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THE METAL ION CATALYSED OXIDATION OF HEXAHYDROCOLUPULONE

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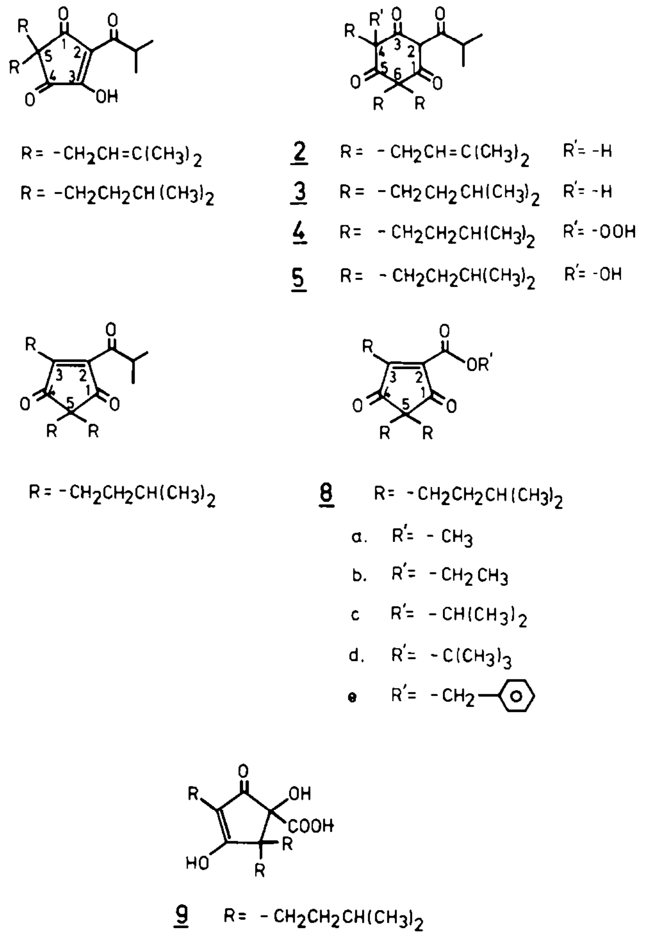
Abstract—The decomposition of 4-hydroperoxyhexahydrocolupulone **4**, catalysed by various metal ions, gives mainly 4-hydroxyhexahydrocolupulone **5** and tetrahydrocohulupone **6** in different ratios, depending on the nature of the metal ion. The maximum yield of the bitter-tasting **6** is 45%, if Co(II) acetate in 1,4-dioxan is used. The oxidation of hexahydrocolupulone **3** in 0.5% alcoholic cyclohexane in the presence of Cu(II) acetate affords two new neutral oxidation products, 2 - (2' - methyl)propanoyl - 3,5,5 - tri(3' - methyl)butyl - 2 - cyclopentene - 1,4 - dione **7** and 2 - carboalkoxy - 3,5,5 - tri(3' - methyl)butyl - 2 - cyclopentene - 1,4 - dione **8**.

Increasing the yield of bitter-tasting hulupones, e.g. cohulupone **1**, in the oxidation of non-bitter hop β-acids, e.g. colupulone **2**, has been the incentive to many studies.[2] The hydrogenated hop β-acids give less complex oxidation reaction mixtures and are therefore the most suitable substrates to be studied with various oxidants. We therefore investigated the oxidation of hexahydrocolupulone **3**, which can be converted[3] in high yield into the hydroperoxy **4** and subsequently the hydroxy derivative **5**.

Tetrahydrocohulupone **6** can be obtained by further oxidation of **4** in low conversion, comparable to the yield of cohulupone **1** in the oxidation of **2**.[2] Product **5** however cannot be transformed into **6**. Thermal decomposition of the hydroperoxide **4** also leads to a certain amount of **6**. This reaction is catalysed by several metal ions[4] and proceeds about ten times faster compared to the uncatalysed reaction. Conditions were standardised at 75°C with 2% hydroperoxide solution in either cyclohexane, carbon tetrachloride, benzene, 1,4-dioxan or ethyl



1 R = $-CH_2CH{=}C(CH_3)_2$
6 R = $-CH_2CH_2CH(CH_3)_2$

2 R = $-CH_2CH{=}C(CH_3)_2$ R' = $-H$
3 R = $-CH_2CH_2CH(CH_3)_2$ R' = $-H$
4 R = $-CH_2CH_2CH(CH_3)_2$ R' = $-OOH$
5 R = $-CH_2CH_2CH(CH_3)_2$ R' = $-OH$

