[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KALAMAZOO COLLEGE]

Synthetic Furocoumarins. II.[1] Synthesis of Several Alkylated Psoralenes and of a Dihydroisopsoralene

KURT D. KAUFMAN, FRED J. GAISER, THOMAS D. LETH, AND LEONARD R. WORDEN

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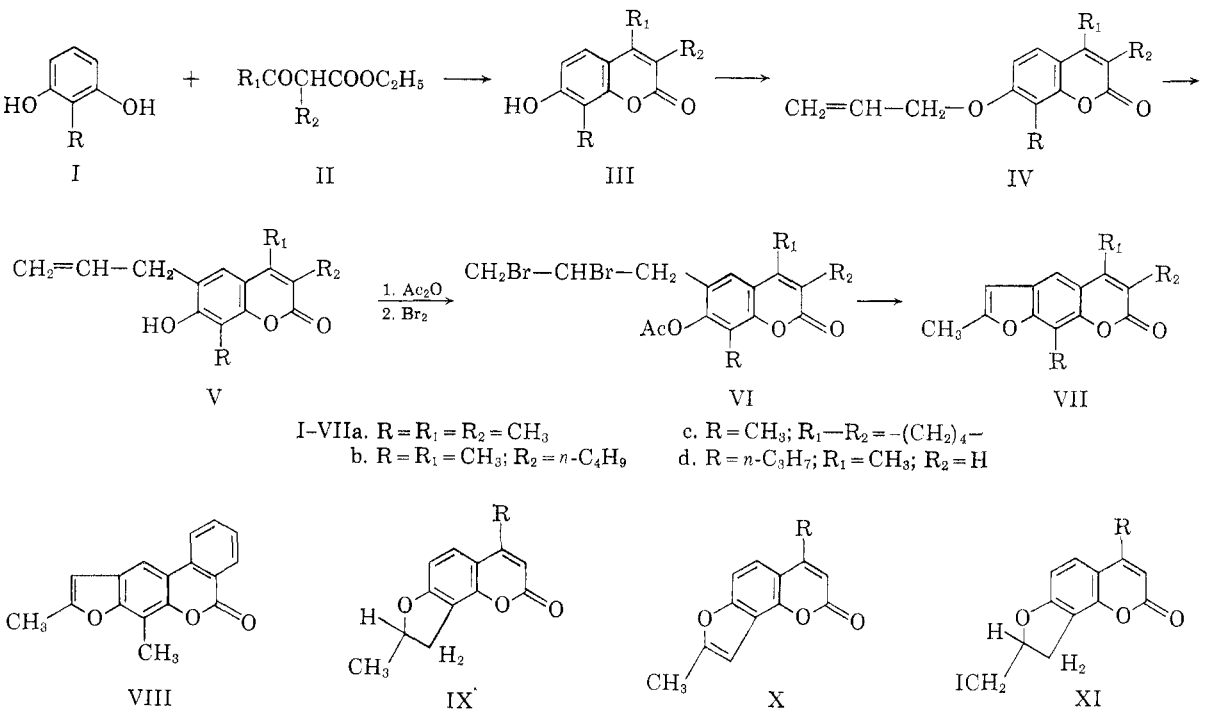
Five new alkylated psoralenes have been synthesized *via* 6-allyl-7-hydroxycoumarins to enable comparing their photosensitizing activity with psoralene. A dihydroisopsoralene has been prepared and it is suggested that two compounds, previously assigned the structures of dihydroisopsoralenes, are actually isopsoralenes.

The synthetic method described in Part I[1] of this series has been utilized for the synthesis of several psoralenes bearing alkyl substituents in the 3-, 4-, 8-, or 5′- positions.[2] Wide applicability of the process has thereby been illustrated and, at the same time, a variety of methyl and higher alkyl psoralenes have been made available for biological studies directed toward a better understanding of their photosensitizing action. The results of the biological studies are reported elsewhere.[3]



I–VIIa. $R = R_1 = R_2 = CH_3$
b. $R = R_1 = CH_3$; $R_2 = n\text{-}C_4H_9$
c. $R = CH_3$; $R_1—R_2 = -(CH_2)_4-$
d. $R = n\text{-}C_3H_7$; $R_1 = CH_3$; $R_2 = H$

The general synthetic method is summarized by structures I through VII and all of the new compounds actually isolated and characterized are listed in Table I at the end of this section. Five new substituted psoralenes have been obtained and are listed in the last part of the table. One of them, 3,4-benzo-5′,8-dimethylpsoralene (VIII), was obtained by dehydrogenation of 5′,8-dimethyl-3,4-cyclohexenopsoralene (VIIc) over palladium on charcoal in refluxing diphenyl ether.

