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^{1}H NMR SPECTRAL PARAMETERS AND CONFIGURATIONAL ASSIGNMENT OF THE ISOMERIC 1,4-DIACETOXY-2-t-BUTYL-3-METHYLCYCLOPENTANES

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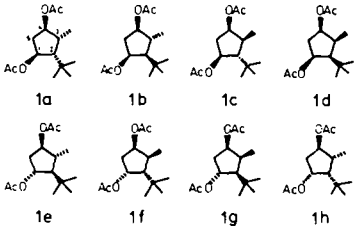
Abstract—The isomeric 1,4-diacetoxy-2-t-butyl-3-methylcyclopentanes have been prepared starting from 2-t-butyl-3-methyl-4-hydroxy-2-cyclopentenone and 3-t-butyl-2-methyl-4-hydroxy-2-cyclopentenone. Configurational assignments are made on the basis of ^{1}H NMR data.

Configurational and conformational studies in our laboratory of 2,3 - dialkyl - 1,4 - diacetoxycyclopentanes[1,2] continue with the present paper, describing the preparation of all eight isomeric 1,4 - diacetoxy - 2 - t - butyl - 3 - methylcyclopentanes (Scheme 1).

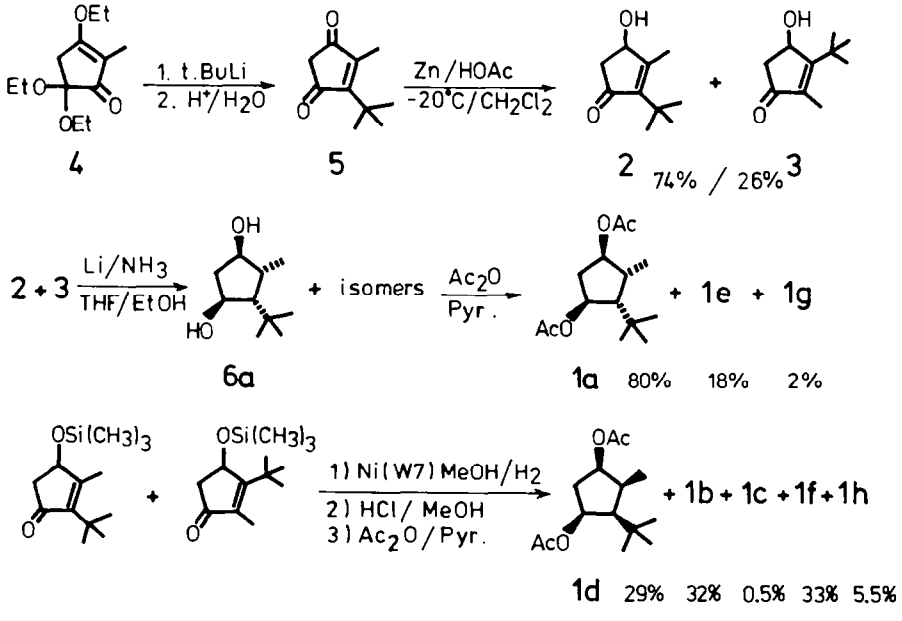


Scheme 1.

The synthesis of the title compounds is outlined in Scheme 2. Reaction of 3,5,5 - triethoxy - 2 - methyl - 2 - cyclopentenone 4[3] with t-butyllithium affords after working up in acidic medium 2 - t - butyl - 3 - methyl - 2 - cyclopentene - 1,4 - dione 5. Reduction of 5 with zinc–acetic acid in methylenechloride at −20°C yields a mixture of the isomers 2 and 3 in a ratio of 74/26. They can be separated by preparative gaschromatography of the more volatile acetoxy derivatives, which are then hydrolysed back with hydrochloric acid–methanol. The pure isomers 2 and 3 were needed to elucidate the stereochemical outcome of the lithium–liquid ammonia reduction as described in the foregoing paper.[4] As the isomeric compounds 1 obtained upon reduction of 2 and/or 3 have to be separated by preparative gaschromatography the presently described reductions were performed on the isomeric mixture of 2 and 3.

