Synthesis of 3,5-Dihydroxytropone

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Starting from tropone, the hitherto unknown 3,5-dihydroxytropone (**6**) is prepared in a four-step synthesis including a [4 + 2] cycloaddition reaction of singlet oxygen.

Synthese von 3,5-Dihydroxytropon

Wir beschreiben eine vierstufige Synthese des bisher unbekannten 3,5-Dihydroxytropons (**6**), die von Tropon ausgeht und eine [4 + 2]-Cycloaddition mit Singulett-Sauerstoff einschließt.

Since 2,3-dihydroxytropone (**7a**) was noted for its synergism with aminoglycoside antibiotics[1], novel improved syntheses of several hydroxytropones were published, showing both the increased interest in these systems and their relatively difficult accessibility[2-4].

We have now succeeded in preparing 3,5-dihydroxytropone (**6**) by the sequence of transformations shown in Scheme 1. Surprisingly, of the four dihydroxytropones, **6** was hitherto unknown, and furthermore very few 1,3,5-trisubstituted derivatives of cycloheptane and cycloheptatriene have been reported[5-8].

In the first step of our synthesis, we reduced tropone[9] (**1**) to 1,3-cycloheptadien-6-ol (**2**) and were able to improve the yield of this procedure[10] substantially.

2[11] was then treated with singlet oxygen, yielding the endoperoxides **3a** and **3b** which could be separated and characterized. Floyd and Cimarusti also performed this conversion, but did not characterize the endoperoxides. However, they converted **3a**, the main product, to 3-acetoxy-1,5-cycloheptanediol and showed by X-ray analysis that the oxygen substituents have *cis* configuration[11].

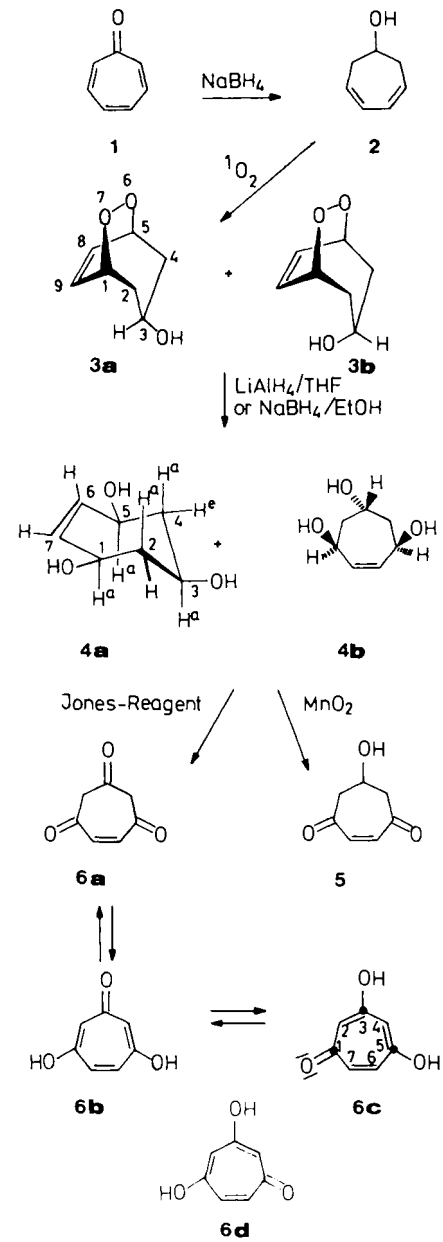
We then reduced **3a/b** to the new triols **4a** and **4b**. They are very sparingly soluble in ethyl acetate or acetone; actually, **4a** could be precipitated in cold acetone by stirring and irradiating with ultrasound. The ^{1}H-NMR spectrum of **4a** can be interpreted in terms of the chair conformation depicted in Scheme 1.

Activated manganese dioxide[12] oxidized the allylic hydroxyl groups of the triols **4a/b**, yielding – the as yet unknown – 6-hydroxy-2-cycloheptene-1,4-dione (**5**).

