Osage Orange Pigments. XV. Structure of Osajaxanthone. Synthesis of Dihydroosajaxanthone Monomethyl Ether[1a]

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Osajaxanthone, a pigment obtained from the root bark of the osage orange (*Maclura pomifera* Raf.), is shown to be 5,8-dihydroxy-2,2-dimethyl-2H,6H-pyrano[3,2-*b*]xanthen-6-one (**1**). Dihydroosajaxanthone monomethyl ether (**7**) and an isomer are synthesized.

In a previous paper[2] in this series, we have described the isolation and partial characterization of three new, yellow pigments from the root bark of the osage orange (*Maclura pomifera* Raf.). These were tentatively assigned substituted polyhydroxyxanthone structures on the basis of their ultraviolet spectra and various diagnostic tests and were accordingly designated macluraxanthone, osajaxanthone, and alvaxanthone. Subsequently,[1a] macluraxanthone was shown to be 12-(1,-1-dimethylallyl)-5,9,10-trihydroxy-2,2-dimethyl-2H,6H-pyrano[3,2-*b*]xanthen-6-one.

We report herein the elucidation of the structure of the pigment found in least amount, osajaxanthone, and the synthesis of dihydroosajaxanthone monomethyl ether and one of its isomers.

As reported previously,[2] osajaxanthone, $C_{18}H_{14}O_5$, can be obtained in 0.02% average yield from the dry root bark of the osage orange. Further, osajaxanthone was found to be optically inactive, methoxyl free, and to possess only phenolic acidity. Positive Perkin and Wilson boric acid tests indicated a γ-pyrone structure with an auxochrome (presumably a hydroxyl) *peri* to the carbonyl group. Finally, the ultraviolet spectrum of osajaxanthone indicated a xanthone nucleus.

Hydrogenation of osajaxanthone or its monomethyl ether yielded dihydro derivatives. The hypsochromic shifts in the ultraviolet spectra (Table I) of these compounds, compared with the spectra of their unsaturated analogs, revealed the single olefinic double bond of osajaxanthone to be conjugated with the aromatic nucleus.[4]

Since our previous work on macluraxanthone[1a] had demonstrated the utility of ultraviolet spectral studies in assigning the oxygenation pattern of a xanthone, the spectra of dihydroosajaxanthone and its monomethyl ether were compared with those of various known trioxygenated xanthones.[5,6] A close resemblance was noted between the spectra of our compounds and derivatives of 1,3,7-trihydroxyxanthone,[5-7] thus implying that osajaxanthone had the 1,3,7-oxygenation pattern (Table I).[3] It should be noted that the spectra recorded in Table I for 1-hydroxy-3,7-dimethoxyxanthone[8] and 1,3-dihydroxy-7-methoxyxanthone,[8] which were obtained in the present work, differ from those published[5,7] in that the longest wave-length bands are included and some bands differ slightly as to intensity and wave length. A visual comparison (Figure 1) of the spectra of 1-hydroxy-3,7-dimethoxyxanthone and

TABLE I

ULTRAVIOLET SPECTRA OF OSAJAXANTHONE DERIVATIVES AND KNOWN XANTHONES

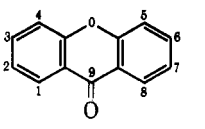
Compd.	λ_{max}, mμ (log ϵ)
Osajaxanthone	240 (4.27), 249 (4.26), 285 (4.67), 339 (3.90), 382 (3.68)
Osajaxanthone monomethyl ether	240 (4.33), 248 (4.30), 286 (4.64), 339 (3.96), 375 (3.65)[a]
Dihydroosajaxanthone	237 (4.49), 262 (4.55), 316 (4.21), 380 (3.78)
1,3-Dihydroxy-7-methoxyxanthone	235 (4.45), 259 (4.51), 311 (4.14), 369 (3.80)
Dihydroosajaxanthone monomethyl ether	233 (4.50), 263 (4.55), 316 (4.22), 375 (3.79)
1-Hydroxy-3,7-dimethoxyxanthone	236 (4.44), 259 (4.60), 306 (4.15), 369 (3.80)

[a] Inflection.

Acetylation of osajaxanthone under mild or severe conditions yielded a colorless diacetate which gave a negative ferric chloride test. Methylation with diazomethane yielded a yellow monomethyl ether while more severe conditions gave a colorless dimethyl ether. The nuclear magnetic resonance spectrum of the monomethyl ether included a sharp singlet at τ 3.46, which in this case can only be due to a strongly hydrogen-bonded phenolic proton. Thus it was concluded that osajaxanthone possesses a hydroxyl on C-1 of the xanthone nucleus,[3] as was previously indicated by the Wilson boric acid test.[2]

dihydroosajaxanthone monomethyl ether demonstrates especially convincingly that our pigment has a 1,3,7-oxygenation pattern. As expected, the spectra of unsaturated derivatives of osajaxanthone depart from this

(3) The numbering system used in this discussion is based on xanthen-9-one as the parent compound, as below, not on 2H,6H-pyrano[3,2-*b*]xanthen-6-one which is later shown to be the parent system.



