under reflux for 3 hr., resulting in complete solution. The chilled mixture gave 1.0 g. (74%) of crude product, m.p. 230–234°. The solid was recrystallized from 40 ml. of hot methanol to give 0.60 g. (44%) of product, m.p. 237–239°; $\lambda_{max(\mu)}^{KBr}$ 3.11 (NH); 5.70–5.80 (uracil and ester C=O), 6.60 (NH and pyrimidine ring); 6.13, and 6.99 (pyrimidine ring), 8.15 (ester C—O—C); $\lambda_{max(m\mu)}^{pH\ 1}$ 270 (ε 13300); $\lambda_{max(m\mu)}^{pH\ 7}$ 272 (ε 11900); $\lambda_{max(m\mu)}^{pH\ 13}$ 239 (ε 13700), 291 (ε 17900). On paper chromatography in solvent A, the product moved as a single spot with R_{Ad} 1.57.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.9; H, 5.70; N, 13.2. Found: C, 51.1; H, 5.79; N, 13.0.

Uracil-5-carboxyhydrazide (IX). A stirred suspension of 0.50 g. (2.36 mmoles) of the ester (VIII) in 5 ml. of hydrazine hydrate was heated under reflux for 15 min. and the resulting solution cooled to room temperature. Methanol (10 ml.) was added to the solution and, on chilling, 0.30 g. (75%) of product, m.p. >300°, was obtained. The solid was recrystallized from 40 ml. of water with the aid of Norit to give 0.20 g. (50%) of product, m.p. >300°; $\lambda_{max(\mu)}^{Nujol}$ 3.09 and 6.30 (NH_2), 3.25 and 3.30 (NH), 5.65 and 5.78 (uracil C=O), 5.99 (amide C=O), 6.65 (NH and pyrimidine ring), 6.09 and 6.92 (pyrimidine ring); $\lambda_{max(m\mu)}^{pH\ 1}$ 219 (ε 12800), 273 (ε 12000); $\lambda_{max(m\mu)}^{pH\ 7}$ 223 (ε 8500), 278 (ε 10800); $\lambda_{max(m\mu)}^{pH\ 13}$ 244 (broad ε 10200), 292 (ε 16800). On paper in solvent B the product moved as a single spot with R_{Ad} 0.43.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.2; H, 3.52; N, 32.8. Found: C, 35.3; H, 3.74; N, 32.8.

N-(2-Hydroxyethyl)uracil-5-carboxamide (XI). A mixture of 1.0 g. (4.7 mmoles) of 5-carbo-*n*-butoxyuracil (VIII), 0.86 g. (14.2 mmoles) of 2-aminoethanol, and 15 ml. of absolute ethanol was heated in a stainless steel bomb at 150–155° for 15 hr. The bomb was cooled and the contents were evaporated to dryness *in vacuo* at 50–60°. Water (6 ml.) was added to the residual sirup and the solution was adjusted to *p*H 1 with 6*M* hydrochloric acid. On chilling, the solution deposited 0.45 g. (48%) of product, m.p. 244–246°. This was recrystallized from 30 ml. of hot water to yield 0.25 g. (26%) of material, m.p. 284–285°; $\lambda_{max(\mu)}^{Nujol}$ 2.98, 3.09, 3.19, 3.31 (NH, OH), 5.81 and 5.90 (uracil and amide C=O), 6.25 (pyrimidine ring), 9.38 (C—OH); $\lambda_{max(m\mu)}^{pH\ 1}$ 221 (ε 13100), 272 (ε 12700); $\lambda_{max(m\mu)}^{pH\ 7}$ 221 (ε 13100), 273 (ε 12000); $\lambda_{max(m\mu)}^{pH\ 13}$ 244 (ε 11000), 290 (ε 17000). On paper chromatography in solvent A the product moved as a single spot with R_{Ad} 0.83.

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.2; H, 4.55; N, 21.0. Found: C, 42.3; H, 4.77; N, 20.7.

