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TETRAHYDROCANNABINOL ANALOGS. SYNTHESIS OF 2-(3-METHYL-2-OCTYL)-3-HYDROXY-6,6,9-TRIMETHYL-7,8,9,10-TETRAHYDRODIBENZO(b,d)PYRAN[1a]

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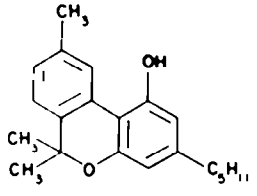
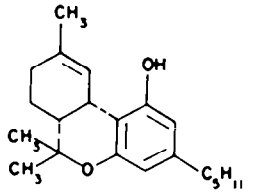
Abstract—The title compound, a positional isomer (in the phenolic ring) of a compound (IV) previously known to possess potent "marijuana-like"activity, has been synthesized in seven steps from 4-acetylresorcinol; surprisingly, it was found to be physiologically inactive. An alternative, potentially versatile synthetic route to structural analogs of THC was explored which involved application of the Fries rearrangement of esters of hydroxytetrahydrodibenzopyrones (XVIII) and -pyrans (XX).

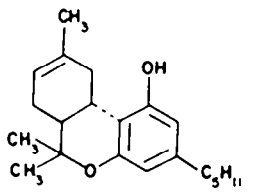
"TETRAHYDROCANNABINOL" is a tetrahydro derivative of the hashish component cannabinol (I), but the position of the alicyclic double bond may vary depending upon the origin of the hemp. Of the two active, naturally-occurring "tetrahydrocannabinols" which have thus far been isolated from hemp, the Δ^1 isomer (II) is by far the most common,[2] while the Δ^6 isomer (III) has been found in some varieties of Mexican hemp.[3] It has been suggested[4] that the physiological effects observed upon smoking of marijuana may be due to the Δ^6 isomer, which is readily formed by heat isomerization of the Δ^1 isomer. The synthesis of both isomers has recently been reported.[4,5]



I



II



III

In the course of a synthetic study of structure-activity relationships in tetrahydrocannabinol (THC) analogs, Adams[6] prepared a compound (IV) which was some 70 times more potent that the active THC fraction from marijuana. It differed from natural THC by the replacement of the n-pentyl side chain in the phenolic ring by a 1,2-dimethylheptyl group, and by the placement of the aliphatic double bond in the conjugated position. In further studies of structure-activity relationships in this series, Avison and coworkers in 1949[7] described other tetrahydrodibenzopyran derivatives

[1a] This work was supported by a grant to Princeton University from the Smith Kline and French Laboratories, Philadelphia, Pa. [b] Smith Kline and French Laboratories.

[2] Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.* **86**, 1646 (1964).

[3] R. Hively, F. Hoffmann and W. A. Mosher, *J. Amer. Chem. Soc.* **88**, 1832 (1966).

[4] E. C. Taylor, K. Lenard and Y. Shvo, *J. Amer. Chem. Soc.* **88**, 367 (1966).

[5] R. Mechoulam and Y. Gaoni, *J. Amer. Chem. Soc.* **87**, 3273 (1965).

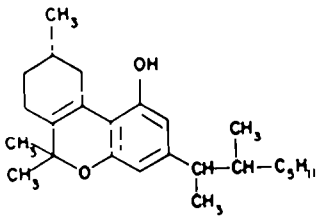
[6] R. Adams, S. MacKenzie and S. Loewe, *J. Amer. Chem. Soc.* **70**, 664 (1948).

[7] A. W. D. Avison, A. L. Morrison and M. W. Parkes, *J. Chem. Soc.* 952 (1949).

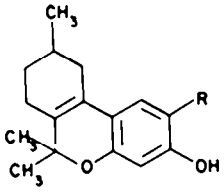
which differed from THC not only in having the double bond in the conjugated position but, more significantly, in possessing altered positions for the hydroxyl and alkyl groups in the aromatic ring (Va–e).

In pharmacological investigations, these structural analogs showed significant analgetic activity when compared with natural THC as standard.

