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Dihydrofurocoumarins

Synthesis of some Long Chain 4-*n*-Alkyl Substituted Dihydroxanthotoxins, 4-Phenyl-dihydroxanthotoxin and Methyl 8-(Dihydroxanthotoxin-4)-*n*-octanoate

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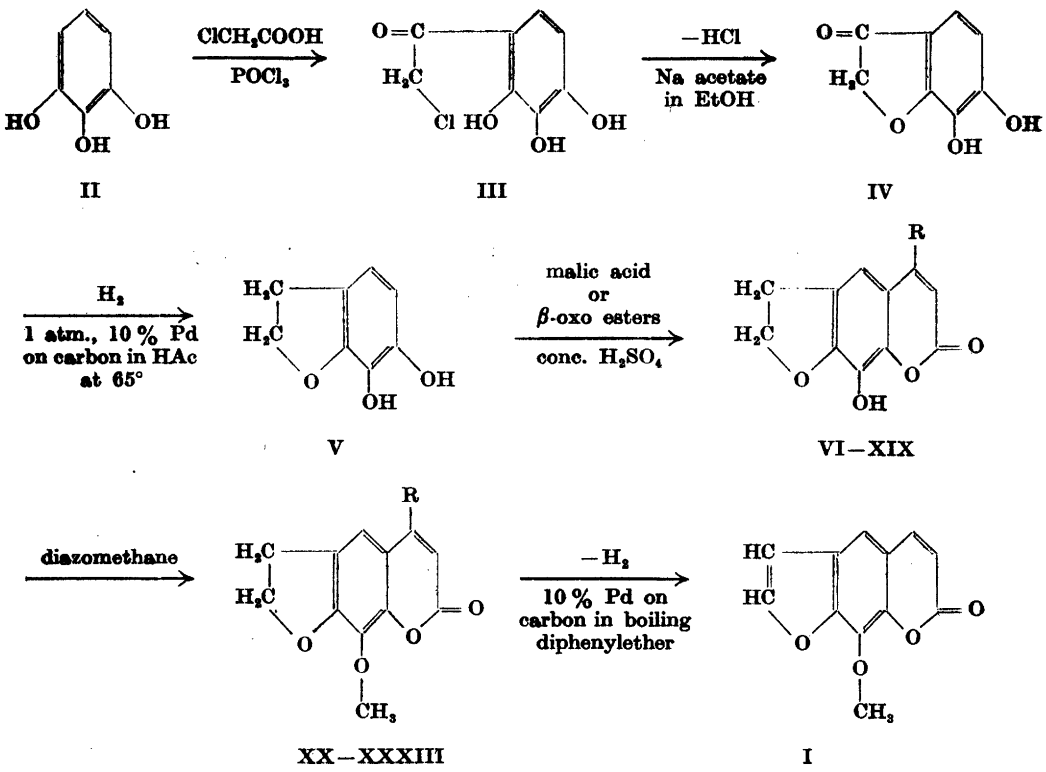
A number of long chain 4-*n*-alkyl substituted dihydroxanthotoxols and dihydroxanthotoxins have been synthesized together with some other substituted dihydroxanthotoxols and dihydroxanthotoxins. Xanthotoxin has been prepared by a modification of the method described by Späth and Pailer [4].

Since old times in Egypt a drug obtained from the plant *Ammi majus* L. has been used as treatment for *leucoderma idiopathicum*. The active principle of this drug was crystallized by Fahmy and Abushady [1] and was shown by Schönberg and Sina [2] to be identical with the methoxyfurocoumarin xanthotoxin (I) previously isolated by Thoms [3] from the fruits of *Fagara xanthoxyloides*. The total synthesis of xanthotoxin was performed by Späth and Pailer [4].

For the knowledge of the etiology of *leucoderma idiopathicum*, it would seem important to study the effect of furocoumarins and related compounds on the pigment metabolism. In this connection a number of new derivatives of dihydroxanthotoxin has been prepared. This report describes the synthesis of some 4-alkyl substituted dihydroxanthotoxols and dihydroxanthotoxins, 4-phenyl-dihydroxanthotoxol and 4-phenyl-dihydroxanthotoxin and methyl 8-(dihydroxanthotoxin-4)-*n*-octanoate. Xanthotoxin was prepared according to Späth and Pailer [4] with some minor modifications of the original method. The accompanying chart shows the route by which the synthesis of xanthotoxin and the derivatives of dihydroxanthotoxin were carried out.