Lithium–liquid ammonia–ethanol reduction[5] yields three isomeric diols which were separated as their diacetates **1a**, **1e** and **1g**. Catalytic hydrogenation of the trimethylsilylethers with Raney Nickel (W7) catalyst in methanol (a solvent giving a low stereoselectivity of reduction[1]) gave after acetylation and separation five isomers. Only isomer **1c** could not be purified well enough in order to record an interpretable ^{1}H NMR spectrum. Experiments for obtaining **1c** by a S_N2-reaction with tetraethylammonium acetate on appropriate tosylates of other isomers gave only elimination products.

Table 1 gives the ^{1}H NMR parameters of the seven



Scheme 2.

Table 1.

Solvent CCl_4	1a	1b	1d	1e	1f	1g	1h	6a
δH-5[a]	1.48	1.53	1.55	1.89	1.85[d]	2.17	2.08	1.64
δH-5'[a]	2.64	2.29	2.64	1.89	2.02[d]	1.83	2.08	2.35
δH-1	5.13	5.08	5.16	5.07	5.19	5.12	5.37	4.23
δH-4	4.61	4.58	4.78	4.67	5.14	4.98	4.78	3.88
δH-2	2.16	1.27	1.49	1.42	1.56	1.93	1.81	2.08
δH-3	2.24	2.23	2.51	1.81	2.35	2.52	2.20	2.25
δMe-3	0.98	1.15	1.04	1.15	1.00	0.87	1.23	0.86
δt.Bu	0.99	1.00	1.06	0.90	1.00	0.99	1.05	1.04
J5,5'[b]	-16.1	-15.8	-15.3	-	-15.3	-14.6	-	-15.2
J1,5	3.9	0.6	2.4	5.9[e]	5.4	9.5	4.6[e]	2.0
J4,5	1.8	3.2	8.4	5.9[e]	5.6	10.1	4.6[e]	2.0
J1,5'	9.0	5.4	7.4	5.9[e]	1.2	2.8	4.6[e]	8.6
J4,5'	6.1	8.4	9.2	5.9[e]	6.9	8.6	4.6[e]	4.8
J1,2	9.0	4.4	5.4	5.2	4.7	8.9	4.9	6.8
J3,4	1.0	6.4	6.5	4.5	7.0	5.9	0.7	1.0
J2,3	6.5	11.4	5.4	6.3	10.7	6.0	6.6	6.8
J3,Me-3	7.4[c]	6.6	7.4	7.0	6.9	7.3	7.5	7.4
J3,5	-0.9	-	-	-	-	-	-	c.s
J3,5'	-	-	-	-	-	-0.9	-	-

[a]H-5: cis with Ac-4; H-5': trans with Ac-4 (Scheme 1); [b]coupling constants are given in Hz; [c]could not be measured: the noted value was taken from a spectrum recorded in C_6D_6; [d]the assignment was done arbitrarily; [e]see text.

isomers obtained at 300 MHz in carbon tetrachloride solution (TMS internal standard, room temp.). As the two side chains are different, all isomers lack any kind of symmetry and thus belong to the point group C_1. A classification of the isomers according to a cis or trans relationship of the 1- and 4-acetoxy function can easily be made on inspection of Table 1. A large shift difference (0.5–1 ppm) of the C-5 methylene hydrogens is a diagnostic feature for cis-1,4-diacetoxy groups.[1,2] This criterion divides the seven isomers into two sets: one composed of **1a**, **1b**, **1d** (cis) and the other composed of **1e**, **1f**, **1g**, **1h** (trans). The 1,4-cis-relation in the former was confirmed by positive boric acid complex formation of the corresponding diols **6a**, **6b** and **6d** (GCMS analysis).

