Improved *O*-Methylation of Carotenoids

GERD NYBRAATEN and SYNNØVE LIAAEN-JENSEN

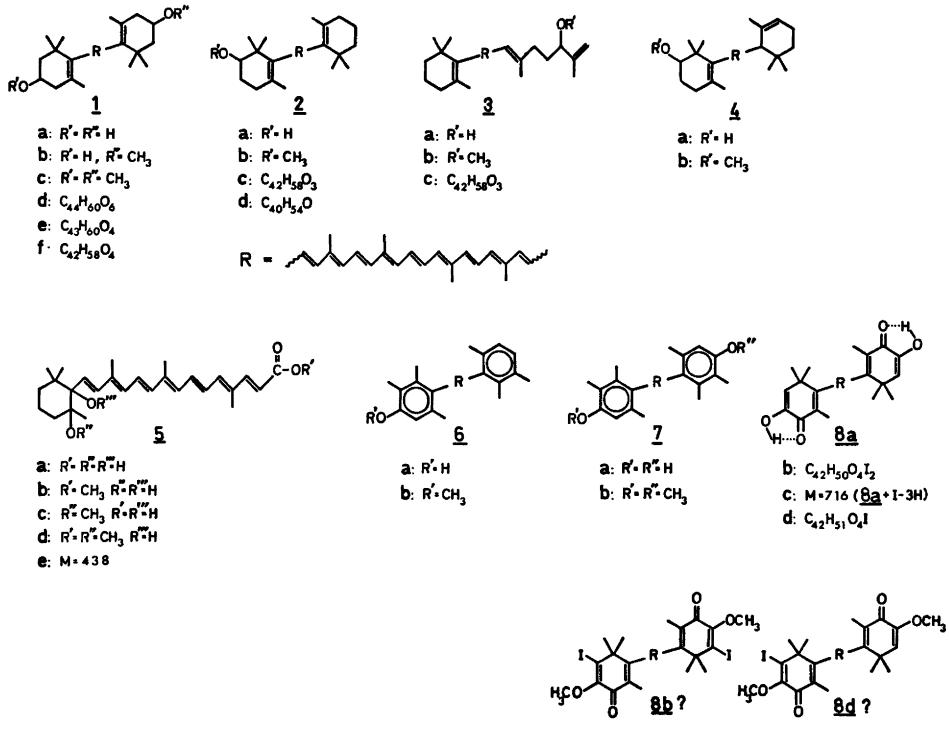
Organic Chemistry Laboratories, Norwegian Institute of Technology, University of Trondheim, N-7034-Trondheim, Norway

Methods available for *O*-methylation of carotenoids have recently been reviewed.[1] These include selective methylation of allylic, secondary hydroxy groups by hydrogen chloride in methanol [2–4] and methylation of non-allylic secondary hydroxy groups with methyl iodide and potassium *t*-amyloxide [5] or better by the Kuhn procedure [6–10] with methyl iodide and silver oxide or barium oxide in dimethylformamide or dimethylformamide/dimethyl sulfoxide. By the latter procedure tertiary hydroxy group may also be methylated.[11] Methylation of enolic and phenolic hydroxy groups in the carotenoid series is not achieved with diazomethane.[12–13]

In the present work, the original Kuhn procedure with silver oxide [6] was shown to result in abnormal products for zeaxanthin (*1a*) and *β,β*-caroten-2-ol (*2a*), Scheme 1. Zeaxanthin (*1a*) gave three products *1d, e, f* more polar than zeaxanthin dimethyl ether (*1c*) with unchanged electronic spectrum and molecular ion *m/e* 684.4392 (684.4390 calc. for $C_{44}H_{60}O_6$), 640 and 626 respectively, and with fragment ions M − 14, M − 30, M − 44, and M − 60 in addition to M − 92 and M − 106 ascribed to eliminations from the polyene chain.[14] Product *1d* has formally added $2 \times C_2H_2O_2$, and the molecular ions of *1e* and *1f* are compatible with the addition of ($C_2H_2O_2 + CH_2$) and $C_2H_2O_2$, respectively. *β,β*-Caroten-2-ol (*2a*) gave a product *2c* (20 % of recovered carotenoid; 45 % total recovery), more polar than the methyl ether *2b*, with molecular ion *m/e* 610, again compatible with a formal addition of $C_2H_2O_2$. The same type of abnormal product has recently been observed for aleuriaxanthin (*3a*).[15]

