[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF OKLAHOMA]

THE USE OF N-BROMOSUCCINIMIDE AND PYRIDINIUM BROMIDE PERBROMIDE IN THE CONVERSION OF FLAVANONES INTO FLAVONES

N. B. LORETTE,[1] THOMAS B. GAGE, AND SIMON H. WENDER

Received February 2, 1951

The bromination of flavanones and flavanone glycosides, followed by dehydrobromination, offers a convenient method for the preparation of the more difficultly obtainable flavones and flavone glycosides. Kostanecki and his coworkers (1, 2, 3) prepared 6-ethoxyflavone, 3′-methoxy-4′,6-diethoxyflavone, and flavone(2-phenylbenzopyrone) by bromination of the corresponding flavanones with liquid bromine in carbon disulfide solution. This was followed by removal of hydrogen bromide with alcoholic potassium hydroxide. These workers failed to report any yields for their procedure. More recently, Zémplen and Bognár (4) indicated that Kostanecki's method was unsatisfactory for the conversion of hydroxyflavanones or flavanone glycosides due to excessive nuclear bromination. Zémplen and Bognár reported successful monobromination of acetylated flavanones by means of liquid bromine in chloroform solution with the aid of ultraviolet light. The desired flavone derivative was obtained following loss of hydrogen bromide and de-acetylation with alcoholic alkali. Using this method, they obtained a 37% conversion of hesperidin (I) into diosmin (II).

Narasimhachari and Seshadri (5) recently reported the use of excess acetate and iodine to dehydrogenate alcoholic solutions of flavanones. Yields up to 60–70% were cited for some of their reactions. No yields were given, however, for the conversion of the two flavanone glycosides listed in the present paper, although both reactions were reported by them.

In this laboratory, the authors have been concerned with the preparation of 50–100-g. samples of certain flavone glycosides from the more readily available flavanone glycosides. These were needed for evaluation of their protective action against radiation sickness. This paper reports for the first time the finding that N-bromosuccinimide and pyridinium bromide perbromide are satisfactory brominating agents for the two step bromination-dehydrobromination of flavanone glycosides. Yields of flavone glycosides ranging from 35–55% have been obtained by this method. Additional advantages of the method are: (a) the brominating agent is easily handled, (b) only simple equipment is required (ultraviolet light is unnecessary), and (c) the final product is obtained in relatively pure form without difficulty.

Bromination failed to take place with N-bromosuccinimide and pyridinium bromide perbromide in the absence of peroxide catalyst. Benzoyl peroxide was used successfully, however, as a catalyst for the reaction.

[1] Present address: Dow Chemical Company, Freeport, Texas.

EXPERIMENTAL

Diosmin. N-bromosuccinimide (Arapahoe Chemicals, Inc., Boulder, Colorado) (3 g.) in 75 ml. of chloroform, was heated to boiling on a sand-bath and 75 ml. of chloroform containing 10 g. of acetylated hesperidin (I) and 0.2 g. of benzoyl peroxide was added. The solution was refluxed four hours and then poured into an evaporating dish and allowed to evaporate at room temperature with the aid of a fan. The residual, viscous mass was dissolved in 150 ml. of 95% ethyl alcohol and rendered basic with 55 ml. of 15% sodium hydroxide. The alkaline solution was heated to near boiling for five minutes, cooled, and neutralized to *p*H 6–7 with sulfuric acid. The color changed from a deep red to an orange-yellow. Additional alcohol was added to precipitate inorganic salts (sodium acetate and sodium sulfate). The filtrate was concentrated to small volume at room temperature. As the solution evaporated, a yellow crystalline precipitate of diosmin (II) appeared. The precipitate was collected by centrifugation and washed with water and alcohol until the washings were clear. The yield of diosmin was 2.95 g. (44%), m.p. 272–280°. Recrystallization from 1% sodium hydroxide by the addition of carbon dioxide (6), raised the melting point to 278–281°; reported m.p. 280° (6).

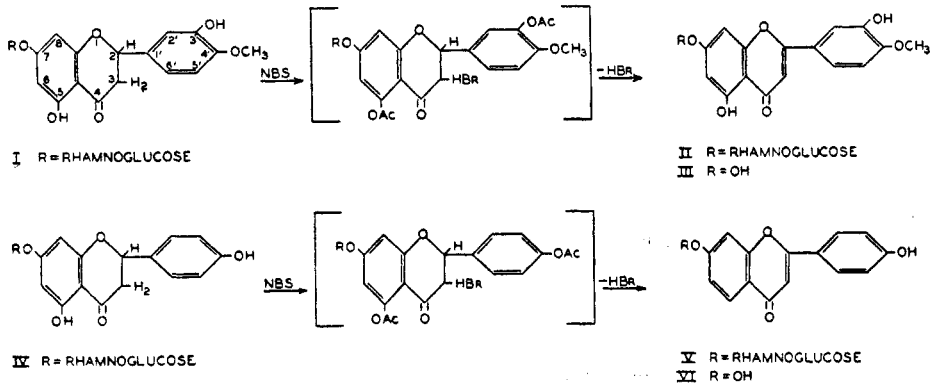

Fig. 1[2]

Hydrolysis of a portion of the diosmin in a sulfuric acid-acetic acid-water solution (2-65-38 volume-%, respectively) yielded diosmetin (III), m.p. 251°; reported m.p. 253° (4) and 256–257° (5).

