NEW CYCLODIMERIZATION REACTION OF (3,5-DI-*tert*-BUTYL-4-OXOCYCLOHEXA-2,5-DIENYLIDENE)ACETIC ACID

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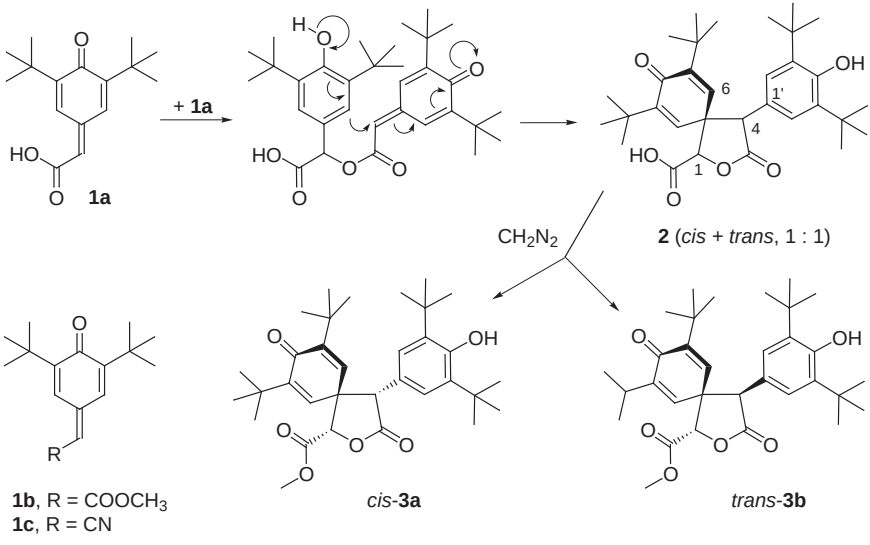
(3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)acetic acid **1a** underwent on heating a new cyclodimerization reaction affording a 1 : 1 mixture of the racemic *cis*- and *trans*-isomeric lactone-acids **2**. The decisive structure elucidation of **2** was carried out after its mild esterification with diazomethane and separation of the racemic isomeric methyl esters **3a** and **3b**. The attempted esterification of **2** with methanol and sulfuric acid gave only the methyl diarylacetate **4**. In contrast to **1a**, which contains the carboxylic acid functionality no cyclodimerization was observed with the corresponding methyl ester **1b** or nitrile **1c**.
Keywords: Quinone methides; Cyclodimerization; Diaryl acetates; Butyrolactones; Esterification; Glyoxylic acid; Reaction mechanism.

Quinone methides[1] being highly reactive compounds are very useful as synthetic intermediates[2]. They also play an important role in biochemical reactions[3] and have also industrial importance, for instance, as polymerization inhibitors[4] or transformation products[5] of phenolic antioxidants. The strong dipolar character of quinone methides imparted by the presence of two electronically different substituents, carbonyl and methylidene, on the cyclohexadiene ring determines their reactivity. Indeed, the addition of a broad range of nucleophiles, *e.g.* thiols[6], dialkyl phosphites[7], ammonia[8], amines[9] or phenoxides[10] to the electrophilic exocyclic alkylidene carbon is the predominant reaction of quinone methides. Additions of free radicals[6] to quinone methides or their involvement in Diels–Alder reaction[11,2a] are also known.

RESULTS AND DISCUSSION

Recently, one of us published a new large-scale synthesis[12] of quinone methides[13] **1a**–**1c**. When working with **1a** we observed that this compound

was partially transformed into a new product during crystallization from octane. This prompted us to investigate this reaction in more detail. Indeed, when refluxed in octane for 20 h, **1a** afforded 81.6% of a new, colorless, sparingly soluble compound. The ^{1}H NMR, ^{13}C NMR, MS and IR spectra and elemental analysis suggested the presence of two diastereoisomeric lactone-acids *cis*- and *trans*-**2** in 1 : 1 ratio. Unfortunately, separation of the diastereoisomers by crystallization or chromatography was not possible because of their very low solubility. Therefore, the mixture of *cis*- and *trans*-**2** was esterified with diazomethane and the resulting much more soluble diastereoisomeric methyl esters were separated by column chromatography on silica gel to afford the pure diastereoisomeric racemates *cis*-**3a** and *trans*-**3b**. Their structures were conclusively elucidated with the same techniques as for *cis*- and *trans*-**2**. The relative configurations of *cis*-**3a** and *trans*-**3b** were determined with the help of ^{1}H-NOE NMR spectroscopy. Indeed, only the higher melting *cis*-**3a** isomer showed strong NOE between the protons H-1 and H-4 (see Scheme 1 for numbering). The assignments of the ^{1}H NMR resonances for *cis*- and *trans*-**2**, *cis*-**3a** and *trans*-**3b** are compiled in the Table I. The unambiguous assignment of the H-6 and H-10 resonances in both *cis*-**3a** and *trans*-**3b** was also achieved using NOE's (see Table I). The rather complex spectra of the mixture *cis*- and *trans*-**2** were interpreted by analogy with the data obtained for the pure isomers *cis*-**3a** and



