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Studies on the Chlorinated α-Santonins. I

It has been reported that Wedekind, *et al.*[1] obtained an α-santonin dichloride when chlorine was passed through a chloroform solution of α-santonin. According to Sestini[2] a trichloro-α-santonin was obtained by the chlorination of an aqueous suspension of α-santonin. On the other hand, Hendrickson and Bogard[3] re-examined the chlorination and epoxidation of α-santonin which yielded several chlorohydrins, epoxides and santonin dichlorides, and studied their configurations and conformations.

In this paper we wish to report a structure of newly obtained tetrachloro-α-santonin (III) based on nuclear magnetic resonance (NMR) and mass spectra, and X-ray analysis. This compound (III) is a key-compound for the determination of halogenated α-santonin derivatives. From our experimental data on its structure, it is suggested that 1β,2α-dichloro-α-santonin which was previously reported by Hendrickson, *et al.*[3] will be revised to 1α,2β-dichloro-compound (II), and this result cleans up the confused stereochemical relationship in the halogenated α-santonin derivatives.

When gaseous chlorine was led through a solution of α-santonin (I) in chloroform, dichlorosantonin (II) was formed. II was further chlorinated with chlorine gas in a mixture of chloroform-acetic acid to give tetrachlorosantonin (III). The elementary analysis[4] and mass spectrum [*m/e* 386 (M^+)][5] of III were in agreement with the formula $C_{15}H_{18}O_3Cl_4$. Carbonyl absorption at 1755 cm^{-1} ($CHCl_3$) in infrared (IR) spectrum, and ultraviolet spectrum (UV) absorption in $CHCl_3$ at 253 nm (log ε 3.81) and 301 nm (log ε 1.82) indicate the presence of saturated carbonyl group.

The configuration of the chlorine atoms at 1 and 2 positions of II should be the same as that of III. This was further confirmed by dechlorination of III in methanol over palladium

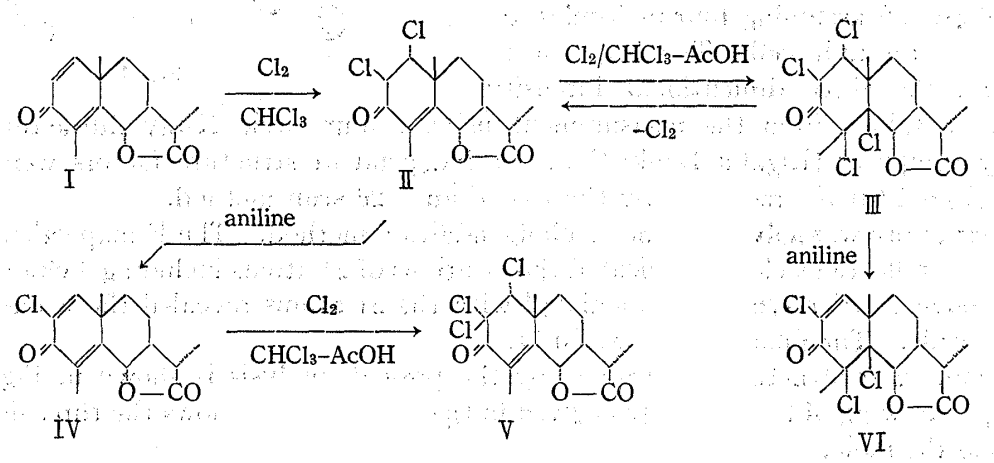

Chart 1

on charcoal under an atmosphere of hydrogen or with zinc dust in acetic acid to regenerate II. The NMR spectra (δ, 100 MHz, $CDCl_3$) of II and III for C-2 proton showed signals at 4.72 ppm (d, J=11.0 Hz) and 4.35 ppm (d, J=12.2 Hz), respectively, and those for C-1 proton showed at

1) E. Wedekind and A. Koch, *Ber.*, **38**, 429, 1848 (1905).
2) For a review see J. Simonsen and D.H.R. Barton, "The Terpenes," Vol. III, 2nd Ed. Cambridge Univ. Press, Cambridge, 1961, p. 275.
3) J.B. Hendrickson and T.L. Bogard, *J. Chem. Soc.*, **1962**, 1678.
4) Satisfactory elemental analyses were obtained.
5) Mass spectra were determined with a JEOL-OlS spectrometer by a direct inlet system at 75 eV.

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4.72 ppm (d, J=11.0 Hz) and 5.65 ppm (d, J=12.2 Hz), respectively. By the coupling constant of 12.2 Hz for III, the dihedral angle between 1-H and 2-H is proposed to be nearly 180°. From this fact, in the compound II having the coupling constant 11.0 Hz, the dihedral angle between 1-H and 2-H should be closed to 180°.