It will be noted that the 1,2-dimethylheptyl side chain was missing from the 4-alkylresorcinol-derived derivatives (Va–e) listed above. As an initial objective in our program to obtain information on structure-activity relationships in THC-related



IV



V a R = n-hexyl
b R = cyclohexyl
c R = n-heptyl
d R = n-octyl
e R = sec-octyl

compounds, we directed our efforts towards the synthesis of compound VII. In brief, the synthetic scheme to be explored involved the condensation of ethyl 5-methylcyclohexanone-2-carboxylate with the appropriate alkyl-substituted resorcinol to give the coumarone derivative (VI) which by subsequent treatment with methyl magnesium iodide followed by cyclization would lead to the desired tetrahydrodibenzopyran (VII). Available information on the position of condensation of ethyl 5-methyl-cyclohexanone-2-carboxylate with substituted resorcinols indicated that the construction of the coumarone VI would probably take place as shown. Thus, condensation takes place between the two hydroxyl groups (position 2) in 5-substituted resorcinols,[8] at position 4 with unsubstituted resorcinols[9] and at position 6 with 4-substituted resorcinols.[10] The same substitution pattern is observed with ethyl cyclohexanone-2-carboxylate itself.[11]

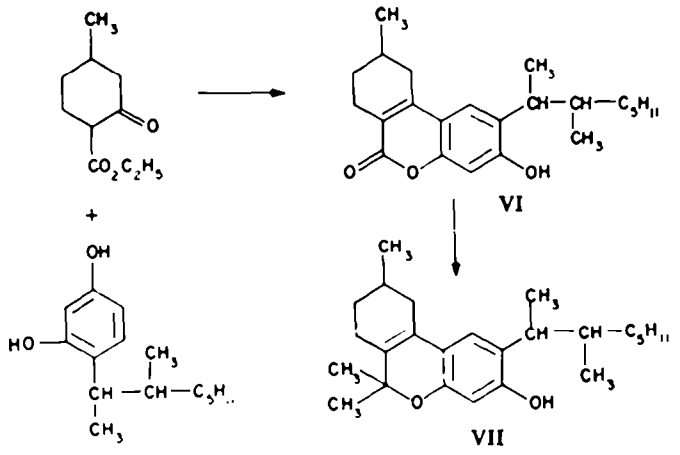
The route indicated in the accompanying flow sheet was successfully employed for the preparation of 2-(2,4-dihydroxyphenyl)-3-methyloctane (XIII). 4-Acetylresorcinol (VIII) was first methylated with dimethyl sulfate to give the dimethoxy derivative IX which was then treated with the Grignard reagent from 2-bromoheptane to give the tertiary alcohol X. This was dehydrated under acid conditions to the olefin XI, which was reduced with hydrogen in the presence of palladium catalyst to give the

[8a] R. Adams, S. Loewe, C. Jelinek and H. Wolff, *J. Amer. Chem. Soc.* **63**, 1971 (1941), [b] R. Adams, C. M. Smith and S. Loewe, *J. Amer. Chem. Soc.* **63**, 1973 (1941). [c] P. B. Russell, A. R. Todd, S. Wilkinson, A. D. MacDonald and G. Woolfe, *J. Chem. Soc.* 169, 826 (1941).

[9a] R. Ghosh, A. R. Todd and S. Wilkinson, *J. Chem. Soc.* 1121 (1940); [b] S. Z. Ahmad and R. D. Desai, *Chem. Abstr.* **32**, 4562 (1938); [c] N. A. Chowdhry and R. D. Desai **32**, 9066 (1938).

[10] N. A. Chowdhry and R. D. Desai, *Chem. Abstr.* **32**, 9065 (1938).

[11a] W. Dieckmann, *Liebigs. Ann.* **317**, 27 (1901). [b] H. K. Sen and U. P. Basu, *J. Ind. Chem. Soc.* **5**, 467 (1928).

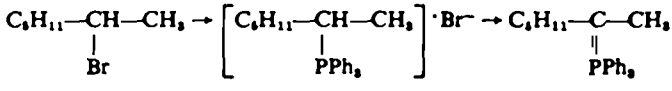


desired dimethoxy alkyl derivative XII. Demethylation with hydrogen bromide in acetic acid gave the alkyl resorcinol XIII.

An attempt to use the benzyl rather than the methyl blocking group was disappointing. Although the required dibenzyloxy ketone was readily prepared, the subsequent Grignard addition went in very poor yield, perhaps because of the bulk of the *o*-situated benzyloxy grouping. Difficulty was also encountered in reductive removal of the benzyl groupings, and mixtures were always obtained of debenzylated and benzylated derivatives of XIII.

Condensation of ethyl 5-methylcyclohexanone-2-carboxylate with the resorcinol derivative XIII in benzene solution, using phosphorus oxychloride as condensing agent, gave VI as a white crystalline solid. The structure of VI was confirmed by its NMR spectrum in which the aromatic protons at C_1 and C_4 appear as sharp singlets at τ 2·96 and 2·73 respectively. This compound upon treatment with excess methyl magnesium iodide and subsequent cyclization with hydrobromic acid gave the desired THC analog VII as a yellow resin.