SCHEME 1

trans-**3b**. The as far as possible assignment of ^{13}C-resonances was accomplished with the help of additional ^{13}C NMR-DEPT spectra. The corresponding data are summarized in Table II.

A proposal of a plausible mechanism explaining the formation of *cis*- and *trans*-**2** is presented in Scheme 1. Thereafter, the cyclodimerization of **1a** commences by the nucleophilic addition of the carboxylic group of one molecule of **1a** to the electrophilic exocyclic methine carbon of another **1a** yielding the intermediate having both the nucleophilic phenolic and the electrophilic quinone methide moiety. The attack of the former on the exocyclic methine carbon leads to the product *cis*- and *trans*-**2**. The mechanism according to Scheme 1 is supported by the fact that the quinone methides **1b** and **1c** which cannot undergo the initial nucleophilic addition of the carboxylic group were entirely stable during refluxing in octane. Interestingly, intramolecular cyclizations between the exocyclic quinone

TABLE I
Assignment of the ^{1}H NMR (360.13 MHz) resonances for *cis*- and *trans*-**2**, *cis*-**3a** and *trans*-**3b**

Assignment	**2** (*cis* + *trans*, 1 : 1), δ, ppm		*cis*-**3a** δ, ppm	*trans*-**3a** δ, ppm
	cis	*trans*		
COOH, bs	7.5–7.9		–	–
H-2′ and H-6′, s	6.84	6.78	6.84	6.77
H-6, d, J = 3 Hz	6.65	6.33	6.66	6.32
H-10, d, J = 3 Hz	6.39	6.48	6.36	6.37
–O–H, s	5.18	5.18	5.17	5.18
H-1, s	4.99	4.77	4.94[a]	4.73[b]
H-4, s	4.19	4.22	4.18[c]	4.23[d]
–$COOCH_3$, s	–	–	3.61	3.86
t-Bu-3′ and *t*-Bu-5′, s	1.36	1.36	1.36	1.36
t-Bu-7 or *t*-Bu-9, s	1.27	1.24	1.28	1.23
t-Bu-7 or *t*-Bu-9, s	0.95	0.98	0.94	0.98

[a] Strong NOE from H-1 to H-4 and H-6. [b] Strong NOE from H-1 to H-6. [c] Strong NOE from H-4 to H-1, H-6 and H-2′ + H-6′. [d] Strong NOE from H-4 to H-10 and H-2′ + H-6′.

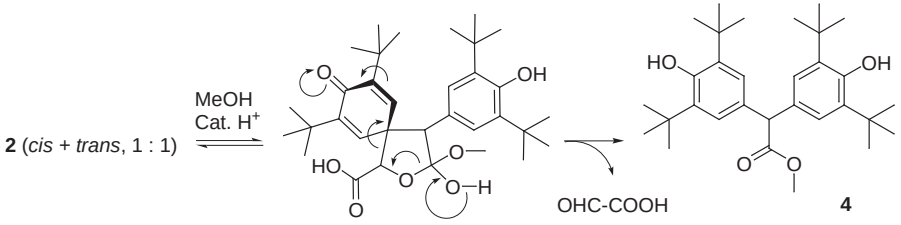
TABLE II
Assignment of the ^{13}C NMR (90.55 MHz) signals for *cis*- and *trans*-**2**, *cis*-**3a** and *trans*-**3b**

