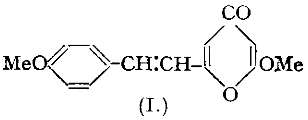
719. *Researches on Acetylenic Compounds. Part XXV. Synthesis of (±)-Kawain.*

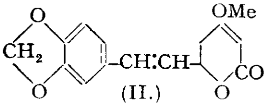
By (Mrs.) E. M. F. Fowler and H. B. Henbest.

(±)-Kawain has been synthesised from cinnamaldehyde. Its infra-red and ultra-violet spectra and chemical properties are identical with those of the naturally occurring (+)-kawain isolated by Borsche and Peitzsch (*Ber.*, 1930, **63**, 2414) from kawa root.

During a very thorough investigation into the constituents of kawa root, Borsche and his co-workers (*Ber.*, 1929—1933) isolated the three crystalline compounds, yangonin, methysticin, and kawain, and by degradation showed them to possess the closely related structures (I), (II), and (III) respectively. The structure (I) for yangonin was confirmed by synthesis (Borsche and Bodenstein, *Ber.*, 1929, **62**, 2515), but attempts to synthesise methysticin and kawain were unsuccessful. Kawain has been used in the treatment of gonorrhœa, but detailed antibiotic tests do not appear to have been made (cf. Haynes, *Quart. Reviews*, 1948, **2**, 72).



(I.)



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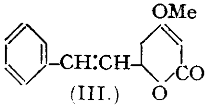
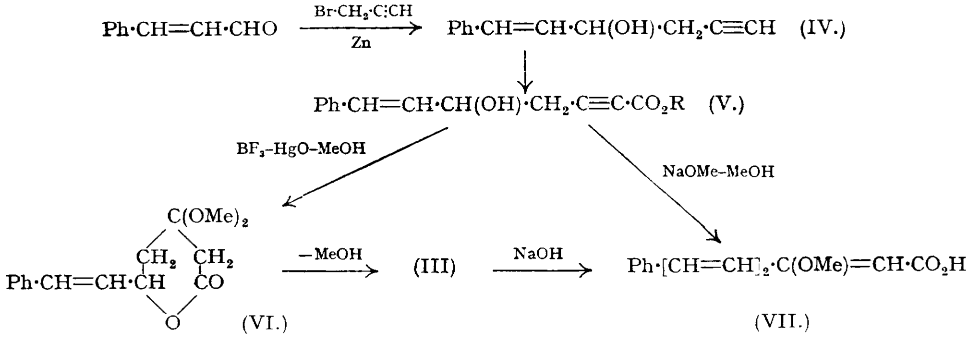


(III.)

Possible routes for the synthesis of these compounds from readily accessible starting materials presented themselves during work designed to build up the side-chain of auxin-b (see *J.*, 1950, 3628, 3634):

