Chemistry of Dihydroquercetin. II. Reaction of Partially Acetylated Polyhydroxyflavanones with N-Halosuccinimides

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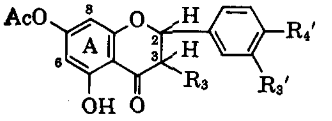
The reactions of partially acetylated polyhydroxyflavanones of natural occurrence with N-bromo- and N-iodosuccinimide were investigated as a synthetic method for the preparation of halogenated flavanone derivatives. One molar equivalent of NBS led to formation of the corresponding flavone ester, while 2 moles gave mixtures of mono- and dibromoflavanone and -bromoflavone esters. One and two molar equivalents of NIS gave only the mono- and diiodoflavanone esters. Certain product–flavanone structure relationships regarding the site of molecular reaction are described.

Conversion of fully acetylated polyhydroxyflavanones to the corresponding flavone esters in almost quantitative yield using N-bromosuccinimide (NBS) has been reported recently.[1] The reaction sequence proposed involves bromination at the 2- or 3-position in the dihydro-γ-pyrone ring *via* a free-radical mechanism and subsequent dehydrobromination to yield the flavone ester.

The 7-glycosides of these same polyhydroxyflavanones, having a phenolic hydroxyl group in the 5-position, reacted with NBS under the same conditions to yield a mixture of the corresponding flavone glycoside and brominated compounds, the nature of which were not determined.[2,3] Dimethyl and diethyl ethers of 5,7-dihydroxyflavanone react with NBS to give the 8-bromoflavanone and 8-bromoflavone ethers, the composition of the product mixture being dependent upon the molar equivalent of NBS employed. One mole gives primarily the 8-bromoflavanone ether; 2 moles results in a predominance of the 8-bromoflavone ether.[4,5] Thus retention of phenolic activity in the A-ring of 5,7-dihydroxyflavanones leads to bromination of this ring in preference to the dihydro-γ-pyrone ring.

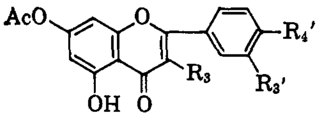
For the preparation of a series of acetylated halogen derivatives of naturally occurring polyhydroxyflavanones (having hydroxyl groups in the 5- and 7-positions), desired for fungicidal studies[6] and as synthetic intermediates, the simplest and most direct synthetic route appeared to be the reaction of NBS with the partial acetate esters of these polyhydroxyflavanones. In these partial esters, recently characterized,[7] the 5-hydroxyl group remains unesterified, thereby retaining the phenolic character of the A-ring. Examination of the reaction of these esters with N-halosuccinimides was therefore undertaken.

The partial acetate esters of naringenin (4′,5,7-trihydroxyflavanone), hesperetin (4′-methoxy-3′,5,7-trihydroxyflavanone), homoeriodictyol (3′-methoxy-4′,5,7-trihydroxyflavanone), and dihydroquercetin (3,3′,4′,5,7-pentahydroxyflavanone), Ia, Ib, Ic, and Id, respectively, were prepared by room temperature reaction with acetic anhydride.[7] Analytical data, yield, and ultraviolet spectral data are presented in Table I. The identity of the ultraviolet spectra of these flavanone esters is consistent with an earlier observation[7] that variation in substitution in the side phenyl ring or at the 3-position has little effect on their spectra.

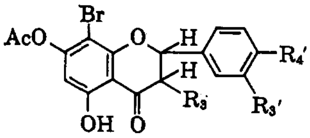


Ia, $R_3 = R_3' = H$; $R_4' = OAc$
b, $R_3 = H$; $R_4' = OCH_3$; $R_3' = OAc$
c, $R_3 = H$; $R_3' = OCH_3$; $R_4' = OAc$
d, $R_3 = R_3' = R_4' = OAc$

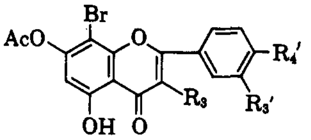
The reaction of Ia, Ib, and Ic with 1 mole of NBS under the conditions employed in the earlier studies,[4,5] using carbon tetrachloride in the presence of catalytic amounts of benzoyl peroxide, gave the corresponding flavone esters, IIa, IIb, and IIc in excellent yield (Table II); no other product was isolated. Dihydroquercetin tetraacetate (Id), however, gave a mixture of products from which, by fractional crystallization, were isolated the 8-bromo derivative IIId as the major product and a smaller amount of 8-bromoquercetin tetraacetate (IVd, the corresponding bromoflavone). Physical data for these bromo compounds are presented in Table III.



