[Contribution from the Chemical Laboratory of the University of Illinois]

SYNTHESIS OF SOME CHALKONES

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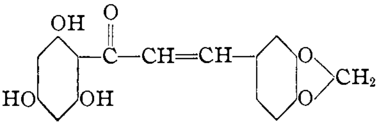
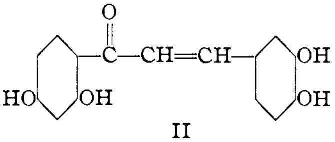
A yellow coloring matter, hyssopin, first isolated from *Herba Hyssopi* by Tunmann,[1] was shown to be a rhamnoside of a chalkone by Oesterle and Kueny.[2] Oesterle[3] also prepared it from *Capsella Bursa Pastoris* and studied its decomposition by 33% potassium hydroxide. Since piperonal, acetopiperone and phloroglucinol were obtained by this alkaline degradation, Oesterle decided that the chalkone was 2,4,6-trihydroxyphenyl-3,4-methylenedioxystyryl ketone (I). This structure was analogous to that assigned to butein (II) by Perkin and Hummel,[4] and Göschke and Tambor,[5] who have synthesized the latter compound. It is also similar to the structure given to eriodictyol (III) by Tutin.[6]


I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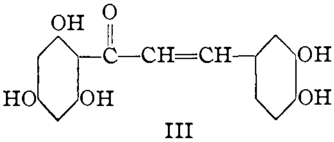
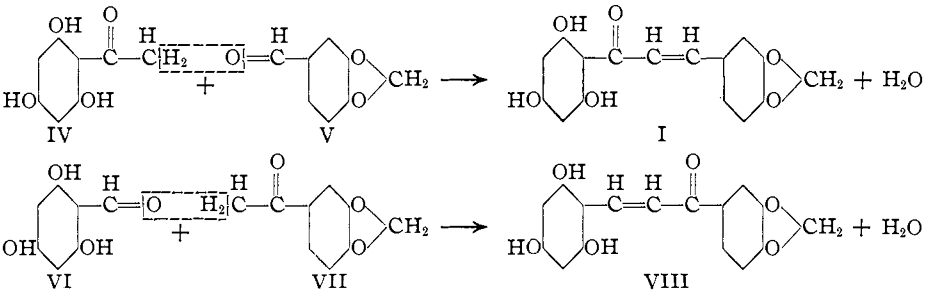

III

However, since only a small amount of piperonal was obtained and acetopiperone predominated among the decomposition products, it would seem that the chalkone should be 2,4,6-trihydroxystyryl-3,4-methylenedioxyphenyl ketone (VIII). The purpose of the present investigation was to synthesize the two isomeric chalkones represented by Formulas (I) and (VIII).



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[1] Tunmann, *Pharm. Post.*, **90**, 773 (1917).

[2] Oesterle and Kueny, *Schweiz. Apoth.-Ztg.*, **59**, 548 (1921).

[3] Oesterle, *ibid.*, **60**, 441 (1922).

[4] Perkin and Hummel, *J. Chem. Soc.*, **85**, 1459 (1904).

[5] Göschke and Tambor, *Ber.*, **44**, 3502 (1911).

[6] Tutin, *J. Chem. Soc.*, **97**, 2054, 2062 (1910).

The first isomer (I) was prepared by condensing 2,4,6-trihydroxyacetophenone (IV) with piperonal (V) by means of alcoholic potassium hydroxide. The 2,4,6-trihydroxyacetophenone was made by condensing phloroglucinol with acetyl chloride by means of aluminum chloride in nitrobenzene as a solvent.[7]

The second isomer (VIII) was synthesized by the condensation of phloroglucinaldehyde (VI) with acetopiperone (VII). The phloroglucinaldehyde was prepared by means of the Gattermann reaction using the modified procedure of Adams and Levine.[8] Dry hydrogen chloride was passed into a suspension of zinc cyanide in an ether solution of phloroglucinol. The resulting imidohydrochloride was then hydrolyzed to phloroglucinaldehyde. Acetopiperone was prepared by the ketonic hydrolysis of piperonyl acetic ester[9] obtained by condensing methyl piperonylate with ethyl acetate by the use of sodium. The chalkone was obtained by condensing together the above aldehyde (VI) and ketone (VII) with alcoholic alkali.