(1) (a) Preceding paper in this series: M. L. Wolfrom, F. Komitsky, Jr., G. Fraenkel, J. H. Looker, E. E. Dickey, P. McWain, A. Thompson, P. M. Mundell, and O. M. Windrath, *J. Org. Chem.*, **29**, 692 (1964); (b) National Science Foundation Cooperative Graduate Fellow, 1961–1964.

(2) M. L. Wolfrom, E. E. Dickey, P. McWain, A. Thompson, J. H. Looker, O. M. Windrath, and F. Komitsky, Jr., *J. Org. Chem.*, **29**, 689 (1964).

(4) *Cf.*, for example, M. L. Wolfrom, W. D. Harris, G. F. Johnson, J. E. Mahan, S. M. Moffett, and B. S. Wildi, *J. Am. Chem. Soc.*, **68**, 406 (1946).

(5) J. C. Roberts, *Chem. Rev.*, **61**, 591 (1961).

(6) P. Yates and G. H. Stout, *J. Am. Chem. Soc.*, **80**, 1691 (1958).

(7) L. Cononica and F. Pellizzoni, *Gazz. chim. ital.*, **85**, 1007 (1955).

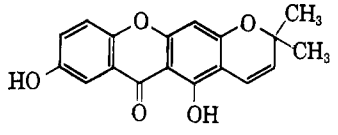
(8) P. K. Grover, G. D. Shah, and R. C. Shah, *J. Chem. Soc.*, 3982 (1955).

similarity owing to the effect of the conjugated olefinic double bond.

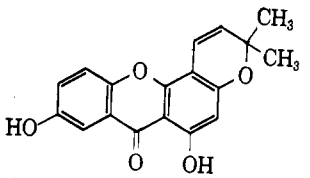
With the placement of the three oxygen functions on the xanthone nucleus, it remained to prove the structure and location of the C_5 fragment remaining, which was assumed to be a terpenoid substituent.[2] Inspection of the molecular formula showed this fragment to be part of a ring. Since the previously discussed ultraviolet studies showed the olefinic double bond to be conjugated with the aromatic nucleus, the presence of a 2,2-dimethylchromene ring was suspected since this is the only common terpenoid substituent which has such a double bond.[9,10]

To be sure, the presence of the 2,2-dimethylchromene ring was proved by the occurrence of a sharp singlet of relative area six, due to the geminal methyls, at τ 8.50, and two doublets, each of relative area one, at 3.51 and 4.29 (J = 10.8 c.p.s.), due to the olefinic protons,[1a,11,12] in the nuclear magnetic resonance spectrum of osajaxanthone diacetate (Figure 2). The acetate methyl protons gave two sharp singlets at τ 7.48 and 7.60. The aromatic protons gave a multiplet of relative area one at τ 2.08, a multiplet of area two at 2.60, and a sharp singlet of area one at 3.29. By virtue of its high shift, the last signal must be due to a proton on the electron-rich phloroglucinol ring of osajaxanthone diacetate. Furthermore, since this signal is a singlet, the phloroglucinol ring can have only one substituent proton, and therefore the 2,2-dimethylchromene ring must be fused to it. Conversely, the multiplet at τ 2.08, by virtue of its low shift, can only be due to the C-8 proton[3] which is adjacent to the xanthone carbonyl. Since its signal is a multiplet, the C-8 proton must be coupled with at least two more protons. Therefore the hydroquinone ring of osajaxanthone must have three aromatic protons, at C-5, C-6, and C-8, besides the C-7 hydroxyl group[3] which precludes any consideration of the 2,2-dimethylchromene ring as fused to it. The nuclear magnetic resonance data, including the proof of a C-1 hydroxyl, coupled with the ultraviolet data, which indicates a 1,3,7-oxygenation pattern, narrows the possible structures for osajaxanthone to **1** and **2**.

The two possible structures would be expected to differ as to reactivity of the C-1 hydroxyl group. The C-1



1



2

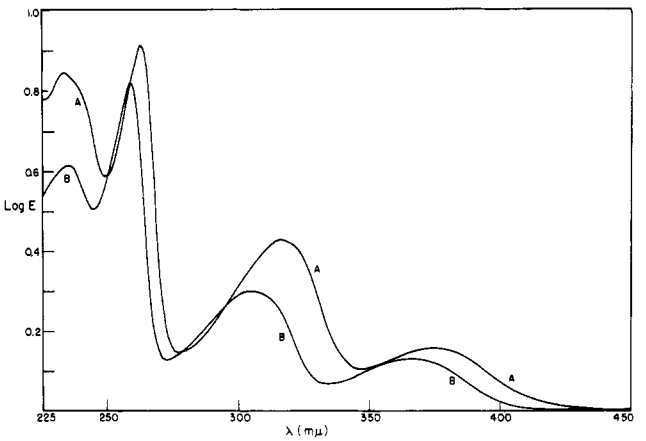


Figure 1.—Ultraviolet spectra of dihydroosajaxanthone monomethyl ether (A) and 1-hydroxy-3,7-dimethoxyanthone (B).