IIa, b, and c



IIId



IVa and d

This difference in products strongly suggests that the 3-position carbon of the dihydro-γ-pyrone ring is the site of attack by the brominating species. Since this carbon atom in Id holds an acetoxyl group, in contrast to the methylene carbon in Ia, Ib, and Ic, attack at this position must be slowed to the extent that A-ring bromination predominates. However, since some of the bromoflavone ester is also present, it must mean either that some bromination of this position still does occur, or that the 2-position carbon may also undergo bromination slowly and with subsequent dehydrobromination gives the flavone ester.

Acid hydrolysis[8] of the reaction products of Ia, Ib, and Ic gave only a single compound, shown by paper chromatographic analysis, in each instance, identical

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[1] J. H. Looker and M. J. Holm, *J. Org. Chem.*, **24**, 567 (1959).

[2] N. B. Lorette, T. B. Gage, and S. H. Wender, *ibid.*, **16**, 930 (1951).

[3] R. M. Horowitz, *ibid.*, **21**, 1184 (1956).

[4] T. S. Chen, Y. S. Lin, and F. C. Chen, *Formosan Sci.*, **16**, 31 (1959).

[5] C. T. Chang, *ibid.*, **16**, 117 (1962).

[6] K. Nishida, T. Kondo, and K. Funaoka, *J. Japan. Forestry Soc.*, **33**, 390 (1951).

[7] H. Aft, *J. Org. Chem.*, **26**, 1958 (1961).

[8] V. Deulofeu and N. Schopflocher, *Gazz. chim. ital.*, **83**, 449 (1953).

TABLE I

ACETATE ESTERS OF POLYHYDROXYFLAVANONES

Compd.	M.p., °C.	Yield, %	% C Calcd.	% C Found	% H Calcd.	% H Found	% acetyl Calcd.	% acetyl Found	Ultraviolet spectra, mμ λ_{max} (log ε)	Ultraviolet spectra, mμ λ_{min} (log ε)
Ia ($C_{19}H_{16}O_7$)	145.5–146	79	64.04	63.64	4.52	4.22	24.15	24.19	276 (4.10) 340 (3.59)	245 (3.39) 304 (3.28)
Ib ($C_{20}H_{18}O_8$)	102.5–103[a]	52	62.17	62.16	4.69	4.39	22.28	22.14	275 (4.15) 339 (3.54)	245 (3.52) 305 (3.20)
Ic ($C_{20}H_{18}O_8$)	129.5–130	62	62.17	62.19	4.69	4.71	22.28	22.95	276 (4.17) 339 (3.54)	245 (3.40) 305 (3.23)
Id ($C_{23}H_{20}O_{11}$)	153–154[b]	45							277 (4.13) 340 (3.57)	245 (3.39) 307 (3.35)

[a] M.p. 103–105°, M. Simokoriyama, *Bull. Chem. Soc. Japan*, **16**, 284 (1941). [b] See ref. 7.