The configurational assignment within each set can be made with the aid of criteria concerning chemical shifts and coupling constants derived from the analogous 1,4-diacetoxy-2,3-dimethylcyclopentane[1] series and according to empirical rules for shift values[6] recently become available. Especially the exo coupling constant (J_3, Me-3) is significant; it is at its highest value when the alkyl groups have a cis relation, this effect being associated with the higher strain[7] imposed by this situation. For the set with trans-1,4-diacetoxy groups the relative shift increments for the four indicated hydrogen atoms are summarised in Table 2; for comparison the zero value has been taken for the hydrogen atom with the highest δ-value.

Isomer **1e** shows maximal upfield shifts for all hydrogens which points to the all-trans configuration; the lower value for the exo coupling constant is in agreement with this structure. The low value for $J_{2,3} = 6.3$ Hz (a "normal" value would be > 10 Hz) is not yet fully understood and is probably due to a conformational effect. The other isomer with a small exo coupling supported by a large $J_{2,3}$ value, indicating a trans relation of both alkyl groups is **1f**; inspection of the shift increments determines a cis relation of the acetoxy groups with the vicinal alkyl substituent. Of both compounds with the alkyl groups in cis position (J_3, Me-3 high; $J_{2,3}$ low), the isomer **1h** shows a large upfield shift for H-4, which together with $\Delta\delta$H-1 = 0 assigns the configuration; the remaining isomer of this set has therefore structure **1g** for which the parameters in Table 2 are in agreement. The long range coupling $^4J_{3,5'} = -0.9$ Hz ("M" or "W" pattern[8]) allows the assignment of the high field multiplet of the C-5 methylene hydrogens to H-5' (see Table 1).

Table 2.

	1e	1f	1g	1h
Δδ2[a]	0.51	0.37	0	0.12
Δδ3	0.71	0.17	0	0.32
Δδ1	0.30	0.18	0.25	0
Δδ4	0.47	0	0.16	0.36
J3,Me-3	7.0 Hz	6.9 Hz	7.3 Hz	7.5 Hz

[a] Shift increment relative to highest δ-value.

The spectra of only three of the four isomers of the other set (cis diacetoxy functions) are available. The study of the shift values and exo coupling constants however allows assignment of the configuration (see Table 3).

Table 3.

	1a	1b	1d
$\Delta\delta 2$[a]	0	0.89	0.67
$\Delta\delta 3$	0.27	0.28	0
$\Delta\delta 1$	0.03	0.08	0
$\Delta\delta 4$	0.17	0.20	0
J3,Me-3	7.4 Hz	6.6 Hz	7.4 Hz

[a] Shift increments relative to highest δ-value.

The all-cis isomer **1d** can easily be distinguished; the large exo coupling, the small $J_{2,3}$ value and the large δ-values for H-1 and H-4 are clearly demonstrative. Due to the low value for J_3, Me-3 the alkyl groups in isomer **1b** must have a trans relationship; taking into account the large shift increment for H-4 the structure must be 1 - r - acetoxy - 2 - c - t - butyl - 3 - t - methyl - 4 - c - acetoxycyclopentane.

This leaves only two configurations for the remaining isomer. The structure **1a** is suggested by the relative high shift increment for H-4, the large value for the exo coupling and the relative small coupling constant $J_{2,3}$ = 6.5 Hz (see Table 1). However, not only for the sake of the present argument but also for the elucidation of the mechanism of the lithium–liquid ammonia reduction[4] (**1a** is the major product; see Scheme 2), an independent proof of the configuration **1a** was needed. This was provided by the X-ray diffraction analysis of the corresponding 2 - t - butyl - 3 - methyl - 1,4 - cyclopentanediol **6a**. This analysis will be described in detail elsewhere.[9] The ring torsional angles found in the crystal are shown in Table 4. As demonstrated by Altona *et al.*,[10] the torsional angles ϕ, in a given cyclopentane conformation can be calculated from the maximum torsional angle ϕ_m and the phase angle of pseudorotation[11] Δ with the aid of equation (1). The experimental torsional angles can be reproduced fairly accurate (see Table 4)

