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The Influence of Hydrate Formation on the Clemmensen Reduction of Pentacyclo [5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]Undecane-8,11-Dione and Pentacyclo[6.4.0.0^{2,7}.0^{3,11}.0^{6,10}]Dodecane-9,12-Dione

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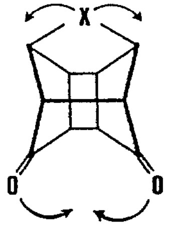
Abstract *Hydration of pentacyclo[5.4.0.0^{2,6}.0^{3,10} 0^{5,9}]undecane-8,11-dione led to the formation of a mixture of a geminal diol (80%) and a transannular hydrate (20%) and not to only the latter as previously accepted Compounds with smaller intercarbonylic distances formed only transannular hydrates which promoted rearrangement reactions during Clemmensen reduction. The transannular hydrate of pentacyclo[6.4 0 0^{2,7} 0^{3,11} 0^{6,10}]dodecane- 9,12-dione produced pentacyclo[6 4 0 0^{2,6} 0^{5,9}.0^{4,12}]-2-dodecanol*

Several reports in the recent literature have dealt with hydrate formation in cage-like structures containing carbonyl groups. Cookson and coworkers[1] already in 1964 pointed out that the ease of hydration in cage compounds with carbonyl groups in a 1,4-position is dependent on the proximity of the carbonyl groups. The intercarbonylic distance as well as the orientation angle of the two carbonyl groups relative to each other in 1 is dependent on the size of the bridge X It was observed[1] that compounds with two-carbon bridges (3) were readily hydrated on exposure to air, especially in solution, but temperatures above 150° were needed before they lost water, whereas, compounds such as (2) were comparatively slowly hydrated and was completely dehydrated after being heated for a few hours at 80°C. The two-carbon bridge compound (3) having the greater carbonyl π-π repulsion find hydrate formation a more energetically favourable process than the one-carbon bridge diketone (2) since the carbonyl carbon atoms are more easily spanned by an oxygen atom. It was concluded[1] that both the hydrates of 2 and 3 possessed transannular structures (4 and 5 respectively)



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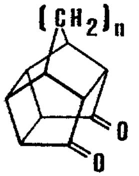
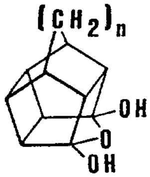


2 (n=1)

3 (n=2)

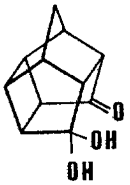


4 (n=1)

5 (n=2)

More recently Sasaki and coworkers[2] reported that when diketone 2 was heated in aqueous ethyl acetate at 60°C for 3 days the hydrate 6 was obtained. The presence of a CO group and an OH group in 6 was demonstrated by characteristic IR absorptions at 3 300 and 1 715 cm^{-1} Although it is not clear if the possibility of the presence of both 2 and 4 was considered, it was pointed out[2] that the known ketol 7[1] did not cyclise to 8, even at 270°C, indicating that the system 2 has a low transannular cyclisation reactivity.

This observation appears to have been questioned more recently[3] without specific arguments why a transannular hydrate structure 4 is supported instead of the hydrate 6 as proposed by Sasaki[2] and coworkers



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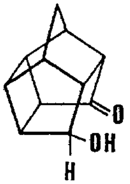

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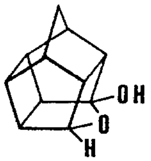

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In order to evaluate the influence of hydrate formation on the Clemmensen reduction of 2 and 3, we conducted an extensive investigation on the structures of the corresponding hydrates.