TABLE II

ACETATE ESTERS OF POLYHYDROXYFLAVONES

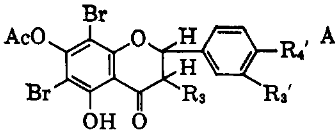
Compd.	M.p., °C.	Yield, %	% C Calcd.	% C Found	% H Calcd.	% H Found	% acetyl Calcd.	% acetyl Found	Ultraviolet spectra, mμ λ_{max} (log ε)	Ultraviolet spectra, mμ λ_{min} (log ε)	M.p. of acetate, °C.
IIa ($C_{19}H_{14}O_7$)	202–203[a]	75	64.41	63.85	3.98	4.14	24.29	23.41	271 (4.42) 301 (4.21) ~331 (4.02)	241 (3.88) 293 (4.19)	181–182[b]
IIb ($C_{20}H_{16}O_8$)	209–210	70	62.50	62.68	4.19	4.18	22.39	21.61	271 (4.27) 324 (4.35)	250 (4.02) 292 (4.07)	195–196[c]
IIc ($C_{20}H_{16}O_8$)	176–177	70	62.50	62.46	4.19	4.25	22.39	22.83	243 (4.45) 272 (4.36) 324 (4.16)	235 (4.19) 252 (4.16) 295 (4.08)	198–199[d]

[a] M.p. 203–204°, S. Heitz and C. Mentzer, *Compt. Rend.*, **252**, 4214 (1961). [b] M.p. 181–182°, M. K. Seikel, *J. Am. Chem. Soc.*, **77**, 5685 (1955). [c] M.p. 195–196°, A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 817 (1930). [d] M.p. 198–199°, F. Tutin and H. W. B. Clewer, *ibid.*, **95**, 81 (1909).

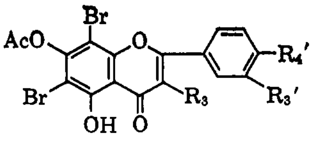
with authentic samples of apigenin, diosmetin, and chrysoeriol, respectively (IIa, IIb, and IIc where OAc is now OH). Acetylation of these reaction products with acetic anhydride at 100° gave compounds whose melting points (Table II) and ultraviolet spectra agree with those reported for the fully acetylated flavones.[9] Furthermore, the ultraviolet spectra of each of the reaction products is consistent for that of the partial acetate ester of the flavone corresponding to each of the three flavanones.[9]

Reaction of the esters Ia, Ic, and Id with 2 molar equiv. of NBS resulted, in each instance, in mixtures of brominated products. Acid hydrolysis[8] and paper chromatographic analysis of the crude reaction mixture obtained from each flavanone ester showed the presence of at least three compounds, none of which appeared to be the corresponding nonbrominated flavone.

By fractional crystallization of the crude reaction products obtained from these three esters, the 8-bromoflavone esters (IV), 6,8-dibromoflavanone esters (V), and 6,8-dibromoflavone esters (VI) were isolated. Analytical and spectral data for these brominated compounds are presented in Table III.



Vc and d



VIa and c

Assignment of structure to the brominated compounds obtained from these reactions was made on the basis of their ultraviolet spectra. The spectra of the mono and dibromo compounds IIId and Vd have retained the spectral character of the flavanone esters, *i.e.*, absorption curve shape and extinction coefficient values at absorption maxima. However, in the spectrum of each of these compounds there is a consistent bathochromic displacement of the second absorption maximum from that of the parent flavanone ester Id (340 mμ), IIId (348 mμ), and Vd (359 mμ), as well as a slight bathochromic displacement of the parent 275-mμ maximum in Vd. Since the spectral data in Table I indicate that only A-ring substitution could materially affect the spectra of flavanone esters, this consistent displacement in the spectra of these compounds may, most reasonably, be attributed to consistent mono- and dibromination of this ring. The dibromo compound Vd may thus be assigned the 6,8-dibromoflavanone ester structure. The compound Vc, despite differences in side phenyl-ring substitution which could affect the reactivity of this ring to further substitution, has a spectrum almost identical with that of Vd. The only reaction sites common to both flavanone esters which could account for the absorption maxima displacement are the 6- and 8-positions.

In the spectra of the flavone esters (Table II) there is a consistent absorption maximum at 271–272 mμ, which has been attributed to the resonating system of the A-ring carbonyl moiety.[9] (Note a corresponding maximum at 275 mμ in the spectra of the flavanone esters.) Assignment of the 6,8-dibromo structure to the dibromo compounds having the general spectral character of the corresponding flavone ester (curve shape and extinction coefficient values) was made on the basis of the bathochromic displacement of this absorption maximum to 284 (VIa) and 281 mμ (VIc).[10]

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(9) L. Jurd, "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., The Macmillan Co., New York, N. Y., 1962, p. 107.

