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226. Novel Synthesis of 3,5,5-Trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one, a Major Constituent of *Burley* Tobacco Flavour

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(2. IX. 74)

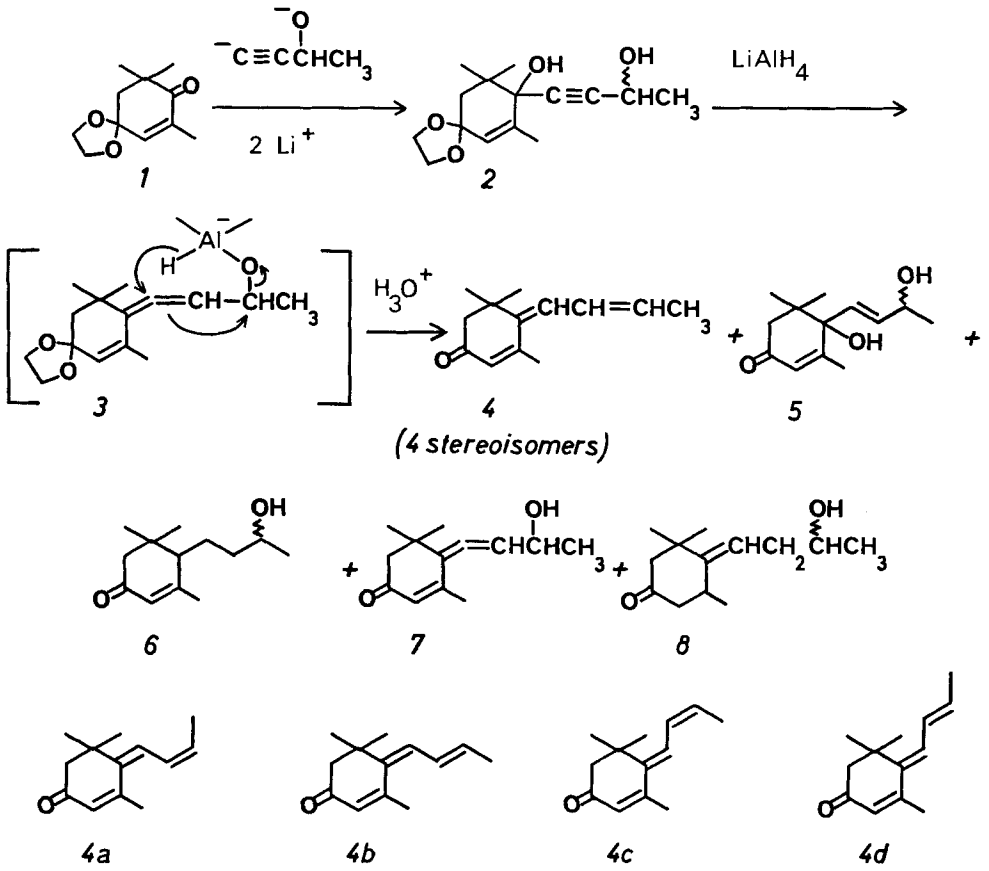
Summary. The acetylenic diol **2**, prepared by reaction of but-3-yn-2-ol dianion with 2,6,6-trimethyl-4,4-ethylenedioxy-cyclohex-2-en-1-one (**1**), afforded 3,5,5-trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one (**4**), a major constituent of *Burley* tobacco flavour, upon $LiAlH_4$ reduction and hydrolysis. Vomifoliol (**5**) and blumenol C (**6**) were major by-products in this reaction.

Burley tobacco condensate contains as much as 10% of 3,5,5-trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one (**4**) [1] [2]. This key flavouring compound, which also occurs in Greek [3a] and Turkish [4] tobaccos, was first synthesized by *Rowland* in 1965 [5] (from dehydroionone), and more recently by *Enzell*'s group [3] (from α-ionone). Both these syntheses, however, constitute unpractical processes hardly applicable to a desired 10–100 g scale production of **4**.

