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Cycloadditions of Allyl Cations, 25[1]

Acid Catalyzed Dehydrative Cyclodimerization of 2,4-Dimethyl-3-penten-2-ol in Two Phases. Biomimetic One-Pot Preparation of 3,3,5,5-Tetramethyllimonene (4-Isopropenyl-1,3,3,5,5-pentamethyl-1-cyclohexene)

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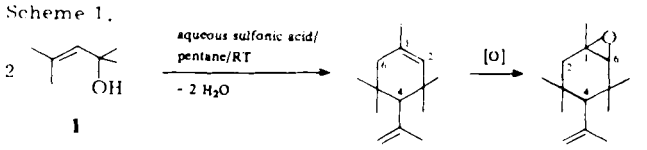
Cycloadditionen von Allyl-Kationen, 25[1]

Säurekatalysierte dehydrative Cyclodimerisierung von 2,4-Dimethyl-3-penten-2-ol in zwei Phasen. Biomimetische Eintopfdarstellung von 3,3,5,5-Tetramethyllimonen (4-Isopropenyl-1,3,3,5,5-pentamethyl-1-cyclohexen)

2,4-Dimethyl-3-penten-2-ol (**1**) wurde in einer Mischung von wäßriger Sulfonsäure/Pentan bei Raumtemperatur gerührt. Es bildete sich 3,3,5,5-Tetramethyllimonen (**2**) in hoher Ausbeute. **2** wurde in sein Epoxid (**3**) (4-Isopropenyl-1,3,3,5,5-pentamethyl-7-oxabicyclo[4.1.0]heptan) umgewandelt.

Previously, we have shown the utility of generating allyl cations in two phase conditions. For example, 2,4-dimethyl-3-penten-2-ol (**1**), when allowed to react with cyclopentadiene in aqueous sulfonic acid/pentane at 0 and 25 °C, gave inter al. bridged cyclohexenes, or, more specifically, norbornene derivatives[2]. We now report the acid promoted dehydrative dimerization of **1**, which proceeds under similar conditions and produces three isomeric hydrocarbons $C_{14}H_{24}$ in nearly 80% yield (Table 1) in addition to a minor amount of alcohols. The major $C_{14}H_{24}$ hydrocarbon was 3,3,5,5-tetramethyllimonene (**2**) which was identified by ^{1}H NMR, MS, and microanalysis as well as by conversion into its epoxide **3** (Scheme 1). **2** was accompanied by just two minor isomers **5b** and **5c** (**2**:**5b**:**5c** = 92:3:5) which are considered to be acyclic trienes.

Scheme 1.



1 **2** **3**

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Table 1. Dehydrative Dimerization of 2,4-Dimethyl-3-penten-2-ol (**1**) in an Acidic Two Phase System at Room Temperature

Educt **1** (g)	Reaction time (h)	Product $C_{14}H_{24}$ (g)	Yield (%)
2.2	24	1.30	70
5	24	3.10	74
2.85[a]	24	1.67 – 1.71	70 – 71
5.7[a]	24	3.42 – 3.82	71 – 80
2.85[a]	4	0.60 – 0.79	26 – 33

[a] Duplicate experiments.

Interestingly, it is not essential to start the dimerization with the allyl alcohol **1**. When 2,4-dimethyl-1,3-pentadiene (**4**) was treated with aqueous acid under the same conditions, a similar mixture of products was obtained, although the reaction took longer and yields were lower, when the reaction was carried out at room temperature (Table 2).