In this chart R is equal to: VI and XX = H, VII and XXI = methyl, VIII and XXII = ethyl, IX and XXIII = *n*-pentyl, X and XXIV = *n*-hexyl, XI and XXV = *n*-heptyl, XII and XXVI = *n*-octyl, XIII and XXVII = *n*-nonyl, XIV and XXVIII = *n*-hendecyl, XV and XXIX = *n*-tridecyl, XVI and XXX = *n*-pentadecyl, XVII and XXXI = *n*-heneicosyl, XVIII and XXXII = phenyl, XIX and XXXIII = *n*-heptyl-7-methoxycarbonyl.

Späth and Pailer [4] carried out the conversion of 6,7-dihydroxy-coumaran-3-one (IV) to the corresponding 6,7-dihydroxy-coumaran (V) by low pressure hydrogenation at elevated temperature using a palladium on carbon catalyst. The calculated amount of hydrogen was absorbed, but the yield of (V) was only about one third of the theoretical one, indicating that other reactions than conversion of the carbonyl group to a methylene group took place. Attempting to convert 6-hydroxy-coumaran-3-one to 6-hydroxy-coumaran, Horning and Reisner [5] completely failed to isolate the desired product, and they noted that an excess of about 40 % hydrogen was absorbed in the reaction. After acetylation of the free hydroxy group, however, 6-acetoxy-coumaran was obtained in nearly quantitative yield, indicating that the free hydroxy group is involved in these side reactions. However, reduction of the carbonyl group

of hydroxy-coumaran-3-ones and their acetoxy derivatives is perhaps still more complex. Davies and Deegan [6] have shown that acetylation of 6,7-dihydroxy-coumaran-3-one (IV) with acetyl chloride in ethyl acetate solution gives two different products, *i. e.* 6,7-diacetoxy-coumaran-3-one and 3,6,7-triacetoxy-coumarone. The last compound was successfully hydrogenated to give 6,7-diacetoxy-coumaran. Thus, in this case acetylation involves an enolization on the carbonyl group with introduction of a double bond in the heterocyclic ring prior to the hydrogenation reaction. Similar conditions seem to be valid for the acetylated product of 6-hydroxy-coumaran (Davies *et al.*[7]).

When converting 6,7-dihydroxy-coumaran-3-one (IV) to 6,7-dihydroxy-coumaran (V), the overall yield appears to be about the same, either direct hydrogenation is used, or the route is followed which includes acetylation of IV, hydrogenation of the acetylated product and finally deacetylation of the hydrogenated compound. Consequently, the present author preferred to carry out the reaction in one step. In order to avoid poisoning of the catalyst, it is essential that the 6,7-dihydroxy-coumaran-3-one is very pure (recrystallization several times with active carbon), and that efficient stirring is employed when dissolving the substance in the acetic acid used as solvent in the hydrogenation reaction. With these precautions fulfilled, the theoretical amount of hydrogen is rapidly absorbed on hydrogenation at 65° and one atmosphere pressure with 10 % palladium on carbon as catalyst. Very constant yields are obtained, which are somewhat higher than those reported by Späth and Pailer [4].

The condensation of 6,7-dihydroxy-coumaran with malic acid in the presence of concentrated sulphuric acid at 114° gives dihydroxanthotoxol (VI). In this reaction the present author obtained a yield of about 38 % of the theoretical in good agreement with the result reported by Späth and Pailer [4]. In this connection it may be remarked that condensation of phenols with malic acid generally gives lower yields than those obtained when condensating the same phenols with a β-oxo ester as ethyl acetoacetate (*cf.* Sethna and Phadke[8]). Horning and Reisner [5] got pure dihydropsoralene only in a yield of 11 % condensing 6-hydroxy-coumaran with malic acid.