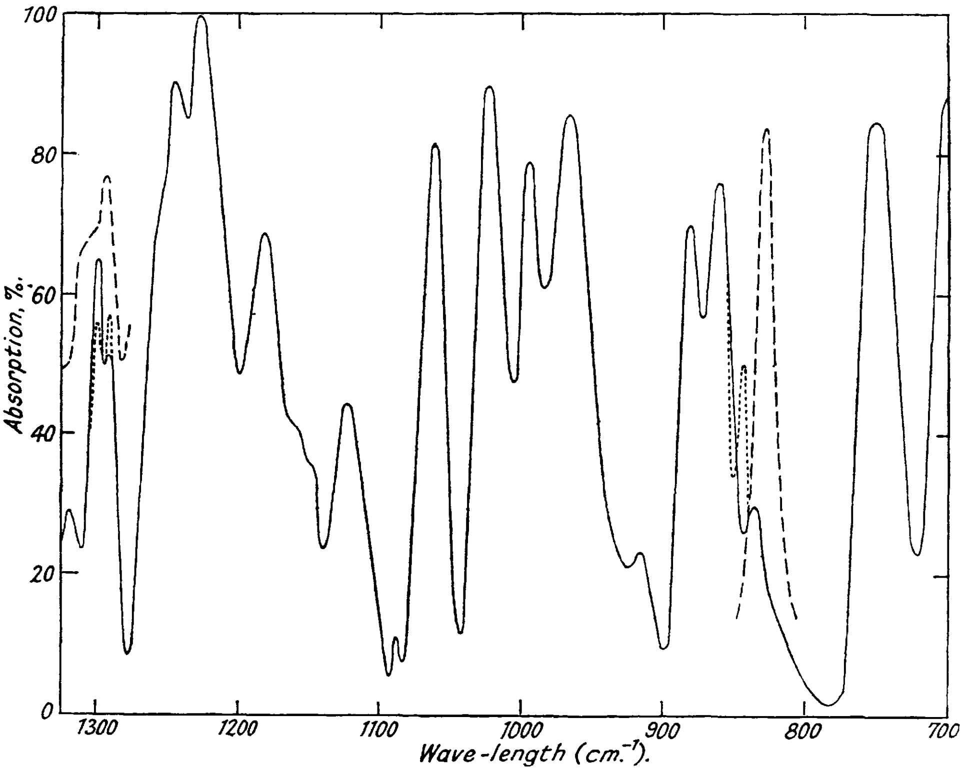


The modified Reformatsky reaction between cinnamaldehyde and propargyl bromide proceeded smoothly under the conditions described by Henbest, Jones, and Walls (*J.*, 1949, 2696). In order to obtain the carbinol (IV) in a state of purity it was necessary to chromatograph the liquid product obtained after a preliminary vacuum-distillation; in this way a complete separation of (IV) (45% overall yield) from unchanged cinnamaldehyde and a hydrocarbon impurity (probably $Ph\cdot[CH{=}CH]_2\cdot C{\equiv}CH$) was achieved. The relatively non-volatile product from the Reformatsky reaction yielded the crystalline glycol (VIII) as a mixture of two stereoisomeric forms, from which the higher-melting isomer was readily separated by crystallisation.

$$CHPh{=}CH\cdot CH(OH)\cdot CH_2\cdot C{\equiv}C\cdot CH(OH)\cdot CH{=}CHPh \qquad \text{(VIII.)}$$

Carboxylation of the carbinol (IV) was effected by treating the di-Grignard complex with carbon dioxide under pressure as described by Haynes and Jones (*J.*, 1946, 503), although it was preferable to convert the carbinol into the Grignard complex at 0° instead of refluxing in ethereal solution. The total yield of acidic material obtained by carboxylation of the chromatographically purified carbinol was satisfactory (60—65%), but only a part of it could be induced to crystallise, giving the acid (V; R = H) in 30% yield. No other definite compound could be isolated from the remainder of the acidic material even after esterification with methanol and attempted distillation of the ester. Carboxylation of the crude carbinol (IV) gave the crystalline acid (V; R = H) in smaller yield (12—20%) but this method was generally preferable for the preparation of the acetylenic acid in quantity since it obviated the chromatographic purification.

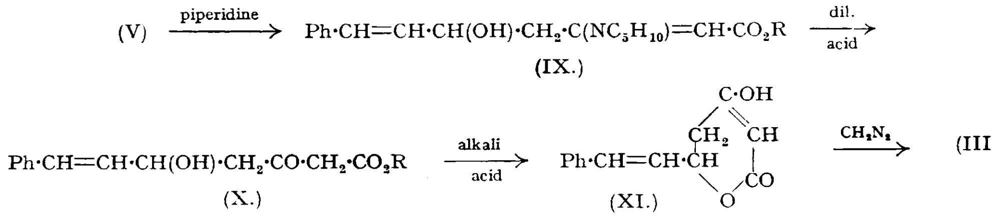
The acetylenic acid was converted into its methyl ester (V; R = Me), and the latter was treated with methanol in the presence of a mercuric oxide–boron trifluoride catalyst in the manner described by Hennion and Zoss (*J. Amer. Chem. Soc.*, 1941, **63**, 1151; cf. Jones and Whiting, *J.*, 1949, 1423). Addition of methanol took place exothermally and the liquid product, obtained in good yield, was shown to be the dimethoxy-lactone (VI) by analysis and by its ultra-violet absorption spectrum. Many attempts were made to eliminate methanol from this dimethoxy-lactone to give kawain (III), but only one was successful. This involved heating the dimethoxy-lactone at 150° for a short time followed by vacuum-sublimation, and gave crystalline (±)-kawain, but only in poor yield. Attempts to prepare kawain directly from the acetylenic ester by modifying the experimental conditions under which the addition of methanol was carried out or by storing the reaction mixture for some time in the expectation that the dimethoxy-lactone would be converted into kawain were also unsuccessful (cf. Jones and Whiting, *loc. cit.*).



