4-benzyloxy-3-methoxyphenylpyruvic acid[5] in 3.5 l. of 1-butanol was heated under reflux for 2 hr. The cooled solution was diluted with 2.0 l. of acetone and chilled. White fluffy needles precipitated and were collected. The product weighed 78 g. (55%) and melted at 223–226°. Recrystallization from glacial acetic acid, or from aqueous ethanol, raised the melting point to 226–227°.

Anal. Calcd. for $C_{26}H_{26}N_2O_2 \cdot HCl$: C, 71.79; H, 6.26; Cl, 8.15. Found: C, 71.76; H, 6.34; Cl, 8.27.

18-Benzyloxy-17-methoxy-15,16,17,18,19,20-hexadehydroyohimbane hydrochloride (IVa). A mixture of 43 g. (0.1 mole) of IIIa and 1.0 l. of 50% ethanol was heated on the steam bath until the solid dissolved. After adding 100 ml. of 36% formaldehyde, the solution was heated on the steam bath for 3 hr. The hot reaction mixture was filtered to remove a yellow solid which was washed with hot 50% ethanol. The product weighed 37 g. (83%) and melted at 265–268°.

Anal. Calcd. for $C_{27}H_{26}N_2O_2 \cdot HCl$: C, 72.55; H, 6.09; Cl, 7.93; N, 6.27; O, 7.16. Found: C, 72.34; H, 6.27; Cl, 7.68; N, 6.07; O, 7.26.

1-(4-Hydroxy-3-methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride (IIIb). A suspension of 2.75 g. (0.005 mole) of IIIa and 0.3 g. 5% palladium on carbon in 100 ml. of 50% ethanol was hydrogenated at 1.7 atm. at 60°. Theoretical uptake occurred in 1 hr., and all of the solid was in solution. The catalyst was removed and the solution was chilled to obtain a solid, m.p. 254–255°. The filtrate was taken to dryness, and the residue was triturated with ether to obtain more product, m.p. 253–254°. The total yield was 1.45 g. (84%). The recorded melting point is 253–254°.[3]

On larger scale runs, it was necessary to extract the catalyst thoroughly with hot 75% ethanol to insure good yields. In a combined workup of four 16-g. (0.0368 mole) runs a 75% yield was obtained.

18-Hydroxy-17-methoxy-15,16,17,18,19,20-hexadehydroyohimbane hydrochloride (IVb).[9] A suspension of 44.7 g. (0.1 mole) of IVa and 7.5 g. of 5% palladium on carbon in 250 ml. of dimethylformamide was hydrogenated at 2 atm. at about 70°. When hydrogen uptake was complete (8–15 hours) product had begun to precipitate. The product was dissolved by heating to boiling with addition of 65 ml. of dimethylformamide and 360 ml. of water. The hot solution was filtered to remove the catalyst, and the filtrate chilled to obtain 26 g. (73%) of bright yellow solid melting at 277–279°. Recorded melting points are 254–256°,[1] 256–257°,[3] and 254–256°.[4]

Anal. Calcd. for $C_{20}H_{20}N_2O_2 \cdot HCl$: C, 67.31; H, 5.93; Cl, 9.93; N, 7.85; O, 8.96. Found: C, 67.27; H, 5.82; Cl, 10.00; N, 7.87; O, 9.27.

Consensation of IIIb with formaldehyde as described previously[1,3,4] gave a bright yellow solid, m.p. 277–279°, identical in every respect with the material described above. Although the melting point varied somewhat with the rate of heating, and also on whether an oil bath or metal block was used, pure material was never observed to melt below 270°.

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(9) The preferred *Chemical Abstracts* name for this compound is 5,7,8,13,13b,14-hexahydro-2-methoxybenz[g]-indolo[2,3-a]quinolizin-3-ol hydrochloride.

Spectral Studies on Flavonoid Compounds. III. Polyhydroxychalcones

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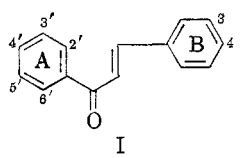
The ultraviolet spectra of most of the known, naturally occurring, hydroxylated chalcone (I) derivatives have been reported.[2] However, as an aid in the identification of new pigments, the spectra of a number of additional hydroxychalcones in neutral and in alkaline solutions are presented in this note.