A possible alternative route to the resorcinol intermediate XIII involved the use of the Wittig reaction instead of the Grignard reaction for the attachment of the desired alkyl side chain. 2-Bromoheptane was converted by reaction with triphenyl phosphine into the phosphonium salt (XIV) which was converted into the Wittig reagent (XV) by sodium hydride in dimethyl sulfoxide.[12] The above quaternization step required



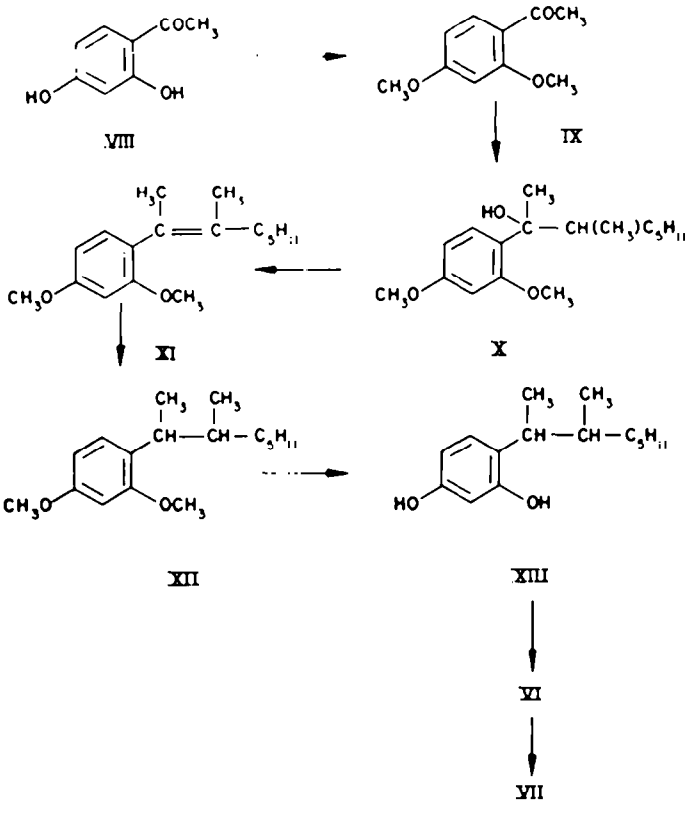
XIV XV

drastic conditions (190–200° for 20 hr) giving a mixture of the desired quaternary salt, heptene-1 and heptene-2. Subsequent attempts to carry out the Wittig condensation with 2,4-dimethoxyacetophenone were completely unsuccessful. Other workers have failed to effect similar Wittig reactions.[13]

[12] R. Greenwald, M. Chaykovsky and E. J. Corey, *J. Org. Chem.* **28**, 1128 (1963).

[13] S. D. Koch, J. L. Dever and P. F. Donovan, U.S. Dept. Com. Office Tech. Serv. AD 278, 052, 189 pp. (1962); *Chem. Abstr.* **59**, 15201 (1963).

A possible alternate route involving unprotected resorcinol intermediates was not attempted because of the probability that the unprotected *o*-hydroxyl group would cyclize with the olefin produced either by dehydration of the glycol or directly from the Wittig reaction.[14]

