An Alternative Synthesis of (7-Methoxy-3,7-dimethyloct-2-enyl)triphenylphosphonium Bromide

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(7-Methoxy-3,7-dimethyloct-2-enyl)triphenylphosphonium bromide (*1*) is a convenient intermediate in the total synthesis of various carotenoids containing the 1-methoxy-1,2-dihydro end group.

This Wittig salt (*1*) was first prepared by Surmatis and Ofner [1] in four steps from methyl heptenone (*2*) according to scheme 1. The initial step involved acid-catalysed addition of methanol to give 6-methoxy-6-methyl-2-heptanone (*3*). Aasen and Liaaen Jensen [2] later prepared *1* from *3* according to scheme 2, the Wittig reaction of the ketone (*3*) proceeding with low yield. By using a Horner reaction [3,4] of *3* with triethylphosphonoacetate the yield in this step has now been increased to 73 % (with E. Øverland).

A one step synthesis of (7-methoxy-3,7-dimethyloct-2-enyl)triphenylphosphonium bromide (*1*) from linalool (*4*) and triphenylphosphonium bromide with simultaneous acid-catalysed addition of methanol to the isopropylidene double bond is now reported, scheme 3. Under optimal conditions the reaction product contained *1* (85 %) and geranyltriphenylphosphonium bromide (*5*, 15 %). Separation of *1* and *5* could not be achieved by TLC or fractional crystallisation, but provided the final products of the Wittig reaction can be readily separated, the present method appears to be a convenient alternative for the synthesis of *1*.

The reaction was discovered incidentally during the synthesis of 7,7'-[^{2}H$_2$]-lycopene [5] when two carotenoids having added one and two moles of methanol in 1,2(1',2')-positions were isolated. This result could be ascribed to a methoxylated component in the deuterated geranyl Wittig salt used. The Wittig salt had been prepared in methanol,[1] and it was assumed that methanol addition to the isopropylidene double bond was catalysed by hydrogen bromide derived from triphenylphosphonium bro-

mide, *cf.* steps *2-3* in scheme 1. The optimal conditions for the formation of *1* were further studied.

By an elegant method Surmatis and Ofner [1] have obtained (7-hydroxy-3,7-dimethyloct-2-enyl)triphenylphosphonium bromide in 90 % yield on boiling the geranyl Wittig salt (*5*) in water. Treatment of *5* with methanol and catalytic amounts of acid did not give high yields of the methoxylated derivative (*1*), and it appears that the addition of methanol preferentially occurs during the formation of the Wittig salt from linalool (*4*). Linalool (*4*) could be replaced by geraniol (*6*). Selective addition of methanol to *4* and *6* did not occur at the conditions used for the preparation of *1*.

Experimental. The mixed Wittig salts were precipitated from methylene chloride-ethyl acetate and the ratio of (7-methoxy-3,7-dimethyloct-2-enyl)triphenylphosphonium bromide (*1*) and geranyltriphenylphosphonium bromide (*5*) determined from the PMR spectrum using the methoxy signal of *1* and the allylic methylene signals for *1* and *5* as main indicators.

Addition of methanol to geranyltriphenylphosphonium bromide (5). Stirring of *5* (3 g) in methanol (24 ml) and 0.01 M HBr in methanol (1 ml) for 20 h at room temperature, or for 28 h at reflux, gave no *1*. Stirring of *5* (5 g) in methanol (50 ml) containing conc. H$_2$SO$_4$ (4 drops) for 70 h at room temperature gave *1:5* = 16:84. Refluxing of *5* (3.5 g) in methanol (25 ml) containing conc. H$_2$SO$_4$ (2 drops) gave *1:5* = 36:65.