I

The spectra of twenty-five hydroxychalcones are collected in Table I. These chalcones absorb strongly in the 300–400 mμ region and less strongly in the 220–270 mμ region. In alcoholic sodium ethylate solution the long wave-length band of those chalcones which contain a free hydroxyl group in the 4- position undergoes a bathochromic shift of 70–90 mμ and a considerable *increase* in its intensity (Table I; compounds I–II). This spectral shift is sufficiently characteristic of the 4-hydroxychalcones to be used as evidence for the the presence of this grouping in chalcones. The alkali spectrum of the natural chalcone, xanthohumol (II), reported by Verzele and his co-workers,[3] provides a good example of this shift.

Chalcones which contain a free 4'-hydroxyl *and* either a free 2'-hydroxyl or an alkylated or glycosidated 4-hydroxyl show a bathochromic shift of only 40–50 mμ in sodium ethylate (Table I; compounds 12–18). On the other hand, when the 2'- and 4- positions are unsubstituted, 4'-hydroxychalcones give a bathochromic shift of 65–70 mμ in sodium ethylate (Table I; compounds 19, 20). This shift is easily distinguished from that given by the 4-hydroxychalcones, however, since it is accompanied by a considerable *decrease* in the intensity of the long wave-length band. The difference is illustrated by the spectra of 4-hydroxychalcone and 4'-hydroxychalcone (Fig. 1). The influence of a 2'-hydroxy group on the alkali spectrum of a 4'-hydroxychalcone is probably to be attributed to chelation with the carbonyl group, while the influence of a 4-alkoxy group may be accounted for by assuming a cross-conjugation effect similar to that proposed by Geissman and Harborne[4] for hydroxyaurones.

(1) (a) Western Regional Research Laboratory, Albany, Calif.[1c]; (b) Fruit and Vegetable Chemistry Laboratory, Pasadena, Calif.[1c]; (c) Laboratories of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) For examples, see J. B. Harborne and T. A. Geissman, *J. Am. Chem. Soc.*, **78**, 829 (1956); T. A. Geissman, J. B. Harborne, and M. K. Seikel, *J. Amer. Chem. Soc.*, **78**, 825 (1956); T. A. Geissman, *Modern Methods of Plant Analysis*, Vol. 3, eds. K. Paech and M. V. Tracey, Springer-Verlag, 1955, p. 450.

(3) M. Verzele, J. Stockx, F. Fontijin, and M. Anteunis, *Bull. Soc. Chim. Belg.*, **66**, 452 (1957).

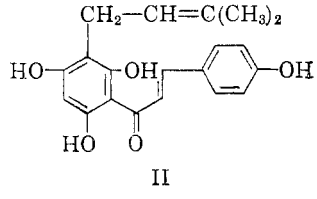
(4) T. A. Geissman and J. B. Harborne, *J. Am. Chem. Soc.*, **78**, 832 (1956).

TABLE I

SPECTRA OF CHALCONES IN ETHANOL AND IN SODIUM ETHOXIDE

Chalcone	C_2H_5OH λ_{max}, mμ	0.002*M* $NaOC_2H_5$ λ_{max}, mμ	Δλ[b]
1. 4-Hydroxy-	350, 248	438, 286	88
2. 4,4′-Dihydroxy-	348, 240	427, 250	79
3. 3,4-Dihydroxy-	367, 266	452, 267	85
4. 2′,4-Dihydroxy-3′-methoxy-	380, 267, 249	458, 273, 238	78
5. 2′,4-Dihydroxy-4′-methoxy-	370, 303, 242	441, 293, 250	71
6. 4-Hydroxy-2′,4′-dimethoxy-	350	423	73
7. 2′,3,4-Trihydroxy-	384, 320,[a] 271, 249	460, 280	76
8. 4,2′,4′-Trihydroxy-3-methoxy-	378, 307,[a] 260	451, 354, 280,[a] 253	73
9. Coreopsin[2]	385, 305,[a] 265, 245	450	65
10. 4-Hydroxy-2′,4′,3-trimethoxy-	360	440	80
11. Xanthohumol[3]	370	438	68
12. 2′,4′-Dihydroxy-	345,[a] 317, 267	394, 300, 279	49
13. 2′,4′-Dihydroxy-4-methoxy-	362, 307,[a] 237	400, 282, 234[a]	38
14. 4′-Hydroxy-2′,4-dimethoxy-	350	395	45
15. 4′,3-Dihydroxy-4-methoxy-	358, 314,[a] 262,[a] 235	404, 327,[a] 276, 250	46
16. 2′,4′-Dihydroxy-3,4-dimethoxy-	371, 310,[a] 259	407, 337,[a] 283, 258[a]	36
17. 4′-Hydroxy-2′,3,4-trimethoxy-	357	395	38
18. 4′-Hydroxy-2′,6′,3,4-	341, 320,[a] 252,[a] 239	389, 334, 250	48
19. 4′-Hydroxy-	320, 230	388, 297, 272[a]	68
20. 4′,3-Dihydroxy-	321, 242	385, 311, 267	64
21. 2′-Hydroxy-	366,[a] 316, 221	428, 303, 250	
22. 2′,3-Dihydroxy-	356, 316, 257	317, 273, 241	
23. 2′-Hydroxy-4′,6′-dimethoxy-	338, 236[a]	383, 295, 250	
24. 2′-Hydroxy-4,4′-dimethoxy-	362, 295,[a] 239	419, 321, 251	
25. 2′-Hydroxy-3,4-dimethoxy-	371, 316,[a] 264, 247	422, 341, 297,[a] 242	