We have devised a more efficient, two-step procedure starting from 2,6,6-trimethyl-4,4-ethylenedioxy-cyclohex-2-en-1-one (**1**) [6]. According to *Pearson*'s theory [7], this unsaturated ketoacetal may be expected to add soft bases in the 1,4-manner, while relatively hard bases of little steric requirement should preferentially give 1,2-addition products. Accordingly, we found that acetylenic diol **2** was produced in excellent yield (90%, mixture of diastereoisomers) when but-3-yn-2-ol dianion [8] was allowed to react with acetal **1** in a *Nef*-type reaction. Subsequent reduction of the 2-yn-1,4-diol structure in **2** could be accomplished in about 30% yield through a one-step conjugate displacement of *both* OH groups by hydride ion, a reaction which most likely involves the intermediacy of the allenoxyaluminohydride complex **3**. Such a two-fold hydrogenolysis of propargylic hydroxyl groups, first rationalised by *Lutz et al.* [9] in the case of the $LiAlH_4$ reduction of 1,1,4,4-tetraphenylbut-2-yn-1,4-diol, has been proposed by *Claesson & Bogentoft* [10] as a procedure for preparing conjugated dienes from acetylenic, tertiary diols.

3,5,5-Trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one (**4**) was thus obtained in a 27% yield from acetal **1**. Gas liquid chromatography showed this ketone to be a (readily equilibrating?) 1:7:1,5:10 mixture of the four stereoisomers **4a–d**, the structures of which were recently resolved by *Aasen et al.* [3a]. Ketone **4** occurs in tobacco as a mixture of stereoisomers too.

The above synthesis afforded *vomifoliol* (**5**) [11] and *blumenol C* (**6**) [11b] (or stereoisomers thereof) as major by-products, together with allenic alcohol **7**, a logical intermediate in the $LiAlH_4$ reduction of **2**, and its tetrahydro-derivative **8**. Worthy of mention is the fact that both vomifoliol and blumenol C were also isolated from *Burley* tobacco flavour[1]).



Experimental Part

The spectra were measured on the following instruments: IR. spectrometer *Perkin-Elmer* 720; UV. spectrometers *Optica* CF4 N.I. and *Beckmann*; mass spectrometer *Atlas* CH4 IV 58 (*Atlas Werke* AG); NMR. spectrometers *Bruker* HFX-90/3–15 inch (90 MHz) and *Hitachi Perkin-Elmer*

[1]) *E. Demole & D. Berthet*, unpublished results. Blumenol C (**6**) was also independently identified as a new tobacco constituent by *A. J. Aasen et al.* (*Swedish Tobacco Co*) [12], and by *D. L. Roberts et al.* (*R. J. Reynolds Tobacco Co*) (private communications).

R 20 B (60 MHz). The melting points were determined in vacuum sealed capillary tubings and are not corrected.

1. *1-(3-Hydroxybut-1-yn-1-yl)-2, 6, 6-trimethyl-4, 4-ethylenedioxy-cyclohex-2-en-1-ol* (**2**). But-3-yn-2-ol (63 g, 0.9 mol) was added over a 30 min period to a stirred solution of lithium (12.5 g, 1.8 mol) and ferric nitrate (1.2 g) in liquid ammonia (2.5 l) (temperature $-35/-40°$). After 1.5 h of additional stirring, there was added 2,6,6-trimethyl-4,4-ethylenedioxy-cyclohex-2-en-1-one (**1**) [6] (117.5 g, 0.6 mol, in 250 ml of anhydrous ether) over 1 h at the same temperature and the mixture was further stirred for 15 h at $-35°$. Ammonium chloride (200 g) was added in several portions, and the reaction mixture allowed to warm up to room temperature while the evaporated ammonia was progressively replaced by the same volume of ether. After filtration, evaporation to dryness and thorough drying of the residue at 50°/0.001 Torr, there was obtained 144 g (90% yield) of crude acetylenic diol **2**.

