Carotenoids and Related Compounds. Part XXVI.[1] Synthesis of Methyl Natural Bixin

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A stereochemically controlled synthesis of the *cis*-(*Z*)-4-isomer (26; R = Me) of methylbixin is described, which involves 5-methoxycarbonyl-3-methylpenta-*cis*-(*Z*)-2,*trans*-(*E*)-4-dien-1-al (6) as the key intermediate. The product is shown to be identical with the methyl ester of natural bixin.

Bixin (26; R = H) is the principal pigment in seeds of *Bixa orellana*, and was the first carotenoid in which geometrical isomerism was encountered (for a review see ref. 2). Iodine-catalysed isomerisation of natural bixin gives the all-*trans* isomer (27; R = H) the structure of which has been proved by synthesis of the related all-*trans* dimethyl ester (27; R = Me).[3-5] Several geometrical formulations have been considered for natural bixin, but an n.m.r. study of the bixins, and related compounds, led to the assignment of the *cis*-(*Z*)-4 structure (26; R = Me) to methyl natural bixin, and the *cis*-(*Z*)-16-structure (26; R = H) to natural bixin.[2,†]

As part of our programme directed towards the controlled synthesis of carotenoids containing *cis*-double bonds, and particularly those containing methylated *cis*-double bonds, we now report an unambiguous synthesis of methyl natural bixin. This not only confirms the configuration assigned previously to this compound on the basis of the n.m.r. studies, but also represents the first stereochemically controlled direct total-synthesis of a carotenoid containing a methylated *cis*-double bond.

Our previous investigations[6] on the suitability of Wittig and related condensations for the introduction of *cis*-double bonds, suggested that a condensation between the *cis*-aldehyde (6) and the phosphoran (25) might provide a suitable route to the required *cis*-(*Z*)-4 methylbixin. This proved to be the case.

The *cis*,*trans*-β-methylmuconic half ester (4) is conveniently prepared by condensing the lactol (1)[6] with the phosphonate (2)[7] derived from methyl bromoacetate. It is also obtained by treating 3-nitro-*p*-cresol with concentrated sulphuric acid to give the lactonic acid (3; R = H), followed by esterification and treatment of the resulting ester (3; R = Me) with base.[8]

† The numbering of carbon atoms indicated in compound (26) refers to the diester (R = Me). However, in the half-ester (R = H), CO_2H is designated C-1 by convention. Thus, a *cis* double band at 4,5 in methyl bixin corresponds to one at 16,17 in bixin.

[1] Part XXIV, L. Bartlett, W. Klyne, W. P. Mose, P. M. Scopes, G. Galasko, A. K. Mallams, B. C. L. Weedon, Gy. Tóth, and J. Szabolcs, *J. Chem. Soc.* (*C*), 1969, 2527; Part XXV, O.B. Weeks, A. G. Andrewes, B. O. Brown, and B. C. L. Weedon, *Nature*, in the press.

[2] M. S. Barber, A. Hardisson, L. M. Jackman, and B. C. L. Weedon, *J. Chem. Soc.*, 1961, 1625.

[3] R. Ahmad and B. C. L. Weedon, *J. Chem. Soc.*, 1953, 3286.

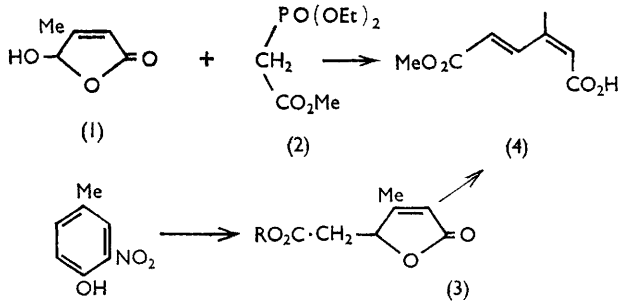
[4] H. Inhoffen and G. Raspé, *Annalen*, 1955, **592**, 214; E. Buchta and F. Andree, *Chem. Ber.*, 1959, **92**, 3111; H. Pommer, *Angew. Chem.*, 1960, **72**, 911.

[5] O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, 1957, **40**, 1242.

[6] G. Pattenden and B. C. L. Weedon, *J. Chem. Soc.* (*C*), 1968, 1984, 1997.

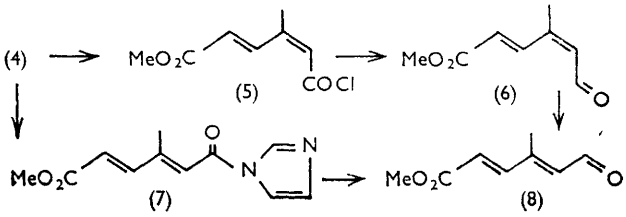
[7] W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.

[8] J. A. Elvidge, R. P. Linstead, and P. Sims, *J. Chem. Soc.*, 1951, 3386.



(1) (2) (4) (3)

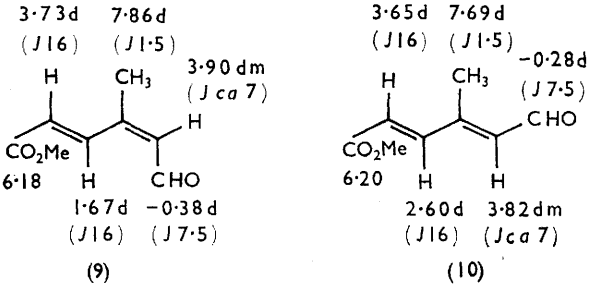
Conversion of the acid (4) into the corresponding acid chloride (5) and subsequent reduction of the latter in diglyme at −78° with lithium tri-t-butoxyaluminium hydride,[9] yielded the aldehyde (6) with complete retention of stereochemistry. Iodine-catalysed isomerisation of the *cis,trans*-aldehyde (6) then gave the corresponding



(5) (6) (7) (8)

trans,trans-isomer (8). The latter was also obtained during attempts to prepare the *cis,trans*-aldehyde (6) from the *cis,trans*-acid (4) by the imidazolide route. Presumably stereomutation occurred during the formation of the imidazolide, and subsequent reduction of (7), with lithium aluminium hydride, then furnished the *trans,trans*-aldehyde (8).

