Alkylation of Dimedone with 1,4-Dibromobutyne-2 and *trans*-1,4-Dibromobutene-2

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Dimedone on treatment with 1,4-dibromobutyne-2 gave the 1,4-disubstituted butyne-2 derivative *1* as well as an unexpected dibromide *2*. On hydrogenation under appropriate conditions *1* was converted into the corresponding *cis*-butene-2 or butane derivatives, *3* and *4*, respectively. Dimedone and *trans*-1,4-dibromobutene-2 in the presence of copper catalyst gave the *trans*-1,4-disubstituted butene-2 derivative *5b* which on hydrogenation gave *4*. On similar treatment but without copper catalyst no *5b* was obtained. The exclusive acidic product was 1,2-bis(2,6-diketo-4,4-dimethylcyclohexyl)butene-3 (*6*), isomeric with *5b*. On hydrogenation *6* gave the butane derivative *7*. The suggested mechanism for the formation of *6* involves internal S_N2' displacement and nucleophilic ring opening of a cyclopropane intermediate.

In our studies on oxidative coupling of cyclic β-diketones with iron(III) hexacyanoferrate(III)[1–4] we wanted to investigate how a lengthened carbon chain between the two active 1,3-cyclohexanedione rings would influence the course of reaction. We now report on the synthesis of some model compounds for such studies derived from dimedone and 1,4-dibromobutyne-2 or *trans*-1,4-dibromobutene-2.

The formulae and the NMR spectra of the compounds described here are given in Table 1.

The potassium salt of dimedone was allowed to react with 1,4-dibromobutyne-2 in methanol-water (3:2) at room temperature. The acidic fraction from the complex reaction mixture was shown to contain four major and at least seven minor components by TLC. Careful acidification and fractional crystallization of the mixture resulted in the isolation of three of the major components, unchanged dimedone, a dibromide, $C_{12}H_{16}Br_2O_2$, and the desired 1,4-disubstituted butyne-2 derivative *1*.

The dibromide gave no reaction with silver nitrate even on prolonged boiling. The UV spectrum indicated the presence of one enolisable dimedone

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Table 1. NMR parameters for compounds *1—7*.

Compound		Chemical shifts, ppm			
No.	Solvent	(a)	(b)	(c)	(d)
1	CD_3OD	1.02 (12H)s	2.28 (8H)s	3.02 (4H)s	
2	CD_3OD	1.10 (6H)s	2.32 (4H)s	3.62 (2H)s(br)	2.40 (3H)tr $J = 1.5$ cps
3	CD_3OD	1.05 (12H)s	2.30 (8H)s	3.12 (4H)d(br) $J \sim 5$ cps	5.19 (2H)qua $J_{cis} \sim 7$ cps $J_{cd} \sim 5$ cps
4	$CDCl_3$	1.09 (12H)s	2.34 (4H)s 2.38 (4H)s	~ 2.5 (4H)m	~ 1.1 (4H)m
5a	DMSO-d_6			2.73 (4H)d(br) $J \sim 5$ cps	5.26 (2H)m
5b	CD_3OD	1.04 (12H)s	2.27 (8H)s	2.89 (4H)d(br) $J \sim 5$ cps	5.38 (2H)m
6	CD_3OD	1.02 (12H)s	2.23 (8H)s	2.62 (2H)qua	3.72 (1H)qua (e) 6.17 (1H)m (f) 4.82 (1H)m (g) 4.98 (1H)m
7		Spectrum not determined due to solubility difficulties.			
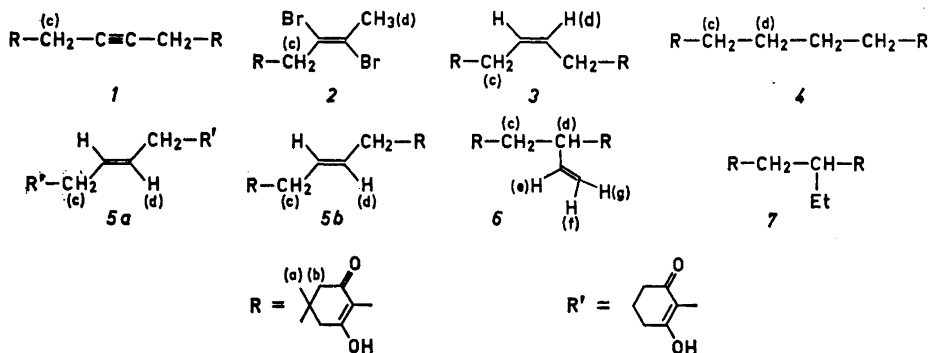
ring.[5] On these grounds the dibromide was formulated as the *trans* structure *2* or the corresponding *cis* structure.