It proved to be very difficult to accomplish the oxidation of all hydroxy groups of **4a/b**. Of many tested reagents and reaction conditions, Jones oxidation[13] gave the best, though still fairly low yield of 3,5-dihydroxytropone (**6**). ^{1}H-NMR monitoring of the course of the reaction revealed, as was to be expected, that **4a/b** are initially oxidized to give **5** very rapidly, which is then slowly converted into **6**, but with accompanying substantial decomposition.

The by-products could not be characterized; they gave rise to a lot of peaks between δ = 1 and 5 in the ^{1}H-NMR spectrum of the reaction mixture.

Scheme 1



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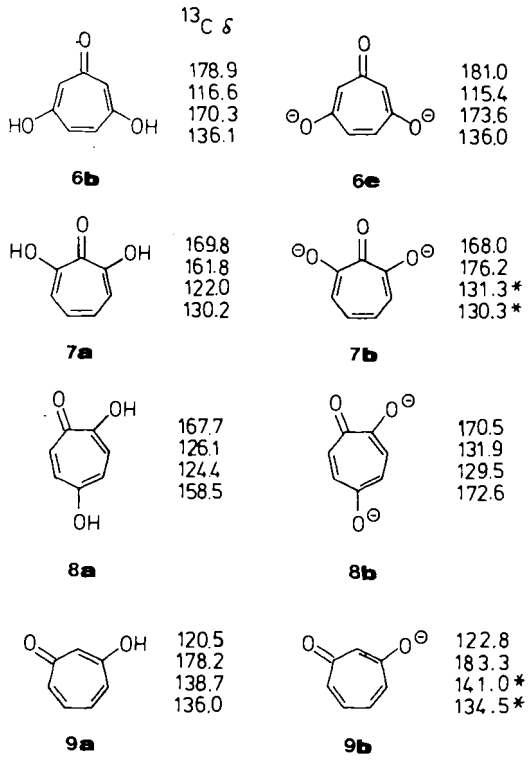
The ^1H- and ^{13}C-NMR spectra of **6**, in methanol, can be rationalized by the depicted dihydroxy ketone constitution, **6b/c/d**. When **6** was left standing in [D_4]methanol for two days, about 75% of 2/4-H had been exchanged for deuterium.

Scheme 2. ^{13}C-NMR data of **6b**–**9a** in CD_3OD and **6e**–**9b** in D_2O/KOH.



* The assignment could be reversed.

The ^{13}C-NMR data of **6** in deuterium oxide after addition of excess potassium hydroxide are shown in Scheme 2, together with the analogous data of 2,3-dihydroxytropone (**7**), 2,5-dihydroxytropone (**8**), and 3-hydroxytropone (**9**). We assume formation of the dianions because the pK_a values of **7** and **8** range in the region of 11 for the second deprotonation step[14].

The deprotonation of **6** hardly affects C-6/7. We propose that **6e** is another example of a Y-delocalized aromatic system[15].

The new compounds **4a/b**, **5**, and **6** offer an attractive entry to unusually and/or multiply substituted derivatives of cycloheptene and tropone. One can easily devise synthetic plans that will lead both to the introduction of hetero substituents other than oxygen and to the substitution of the cycloheptane nucleus with five or even seven hydroxyl/keto groups. Investigations along these lines are under way.

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Experimental

All reagents were of commercial quality. – Analytical TLC plates and silica gel (230–400 mesh) were purchased from Merck. Preparative TLC was performed using a Harrison Research (Palo Alto, California) Chromatotron® using Merck silica gel 60 PF_{254} "gipshaltig". – Melting points were taken using a Dr. Tottoli apparatus (Büchi) and are uncorrected. – Microanalyses were obtained using a CH analyser Dr. Salzer (Labormatic/Wösthoff). – Mass spectra were obtained with a VG model 7070 spectrometer at 70 eV. – IR spectra were obtained using Perkin-Elmer spectrometers models 257 and 398. – NMR spectra were obtained using Varian T 60 (^1H), Jeol JNM-FX-100 (^1H, ^{13}C), and Jeol JNM-GX-400 (^1H, ^{13}C) spectrometers. – The ultrasonic bath was a Sonorex Super RK 106 (Bandelin; 35 kHz, max. 2 × 240 W/period).

