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A Method for the Selective Deacetylation of the 5-Acetoxy Group in Acetoxyflavones (1,2)

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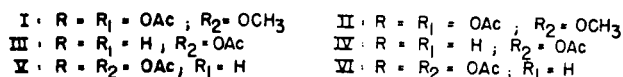
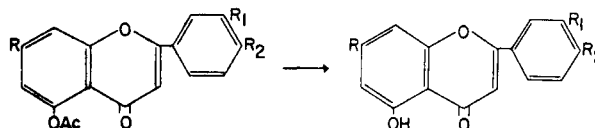
In a previous paper (4), we reported the reaction of 3-bromohesperetin triacetate (3-bromo-3',5,7-triacetoxy-4'-methoxyflavanone) (5) with silver acetate in acetic anhydride to give diosmetin triacetate (I). Subsequently, it was found that addition of acetic acid and a marked reduction in the quantity of acetic anhydride in this reaction mixture led to a phenolic, bromine-free substance, which obviously was not I, in which all hydroxyl groups are blocked. In the present paper we report data supporting formulation of this phenolic substance as the diosmetin diacetate (II). In addition a procedure for the selective deacetylation of the acetoxyflavones (I, III, V) at the 5-acetoxy group is reported. The method appears of added significance in view of the small number of examples of selective partial deacetylation in the flavonoid area (6).

Inasmuch as diosmetin triacetate (I) results from reactions of 3-bromohesperetin triacetate in basic media (4, 7), it is possible that I is an intermediate in the formation of II. In any event, I has been used as a more convenient source of II than the difficultly accessible 3-bromohesperetin derivative. Analytical data obtained for II include carbon-hydrogen, methoxyl, and molecular weight determinations (by two different methods), which indicates the molecular formula to be $C_{20}H_{16}O_8$. Acetyl analysis shows the presence of only two acetyl groups. Since II gives a positive ferric chloride test, the presence of a 5-hydroxyl group is strongly indicated (8). Absence of a distinct peak in the solid state infrared spectrum in the O-H stretching region also confirms this indication, since among 3',5-, and 7-hydroxyflavones, only 5-hydroxyflavone shows this spectral property (9). The infrared spectrum also contains the expected flavone and ester carbonyl bands.

The partial deacetylation procedure developed with I has been extended to 4',5-diacetoxyflavone (III) and apigenin triacetate (V). In both cases, products IV and VI resulting from selective deacetylation at the 5-position were obtained. The substances IV and VI gave positive ferric chloride tests. Their infrared spectra exhibit no distinct O-H stretching band, but do contain flavone and ester carbonyl bands. The crude deacetylation products II and VI were obtained in 58 and 25% yields respectively, and IV in 59% yield if a correction is made for recovered starting material.

A modified deacetylation procedure in which anhydrous sodium acetate is substituted for silver acetate resulted in a somewhat lower yield of II, as well as recovery of 50% of I and an unidentified

reddish-orange oil. Omission of the acetic anhydride from the silver acetate reaction mixture markedly lowers the yield, from 58% to 20%. In the latter instance other products were obtained, which apparently resulted from extensive deacetylation. The infrared spectrum of the mixture of such products, which shows strong broad general absorption in the 3600 to 2000 cm^{-1} region, indicates the presence of hydroxyl groups in addition to the one at the 5-position.



EXPERIMENTAL (10)

Diosmetin Diacetate (3',7-Diacetoxy-5-hydroxy-4'-methoxyflavone).

A mixture of 25 ml. of glacial acetic acid, 2.5 ml. of acetic anhydride, and 185 mg. of silver acetate, in an apparatus permitting protection from atmospheric moisture, was heated for four hrs. at 120° in an oil bath. Then 500 mg. of diosmetin triacetate was added and heating was continued for twenty hrs. The reaction mixture was cooled, precipitated silver acetate removed by filtration, and the filtrate evaporated to dryness under reduced pressure. Solution of the residue in hot ethanol with subsequent cooling gave 260 mg. (58%) of product, m.p. 203-205°. Two recrystallizations of the substance from acetone gave 200 mg. of diosmetin diacetate, m.p. 210-211°.

Anal. Calcd. for $C_{15}H_{10}O_5(OCH_3)_2$: C, 62.50; H, 4.20; $COCH_3$, 22.40; OCH_3 , 8.08; mol. wt. 384. Found: C, 62.60, 62.32; H, 4.34, 4.21; $COCH_3$, 21.59; OCH_3 , 7.96; mol. wt. (Rast), 390, [Barger-Signer (11)], 371.