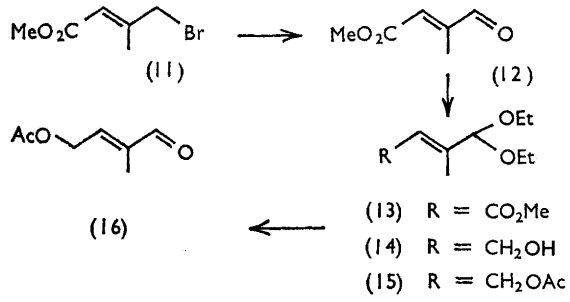
The configurations assigned to the aldehydes (6) and (8) follow conclusively from their n.m.r. properties which are summarised in the accompanying formulae (9) and (10). The olefinic proton resonances are readily assigned



(9) (10)

from the observed spin–spin coupling. The 4- and 5-protons in each isomer are observed as doublets (J 16 Hz) at τ 1·67 and 3·73 for (9), and at τ 2·60 and 3·65 for (10); the observed coupling constant is typical of *trans*-disubstituted double bonds.[10] The 4-proton in the *cis*-(*Z*)-2,*trans*-(*E*)-4 isomer (9) resonates at lower field (τ 1·67) than the corresponding proton in the *trans*-(*E*)-2,*trans*-(*E*)-4 isomer (10) (τ 2·60) owing to deshielding by both the methoxycarbonyl and the aldehyde groups. Resonances due to the olefinic 2-protons occur as doublets (J *ca.* 7 Hz) of unresolved multiplets for each isomer. The 2-proton in the *trans*-(*E*)-2-isomer (10) resonates at lower field (τ 3·82) than the corresponding proton in the *cis*-(*Z*)-2-isomer (9) (τ 3·90), because of deshielding by the 4,5-double bond. The methyl protons in the two isomers also give n.m.r. bands at different fields; as expected, the methyl band for the *trans*-(*E*)-2-isomer (10), in which the methyl group is close to (and therefore deshielded by) the aldehyde group, occurs at lower field (τ 7·69) than the corresponding band (τ 7·86) in the *cis*-(*Z*)-2-isomer (9). This difference is a convenient and unambiguous means of determining stereochemical homogeneity in this series. The aldehyde protons resonate as doublets (J 7·5 Hz) in both isomers, at τ −0·38 for (9) and τ −0·28 for (10), the former deshielded by virtue of its *cis*-relationship to the 4,5-double bond.

The phosphoran (25) required for the proposed methylbixin synthesis was obtained by the following routes. A Kröhnke reaction on methyl 4-bromo-3-methylcrotonate (11) [11] gave the *trans*-(*E*)-aldehydo-ester (12) [12] without detectable loss of stereochemistry about the carbon–carbon double bond. The aldehydo-ester (12) was converted into the corresponding acetal (13) which was reduced with lithium aluminium hydride to the hydroxy-acetal (14). Acetylation of the latter, and subsequent acid hydrolysis of the resulting acetate (15), then gave the *trans*-(*E*)-acetoxy-aldehyde (16). Makin *et al.*[13] claim to have prepared this compound by an alternative route, but its stereochemical purity was not established.



(11) (12) (16)

(13) R = CO_2Me
(14) R = CH_2OH
(15) R = CH_2OAc

A Wittig condensation between *trans*-(*E*)-acetoxy-aldehyde (16) and the phosphoran (17) [5] derived from methyl bromoacetate furnished the *trans*-(*E*)-2,*trans*-(*E*)-4-acetoxy-ester (18). Stabilised phosphorans such as (17) are well known [6,14] to yield predominantly *trans*-

[9] (*a*) H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, 1966, **88**, 1458; (*b*) H. C. Brown and P. M. Weissman, *Israel J. Chem.*, 1963, **430**, 1.

[10] Nuclear Magnetic Resonance for Organic Chemists, ed. D. W. Mathieson, Academic Press, 1967.

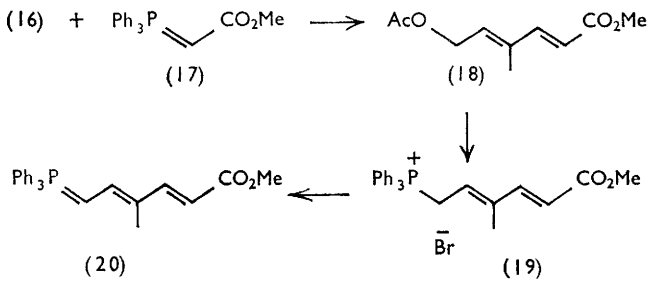
[11] R. E. Buckles, G. V. Mock, and L. Locatell, *Chem. Rev.*, 1955, **55**, 659.

[12] K. Sisido, K. Kondô, H. Nozaki, M. Tuda, and Y. Udô, *J. Amer. Chem. Soc.*, 1960, **82**, 2286.

[13] S. M. Makin, D. V. Nazarova, E. A. Kirsanova, and L. N. Smirnova, *Zhur. obshchei Khim.*, 1962, **32**, 1111; *Chem. Abstr.*, 1963, **58**, 3309.

[14] (*a*) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, 1962, **27**, 2666; (*b*) L. D. Bergelson, L. I. Barsukov, and M. M. Shemyakin, *Tetrahedron*, 1967, **23**, 2709.