3,5-Cycloheptadien-1-ol (**2**) is synthesized by the procedure of Schuster et al.[10]. The yield is increased to 80% by distillation in a short-path distillation apparatus (Leybold-Heraeus), b.p. 70°C/16 mbar (ref.[10] 50–55°C/5 mbar).

6,7-Dioxabicyclo[3.2.2]non-8-en-3-ol (**3a/b**): 12.00 g (110 mmol) of **2** and 0.25 g (0.40 mmol) of hematoporphyrine are dissolved in 350 ml of methanol. The solution is irradiated in a falling-film apparatus with a sodium vapour lamp (250 W) under a stream of oxygen. The reaction is monitored by TLC and is completed after approximately 15 h. The solvent is evaporated under reduced pressure, and the oily residue chromatographed twice on silica gel, eluting with ethyl acetate; yield 15.2 g (89%), ratio of **3a**:**3b** approx. 9:1 (according to ^1H-NMR integration of the olefinic protons).

(1α,3α,5α)-6,7-Dioxabicyclo[3.2.2]non-8-en-3-ol (**3a**): **3a** is separated from the product mixture (**3a/3b**; 1.0 g) by preparative TLC (Chromatotron®, 2-mm plates) with ethyl acetate. Evaporation of the eluent yields a colourless oil which is dissolved in boiling diethyl ether. Upon standing at –20°C, colourless needles are precipitated; yield 0.6 g (67%), m.p. 62–63°C. – IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1}, 1040. – ^1H NMR ($CDCl_3$): δ = 6.42 (dd, 2H, CH=CH), 4.72 (br. m, 2H, CH), 3.73 (m, 1H, CHOH), 2.13 (m, 4H, CH_2). – ^{13}C NMR ($CDCl_3$): δ = 128.6 (d, $^1J_{CH}$ = 169 Hz, C-8/9), 73.4 (d, $^1J_{CH}$ = 149 Hz, C-1/5), 65.7 (d, $^1J_{CH}$ = 146 Hz, C-3), 40.5 (t, $^1J_{CH}$ = 128 Hz, C-2/4). – MS (70 eV): *m/z* (%) = 142 (21) [M^+], 110 (100).

$C_7H_{10}O_3$ (142.2) Calcd. C 59.14 H 7.09
Found C 59.12 H 7.03

(1α,3β,5α)-6,7-Dioxabicyclo[3.2.2]non-8-en-3-ol (**3b**): **3b** is separated from the product mixture by preparative TLC (see above **3a**); it was always contaminated with some **3a**. Knowing the spectra of **3a**, the NMR data of **3b** can be extracted from the spectra of the mixture of the isomers. – ^1H NMR ($CDCl_3$): δ = 2.30 (m, 4H, CH_2), 4.05 (m, 1H, CHOH), 4.70 (br. m, 2H, CH), 6.60 (dd, 2H, CH=CH). – ^{13}C NMR ($CDCl_3$): δ = 41.7 (t, $^1J_{CH}$ = 126 Hz, C-2/4), 66.9 (d, $^1J_{CH}$ = 148 Hz, C-3), 74.5 (d, $^1J_{CH}$ = 147 Hz, C-1/5), 131.7 (d, $^1J_{CH}$ = 174 Hz, C-8/9).