Addition of methanol during formation of (7-methoxy-3,7-dimethyloct-2-enyl)triphenylphosphonium bromide (1) from linalool (4). Stirring of *4* (10 g) and ϕ_3PHBr (20 g) in methanol (50 ml) containing 0.01 M HBr in methanol (2 ml) gave *1:5* = 28:72. Further treatment of the product (3 g) in methanol (50 ml) containing 0.01 M HBr (4 ml) in a sealed tube at 100°C for 24 h gave *1:5* = 33:67. *4* (2.5 g) and ϕ_3PHBr (5 g) in methanol (25 ml) containing conc. H$_2$SO$_4$ (2 drops) was refluxed for 24 h, ratio *1:5* = 50:50. *4* (2 g) and ϕ_3PHBr (5 g) in methanol (50 ml) containing conc. H$_2$SO$_4$ (4 drops) was refluxed and aliquots withdrawn. After 96 h the ratio *1:5* = 85:15, and after 140 h *1:5* = 96:4. However, after 140 h a contaminant identified by PMR as methyltriphenylphosphonium bromide had appeared. This contaminant could be partly removed by fractional crystallisation.

Addition of methanol during the formation of (7-methoxy-3,7-dimethyloct-2-enyl)triphenylphosphonium bromide (1) from geraniol (6)
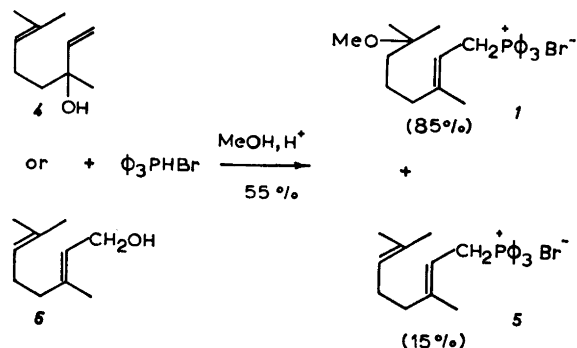
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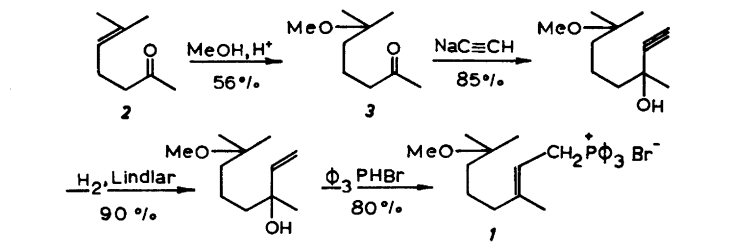
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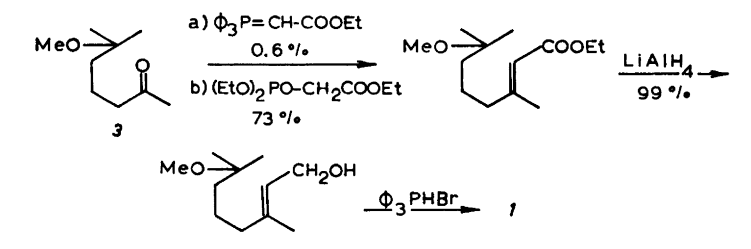
SCHEME 3

Geraniol (*6*, 1.54 g) and ϕ_3PHBr (3.43 g) in methanol (25 ml) containing conc. H_2SO_4 (2 drops) was refluxed for 96 h, ratio *1:5* = 80:20.

Characterisation of (7-methoxy-3,7-dimethyloct-2-enyl)triphenylphosphonium bromide (1). Equimolar amounts of *4* and ϕ_3PHBr (0.02 moles) in acidic methanol (50 ml, 4 drops H_2SO_4) at optimal conditions (96 h, reflux) gave

55 % of the mixed Wittig salts after recrystallisation from $CHCl_3$-ethyl acetate. In mixture with geranyltriphenylphosphonium bromide (*5*, *ca.* 15 %) *1* was a white solid, m.p. 149—152°C (reported[1] 168—171 for pure *1*) and exhibited characteristic signals (C_2HCl_3) at τ 3.2 m (15 H, aromatic), 4.85 t (1 H, olefinic, $J = 6$ cps), 5.4 dd (2 H, CH_2-P, $J_{CH-CH_2} = 6$

cps, $J_{CH_3-P}=15$ cps), 6.87 s (3 H, OCH₃), 8.0 m (2 H, allylic CH₂), ca. 8.6 m (ca. 7 H, CH₂ and 2 CH₂), and 8.92 s (6 H, 2 CH₂ at tert. OCH₃).