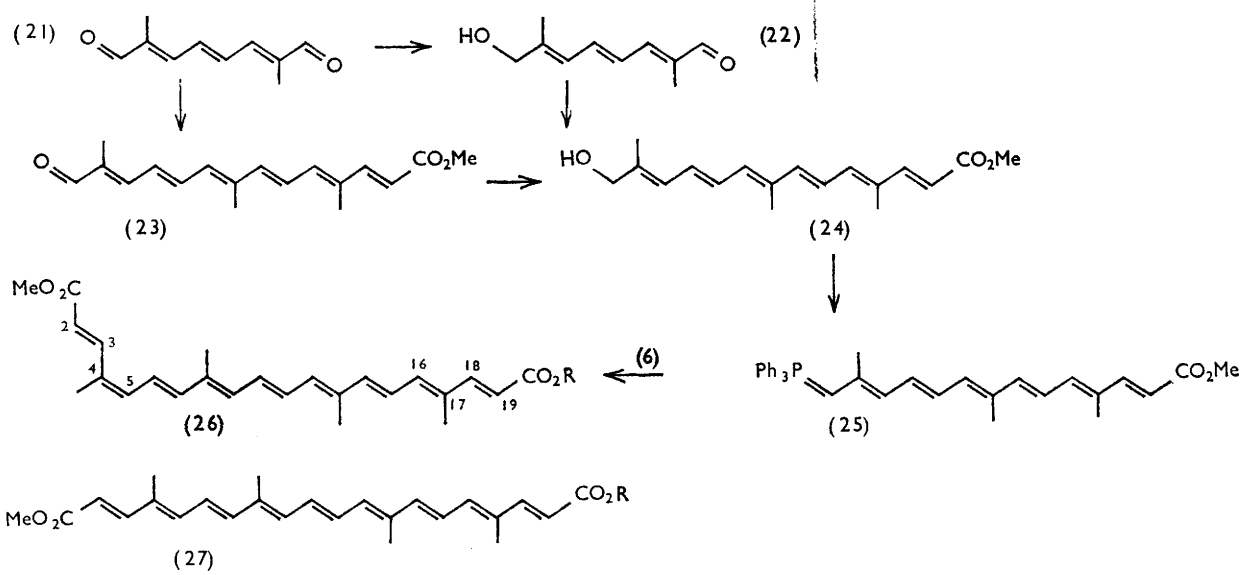
olefination products. However the configuration assigned to (18) was readily confirmed by n.m.r. spectroscopy. This revealed a typical AB system attributable to the olefinic protons at C-2 and C-3. The observed doublets (τ 4·06 and 2·66) had a coupling constant (16 Hz) which proved conclusively the *trans*-(*E*) configuration about the 2,3-double bond. The remaining bands were those expected for (18), and no evidence was obtained for the presence of geometrical isomers.



Reaction of the *trans*-(*E*)-2,*trans*-(*E*)-4 acetoxy-ester (18) with triphenylphosphonium bromide gave the Wittig salt (19) which, on treatment with base, yielded the phosphoran (20). Under suitable conditions, the latter reacted with the triene-dial (21) [15] to give the aldehydo-ester (23) in good yield. Selective reduction with sodium borohydride then furnished the hydroxy-ester (24). The latter was also prepared by partial reduction of the triene-dial (21) with sodium borohydride, followed by a Wittig condensation between the resulting hydroxy-aldehyde (22) and the phosphoran (20).

Reaction of the hydroxy-ester (24) with triphenylphosphonium bromide, and treatment of the Wittig salt thus formed with base, gave the corresponding phosphoran (25). This was condensed with the *cis*,*trans*-aldehyde (6) under carefully controlled conditions to give a mixture of methylbixin isomers which were separated by chromatography. The major constituent (*ca.* 80%) was the expected *cis*-(*Z*)-4 isomer (26; R = Me) and proved to be identical with an authentic specimen of methyl natural bixin in all respects (m.p. and mixed m.p., t.l.c., visible and i.r. light absorption spectra, n.m.r. and mass spectra). Two minor *cis*-isomers (which together constituted *ca.* 5% of the mixture) were isolated. These were not fully characterised, but their n.m.r. spectra indicated that they retained the *cis*-double bond derived from the starting aldehyde (6). The positions of their light absorption maxima suggested that both contained an additional (' unhindered ') *cis*-double bond. These probably resulted from stereomutation in the phosphoran (25), but *cis*-olefination and stereomutation during isolation of the main product cannot be excluded. The remaining, most strongly adsorbed, product (*ca.* 10%) was identified as all-*trans* methylbixin (27; R = Me) by direct comparison with an authentic specimen. The formation of this isomer is attributed to partial loss of configuration in the labile *cis*,*trans*-aldehyde (6) under the condensation conditions.

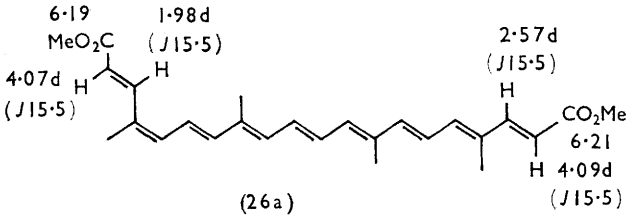
The salient n.m.r. properties of methyl natural bixin (26; R = Me) and all-*trans*-methylbixin (27; R = Me) are summarised in formulae (26a) and (27a). These