(10) A corresponding displacement of this maximum is observed in the spectra of other 6,8-dihaloflavone esters: the 6,8-diiodoflavone esters IXa and b (Table IV) and 6-bromo-8-iodoflavone ester XIa (Table V).

TABLE III

ACETATE ESTERS OF BROMOFLAVONOID COMPOUNDS

Compd.	M.p., °C.	Yield, g.[a]	% C		% H		% Br		Ultraviolet spectra, mμ	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	λ_{max} (log ε)	λ_{min} (log ε)
IIId ($C_{23}H_{19}BrO_{11}$)	144–145	0.3	50.11	49.95	3.47	3.64	14.49	14.73	275 (4.11) 348 (3.63)	251 (3.79) 314 (3.42)
IVd ($C_{23}H_{17}BrO_{11}$)	164–165	0.1[b] 0.3[c]	50.29	50.65	3.12	3.24	14.50	15.02	272 (4.48) ~302 (4.21) ~340 (3.97)	245 (4.09)
IVa ($C_{19}H_{13}BrO_7$)	182–183	0.15	52.67	51.23	3.02	2.98	18.45	19.85	275 (4.43) ~303 (4.23) ~335 (4.01)	244 (3.94)
Vc ($C_{20}H_{16}Br_2O_8$)	166.5–167	0.14	44.14	44.40	2.96	2.91	29.37	29.42	278 (4.16) 357 (3.72)	252 (3.79) 308 (3.26)
Vd ($C_{23}H_{18}Br_2O_{11}$)	203–204	0.13	43.83	43.85	2.87	3.02	25.36	25.36	278 (4.13) 359 (3.68)	251 (3.81) 326 (3.43)
VIa ($C_{19}H_{12}Br_2O_7$)	243.5– 244.5	0.3	44.55	44.31	2.36	2.81	31.21	31.93	284 (4.43) ~312 (4.23) ~342 (3.99)	247 (3.95)
VIc ($C_{20}H_{14}Br_2O_8$)	227.5–228	0.5	44.30	44.68	2.60	3.04	29.48	28.17	~235 (4.16) 281 (4.32) 330 (4.15)	246 (4.08) 309 (4.07)

[a] In grams from reaction of 1 g. of parent flavanone ester. [b] From 1-mole NBS reaction. [c] From 2-mole NBS reaction.

TABLE IV

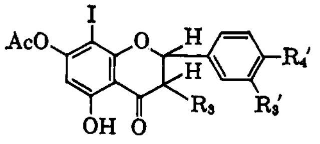
ACETATE ESTERS OF IODOFLAVONOID COMPOUNDS

Compd.	M.p., °C.	Yield, %	% C		% H		% I		Ultraviolet spectra, mμ	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	λ_{max} (log ε)	λ_{min} (log ε)
VIIa ($C_{19}H_{15}IO_7$)	142–143	43	47.32	46.70	3.13	3.26	26.31	27.35	278 (4.00) 355 (3.59)	258 (3.74) 309 (3.04)
VIIb ($C_{20}H_{17}IO_8$)	90.5–91	41	46.89	47.00	3.35	3.40	24.77	24.65	277 (4.07) 352 (3.68)	256 (3.91) 309 (3.28)
VIId ($C_{23}H_{19}IO_{11}$)	113–114	39	46.17	45.76	3.20	3.16	21.21	20.90	279 (4.02) 355 (3.58)	259 (3.89) 316 (3.36)
VIIIa ($C_{19}H_{14}I_2O_7$)	209–210	41	37.53	37.46	2.32	2.49	41.74	41.44	285 (3.96) 365 (3.67)	263 (3.75) 314 (2.97)
VIIIb ($C_{20}H_{16}I_2O_8$)	198.5–199.5	40	37.64	37.56	2.53	2.55	39.77	39.34	280 (4.03) 364 (3.68)	262 (3.86) 312 (3.11)
VIIId ($C_{23}H_{18}I_2O_{11}$)	200–201	42	38.14	38.13	2.51	2.35	35.05	34.30	286 (3.99) 366 (3.65)	263 (3.81) 318 (2.99)
IXa ($C_{19}H_{12}I_2O_7$)	237.5–239	80	37.65	37.69	1.99	2.04	41.87	41.60	288 (4.49) ~320 (4.18) ~340 (3.87)	254 (4.12)
IXb ($C_{20}H_{14}I_2O_8$)	246–247	58	37.75	37.77	2.21	2.31	39.90	38.98	229 (4.48) 282 (4.27) 307 (4.30) 332 (4.44)	221 (4.45) 256 (4.02) 290 (4.26) 310 (4.30)