On reaction with crocetindial the mixed Wittig salts (1 and 5) gave lycopene, 1-methoxy-1,2-dihydro-lycopene and 3,4,3′,4′-tetrahydrospirilloxanthin.[5]

Effect of acidic methanol on linalool (4) and geraniol (6). 4 (2 g) and 6 (2 g) in methanol (10 ml) containing conc. H_2SO_4 (1 drop) were treated separately at room temperature for 20 h. No new products were formed (no allylic rearrangement of 4). 4 (6 g) and 6 (6 g) in methanol (25 ml) containing conc. H_2SO_4 (2 drops) were refluxed separately for 34 h. A complex mixture of methoxylated and cyclised products was obtained.

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1. Surmatis, J. D. and Ofner, A. *J. Org. Chem.* **28** (1963) 2735.
2. Aasen, A. J. and Liaaen Jensen, S. *Acta Chem. Scand.* **21** (1967) 371.
3. Horner, L., Hoffman, H. and Wippel, H. G. *Chem. Ber.* **91** (1958) 61.
4. Wadsworth, W. S. and Emmonds, W. D. *J. Am. Chem. Soc.* **83** (1961) 1733.
5. Kjøsen, H., Liaaen-Jensen, S. and Enzell, C. R. *Acta Chem. Scand.* To be published.

Studies on Flavin Derivatives

VIII.* The Crystal and Molecular Structure of 9-Bromo-3,7,8,10-tetramethylisoalloxazine Monohydrate

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In connection with studies on flavin derivatives undertaken at this Institute the crystal and molecular structure of 9-bromo-3,7,8,10-tetramethylisoalloxazine monohydrate, $C_{14}H_{13}BrN_4O_2 \cdot H_2O$, has been determined by X-ray diffraction

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methods in order to obtain structural information about a flavin derivative in an oxidized, neutral state.

Single crystals suitable for X-ray work were obtained by recrystallization from an acetic acid solution of a specimen prepared by L. Maron[1] at this Institute. The crystal structure ($P2_1/c$, $a=13.047\pm5$ Å, $b=7.053\pm5$ Å, $c=17.957\pm5$ Å, $\beta=120.40\pm5°$, $Z=4$) was solved by the heavy-atom method on the basis of the 1381 independent, most significant reflections registered
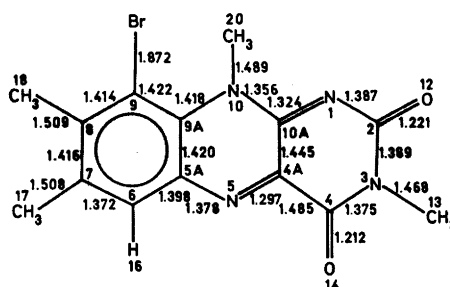

Fig. 1.

with Cu$K\alpha$ radiation using a Siemens automatic single-crystal diffractometer. The structure was refined by full-matrix least-squares techniques including anisotropic thermal parameters for the non-hydrogen atoms and isotropic parameters for the hydrogens to a final R value of 0.052.

The dimensions of the molecule are given in Fig. 1. The estimated standard deviations are 0.012 Å for distances between non-hydrogen atoms and around 0.25° for the the angles (Fig. 2).

The ring skeleton is essentially planar. The largest deviation of any atom from a least-squares plane through all fourteen non-hydrogen atoms in the three rings is less than 0.1 Å.

The bond lengths within the molecule obtained in the present study are in good agreement with the values for 7,8,10-trimethylisoalloxazine calculated by Grabe[2] using Pariser-Parr-Pople selfconsistent-field molecular orbital method on the π-system of the molecule. The calculated values of distances and π-bond orders and the corresponding observed bond lengths are: