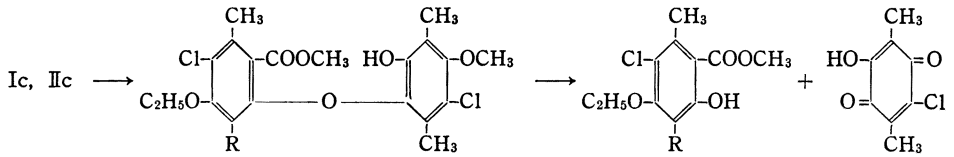
III: R^1=R^2=CH_3 (parietin)
IV: R^1=CH_3, R^2=CHO (fallacinal)
V: R^1=CH_3, R^2=CH_2OH (fallacinol)
VI: R^1=H, R^2=CH_3 (emodin)



[A] R^1, R^2=H or CH_3



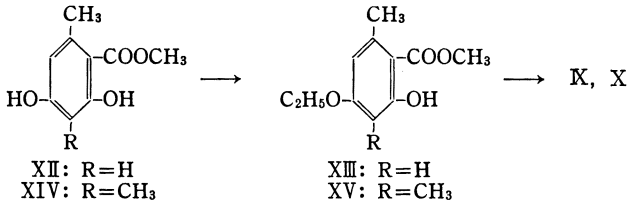
[B]



VII: R=Cl
VIII: R=CH_3

IX: R=Cl
X: R=CH_3

XI



XII: R=H
XIV: R=CH_3

XIII: R=H
XV: R=CH_3

Chart 1

5) For the NMR assignment of depsidones, *cf.* S. Huneck and P. Linscheid, *Z. Naturforsch.*, **23b**, 717 (1968).
6) *a*) S. Shibata, "Festschrift Kurt Mothes zum 65 Geburtstag," Gustav Fischer Verlag, Jena, 1965, p. 332; *b*) K. Mosbach, *Angew. Chem. Intern. Ed. Engl.*, **8**, 240 (1969).

7.38 (3H each, s, arom. $C\underline{H}_3\times3$), 6.23 (3H, s, $OC\underline{H}_3$), prepared by ethylation of Ca-III with ethyl iodide–K_2CO_3–acetone, afforded, upon treatment with KOH–MeOH, a hydroxy methyl ester (VII) (amorphous); IR ($CHCl_3$): 3550, 3260 (br, OH), 1737, 1708, 1284 (br) (Ar-$COOCH_3$); NMR: 8.55 (3H, t, J=7 Hz), 5.90 (2H, q, J=7 Hz) ($OC\underline{H}_2C\underline{H}_3$), 7.83 (6H, s), 7.69 (3H, s) (arom. $C\underline{H}_3\times3$), 6.27, 6.22 (3H each, s, $OC\underline{H}_3\times2$), 3.35 (1H, br s, $W^h/_2$=8 Hz, O$\underline{H}$).

Nitric acid oxidation [7,8] of the ester (VII) in acetic acid furnished methyl 3,5-dichloro-4-O-ethyl-orsellate (IX),[9] $C_{11}H_{12}O_4Cl_2$, mp 87.5—88°. Mass Spectrum[10] *m/e*: 278 (M^+); IR (CCl_4): 1668, 1440, 1390, 1308, 1230; NMR: 8.52 (3H, t, J=7 Hz), 5.84 (2H, q, J=7 Hz) ($OC\underline{H}_2C\underline{H}_3$), 7.51 (3H, s, arom. $C\underline{H}_3$), 6.02 (3H, s, $OC\underline{H}_3$), −1.44 (1H, s, O$\underline{H}$) and an orange yellow chloroquinone (XI),[11] $C_8H_7O_3Cl$, mp 124—125°; Mass Spectrum *m/e*: 186 (M^+); IR (CCl_4): 3420, 1663, 1653, 1606, 1290, 1210, 1132, 1060; UV $\lambda_{max}^{isopentane}$ mμ (log ε): 274 (4.23), 283 (4.29). NMR: 8.01, 7.81 (3H each, s, vinyl $C\underline{H}_3\times2$), 2.95 (1H, br s, $W^h/_2$=5 Hz, O$\underline{H}$). Consequently Ca-III is now formulated as I. Since it seems to be unprecedented, we propose the name "caloploicin" for Ca-III.