Table 2. Dimerization of **4** in an Acidic Two Phase System at Room Temperature

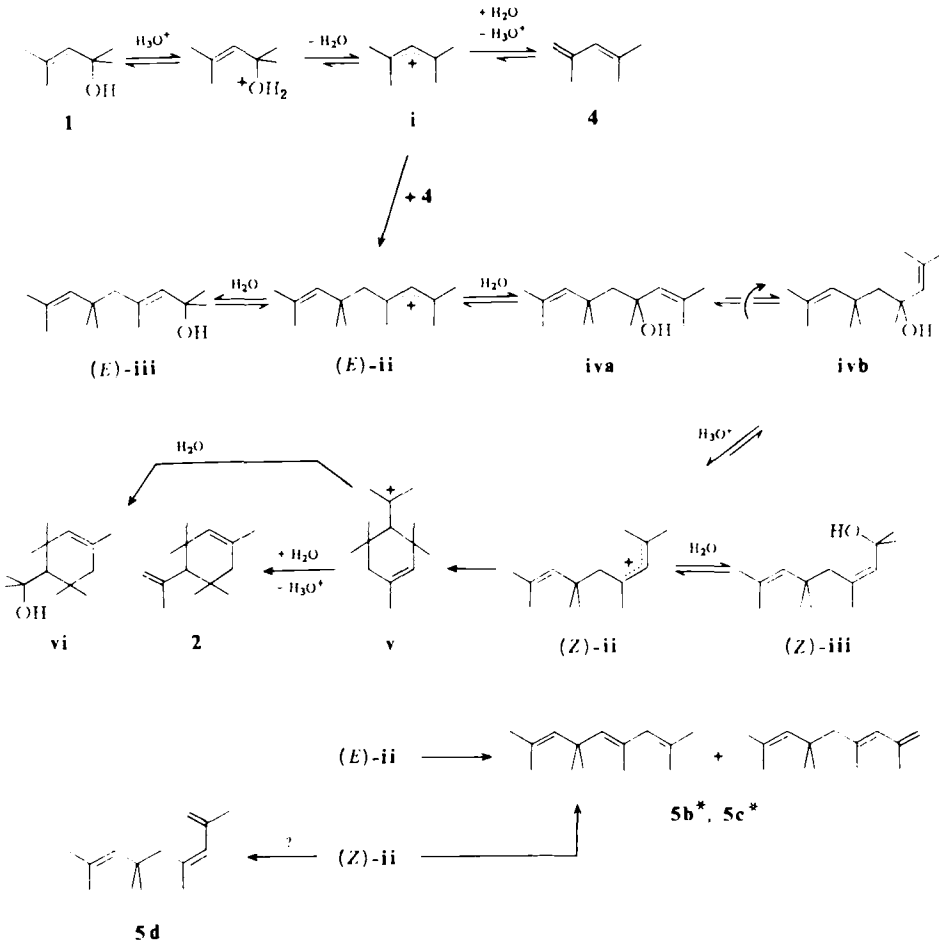
Educt **4** (g)	Reaction time (h)	Dimer $C_{14}H_{24}$ (g)	(%)
2.4	24	0.67	28
2.4	24	0.79	33
1.1	24	0.33	30
2.4	4	0.57 – 0.75	24 – 31

Discussion

The various products formed on dimerization of **1** can be rationalized by Scheme 2. In the presence of dilute aqueous acid at room temperature, **1** forms the 1,1,3,3-tetramethylallyl cation **i**, which is assumed to suffer partial deprotonation to diene **4**. The combination of allyl cation **i** and **4** gives a second allyl cation, which can be either *E*-configurated as in (*E*)-**ii** or *Z*-configurated as in (*Z*)-**ii**. (*E*)-**ii** has the lower energy of the two cations, but cannot cyclize to **v**. For cyclization to occur, (*E*)-**ii** must isomerize to (*Z*)-**ii**. This isomerization is formulated via recombination of (*E*)-**ii** with water at the more hindered allylic terminus to give **iva**, rotation about a single bond (**iva** ⇌ **ivb**) and re-ionization to the isomeric allyl cation, in this instance (*Z*)-**ii**, which has a higher energy than (*E*)-**ii** and can cyclize to **v**. Finally, loss of a proton from **v** gives the observed 3,3,5,5-tetramethyllimonene (**2**) and is preferred to recombination with water (**v** → 3,3,5,5-tetramethyl-α-terpineol (**vi**)) on steric grounds.

What are the two minor $C_{14}H_{24}$ isomers which are formed together with **2**? Tetramethyllimonene (**2**) undergoes a retro-Diels-Alder reaction in the mass spectrum. In fact, the peak $M^+/2 = 96$ is also the base peak, whereas its two minor isomers which are less volatile (GC-SE 30 column), show a less intense parent peak (cf. **5b**) or no parent peak at all (cf. **5c**). The base peak is now $m/e = 97$ for both isomers. These facts suggest the possibility that **5b** and **5c** are acyclic trienes.