7 R = $-CH_2CH_2CH(CH_3)_2$

8 R = $-CH_2CH_2CH(CH_3)_2$
a. R' = $-CH_3$
b. R' = $-CH_2CH_3$
c R' = $-CH(CH_3)_2$
d. R' = $-C(CH_3)_3$
e R' = $-CH_2-C_6H_5$

9 R = $-CH_2CH_2CH(CH_3)_2$

Scheme 1.

acetate. To 1 ml of these solutions 90 μl of 0.1 M metal salt solution in methanol was added. A number of cobalt, copper, lead and manganese salts were investigated. The reaction mixture was analysed by HPLC on a styrene-divinylbenzene anion exchange column with UV detection at 254 nm. Only two major products are formed: **5** and **6**. The ratio of **6** to **5** depends on the nature of the metal ion and varies between 0.05 for Pb(IV) acetate in cyclohexane and 3.5 for Co(II) acetate in 1,4-dioxan. In the latter case, the yield of **6** is 45% and the time to decompose all the peroxide is then only 4 h. In the absence of metal ions, the peroxide is completely decomposed in 55 h. At other concentrations of substrate or catalyst and at different temperatures the yields of **6** are lower.

Direct metal ion catalysed oxidation experiments on **3** using Cu(I) chloride, Cu(II) acetate, Cu(II) phtalocyanine, Co(II) acetate, Mn(II) nitrate and Pb(IV) oxide, gave **5** and **6** again, but in lower yields compared to the decomposition of the hydroperoxide **4**. The most interesting results were obtained with Cu(II) acetate. Two compounds, **7** and **8**, so far unknown in hop chemistry, are formed. Thin layer chromatography in benzene: isooctane 8:2 reveals the gradual formation of the two new oxidation products.

Compound **7**, a light yellow oil, is not acidic and has an UV absorption maximum of 243 ($\epsilon = 21{,}400$) nm in CH_3OH, which represents a cyclopentene - 1,4 - dione chromophore. The ^{1}H NMR spectrum has all absorption frequencies below $\delta = 1.6$, except for a triplet at $\delta = 2.53$, accounting for an allylic methylene unit, and a septuplet at $\delta = 3.3$ for the proton in the 2-methylpropanoyl sidechain. The molecular ion in the mass spectrum at *m/e* 376 is at the same time the most intense ion. The fragment ion at *m/e* 307 (73%) arises from the loss of a 4-methylpentyl radical. The yield of **7** is between 10 and 20%, depending on the nature of the alcohol, used as a cosolvent.

Compounds **8a–8d** occur as yellow oils, while **8e** is crystalline (m.p. 36°C). The yield is highest for **8a** (55%) and decreases with increasing volume of the alkoxy moiety. The compounds are not acidic and show UV absorption maxima between 230 and 240 nm in CH_3OH, in agreement with the expected values for a substituted cyclopentene - 1,4 - dione chromophore. The ^{1}H NMR spectra are very similar to that of **7**, except for the absence of the septuplet at $\delta = 3.3$. This indicates that the acyl sidechain at C_2 in **3** is no longer present, but is eventually replaced by a carboalkoxy group. The change in the alkoxy moiety of **8** with the changing nature of the alcohol, is easily recognised by the appropriate signals in each spectrum. The most intense ion in the mass spectra is generated by losing an alcohol molecule, except for **8d**. Here, the main fragment ion is formed by splitting off two alkyl sidechains consecutively, once as the corresponding alkene, once as the radical.

