

tions of these materials. Dried aluminum hydroxide gel U.S.P. was selected as an example of a powdered material which cannot be compressed directly. Blends containing 25 and 50% by weight of the aluminum compound were prepared with fused mannitol, mannitol and sucrose (50:50), and mannitol and lactose (50:50) in a Twin Shell blender. Magnesium stearate (1%) was included as a lubricant. These blends continued to exhibit the excellent flow and compression characteristics which had been observed with the vehicles alone. Tablets weighing 0.5 Grn. prepared on a model F compression machine gave Strong-Cobb hardness tester values of up to 10-11 with no signs of capping. The tablets were satisfactory in all other respects.

Comparison of Fused Spray-Congeaed and Screened Mannitol.—To compare the relative compressibility of the two physical states of mannitol obtained by either spray-congealing or screening, a Carver laboratory hydraulic press was employed. This press was modified to operate a specially constructed rig containing a set of 13/32 in. F.F. punches and a die. Accurately weighed 500-mg. portions of the different batches of mannitol were compressed at pressure levels of 1000, 2000, 3000, and 4000 p.s.i. Tablets produced at each level were tested for hardness. It was determined that the spray-congealed mannitol produced softer tablets at corresponding pressure levels than did the 20-mesh screened material (Table II).

SUMMARY AND CONCLUSIONS

The unusual heat stability of mannitol has led to the development of several new applications which possess a high degree of potential. Foremost among these is the discovery that fused mannitol, which is recrystallized and processed by either spray-congealing or screening, possesses exceptionally good tableting characteristics.

The liquid state of mannitol has been shown capable of dissolving or dispersing a number of pharmaceutical adjuvant or physiologically active drugs. Phase diagrams of several of these combinations have indicated that solid-solid solutions are obtained. In at least one

instance (mannitol-diphenhydramine HCl) the phase diagram indicates the probable formation of a new compound. New compounds formed in this manner may conceivably possess different physical, chemical, and physiological properties.

In view of present day considerations of the effect of particle size on the biological availability of drugs, these solid-solid solutions or microcrystalline dispersions offer a unique opportunity of making available an extremely fine state of subdivision of active ingredients in tablet form. Moreover, these solid solutions, capable of being directly compressed into tablets, obviate the necessity for blending procedures and assure complete uniformity of dosage.

Additional investigations are under consideration which will explore more thoroughly the nature of the interaction involved in the solid-solid solution in fused mannitol and will quantify the extent of solubilities of various chemicals and drugs.

Fused mannitol has also been utilized to produce eutectic mixtures with other less costly carbohydrates, such as sucrose and lactose. These mixtures have also been found to possess excellent flow and compression properties when used either as solvents for active principles or when admixed with them as a dry tablet binder.

Fused mixtures of mannitol with other sugars advance the possibility of large-scale production of an inexpensive, efficient vehicle for the direct compression of tablets.

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4',5,6,7-Oxygenated Flavones and Flavanones

By MASON G. STOUT, HANS REICH, and MAX N. HUFFMAN

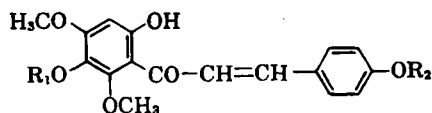
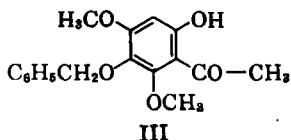
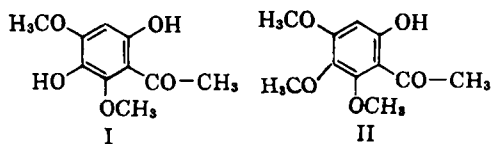
The preparation of 4'-hydroxy-5,6,7-trimethoxyflavanone, 6-hydroxy-4',5,7-trimethoxyflavanone, and the corresponding flavones is described as well as a new synthesis of 4',6-dihydroxy-5,7-dimethoxyflavone. The results of the biological tests of these and other closely related bioflavonoids in our general endocrine screening assay are tabulated.

