UDC 547.913 : 582.998

158. **Itiro Yosioka, Hiroshi Hikino, and Yasuko Sasaki**: Studies on the Constituents of *Atractylodes*. VII.1) The Structure of Atractylodin. (2). The Chromophores.[*1]

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

A crystalline component, atractylodin, $C_{13}H_{10}O$, of the essential oil from the rhizomes of an *Atractylodes* species (Compositae) growing in Manchuria was recently isolated.2) The preceding communication,1) outlined below, established the carbon skeleton: On complete hydrogenation, atractylodin, with consumption of 8 moles of hydrogen, gave a saturated oxide, $C_{13}H_{26}O$, which was found to be identical with 2-nonyltetrahydrofuran prepared synthetically. It then remained to arrange the orientation of the chromophres in this skeleton.

The present paper summarises new experimental and spectral works which have shown that atractylodin has the structure formulated as (I). This structure is fully justified by the following experimental facts.

There was no doubt that two of the ethylenic linkages in atractylodin must be present as a furan ring from the infrared maxima in CCl_4 at 3135, 1550, 1484, 1014, and 883 cm^{-1}, and in Nujol at 1014, 882, and 735 cm^{-1}, as had previously been pointed out.1) If it contained a furan ring, a conjugated diene system, an adduct by the Diels-Alder reaction must be formed when heated with an excess of maleic anhydride, but attempts to obtain such an adduct were abortive. This fact, together with the weakness of infrared band at 1550 cm^{-1}, was undoubtedly due to the effect of direct linkage of unsaturated system to α-position of the furan ring3) as indicated below. This was also supported by the fact that atractylodin showed a strong Ehrlich reaction (a green coloration) but gave no color by the pine-splinter test or with vanillin and hydrochloric acid.

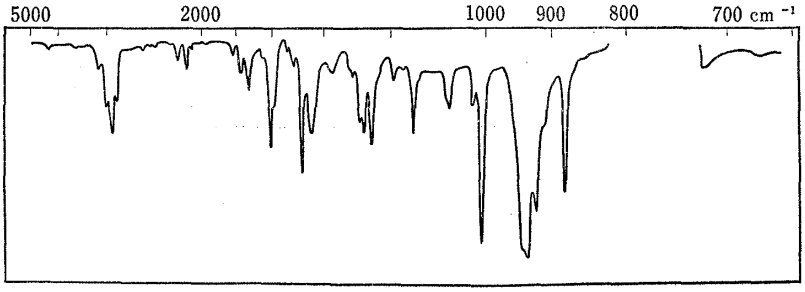

Fig. 1. Infrared Absorption Spectrum of Atractylodin (in CCl_4)

Thus, two of the double bonds were attributed to the furan ring and residual six of unsaturated degree ought to be located in the nonyl side chain. It was immediately clear that this unsaturated system was not a simple polyene type, because, if atractylodin contained only olefinic links, nonyl radical must not theoretically retain six of them but only four, even if all were conjugated. Hence, there must be allene systems or triple bonds.

Here infrared spectroscopic evidence provided a valuable indication about the chromo-

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[*1] Paper presented at the Kinki Local Monthly Meeting of the Pharmaceutical Society of Japan, Kyoto, September 19, 1959.

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

1) Part VI. I. Yosioka, H. Hikino, Y. Sasaki: This Bulletin, 8, 949(1960).

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

3) M. G. Campen, Jr., J. R. Johnson: J. Am. Chem. Soc., **55**, 430(1933).

phores of the side chain. The presence of disubstituted diacetylenic linkages in conjugation was represented by the bands in CCl_4 at 2193 cm^{-1}, associated with disubstituted acetylenic linkage, and at 2120 cm^{-1}, assigned to diacetylene system.[4] Further, the presence of ethylenic bonds in the side chain was confirmed from maxima appearing at 1616 cm^{-1}, attributed to ethenoid linkages located outside the furan ring, and at 940 with a shoulder at 947 cm^{-1}, belonging to two *trans*-RCH=CHR′ groups; the normal value for this feature is about 965 cm^{-1} and the displacement, by as much as 18∼25 lower wave number than usually observed, is definitely due to the effect of conjugation with acetylenic linkage.[5] Absorption peaks indicative of allene system or of vinyl feature were absent. This compound contained no terminal ethynyl group since it did not show any band near 3300 cm^{-1} and failed to afford silver derivatives.

