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# 159. **Itiro Yosioka, Hiroshi Hikino, and Yasuko Sasaki**: Studies on the Constituents of *Atractylodes*. VIII.[1] The Structure of Atractylodin. (3). Synthesis.[*1]

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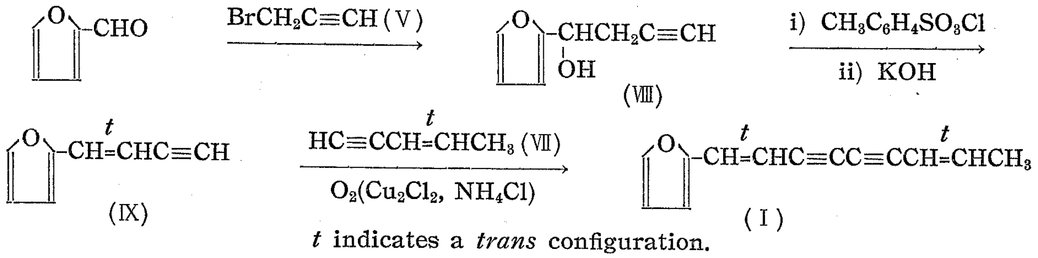
Atractylodin, a novel type of a polyenyne containing furan ring, was first isolated from the rhizomes of an *Atractylodes* species of Manchurian origin.[2] A series of investigations[1,3] led to the proposal that the formula (I), 1-(2-furyl)-*trans*-1,*trans*-7-nonadiene-3,5-diyne, represented the structure of atractylodin. A total synthesis of atractylodin, in the present series of work, confirmed that this oxide actually had the structure (I).

Possible route for the synthesis of this compound (I) from readily accessible starting materials was designed as shown in Chart 1.



*t* indicates a *trans* configuration.

Chart 1.

The condensation of 1,2-epoxypropane with ethynylsodium in liquid ammonia had been reported[4] for the preparation of 4-pentyn-2-ol, the starting material for the first intermediate, *trans*-3-penten-1-yne. In the present work, however, modified Reformatsky reaction[5] was newly adapted: Condensation of acetaldehyde with 3-bromo-1-propyne (V) successfully gave the required product, 4-pentyn-2-ol (VI), $C_5H_8O$, characterised as its 3,5-dinitrobenzoate of m.p. 68~69°. This acetylenic alcohol was dehydrated according to the method described by Whiting, *et al.*[6] and afforded *trans*-3-penten-1-yne (VII).

On the other hand, like acetaldehyde, 2-furaldehyde was also condensed with 3-bromo-1-propyne (V) by the modified Reformatsky reaction to yield 1-(2-furyl)-3-butyn-1-ol (VIII), $C_8H_8O_2$, characterised as its 3,5-dinitrobenzoate of m.p. 81~82°. Removal of the hydroxyl group in this carbinol by the same manner as mentioned above, via esterification with tosyl chloride followed by treatment with aqueous alkali solution, furnished the second intermediate, 1-(2-furyl)-1-buten-3-yne (IX) which was characterised by the infrared absorption bands (in $CCl_4$) at 3306, 2105 (terminal ethynyl), 947 (*trans*-disubstituted olefinic linkage: shifted by conjugation with acetylenic link), and at 3096, 1493, 1018, and 885 (furan nucleus) $cm^{-1}$. Therefore, ethylenic bond thus introduced had apparently *trans*-configuration.

Finally, oxidation of the two different acetylenic intermediates, (VII) and (IX), with an

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aqueous copper(I) chloride–ammonium chloride solution in oxygen atmosphere at room temperature resulted in a smooth coupling reaction. The products were separated by careful chromatography on alumina and each fraction was traced by ultraviolet spectroscopy (Table I). As was expected, first elution gave 2,8-decadiene-4,6-diyne, a couple of two 3-penten-1-yne, ultraviolet spectrum of which was in good agreement with authentic data,[7,8] and the most firmly adsorbed product was a pair of furan-containing components, 1,8-di(2-furyl)-1,7-octadiene-3,5-diyne, whose absorption curve closely resembled that of 1,12-di(1-cyclohexenyl)-1,3,9,11-dodecatetraëne-5,7-diyne[5] which possessed the same mixed chromophores, though the peaks were in general displaced by about 10 mμ to a shorter wave-length region. Several fractions, eluted between above two symmetrical by-products, had ultraviolet maxima at 255, 260, 272, 336, and 354 mμ, indicative of the occurrence of the desired cross-coupling which would give the substance having the structure (I). These fractions were combined and afforded a viscous oil which readily crystallized into faintly yellow needles, m.p. 52°, $C_{13}H_{10}O$, and identified with atractylodin by admixture and by comparison of ultraviolet and infrared spectra.

