SYNTHESIS OF 2.4-DIHYDROXY-6-PENTYL-BENZOIC-6-^{14}C ACID. ETHYL ESTER. (OLIVETOLIC-6-^{14}C ACID. ETHYL ESTER)

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SUMMARY

In a first step, Δ1-trans-octenoic-3-^{14}C acid was prepared by a Grignard reaction with $BaCO_3$-^{14}C and 1-bromo-pentane, followed by reduction of the obtained hexanoic-1-^{14}C acid to hexanal-1-^{14}C via the n-hexanol-1-^{14}C. The produced hexanal-1-^{14}C, by condensing with malonic acid gives the request Δ1-trans-octenoic-3-^{14}C acid. In a second step, olivetolic-6-^{14}C acid, ethyl ester was prepared by condensing the Δ1-trans-octenoic-3-^{14}C acid, methyl ester with ethyl acetoacetate followed by bromination and catalytic hydrogenation.

Discussion

In 1946 [1] Todd suggested that the cannabinoids may be formed initially in Cannabis Sativa by condensation of menthatriene with olivetol. Later on, Schultz and Hoffner [2] examined numerous fresh cannabis plants and reported that cannabidiolic acid is by far more predominant than cannabidiol. They assumed that olivetolic acid, and not olivetol, is the aromatic species involved in the primary condensation. The isolation of numerous new cannabinoids, in particular cannabigerol and cannabigerolic acid, has made possible a more detailed formulation of the biogenetic process, presented by Mechoulam in 1970. [3] That scheme, which relates mainly to the neutral cannabinoids, implies the olivetolic acid as initial aromatic precursor of the sequence. In our investigation of the cannabinoids biogenesis, it was necessary to find an easy way to synthetize both olivetolic acid and olivetol, and no the single olivetol as described in another intention by Liebman et al. [4]

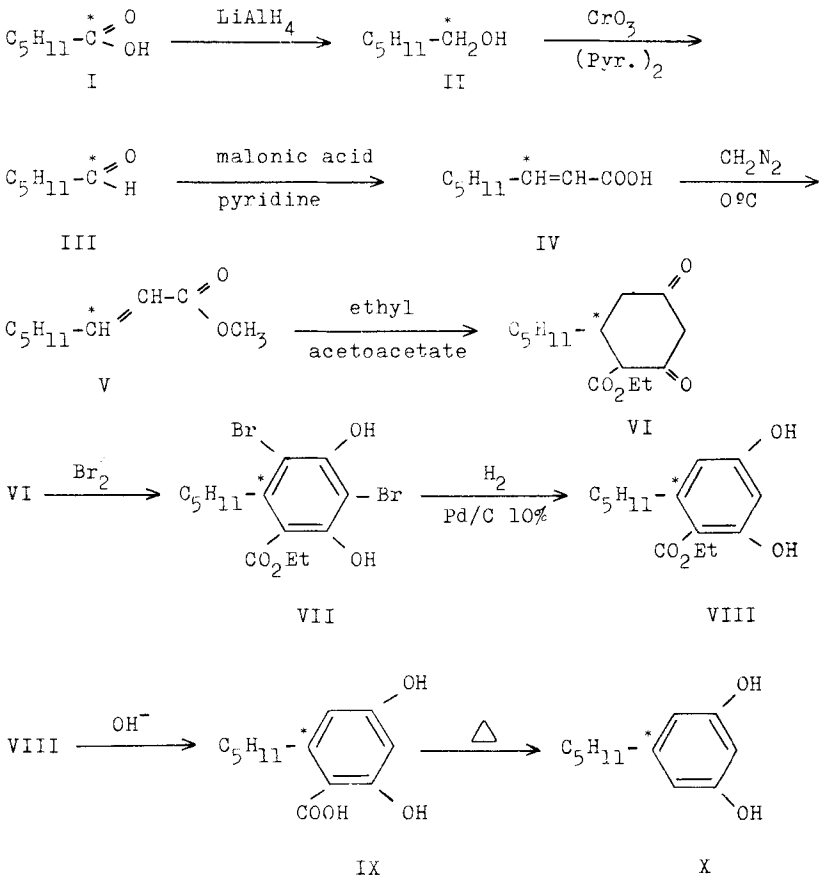

fig. 1.

After several trials, only one scheme (fig. 1), involving condensation of ethyl acetoacetate and Δ1-trans-octenoic acid, methyl ester ^{14}C labelled, [5] was retained for its relative easiness and its yields. Carboxylic labelled hexanoic acid (I) was obtained by a classic Grignard reaction with 1-bromo-pentane and radioactive $^{14}CO_2$. [6] Although the Rosenmund reaction [7] and its variants, can give hexanal in one step, the experience has given better yields in a two steps way, the first as a reduction to the corresponding alcohol with lithium aluminium hydride, and the second as an oxydation with a chromium trioxide pyridine complex [8] to the desired hexanal (III). A condensation with

malonic acid [9] gives the Δ1-trans-octenoic acid (IV), 3-^{14}C labelled. The methyl ester (V) of this latter was condensed with ethyl acetoacetate to ethyl dihydro-olivetolcarboxylate (VI) with a yield of more than 70 %.

Finally a succession of two steps gives successively ethyl dibromo-olivetolcarboxylate (VII) and ethyl olivetolcarboxylate (VIII). On the other hand, Anker and Cook [5] in the usual way, have hydrolysed and decarboxylated the obtained ester (IX), to olivetolic acid and olivetol with a yield of 92 %.