Further important evidence as to the conjugated system in the chromophores of atractylodin was obtained from the ultraviolet spectrum (Fig. 2). First, the intense absorption bands in the longer wave-length region displayed the presence of conjugated six units of unsaturated centers and this eliminated the possibilities that the unsaturated series in the side chain was insulated or was not conjugated with the furan system. It followed, therefore, that the chromophores in the nonyl chain must consist of none other than two acetylenic and two ethylenic linkages in conjugation, which was in harmony with the fact that the unsaturated system had neither allene, terminal methylene, nor ethynyl mode.

Unambiguous confirmation, the number of the acetylenic linkages in the chromophores being two, was obtained by semihydrogenation over the Lindlar catalyst. Hydrogenation showed a definite break in the rate of hydrogen uptake after rapid absorption of the theoretical volume of 2 moles. The change in the ultraviolet extinction curve of the substance after absorption of 1, 2, and 3 moles of hydrogen is illustrated in Fig. 2. After 2 moles of hydrogen had been absorbed, the shorter wave-length bands decreased; the main longer wave-length band system was replaced by a second system which was more intense and in a longer wave-length region than the original system and represented the conjugated hexaëne type. It had been well known that a triple bond causes a reduction in intensity and a hypsochromic shift of the main absorption band in the ultraviolet absorption spectra of polyenynes and polyenes as long as they have the same number of unsaturated centers. Therefore, this kind of transition in absorption observed as above could be taken to show a partial hydrogenation of two triple bonds forming two double bonds, completing a conjugated hexaëne system. This change of absorption was incomplete when only one mole of hydrogen was consumed. When 3 moles had been absorbed, intensity of the polyene band system decreased considerably. This indicated a slow general reduction of the whole unsaturated system. Attempts to isolate a partially hydrogenated product, tetrahydro-atractylodin, failed owing to rapid polymerisation.

To establish the conjugation of the two acetylenic linkages, partial ozonolysis was tried besides the infrared spectral evidence. When the reaction process was followed by the change in ultraviolet absortion spectrum, the intense maxima in longer wave-length region in the starting material, atractylodin, rapidly disappeared and the second band system appeared (Fig. 3). Though considered to be influenced by some other substances, the secondarily furnished absorption curve exhibited the presence of a diacetylenic dicaboxylic acid,[6] whose isolation however failed. This observation suggested that atractylodin had the conjugated diacetylenic system in its mixed chromophores. This was further supported by the fact that atractylodin showed a well-defined structure in the shorter wave-

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[4] E. F. L. J. Anet, B. Lythgoe, M. H. Silk, S. Trippett: J. Chem. Soc., **1953**, 309.

[5] N. H. E. Ahlers, S. P. Ligthelm: *Ibid.*, **1952**, 5039; J. L. H. Allan, G. D. Meakins, M. C. Whiting: *Ibid.*, **1955**, 1874; W. D. Celmer, I. A. Solomons: J. Am. Chem. Soc., **75**, 1372, 3430(1953).

[6] F. Bohlmann, H. Sinn: Chem. Ber., **88**, 1869(1955).

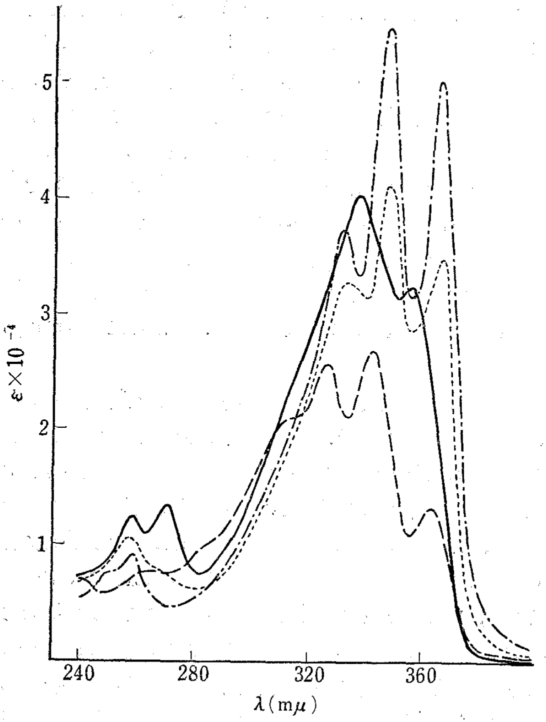


Fig. 2. Effect of Partial Hydrogenation on the Ultraviolet Absorption of Atractylodin

Atractylodin ———
After Consumption of 1 mole ---------
〃 2 moles -·-·-·-
〃 3 moles — — —

