[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

Allokhellin[1]

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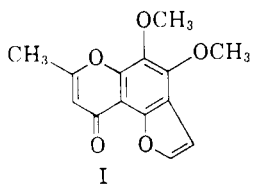
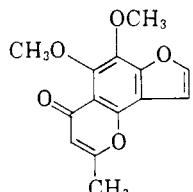
The synthesis of allokhellin from antiarol is reported. It was found that boric acid fails to give a hypsochromic shift of the spectra of a 2,3-dihydroxyacetophenone in alcoholic sodium ethoxide, contrary to dihydroxy compounds which do not permit hydrogen bonding.

The hydrogen iodide demethylation of khellin followed by remethylation[3,4] gave an isomer by rearrangement, for which structure I or II was proposed[3,5] and the latter, isokhellin, was then synthesized.[5]

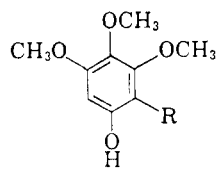


I

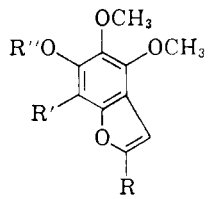


II

We have now prepared I from antiarol, III, and propose the name, *allokhellin*, by analogy to allobergapten.



III. R, H
IV. R, CH(=O)



V. R, CO_2CH_3; R′, H; R″, CH_3
VI. R, CO_2CH_3; R′, CCH_3(=O); R″, CH_3
VII. R, CO_2CH_3; R′, CCH_3(=O); R″, H
VIII. R, R″, H; R′, CCH_3(=O)

Antiarol was converted to the aldehyde IV using *N*-methylformanilide and the aldehyde gave V by reaction with methyl bromoacetate and sodium methoxide.[6] The coumarilic ester V formed the acetyl compound VI by acetylation in polyphosphoric acid (PPA). Selective cleavage of VI in hydrogen bromide–acetic acid at room temperature[7] gave the desired hydroxyketone, VII. The direct production of VII from V was also possible by acetylation using boron trifluoride and acetic acid analogous to an acetylation with cleavage on a dihydrobenzofuran.[8] After saponification of the ester VII, the acid was decarboxylated *via* quinoline and copper powder. The product unexpectedly gave analytical values supporting a dihydroxy compound. Further, no chromone could be obtained from this material. Ethereal diazomethane converted the dihydroxy compound to VIII and this gave an acetoacetyl compound when condensed with sodium hydride and ethyl acetate.[9] The chromone was then formed using alcoholic sulfuric acid.[10]

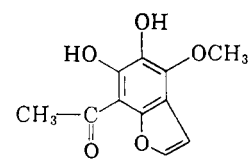
TABLE I

SUMMARY OF DATA ON KHELLINS

	M.P.	λ_{max}^{alc} (log ϵ)
Khellin	153[a]	247 (4.57)[b]
	152–153[c]	281 (3.67)
		331 (3.67)
Isokhellin	176[a]	243 (4.47)[b]
	180[b,d]	319 (3.66)
Allokhellin	152.2–153.2	255.5 (4.37)
		294.5 (3.93)
		~244 (4.29)[e]
		~261 (4.33)

[a] Ref. 3. [b] Ref. 5. [c] Ref. 9. [d] Undepressed when mixed with a sample prepared as in Ref. 3. [e] Inflection.

In order to test the possibility that IX represents the above dihydroxy compound, we investigated the hypsochromic shift of the long wave length band caused by the addition of boric acid to IX in ethanolic sodium ethoxide as proposed by Swain[11]



IX

(1) This investigation was supported by a Public Health Service Grant CY-4817 from the National Cancer Institute, Public Health Service.

(2) A part of the Doctoral dissertation of M. G. Stout.

(3) J. R. Clarke and A. Robertson, *J. Chem. Soc.*, 302 (1949).

(4) S. K. Mukerjee and T. R. Seshadri, *J. Sci. Ind. Research (India)*, **13B**, 400 (1954). *Chem. Abstr.*, **49**, 12454 (1955).

(5) H. Abu-Shady and T. O. Soine, *J. Am. Pharm. Assoc.*, **41**, 403 (1952).

(6) T. Reichstein, *et al.*, *Helv. Chim. Acta*, **18**, 816 (1935).

(7) W. J. Horton and J. T. Spence, *J. Am. Chem. Soc.*, **77**, 2894 (1955).

(8) W. J. Horton and E. G. Paul, *J. Org. Chem.*, **24**, 2000 (1959).

(9) T. A. Geissman, *J. Am. Chem. Soc.*, **71**, 1498 (1949).