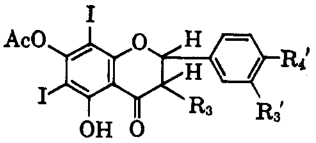
Isolation of the 6,8-dibromoflavanone ester Vc as a product of the reaction of Ic with 2 moles of NBS is particularly interesting since the 1-mole NBS reaction of this ester gave only the flavone ester IIc. Apparently, in the presence of an excess of the brominating species, A-ring bromination becomes competitive with the bromination of the dihydro-γ-pyrone ring.

Use of N-iodosuccinimide (NIS) as a halogenating reagent has not been extensive. It has been reported,[11] however, that NIS showed no free-radical activity and that the iodination reaction discussed proceeded *via* an ionic mechanism.

Treatment of Ia with 1 mole equiv. of NIS in either dry dioxane[11] or carbon tetrachloride in the absence of benzoyl peroxide gave no reaction. However, in the presence of catalytic amounts of benzoyl peroxide, iodination did occur and the 8-iodoflavanone ester VIIa was isolated. Similar reactions were undergone by Ib and Id. Use of 2 mole equiv. of NIS under identical conditions gave the 6,8-diiodoflavanone esters VIII. Analytical and spectral data for these reaction products are presented in Table IV. That diiodination of the A-ring has occurred giving the 6,8-diiodoflavanone esters as the products of this reaction is indicated by the identity of the spectra of these diiodo compounds despite molecular variations in methoxyl and acetoxyl substitution, and retention of the spectral character of the flavanone esters with the consistent bathochromic displacement of absorption maxima and minima from those observed in the parent and monoiodoflavanone esters.



VIIa, b, and d



VIIIa, b, and d

In all instances, the only products isolated were the 8-iodo- and 6,8-diiodoflavanone esters. During the

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(11) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **75**, 3493 (1953).

TABLE V

ACETATE ESTERS OF BROMOIODOFLAVONOID COMPOUNDS

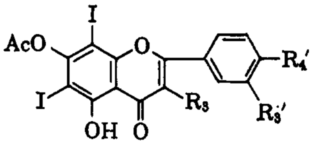
Compd.	M.p., °C.	Yield, %	% C Calcd.	% C Found	% H Calcd.	% H Found	% acetyl Calcd.	% acetyl Found	Ultraviolet spectra, mμ λ_{max} (log ε)	Ultraviolet spectra, mμ λ_{min} (log ε)
Xa ($C_{19}H_{14}BrIO_7$)	195–196	53	40.66	40.44	2.51	2.30	15.34	14.33	282 (4.13) 358 (3.69)	258 (3.83) 332 (3.52)
Xb ($C_{20}H_{16}BrIO_8$)	197.5–198.5	50	40.63	40.63	2.73	3.03	14.56	14.74	280 (4.04) 357 (3.73)	258 (3.80) 311 (3.39)
XIa ($C_{19}H_{12}BrIO_7$)	237.5–238	62	40.81	40.93	2.16	2.16	15.39	15.60	288 (4.51) ~315 (4.28) ~344 (3.99)	250 (4.10)

course of the reaction there was no evolution of hydrogen iodide from the refluxing mixture, which would indicate dihydro-γ-pyrone-ring iodination and subsequent dehydroiodination to give the flavone ester, as was found with NBS.