Condensation of phenols with β-oxo esters in the presence of sulphuric acid almost always produces coumarins (*cf.* Sethna and Phadke [8]) and consequently γ-substituted β-oxo esters form coumarins substituted in position 4. Long chain β-oxo esters do not seem to have been used for such condensation to any large extent. The reactivity of the β-oxo esters is generally assumed to decrease with increasing length of the carbon chain. When condensing 6,7-dihydroxy-coumaran (V) with a number of β-oxo esters, which have straight chains of a length varying from four to twenty-four carbon atoms, however, 4-*n*-alkyl substituted dihydroxanthotoxols (VII—XVII) were obtained as crystalline products in rather good yields. The condensation between 6,7-dihydroxy-coumaran and the higher β-oxo esters were generally carried out as follows. After dissolving the phenol and the β-oxo ester in each other by heating, the solution was slowly poured into concentrated sulphuric acid and the mixture was kept at room temperature for three to five days before the product was isolated. Condensing methyl 3-oxo-hendecane-1, 11-dioate with 6,7-dihydroxy-coumaran yielded 8-(dihydroxanthotoxol-4)-*n*-octanoic

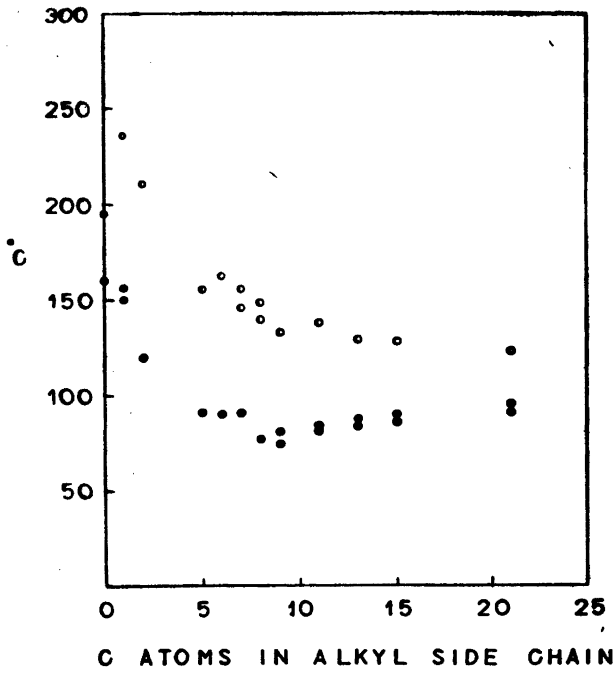


Fig. 1. Melting points of 4-n-alkyl substituted dihydroxanthotoxols, O, and 4-n-alkyl substituted dihydroxanthotoxins, ●, as a function of the number of carbon atoms in the side chain.

acid together with the corresponding methyl ester (XVIII) due to partial hydrolysis during the condensing reaction.

Methylation of the phenolic hydroxy group with diazomethane converted the dihydroxanthotoxols to the corresponding dihydroxanthotoxins (XX—XXXIII). Many of the alkyl substituted dihydroxanthotoxols and dihydroxanthotoxins are dimorphous and possess two melting points. Fig. 1 gives the melting points of these substances as a function of the number of carbon atoms in the alkyl side chain. The melting points of the alkyl substituted dihydroxanthotoxols are generally much higher than the corresponding dihydroxanthotoxins and decrease with increasing length of the side chain. An increase of the alkyl side chain of the dihydroxanthotoxins to about eight carbons continously depresses the melting points. With further lengthening of the side chain the melting points are slowly raised in a rather regular manner.

The last step in the preparation of xanthotoxin involves a dehydrogenation of the dihydrofuran ring. By heating a mixture of dihydroxanthotoxin and a palladium catalyst at 170° Späth and Pailer [4] carried out this reaction with a yield of about 10 % of the theoretical one. Horning and Reisner [9] successfully dehydrogenated dihydropsoralene (2′,3′-dihydrofurocoumarin) to psoralene with a yield of about 50 % by refluxing the substance during four hours together with a 5 % palladium on carbon catalyst in a high boiling medium,

viz. diphenyl ether (b. p. 259°). By employing this technique, the present author could dehydrogenate dihydroxanthotoxin to xanthotoxin in a yield of 37 % of the theoretical. An attempt to dehydrogenate 4-methyl-dihydroxanthotoxin (XXI) with the same technique was unsuccessful. The corresponding xanthotoxin could not be isolated and the starting material had almost completely decomposed. When mesitylene (b. p. 165°) was used as an indifferent medium, only an almost quantitative recovery of 4-methyl-dihydroxanthotoxin was obtained.