A solution of 2 (n = 1) in ethyl acetate was allowed to evaporate in an open container at room temperature. A crystalline product was obtained of which the infrared spectrum exhibits two absorptions at 3 336 and 3 377 cm^{-1} associated with two different hydroxyl groups. A carbonylic absorption appears at 1 712 cm^{-1} As expected, the electron impact induced (EI) mass spectrum shows a molecular ion at m/z 174 indicating that dehydration must have taken place during EI operating conditions. Under milder ionisation conditions a molecular ion associated with the hydrate should be obtained. The presence of two hydroxyl groups was clearly demonstrated by a fast atom bombardment (FAB) mass spectrometric analysis Pre-ionisation was achieved by using a solution of the hydrate in glycerol containing sodium iodide as matrix Bombardment with a 1 mA beam of 8 keV accelerated neutral xenon atoms produced a mass spectrum which showed a pseudo molecular ion at m/z 237 and a fragment peak at m/z 215 relating to the association of two sodium ions.

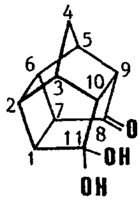
The presence of two hydroxyl groups was finally confirmed by using cesium iodide as ionisation agent instead of sodium iodide. The FAB mass spectrum exhibits two strong peaks at m/z 458 [$(M+2Cs)^+$] and m/z 325 [$(M+Cs)^+$] in a region where no matrix interference occurred.

To gain more information on the structure of the hydrate of 2 a ^{1}H and ^{13}C n.m.r. investigation was conducted. The ^{13}C n.m.r. spectrum in DMSO-d_6 initially, after dissolution of the substrate showed two sets of signals in a relative intensity ratio of 4:1. The ^{13}C n.m.r. spectrum of the main component (6) of the mixture exhibits a carbonylic resonance at δ_C 213.27, a resonance at δ_C 99.54 which can be associated with a quaternary carbon atom bearing two oxygen atoms, a methylene carbon resonance at δ_C 37.80 and eight different methine carbon signals.

In direct contrast to the asymmetric character of 6 the ^{13}C n.m.r. spectrum of the minor component (4) of the hydrate mixture showed only six signals. The ^{13}C n.m.r. data of 4 and 6 are given in Table 1.

The ^{1}H n.m.r. spectra of compounds such as 4 and 6 are very complex. Only from a few proton resonances can proton-proton coupling constants be obtained. In addition to geminal and vicinal proton-proton couplings, long range proton-proton interactions are also operative, resulting in fairly broad unresolved resonance peaks. The ^{1}H n.m.r. data of 6 are also given in Table 1. The concentration level of 4 was too low to enable any ^{1}H n.m.r. assignments.

The assignment of the different resonance signals in the ^{1}H and ^{13}C n.m.r. spectra of 4 and 6 to certain nuclei was made from proton-proton 2D chemical shift correlation (COSY) and hetero-nuclear (^{13}C, ^{1}H) 2D correlation (HETCOR) experiments. The assignment was verified by ^{13}C- ^{1}H selective population inversion (SPI) experiments.[4] Application of a selective π-pulse to the high-field C-4 proton resonance of 6 affected the ^{13}C resonances of C-9 and C-10. Irradiation of the low-field C-4 proton resonance affected the ^{13}C resonances of C-2 and C-6. Irradiation of the two hydroxyl proton resonances of 6 affected in both cases the ^{13}C resonance of C-11, C-1 and C-10, indicating that the two hydroxyl groups in 6 are both coupled to the same carbon atom.



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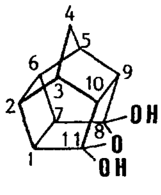

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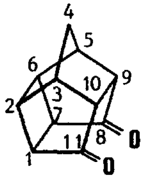

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Table 1 ^1H and ^{13}C n.m.r. data[a] of 2, 4 and 6

^{13}C

	6			4[c]	2[c]
Carbon	δ_C^b(ppm)	J(Hz)	$^{>1}J$(Hz)	δ_C^b(ppm)	δ_C^b(ppm)
1	45.84 Dm	147.8		43.72	
2	42.07 Dm	148.1		41.33	
3	46.23 Dd	145.0	8.0	47.47	
4	37.80 T	131.7		42.92	40.06
5	42.07 Dd	145.0	8 5		44.26
6	34.93 Dm	151.2			38.00
7	40.76 Dm	150.0			43.45
8	213.27 S				212.98
9	49.70 Dm	142.7			54.45
10	56 47 Dm	142.1		57.40	
11	99.54 Sm			112.23 Sm	