In addition, the infrared spectroscopic examination of the intermediates in the above synthetic process provided a valuable evidence for assignment of the bands in the CH deformation region of atractylodin. The normal value for the out-of-plane =C–H bending vibrations of a *trans*-disubstituted ethylenic double bond lies close to 965 $cm^{-1}$ and a slight decrease to 959 $cm^{-1}$ had been observed when conjugated with a furan ring.[3] It is well known that conjugation with acetylenic link causes a displacement of the 965 $cm^{-1}$ band toward lower frequencies. In the present case, 3-penten-1-yne (VIII) and 1-(2-furyl)-1-buten-3-yne (IX) absorbed as much as 12 $cm^{-1}$ below the above-mentioned levels, at 953 and 947 $cm^{-1}$. Further shift to lower wave-numbers was expected to occur when conjugated with another triple bond accompanying a few ethylenic linkages. Returning to the spectrum of the coupling product, atractylodin, the maxima are in fact displaced by about 7 wave-numbers lower than the peaks in the above two intermediates; the bands at 947 and 940 $cm^{-1}$ may therefore be assigned to the terminal olefinic link at C-7 and C-1 conjugated with furan ring and diacetylene linkages, respectively.

## Experimental[*3]

**3-Bromo-1-propyne (V)**—2-Propen-1-ol was treated with HBr,[9] followed by addition with $Br_2$, to give 1,2,3-tribromopropane.[10] This, on boiling with AcOK in AcOH according to the method of Mereschkowsky,[11] afforded 2-bromo-2-propenyl acetate which was heated with 1.1 moles of KOH by Henry's method[12] and yielded 2-propyn-1-ol. This alcohol was brominated with $PBr_3$[13] to furnish 3-bromo-1-propyne (V), b.p. 80~82°.

**4-Pentyn-2-ol (VI)**—3-Bromo-1-propyne (V) (10.0 g.) and AcH (10.0 g.) in dehyd. $Et_2O$ (20 cc.) was slowly added to a well-stirred suspension of activated Zn wool[5] (6.5 g.) with a small amount of $HgCl_2$ in tetrahydrofuran (20 cc.) under reflux, using a condenser chilled by solid $CO_2$. After being refluxed for a further 15 min., the reaction mixture was decomposed with crushed ice and 10% AcOH, and extracted with $Et_2O$. The extract was washed with 10% $Na_2CO_3$ solution and $H_2O$, dried ($Na_2SO_4$), evaporated, and the residue was fractionated. 4-Pentyn-2-ol (VI) had b.p.$_{50}$ 55~60°, $n_D^{25}$ 1.441. IR (in a

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[*3] Whenever possible, handling of unsaturated substances was made under a diffused light, in $N_2$ atmosphere. All m.p.s and b.p.s are uncorrected. Ultraviolet absorption spectra were determined in EtOH solution. Light petroleum refers to the fraction of b.p. 35~40°.

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10) Org. Syntheses, Coll. Vol. 1, 521(1948).
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liquid film) cm$^{-1}$: 3333 (O–H), 3289, 2110 (C≡CH). 3,5-Dinitrobenzoate: Faintly yellow flat needles (from EtOH), m.p. 68～69°. *Anal.* Calcd. for $C_{12}H_{10}O_6N_2$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.50; H, 3.51; N, 9.99.

**3-Penten-1-yne (VII)**—4-Pentyn-2-ol (VI) was esterified with tosyl chloride.[6] The sulfonate was treated with aqueous KOH solution[6] and fractionally distilled to give 3-penten-1-yne (VII) as a colorless mobile oil, b.p. 52°, $n_D^{25}$ 1.441. IR (in $CCl_4$) cm$^{-1}$: 3300, 2092 (C≡CH), 953 (*trans*-HC=CH conjugated with C≡C). UV: $\lambda_{max}$ 222 mμ.

**1-(2-Furyl)-3-butyn-1-ol(VIII)**—Tetrahydrofuran (20 cc.) together with activated Zn wool (6.5 g.) and $HgCl_2$ (trace) was heated to a gentle reflux. A solution of 3-bromo-1-propyne (V) (10.0 g.) and 2-furaldehyde (10.0 g.) in dehyd. $Et_2O$ (20 cc.) was added dropwise with good agitation. The stirring was continued under reflux for further 15 min., the mixture was poured into a mixture of crushed ice and 10% AcOH, and the product was extracted with $Et_2O$. The extract was washed, dried, and evaporated. Distillation of its residue furnished 1-(2-furyl)-3-butyn-1-ol (VIII) as a colorless mobile liquid, b.p$_9$ 79°, $d_4^{25}$ 1.098, $n_D^{25}$ 1.509. IR (in a liquid film) cm$^{-1}$: 3356 (O–H), 3289, 2110 (C≡CH), 3145, 1505, 1010, 883, 741 (furan). 3,5-Dinitrobenzoate: Pale yellow flat needles (from EtOH), m.p. 81～82°. *Anal.* Calcd. for $C_{15}H_{10}O_7N_2$: C, 54.55; H, 3.05; N, 8.48. Found: C, 54.40; H, 3.31; N, 8.39.