hydroxyl of **1**, since it is hydrogen bonded and *ortho* disubstituted, probably would not be acetylated if **1** were treated with a slight excess of pyridine–acetic anhydride at 0° overnight. This is true of such a hydroxyl in the γ-pyrone series in general[4] and has been extended to xanthones also.[1a] On the other hand, these same conditions would be expected to acetylate the C-1 hydroxyl of **2** since, although it is hydrogen bonded, it is not hindered by a second *ortho* substituent. For instance, 1,3,-5,6-tetrahydroxyxanthone is fully acetylated by pyridine–acetic anhydride at 0° overnight.[1a] However, it was difficult to apply this reaction to osajaxanthone due to its insolubility in the pyridine–acetic anhydride reagent. If a sample was treated with the usual small excess of reagent, solution was not achieved and an inhomogeneous product resulted. If enough of the reagent was used to keep the pigment in solution, a diacetate resulted. However, this required a huge excess of reagent and the crude product was not as pure as would be expected so this result was treated with caution. Indeed, when a sample of the easily soluble dihydroosajaxanthone monomethyl ether was treated with the usual small excess of pyridine–acetic anhydride at 0° overnight, it was recovered unchanged, indicating the linear constitution **1** for osajaxanthone. Moreover, the dihydromonomethyl ether yielded an acetate when the same large excess was used which converted osajaxanthone itself to the diacetate. Thus it was tentatively concluded that osajaxanthone possessed structure **1**.

Confirmation of this point was obtained by use of the Gibbs test, used to detect unsubstituted positions *para* to a free hydroxyl. This method was utilized to decide between linear and angular isomers, analogous to **1** and **2**, which were possible structures for the xanthone jacareubin.[13] First used as a quantitative method for phenol itself,[14] the method was put on a firm basis by King, King, and Manning,[13] who tested many phenols and noted the invariable appearance of a strong maximum (log ϵ is usually about 4) in the region 590–665 mμ if a monohydric phenol had an unsubstituted *para* position and no maximum in this region if there was no such position. More complex phenols gave the same results except that the maxima sometimes occurred outside this range. Application of this test to osajaxanthone and the monomethyl ether of its dihydro deriva-

(9) W. D. Ollis and I. O. Sutherland, "Recent Developments in the Chemistry of Natural Phenolic Compounds," W. D. Ollis, Ed., Pergamon Press Ltd., London, 1961, p. 74.

(10) M. L. Wolfrom and F. Komitsky, Jr., "Recent Progress in the Chemistry of Natural and Synthetic Colouring Matters and Related Fields," T. S. Gore, B. S. Joshi, S. V. Sunthankar, and B. D. Tilak, Ed., Academic Press, Inc., New York, N. Y., 1962, p. 287.

(11) B. F. Burrows and W. D. Ollis, *Proc. Chem. Soc.*, 177 (1960).

(12) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Varian High Resolution Nuclear Magnetic Resonance Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, No. 344.

(13) F. E. King, T. J. King, and L. C. Manning, *J. Chem. Soc.*, 563 (1957).

(14) H. D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927).

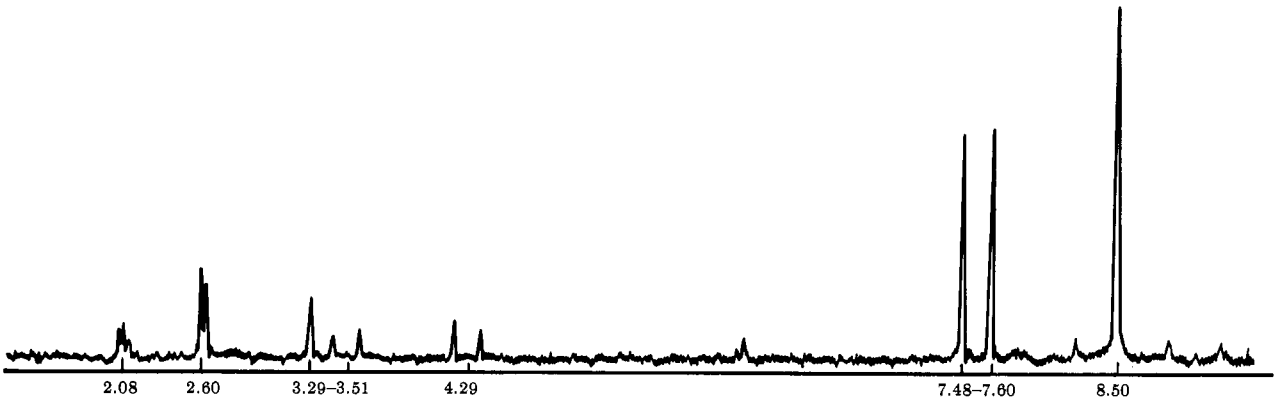


Figure 2.—N.m.r. spectrum of osajaxanthone diacetate. The spectrum of the monomethyl ether includes a singlet at τ 3.46.

tives resulted in a blue color in each case due to maxima at 715 mμ (log ε 4.0) and 690 mμ (log ε 4.1), respectively. The parent compound, 1-hydroxy-3,7-dimethoxyxanthone, gave a maximum at 667 mμ (log ε 4.0). Although certain workers have found this test to be unreliable,[15,16] in our hands uniform results were obtained if the Gibbs reagent, 2,6-dichlorobenzoquinone chlorimide,[14] was carefully purified.