Curve ————. (±)-*Kawain* (*suspension in* " *Nujol* ").
Curve - - - - - - -. (+)-*Kawain* (*suspension in* " *Nujol* "), *part of spectrum different from* (±)-*kawain*.
Curve — — — —. (+) *or* (±)-*Kawain in chloroform solution.*

Borsche and Peitzsch (*Ber.*, 1930, **63**, 2414) observed that natural kawain was isomerised into kawaic acid (VII) on treatment with alkali under mild conditions. It was found possible to prepare kawaic acid directly from the acetylenic ester (V; R = Me) by the action of sodium methoxide in methanol—addition of methanol to the triple bond being (presumably) followed by dehydration and hydrolysis.

Another route for the synthesis of kawain was opened up by the work of Brown, Henbest, and Jones (*J.*, 1950, 3634) on the preparation of 5 : 6-dihydro-4-hydroxy-2-pyrones from αβ-unsaturated aldehydes. Application of the method to the acetylenic ester (V; R = Me), derived from cinnamaldehyde, proceeded through the stages shown. The crystalline 5 : 6-dihydro-4-hydroxy-6-styryl-2-pyrone (XI) reacted readily with diazomethane in dioxan, but the expected product, kawain, was only obtained in small yield (5%). A better yield (30%) was obtained by conducting the diazomethane reaction in the presence of methanol (cf. Schönberg and Mustafa, *J.*, 1946, 746).



The melting point of synthetic (±)-kawain is considerably higher (146—147°) than that of the natural (+)-isomer (105—107°), but their chemical identity is clearly shown by a comparison of their ultra-violet (see Experimental) and infra-red light absorption spectra. From the latter, shown in the Figure, it can be seen that the crystalline (+)- and (±)-kawain have nearly identical spectra, the small differences in two regions being probably due to differing molecular orientation in the crystal structure. In chloroform solution, in the regions where the spectra of the crystalline forms were different, the absorption curves were identical.

EXPERIMENTAL.

(All m. p.s were taken on a Köfler block and are corrected, and all light-absorption data were determined in ethanol solution with a Beckman spectrophotometer.)

1-*Phenylhex*-1-*en*-5-*yn*-3-*ol* (IV).—This was prepared from cinnamaldehyde by the procedure of Henbest, Jones, and Walls (*loc. cit.*). A mixture of redistilled cinnamaldehyde (40 g.), propargyl bromide (36 g.), dry ether (40 c.c.), and dry tetrahydrofuran (40 c.c.) was added at a fast rate to freshly activated zinc (21 g.). The exothermic reaction started readily and was kept under control by external ice-cooling as necessary. When the reaction subsided, the solution was finally heated under reflux for 1 minute, cooled, and added to dilute acetic acid and ice, and the crude carbinol (48 g.) was isolated with ether in the usual way. Distillation from a Claisen flask gave (*a*) impure cinnamaldehyde (0·6 g.), b. p. 90—110°/0·1 mm., n_D^{18} 1·598, and (*b*) impure carbinol (31 g.), b. p. 110—130°/0·1 mm., n_D^{18} 1·582. For purification, the impure carbinol (19·8 g.) in benzene (25 c.c.) was adsorbed on a column of alumina (Peter Spence, Grade O; 40 × 3·6 cm.). Development with benzene gave a chromatogram with the following appearance: (*a*) a small orange band at the top, (*b*) a large yellow zone in the middle, and (*c*) two dark yellow bands at the bottom. The two yellow bands in zone (*c*) were eluted through with benzene and rejected—they probably corresponded with unchanged cinnamaldehyde and 1-phenylhexa-1 : 3-dien-5-yne. After the column had been allowed to drain, the top zone (*a*) was removed with a spatula and rejected, and the alumina of the middle zone (*b*) was eluted with ether–methanol (9 : 1) to give pure 1-*phenylhex*-1-*en*-5-*yn*-3-*ol* (IV) (14·2 g., 45%), b. p. 85—87° (bath temp.)/10^{-4} mm., n_D^{15} 1·5777 (Found: C, 82·5; H, 7·0. $C_{12}H_{12}O$ requires C, 83·75; H, 7·05%—low carbon values are often given by $\beta\gamma$-acetylenic carbinols, cf. Henbest, Jones, and Walls, *loc. cit.*). Light absorption: Maxima, 2485, 2825, and 2920 A.; ε = 16,000, 1300, and 900 respectively. [For the light absorption of the related 1-phenylbut-1-en-3-ol, Braude, Jones, and Stern (*J.*, 1946, 396) give: Maxima, 2480, 2510, 2810, and 2910 A.; ε = 19,000, 19,500, 2000, and 1550 respectively.] Further attempted purification of the carbinol by treatment with sodium hydrogen sulphite or by partition between light petroleum (b. p. 40—60°) and aqueous methanol did not alter the above physical constants.