These chalkones decompose on heating and do not possess definite melting points. Their acetates, however, melt sharply and hence the triacetate of each of the isomers was prepared. The natural product decomposed at 262–263° and its triacetate melted at 196–197° according to Oesterle.[3] The synthetic chalkone corresponding to Formula (I) decomposed above 300° and yielded an acetyl derivative melting at 218–220°. Compound VIII decomposed at 265–270° and yielded an acetate melting at 205–206°. It will be noted that the synthetic chalkone (VIII) decomposed at very nearly the same temperature as the natural product. It also possessed properties which agreed with those given by Oesterle for his compound, but the triacetate of this synthetic chalkone melted ten degrees higher than the acetate prepared from the natural substance. Since it is very difficult to purify these natural coloring matters it may be that the natural product was not quite pure. It is very evident that chalkone I differs markedly from the natural product. Its decomposition point and the melting point of its triacetate are very much higher than the values for the natural chalkone. Unfortunately, no sample of the natural product could be obtained for direct comparison.

Experimental

Piperonal.—The piperonal was a commercial product and was purified by vacuum distillation. It melted at 36°.

2,4,6-Trihydroxyacetophenone.—Fifteen grams of phloroglucinol and 20 g. of acetyl chloride were dissolved in a mixture of 200 cc. of dry nitrobenzene and 200 cc. of absolute ether. Thirty grams of aluminum chloride was then added in small portions

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[7] Rosenmund and Schulz, *Arch. Pharm.*, **265**, 318 (1927).

[8] Adams and Levine, THIS JOURNAL, **45**, 2373 (1923).

[9] Mauthner, *J. prakt. Chem.*, **116**, 321 (1917).

during a period of half an hour. The ether was distilled and an additional 30 g. of aluminum chloride was added to the solution, which was stirred vigorously and allowed to stand overnight. The mass was decomposed with ice and the nitrobenzene removed by steam distillation. The aqueous residue was filtered while still hot. On cooling the filtrate, trihydroxyacetophenone crystallized out. After two crystallizations from water with the aid of Norite, 5 g. of light yellow needles was obtained which melted at 213–214° (corr.). The compound gave a wine-red color with ferric chloride, which differentiates it from phloroglucinol, which melts at 217–218°.

Anal. Subs., 0.1341: H_2O, 0.0563; CO_2, 0.2819. Calcd. for $C_8H_8O_4$: H, 4.76; C, 57.14. Found: H, 4.69; C, 57.33.

2,4,6-Trihydroxyphenyl-3,4-methylenedioxystyryl Ketone (I).—This chalkone was obtained by mixing together 2 g. of piperonal, 2 g. of chloro-acetophenone and 20 cc. of 50% alcohol in which 5 g. of potassium hydroxide had been dissolved. The mixture was heated for one hour at 95–100°. After cooling, it was poured into dilute hydrochloric acid and the yellow precipitate filtered off. After recrystallization from 75% methyl alcohol, a yellow powder was obtained which decomposed around 300–310°.

Anal. Subs., 0.0986: H_2O, 0.0365; CO_2, 0.2309. Calcd. for $C_{16}H_{12}O_6$: H, 4.03 C, 64.00. Found: H, 4.13; C, 63.85.

The acetate was prepared by refluxing 1 g. of the above chalkone with 15 cc. of acetic anhydride and 1 g. of anhydrous sodium acetate for one hour. On pouring into water the acetate separated as a light yellow solid. It was recrystallized from 90% alcohol and consisted of light yellow needles melting at 218–220°.

Anal. Subs., 0.1071: H_2O, 0.0386; CO_2, 0.2419. Calcd. for $C_{22}H_{18}O_9$: H, 4.22; C, 61.97. Found: H, 4.03; C, 61.56.

Phloroglucinaldehyde.—Dry hydrogen chloride was passed into a mixture of 30 g. of phloroglucinol dissolved in 250 cc. of dry ether with 30 g. of zinc cyanide with vigorous mechanical stirring. At the end of two hours the imido-hydrochloride separated as an oil. The supernatant liquid was decanted and the crude imido-hydrochloride washed with ether. The product then solidified. It was boiled with 250 cc. of water for three minutes and the solution cooled. Orange-red crystals of the crude aldehyde separated and were purified by two crystallizations from hot water in the presence of Norite. Long, white needles were obtained which possessed no definite melting point. This compound gave a wine-red color with ferric chloride and yielded a phenylhydrazone melting at 120°; yield 18 g. or 49% of the theoretical.

