225. The [2,3] Sigmatropic Reaction of Acetonyl Allyl Ethers, a New Method for Preparing Certain 2-Hydroxyketones

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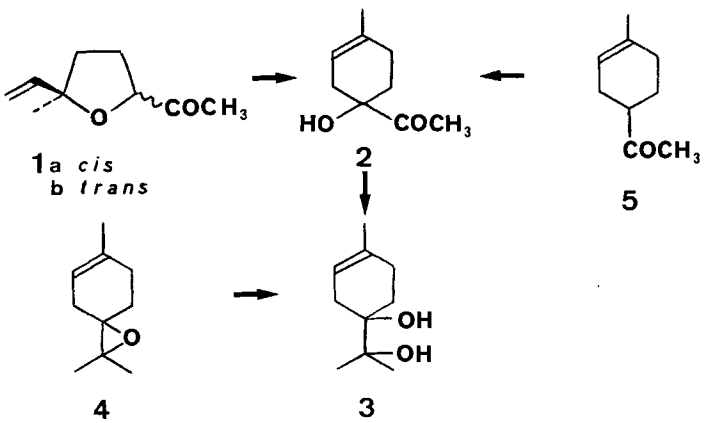
Summary. A new [2] [3] sigmatropic rearrangement is described, enabling the conversion of acetonyl allyl ethers to 3-hydroxy-5-en-2-ones.

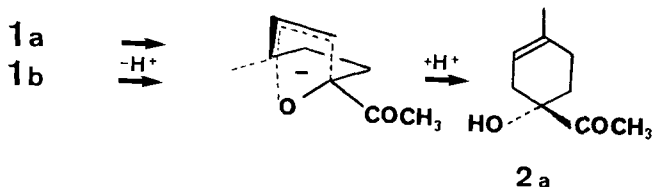
There are many papers about [2] [3] sigmatropic reactions, using allylic ammonium ylides [1], sulfonium ylides [2], sulfide carbanions [3], and other modifications. A recent publication *Cazes & Julia* [4] concerning the rearrangements of allyl ethers of cyanhydrins describes how the cyano group can activate the formation of a carbanion next to an oxygen atom thus enabling a [2] [3] sigmatropic rearrangement to occur. We have also been able to achieve such a rearrangement by placing a carbonyl function at the position occupied by a cyano group in *Julia*'s case, and it is this which we report here.

We first suspected the rearrangement when it was observed that 5-methyl-5-vinyltetrahydrofur-2-yl methyl ketone (**1**) did not react normally in the *Grignard* reaction [5], giving instead, as the main product, 1-acetyl-cyclohex-3-enol (**2**). Proof for the structure of the latter was obtained in two ways. Excess of methyl magnesium iodide yielded a diol (**3**) identical with the product obtained on acid-catalyzed ring opening of terpinolene epoxide (**4**). Alternatively, oxidation of 4-methylcyclohex-3-



enyl methyl ketone (**5**) [6] with oxygen in the presence of potassium *t*-butoxide and triethyl phosphite [7] also led to the diol **3**.

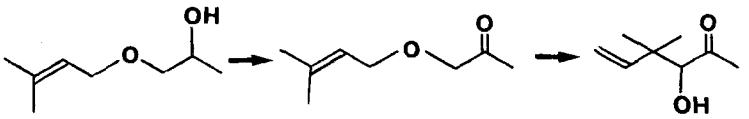
The reaction was shown to be a genuine suprafacial [2] [3] sigmatropic rearrangement by the fact that both (–)-*cis*-5-methyl-5-vinyltetrahydrofur-2-yl methyl



2a

ketone (**1a**) and its (+)-*trans* isomer (**1b**) yielded the same (+)-hydroxyketone, to which we ascribe the (*S*)-configuration **2a**.

In order to test the generality of the method for making hydroxyketones, we prepared the acetonyl 3-methylbut-2-enyl ether (**6**) as follows. 3-Methylbut-2-enolate was treated with propylene oxide [8] to give the corresponding monoether of propylene 1,2-glycol (**7**). The oxidation of the hydroxyl group was not easy, but using *Brown*'s two-phase system [9] we were able to achieve about 30% of the desired ketone (**6**). The latter reacted smoothly with potassium *t*-butoxide, to give 3-hydroxy-4,4-dimethylhex-5-en-2-one (**8**) as the only isolable product.



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Experimental Part

NMR.-spectra were recorded on a *Hitachi Perkin-Elmer* R-20B instrument, and chemical shifts are given in ppm with tetramethylsilane as 0.00 ppm. IR.-spectra were measured with a *Perkin-Elmer* type 125 spectrophotometer. Mass spectra were measured on an *Atlas* CH 4 mass spectrometer, using an inlet temperature of about 150° and electrons of 70 eV. Results are quoted in *m/e* (% most important fragment), and generally the ten most important fragments are quoted. Gas chromatography (GLPC.) was carried out on a *Carlo Erba* type GT instrument, using Carbowax 20M, 15% on Chromosorb W 60–80 mesh, acid-washed, unless otherwise stated.

