SUMMARY

1. The present study was undertaken to determine whether or not the activity and toxicity of Amytal Sodium and Seconal Sodium would be changed by 60 and 50 per cent, respectively, of polyethylene glycol 200.
2. Amytal Sodium in 60 per cent polyethylene glycol 200 and Seconal Sodium in 50 per cent polyethylene glycol 200 showed approximately the same potency and toxicity as aqueous solutions of these barbiturates. The median anesthetic dose (AD_{50}) by vein in rats was 75.0 ± 3.5 mg. per Kg. for Amytal Sodium and 39.0 ± 1.2 mg. per Kg. for Seconal Sodium. The median lethal doses (LD_{50}) were approximately twice as large as the AD_{50}'s. This is a ratio of nearly 2:1, which is common to most barbiturates now in clinical use.
3. In the subacute toxicity experiments both barbiturates in polyethylene glycol 200 produced no obvious pathological changes.
4. When injected intramuscularly in rabbits, the aqueous solutions of the two barbiturates produced more irritation in the tissues than solutions of the two compounds in polyethylene glycol 200.

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Experiments with Khellin. V. The Structure of Desmethylisokhellin*

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Chemical evidence is presented to show that desmethylisokhellin is 5-hydroxy-6-methoxy-2-methylfuro(2′,3′,7,8)chromone as had been predicted previously. Several new compounds incidental to the proof of structure have been prepared and the concept of the structure of desmethylisokhellin is supported by the infrared spectrum which shows a band attributed to a bonded hydroxyl group.

IN A RECENT communication the preparation of the phenol, desmethylisokhellin, has been described (1). Under the influence of 48 per cent hydrobromic acid, khellin undergoes a series of transformations to yield the monophenol (desmethylisokhellin) as the main component of the reaction mixture. When methylated in the usual way by the methyl iodide-potassium carbonate method, desmethylisokhellin was converted to isokhellin, the structure of which had been established in an earlier communication (2). On the other hand, desmethylisokhellin would not methylate with diazomethane, a fact indicative of the low acidity of the phenolic group which was believed to be hydrogen bonded with an adjacent carbonyl group. This concept of the structure of desmethylisokhellin was supported by the infrared spectrum which showed a band at 3,100 cm.$^{-1}$ that was attributed to a bonded hydroxyl group.

In this paper, however, chemical evidence is presented to prove beyond doubt that desmethylisokhellin is II and not I. Desmethylisokhellin was converted to its benzyl ether (III) by the

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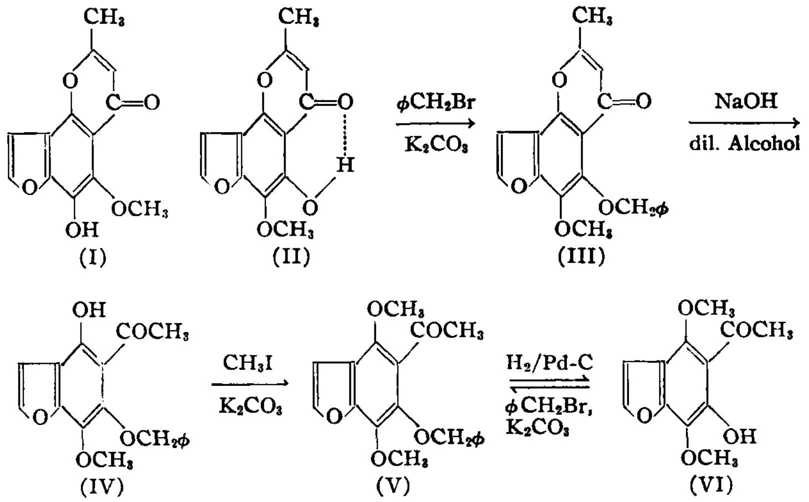

action of benzyl bromide and potassium carbonate. The benzyl ether was then treated with sodium hydroxide solution to hydrolyze the γ-pyrone ring. The resulting *o*-hydroxyketone (IV) was characterized as its 2,4-dinitrophenylhydrazone and was methylated with methyl iodide and potassium carbonate to yield benzylkhellinone (V). This derivative of khellinone was found to be identical with a sample prepared from authentic khellinone. Furthermore, benzylkhellinone (V) was hydrogenolyzed to yield khellinone (VI) which was identical with authentic khellinone (mixed m. p.).

The ultraviolet spectra of khellin and isokhellin together with the corresponding desmethyl compounds are shown in Figs. 1 and 2. The maxima of all compounds are presented in Table I. It is interesting to note the 8 mμ shift toward the longer wave length in passing from the methyl ether to the phenol in each case in the first maximum.

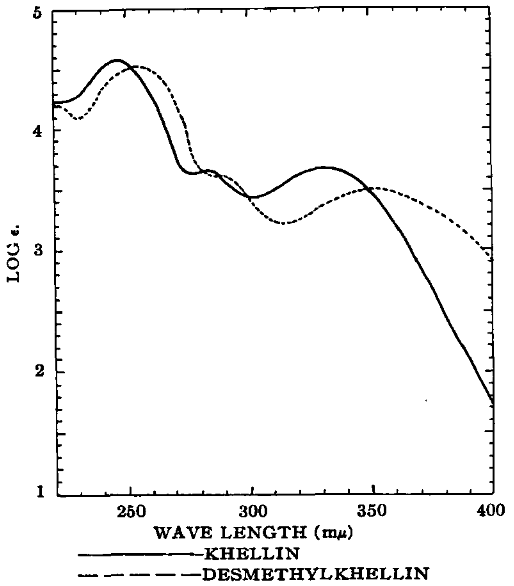

FIGURE 1.