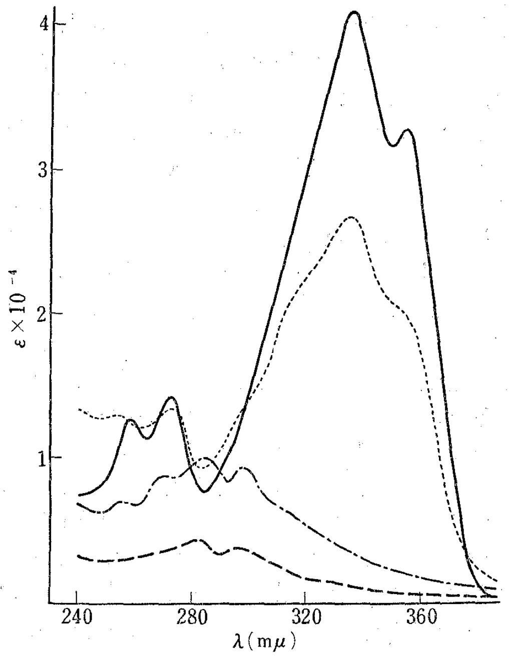


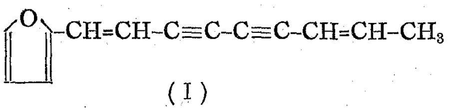
Fig. 3. Effect of Partial Ozonolysis on the Ultraviolet Absorption of Atractylodin

In original state ———
After 5 min. ---------
〃 10 min. -·-·-·-
〃 15 min. — — —

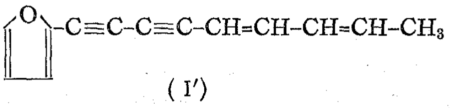
length region of its ultraviolet spectrum, characteristic to a conjugated poly-yne, and the spacing of the maxima (ca. 2000 cm^{-1}) fitted well with the stretching frequency of a triple bond$^{7)}$ while the spacing of the lower wave-number bands (ca. 1500 cm^{-1}) corresponded to the stretching frequency of the ethylenic and not the acetylenic linkages.

Unequivocal proof of the terminal feature in the side chain was obtained by liberation of acetaldehyde on ozonolysis, showing that the CH_3-CH=CH- system must be located terminally in the original chromophores.

Above observations lead to the most probable formulation of atractylodin as (I) or (I′).



(I)



(I′)

A decision had to be made as to which of these two alternative formulae represented atractylodin. Inability to isolate an adduct with maleic anhydride suggested that there was also no conjugated diene system in the side chain. Furthermore, infrared absorption spectrum of atractylodin showed bands at 940 and 947 cm^{-1}, due to two isolated *trans*-RCH=CHR′ conjugated with triple bonds, but no maxima attributed to a diene system. These results were not in agreement with the structure (I′).

Returning to the ultraviolet spectrum of atractylodin, further additonal support for the arrangement of the chromophores was provided. It has often been found that ultraviolet absorption spectrum furnishes an important key point in elucidating the orientation

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7) M. Anchel: J. Am. Chem. Soc., **74**, 1588(1952); W. C. Clemer, I. A. Solomons: *Ibid.*, **74**, 3838 (1952); T. Bruun, C. M. Haug, N. A. Sörensen: Acta Chem. Scand., **4**, 850(1950); E. R. H. Jones, M. C. Whiting, J. B. Armitage, C. L. Cook, N. Entwhistle: Nature, **168**, 900(1951).

of a conjugated polyenyne. Then comparison in the ultraviolet spectrum of atractylodin with that of triene–diyne–ene mode representing the chromophores of the structure (I) and with that of diene–diyne–diene series representing the unsaturated system of (I′), both of which were expected to show considerably different ultraviolet absorption, could be taken as the key point of discrimination. As the model compound for the triene–diyne–ene system, 1,3,5,11–tridecatetraëne–7,9–diyne[8] (Ⅲ) could be selected. In some polyene series, so far as containing the same number of unsaturated centers, the replacement of butadienyl unit with furyl group seemed to show no fundamental change in the position of the absorption bands but only the general reduction in intensity.[9] Therefore, it has been suggested that it would appear to be immaterial whether the two ethylenic linkages are in an open chain or in a furan ring. Close resemblance of the positions of maxima in the ultraviolet absorption spectrum of atractylodin with that of the polyenyne (Ⅲ), as tabulated in Table I, must reveal that both had the same mixed chromophores and moreover the relationship in the intensity in those of the two compounds was in accordance with the observation cited above.