[a] Inflection.
[b] $\Delta\lambda = \lambda_{max}$ (0.002*M* $NaOC_2H_5$) $= \lambda_{max}$ (EtOH) of the long wave-length band.
The most intense band in each spectrum is underlined.



II

TABLE II

SPECTRA OF ALUMINUM CHLORIDE-2′-HYDROXYCHALCONE COMPLEXES

Chalcone	C_2H_5OH λ_{max}, mμ	$AlCl_3$ λ_{max}, mμ	Δλ
2′-Hydroxy-	366[a]	425	59
2′,4′,4-Trihydroxy-	370	422	52
2′,4′-Dihydroxy-4-methoxy-	362	415	53
2′,3,4-Trihydroxy-	384	447	63
2′-Hydroxy-3,4-dimethoxy	371	437	66
2′,4′,3,4-Tetrahydroxy(coreopsin) (2)	385	450	50
2′,4′-Dihydroxy-3,4-methylenedioxy-	370	416	46
2′,3′,4′,3,4-Pentahydroxy-(okanin) (4)	381	420	39
Marein (4)	383	422	39
2′,3′,4′-Trihydroxy-	347	384	37

[a] Inflection.

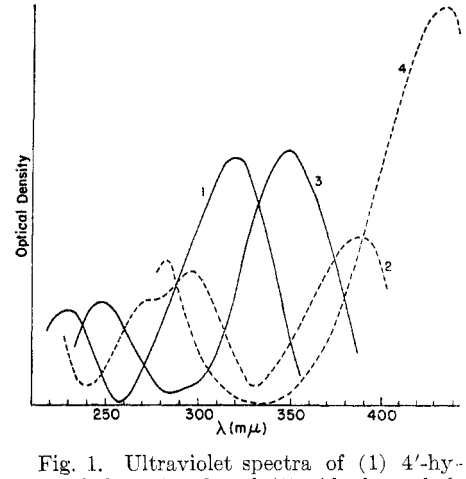


Fig. 1. Ultraviolet spectra of (1) 4′-hydroxychalcone in ethanol, (2) 4′-hydroxychalcone in 0.002*M* sodium ethoxide, (3) 4-hydroxychalcone in ethanol, (4) 4-hydroxychalcone in 0.002*M* sodium ethoxide

Chalcones whose only free hydroxyl group is in the 2′- position are readily distinguished by their characteristic spectral curves in sodium ethylate. The principal long wave-length band appears at a somewhat shorter wave length than in neutral solution, while the absorption in the short wave-

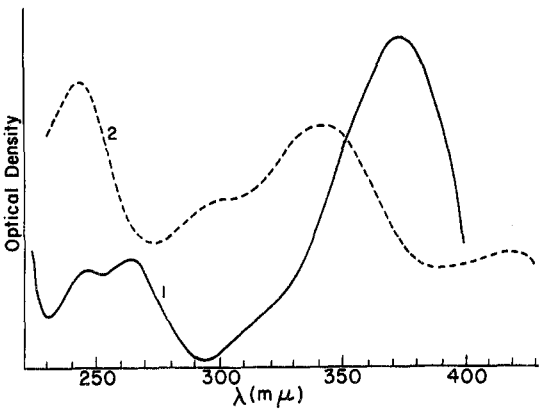


Fig. 2. Ultraviolet spectra of 2′-hydroxy-3,4-dimethoxychalcone in (1) ethanol, (2) 0.002*M* sodium ethoxide

length region undergoes a marked increase in intensity. A low intensity band may appear in the 400 mμ region (Fig. 2).