The infrared spectrum (potassium bromide disk) contained bands at 1765 (ester CO), 1755 (ester CO), and 1658 cm^{-1} (flavone CO). The chloroform solution spectrum contained the flavone CO band at 1655 cm^{-1} .

In ethanol solution, diosmetin diacetate gave a wine color with 1% ethanolic ferric chloride. With magnesium-ethanolic hydrochloric acid, an orange-yellow color resulted.

Diosmetin diacetate (30.49 mg.) was dissolved in 10 ml. of methanol and one drop of concentrated hydrochloric acid added. The solution was stored in an evacuated desiccator over potassium hydroxide until evaporated to dryness. The residue was dissolved in 10 ml. of hot methanol and poured quantitatively into 100 ml. of hot water. Cooling the mixture gave a precipitate, which was collected quantitatively in a sintered glass funnel and dried in a desiccator over concentrated sulfuric acid; mass, 24.08 mg. The weight loss on deacetylation is thus 21.7% (theory for the reaction, diosmetin diacetate to diosmetin, is 22.4%). Recrystallization of the precipitate from aqueous methanol gave diosmetin, m.p. 259-260°, with a change in crystal form at 230-240° (lit. (12) m.p., 253-254°). The ultraviolet spectrum was identical

with that previously reported for diosmetin (13). Diosmetin also was obtained from diosmetin diacetate upon treatment for ten min. with hot 1 N alcoholic potassium hydroxide and subsequent acidification.

Application of the deacetylation procedure described herein to quantities of starting material up to 2.0 g. gave similar yields of diosmetin diacetate. Similar yields also were obtained from isolation procedures involving only a non-hydroxylic solvent (acetone), or by chromatography of the benzene solution of the product on silicic acid-celite, with benzene-ethanol (100:1 v/v) being used as developer. Two moveable zones were obtained, of which the diosmetin diacetate band (orange) was the more mobile. The trailing moveable band was unreacted diosmetin triacetate, which was colorless under visible light but showed blue fluorescence under ultraviolet light.

4'-Acetoxy-5-hydroxyflavone.

A mixture of 25 ml. of acetic acid, 2.5 ml. of acetic anhydride, and 200 mg. of silver acetate was heated in oil bath at 120-130° for three hrs. in an apparatus protected from atmospheric moisture by a calcium chloride drying tube. Then 400 mg. of 4',5-diacetoxyflavone, m.p. 180-181°, was added, and heating continued sixteen hrs. The mixture then was cooled, filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved partially in 10 ml. of acetone and the insoluble fraction collected and recrystallized to give 130 mg. (59% based on 250 mg. of starting material) of substance m.p. 209-210°. A 150 mg. quantity of 4',5-diacetoxyflavone, m.p. 173-177°, was recovered by concentration of the mother liquor. One additional crystallization of the substance, m.p. 209-210°, gave 4'-acetoxy-5-hydroxyflavone as light yellow needles, m.p. 210.5-211°.

Anal. Calcd. for $C_{15}H_{10}O_4(COCH_3)$: C, 68.91; H, 4.08; CH_3CO , 14.50. Found: C, 68.44, 68.60; H, 4.22, 4.22; CH_3CO , 13.51.

The infrared spectrum (potassium bromide disk) contained bands at 1749 (ester CO) and 1659 cm^{-1} (flavone CO). 4'-Acetoxy-5-hydroxyflavone gave positive ferric chloride and magnesium-hydrochloric acid tests.

Apigenin Diacetate (4',7-Diacetoxy-5-hydroxyflavone).

Apigenin triacetate, m.p. 186-187° (500 mg.), was added to a mixture of 25 ml. glacial acetic acid, 2.5 ml. acetic anhydride, and 150 mg. of silver acetate, which had been maintained at 120° for four hrs. Heating was continued for fourteen hrs. Isolation of the crude deacetylation product as before gave a residue which was leached with 30 ml. of acetone to give 110 mg. (25%) of insoluble solid, melting 200-205°, with darkening at 186°. Two recrystallizations from acetone gave 30 mg. of apigenin diacetate, m.p. 205-206° (lit. (14) m.p., 203-204°).

Anal. Calcd. for $C_{15}H_{10}O_5(COCH_3)_2$: CH_3CO , 26.1; Found: CH_3CO , 25.7.

The infrared spectrum (potassium bromide disk) contained absorption bands at 1745 (ester CO) and 1649 cm^{-1} (flavone CO). Apigenin diacetate gave a wine color with alcoholic ferric chloride.

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- (3) Du Pont Postgraduate Teaching Assistant, 1956-57; Standard Oil of Indiana Foundation Fellow, 1957-58.
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