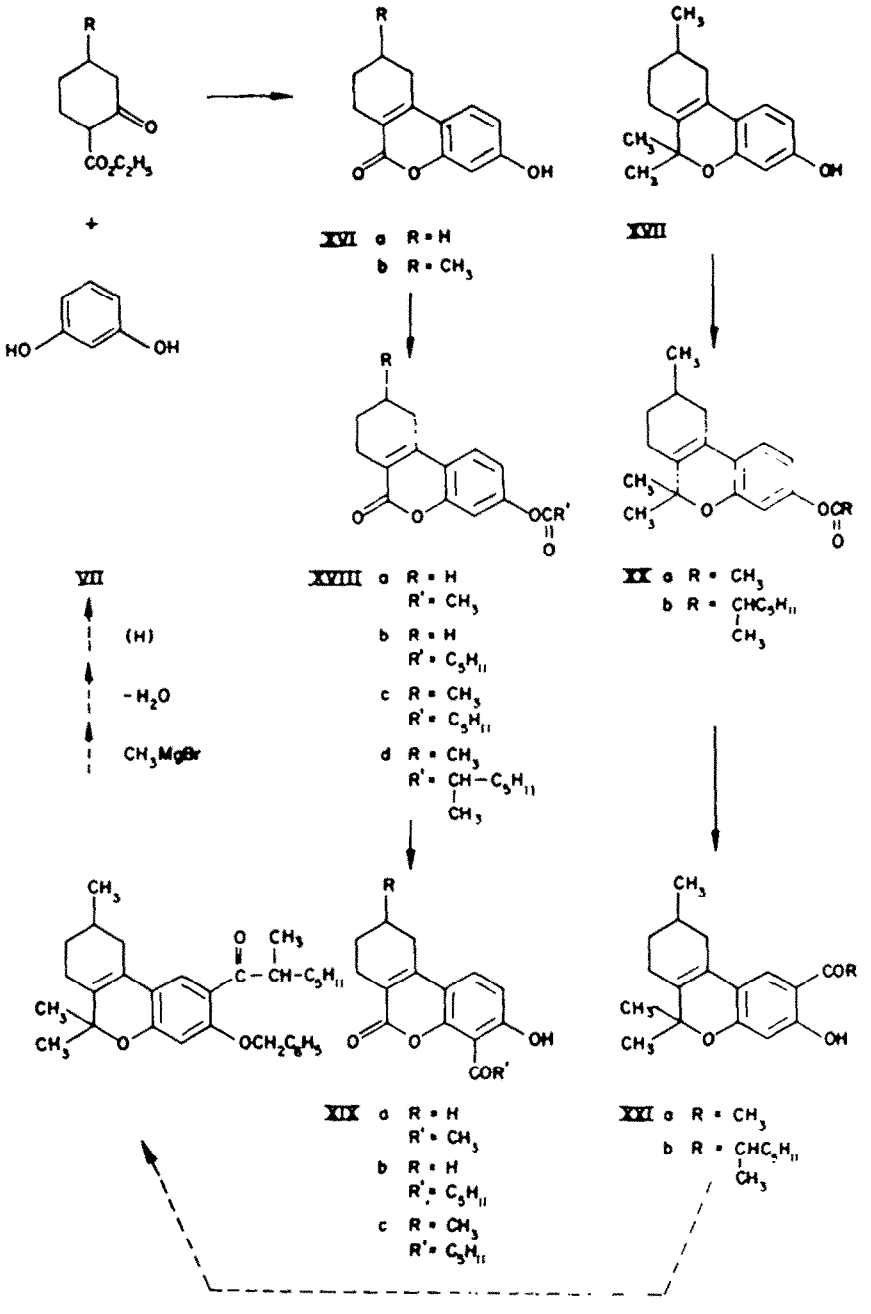


A second and possibly more general synthetic route to THC analogs related to VII involved the application of the Fries rearrangement to esters (XVIIIa,[15] b–d, XXa,[9a] b) of appropriate hydroxy tetrahydrodibenzopyrones (XVIa,[11] XVIb[9]) and hydroxy tetrahydrodibenzopyrans (XVII).[9a] It has been claimed[15] that treatment of 3-acetoxy 7,8,9,10-tetrahydrodibenzo(b,d)pyrone (XVIIIa) under Fries rearrangement conditions resulted in the migration of the acetoxy group to the 4 position (XIXa). However, since this conclusion was based only on apparent differences between the product and the 2-acetyl compound (which they had obtained from the condensation of 4-acetyl-resorcinol with ethyl cyclohexanone-2-carboxylate), we repeated this reaction, confirmed the above structural assignment by NMR and extended the rearrangement to the preparation of the acyl derivatives XIXb, c and XXIa, b.

The esters (XVIIIa–d) of the phenols (XVIa, b) were readily prepared using acetic anhydride, caproyl chloride or 2-methylheptanoyl chloride. All of the esters were crystalline but were most conveniently purified by distillation under reduced pressure.

[14] W. M. Lauer and E. E. Renfrew, *J. Amer. Chem. Soc.* **67**, 808 (1945).

[15] R. D. Desai, M. M. Gaitonde, S. M. Hansan and R. C. Shah, *Proc. Indian Acad. Sci.* **25A**, 345 (1947); *Chem. Abstr.* **42**, 1914 (1948).


R
CO2C2H5
O
HO
OH
XVI a R = H
b R = CH3
CH3
CH3
CH2
XVII
OCR'
O
XVIII a R = H
R' = CH3
b R = H
R' = C5H11
c R = CH3
R' = C5H11
d R = CH3
R' = CH-C5H11
CH3
VII
(H)
-H2O
CH3MgBr
OCR
XX a R = CH3
b R = CHC5H11
CH3
COR
XIX a R = H
R' = CH3
b R = H
R' = C5H11
c R = CH3
R' = C5H11
XXI a R = CH3
b R = CHC5H11
CH3

