[CONTRIBUTION FROM THE FRUIT AND VEGETABLE CHEMISTRY LABORATORY, WESTERN UTILIZATION RESEARCH AND DEVELOPMENT DIVISION, AGRICULTURAL RESEARCH SERVICE, UNITED STATES DEPARTMENT OF AGRICULTURE]

Flavonoids of Citrus. IV. Isolation of Some Aglycones from the Lemon (*Citrus limon*)

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The isolation of a number of flavonoids, coumarins, and cinnamic acids from lemon peel is described. Separation of the compounds was accomplished by chromatography on silicic acid. The following compounds are reported: apigenin, luteolin, chrysoeriol, quercetin, isorhamnetin, the new flavonols limocitrin and limocitrol, sinapic acid, *p*-coumaric acid, scopoletin, and umbelliferone. Absorption spectra of 6- and 7-hydroxylated coumarins are discussed.

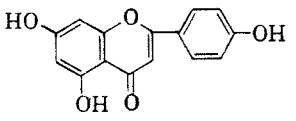
In earlier papers on the flavonoid constituents of lemons we reported the occurrence of hesperidin, diosmin,[1] limocitrin,[2] and eriodictyol rutinoside.[3] We now describe the isolation of six additional flavonoid aglycones as well as several coumarins and cinnamic acid derivatives. The flavonoids occur in the peel in the glycosidic form only and were obtained from extracts which had been hydrolyzed enzymatically. It has not been determined whether the coumarins occur in the free or combined form. Separation of the compounds was accomplished on columns of silicic acid which were developed and eluted with chloroform, chloroform-acetone or chloroform-methanol. This method of separating flavonoids and related phenolic substances gives very satisfactory results and appears to us to be superior to previously described procedures.

The aglycones isolated in the present work are apigenin (I),[4] luteolin (II), chrysoeriol (III), quercetin (IV),[5] isorhamnetin (V), and the new flavonols limocitrin (VI) and limocitrol (VII). The known compounds (I–V) were identified unequivocally by melting point, absorption spectra, preparation and analysis of appropriate derivatives, R_f values and comparison with authentic samples. The structure of limocitrin was shown earlier[2] to be 3,5,7,4′-tetrahydroxy-8,3′-dimethoxyflavone (VI). The other new flavonol, limocitrol, appears to be 3,5,7,4′-tetrahydroxy-6,8,3′-trimethoxyflavone (VII), which is the 6-methoxy derivative of limocitrin.[6] It should be noted that limocitrin and limocitrol (as well as chrysoeriol and isorhamnetin) are related in that they all yield vanillic acid on alkaline hydrolysis. To complete the summary of aglycones from the lemon, the structures of hesperetin (from hesperidin), diosmetin (from diosmin) and eriodictyol are shown as VIII, IX, and X, respectively.

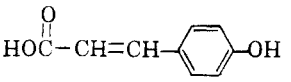
The C_6–C_3 compounds isolated and crystallized are *p*-coumaric acid (XI), sinapic acid (XII), and the coumarins scopoletin (XIII) and umbelliferone(XIV). With the exception of umbelliferone these compounds were identified by ultraviolet and infrared spectra, melting point determination, and by comparison with authentic samples. Umbelliferone was obtained in very low yield and was identified by ultraviolet spectra and R_f values alone. Since study of the C_6–C_3 compounds was incidental to the rest of the work and was not pursued in detail, it is likely that a number of them remain to be isolated.

Ultraviolet spectra were used extensively for preliminary structural studies of the compounds described. Characteristic shifts, or lack of shifts, were observed in the spectra of the flavonols and flavones on addition of sodium acetate,[7] sodium hydroxide,[7] sodium acetate–boric acid[8] or aluminum chloride,[9] as shown in Table I. In many instances the spectral data alone were adequate to identify the compound even before crystallization had occurred. Similar spectral shifts, of value in identifying scopoletin and umbelliferone, were observed on adding these reagents (except aluminum chloride) to a series of coumarins substituted at the 6- and 7-positions, as shown in Table II. The long wave-length band of coumarins having a free 7-hydroxyl group (compounds 1–5, Table II) undergoes a marked bathochromic shift in the presence of sodium acetate or sodium hydroxide; when a free 6-hydroxyl combined with a protected 7-hydroxyl is present (compounds 6 and 7) the spectrum is altered with sodium hydroxide but

