136. *Some Alkyl Quinols and Related Compounds.*

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The preparation of long-chain acyl quinol diethers is described. These have been reduced to alkyl quinol ethers, which were hydrolysed to alkyl quinols; the last were oxidised to alkyl benzoquinones.

The intermediate acyl quinol ethers were treated with methylmagnesium iodide, olefinic and not *tert.*-alcoholic quinol ethers being obtained; representative *sec.*-alcoholic quinol ethers were prepared by reducing the acyl compounds. The olefinic or alcoholic ethers were also hydrolysed with halogen hydride, but the products were evidently coumarans or chromans. Efforts to synthesise analogues of vitamin E by a similar method were unsuccessful.

Quinols bearing a higher alkyl side chain were required for technical purposes. No success attended attempts to alkylate quinol with *n*-propyl or *tert.*-butyl alcohol in presence of boron trifluoride (cf. Kolka and Vogt, *J. Amer. Chem. Soc.*, **1939**, **61**, **1463**; Calcott, Tinker, and Weinmayer, *ibid.*, p. 1010) or with *n*-butyl, amyl, or cetyl alcohol or 1-methyl*cyclo*hexanol in presence of zinc chloride (cf. B.P. 470,852); similar attempts with quinol diethyl ether (Hinton and Nieuwland, *J. Amer. Chem. Soc.*, **1932**, **54**, 2017) were also abandoned. Stearic acid or stearoyl chloride could not be condensed with quinol in presence of zinc chloride (cf. B.P. 287,967); *quinol distearate*, *4-methoxyphenyl palmitate* or *stearate* could not be induced to undergo the Fries reaction.

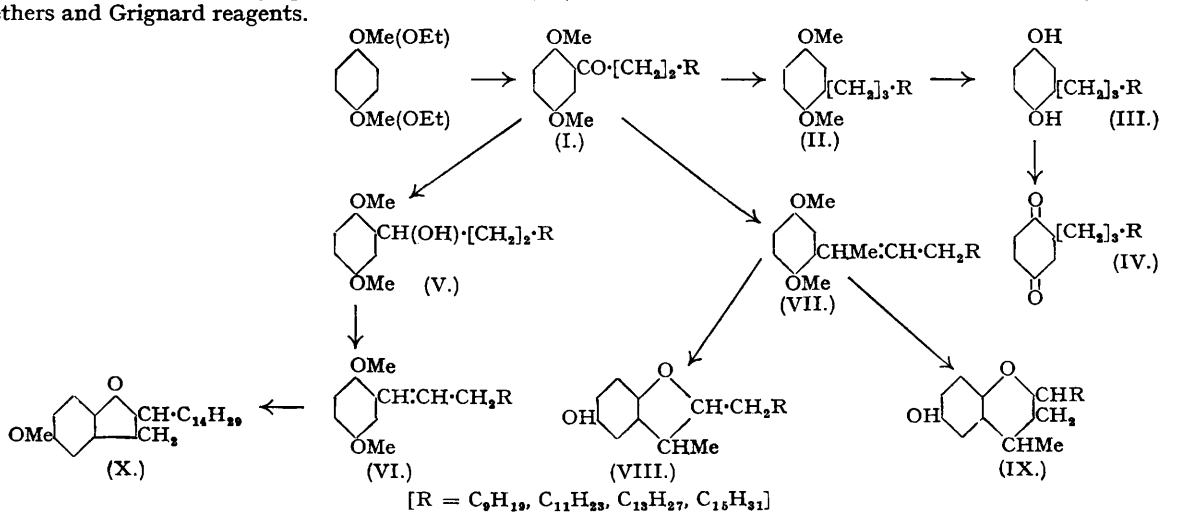
Success in preparing derivatives of acyl quinols was at length achieved by minor modification of the method employed by Cruikshank and Robinson (J., **1938**, 2064; cf. also Gulland, *Biochem. J.*, **1932**, **26**, **43**) to obtain 2-hydroxy-5-methoxy-*n*-valerophenone. Cruikshank and Robinson allowed quinol dimethyl ether, valeryl chloride, and aluminium chloride to interact at the b. p. of carbon disulphide, whereby removal of one ether group ensued. In the present work, we treated quinol dimethyl ether and quinol diethyl ether with stearoyl, palmitoyl, myristoyl, and lauroyl chlorides in an inert solvent at 0° and in presence of aluminium chloride. In each case an excellent yield of the crystalline *acyl quinol diether* (I) was obtained and only negligible amounts of the monoethers appeared to be formed; this statement is based on the absence of phenolic properties and appreciable active hydrogen content, and quantitative dealkylations; alkyl iodide was only slowly evolved and usually amounted to 85% of that theoretically required (cf. Bateman and Robinson, J., **1941**, 402).