Assignment	**2** (*cis* + *trans*, 1 : 1), δ, ppm			*cis*-**3a** δ, ppm	*trans*-**3a** δ, ppm
	cis		*trans*		
C-8	185.01		184.68	185.13	184.76
C-3	172.56		174.17	172.68	174.25
$COOCH_3$	169.14		171.21	165.85	168.37
C-4′	153.94		153.87	153.84	153.80
C-7 or C-9	151.88		151.56	151.53	151.39
C-7 or C-9	150.44		148.64	149.90	148.39
C-6 or C-10	136.67[a]		136.15[a]	137.17[a]	136.42[a]
C-3′ and C-5′	135.97		136.12	135.93	136.07
C-6 or C-10	132.73[a]		135.00[a]	133.46[a]	135.31[a]
C-2′ and C-6′	125.37[a]		125.37[a]	125.25[a]	125.37[a]
C-1′	120.66		121.18	120.95	121.39
C-1	78.83[a]		78.83[a]	79.20[a]	79.15[a]
C-4	56.40[a]		53.83[a]	56.22[a]	53.75[a]
C-5	52.50		50.74	52.51	52.72
CH_3OOC	–		–	52.28[b]	50.92[b]
$(CH_3)_3$-C-7 or $(CH_3)_3$-C-9	35.27	or	35.20	35.16	35.19
$(CH_3)_3$-C-7 or $(CH_3)_3$-C-9	35.04	or	34.88	34.95	34.84
$(CH_3)_3$-C-3′ or $(CH_3)_3$-C-5′	34.26	or	34.25	34.25	34.25
$(CH_3)_3$-C-3′ or $(CH_3)_3$-C-5′	30.08[b]	or	29.43[b]	30.08[b]	30.09[b]
$(CH_3)_3$-C-7 or $(CH_3)_3$-C-9	28.89[b]		28.89[b]	29.41[b]	29.46[b]
$(CH_3)_3$-C-7 or $(CH_3)_3$-C-9	28.87[b]		28.87[b]	28.89[b]	28.89[b]

[a] DEPT resonance indicates 1 directly bonded H. [b] DEPT resonance indicates 3 directly bonded H.

methide methine carbon and a suitable nucleophile incorporated in the substituent of this methine carbon were described[2b] some time ago.

When larger samples of isomers *cis*-**3a** and *trans*-**3b** were needed for further work, a simpler esterification of *cis*- and *trans*-**2** with methanol and sulfuric acid was attempted. Surprisingly, the only product obtained was the methyl diarylacetate **4**. A mechanistic proposal for the formation of **4** is outlined in Scheme 2. Thereafter, the reaction starts with an acid-catalyzed addition of methanol on the lactone carbonyl group. The depicted fragmentation, with elimination of glyoxylic acid (or its methyl ester), affords **4**.



SCHEME 2

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AM-300 or AM-360 spectrometers. Chemical shifts are given in ppm (δ-scale). The MS spectra were measured on a Finnigan SSQ 710 apparatus at 70 eV. IR spectra (wavenumbers in cm^{-1}) were taken on a Nicolet Magna-IR 750 spectrometer in KBr pills. The melting points were determined on a hot stage microscope and are not corrected.

(*cis*- and *trans*)-7,9-Di-*tert*-butyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3,8-dioxo-2-oxaspiro[4.5]deca-6,9-diene-1-carboxylic Acid (**2**)

A solution of (3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)-acetic acid[12] (**1a**) (13.12 g, 0.05 mol) in 100 ml of an octane fraction (b.p. 124–128 °C) was refluxed with stirring under nitrogen for 21 h. A white solid precipitated out during this time. The reaction mixture was then cooled to room temperature, the solid was filtered off, washed with octane (50 ml) and dried to afford 10.71 g (81.6%) of **2** as a white powder, m.p. 228–230 °C. MS (*m/z*, %): 524 (M^+, 5), 263 (20), 246 (100), 233 (10), 219 (23). IR: 3 638, 2 961, 1 795, 1 756, 1 648, 1 439, 1 371, 1 203, 1 140, 1 079, 1 058. For $C_{32}H_{44}O_6$ (524.7) calculated: 73.25% C, 8.45% H; found: 73.17% C, 8.47% H.

The red residue (2.2 g), obtained after evaporation of the mother liquor, contained the practically pure (^{1}H NMR, 300.13 MHz) starting **1a**.

