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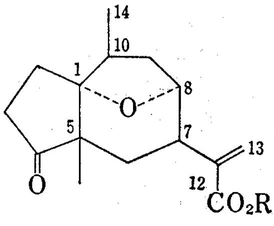
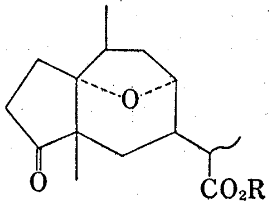
# Ambrosic Acid, a New Irritant Principle from *Ambrosia arthemisiifolia*[1]

In connection with our studies on the physiologically active substance in the genus of *Gaillardia*, *Arthemisia* and their relatives in Compositae, we have recently investigated a poisonous principle in the common rag weed, *Ambrosia arthemisiifolia* (Butakusa). Since this plant was introduced into Japan from North America almost one century ago, it has made a wide distribution over Japan island and been notorious for a cause of the pollen allergy (hay fever) and also as a poisonous weed in cattle feeds.

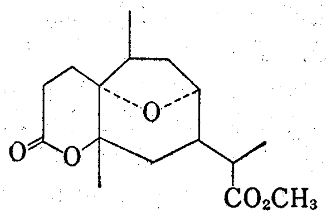
The sesquiterpene constituents so far isolated from several populations of the same plant were found to be pseudoguaianolides such as coronopilin,[2] psilostackyne,[3] pervin,[3] cumanin[4] and dihydrocumanin,[4] and germacranolides such as dihydroparthenolide,[3] arthemisiifolin[5] and isabelin.[5] In our own investigation with few collections of the title plant in the environs of Tokyo, none of the known sesquiterpene lactones[2-5] could be found, but a new modified pseudoguaianoid named ambrosic acid was isolated pure, especially most from the pollen. The present communication concerns with the isolation and a preliminary account for the structure of ambrosic acid formulated as **1a**.



1a : R=H
1b : R=$CH_3$



2a : R=H
2b : R=$CH_3$



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The fresh pollen collected from the flowers, air-dried chipped stems and leaves were submitted to individual percolation with hot chloroform. The acidic part of each extraction furnished the identical crystalline substance in a yield of 0.21%, 0.08% and 0.02%, respectively.

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1) Presented to the 92nd annual meeting of Pharmaceutical Society of Japan, Osaka, Apr. 6, 1972, Abstracts II, p. 191, and to the 17th Symposium of Perfume, Terpene and Ethereal Oil, Okayama, Oct. 7, 1973, Abstracts p. 77.

2) W. Herz and G. Högenauer, *J. Org. Chem.*, **26**, 5011 (1961).

3) E. Bianchi, C.C.J. Culvenor, and J.W. Loder, *Aust. J. Chem.*, **21**, 1109 (1968).

4) T.H. Porter and T.J. Mabry, *Phytochemistry*, **8**, 793 (1969).

5) T.H. Porter, T.J. Mabry, H. Yoshioka, and N.H. Fisher, *Phytochemistry*, **9**, 119 (1970).

$C_{15}H_{20}O_4$[6] ($M^+$ 264); mp 211—213°; $[\alpha]_D$ +77.0° ($CHCl_3$); $\nu_{max}^{KBr}$ ($cm^{-1}$) 3380, 1701 (COOH), 1732 (cyclopentanone), 1622, 880 ($C{=}CH_2$); $\delta$ ($CDCl_3$) 1.07 s ($\geqslant C{-}C\underline{H}_3$), 1.22 d 6.2 ($>CH{-}C\underline{H}_3$), 3.00 m($>C\underline{H}{-}C(=CH_2)COOH$), 4.42 m ($>C\underline{H}{-}O{-}C\leqslant$), 5.68 d 1.0, 6.44 d 1.0 ($>C{=}C\underline{H}_2$), 10.22 s (–COOH). The methyl ester (**1**b) was readily formed with $CH_2N_2$ or $MeOH/H_2SO_4$ as usual. $C_{16}H_{22}O_4$ ($M^+$ 278); mp 88—90°; $[\alpha]_D$ +64.4° (EtOH); $\lambda_{max}^{EtOH}$ (nm) ($\varepsilon$) 201 (9000), 286 (30); $\nu_{max}^{KBr}$ ($cm^{-1}$) 1748 (cyclopentanone), 1702, 1622 ($\Delta^{\alpha,\beta}$–COOMe); $\delta$ ($CDCl_3$) 1.10 s ($\geqslant C{-}C\underline{H}_3$), 1.26 d 6.5 ($>CH{-}C\underline{H}_3$), 3.80 s ($-COOC\underline{H}_3$), 2.98 m ($>C\underline{H}{-}C(=CH_2)COOMe$), 4.37 m ($\geqslant C{-}O{-}C\underline{H}<$), 5.56 t 1.2, 6.29 d 1.0 ($>CH{-}C(=C\underline{H}_2)COOMe$). Catalytic hydrogenation with 5%-Pd/C or $NaBH_4$ reduction of **1**b in MeOH gave in moderate yield methyl dihydroambrosiate (**2**b): $C_{16}H_{24}O_4$ ($M^+$ 280); mp 130—132°; $[\alpha]_D$ +130° (EtOH); $\lambda_{max}^{EtOH}$ (nm) ($\varepsilon$) 287 (35); $\nu_{max}^{KBr}$ ($cm^{-1}$) 1745 (cyclopentanone), 1732 (ester); $\delta$ ($CDCl_3$) 0.97 s ($\geqslant C{-}C\underline{H}_3$), 1.10 d 6.0 ($>CH{-}C\underline{H}_3$), 1.20 d 6.0 ($>CH{-}C\underline{H}_3$), 3.72 s ($-COOC\underline{H}_3$), 4.33 m ($\geqslant C{-}O{-}C\underline{H}<$). The corresponding dihydro acid (**2**a) was obtained on hydrolysis of **2**b or hydrogenation of **1**a with 5%-Pd/C in a reasonable yield: $C_{15}H_{22}O_4$ ($M^+$ 266); $bp_{1.5}$ 155—165° (bath temp.). Ozonolysis of **1**a in MeOH yielded bisnorambrosic acid (**3**a) with liberation of $CH_2O$ being detectable by formol dimedon: $C_{13}H_{18}O_4$ ($M^+$ 238); mp 113—115° [methyl ester (**3b**): $C_{14}H_{20}O_4$ ($M^+$ 252); mp 59—61°)].