The BaO/DMF modification [7] gave for *β,β*-caroten-2-ol (*2a*) 49 % pigment recovery, 25 % thereof was a didehydro-*2a* = *2d* (4 nm hypsochromic shift in methanol, *m/e* 550.4170 = M = $C_{40}H_{54}O$).

The BaO-DMF/DMSO procedure,[8] tested for zeaxanthin (*1a*), *β,β*-caroten-2-ol (*2a*),[10] and *β,ε*-caroten-2-ol (*4a*) gave the desired methyl ethers. Thus zeaxanthin (*1a*) gave the dimethyl ether (*1c*, 30 % of recovered carotenoid), the mono-



Scheme 1.

methyl ether (*1b*, 20 %), and unreacted *1a* (50 %); total pigment recovery 50 % after 40 h. β,ε-Caroten-2-ol (*4a*) gave the methyl ether *4b* (35 % of recovered carotenoid) and unreacted *4a*; total pigment recovery 48 %.

These results demonstrate that the Kuhn procedures[6,7] may give abnormal products in the carotenoid series. Yields of methylated products are variable, *cf.* Refs. 9 and 4, and particularly unsatisfactory for secondary, sterically hindered alcohols (*2a*[10] and *4a*) and tertiary alcohols.[11]

Recently Stoochnoff and Benoiton[16] reported that methyl iodide and sodium hydride in tetrahydrofuran effect methylation of weakly acidic or sterically hindered hydroxy groups. The potentiality of this method in the carotenoid series has now been studied:

Secondary, allylic hydroxyl. Aleuriaxanthin (*3a*) gave the methyl ether *3b* (60 % of recovered carotenoid) besides unreacted *3a*; total pigment recovery 66 %.

The methyl ether *3b* had *m/e* 566 (M), 550.4176 (M−CH_4; calc. for $C_{40}H_{54}O$ 550.4175), M−28, M−79, M−92, M−106, M−158.

Secondary, non-allylic hydroxyl. Zeaxanthin (*1a*) gave the monomethyl ether *1b* (15 % of recovered carotenoid) and the dimethyl ether *1c* (85 %); total recovery 92 %. Both methyl ethers exhibited the predicted molecular ions and M−31, M−92, M−106, and M−158 fragment ions; *1b* also an M−18 ion.

Sterically, hindered hydroxyl. β,ε-Caroten-2-ol (*4a*) gave the methyl ether *4b* (60 % of recovered carotenoid) and unreacted *4a*; total recovery 72 %.

Azafrin (*5a*) gave (24 h, room temperature) the methyl ester *5b* (50 % of recovered pigment), *5e* (20 %) and unreacted *5a*; total recovery 85 %. Modified conditions (45 °C, 5 h, 20 °C, 12 h) gave small amounts of the presumed monomethyl ether *5c* and the presumed methyl ester monomethyl ether *5d*; total recovery 75 %.

The methyl ester *5b* had electronic spectrum like azafrin (*5a*), *m/e* 440 (M), M−18, M−31 *etc.*; inseparable from authentic *5b* on cochromatography. Silylation afforded the mono(trimethylsilyl) ether, *m/e* 512 (M); *cf.* Ref. 17.

Phenolic hydroxyl. 3-Hydroxyisorenieratene (*6a*) gave the methyl ether *6b* (100 % of recovered carotenoids) and unreacted *6a*; pigment recovery 80 %. 3,3′-Dihydroxyisorenieratene (*7a*) provided the dimethyl ether *7b* (100 % of recovered carotenoid); pigment recovery 30 %.

Enolic hydroxyl. Astacene (*8a*), see Scheme 1, gave products *8b* (60 % of recovered carotenoid), *8c* (15 %) and *8d* (25 %); pigment recovery 25 %. All products had electronic spectra (round) like canthaxanthin (β,β-caroten-4,4′-dione).