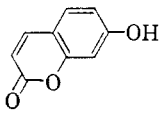
(1) R. M. Horowitz, *J. Org. Chem.*, **21**, 1184 (1956).
(2) R. M. Horowitz, *J. Am. Chem. Soc.*, **79**, 6561 (1957).
(3) R. M. Horowitz and B. Gentili, *J. Am. Chem. Soc.*, **82**, 2803 (1960).
(4) Apigenin 7-rhamnoglucoside (rhoifolin) has been isolated from the sour orange (*Citrus aurantium*) by S. Hattori, M. Shimokoriyama, and M. Kanao, *J. Am. Chem. Soc.*, **74**, 3614 (1952).
(5) Quercetin 3-rutinoside (rutin) has been isolated from the "Satsumelo" hybrid, which is regarded as a cross between grapefruit and the Satsuma orange: C. F. Krewson and J. F. Couch, *J. Am. Chem. Soc.*, **70**, 257 (1948).
(6) The chemistry of limocitrin and limocitrol will be described in a later paper.
(7) L. Jurd and R. M. Horowitz, *J. Org. Chem.*, **22**, 1618 (1957).
(8) L. Jurd, *Arch. Biochem. Biophys.*, **63**, 376 (1956).
(9) L. Jurd and T. A. Geissman, *J. Org. Chem.*, **21**, 1395 (1956).



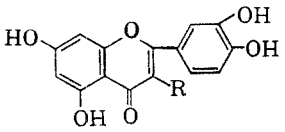
I. Apigenin



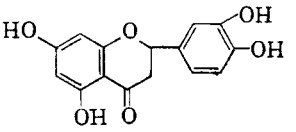
XI. *p*-Coumaric Acid



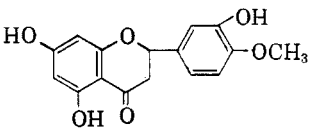
XIV. Umbelliferone

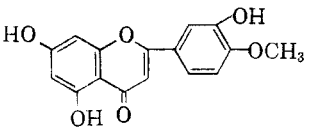


II. R = H, Luteolin
IV. R = OH, Quercetin

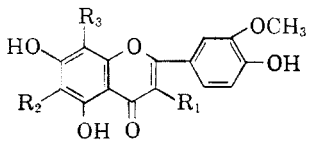


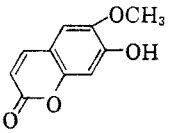
X. Eriodictyol



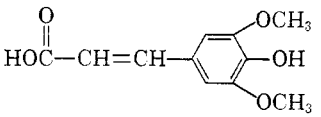


VIII. Hesperetin
IX. Diosmetin





III. $R_1 = R_2 = R_3 = H$, Chrysoeriol
V. $R_1 = OH$; $R_2 = R_3 = H$, Isorhamnetin
VI. $R_1 = OH$; $R_2 = H$; $R_3 = OCH_3$, Limocitrin
VII. $R_1 = OH$; $R_2 = R_3 = OCH_3$, Limocitrol
XIII. Scopoletin



XII. Sinapic Acid

not with sodium acetate; while the presence of both 6- and 7-hydroxyl groups (compound 2) results in a shift with sodium acetate–boric acid as well as sodium acetate and sodium hydroxide. No changes are observed with coumarins lacking any free hydroxyl group (compounds 8–10). As with flavonols and flavones, it is clear that the conjugated 7-hydroxyl group of coumarins is sufficiently acidic to be ionized with sodium acetate, while the 6-hydroxyl group is affected only by sodium hydroxide. The effect of sodium acetate–boric acid on esculetin is apparently to chelate with the *ortho* hydroxyl groups. It is thus possible, by applying these reagents, to discern the presence and position of hydroxyl groups in this type of coumarin.

The flavanones, flavones, and flavonols shown here are probably the most important flavonoids in the common (Eureka) lemon, although the possibility cannot be ruled out that closer scrutiny would yield further examples. It is likely that many of these aglycones occur in more than one glycosidic combination and we have evidence that this is true for diosmetin. Hesperidin, eriodictyol rutinoside, and diosmin are, in that order apparently, the most abundant glycosides in lemons.

In certain plant tissues, such as the flowers of *Coreopsis maritima*,[10] it has been found that the C_6–C_3 compounds and B-rings of the flavonoids all have the same pattern of hydroxylic substitution. With regard to biosynthesis, this is often considered as evidence that the pattern of hydroxylation of a C_6–C_3 unit (which later becomes B-ring-C_3 of the flavonoid) is established before elaboration of the A-ring occurs.[11] Five different patterns of hydroxyl substitution were present in the coumarins, cinnamic acids, and B-rings of the flavonoids described here, *i.e.* 4-hydroxy, 3,4-dihydroxy, 3-methoxy-4-hydroxy, 3-hydroxy-4-methoxy, and 4-hydroxy-3,5-dimethoxy. These results appear neither to support nor disprove the hypothesis in quesion. On the one hand, it might be considered that the large number of hydroxylation patterns in the lemon compounds indicates that modifications of a preformed C_6–C_3–C_6 unit take place to yield the array of flavonoids. On the other hand, the fact that several different coumarins and cinnamic acids were isolated from the same source confirms that C_6–C_3 units can be modified by hydroxylation and methoxylation and these variously substituted C_6–C_3 compounds might then be intermediates in the formation of flavonoids. As pointed out by Bogorad,[11] enzymological studies will probably be required to resolve the problem.

EXPERIMENTAL

Hydrolysis of the glycosides. "Calcium Flavonate Glycoside, Lemon"[12] (200 g.) was warmed briefly in 0.1*M* acetate buffer (3600 ml.) (*p*H 4.6) and was then filtered to remove a large quantity of insoluble material. The filtrate, readjusted to *p*H 4.6 with acetic acid, was treated with hemicellulase (12 g., Nutritional Biochemicals Corporation) and kept at room temperature for 2 days, when it was extracted with ethyl acetate (8 × 250 ml.). The solid yellow residue obtained by evaporating the combined ethyl acetate was broken up and extracted with two 200-ml. portions of boiling ether for 1 hr. each. The solid undissolved by ether consisted mainly of eriodictyol (4.75 g.).[3] The combined ether extracts were reduced to a volume of about 30 ml. and allowed to stand several days until limocitrin[2] had crystallized. On further standing a mixture of brown-yellow crystals separated (0.45 g., melting range 175–200°). This mixture was used on the column for separating the flavonoid aglycones.

Separation of the flavonoid aglycones. Examination of a large number of solvents and solvent combinations on

(10) T. A. Geissman, J. B. Harborne, and M. K. Seikel, *J. Am. Chem. Soc.*, **78**, 825 (1956).

(11) L. Bogorad, *Annual Review of Plant Physiology*, Vol. 9, A. S. Crafts, ed., Annual Reviews, Inc., Palo Alto, 1958, p. 417.

(12) This is a mixture of the flavonoid glycosides of lemon peel prepared as calcium salts (Exchange Lemon Products Company, Corona, Calif.). It contains relatively little hesperidin and diosmin.

TABLE I

ABSORPTION SPECTRA OF FLAVONES AND FLAVONOLS

Compound	λ_{max} in mμ: C_2H_5OH[a]	Short wave-length band in NaOAc–C_2H_5OH[b]	Long wave-length band in NaOH–C_2H_5OH[c]	Long wave-length band in NaOAc–H_3BO_3–C_2H_5OH[d]	Long wave-length bands in $AlCl_3$–C_2H_5OH[e]
Apigenin	270, 334	278	398		346, 382
Luteolin	255, 268,[f] 350	271	407	372	361, 389
Chrysoeriol	252, 270, 346	278	410	346	358, 385
Quercetin	256, 370	268	dec.	386	440
Isorhamnetin	254, 368	276	dec.		433
Limocitrin	259, 273,[f] 340,[f] 378	282	dec.	379	442
Limocitrol	260, 275,[f] 350,[f] 378	282	dec.		441

[a] Absolute ethanol. [b] Absolute ethanol saturated with fused sodium acetate. [c] One drop of 1% sodium hydroxide added to 2.5 ml. cuvette. [d] Ref. 8. [e] Ethanol solution saturated with aluminum chloride. [f] Inflection.