$$\phi_j = \phi_m \cos\left(\frac{\Delta}{2} + j\delta\right) \qquad (1)$$

$$j = 0, 1, 2, 3, 4, \quad \delta = 144°$$

with ϕ_m = 44.0°, taken from the basic models derived by Hendrickson.[12] If Δ is taken as 0° for the C_2 form presented in Fig. 1, fixing one of the two neighbouring C_s forms at Δ = 36°, then the intermediate conformation shown by the X-ray determination is at Δ = 6°. This "half-chair" conformation is in agreement with the consideration that the substituents with the highest torsional energy between them (the methyl and the t-butyl group), in order to release this strain will tend to occupy the most puckered part of the ring. As could be expected the t-butyl group takes the equatorial position. A ^{1}H NMR spectroscopic study of the conformational behaviour in solution is currently in progress.

EXPERIMENTAL

2-t-Butyl-3-methyl-2-cyclopentenone **5**

To a solution of t-butyllithium in pentane (Alfa product; 0.35 mol) dry ether (250 ml) was added and the solution was cooled to −40°C. A solution of **4** (40 g; 0.175 mol) in ether (250 ml) was added under stirring over a period of 2 h. After 3 h the reaction mixture was poured in cold HCl (1000 ml: 6 N) and stirred for 1 h. The solution was extracted with ether, washed with sodium bicarbonate and brine. After drying ($MgSO_4$) and evaporation **5** was obtained as a red oil which was purified by destillation. B.p. 95°C (3 mm Hg). Yield 65%. TLC; R_f = 0.62 (ether–benzene 1 : 1 as eluent). UV (MeOH): 243 nm. IR: peaks at 3420, 2960, 2880, 1740, 1700, 1600, 1375, 1310, 1250, 1215, 1070, 925, and 790 cm^{-1}. ^{1}H NMR (60 MHz–CCl_4); 3-CH_3: δ = 2.13; 2-t-Bu: δ = 1.36; 5-CH_2: δ = 2.69. MS (peaks > 30%): *m/e* at 166 (M^+; 38%), 124 (67%),

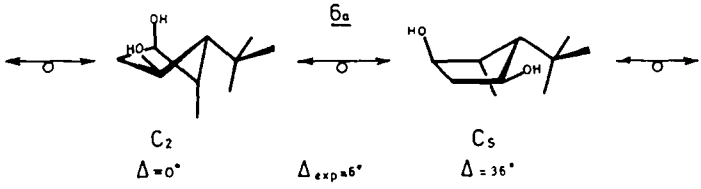


Fig. 1.

Table 4.

6a	Experimental X-ray	Calculated[a] ϕ_m = 44.0° ; Δ = 6°
ϕ_0 (C-2 - C-3)	43.82°	43.94°
ϕ_1 (C-1 - C-2)	-37.11°	-36.90°
ϕ_2 (C-1 - C-5)	15.72°	15.77°
ϕ_3 (C-4 - C-5)	11.58°	11.39°
ϕ_4 (C-3 - C-4)	-34.41°	-34.19°

[a] See text.

123 (30%), 109 (36%), 81 (100%) and 53 (32%). Found: C, 72.38; H, 8.63. $C_{10}H_{14}O_2$ requires: C, 72.27; H, 8.49%.