Spectral procedures for detecting *o*-dihydroxyl and 2′-hydroxyl groups in chalcones have been reported previously. Thus, chalcones which contain an *o*-dihydroxyl grouping in the B-ring give a characteristic bathochromic shift with boric acid–sodium acetate.[5] 2′-Hydroxychalcones form complexes with aluminum chloride in alcoholic solution,[2,6] the λ_{max} of the long wave-length band undergoing a bathochromic shift of 40–60 mμ (Table II). It is important that a large excess of aluminum chloride be employed in this test for a 2′-hydroxyl.[7] In Table II, it will be noted that 2′,3′,4′-trihydroxychalcone derivatives give a remarkably consistent bathochromic shift of only 37 mμ with aluminum chloride. This suggests that these compounds form aluminum complexes of a different type from those given by other 2′-hydroxychalcones.

Acknowledgment. The authors are indebted to Dr. T. A. Geissman for specimens of many of the chalcones used in this study.

(5) L. Jurd, *Arch. Biochem.*, **63**, 376 (1956).

(6) E. C. Bate-Smith and T. Swain, *J. Chem. Soc.*, 2185 (1953).

(7) L. Jurd and T. A. Geissman, *J. Org. Chem.*, **21**, 1395 (1956).

Potential Cancerocidal Agents. III. Formanilides[1,2]

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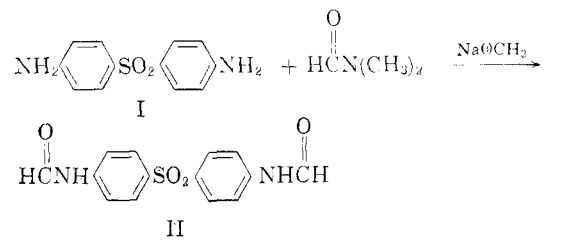
As part of a study directed at defining the scope of a new procedure[3] for the preparation of formanilides it was considered of importance to submit several of these substances for evaluation as cancer chemotherapeutic agents.[4] One of the first compounds prepared was 2,5-dimethoxyformanilide (Table I) and this substance was subsequently found to inhibit growth of the Ehrlich Ascites tumor in preliminary screening studies.[5] Consequently, it appeared desirable to prepare a number of related formanilides.

Initial emphasis was placed on the preparation of alkylated, alkoxy, and halogenated derivatives of formanilide (Table I). In each case, the corresponding aniline was formylated (*cf.*, I → II) employing dimethylformamide in the presence of sodium methoxide.[3] Acylation was conveniently accomplished using excess dimethylformamide and



a 2:1 molar ratio of sodium methoxide to amine Generally the reaction was complete after fifteen to thirty minutes at reflux and was accompanied by evolution of dimethylamine. The structure of the first product, *p*-chloroformanilide (Table I), prepared by this new reaction was suggested on the basis of its infrared spectrum and elemental composition. Unequivocal evidence for this structure was obtained following comparison (infrared spectra and mixture melting point) with an authentic specimen of *p*-chloroformanilide.[6]

Although the substances illustrated in Table I

(1) Refer to G. R. Pettit and M. V. Kalnins, *J. Org. Chem.*, **25**, 1365 (1960) for the preceding contribution.

(2) This investigation was aided by Grant No. T-79A from the American Cancer Society and in part by a Frederick Gardner Cottrell grant from the Research Corporation.

(3) Consult: G. R. Pettit and E. G. Thomas, *J. Org. Chem.*, **24**, 895 (1959) for a preliminary report of this reaction.

(4) The known inhibition of Sarcoma 180 by *N*-methylformamide emphasized the advisability of a concurrent biological investigation. An account of the tumor inhibitory activity of *N*-methylformamide has been prepared by D. A. Clarke, F. S. Philips, S. S. Sternberg, R. K. Barclay, and C. C. Stock, *Proc. Soc. Exptl. Biol. Med.*, **84**, 203 (1953). This substance has also been shown to prolong the survival time of mice with Leukemia L1210 and inhibit the growth of Adrenocarcinoma E0771; H. E. Skipper, F. M. Schable, V. Binns, J. R. Thomson, and G. P. Wheeler, *Cancer Research*, **15**, 143 (1955). An increase in the survival time of mice bearing Ehrlich Ascites tumor following treatment with *N*-methylformamide has been reported by A. Furst, W. C. Cutting, and H. Gross, *Cancer Research*, **15**, 294 (1955).

(5) Evaluation of 2,5-dimethoxyformanilide (NSC 30098) is being carried out by the Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda, Md.

(6) M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2552 (1924).