EXPERIMENTAL *

6,7-Dihydroxy-coumaran-3-one (IV) was prepared by the method of Davies and Deegan [9]. In the reaction leading to ω-chloro-gallacetophenone (III), a minimum of tarry products was obtained when the temperature was kept below 61° (Davies and Deegan give 60—70°). The overall yield of 6,7-dihydroxy-coumaran-3-one crystallized twice (charcoal) from water was about 16 % of the theoretical calculated on the pyrogallol used.

6,7-Dihydroxy-coumaran (V). 6,7-Dihydroxy-coumaran-3-one (36 g) was dissolved in hot acetic acid (850 ml) with careful stirring. The yellow solution was transferred to a hydrogenation vessel previously filled with hydrogen and containing 15 g 10 % palladium on carbon (*Organic Syntheses*, Vol. 26, method D). The vessel, which was placed in a large flask shaker, was equipped with a jacket through which water maintained at 65° was circulated from a thermostat. The gas burette and other devices for supply of hydrogen gas were of a construction similar to those described by Parrette [10]. The theoretical amount of hydrogen was absorbed in about two hours, but in some runs it was necessary to add more catalyst in order to complete the reaction. After removal of the catalyst and evaporation of the acetic acid, the residue (a brown oil) was distilled at 125—132° at 0.05 mm pressure to give a nearly colourless oil (25 g) that immediately solidified on cooling. This material was redistilled to give a colourless substance (24 g) that was further purified by crystallization from a mixture of light petroleum (b. p. 20—40°) and benzene (1:1 by volume) as follows. The finely powdered substance was extracted with 500 ml light petroleum-benzene by refluxing with stirring for 15 minutes. The liquid was decanted off and discarded. The remaining amount of substance was dissolved in about 3 000 ml light petroleum-benzene. After being kept at —8° overnight, 6,7-dihydroxy-coumaran (16.8 g) crystallized as long beautiful needles. Melting point 112° (Kofler "Heizbank"). The yield was about 50 % of the theoretical.

Dihydroxanthotoxol (VI) (*cf.* Späth and Pailer [4]). A mixture of 6,7-dihydroxy-coumaran (5 g), malic acid (5 g), and concentrated sulphuric acid (25 ml) was kept at 114° in an oil bath with constant stirring until foaming stopped (about 7 minutes). After cooling the mixture was poured with stirring into 250 ml of cold water to give a dark tarry product suspended in the aqueous layer. After extraction with eight 100 ml portions of chloroform, the combined organic solutions were dried over anhydrous sodium sulphate and the solvent evaporated to yield 3.5 g of a yellow powder. Crystallization from water (charcoal) gave 2.3 g (38 % of the theoretical) of slightly yellow long beautiful needles. The melting point was 195° (Kofler "Heizbank", odour of coumarin) and could not be raised after sublimation *in vacuo*. Späth and Pailer [4] reported a melting point of 202°.

4-n-Alkyl-dihydroxanthotoxols (VII—XVII) and 4-phenyl-dihydroxanthotoxol (XVIII). 6,7-Dihydroxy-coumaran was condensed with a number of β-oxo esters in the presence of concentrated sulphuric acid. The data of these preparations are collected in Table 1. Generally the condensation was performed as follows.

* If not otherwise stated, the melting points up to about 200 °C recorded in this paper were taken in sealed capillary tubes using calibrated Anschütz type thermometers completely immersed in a well stirred bath of silicon oil (DC 710 Fluid, Dow Corning Co.). The heating was carried out very slowly (1° per 3 minutes). The melting points over 200 °C were taken by use of a Kofler type hot stage microscope.

Table 1. Dihydroxanthotoxols substituted in position 4.