By treatment of II with aniline in methanol 2-chloro-α-santonin (IV) was obtained. Further chlorination of IV in chloroform–acetic acid solution led to 1,2,2-trichloro-α-santonin[4] (V). On the other hand, by the treatment of III with aniline in methanol 2,4,5-trichloro-α-santonin[4] (VI) was formed. Structural elucidation of trichlorosantonins (V and VI) was studied by the means of their NMR spectra. The former isomer (V) showed C-1 proton at 4.44 ppm. However, the latter isomer (VI) did at 6.50 ppm because of a proton bound to a double bond, while the former proton is bound to a single bond. V showed 4-methyl protons at 2.20 ppm and the splitting of a peak to doublet (J=1.5 Hz) indicates the long-range coupling with 6-H at 4.85 ppm (dd, $J_{6,7}$=10.0 Hz). On the other hand, VI showed 4-methyl protons at 2.18 ppm and no splitting of a peak indicates no long-range coupling with 6-H at 4.50 ppm (d, $J_{6,7}$=12.0 Hz). Chemical shift (6.94 ppm) of C-1 proton of IV was similar to that of VI.

Since the configuration of the chlorine atoms at 1, 2, 4, and 5 positions could not be decided unequivocally by physical methods as mentioned above, an X-ray crystal structure analysis was performed. III was crystallized from ethyl acetate solution as colorless plates. Weissenberg and precession photographs indicated that the crystal belongs to the orthorhombic system with the lattice constants of a= 14.88, b=14.37, c=7.595 Å. The space group was determined to be $P2_12_12_1$. The density was 1.596 g·cm^{-3} assuming four molecules are contained in an unit cell. The lattice constants and the three dimensional intensity data were obtained from the measurement using a four circle X-ray diffractometer controlled by computer (Rigaku Denki Co.). 882 independent structure factors were obtained with Ni-filtered Cu Kα radiation by the use of an ω-2θ scan method.

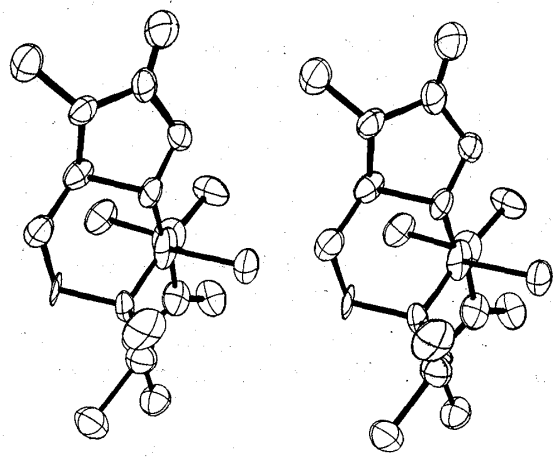

Fig. 1

The structure was solved by the symbolic addition method. The E map calculated with phases of 149 reflections clearly indicated the locations of 21 atoms including 4 chlorine atoms. The successive Fourier syntheses calculated with the 21 atoms revealed the whole structure of the molecule. The final R value was 0.11.

The molecular structure determined by the present analysis is shown in Figure 1. A stereoscopic drawing of the structure is given in the Figure which shows the three dimensional structure of the molecule.[6]

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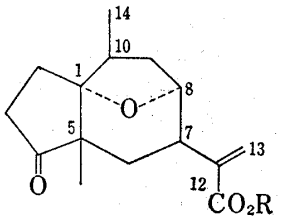
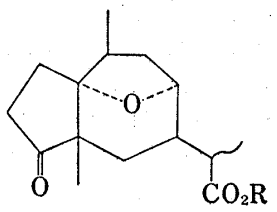
Ambrosic Acid, a New Irritant Principle from *Ambrosia arthemisiifolia*[1]

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.

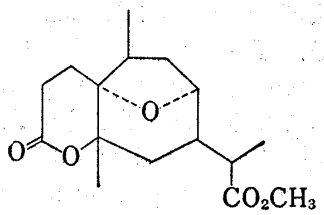
The sesquiterpene constituents so far isolated from several populations of the same plant were found to be pseudoguaianolides such as coronopilin,[2] psilostackyne,[3] pervin,[3] cumanin[4] and dihydrocumanin,[4] and germacranolides such as dihydroparthenolide,[3] arthemisiifolin[5] and isabelin.[5] 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.

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).

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