Experimental

Hexanoic-1-^{14}C acid. (I)

In a vacuum apparatus, 1.9652 g (9.98 mmole) of inactive barium carbonate were added to 1.6 mg of active carbonate (specific activity .281 mC/mg) and later treated by 15 ml of perchloric acid, as described by J.D. Cox et al. [10] Then the generated labelled carbon dioxide was frozen at -196 ºC and purified by static vacuum distillation (10^{-4} mm) through a 4 Å molecular sieve. The dried carbon dioxide was led, always in vacuum, in contact to a magnetically stirring solution of 1-bromo-pentane Grignard reagent (12.1 mmole and 9.9 mmole Mg) in ether at -35 ºC. After 30 min, the system was opened to atmospheric pressure, hydrolysed with a solution of 15 ml(5 N)H_2SO_4 and extracted with ether. The organic layer was then dried over anhydrous Na_2SO_4 and the ether evaporated in vacuo. 0.9 g (7.76 mmole) of labelled hexanoic acid were isolated. Yield 78 %.
Specific activity 10.1 10^7 DPM/mmole.

1-Hexanol-1-^{14}C. (II)

Under nitrogen atmosphere, to 1.9 g (5 mmole) of $LiAlH_4$ in dried ether, were slowly added 7.76 mmole of the previously synthetized hexanoic acid. During the addition, the solution was maintained at 0ºC with an ice bath and magnetically stirred for 30 min. The excess of $LiAlH_4$ was then decomposed with moist ether, the solution neutralized with dilute sulfuric acid and the alcohol extracted with ether. After drying the solution over anhydrous Na_2SO_4, the ether was evaporated and 0.581 g (5.7 mmole) isolated. Yield 73 %. Specific activity 7.8 10^7 DPM/mmole.
In another labelled synthesis, a yield of 92 % was obtained.

Hexanal-1-^{14}C. (III)

A round-bottomed flask with three necks was fitted with a drying $CaCl_2$ tube and two bent tubes, containing respectively 7 g (70 mmole) of chromium trioxide and 0.5818 g (5.7 mmole) of labelled hexanol in 1 ml of pyridine. To the magnetically stirred solution (11 ml) of anhydrous pyridine in 150 ml of methylene chloride, was slowly added the chromium trioxide. After stirring the solution in an ice bath during 15 min, the solution of labelled hexanol was then quickly added. After stirring another 15 min at room temperature, the solution was decanted and filtered, and the filtrate washed with ether. 2.165 g (21.7 mmole) of inactive hexanal were added as isotopic dilution. The combined organic layers were washed with a 10 % aqueous NaOH solution, a 10 % aqueous hydrochloric acid solution, three times with water, and finally dried over anhydrous Na_2SO_4. Yield 75 %. Specific activity after isotopic dilution 2. 10^7 DPM/mmole.

Anhydrous pyridine was prepared by drying with KOH and distillation. Methylene chloride was dried over calcium chloride and distillated. Chromium trioxide was dried in a vacuum desiccator during 4 days, at 80°C.

1-trans-octenoic acid. (IV)

2.5 g (25 mmole) of n-hexanal, 1.5 g (14.4 mmole) of malonic acid, and 10 ml of pyridine were heated at 70 °C during 20 h. 0.865 g (1 ml) of inactive Δ1-trans-octenoic acid was then added and the cooled solution treated with 5 ml of 50 % (vol) sulfuric acid, extracted with ether and the obtained Δ1-trans-octenoic acid distilled at 142°C under 35 mm Hg. 3.29 g (23 mmole) of acid was collected. Yield 66 %. Specific activity 1.218 10^7 DPM/mmole.

Olivetolic-6-^{14}C acid, ethyl ester. (VIII)

4.03 g (28 mmole) of the acid (IV), specific activity 0.19 10^7 DPM/mmole, was converted into its methyl ester by diazomethane in ether. Yield 90 %.

A boiling solution of ethylacetoacetate (4 ml) in ethanol (7.7 ml) in which sodium (0.7 g) had been dissolved, was treated dropwise with 4.0779 g (25.6 mmole) of Δ1-trans-octenoic acid methyl ester and the whole refluxed during 10 hours. The cold solution was filtrated, the precipitate dissolved in dilute hydrochloric acid, extracted with ether, dried over anhydrous

Na_2SO_4 and 4.6792 g (18.4 mmole) collected after removing the ether. Yield 72 %.
The crude ester in acetic acid (10 ml) was slowly treated with stirring at room temperature, with 2.5 ml of bromine in acetic acid (10 ml), and the solution heated overnight at 60°C. The cooled solution gave ethyl-dibromo-olivetol carboxylate by evaporating the filtrate. The crude dibromo compound in N sodium hydroxyde aqueous solution (8.5 ml) was hydrogenated at room temperature and 1 atmosphere, over 10 % palladium/carbon (46 mg) as far as the theoretical quantity of hydrogen was absorbed. Olivetolic acid, ethyl ester and the catalyst were then salted out from the acidified solution, and the ester extracted with ether. Collected 2.75 g (10.9 mmole). Yield 59 % on Δ1-trans-octenoic acid. Specific activity 0.0919 10^7 DPM/mmole.

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