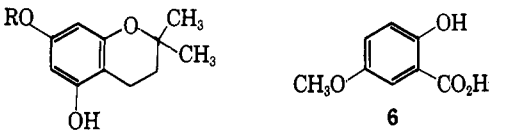
Thus, since structure **2** has no unsubstituted position *para* to a free hydroxyl, structure **1** is confirmed as osajaxanthone.

The classical method for establishing the structure of an organic compound requires that, as a final step, the structure assigned by degradative or other methods be verified by a synthesis from intermediates of known structure. Although it has not been possible to synthesize osajaxanthone itself, the monomethyl ether of its dihydro derivative has been obtained in such a way as to eliminate consideration, in a classical sense, of all possible structures for the pigment except **1** and **2**.

The synthesis of Grover, Shah, and Shah[8] is probably the best general route to xanthones. Unfortunately, these workers were unable to synthesize the parent compound of osajaxanthone, 1,3,7-trihydroxyxanthone, since 2,5-dihydroxybenzoic acid failed to condense with phloroglucinol. However, the use by them of 2-hydroxy-5-methoxybenzoic acid led to a fair yield of 1,3-dihydroxy-7-methoxyxanthone. In the present work, these results were confirmed and attempts were made to condense phloroglucinol carboxylic acid with hydroquinone which, however, yielded none of the desired xanthone. Thus it was concluded that any synthetic efforts directed toward osajaxanthone or one of its derivatives would require condensation of 2-hydroxy-5-methoxybenzoic acid with a properly substituted phloroglucinol derivative.

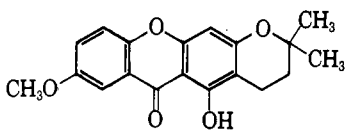
While this work was in progress, a similar synthesis of related dihydrojacareubin was published,[17] which involved condensation of the chroman **3** with 2,3,4-trihydroxybenzoic acid. Although three products would be expected, only the desired linear isomer was obtained.

Thus the chroman **3**, obtained by diborane reduction[17] of its corresponding chromanone, made by a modification of a known method,[17] was condensed with 2-hydroxy-5-methoxybenzoic acid (**6**) in phosphorus oxychloride solutions under zinc chloride catalysis. Only two products were isolated, although three, **7**, **8**, and **9**, would be expected. One of these, long, yellow needles, was found to be identical in every way with a sample of dihydroosajaxanthone monomethyl ether prepared from the natural product.



3, R = H
4, R = CH_3
5, R = $CH_2C_6H_5$

6



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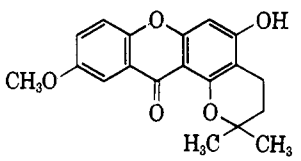

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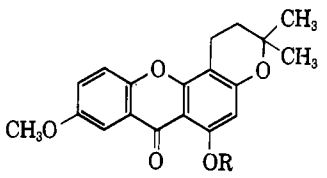


9, R = H
10, R = CH_3
11, R = $CH_2C_6H_5$

This shows, in a completely independent manner, that osajaxanthone must be **1**, **2**, or the unsaturated, unmethylated analog of **8**.

The second of the synthetic products, tiny, yellow plates, was insoluble in all solvents with the exception of hot acetic acid, melted at 323–325°, had an infrared spectrum very similar to dihydroosajaxanthone monomethyl ether, and gave an analysis compatible with one of the isomeric structures **7**, **8**, or **9**. The nuclear magnetic resonance spectrum (Figure 3) of its easily soluble acetate confirmed its structure as one of these. The above properties immediately pointed to structure **8** since the insolubility and the high melting point of 323–325°, *vs.* 173.5–174° for dihydroosajaxanthone monomethyl ether, can only be explained by intermolecular hydrogen bonding in the crystal lattice. This is possible in **8** between the carbonyl of one molecule and the 3-hydroxyl in an adjacent molecule, but not in **7** or **9** since there would be strong intramolecular hydrogen bonding between the C–1 hydroxyl and the xanthone

(15) H. Inouye, Y. Kanaya, and Y. Murata, *Chem. Pharm. Bull.* (Tokyo), **7**, 573 (1959).
(16) E. D. Burling, A. Jefferson, and F. Scheinmann, *Tetrahedron Letters*, 599 (1964).
(17) H. B. Bhat and K. Venkataraman, *Tetrahedron*, **19**, 77 (1963).

