

SOME STUDIES ON CAROTENOID SYNTHESIS

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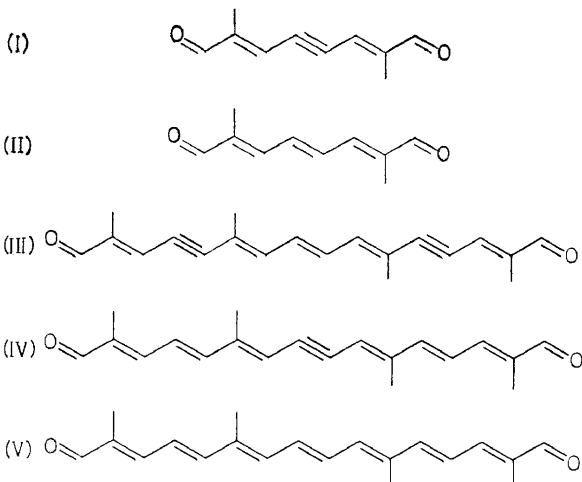
INTRODUCTION

Traditionally synthesis is invoked as the final proof of a structure deduced by other means. In the carotenoid field synthesis is being used increasingly as an integral part of structural studies in order to elucidate some molecular feature for which the other evidence is inconclusive or ambiguous. Synthesis also fulfils the very important rôle of making many carotenoids much more readily available for further investigations than they would be if it were necessary to rely entirely on natural sources.

The variety of natural carotenoids presents many intriguing problems in synthesis, and it is impossible in the space of a short review to do justice to all the work which has been carried out in this field in an attempt to solve them. Attention will therefore be largely confined to problems that have been tackled by the group of which I am, today, the spokesman.

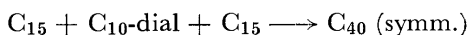
SYNTHESIS OF CAROTENOIDS

Symmetrical C_{10} - and C_{20} -dials offer very versatile routes for the synthesis of carotenoids. We first prepared the C_{10} -dials (I) and (II) from α -methacrolein and acetylene¹, and devised a route to the C_{20} -dial (III)². Routes to the C_{10} -dials (I) and (II) have also been developed in other laboratories³⁻⁶, and both compounds can now be regarded as readily available intermediates. Moreover, Isler *et al.*⁷ have shown that, by application of their vinyl ether syntheses⁸, these C_{10} -dials may be converted into crocetinindial (V) and dehydrocrocetinindial (IV). These C_{20} -dials thus

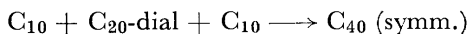


become much more readily available than the earlier C₂₀-dial (III) which was used in the first direct total synthesis of an oxygenated carotenoid^{2, 9}.

To build up the C₄₀ carbon skeleton of a typical carotenoid from these key intermediates we have used two main reactions: the aldol condensation for converting an aldehyde into the vinylogous ketone, and the Wittig reaction for converting a carbon–oxygen double bond into a carbon–carbon double bond. Under appropriate conditions, we find that the Wittig reaction with the C₁₀- and C₂₀-dials can be carried out in two steps: first at one end of the molecule, and then at the other. The Wittig reaction therefore affords a convenient way of building up both symmetrical and unsymmetrical carotenoids. The routes to the former may be represented as:



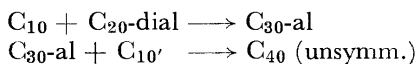
and



and those to the unsymmetrical compounds as:



and



where C_{15'} and C_{10'} represent Wittig reagents different from those used in the first step to produce the C₂₅ and C₃₀ aldehydes respectively.

Syntheses based on the C₁₀-dials

Of recent years there has been much discussion on the structures of the hydrolycopenes now recognized as intermediates in the biosynthesis of carotenoids. Even when the main structural features of ζ-carotene had been determined, a decision in favour of the symmetrical formulation (VIII), as opposed to the unsymmetrical alternative (IX), was only possible on the basis of a synthesis (*Figure 1*) of the former from the C₁₀-dial (II) and the farnesyl Wittig reagent (VII) derived from nerolidol (VI)^{10, 11}. By partial hydrogenation of the product obtained similarly from the acetylenic C₁₀-dial (I), central-*cis* ζ-carotene was obtained^{10, 11}, and identified with a pigment isolated from *Chlorella* mutants¹². A two step Wittig synthesis (*Figure 2*) was used to confirm the structure deduced for the key compound, neurosporene (XII)¹¹. As a result of these and related studies, the nature of the main dehydrogenation sequence in the biosynthesis of carotenoids became clear.

By similar Wittig syntheses a number of 7,8-di- and 7,8,7',8'-tetrahydrocarotenes have been prepared, including (±)-*α*-zeacarotene (XVa) and β-zeacarotene (XVb) from *α*- and β-ionone (XIIIa and XIIIb) respectively (*Figure 3*), and the tetrahydro-β- and ε-carotenes from the corresponding dihydro-ionones^{13, 14}. An alternative synthesis of β-zeacarotene has been reported by Isler *et al.*¹⁵. The characterization of authentic hydrocarotenes will, it is hoped, facilitate the detection of some of these compounds in Nature, and thus help to identify the stage at which ring closure occurs in the biosynthesis of carotenoids.