(10) R. A. Baker, G. R. Ramage, and J. A. Timson, *J. Chem. Soc.*, S30 (1949).

(11) T. Swain, *Chem. & Ind. (London)*, 1480 (1954).

for 1,2-dihydroxy compounds. No hypsochromic shift was found (Table II). Further, known 2,3-dihydroxy-4-methoxyacetophenone[12] gave no such shift. As a check on our handling of Swain's method, protocatechuic aldehyde gave results essentially as reported[11] (Table II). It is therefore concluded that this test fails in cases capable of hydrogen bonding. Such cases are not reported in the original work.[11]

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA[a]

	$\lambda_{max}^{abs.\ alc.}$	mμ (ε)	$\lambda_{max}^{0.200M\ NaOC_2H_5}$	mμ (ε)
Dihydroxy compound above (IX or isomer)	239	(15700)	223	(16400)
	303.5	(13800)	~245	(7680)[b,c]
	347	(8620)	262	(8350)[c]
			350	(29800)[c]
2,3-$(OH)_2$-4-CH_3O-acetophenone	236.5	(13100)	243	(4930)[c]
	298	(15400)	~320	—[c,d]
			357	(5940)[c]
Protocatechuic aldehyde[e]	233	(12900)	251.5	(8870)
	278.5	(9190)	~295	—[d]
	314	(8520)	350	(23000)

[a] The solvent was absolute ethanol throughout. [b] Indicates an inflection. [c] Identical in position and intensity in 0.002*M* sodium ethoxide-0.002*M* boric acid. [d] Unstable solution. [e] In 0.002*M* sodium ethoxide-0.002*M* boric acid, 245 mμ (14,200), 292 mμ (6690) and 338 mμ (14,300).

EXPERIMENTAL[13]

Antiarolaldehyde (IV). A solution containing 15.2 g. of phosphorus oxychloride and 13.4 g. of *N*-methylformanilide, after mixing and standing for 35 min. was treated at 25° with 18.2 g. of antiarol[14] over a period of 40 min. The solution was stirred for 3.25 hr. and allowed to stand for 18 hr. The dark red complex was poured into 500 ml. of water, allowed to stand for 1 hr., and filtered. The collected solid, dissolved in hot benzene, gave 7.34 g. of antiarol on cooling. The filtrate was evaporated and the residue, crystallized from aqueous methanol, gave 10.2 g. (81%) of pale yellow solid m.p. 60–62°; reported[14] m.p. 65°.

Methyl 4,5,6-trimethoxycoumarone-2-carboxylate (V). A solution of 12.3 g. of antiarolaldehyde and 12.2 ml. of methyl bromoacetate in 153 ml. of absolute methanol was refluxed (1.3 hr.) during the addition of a solution of 3.1 g. of sodium in 40 ml. of methanol. After 7 hr. at the boiling point the solution was allowed to stand overnight. When poured into 800 ml. of water and acidified, 9.12 g. (60%) of the ester was obtained, m.p. 98–99°. Crystallization from aqueous methanol gave material m.p. 98.8–99.1°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.63; H, 5.36.

After saponification, the *acid* was obtained as light tan needles m.p. 156.9–157.5° from cyclohexane-benzene or cyclohexane-acetone.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.60; H, 5.10.

Methyl 4,5,6-trimethoxy-7-acetylcoumarone-2-carboxylate (VI). A mixture containing 3.9 g. of the above ester and 1.33 ml. of acetic acid in 104 ml. of polyphosphoric acid became dark red after 30 min. at 70–75°. The solution after cooling and dilution with water gave a solid which was crystallized from cyclohexane. The yellow material (3.97 g.; 93.5%) melted at 90–110° and after further crystallization from cyclohexane at 111.1–111.6°.

Anal. Calcd. for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.60; H, 5.34.

The *2,4-dinitrophenylhydrazone*, from ethyl acetate, melted at 215.5–216.1°.

Anal. Calcd. for $C_{21}H_{20}O_{10}N_4$: C, 51.64; H, 4.13. Found: C, 51.72; H, 4.26.

Methyl 4,5-dimethoxy-6-hydroxy-7-acetylcoumarone-2-carboxylate (VII). (a) The hydrogen bromide-acetic acid cleavage[7] on VI produced a large amount of precipitate within 10 min. After 4.5 hr. standing, the product, crystallized from benzene, weighed 3.27 g. (86%) m.p. 174–180°. Further recrystallization from methanol gave pearly needles m.p. 182.6–182.9°. These gave a dark rose color with alcoholic ferric chloride.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.80. Found: C, 57.21; H, 4.85.