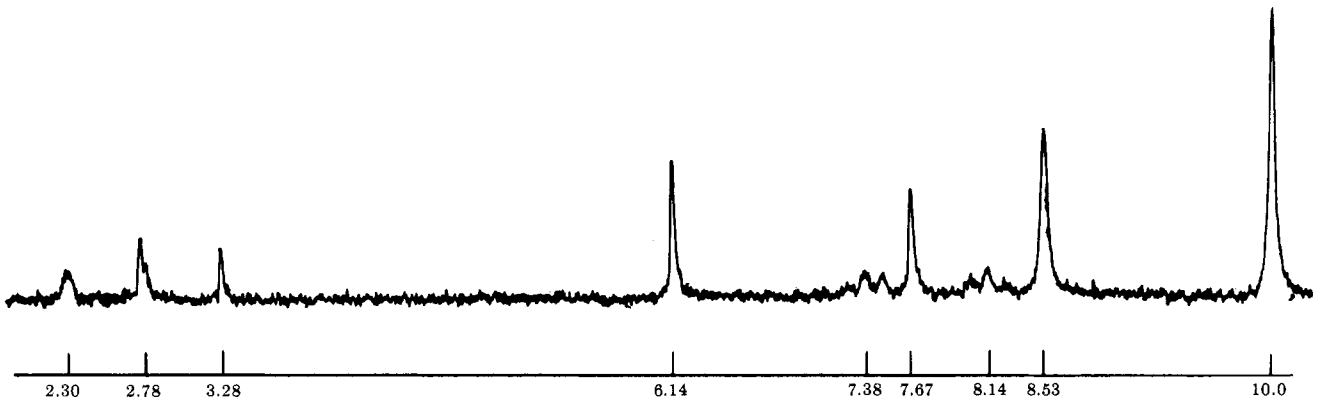


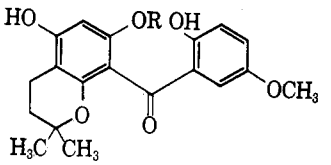
Figure 3.—N.m.r. spectrum of dihydroleucoosajaxanthone monomethyl ether acetate. Assignments are as follows: geminalmethyl protons, τ 8.53; C-1 acetate methyl protons, τ 7.67; C-7 methoxyl protons, τ 6.14; chroman ring benzylic protons, τ 7.38; other chroman ring protons, τ 8.14; C-4 proton, τ 3.28; C-8 proton, τ 2.30; and C-5 and C-6 protons, τ 2.78.

carbonyl in these molecules. However, despite repeated recrystallizations from acetic acid, the high-melting product remained yellow, and compound **8**, called dihydroleucoosajaxanthone monomethyl ether, would be expected to be white, since the C-1 oxygen is an ether.[8] That this color was due to a minor impurity was demonstrated by acetylation of the high-melting compound, purification of the resulting acetate, and saponification which gave a pure white product, confirming its structure as **8**. Finally, treatment of the white product with boroacetic anhydride[18] gave no boron complex, but yielded an acetate identical with that obtained by pyridine–acetic anhydride acetylation of the high-melting product. This again rules out structures **7** and **9** since boroacetic anhydride would form a complex with these and would not acetylate them because both have only a C-1 hydroxyl.[1a,5,18] Thus, in a completely independent manner, the possible structures for dihydroosajaxanthone monomethyl ether are narrowed to **7** and **9** and thus again to **1** and **2** for osajaxanthone itself.

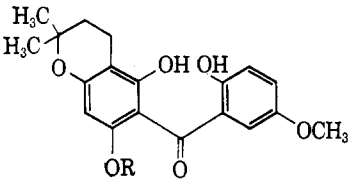
As previously discussed, acetylation studies and the Gibbs test lead to **1** as the structure of osajaxanthone and thus to **7** for the dihydroosajaxanthone monomethyl ether. The synthetic work in no way confirmed this last conclusion since no **9**, which can be termed dihydroisoosajaxanthone monomethyl ether, was produced, as verified by thin layer chromatography, and thus no comparisons of the behavior of **7** and **9** could be made. The fact that no **9** was produced is surprising but parallels the synthetic work on dihydrojacareubin, where only one product, the linear isomer, was obtained of the three possibilities, analogous to **7**, **8**, and **9**.[17]

In any case, it was felt that perhaps a sample of **9** or a derivative could be obtained by condensation of a suitable blocked chroman with 2-hydroxy-5-methoxybenzoic acid. Thus the chromans **4** and **5** were prepared by diborane reduction[17] of their respective chromanone analogs[19] and attempts were made to condense them with **6** to obtain **10** and **11**, the methyl and benzyl ether of **9**, respectively.

In both cases, only a small amount, less than 1%, of **8** was produced and no derivatives of **9** were obtained. Apparently some of the benzophenone intermediates **12** and **13** are formed.[8] The only mode of ring closure open to them requires elimination of benzyl or methyl alcohol, yielding insoluble, easily isolated, **8**. If any of the intermediate benzophenones **14** or **15** were formed, they could close with elimination of water to the base-insoluble **10** or **11**, respectively. Alternately, elimination of methyl or benzyl alcohol would lead to **7**, which is soluble in base owing to its free hydroxyl. However, in both cases, the base-insoluble fractions yielded only amorphous material. The apparent inability of the benzophenones **14** and **15** to close to **10** and **11** has no ready explanation apparent to us. Possibly such intermediates are not formed but **16** must certainly be an intermediate in the condensation of **3** and **6**,[8] and of the



12, R = CH_3
13, R = $CH_2C_6H_5$



14, R = CH_3
15, R = $CH_2C_6H_5$
16, R = H

two modes of ring closure available, only that leading to the linear isomer **7** proceeds.