TABLE I.—ULTRAVIOLET ABSORPTION DATA[a]

Compound	Ethanol, 95% λMax., mμ	Log ε
Khellin[b]	247	4.57
	281	3.67
	331	3.67
Desmethylkhellin	255	4.52
	~287.5	. . .
	353	3.49
Isokhellin	243	4.47
	319	3.66
Desmethylisokhellin	251	4.45
	344	3.45

[a] The authors wish to acknowledge the assistance of H. J. Rhodes of this laboratory in the checking and reproduction of the ultraviolet data.

[b] These values agree closely with those of Bailey, S. D., Geary, P. A., and deWald, A. E., THIS JOURNAL, 40, 280 (1951).

EXPERIMENTAL

5-Hydroxy-6-methoxy-2-methylfuro(2′,3′,7,8)-chromone (Desmethylisokhellin, II).—This phenol (m. p. 177°) was prepared from khellin by the action of 48% hydrobromic acid (sp. gr. 1.49) according to the method of Abu-Shady and Soine (1).

5-Benzyloxy-6-methoxy-2-methylfuro(2′,3′,7,8)-chromone (Benzyldesmethylisokhellin, III).—Desmethylisokhellin (10 Gm.) was refluxed for seventy hours with benzyl bromide (7 cc.), anhydrous potassium carbonate (20 Gm.), and acetone (200 cc.). The reaction mixture was filtered and evaporated to a small volume to yield 6.5 Gm. of slightly yellow crystals. These crystals were washed with ether and then crystallized three times from methyl alcohol to give an analytical sample, m. p. 140°.

Anal.—Calcd. for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.40; H, 4.94.

5-Acetyl-6-benzyloxy-4-hydroxy-7-methoxycoumarone (IV).—Benzyldesmethylisokhellin (5 Gm.) was refluxed for thirty minutes with a solution containing 10 Gm. of sodium hydroxide in a mixture

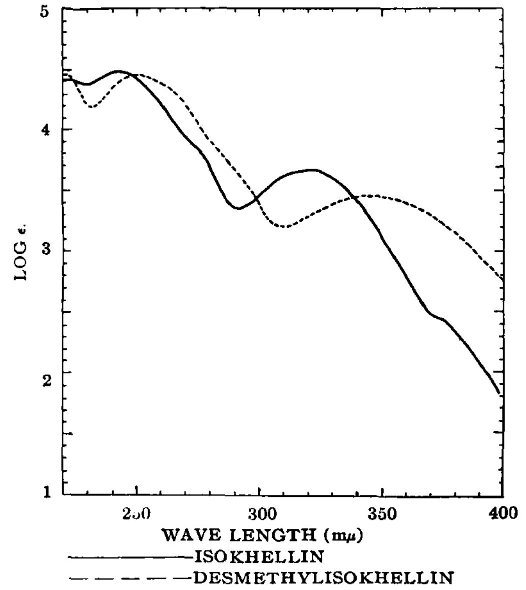

FIGURE 2.

of 50 cc. of alcohol and 50 cc. of water. The refluxed mixture was cooled, carefully acidified with acetic acid, and then extracted thoroughly with ether. The ethereal solution was dried over anhydrous sodium sulfate and then evaporated to dryness to yield a yellow liquid that failed to crystallize. In order to obtain an analysis on this compound a small portion of it was converted in the usual way to the 2,4-dinitrophenylhydrazone, m. p. 156.5–157°, which was then analyzed.

Anal.—Calcd. for $C_{24}H_{20}O_8N_4$: C, 58.53; H, 4.09. Found: C, 58.83; H, 4.30.

5-Acetyl-6-benzyloxy-4,7-dimethoxycoumarone (Benzylkhellinone, V).—A portion of the uncrystallizable, yellow liquid from the preceding experiment was subjected to the usual methyl iodide-potassium carbonate treatment in acetone and yielded a colorless, crystalline product, m. p. 86°. On comparison with a sample of benzylkhellinone prepared from khellinone by the action of methyl iodide and potassium carbonate in acetone, it was found that they were identical. A mixed melting point with the known benzylkhellinone failed to depress the melting point.

Anal.—Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.23; H, 5.85.

5-Acetyl-4,7-dimethoxy-6-hydroxycoumarone (Khellinone, VI).—A small sample of benzylkhellinone in alcohol was hydrogenolyzed in the usual way (2) in the presence of a palladium-on-charcoal (10%) catalyst. The alcoholic solution was then freed from the catalyst by filtration and evaporated on a steam bath to dryness. The residue was taken up in 10% sodium hydroxide solution and the yellow alkaline solution was then shaken successively with small volumes of ether to remove the unchanged benzyl ether. The alkaline solution, after being freed of ether on a steam bath, was acidified with dilute hydrochloric acid and again extracted completely with ether. The combined ethereal extracts were washed with water, dried, and concentrated to a small volume. The yellow crystals that separated on cooling melted at 95° and were identified as khellinone on the basis of a mixed melting point determination with an authentic sample of khellinone prepared from khellin by hydrolysis using the method of Spaeth and Gruber (3).

Ultraviolet Spectra.—The ultraviolet absorption spectra reproduced in Table I were determined in alcoholic solution with a Beckman Model DU Quartz Spectrophotometer; $\epsilon = 1/c \log_{10} I_0/I$ where c represents moles per liter.

SUMMARY

1. A chemical proof has been established to show that desmethylisokhellin is, indeed, 5-hydroxy-6-methoxy-2-methylfuro(2′,3′,7,8)chromone as had previously been predicted.

2. Several new compounds incidental to the proof of structure have been prepared.

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