Treatment of the ester XVIIIa with anhydrous aluminum chloride gave a methyl ketone which was shown conclusively to have the acetyl grouping in position 4 (XIXa) by NMR; the vicinal aromatic protons at C_1 and C_2 appear as a pair of doublets at τ 2·41 (J = 10 c/s) and τ 3·19 (J = 10 c/s). With the caproyl derivatives (XVIIIb, c), the Fries rearrangement with aluminum chloride as catalyst again gave the 4-substituted derivatives (XIXb, c), as shown by the appearance of the vicinal hydrogens at C_1 and C_2 as doublets at τ 2·45 (J = 10 c/s) and τ 3·20 (J = 10 c/s). However, attempts to obtain higher yields in the Fries rearrangement by replacing aluminum chloride with boron trifluoride etherate led to cleavage of the ester with reformation of the starting phenol. All efforts to carry our a Fries rearrangement with the methylheptanoyl ester (XVIIId), either with aluminum chloride or boron trifluoride etherate, resulted solely in ester cleavage.

Conversion of XVIb to XVII with methyl magnesium iodide was effected under much simpler conditions than those previously described;[9a] i.e., the Grignard reaction was carried out without protection of the 3-hydroxy group, using ether–benzene as solvent. Although the dibenzopyrone (XVIb) is not soluble in this solvent mixture, the Grignard complex is and a homogeneous solution results. The 3-acetoxy derivative (XXa) of the resulting tetrahydrodibenzopyran was readily formed by treatment with excess acetic anhydride. Compound XXa has been prepared previously by a different procedure.[9a] The methyl heptanoyl ester (XXb) was readily formed by treatment of XVII with the appropriate acid chloride (from 2-bromoheptane by the Grignard method, followed by formation of the acid chloride with $SOCl_2$). The acetoxy ester (XXa) was a solid, but the methyl heptanoyl ester (XXb) was a yellow liquid which could, however, be distilled under reduced pressure. Attempted Fries rearrangement of these esters with aluminum chloride led only to tarry products, but it was found that rearrangement could be effected in reasonable yields (about 60%) by treatment with boron trifluoride etherate at 80–90° for 30–50 min. The Fries rearrangement product from XXa was shown to have structure XXIa by examination of its NMR spectrum, which showed two sharp singlets at τ 2·65 and τ 3·67 for the aromatic protons. In contrast to the results obtained in the dibenzopyrone series, no hydrolytic cleavage occurred when the Fries rearrangement of the methyl heptanoyl ester (XXb) was carried out with boron trifluoride etherate and the desired ketone (XXIb) (NMR: C_1–H, singlet at τ 2·58; C_4–H: singlet at τ 3·70) was thus prepared. Conversion of this ketone to VII could presumably be effected by the sequence of steps indicated (dotted arrows), but this was not done in view of the biological inactivity of the THC analog VII.

EXPERIMENTAL[10]

2-(2,4-Dimethoxyphenyl)-3-methyl-2-octene (XI). To a suspension of 24·0 g (1·0 mole) Mg ribbon and one small crystal I_2 in 100 ml abs ether was added dropwise, and under N_2, a solution of 180 g (1·0 mole) 2-bromoheptane in 100 ml abs ether. After addition was complete (1 hr), the mixture was heated under reflux for 2 hr to complete formation of the Grignard reagent, and a solution of 90·1 g (0·5 mole) 2,4-dimethoxyacetophenone in 200 ml tetrahydrofuran added over a period of 1·5 hr. The mixture was heated under reflux for 10 hr, cooled and 180 ml saturated NH_4Claq added to decompose the excess Grignard reagent. The solvents were decanted, the residual paste extracted with tetrahydrofuran, and the combined solvents dried ($CaCl_2$) and evaporated under red. press. The residual oil (the tertiary alcohol X) was distilled at a pressure of 10 mm and at an oil bath temp of 120–130° in the presence of a few drops 20% H_2SO_4. After the water had been removed, the residue

[10] We are indebted for the microanalyses to the Robertson Microanalytical Laboratory, Florham Park, N.J. All m.ps are uncorrected.

was distilled at 0·2 mm and at an oil bath temp of 285°, and the fraction boiling at 128–140°/0·2 mm collected (60 g). When this material was redistilled it boiled at 215°/0·2 mm, presumably due to thermal isomerization of the *cis* to the *trans* isomer. A higher boiling fraction from the original distillation boiled at 170–190°/0·2 mm and appeared to be a mixture of *cis* and *trans* isomers; redistillation gave the same high-boiling component obtained by redistillation of the lower boiling (main) fraction. (Found: C, 77·35; H, 9·92. $C_{17}H_{26}O_2$ requires: C, 77·82; H, 9·99%.)