Anal. Subs., 0.1268: H_2O, 0.0451; CO_2, 0.2521. Calcd. for $C_7H_6O_4$: H, 3.89; C, 54.50. Found: H, 3.98; C, 54.28.

Acetopiperone.—A mixture of 24 g. of methyl piperonylate, 3.1 g. of powdered sodium and 18 g. of ethyl acetate was heated on the steam-bath for two hours. At the end of this time an additional 2 g. of sodium and 10 g. of ethyl acetate were added and the heating was continued for another two hours, at which time 10 g. of ethyl acetate was again added and the heating allowed to continue for four hours. The addition of the ethyl acetate in this manner is necessary in order to get the methyl piperonylate to condense, since a considerable portion of the ethyl acetate condenses with itself to give ethyl acetoacetate.

The reaction mixture was decomposed with water and acidified with acetic acid. The oil which separated was crude 3,4-methylenedioxybenzoylacetic ester. This was washed with water and then hydrolyzed by refluxing with 300 cc. of 10% sulfuric acid for eight hours. After cooling, the solution was made alkaline with sodium hydroxide and extracted with ether. The ether was distilled and the acetopiperone recrystallized from 50% alcohol. Eight grams of white crystals was obtained which melted at 87–88°.

The compound yielded a *p*-nitrophenylhydrazone melting at 201–203°, which agrees with the value given by Mauthner.[9]

Anal. Subs., 0.1011: H_2O, 0.0457; CO_2, 0.2424. Calcd. for $C_9H_8O_3$: H, 4.88; C, 65.90. Found: H, 5.05; C, 65.45.

2,4,6-Trihydroxystyryl-3,4-methylenedioxyphenyl Ketone (VIII).—Two grams of phloroglucinaldehyde and 2 g. of acetopiperone were condensed by the method described above for the other isomer. Crystallization from 75% methyl alcohol yielded an orange powder which decomposed at 265–270°. In its decomposition point, color (deep orange) and also its insolubility in dilute ammonia, this compound resembled the natural product described by Oesterle.

Anal. Subs., 0.0770; H_2O, 0.0289; CO_2, 0.1798. Calcd. for $C_{16}H_{12}O_6$: H, 4.03; C, 64.00. Found: H, 4.20; C, 63.71.

The triacetate was prepared by refluxing 1 g. of the above ketone with acetic anhydride and sodium acetate for one hour. After decomposition with and crystallization from alcohol, light yellow needles were obtained which melted at 205–206°.

Anal. Subs. 0.0876: H_2O, 0.0328; CO_2, 0.1995. Calcd. for $C_{22}H_{18}O_9$: H, 4.22; C, 61.97. Found: H, 4.18; C, 62.08.

Summary

The two isomeric chalkones, 2,4,6-trihydroxystyryl-3,4-methylenedioxyphenyl ketone and 2,4,6-trihydroxyphenyl-3,4-methylenedioxystyryl ketone, corresponding to the possible structures for the chalkone previously isolated from natural sources, have been synthesized. A comparison of the properties of the natural chalkone with those of the synthetic isomers indicates that the natural compound is 2,4,6-trihydroxystyryl-3,4-methylenedioxyphenyl ketone. The other isomer, which possesses the structure originally assigned to the natural chalkone, differs markedly from the compound found in nature.

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DIFURYLETHYLENE

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In making a study of the disappearance of furfural in alcohol fermentation, Lintner[1] found that furfural in dilute aqueous solution reacts with hydrogen sulfide to form a milky emulsion of polythiofurfuraldehyde which has a peculiar penetrating bread-like odor. The emulsion which was formed could be coagulated to a rubbery mass on the addition of a few drops of sulfuric or hydrochloric acid.

A study of this reaction has been made and an attempt to identify the product has brought about the discovery of a method whereby difurylethylene may easily be prepared. By the vacuum distillation of

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[1] Lintner, *Z. ges. Brauw.*, **15**, 189 (1910); *C. A.*, **5**, 755 (1911).