Scheme 2. Postulated Routes for Acid-Induced Dimerization of **1**

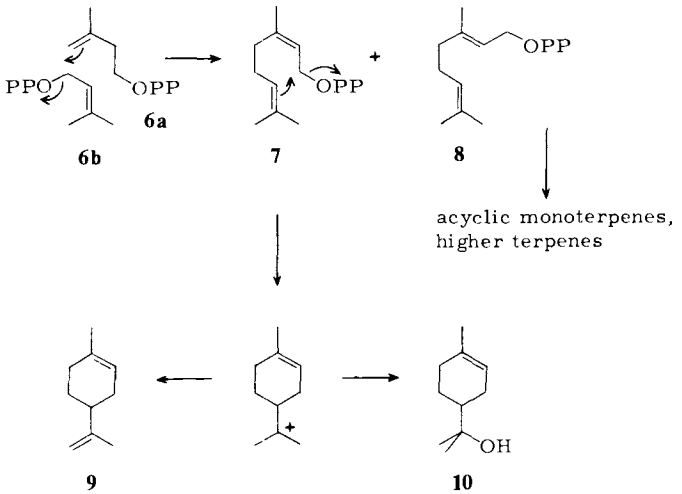


Trienes **5b*** and **5c*** (Scheme 2), which can be formed by loss of a proton from the stereoisomeric allyl cations (*E*)-**ii** and (*Z*)-**ii**, and cannot cyclize immediately on protonation because of the *E*-configurated central C = C double bond, are candidates for the minor $C_{14}H_{24}$ isomers **5b** and **5c**. Whilst **5b*** has an *E*-configurated central C = C double bond, the direct formation of its *Z*-configurated isomer from (*E*)-**ii** is also feasible. Acyclic triene **5d** with the *Z*-configurated central C = C double bond is considered less likely as it should be less stable than either **5b*** or **5c***.

No attempts were made to identify the mixture of the many minor alcohols formed in the dimerization of **1**, although (*E*)-**iii** and **iv** can be expected to have been present. Our mechanistic Scheme 2 and the type of products formed find analogy in the reaction of 2,4-dimethyl-3-penten-2-ol (**1**) and cyclopentadiene, studied in a previous paper[2]. The Scheme is also related to the biogenesis of monocyclic terpenes, for example to the combination of isopentyl pyrophosphate (**6a**) and 3,3-dimethylallyl pyrophosphate (**6b**) to give geranyl (**8**) as well as neryl pyrophosphate

(7), and cyclization of 7 to limonene (9) and α-terpineol (10) (Scheme 3). In fact, our experimental conditions – dilute aqueous acid, hydrocarbon solvent, and room temperature – are very mild and mimic intracellular conditions. Clearly, 3,3,5,5-tetramethyllimonene (2) can now be prepared readily. The approach is so simple that it should also be feasible on a larger, technical scale*).

Scheme 3. Biogenesis of Monoterpenes



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Experimental Part

The solution of 2,4-dimethyl-3-penten-2-ol (**1**)[3] (25 – 50 mmol) in pentane (5 ml) was stirred at room temperature with water (5 ml) containing *p*-toluenesulfonic acid (2.4 g, ca. 13 mmol) as set out in Table 1. The reaction mixture was neutralized with aqueous $NaHCO_3$, the organic phase separated, and the aqueous phase extracted with three further portions of pentane. The combined organic layer was washed with water, dried (Na_2SO_4), and the solvent removed at reduced pressure to leave an oil which was chromatographed on silica gel (20 g) to separate the olefinic from a minor amount of alcoholic products: Elution with pentane gave the olefins, which were isolated by distillation at the Kugelrohr (60 – 100°C, water pump vacuum). GC-MS showed the presence of just three $C_{14}H_{24}$ isomers in a ratio of 92 : 3 : 5, the major isomer being:

4-Isopropenyl-1,3,3,5,5-pentamethyl-1-cyclohexene (**2**): 90 MHz ^1H NMR (CCl_4): δ = 0.94 (s, 6H), 0.99 (s, 3H), 1.04 (s, 3H), 1.61 (m, 3H), 1.82 (m, 3H), 1.61 – 2.00 (m, 3H), 4.66 – 4.76 (m, 1H), 4.84 – 4.97 (m, 1H), 4.97 – 5.10 (m, 1H). – GC-MS (70 eV): *m/e* = 192 (6%, M^+), 177 (6), 149 (7), 135 (8), 121 (14), 119 (2), 107 (5), 105 (6), 96 (100), 91 (8), 81 (38).

$C_{14}H_{24}$ (192.3) Calcd. C 87.42 H 12.58 Found C 86.92 H 12.59

*) *Note added in proof (25. 11. 1980):* Since the above was written we have prepared tetramethyllimonene (**2**) by various acid-catalyzed reactions of the allylic alcohol **1** and also diene **4**, in quantities of 25 g per batch (*U. Gibbels, R. J. Giguere,* and *G. von Ilsemann,* unpublished work).

Isomer **5b**: GC-MS (70 eV): *m/e* = 192 (< 1%, M^+), 177 (4), 149 (60), 135 (1), 121 (13), 119 (< 1), 107 (11), 105 (4), 97 (100), 55 (73). – *Isomer* **5c**: 177 (< 1%), 149 (3), 135 (< 1), 121 (< 1), 107 (< 1), 105 (< 1), 97 (100), 55 (53). The more polar product alcohols were eluted from the column with light petroleum (bp. 40 – 60°C)/ether (10 vol %) and isolated by distillation at the Kugelrohr (100 – 150°C, ca. 1 Torr). Starting from **1** (2.85 g, see Table 1) we obtained some residue (0.05 – 0.22 g) and a yellow oil (0.10 – 0.20 g) with an intensive smell (GC: many peaks).