FOR BIOLOGICAL experiments, the 4',5,6,7-substituted flavanones X, XII, XIV, and XV and the corresponding flavones XVI, XVIII,

XX, and XXII were required. Compounds X and XVI had been prepared previously (1) from the acetophenone derivative II and anisaldehyde via the chalcone IV, and the flavanone XV had been obtained from the acetophenone derivative I by condensation with *p*-hydroxybenzaldehyde (2). This flavanone was later used as starting material for the preparation of the flavone XXII

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- IV $R_1 = R_2 = \text{CH}_3$
 V $R_1 = \text{CH}_3$; $R_2 = \text{CH}_2\text{C}_6\text{H}_5$
 VI $R_1 = \text{H}$; $R_2 = \text{CH}_3$
 VII $R_1 = \text{CH}_2\text{C}_6\text{H}_5$; $R_2 = \text{CH}_3$
 VIII $R_1 = R_2 = \text{H}$
 IX $R_1 = R_2 = \text{CH}_2\text{C}_6\text{H}_5$

which was accomplished by bromination and dehydrobromination with alkali (3). For the synthesis of this flavone XXII, we chose the condensation of the benzyloxyacetophenone derivative III with *p*-benzyloxybenzaldehyde, oxidation of the resulting chalcone IX with selenium dioxide to the flavone XXI, and debenzoylation with hydrochloric acid in acetic acid.

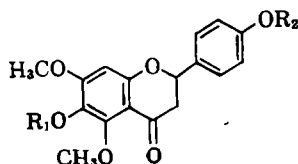
The flavanone XII and the flavone XVIII were synthesized in the following manner. The trimethoxyhydroxyacetophenone II was brought into reaction with *p*-benzyloxybenzaldehyde, and the chalcone V thus obtained was either cyclized or oxidized with selenium dioxide to give XI and XVII, respectively. Removal of the benzyloxy group in XI was achieved by hydrogenation and debenzoylation of XVII with hydrochloric acid in acetic acid.

Condensation of III with anisaldehyde gave a mixture of the chalcone VII and the flavanone XIII which could be separated by crystallization. Oxidation of the chalcone with selenium dioxide led to the formation of flavone XIX and acidic debenzoylation of the latter to the required flavone XX. Since the flavanone XIII could not be debenzoylated by hydrogenation or with acids, it was necessary to condense the dihydroxy-dimethoxyacetophenone I with anisaldehyde. Also in this case, the reaction product was a mixture of the chalcone VI and the flavanone XIV which had to be separated by fractional crystallization.

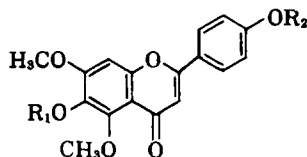
EXPERIMENTAL¹

Aldehydes.—*p*-Hydroxybenzaldehyde and anisaldehyde were commercial preparations (Eastman).

¹ All melting points are uncorrected. The microanalyses were carried out by Huffman Microanalytical Laboratories, Wheatridge, Colo., and Galbraith Laboratories, Knoxville, Tenn.



- X $R_1 = R_2 = \text{CH}_3$
 XI $R_1 = \text{CH}_3$; $R_2 = \text{CH}_2\text{C}_6\text{H}_5$
 XII $R_1 = \text{CH}_3$; $R_2 = \text{H}$
 XIII $R_1 = \text{CH}_2\text{C}_6\text{H}_5$; $R_2 = \text{CH}_3$
 XIV $R_1 = \text{H}$; $R_2 = \text{CH}_3$
 XV $R_1 = R_2 = \text{H}$



- XVI $R_1 = R_2 = \text{CH}_3$
 XVII $R_1 = \text{CH}_3$; $R_2 = \text{CH}_2\text{C}_6\text{H}_5$
 XVIII $R_1 = \text{CH}_3$; $R_2 = \text{H}$
 XIX $R_1 = \text{CH}_2\text{C}_6\text{H}_5$; $R_2 = \text{CH}_3$
 XX $R_1 = \text{H}$; $R_2 = \text{CH}_3$
 XXI $R_1 = R_2 = \text{CH}_2\text{C}_6\text{H}_5$
 XXII $R_1 = R_2 = \text{H}$

p-Benzyloxybenzaldehyde was prepared from *p*-hydroxybenzaldehyde according to the method of Bergmann and Sulzbacher (4).

