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157. **Itiro Yosioka, Hiroshi Hikino, and Yasuko Sasaki :** Studies on the Constituents of *Atractylodes*. VI.[1] The Structure of Atractylodin. (1). The Skeleton.*1

(*Faculty of Pharmacy, University of Osaka**2)

In the previous paper[1] was described the isolation of a crystalline oxide, atractylodin (I), $C_{13}H_{10}O$, from the essential oil in the rhizomes of an *Atractylodes* species (Compositae) from Manchuria. The rigid identification of this original plant is awaiting further taxonomical work. This compound (I) showed very unusual and disagreeable properties, such as instability toward air and light, probably due to notable unsaturation. Polymerisation into brown insoluble resin occurred rapidly in air even at room temperature. Combustion suddenly took place on heating, followed by the formation of a tar, leaving porous coal. The present investigation was undertaken to obtain full information about the carbon skeleton of atractylodin.

The nature of the oxygen function was first indicated by the infrared spectrum. It showed no bands indicative of oxygen functions such as hydroxyl or carbonyl groups, but exhibited marked maxima (in Nujol) at 1014, 882, and 735 cm^{-1}, providing useful evidence for the presence of furan ring, which was further suggested by the positive Ehrlich test. This evidence was confirmed by the hydrogenation experiment, summarized below, which also revealed the nature of the carbon skeleton.

Catalytic hydrogenation of atractylodin in the presence of palladium-charcoal in methanol, with absorption of 8 moles of hydrogen, furnished hexadecahydro derivative (II), $C_{13}H_{26}O$, which was considered to be a key compound in the structural investigation of atractylodin. Besides above saturated oxide (II), a keto-alcohol, $C_{13}H_{26}O_2$, m.p. 45~46°, was obtained, which must be one of the hydrogenolysed products, but the quantity was insufficient for further examination. In the infrared absorption spectrum, as indicated in Fig. 1, the saturated derivative (II) exhibited maxima (without a solvent) at 1068 and 917 cm^{-1} associated with tetrahydrofuran ring, as would have been anticipated. A band at 720 cm^{-1}, due to rocking frequency of a normal paraffinic chain, was also detected. These infrared spectral evidences suggested the most probable formulation of hexadecahydro-atractylodin as nonyltetrahydrofuran and left undecided only the point of attachment of normal carbon side-chain at 2- or 3-position in the furan ring. It was necessary to confirm by synthesis of 2- and 3-nonyltetrahydrofuran, to see which of these would be identical with saturated atractylodin (II).

The synthesis of 2-nonyltetrahydrofuran was at first tried. In the present work, the route adopted was as follows : 2-Furaldehyde and 1-bromoöctane were coupled by the Grignard reaction giving 1-(2-furyl)-1-nonanol which was converted into the chloride followed by dehydrochlorination, and finally reduced to the desired compound, 2-nonyltetrahydrofuran.

The infrared spectrum of the condensation product, 1-(2-furyl)-1-nonanol, $C_{13}H_{22}O_2$, showed bands assigned to the furan ring at 1504, 1007, 883, and 732 cm^{-1}, which possessed the same relative intensities as those in atractylodin. A close relationship between these intensities was considered to suggest that both had the same substitution point, 2-position of the furan ring. This carbinol was chlorinated with thionyl chloride in

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*2 Toneyama, Toyonaka, Osaka-fu (吉岡一郎, ヒキノヒロシ, 佐々木靖子).

1) Part V. I. Yosioka, S. Takahashi, H. Hikino, Y. Sasaki : Yakugaku Zasshi, **80**, 1564(1960).

pyridine to give the second intermediate, 2-(1-chlorononyl)furan. The infrared absorption spectrum of this product no longer showed the band at 3333 cm^{-1} attributed to hydroxyl grouping but a maximum at 755 cm^{-1}, characteristic to a chloride. Dehydrochlorination was carried out with aniline affording the triene, 2-(1-nonenyl)furan, which was hydrogenated in a neutral medium in the presence of palladized charcoal, smoothly taking up 3 moles of hydrogen, to furnish the final compound, 2-nonyltetrahydrofuran, $C_{13}H_{26}O$.

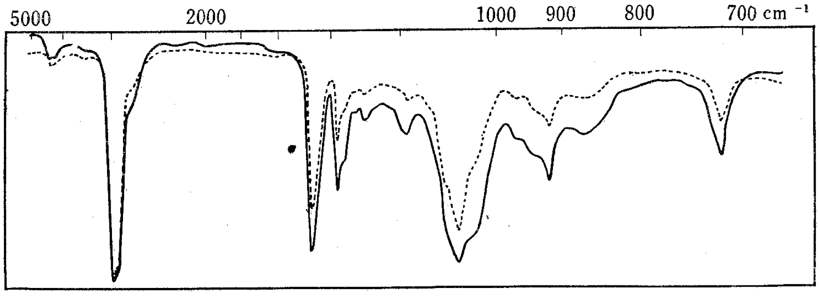

Fig. 1. Infrared Absorption Spectra of Hexadecahydro-atractylodin (——) and 2-Nonyltetrahydrofuran (------)

Comparison of the physical constants and infrared absorption spectrum of the synthesized product with those of hexadecahydro-atractylodin offered strong ground for the identity of the two substances.

These experiments showed that the structure of atractylodin has a 2-nonyltetrahydrofuran skeleton.