This product proved to be a mixture of the two expected diastereoisomers which could be separated by shaking crude **2** (30 g) with 100 ml of ether/hexane 3:1, keeping the resulting suspension overnight at $-30°$, and collecting the crystals (14.1 g, m.p. 125–130–133°). The *erythro*-structure was assigned[2]) to this diastereoisomer, the m.p. of which rose to 143–145° after five further crystallizations carried out alternatively in ether/ethyl acetate and benzene as solvents. The *threo*-diastereoisomer[2]) was obtained by evaporating the mother liquors of the *erythro*-isomer, thus affording 14.5 g of an amorphous substance, b.p. 158–162°/0.001 Torr. Both diastereoisomers displayed virtually identical spectral properties in agreement with structure **2**. The *erythro*-isomer had IR. (KBr): ν = 940, 975, 1015, 1080, 1660, 3250 cm^{-1}; MS.: M^+ = 266, base peak *m/e* 210, prominent *m/e* 43 fragment; NMR. (DMSO-d^6): δ = 0.93 (3 H, *s*), 1.03 (3 H, *s*), 1.30 (3 H, *d*, J = 7 Hz), 1.80 (5 H, narrow *m*), 3.80 (4 H, *s*), 4.35 (1 H, br. *m*), 5.03 (2 H, br. *s*, OH), 5.20 (1 H, br. *s*).

$C_{15}H_{22}O_4$ (266.33) Calc. C 67.64 H 8.33% Found C 67.86 H 8.28%

2. *3,5,5-Trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one* (**4**). Crude diol **2** (72 g, 0.27 mol, in 375 ml of anhydrous tetrahydrofuran) was added over a 30 min period to a refluxing solution of lithium aluminium hydride (25 g, 0.659 mol) in anhydrous ether (1.5 l) with efficient stirring. The reaction mixture was still refluxed and stirred for 52 h, cooled at 0°, and decomposed by cautiously adding 100 ml of water over 45 min. After 30 min of further stirring, the mixture was filtered, the solvents were removed *in vacuo*, and the residue was taken up in 100 ml of 5% sulfuric acid and 1 l of acetone. The resulting solution was set aside for 15 h at room temperature, an excess of 10% solution of sodium carbonate was added under efficient stirring, most of the acetone solvent was evaporated and the concentrate extracted twice with ether. After usual work-up, there remained 41 g of crude 3,5,5-trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one (**4**) giving the characteristic gas liquid chromatogram shown below (*fig.*). This mixture was first distilled (b.p. 65–100°/0.001 Torr, 30 g; residue 11 g) and the distillate subjected to a chromatographic fractionation on 600 g of silicagel[3]). Ketone **4** was eluted with 2:1 to 2:3 toluene/ethyl acetate mixture: b.p. 84–88°/0.005 Torr, 15 g (29.2% yield); d_4^{20} = 0.973; n_D^{20} = 1.5846; IR. (neat): ν = 965, 1280, 1580, 1625, 1660 cm^{-1}; MS.: M^+ = 190 (base peak), other prominent fragments at *m/e* 175, 148, 147, 133, 119, 105, 91, 77, 69; NMR. (CCl_4): δ = 1.18 (3 H, 2 *s*), 130 (3 H, *s*), 1.7–2.0 (3 H, *m*), 2.0–2.4 (5 H, *m*), 5.5–7.0 (4 H, *m*).