TABLE II

ABSORPTION SPECTRA OF COUMARINS

No.	Compound	λ_{max} in mμ of long wave-length band in: C_2H_5OH[a]	NaOAc–C_2H_5OH[b]	NaOH–C_2H_5OH[c]	NaOAc–H_3BO_3–C_2H_5OH[d]
1	Umbelliferone (7-hydroxycoumarin)	325	373	374	326
2	Esculetin (6,7-dihydroxycoumarin)	352	376	393	370
3	Esculin (esculetin 6-glucoside)	336	379	382	339
4	Scopoletin (6-methoxy-7-hydroxycoumarin)	345	391	393	346
5	6-*O*-Benzoylesculetin	330	381		
6	7-*O*-Methylesculetin	348	348	402 (low	
7	7-*O*-Benzylesculetin	349	349	403 (low)	
8	7-*O*-Benzylesculin	335		335	
9	7-*O*-Acetylscopoletin	337			
10	7-*O*-Benzyl-6-*O*-benzoylesculetin	325		323	

[a] Absolute ethanol. [b] Absolute ethanol saturated with fused sodium acetate. [c] One drop 1% sodium hydroxide added to 2.5 ml. cuvette. [d] Ref. 8.

chromatostrips[13] coated with silicic acid showed that chloroform-acetone would give good separation of the aglycones. Accordingly, a slurry of 100 mesh silicic acid (1100 g., Mallinckrodt analytical reagent) in U.S.P. chloroform (4000 ml.) was poured into an 8-cm. (diameter) tube forming a column 45 cm. high. The mixture of flavonoid aglycones (1.67 g.) dissolved in a minimum of acetone was added to the column and washed with (a) chloroform (1000 ml.) and (b) 7% (v./v.) acetone in chloroform (3000 ml.). A total of 385 fractions (*ca.* 25 ml. per fraction) was then collected using increasing concentrations of acetone in chloroform, as shown in Table III. Every tenth fraction was examined on duplicate paper chromatograms developed with 50% acetic acid and sprayed with sodium borohydride–hydrogen chloride[14] and ammoniacal silver nitrate, respectively. Crystallization and identification of the compounds was carried out as described below. It is of interest to note that the order of elution of the compounds seems to be related to the substitution pattern in the B-ring, those having a 3′-methoxy-4′-hydroxy group being eluted first, those having a 4′-hydroxy group next and those having a 3′,4′-dihydroxy group last.

(13) J. G. Kirchner, J. M. Miller, and G. J. Keller, *Anal. Chem.*, **23**, 420 (1951).

(14) R. M. Horowitz, *J. Org. Chem.*, **22**, 1733 (1957).

TABLE III

ELUTION OF AGLYCONES FROM SILICIC ACID

Fractions	Volume of Solvent in ml.	% Acetone in Chloroform (v./v.)	Components
1–45	1125	7	(Trace)
46–65	475	7	Limocitrin
66–175	2750	7–10	Limocitrol and Isorhamnetin
176–250	1850	10	Chrysoeriol
251–300	1250	10	Apigenin
301–344	1100	10–15	Eriodictyol
345–365	500	15	Quercetin
366–385	500	15	Luteolin

Limocitrin. The combined fractions 46–65 were evaporated and the residue was crystallized from methanol. The product (110 mg.) was identical spectroscopically and chromatographically with earlier specimens of limocitrin, m.p. 271–275°, undepressed on mixing.

Limocitrol.[6] The combined fractions 66–175 were evaporated to dryness and the residue (598 mg.) was crystallized

once from ethanol and twice from methanol. Limocitrol was thereby obtained as fine yellow needles (172 mg.), m.p. 221–222°. It gave a magenta color with magnesium in ethanolic hydrochloric acid and a green color with ferric chloride. Vanillic acid was obtained as one of the products of alkaline hydrolysis (60% potassium hydroxide boiled under reflux for 45 min.).

Anal. Calcd. for $C_{16}H_{16}O_9$: C, 57.4; H, 4.29; 3 CH_3O, 24.7. Found: C, 57.5; H, 4.29; CH_3O, 25.0.

Isorhamnetin. The methanolic liquors from limocitrol yielded, on concentration and standing, tiny yellow needles (46 mg.), m.p. 307–310° from methanol, not depressed on mixing with a specimen of synthetic isorhamnetin.[15] The ultraviolet spectra and R_f value (0.37 in 50% acetic acid) were identical with those of isorhamnetin.

The *tetraacetyl* derivative was obtained as a colorless solid, m.p. 211–212° from ethyl acetate–ether. 3,5,7,4′-Tetra-*O*-acetylisorhamnetin melted at 210–211° and gave no depression on mixing.

Anal. Calcd. for $C_{15}H_5O_5(OCH_3)(COCH_3)_4$: C, 59.5; H, 4.17; CH_3O, 6.42. Found: C, 59.0; H, 4.23; CH_3O, 6.52.