The formation of **7** and **8** requires that the triacylmethane system of **3**, which is encountered in most derivatives of the hop bitter acids, be removed. A ring contraction, most probably between C_2 and C_4, followed by an elimination reaction, would afford the substituted enedione structural unit. These prerequisites are fulfilled if C_2 is the reacting centre. Oxidation of **3** at C_2 has been observed with H_2O_2 in strong alkaline medium, whereby hexahydrolupuloxinic acid **9** is the reaction product.[5] It is also likely that oxidation within the triacylmethane system occurs preferentially, when this group is being complexed by the Cu(II) ion. Decomposition of the initially formed hydroperoxide **10** and of the resulting radicals is critically influenced by the Cu(II)–Cu(I) redox couple (Scheme 2). Oxidative splitting of **10** by Cu(II) acetate generates a peroxyradical (reaction 1), which can give an alcohol and an oxyradical upon oxidation of the substrate (reaction 2). Further reaction of the oxyradical yields again the corresponding alcohol together with a carbon radical (reaction 3). In this way two equivalents of the alcohol are formed and only one equivalent of the carbon radical. Since the reaction products **7** and **8** are formed directly from the carbon radical (reaction 5), the maximum yield would be about 33%. The actually observed combined chemical yields of **7** and **8** are much higher than this value, hence further reduction of the alcohol must occur. Therefore, it is quite likely that the Cu(I) ion, which behaves as a reasonably good reducing agent,[6] converts the alcohol, at least partially, into the reactive carbon radical (reaction 4). This mechanism accounts also for the activity of Cu(II) acetate in only catalytic quantities and is analogous to the reaction of arene diazonium compounds with Cu(I) salts.[7]

$$\mathrm{ROOH} + \mathrm{Cu}^{2+} \rightarrow \mathrm{ROO}^{\cdot} + \mathrm{Cu}^{1+} + \mathrm{H}^{+} \qquad (1)$$

$$\mathrm{ROO}^{\cdot} + \mathrm{RH} \rightarrow \mathrm{ROH} + \mathrm{RO}^{\cdot} \qquad (2)$$

$$\mathrm{RO}^{\cdot} + \mathrm{RH} \rightarrow \mathrm{ROH} + \mathrm{R}^{\cdot} \qquad (3)$$

$$\mathrm{ROH} + \mathrm{Cu}^{1+} \rightarrow \mathrm{R}^{\cdot} + \mathrm{Cu}^{2+} + \mathrm{OH}^{-} \qquad (4)$$

$$\mathrm{R}^{\cdot} \rightarrow \text{reaction products } \mathbf{7} \text{ and } \mathbf{8} \qquad (5)$$

Scheme 2.

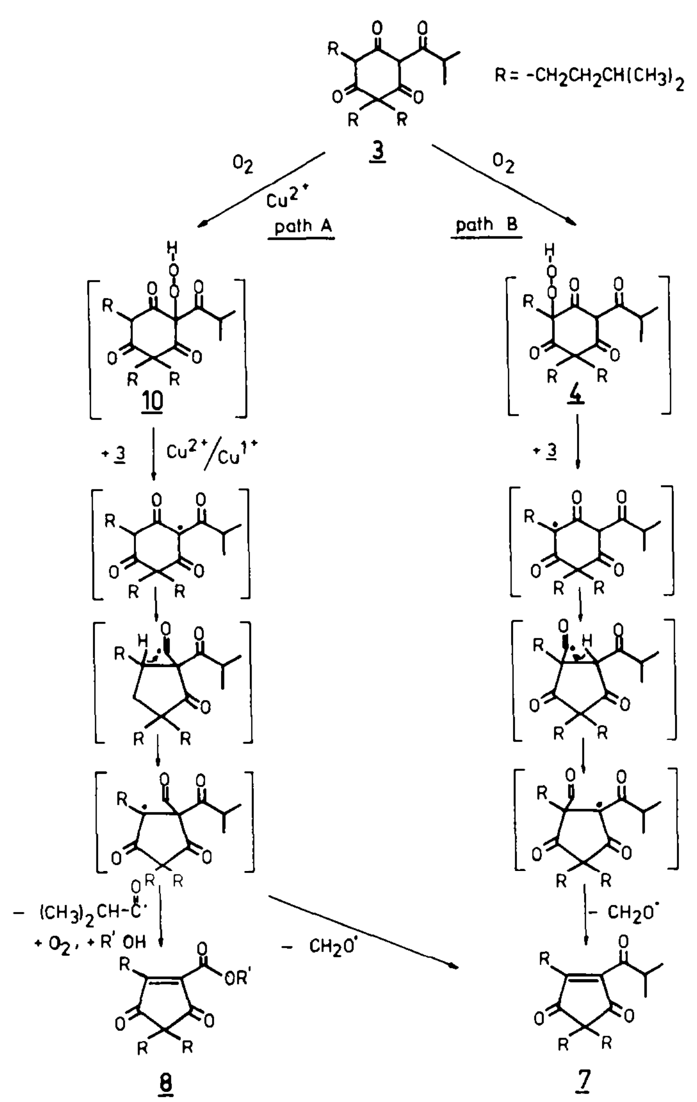
Intramolecular rearrangement of the carbon radical species leads to the stable products **7** and **8** (Scheme 3, path A). Intramolecular hydrogen abstraction by the carbonyl radical, formed after ring contraction, is to be followed by two alternative carbonyl α-cleavages. Splitting off a formyl radical results in formation of **7**, while loss of the acyl radical produces the series **8** after oxidation and esterification with the various alcohols used. The role of Cu(II) acetate in the oxidation reaction described here is double: activating the triacylmethane system for oxidation through coordination and producing the reactive triacylmethyl radical through a coupled redox reaction. The proposed mechanism of the Cu(II) acetate catalysed oxidation of the triacylmethane group finds support in the fact that **7** is present in the autoxidation reaction mixture of **3**, while **8** is absent.[8] Autoxidation occurs at ring carbon atom C-4. The radical species are, in these conditions, produced within the ring 1,3-dicarbonyl system and can only afford **7**, when reacting in an analogous manner as described before (Scheme 3, path B).

