Bromination of Flavanones. III. Bromodeacetylation of Two Triacetoxyflavanones. Revised Configuration for a 3-Bromohesperetin Triacetate

James H. Looker, Myron J. Holm, Loren L. Braun, Sharad Kagal, and J. Woodson Mader

Department of Chemistry, The University of Nebraska, Lincoln, Nebraska 68508

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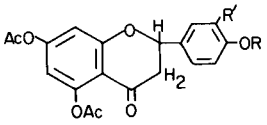
The bromination of hesperetin triacetate (Ia), resulting in 3-bromohesperetin triacetate (II), was reported several years ago (1). We attempted to assign configuration and conformation to II from chemical and infrared spectral data (2). The importance of removing product bromine in preparation of flavones from *N*-bromosuccinimide dehydrogenation of flavanones has been noted (3). In the present paper, we report a second product from the bromination of Ia, and the characterization of two products from the interaction of naringenin triacetate (Ib) with bromine in absolute chloroform. Nuclear magnetic resonance spectral data leading to a revised configurational assignment for II are included.

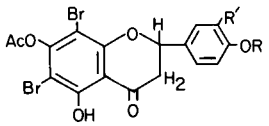
The second crystalline bromination product (IIIa) of Ia has been obtained in low yield, but consistently, from interaction of Ia with bromine in absolute chloroform or methylene chloride, and was purified by column chromatography on silicic acid. Analysis indicated the presence of two bromine atoms. The solution infrared spectrum contained a band at 1651 cm^{-1}, suggestive of a carbonyl group in either a flavone or a 5-hydroxyflavanone. A subsequent positive ferric chloride test indicated a free 5-hydroxyl group, and obvious hydrogen-bonding in a 5-hydroxyflavanone derivative. The solution infrared spectrum of an acetylation product of IIIa contained a band near 1700 cm^{-1}, indicative of a flavanone carbonyl. That IIIa is indeed a dibromoflavanone has been confirmed by nmr spectral data.

A one-proton quartet (2-H of flavanone) at δ 5.81 and a two-proton octet (methylene hydrogens) near δ 3.23 were observed. Similar peaks for Ia were located at δ 5.61 and δ 3.14 respectively. The spectrum of Ia contained two one-proton doublets at δ 6.65 and δ 6.83, with J = 2 Hz. Such a value is satisfactory for *meta*-coupling (4). These latter peaks accordingly originate from protons at 6- and 8-positions, and their absence in the spectrum of IIIa supports bromine atoms as substituents at 6- and 8-positions in the IIIa molecule. The ultraviolet spectrum is quite similar to that of 6,8-dibromohomoeriodictyol diacetate (5). Accordingly, on the basis of these combined infrared, nmr and ultraviolet spectral data, IIIa is formulated as 6,8-dibromohesperetin-3′,7-diacetate.

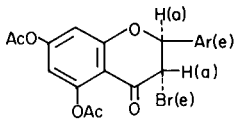
CHART I



Ia: R=CH_3; R′=OAc
Ib: R=Ac; R′=H

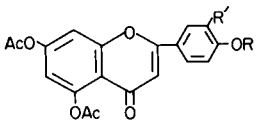


IIIa: R=CH_3; R′=OAc
IIIb: R=Ac; R′=H



II

Ar=3-Acetoxy-4-methoxyphenyl



IVa: R=CH_3; R′=OAc
IVb: R=Ac; R′=H

The reaction of naringenin triacetate (Ib) with bromine in absolute chloroform was more complex. By column chromatography there were obtained seven different substances, of which two were crystalline. Of the latter, one obtained in 3% yield was apigenin triacetate (IVb). It is evident that reaction of Ib with bromine is more complex than that in a bromine-excluded NBS procedure, from which IVb was obtained in 95% yield (3).

The second crystalline bromination product (IIIb) was obtained from Ib somewhat more conveniently in methylene chloride. Although IIIb was the major product, it was received in very modest yield. The substance was obtained initially by chromatographic procedures, but was prepared subsequently in reasonably pure state by crystallization techniques alone. Analytical data indicate the presence of two bromine atoms. The combined data of a strong band in the solution infrared spectrum at 1658 cm^{-1} and a positive ferric chloride test support IIIb as a 5-hydroxyflavanone. The nmr spectrum confirmed that IIIb is a flavanone, and the absence of one-proton aromatic peaks indicated the 6,8-substitution pattern for the bromine atoms. The uv spectrum of IIIb is very similar to that of IIIa. Accordingly, IIIb is considered to be 6,8-dibromonaringenin-4′,7-diacetate.

