# Synthesis of 3-Substituted Furans and the Formation of 3-(4,8,12-Tri-methyltridecyl)furan

By **Derek L. Dare, Ian D. Entwistle**, and **Robert A. W. Johnstone**,* The Robert Robinson Laboratories, The University, Liverpool L69 3BX

3-(4,8,12-Trimethyltridecyl)furan (I) was isolated from cigarette smoke condensate and its structure was confirmed by synthesis. During attempts at synthesis, two general routes to 3-substituted furans were investigated. In the first, greatly improved procedures for the preparation of 3-furoic acid were devised; the second involved thermal cyclisation and dehydration of 1,2,3,4-tetraols.

THE neutral fraction of cigarette smoke condensate [1] afforded an oil which, from its spectroscopic properties, has now been assigned the structure (I). This structure is homologous with that of dendrolasin (II), isolated from

(I) R =

(II) R =

(III) R =

(IV) R = OC

(X)

(XI) R =
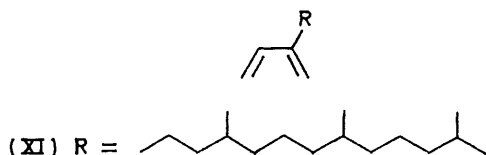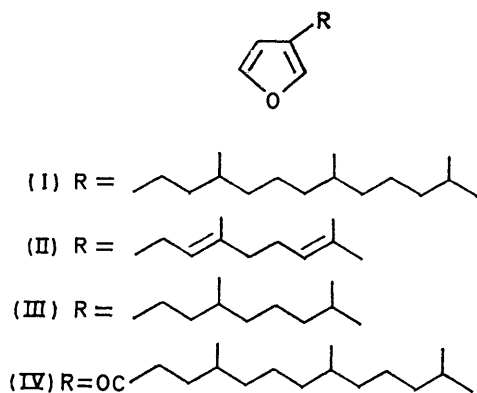
ants.[2] Attempts to synthesise structure (I) revealed a paucity of good routes to 3-substituted furans in general and most of the synthetic work described here centred on the development of routes to these compounds. Two promising routes were established and the structure (I) was obtained by each method.

RESULTS AND DISCUSSION

The furan (I) was prepared by a route analogous to the synthesis of tetrahydrodendrolasin [2] (III), involving condensation of 3-furoyl chloride with bis-3,7,11-tri-methyldodecylcadmium to give the ketone (IV) followed by reduction of the keto-function. The resulting

3-(4,8,12-trimethyltridecyl)furan was identical with the oil isolated from cigarette smoke condensate. This intrinsically useful route to 3-substituted furans is made less attractive by the relative difficulty of preparing 3-furoic acid. Of the methods available for the preparation of this acid, the one shown in Scheme 1 is capable

(V)

(VI)

(VII)
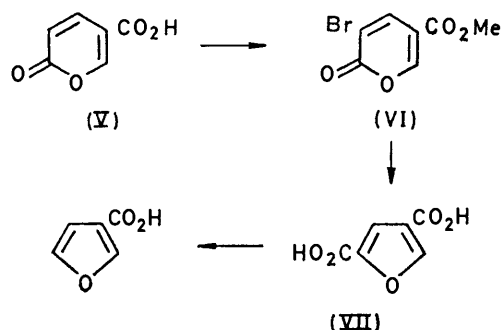
Scheme 1

of giving an overall 75% yield from methyl coumalate or 58% overall from coumalic acid. However, in our hands, the experimental conditions reported previously [3] left much to be desired since the yields at each step varied a great deal from one preparation of 3-furoic acid to the next, even with apparently identical reaction conditions. Accordingly, we worked out alternative or improved methods for effecting each step of the sequence in Scheme 1; we then obtained consistently good overall yields of 3-furoic acid. Recently, a good route to this acid from the commercially available furan-3,4-di-carboxylic acid has been described.[4]

Coumalic acid (V) [5] was converted into methyl coumalate in 78% yield with acetyl chloride in methanol and the ester was brominated with pyridinium bromide perbromide to give an 83% yield of methyl 3-bromo-coumalate (VI). Treatment of this bromo-ester with base by the previously reported procedure [3] often gave none of the diacid (VII) and sometimes a fair yield of it. We found that a close control of reaction times and temperature was necessary and we were then able to obtain consistently high (90%) yields of the dicarboxylic acid (VII). The action of base on the bromo-ester (VI) was examined in more detail; this revealed the probable