N-(n-butyl)uracil-5-carboxamide (XII). A mixture of 0.50 g. (2.36 mmoles) of ester (VIII) and 2.0 g. (27 mmoles) of *n*-butylamine was heated in a stainless steel bomb at 170° for 15 hr. The bomb was cooled and the contents were evaporated to dryness *in vacuo* at 70–80°. Water (20 ml.) was added to the semi-crystalline residue and the mixture was adjusted to *p*H 1 with 6*M* hydrochloric acid, causing the precipitation of a solid, 0.35 g. (73%), m.p. 290–293°. The solid was recrystallized from 50 ml. of hot water to yield 0.30 g. (63%) of the analytical sample, m.p. 290–291°; $\lambda_{max(\mu)}^{Nujol}$ 3.06 and 3.22 (NH), 5.78 and 5.89 (uracil C=O), 6.19 (pyrimidine ring); surprisingly, there was no amide carbonyl band near 6.0 μ; $\lambda_{max(m\mu)}^{pH\ 1}$ 222 (ε 12600), 272 (ε 12200); $\lambda_{max(m\mu)}^{pH\ 7}$ 222 (ε 13000), 273 (ε 12600); $\lambda_{max(m\mu)}^{pH\ 13}$ 243 (ε 12000), 290 (ε 17600). On paper chromatography in solvent A the product moved as a single spot with R_{Ad} 1.45.

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.1; H, 6.19; N, 19.9. Found: C, 51.3; H, 6.21; N, 19.9.

Acknowledgment. The authors are indebted to Dr. P. Lim for interpretation of the infrared spectra and to his staff for the paper chromatographic results. They also wish to thank Mr. O. P. Crews, Jr., and his group for the large-scale preparation of certain intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

Guanidines with Antihypertensive Activity

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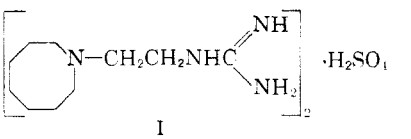
[2-(Octahydro-1-azocinyl)ethyl]guanidine sulfate was found to have protracted antihypertensive properties with the capacity to block sympathetic efferent transmission, presumably at the nerve terminals. Alterations of the ring, side chain, and terminal grouping were investigated and the relationship of these modifications to activity ascertained.

The observation that hexahydro-1-azepinylpropionamidoxime[1] possessed protracted antihypertensive activity with an unusual mechanism of action has prompted a wider search for large-membered heterocyclic compounds which might display similar unique pharmacological properties. Previous communications[2] on this study disclosed that [2-(octahydro-1-azocinyl)ethyl]guanidine sulfate (I) markedly lowered the arterial pressure of unanesthetized renal and neurogenic dogs and



I

blocked sympathetic efferent transmission, presumably at the nerve terminals. The protracted

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antihypertensive properties of this compound were corroborated in man when it was submitted for clinical trial.

From the variety of guanidine compounds investigated, some conclusions regarding structure and activity could be drawn. With reference to ring size, it was found that whereas the pyrrolidyl and piperidyl compounds exhibited moderate pharmacological properties, a significant increase in antihypertensive activity occurred when the hexahydroazepinyl moiety was present. The eight-membered ring derivative, [2-(octahydro-1-azocinyl)ethyl]guanidine sulfate, possessed maximum activity. Further increase in ring size was accompanied by diminution of activity. These findings are similar to those in the amidoxime series except that maximum activity, in that instance, was associated with the hexahydroazepine ring system. A variety of other ring systems, *e.g.*, the thiazepinyl, morpholinyl, phenothiazinyl, and pyridyl, were used in place of the octahydroazocinyl moiety, but only the pyridyl had noteworthy activity; the dialkylaminoalkyl guanidines were inactive.

Side chain variations disclosed that for optimal activity the ethyl side chain was essential. Alteration of the chain produced less active compounds, frequently with more pronounced pharmacological side effects. These findings, too, are similar to those noted with the amidoximes except that peak activity in that case was noted with the propyl side chain. Replacement of the guanidino portion of the molecule by those functional groups described in the Experimental section gave inactive compounds.