^1H

	6	
Proton	δ_H^b(ppm)	J(Hz)
1	2.515	
2	2.793	
3	2.668	
4a	1.407	J(a,b)10.5
4b	1.721	
5	2.400	
6	2.666	
7	2.290	
9	2.142	
10	2.405	
11a	5.995(OH)	
11b	5.535(OH)	

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[a] Solvent $(CD_3)_2SO$, 300 MHz for ^1H and 75 MHz for ^{13}C.

[b] Relative to internal TMS Symbols in capital letters refer to patterns resulting from directly bonded protons and lower case letters to (C,H)-couplings over more than one bond. S = singlet, D or d = doublet, T = triplet and m = multiplet.

[c] Proposed assignment.

The composition of the hydrate mixture of 4 and 6 gradually changes in DMSO solution at room temperature due to spontaneous dehydration After 10 days the mixture consisted of a mixture of 2, 6 and 4 in a 6 3 1 ratio demonstrating the instability of the hydrates 4 and 6 In DMSO at equilibrium the formation of 6 is favoured over 4. Hence 6 is thermodynamically more stable.

As expected, the dione 3 (n = 2) behaved differently towards hydration and rendered only one product (5) on treatment with ethyl acetate as described above. The same hydrate (5) was obtained from evaporation of an acetic acid solution of 2 The infrared spectrum of the hydrate (5) exhibits a strong hydroxylic absorption at 3 377 cm^{-1} and no absorptions in the carbonylic region. The FAB mass spectrum of 5 with sodium iodide and glycerol as matrix shows the presence of two hydroxyl groups with peaks at m/z 251 $[(M+2Na)^+]$ and m/z 229 $[(M+Na)^+]$. With cesium iodide as ionisation agent peaks at m/z 458 $[(M+2Cs)^+]$ and m/z 325 [(M+Cs)] are observed. As expected, no molecular ion associated with the hydrate molecule could be obtained with an EI mass spectrometrical analysis due to spontaneous dehydration during EI operating conditions.

Confirmatory evidence for the correctness of the structure of 5 was obtained from a ^1H and ^{13}C n.m.r. study. The n.m.r. data of 5 are given in Table 2.

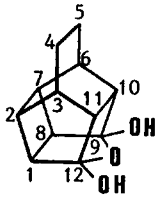

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Table 2 ^{1}H and ^{13}C n.m.r. data[a] of 5

	^{13}C		^{1}H	
Carbon/ Proton	δ_C^b(ppm)	^{1}J(Hz)	δ_H^b(ppm)	COSY[c]
1 (8)	48.54 Dm	149.5	2.391	2,11
2 (7)	36.96 Dm	144.9	2.357	1,11,3
3 (6)	31 19 Dm	133.2	1.868	2,11,4
11(10)	48.74 Dm	142.0	1.980	1,2;3
12 (9)	110.50 Sm		6.610 (OH)	
4 (5)	17.11 Tm	129.2	1.482 1.359 } d	3

[a] Solvent $(CD_3)_2SO$, 300 MHz for ^{1}H and 75 MHz for ^{13}C.

[b] Relative to internal TMS. Symbols in capital letters refer to patterns resulting from directly bonded protons and lower case letters to (C,H)-couplings over more than one bond. S = singlet, D = doublet, T = triplet and m = multiplet

[c] Numbers refer to correlations with the protons in column 1.

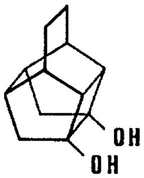
[d] ABCD part of an ABCD(XY) spin system.