The acyl quinol ethers were reduced to *alkyl quinol ethers* (II) in yields of 42—50%; 2 : 5-dimethoxymyristylbenzene was obtained in crystalline form. The action of hydrazine hydrate and sodium methoxide was unsuccessfully attempted and the greatest measure of success in reducing the ketones resulted on applying the original method of Clemmensen; attempts to improve this by adding solvents such as acetic acid or dioxan to the reducing medium resulted in decreased rather than increased yield.

In attempting dealkylation, aluminium chloride in carbon disulphide or hydriodic acid appeared to initiate deep-seated changes and the method finally adopted was to reflux the diethers for a short time with hydrobromic acid.

These crystalline *myristyl-*, *lauryl-*, *palmityl-*, and *stearyl-quinols* (III) were characterised by oxidation with silver oxide to the corresponding *quinones* (IV). The two lower homologues were indefinitely stable, but palmityl- and more particularly stearyl-benzoquinone tended to resinify on crystallisation; this behaviour is shown by some lower alkyl benzoquinones also. Stearylbenzoquinone reacted normally with acetic anhydride to give a colourless triacetoxy-compound, 2 : 4 : 5-*triacetoxystearylbenzene*.

Whilst the difficulties of reducing the above acyl compounds were being overcome, experiments to circumvent this obstacle were begun. 2 : 5-Dimethoxy-stearo- and -palmito-phenone were reduced quantitatively to sec.-*alcohols* (V) by aluminium *iso*propoxide, but, as dehydration of these (with sodium bisulphate) afforded only poor yields of *alkenyl quinol dimethyl ethers* (VI), attention was turned to the interaction of acyl quinol ethers and Grignard reagents.



[R = C_9H_{19}, $C_{11}H_{23}$, $C_{13}H_{27}$, $C_{15}H_{31}$]

2 : 5-Dimethoxy-lauroyl-, -myristoyl-, -palmitoyl-, and -stearoyl-benzene and methylmagnesium iodide furnished not tertiary alcohols but the corresponding *alkenyl quinol dimethyl ethers* (VII), usually obtained at the ordinary temperature as oils. These olefins were demethylated with hydrobromic acid, but the oils were not unsaturated quinols, though the analytical figures were in agreement with such structures. They contained no unsaturated groups and no absorption took place on shaking with platinum in an atmosphere of hydrogen; instead of two hydroxyl groups, only one was present, as was shown by determination of active hydrogen; any possibility of incomplete demethylation could be disregarded on the results of (negative) methoxyl estimations. There can be no doubt, therefore, that these products are to be formulated as *coumarans* or *chromans* (VIII, IX) with structures recalling those of vitamin E. It must be considered probable that their persistence as oils and their reluctance to give crystalline derivatives is due to the co-existence of five- and six-membered oxygen ring structures, and perhaps also to the existence of stereoisomerides. Cyclisation of the olefin from the secondary alcohol obtained by reducing dimethoxypalmitophenone was exceptional; elementary analysis, methoxyl estimations, absence of olefinic linkages and absence of hydroxyl groups all went to confirm that again cyclisation had occurred but with removal of only one methoxyl group; the product is therefore formulated as (X).

(IX; R = $C_{13}H_{27}$) is closely related to vitamin E, from which it differs only in the lack of nuclear and side-chain methyl groups. We were therefore interested to carry out a similar series of reactions starting from ψ-cumoquinol dimethyl ether and palmitoyl chloride. Unfortunately all attempts to prepare the acyl derivative failed. The failure might have been due to "steric hindrance" or to electronic incompatibility occasioned by the presence of nuclear methyl groups. As there seems to be no inhibitory factor in the known syntheses of vitamin E, electronic inhibition seems to be the more acceptable explanation of the difference between quinol and ψ-cumoquinol ethers.

Experimental.