Apigenin-7-rhamnoglucoside. Three grams of acetylated naringin (IV) was brominated by refluxing for 3 hours with 0.2 g. of pyridinium bromide perbromide and 0.2 g. of benzoyl peroxide in 50 ml. of chloroform. The chloroform was removed by evaporation at room temperature and the residue dissolved in 25 ml. of 95% ethyl alcohol. Then 15 ml. of 15% sodium hydroxide was added and the red solution was heated to near boiling for five minutes. The reaction mixture was cooled and then neutralized with 5% sulfuric acid. The residue was treated with 200 ml. of boiling ethyl alcohol, cooled, and filtered to remove inorganic salts. The alcohol was removed by evaporation and the precipitate recrystallized from water. The yield of apigenin-7-rhamnoglucoside (V) was 1.12 g. (55%, m.p. 195–200°; reported m.p. 198–200°) (5).

Hydrolysis of a portion of the above product with 2% sulfuric acid, yielded apigenin (VI), m.p. 340°; reported m.p. 340–342° (5).

Adsorption on an ion exchange resin. Apigenin-7-rhamnoglucoside is only slightly soluble in water. In the above procedure, however, the product obtained after deacetylation with

[2] Erratum: OH to be inserted at position 5 in Formulas V and VI.

base and subsequent neutralization was initially very water-soluble. On standing for several hours, however, apigenin-7-rhamnoglucoside precipitated from the water solution. Passage of a freshly prepared aqueous solution through a column of Amberlite IRC-50(H) cation exchange resin (The Resinous Products Division, Rohm and Haas Co.) resulted in adsorption of the flavonoid on the resin. The glycoside was subsequently eluted with 95% ethyl alcohol. The product obtained by evaporation of this alcoholic solution was only slightly soluble in water and contained less than 0.1% ash. The crude glucoside, prior to recrystallization from water or ion exchange treatment, contained gross quantities of ash.

Bromination using pyridinium bromide perbromide. Diosmin and apigenin-7-rhamnoglucoside were prepared from hesperidin and naringin, respectively, using 0.2 g. of pyridinium bromide perbromide (Jasons Drug Co., Brooklyn, N. Y.) for each 3 g. of acetylated flavanone. The amount of catalyst, details of the procedure, and properties of the products were the same as previously described for the reactions using N-bromosuccinimide. The yield of diosmin by this reaction was 35%; the yield of apigenin-7-rhamnoglucoside was 54%.

TABLE I

RESULTS OF PAPER PARTITION CHROMATOGRAPHY

FLAVONOID	R_f VALUES[b]		
	Authentic values from other sources	Prepared by N-bromosuccinimide reaction	Prepared by pyridinium bromide perbromide reaction
Diosmin	0.55	0.57	0.52
Diosmetin	.89	.92	.92
Apigenin-7-rhamnoglucoside	[a]	.60	.60
Apigenin	.92	.93	.94
Hesperidin	.40		
Naringin	.70		

[a] Not available. [b] Solvent system: Butanol-acetic acid-water (40-10-50 volume-per cent, respectively).

Paper partition chromatography. The confirmation of the identity of the flavone glycosides (and the aglycones produced on hydrolysis) was made by means of paper partition chromatography (7). The R_f values obtained in a butanol-acetic acid-water system (40-10-50 volume-per cent, respectively) are listed in Table I. The R_f values of the flavanone glycosides used in the reaction are also included in this table. The values listed for "authentic" diosmin and diosmetin were reported by Bate-Smith (8). The R_f value of "authentic" apigenin was determined with a sample of apigenin prepared in this laboratory from fresh parsley.

Paper partition chromatography was also used to demonstrate the presence of rhamnose and glucose in the aqueous hydrolysates of diosmin and apigenin-7-rhamnoglucoside. The technique of Gage, Douglass, and Wender (9) was combined with a solvent system described by Partridge (10) for this purpose.

Acknowledgments. The authors wish to express their gratitude to the Research Department of the California Fruit Growers Exchange, Ontario, California, for the donation of the naringin used in this research.

This research was supported in part by a grant-in-aid from the Atomic Energy Commission (AT-(40-1)-235).

SUMMARY

Acetylated hesperidin and naringin have been converted into diosmin and apigenin-7-rhamnoglucoside, respectively, by bromination with N-bromosuccinimide and pyridinium bromide perbromide followed by removal of hydrogen bromide and acetyl groups with alcoholic alkali.

The method presented, in addition to giving satisfactory yields, has additional advantages over older procedures from the standpoint of the ease of handling of the brominating agent, the simple equipment required, and the ease of purification of the product.

NORMAN, OKLAHOMA

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