EXPERIMENTAL

The UV spectra were recorded on a Cary 15 spectrophotometer; the mass spectra were obtained on a CEC 21-104 instrument and the 300 MHz ^{1}H NMR spectra were taken on a Varian HR-300 machine as a 10% solution, TMS being the internal reference. Elemental analyses were carried out with a Perkin Elmer 240 Elemental Analyzer. At the time of analysis, samples **8b** and **8d** were no longer available.

The metal ion (Cu(II) *acetate*) *catalysed oxidation of* 3

0.812 g (2×10^{-3} mole) of **3** was dissolved in 200 ml cyclohexane (10^{-2} M) and 0.0363 g (2×10^{-4} mole) of metal ion (Cu(II) acetate)



Scheme 3.

was added in 1 ml alcohol (methanol, ethanol, isopropanol, tertiary butanol and benzylalcohol, respectively). The reaction vessel, which is kept at a constant temperature of 45°C, is vigorously shaken in pure oxygen atmosphere. The reaction is followed by the measurement of oxygen uptake and by TLC chromatography in benzene: iso-octane 8:2. The reaction mixture is separated by column chromatography (21 cm × 2 cm) on silicagel (30 g). The products are eluted with the same solvent mixture, used in the TLC chromatography. The appropriate fractions were collected and afforded, after evaporation of the solvent, two pure compounds. Compound **6** had in each case a R_f-value of 0.5 in TLC, while the R_f-values of compounds **8** vary: 0.3 for **8a**; 0.34 for **8b**; 0.365 for **8c**; 0.38 for **8d** and 0.36 for **8e**.

Found for **7**, C, 75.95; H, 10.42; $C_{24}H_{40}O_3$ requires: C, 76.6; H, 10.64%. UV: $\lambda_{max}(\epsilon)$: 243 nm (21,400) in 0.1 N HCl/CH_3OH; 222 nm (29,300), 240 nm (sh) and 314 nm (24,000) in 0.1 N $NaOH/CH_3OH$. ^1H NMR: $\delta(CCl_4)$: 0.83 (12 H, d, J = 7 Hz); 0.96 (6 H, d, J = 7 Hz); 1.11 (6 H, d, J = 7 Hz); 1.39–1.41 (7 H, m); 1.6 (6 H, t, J = 7 Hz); 2.53 (2 H, t); 3.3 (1 H, sept., J = 7 Hz). MS: *m/e* (%): 376 (100); 361 (8); 333 (12); 320 (4); 307 (73); 306 (21); 305 (26); 264 (4); 263 (10); 251 (12); 250 (18); 249 (5); 237 (14); 207 (6); 181 (3); 180 (2); 179 (3).

Found for **8a**: C, 72.42; H, 10.07; $C_{22}H_{36}O_4$ requires: C, 72.52; H, 9.9%. UV: $\lambda_{max}(\epsilon)$: 240 nm (12,000) in 0.1 N HCl/CH_3OH; 230 nm (sh), 300 nm (sh) and 370 nm (1,800) in 0.1 N $NaOH/CH_3OH$. ^1H NMR: δ (CCl_4): 0.83 (12 H, d, J = 7 Hz); 0.95 (6 H, d, J = 7 Hz); 1.4–1.6 (13 H, m); 2.6 (2 H, t, J = 8 Hz); 3.92 (3 H, s). MS: *m/e* (%): 364 (11); 336 (16); 333 (29); 332 (100); 304 (3); 295 (5); 294 (7); 293 (5); 276 (4); 264 (46); 263 (81); 262 (80); 238 (10); 235 (6); 207 (15); 206 (38); 195 (6); 182 (6); 181 (5); 167 (3).