In certain runs in which the compounds were eluted from the column more slowly, starting with 2% acetone in chloroform, limocitrol separated cleanly from isorhamnetin, limocitrol preceding isorhamnetin.

Chrysoeriol. The combined fractions 176–250 were taken to dryness and the residue was crystallized from ethanol as clusters of fine yellow needles (66 mg.), m.p. 325–330°. The melting point was not depressed on mixing with a specimen of synthetic chrysoeriol (m.p. 328–335°).[16] The ultraviolet spectra and R_f value (0.55 in 50% acetic acid) were identical with those of the authentic sample.

The *triacetyl* derivative was obtained as a colorless compound, m.p. 223–224° from ethanol. 5,7,4′-Tri-*O*-acetylchrysoeriol melted at 221–223° and gave no depression on mixing.

Anal. Calcd. for $C_{15}H_6O_5(OCH_3)(COCH_3)_3$: C, 62.0; H, 4.26; CH_3O, 7.28. Found: C, 62.1; H, 4.23, CH_3O, 7.28.

Apigenin. The residue obtained by evaporating the combined fractions 251–300 was dissolved in methanol and allowed to stand. Small yellow crystals (30 mg.) were obtained, m.p. 348–355°, not depressed on admixture with synthetic apigenin. The ultraviolet spectra and R_f value (0.58 in 50% acetic acid) were identical with those of synthetic apigenin.

The *triacetyl* derivative crystallized as large needles from ethanol, m.p. 183–184°; reported[17] m.p. of 5,7,4′-tri-*O*-acetylapigenin 181–182°.

Anal. Calcd. for $C_{15}H_7O_5(COCH_3)_3$: C, 63.6; H, 4.07, $COCH_3$, 32.6. Found: C, 63.5, H, 4.16, $COCH_3$, 32.0.

Eriodictyol.[3] This was identified in fractions 301–344 by R_f values, reduction of ammoniacal silver nitrate and color with the sodium borohydride–hydrogen chloride reagent.

Quercetin. Evaporation of the combined fractions 345–365 yielded a gum which was dissolved in a small volume of methanol. Small yellow crystals (14 mg.) were obtained, m.p. 295–301°; reported[11] m.p. of quercetin 313–314°. The ultraviolet spectra and R_f value (0.31 in 50% acetic acid) were very close to those of authentic quercetin.

The *pentaacetyl* derivative was obtained as colorless needles after several recrystallizations from ethanol, m.p. 197–198°. A sample of authentic 3,5,7,3′,4′-penta-*O*-acetylquercetin melted at 200–201° and gave no depression on mixing.

Anal. Calcd. for $C_{15}H_5O_7(COCH_3)_5$: C, 58.6; H, 3.93; $COCH_3$, 42.0. Found: C, 58.5; H, 3.92; $COCH_3$, 41.8.

The *pentamethyl ether* was obtained by treatment with methyl iodide in acetone containing potassium carbonate. The product separated as small needles from ethanol, m.p. 148–149°, not depressed on mixing with a sample of authentic 3,5,7,3′,4′-penta-*O*-methylquercetin (m.p. 148–149°).

Luteolin. The residue from the combined fractions 366–385 was placed in ethanol and allowed to stand. Small yellow plates were obtained (122 mg.), softening at 322° and melting at 332°. A specimen of authentic luteolin melted at 331–333° and gave no depression on mixing. The ultraviolet spectra and R_f value (0.47 in 50% acetic acid) were identical.

The *tetraacetyl* derivative was obtained as slender needles, m.p. 232–233° from ethanol, not depressed on mixing with a sample of 5,7,3′,4′-tetra-*O*-acetylluteolin (m.p. 231–233°).

Anal. Calcd. for $C_{15}H_6O_6(COCH_3)_4$: C, 60.8; H, 3.99; $COCH_3$, 37.9. Found: C, 60.6; H, 4.06; $COCH_3$, 37.6.

