[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Cannabinol. V. A Second Method of Synthesis of Cannabinol[1]

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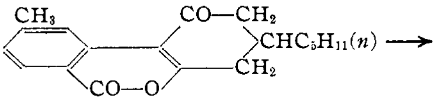
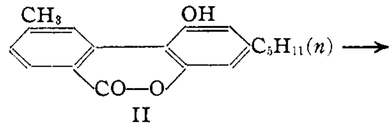
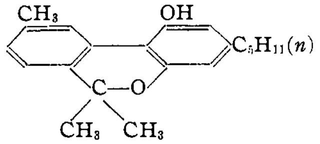
Cannabinol was shown to be 1-hydroxy-3-*n*-amyl-6,6,9-trimethyl-6-dibenzopyran (III) by a synthesis[2] involving (1) the condensation of 4-methyl-2-bromobenzoic acid with dihydroolivetol to 1-keto-3-*n*-amyl-9-methyl-1,2,3,4-tetrahydro-6-dibenzopyrone (I), (2) dehydrogenation of I to 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone (II), (3) conversion of II by means of methylmagnesium iodide to cannabinol (III).



I

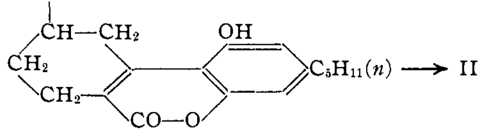


II



III

A second method for synthesizing cannabinol has now been devised. Ethyl 5-methylcyclohexanone-2-carboxylate was condensed with olivetol in the presence of phosphorous oxychloride[3] to give 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (IV). This last compound was dehydrogenated with ease in the presence of sulfur to give the pyrone (II), identical in all respects with the substance previously described. Since this latter is converted with methylmagnesium iodide to cannabinol (III), a second course for the synthesis of cannabinol, new except for the last step, becomes available. The dehydrogenation reaction in this new procedure gives better yields than in the process previously described.



IV

Experimental

1 - Hydroxy - 3 - *n* - amyl - 9 - methyl - 7,8,9,10 - tetrahydro-6-dibenzopyrone.—A solution of 4.5 g. of olivetol (5-*n*-amylresorcinol), 6 g. of ethyl 5-methylcyclohexanone-2-carboxylate and 4.6 cc. of phosphorous oxychloride in 25 cc. of dry benzene protected from moisture was refluxed for three hours in an all-glass apparatus on the steam-bath. The solution rapidly turned deep red. It was washed with dilute aqueous sodium bicarbonate, which caused the benzene layer to become green, then with water. After evaporation of the benzene, the residue was purified by recrystallization from ethyl acetate; white needles, m. p. 180–181° (cor.); yield 4.3 g. (57%).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.03. Found: C, 76.16; H, 8.00.

1 - Acetoxy - 3 - *n* - amyl - 9 - methyl - 7,8,9,10 - tetrahydro-6-dibenzopyrone.—A solution of 0.2 g. of the above compound and 0.1 g. of fused sodium acetate in 2 cc. of acetic anhydride was refluxed for two hours. The solution was poured into water, a small amount of the separated oil removed on a spatula and suspended in a little methanol. Crystals immediately formed which were used to seed the aqueous suspension. The product was purified by recrystallization from methanol, white needles, m. p. 82.5–84° (cor.).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.63. Found: C, 73.50; H, 7.80.

1 - Hydroxy - 3 - *n* - amyl - 9 - methyl - 6 - dibenzopyrone.—A mixture of 0.60 g. of 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone and 0.13 g. of sulfur was heated in a sidearm test-tube at 255–260° for ten minutes with occasional mixing. A cold finger was inserted and the product sublimed at 230–240° (3 mm.). It was recrystallized from toluene, then acetic acid, white needles, m. p. 184–185° (cor.); yield 0.36 g. (61%). A mixed melting point of this product and that with the same structure prepared in another way[2] gave no depression.

Summary

A second method of synthesis of cannabinol has been devised. It consists in the condensation of ethyl 5-methylcyclohexanone-2-carboxylate with olivetol in the presence of phosphorous oxychloride to give 1-hydroxy-3-*n*-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone. Dehydrogenation of this product with sulfur gives 1-hydroxy-3-*n*-amyl-9-methyl-6-dibenzopyrone which has been shown previously to give cannabinol when treated with methylmagnesium iodide.

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[1] For previous paper in this series, see Adams and Baker, THIS JOURNAL, **62**, 2208 (1940).

[2] Adams, Baker and Wearn, *ibid.*, **62**, 2204 (1940).

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