[1] R. A. W. Johnstone and P. M. Quan, *J. Chem. Soc.*, 1963, 5706.
[2] (a) P. Grunanger and F. Piozzi, *Gazzetta*, 1959, **89**, 897; (b) A. Quilico, F. Piozzi, and M. Pavan, *Tetrahedron*, 1957, **1**, 177; A. Quilico, P. Grunanger, and F. Piozzi, *ibid.*, p. 186.
[3] (a) F. Feist, *Ber.*, 1901, **34**, 1992; (b) H. Gilman and R. R. Burtner, *J. Amer. Chem. Soc.*, 1933, **55**, 859, 2903.
[4] M. R. Boyd, T. M. Harris, and D. J. Wilson, *Synthesis*, 1971, 545; L. W. Deady and R. A. Shanks, *ibid.*, 1972, 571.
[5] R. H. Wiley and N. R. Smith, *Org. Synth.*, 1963, Coll. Vol. IV, p. 201.

reason for the close control of reaction conditions necessary to obtain these high yields (see later). The diacid (VII) can be converted into 3-furoic acid directly by monodecarboxylation with copper chromite in quinoline, but close control of reaction conditions was again necessary to obtain even modest (50%) yields. Conversion of the diacid (VII) into the half ester, 4-methoxycarbonylfuran-2-carboxylic acid, followed by

aldehyde-ester (IX) were then isolated and readily identified by n.m.r., mass, and i.r. spectra. The two structures suggest that the reaction of the bromo-ester with base can follow two main paths as shown in Scheme 2. In Scheme 2, the use of potassium hydroxide instead of sodium methoxide could be expected to lead to the cyclised product, furan 2,4-dicarboxylic acid (VII), instead of the diester (VIII) by a mechanism analogous
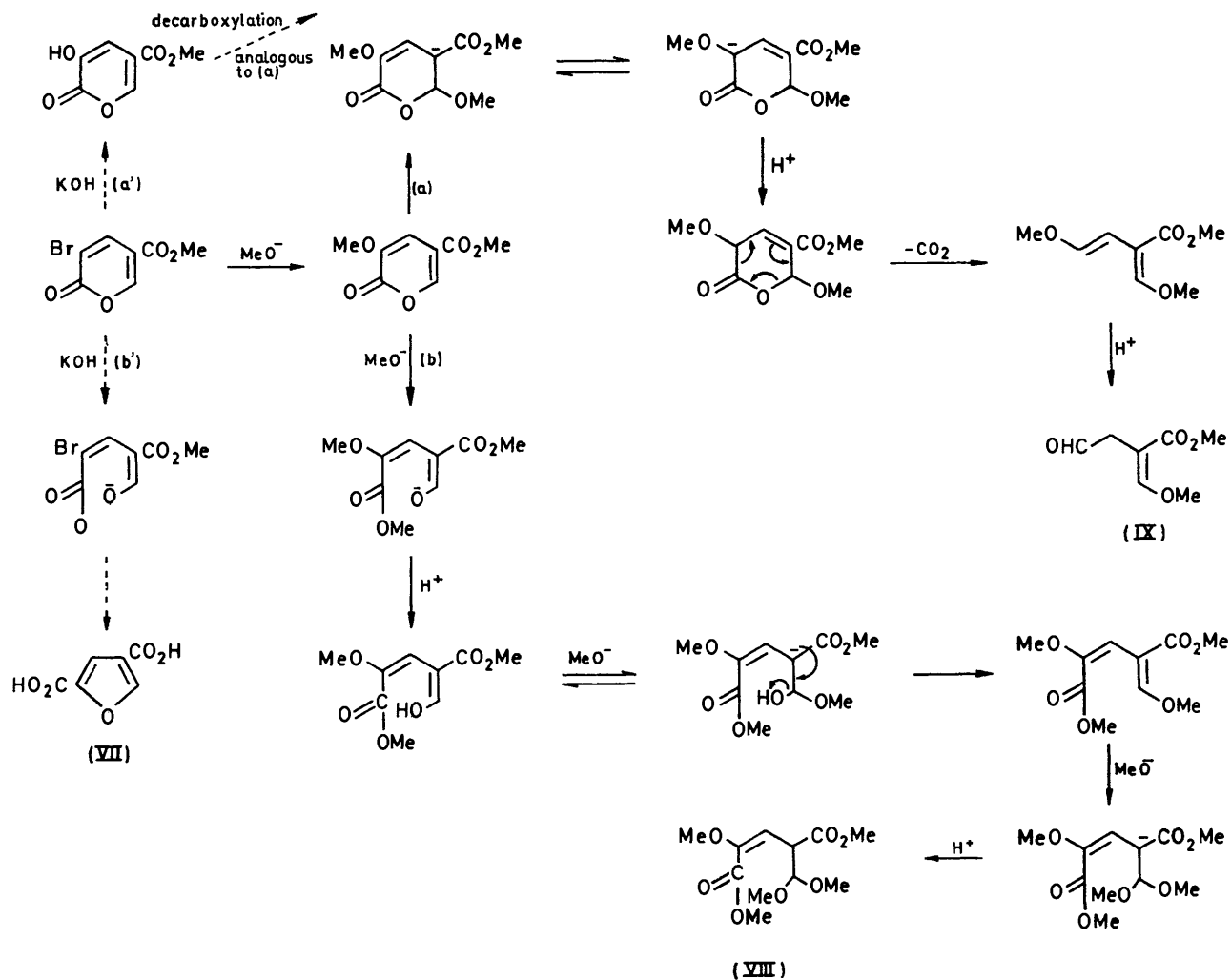
SCHEME 2