4-Methoxyphenyl Stearate.—Stearoyl chloride (30 g.) and quinol monomethyl ether (11 g.), dissolved in ether (50 c.c.), were treated slowly in the cold with pyridine (20 c.c.). After 2 hours, ether (100 c.c.) was added, and the whole extracted with 10% hydrochloric acid and then with 10% caustic soda solution. The ethereal layer was dried and evaporated; the residual *ester* crystallised from ethanol; yield 25 g., m. p. 50° (Found: C, 76·7; H, 10·8. $C_{25}H_{42}O_3$ requires C, 76·9; H, 10·8%). The *palmitate* was obtained similarly; it crystallised from ethanol, m. p. 51·5° (Found: C, 76·5; H, 10·7. $C_{23}H_{38}O_3$ requires C, 76·3; H, 10·5%).

Acyl Quinol Dimethyl or Diethyl Ethers.—Quinol dimethyl or diethyl ether (1 g.-mol.) in ice-cold tetrachloroethane (500 c.c.) was treated with aluminium chloride (134 g.) with stirring. The fatty acid chloride (C_{12}, C_{14}, C_{16}, C_{18}) (1 g.-mol.) was added slowly, and the whole stirred for a further 12 hrs. The deep red solution was then poured on ice (500 g.), and solvent distilled in steam. The non-volatile ketone was taken up in ether and freed from fatty acid by washing repeatedly with 10% caustic soda solution; it was finally distilled in a vacuum, and the solid product crystallised from methanol.

The following compounds were prepared: 2 : 5-*Dimethoxystearophenone*, m. p. 46°; yield, 60% (Found: C, 77·2; H, 11·0. $C_{26}H_{44}O_3$ requires C, 77·2; H, 10·9%). 2 : 5-*Dimethoxypalmitophenone*, b. p. 205°/0·18 mm., m. p. 51·5°; yield, 69% (Found: C, 76·9; H, 10·7. $C_{24}H_{40}O_3$ requires C, 76·6; H, 10·6%). 2 : 5-*Dimethoxymyristophenone*, b. p. 209°/0·5 mm., m. p. 43°; yield, 62% (Found: C, 75·8; H, 10·4. $C_{22}H_{36}O_3$ requires C, 75·9; H, 10·4%). 2 : 5-*Dimethoxylaurophenone*, b. p. 175—178°/0·2 mm., m. p. 27·5°; yield, 76% (Found: C, 75·3; H, 10·0. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·0%). 2 : 5-*Diethoxymyristophenone*, b. p. 204°/0·29 mm., m. p. 44·5°; yield, 62% (Found: C, 76·9; H, 10·8. $C_{24}H_{40}O_3$ requires C, 76·6; H, 10·6%). 2 : 5-*Diethoxylaurophenone*, b. p. 180—190°/0·34 mm., m. p. 34—35°; yield, 65% (Found: C, 75·6; H, 10·1. $C_{22}H_{36}O_3$ requires C, 75·8; H, 10·4%). 2 : 4 : 5-*Trimethoxylaurophenone*, m. p. 53°; yield, 60% (Found: C, 72·3; H, 9·7. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·7%).

The 2 : 4-*dinitrophenylhydrazones* of 2 : 5-diethoxypalmitophenone, 2 : 5-diethoxymyristophenone, and 2 : 5-diethoxylaurophenone were obtained in the normal manner. They formed bright red crystals from ethanol, m. p. 75° (Found: N, 9·9. $C_{32}H_{48}O_6N_4$ requires N, 9·6%), 78° (Found: N, 10·4. $C_{30}H_{44}O_6N_4$ requires N, 10·1%), and 77·5° (Found: N, 10·4. $C_{28}H_{40}O_6N_4$ requires N, 10·6%), respectively.