SOME STUDIES ON CAROTENOID SYNTHESIS

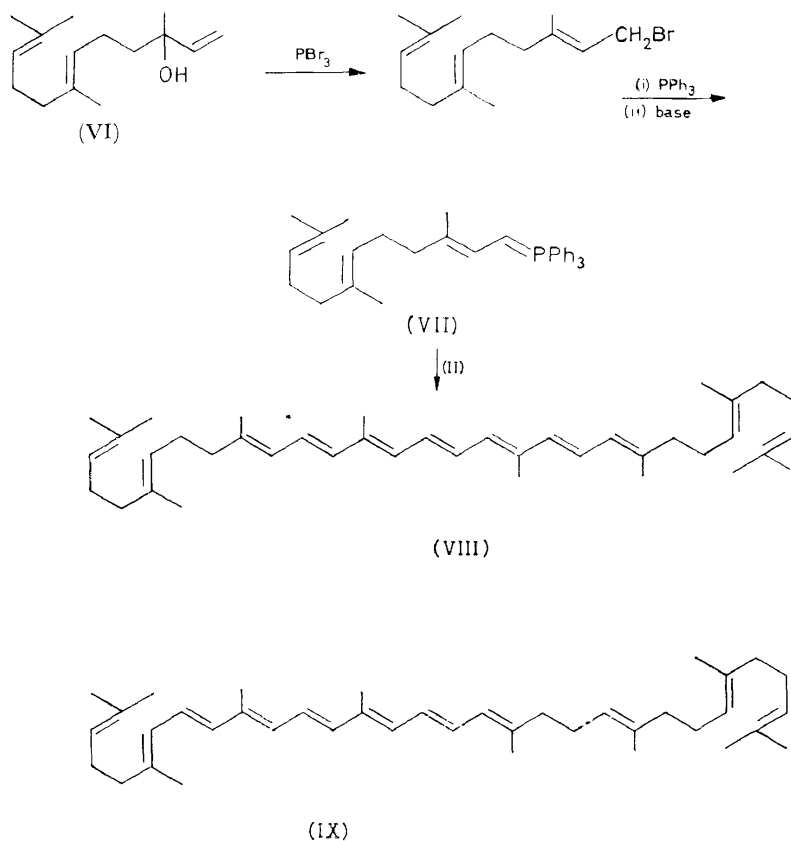


Figure 1. Synthesis of ζ -carotene (VIII)

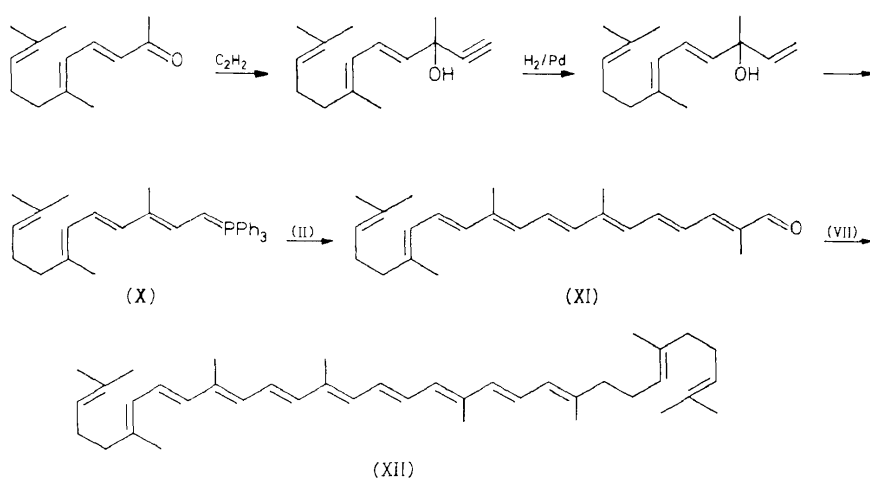


Figure 2. Synthesis of neurosporene

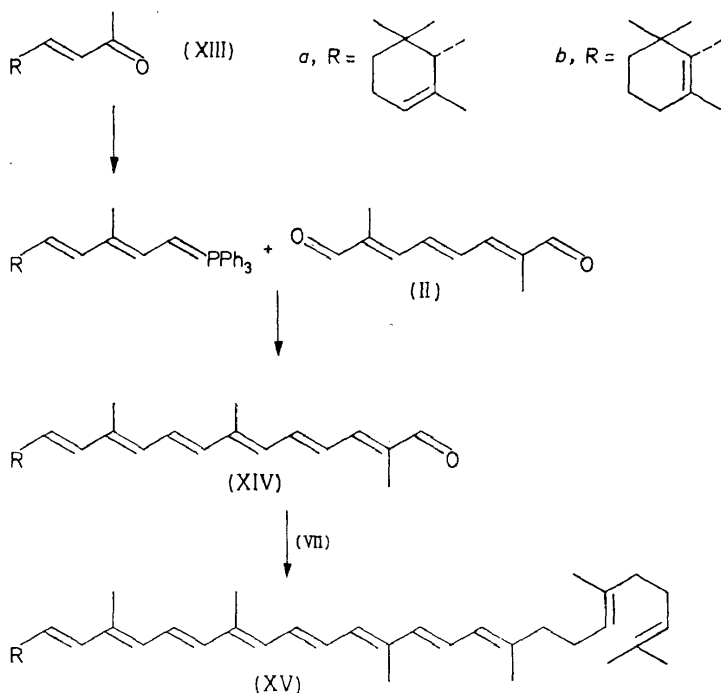
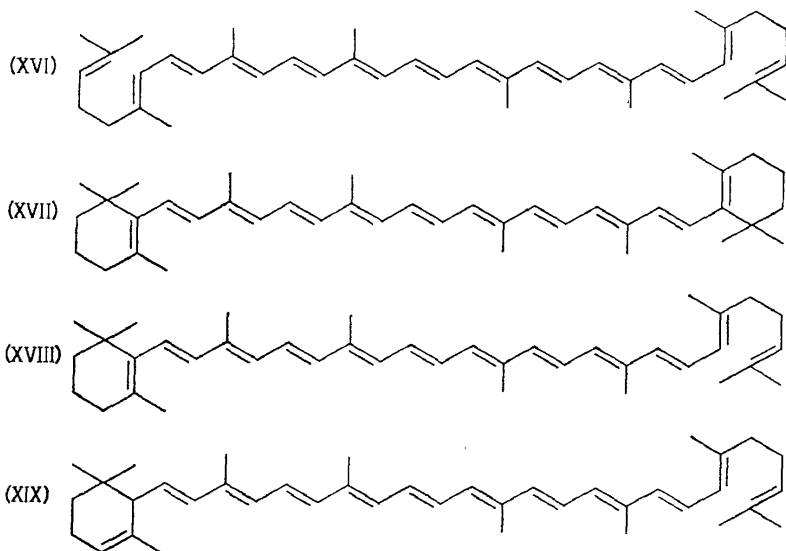
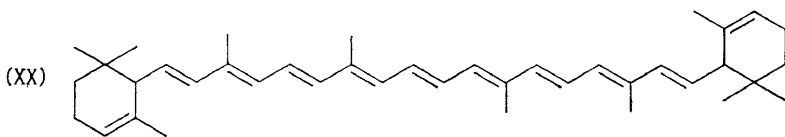


Figure 3. Synthesis of (\pm)- α - and β -zeacarotene (XVa and XVb respectively)

Wittig reactions based on the same C₁₀-dial (II) again provide convenient syntheses of lycopene (XVI)¹⁶, β -carotene (XVII)¹⁷, γ -carotene (XVIII)¹⁶, δ -carotene (XIX)¹⁶, and ϵ -carotene (XX)¹⁶.