monodecarboxylation, was found to be an easier route to 3-furoic acid than the controlled decarboxylation of the diacid (VII).

Poor yields of the diacid (VII) were usually obtained either when the bromo-ester (VI) was slightly impure or when a deep brown colour developed immediately after addition of the base required for the conversion. Also, when these poor yields were obtained, vigorous evolution of carbon dioxide was observed on acidification of the reaction mixture. To investigate the reaction more closely, the bromo-ester (VI) was treated with sodium methoxide in methanol instead of the aqueous potassium hydroxide normally used. The diester (VIII) and the

to path (b), indicated as (b') and by the dotted line. Paths (a) and (a') with either sodium methoxide or aqueous potassium hydroxide can be expected to lead to decarboxylation; the balance held between paths (a') and (b') when potassium hydroxide is used as base might therefore be expected to determine whether or not good yields of the furandicarboxylic acid (VII) are obtained; hence the need for tight control of reaction conditions. Also, in the first step of the reaction with aqueous potassium hydroxide, replacement of the bromine in the bromo-ester (VI) by hydroxy [path (a')] before cyclisation takes place [path (b')] would effectively stop any cyclisation to a furan because hydroxy is a poor leaving

group; a decarboxylation path similar to (a) of Scheme 2 would then be favoured.

An alternative, more direct route to 3-substituted furans lies in the dehydration of tetraols (X), which can be prepared from 1,3-dienes. Neophytadiene (XI) [6] was treated with *m*-chloroperbenzoic acid to yield the di-epoxide. Previous attempts to prepare this diepoxide have been reported to lead only to a monoepoxide.[7] Neophytadiene diepoxide with acid yielded the tetraol (X; R = 4,8,12-trimethyltridecyl). The same tetraol was also prepared by hydrolysis of the dihydroxy-diformate derivative of neophytadiene formed by the action of performic acid. The tetraol was heated to 160—200° under reduced pressure to yield a distillate of unchanged tetraol and the required furan (I). A re-distillation of the distillate afforded the furan (I) in 25% yield. This direct route to furans, resembling the similar conversion of carbohydrates into furans,[8] was attempted with other dienes. Isoprene diepoxide was converted into the tetraol (X; R = Me) but all attempts to convert this into 3-methylfuran failed. Heating this tetraol alone or with concentrated or dilute acid appeared to give only polymeric material and unchanged tetraol. The tetraol (X; R = H) has been converted into erythritan [9] but we found no evidence for a similar reaction with the tetraol (X; R = Me).