2-(2,4-*Dimethoxyphenyl*)-3-*methyloctane* (XII). A solution of 50 g XI (redistilled) in 100 ml EtOH was shaken under 2–3 atms. of H_2, in the presence of 0·6 g 10% Pd–C, for 2 hr (until cessation of H_2 uptake). The catalyst was removed by filtration and the filtrate evaporated under red. press. The residual colorless oil was distilled and the main fraction boiling at 110–117°/0·1 mm collected to give 42 g (80%). (Found: C, 77·97; H, 10·95; OCH_3, 24·11. $C_{17}H_{28}O_2$ requires: C, 77·22; H, 10·67; OCH_3, 23·46%.)

Assuming the redistilled olefin XI to be *trans*, its reduction product XII would be the *d, l*-racemate. The fact that the dibenzopyrone VI was obtained as a homogeneous, crystalline material supports the presumed homogeneity of XII.

2-(2,4-*Dihydroxyphenyl*)-3-*methyloctane* (XIII). Demethylation of XII was carried out as described for similar cases by Suter and Weston.[17] A mixture of 40 g XII 100 ml 48% HBr and 320 ml glacial AcOH was heated under reflux for 4 hr, poured into ice, the resulting mixture neutralized to pH 4–5 by addition of 10N NaOH and extracted with ether. The ether extracts were combined and extracted with 3 150-ml portions of 2N NaOH, the extracts acidified with AcOH and re-extracted with ether. After drying ($MgSO_4$), the ether was evaporated and the residual oil distilled. The main fraction boiled at 158–160°/0·1 mm and weighed 20 g (60%). (Found: C, 75·88; H, 10·15. $C_{16}H_{24}O_2$ requires: C, 76·22; H, 10·24%.)

2-(3-*Methyl*-2-*octyl*)-3-*hydroxy*-9-*methyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (VI). A mixture of 11·6 g (0·05 mole) XIII, 9·2 g (0·05 mole) ethyl 5-methylcyclohexanone-2-carboxylate and 5·0 g $POCl_3$ in 70 ml anhydrous benzene was heated to boiling for 5 min. The solution turned deep red and evolution of HCl commenced. The reaction mixture (protected from atmospheric moisture with a $CaCl_2$ tube) was then allowed to stand at room temp for 20 hr, poured into 10% $NaHCO_3$aq and the benzene layer separated and washed with 3 50-ml portions of 10% $NaHCO_3$aq (the color of the benzene layer changed from red to yellow during the alkaline washing). The benzene was then dried ($MgSO_4$) and evaporated under red. press. The residual crystalline mass was recrystallized from 50 ml of AcOEt to give 6·6 g (40%) of colorless crystals, m.p. 192–193°. (Found: C, 77·41; H, 9·07. $C_{23}H_{30}O_3$ requires: C, 77·49; H, 9·05%.)

2-(3-*Methyl*-2-*octyl*)-3-*hydroxy*-6,6,9-*trimethyl*-7,8,10-*tetrahydrodibenzo*(b,d)*pyran* (VII). The Grignard reaction was carried out essentially as described for similar conversions.[18] Thus, a solution of 4·5 g VI in 150 ml dry benzene was added dropwise to a solution of MeMgI (prepared from 7·8 g Mg ribbon and 18 ml MeI in 90 ml dry ether). After addition was complete, the mixture was heated under reflux for 20 hr, the excess Grignard reagent decomposed by the addition of 45 ml saturated NH_4Claq, the organic layer separated and the aqueous phase extracted with benzene. The combined benzene extracts and organic layer were washed successively with water, dil. $NaHCO_3$aq and water, and then dried and evaporated under red. press. The residue was suspended in 300 ml pet. ether (30–60°) and 1·0 ml 48% HBraq added. The solution was heated under reflux for 1 hr, evaporated under red. press. and the residue sublimed at 200–240°/0·05 mm to give 2·5 g (57%) of a yellow resin. (Found: C, 80·79; H, 10·23. $C_{24}H_{36}O_2$ requires: C, 81·03; H, 10·34%.)

3-*Hydroxy*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (XVIa). A mixture of 22·0 g resorcinol, 34·0 g ethyl 2-cyclohexanonecarboxylate and 20 g polyphosphoric acid[19] was heated to 100–110°, at which point an exothermic reaction took place and the temp rose to 140°. After the exothermic reaction had subsided, the reaction mixture was maintained by external heating at 140° for 30 min, cooled and poured into ice-water. The crude product was filtered off, washed thoroughly with water and recrystallized from EtOH to give 34·0 g (80%) of a pale yellow solid, m.p. 201–202° (lit.[11] m.p. 203–204°). This comp had previously been prepared from the same reactants by condensation in conc. H_2SO_4.[11]

3-*Hydroxy*-9-*methyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (XVIb) was prepared in 68% yield

[17] C. M. Suter and A. W. Weston, *J. Amer. Chem. Soc.* **61**, 232 (1939).