6-Cycloheptene-1,3,5-triols **4a** *and* **4b**: 15.2 g (0.107 mol) of **3a/b** and 1.2 g (0.032 mol) of $NaBH_4$ are stirred in 200 ml of dried 2-propanol or ethanol at room temp. for approx. 12 h. Initially, the reaction mixture is cooled with an ice bath for about 1 h. The solvent is evaporated under reduced pressure, the semisolid residue dissolved in methanol, and chromatographed on a silica gel column, eluting with methanol. The eluent is concentrated, filtered, and thoroughly freed of methanol by evaporation under reduced pressure. The colourless, very viscous residue is stirred and irradiated in an ultrasonic bath in cold, dry acetone, resulting in the precipitation of the main product, (1α,3α,5α)-6-cycloheptene-1,3,5-triol (**4a**); **4b** could not be obtained purely. Yield (**4a** and **4b**, oil) 14.3 g (93%).

Data for **4a**: Mp. 113–116°C. – IR (KBr): $\tilde{\nu}$ = 3150–3550 cm^{-1}, 2920, 2850. – ^1H NMR (CD_3OD): δ = 5.62 (s, 6/7-H) 2 Hz, 4.16 (dd, J_{aa} = 12, J_{ae} = 1.5 Hz, 1/5-H), 3.78 (dt, J_{aa} = 11, J_{ae} = 3.5 Hz, 3-H), 2.09 (br. d, J_{gem} = 11 Hz, 2/4-H_e), 1.46 (dd, J_{gem} = 11, J_{ae} = 11, J_{aa} = 12 Hz, 2/4-H_a). – ^{13}C NMR (CD_3OD): δ = 136.09 (d; $^1J_{CH}$ = 162 Hz, C-6/7), 69.08 (d, $^1J_{CH}$ = 140 Hz, C-3), 67.45 (d, $^1J_{CH}$ = 138 Hz, C-1/5), 46.27 (t, $^1J_{CH}$ = 131 Hz, C-2/4). – MS (CI with NH_3): *m/z* (%) = 145 (19) [M^+ + 1], 127 (17), 109 (100).

$C_7H_{12}O_3$ (144.2) Calcd. C 58.32 H 8.39
Found C 58.30 H 8.20

6-Hydroxy-2-cycloheptene-1,4-dione (**5**): 1.0 g (6.9 mmol) of **4a/b** and 10.0 g of freshly prepared MnO_2[12] are stirred in 30 ml of dried acetone at room temp. for 42 h. The mixture is filtered, the solvent evaporated under reduced pressure, and the residue chromatographed on a silica gel column, eluting with ethyl acetate, to give **5** as a pale yellow oil; yield 0.3 g (31%). – IR (neat): $\tilde{\nu}$ = 3420 cm^{-1}, 1660. – UV (CH_2Cl_2): λ_{max} (lg ε) = 275 nm (1.86), 343 (1.94). – ^1H NMR (CD_3OD): δ = 6.50 (s, 2H, 2/3-H), 4.37 (quint, *J* = 4.5 Hz, 1H, 6-H), 3.08 (d, *J* = 4.5 Hz, 4H, 5/7-H). – ^{13}C NMR ($CDCl_3$): δ = 198.53 (m, *J* = 7 Hz, C-1/4), 137.97 (d, $^1J_{CH}$ = 164 Hz, C-2/3), 62.76 (d, $^1J_{CH}$ = 146 Hz, C-6), 51.36 (t, $^1J_{CH}$ = 129 Hz, C-5/7). – MS (70 eV): *m/z* (%) = 140 (9) [M^+], 68 (100).