Conclusive evidence for structure *2* was given by the NMR spectrum (Table 1). The methyl and the methylene protons of the dimedone ring give rise to singlets at δ 1.10 (6H) and δ 2.32 (4H), respectively.[2] The triplet ($J = 1.5$ cps) at δ 2.40 (3H) is assigned to the methyl protons in the side chain.[6] These protons couple homoallylically with the methylene protons (δ 3.62, 2H, broad singlet) between the dimedone ring and the double bond. Methylene protons of that type are found around δ 3.0, if the double bond is unsubstituted (*cf.* Table 1, compounds *3*, *5a*, and *5b*). A bromine in the α-position would be expected to cause a downfield shift of about 0.6—0.7 ppm.[6] The large coupling constant ($J = 1.5$ cps) exhibited by the methyl protons is clear evidence for the *trans* configuration.

No rational mechanism for the unexpected formation of *2* can at present be proposed.

The butyne derivative *1* on hydrogenation at atmospheric pressure over Pd/BaSO$_4$ poisoned with quinoline [7] consumed one mole of hydrogen and gave *cis*-1,4-bis(2,6-diketo-4,4-dimethylcyclohexyl)butene-2 (*3*), m.p. 188 − 190°C. On hydrogenation under similar conditions using PdO/BaSO$_4$ as catalyst,[8] compound *1* consumed two moles of hydrogen and gave the corresponding butane derivative *4*, m.p. 250 − 251°C.

Stetter and Dierichs [9] have described a procedure to prepare *trans*-1,4-bis(2,6-diketocyclohexyl)butene-2 (*5a*) in good yield (69 %). Attempts were made to obtain the corresponding dimedone derivative *5b* by a similar procedure. The potassium salt of dimedone was allowed to react with *trans*-1,4-dibromobutene-2 in methanol-water (3:2) at room temperature in the presence of catalytic amounts of Cu$_2$Cl$_2$ (alternatively Cu powder). The desired product *5b*, m.p. 216 − 218°C (decomp.), 21 % yield, could easily be isolated from the complex acidic fraction of the reaction mixture. Although *5b* was the only isolated reaction product, IR spectra were recorded for all the crude fractions obtained.

On hydrogenation of *5b* at atmospheric pressure using PdO/BaSO$_4$ catalyst the uptake of hydrogen was slow and complete hydrogenation could not be effected. However, a product, C$_{20}$H$_{30}$O$_4$, identical with compound *4* was isolated in low yield. The same slow reaction was observed on the attempted hydrogenation of *5a*.

The poor yield of *5b* obtained from the reaction described above, prompted us to change the reaction conditions. Thus, when we repeated the alkylation experiment without copper catalyst we obtained a completely different acidic fraction containing only one acidic compound besides dimedone. This compound, m.p. 182 − 183°C, 52 % yield, had the composition C$_{20}$H$_{28}$O$_4$ and is isomeric with *5b*. The compound shows a UV spectrum practically identical with that of *5b*. The IR spectra of the isomers are also similar. However, two sharp bands at 900 and 1000 cm^{-1} not present in the spectrum of *5b* can be attributed to a vinyl group, suggesting structure *6* for the product. The NMR spectrum of the compound gives conclusive evidence in favour of structure *6* (Table 1). The protons of the two dimedone rings give rise to two singlets at δ 1.02 (12H) and δ 2.23 (8H), respectively. A quartet at δ 2.62 (2H) is assigned to the diastereomeric methylene protons. The methine proton at the asymmetric carbon gives rise to a 1:3:3:1 quartet ($J = 7.5$ cps) at δ 3.72. The vinyl group shows the expected multiplets at δ 4.82, δ 4.98 and δ 6.17.[10]

