sodium hydroxide (250 ml.). for 1 hr. at 65°. Acidification and crystallization from methanol yielded 3.1 g. of Vf as colorless needles (m.p. 274–280°; R_f 0.35). A sample recrystallized for analysis had the same melting point range.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.8; H, 4.24.

4,7,4'-Triacetoxy-3-phenylcoumarin (Vd) was obtained by boiling a mixture of Ve (700 mg.) and fused sodium acetate (2 g.) in acetic anhydride (20 ml.) for 10 min. The triacetate Vd crystallized from a small volume of methanol as colorless needles (630 mg.), m.p. 189–191° (R_f 0.55).

Anal. Calcd. for $C_{21}H_{16}O_8$: C, 63.63; H, 4.07. Found: C, 63.9; H, 4.04.

4-Alkylcoumarins.[34]

	M.p., °C. (ref.)	M.p., °C. (found)	R_f
Vh	200[34a]	203–204 (Kofler block)	0.67
Vi	156[34a]	153–153.5	0.86
Vj	265[34a]	265 dec.	0.46
Vk	317[34b]	310 dec. (Kofler block)	0.37
Vl	279[34b]	274 (Kofler block)	0.71
Vm	232[34a]	227–230	0.62

Acknowledgment.—We are indebted to Mrs. A. Gramps for technical assistance, to Mr. A. P. Hendrickson for performing the bioassays, to Dr. R. L. Lundin for nuclear magnetic resonance data and interpretation, and to Mr. L. M. White and Miss G. E. Secor for microanalyses. We also wish to thank Professors W. G. Dauben and W. B. Whalley for helpful discussions.

Oxazolocoumarins

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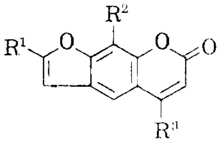
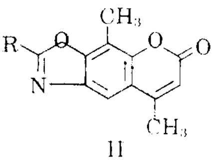
Nine oxazolocoumarins (II) (nitrogen analogs of psoralens) were prepared from 6-amino-7-hydroxy-4,8-dimethylcoumarin. These compounds have been subjected to a number of biological tests. Some of them have been found to be mild central nervous system depressants. One (II, R = CH_3) is active against powdery mildew on cucumbers. None shows psoralen-like activity on skin.

Psoralen (Ia) and its simple substitution products (*e.g.*, Ib, Ic) are highly active in promoting erythema and pigmentation in skin exposed to sunlight. The present paper reports the synthesis of related compounds (II) in which one CH group has been replaced by a nitrogen atom.

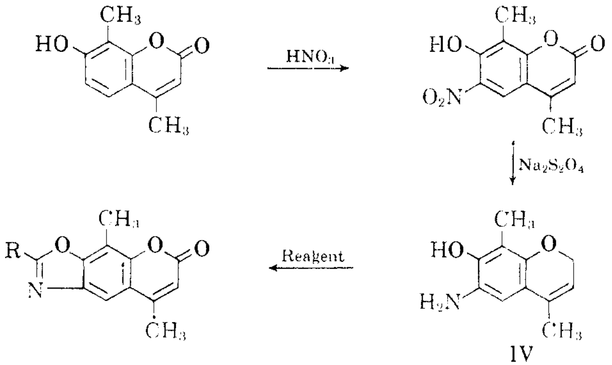




II

Ia, R^1, R^2, R^3 = H (Psoralen)
b, R^1, R^3 = H; R^2 = OCH_3[1]
c, R^1, R^2, R^3 = CH_3[2,3]

The oxazolocoumarins[4] (II) were prepared from 6-amino-7-hydroxy-4,8-dimethylcoumarin (IV) by reaction with the appropriate carboxylic acid. The same key intermediate was used to prepare the 2-hydroxy (V), 2-mercapto (VI), and 2-amino (VII), compounds. Infrared and ultraviolet spectra indicate that V and VI exist mostly in their keto forms in neutral media.



IV

II, Reagent used, RCOOH
V, R = OH; reagent, $(H_2N)_2CO$
VI, R = SH; reagent, CS_2 + KOH
VII, R = H_2N; reagent, BrCN

Most of these oxazolocoumarins were tested for erythemal activity (photosensitization) on albino guinea-pig skin. In spite of their

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(1) Meloxine®, brand of methoxsalen.