Experimental*[3]

Atractylodin—$C_{13}H_{10}O$, m.p. 52°, $[\alpha]_D \pm 0°$ (c=10.0, $CHCl_3$); shows a green color with Ehrlich reagent and negative to the pine-splinter or vanillin-HCl test.

Complete Hydrogenation of Atractylodin—Atractylodin (700 mg.) was hydrogenated over Pd-C (5%, 2.0 g.) in dehyd. MeOH (40 cc.) at atmospheric temperature and pressure. The original faint yellow solution first became dark green and finally colorless. H_2 uptake was 707 cc. (theor. for 8 double bonds: 688 cc., calcd. for $C_{13}H_{10}$ (8╒)). After filtering off the catalyst, the solvent was evaporated. The oily hydrogenation product was separated by chromatography through alumina (15 g.). (i) Light petroleum eluate was distilled over Na under a reduced pressure to give hexadecahydroatractylodin (II) as a colorless oil, b.p$_6$ 98°, d_4^{25} 0.852, n_D^{25} 1.443, $[\alpha]_D \pm 0°$. *Anal.* Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.56; H, 13.10. The infrared spectrum was discussed in the main text. (ii) Elution with EtOH followed by crystallization from light petroleum afforded a ketol as white needles, m.p. 45~46°. *Anal.* Calcd. for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23. Found: C, 72.94; H, 12.03. IR (in Nujol) cm^{-1}: 3315, 3260 (O-H), 1695 (C=O), 726 ($(CH_2)_n$).

Preparation of 1-(2-Furyl)-1-nonanol—2-Furaldehyde (10.0 g.) in dehyd. Et_2O (25 cc.) was added slowly to a well-stirred solution of octylmagnesium bromide (from 1-bromoöctane (25.0 g.), Mg (3.5 g.), and Et_2O (75 cc.)), heated under reflux for 30 min., cooled, poured on crushed ice, and decomposed by saturated NH_4Cl solution. The Et_2O layer was washed with H_2O, dried, and evaporation of the solvent left an oily residue. Distillation of the residue under a diminished pressure afforded the main fraction, b.p$_{2.5}$ 125~127°, whose crystallization from light petroleum gave 1-(2-furyl)-1-nonanol as white needles, m.p. 16~17°, d_4^{25} 0.948, n_D^{25} 1.467. *Anal.* Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.42; H, 10.37. IR (in a liquid film) cm^{-1}: 3333 (O-H), 1504, 1007, 883, 732 (furan, the last superimposed with band due to $(CH_2)_n$). 3,5-Dinitrobenzoate: Slightly yellow needles (from light petroleum), m.p. 44~45°. *Anal.* Calcd. for $C_{20}H_{24}O_7N_2$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.73; H, 5.98; N, 6.70.

Chlorination of 1-(2-Furyl)-1-nonanol—$SOCl_2$ (6.5 g.) was added dropwise with stirring to ice-cold solution of 1-(2-furyl)-1-nonanol (10.0 g.) in pyridine (10 cc.). The mixture was agitated for further 3 hr. at room temperature, H_2O (50 cc.) was added, and the mixture was warmed on a hot water bath for 1 hr. The product was extracted into Et_2O, washed with H_2O, dried, evaporated, and distilled to

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*[3] All m.p.s and b.p.s are uncorrected.

give 2-(1-chlorononyl)furan as a colorless liquid, b.p$_3$ 110°. IR (in a liquid film) cm^{-1}: 3247, 1506, 1010, 883, 722 (furan, the last overlapped with maximum assigned to $(CH_2)_n$), 755 (C-Cl).

Dehydrochlorination of 2-(1-Chlorononyl)furan—A mixture of the chloride (5.1 g.) and aniline (5.2 g.) was heated at 150~160° for 3 hr. After acidification with AcOH, the resulting mixture was steam-distilled. The distillate was neutralized with $NaHCO_3$ and extracted with Et_2O. The Et_2O extract, after being washed with H_2O, was dried and evaporated. The residue was purified by fractional distillation yielding 2-(1-nonenyl)furan as a colorless oil, b.p$_3$ 100~103°, d_4^{25} 0.926, n_D^{25} 1.472. IR (in a liquid film) cm^{-1}: 3125, 1506, 1010, 883, 728 (furan, the last was in combination with peak attributed to $(CH_2)_n$), 959 (*trans* HC=CH).

Catalytic Hydrogenation of 2-(1-Nonenyl)furan—2-(1-Noneny)furan (1.7 g.) was hydrogenated over Pd-C (5%, 2.0 g.) in AcOEt (30 cc.) the reaction ceased after absorption of 618 cc. of H_2 (theor. for 3 double bonds: 597 cc., calcd. for $C_{13}H_{20}O$ (3╒)). After removal of the catalyst and solvent, the saturated oxide, 2-nonyltetrahydrofuran, was distilled to a colorless oil, b.p$_4$ 90°, d_4^{25} 0.850, n_D^{25} 1.441, $[\alpha]_D \pm 0°$. *Anal.* Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.98; H, 13.14. It gave negative reaction with $C(NO_2)_4$ and Br_2 solution. IR (in a liquid film) cm^{-1}: 1070, 918 (tetrahydrofuran), 722 ($(CH_2)_n$). Thus the infrared spectrum agreed completely with that of hexadecahydro-atractylodin (II) as reproduced in Fig. 1.

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Summary

Complete hydrogenation of atractylodin (I) with consumption of 8 moles of hydrogen gave a saturated oxide (II) which was identified with synthesized 2-nonyltetrahydrofuran.

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