Esterification of **2** with Diazomethane

An etheral solution (approximately 0.4 mol l^{-1}) of diazomethane was added dropwise at room temperature to a stirred solution of **2** (7.87 g, 0.015 mol) in 150 ml of dichloromethane until the yellow color of diazomethane persisted for 2 min. The excess of diazomethane was then destroyed by addition of 5 drops of acetic acid and the colorless solution was evaporated on a rotary evaporator to give 8.12 g (≈100%) of the **3a** + **3b** mixture, m.p. 192–226 °C. After chromatography on a silica gel (200 g) column with dichloromethane pure **3a** and **3b** were isolated, see below.

cis-7,9-Di-tert-butyl-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-3,8-dioxo-2-oxa-spiro[4.5]deca-6,9-diene-1-carboxylic acid methyl ester (**3a**): 3.96 g (49% based on **2**), m.p. 232–235 °C, single spot on silica gel plate (R_F 0.42, methylene chloride). Recrystallization of 2.96 g of crude **3a** from 20 ml toluene afforded 2.82 g of the analytically pure **3a**, m.p. 234–236 °C. MS (*m/z*, %): 538 (M^+, 7), 450 (5), 293 (20), 277 (8), 246 (100), 233 (18), 219 (25). IR: 3 637, 2 954, 1 791, 1 751, 1 665, 1 645, 1 485, 1 460, 1 438, 1 370, 1 251, 1 216, 1 164, 1 120, 1 090. For $C_{33}H_{46}O_6$ (538.7) calculated: 73.57% C, 8.61% H; found: 73.45% C, 8.70% H.

trans-7,9-Di-tert-butyl-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-3,8-dioxo-2-oxa-spiro[4.5]deca-6,9-diene-1-carboxylic acid methyl ester (**3b**): 4.02 g (49.7% based on **2**), m.p. 195–198 °C, single spot on silica gel plate (R_F 0.63, methylene chloride). Recrystallization of 3.53 g of crude **3b** from 20 ml toluene afforded 2.58 g of the analytically pure **3b**, m.p. 197–199 °C. MS (*m/z*, %): 538 (M^+, 7), 450 (5), 293 (20), 277 (8), 246 (100), 233 (18), 219 (25). IR: 3 640, 2 956, 1 799, 1 749, 1 665, 1 645, 1 438, 1 368, 1 333, 1 253, 1 238, 1 209, 1 152, 1 136, 1 122, 1 101, 1 081. For $C_{33}H_{46}O_6$ (538.7) calculated: 73.57% C, 8.61% H; found: 73.53% C, 8.68% H.

Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetic Acid Methyl Ester (**4**)

A solution of **2** (1.31 g, 0.0025 mol) in 25 ml of anhydrous methanol containing 0.25 ml of 98% H_2SO_4 was refluxed under nitrogen atmosphere for 20 h. The reaction mixture was then cooled to room temperature, diluted with 50 ml dichloromethane and washed with 200 ml water. The organic layer was dried over $MgSO_4$ and evaporated on a rotary evaporator to give 1.17 g (97%) of **4**, m.p. 139–141 °C, single spot on silica gel plate (R_F 0.84, methylene chloride). Recrystallization from 10 ml octane afforded 1.03 g of the analytically pure **4**, m.p. 139–141 °C. MS (*m/z*, %): 482 (M^+, 13), 423 (100), 277 (5), 226 (10). ^{1}H NMR (300.13 MHz): 7.19 s, 4 H (ArH); 5.13 s, 2 H (OH); 4.82 s, 1 H; 3.71 s, 3 H (OCH_3); 1.41 s, 36 H (*t*-Bu). ^{13}C NMR (75.47 MHz): 174, 152.9, 135.7, 129.5, 125.3, 56.7, 52.1, 34.4, 30.3. IR: 3 611, 2 959, 1 723, 1 434, 1 237, 1 198, 1 161. For $C_{31}H_{46}O_4$ (482.7) calculated: 77.14% C, 9.61% H; found: 76.91% C, 9.67% H.

Attempted Cyclodimerization of **1b** and **1c**

A solution of (3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)acetic acid methyl ester[12] (**1b**) (0.69 g, 0.0025 mol) or (3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dienylidene)acetonitrile[12] (**1c**) (0.61 g, 0.0025 mol) in 5 ml of octane fraction (b.p. 124–128 °C) was refluxed with stirring under nitrogen for 21 h. The ^{1}H NMR (300.13 MHz) spectra of the residues after evaporation of octane were identical with those of the starting **1b** and **1c**.

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