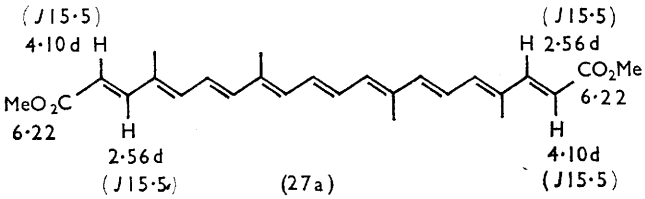
results are in good agreement with, but amplify, those reported earlier as the basis for assigning the *cis*-4 configuration to methyl natural bixin.[2] Both isomers show ' in-chain ' methyl resonances (at 8·01 and 8·04 for the *cis*-isomer, and 8·00 and 8·03 for the all-*trans*), and a broad complex band centred near τ 3·45 attributable to the 10 olefinic protons along the C-5 to C-16 portion of the polyene chain. The olefinic protons in the α- and β-positions to the ester groups in all-*trans* methyl bixin constitute two identical AB systems. Of the resulting two doublets (each equivalent to two protons) that at higher fields (τ 4·10) may be assigned to the two

[15] P. Mildner and B. C. L. Weedon, *J. Chem. Soc.*, 1953, 3294; H. H. Inhoffen, O. Isler, G. von der Bey, G. Raspé, P. Zeller, and R. Ahrens, *Annalen*, 1953, **580**, 7.

α-protons, and that at lower fields (τ 2·56) to the two β-protons, and the observed coupling constant (15·5 Hz) confirms the *trans* configuration of the two terminal carbon–carbon double bonds.[2] In methyl natural bixin



(26a)



(27a)

the 18,19-double bond provides a similar AB system and results in a pair of doublets (τ 4·09 and 2·57; *J* 15·5 Hz) closely resembling those in the all-*trans*-isomer, but with only half the intensity. The 2,3-double bond furnishes another AB system, and leads to a second pair of doublets, each of which is also equivalent to only one proton. The doublet at higher fields (τ 4·07) may again be attributed to the α-proton and differs only slightly from that due to the α-proton in the 'all-*trans* end'. The position (τ 1·98) of the remaining doublet clearly reveals the deshielding of the C-3 proton by the 6,7-double bond in the isomer with the *cis*-4 configuration.[2] That both terminal carbon–carbon double bonds in methyl natural bixin have the *trans*-configuration is again shown by the coupling constant (15·5 Hz) observed for all four doublets. The difference in configuration between all-*trans* methyl bixin and methyl natural bixin is also revealed by small differences in the resonances due to the methyl ester protons. The former isomer exhibits a sharp peak at τ 6·22 whereas the latter has two signals (τ 6·19 and 6·21).

EXPERIMENTAL

For general experimental details see Part XVIII.[6] Alumina for chromatography was Grade IV unless stated otherwise.

Except where indicated to the contrary, n.m.r. spectra were determined on a Varian A60 instrument for dilute solutions in deuteriochloroform, with tetramethylsilane as an internal standard. Bands were sharp singlets, except where one of the following designations is used: br, broad; d, doublet; dd, doublet of doublets; dm, doublet of multiplets; dq, doublet of quartets; dt, doublet of triplets; m, multiplet; q, quartet; t, triplet; td, triplet of doublets; tm, triplet of multiplets; tq, triplet of quartets. Relative intensities are not normally quoted as these had the expected values.

Mass spectra were recorded on an AEI MS902 mass spectrometer, using the direct insertion technique. High resolution measurements were made relative to heptacosafluorotributylamine.

4-Carboxymethyl-3-methylbut-2-enolide (3; R = H).—Treatment of 3-nitro-*p*-cresol [16] with concentrated sulphuric acid, according to the method of Pauly *et al.*[17] gave (70%) the lactonic acid, m.p. 128—130° (lit.,[8] m.p. 129—130°); $\nu_{max.}$ (ether) 1780 and 1750 cm.$^{-1}$; τ (deuterioacetone) 4·60 (q, *J* 1·5, =C*H*), 5·16 (m, C*H*–), 7·43 (dd, *J* 16·5 and 5, CH–C*H*H–), 7·95 (dd, *J* 16·5 and 7, CH–CH*H*–), and 8·32 (m, =C·CH_3).

4-Methoxycarbonylmethyl-3-methylbut-2-enolide (3; R = Me).—Treatment of the lactonic acid in ether–methanol (95 : 5) with ethereal diazomethane gave (75%) the methyl ester, m.p. 31—32° (lit.,[8] m.p. 34—35°); $\nu_{max.}$ (CCl_4) 1770, 1740, and 1645 cm.$^{-1}$; τ 4·12 (q, *J ca.* 1·5, =C*H*), 4·73 (m, C*H*–), 6·24 (OCH_3), 7·2—7·4 (m, CH_2), and 7·9 (dd, *J* 1·5 and 1, =C·CH_3).

5-Methoxycarbonyl-3-methylpenta-cis-(Z)-2,trans-(E)-4-*dienoic Acid* (4).—The lactonic ester (6·0 g.) was treated with sodium methoxide (from 1·0 g. sodium) in methanol (60 ml.), according to the method of Elvidge *et al.*,[8] and gave the half-ester (5·0 g., 80%) as needles, m.p. 134—134·5° (benzene) identical in all respects (mixed m.p., u.v., i.r., and n.m.r.) with the product described previously [6] from 4-hydroxy-3-methylbut-2-enolide (Elvidge *et al.*,[8] give m.p. 126—127°).