In general, the guanidines were prepared from the appropriate amines and a 2-methylthiopseudourea salt according to the method of Rathke.[3] The amines were obtained by lithium aluminum hydride reduction of the nitriles which in turn were readily synthesized by condensation of an aliphatic or cyclic imine with a halonitrile. The preparation of the larger ring systems has been previously described.[1,4,5] Hexahydro-5-oxo-1,4-thiazepine was prepared from tetrahydro-1-thiopyran-4-one by utilizing the Schmidt reaction for the ring expansion; reduction of this lactam with lithium aluminum hydride gave the desired 1,4-hexahydrothiazepine. All other compounds were prepared by established synthetic methods and are given in the Experimental or tables.

EXPERIMENTAL[6]

Tables I and II list those nitriles and amines not previously reported in the literature. 1-Pyrrolidylacetonitrile,[7] 1-piperidylacetonitrile,[8] hexahydro-1-azepinylacetonitrile,[9] octahydro-1-azocinylacetonitrile,[1b] 2-(1-pyrrolidyl)ethylamine,[10] 2-(1-piperidyl)ethylamine,[10] 2-(hexahydro-1-azepinyl)ethylamine,[9] 2-(2-pyridyl)ethylamine,[11] 2-(4-pyridyl)ethylamine,[12] and 3-(10-phenothiazinyl)propylamine[13] have been previously characterized.

The preparation of [2-(octahydro-1-azocinyl)ethyl]guanidine sulfate is given to illustrate the general method used in preparing the guanidines listed in Table III.

Octahydro-1-azocinylacetonitrile (II). Octahydroazocine[5] (109.2 g.; 0.96 mole) in 280 ml. of benzene was added to a solution of 73 g. (0.96 mole) of chloroacetonitrile in 500 ml. of benzene containing a suspension of 51.5 g. (0.48 mole) of anhydrous sodium carbonate. Vigorous stirring and refluxing was continued for 4 hr. The reaction mixture was then cooled, filtered, concentrated *in vacuo*, and fractionated. See Table I footnote for reference to physical properties of this material.

2-(Octahydro-1-azocinyl)ethylamine (III). While stirring, 127.5 g. (0.83 mole) of octahydro-1-azocinylacetonitrile in 300 ml. of ether was added slowly to 44.5 g. (1.17 mole) of lithium aluminum hydride in 2 l. of ether. The solution was then refluxed for 3 hr. and stirred at room temperature overnight. The solution was cooled and decomposed by carefully adding 40 ml. of water, 50 ml. of 20% sodium hydroxide, and 125 ml. of water to the solution. After filtration and concentration of the ether solution, the residual oil was fractionated. See Table II footnote for reference to physical properties of this material.

[2-(Octahydro-1-azocinyl)ethyl]guanidine sulfate (I). 2-Methylthiopseudourea sulfate (86 g.; 0.31 mole) was added to 98 g. (0.62 mole) of 2-(octahydro-1-azocinyl)ethylamine dissolved in 300 ml. of water and the mixture refluxed for 8 hr. Vigorous evolution of methyl mercaptan took place and solid separated. After cooling, the solid was removed by filtration and recrystallized from ethanol-water. See Table III, footnote c, for reference to physical properties of this material.

1-(Octahydro-1-azocinyl)-1-phenyl-2-propanone. A solution of 36.2 g. (0.17 mole) of 1-bromo-1-phenyl-2-propanone[14] in 100 ml. of benzene was slowly added to a stirring mixture of 38 g. (0.34 mole) of octahydroazocine in 125 ml. of benzene. After refluxing for 3 hr. the solution was stirred an additional 21 hr. at room temperature. After filtration and concentration *in vacuo*, the residual oil was fractionated to give a yellow oil, b.p. 115–128° (0.4 mm.), yield 12.4 g. (30%), n_D^{28} 1.5312.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.37; H, 9.39; N, 5.71. Found: C, 78.17; H, 9.20; N, 5.91.

The *oxime* was recrystallized from ethanol-water and melted at 85–88°.

Anal. Calcd. for $C_{16}H_{24}N_2O$: C, 73.91; H, 9.30; N, 10.78. Found: C, 73.30; H, 9.16; N, 11.29.