To investigate further the difference in cyclisation behaviour between the tetraols (X; R = Me) and (X; R = 4,8,12-trimethyltridecyl), the tetraol (X; R = n-pentyl) of intermediate chain length was prepared. On distillation, this tetraol gave a 30% yield of 3-n-pentylfuran. In similar experiments with the tetraol (X; R = Et) a low yield of 2-ethylfuran was obtained together with much polymeric material and unchanged tetraol. These results suggest that 3-substituted furans having more than three or four carbon atoms in the side-chain can be prepared in satisfactory yields despite competitive polymerisation reactions.

This route to furans depends on the availability of the required dienes, and we have developed a route to them from readily available methyl ketones (Scheme 3). The dehydration of the unsaturated alcohol (XIV; R = n-pentyl) was investigated in some detail because this reaction can potentially give rise to several dienes if dehydration and bond migration into the side-chain (R) occurs. The mixture of isomeric unsaturated esters (XIII; R = n-pentyl) obtained by reaction of the phosphorane (XII) on methyl n-pentyl ketone was separated into *cis*- and *trans*-forms by preparative-scale g.l.c. Reduction of the *cis*- or *trans*-unsaturated ester yielded the corresponding *cis*- or *trans*-unsaturated alcohol. In view of reports of the successful base-catalysed dehydration of phytol to neophytadiene [1,6] and the similar dehydration of similar alcohols,[10] we attempted the base-catalysed dehydration of the *cis*-

and *trans*-unsaturated alcohols (XIV; R = n-pentyl). The crude dehydration products from either *cis*- or *trans*-alcohol were similar and were mixtures of many components (i.r., g.l.c., t.l.c.). The almost identical behaviour on dehydration of the *cis*- and *trans*-alcohols is not expected from the proposed mechanism [6,10] of dehydration through a cyclic transition state. We have repeated the base-catalysed dehydration of phytol both in this work and earlier,[1] and have confirmed the earlier preparation of neophytadiene [6] as giving almost the only diene reaction product. The discrepancy between the earlier work [10] and our own recent work is confusing.
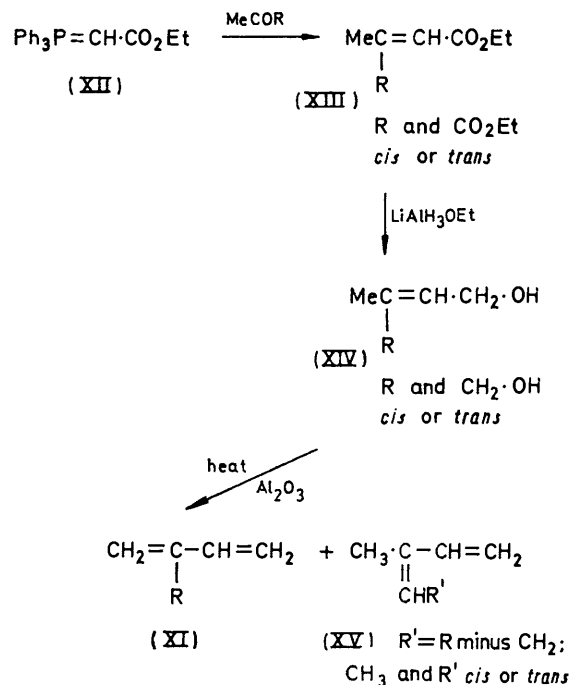
SCHEME 3

The reason why phytol yields only one diene on base-catalysed dehydration whereas the alcohol (XIV; R = n-pentyl) yields several is not clear.

We have found that the unsaturated alcohol (XIV; R = n-pentyl) can be dehydrated by passage over heated alumina [11] using very short contact times. In this way, either the *cis*- or the *trans*-alcohol (XIV; R = n-pentyl) gave the required diene (XI; R = n-pentyl) in 50—60% yield; small quantities were obtained of two other dienes (XV) in which dehydration into the chain (R) had occurred. The three dienes were separated easily by g.l.c.; the two minor components proved to be geometrical isomers (see Experimental section). Since both *cis*- and *trans*-alcohols afforded the same mixture of dienes, a common intermediate may well be involved in the reaction, possibly an allylic cation stabilised on the alumina. Thus, separation of the

[6] A. Bhati, *Perfumery Essent. Oil Record*, 1963, **54**, 376.
[7] A. Bhati, *Perfumery Essent. Oil Record*, 1966, **57**, 563.
[8] See for example, W. N. Haworth and W. G. M. Jones, *J. Chem. Soc.*, 1944, 667.