β-Oxo ester condensed with 6,7-dihydroxy-coumaran	Time of reaction h = hours d = days	Substituent	No.	Yield %	Empirical formula	Composition, %				Melting point °C	
						Calc.		Found			
						C	H	C	H		
Ethyl 3-oxo-butanoate	1 h	4-methyl-	VII	43	$C_{13}H_{10}O_4,H_2O$*	61.01	5.12	60.96	5.13	236	—237
Ethyl 3-oxo-pentanoate	1 h	4-ethyl-	VIII	44	$C_{13}H_{12}O_4$	67.23	5.21	67.07	5.30	210	—212
Methyl 3-oxo-octanoate	1 h	4-*n*-pentyl-	IX	44	$C_{16}H_{18}O_4$	70.05	6.61	69.89	6.57	155.7	—157.0
Methyl 3-oxo-nonanoate	1 h	4-*n*-hexyl-	X	66	$C_{17}H_{20}O_4$	70.81	6.99	70.83	6.55	162.0	—163.3
Methyl 3-oxo-decanoate	1 h	4-*n*-heptyl-	XI	54	$C_{18}H_{22}O_4$	71.50	7.33	71.50	7.40	145.7 156.2	—147.2 —157.3
Methyl 3-oxo-hendecanoate	2 h	4-*n*-octyl-	XII	51	$C_{19}H_{24}O_4$	72.12	7.65	72.34	7.69	139.6 148.6	—140.6 —149.6
Methyl 3-oxo-dodecanoate	3 d	4-*n*-nonyl-	XIII	32	$C_{20}H_{26}O_4$	72.70	7.93	72.93	7.97	132.2	—134.2
Methyl 3-oxo-tetradecanoate	3 d	4-*n*-hendecyl-	XIV	27	$C_{22}H_{30}O_4$	73.71	8.44	73.44	8.47	138.2	—138.8
Methyl 3-oxo-hexadecanoate	3 d	4-*n*-tridecyl-	XV	33	$C_{24}H_{34}O_4$	74.57	8.87	75.11	8.85	128.6	—130.0
Methyl 3-oxo-octadecanoate	5 d	4-*n*-pentadecyl	XVI	18	$C_{26}H_{38}O_4$	75.32	9.24	75.21	9.38	127.2	—128.4
Methyl 3-oxo-tetracosanoate	5 d	4-*n*-heneicosyl-	XVII	11	$C_{32}H_{50}O_4$	77.06	10.11	77.26	10.51	123.7	—124.5
Ethyl 3-oxo-3-phenyl-propionate	1 h	4-phenyl-	XVIII	29	$C_{17}H_{18}O_4$	72.85	4.32	73.13	4.39	245.5	—247.0

* When crystallized from aqueous methanol, one mole of substance VII contains one mole of water that could be quantitatively removed after drying overnight at 120°.

A mixture of 6,7-dihydroxy-coumaran and an excess (10—20 %) of the β-oxo ester was dissolved by heating. The solution was poured into concentrated sulphuric acid with constant stirring. The mixture was kept standing at room temperature for one hour to five days (see Table 1) and was then slowly poured with stirring into ice water. The precipitate formed was collected and suspended in water. The excess of ester was removed by steam distillation. The material collected was recrystallized several times from acetone and from methanol (charcoal).

Table 2. Dihydroxanthotoxins substituted in position 4.