1-Methyl-2-(octahydro-1-azocinyl)-2-phenethylamine. 1-Octahydro-1-azocinyl)-1-phenyl-2-propanone oxime (13.38 g.; 0.05 mole) in 100 ml. of ether was added to a refluxing solution of 4.35 g. (0.114 mole) of lithium aluminum hydride in 150 ml. of ether. The solution was refluxed for an additional 3 hr. and decomposed by successive additions of 10 ml. of water, 12 ml. of 20% sodium hydroxide and 30 ml.

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TABLE I

PHYSICAL PROPERTIES OF THE NITRILES R—$(CH_2)_m$CN

R	m	Yield, %	B.P.	mm.	n_D^t	t	Molecular Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Octahydro-1-azocinyl[a]	1	87	114–118	14	1.4720	24	$C_9H_{16}N_2$	71.11	71.17	10.61	10.62	18.43	18.36
Octahydro-1-azocinyl	3	71	140–144	15	1.4751	28	$C_{11}H_{20}N_2$	73.39	73.56	11.20	11.21	15.56	15.26
Octahydro-1-azoninyl	1	83	120–125	13	1.4783	27	$C_{10}H_{18}N_2$	72.35	72.28	10.93	11.13	16.88	16.76
1-Azacycloundecyl	1	63	149–153	15	1.4849	25	$C_{12}H_{22}N_2$	74.29	74.32	11.43	11.44	14.44	14.32
Hexahydro-1,4-thiazepin-4-yl	1	56	148–150	13	1.5268	24	$C_7H_{12}N_2S$	53.89	53.93	7.75	7.77	17.95	17.90

[a] Designated as compound II under Experimental.

TABLE II

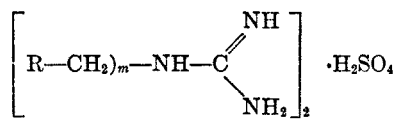
PHYSICAL PROPERTIES OF THE AMINES R—$(CH_2)_m$$NH_2$

R	m	Yield, %	B.P.	mm.	n_D^t	t	Molecular Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Octahydro-1-azocinyl[a]	2	89	108–111	14	1.4830	22	$C_9H_{20}N_2$	69.29	69.26	12.92	12.92	17.96	17.89
Octahydro-1-azocinyl	3	70	94–98	0.4	1.4858	25	$C_{10}H_{22}N_2$	70.65	70.98	13.04	13.70	16.48	16.88
Octahydro-1-azocinyl	4	74	70–77	0.35	1.4818	28	$C_{11}H_{24}N_2$	71.80	71.97	13.15	12.97	15.23	15.24
Octahydro-1-azoninyl	2	76	64–68	0.7	1.4859	26	$C_{10}H_{22}N_2$	70.65	70.88	13.04	12.93	16.48	16.61
1-Azacycloundecyl	2	70	87–90	0.3	1.4880	28	$C_{12}H_{26}N_2$	72.79	72.94	13.24	13.11	14.15	14.11
Hexahydro-1,4-thiazepin-4-yl	2	33	120–122	13	1.5293	24	$C_7H_{16}N_2S$	52.54	52.86	10.08	10.33	17.51	17.46

[a] Designated as Compound III under Experimental.

TABLE III

PHYSICAL PROPERTIES OF THE GUANIDINES



R	m	Yield, %	M.P.,[a] dec.	Molecular Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1-Pyrrolidyl	2	80	159–162	$C_{14}H_{34}N_8O_4S$[b]	41.01	40.92	8.36	8.76	27.33	27.05
1-Piperidyl	2	53	204–207	$C_{16}H_{38}N_8O_4S$	43.77	43.37	8.73	8.64	25.53	25.54
Hexahydro-1-azepinyl	2	83	208–215	$C_{18}H_{42}N_8O_4S$	46.29	46.33	9.07	9.16	24.00	24.39
Octahydro-1-azocinyl	2	74	276–281	$C_{20}H_{46}N_8O_4S$[c]	48.55	48.49	9.37	9.51	22.64	22.49
Octahydro-1-azocinyl	3	82	248–252	$C_{22}H_{50}N_8O_4S$	50.52	50.14	9.64	9.74	21.43	20.61
Octahydro-1-azocinyl	4	66	215–235	$C_{24}H_{56}N_8O_5S$[d]	50.66	50.69	9.92	9.73	19.69	19.40
Octahydro-1-azoninyl	2	70	272–275	$C_{22}H_{50}N_8O_4S$	50.52	50.86	9.64	9.70	21.43	20.88
1-Azacyloundecyl	2	70	260–273	$C_{26}H_{58}N_8O_4S$	53.93	54.08	10.10	10.10	19.35	19.25
Hexahydro-1,4-thiazepin-4-yl	2	63	207–214	$C_{16}H_{38}N_8O_4S_2$	38.20	37.59	7.62	7.60	22.28	21.94
4-Morpholinyl	2	41	177–189	$C_{14}H_{34}N_8O_6S$	38.04	38.12	7.75	7.77	25.35	24.41
10-Phenothiazinyl	3	52	127–130	$C_{32}H_{38}N_8O_4S_3$	55.30	54.95	5.51	5.70	16.12	15.73
2-Pyridyl	2	48	147–150	$C_{16}H_{26}N_8O_4S$	45.11	45.50	6.15	6.06	26.31	26.49
4-Pyridyl	2	56	256–257	$C_{16}H_{26}N_8O_4S$	45.11	45.36	6.15	6.48	26.31	26.17
Diethylamino	2	66	210–215	$C_{14}H_{38}N_8O_4S$[e]	40.52	40.82	9.23	9.20	27.00	26.95
Di-*n*-butylamino	2	63	120–123	$C_{22}H_{54}N_8O_4S$[f]	50.23	50.39	10.35	10.92	21.30	21.51
Di-*n*-propylamino	2	73	190–205	$C_{18}H_{46}N_8O_4S$[e]	46.00	46.05	9.87	9.96	23.84	23.81

[a] The recrystallizations were from ethanol-water unless otherwise noted. [b] Prepared by permitting the reactants to stand at room temperature for several days after which the product crystallized from the reaction mixture as an analytically pure sample. [c] Designated as Compound I under Experimental. [d] Monohydrate, recrystallized from ethanol. [e] Recrystallized from ethanol-ether. [f] Recrystallized from water.

of water. After filtration, concentration *in vacuo*, and fractionation of the residual oil, 6.5 g. (51%) of product was obtained, b.p. 136–146° (0.6 mm.), n_D^{28} 1.5353.

Anal. Calcd. for $C_{16}H_{26}N_2$: C, 78.11; H, 10.65; N, 11.39. Found: C, 78.52; H, 10.25; N, 10.81.

[1-Methyl-2-(octahydro-1-azocinyl)-2-phenethyl]guanidine sulfate was prepared from 5 g. (0.02 mole) of 1-methyl-2-(octahydro-1-azocinyl)-2-phenethylamine and 2.83 g. (0.01 mole) of 2-methylthiopseudourea sulfate. Recrystallization from ethanol-ether gave 4.1 g. (61%) of crystalline material, m.p. 145–155° dec.

Anal. Calcd. for $C_{34}H_{42}N_8O_4S$: C, 60.49; H, 8.66; N, 16.60. Found: C, 60.40; H, 8.37; N, 16.81.

Hexahydro-5-oxo-1,4-thiazepine. With moderate cooling, 12.7 g. (0.19 mole) of sodium azide was slowly added to 15 g. (0.13 mole) of tetrahydro-1-thiopyran-4-one[15] in 65 ml. of concd. hydrochloric acid. After the addition was completed, stirring was continued for an additional 4 hr. at room temperature. Solid sodium carbonate was then added until the solution was slightly alkaline, sufficient water being added to dissolve salts present. After extraction with chloroform, drying, and concentrating to a low volume, petroleum ether was added to precipitate the product. Recrystallization was from carbon tetrachloride–heptane to give 11.5 g. (63%) of product, m.p. 115–118°.

Anal. Calcd. for C_5H_9NOS: C, 45.84; H, 6.93; N, 10.69; S, 24.48. Found: C, 45.13; H, 6.79; N, 10.10; S, 24.23.

1,4-Hexahydrothiazepine. To a solution of 5.9 g. (0.15 mole) of lithium aluminum hydride in 800 ml. of ether was added, with stirring, 12 g. (0.09 mole) of solid hexahydro-5-oxo-1,4-thiazepine. After refluxing for 24 hr., the mixture was carefully decomposed with 20 ml. of water. After filtration and concentration of the filtrate, the residue was fractionated to give 9.5 g. (88%) of product, b.p. 192–193° n_D^{27} 1.5342.

Anal. Calcd. for $C_5H_{11}NS$: C, 51.32; H, 9.48; N, 11.97; S, 27.41. Found: C, 51.23; H, 8.96; N, 11.22; S, 27.85.

The *hydrochloride salt* was recrystallized from isopropyl alcohol–ether to give material which melted at 210–212°.

Anal. Calcd. for $C_5H_{12}ClNS$: C, 39.25; H, 7.91; N, 9.16; Cl, 23.17. Found: C, 39.08; H, 7.89; N, 9.06; Cl, 23.04.

[2-(Octahydro-1-azocinyl)ethylamino]-2-imidazoline hydroiodide. To 4 g. (0.025 mole) of 2-(octahydro-1-azocinyl)-ethylamine in 10 ml. of water was added 6.26 g. (0.025 mole) of 2-methylthio-2-imidazoline[16] hydroiodide and the mixture warmed on the steam bath until evolution of methyl mercaptan ceased. The oil which separated on cooling was dissolved in ethanol and reprecipitated by addition of ether. This low melting material amounted to 6 g. (67%).

Anal. Calcd. for $C_{12}H_{25}IN_4$: C, 40.91; H, 7.16; N, 15.92. Found: C, 39.66; H, 7.25; N, 15.65.

[2-(Octahydro-1-azocinyl)ethyl]-2-thiopseudourea dihydrochloride. 2-(Octahydro-1-azocinyl)ethylchloride hydrochloride[5] (2 g.; 0.01 mole) was added with stirring to a solution of 0.8 g. (0.01 mole) of thiourea in 26 ml. of ethanol and refluxed for 6 hr. The solid which separated after cooling was recrystallized from ethanol to give 1.6 g. (56%) of material, m.p. 212–215°.

Anal. Calcd. for $C_{10}H_{23}Cl_2N_3S$: C, 41.70; H, 8.05; N, 14.59. Found: C, 41.59; H, 7.96; N, 14.37.

Acknowledgment. The authors wish to express their appreciation to Mr. Louis Dorfman and his associates for the microanalyses.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Anthochlor Pigments. XIV. The Pigments of *Viguiera multiflora* (Nutt.) and *Baeria chrysostoma* (F. and M.)

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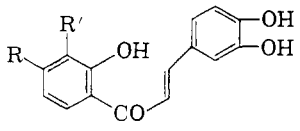
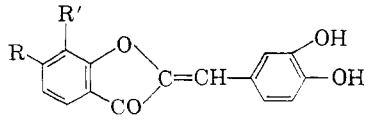
The flower petals of two composites, neither of which is a member of the subtribe Coreopsidinae, have been found to be pigmented with chalcones and aurones. The presence of these (anthochlor) pigments in plants not in the subtribe of which they have heretofore seemed to be characteristic offers further evidence concerning their biosynthetic relationships. As in earlier examples, a chalcone is accompanied by the structurally corresponding aurone in each instance of its occurrence.

The designation "anthochlor" has been applied to the polyhydroxychalcones and -aurones (2-benzal-3-coumaranones) typified by the widely distributed compounds butein (I) and sulfuretin (V):



I. Butein, R = OH, R′ = H
II. Coreopsin, R = *O*-glucosyl, R′ = H
III. Okanin, R = R′ = OH
IV. Marein, R = *O*-glucosyl, R′ = OH



V. Sulfuretin, R = OH, R′ = H
VI. Sulfurein, R = *O*-glucosyl, R′ = H
VII. Maritimetin, R = R′ = OH
VIII. Maritimein, R = *O*-glucosyl, R′ = OH

Pigments of these classes that contain a resorcinol-derived ring (as in I and II) rather than one derived from phloroglucinol[1] occur in numerous genera of compositae, and most characteristically