4-Hydroxy-2,3-methyl t-butyl-2-cyclopentenones **2** *and* **3**

A solution of **5** (18 g; 0.11 mol) in dry CH_2Cl_2 (50 ml) and glacial AcOH (50 ml) at −20°C was added dropwise to a suspension of zinc powder (29 g, 0.44 mol) in CH_2Cl_2 (150 ml) and glacial AcOH (150 ml) at −20°C. After stirring for 3 h at −20°C, the reaction mixture was concentrated *in vacuo*. Ether was added and the zinc was filtered off and washed thoroughly with ether. The combined filtrates were washed with a sodium carbonate solution (10% in water), dried (Na_2SO_4) and evaporated. The residual yellow oil was sufficiently pure for transformation into the acetate. Purification can however be done by column chromatography (silica gel; ethylacetate–iso octane 75:25). TLC; R_f = 0.49 and 0.53 (ethylacetate as eluent).

The acetates of **2** *and* **3**

The mixture of enolones **2** and **3** (10 g) dissolved in acetic anhydride (150 ml) and pyridine (150 ml) was stirred for 3 h at room temp. The reaction mixture was poured on ice and extracted (after 30 min) with n-pentane. The extract was washed with 2% aq HCl, dried (Na_2SO_4) and evaporated (yield 95%). TLC: R_f = 0.57 and 0.63 (ether–benzene 1:1 as the eluent). IR: strong absorptions at 2960, 1740, 1710, 1625, 1370, 1250, 1230 and 1020 cm^{-1}. Preparative GC of the acetates was performed on SE-30 (10% on Chromosorb G, 6 m, 200°C).

4-Hydroxy-2-t-butyl-3-methyl-2-cyclopentenone **2**

4 - Acetoxy - 2 - t - butyl - 3 - methyl - 2 - cyclopentenone (3 g) dissolved in 20% HCl in methanol (50 ml) was stirred for 5 h at room temp. the reaction mixture was neutralised with 5% NaOH in methanol solution at pH = 7. The solvent was evaporated, the residue was dissolved in ether and the inorganic salts were filtered off. The combined ether fractions were washed with brine, dried (Na_2SO_4) and evaporated. Purification by column chromatography with ethylacetate–iso-octane (1:1) as eluent yielded a colourless oil. Yield 95%. TLC; R_f = 0.20 (ether–benzene as the eluent). UV (MeOH) 230 nm. IR: 3390 (broad), 2960, 1690 (broad), 1620, 1480, 1460, 1390, 1370, 1360, 1310, 1240, 1220, 1200, 1170, 1140, 1080, 1050, 1025, 1010, 970, 920, 860, 825 and 720 cm^{-1}. ^{1}H-NMR (100 MHz, CCl_4); 2-t-Bu: δ = 1.25; 3-C$\underline{H}_3$: δ = 2.21 (m = 4, ^4J = −0.7 Hz); 4-C$\underline{H}$: δ = 4.42; 5-C$\underline{H}_A\underline{H}_B$/$\delta$ = 2.12 (m = 4) and 5-C$\underline{H}_A\underline{H}_B$/$\delta$ = 2.54 (m = 4); ABX-system (J_{AB} = −17.9 Hz; J_{AX}(trans) = 2.5 Hz; J_{BX}(cis) = 6.2 Hz). MS (peaks > 30%): *m/e* at 168 (M^+; 53%), 153 (32%), 125 (39%), 111 (64%), 81 (48%), 67 (34%), 57 (31%), 53 (36%) and 43 (100%). Found: C, 71.72; H, 9.70. $C_{10}H_{16}O_2$ requires: C, 71.40; H, 9.59%.