Work is proceeding on an unequivocal synthesis of an osajaxanthone derivative and on the structure of alvaxanthone, the last of the osage orange root bark pigments.

Experimental[20]

Osajaxanthone Monomethyl Ether.—A solution of 75 mg. of osajaxanthone[2] in methylene chloride, cooled to 0°, was treated with an excess of ethereal diazomethane. The solution was kept

(18) A. Pictet and A. Geleznoff, *Ber.*, **36**, 2219 (1903).
(19) S. W. George and A. Robertson, *J. Chem. Soc.*, 1535 (1937).

(20) Melting points were taken in a Hershberg apparatus using total immersion thermometers. Nuclear magnetic resonance spectra were taken on saturated deuteriochloroform solutions with a tetramethylsilane internal reference standard, using a Varian A-60 nuclear magnetic resonance spectrometer. Ultraviolet spectra were taken in absolute ethanol on a Cary Model 14 recording spectrophotometer. These are recorded in Table I as λ_{max}^{EtOH} in $m\mu$ (log ϵ). Infrared spectra were taken in potassium bromide pellets on a Perkin-Elmer Infracord spectrophotometer. Analyses were by Mr. William Rond of this laboratory.

at 0° for several hours, then overnight at room temperature. Filtration, evaporation, and recrystallization of the resulting residue gave yellow needles, yield 61 mg., m.p. 181–182°.

Anal. Calcd. for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.48; H, 4.79.

Osajaxanthone Dimethyl Ether.—A solution of 100 mg. of osajaxanthone[2] in 10 ml. of acetone, 1.6 ml. of dimethyl sulfate, and 0.9 ml. of 50% potassium hydroxide was brought to reflux. Three separate portions of 0.8 ml. of dimethyl sulfate and 1.0 ml. of 50% potassium hydroxide were added as rapidly as possible, followed by a final 1.6 ml. of dimethyl sulfate and 2.0 ml. of 50% potassium hydroxide. The solution was refluxed for 2 hr. and poured into 200 ml. of iced water, and the resulting residue was recrystallized from methanol–water, giving colorless columns, yield 72 mg., m.p.167–168°.

Anal. Calcd. for $C_{18}H_{12}O_3(OCH_3)_2$: C, 70.99; H, 5.36; OCH_3, 18.35. Found: C, 71.40; H, 5.31; OCH_3, 15.80.

Dihydroosajaxanthone.—A solution of 25 mg. of osajaxanthone in absolute ethanol with a 5% palladium-on-charcoal catalyst was hydrogenated overnight at room temperature and under 3 atm. Filtration from the catalyst, evaporation, and recrystallization of the residue from ethanol–water gave long, yellow needles, yield 22 mg., m.p. 299–300° dec.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.46; H, 5.12.

Dihydroosajaxanthone Monomethyl Ether (7).—Osajaxanthone monomethyl ether (25 mg.) was hydrogenated as described for the preparation of dihydroosajaxanthone. Recrystallization of the crude product from ethanol gave matted, yellow needles, yield 19 mg., m.p. 172–174°. An analysis was obtained on the synthetic sample, which was shown to be identical with the above.

Osajaxanthone Diacetate.—A mixture of 45 mg. of osajaxanthone,[2] 0.5 g. of sodium acetate, and 5 ml. of acetic anhydride was refluxed for 2 hr. and poured into 50 ml. of water. Recrystallization of the resulting precipitate from 95% ethanol gave white needles, yield 45 mg., m.p. 203–204°.

A solution of 50 mg. of osajaxanthone in 10 ml. of pyridine was cooled to 0° and 10 ml. of precooled acetic anhydride was added. After standing overnight at 0°, the solution was poured into 100 ml. of water. Recrystallization of the resulting precipitate from ethanol–water gave a product shown to be identical, by infrared spectrum, with the substance obtained by sodium acetate–acetic anhydride acetylation of osajaxanthone, yield 17 mg., m.p. 203–204°.

Anal. Calcd. for $C_{18}H_{12}O_5(COCH_3)_2$: C, 67.00; H, 4.60; $COCH_3$, 21.80. Found: C, 67.28; H, 4.50; $COCH_3$, 19.33.

Acetylation of Dihydroosajaxanthone Monomethyl Ether.—A mixture of 100 mg. of dihydroosajaxanthone monomethyl ether, 0.5 g. of sodium acetate, and 5 ml. of acetic anhydride was refluxed for 2 hr. and poured into 50 ml. of water. Filtration of the resulting precipitate and recrystallization from ethanol–water gave tiny, light yellow needles, yield 78 mg., m.p. 204–206°.

A solution of 50 mg. of dihydroosajaxanthone monomethyl ether in 10 ml. of pyridine was cooled to 0° and 10 ml. of precooled acetic anhydride was added. After standing overnight at 0°, the solution was poured into 100 ml. of water. Recrystallization of the resulting precipitate from ethanol–water gave an acetate which was proved identical by infrared spectra with the above, yield 21 mg., m.p. 204–206°.