Upon interaction of 3-bromohesperetin triacetate (II)

with NBS at reflux temperature in carbon tetrachloride, dehydrogenation was not the major reaction path. Instead there was obtained in approximately 60% yield diosmetin triacetate (IVa), from apparent dehydrobromination of II. In a separate experiment, an analytical technique indicated the presence of product bromine in 75% yield, assuming sequential dehydrobromination and oxidation of hydrogen bromide by NBS. Although these steps seem reasonable possibilities, the present study is not sufficiently detailed to establish them as the only reaction paths, nor to permit evaluation of any mechanistic significance. In view of the revised configurational assignment to II (sequel), IVa would result from a *cis*-elimination process. The formation of IVa from II under silver ion catalysis in acetic anhydride has been previously observed (6).

In a previous study (2), infrared carbonyl bands of Ia and II were interpreted as supporting a conformation in which the 3-bromine atom was axial. We now have reinvestigated the configuration and conformation of II through nmr spectral data. An initial spectrum of II in dimethyl sulfoxide-d_6 proved anomalous, showing a sharp two-proton singlet at δ 5.72. However, a spectrum of a deuteriochloroform solution of II shows two one-proton peaks at δ 5.30 and δ 4.68, from proton resonances at $C_{(2)}$ and $C_{(3)}$ respectively, with $J_{2,3}$ = 8.8 Hz. These data establish not only that the bromine atom is at the 3-position, but also indicates that the hydrogen atoms at positions-2 and 3 are *trans*-diaxial (7-9). Accordingly, it is necessary to revise the previous configurational assignment (2) for II from a *cis*-configuration in which the bromine is axial, to a *trans*-configuration in which the halogen is equatorial. Although the small shift in the infrared $\nu_{C=O}$ is rather surprising, and cannot be correlated with the relatively large shifts observed in corresponding infrared carbonyl bands of equatorial α-bromocyclohexanones (10), an explanation has been advanced (7).

The DMSO-d_6 nmr spectrum of II apparently is an example of accidental magnetic equivalence of the chemically nonequivalent protons at positions-2 and 3. A similar case has been reported in the nmr spectrum of 3,5,7,2′,4′-pentaacetoxyflavanone (9).

In brief summary, the present work indicates that bromodeacetylation is a significant reaction path in the bromination of two triacetoxyflavanones. A *trans*-3-bromoflavanone undergoes apparent thermal dehydrobromination in the presence of *N*-bromosuccinimide.

EXPERIMENTAL (11)

6,8-Dibromohesperetin-3′,7-diacetate (IIIa).

Bromination of hesperetin triacetate with bromine in absolute chloroform was carried out as previously described (1,6). The product 3-bromohesperetin triacetate was removed by crystallization from ethanol. Partial evaporation and subsequent chilling of the mother liquors yielded a second crystalline fraction, which, however, resisted all purification attempts involving crystallization from ethanol or benzene.

Chromatography of 0.9 g. of this second bromination product, m.p. 170-184°, in benzene solution on silicic acid-Celite 535 (5:1 wt.) with development by benzene-ethanol (100:1 vol.) gave a chromatogram with two colored zones. The leading diffuse yellow zone was eluted from the column, collected by evaporation of the effluent solution and rechromatographed using the same general procedure. The bromination product, which crystallized from the effluent solution, was recrystallized repeatedly from benzene-isooctane and obtained as colorless needles, m.p. 202-203°.

Anal. Calcd. for $C_{20}H_{16}Br_2O_8$: C, 44.18; H, 2.97; Br, 29.32. Found: C, 44.28; H, 2.83; Br, 28.78.

The infrared spectrum (carbon tetrachloride) contained a band at 1651 cm^{-1} (H-bonded flavanone CO). Nmr peaks (DMSO-d_6) were present at δ 2.28 (3H singlet, acetoxyl), δ 2.42 (3H singlet, acetoxyl), δ 3.23 (center of 2H octet, methylene), δ 3.80 (3H singlet, methoxyl), δ 5.81 (center of 1H quartet, carbon-2 hydrogen), δ 7.1-7.52 (3H multiplet, aromatic), δ 12.70 (1H singlet, 5-hydroxyl).

The ultraviolet spectrum (1.95 mg. per 100 ml. of 95% ethanol solution) showed absorption maxima at 227 nm (ϵ 36.8 x 10^3), 276 nm (ϵ 12.9 x 10^3), and 356 nm (ϵ 4.94 x 10^3). In alcoholic solution, the substance gave a brownish color with ferric chloride solution.

Acetylation of 100 mg. of 6,8-dibromohesperetin-3′,7-diacetate in 0.8 ml. acetic anhydride containing three drops of pyridine overnight at room temperature, isolation of acetylation product upon admixture with ice-water, and four recrystallizations from 95% ethanol gave the triacetate, m.p. 175.5-180°. The infrared spectrum of its methylene chloride solution contained a strong band at 1700 cm^{-1} (flavanone CO).

6,8-Dibromonaringenin-4′,7-diacetate.