Sinapic acid. A mixture of compounds (6 g.), which was obtained by extracting an aqueous solution of unhydrolyzed "Calcium Flavonate Glycoside, Lemon" with butanol, was chromatographed on a column of silicic acid (1090 g.) eluted with 9 l. of chloroform-methanol (3 to 7% methanol). The extraction and chromatographic procedures have been described in detail.[3]

Fractions 130–160 (6% methanol) were obtained as pale yellow solutions which changed to pink on standing for several days in air. Paper chromatograms prepared with 10% acetic acid showed a single deep blue spot in ultraviolet light. When the chromatograms were sprayed with ammoniacal silver nitrate a deep magenta color formed which, after about 10 min., changed to the characteristic brown-black of reduced silver nitrate. A specimen of sinapic acid had the same R_f value (0.44 in 10% acetic acid) and gave the same color reaction.[18] The combined fractions were taken to dryness and the residue was crystallized from a small volume of ethyl acetate. Grayish white needles were obtained, m.p. 192° after recrystallization and sublimation. The melting point was not depressed on mixing with sinapic acid and both the infrared and ultraviolet spectra were identical with those of sinapic acid: $\lambda_{max}^{C_2H_5OH}$ 238, 324 mμ.

p-Coumaric acid. Fractions 210–230 from the previous run (7% methanol) were allowed to stand several days during which feathery white crystals separated, m.p. 217–219°, not depressed on mixing with *p*-coumaric acid. The infrared and ultraviolet spectra were identical with those of *p*-coumaric acid: $\lambda_{max}^{C_2H_5OH}$ 228, ~293, ~300, 312 mμ.

Umbelliferone. A sample of dried lemon peel was extracted successively in a Soxhlet type extractor with petroleum ether, ether, acetone, and methanol, as described earlier.[1] The methanol extract was filtered to remove hesperidin, then was taken to dryness and the residue hydrolyzed in acetate buffer with hemicellulase, as described above. The mixture of aglycones (1.25 g.) was chromatographed on a 5 × 32 cm. column of 100 mesh silicic acid, using 6 l. of chloroform as eluant. Fractions 160–200 yielded a very small amount of material which crystallized from benzene. This had the same R_f value as umbelliferone (0.61 in 10% acetic acid) and gave the same intense blue fluorescence under ultraviolet light when exposed to ammonia vapor. The ultraviolet spectra in ethanol and with the various diagnostic reagents added were identical with those of umbelliferone.

Scopoletin. Fractions 100–106 of the immediately preceding run contained several compounds, one of which fluoresced blue under ultraviolet light and another of which gave a red color with vanillin–hydrochloric acid. The material from the combined fractions was rechromatographed on a small column of silicic acid which was eluted with 10% acetone in chloroform. The blue fluorescing substance was thus obtained pure as pale yellow crystals, m.p. 203–205° from benzene, not depressed on mixing with synthetic scopoletin.

(15) Prepared by Dr. Leonard Jurd.

(16) Prepared by the procedure of A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 817 (1930).

(17) *Dictionary of Organic Compounds*, I. Heilbron and H. M. Bunbury, eds., Oxford University Press, New York, 1953.

(18) Ferulic acid also reduces ammoniacal silver nitrate but fails to give the transient magenta color. The color is probably due to an oxidative dimerization of sinapic acid. The reaction is now being examined in detail.

The infrared and ultraviolet spectra (the latter in ethanol and with the diagnostic reagents added) agreed closely with those of scopoletin, as did R_f values in several solvents (0.51 in 10% acetic acid; 0.85 in 50% acetic acid).

Synthesis of scopoletin. A mixture of esculin (0.3 g.), benzyl chloride (1.2 ml.), potassium carbonate (3 g.), potassium iodide (1.4 g.), and acetone (200 ml.) was boiled under reflux for 24 hr., then was filtered and evaporated. The residue crystallized as needles from methanol (0.26 g.), m.p. 177–178°; reported[19] m.p. of 7-*O*-benzylesculin: 177.5°. Hydrolysis of this compound in boiling aqueous methanol-hydrochloric acid (2 hr.) afforded 7-*O*-benzylesculetin, m.p. 189.5–190.5°; reported[20] m.p. 189–189.5°. This was methylated in the usual manner with methyl iodide and potassium carbonate in acetone to give 6-*O*-methyl-7-*O*-benzylesculetin, colorless needles from methanol, m.p. 124–125°; reported[21] m.p. 126–127°. Treatment of this compound with hot acetic acid–concentrated hydrochloric acid (1:1) gave scopoletin (prisms from aqueous methanol), m.p. 204–206°; reported[21] m.p. 203–204°. The *acetyl* derivative melted at 178–179° (ethyl acetate–ether); reported[21] m.p. 176–177°.

Acknowledgment. We should like to thank L. M. White for the analytical data and L. Jurd for a sample of isorhamnetin.