5-Methoxycarbonyl-3-methylpenta-cis-(Z)-2,trans-(E)-4-*dienoic Acid Chloride* (5).—A mixture of the preceding acid (4) (2·0 g.) and thionyl chloride (13 ml.) was boiled, under reflux for 1 hr., and then evaporated to dryness under reduced pressure. The residue was treated with dry benzene, and the solution was again evaporated; this procedure was repeated twice more. Crystallisation of the residue from benzene–light petroleum (b.p. 60—70°) gave the acid chloride (1·2 g.) as feathery needles, m.p. 45—47°; $\nu_{max.}$ ($CHCl_3$) 1742, 1710, 1622, 1580, 1318, 1290, 1000, and 880 cm.$^{-1}$; τ 1·77 (d, *J* 16, 4-*H*), 3·65 (d, *J* 16, 5-*H*), 3·72 (m, 2-*H*), 6·19 (OCH_3), and 7·89 (d, *J* 1·5, =C·CH_3). The acid chloride [from acid (1·5 g.), and thionyl chloride (10 ml.)], when stirred vigorously with ammonia (*d* 0·880; 2 ml.) at 0°, gave the corresponding *cis*-(*Z*)-amide which crystallised from ethanol and had m.p. 138—140° (lit.,[8] m.p. 141°); $\lambda_{max.}$ (EtOH) 266 nm.; $\nu_{max.}$ ($CHCl_3$) 3500, 3400, 1710, 1668, 1630, 1585, 1315, 1290, 995, and 890 cm.$^{-1}$; τ 1·67 (d, *J* 16, 4-*H*), 3·3—4·0br (–NH_2), 3·88 (d, *J* 16, 5-*H*), 4·00 (m, 2-*H*), 6·23 (OCH_3), and 8·00 (d, *J* 1·5, =C·CH_3).

5-Methoxycarbonyl-3-methylpenta-cis-(Z)-2,trans-(E)-4-*dien*-1-*al* (6).—A solution of t-butyl alcohol (1·25 g.) in diglyme (2 ml.) was added during 1 hr. to a stirred solution of lithium aluminium hydride (190 mg.) in diglyme (10 ml.) at 25°. The mixture was stirred for 30 min., and was then added during 45 min. to a stirred solution of the acid chloride (5) (1·0 g.) in diglyme (20 ml.) at −78° under nitrogen. The mixture was stirred between −50° and −20° for 45 min., and was then diluted with N-sulphuric acid and extracted with ether. The ether extracts were washed with sodium hydrogen carbonate solution and water, and then dried and evaporated to dryness. Chromatography of the residue in benzene on alumina and crystallisation from benzene–light petroleum (b.p. 60—70°) gave the *aldehyde* (400 mg., 50%) as feathery needles, m.p. 47·5—

[16] G. Schultz, *Ber.*, 1907, **40**, 4324.
[17] H. Pauly, R. Gilmour, and G. Will, *Annalen*, 1914, **403**, 119.

48°; $\lambda_{max.}$ (95% EtOH) 273·5 nm. (ε 24,200); $\nu_{max.}$ ($CHCl_3$) 1710, 1670, 1630, 1590, 1318, 1290, 1118, 975, and 888 cm.$^{-1}$; τ, see Formula 9 (Found: C, 62·1; H, 6·55. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%). The 2,4-*dinitrophenylhydrazone* (85% yield), purified by chromatography in benzene on alumina, crystallised from benzene and had m.p. 232—233°; $\lambda_{max.}$ (benzene) 389·5 nm. (ε 36,300) (Found: C, 50·2; H, 4·4; N, 16·9. $C_{14}H_{14}N_4O_6$ requires C, 50·3; H, 4·2; N, 16·8%).

5-*Methoxycarbonyl*-3-*methylpenta*-trans-(E)-2,trans-(E)-4-*dien*-1-*al* (8).—(a) *From* 5-*methoxycarbonyl*-3-*methylpenta*-cis-(Z)-2,trans-(E)-4-*dien*-1-*al*. A solution of the *cis*-aldehyde (100 mg.) in benzene (15 ml.) containing a crystal of iodine was kept in daylight for 4 hr. The solution was then washed with aqueous sodium thiosulphate, dried, and evaporated. Crystallisation of the residue from benzene–light petroleum (b.p. 60—70°) gave the *aldehyde* (65 mg.) as needles, m.p. 84—85°, depressed to m.p. 33—43° on admixture with the *cis*-(Z)-aldehyde; $\lambda_{max.}$ (95% EtOH) 277·5 nm. (ε 29,100); $\nu_{max.}$ ($CHCl_3$) 1710, 1670, 1630, 1600, 1318, 1300, 1108, 982, 872, and 860 cm.$^{-1}$; τ, see Formula 10 (Found: C, 61·8; H, 6·5. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%). The 2,4-*dinitrophenylhydrazone* (80% yield), purified by chromatography in benzene on alumina, crystallised from benzene and had m.p. 234° [depressed to m.p. 214—216° on admixture with the derivative from the *cis*-(Z)-aldehyde]; $\lambda_{max.}$ (benzene) 391 nm. (ε 38,700) (Found: C, 50·4; H, 4·35; N, 16·7. $C_{14}H_{14}N_4O_6$ requires C, 50·3; H, 4·2; N, 16·8%).

(b) *From* 5-*methoxycarbonyl*-3-*methylpenta*-cis-(Z)-2,trans-(E)-4-*dienoic acid*. A solution of the *cis,trans* half-ester (5) (2·0 g.) and *NN'*-carbonyldi-imidazole [18] (2·05 g.) in tetrahydrofuran (60 ml.) was stirred at 25° for 6 hr., and was then evaporated to dryness under high vacuum. The residue, which consisted largely of the imidazolide derivative showed $\nu_{max.}$ ($CHCl_3$) 1710 and 1600 cm.$^{-1}$; τ 2·55, 3·29, 3·62, 6·19, and 7·61 (relative intensities *ca.* 1 : 1 : 1 : 3 : 3).