The minor chloro-depsidone, Ca-II (II), $C_{18}H_{16}O_5Cl_2$, mp 239—240° (colorless needles from benzene); Mass *m/e*: 382, 384, 386 (molecular ion peaks with the ratio of 9:6:1). IR ($CHCl_3$): 3520 (OH), 1730, 1260 (-COO-); NMR: 7.66, 7.55 (3H each, s), 7.48 (6H, s) (arom. $C\underline{H}_3\times4$), 6.22 (3H, s, $OC\underline{H}_3$), 3.80 (1H, br, O$\underline{H}$) gave smoothly a monoacetate (IIa), $C_{18}H_{15}O_4Cl_2$ ($OCOCH_3$), mp 211—211.5°; IR (CCl_4): 1785, 1752, 1260, 1189 ($OCOCH_3$, -COO-); NMR: 7.69, 7.64, 7.60 (3H each, s), 7.50 (6H, s) (arom. $C\underline{H}_3\times4$ and $OCOC\underline{H}_3\times1$), 6.23 (3H, s, $OC\underline{H}_3$), and a monomethyl ether (IIb), $C_{18}H_{15}O_4Cl_2$ (OCH_3); Mass Spectrum *m/e*: 396 (M^+), mp 191—192°, thus suggesting that Ca-II is a depsidone possessing one more methyl and one less chlorine substituents as compared with caloploicin (I). The basis supporting the structure II for Ca-II was achieved as described below.

Thus, the alkaline treatment of the monoethyl ether (IIc), $C_{18}H_{15}O_4Cl_2$ (OC_2H_5), mp 196—197°; IR (KBr): 1735, 1270 (-COO-), as for Ic (*vide supra*) gave a hydroxy methyl ester (VIII); IR ($CHCl_3$): 3520 (OH), 1730, 1700, 1275 (Ar-$COOCH_3$), which, on the subsequent oxidation with nitric acid, yielded methyl 5-chloro-4-O-ethyl-β-orcinolcarboxylate (X),[12] mp 64—64.5°, $C_{12}H_{15}O_4Cl_2$; Mass Spectrum *m/e*: 258 (M^+); IR (CCl_4): 1663, 1440, 1388, 1308, 1250, 1194, 1164 and an orange yellow chloroquinone identical with XI (IR and TLC). Accordingly, Ca-II is now expressed as II being identical with the revised structure[13] of vicanicin,[8] although the direct comparison of both samples has been unavailable (in lit.[8]: vicanicin, mp 248—250°; methyl ether, mp 193—194°; acetate, mp 211—214°).

Caloploicin (I) is the additional instance among the naturally occurring chloro-depsidones such as vicanicin,[8,13] gangaleoidin,[14a] diploicin,[14b] pannarin,[14c] nidurin,[7] and nornidurin.[7] In addition, caloploicin and vicanicin are the first examples of the chloro-depsidones isolated from the genus *Caloplaca*. Furthermore, it is interestingly assumed that a compound noticed

7) *a*) F.M. Dean, J.C. Roberts, and A. Robertson, *J. Chem. Soc.*, **1954**, 1432; *b*) F.M. Dean, D.S. Deorha, A.D.T. Erni, D.W. Hughes, and J.C. Roberts, *ibid.*, **1960**, 4829.

8) S. Neelakantan, T.R. Seshadri, and S.S. Subramanian, *Tetrahedron*, **18**, 597 (1962).

9) Identified by TLC, mixed mp, and IR with the sample prepared from methyl orsellate (XII) through the unequivocal process (XII→XIII→IX).

10) Molecular ions of the chlorine containing substances are calculated on the basis of Cl=35, and they are all accompanied by the satelite ions due to the isotopes with the reasonable intensities.

11) Assigned on the basis of the physical data given here and the biogenetic point of view.