The ^{1}H n.m.r. spectrum of 5 exhibits a signal pattern which can be attributed to the ABCD part of an ABCD(XY) spin system and can be assigned to the protons on C-4 and C-5. The hydroxyl protons resonate at δ 6,610. The assignment of the different resonance signals in the ^{1}H n.m.r. spectrum of 5 was made from a COSY experiment. Protons between which a correlation was observed are also given in Table 2.

Six different resonances are registered in the ^{13}C n.m.r. spectrum of 5. The resonance at δ 110,50 can be assigned to the quaternary carbon atom C-9(C-12) bearing two oxygen atoms The methylene carbon atoms C-4 and C-5 are registered at δ 17,11. Assignment of the remaining four methine carbon resonances was made from a HETCOR experiment from the previously assigned ^{1}H n.m.r. spectrum.

No dehydration of the hydrate 5 was observed in solution at room temperature. As previously reported[1] temperatures of above 150°C are needed for dehydration towards 3. These observations suggested that 5 ought to play a role in the formation of some of the products reported[5] to be obtained from the Clemmensen reduction of 3.

It was previously reported[5] that the Clemmensen reduction of the dione 3 produces mainly the pinacol 9 (30%) and the alcohol 10 (45%) while small quantities of 11 (15%) and 12 (10%) are also formed. The yield of 10 can be increased to 60% when 3 is subjected to a Clemmensen reduction at increased acid concentration.[5] (Increased from 6 mol dm^{-3} to 11 mol dm^{-3}). It was suspected by us that this is an indication that 10 originates from the hydrate 5 as increased acid concentration probably favours hydrate formation.



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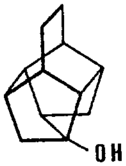

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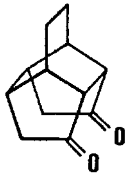

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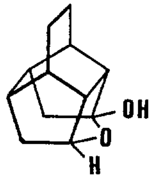

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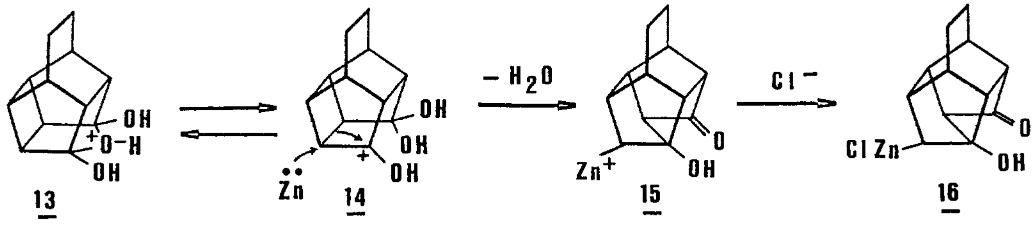
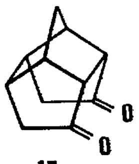
Treatment of 5 with amalgamated zinc and hydrochloric acid (6 mol dm^{-3}) indeed resulted in the formation of 10 in 85% yield confirming that 10 originates from the hydrate 5 and not from the dione 3 as previously reported.[5] Treatment of 5 with hydrochloric acid in the absence of amalgamated zinc produced no rearranged product and only the starting material could be isolated from the reaction mixture. Protonation of the ether oxygen atom in 5 followed by cleavage of the C-O-bond of 13 and rearrangement of 14 in the presence of zinc atoms leads probably to the less strained 15. Normal Clemmensen reduction of 16 produces 10



Due to unfavourable intercarbonylic distance in 2 (n = 1) the corresponding transannular hydrate 4 (as well as the hydrate 6) is unstable and is easily dehydrated as shown before. As expected, the Clemmensen reduction of the hydrate mixture of 2 is dominated by the diketone 2 Typical cyclobutane ring cleavage of 2 to produce 17 is followed by pinacol formation whereby 18 is obtained [6,7] Treatment of the hydrate mixture of 2 with zinc powder in acetic acid produced only 17.