4,5′-Dimethyl-8-*n*-propylpsoralene (VIId) was obtained from 7-hydroxy-4-methyl-8-*n*-propylcoumarin (IIId), which was prepared by catalytic hydrogenation of 8-allyl-7-hydroxy-4-methylcoumarin (III. R = allyl; $R_1 = CH_3$; $R_2 = H$).[1] When the synthesis of the latter compound was repeated (by Claisen rearrangement of 7-allyloxy-4-methylcoumarin), a small amount of an alkali insoluble side product, m.p. 117.6–117.8°, was obtained. The structure of 4′,5′-dihydro-4,5′-dimethylisopsoralene (IX. R = CH_3) has been assigned to this compound on the basis of micro-combustion analysis and the fact that it was dehydrogenated to give 4,5′-dimethylisopsoralene (X. R = CH_3).[1]

Krishnaswamy and Seshadri[4] have previously obtained a substance, m.p. 182–183°, which they alleged to be 4′,5′-dihydro-4,5′-dimethylisopsoralene

(1) Part I. K. D. Kaufman, *J. Org. Chem.*, 26, 117 (1961).
(2) For numbering of the psoralene system, see Part I of this series.
(3) M. A. Pathak, J. B. Fellman, and K. D. Kaufman, *J. Invest. Dermatol.*, 35, 165–183 (1960).
(4) B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 13A, 43–48 (1941).

TABLE I

Compound	Yield, %	Recrystn. Solvent[a]	M.P.[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
7-Hydroxycoumarins (III)								
IIIa[c]	65	C	279–280	$C_{12}H_{12}O_3$	70.57	70.58	5.92	5.85
IIIb[c]	22	B	156–157	$C_{15}H_{18}O_3$	73.15	73.19	7.32	7.34
IIIc[d]	47	C	279–281	$C_{14}H_{14}O_3$	73.02	73.26	6.13	5.99
IIId[e]	96[f]	A	186–186.5	$C_{13}H_{14}O_3$	71.60	71.49	6.47	6.06
7-Allyloxycoumarins (IV)								
IVa	97[f]	A	126–126.5	$C_{15}H_{16}O_3$	73.75	73.41	6.60	6.57
IVb	98[f]	B	94.5–95	$C_{18}H_{22}O_3$	75.52	75.59	7.69	7.67
IVc	84	A	143.5–144	$C_{17}H_{18}O_3$	75.53	75.85	6.71	6.69
IVd	90	D	89	$C_{16}H_{19}O_3$	74.40	74.69	7.02	7.42
6-Allyl-7-hydroxycoumarins (V)								
Va	78[f]	E	179–181	$C_{15}H_{16}O_3$	73.75	73.81	6.60	6.71
Vb	86[f]	B	133.5–134	$C_{18}H_{22}O_3$	75.52	75.39	7.69	7.85
Vc	35[f]	E	162.5–165	$C_{17}H_{18}O_3$	75.53	75.32	6.71	6.66
Vd	50[g]	A, E	145–145.5	$C_{16}H_{18}O_3$	74.40	74.88	7.02	7.37
7-Acetoxy-6-allylcoumarins								
Va Acetate[h]	66	C	127–127.5	$C_{17}H_{18}O_4$	71.06	70.98	6.31	6.30
Vb Acetate[i]	56	F	97–98	$C_{20}H_{24}O_4$	73.14	73.35	7.37	7.43
Vc Acetate[h]	96	A	125.5	$C_{19}H_{20}O_4$	73.06	73.15	6.45	6.55
Vd Acetate[i]	97	D	112–113	$C_{18}H_{20}O_4$	71.99	71.84	6.71	6.46
7-Acetoxy-6-(2′,3′-dibromopropyl)coumarins (VI)								
VIa	98[f]	A	148–149	$C_{17}H_{15}O_4Br_2$	45.76	45.92	4.07	4.34[j]
VIb	74	G	100.5–101	$C_{20}H_{24}O_4Br_2$	49.20	49.58	4.96	5.22[j]
VIc	83	A	154.5–155.5	$C_{19}H_{20}O_4Br_2$	48.32	48.26	4.27	4.14
VId	100[f]	A	119–120	$C_{18}H_{20}O_4Br_2$	46.98	46.67	4.38	4.31[j]
Furocoumarins (VII, VIII, and IX)								
VIIa	74	A, E	203.5–204.5	$C_{15}H_{14}O_3$	74.36	74.63	5.82	5.47
VIIb	69	A	119–120	$C_{18}H_{20}O_3$	76.02	75.68	7.10	6.96
VIIc	59	A	176.5–178	$C_{17}H_{16}O_3$	76.10	76.01	6.01	5.73
VIId	61	A	171.3–171.8	$C_{16}H_{16}O_3$	74.98	74.99	6.29	6.86
VIII	25[k]	E	232–233	$C_{17}H_{12}O_3$	77.25	76.91	4.58	4.21
IX (R = CH_3)	8[l]	A	117.6–117.8	$C_{13}H_{12}O_3$	72.20	72.20	5.60	5.81