[18] R. Adams, K. H. Chen and S. Loewe, *J. Amer. Chem. Soc.* **67**, 1534 (1945).

[19a] J. Koo, *Chem. and Ind.* 445 (1955); [b] S. S. Israelstam and E. Barris, *Ibid.* 1430 (1958).

by condensation of resorcinol with ethyl 5-methyl-2-cyclohexanonecarboxylate in polyphosphoric acid, as described above. The product melted at 198–200° (lit.[8a] m.p. 199–200°) after recrystallization from EtOH. This material had previously been prepared from the same reactants by condensation in conc. H_2SO_4.[8a]

3-*Hydroxy*-4-*acetyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (XIXa). A mixture of 2·0 g 3-acetoxy derivative XIV[8a] and 4·0 g anhydrous $AlCl_3$ was heated in an oil bath at 170° for 1 hr. The melt was cooled, decomposed by the addition of HCl and the precipitated solid collected by filtration and washed with water. The crude ketone was recrystallized from EtOH to give 1·0 g (50%) of yellow crystals, m.p. 164–166°. (Found: C, 69·59; H, 5.51. $C_{14}H_{14}O_4$ requires: C, 69·75; H, 5·46%.)

3-*Caproyloxy*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (XVIIIb). A mixture of 6·3 g XVIa[11] and 8·0 ml caproyl chloride was heated in an oil bath at 120°. After a few min a vigorous exothermic reaction took place and the temp of the mixture rose to 160–170°, with concomitant HCl evolution. After 30 min HCl evolution ceased, and the reaction mixture was then cooled and poured into EtOH. The yellow crystals which separated were collected by filtration to give 7·8 g (88%), m.p. 92–94°. (Found: C, 72·97; H, 7·18. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%.)

3-*Hydroxy*-4-*caproyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (XIXb). A mixture of 3·2 g XVIIIb and 4·4 g anhydrous $AlCl_3$ was heated in an oil bath at 170° for 1 hr, cooled and excess $AlCl_3$ decomposed by the addition of HCl. The crude product was collected by filtration, dissolved in 7 ml 2N NaOH and a small amount of insoluble material removed by filtration. Acidification of the filtrate resulted in the separation of the crude ketone, which was recrystallized from EtOH and then sublimed at 130–140°/0·01 mm to give 1·4 g, m.p. 118–119°. (Found: C, 72·65; H, 7·28. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%.)

3-*Caproyloxy*-9-*methyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (XVIIIc). Acylation of XVIb with caproyl chloride was carried out in the same manner as described above for the preparation of XVIII. The product was obtained in 76% yield; m.p. 76–78°. (Found: C, 73·18; H, 7·60. $C_{20}H_{24}O_4$ requires: C, 73·14; H, 7·37%.)

3-*Hydroxy*-4-*caproyl*-9-*methyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (XIXc). The Fries rearrangement was carried out as described above for the rearrangement of XVIII to XIX; the product melted at 124–126° after recrystallization from EtOH; yield 50%. (Found: C, 72·87; H, 7·37. $C_{20}H_{24}O_4$ requires: C, 73·14; H, 7·37%.)

2-*Methylheptanoic acid.* 2-Heptylmagnesium bromide was prepared by adding 108 g (0·6 mole) 2-bromoheptane in 100 ml abs ether to a suspension of 13·8 g (0·6 mole) Mg ribbon in 100 ml ether and refluxing for 2 hr. The mixture was then carbonated by pouring over dry ice. After 2 hr the mixture was decomposed by addition of 200 ml 20% HCl aq, and extracted with ether. The ether extract was washed once with water and then extracted with 2 100-ml portions of 2N NaOH. The alkaline extracts were then acidified and extracted with ether, and the ether extracts dried ($MgCl_2$) and evaporated under red press. The remaining colorless oil was distilled at 85–87°/0·5 mm to give 47 g (54%). (Found: C, 67·07; H, 11·20. $C_9H_{18}O_2$ requires: C, 66·63; H, 11·18%.)

2-*Methylheptanoyl chloride:* To 72 g (0·6 mole) $SOCl_2$ was added with stirring during the course of 1 hr 72 g 2-methylheptanoic acid; the temp of the mixture was maintained at 40–45°. After addition was complete, the mixture was heated under reflux for 1 hr and then distilled under water aspirator pressure. After removal of excess $SOCl_2$, the main fraction distilled at 104–105°/70–75 mm to give 75 g (94%). (Found: C, 59·37; H, 9·29; Cl, 22·37. $C_9H_{17}OCl$ requires: C, 59·07; H, 9·29; Cl, 21·79%.)