The $\alpha,\alpha$-disubstituted cyclopentanone moiety in **1**a is recognized by the positive Zimmermann test shown with **1**, **2** and **3**, and the parent peak at *m/e* 282 for deuterated compound of **2**b, indicating an uptake of two deuterium atoms in the molecule. Another substantial support was provided by *m*-chloroperbenzoic acid oxidation of **2**b resulting in formation of $\delta$-lactone (**4**) [$C_{16}H_{24}O_5$ ($M^+$ 296); mp 168—170°]. The tertiary methyl signal of **4** shifts to the lower field than that of **2**b, which should make it obvious only to enlarge the partial structure from the cyclopentanone to a pseudoguaian-4-one. The dehydrogenation of the diol (**5**a) [diacetate (**5**b): $C_{19}H_{30}O_5$ ($M^+$ 338); $bp_{0.45}$ 200—210° (bath temp.)] prepared by treatment of **1**b with $LiAlH_4$ in hot tetrahydrofuran, afforded in a poor yield chamazulene (trinitrobenzene adduct: mp 130—131°), which was coincident with the authentic sample in every respects.[7] The forth oxygen atom of the molecule should be involved in an ether linkage survived on the $LiAlH_4$ reduction of **1**b.

The above mentioned facts should permit us to accomodate the pseudoguaian-4-one-7-methacrylic acid including one possible ether bridge located most probably between $C_1$ and $C_8$ in the structure of ambrosic acid (**1**a). The positive rotatory dispersion Cotton effects of **1**b (a = +21.1) and **2**b (a = +21.0) in MeOH solution were found to be very comparable with that of coronopilin[8] (a = +61.5), suggesting *trans* ring fusion of the pseudoguaian skeleton of **1**a ($5\beta$–$CH_3$/$1\alpha$–OR). The final proof of the whole structure of **1**a including the exact location of the ether bridge was obtained from proton-nuclear magnetic resonance ($^1H$–NMR) spin-decoupling experiments (100 M Hz, $CDCl_3$) with **1**b, except the configuration of $C_{10}$-$\beta$-methyl group.[9] The multiplet signal appeared at 4.37 ($H_8$) changed to a doublet ($J$=6 Hz) when irradiated at 3.22 ($H_7$), and to a singlet on simultaneous irradiation at 2.98 ($H_7$) and 2.22 ($H_{9e}$). On the other hand, the multiplet of $H_7$ became sextet ($J$=3.6 Hz) and quartet on respective irradiation of $H_{13}$ and $H_8$, sharpened considerably on double irradiation of $H_{13}$ and $H_8$, and changed to a doublet ($J$=6 Hz) when irradiated both at 4.37 ($H_8$) and ~2.22 ($H_{6e}$). The doublet of $C_{14}$-methyl protons appeared at 1.26 changed to a singlet on irradiation at ~2.22 ($H_{10}$), and the complex of $H_{9a}$ and $H_{6a}$ was contracted on simultaneous irradiation of $H_7$ and $H_8$. The following $^{13}C$–NMR data with **1**b ($CDCl_3$) also support the structure of **1**a mentioned above; $\delta$ ppm ($I^{rel}$) 14.92 (139) ($C_{15}$), 20.99 (129) ($C_{14}$), 26.82 (154) ($C_6$),* 27.91 (185) ($C_9$),* 33.61 (190)

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[6] All the compounds given with the chemical formulae gave the satisfactory analytical values.

[7] A sample of chamazulene trinitrobenzene complex was kindly donated from Drs. K. Takeda and H. Minato of Shionog iPharmaceutical Co., Ltd., to whom we are indebted.

[8] A sample of coronopilin was provided by coutesy of Prof. W. Herz of Florida State University, to whom our thanks are due.

[9] S. Inayama, A. Itai, and Y. Iitaka, *Tetrahedron Letters*, 1974, 809.

($C_2$),* 33.98 (180) ($C_3$),* 39.07 (184) ($C_{10}$), 40.53 (166) ($C_{16}$), 51.81 (97) ($C_7$), 53.03 (74) ($C_5$), 74.14 (173) ($C_8$), 89.55 (56) ($C_1$), 124.50 (154) ($C_{13}$), 140.15 (60) ($C_{11}$), 167.21 (26) ($C_{12}$), 216.72 (40) ($C_4$) [*tentative assignment].

The structure of ambrosic acid represented by **1a** is thus established on the above all chemical and spectral evidences.

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