A solution of 1.00 g. (2.51 millimoles) of naringenin triacetate, m.p. 117-119°, in 14 ml. of methylene chloride was placed in an ultraviolet-transmitting flask (Vycor). The mixture was cooled strongly in ice and irradiated with a Hanovia Model 30600 quartz-mercury vapor lamp while a solution of 0.4 g. (2.5 millimoles) of bromine in 6 ml. of methylene chloride was added all at once. After irradiation for 20 minutes, with cooling as necessary to maintain temperature below 20°, the bromine color had disappeared. Irradiation was continued 20 minutes. The mixture then was washed three times with water, the solvent removed under reduced pressure, and the residual solid crystallized twice from absolute ethanol, yield, 170 mg., m.p. 184-189°. After several additional crystallizations, analytically pure 6,8-dibromonaringenin-4′,7-diacetate was obtained as pale yellow crystals, m.p. 192-194.5°.

Anal. Calcd. for $C_{19}H_{14}Br_2O_7$: C, 44.39; H, 2.74; Br, 31.09. Found: C, 44.58; H, 2.70; Br, 31.29.

The infrared spectrum (methylene chloride) contained a band at 1658 cm^{-1} (H-bonded flavanone CO). Nmr peaks (deuteriochloroform) were present at δ 2.31 (3H singlet, acetoxyl), δ 2.42 (3H singlet, acetoxyl), δ 3.02 (1H incompletely resolved doublet, methylene), δ 3.16 (1H doublet, methylene), δ 5.60 (center of 1H quartet, carbon-2 hydrogen), and δ 7.37 (center of 4H multiplet, aromatic). In alcohol solution, the compound gave an olive color with aqueous ferric chloride solution.

The ultraviolet spectrum (2.48 mg. per 100 ml. of 95% ethanol solution) contained absorption maxima at 220 nm (ϵ 40.5 x 10^3), 275 nm (ϵ 13.2 x 10^3), and 356 nm (ϵ 5.85 x 10^3).

The bromination products of naringenin triacetate also were

examined chromatographically. Bromination was effected as previously described (6). The bromination products in benzene solution were chromatographed on silicic acid-celite (5:1 wt.) and developed with benzene-ethanol (100:1 vol.). 6,8-Dibromonaringenin-4′,7-diacetate was obtained as the leading, most mobile band in 24% yield. After repeated crystallization from benzene-isooctane, the substance melted at 199-200°. Apigenin triacetate, m.p. and mixture m.p. 181-183°, was obtained as the fourth fraction eluted from the column. Other fractions were not crystalline.

Reaction of 3-Bromohesperetin Triacetate with NBS.

A 200 mg. quantity (0.393 millimole) of 3-bromohesperetin triacetate was placed in 80 ml. of carbon tetrachloride and 70 mg. (0.393 millimole) of *N*-bromosuccinimide added. The mixture was heated under reflux for 150 minutes. The solvent then was removed *in vacuo*, and the residual solid washed well with water. Recrystallization from absolute ethanol gave 100 mg. (59%) of diosmetin triacetate, m.p. 191-194° [lit. (12) m.p. 195-196°]. Admixture with authentic diosmetin triacetate caused no m.p. depression.

3-Bromohesperetin Triacetate. Spectral Data.

Bromination of hesperetin triacetate in dry methylene chloride was more convenient than the previously described bromination in extremely pure absolute chloroform (6). Dropwise addition of bromine was essential, inasmuch as addition of bromine all at once caused 6,8-dibromohesperetin diacetate to be the predominant product.

In DMSO-d_6, the nmr spectrum contained two peaks near δ 2.25 (integrating for nine protons of the three acetoxyl groups), a peak at δ 3.72 (3H singlet, methoxyl), one at δ 5.72 (2H singlet, an anomalous singlet associated with proton resonances at $C_{(2)}$ and $C_{(3)}$), two peaks at δ 6.72 (1H doublet, J = 2) and δ 6.88 (1H doublet, J = 2) from resonances involving protons at $C_{(6)}$ and $C_{(8)}$, and peaks from δ 7.02-7.44 (3H multiplet, aromatic protons at $C_{(2')}$, $C_{(5')}$, and $C_{(6')}$.

In deuteriochloroform, the nmr spectrum was markedly similar to that in DMSO-d_6 with exception of the important proton resonances at positions-2 and 3 of the flavanone. Thus, peaks were present at δ 4.68 (1H doublet, $C_{(3)}$ proton, J = 8.8) and at δ 5.30 (1H doublet, $C_{(2)}$ proton, J = 8.8). Other peaks were shifted downfield slightly from corresponding peaks in the DMSO-d_6 spectrum.

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(11a) Partial support of this work through a grant (AI-01703) from the U. S. Public Health Service is gratefully acknowledged. (b) Infrared spectra were recorded on a Perkin-Elmer model 21 or 621 spectrophotometer. Nmr spectral data were obtained with a Varian Model A60 spectrometer, using tetramethylsilane as internal standard. Deuteriochloroform solutions were warmed gently if necessary to effect complete solution. The nmr spectrum of DMSO-d_6 neat contained impurity peaks near δ 2.50, necessitating an appropriate correction of DMSO-d_6 spectra.

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