[a] A, 95% ethanol; B, ligroin (*d* 0.69–0.72); C, acetic acid; D, *n*-hexane; E, benzene; F, methanol-water; G, methanol. [b] All melting points were determined in soft glass capillaries and are corrected. [c] Condensing medium: polyphosphoric acid. [d] Condensing medium: concd. sulfuric acid. [e] Obtained by hydrogenation of 8-allyl-7-hydroxy-4-methylcoumarin[2] as described in the experimental section. [f] Yield of crude material, suitable for use in the next step. [g] Based on recovery of unchanged starting material after refluxing for only one hour. [h] From acetic anhydride-pyridine. [i] From acetic anhydride–sodium acetate. [j] Bromine analyses: (a) Calcd. 35.82; found 35.69. (b) Calcd. 32.73; found 32.13. (d) Calcd. 34.72; found 34.81. [k] From the dehydrogenation of VIIc. [l] A side product in the preparation of 8-allyl-7-hydroxy-4-methylcoumarin.

(IX. R = CH_3). Their compound was obtained by the treatment of 4′,5′-dihydro-5′-iodomethyl-4-methyl-isopsoralene (XI. R = CH_3) with sodium in ethyl alcohol, which they assumed reduced the iodomethyl group. We suggest that sodium ethoxide, produced by the reaction of sodium with ethyl alcohol, caused the elimination of hydrogen iodide followed by prototropic rearrangement to give 4,5′-dimethylisopsoralene (X. R = CH_3), which has been reported[1] to have m.p. 182–183°. Furthermore, the same authors[4] report m.p. 148–149° for the compound obtained by treatment of XI (R = H) with sodium in ethyl alcohol and they propose structure IX (R = H) for it. Very probably, they obtained instead 5′-methylisopsoralene (X. R = H), reported[1] to have m.p. 153–154°. Whether or not their products were isopsoralenes, as seems likely, there can be no doubt that their compound, m.p. 182–183°, is not 4′,5′-dihydro-4,5′-dimethyl-isopsoralene, as our sample of that compound melts over 60° lower.

Three of the new psoralenes were obtained from 2-methylresorcinol (I. R = CH_3) using different β-keto esters (II) in the first step, which is a v. Pechmann condensation. With methylacetoacetic ester (IIa) and *n*-butylacetoacetic ester (IIb) condensation was effected by heating the reactants in polyphosphoric acid on a steam bath as suggested by Koo.[5] With ethyl cyclohexanone-2-carboxylate (IIc) condensation occurred readily in concentrated sulfuric acid at 0–10°. In all cases, the 7-hydroxycoumarins (III) were converted smoothly to 7-

(5) J. Koo, *Chem. & Ind.*, 445 (1955). The polyphosphoric acid was donated by the Victor Chemical Co., Chicago, Ill.

allyloxycoumarins (IV) by reaction with allyl bromide and anhydrous potassium carbonate in refluxing acetone.

Claisen rearrangement of the 7-allyloxycoumarins was effected in two different ways. 7-Allyloxy-3-*n*-butyl-4,8-dimethylcoumarin (IVb) was heated alone for three hours at 215° to give the 6-allyl product (Vb), which was very discolored and difficult to purify. The other 7-allyloxycoumarins were refluxed from sixty to ninety minutes in diethylaniline (b.p. 213–216°), which produced 6-allyl compounds that were less discolored and easier to purify. In one case, a sixty-minute reflux period left a large quantity of unchanged starting material, indicating that a longer reflux period is, in general, a safer procedure. Acetylation of the 6-allyl-7-hydroxy coumarins (V) was accomplished either with acetic anhydride and sodium acetate or with acetic anhydride and pyridine.

Chloroform solutions of the acetylated compounds readily absorbed one mole of bromine per mole of reactant to give 7-acetoxy-6-(2′,3′-dibromopropyl)coumarins (VI). In one experiment, designed to test whether acetylation is necessary before the bromine addition step, 6-allyl-7-hydroxy-4-methyl-8-*n*-propylcoumarin (Vd) in chloroform was treated with bromine. Hydrogen bromide was evolved and the product was a mixture of bromo derivatives which was not purified. These observations indicate that deactivation of the hydroxyl group, through acetylation, is necessary even when both of the positions *ortho* to the hydroxyl group are occupied. Cyclization of the dibromopropyl acetates (VI) to psoralenes (VII) was accomplished in each case by treatment with sodium ethoxide in absolute ethanol.

EXPERIMENTAL

Data for the new compounds described in this paper are summarized in Table I. Typical procedures are given in this section. Although the data are not given, infrared and ultraviolet spectra were determined for all of the psoralenes and most of the intermediate coumarins and were consistent with the structures proposed.

7-Hydroxy-3,4,8-trimethylcoumarin (IIIa). Polyphosphoric acid (250 g.) was added to a solution of 2-methylresorcinol (82.30 g., 0.66 mole) in ethyl α-methylacetoacetate (94.80 g., 0.66 mole). The mixture was stirred and heated on the steam bath at a temperature between 75–80°. In a few minutes, the mixture had solidified and, after 20 min., water was added and the mixture was stirred and refluxed for 8 hr. to ensure dissolution of all polyphosphoric acid. The tan solid, which was isolated by filtration, crystallized from glacial acetic acid to give the product reported in Table I.

7-Hydroxy-8-methyl-3,4-cyclohexenocoumarin (IIIc). 2-Methylresorcinol (68.30 g., 0.55 mole), followed by ethyl cyclohexanone-2-carboxylate (IIc) (95.00 g., 0.56 mole), was dissolved in stirred coned. sulfuric acid (500 ml.) at such a rate as to keep the temperature below 10° (ice-salt bath). After stirring for 6 hr. the chilled solution was poured into *ca.* 8 l. of ice water with constant stirring. After standing for a few minutes, a brown solid was isolated by filtration and it crystallized from glacial acetic acid as long prisms, m.p. 279–281°. Yield and analytical data are reported in Table I.

7-Hydroxy-4-methyl-8-n-propylcoumarin (IIId). A mixture of 8-allyl-7-hydroxy-4-methylcoumarin[1] (35.94 g., 0.166 mole), pyridine (200 ml.), and 5% palladium on charcoal (1.66 g.) was shaken with hydrogen at an initial pressure of 65.2 lbs./in.^{2} After 3.75 hr., 0.166 mole of hydrogen had been absorbed, and the catalyst was removed by filtration before diluting the reaction mixture to *ca.* 1.5 l. with dilute hydrochloric acid. The white precipitate, which was collected, weighed 34.28 g. and was suitable for use in the next step. Crystallization from 95% ethanol gave the material of analytical purity reported in Table I.

7-Allyloxy-3,4,8-trimethylcoumarin (IVa). A mixture of 7-hydroxy-3,4,8-trimethylcoumarin (88.00 g., 0.431 mole), anhydrous potassium carbonate (235 g., 1.7 mole), and allyl bromide (314.1 g., 2.6 mole) was stirred and heated in refluxing acetone (2 l.) for 8 hr. Evaporation of the acetone under reduced pressure left a residue, which was washed thoroughly with water, dried, and washed once with petroleum ether (b.p. 30–60°) to remove excess allyl bromide. This procedure gave 101.5 g. (96.5% yield) of product, m.p. 122–125°, free of starting material and suitable for use in the next step. Starting material, if present, can be removed by washing with 5% sodium hydroxide solution. Crystallization from 95% ethanol gave the material of analytical purity reported in Table I.