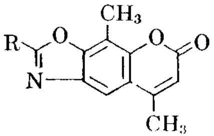
(2) K. D. Kaufman, *J. Org. Chem.*, **26**, 117 (1961).

(3) M. A. Pathak, J. H. Fellman, and K. D. Kaufman, *J. Invest. Dermatol.*, **35**, 165 (1960).

(4) Systematically named (II, R = alkyl): 5-benzoxazoleacrylic acid, 2-alkyl-6-hydroxy-β,7-dimethyl-, γ-lactone; or 7H-pyrano[3,2-f]benzoxazol-7-one, 2-alkyl-5,9-dimethyl-.

TABLE I

OXAZOLOCOUMARINS



R	Yield, %[a]	M.p., °C.[b]	Crystallizing solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found[b]	Nitrogen, % Calcd.	Nitrogen, % Found[b]
H	68	230–231	DMF[c]	$C_{12}H_9NO_3$	66.97	66.94	4.22	4.45	6.51	6.42
CH_3	72	241–243	DMF[d]	$C_{13}H_{11}NO_3$	68.11	68.28	4.84	4.68	6.11	6.15
C_2H_5	62	172–173	EtOH	$C_{14}H_{13}NO_3$	69.12	68.98	5.39	5.75	5.76	5.86
$(CH_3)_2CH$	80	161–162	EtOH	$C_{15}H_{15}NO_3$	70.02	70.12	5.88	5.99	5.44	5.42
$C_6H_{11}CH_2$[e]	68	180.5–181	EtOH + MeOH	$C_{19}H_{21}NO_3$	73.29	72.97	6.80	6.49	4.50	4.51
$C_2H_5OCH_2$	41	176–177.5	EtOH	$C_{15}H_{15}NO_4$	65.92	66.25	5.53	5.73	5.13	5.00
OH	34	352–353	DMF[c]	$C_{12}H_9NO_4$	62.34	62.48	3.92	3.92	6.06	6.08
SH	51	342.5–343.5	...	$C_{12}H_9NO_3S$[f]	58.28	58.21	3.67	3.86	5.67	5.66
NH_2	47	>365	DMF[c]	$C_{12}H_{10}N_2O_3$	62.60	62.51	4.38	4.46	12.17	11.92
$NH_2.HCl$	95[g]	>345	H_2O + HCl	$C_{12}H_{11}ClN_2O_3\cdot 1.5H_2O$[h]	49.07	49.34	4.80	4.82	9.54	9.38

[a] Unless specifically described in the experimental section, these compounds were prepared as described for 6-hydroxy-β,7-dimethyl-5-benzoxazoleacrylic acid γ-lactone. The yields are calculated from 6-amino-7-hydroxy-4,8-dimethylcoumarin. [b] See footnote 5. [c] DMF is dimethylformamide. [d] The crude sublimed product was recrystallized first from benzene, then from dimethylformamide. [e] C_6H_{11} = cyclohexyl. The excess cyclohexaneacetic acid was removed under reduced pressure and the product was sublimed at somewhat higher temperature and lower pressure than in the model case (230–240°, bath at 0.6 mm.). [f] Calcd.: S, 12.97. Found: S, 12.70. [g] Yield calculated from the free base. [h] Calcd.: Cl, 12.07; O, 24.51. Found: Cl, 11.80; O, 24.64.

close relationship to the psoralens, they were found to be completely inactive.[3] All the compounds reported herein were tested in other biological assays. The trimethyl oxazolocoumarin (II, R = CH_3) proved to be highly active against powdery mildew on cucumbers but was deemed economically impractical for this use. Strangely, even the closest analogs (II, R = H, C_2H_5) are not active in this respect. A number of the oxazolocoumarins exhibited a moderate degree of activity as central nervous system depressants, as determined by gross observation of intact mice.

Experimental[5]

7-Hydroxy-4,8-dimethyl-6-nitrocoumarin.—A solution of 95.1 g. (0.5 mole) of 7-hydroxy-4,8-dimethylcoumarin[6] in 250 ml. of concentrated sulfuric acid was cooled by an ice-salt bath to 0°. A solution of 37.3 ml. (0.75 mole) of concentrated nitric acid in 112 ml. of concentrated sulfuric acid was cooled to 0° and slowly added during 30 min. at such a rate that the temperature was kept at 0–6°. After stirring at −5 to 0° for 1 hr., the dark solution was poured into ice, giving a yellow precipitate. This was collected, washed well with water and dried, yielding 110.5 g. of nitro compound, m.p. 222–226°. This was recrystallized from 1.5 l. of glacial acetic acid with filtration of the hot solution, giving 9.16 g. (78%) of dark yellow crystals, m.p. 229.5–231.5°.

