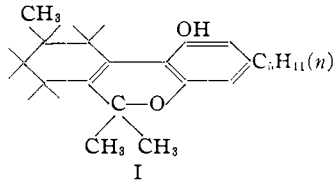
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND FROM THE DEPARTMENT OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE]

Tetrahydrocannabinol Analogs with Marihuana Activity. XI[1]

BY ROGER ADAMS, C. K. CAIN AND S. LOEWE

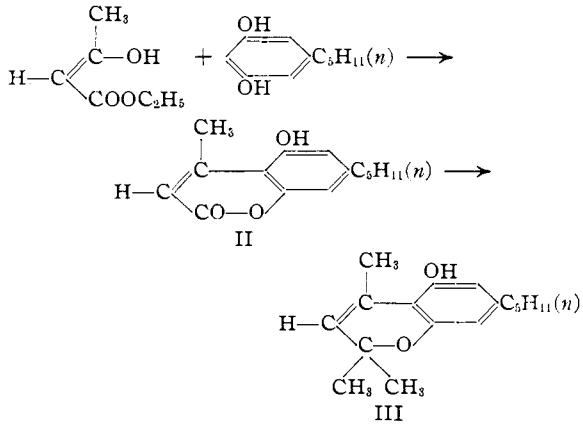
IN COLLABORATION WITH THE TREASURY DEPARTMENT, NARCOTICS LABORATORY, WASHINGTON, D. C.

The observation that such changes in the tetrahydrocannabinol (I) molecule as introduction of various sized alkyl groups in place of the *n*-amyl, the replacement of the methyl groups in the pyran ring by ethyls or *n*-propyls and the shifting or replacement by hydrogen of the methyl group in the left-hand ring sometimes increased, more often decreased but did not eliminate the marihuana activity,[1,2] has led to a study of more radical modifications of the molecule.



I

The elimination of the left-hand ring has now been effected. Olivetol was condensed with ethyl acetoacetate with formation of the coumarin (II). Excess methylmagnesium iodide converted the coumarin to the pyran (III). That

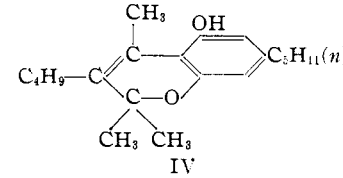


II

III

the initial condensation took place in the manner indicated was assumed on account of previous condensations described with orcinol in which the position of the pyrone ring was proved.[3] The compound showed marihuana activity though only about one-thirtieth that of compound I. The decrease in activity was suspected to be due perhaps to the loss of four carbon atoms or to the presence of the hydrogen atom on the 3-carbon. As a consequence ethyl *n*-butylacetoacetate was condensed with olivetol. By the procedure used for ethyl acetoacetate, the yields were very poor.

Using orcinol as a raw material for a study to improve this reaction, a procedure was found which gave 80% yields or better of the crude pyrone in such condensations. A mixture of orcinol and ethyl *n*-butylacetoacetate in equimolecular amounts was merely treated in the cold with twice the molar concentration of phosphorus oxychloride and allowed to stand at room temperature for forty-eight hours. Olivetol condensed equally well with these substituted ethyl acetoacetates. A feasible method is thus available for the preparation of a variety of substituted coumarins from olivetol or its homologs which can then be converted into the corresponding pyrans. An investigation of such compounds with various alkyl and alkylene groups in the 3- and 4-positions is now in progress. The butyl derivative (IV), which has the same number of



IV

carbons as tetrahydrocannabinol (I) and differs merely by two hydrogen atoms proved, however, to have only about the same effectiveness (5 expts. 0.04 ± 0.01) as the corresponding unsubstituted pyran (III) (10 expts., 0.033 ± 0.01).

Experimental

4,7-Dimethyl-5-hydroxycoumarin.—This compound was prepared by the general directions of Chakravarti.[4] A solution of 5 g. of orcinol in 6 g. of ethyl acetoacetate was cooled and 30 cc. of 85% phosphoric acid added. After standing for twenty hours, the mixture was treated with cold water and the crystals filtered off. Upon recrystallization by dissolving in 50 cc. of hot ethanol and adding water until precipitation just started the product formed white crystals, m. p. 258–259° (cor.); yield, 4.17 g. (55%). Chakravarti reports a melting point of 250°.

(1) For previous paper see Adams, Smith and Loewe, THIS JOURNAL, **63**, 1973 (1941).

(2) Adams, Loewe, Jelinek and Wolff, *ibid.*, **63**, 1971 (1941).

(3) Adams and Baker, *ibid.*, **62**, 2405 (1940).

(4) Chakravarti, *J. Indian Chem. Soc.*, **12**, 536 (1935).

4-Methyl-5-hydroxy-7-*n*-amylcoumarin.—A solution of 4.5 g. of olivetol, 4.5 g. of ethyl acetoacetate and 3.4 g. of phosphorus oxychloride in 75 cc. of dry benzene was refluxed for four hours in an all glass apparatus. Water was added and the mixture cooled. The crystals which separated were filtered off and the benzene layer of the filtrate evaporated, giving an additional crop of crystals. Upon recrystallization by dissolving in 50 cc. of hot ethanol and adding water until precipitation just started, the product formed plates, m. p. 178–179° (cor.); yield, 5.23 g. (85%).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.19; H, 7.44.