SOME STUDIES ON CAROTENOID SYNTHESIS



The unique carotenoids of the photosynthetic bacteria have also attracted a great deal of attention in recent years. Three such pigments from *Rhodospseudomonas* species, chloroxanthin, spheroidene, and spheroidenone, were formulated as (XXII), (XXIII), and (XXVII) respectively on the basis of structural studies^{10, 11}, but the evidence was not conclusive until backed by synthesis (Figures 4 and 5)^{11, 18, 19}. It is clear from these structures that the

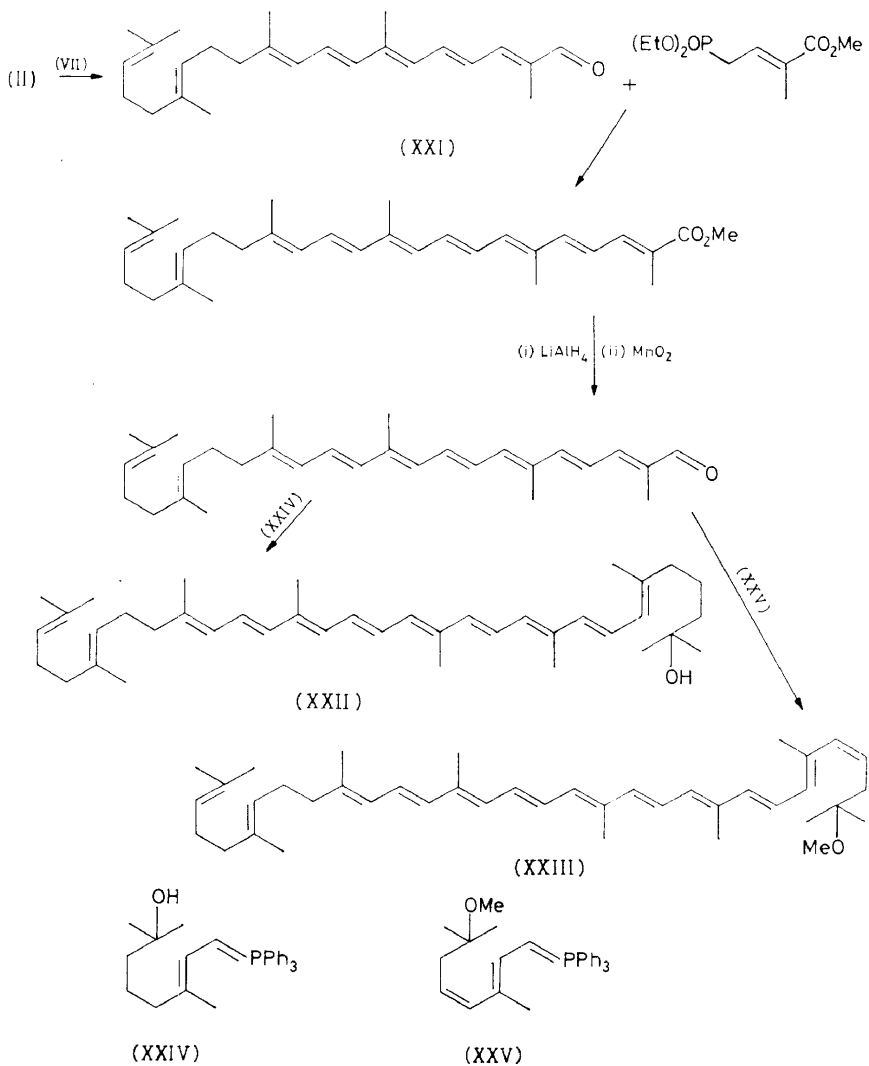


Figure 4. Synthesis of chloroxanthin (XXII) and all-trans spheroidene (XXIII).

B. C. L. WEEDON

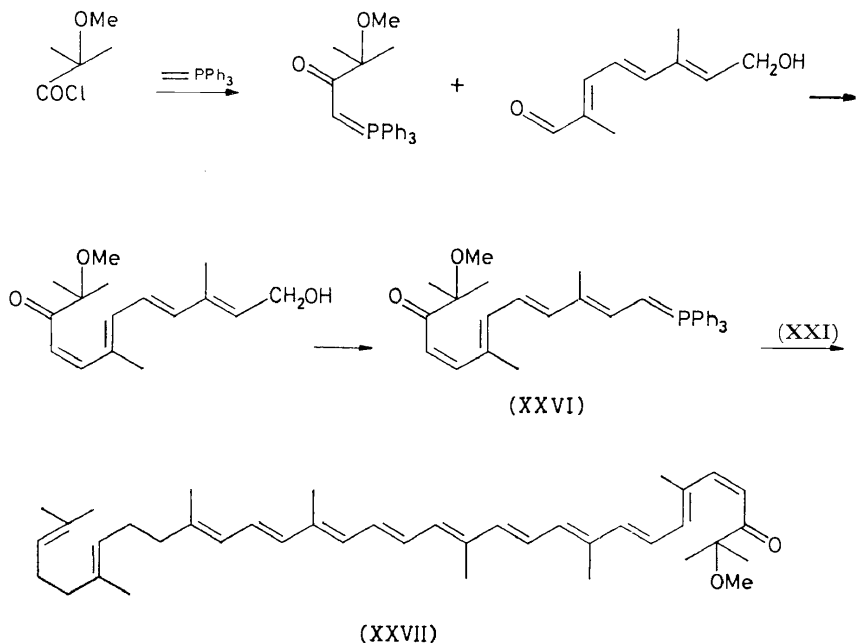
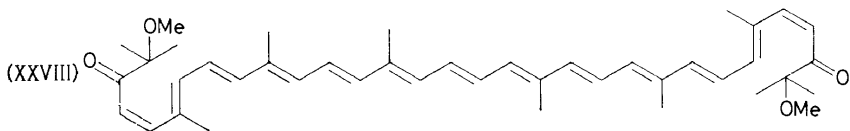


Figure 5. Synthesis of all-*trans* spheroidenone

main *Rhodospseudomonas* pigments are formed from neurosporene (XII) by processes analogous to those involved in the formation of spirilloxanthin (XLVIII; R = Me) from lycopene (XVI) in purple photosynthetic bacteria^{11, 20}. The structure (XXVIII) assigned²¹ to "P 518", a rare pigment from some *Rhodospseudomonas* species, has also been confirmed by synthesis from the C₁₀-dial (II) and the Wittig reagent (XXVI)¹⁹; an alternative route to (XXVIII) has been described by Isler *et al.*²²



Syntheses based on the C₂₀-dials

After many alternative structures had been rejected, capsanthin, capsorubin and kryptocapsin, three pigments found in paprika, were shown to possess an unique cyclopentane end group²³⁻²⁷. Synthesis²⁸ (Figure 6) of an optically inactive form of capsorubin (XXIX) by aldol condensation of crocetinindial (V) with the (\pm)-methyl ketone (XXX) confirmed the position of the substituents on the five membered rings, and proved that the two oxygen substituents are *trans* (cf. ref. 24) and not *cis* (cf. ref. 29) to one another.

SOME STUDIES ON CAROTENOID SYNTHESIS

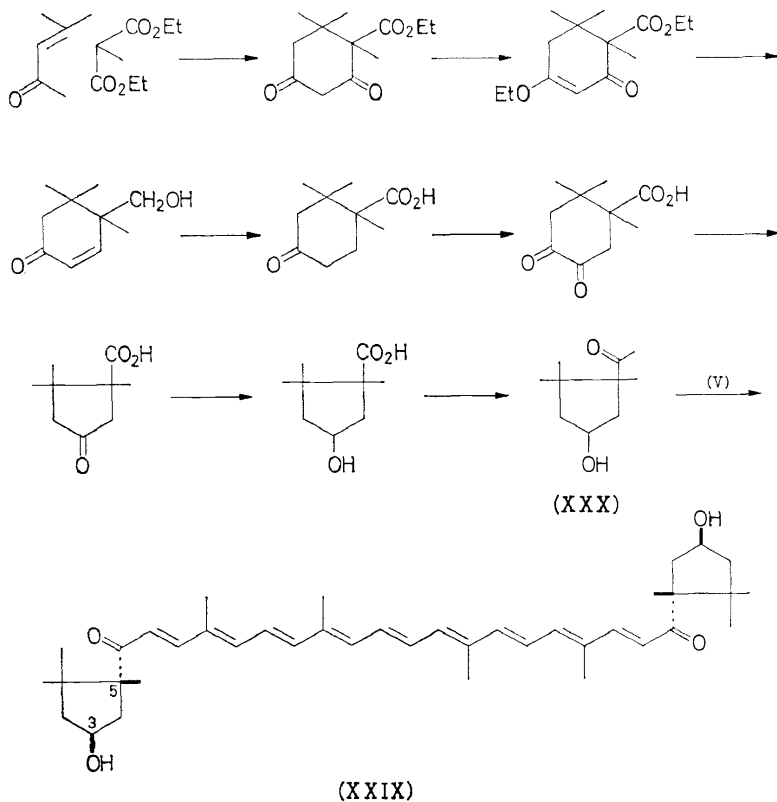
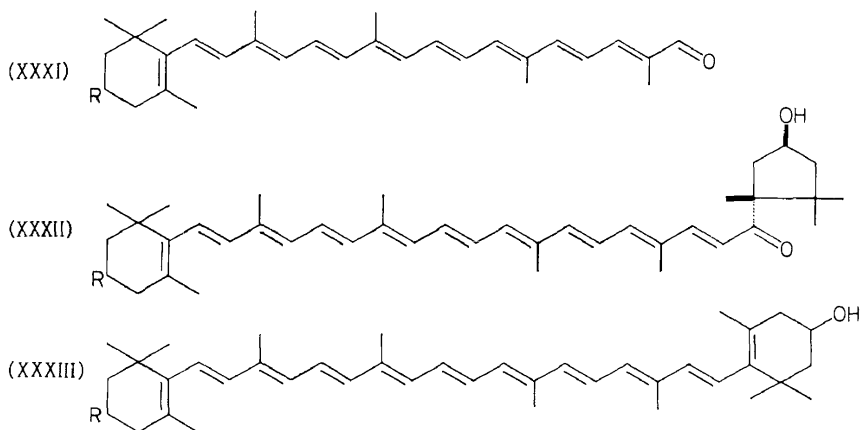


Figure 6. Synthesis of capsorubin

Similarly kryptocapsin (XXXII; R = H) was prepared from C₃₀-apo-8'-β-carotenal (XXXI; R = H)²⁷, and capsanthin (XXXII; R = OH), on a spectral scale, from natural β-citraurin (XXXI; R = OH)³⁰.



Several total syntheses of the (\pm)-methyl ketone (XXX) have been developed^{28, 31}. Recently an enantiomorph of (XXX) has been prepared from natural camphor³¹ and this opens the way to the synthesis of optically active forms of the paprika ketones. It should thus be possible to check the conclusion^{28, 32} that the characteristic end groups of the paprika ketones have the 3 S, 5 R configuration shown in (XXIX)[†] and (XXXII).

Oxygenated derivatives of β -carotene (XXXIV; X = Y = a) occur widely in Nature. The first unambiguous synthesis of canthaxanthin (XXXIV; X = Y = d) and echinenone (XXXIV; X = a, Y = d) was achieved by an aldol route from crocetindial (V) and C₃₀-apo-8'- β -carotenal (XXXI; R = H) respectively³⁴. A superior route³⁵ to both carotenoids is summarized in Figure 7. Methods based on the reaction of β -carotene with N-bromosuccinimide in the presence of alcohol or acetic acid have received much attention by other workers (cf. Figure 8)³⁶⁻³⁸.

The availability of 4- and 4,4'-oxygenated derivatives of β -carotene has prompted a number of investigations on their conversion into other carotenoids. Some transformations that have been carried out on several of the

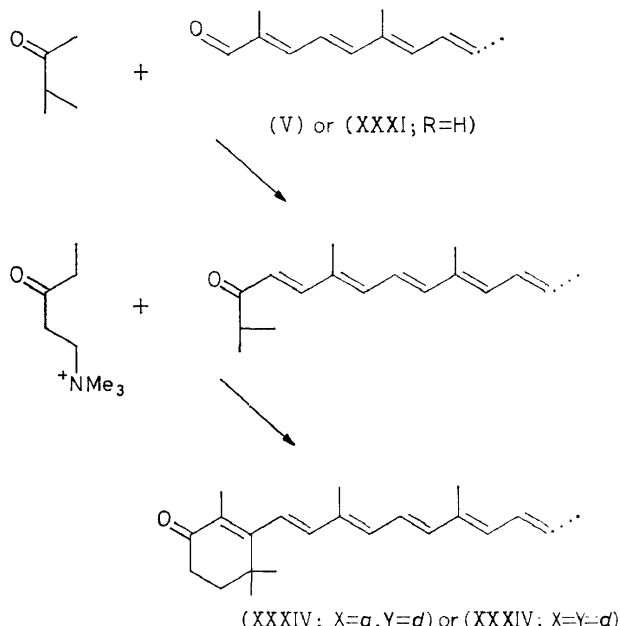
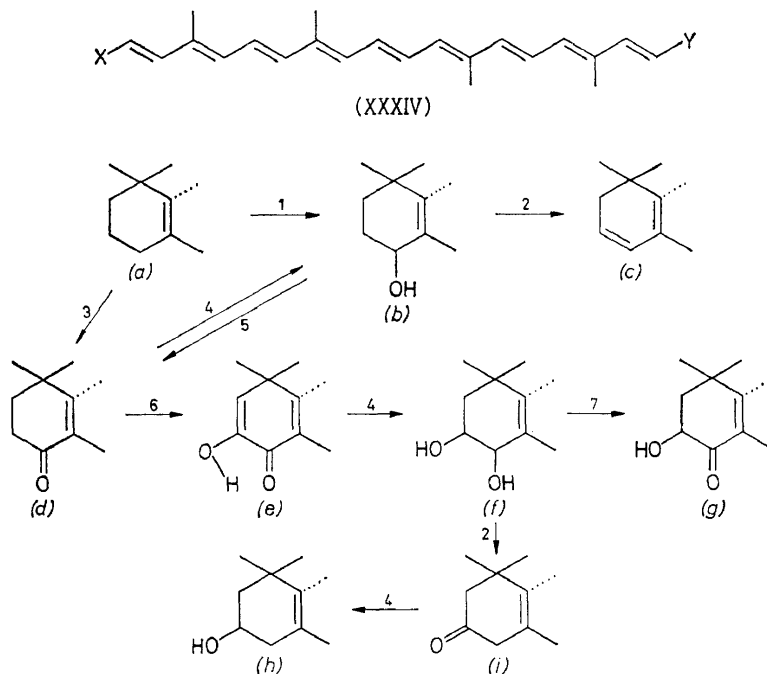


Figure 7. Synthesis of echinenone (XXXIV; X = a, Y = d) and canthaxanthin (XXXIV; X = Y = d) from C₃₀-apo-8'- β -carotenal (XXXI; R = H) and crocetindial (V) respectively

[†] The formula for capsorubin given in ref. 14 indicates the *trans* arrangement of the two oxygen substituents on the five membered rings; it does not correctly represent the conclusion concerning absolute configuration. Since the paprika ketones are believed to be derived in Nature from zeaxanthin (XXXIII; R = OH) and kryptoxanthin (XXXIII; R = H) by transformations not involving the oxygen substituent at C-3²³⁻²⁵, it is probable that the hydroxylated end groups in zeaxanthin and kryptoxanthin have a 3 R configuration^{14, 28} (the same stereochemistry at C-3 is represented as S in one series and R in the other on the purely conventional application of the sequence rule³³).

SOME STUDIES ON CAROTENOID SYNTHESIS

compounds in this series, or their 15,15'-dehydro-analogues, are summarized in *Figure 8*. The 4-oxo end groups (*d*) are readily converted into the diosphenols (*e*) by autoxidation in the presence of potassium *t*-butoxide^{14, 39}; thus canthaxanthin (XXXIV; X = Y = *d*) yields astacene (XXXIV; X = Y = *e*) almost quantitatively^{14, 39}. Under appropriate conditions the intermediate tri-ketone (XXXIV; X = *e*, Y = *d*) may be isolated¹⁴, and has been used to confirm the structure (XXXIV; X = *g*, Y = *d*) proposed⁴⁰ for phoenicoxanthin, which is probably identical with adonirubin⁴¹. By appropriate combinations of the reactions indicated in *Figure 8*, the first total synthesis of astaxanthin (XXXIV; X = Y = *g*) has been achieved⁴².

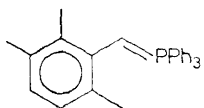


- | | |
|--|--|
| 1. (i) NBS/CHCl ₃ -HOAc. (ii) KOH | 5. dichlorodicyanoquinone |
| 2. HCl/CHCl ₃ | 6. O ₂ / <i>t</i> -BuOK |
| 3. NBS/CHCl ₃ -EtOH | 7. CH ₃ ·CO·CH ₃ /(<i>t</i> -BuO) ₃ Al |
| 4. KBH ₄ | |

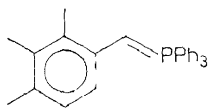
Figure 8. Syntheses of oxy- and oxo-derivatives of β -carotene

Autoxidation of echinenone (XXXIV; X = *a*, Y = *d*) gives the diosphenol (XXXIV; X = *a*, Y = *e*)¹⁴, which may be converted into hydroxy-echinenone (XXXIV; X = *a*, Y = *g*)⁴². The latter has not as yet been compared directly with either the pigment from *Euglena gracilis*⁴³ or that from *Adonis annua* L.⁴¹ for which this structure has been proposed, but comparison of the authentic diosphenol (XXXIV; X = *a*, Y = *e*) with euglenanone shows that the structure suggested⁴³ for this carotenoid is untenable¹⁴. Similarly it is hoped to examine many of the other structures

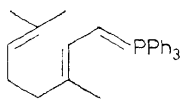
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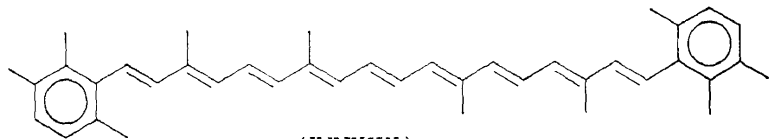
(XXXV)



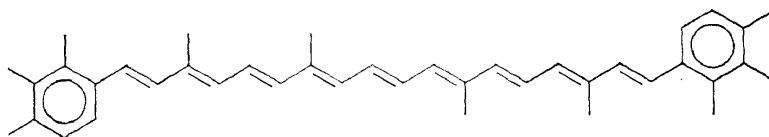
(XXXVI)



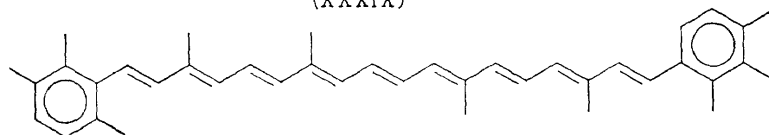
(XXXVII)



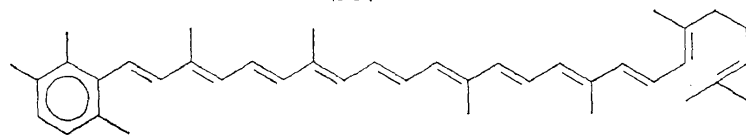
(XXXVIII)



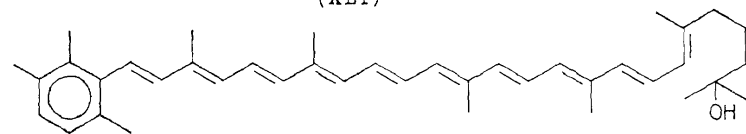
(XXXIX)



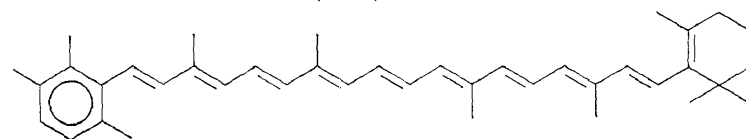
(XL)



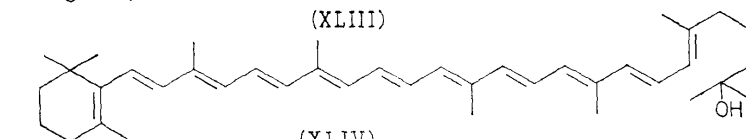
(XLI)



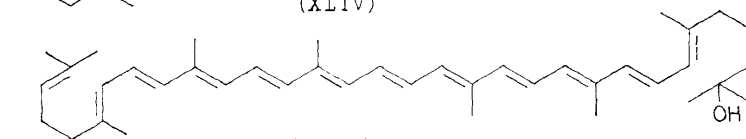
(XLII)



(XLIII)



(XLIV)



(XLVII)

SOME STUDIES ON CAROTENOID SYNTHESIS

which have been put forward for compounds involved in the biosynthesis of phoenicoxanthin and astaxanthin. New syntheses of kryptoxanthin (XXXIV; $X = h, Y = a$) and zeaxanthin (XXXIV; $X = Y = h$)^{14, 44} by the routes summarized in *Figure 8* also deserve mention.

A few years ago Yamaguchi⁴⁵ reported the first examples of natural aromatic carotenoids. By reacting crocetindial (V) with the Wittig reagents (XXXV) and (XXXVI) derived from the appropriate benzyl halides, we were able to make isorenieratene (XXXVIII), renierapurpurin (XXXIX) and renieratene (XL) comparatively readily available⁴⁶. Subsequently, in collaboration with Dr. S. L. Jensen⁴⁷, Grundmann and Takeda's leptotene from *Mycobacteria*⁴⁸ was identified with synthetic isorenieratene (XXXVIII), thus solving one further long outstanding structural problem.

Recently Jensen *et al.*⁴⁹ reported the occurrence of aromatic carotenoids

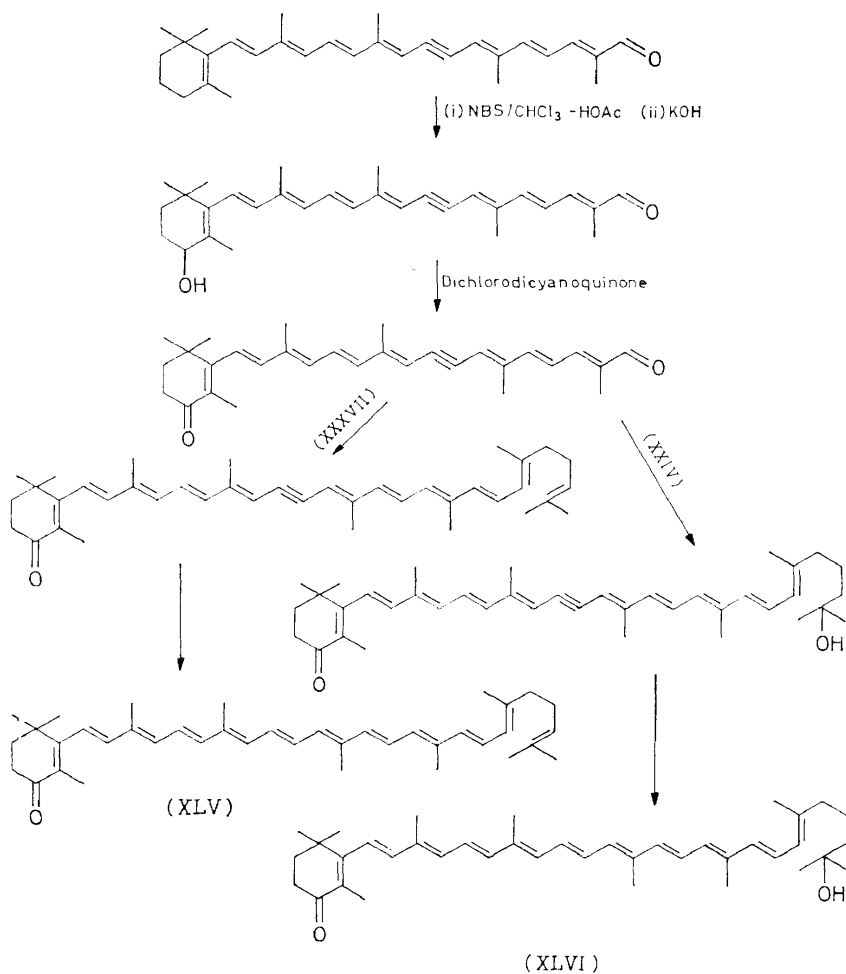


Figure 9. Synthesis of 4-oxo- γ -carotene (XLV) and its 1'-hydroxy-1',2'-dihydro derivative (XLVI)

in green photosynthetic bacteria (*Chlorobia*). Using the two step Wittig synthesis with the reagents (XXXVII) or (XXIV) and (XXXV), the structures which they proposed for chlorobactene (XLI) and "OH-chlorobactene" (XLII) were confirmed, dispelling the slight doubt concerning the location of one of the aromatic methyl groups⁵⁰.

It is interesting to note that β -isorenieratene (XLIII), a pigment of *Phaeobium*⁵¹, and the hydroxy-dihydro- γ -carotene (XLIV), a minor pigment of *Mycobacterium phlei* strain Vera⁵², were first identified by direct comparisons with specimens which we had synthesized previously in other connections^{46, 50}. The structures (XLV) and (XLVI) of two other carotenoids from *Mycobacterium phlei*⁵² were also confirmed by synthesis (Figure 9)⁵³.

The revised structure (XLVII) of rhodopin⁵⁴, a key intermediate in the biosynthesis of many bacterial carotenoids, has been rigorously proved by synthesis from crocetinindial (V) and the reagents (XXXVII) and (XXIV)⁵⁰. Subsequently the synthesis of rhodopin, and some related pigments, was reported by Surmatis *et al.*⁵⁵ Earlier Surmatis and Ofner⁵⁶ used Wittig routes based on crocetinindial (V) to prepare spirilloxanthin (XLVIII; R = Me), an important constituent of many purple photosynthetic bacteria. An alternative synthesis⁵⁷ of this pigment is outlined in Figure 10. This route has also been

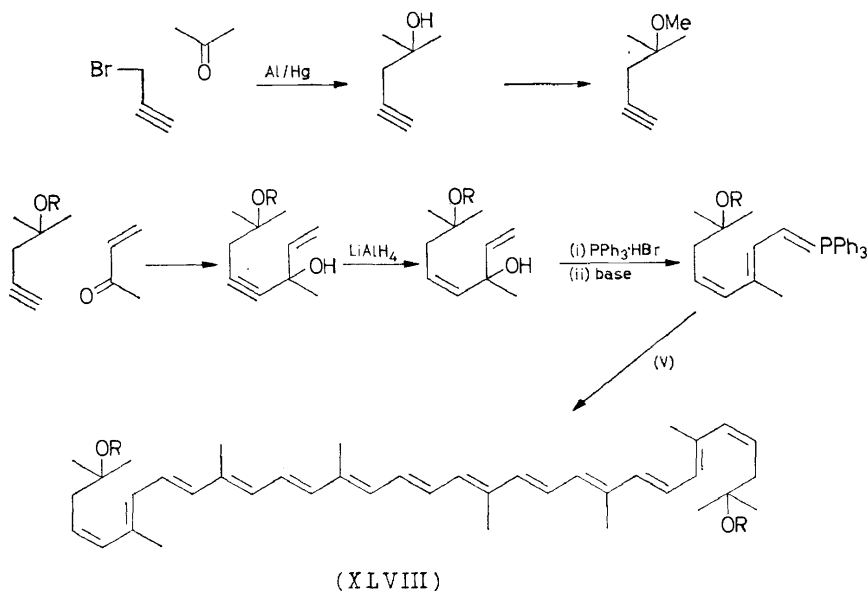


Figure 10. Synthesis of all-*trans* spirilloxanthin (XLVIII; R = Me) and " α -bacterioruberin" (XLVIII; R = H)

used⁵⁷ to obtain a compound with the structure (XLVIII; R = H) proposed⁵⁸ for α -bacterioruberin, the pigment of many *Halobacteria*; in this case, however, significant differences in properties between the synthetic and natural carotenoids point to the need for a reinvestigation of the latter compound. Many similar situations will doubtless arise the more we use

SOME STUDIES ON CAROTENOID SYNTHESIS

synthesis to probe the tentative structures assigned to various carotenoids. We shall still regard such results as positive contributions by the synthetic method to the study of these important, but often rare, natural compounds.

Finally I should like to thank my many collaborators to whose skill and enthusiasm any success we have achieved has been largely due. In particular I would like to mention Drs. R. Ahmad, P. Mildner, C. K. Warren, and M. Akhtar who were responsible for much of the early work, Drs. J. B. Davis, R. D. G. Cooper, and P. T. Siddons who opened up many new areas, and Messrs. A. A. Spark, C. W. Price, P. S. Manchand, R. Bowden, A. P. Leftwick, and Dr. D. F. Schneider who have carried out our more recent work.

References

- 1 P. Mildner and B. C. L. Weedon. *J. Chem. Soc.* 3294 (1953); cf. *Chem. and Ind.* 239 (1953).
- 2 R. Ahmad and B. C. L. Weedon. *J. Chem. Soc.* 3286 (1953).
- 3 H. H. Inhoffen, O. Isler, G. von der Bey, G. Raspé, P. Zeller, and R. Ahrens. *Liebigs Ann. Chem.* **580**, 7 (1953).
- 4 H. H. Inhoffen and G. von der Bey. *Liebigs Ann. Chem.* **583**, 100 (1953).
- 5 R. Rüegg, H. Lindlar, M. Montavon, G. Saucy, S. F. Schaeren, U. Schwieter, and O. Isler. *Helv. Chim. Acta* **42**, 847 (1959).
- 6 H. Pommer. *Angew. Chem.* **72**, 911 (1960).
- 7 O. Isler, H. Gutmann, H. Lindlar, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller. *Helv. Chim. Acta* **39**, 463 (1956).
- 8 O. Isler, H. Lindlar, M. Montavon, R. Rüegg, and P. Zeller. *Helv. Chim. Acta.* **39**, 249 (1956).
- 9 R. Ahmad and B. C. L. Weedon. *Chem. and Ind.* 882 (1952).
- 10 J. B. Davis, L. M. Jackman, P. T. Siddons, and B. C. L. Weedon. *Proc. Chem. Soc.* 261 (1961).
- 11 J. B. Davis, L. M. Jackman, P. T. Siddons, and B. C. L. Weedon. *J. Chem. Soc. C* 2154 (1966).
- 12 H. Claes, *Z. Naturforsch.* **16B**, 445 (1961).
- 13 P. S. Manchand, P. T. Siddons, and B. C. L. Weedon, unpublished results.
- 14 B. C. L. Weedon. In *Chemistry and Biochemistry of Plant Pigments*, (Ed. T. W. Goodwin), Academic Press, London, 1965.
- 15 R. Rüegg, U. Schwieter, G. Ryser, P. Schudel, and O. Isler. *Helv. Chim. Acta* **44**, 994 (1961).
- 16 P. S. Manchand, R. Rüegg, U. Schwieter, P. T. Siddons, and B. C. L. Weedon. *J. Chem. Soc.* 2019 (1965).
- 17 H. Freyschlag, H. Grassner, A. Nürrenbach, H. Pommer, W. Reif, and W. Sarnecki. *Angew. Chem. internat. Edit.* **4**, 287 (1965).
- 18 P. S. Manchand and B. C. L. Weedon. *Tetrahedron Letters* No. 37, 2603 (1964).
- 19 P. S. Manchand and B. C. L. Weedon. *Tetrahedron Letters* No. 9, 989 (1966).
- 20 S. L. Jensen. *Ann. Rev. Microbiol.* **19**, 163 (1965).
- 21 L. M. Jackman and S. L. Jensen. *Acta Chem. Scand.* **18**, 1403 (1964).
- 22 U. Schwieter, R. Rüegg, and O. Isler. *Helv. Chim. Acta* **49**, 992 (1966).
- 23 M. S. Barber, L. M. Jackman, C. K. Warren, and B. C. L. Weedon. *Proc. Chem. Soc.* 19 (1960).
- 24 M. S. Barber, L. M. Jackman, C. K. Warren, and B. C. L. Weedon. *J. Chem. Soc.* 4019 (1961).
- 25 R. Fentschel and P. Karrer. *Helv. Chim. Acta* **43**, 89 (1960).
- 26 L. Cholnoky and J. Szaboles. *Experientia* **16**, 483 (1960).
- 27 L. Cholnoky, J. Szaboles, R. D. G. Cooper, and B. C. L. Weedon. *Tetrahedron Letters* No. 19, 1257 (1963).
- 28 R. D. G. Cooper, L. M. Jackman, and B. C. L. Weedon. *Proc. Chem. Soc.* 215 (1962).
- 29 H. Faigle and P. Karrer. *Helv. Chim. Acta* **44**, 1257 (1961).
- 30 R. D. G. Cooper and B. C. L. Weedon, unpublished results.
- 31 R. D. Bowden and B. C. L. Weedon, unpublished results.
- 32 J. W. Faigle, H. Müller, W. von Philipsborn, and P. Karrer. *Helv. Chim. Acta.* **47**, 741 (1964).
- 33 R. S. Cahn, C. K. Ingold, and V. Prelog. *Experientia* **12**, 81 (1956).
- 34 C. K. Warren and B. C. L. Weedon. *J. Chem. Soc.* 3986 (1958).
- 35 M. Akhtar and B. C. L. Weedon. *J. Chem. Soc.* 4058 (1959).
- 36 F. J. Petracek and L. Zechmeister. *J. Amer. Chem. Soc.* **78**, 1427 (1956).
- 37 R. Fentschel and P. Karrer. *Helv. Chim. Acta* **41**, 402 (1958).

B. C. L. WEEDON

- ³⁸ P. Zeller, F. Bader, H. Lindlar, M. Montavon, P. Müller, R. Rüegg, G. Ryser, G. Saucy, S. F. Schaeren, U. Schwieter, K. Stricker, R. Tamm, P. Zürcher, and O. Isler. *Helv. Chim. Acta* **42**, 841 (1959).
- ³⁹ J. B. Davis and B. C. L. Weedon. *Proc. Chem. Soc.* 182 (1960).
- ⁴⁰ D. L. Fox and T. S. Hopkins. *Comp. Biochem. Physiol.* **17**, 841 (1966).
- ⁴¹ L. K. Egger. *Phytochem.* **4**, 609 (1965).
- ⁴² A. P. Leftwick and B. C. L. Weedon. *Chem. Comm.* 49 (1967).
- ⁴³ N. I. Krinsky and T. H. Goldsmith. *Arch. Biochem. Biophys.* **91**, 271 (1960).
- ⁴⁴ C. W. Price and B. C. L. Weedon, unpublished results.
- ⁴⁵ M. Yamaguchi. *Bull. Chem. Soc. Japan* **30**, 111, 979 (1957); **31**, 51, 739 (1958); **32**, 1171 (1959); **33**, 1560 (1960).
- ⁴⁶ R. D. G. Cooper, J. B. Davis, and B. C. L. Weedon. *J. Chem. Soc.* 5637 (1963).
- ⁴⁷ S. L. Jensen and B. C. L. Weedon. *Naturwiss.* **51**, 482 (1964); cf. O. Okukado and M. Yamaguchi. *Bull. Chem. Soc. Japan* **38**, 1043 (1965).
- ⁴⁸ C. Grundmann and Y. Takeda. *Naturwiss.* **25**, 27 (1937).
- ⁴⁹ S. L. Jensen, E. Hegge, and L. M. Jackman. *Acta Chem. Scand.* **18**, 1703 (1964).
- ⁵⁰ R. Bonnett, A. A. Spark, and B. C. L. Weedon. *Acta Chem. Scand.* **18**, 1739 (1964).
- ⁵¹ S. L. Jensen. *Acta Chem. Scand.* **19**, 1025 (1965).
- ⁵² S. Hertzberg and S. L. Jensen. *Acta Chem. Scand.* **20**, 1187 (1966).
- ⁵³ A. P. Leftwick and B. C. L. Weedon. *Acta Chem. Scand.* **20**, 1195 (1966).
- ⁵⁴ S. L. Jensen. *Acta Chem. Scand.* **13**, 842, 2142 (1959).
- ⁵⁵ J. D. Surmatis, A. Ofner, J. Gibas, and R. Thommen. *J. Org. Chem.* **31**, 186 (1966).
- ⁵⁶ J. D. Surmatis and A. Ofner. *J. Org. Chem.* **28**, 2735 (1963).
- ⁵⁷ D. F. Schneider and B. C. L. Weedon. *J. Chem. Soc.* in the press.
- ⁵⁸ S. L. Jensen. *Acta Chem. Scand.* **14**, 950 (1960).