Treatment of the carbinol with *p*-nitrobenzoyl chloride in pyridine at room temperature overnight gave, after crystallisation from methanol and then from light petroleum (b. p. 60—80°), the p-*nitrobenzoate*, as pale yellow prisms, m. p. 77—78° (Found: C, 71·05; H, 4·85. $C_{19}H_{15}O_4N$ requires C, 71·05; H, 4·7%). Light absorption: Maximum, 2550 A.; ε = 30,000.

1 : 9-*Diphenylnona*-1 : 8-*dien*-4-*yne*-3 : 7-*diol*.—The dark undistilled residue from the carbinol preparation was dissolved in benzene, whereupon the glycol (2·3 g.) rapidly crystallised. Examination of the melting behaviour of this glycol on the Köfler stage showed that it was a mixture of two stereoisomers with a melting point range of 124—138°. It was found possible to concentrate the higher-melting isomer by triturating the mixture with warm ether. Recrystallisation of the insoluble part from aqueous methanol then gave the *glycol*, m. p. 147—148°, as long needles (Found: C, 82·65; H, 6·55. $C_{21}H_{20}O_2$ requires C, 82·85; H, 6·6%). Light absorption: Maxima, 2510, 2830, and 2920 A.; ε = 37,000, 2500, and 1500 respectively.

4-*Hydroxy*-6-*phenylhex*-5-*en*-1-*yne*-1-*carboxylic Acid* (V; R = H) *and its Methyl Ester* (V; R = Me).—A solution of ethylmagnesium bromide was prepared from magnesium (6 g.) in ether (50 c.c.). This solution was cooled to 0° and pure 1-phenylhex-1-en-5-yn-3-ol (17·2 g.) in benzene (150 c.c.) was added with stirring during an hour at 0°. Stirring was then continued for 1 hour at 20°. All the above operations were carried out in the presence of dry nitrogen. The Grignard complex was carboxylated in an autoclave by the method of Haynes and Jones (*loc. cit.*); the carbon dioxide pressure rose to 43 atmospheres and remained at this value for 18 hours. The organic acid fraction was obtained as a brown syrup (13·5 g.) by evaporation of an ethereal extract under reduced pressure at $\ngtr$ 20°. Addition of benzene gave a tan-coloured crystalline product (6·2 g., 30%), m. p. 105—110°. Recrystallisation from benzene or ethyl acetate–light petroleum (b. p. 60—80°) gave the *acid* as small needles, m. p. 120—123° (Found: C, 71·9; H, 5·6. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%). Light absorption: Maxima, 2520, 2830, and 2920 A.; ε = 19,000, 1300, and 800 respectively. No crystalline material could be obtained from the remainder of the acid fraction and conversion of the latter into the methyl ester (methanol–sulphuric acid) followed by attempted distillation at 10^{-5} mm. from a short-path still gave no volatile product.

Two carboxylations of the impure carbinol (17·2 g. each time; $n_{\rm D}^{18}$ 1·582) by the above procedure gave the crystalline acid (m. p. *ca.* 110°) in yields of 2·6 and 4·4 g. respectively.

The *methyl* ester (V; R = Me) was obtained by dissolving the acid (1 g.) in methanol (10 c.c.) containing sulphuric acid (1%) and keeping the solution overnight at 20°. Isolation with ether gave a nearly quantitative yield of ester, b. p. 130° (bath-temp.; short-path still)/10^{-5} mm., $n_{\rm D}^{18}$ 1·5680 (Found: C, 72·6; H, 6·3; $C_{14}H_{14}O_3$ requires C, 73·05; H, 6·15%). Light absorption: Maxima, 2510, 2830, and 2920 A.; ε = 18,500, 1300, and 800 respectively.

Reactions of Methyl 4-*Hydroxy*-6-*phenylhex*-5-*en*-1-*yne*-1-*carboxylate* (V; R = Me).—(a) *Conversion into kawaic acid* (VII). The ester (100 mg.) was added to sodium methoxide solution [prepared from sodium (50 mg.) and methanol (0·5 c.c.)]; a temperature rise of 8° was observed. After 3 minutes, the solution was acidified with dilute hydrochloric acid. The precipitated solid was purified by extracting impurities with boiling methanol, followed by crystallisation from *n*-butanol or ethyl acetate–ethanol. The kawaic acid had m. p. 198—199° (decomp.) on the Köfler stage and m. p. 183—184° (decomp.) in a capillary tube (Found: C, 73·05; H, 6·3. Calc. for $C_{14}H_{14}O_3$: C, 73·05; H, 6·15%). Light absorption: Maxima, 2510 and 3220 A.; ε = 9500 and 40,000 respectively. Borsche and Peitzsch (*Ber.*, 1930, **63**, 2314) give m. p. 184—185°, and Borsche and Blount (*ibid.*, p. 2418) give m. p. 186° (decomp.). Kawaic acid obtained from natural (+)-kawain by the method of Borsche and Peitzsch (*loc. cit.*) was identical in melting behaviour (and mixed m. p.) with the synthetic material.