On hydrogenation compound *6* consumed one mole of hydrogen and gave *7*. The structure of *7* was confirmed by spectroscopic data, especially the mass spectrum.[11] The reaction of *7* with iron(III) hexacyanoferrate(III) has been described elsewhere.[3]

Examination of the IR spectra of the crude fractions obtained from the reaction mixture of *5b* mentioned above, gave no indication that *6* was present when copper catalyst was used. Compound *6* gives distinct IR absorption bands at 900, 1000, 1210, and 1308 cm^{-1} whereas *5b* lacks pronounced absorption at these positions.

Further attempts to improve the yield of *5b* were unsuccessful.

It is noteworthy that in the absence of copper the reaction between dimedone and *trans*-1,4-dibromobutene-2 proceeds with the exclusive formation of *6*. A plausible mechanism of formation (Fig. 1) involves an initial S_N2
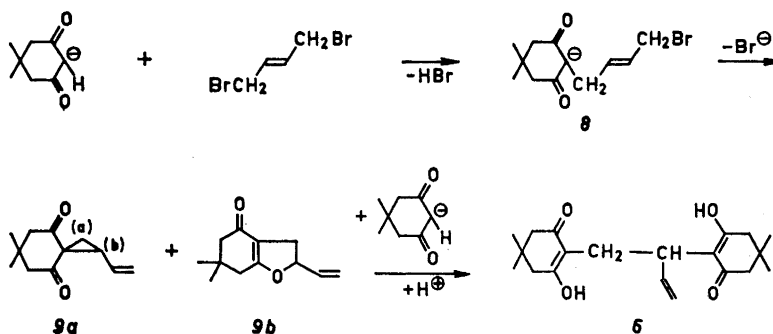

Fig. 1.

reaction to give a monobromo derivative as its anion *8*. The possibility that *8* reacts directly with a second dimedone anion by an S_N2' reaction to *6* is highly unlikely. There are a few exceptional examples reported of primary allylic halides in which the S_N2' reaction is favoured over S_N2. Strong electron-withdrawing substituents on the $C=C$ bond might give predominant S_N2' attack.[12,13] However, the structure of *8* would favour an internal S_N2' displacement to give the spiro cyclopropane derivative *9a* or the cyclic enol ether *9b*. The S_N2 ring closure alternatives can be excluded for steric reasons.

In the last step one possible route involves a nucleophilic attack of a dimedone anion on the cyclopropyl ring of *9a*. The attack can occur either on carbon (a) or carbon (b), in both cases leading to *6*. Analogous nucleophilic ring opening reactions of cyclopropane derivatives having one or more electron-withdrawing substituents have been reported. In these cases, *e.g.*, diethyl sodiomalonate,[14] amines,[15] and halides [16] were used as nucleophiles.

An alternative route to *6* involves a similar ring opening of the enol ether *9b*.

In the presence of copper catalyst the course of reaction is completely changed. The effect of the catalyst might involve an increase in the rate of the normal S_N2 reaction of *8*. Alternatively the rate of the intramolecular S_N2' reaction of *8* is decreased. Klingenfuss [17] reported that copper increases the rate of reaction between allyl bromide and 1,3-cyclohexanedione but gave no experimental details. We believe that both factors are involved, although further studies are necessary to clarify the entire role of the copper catalyst.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. IR spectra were recorded on a Perkin-Elmer No. 221 or a 257 instrument. UV spectra were measured in 99.5 % ethanol with a Beckman DK 2 spectrophotometer. The NMR spectra were obtained on

a Varian A-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are given in δ (ppm) units. The analyses were made by A. Bernhardt, Mikro-analytisches Laboratorium, Elbach über Engelskirchen, West Germany.