6-Allyl-7-hydroxy-3,4,8-trimethylcoumarin (Va). A solution of crude 7-allyloxy-3,4,8-trimethylcoumarin (100.5 g.) in boiling diethylaniline (275 ml.) was refluxed for 1 hr. After cooling, the product crystallized from the reaction mixture and was collected, washed with fresh diethylaniline, and then with petroleum ether (b.p. 30–60°). The crude product, m.p. 165–181°, weighed 78.1 g. (78% yield) and was completely soluble in 5% sodium hydroxide solution. It was suitable for use in the next step, but crystallization from benzene gave the material of analytical purity, m.p. 179–181°, reported in Table I.

6-Allyl-3-n-butyl-4,8-dimethyl-7-hydroxycoumarin (Vb). Crude 7-allyloxy-3-*n*-butyl-4,8-dimethylcoumarin (12.33 g.) was heated at 215° for 3 hr. in an oil bath. The cooled reaction mixture dissolved in boiling 95% ethanol, and the hot solution was filtered and diluted with excess water which caused the precipitation of 10.64 g. (86% yield) of crude product, m.p. 121–124°. This material was used in the acetylation step, although it was sufficiently impure that difficulty was encountered in purifying the acetate. A portion of the crude product was further purified by dissolving it in 5% sodium hydroxide solution, filtering, and reprecipitating with hydrochloric acid. The precipitate crystallized from a large volume of ligroin (*d.* 0.69–0.72) to give the material of analytical quality reported in Table I.

7-Acetoxy-6-allyl-4-methyl-8-n-propylcoumarin (Vd acetate). A mixture of 6-allyl-7-hydroxy-4-methyl-8-*n*-propyl coumarin (4.73 g.) and acetic anhydride (25 ml.) containing a few crystals of fused sodium acetate was heated under reflux for 4 hr. Excess anhydride decomposed on stirring for an hour with water (300 ml.) and the product (5.32 g., 97% yield), m.p. 112–113°, was collected by filtration. Crystallization from *n*-hexane did not change the melting point, but gave the sample of analytical purity reported in Table I.

7-Acetoxy-6-allyl-3,4,8-trimethylcoumarin (Va acetate). Acetic anhydride (35.0 g.) was added rapidly to a solution of crude (6-allyl-7-hydroxy-3,4,8-trimethylcoumarin (77.0 g., 0.317 mole) in pyridine (470 ml.) which was stirred for 1 hr. at room temperature. A mixture of ice and 5% hydrochloric acid (3.5 l.) was added and, after brief stirring to allow decomposition of excess acetic anhydride, the precipitate was collected and recrystallized from acetic acid to give 59.7 g. (66% yield) of product, m.p. 125–126.5°. Another crystallization from acetic acid gave the analytical sample reported in Table I.

7-Acetoxy-6-(2′,3′-dibromopropyl)-3,4,8-trimethylcoumarin (VIa). A solution of bromine (2.78 g., 0.0174 mole) in

chloroform (35 ml.) was added dropwise to a stirred solution of 7-acetoxy-6-allyl-3,4,8-trimethylcoumarin (5.00 g., 0.0174 mole) in chloroform (50 ml.). Evaporation of solvent left 7.6 g. (98% yield) of an off-white solid, m.p. 141–145°, which was suitable for use in the next step. Crystallization from ethanol gave the material reported in Table I.

2',3,4,8-Tetramethylpsoralene (VIIa). A solution of crude 7-acetoxy-6-(2',3'-dibromopropyl)-3,4,8-trimethylcoumarin (74.5 g., 0.167 mole) in ethanolic sodium ethoxide (19.2 g. sodium in 750 ml. absolute ethanol) was heated under reflux for 1.75 hr., allowed to cool for 15 min., and poured into a mixture of ice (3 kg.) and 3.5% hydrochloric acid (3 l.). The resulting precipitate was washed three times with 5% sodium hydroxide (1-l. portions) and then with water to yield 36.2 g. (89% yield) of crude product, m.p. 190–196°. Crystallization from ethanol and then from benzene gave the material reported in Table I.