Table I. Ultraviolet Spectral Data

Atractylodin					
λ_{max} (mμ)	258	272		336	354
ε	12,700	14,300		40,800	32,500
1,3,5,11-Tridecatetraëne-7,9-diyne					
λ_{max} (mμ)	264	274	310	330	353.5
ε	32,000	26,700	36,000	57,200	42,200
2,7-Dimethyl-1,8-bis(1-cyclohexenyl)-1,7-octadiene-3,5-diyne					
λ_{max} (mμ)	250	264	296	313	337
ε	13,800	14,000	16,800	18,700	15,000

On the other hand, 2,7–dimethyl–1,8–bis(1–cyclohexenyl)–1,7–octadiene–3,5–diyne (Ⅳ),[10] selected as a model substance having the diene–diyne–diene system, exhibited a remarkably different extinction curve from that of atractylodin (Table I) by which, therefore, the structure (I′) should be ruled out.

On the basis of all these experimental facts recorded above, it is concluded that the structure (I), 1–(2–furyl)–*trans*, 1–*trans*–7–nonadiene–3,5–diyne, for atractylodin can only be accommodated.

Experimental[*3]

Attempted Reaction of Atractylodin with Maleic Anhydride—A mixture of atractylodin (0.5 g.) and a large excess (1.0 g.) of maleic anhydride was sealed in a tube and heated at 80° for 1 hr. Treatment of the resulting brown mass with light petroleum gave the original oxide (0.4 g.).

Partial Hydrogenation of Atractylodin—A mixture of atractylodin (148 mg.), the Lindlar catalyst (80 mg.), and EtOH (30 cc.) was stirred in H_2 stream at atmospheric temperature and pressure. After each of the theoretical volume of 1, 2, and 3 moles of H_2 was absorbed, 0.05-cc. aliquot of the clear supernatant solution was diluted to 100 cc. with EtOH. Ultraviolet absorption spectrum for each is given in Fig. 2.

Attempted Isolation of Tetrahydro-atractylodin—Atractylodin (500 mg.) in AcOEt (20 cc.) was hydrogenated in the presence of the Lindlar catalyst (200 mg.) and quinoline (3 drops). The theoretical volume of 2 moles of H_2 (123 cc.) was consumed in 90 min. After filtering off the catalyst, the solution

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

8) F. Bohlmann, H. J. Mannhardt : Chem. Ber., 88, 1330(1955); J. S. Sörensen, N. A. Sörensen: Acta Chem. Scand., 8, 1741(1954).

9) A. E. Gillam, E. S. Stern : "An Introduction to Electric Absorption Spectroscopy in Organic Chemistry," 85(1958), Edward Arnold, Ltd., London.

10) F. Bohlmann : Chem. Ber., **84**, 545(1951).

was evaporated to dryness under a reduced pressure. The product was crystallised several times from EtOH during which the m.p. rose up to 130° while polymerisation occurred rapidly to form a brown resin.

Partial Ozonisation of Atractylodin—Ozonised O_2 was passed through a solution of atractylodin (50 mg.) in AcOEt (10 cc.), cooled with ice and salt. After every 5 min., 0.05-cc. aliquot of the solution was taken out and evaporated. The residue, added with dioxane (0.5 cc.) and 10% H_2O_2 (0.05 cc.), was warmed at 50° for 10 min. and diluted to 50 cc. with MeOH. Ultraviolet absorption curve for each product is indicated in Fig. 3.

Ozonolysis of Atractylodin—Atractylodin (118 mg.) in AcOEt (10 cc.) was ozonised at 0° until a test portion no longer decolorised CCl_4 solution of Br_2. Then AcOEt was removed by distillation *in vacuo*. After the ozonide was reduced by refluxing with H_2O (20 cc.) and Zn dust (0.5 g.), the volatile fragment was steam-distilled and the distillate was treated with a solution of 2,4-dinitrophenylhydrazine hydrochloride. The 2,4-dinitrophenylhydrazone formed (60 mg.) was isolated and crystallised from EtOH to give acetaldehyde 2,4-dinitrophenylhydrazone as orange-yellow needles, m.p. 160~160.5°, *Anal.* Calcd. for $C_8H_8O_4N_4$: N, 24.99. Found : N, 24.92. Undepressed in m.p. on admixture with an authentic specimen.

The authors express their indebtedness to Prof. T. Shimanouchi, Faculty of Science, University of Tokyo, Dr. K. Hirayama, Fuji Photo Film Co., Ltd., and Dr. M. Yamaguchi, Wakayama Medical College, for valuable advices in the interpretation of the spectral data. Light absorption spectral measurements and microanalyses were carried out by the members of Photometric and Microanalytical Laboratories of this Faculty, to whom the authors are grateful.

Summary

The structural formula (I), 1-(2-furyl)-*trans*-1,*trans*-7-nonadiene-3,5-diyne, was deduced as the structure for atractylodin based on the 2-nonyltetrahydrofuran skeleton, for which the precise designation of the unsaturated bonds was provided by degradative and spectral evidences.

(Received March 1, 1960)