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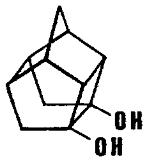

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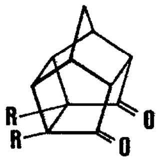
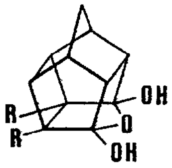
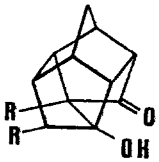
The dimethyl derivative 19[8] behaved remarkably different towards dissolving metal reduction in acidic medium. Evaporation of an acetic acid solution of 19 produced only the stable transannular hydrate 20 which does not dehydrate in DMSO solution The infrared spectrum of 20 exhibits a strong hydroxylic absorption at 3 418 cm^{-1} while no absorptions are observed in the carbonylic region. The FAB mass spectrum (CsI-glycerol matrix) shows a pseudo molecular ion at m/z 486 $[(M+2Cs)^+]$ and a strong peak at m/z 353 $[(M+Cs)^+]$ indicating the presence of two hydroxyl groups and a molecular formula of $C_{13}H_{16}O_3$.



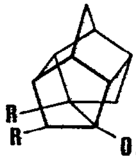
19 ; R = CH_3



20 ; R = CH_3

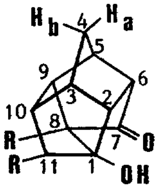


21 ; R = CH_3



22 ; R = CH_3

Treatment of 20 with zinc powder in acetic acid led to the formation of 21[8] in quantitative yield. As expected, the Clemmensen reduction of 20 produced 22 as sole product confirming that transannular hydrates are responsible for the rearrangement reactions during the Clemmensen reduction of the diones 3 and 19. The ^1H and ^{13}C n.m.r. data of 21 are also given in Table 3. The assignment of the different resonace signals in the ^1H and ^{13}C n.m.r. spectra of 21 to certain nuclei was made from homo- and heteronuclear SPI experiments[4] by applying selective π-pulses to certain nuclei as well as COSY and HETCOR experiments.



21 ; R = CH_3

Table 3 ^1H and ^{13}C n m.r. data[a] of 21

	^1H		^{13}C		
Carbon/ Hydrogen	δ_H(ppm)	J(Hz)	δ_C^b(ppm)	^1J(Hz)	$^{>1}J$(Hz)
1			84.41 Sm		
2	2 454		51.48 Dq	148.1	7 1
3	2.560		46.67 Dm	145.6	
4 a b	1.483 1.579 } $J_{(AB)}$	10.5	37.21 T	132 8	
5	2.454		40.96 Ddm	147.4	9.7
6	2 055		49.74 Dm	152.5	
7			218.40 Sm		
8			52.71 Sm		
9	2.258 t	5.6	48.26 Dm	149.5	
10	2.055		50.25 Dm	146.3	
11	2.149 q	7 0	45.78 Dq	129.6	4.3
CH_3 (8)	1.102 s		10.38 Qd	126.7	3.1
CH_3(11)	1.078 d	7.2	12.63 Q	125.4	

[a] Solvent $CDCl_3$; 300 MHz for ^1H and 75 MHz for ^{13}C.

[b] Relative to internal TMS. Symbols in capital letters refer to patterns resulting from directly bonded protons and lower case letters to (C,H)-couplings over more than one bond. S = singlet, D or d = doublet, T = triplet, m = multiplet and Q or q = quartet.

EXPERIMENTAL

Infrared spectra (KBr-disc) were recorded on a Nicolet 5 DX FT-spectrophotometer. FAB mass spectra were recorded on a VG Analytical 7070-E mass spectrometer equipped with an Ion-Tech FAB gun, operating at 8 keV accelerating potential, resolving power approximately 1000 and scanned at 10 s per decade in the positive ion mode. N.m.r. spectra were recorded on a Bruker AC 300 spectrometer.