Compound	No.	Empirical formula	Composition, %				Melting point °C
			Calc.		Found		
			C	H	C	H	
4-Methyl-dihydroxanthotoxin	XXI	$C_{13}H_{12}O_4$	67.23	5.21	67.44	5.35	149.5—151.2 156.2—157.1
4-Ethyl- »	XXII	$C_{14}H_{14}O_4$	68.26	5.73	68.44	5.79	119.6—121.4
4-*n*-Pentyl- »	XXIII	$C_{17}H_{20}O_4$	70.81	6.99	70.73	7.06	90.2— 91.6
4-*n*-Hexyl- »	XXIV	$C_{18}H_{22}O_4$	71.50	7.33	71.22	7.44	90.3— 91.9
4-*n*-Heptyl- »	XXV	$C_{19}H_{24}O_4$	72.12	7.65	72.21	7.71	91.2— 92.6
4-*n*-Octyl- »	XXVI	$C_{20}H_{26}O_4$	72.70	7.93	72.66	7.91	75.6— 78.1
4-*n*-Nonyl- »	XXVII	$C_{21}H_{28}O_4$	73.20	8.19	73.55	8.20	74.0— 75.0 80.4— 81.9
4-*n*-Hendecyl- »	XXVIII	$C_{23}H_{32}O_4$	74.16	8.66	74.34	8.71	80.6— 81.5 83.8— 84.7
4-*n*-Tridecyl- »	XXIX	$C_{25}H_{36}O_4$	74.96	9.06	74.88	9.07	83.6— 84.5 87.4— 88.8
4-*n*-Pentadecyl- »	XXX	$C_{27}H_{40}O_4$	75.66	9.41	75.68	9.52	86.5— 86.9 89.6— 89.9
4-*n*-Heneicosyl- »	XXXI	$C_{33}H_{52}O_4$	77.29	10.22	77.04	10.44	91.2— 92.3 95.1— 96.4
4-Phenyl- »	XXXII	$C_{18}H_{14}O_4$	73.46	4.80	73.60	4.93	198 —199
Methyl 8-(dihydroxanthotoxin-4)-*n*-octanoate	XXXIII	$C_{21}H_{26}O_6$	67.36	7.00	67.42	7.06	71.8— 73.2 76.6— 77.8

Ethyl 3-oxo-pentanoate was prepared as described by Brändström [11]. The higher β-oxo esters were those prepared by Mrs. Ställberg-Stenhagen (Ställberg-Stenhagen [12]).

Methyl 8-(dihydroxanthotoxol-4)-n-octanoate (XIX). 6,7-Dihydroxycoumaran (5 g) was dissolved by heating in methyl 3-oxo-hendecane-1,11-dioate (10 g, prepared by the author as described by Ställberg-Stenhagen [12]) and was poured with stirring into 25 ml of concentrated sulphuric acid. The reaction mixture was kept at room temperature for three days. Proceeding as usual gave 3.65 g (about 30 % of the theoretical) of a crystalline material melting between 80 and 95° (recrystallized once from acetone, twice from methanol, charcoal). This substance is most likely a mixture of the ester and the corresponding free acid. No attempts were made to separate the substances.

Derivatives of dihydroxanthotoxin. The 4-substituted dihydroxanthotoxols were converted to the corresponding dihydroxanthotoxins by methylation with diazomethane in a mixture of methanol and ether (1:1 by volume). The solutions were chilled to about +15° before an excess of cold solution (−5°) of diazomethane in ether was added. The reaction mixtures were kept at room temperature overnight. After evaporating the solvent, the methylated products were recrystallized from methanol. The yields were in general between 70 and 85 % of the theoretical. The analytical figures and the melting points of these substances are collected in Table 2. After methylation the mixture of free acid and ester (XIX) was converted to a homogeneous substance, methyl 8-(dihydroxanthotoxin-4)-*n*-octanoate of m. p. 71.8—73.2° and 76.6—77.8° (for analytical figures see Table 2 XXXIII).

Xanthotoxin (I) (*cf.* Späth and Pailer [4]). A mixture of dihydroxanthotoxin (XX) (0.165 g) (m. p. 160.4—161.2°, obtained by methylating VI), 10 % palladium on carbon catalyst (0.165 g), and diphenyl ether (11 g) was heated under reflux for four hours. The catalyst was removed by filtration and washed with hot diphenyl ether (20 g). After removing the diphenyl ether with steam distillation, the hot aqueous solution was filtered. Crystalline xanthotoxin was obtained from the chilled solution as slightly yellow needles. Recrystallization from methanol (charcoal) yielded 0.061 g (37 % of the theoretical) of colourless needles of m. p. 145.7—146.2° in good agreement with that given by Späth and Pailer [4] (146°).

4-Methyl-xanthotoxin. 4-Methyl-dihydroxanthotoxin (XXI) (0.3 g), 10 % palladium on carbon catalyst (0.3 g), and diphenyl ether (17 g) were heated under reflux with mechanical stirring for four hours. Proceeding as just described only 0.08 g of a substance could be isolated that was identical with the starting material. When the same procedure was performed with mesitylene as an indifferent solvent, only a nearly quantitative yield of the starting material was obtained.

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