4-Hydroxy-3-t-butyl-2-methyl-2-cyclopentenone **3**

From the 4 - acetoxy - 3 - t - butyl - 2 - methyl - 2 - cyclopentenone as described for **2**. Yield: 95%. TLC: R_f = 0.19 (ether–benzene 1:1 as the eluent). UV (MeOH) 230 nm. IR: 3420 (broad), 2900, 1690 (broad), 1615, 1465, 1395, 1375, 1360, 1315, 1245, 1155, 1070, 1040, 1020, 980, 890, 860, 795 and 760 cm^{-1}. ^{1}H NMR (100 MHz–CCl_4); 3-t-Bu: δ = 1.33; 2-C$\underline{H}_3$: δ = 1.79 (m = 2, ^5J = 1.1 Hz); 4-C$\underline{H}$: δ = 4.85; 5-C$\underline{H}_A\underline{H}_B$/$\delta$ = 2.10 (m = 4) and 5-C$\underline{H}_A\underline{H}_B$/$\delta$ = 2.54 (m = 4); ABX-system (J_{AB} = −18.2 Hz; J_{AX}(trans) = 1.2 Hz; J_{BX}(cis) = 5.9 Hz). MS (peaks > 30%): *m/e* at 168 (M^+; 14%), 124 (45%), 112 (72%), 111 (51%), 109 (50%), 81 (93%), 57 (64%), 53 (32%), 43 (61%) and 41 (100%).

Catalytic hydrogenation of the trimethylsiloxycyclopentenones **7** *and* **8**

The trimethylsiloxy derivatives **7** and **8** were prepared with hexamethyldisilazane as described in Ref. 1. To a solution of **7** and **8** (10 g, 0.041 mol) in dry MeOH (300 ml) was added about 10 g of freshly prepared Raney-Ni catalyst, modification W7,[13] and the pH of the solution was adjusted to 8–8.5 with NaOH. The reduction was carried out in a Parr apparatus (starting pressure: 40 lb in^{-2} H_2) and was almost complete after 24 h. The catalyst was filtered off and the filtrate was acidified with dil HCl. The MeOH was removed under reduced pressure and the remaining aqueous solution was extracted with ether. The ether extract was washed with brine, dried ($MgSO_4$) and evaporated. The mixture of isomeric 2 - t - butyl - 3 - methyl - 1,4 - cyclopentanediols, obtained as a viscous oil, was sufficiently pure for further reaction. Yield 92%. Preparative GC after formation of the diacetates yielded **1d** (29%), **1b** (32%), **1c** (0.5%), **1f** (30%) and **1h** (5.5%).

Dissolved metal reduction of the cyclopentenolones **2** *and* **3**

The mixture of **2** and **3** (8.4 g; 0.05 mol) dissolved in super-dry ethanol (15 ml) and dry tetrahydrofuran (70 ml) was added to liquid ammonia (250 ml; distilled from sodium). Lithium (2.8 g; 0.4 mol) was then added in small pieces. After 45 min the excess lithium was destroyed with ammonium chloride. The ammonia was evaporated, ether was added and the inorganic salts were filtered off. After acidifying with dil HCl, the water layer was thoroughly extracted with ether and the extracts dried (Na_2SO_4) and evaporated. The diol mixture was purified by column chromatography (silica gel; ether:benzene 60:40). Yield 77%. TLC; R_f = 0.28 with ethylacetate as eluent. Preparative GC after formation of the di-acetates yielded **1a** (80%), **1e** (18%) and **1g** (2%). The diol **6a** could be obtained by crystallisation of the crude reaction mixture by adding dry ether (m.p. 116°C). Found: C, 70.12; H, 11.95. $C_{10}H_{20}O_2$ requires: C, 69.73; H, 11.70%.

^{1}H NMR spectral analysis

The spin system formed by the ring hydrogen atoms is in principle of the type ABMNXY. Since the spectrometer was a 300 MHz apparatus, the $\Delta\nu$/J ratios were in most cases sufficiently large to justify a first order analysis. Where needed, a subspectral second order analysis ABXY (JX,Y ~ 0) was applied. In the isomers **1e** and **1h** the C-5 methylene hydrogens were accidentally isochronous and appeared as a "triplet" with a reduced and broadened central line. As they are probably not magnetically equivalent in the spin coupling sense and form, say, a subspectral AA′ system, the individual coupling constants could not be determined because certain lines needed for the analysis were of too low intensity to be found. Only the sum of the coupling constants (measured between the outer lines of the "triplet") could be established and the values presented in Table 1 equal ΣJ/2.

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