A solution of lithium aluminium hydride (225 mg.) in ether (250 ml.) was added during 1·5 hr. to a stirred solution of the imidazolide in tetrahydrofuran (100 ml.) at −20°. The mixture was stirred at −20° for a further 1 hr. and was then treated with water and dilute hydrochloric acid; finally it was extracted with ether. The ether extracts were washed with sodium hydrogen carbonate solution and water, and were then dried and evaporated. Chromatography of the residue in benzene on alumina, and crystallisation from benzene–light petroleum (b.p. 60—80°), gave the *trans*-(E)-aldehyde (150 mg.), m.p. 78—83° [and mixed m.p. 80—84° with the aldehyde from (a)]; $\lambda_{max.}$ (95% EtOH) 277 nm.; the n.m.r. and i.r. spectral data were identical with those of the product from (a). The 2,4-dinitrophenylhydrazone had m.p. 232—234°; $\lambda_{max.}$ (benzene) 391 nm.

Methyl trans-(E)-4,4'-*Diethoxy*-3-*methylbut*-2-*enoate* (13).—Methyl *trans*-(E)-3-formyl-3-methylacrylate [15] was prepared from methyl 4-bromo-3-methylcrotonate, by a Kröhnke synthesis, as described previously.[6] A stirred mixture of the aldehyde (33 g.) and ethyl orthoformate (44 g.) was treated with a hot solution of ammonium nitrate (1·0 g.) in ethanol (27 ml.), and the mixture was stirred for 3 days. Anhydrous potassium carbonate was then added and the mixture was distilled to give the trans-(E)-*acetal* (45·3 g., 86%), b.p. 61—64°/0·5 mm., n_D^{21} 1·4408; $\nu_{max.}$ (film) 1720, 1660, 1115, and 1060 cm.$^{-1}$; τ 3·78 (q, *J* 1·5, =C*H*), 5·14 (C*H*−), 6·19 (OCH_3), 6·37 (m, 2 × CH_2CH$_3$), 7·80 (d, *J* 1·5, =C·CH_3), and 8·76 (t, *J* 7·5, 2 × CH$_2$CH_3) (Found: C, 59·65; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·95%). Condensation between the diethyl acetal of methylglyoxal and methyl diethylphosphonoacetate, as described previously,[6] gave a 1 : 2 mixture of the *cis*-(Z)-, and *trans*-(E)-isomers of the product.

trans-(E)-4,4-*Diethoxy*-3-*methylbut*-2-*en*-1-*ol* (14).—The preceding ester (45·0 g.) in ether (500 ml.) was added during 1·5 hr. to a stirred mixture of lithium aluminium hydride (5 g.) and ether (500 ml.) at 0°. The mixture was stirred at 25° for 2 hr., after which the excess of lithium aluminium hydride was decomposed by the dropwise addition of water. The mixture was treated with saturated aqueous ammonium chloride; the ether extract was then separated, washed (H_2O), and dried. Distillation gave the *alcohol* (32 g., 85%), b.p. 67—70°/0·1 mm., n_D^{21} 1·4474; $\nu_{max.}$ (film) 3420, 1675, 1120, and 1070 cm.$^{-1}$; τ 4·27 (tm, *J* 6·5, =C*H*−), 5·38 (C*H*−), 5·80 (d, *J* 6·5, CH_2O), 6·48 (m, 2 × CH_2CH$_3$), 7·27 (O*H*), 8·35 (=C·CH_3), 8·80 (t, *J* 6·5, 2 × CH$_2$CH_3) (Found: C, 61·6; H, 10·0. $C_9H_{18}O_3$ requires C, 62·0; H, 10·4%).

trans-(E)-4-*Acetoxy*-2-*methylbut*-2-*en*-1-*al* (16).—Acetic anhydride (19 g.) was added at 0° during 5 min. to the preceding alcohol (32 g.) in pyridine (17 ml.), and the mixture was stirred at 25° for 96 hr. The mixture was diluted with water and then extracted with ether. Distillation of the washed (H_2O) and dried ether extracts gave the acetal-acetate (*ca.* 26 g.) (containing varying amounts of the aldehyde-acetate), b.p. 46—52°/8·5 × 10^{-3} mm. This mixture (16 g.) was shaken with saturated aqueous tartaric acid (50 ml.) for 12 hr. Saturated aqueous sodium chloride (100 ml.) was added and the mixture was then extracted with ether. The combined ether extracts were washed with 5% potassium carbonate solution and then with water; they were then dried. Distillation gave the aldehyde (10 g.), b.p. 66—72°/2 mm., n_D^{22} 1·4647. A sample purified by g.l.c. (Ucon-polar, 215°) had n_D^{20} 1·4651; $\lambda_{max.}$ (95% EtOH) 224 nm. (ε 11,000); $\nu_{max.}$ (film) 2715, 1735, 1690, and 1648 cm.$^{-1}$; τ 0·45 (−C*H*O), 3·48 (tq, *J* 6·5 and 1·5, =C*H*−), 5·07 (dq, *J* 6·5 and 1, CH_2−O), 7·88 (COCH_3), and 8·19 (dt, *J* 1·5 and 1, =C·CH_3) (lit.,[13] b.p. 52—55°/2 mm., n_D 1·4600). The 2,4-dinitrophenylhydrazone, purified by chromatography in benzene on alumina, crystallised from benzene and had m.p. 168—169° (lit.,[13] m.p. 166°); $\lambda_{max.}$ (EtOH) 370 nm.