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.68; H, 5.75.

An amount of 90 mg. of dihydroosajaxanthone was dissolved in 3.6 ml. of pyridine and cooled to 0°; 2.0 ml. of acetic anhydride was added. The solution was processed as above after standing overnight. Recrystallization of the crude product gave long yellow needles which infrared spectra revealed to be starting material, recovery 71 mg., m.p. 171–173°.

2,2-Dimethyl-5,7-dihydroxychroman-4-one.—This compound was prepared by the method of Bhat and Venkataraman[17] with the modification that 3,3-dimethylacrylic acid was used in place of 3-hydroxyisovaleric acid. Yields were comparable.

The Synthesis of Dihydroosajaxanthone Monomethyl Ether and Dihydroleucoosajaxanthone Monomethyl Ether.—A mixture of 10.0 g. of **3**, 2,2-dimethyl-5,7-dihydroxychroman,[17] 10.0 g. of **6**, 2-hydroxy-5-methoxybenzoic acid, 30 g. of freshly fused and pulverized zinc chloride, and 80 ml. of phosphorus oxychloride was stirred at 75° for 2 hr.[8] The red solution was poured into 2000 ml. of ice and water and stirred for 1 hr.; the resulting precipitate was air dried. The crude product was treated with 1000 ml. of boiling methanol and then filtered. Recrystallization of the insoluble residue from acetic acid gave dihydroleucoosajaxanthone monomethyl ether (**8**), tiny yellow plates, yield 1.19 g., m.p. 323–325° dec.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 70.05; H, 5.43.

The methanol filtrate was reduced in volume by boiling. On cooling, long, yellow, matted needles separated. Recrystallization from methanol–water gave dihydroosajaxanthone monomethyl ether (**7**), proved identical with the natural product derivative by infrared spectrum, X-ray powder pattern, and mixture melting point, yield 1.05 g., m.p. 173.5–174.0°.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.78; H, 5.52.

This preparation was repeated twice with identical results. Thin layer chromatography of the methanol mother liquor on silica gel with 1.5% methanol in benzene showed the presence of some dihydroosajaxanthone monomethyl ether as the only mobile spot.

Dihydroleucoosajaxanthone Monomethyl Ether Acetate.—A solution of 1.0 g. of dihydroleucoosajaxanthone monomethyl ether (**8**) in 100 ml. of pyridine and 100 ml. of acetic anhydride was warmed at 100° for 2 hr. The solution was poured into ice and water and the resulting white precipitate was filtered and air dried. The crude product was dissolved in boiling ethanol and filtered from a small amount of residue. The filtrate was reduced in volume and cooled, depositing long, white needles of the acetate, yield 973 mg., m.p. 173–174°.

Anal. Calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.31; H, 5.39.

Pure Dihydroleucoosajaxanthone Monomethyl Ether.—An amount of 100 mg. of sodium was added to a solution of 400 mg. of dihydroleucoosajaxanthone monomethyl ether acetate in 50 ml. of methanol. After refluxing for 30 min., 5 ml. of water was added, followed by 5 ml. of acetic acid. The resulting white precipitate was recrystallized from acetic acid, giving tiny, white plates of dihydroleucoosajaxanthone monomethyl ether (**8**), yield 310 mg., m.p. 323–325° dec. An infrared spectrum of this product proved its identity with the slightly yellow material not purified by acetylation and saponification.

Triacetyl Borate Acetylation of Dihydroleucoosajaxanthone Monomethyl Ether.—Triacetyl borate (500 mg.)[18] was added to a solution of 100 mg. of pure, white, dihydroleucoosajaxanthone monomethyl ether in 5 ml. of acetic anhydride and the mixture was refluxed for 15 min. The solution was cooled and diluted with 20 ml. of ether. After 8 hr., as no boron complex had separated, 25 ml. of water was added and the resultant mixture was extracted in portions with 150 ml. of ether. The ether extract was dried and evaporated. Recrystallization of the residue from methanol–water gave white needles, shown by infrared spectra to be identical with the acetate obtained from the pyridine–acetic anhydride acetylation of dihydroleucoosajaxanthone monomethyl ether, yield 31 mg.

2,2-Dimethyl-7-benzyloxy-5-hydroxychroman and 2,2-Dimethyl-7-methoxy-5-hydroxychroman.—These compounds **4** and **5** were prepared by diborane reduction of the respective chromanones[19] according to the method of Bhat and Venkataraman.[17] The yield of **4** was comparable with that obtained using the Clemmensen reduction.[19] The benzyl compound **5** is apparently unknown, yield 62.5%, m.p. 128–129°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.91; H, 6.94.