Hydration of 2 and 3

A solution of 2 or 3 (0.5 g) in ethyl acetate (50 cm^3) was allowed to evaporate to dryness in an open container at room temperature. A hydrate mixture of 4 and 6 was obtained from 2 whereas 3 produced only 5.

4 and 6: Dehydration temperature· 80°C
λ_{max} 3 336, 3 377, 2 993, 1 712, 1 138 and 1 069 cm^{-1}
FAB MS (NaI) m/z 237 $[(M+2Na)^+]$ and 215 $[(M+Na)^+]$
(CsI) m/z: 458 $[(M+2Cs)^+]$ and 325 $[(M+Cs)^+]$
Calc. for $C_{11}H_{12}O_3$ C, 68.75, H, 6.25%. Found C, 68.72; H, 6.26%

5. Dehydration temperature: 152°C
λ_{max} 3 377, 2 920, 1 300, 1 140 and 1 079 cm^{-1}
FAB MS (NaI) m/z: 251 $[(M+2Na)^+]$ and 229 $[(M+Na)^+]$
(CsI) m/z 458 $[(M+2Cs)^+]$ and 325 $[(M+Cs)^+]$
Calc. for $C_{12}H_{14}O_3$. C, 69.90, H, 6.80%. Found C, 69.87, H, 6.76%

Clemmensen Reduction of 5

A mixture of 5 (4 g), zinc amalgam (40 g), 6 mol dm^{-3} hydrochloric acid (70 cm^3) and methanol (10 cm^3) was boiled under reflux for 0.5 h. Steam distillation of the reaction mixture produced 10 (2.9 g, m.p 141-143°C) as the sole product in the distillate. The residue contained no isolatable organic compounds.

Hydration of 19

A solution of 19 (0.5 g) in acetic acid (30 cm^3) was allowed to evaporate to a small volume (5 cm^3) under reduced pressure The hydrate 20 (0.42 g) was filtered off, washed with water and dried

Dehydration temperature 125°C
λ_{max} 3 418, 2 976, 2 959, 2 927, 2 861, 1 114 and 1 081 cm^{-1}
FAB MS (CsI) m/z 486 $[(M+2Cs)^+]$ and 353 $[(M+Cs)^+]$
Calc for $C_{13}H_{10}O_3$ C, 72.90, H, 4.67%. Found: C, 72.86, H, 4.65%

Zinc and Acetic Acid Reduction of 20

A mixture of activated zinc powder (20 g), 20 (1 7 g) and acetic acid (150 cm^3) was boiled under reflux for 0.5 h. The reaction mixture was cooled and diluted with water (100 cm^3). The product 21 (1.28 g, m.p. 85°C) was extracted with dichloromethane and recrystallised from methanol.

λ_{max} 3 320, 2 992, 1 748, 1 270 and 1 165 cm^{-1}
EI MS, m/z 204 (M^+), 202, 189, 174, 159, 136 and 110
Calc. for $C_{13}H_{16}O_2$. C, 76.47, H, 70 84%. Found. C, 76 43, H, 7 81%

Clemmensen Reduction of 20

A mixture of 20 (4 g), zinc amalgam (40 g), 6 mol dm^{-3} hydrochloric acid (70 cm^3) and methanol (10 cm^3) was boiled under reflux for 1 h. The reaction mixture was cooled, neutralised with sodium bicarbonate and the organic phase extracted with dichloromethane Flash chromatography[9] with silika gel (E. Merck Kieselgel 60, 38-63 µm) as stationary phase and a 1:1·1 mixture of benzene, diethyl ether and ethyl acetate as eluant produced 21 (0.65 g) and 22 (2.33 g, m.p. 110°C) consecutively.

22 λ_{max} 3 315, 2 950 and 1 295 cm^{-1}
EI MS, m/z· 190 (M^+), 175, 172
Calc. for $C_{13}H_{18}O$ C, 82 11, H, 9 47% Found: C, 82.06, H, 9.44%

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