Methyl 6-*Acetoxy*-4-*methylhexa*-trans-(E)-2,trans-(E)-4-*dienoate* (18).—A solution of the preceeding aldehyde (16) (7·0 g.) and methoxycarbonylmethylenetriphenylphosphoran [5] (17 g.) in methylene chloride (300 ml.) was stirred at 25° for 5 days; the course of the reaction was followed by the appearance of a band at 1700 cm.$^{-1}$ (conj. ester C=O), and the disappearance of the band at 1682 (aldehyde C=O) in the i.r. spectrum (CH_2Cl_2) of the mixture. The solution was evaporated to dryness and the residue was treated with light petroleum (b.p. 60—80°). The precipitated phosphine oxide was filtered off and the filtrate was distilled to give the *acetoxy-ester* (8·0 g., 80%), b.p. 76—78°/8 × 10^{-4} mm., n_D^{21} 1·5061; $\lambda_{max.}$ (95% EtOH) 258·5 nm. (ε 25,500); $\nu_{max.}$ (film) 1730, 1710, 1620, 985, and 860 cm.$^{-1}$; τ 2·66 (d, *J* 16, 3-*H*), 4·06 (d, *J* 16, 2-*H*), 4·15 (tm, *J* 7, 5-*H*), 5·25 (d, *J* 7, CH_2−O), 6·23 (OCH_3), 7·93 (COCH_3), and 8·14 (d, *J* 1, =C·CH_3); *m/e* 198 ($C_{10}H_{14}O_4$ requires 198) (Found: C, 60·7; H, 7·2. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

[18] H. A. Staab and H. Bräunling, *Annalen*, 1962, **654**, 119.

13-*Methoxycarbonyl*-2,7,11-*trimethyltrideca*-2,4,6,8,10,12-*hexaen*-1-*al* (23).—The above acetoxy-ester (0·6 g.) and triphenylphosphonium bromide [19] (1·2 g.) in methanol (40 ml.) was stirred at 20° for 5·5 days. The methanol was removed under reduced pressure and the oily residue was washed several times with ether. Solvents were removed under high vacuum to leave the triphenylphosphonium salt as a glassy solid which was used without further purification.

Sodium methoxide [from sodium (0·1 g.)] in methanol (5 ml.) was added during 4 hr., to a stirred solution of the above phosphonium salt and 2,7-dimethylocta-2,4,6-triene-1,8-dial [15] (0·3 g.) in dimethylformamide at 20°; the reaction was followed by light absorption analysis of aliquots taken at intervals throughout the addition of base. The mixture was diluted with water, saturated with sodium chloride, and extracted with benzene. The extracts were washed with water, dried, and evaporated. Chromatography of the residue in benzene on alumina, isolation of the product from the main band, and crystallisation from benzene gave the *aldehydo-ester* (150 mg.) as purple-red rhombs, m.p. 148—150°; $\lambda_{max.}$ ($CHCl_3$) 397infl, 416, and 441 nm. (ε 55,800, 84,600, and 79,500); $\nu_{max.}$ ($CHCl_3$) 1693, 1660, 1615, and 1592 cm.$^{-1}$; τ 0·55 (C*H*O), 2·5—4·2 (m, 9 × =C*H*), 2·62 (d, *J* 15·5, 12-*H*), 4·10 (d, *J* 15·5, 13-*H*), 6·26 (OCH_3), 7·97, 8·06 (2- and 7-Me) and 8·12 (11-Me); *m/e* 286·1567 ($C_{18}H_{22}O_3$ requires 286·1568) (Found: C, 75·6; H, 7·6. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%).

2,7-*Dimethyl*-8-*hydroxy-octa*-2,4,6-*trien*-1-*al* (22).—Sodium borohydride (75 mg.) in methanol (25 ml.) was added during 2 hr. to a stirred solution of 2,7-dimethylocta-2,4,6-triene-1,8-dial [15] (0·95 g.) in methanol (75 ml.); the reaction was followed by light absorption analysis of samples of the reaction mixture taken throughout the addition of borohydride. The mixture was concentrated to 5 ml. and was then diluted with water and extracted with ether. The extracts were washed with 0·5N-hydrochloric acid and water and then dried and evaporated. The residue was chromatograped in benzene on alumina, and the product was isolated from the main band; it crystallised from ether to give the *alcohol* (730 mg.), m.p. 58—62°. Sublimation of a small sample at *ca.* 55°/3·17 × 10^{-3} mm. gave the alcohol as yellow needles, m.p. 61—62°; $\lambda_{max.}$ (light petroleum, b.p. 60—80°) 294, 309, and 324 nm. (ε 25,900, 44,300, and 42,400); $\nu_{max.}$ ($CHCl_3$) 1622 and 1605 cm.$^{-1}$; τ 0·57 (C*H*O), 3·0—3·8 (m, 4 × =C*H*), 5·83 (CH_2–O), 7·86 (O*H*), and 8·13 (2 × =C·CH_3) (Found: C, 72·0; H, 8·35. $C_{10}H_{14}O_2$ requires C, 72·25; H, 8·5%).

Methyl 14-*Hydroxy*-4,8,13-*trimethyltetradeca*-2,4,6,8,10,12-*hexaenoate* (24).—(a) *From* 13-*methoxycarbonyl*-2,7,11-*trimethyltrideca*-2,4,6,8,10,12-*hexaen*-1-*al* (23).—Sodium borohydride (50 mg.) in methanol (25 ml.) was added, during 2 hr., to a stirred solution of the aldehydo-ester (110 mg.) in methanol (25 ml.) and ether (5 ml.); the reaction was followed by light absorption analysis of samples of the reaction mixture taken at intervals throughout the addition of borohydride. The mixture was stirred for 1 hr., and was then evaporated to dryness; the residue was extracted with ether. The extracts were washed with 0·5N-hydrochloric acid and water and were then dried and evaporated to dryness. Chromatography of the residue in benzene on alumina, and crystallisation from benzene, gave the *alcohol* (100 mg.), m.p. 138—140°; $\lambda_{max.}$ ($CHCl_3$) 381infl, 399, and 419 nm. (ε 44,200, 57,800, and 54,500); $\nu_{max.}$ ($CHCl_3$) 3500, 1700, 1620, 1600, and 1560 cm.$^{-1}$; τ 2·53—4·3 (m, 9 × =C*H*), 2·65 (d, *J* 15·5, 3-*H*), 4·17 (d, *J* 15·5, 2-*H*), 5·89 (CH_2–O), 6·28 (OCH_3), 8·09 (4- and 8-Me), and 8·18 (13-Me); *m/e* 288·1730 ($C_{18}H_{24}O_3$ requires 288·1725).