PASADENA, CALIF.

(19) This was obtained by glucosidation of 7-*O*-benzylesculetin: K. W. Merz and W. Hagemann, *Arch. Pharm.*, 282, 79 (1944).

(20) This, together with 6,7-di-*O*-benzylesculetin, was obtained (ref. 19 and 21) by direct benzylation of esculetin. The procedure described here is preferable since it does not give mixtures.

(21) K. Aghoramurthy and T. R. Seshadri, *J. Sci. Ind. Research (India)*, 11B, 411 (1952).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUQUESNE UNIVERSITY]

Divinyl Ethers. Preparation and Spectra[1]

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The preparation of diisobutenyl ether (III) was accomplished by the dehalogenation of $\alpha,\alpha',\beta,\beta'$-tetrabromodiisobutyl ether (II) with magnesium iodide. Diisopropenyl ether (IV) and dipropenyl ether (V) were prepared by the dehydrohalogenation of the corresponding β,β'-dichloro ethers. The reaction of $\alpha,\alpha',\beta,\beta'$-tetrabromodiethyl ether (I) and the tetrabromo ether (II) with Grignard reagents resulted in dehalogenation to their corresponding divinyl ethers. The reaction of II with *n*-butyllithium proceeded *via* a transmetallation reaction to furnish diisobutenyl ether. The infrared spectra of this series of divinyl ethers showed characteristically strong absorption bands between 6.0 and 6.1 μ. The ultraviolet absorption maximum for divinyl ethers was shown to be between 227 and 228 mμ in tetrahydrofuran.

The purpose of this investigation was to prepare a series of divinyl ethers and to investigate their spectra and reactions. The parent compound and only known member of this series, divinyl ether, had been prepared by Hibbert and coworkers in 1929.[2] The reactions of the divinyl ether with various reagents, such as bromine to form the tetrabromodiethyl ether (I), sulfuric acid to form a black polymer, permanganate oxidation, and a polymerization reaction with benzoyl peroxide were discussed thoroughly by Shostakovskii and Dubrova.[3] The chief use of this compound today is as an anesthetic and it is prepared commercially by dehydrohalogenation.[4]

The most attractive method for the preparation of other divinyl ethers in addition to dehydrohalogenation was dehalogenation. A compound reported as $\alpha,\alpha',\beta,\beta'$-tetrabromodiisobutyl ether (II) had been prepared by Dworzak and Prodinger.[5] This compound represented a potential starting material for the synthesis of a divinyl ether; hence, its preparation was attempted. Direct bromination of isobutyraldehyde in carbon disulfide at 0° formed a white, crystalline solid, m.p. 81–82°, in 80% yield subsequently identified as II. The structure of the compound was elucidated by its reaction with ethanol and with acetic acid to furnish respectively α-bromoisobutyraldehyde diethyl acetal, and α-bromoisobutylidene diacetate. When the tetrabromo ether II was treated with 2,4-dinitrophenylhydrazine solution, the red 2,4-dinitrophenylhydrazone of methacrolein was obtained.[6] The tetrabromo ether II could be stored indefinitely under nitrogen; however, atmospheric moisture slowly catalyzed its decomposition to α-bromoisobutyraldehyde and hydrogen bromide.

To obtain diisobutenyl ether (III) from II, dehalogenation was carried out by a technique similar to that used by Summerbell and Umhoffer[7] in the

(1) This research was sponsored by a Frederick Gardner Cottrell Grant from Research Corporation.

(2) H. Hibbert, S. Z. Perry, and K. A. Taylor, *J. Am. Chem. Soc.*, 51, 1551 (1929).

(3) M. F. Shostakovskii and E. V. Dubrova, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 339 (1958).

(4) R. T. Major and W. L. Ruigh, U. S. Patent 2,021,872, Nov. 19, 1935.

(5) R. Dworzak and W. Prodinger, *Monatsh.*, 53, 588 (1929) reported a compound, m.p. 82.5°, formed in low yield on bromination of isobutyraldehyde at 70°, which they formulated correctly as II on the basis of analyses and a molecular weight determination.

(6) F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, 75, 6026 (1953) have shown that at higher temperatures certain α-halo-2,4-dinitrophenylhydrazones eliminate the halogen readily.

(7) R. K. Summerbell and R. R. Umhoffer, *J. Am. Chem. Soc.*, 61, 3019 (1939).