Fully acetylated derivatives of Ia, Ib, and Id did not react with 1 or 2 mole equiv. of NIS under identical reaction conditions. NBS, on the other hand, does react with these esters[1] to give the corresponding flavone esters by bromination of the dihydro-γ-pyrone ring and subsequent dehydrobromination. Apparently, the iodinating species from NIS does not attack the dihydro-γ-pyrone ring in reaction with these flavanone esters.

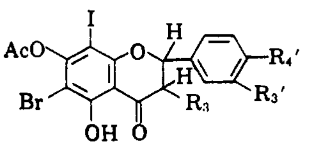
Some indication that the iodination reaction of NIS with esters of phenolic compounds may be subject to limitations of phenolic reactivity also was noted. Resacetophenone monoacetate (4-acetoxy-2-hydroxyacetophenone) did not react with 2 moles of NIS under conditions of reaction in which the flavanone esters Ia, Ib, and Id were iodinated.

Reaction of the 6,8-diiodoflavanone esters VIIIa and b with 1 mole equiv. of NBS gave the corresponding diiodoflavone esters IXa and b in good yield. Analytical and spectral data for these compounds also are presented in Table IV.

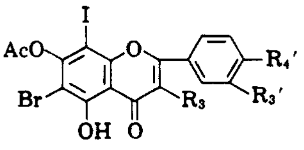


IXa and b

Attempted conversion of the 8-iodoflavanone esters VIIa and b to the corresponding 8-iodoflavone esters, again using 1 mole equiv. of NBS under identical conditions, gave instead, the 6-bromo-8-iodoflavanone esters (Xa and b) as the major products of reaction. Bromination of the A-ring in the 6-position is indicated by the spectral similarity of the two products, retention of the absorption characteristics of flavanone esters, and the slight bathochromic displacement of the absorption maxima from those observed in the spectra of the 8-iodoflavanone esters VIIa and b. Analytical and spectral data for these compounds are presented in Table V. During the course of these reactions, no hydrogen bromide was evolved, which would ordinarily signal formation of the flavone ester. Thus, in contrast to the reactions of the esters Ia and Ib with 1 mole equiv. of NBS which gave the corresponding flavone esters IIa and b, the presence of the iodine substituent in the A-ring has altered the site of reaction of the brominating species from the dihydro-γ-pyrone ring to the A-ring. This alteration of reaction site also is suggested by the isolation of the 6,8-dibromoflavanone ester Vc, as one product of the reaction of the flavanone ester Ic with 2 mole equiv. of NBS.



Xa and b



XIa

Subsequent treatment of the 6-bromo-8-iodoflavanone Xa with 1 mole equiv. of NBS gave the corresponding flavone ester XIa in good yield. This compound is also described in Table V.

Experimental

Materials.—The hydroxyflavanones, naringenin and hesperetin, were obtained from Aldrich Chemical Co.; homoeriodictyol was obtained from Bios Chemical Co. Dihydroquercetin was obtained from Douglas fir (*Pseudotsuga menziesii*) bark.[7] N-bromo- and N-iodosuccinimides were obtained from Arapahoe Chemical Co. Reagent grade benzoyl peroxide and solvents were used; the carbon tetrachloride was redistilled prior to use.

Analyses.—Melting points were determined on a Fisher-Johns melting point apparatus and are not corrected. Microanalyses were performed by Pascher and Pascher, Bonn, West Germany. All ultraviolet spectra were measured in 95% ethanol with a Cary recording spectrophotometer. In the paper chromatographic analyses, Whatman No. 1 paper was used in the descending technique. Solvents employed were acetic acid–water (6:1 v./v.), and butanol–acetic acid–water (4:1:5, upper layer). Detection agents used were ultraviolet light, bisdiazotized benzidine, and ferric chloride–potassium ferricyanide.