The *acetate* after repeated crystallization from aqueous methanol and from cyclohexane formed colorless fleecy needles m.p. 123.4–124.9°.

Anal. Calcd. for $C_{16}H_{16}O_8$: C, 57.14; H, 4.80. Found: C, 56.53; H, 4.74.

(b) Boron trifluoride was added at a temperature below 35° to a solution of 3.46 g. of methyl 4,5,6-trimethoxycoumarone-2-carboxylate V in 70 ml. of acetic acid. After addition of 75.3 g. of the gas, the dark green solution was allowed to stand at room temperature for 20.5 hr. By addition of 600 ml. of water, the solid boron complex was obtained and after boiling in 100 ml. of methanol and cooling, 3.57 g. (93%) of colorless needles m.p. 181–183° was obtained, identical by mixed melting point to VII above.

4,5-Dimethoxy-6-hydroxy-7-acetylcoumarilic acid. Saponification of the ester gave the *acid* (94.5%) m.p. 264–267° which produced a dark wine-colored ferric chloride test. From ethanol, light yellow needles m.p. 271–271.5° (uncor.—Fisher-Johns block) were obtained.

Anal. Calcd. for $C_{13}H_{12}O_7$: C, 55.72; H, 4.32. Found: C, 56.02; H, 4.41.

The *oxime* from ethanol formed colorless needles, m.p. 265–267.5°, dec. (uncor.—Fisher-Johns block) with an emerald green ferric chloride reaction.

Anal. Calcd. for $C_{13}H_{13}O_7N$: C, 52.88; H, 4.44. Found: C, 53.10; H, 4.60.

4,5-Dimethoxy-6-hydroxy-7-acetylbenzofuran (VIII). A mixture of 2.28 g. of the hydroxycoumarilic acid with 1.14 g. of copper powder in 65 ml. of quinoline was heated for 30 min. in a metal bath at 230–240°. The cooled and filtered solution in 1 l. of ether was washed three times with 5% hydrochloric acid and eight times with 8% sodium hydroxide. Acidification of the alkaline extract gave a red precipitate which was extracted repeatedly with boiling cyclohexane. The concentrated cyclohexane gave 1.23 g. (68%) of *4-methoxy-5,6-dihydroxy-7-acetylbenzofuran* (IX) *or the isomer* as a yellow solid, m.p. 175–177°, giving an emerald green ferric chloride test. The sample from further cyclohexane crystallization melted at 176.2–176.6°. The ultraviolet absorption spectral data are given in Table II.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.57; H, 4.71.

The compound (2.22 g.) gave *4,5-dimethoxy-6-hydroxy-7-acetylbenzofuran* when allowed to stand with ethereal diazomethane for 1 hr. The residue after evaporation of the solvent was crystallized from methanol to give a light brown solid (2.02 g. 86%), m.p. 109–110°. Purification from methanol gave VIII, m.p. 109.4–110.0°.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.23; H, 5.15.

Allokhellin (I). To 500 mg. of VIII in 5 ml. of dry ethyl acetate was added 500 mg. of sodium hydride in five portions. After standing overnight, ice was added followed by

(12) P. D. Gardner, W. J. Horton, and R. E. Pincock, *J. Am. Chem. Soc.*, 78, 2541 (1956).

(13) Melting points of analytical samples, except as noted, are corrected.

(14) E. Chapman, A. G. Perkin, and R. Robinson, *J. Chem. Soc.*, 130, 3015 (1927).

25 ml. of dilute hydrochloric acid. The ethyl acetate was removed at room temperature in an air stream and the resultant solid collected, m.p. 95–103°, depressing the melting point of VIII. The crude solid, dissolved in a solution containing 16 ml. of alcohol and 4 ml. of concd. sulfuric acid, was heated on the steam bath for 1 hr. The solution was poured into 50 ml. of ice water, held for 16 hr. at 5°, and extracted with ether. The product obtained after washing the ether with 5% sodium hydroxide, saturated salt, and evaporation of the ether weighed 160 mg. Crystallization from cyclohexane gave 130 mg., m.p. 149.5–153°. Further crystallization brought the melting point to 152.2–153.2°. λ_{max}^{alc} 255.5, 294.5 mμ (ε 23,400, 8470); $\lambda_{inflect.}^{alc}$ 244, 261 mμ (ε 19,500, 21,500).

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 65.00; H, 4.99.