(b) *Conversion into kawain* (III) via *the dimethoxy-lactone* (VI). The methyl ester (0·9 g.) was treated with a solution of mercuric oxide (10 mg.) and boron trifluoride–ether complex (0·2 g.) in methanol (2 c.c.). The temperature of the mixture slowly rose from 20° to 45°. After allowing the solution to cool to 25°, the product was isolated with ether; distillation then gave the *lactone* (VI) (0·65 g.) of 4-hydroxy-2 : 2-dimethoxy-6-phenylhex-5-ene-1-carboxylic acid. This had b. p. 120° (bath temp.)/10^{-5} mm., $n_{\rm D}^{20}$ 1·5418 (Found: C, 68·45; H, 7·0; OMe, 23·5. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9; OMe, 23·5%). Light absorption: Maxima, 2520, 2820, and 2910 A.; ε = 16,000, 1200, and 900 respectively.

The dimethoxy-lactone was heated at 150° for 15 minutes at 20 mm. in a short-path still. It was then distilled at 120° by lowering the pressure to 10^{-5} mm. The partly crystalline distillate was treated with a little dry ether, and the resulting solid was crystallised twice from aqueous methanol to give (±)-*kawain* (3—5% yield) as needles, m. p. 146—147° (Found: C, 73·0; H, 6·3. $C_{14}H_{14}O_3$ requires C, 73·05; H, 6·15%). Light absorption: Maximum, 2440 A.; ε = 25,500; cf. light absorption of natural (+)-kawain: Maximum, 2450 A.; ε = 25,500.

Attempts to convert (III) into (±)-kawain by (*a*) heating or distilling it with toluene-*p*-sulphonic acid, (*b*) heating it with acetic anhydride, (*c*) treating it with boron trifluoride–ether complex, or (*d*) treating it with dilute sulphuric acid, were unsuccessful.

(c) *Conversion into kawain* (III) via 5 : 6-*dihydro*-4-*hydroxy*-6-*styryl*-2-*pyrone* (XI).—Piperidine (0·6 c.c.) was added to a solution of the methyl ester (0·78 g.) in dry ether (4 c.c.) at 15°, the temperature rising to 24°. The solution was kept at room temperature (*ca.* 20°) for 1 hour, and the piperidine-adduct (IX) was then extracted three times with 0·25N-hydrochloric acid. Ether (20 c.c.) was added to the slightly cloudy acid extract, and after being occasionally shaken during 2 hours the mixture was set aside overnight. The ethereal layer was separated and the acid layer extracted once with ether. The combined ethereal solutions were dried and evaporated *in vacuo*, and the residual crude keto-ester (X) was shaken with 0·1N-sodium hydroxide giving a slightly turbid solution. After 2 hours at room temperature, the solution was extracted with ether to remove neutral materials, and the extract discarded. More ether was added, followed by 2N-hydrochloric acid until the solution was acid to Congo-red. The ethereal extract was processed in the usual way to give a solid product which after two crystallisations from ethyl acetate–light petroleum (b. p. 60—80°) (5 : 1) gave the *pyrone* (XI) (0·12 g.), m. p. 142—144° (decomp.) (Found: C, 72·05; H, 5·7. $C_{13}H_{12}O_3$ requires C, 72·1; H, 5·55%). Light absorption: Maximum, 2470—2480 A.; ε = 29,000. Like other members of the same class of compound it gave a violet colour with neutral ferric chloride solution in aqueous methanol.

A solution of the pyrone (100 mg.) in a mixture of methanol (1 c.c.) and ether (2 c.c.) was treated with a solution of diazomethane in ether until the solution became permanently yellow. The methylation was very rapid. Removal of the solvents *in vacuo* gave a solid, which after two recrystallisations from methanol yielded (±)-kawain (30 mg.) as needles, m. p. 146—147° (undepressed on admixture with the product obtained previously). Substitution of dioxan for methanol–ether in this methylation experiment gave a much poorer yield of kawain (5 mg.).

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