Partial Acetate Esters of the Polyhydroxyflavanones (Ia, b, c, and d).—These esters were prepared by room-temperature reaction of the flavanone with acetic anhydride and pyridine as described earlier.[7] Recrystallization from ethanol–water three to four times gave the pure esters as colorless or white glistening needles. Prior to further use, these esters always were dried *in vacuo* over potassium hydroxide pellets.

Reaction of the Flavanone Esters with N-Halosuccinimides.—The reactions of the flavanone esters with both NBS and NIS were performed under conditions as nearly identical as possible. Therefore, a typical reaction, with appropriate descriptions of variations in procedure where these were warranted because of differences in individual reactions, will be described in each instance.

Reaction of Ia with 1 Mole of NBS.—One gram (0.0028 mole) of Ia, 0.5 g. of NBS (0.0028 mole), and 10–15 mg. of benzoyl peroxide were added to 100 ml. of carbon tetrachloride. The mixture was heated to reflux, during which time most of the ester and NBS dissolved. The solution darkened almost immediately, becoming a deep red-brown within 5–10 min. after reflux began.[12] At this point, the color began to fade rapidly and hydrogen bromide (HBr) was evolved copiously. Reflux was continued until evolution of HBr ceased and succinimide was noted floating throughout the solution, now yellow-green in color. Generally from 60 to 90 min. of refluxing brought the reaction to this point. The solution was then filtered, still hot,

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[12] A similar development in color has been described in the course of reaction of the fully acetylated flavanone ester with 2 moles of NBS by Looker and Holm.[1]

and the carbon tetrachloride was removed on a steam bath under a gentle stream of air. The residue, generally a light brownish green, was washed with water and recrystallized from acetone–methanol–water (solution of the residue in the minimum amount of boiling acetone, addition of 2–3 vol. of boiling methanol, treatment with Norit and filtration, reheating to boil to redissolve any separated solid, and addition of a few drops of hot water). Five recrystallizations gave 0.75 g. (75% theoretical yield) of the pure flavone ester, shining light yellow-green needles, m.p. 202–203°. No other product was obtained by work-up of the mother liquors.

A similar procedure and sequence in development of color was observed in the reaction of Id. However, the crop of material recovered from the first recrystallization was so small that a second crop of material from the mother liquor was obtained by flooding with water. Recrystallization of both crops then was made from ethanol–water. After six recrystallizations, the two compounds, IIId and IVd, described in Table III, were obtained. Crop 1, about 100 mg., small light yellow-green needles, was IVd, and crop 2, 0.4 g., fine off-white needles, was IIId.

Hydrolysis of the Polyhydroxyflavone Esters IIa, b, and d.—IIa (200 mg.) was refluxed with 35 ml. of concentrated hydrochloric acid for 1 hr. The solution was cooled to room temperature and 40 ml. of cold water was added. The mixture then was refrigerated until no further solid separated (generally 12–16 hr.). The solid was collected by filtration and recrystallized three times from acetone–methanol–water, giving about 100 mg. of yellow-green microcrystals. The material was identical with an authentic sample of apigenin (4′,5,7-trihydroxyflavone) both spectrally and chromatographically.

Acetylation of the Partial Esters of the Polyhydroxyflavones IIa, b, and d.—IIa (300 mg.), 5 ml. of acetic anhydride, and 60 mg. of anhydrous sodium acetate were heated on a steam bath for 3 hr. The reaction mixture was flooded with cold water (about 200 ml.), and refrigerated for 12–16 hr. The solid collected by filtration was recrystallized five times from ethanol–water giving 0.3 g. of fine white needle crystals, m.p. 181–182° (Table II).

Reaction of Ia with 2 Moles of NBS.—Ia (1 g., 0.0028 mole), 1 g. of NBS (0.0056 mole), 10–15 mg. of benzoyl peroxide, and 100 ml. of carbon tetrachloride were refluxed together for 1 hr. A sequence of events in the reaction similar to that of the 1 mole of NBS reaction was observed. Work-up of the reaction mixture was identical with that described for the 1 mole of NBS reaction. Recrystallization from acetone–methanol–water gave two crops of material, the second by the further addition of water to the mother liquor from crop I. Five to six recrystallizations of both crops from acetone–methanol–water gave the two compounds, IVa and VIa, described in Table III. Crop 1 (VIa), about 0.3 g., was obtained as bright yellow, fine small needles, and crop 2 (IVa), as greyish green needles.