[9] A. Henninger, *Ann. Chim. phys.*, 1886, **7**, 224; P. Carré, *ibid.*, 1905, **5**, 345; *Compt. rend.*, 1903, **136**, 456.
[10] G. Ohloff, *Annalen*, 1959, **627**, 79.
[11] G. Brieger, *J. Org. Chem.*, 1967, **32**, 3720.

mixture of *cis*- and *trans*-alcohols before dehydration is unnecessary.

EXPERIMENTAL

Isolation of 3-(4,8,12-*Trimethyltridecyl*)*furan.*—T.l.c. of the neutral, paraffin-like material from cigarette smoke condensate [1] afforded a substance which gave a blue spot on developing the plate with conc. H_2SO_4. Chromatography on argentated silica gel in petroleum (b.p. 40—60°) gave the substance responsible for the blue spot as a colourless oil after distillation under reduced pressure; the oil was almost pure by g.l.c. Mass spectrometry gave the molecular formula as $C_{20}H_{36}O$; the base peak occurred at m/e 82 (C_5H_6O) with major fragment ions at m/e 95, 81, and 53. The remainder of the mass spectrum consisted of groups of ions 14 mass units apart, very similar to the mass spectra of long-chain alkanes. The i.r. spectrum contained sharp, strong bands at 784, 884, 1032, 1070, 1162, 1504, and 1560 cm^{-1} and, along with the mass spectrum, suggested the presence of a furan ring (no CO or OH present).[12] The i.r. spectrum contained a doublet at 1370 and 1380 cm^{-1} (Pr^i) and the compound formed an inclusion complex with thiourea but not with urea. These properties are consistent with a furan ring having a saturated, isoprenoid side-chain; the i.r. and n.m.r. spectra indicated a 3-substituted furan. Since the diterpene neophytadiene is a major constituent of cigarette smoke condensate [10,13] and tobacco leaf,[14] the evidence suggested that the compound was 3-(4,8,12-trimethyltridecyl)furan. Synthesis of this furan and comparison of spectroscopic (i.r., n.m.r., mass) and chromatographic (g.l.c., t.l.c.) properties confirmed the identification.

Synthesis of 3-(4,8,12-*Trimethyltridecyl*)*furan.*—(*a*) To a solution of hexahydrofarnesylmagnesium bromide (0·008 mol) in ether, prepared in the usual way from hexahydrofarnesyl bromide, was added freshly melted, powdered cadmium chloride (0·004 mol), and the mixture was stirred and heated under reflux for 45 min. The ether was replaced by benzene and the resulting solution was treated with 3-furoyl chloride (0·008 mol) in benzene at room temperature. The mixture was refluxed for 1 h, cooled, and treated with H_2SO_4 to yield, after chromatography on silica gel in petroleum (b.p. 40—60°), 3-(4,8,12-*trimethyltridecanoyl*)*furan* (14%), b.p. 180° (air bath) at 0·1 mmHg (Found: C, 78·5; H, 11·3. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%). The ketone was treated with hydrazine and sodium in ethylene glycol under reflux for 4 h and then, after removal of the condenser, at 210—215° for 21 h to give 3-(4,8,12-*trimethyltridecyl*)*furan* (8%) (Found: C, 81·8; H, 12·3. $C_{20}H_{36}O$ requires C, 82·1; H, 12·4%).

(*b*) 2-(4,8,12-Trimethyltridecyl)butane-1,2,3,4-tetraol (0·5 g) was distilled at 170—190° (air bath) and 0·1 mmHg to yield a colourless distillate containing starting material (i.r.). The whole distillate was redistilled under the same conditions to give 3-(4,8,12-trimethyltridecyl)furan (25%), b.p. 170° (air bath) at 0·1 mmHg (pure by g.l.c. on silicone elastomer at 200°).

Similarly, 2-n-pentylbutane-1,2,3,4-tetraol was distilled twice to give 3-*n*-*pentylfuran* (20%), b.p. 160° (air bath) (Found: C, 78·3; H, 10·2. $C_9H_{14}O$ requires C, 78·2; H, 10·2%).