Chromatographic investigations. All reactions were followed by TLC on polyamide (Merck) or silica gel HF plates with 1,2-dichloroethane-methanol in different proportions as solvents. The spots were detected as previously described.[2]

trans-1-(2,6-Diketo-4,4-dimethylcyclohexyl)-2,3-dibromobutene-2 (2). To a stirred solution of dimedone (14 g, 100 mmol) and KOH (6.46 g, 86 %, 100 mmol) in methanol-water (3:2) (20 ml) was added dropwise 1,4-dibromobutyne-2[18] (8.69 g, 41 mmol). The mixture was stirred overnight. After addition of 15 % NaOH (20 ml) and filtration, the filtrate was extracted with ether (3 × 20 ml) and acidified with 2 M HCl to pH 6. The precipitate (5.2 g) was recrystallized several times from acetone to yield *2* (2.60 g, 18 %), m.p. 185−187°C, λ_{max} in acidic solution 261 nm (ε 17 600), λ_{max} in basic solution 289 nm (ε 28 000), ν_{max} (KBr) 2500(br), 1640(w), 1552, 1375, 1352, 1259 cm^{-1}. (Found: C 41.1; H 4.66; Br 45.3. $C_{12}H_{16}Br_2O_2$ (352.08) requires C 40.9; H 4.58; Br 45.4).

1,4-Bis(2,6-diketo-4,4-dimethylcyclohexyl)butyne-2 (1). The mother liquor from the isolation of *2* was further acidified to pH 5. A second crop of crystalline material was obtained (7.2 g). TLC showed the presence of a number of components in this material. However, repeated recrystallization from methanol-water (1:1) gave *1* (2.5 g, 19 %), m.p. 180−186°C (decomp.), λ_{max} in acidic solution 259 nm (ε 29 400), λ_{max} in basic solution 284 nm (ε 50 500), ν_{max} (KBr) 3150(br), 1600, 1385, 1255, 1048 cm^{-1}, mass spectrum M$^+$ = 330 m.u. (Found: C 72.1; H 7.82. $C_{20}H_{26}O_4$ (330.43) requires C 72.7; H 7.93).

cis-1,4-Bis(2,6-diketo-4,4-dimethylcyclohexyl)butene-2 (3). A solution of *1* (330 mg, 1 mmol) and sodium methoxide (from Na, 46 mg, 2 mmol) in methanol (6 ml) was hydrogenated at room temperature and atmospheric pressure using Pd/BaSO$_4$ (30 mg) poisoned with quinoline (30 mg) as catalyst.[7] The uptake of hydrogen ceased after 4 h when 1 mmol of hydrogen had been consumed. The catalyst was removed by filtration and after evaporation of the solvent a residue was obtained which was dissolved in a minimum of water. The solution was acidified with 2 M HCl to pH 5. The crystals obtained were recrystallized from methanol-water (3:2) to yield *3* (265 mg, 80 %), m.p. 188−190°C, λ_{max} in acidic solution 263 nm (ε 25 500), λ_{max} in basic solution 288 nm (ε 44 000), ν_{max} (KBr) 3100(br), 2620(br), 1570, 1378, 1250, 1221, 1150, 1095 cm^{-1}, mass spectrum M$^+$ = 332 m.u. (Found: C 71.9; H 8.71. $C_{20}H_{28}O_4$ (332.45) requires C 72.3; H 8.49).