Attempted Syntheses of Dihydroisoosajaxanthone Methyl Benzyl Ether and Dihydroisoosajaxanthone Dimethyl Ether.—Attempts were made to condense 5.0-g. amounts of 2,2-dimethyl-7-methoxy-5-hydroxychroman (**4**) and 2,2-dimethyl-7-benzyloxy-5-hydroxychroman (**5**) with 5.0-g. amounts of 2-hydroxy-5-methoxybenzoic acid (**6**) in the same manner used[8] for the synthesis of dihydroosajaxanthone monomethyl ether (**7**) and its leuco isomer (**8**). In both cases, the crude products were taken up in methanol and cooled, yielding 25 mg. and 20 mg., respectively, of dihydroleucoosajaxanthone monomethyl ether (**8**). The filtrates were reduced to dryness under vacuum and the resulting residues were taken up in large volumes of ether. The ether solutions were exhaustively extracted with 2 *N* sodium hydroxide, then washed

with water. Evaporation of the ether solutions gave 114 mg. and 179 mg., respectively, of an amorphous light brown powder which would not crystallize from methanol. Acidification of the basic extracts in both cases, yielded reddish tar.

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New Syntheses of Nucleosides.[1a] The Syntheses of Glycopyranosides of Purines, Pyrimidine, and Benzimidazole

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Syntheses of nucleosides of chloropurines, 6-benzamidopurine, theophylline, N^6-benzoylcytosine, and benzimidazole are presented. The method developed involved the direct condensation of the heterocyclic imino compounds such as free acylaminopurine, chloropurines, theophylline, N^6-benzoylcytosine, and benzimidazole with acylglycosyl halides in nitromethane containing hydrogen halide acceptors to give the corresponding crystalline, acylated nucleosides.

The reaction described in this paper provides a new synthesis for purine nucleosides and analogous compounds, particularly for the glycosidation of heterocyclic compounds having an imino group, *e.g.*, purines, pyrimidines, and benzimidazoles.

Several methods have been reported previously for the syntheses of purine nucleosides. In the first of these Fischer and Helferich[2] condensed silver 2,8-dichloroadenine or theophylline with 2,3,4,6-tetra-O-acetylglucopyranosyl bromide to give 2,8-dichloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)adenine or 7-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)theophylline.

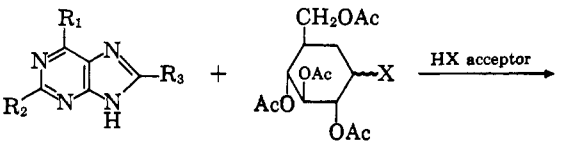
Davoll, Lythgoe, and Todd[3] observed that tri-O-acetylpentafuranosyl chlorides, due to their increased stability, gave higher yields of nucleosides than the corresponding furanosyl bromides. Another major improvement was the introduction of the use of chloromercuri derivatives of purines, rather than silver purines by Davoll and Lowy.[4] The third major improvement was the introduction of O-benzoyl blocking groups, rather than O-acetyl for the sugar moiety by Kissman, Pidacks, and Baker.[5]

Sato, Shimadate, and Ishido[6] proposed a method for the synthesis of purine nucleosides by melting a mixture of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose with purines in the presence of *p*-toluenesulfonic acid or zinc chloride *in vacuo*.

Robins and co-workers[7] have also reported the condensation of certain 2,3-dihydro-4H-pyrans with 6-substituted purines in the presence of a catalytic amount of acid to give the corresponding 6-substituted 9-(tetrahydro-2-pyranyl)purines.

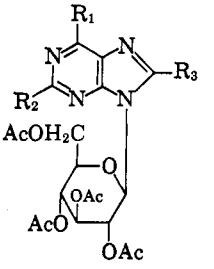
Schramm, Grötsch, and Pollmann[8] observed that the condensation of adenine with D-ribose in the presence of polyphosphate ester gave adenosine. A riboside of uric acid was synthesized from tetrakistriethylsilyluric acid and tri-O-benzoylribosyl bromide in the presence of silver perchlorate by Birkofer, Ritter, and Kühlthau.[9] Spongoadenosine was prepared by the condensation of 2,3,5-tri-O-benzyl-D-arabinofuranosyl chloride with N-benzoyladenine,[10] but Coxon and Fletcher[11] observed that the condensation of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide with mercuric cyanide in nitromethane gave 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl cyanide.

Our method of synthesis allows us to eliminate the step for formation of the metal salt of purine or benzimidazole, the preparation of heavy metal salts being generally quite difficult. This reaction assured us an improved yield 20–40% higher than the conventional processes.[2,4,6,12]



Ia, $R_1 = R_2 = R_3 = Cl$
b, $R_1 = R_2 = Cl$; $R_3 = H$
c, $R_1 = R_3 = Cl$; $R_2 = H$
d, $R_1 = Cl$; $R_2 = R_3 = H$

II, Ac = $-\overset{\overset{O}{\|}}{C}CH_3$;
X = Cl or Br



IIIa, $R_1 = R_2 = R_3 = Cl$
b, $R_1 = R_2 = Cl$; $R_3 = H$
c, $R_1 = R_3 = Cl$; $R_2 = H$
d, $R_1 = Cl$; $R_2 = R_3 = H$

(1) (a) This paper was presented at the annual meeting of Agricultural Chemical Society of Japan, Tokyo, April 1963. (b) Deceased.

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