UV for **8b**: $\lambda_{max}(\epsilon)$: 235 nm (12,500) in 0.1 N HCl/CH_3OH; 235 (sh), 300 nm (12,900) and 366 nm (1,900) in 0.1 N $NaOH/CH_3OH$. ^1H NMR: δ (CCl_4): 0.84 (12 H, d, J = 7 Hz); 0.96 (6 H, d, J = 7 Hz); 1.3–1.6 (13 H, m); 1.42 (3 H, t, J = 7 Hz); 2.59 (2 H, t, J = 7 Hz); 4.36 (2 H, q, J = 7 Hz). MS: *m/e* (%): 378 (10); 363 (6.5); 351 (4); 350 (14); 333 (31); 332 (100); 309 (5); 308 (9); 307 (7); 290 (5); 276 (4); 265 (12); 264 (46); 263 (83); 262 (80); 261 (13); 220 (12); 207 (14); 206 (33); 205 (12); 194 (19); 193 (11).

Found for **8c**: C, 73.40; H, 9.94; $C_{24}H_{40}O_4$ requires: C, 73.47; H, 10.2%. UV: $\lambda_{max}(\epsilon)$: 238 nm (12,300) in 0.1 N HCl/CH_3OH; 235 (sh), 299 nm (13,700) and 370 nm (1,600) in 0.1 N $NaOH/CH_3OH$. ^1H NMR: δ (CCl_4): 0.84 (12 H, d, J = 7 Hz); 0.95 (6 H, d, J = 7 Hz); 1.39 (6 H, d, J = 6.25 Hz); 1.3–1.6 (13 H, m); 2.57 (2 H, t, J = 8 Hz); 5.21 (1 H, d, J = 6.25 Hz). MS: *m/e* (%): 392 (12); 377 (4); 333 (34); 332 (100); 265 (9); 264 (32); 263 (64); 262 (71); 207 (10); 206 (24); 194 (12); 150 (11); 149 (12).

UV for **8d**: $\lambda_{max}(\epsilon)$: 230 nm (11,000) in 0.1 N HCl/CH_3OH; 235 (sh), 300 nm (12,200) and 365 nm (1,400) in 0.1 N $NaOH/CH_3OH$. ^1H NMR: δ (CCl_4): 0.84 (12 H, d, J = 7 Hz); 0.955 (6 H, d, J = 7 Hz); 1.3–1.65 (13 H, m); 1.575 (9 H, s); 2.53 (2 H, t, J = 8 Hz). MS: *m/e* (%): 406 (21); 391 (1); 388 (1), 351 (1); 335 (9); 333 (13); 332 (35); 322 (4); 306 (5); 300 (24); 298 (22); 296 (14); 288 (4); 277

(3); 264 (10); 263 (19); 262 (20); 245 (4); 244 (12); 243 (100); 241 (96); 239 (55); 238 (22); 220 (4); 202 (26); 150 (4).

Found for **8c**: C, 76.14; H, 9.18; $C_{28}H_{40}O_4$ requires: C, 76.36; H, 9.09%. UV: $\lambda_{max}(\epsilon)$: 240 nm (11,900) in 0.1 N HCl/CH_3OH; 230 (sh), 300 nm (17,600) and 370 nm (2,200) in 0.1 N $NaOH/CH_3OH$. ^1H NMR: δ (CCl_4): 0.83 (12 H, d, J = 7 Hz); 0.875 (6 H, d, J = 7 Hz); 1.25–1.6 (13 H, m); 2.55 (2 H, t, J = 8 Hz); 5.33 (2 H, s); 7.2–7.45 (5 H, m). MS: *m/e* (%): 440 (19); 425 (4); 413 (8); 412 (24); 377 (5); 376 (15); 370 (9); 349 (16); 333 (27); 332 (100); 331 (22); 310 (9); 307 (13); 279 (9); 265 (6); 264 (21); 263 (41); 262 (27); 237 (7); 235 (6); 222 (5); 207 (8); 206 (15); 205 (3); 178 (10); 149 (6).

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