12) Identified by TLC, mixed mp, and IR with the sample prepared from methyl β-orcinolcarboxylate (XIV) through the unequivocal process (XIV→XV→X).

13) C.F. Culberson, "Chemical and Botanical Guide to Lichen Products," The Univ. of North Carolina Press, 1968, p. 165.

14) *a*) Y. Asahina and S. Shibata, "Chemistry of Lichen Substances," Japan Society for the promotion of Science, Tokyo, Japan, 1954, p. 123, *b*) *Idem*, *ibid.*, 1954, p. 127; *c*) *Idem*, *ibid.*, 1954, p. 146.

by Santesson[1] in some *Caloplaca* species on account of its significant molecular ion peak at 402 *m/e* might be identical with the present caloploicin (I).

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Synthesis of 3-Suberoylalanine Ester of Digitoxigenin

Since the first discovery by Wieland, *et al.*,[1] the so-called "bufotoxin" isolated from the toad venom drug, *Ch'an Su*, has been assigned to the structure 14-suberoylarginine ester of bufotalin.[2] Kamano, *et al.*[3] isolated 3-suberoylbufogenins from *Ch'an Su*, and Linde-Tempel[4] revised the structure of "bufotoxin" to be the 3-suberoylarginine ester from the evidence of enzymatic degradation. In addition the isolation of the 3-(hydrogen suberate) as well as cardenolide itself from *Ch'an Su* has recently been reported.[5] These findings together led to the assumption that the suberoylamino acid ester of cardenolide may possibly occur as the natural product. The physiological activity of the potential cardenolide conjugate also appeared to be of interest to us. In this paper we wish to report the synthesis of the titled compound starting from digitoxigenin (Ia).

As a preliminary experiment an attempt was initiated on the preparation of the 3-succinoylglycine ester. Reaction of digitoxigenin 3-(hydrogen succinate) (Ib)[6] with ethyl chlorocarbonate in tetrahydrofuran gave the carbonic-carboxylic acid anhydride, which in turn was condensed with *tert*-butyl glycinate to give the 3-succinoylglycine ester (IIa), mp 185—187°, as colorless leaflets (from ethyl acetate). Upon brief exposure to hydrogen bromide in acetic acid[7] elimination of the *tert*-butyl group was readily attained, but undesirable dehydration of the 14-hydroxyl function was accompanied to a considerable extent. Some other attempts for the selective hydrolysis without affecting any disturbance on the steroidal moiety also resulted in failure. Accordingly an alternative synthetic route, that is the *p*-nitrophenyl ester method,[8] was undertaken. Being treated with *p*-nitrophenol in the presence of N,N-dicyclohexylcarbodiimide, Ib was transformed into the *p*-nitrophenyl ester (IIIa), mp 172—174°, colorless prisms (from MeOH). When stirred with glycine in aqueous pyridine, IIIa

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2) K. Meyer, *Helv. Chim. Acta*, **32**, 1993 (1949); H.R. Urscheler, Ch. Tamm, and T. Reichstein, *ibid.*, **38**, 883 (1955).
3) Y. Kamano, H. Yamamoto, Y. Tanaka, and M. Komatsu, *Tetrahedron Letters*, **1968**, 5673.
4) H.O. Linde-Tempel, *Helv. Chim. Acta*, **53**, 2188 (1970).
5) *a*) N. Höriger, H.H.A. Linde, and K. Meyer, *Helv. Chim. Acta*, **53**, 1503 (1970); *b*) N. Höriger, D. Zivanov, H.H.A. Linde, and K. Meyer, *ibid.*, **53**, 1993 (1970); *c*) *idem*, *ibid.*, **53**, 2051 (1970).
6) M. Zingg and K. Meyer, *Pharm. Acta Helv.*, **32**, 393 (1957); A. Yamada, *Yakugaku Zasshi*, **79**, 1440 (1959).
7) G.W. Anderson and F.M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).
8) M.A. Ondetti, *J. Med. Chem.*, **6**, 10 (1963).