1-Acetylcyclohex-3-enol (**2**). a) A solution of potassium *t*-butoxide was prepared from 3.9 g of potassium and 100 ml of *t*-butylalcohol, and 15.4 g of a mixture of *cis*- and *trans*-isomers of 5-methyl-5-vinyltetrahydrofur-2-yl methyl ketone [5] was added. After 26 h, the reaction was complete, and the product was isolated in ether, and washed to neutrality. The residue was distilled, b.p. 60°/0.01 Torr, to yield 3.4 g of material consisting mainly of the title compound, and 9.3 g of residue. Redistillation of the title compound did not result in extensive formation of residue. For analysis, the substance was purified by GLPC. – NMR. (CCl_4): 1.69 (3H, broad *s*, CH_3—C=); 2.18 (3H, *s*, CH_3CO); *ca.* 5.27 (1H, broad, CH_2CH=C); 6 other CH protons. – MS.: 111 (100), 43 (97), 93 (94), 55 (59), 41 (39), 81 (35), 77 (33), 67 (29), 91 (25), 39 (23) ... 136 (M – 18$^+$, 20). – IR.: $\nu_{CCl_4}^{max}$ 3490 (OH), 1705 (C=O) cm^{-1}.

$C_9H_{14}O_2$ (154.2) Calc. C 70.09 H 9.15% Found C 69.88 H 9.39%

Using (–)-*cis*-5-methyl-5-vinyltetrahydrofur-2-yl methyl ketone, (*S*)-1-acetylcyclohex-3-enol of $[\alpha]_D^{20} = +19.5°$ ($c = 10$, CCl_4) was obtained, while from the (+)-*trans* isomer, the same (*S*)-1-acetylcyclohex-3-enol of $[\alpha]_D^{20} = +22.4°$ ($c = 8.4$, CCl_4) was obtained.

b) (*cf.* [7]). A solution of 15 g of sodium hydride in a mixture of 50 ml of *t*-butyl alcohol and 200 ml of dimethylformamide was stirred while 25 ml of triethyl phosphite in 200 ml of dimethylformamide was added at room temperature. The solution was cooled to – 20°, and a current of oxygen was passed through while 11 g of 4-methylcyclohex-3-enyl methyl ketone was added over

$2^1/_2$ h, keeping the temperature below – 15°. When the addition was complete, the mixture was stirred for a further 30 min at – 20°, then acetic acid added until it was acid. After extraction in ether and washing ($NaHCO_3$, water), the residue was distilled to give 17.5 g of material still containing reagents. Chromatography in hexane/ether 8:2 on silica gel (250 g) gave 8.4 g of pure acetylcyclohexenol, identical with that prepared by method A.

(±)-*Menth-1-ene-4,8-diol* (**3**). a) A suspension of 1 g of 4,8-epoxymenth-1-ene (terpinolene epoxide, prepared by the action of peracetic acid on mentha-1,4(8)-diene [10]) in 10 ml of dioxan and 10 ml of 10% aqueous sulfuric acid was stirred at room temperature for 2 h. Ether was added, and the aqueous phase again extracted with ether. The combined ethereal extracts were washed ($NaHCO_3$, water) and concentrated and the residue distilled, b.p. 81°/0.01 Torr. For analysis the diol was purified by GLPC. on OV 17. – NMR. (CCl_4): 1.05 (6H, *s*, $CHC\lessgtr$); 1.65 (3H, broad *s*, $CH_3-\overset{|}{C}=$); 5.20 (1H, broad *s*, $>C=CHCH_2$); 8 other protons (2 × OH). – MS.: 111 (100), 93 (90), 43 (88), 59 (70), 110 (43), 41, 55, and 94 (35), 81 (25), 67 (23) ... 152 ($M-18^+$, 4).

$C_{10}H_{18}O_2$ (170.2) Calc. C 70.54 H 10.66% Found C 70.48 H 10.64%

b) A *Grignard* solution was prepared from 0.5 g of magnesium and 1.2 ml of methyl iodide in 30 ml of dry ether. A solution of 3 g of 1-acetylcyclohex-3-enol in 30 ml ether was added, and the mixture stirred at reflux for 24 h. A further solution of *Grignard* reagent (from 0.75 g magnesium and 1.8 ml of methyl iodide) was then added, and the mixture again heated at reflux for 24 h. The mixture was poured onto ice, and the ether layer washed to neutrality. The residue was distilled, b.p. 70–90/0.02 Torr, and the product was identical in all respects with that prepared by method a).