Anal. Calcd. for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.96. Found: C, 56.26; H, 3.80; N, 5.99.

6-Amino-7-hydroxy-4,8-dimethylcoumarin.—To a suspension of 23.5 g. (0.1 mole) of 7-hydroxy-4,8-dimethyl-6-nitrocoumarin in 200 ml. of 15% aqueous ammonia was added, with stirring, a solution of 70 g. (0.4 mole) of sodium hydrosulfite in 300 ml. of water. The mixture became warm and the nitro compound dissolved. The solution was then heated to reflux and the bright yellow amine soon began to crystallize. After refluxing for 15 min., the mixture was cooled, the product collected, washed with water and dried. The yield was 19.8 g. (97%) of material pure enough for the next step, m.p. 256–259° dec. This may be recrystallized by dissolving in 1.5 l. of 80% ethanol, filtering hot, concentrating to 900 ml., and cooling. By this procedure 17.15 g. of dark yellow-green crystals were obtained, m.p. 255–258° dec.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.67; H, 5.37; N, 6.85.

6-Hydroxy-β,7-dimethyl-5-benzoxazoleacrylic Acid γ-Lactone (II, R = H).—A solution of 10 g. (0.49 mole) of 6-amino-7-hydroxy-4,8-dimethylcoumarin in

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(5) Melting points were taken in capillary tubes with a partial immersion thermometer and are not corrected. They are reported to the nearest 0.5°. Elemental analyses and spectra are by Dr. R. W. Rinehart and associates of our Department of Physical and Analytical Chemistry. Infrared spectra were obtained on all pure products and in all cases support the proposed structures.

(6) S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **6A**, 112 (1937); **7A**, 8 (1938); *Chem. Abstr.*, **32**, 559^5, 4561^5 (1938).

100 ml. of 98% formic acid in a 2-l. reaction (resin) flask was heated under reflux for 1.5 hr. The excess formic acid was distilled at atmospheric pressure and the residue was heated under nitrogen in a bath at 240–250°. The flask then was adapted for sublimation as described by Wiberg.[7] The inner flask (500-ml. round-bottomed without water inlet or outlet) must be clamped to prevent its being sucked in by the vacuum, and is cooled with Dry Ice and acetone. No difficulty was encountered in using this apparatus under vacuum. The product sublimed at a bath temperature of 150–250° at 12 mm. giving 10 g. of yellow solid, which was recrystallized from 90 ml. of dimethylformamide, yielding 7.13 g. (68%) of yellow crystals, m.p. 230–231°.

6-Acetamido-7-acetoxy-4,8-dimethylcoumarin and 6-Acetamido-7-hydroxy-4,8-dimethylcoumarin.—When acetic anhydride was used instead of acetic acid in the preparation of 6-hydroxy-β,2,7-trimethyl-5-benzoxazoleacrylic acid γ-lactone (II, R = CH_3), varying amounts of this oxazolocoumarin were obtained, mixed with impurities. One by-product was separated by its insolubility in benzene and proved by infrared and ultraviolet spectra and analysis to be 6-acetamido-7-acetoxy-4,8-dimethylcoumarin, m.p. 241–244°. A mixture m.p. with II (R = CH_3) gave a large depression (210–220°). The principal spectral bands are: ultraviolet in ethanol: 243, 287, 333, 393 mμ; infrared (Nujol mull): 3370, 1747, 1732, 1692, 1542, 1598, 1215, 1195, 1103 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.82. Found: C, 62.43; H, 5.54; N, 4.81.

Another by-product was separated by chromatography on Florisil. It was eluted with benzene to which were added increasing amounts of acetone. After recrystallization from 90% ethanol and then from aqueous dimethylformamide, material was obtained, m.p. 258–260°, soluble in dilute sodium hydroxide and reprecipitated by acid. Infrared and ultraviolet spectra and analysis indicated it to be 6-acetamido-7-hydroxy-4,8-dimethylcoumarin. The principal spectral bands are, ultraviolet in ethanol: 243, 292, 335, 392 mμ; infrared (Nujol mull): 3310, 2380, 1685, 1657, 1596, 1555, 1495, 1118 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.04; H, 5.60; N, 5.46.

6-Hydroxy-β,7-dimethyl-2-oxo-5-benzolineacrylic acid γ-Lactone (V is the enol form).—A mixture of 20.5 g. (0.1 mole) of 6-amino-7-hydroxy-4,8-dimethylcoumarin and 92 g. of urea (ground together in a mortar) was heated under nitrogen in a bath at 155–165° for 1.5 hr. The mixture melted and resolidified. The temperature was gradually raised during 2.5 hr. to 215° and then cooled. The solid cake was ground with water and filtered. The solid was dissolved in dilute sodium hydroxide, filtered and the filtrate was acidified. The precipitate was collected, washed with water and dried, giving 27.9 g. of tan solid, m.p. 337–339° dec., which was boiled with 800 ml. of dimethylformamide, filtered while hot through Supercel, giving, on cooling, finely crystalline solid. This was collected, washed with acetone and dried, yielding 7.91 g. (34%) of light tan solid, m.p. 352–353° dec. A small sample fractionally crystallized from dimethylformamide

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[7] K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1960, p. 116.

had a m.p. 355.5–356° dec. Infrared and ultraviolet spectra indicate this exists primarily in the keto form in neutral or acid media and the enol form in base. The principal bands are: ultraviolet in ethanol or 0.01 N H_2SO_4: 232, 281, 335 mμ; in 0.01 N ethanolic KOH: 251, 301, 364 mμ; infrared (Nujol mull): 3170, 1795, 1770, 1660, 1596, 1102 cm.$^{-1}$.

6-Hydroxy-β,7-dimethyl-2-thione-5-benzoxazolineacrylic Acid γ-Lactone (VI is the thienol form).—A mixture of 16.5 g. of 85% potassium hydroxide, 100 ml. of methanol, 15 ml. of water, 20 ml. of carbon disulfide and 12.7 g. (0.062 mole) of 6-amino-7-hydroxy-4,8-dimethylcoumarin was heated under reflux with stirring. The solid soon dissolved and hydrogen sulfide was evolved. After 2.5 hr. a solid separated and 50 ml. more methanol and 10 ml. more carbon disulfide were added to facilitate stirring. After 20.5 hr. of heating most of the solvent was evaporated and the residue was dissolved in 700 ml. of water and filtered. The filtrate was acidified giving a nearly white precipitate which was collected and dried, yielding 14.9 g. (51%) of solid, m.p. 342.5–343.5° dec. Infrared and ultraviolet spectra indicate the compound exists in the thione structure in neutral media. The principal bands are: ultraviolet in ethanol or 0.01 N ethanolic H_2SO_4: 274, 348 mμ; in 0.01 N ethanolic KOH; 278, 366 mμ; infrared (Nujol mull); 3060, 1725, 1710, 1638, 1515, 1410, 1230, 1168, 1135, 1100 cm.$^{-1}$.

2-Amino-6-hydroxy-β,7-dimethyl-5-benzoxazoleacrylic Acid γ-Lactone (VII).—A mixture of 20.5 g. (0.1 mole) of 6-amino-7-hydroxy-4,8-dimethylcoumarin, 21.2 g. (0.2 mole) of cyanogen bromide, and 300 ml. of ethanol was stirred at room temperature for 15 hr. and then heated under reflux for 20 min. The resulting solid was collected and dried giving 14.25 g. of brown crystals, m.p. about 210–220°. This crude product was dissolved in hot dimethylformamide and treated twice with Darco. The solution was made basic with 50% aqueous sodium hydroxide and diluted with water until crystallization started. After cooling the free base was collected, washed with water and dried giving 10.72 g. (47%) of light yellow crystals, m.p. above 365° with sublimation and darkening from 320° up. After another recrystallization from dimethylformamide 9 g. of crystals was obtained with the same melting characteristics.

Hydrochloride.—Eight grams (0.035 mole) of the above free base was dissolved by warming in 20 ml. of concentrated hydrochloric acid plus 180 ml. of water, filtered, and cooled. The hydrochloride was collected and dried giving 9.68 g. of crystals, m.p. above 345° dec.; infrared spectrum and analysis indicate it to be a hydrate. It proved difficult to remove all the water without decomposition of the compound. However a sample dried at 25° (15 mm.) for 4 hr. over calcium chloride showed analysis for approximately 1.5 molecules of water.