In similar experiments 2,4-dimethyl-1,3-pentadiene (**4**) was dimerized (Table 2).

4-Isopropenyl-1,3,3,5,5-pentamethylcyclohexene oxide (4-Isopropenyl-1,3,3,5,5-pentamethyl-7-oxabicyclo[4.1.0]heptane) (**3**): A solution of **2** (1.92 g, 10 mmol) containing less than 10% of **5b** and **5c** (see above) in dichloromethane (100 ml) is stirred vigorously with an aqueous solution (30 ml) of 5% $NaHCO_3$, whilst *m*-chloroperbenzoic acid (85%, 10 mmol) is added in portions. The mixture is stirred for 1 h at room temperature, the organic phase is separated, and the aqueous layer is extracted once with dichloromethane (10 ml). The combined organic phase is washed with 1 N NaOH (30 ml), water (30 ml), and dried (Na_2SO_4). The solvent is distilled off and the residue filtered through silica gel (25 g) with pentane (ca. 150 ml) and eluted with ether. Both phases are dried (Na_2SO_4) and distilled at the Kugelrohr (80 – 100°C, water pump vacuum) after removal of the solvent.

From the pentane phase 10 – 20% of the educt **2** was recovered, whilst the ether eluate yielded 55 – 64% of the product *). GC-MS suggested that three monoepoxides in 0.5, 8.5, and 85% and a diepoxide (1.5%) had been formed. Chromatography on silica gel (250 g) with light petroleum/ether (10 vol%) as eluent allowed separation from the diepoxide to give colorless **3**, solid at room temperature. – 90 MHz ^1H NMR ($CDCl_3$): δ = 0.83 (s, 3H), 1.04 (s, 3H), 1.07 (s, 3H), 1.18 (s, 3H), 1.38 (s, 3H), 1.81 (m, 3H, olefinic CH_3), 1.39 – 1.81 (m, 3H), 2.67 (s, 1H, 6-H), 4.70 – 4.80 (m, 1H), 4.92 – 5.06 (m, 1H).

$C_{14}H_{24}O$ (208.3) Calcd. C 80.71 H 11.61 Found C 80.45 H 11.42

On addition of shift reagent $Eu(fod)_3$ the geminal protons at C-2 appear as a clean AB quartet (^2J = 15 Hz) (see Scheme 1 for numbering of atoms). Further, the 6-H signal moves downfield most strongly followed by the signal of 4-H and then of the geminal protons at C-2, one proton of which (*cis* to 4-H) is shifted more than the other. The greater shift of the more remote 4-H relative to the geminal pair at C-2 suggests a contact shift for 4-H which is only possible in the *trans*-epoxide *trans*-**3** (with *exo*-isopropenyl group). A small amount (< 10%) of an inseparable isomeric epoxide (*cis*-**3**) was probably also present (GC-MS, $Eu(fod)_3$ spectrum)[4].

*) Another epoxidation for 24 h at room temperature gave ca. 70% conversion into a single epoxide (> 95%).

[1] Part 24: *R. J. Giguere, H. M. R. Hoffmann, M. B. Hursthouse* and *J. Trotter*, J. Org. Chem., submitted for publication.

[2] *H. Vathke-Ernst* and *H. M. R. Hoffmann*, Angew. Chem. **92**, 861 (1980); Angew. Chem., Int. Ed. Engl. **19**, 827 (1980).

[3] *H. M. R. Hoffmann* and *H. Vathke-Ernst*, Chem. Ber. **114** (1981), in press.

[4] Epoxidation of the parent limonene with perbenzoic acid has been reported to proceed at the trisubstituted double bond giving *cis*- and *trans*-isomers in a ratio of 50:50 [*R. Wylde* and *J. M. Teulon*, Bull. Soc. Chim. Fr. **1970**, 758; *E. E. Royals* and *J. C. Leffingwell*, J. Org. Chem. **31**, 1937 (1966)]. For the epoxidation with the sterically more demanding *tert*-pentyl hydroperoxide in the presence of hexacarbonylmolybdenum a *cis/trans* ratio of 30:70 was determined: *V. P. Yur'ev, I. Gailiunas, L. V. Spirikhin*, and *G. A. Tolstikov*, Zh. Obshch. Khim. **45**, 2312 (1975) [Chem. Abstr. **84**, 90314s (1976)].

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