2,3-Dihydroxy-4-methoxyacetophenone. A solution of 3.08 g. of 2,6-dimethoxyphenol in 107 ml. of glacial acetic acid with 15.8 ml. of acetic anhydride was treated with anhydrous boron trifluoride, holding the temperature below 30° until 96.5 g. of the gas had been added. The solution was then allowed to stand at room temperature for 48 hr. The reaction mixture was poured into 1 l. of ice and water and the filtered and washed boron complex was decomposed by boiling with 30 ml. of alcohol until it dissolved. On addition of 30 ml. of water and cooling, 2.98 g. (67%) of *2-hydroxy-3-acetoxy-4-methoxyacetophenone*, m.p. 121.5–126°, was obtained. From ethanol-water (3:2) colorless long thin prisms were obtained m.p. 123.4–125.0°.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.96; H, 5.42.

When 1.0 g. of the above was refluxed for 1 hr. with 10 ml. of water, 10 ml. of concd. hydrochloric acid, and 20 ml. of alcohol, 0.68 g. of 2,3-dihydroxy-4-methoxyacetophenone, was obtained m.p. 130–134.5°, undepressed when mixed with a known sample (m.p. 130–132°).[12]

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIV., AMERICAN CYANAMID CO.]

The Synthesis of Certain C-21-Substituted Derivatives of 21-Deoxyhydrocortisone, 21-Deoxy-9α-fluorohydrocortisone, and Progesterone[1]

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The synthesis of certain modified steroidal hormones wherein the primary 21-hydroxy group or a 21-hydrogen is replaced by various nitrogen- and sulfur-containing moieties are reported.

At the time of this investigation it had already been shown that modification of the 21-hydroxymethylene grouping in the corticoid series could give structures retaining biological activity, although no case had been reported [2–11] by that time, or since, wherein such a modification has resulted in a dramatic increase in adrenocorticoid activity. C_{21}-Substituted derivatives of 4-pregnene-3,30-dione have also been described.[11–15] These compounds may be considered analogs of the mineralocorticoid deoxycorticosterone wherein the 21-hydroxy group is replaced, and also of progesterone wherein a 21-hydrogen is replaced.

In this paper we wish to report the synthesis of certain modified steroidal hormones wherein the primary 21-hydrogen is replaced by various nitrogen- and sulfur-containing moieties.

In our investigation, we have prepared C-21-substituted derivatives of 21-deoxyhydrocortisone,

(1) This investigation is part of a broad exploratory research program in the steroid field. For the previous publication from this laboratory on this program see H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, in press.

(2) H. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 4812 (1956) (21-fluoro-21-deoxycortisone).

(3) W. J. Leanza, J. P. Conbere, E. F. Rogers, and K. Pfister 3rd, *J. Am. Chem. Soc.*, **76**, 1691 (1954) (21-aldehydo derivatives).

(4)(a) J. Fried *et al.*, *J. Am. Chem. Soc.*, **77**, 4181 (1955) (21-deoxy-9α-fluoroprednisolone); *J. Am. Chem. Soc.*, **77**, 1068 (1955) (21-deoxy-9α-fluorohydrocortisone). (b) S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, *J. Am. Chem. Soc.*, **81**, 4956 (1959) (21-deoxytriamcinolone).

(5) L. H. Sarett, H. D. Brown, and A. R. Matzuk, U. S. Patent **2,853,486** (Sept. 23, 1958) (21-azido derivatives).

(6) P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955). (21-halo, cyano, thiocyano and acetylthio derivatives).

(7) C. Djerassi and A. L. Nussbaum, *J. Am. Chem. Soc.*, **75**, 3700 (1953) (21-acetylthio derivatives).

(8) A. L. Nussbaum, U. S. Patent **2,814,632** (Nov. 26, 1957) (21-acetylthio derivatives).

(9) B. G. Christensen, N. G. Steinberg, and R. Hirschmann, *Chem. & Ind.*, 1259 (1958) (21-diazo derivatives).

(10) 21-Amino-21-deoxy-9α-fluorohydrocortisone has recently been prepared by L. L. Smith and M. Marx of the Chemical Process Improvement Dept. of these laboratories; to be published.

(11) A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3710 (1959) (21-nitro derivatives).

(12) P. Tannhauser, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956) (21-fluoroprogesterone).

(13)(a) S. Nakanishi, K. Morita, and E. V. Jensen, *J. Am. Chem. Soc.*, **81**, 5259 (1959) (21,21-difluoroprogesterone). (b) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5262 (1959). (c) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960). (d) 21,21,21-Trifluoroprogesterone has also been reported,[12a] however, without testing results.

(14) R. A. Micheli and C. K. Bradsher, *J. Am. Chem. Soc.*, **77**, 4788 (1955) (21-morpholinoprogesterone).

(15) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939) (21-aldehydo derivative).