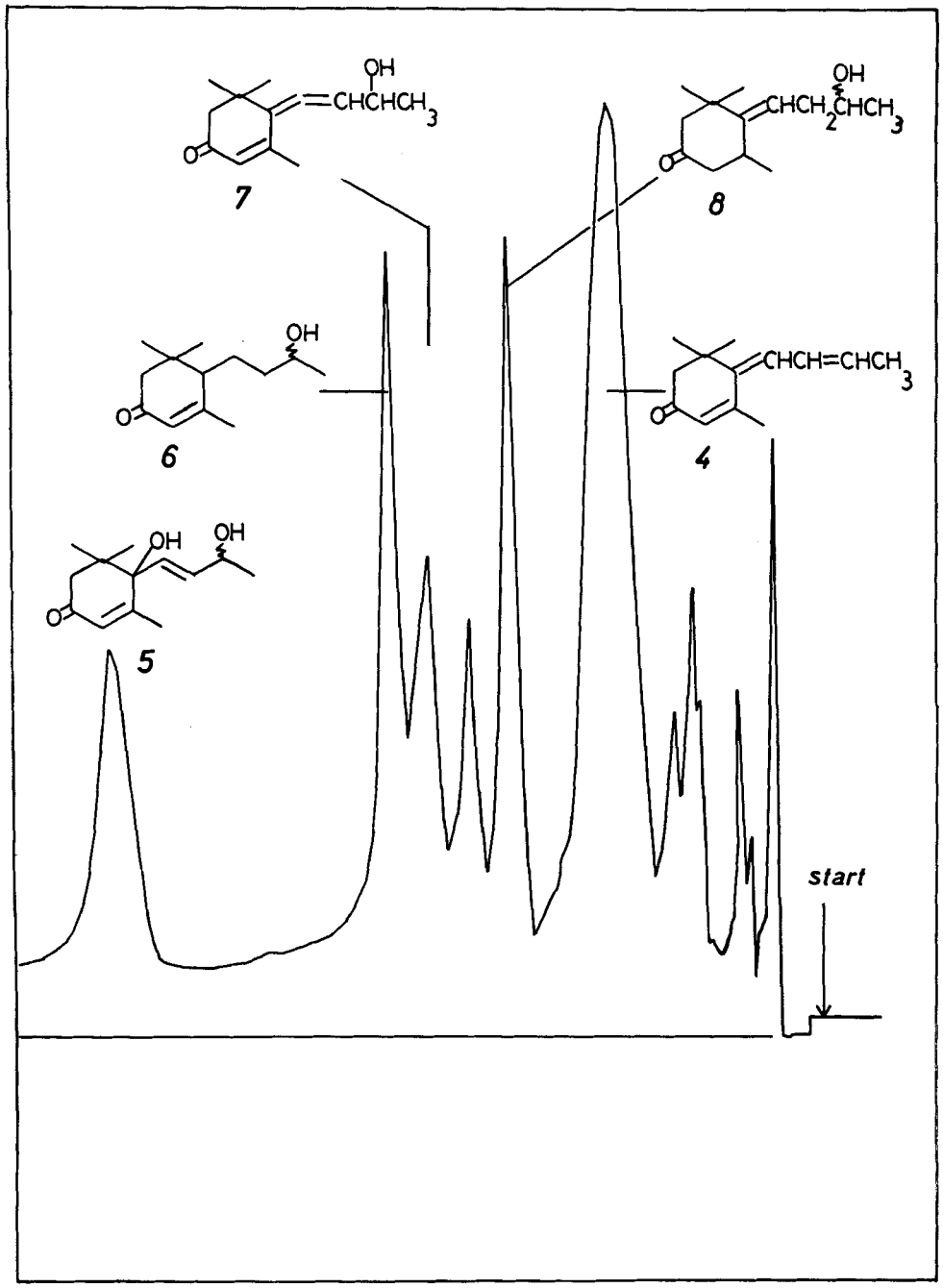
$C_{13}H_{18}O$ (190.28) Calc. C 82.06 H 9.54% Found C 81.86 H 9.82%

GLC. showed this compound to be a 1.0:7.0:1.5:10 mixture of stereoisomers **4a–d** [2.5 m column packed with 5% *Carbowax 20 M* on *Chromosorb W*, 190°; relative retention times: 1.0 (**4a**), 1.15 (**4b**), 1.39 (**4c**), 1.56 (**4d**). A similar separation pattern was observed on a OV-101 50 m × 0.3 mm capillary column at 140°].

3. *Vomifoliol* (**5**). The distillation residue of the crude ketone **4** obtained above (11 g) was taken up in about 100 ml of ether and the solution stored for several days at $-30°$; 3.1 g of crystals were collected and recrystallized twice in ether and benzene, successively, affording pure vomifoliol (**5**): m.p. 89–92°; IR. (KBr): ν = 965, 1015, 1110, 1645, 3380 cm^{-1}; UV.: λ_{max} (EtOH) = 239 nm, ε = 12300; MS.: M^+ = 224 (weak), base peak *m/e* 124; NMR. ($CDCl_3$): δ = 0.98 (3 H, *s*)

[2]) This stereochemical assignment will be discussed in a forthcoming paper.