3',6'-Dihydroxy-2',4'-dimethoxyacetophenone (I).—This compound was prepared from 2,6-dimethoxyhydroquinone diacetate (1) (m.p. 126–127°) in the following manner. A fairly rapid stream of boron trifluoride was introduced into a cooled solution of 75 Gm. of the diacetate in 500 ml. of glacial acetic acid, keeping the temperature below 40°. After 1.5 to 2 hours, the total uptake of boron trifluoride amounted to 393–425 Gm. The yellowish-green solution was allowed to stand at room temperature overnight and was poured into 2.25 L. of water which contained 750 Gm. of ice. After standing for 3 hours in the refrigerator, the yellow precipitate was filtered, washed with water, transferred to a 3-L. flask, and dissolved in 1 L. of 95% ethanol by heating. Then 525 ml. of 10% hydrochloric acid was added and the mixture refluxed for 2 hours. Upon concentration *in vacuo* and cooling overnight, yellow crystals were obtained which were filtered and dried. They weighed 58.7 Gm. (94%), melted at 158–159°, and did not depress the melting point of a sample prepared from 2,6-dimethoxyhydroquinone diacetate by a Fries rearrangement, reported m.p. 162–163° (1, 5), 164–165° (6).

When the hydrolysis with ethanolic hydrochloric acid was omitted, the reaction product proved to be 6'-hydroxy-3'-acetoxy-2',4'-dimethoxyacetophenone, which, after recrystallization from aqueous methanol, melted at 107 to 107.5°.

Anal.—Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_8$: C, 56.59; H, 5.55. Found: C, 56.93; H, 5.61.

2',3',4'-Trimethoxy-6'-hydroxyacetophenone (II).—The methylation of I was carried out with dimethyl sulfate as described by Oliverio and Bargellini (1) and gave a crude product of m.p. 33–36°, reported m.p. 40–41° (1), which was sufficiently pure for the condensation with aldehydes.

2',4'-Dimethoxy-3'-benzyloxy-6'-hydroxyacetophenone (III).—A 110-Gm. quantity of anhydrous potassium carbonate and 32 ml. of benzyl

TABLE I.—CHALCONES

	Yield, %	M.p., ^a °C.	Crystal- lization Media ^b	Color	Empirical Formula	Analysis			
						Calcd. C	H	Found C	H
IV	90	142 ^c	E	Red-orange	C ₁₉ H ₂₀ O ₆				
V	69	123 to 123.5	M	Yellow	C ₂₅ H ₂₄ O ₆	71.42	5.75	71.19	5.58
VI	26 ^d	141–142 ^e	E	Dark red	C ₁₈ H ₁₈ O ₆	65.45	5.49	65.49	5.76
VII	72	139 to 139.5	E	Red-orange	C ₂₅ H ₂₄ O ₆	71.42	5.75	71.32	5.81
VIII	...	198–200 ^f	M-W	Dark red	C ₁₇ H ₁₆ O ₆				
IX	71	121 to 121.5	E	Yellow	C ₂₁ H ₂₈ O ₆	74.98	5.68	74.92	5.68

^a Capillary, uncorrected. ^b E = ethanol; M = methanol; W = water. ^c Reported 140–141° (1); 141–142° (8). ^d An additional 29% of flavanone was obtained; see *Experimental*. ^e Reported 191° (8). ^f Reported 191° (2). This chalcone gave a yellow triacetate, m.p. 182.5 to 183° (from methanol). Calcd. for C₂₅H₂₂O₉: C, 62.44; H, 5.01. Found: C, 62.67, 62.65, 62.67; H, 5.16, 5.00, 5.21.