2-Hydroxy-propyl 3-methylbut-2-enyl ether (**7**, *cf.* [8]). A solution of 0.3 g of sodium in 43 g of 3-methylbut-2-enol was stirred at room temperature while 2.9 g of 1,2-epoxypropane was added over 25 min. The mixture was heated for $1^1/_2$ h at reflux, then about 30 g of the excess alcohol was distilled, and the residue neutralized with 6N sulfuric acid. The product was isolated in ether and distilled, b.p. 72°/11 Torr; yield 5.0 g. For analysis, the substance was purified by GLPC. – NMR. ($CDCl_3$): 1.10 (3H, *d*, $J = 6$ Hz, $CH_3-CH\lessgtr$); 1.65 and 1.72 (each 3H, *s*, $CH_3-\overset{|}{C}=$); 3.0–3.6 (4H, *m*, $OCH_2CHOH-CH_3$); 4.01 (2H, *d*, $J = 7$ Hz, $OCH_2-\overset{|}{C}H=$); 5.38 (1H, *t*, $J = 7$ Hz, + further coupling, $OCH_2-CH=C\lessgtr$). – MS.: 69 (100), 41 (75), 45 and 71 (39), 85 (29), 70 (26), 59 (20), 55 (15), 39, 68 and 129 (13) ... 144 (M^+, 1).

3-Methylbut-2-enyloxymethyl methyl ketone (**6**). To a solution of 50.4 g of **7** (previous experiment) in 300 ml of ether at – 10° was added 350 ml of a solution of 100 g of sodium dichromate ($Na_2Cr_2O_7 \cdot 2H_2O$) in 300 ml water and 136 g conc. sulfuric acid in 500 ml water. The addition was carried out in such a way that the temperature remained at – 5°, and lasted for 75 min. The mixture was stirred for a further 45 min at – 5°, then the ether layer was separated and washed ($NaHCO_3$, water). GLPC. indicated that the residue (30 g) consisted of about 60% of unreacted alcohol and 40% of the desired ketone, but extension of the reaction time or further addition of chromic acid did not increase the amount of product, although the starting material was consumed. The product was purified by slow distillation with ethyl borate, followed by distillation at b.p. 73–76°/11 Torr. – NMR. ($CDCl_3$): 1.69, 1.76 and 2.13 (each 3H, *s*, $CH_3C=$ and CH_3CO); 4.00 (*s*, OCH_2CO) superimposed on 4.05 (*d*, $J = 7$ Hz, $C=CH-CH_2-O$); 5.39 (1H, *t*, $J = 7$ Hz, $C=CH-CH_2$). – MS.: 41 (100), 69 (92), 85 (70), 43 (41), 27 and 39 (16), 29 (15) ... 127 (M – 15$^+$, trace).

3-Hydroxy-4,4-dimethylhex-5-en-2-one (**8**). A solution of 1.17 g of potassium in 18 ml of *t*-butyl alcohol and 10 ml of dry tetrahydrofuran was stirred at 0° while 4.26 g of the ketone from the previous experiment was added over 40 min. After $1^1/_2$ h, there was no further change in the amount of product (*ca.* 65% by GLPC.) and the mixture was poured onto ice and extracted into ether. Distillation of the residue (b.p. 82–85°/18 Torr) gave 2.7 g of material which was mainly the title substance. For analysis it was purified by GLPC. – NMR. ($CDCl_3$): 0.96, 1.10 and 2.13 (each 3H, *s*, $CH-C$ and CH_3CO); 3.91 (1H, *s*, $CO-CH(OH)-C$); 4.9–5.3 (2H, *m*, $CH=CH_2$); 6.00 (1H, $d \times d$, $J = 10$ and 18 Hz, $CH=CH_2$).

$C_8H_{14}O_2$ (142.2) Calc. C 67.57 H 9.93% Found C 67.12 H 9.91%

REFERENCES

[1] *V. Rautenstrauch*, Helv. *55*, 2233 (1972).
[2] *J. E. Baldwin & R. E. Hackler*, J. Amer. chem. Soc. *91*, 3646 (1969).
[3] *J. F. Biellmann & J. B. Ducep*, Tetrahedron Letters *1971*, 33; *V. Rautenstrauch*, Helv. *54*, 739 (1971).
[4] *B. Cazes & S. Julia*, Tetrahedron Letters *1974*, 2077.
[5] *A. F. Thomas & R. Dubini*, Helv. *57*, 2066 (1974).
[6] *E. F. Lutz & G. M. Bailey*, J. Amer. chem. Soc. *86*, 3899 (1964); *W. Kreiser, W. Haumesser & A. F. Thomas*, Helv. *57*, 164 (1974) and references quoted therein.
[7] *J. N. Gardner, F. E. Carlon & O. Gnoj*, J. org. Chemistry *33*, 3294 (1968).
[8] *D. Swern, G. N. Billen & H. B. Knight*, J. Amer. chem. Soc. *71*, 1152 (1949).
[9] *H. C. Brown & C. P. Garg*, J. org. Chemistry *36*, 387 (1971).
[10] *E. Klein, H. Farnow & W. Rojahn*, Dragoco Rept. *12*, 3 (1965); *J. Leffingwell*, Fr. Pat. 2,003,498 Chem. Abstr. *72*, 100934 (1970).

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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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.