Methyl 2-*Oxopyran-5-carboxylate.*—2-Oxopyran-5-carboxylic acid (coumalic acid) [5] (14·5 g) in methanol (415 ml)

was cooled to 0° and treated dropwise with stirring with acetyl chloride (22 ml). The mixture was allowed to warm to room temperature over 3—4 h and then refluxed for 1·5 h to give the methyl ester (75%), m.p. 72—74° (from methanol (lit.,[15] 77°).

Methyl 3-*Bromo-2-oxopyran-5-carboxylate.*—The foregoing ester (9·15 g) in glacial acetic acid (50 ml) was treated with pyridinium bromide perbromide (19 g). The solution was gently refluxed until it was a very pale yellow (about 2 h), then poured into water and extracted with chloroform to give the bromo-ester (85%), m.p. 131—134° (from acetic acid or acetone) (lit.,[3a] 134°); δ 3·89 (3H, s), 8·19 (1H, d), and 8·52 (1H, d) (J 2·5 Hz).

Furan-2,4-dicarboxylic Acid.—The foregoing bromo-ester (0·5 g) in a solution of KOH (0·72 g) in water (1·4 g) was stirred and heated to 60° (thermometer in solution) for 32 min. The solution was diluted with water, cooled in ice, and neutralised with cooled aqueous 10% H_2SO_4 (6·3 ml). The mixture was extracted with ether to give furan-2,4-dicarboxylic acid (300 mg, 90%), m.p. 266° (crystalline with 1 mol H_2O) (lit.,[3a] 266°); after drying at 60—80° for 1—2 h, m.p. 280—284° (anhydrous); δ 7·38 and 8·31 (both 1H, d, $J_{3,5}$ 0·8 Hz).

3-*Furoic Acid.*—(*a*) Furan-2,4-dicarboxylic acid (0·1 g) was heated with copper chromite (0·01 g) in quinoline (3 ml) to 200—220° for 1 h under a slow stream of nitrogen. The cooled solution was acidified and extracted with ether to give 3-furoic acid, m.p. 119—122·5° (40 mg, 55%).

(*b*) Furan-2,4-dicarboxylic acid with diazomethane afforded the dimethyl ester, which was hydrolysed to 4-methoxycarbonylfuran-2-carboxylic acid by refluxing with KOH (0·5 mol) in methanol until there was no colour reaction with phenolphthalein. Acidification and extraction with ether gave the half ester, which was decarboxylated without further purification. Treatment with copper chromite in quinoline at 200—220° for 10 min gave crude methyl 3-furoate, which was hydrolysed to the free acid with aq. 2M-KOH (67% overall yield from the diacid).

Preparation of the Tetraols (X) *from Dienes.*—(*a*) In a typical experiment, 2-(4,8,12-trimethyltridecyl)buta-1,3-diene (neophytadiene) (2·0 g) was treated with *m*-chloroperbenzoic acid in methylene chloride at 0° for 7 days to give the *diepoxide*, b.p. 160—162° at 0·1 mmHg (0·6 g), M 310; $ν_{max.}$ 1250 and 865 cm^{-1} (Found: C, 77·6; H, 12·5. $C_{20}H_{38}O_2$ requires C, 77·3; H, 12·3%). Similarly, isoprene gave its diepoxide as a colourless oil. The n.m.r. spectrum was complex but suggested the presence of diastereoisomers; in fact, the oil could just be resolved into two components by g.l.c. on a 150 ft capillary column of didecylphthalate.

Neophytadiene diepoxide (0·6 g) was warmed at 60° for 2 h with aqueous 10% H_2SO_4 (5 ml) in the minimum quantity of dioxan required to effect complete dissolution. Extraction with ether yielded 2-(4,8,12-*trimethyltridecyl*)*butane*-1,2,3,4-*tetraol* (X; R = 4,8,12-trimethyltridecyl) in 95% yield as a syrup, $ν_{max.}$ 3400 cm^{-1} (Found: C, 69·2; H, 12·1. $C_{20}O_{42}H_4$ requires C, 69·3; H, 12·1%).

(*b*) In a typical experiment, neophytadiene (2·0 g) was treated successively with 90% formic acid (8·7 ml) and 30% H_2O_2 (2·0 ml) and the mixture was heated to 40—50° with stirring for 3 h. After the first hour, a further addition of formic acid (4·3 ml) and H_2O_2 (1 ml) was made. Evaporation under reduced pressure afforded the dihydroxydiformate as a pale yellow syrup, which was immediately

[12] See ref. 2a for data and leading references.
[13] R. L. Rowland, *J. Amer. Chem. Soc.*, 1957, **79**, 5007.

[14] A. Rodgman, *J. Org. Chem.*, 1959, **24**, 1916.
[15] J. Fried and R. C. Elderfield, *J. Org. Chem.*, 1941, **6**, 577.

hydrolysed with ice-cold NaOH (1·75 g) in water (3·25 ml) at room temperature for 1 h to give the tetraol (X; R = 4,8,12-trimethyltridecyl). Similarly, the dienes (XI; R = Me, Et, or n-C_5H_{11}) were converted into the corresponding tetraols (X; R = Me, Et, or n-C_5H_{11}).

Preparation of the Dienes (XI).—Methoxycarbonyl-methylenetriphenylphosphorane (4·5 g) [16] in dry benzene (10 ml) was stirred with methyl n-pentyl ketone (7·4 g) under nitrogen at 60° for 30 h in the presence of dry benzoic acid (0·33 g). To the cooled mixture was added petroleum (b.p. 40—60°) to precipitate triphenylphosphine oxide. After filtration, a mixture of *cis-* and *trans*-ethyl 4-methyl-oct-3-enoate, b.p. 74—77° at 1·5 mmHg, was obtained (58%). The isomers were separated by g.l.c. at 180—185° on a 16 ft × ½ in column of 10% Carbowax 20M. The cis-*isomer* was eluted first (Found: C, 71·9; H, 11·2. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%), followed by the trans-*isomer* (Found: C, 71·9; H, 10·9%). *cis*-Ethyl 4-methyloct-3-enoate (0·8 g) in ether (20 ml) was treated as rapidly as possible with an excess of lithium ethoxytri-hydridoaluminate suspended in ether (5 ml). The mixture was stirred for 10 min and then refluxed for 24 h to give cis-3-*methyloct*-2-en-1-*ol* (0·6 g, 97%) (Found: C, 75·9; H, 12·6. $C_9H_{18}O$ requires C, 76·0; H, 12·8%). Similarly, *trans*-3-methyloct-2-en-1-ol was prepared in 95% yield.

On distilling either of the above alcohols from powdered KOH, a complex mixture of dienes was obtained in which there were no major components. The mixtures appeared to be similar in composition (i.r., g.l.c.) but were not investigated further. Distillation of phytol from powdered KOH afforded only one diene, neophytadiene.[6]

Either *cis-* or *trans*-3-methyloct-2-en-1-ol when injected into a column packed with glass beads and alumina (60—120 mesh; Spence type H) at 260° with nitrogen flowing through afforded a mixture (71%) of three dienes. Optimum gas flow rates through the column were determined by dehydrating geraniol to myrcene and checking the purity of the product by g.l.c. at 60° on a 150 ft capillary column of Carbowax 1540. The mixture of dienes obtained from either *cis-* or *trans*-3-methyloct-2-en-1-ol was separated by preparative-scale g.l.c. into three components, the major one of which was 2-*n-pentylbuta*-1,3-*diene* (XI; R = n-pentyl); $\nu_{max.}$ 1000, 915, and 905 cm^{-1}; δ 0·89 (3H, t), 1·33br (6H, m), 2·19 (2H, t), 4·95 and 5·3 (4H, sharp multiplet of 28 lines), and 6·35 (1H) (Found: C, 86·9; H, 12·8. C_9H_{16} requires C, 87·0; H, 13·0%). Similarly, the two minor components were shown (i.r., n.m.r.) to be cis–trans-isomers of 3-methylocta-1,3-diene (XV).

Treatment of Methyl 3-Bromo-2-oxopyran-5-carboxylate with Sodium Methoxide.—The bromo-ester (1 g) in methanol (10 ml) was refluxed with sodium (0·5 g) in methanol (20 ml) for 30 min. The bulk of the methanol was removed under reduced pressure and the residue was diluted with water, acidified with HCl, and extracted with ether to give a yellow oil. Chromatography on silica gel gave the diester (VIII) and the aldehyde-ester (IX), the structures of which were confirmed by spectroscopy (i.r., n.m.r., mass).

[16] G. Wittig and W. Haag, *Chem. Ber.*, 1955, **88**, 1654.