chloride were added to a solution of 27 Gm. of I and 20 Gm. of sodium iodide in 300 ml. of anhydrous acetone. The mixture was refluxed with stirring for 10 hours, kept an additional 6 hours at room temperature, poured into 400 ml. of water, and concentrated *in vacuo* to remove all the acetone. The aqueous solution was extracted with one 100-ml. and four 50-ml. portions of ether and the combined ether solutions with 20, 20, 10, and 10 ml. of 5% sodium hydroxide. The alkaline solutions were acidified and extracted again with one 50-ml. and five 15-ml. portions of ether. These solutions were dried and evaporated leaving 15.4 Gm. of a red oil which did not solidify and could not be distilled without decomposition. It therefore was used in this impure form. An additional amount of 6.5 Gm. (total yield 56.7%) was obtained by concentration of the first ether extracts and renewed extraction with 5% sodium hydroxide.

Chalcones IV–IX.—These compounds were prepared according to established methods (7) with 50% aqueous KOH as the condensing agent. As a rule, the mixture was allowed to stand at room temperature 3 to 4 days. Only in one case (chalcone VI), it was acidified with HCl after 3 days and kept at room temperature for 3 more days. Consequently, the reaction product was a mixture of chalcone VI and flavanone XIV. The melting points and analyses of six chalcones are listed in Table I.

4',5,6,7-Tetramethoxyflavanone (X).—The conversion of chalcone IV to the corresponding flavanone was carried out according to the method of Seshadri (8). The yield was 33% and the flavanone melted at 119.5 to 120.5° reported m.p. 114–115° (1), 124–125° (8, 9).

Anal.—Calcd. for C₁₉H₂₀O₆: C, 66.27; H, 5.85. Found: C, 66.41; H, 5.98.

5,6,7-Trimethoxy-4'-benzyloxyflavanone (XI).—A

solution of 18.2 Gm. of chalcone V in 830 ml. of ethanol was mixed with 163 ml. of 10% HCl, refluxed for 26 hours, diluted with 300 ml. of boiling water, and cooled slowly. The precipitate consisting of a mixture of chalcone and flavanone was filtered, dried (16.9 Gm.), and extracted three times with 100 ml. of boiling methanol. The combined methanol solutions, upon cooling, gave 6.0 Gm. of crystals, m.p. 152–154°. By further recrystallization from methanol, light yellow needles were obtained, m.p. 155–156°.

Anal.—Calcd. for C₂₅H₂₄O₆: C, 71.42; H, 5.75. Found: C, 71.57; H, 5.62.

4'-Hydroxy-5,6,7-trimethoxyflavanone (XII).—A mixture of 3.8 Gm. of XI, 145 ml. of glacial acetic acid, and 0.72 Gm. of 5% palladium-carbon catalyst was shaken under hydrogen at 24 lb. pressure for 1.5 hours. The suspension was filtered, diluted with 1.5 L. of water, and cooled overnight. The resulting precipitate was filtered, washed with water, and dried (2.7 Gm.; 90.3%). It was dissolved in 25 ml. of acetone, diluted with 50 ml. of benzene, and concentrated to approximately 10 ml. This procedure gave 2.2 Gm. of colorless needles, m.p. 185–187°, which were recrystallized once more from acetone-benzene. They turned red at 187° and melted at 190–192°.

Anal.—Calcd. for C₁₈H₁₈O₆: C, 65.45; H, 5.49. Found: C, 65.50; H, 5.42.

4',5,7-Trimethoxy-6-benzyloxyflavanone (XIII).—Attempts to convert chalcone VII to the corresponding flavanone XIII proved unsuccessful. This flavanone was isolated, however, as a by-product in the preparation of VII. When the crude reaction product of III and anisaldehyde was dissolved in 1:2 acetone-ethanol, concentrated to half the volume, and cooled, the chalcone VII crystallized in 50% yield. After standing at room temperature overnight, the mother liquor contained faintly colored

TABLE II.—FLAVONES

	Yield, %	M.p., ^a °C.	Crystal- lization Media ^b	Color	Empirical Formula	Analysis			
						Calcd. C	H	Found C	H
XVI	49	159–160 ^c	M	Light yellow	C ₁₉ H ₁₈ O ₆	66.66	5.30	66.68	5.41
XVII	77	156	M	Tan	C ₂₅ H ₂₂ O ₆	71.76	5.30	71.72	5.36
XVIII	77.5	226–227	EA ^d	Tan	C ₁₈ H ₁₆ O ₆	65.85	4.91	65.77	4.89
XIX	...	135 or 144 to 144.5	B-C	Light yellow	C ₂₅ H ₂₂ O ₆	71.76	5.30	71.67	5.48
XX	44.5 ^e	217–218	M-B	Yellow	C ₁₈ H ₁₆ O ₆	65.85	4.91	65.98	4.78
XXI	86	155.5 to 156	B-C	Yellow	C ₃₁ H ₂₆ O ₆	75.29	5.30	75.58	5.38
XXII	82.5	283.5 to 284 ^f	M-B	Yellow	C ₁₇ H ₁₄ O ₆	64.96	4.49	64.84	4.55

^a Capillary, uncorrected. ^b M = Methanol; EA = ethyl acetate; B = benzene; C = cyclohexane. ^c Reported 158–160° (10); 162–163° (6, 1); 160° (3). ^d The mother liquor gave crystals, m.p. 243–246°, which were probably 4',5-dihydroxy-6,7-dimethoxyflavone. Calcd. for C₁₇H₁₄O₆: C, 64.96; H, 4.49. Found: C, 64.93; H, 4.29. ^e From chalcone VII via XIX. ^f Reported 283° (3).

TABLE III—GENERAL ENDOCRINE SCREENING ASSAY OF 4',5,6,7-TETRAOXYGENATED FLAVANONES AND FLAVONES^a

	Variation from Control, % ^b								
	Final Body	Vent. Prost.	Testes	Lev. Ani	Adrenals	Left Kid.	Liver	Spleen	Thymus
4',5,6,7-Tetramethoxyflavanone (X)	-4.9	-5.9	-4.0	-5.1	+12	-6.7	-3.4	+6.5	-12
4',5,6,7-Tetramethoxyflavone (XVI)	-7.6	+5.3	0	-6.6	+3.0	-2.8	-8.0	+2.1	-14
4'-Hydroxy-5,6,7-trimethoxyflavanone (XII)	-4.9	+12	+0.74	+4.0	+9.0	-1.3	-6.8	+9.6	-9.5
4'-Hydroxy-5,6,7-trimethoxyflavone (XVIII)	-10	-1.9	-6.0	-3.7	+9.6	-4.0	-5.7	+26	-16
6-Hydroxy-4',5,7-trimethoxyflavanone (XIV)	-4.9	+5.3	-3.7	+2.6	+14	-0.90	-5.7	+14	-2.7
6-Hydroxy-4',5,7-trimethoxyflavone (XX)	-4.9	-1.3	-6.2	+0.37	+13	-3.3	-9.1	+6.7	-3.5
4',6-Dihydroxy-5,7-dimethoxyflavanone (XV)	-5.6	+9.2	-1.6	+11	+18	-5.0	-9.1	+2.1	-6.8
4',6-Dihydroxy-5,7-dimethoxyflavone (XXII)	-1.5	-3.1	-0.23	+2.1	+2.4	+0.69	-2.2	+14	+3.9

^a Twenty-one-day-old intact male Holtzman rats were used at the start of the experiment. Ten animals were in each group and the control group. Administration was at 2 mg./day, s.c., in CMC for 14 days with autopsy on 15th day. Controls given CMC diluent, and initial starting weights matched for the groups. ^b Percentage variation is calculated from the arithmetic mean of each group against the arithmetic mean for the control group.

crystals which were filtered (yield 10%) and recrystallized from benzene-cyclohexane to give colorless plates, m.p. 152 to 152.5°.