$C_7H_8O_3$ (140.2) Calcd. C 60.00 H 5.75
Found C 60.18 H 5.69

3,5-Dihydroxy-2,4,6-cycloheptatrien-1-one (**6**): 144 mg (1.0 mmol) of **4a/b** is stirred in 15 ml of dry 2-propanone at 5–10°C, and 1.1 mol of Jones reagent[13] is added dropwise within 2 h. The mixture is stirred for another 0.5 h. Excess reagent is decomposed with 2-propanol. 10 ml of water are added, and organic solvents are removed by evaporation under reduced pressure; the residual green solution is cooled in an ice bath and adjusted to pH = 5–6 by dropwise addition of a satd. aqueous solution of barium hydroxide. The precipitate is removed by centrifugation and washed twice with 5 ml of water and with 5 ml of methanol. After evaporation of the combined supernatants, the residue is dissolved in 5 ml of water and extracted five times with 10 ml of ethyl acetate. The organic extracts are dried with sodium sulfate, filtered, and evaporated. The residue is redissolved in 0.5 ml of methanol, and the product precipitated with diethyl ether as a pale yellow powder; yield 25 mg (18%), m. p. 220–230°C (dec.). – IR (KBr): $\tilde{\nu}$ = 2800–3500 cm^{-1}, 1642 (w), 1510, 1235. – UV (CH_3OH): λ_{max} (lg ε) = 247 nm (4.33), 257 (4.32), 316 (3.73). – ^1H NMR (CD_3OD): δ = 6.95 (br. s, 6/7-H), 6.41 (t, *J* = 1.6 Hz, 2/4-H). – ^{13}C NMR [CH_3OH/CD_3OD (4:1)]: δ = 178.94 (s, C-3), 170.34 (s, C-1/5), 136.12 (d, $^1J_{CH}$ = 162 Hz, C-6/7), 116.59 (d, $^1J_{CH}$ = 156 Hz, C-2/4). – ^{13}C NMR of the dianion of **6e** [H_2O/D_2O (3:1)]: δ = 181.0 (C-1), 173.6 (C-3/5), 136.0 (C-6/7), 115.4 (C-2/4). – MS (70 eV): *m/z* (%) = 138 (80) [M^+], 10 (70).

$C_7H_6O_3$ (138.1) Calcd. C 60.87 H 4.38
Found C 60.66 H 4.40

CAS Registry Numbers

2: 1121-63-7 / **3a**: 73967-68-7 / **3b**: 74007-09-3 / **4a**: 121289-68-7 / **4b**: 121349-61-9 / **5**: 121289-69-8 / **6**: 121289-70-1

[1] [1a] Anon., *Chem. Eng. News* **59** (1981) 9. – [1b] S. Blechert, *Nachr. Chem. Tech. Lab.* **31** (1983) 788.
[2] M. Cavazza, F. Pietra, *J. Chem. Soc., Chem. Commun.* **1986**, 1480.
[3] A. M. Becker, R. W. Rickards, *Org. Prep. Proced. Int.* **15** (1983) 239.
[4] H. Takeshita, A. Mori, *Synthesis* **1986**, 578.
[5] C. R. Johnson, C. H. Senanayake, *J. Org. Chem.* **54** (1989) 735.
[6] J.-E. Bäckvall, J.-E. Nyström, E. R. Nordberg, *J. Am. Chem. Soc.* **107** (1985) 3676.
[7] M. G. Banwell, R. Onrust, *Tetrahedron Lett.* **26** (1985) 4543.
[8] E. Müller, H. Kessler, H. Fricke, W. Kiedaisch, *Liebigs Ann. Chem.* **675** (1964) 63.
[9] P. Radlick, *J. Org. Chem.* **29** (1964) 960.
[10] D. J. Schuster, S. M. Palmer, S. C. Dickerman, *J. Org. Chem.* **31** (1966) 4281.
[11] D. M. Floyd, C. M. Cimarusti, *Tetrahedron Lett.* **1979**, 4129.
[12] A. J. Fatiadi, K. S. Isbell, W. F. Sager, *J. Res. Natl. Bur. Stand., Sect. A*, **67** (1963) 153.
[13] K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. L. Weedon, *J. Chem. Soc.* **1946**, 39.
[14] N. Yui, *Sci. Rep. Tohoku Univ. [I]* **40** (1956) 114 [Chem. Abstr. **51** (1957) 17354e].
[15] P. Gund, *J. Chem. Educ.* **49** (1972) 100.

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