**1-(2-Furyl)-1-buten-3-yne (IX)**—A solution of tosyl chloride (7.7 g.) in warm pyridine (7 cc.) was cooled and 1-(2-furyl)-3-butyn-1-ol (VIII) (5.0 g.) was added dropwise with mechanical stirring, keeping the temperature at 20～25° by external cooling. The mixture was set aside for 13 hr., poured into $H_2O$, and extracted with $Et_2O$. After repeated washing with dil. $H_2SO_4$ to remove the pyridine, then with $NaHCO_3$ solution and $H_2O$, evaporation of the dried $Et_2O$ layer gave crude 1-(2-furyl)-3-butynyl *p*-toluenesulfonate (2.1 g.). This ester (2.1 g.) was added slowly to a solution of KOH (3.0 g.) in $H_2O$ (10 cc.) containing 1 drop of Teepol, at 110° with vigorous stirring. After the reaction was completely over, isolation with $Et_2O$ afforded the crude product (IX) as brown viscous oil (0.8 g.). The infrared spectrum was discussed previously. UV $\lambda_{max}$ mμ: 295, 305 (inflexion).

**Oxidative Coupling of 3-Penten-1-yne (VII) and 1-(2-Furyl)-1-buten-3-yne (IX)**—A solution of 3-penten-1-yne (VII) (0.2 g.) and 1-(2-furyl)-1-buten-3-yne (IX) (0.3 g.) in MeOH (25 cc.) was added to a solution of $Cu_2Cl_2$ (1.7 g.) and $NH_4Cl$ (5.1 g.) in $H_2O$ (25 cc.), and stirred in a 200-cc. flask with a side-arm, connected to a hydrogenation apparatus which was filled with $O_2$, until the uptake of $O_2$ ceased. The resulting green suspension was extracted with $Et_2O$ and the washed and dried extract was distilled off. The brown oily residue was chromatographed on alumina (20 g.) and 30-cc. fractions were collected. The course of chromatography is presented in Table I.

TABLE I. Course of Chromatography of Products in Oxidative Coupling

| Fraction No. | Solvent | UV: $\lambda_{max}$ mμ | | | | | | Composition |
|---|---|---|---|---|---|---|---|---|
| 1 | Light petroleum | 230 | 236 | 261 | 276 | 292 | 311 | 2,8-Decadiene-4,6-diyne |
| 2 | 〃 | 230 | 261 | 276 | 292 | 311 | | |
| 4 | 〃 | 295 | 341 | | | | | |
| 6 | 〃 | 254 | 273 | 307 | 339 | | | |
| 8 | 〃 | 255 | 272 | 337 | 355 | | | |
| 10 | 〃 | 255 | 260 | 272 | 336 | 354 | | 1-(2-Furyl)-1,7-nonadiene-3,5-diyne |
| 12 | 〃 | 255 | 260 | 272 | 336 | 354 | | |
| 14 | 〃 | 255 | 260 | 272 | 336 | 354 | | |
| 16 | 〃 | 250 | 255 | 260 | 336 | 354 | | |
| 18 | 〃 | 250 | 255 | 261 | 336 | 354 | | |
| 20 | 〃 | 250 | 255 | 336 | | | | |
| 21 | Ether | 251 | 345 | 369 | 396 | | | 1,8-Di(2-furyl)-1,7-octadiene-3,5-diyne |

Evaporation of the solvent from the combined fractions (Fract. Nos. 8～13) *in vacuo*, below 20°, left a viscous oil which crystallized from MeOH to pale yellow needles, m.p. 52°, undepressed on admixture with a specimen of atractylodin isolated from a natural source. *Anal.* Calcd. for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found: C, 85.53; H, 5.53. IR (in $CCl_4$) cm$^{-1}$: 2188, 2114 (C≡C–C≡C), 947, 940 (*trans*-HC=CH: shifted by conjugation with C≡C), 3106, 1484, 1015, 884 (furan). UV $\lambda_{max}$ mμ (log ε): 258 (4.10), 272 (4.16), 336 (4.62), 354 (4.52). Thus the infrared and ultraviolet absorption spectra were identical in every detail with those of atractylodin.

The authors are indebted to the members of Photometric Laboratory and of Microanalytical Laboratory of this Faculty for infrared spectral measurements and elemental analyses.

## Summary

The structure of atractylodin was established as 1-(2-furyl)-*trans*-1,*trans*-7-nonadiene-3,5-diyne by identification with a specimen prepared by unambiguous synthesis.

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