[3]) «Kieselgel 0.05–0.2 mm für die Säulen-Chromatographie» (*Merck* AG).



Gas liquid chromatogram of crude 3,5,5-trimethyl-4-(2-butenylidene)-cyclohex-2-en-1-one (**4**). Instrument: *Perkin-Elmer* 881. Conditions: 2.5 m column packed with 5% *Carbowax 20 M* (*Varian Aerograph AG*) on *Chromosorb W* (*Johns-Manville*); 230°, 4 min isothermal, then +6°/min up to 260°; chart speed $^1/_4$″ min

1.05 (3 H, *s*), 1.27 (3 H, *d*, J = 6.5 Hz), 1.90 (3 H, *d*, $J = \sim 1$ Hz), 2.32 (2 H, *q* AB, J = 17 Hz), 2.55–3.00 (2 H, *m*, OH), 4.37 (1 H, br. *m*), 5.80 (3 H, narrow *m*).

$C_{13}H_{20}O_3$ (224.30) Calc. C 69.61 H 8.99% Found C 69.46 H 8.81%

4. *Blumenol C* (**6**). This compound was isolated from crude ketone **4** by preparative GLC. (see *fig.*). IR. (neat): ν = 1120, 1255, 1295, 1380, 1650, 3450 cm^{-1}; MS.: M^+ = 210, base peak *m/e* 43, other prominent peaks at *m/e* 177, 150, 135, 123, 108, 95, 93, 69; NMR. ($CDCl_3$): δ = 1.00 (3 H, *s*), 1.05 (3 H, *s*), 1.18 (3 H, *d*, J = 6 Hz), 1.98 (3 H, *d*, $J = \sim 1$ Hz), 2.20 (2 H, *q*, *AB*, J = 17 Hz), 1.3–2.2 (5 H, *m*), 3.75 (2 H, *m* + *s*), 5.78 (1 H, *s*).

5. *Allenic ketol* **7**. This compound was also isolated by preparative GLC. (see *fig.*) and exhibited the following properties: IR. (neat): ν = 925, 1075, 1100, 1115, 1265, 1360, 1375, 1595, 1650, 1930, 3430 cm^{-1}; MS.: M^+ = 206, base peak *m/e* 147, other prominent ions at *m/e* 162, 106, 45, 43; NMR. ($CDCl_3$): δ = 1.17 (6 H, *s*), 1.35 (3 H, *d*, J = 6 Hz), 2.00 (3 H, *s*), 2.35 (2 H, *s*), 3.25 (1 H, br. *s*, OH), 4.45 (1 H, *m*), 5.80 (2 H, *s* + *d*).

6. *3,3,5-Trimethyl-4-(3-hydroxybutylidene)-cyclohexan-1-one* (**8**). Like the two preceding compounds, this substance was isolated by preparative GLC. of crude ketone **4** (see *fig.*). IR. (neat): ν = 935, 1040, 1070, 1110, 1235, 1370, 1450, 1700, 3450 cm^{-1}; MS.: M^+ = 210, base peak *m/e* 109, other prominent fragments at *m/e* 166, 151, 82, 81, 69, 67, 45; NMR. (CCl_4): δ = 1.16 (12 H, *m*), 1.9–2.7 (7 H, *m*), 3.20 (1 H, br. *s*), 3.75 (1 H, br. *m*), 5.47 (1 H, *t*, J = 6.5 Hz).

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227. The Wall Effect on Hydrogen Formation in the Vapour-Phase Radiolysis of *c*-C_6D_{12} and *n*-C_7D_{16}

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(7. VIII. 74)

Summary. Vapour-phase radiolysis of *c*-C_6D_{12} and *n*-C_7D_{16} leads to a relatively large HD yield, up to $\sim$ 20% of the total hydrogen, which cannot be accounted for by incomplete deuteration of *c*-C_6D_{12} and *n*-C_7D_{16}. In order to elucidate the mechanism of the HD formation, we have examined the effect of additives and of physical conditions on the HD yield. By coating the vessel with a layer of Aquadag the HD yield is greatly decreased without appreciable variation of the total hydrogen yield. The HD yield from nontreated vessels also decreases remarkably with in-