Product *8b* had *m/e* 872.1762 (calc. 872.1799 for $C_{42}H_{50}O_4I_2$), M−78, M−92, M−106, and M−158 ascribed to elimination from the polyene chain,[14] M−126 (?) and double peaks at both *m/e* 127 and *m/e* 128 partly ascribed to I^+ and HI^+. No phenazine derivative[1] was obtained with *o*-phenylenediamine under conditions where astacene (*8a*) gave such derivatives.

Product *8c* had *m/e* 716 (M), M−15, M−92, M−106, M−126 and double peaks at both *m/e* 127 and *m/e* 128.

Product *8d* had *m/e* 746 (M, compatible with $C_{42}H_{51}O_4I$), M−92, M−126 (?) and double peaks at both *m/e* 127 and *m/e* 128.

Data for products *8b* and *8c* are consistent with the structures suggested in Scheme 1. The assumed mechanism for their formation involves abstraction of a proton by the hydride to a resonance stabilized enolate/carbanion, followed by *O*-methylation by methyl iodide and a synchronous or subsequent Michaeltype addition of iodide to C-2. That hydride, rather than iodide, serves as leaving group on reforming the keto group in 4-position, is unexpected. Alternative *C*-methylation should lead to products capable of forming a phenazine derivative.

Only one other iodine derivative of carotenoids is previously described, namely "isocarotintetraiodid",[18] now considered to be a π-complex.[19]

Conclusion. *O*-Methylation with methyl iodide and sodium hydride seems to represent a rather universal method in the carotenoid series.

Thus methylation of phenolic carotenoids was achieved for the first time. Enolic hydroxy groups like in astacene (*8a*) also appear to undergo *O*-methylation, but complications in form of iodinated products arose.

The results obtained indicate that the CH_3I/NaH procedure is superior to previous methods for methylation of non-allylic and allylic (to one double bond) secondary hydroxy groups, including sterically hindered ones.

Judged by the results for azafrin (*5a*) tertiary hydroxy groups appear to be rather unreactive and carboxylic acids provide methyl esters.

Experimental details are reported elsewhere.[20] General conditions used for *O*-methylation with CH_3I/NaH were: To the carotenoid (0.1−1.0 mg) in dry tetrahydrofuran (2 ml) was added freshly distilled CH_3I (1 ml) and NaH (40 mg). The reaction mixture was kept at room temperature in darkness in inert atmosphere for 16−24 h, and worked up in the usual manner. The products were purified by TLC. R_F-values on kieselguhr paper (Schleicher and Schüll No. 287) of the compounds studied are given below with the percentage acetone in petroleum ether used for development given in parenthesis: *1a* 0.40 (10), *1b* 0.39 (2), *1c* 0.89 (2), *1d* 0.58 (2), *1e* 0.65 (2), *1f* 0.31 (2), *2a* 0.85 (5), *2b* 0.55 (0), *2c* 0.93 (2), *2d* 0.40 (0), *3a* 0.45 (2), *3b* 0.54 (0), *4a* 0.54 (1), *4b* 0.86 (1), *5a* 0.0 (100), *5b* 0.72 (5), *6a* 0.52 (5), *6b* 0.68 (2), *7a* 0.27 (10), *7b* 0.85 (5), *8a* 0.40 (10), *8b* 0.72 (10), *8c* 0.69 (10) and *8d* 0.42 (10 %).

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1. Liaaen-Jensen, S. In Isler, O., Ed., *Carotenoids*, Birkhäuser, Basel 1971, p. 77.
2. Petracek, F. J. and Zechmeister, L. *J. Amer. Chem. Soc. 78* (1956) 1427.
3. Curl, L. *J. Food Res. 21* (1956) 689.
4. Liaaen-Jensen, S. and Hertzberg, S. *Acta Chem. Scand. 20* (1966) 1703.
5. Karrer, P. and Takahashi, T. *Helv. Chim. Acta 16* (1933) 1163.
6. Kuhn, R., Trischmann, H. and Löw, I. *Angew. Chem. 67* (1955) 32.
7. Kuhn, R., Baer, H. H. and Seeliger, A. *Justus Liebigs Ann. Chem. 611* (1958) 236.
8. Wallenfels, K., Bechtler, G., Kuhn, R., Trischmann, H. and Egge, H. *Angew. Chem. 75* (1963) 1014.
9. Müller, H. and Karrer, P. *Helv. Chim. Acta 48* (1965) 291.
10. Nybraaten, G. and Liaaen-Jensen, S. *Acta Chem. Scand. B 28* (1974) 485.
11. Liaaen-Jensen, S. *Kgl. Nor. Vidensk. Selsk. Skr.* (1962) No. 8.
12. Kuhn, R., Lederer, E. and Deutsch, A. *Hoppe-Seyler's Z. Physiol. Chem. 220* (1933) 229.
13. Nybraaten, G. and Liaaen-Jensen, S. *Acta Chem. Scand. 25* (1971) 370.
14. Vetter, W., Englert, G., Rigassi, N. and Schwieter, U. In Isler, O., Ed., *Carotenoids*, Birkhäuser, Basel 1971, Chapter VI.
15. Arpin, N., Kjøsen, H., Francis, G. W. and Liaaen-Jensen, S. *Phytochemistry 12* (1973) 2751.
16. Stoochnoff, B. A. and Benoiton, N. L. *Tetrahedron Lett. 71* (1973) 21.
17. McCormick, A. and Liaaen-Jensen, S. *Acta Chem. Scand. 20* (1966) 1989.
18. Kuhn, R. and Lederer, E. *Ber. Deut. Chem. Ges. B 65* (1932) 639.
19. *Unpublished data.*
20. Nybraaten, G. *Thesis*, Norwegian Inst. Technology, Univ. Trondheim, Trondheim 1973.

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The Reaction between Phosphonium Ylides and Isocyanates, a Convenient Route to Ketenimines

PAUL FRØYEN

Chemical Institute, University of Bergen, N-5014 Bergen, Norway

Reactions of phosphonium ylides with isocyanates have been reported in a few papers. In 1919 Staudinger and Meyer [1] found that triphenyl ketenimine (II) could be prepared from phenyl isocyanate by reaction with diphenylmethylene triphenylphosphorane (I; $R^1 = R^2 =$ Ph)

$$Ph_3P{=}CR^1R^2 + Ph{-}N{=}C{=}O \rightarrow$$

(I)

$$Ph{-}N{=}C{=}C\begin{matrix}R^2\\ \diagup\\ \\ \diagdown\\ R^1\end{matrix} + Ph_3P{=}O$$

(II)

Although this was the first preparation of a ketenimine, no yield was reported and no attempt was made to extend the synthesis to other ketenimines. Later, however, Trippett and Walker [2] studied the reactions of phenyl isocyanate with a series of ylides, but no ketenimine was formed during these reactions. It was reported that the reaction between the "non-stabilized" ylide dimethylmethylene triphenylphosphorane (I; $R^1 = R^2 = CH_3$) and phenyl isocyanate stops at the betaine stage. In other cases, when the ylide under investigation contained an α-hydrogen atom, migration of that hydrogen occurred, a new ylide being formed:

$$Ph_3P{=}CHR + Ph{-}N{=}C{=}O \rightarrow$$

$$Ph_3\overset{+}{P}{-}CHR \quad \overset{-}{O}{-}\overset{|}{C}{=}NPh \rightarrow Ph_3P{=}CR{-}C(O)NHPh$$

Finally, Ratts and Partos [3] attempted the following reaction:

$$Ph_3P{=}C{=}C{=}CPh_2 + CH_3N{=}C{=}O \rightarrow$$

$$Ph_2C{=}C{=}C{=}C{=}NCH_3$$

(III)

and were able to isolate the amide of the cumulene imine (III). As far as the present author knows, there have been no other attempt to make ketenimines along this route. Thus, no ordinary ketenimine, except the one synthesized by Staudinger and Meyer has been prepared by