3-(2-*Methylheptanoyloxy*)-9-*methyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyrone* (XVIIId). A mixture of 6·9 g XVIb and 8·0 ml 2-methylheptanoyl chloride was heated under reflux at an oil bath temp of 160–170° for 30 min. As the temperature of the oil bath reached 150° during the initial heating, vigorous HCl evolution commenced, and the dibenzopyrone went into solution. After heating was complete, the mixture was cooled, poured into excess 1N NaOH solution, and the alkaline solution extracted with ether. The ether extracts were washed with water, 1N NaOH solution and again with water, and then dried and evaporated. The residual white waxy solid was distilled at 180–200°/0·2 mm to give 8·5 g, m.p. 40°. (Found: C, 73·99; H, 7·88. $C_{28}H_{36}O_4$ requires C, 74·13; H, 7·92%.)

An attempted Fries rearrangement of this material with $AlCl_3$ as described above resulted exclusively in cleavage of the ester to regenerate XVIb.

3-*Hydroxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyran* (XVII). The following procedure represents a considerable improvement and simplification over the previously described

preparation of this compound,[84] To a solution of MeMgI prepared from 15·6 g Mg ribbon and 38 ml MeI in 120 ml dry ether was added in small portions 8·0 g crystalline XVIb. The resulting solution was heated under reflux for 12 hr, and then excess Grignard reagent was decomposed by addition of 120 ml 25% H_2SO_4. The acidic solution was extracted with ether and the extracts washed with water, 10% $NaHCO_3$, and water and then dried and distilled. The residual red-brown crystalline mass weighed 8·0 g. It was purified by sublimation at 140–150°/0·5 mm to give 6·8 g (80%) of yellow crystals which after recrystallization from ether melted at 140–142° (lit.[84] m.p. 144–145°). The 3-acetoxy derivative, m.p. 56–58°, (lit.[84] m.p. 58°) was prepared by heating with Ac_2O, followed by recrystallization from EtOH.

2-*Acetyl*-3-*hydroxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyran* (XXIa). A mixture of 4·8 g 3-acetoxy derivative of XVII and 40 ml freshly-distilled BF_3-etherate was heated at 80° for 45 min, then cooled and poured into ice-water. The resulting mixture was extracted with ether, the extracts washed with water, 10% $NaHCO_3$ and again with water, and the ether dried and evaporated. Recrystallization of the residual crystalline solid gave 2·9 g (60%) of yellow crystals, m.p. 128–130°. (Found: C, 75·25; H, 7·78. $C_{18}H_{22}O_3$ requires: C, 75·49; H, 7·74%.)

3-(2-*Methylheptanoyloxy*)-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyran* (XXb). A mixture of 4·8 g XVII and 6·0 ml of 2-methylheptanoyl chloride was heated at an oil bath temp of 160–170° for 30 min and then poured into ice-water. The resulting mixture was extracted with ether, the ether extracts washed with water, then with 2N NaOH and again with water, and finally dried and evaporated. Fractionation of the residual oil gave some fore-run and then 5·5 g (80%) of a main fraction boiling at 207–210°/0·1 mm. (Found: C, 77·52; H, 9·19. $C_{26}H_{34}O_3$ requires: C, 77·80; H, 9·25%.)

2-(2-*Methylheptanoyl*)-3-*hydroxy*-6,6,9-*trimethyl*-7,8,9,10-*tetrahydro*-6-*dibenzo*(b,d)*pyran* (XXIb). A mixture of 5·0 g XXb and 25 ml freshly-distilled BF_3-etherate was heated at 80° for 45 min, then cooled and poured into ice-water. The resulting mixture was extracted with ether, the extracts washed with water, 2N NaOH, and again with water, and the ether dried and evaporated. The residual oil was distilled at 170–180/0·3 mm to give 3·8 g (76%). (Found: C, 77·49; H, 9·31. $C_{24}H_{34}O_3$ requires: C, 77·80; H, 9·25%.)

Tripheny-2-*heptylphosphonium bromide* (XIV). A mixture of 36 g (0·2 mole) 2-bromoheptane and 52 g (0·2 mole) triphenylphosphine was heated at an oil bath temp of 180° for 5 hr, and then at 195–200° for 12 hr. The mixture was then cooled to 60–70° and poured into 400 ml of abs tetrahydrofuran. Refrigeration resulted in the separation of white crystals which were collected by filtration, washed with cold tetrahydrofuran and dried to give 50 g (60%), m.p. 170–172°. (Found: Br, 18·19. $C_{25}H_{30}BrP$ requires: Br, 18·11%.)