Similar recovery was made from the reactions of Ic and Id with 2 moles of NBS, with the exception that in both instances, the second crop of material (Vc and Vd, respectively) was recrystallized from methanol–water.

Hydrolysis[8] of the crude reaction solid and chromatography of the crude hydrolysis products of Ia, Ic, and Id showed the presence of at least three compounds (spots) in each mixture, none of which had R_f values identical with the flavone corresponding to each flavanone.

Reaction of Ia with NIS.—The reactions of Ia, Ib, and Id with both 1 and 2 molar quantities of NIS were run identically. One gram of each flavanone ester, the corresponding molar equivalent weight of NIS, 15–20 mg. of benzoyl peroxide, and 100 ml. of carbon tetrachloride were refluxed together. The reactions with 1 mole of NIS were refluxed for 8 hr., during which time the NIS slowly disappeared from the bottom of the reaction vessel and the color of the solution developed to a dark blue-black color. At the end of this reflux period, all the white solid material had disappeared and a dark brown crust had formed on the walls of the flask at the liquid level. In reactions with 2 moles of NIS, a reflux period of 12–16 hr. was required to reach this reaction point. At no time during the course of these reactions was there any evolution of hydrogen iodide. The solution then was filtered, while still hot, and the solid was washed with a small amount of boiling carbon tetrachloride. The combined filtrates were evaporated on a steam bath under a gentle stream of air, leaving a dark brown solid residue. This residue was recrystallized; the products of the 1 mole of NIS reaction, from ethanol–water five to six times, and the products of the 2 moles of NIS reaction, from acetone–methanol–water a similar number of times. The monoiodoflavanone esters VIIa, b, and d were generally light yellow-green microcrystals, the diiodoflavanone esters VIIIa and b were bright yellow platelets, while VIIId was light yellow-green needles. The yields from these recrystallizations generally ran from 25 to 30% of theoretical; however, work-up of the mother liquors from the recrystallizations gave additional product, generally bringing the total yield to 40–45% of theoretical.

Reaction of Diiodoflavanone Esters VIIIa and b with NBS.—These reactions were run identically with that described for the reaction of the flavanone esters Ia, b, c, and d with a molar equivalent of NBS. The sequence of events, development of color, evolution of HBr, and separation of succinimide, again were observed during refluxing. The residue left after evaporation of the carbon tetrachloride again was recrystallized from acetone–methanol–water; a large volume of acetone (about 150 ml.) was required for solution of the solid. From one-half to one-third volumes of boiling methanol and a few drops of water were added. Four to five recrystallizations gave the diiodoflavone esters IXa and b as bright canary yellow platelets. Again, work-up of the mother liquors gave additional pure product.

Reaction of Monoiodoflavanone Esters VIIa and b with NBS.—The procedure employing 1 mole of NBS again was followed. As refluxing proceeded, the solution darkened in color from a light yellow-green to an intense blue-black. No evolution of HBr was detected. After 4 hr. of refluxing, no NBS was visible in the reaction solution and no changes in color had occurred. Refluxing was stopped and the solution was worked up as previously described. The brown residue, recrystallized from acetone–methanol–water (as for the diiodoflavanone esters) from five to six times gave bright yellow microcrystals (Xa and b). Work-up of the mother liquors gave additional product.

The bromoiodoflavanone ester Xa (0.2 g., 0.00036 mole) again was treated with a molar equivalent weight of NBS (0.063 g.) and 10–15 mg. of benzoyl peroxide in 30 ml. of carbon tetrachloride. Reaction was complete after 30 min. of refluxing, as indicated by change in color of the solution, cessation in evolution of HBr and separation of succinimide from solution. The residue, recrystallized three times from acetone (large volume)–methanol (one-third volume)–water gave 0.125 g. of bright yellow microcrystals (XIa).