Alkyl Quinol Ethers.—The acyl quinol ethers (50 g.) were boiled with concentrated hydrochloric acid (250 c.c.) and water (250 c.c.) for 20 hours in presence of amalgamated zinc (100 g.); 50—100 c.c. of concentrated acid were added after 1, 2, and 3 hours. The oil was diluted with ether, the solution washed with aqueous potassium carbonate, and the alkyl quinol ether fractionally distilled. The following were prepared: 2 : 5-*Dimethoxystearylbenzene*, b. p. 188°/0·2 mm.; yield, 42% (Found: C, 80·4; H, 12·0. $C_{26}H_{46}O_2$ requires C, 80·0; H, 11·8%). 2 : 5-*Dimethoxypalmitylbenzene*, b. p. 210°/0·5 mm.; yield, 40% (Found: C, 79·6; H, 11·8. $C_{24}H_{42}O_2$ requires C, 79·6; H, 11·6%). 2 : 5 : *Dimethoxymyristylbenzene*, b. p. 165°/0·5 mm.; yield, 52% (Found: C, 79·1; H, 11·4; $C_{22}H_{38}O_2$ requires C, 79·1; H, 11·4%). 2 : 5-*Dimethoxylaurylbenzene*, b. p. 154°/0·5 mm.; yield, 42% (Found: C, 78·5; H, 11·2. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·1%). 2 : 5-*Diethoxystearylbenzene*, b. p. 201°/0·06 mm.; yield, 48% (Found: C, 80·2; H, 11·9. $C_{26}H_{50}O_2$ requires C, 80·4; H, 12·0%). 2 : 5-*Diethoxypalmitylbenzene*, b. p. 219°/0·1 mm.; yield, 43% (Found: C, 79·7; H, 11·7. $C_{26}H_{46}O_2$ requires C, 80·0; H, 11·8%). 2 : 5-*Diethoxymyristylbenzene*, b. p. 183°/0·1 mm.; yield, 41% (Found: C, 79·5; H, 11·9. $C_{24}H_{42}O_2$ requires C, 79·6; H, 11·6%). 2 : 5-*Diethoxylaurylbenzene*, b. p. 176°/0·7 mm.; yield, 50% (Found: C, 79·1; H, 11·1. $C_{22}H_{38}O_2$ requires C, 79·1; H, 11·3%).

Alkyl Quinols.—Dialkoxyalkylbenzene (40 g.) was refluxed for 4—6 hours with 50% hydrobromic acid (40 g.) and acetic acid (200 c.c.), a further 20 g. of hydrobromic acid being added after 2 hours. The product was allowed to crystallise either directly or after neutralisation with aqueous sodium bicarbonate. The quinols were crystallised from light petroleum without the aid of charcoal, as this caused catalytic oxidation to blue solids. The following were prepared: *Stearylquinol*, m. p. 100·5° (Found: C, 79·5; H, 11·4. $C_{24}H_{42}O_2$ requires C, 79·6; H, 11·6%). *Palmitylquinol*, m. p. 112° (Found: C, 79·1; H, 11·5. $C_{22}H_{38}O_2$ requires C, 79·1; H, 11·4%). *Myristylquinol*, m. p. 110° (Found: C, 78·2; H, 11·3. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·1%). *Laurylquinol*, m. p. 105° (Found: C, 77·6; H, 10·9. $C_{18}H_{30}O_2$ requires C, 77·7; H, 10·8%).

When hydrolysis was carried out for a shorter time, oils were obtained consisting largely of alkylquinol monoether. Thus palmitylquinol dimethyl ether (45 g.), 50% hydrobromic acid (80 c.c.), and acetic acid (100 c.c.), refluxed for 4 hours and then poured into 1·5 l. of water, gave the oily palmitylquinol monomethyl ether, which was distilled (b. p. 200—210°/0·2 mm.) and then crystallised from ethanol; m. p. 47°, yield 15·5 g. It contained 1 active hydrogen atom/mol. (Zerewitinoff determination) and yielded the quinol on further refluxing with hydrobromic acid.

Alkyl Quinones.—The quinol, dissolved in a small amount of ether, was shaken for 2 hours with twice the theoretical amount of silver oxide at room temperature. The filtered solution was evaporated, and the residual quinone recrystallised from ethanol–ether. *Stearylbenzoquinone*, m. p. 76° (Found: C, 80·1, 79·9; H, 11·3, 10·9. $C_{24}H_{40}O_2$ requires C, 80·0; H, 11·1%), *palmitylbenzoquinone*, m. p. 83° (Found: C, 80·0; H, 11·0. $C_{22}H_{36}O_2$ requires C, 79·5; H, 10·8%), *myristylbenzoquinone*, m. p. 77·5° (Found: C, 78·6; H, 10·4. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·5%), and *laurylbenzoquinone*, m. p. 72° (Found: C, 78·2; H, 10·0. $C_{18}H_{28}O_2$ requires C, 78·3; H, 10·1%), were prepared.

Stearylbenzoquinone (1 g.) dissolved on gentle warming in acetic anhydride (5 c.c.) containing 5 drops of concentrated sulphuric acid. The solution was poured into water, and the precipitated 2 : 4 : 5-*triacetoxystearylbenzene* crystallised from ethanol; it had m. p. 73° (Found: C, 71·4; H, 9·5. $C_{30}H_{48}O_6$ requires C, 71·4; H, 9·5%).

Secondary Alcohols.—Dimethoxypalmitophenone (20 g.), dissolved in a little dry *iso*propyl alcohol, was treated with aluminium *iso*propoxide (5 g.) and the acetone formed was slowly distilled off while dry *iso*propyl alcohol was added at the same rate. On completion (8 hours) the product was poured into dilute hydrochloric acid, and the solid extracted with ether. 1-*Hydroxy*-1-2′ : 5′-*dimethoxyphenylhexadecane* so recovered crystallised from aqueous methanol in colourless leaflets, m. p. 34° (Found: C, 76·3; H, 10·9. $C_{24}H_{42}O_3$ requires C, 76·2; H, 11·1%). It yielded 0·97 mol. of methane with methylmagnesium iodide (Zerewitinoff determination).

The hydroxyhexadecane derivative (12 g.) was heated with anhydrous sodium bisulphate (50 g.) for 3 hours at 200°. The oil was extracted with ether and eventually distilled at 204°/0·015 mm. 1-2′ : 5′-*Dimethoxyphenyl*-Δ^1-*hexadecene* solidified and was crystallised from aqueous ethanol; it had m. p. 43°. It was soluble in the common solvents and was unsaturated towards permanganate, bromine in chloroform, and tetranitromethane (Found: C, 79·7; H, 11·0. $C_{24}H_{40}O_2$ requires C, 80·0; H, 11·1%).

Dimethoxyphenylolefins.—2 : 5-Dimethoxyacylbenzene (40 g.) in dry ether (200 c.c.) was added dropwise to a Grignard reagent prepared from magnesium (2·4 g.), methyl iodide (30 g.), and ether (50 c.c.). The whole was refluxed for 30 mins. and then poured on ice and dilute hydrochloric acid. The ethereal layer was distilled, eventually in a vacuum, to give the olefins; yield, 60—70%. The following were prepared: 1-2′ : 5′-*Dimethoxyphenyl*-1-*methyl*-Δ^1-*octadecene*, b. p. 202°/0·5 mm. (Found: C, 80·5; H, 11·3. $C_{27}H_{46}O_2$ requires C, 80·6; H, 11·5%), 1-2′ : 5′-*dimethoxyphenyl*-1-*methyl*-Δ^1-*hexadecene*, m. p. 35° (from aqueous ethanol) (Found: C, 80·2; H, 11·3. $C_{25}H_{42}O_2$ requires C, 80·2; H, 11·3%), 1-2′ : 5′-*dimethoxyphenyl*-1-*methyl*-Δ^1-*tetradecene*, b. p. 175°/0·2 mm. (Found: C, 79·7; H, 10·9. $C_{23}H_{38}O_2$ requires C, 79·8; H, 11·0%), and 1-2′ : 4′ : 5′-*trimethoxyphenyl*-1-*methyl*-Δ^1-*duodecene*, b. p. 203°/0·5 mm. (Found: C, 75·9; H, 10·4. $C_{22}H_{36}O_3$ requires C, 75·9; H, 10·4%).

Hydroxycoumarans (*Hydroxychromans*).—The dimethoxy-olefins above were demethylated by the same treatment as was used for the dialkoxyalkylbenzenes. The products were repeatedly fractionated in a vacuum; the yields were *ca.* 25% and were reduced on prolonged boiling with hydrobromic acid and acetic acid. The following were prepared: 5-*Methoxycoumaran*-2-*tetradecyl* (6-*methoxy*-2-*tridecylchroman*), b. p. 196°/10·2 mm. (Found: C, 79·4; H, 11·0; OMe, 9·2. $C_{23}H_{38}O_2$ requires C, 79·6; H, 11·0; OMe, 9·0%), 5-*hydroxy*-3-*methyl*-2-*hexadecylcoumaran* (6-*hydroxy*-4-*methyl*-2-*pentadecylchroman*), b. p. 192—194°/0·2 mm. (Found: C, 80·0; H, 10·8. $C_{25}H_{42}O_2$ requires C, 80·2; H, 11·2%), 5-*hydroxy*-3-*methyl*-2-*tetradecylcoumaran* (6-*hydroxy*-4-*methyl*-2-*tridecylchroman*), b. p. 200°/0·2 mm. (Found: C, 79·5; H, 11·0. $C_{23}H_{38}O_2$ requires C, 79·7; H, 11·0%), and 5-*hydroxy*-3-*methyl*-2-*decylcoumaran* (6-*hydroxy*-4-*methyl*-2-*nonylchroman*), b. p. 178—183°/0·2 mm. (Found: C, 78·4; H, 10·3. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%).

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