2,2,4-Trimethyl-5-hydroxy-7-*n*-amyl-1,2-benzopyran.—The Grignard reagent was prepared from 5.80 g. of magnesium and 34 g. of methyl iodide in 75 cc. of dry ether. About 50 cc. of dibutyl ether was added and the diethyl ether distilled off. A solution of 4.92 g. of 4-methyl-5-hydroxy-7-*n*-amylcoumarin in 150 cc. of dry dibutyl ether was added to the methylmagnesium iodide solution. Upon mixing the two solutions, a yellow precipitate was observed which quickly dissolved leaving a clear solution. The mixture was kept at 90° for sixteen hours, after which it was decomposed with dilute hydrochloric acid and the ether layer separated. The ether solution was washed with dilute aqueous sodium bicarbonate followed by water. The residue remaining upon drying and evaporating the ether, was distilled, b. p. 140–142° (0.02 mm.), bath 160–175°. The product was a reddish viscous oil, $n^{20}D$ 1.5462. The yield was 3 g. (58%).

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.07; H, 9.17.

3-*n*-Butyl-4,7-dimethyl-5-hydroxycoumarin.—Although the product was obtained from orcinol and ethyl *n*-butylacetoacetate by refluxing in benzene solution containing phosphorus oxychloride, the yields were very low. The following procedure was found to give better yields of a product which could be easily purified.

A mixture of 2.4 g. of orcinol and 4.12 g. of ethyl *n*-butylacetoacetate was cooled and 5.8 g. of phosphorus oxychloride was added. After standing at room temperature for sixty-five hours, cold water was added to destroy the unreacted phosphorus oxychloride followed by the addition of 50 cc. of benzene. The benzene solution was washed with water and aqueous sodium bicarbonate. The coumarin was extracted by shaking with two 25-cc. portions of 5% sodium hydroxide solution. This solution was acidified with dilute hydrochloric acid and extracted with ether. Upon drying and evaporating the ether, the coumarin crystallized. Upon recrystallization by dissolving in 30 cc. of hot ethanol and adding water until precipitation just started, the product formed white needles, m. p. 191–195° (cor.); yield, 2.92 g. (62%). Several recrystallizations from dilute ethanol, benzene or toluene failed to raise or sharpen the melting point.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.20.

A few milligrams of product with m. p. 158–159° (cor.) and essentially the same analysis was isolated from mother liquors and assumed to be 3-*n*-butyl-4,5-dimethyl-7-hydroxycoumarin resulting from a ring closure to the 4- instead of the 2-position of the orcinol ring.

An attempt to prepare the coumarin by the condensation in the presence of sulfuric acid failed to give any evidence of its formation.

3-*n*-Butyl-4-methyl-5-hydroxy-7-*n*-amylcoumarin.—A mixture of 4.2 g. of olivetol, 4.9 g. of ethyl *n*-butylacetoacetate and 7 cc. of phosphorus oxychloride was allowed to stand at room temperature for thirty hours. After destroying the unreacted phosphorus oxychloride with ice, 50 cc. of ether was added to dissolve the product. The ether solution was washed with water, aqueous sodium bicarbonate, and twice with 25-cc. portions of aqueous sodium hydroxide. Upon acidification of the sodium hydroxide washings no product separated. Evaporation of the ether solution gave crystals of the desired coumarin. Recrystallization from ethyl acetate or benzene gave white plates, m. p. 140.5–141° (cor.); yield, 4.5 g. (66%).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.45; H, 8.67. Found: C, 75.41; H, 8.68.

No by-product similar to that obtained in the orcinol condensation was observed.

2,2,4-Trimethyl-3-*n*-butyl-5-hydroxy-7-*n*-amyl-1,2-benzopyran.—Methylmagnesium iodide was prepared from 3.53 g. of magnesium and 20.7 g. of methyl iodide in 25 cc. of ether. To this solution was added 3.66 g. of 3-*n*-butyl-4-methyl-5-hydroxy-7-*n*-amylcoumarin dissolved in 75 cc. of dry benzene. The yellow precipitate formed on mixing disappeared in a few seconds. The ether was distilled off and the benzene solution was refluxed for ten hours. The excess Grignard reagent was decomposed with iced dilute hydrochloric acid and the benzene layer separated. After washing with water and aqueous sodium bicarbonate, the benzene was boiled off, leaving a purple oil. The oil was distilled, b. p. 176–177° (0.05 mm.), bath 185–195°. The product was a purplish oil, $n^{20}D$ 1.5375; yield, 2.45 g. (64%).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.20; H, 10.29.

The purple color apparently is due to a very small amount of by-product. It is dissipated on addition of a drop of ordinary ethanol with formation of an amber color.

Summary

1. A satisfactory method for condensing ethyl acetoacetate or ethyl *n*-butylacetoacetate with orcinol or olivetol is described. The resulting coumarins were converted into pyrans by means of excess methylmagnesium iodide.

2. The pyrans from olivetol both showed marihuana activity.

URBANA, ILLINOIS RECEIVED MAY 23, 1941