(b) *From* 2,7-*dimethyl*-8-*hydroxy-octa*-2,4,6-*trien*-1-*al* (22). The triphenylphosphonium salt from the acetoxy-dienoate (18) (0·6 g.) and triphenylphosphinium bromide [19] (1·2 g.) was prepared as described above.

Sodium methoxide [from sodium (0·12 g.)] in methanol (10 ml.) was added, during 3 hr., to a stirred solution of the above phosphonium salt and 2,7-dimethyl-8-hydroxy-octa-2,4,6-trien-1-al (300 mg.) in methanol (40 ml.); the reaction was followed by light absorption analysis of samples of the reaction mixture taken at intervals throughout the addition of base. The mixture was evaporated to dryness and the residue was extracted with benzene. The extracts were washed with water, dried, and evaporated. Chromatography of the residue in benzene on alumina, and crystallisation from benzene gave the alcohol (150 mg.) identical (m.p., visible light absorption, and n.m.r.) with that obtained from (a).

Methyl 19-*Methoxycarbonyl*-4,8,13,17-*tetramethylnonadeca*-trans-(*E*)-2,6,8,10,12,14,16,18-cis-(*Z*)-4-*nonaenoate* [cis-(*Z*)-4-*Methylbixin*] (26; R = Me).—A solution of the hydroxy-hexaenoate (24) (205 mg.) and triphenylphosphonium bromide (250 mg.) in methanol (70 ml.) was stirred at 20° for 6 days. The methanol was removed under reduced pressure and the residue was washed several times with ether. Solvents were removed under high vacuum to leave the triphenylphosphonium salt as a solid, $\lambda_{max.}$ ($CHCl_3$) 384, 402, and 425 nm., which was used without further purification.

Solutions of sodium methoxide [from sodium (30 mg.)] in methanol (3 ml.) and of the *cis,trans*-dienal (6) (100 mg.) in methanol (5 ml.), were added separately and simultaneously to a stirred solution of the above phosphonium salt in methanol (10 ml.) at 25° during 0·5 hr. The mixture was stirred for a further 0·5 hr., and was then evaporated to dryness under reduced pressure. The residue was dissolved in benzene and the solution was then washed with water (2 × 100 ml.) and evaporated to dryness at <40° under reduced pressure. Chromatography of the residue in benzene on alumina (Grade III) gave a mixture of methylbixins which was rechromatographed on alumina (Grade III) with benzene–light petroleum (b.p. 60—80°) (9 : 1) as eluant to give, in order of elution: (i) A minor *cis*-isomer (*ca.* 3 mg.), $\lambda_{max.}$ (benzene) 461 and 491 nm.; τ 1·98 (d, *J* 15·5 HC=C*H*), 2·54 (d, *J* 15·5, *H*C=CH), 3·2—3·8 (m, =C*H*), 4·08 (d, *J* 15·5 HC=C*H*), 6·20 (OMe), and 8·01 (=CMe). (ii) A further minor *cis*-isomer (*ca.* 3 mg.), $\lambda_{max.}$ (benzene) 462 and 492 nm.; τ 1·98 (d, *J* 15·5 ,HC=C*H*), 2·54 (d, *J* 15·5, *H*C=CH), 3·2—3·8 (m, =C*H*), 4·08 (d, *J* 15·5, *H*C=CH), 4·11 (d, *J* 15·5, HC=C*H*), 6·20 (OMe), 8·01 (=C·Me. (iii) cis-(Z)-4-*Methylbixin* (61 mg.) which after recrystallisation from ethyl acetate had m.p. 163° (undepressed on admixture with methyl natural bixin, m.p. 163°); $\lambda_{max.}$ (benzene) 442, 468, and 500 nm. (ε 82,500, 122,000, and 110,700) [methyl natural bixin had $\lambda_{max.}$ (benzene) 442, 468, and 500 nm. (ε 83,300, 124,000, and 114,000)]; $\nu_{max.}$ (KBr disc) 1708s, 1610s, 1595m, 1563m, 1436m—w, 1428m, 1395w, 1270m—s, 1167vs, 1130m, 1010m, 983m, 962s, 860w, 850w, and 835w cm.$^{-1}$ (the spectrum was identical with that of methyl natural bixin, determined under the same conditions); τ see formula (26a) and text; *m/e* 408·2306 ($C_{26}H_{32}O_4$ requires 408·2301) (Found: C, 76·2; H, 8·1; O, 15·7. $C_{26}H_{32}O_4$

[19] H. Pommer, *Angew. Chem.*, 1960, **72**, 811.

requires C, 76·4; H, 7·9; O, 15·7%); the synthetic *cis*-4-methylbixin did not separate in mixed t.l.c. [silica gel, light petroleum–acetone (95 : 5)] from methyl natural bixin. (iv) all-*trans*-Methylbixin (9 mg.), which after recrystallisation from ethyl acetate had m.p. 204—205° (undepressed on admixture with an authentic specimen, m.p. 203—204°); $\lambda_{max.}$ (benzene) 446, 473, and 506 nm. (identical with those of the authentic specimen); $\nu_{max.}$ (KBr disc), 1715s, 1615s, 1600m, 1562s, 1435m—w, 1402w, 1392w, 1260m, 1162vs, 1005m—w, 980s, 890w, and 840m—w cm.$^{-1}$ (the spectrum was identical with that of all-*trans* methylbixin, obtained by iodine-catalysed stereomutation of methyl natural bixin); τ see formula (27a) and text.

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