3,4-Benzo-2',8-dimethylpsoralene (VIII). A mixture of 2',8-dimethyl-3,4-cyclohexenopsoralene (3.01 g.), 5% palladium on charcoal (3.00 g.), and diphenyl ether (25 ml.) was heated under reflux for 5 hr. The catalyst was removed from the hot solution by filtration and was washed with 10 ml. of hot diphenyl ether. On cooling, the combined filtrate and wash liquor deposited a crystalline solid, which was washed with 95% ethanol and recrystallized from benzene to yield off-white prisms, (0.75 g., 25% yield), m.p. 232–233°. Analytical data are recorded in Table I.

4',5'-Dihydro-4,5'-dimethylisopsoralene (IX. R = CH_3). 7-Allyloxy-4-methylcoumarin[1] (212.5 g.) was heated at 215° (temperature of reaction mixture) for 3 hr. and the hot melt was poured into ethanol (1.5 l.). Addition of water (10 l.) gave a precipitate, which was treated with 5% aqueous sodium hydroxide (1.5 l.), in several portions, to obtain an alkali insoluble residue that crystallized from 95% ethanol in pale yellow needles (17.0 g., 8% yield), m.p. 117.6–117.8°. Acidification of the alkaline extracts gave crude 8-allyl-7-hydroxy-4-methylcoumarin which was purified in the manner described earlier.[1] Analytical results are included in Table I.

4,5'-Dimethylisopsoralene (X. R = CH_3). A mixture of 4',5'-dihydro-4,5'-dimethylisopsoralene (5.41 g.), 5% palladium on charcoal (5.0 g.), and diphenyl ether (60 ml.) was heated under reflux for 5 hr., filtered, and allowed to cool. The next day, an off-white solid (1.72 g., 32.1% yield), m.p. 179.6–182.2°, was collected by filtration. Dilution of the filtrate to 300 ml. with petroleum ether (b.p. 30–60°) gave a second crop which, when combined with the first crop, crystallized from ethanol in colorless prisms (2.33 g., 43% yield), m.p. 182–183°. A mixture of this material and a sample of 4,5'-dimethylisopsoralene from another method[1] had m.p. 182–183°. The infrared spectra of the two samples were identical.

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KALAMAZOO, MICH.

[CONTRIBUTION FROM THE UNITED STATES DEPARTMENT OF AGRICULTURE]

Spectral Studies on Flavonoid Compounds. II. Isoflavones and Flavanones[1a]

ROBERT M. HOROWITZ[1b] AND LEONARD JURD[1c]

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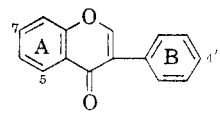
The ultraviolet spectra of isoflavones and flavanones are similar. A free 7-hydroxyl group in these compounds can be detected by spectral changes observed on the addition of sodium acetate, while a free 5-hydroxyl group can be detected by addition of aluminum chloride. Certain specifically substituted flavanones are shown to form chalcones readily in dilute alkali. A number of examples are given.

Although the ultraviolet spectra of many naturally occurring isoflavones and flavanones have been reported,[2] spectral changes in the presence of basic and complexing reagents have not been extensively employed in the structural analysis of these compounds. In view of the success with which spectral shifts produced by certain reagents have been correlated with the location of hydroxyl groups in various flavonol compounds,[1] it was of interest to determine whether similar shifts might provide useful structural information in the isoflavone and flavanone series.

Isoflavones (I) and flavanones (II) differ from flavonols in that the B-ring is not conjugated with



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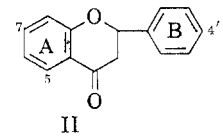

II

the carbonyl group. The spectral characteristics of isoflavones and flavanones are similar, therefore, and are determined primarily by absorption in the A-ring conjugated with the carbonyl group. These compounds usually have only one prominent ab-

(1) (a) Part I: L. Jurd and R. M. Horowitz, *J. Org. Chem.*, 22, 1618 (1957). (b) Fruit and Vegetable Chemistry Laboratory, Pasadena, Calif.[1d]; (c) Western Regional Research Laboratory, Albany 10, Calif.[1d]; (d) a laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) *E.g.*, W. K. Warburton, *Quart. Rev. Chem. Soc.*, 8, 67 (1954); N. L. Dutta, *J. Ind. Chem. Soc.*, **36**, 165 (1959); J. B. Harborne, *Chemistry and Industry*, 1142 (1954); D. H. Curnow, *Biochem. J.*, 58, 283 (1954); P. Crabbe, P. R. Leeming, and C. Djerassi, *J. Am. Chem. Soc.*, 80, 5262 (1958).