Anal.—Calcd. for $C_{28}H_{24}O_6$: C, 71.42; H, 5.75. Found: C, 71.56; H, 5.63.

6-Hydroxy-4',5,7-trimethoxyflavanone (XIV).—

As mentioned above under *Chalcones*, flavanone XIV was obtained in 29% yield, when the alkaline reaction mixture which contained chalcone VI was acidified with HCl and allowed to stand for 3 days. After the chalcone had been precipitated by addition of water (alcohol concentration 40%), the flavanone was obtained from the mother liquor by lowering the alcohol concentration to 15%. One recrystallization from benzene-cyclohexane gave light yellow needles, m.p. 123.5 to 124°.

Anal.—Calcd. for $C_{18}H_{14}O_6$: C, 65.45; H, 5.49. Found: C, 65.66; H, 5.38.

4',6-Dihydroxy-5,7-dimethoxyflavanone (XV).—

Although the directions given by Zemlen (2) were followed very closely, this flavanone could not be prepared according to this method. Usually it was obtained in small yield from the mother liquor after recrystallization of the chalcone VIII. A satisfactory conversion of the chalcone to the flavanone was accomplished by dissolving the chalcone in a mixture of 20 parts of methanol and 1 part of water and adding boiling water (30% by volume). Upon cooling and seeding, the flavanone separated and was recrystallized repeatedly from absolute ethanol. Although its color is reported to be ochre-yellow (2), our preparations were always red-orange, which would indicate that they still contained small amounts of chalcone (dark red). They melted consistently at 205°, reported m.p. 198° (2), and when admixed with the chalcone VIII (m.p. 198–200°), the melting point was strongly depressed (189–196°).

Anal.—Calcd. for $C_{17}H_{14}O_6$: C, 64.55; H, 5.10. Found: C, 64.23; H, 4.99.

Furthermore, the flavanone gave the same diacetate (m.p. 133–135°) as reported in the literature [137° (2)].

Anal.—Calcd. for $C_{21}H_{20}O_8$: C, 63.00; H, 5.04. Found: C, 63.20; H, 5.44.

In contrast, the chalcone VIII, when acetylated under identical conditions, gave an acetate m.p. 182.5 to 183°, which analyzed correctly for a triacetate (see Table I).

Flavones XVI, XVII, XIX, and XXI.—Equal

amounts of chalcones IV, V, VII, and IX and selenium dioxide were dissolved in amyl alcohol (10–14 ml. per gram of chalcone) and refluxed for 12 hours. The solutions were cooled and filtered, the residue washed with ether, the filtrates washed with 20% NaOH and saturated NaCl solution, and the ether removed *in vacuo*. Flavones XVII and XXI crystallized directly from the amyl alcohol solutions, and additional amounts were obtained when the amyl alcohol was removed by steam distillation. This procedure had to be used for flavones XVI and XIX which are too soluble in amyl alcohol. Usually the crude flavones were recrystallized first from dilute methanol or dilute acetic acid, then from the solvents listed in Table II.

Flavones XVIII, XX, and XXII.—The benzyloxy-flavones XVII, XIX, and XXI were dissolved in glacial acetic acid—concentrated HCl 3:1 (30–40 ml. per gram of flavone) and the solutions heated on the steam bath for 1.5 hours. After cooling, they were poured into five or more volumes of water, and the precipitates were filtered and recrystallized from appropriate solvents (Table II).

SUMMARY

The bioflavonoids X, XVI, XII, XVIII, XIV, XX, XV, and XXII were submitted to our general endocrine screening assay, with results as indicated in Table III. Flavone XVIII increased the weight of the spleen in the young intact male rat. The flavanone XV slightly increased the size of the adrenals, but this effect, if real, appeared to be a nonfunctional hypertrophy or hyperplasia. In general, these flavones and flavanones produced no significant endocrine effects.

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