1,4-Bis(2,6-diketo-4,4-dimethylcyclohexyl)butane (4). A solution of *1* (990 mg, 3 mmol) and sodium methoxide (from Na, 136 mg, 6 mmol) in methanol (10 ml) was hydrogenated at room temperature and atmospheric pressure using PdO/BaSO$_4$ (200 mg) as catalyst.[8] The uptake of hydrogen ceased after 3 h, when 6 mmol of hydrogen had been consumed. The catalyst was removed by filtration, the solvent was evaporated and the residue was dissolved in a minimum of water. The solution was acidified to pH 5 with 2 M HCl. The crystals obtained were recrystallized from ethanol-water (3:2) to yield *4* (890 mg, 89 %), m.p. 250−251°C, λ_{max} in acidic solution 265 nm (ε 29 800), λ_{max} in basic solution 293 nm (ε 59 000), ν_{max} (KBr) 3140(br), 1600, 1385, 1248, 1143 cm^{-1}, mass spectrum M$^+$ = 334 m.u. (Found: C 71.6; H 9.01. $C_{20}H_{30}O_4$ (334.46) requires C 71.8; H 9.04).

trans-1,4-Bis(2,6-diketocyclohexyl)butene-2 (5a). The butene derivative was prepared according to Stetter and Dierichs.[9]

trans-1,4-Bis(2,6-diketo-4,4-dimethylcyclohexyl)butene-2 (5b). To a solution of dimedone (7.0 g, 50 mmol), Cu$_2$Cl$_2$ (200 mg) and KOH (3.23 g, 86 %, 50 mmol) in methanol-water (3:2) (15 ml) was added *trans*-1,4-dibromobutene-2 (4.0 g, 19 mmol). The solution was stirred overnight. After addition of 15 % NaOH (20 ml) and filtration, the filtrate was extracted with ether (3 × 20 ml) and acidified with 2 M HCl, first to pH 6, then to pH 5, and finally to pH 1. In this way several crude fractions were collected. The material obtained in the pH interval 5.0−6.0 (1.9 g) was dissolved in hot ethanol-water (1:1). The crystals obtained on cooling were recrystallized from ethanol-water (1:1) to yield *5b* (1.3 g, 21 %), m.p. 216−218°C (decomp.), λ_{max} in acidic solution 262 nm (ε 28 000), λ_{max} in basic solution 288 nm (ε 48 000), ν_{max} (KBr) 3170(br), 1600, 1385, 1250, 1145 cm^{-1}, mass spectrum M$^+$ = 332 m.u. (Found: C 72.0; H 8.74. $C_{20}H_{28}O_4$ (332.45) requires C 72.3; H 8.49).

The material obtained on acidification below pH 5.0 was mainly dimedone according to the IR spectrum. The other products formed as shown by TLC were not further investigated.

Hydrogenation of 5b. Compound *5b* was hydrogenated in the same way as described for compound *1* (preparation of *4*). The uptake of hydrogen was slow. After several days the acidic fraction of the reaction mixture was worked up. It contained mainly starting material recovered unchanged but also a small amount of a new product, $C_{20}H_{30}O_4$, identified as *4* from its IR spectrum, m.p., and mixed m.p.

1,2-Bis(2,6-diketo-4,4-dimethylcyclohexyl)butene-3 (6). To a solution of dimedone (14.0 g, 100 mmol) and KOH (6.46 g, 86 %, 100 mmol) in methanol-water (3:2) (23 ml) was added *trans*-1,4-dibromobutene-2 (8.8 g, 41 mmol). The mixture was stirred at room temperature until it became solid or about 3 h. After addition of 15 % NaOH (20 ml) and filtration, the filtrate was extracted with ether (3 × 20 ml) and acidified with 2 M HCl to pH 6. The solid material separating overnight was filtered and recrystallized from ethanol-water (3:2) to yield *6* (7.1 g, 52 %) as colorless prisms, m.p. 182—183°C, λ_{max} in acidic solution 262 nm (ε 26 000), λ_{max} in basic solution 288 nm (ε 51 000), ν_{max} (KBr) 3135(br), 1600, 1380, 1308, 1210, 1000, 900 cm^{-1}, mass spectrum $M^+ = 332$ m.u. (Found: C 72.2; H 8.62. $C_{20}H_{28}O_4$ (332.45) requires C 72.3; H 8.49).

1,2-Bis(2,6-diketo-4,4-dimethylcyclohexyl)butane (7). Compound *6* was hydrogenated in the same way as described for compound *1* (preparation of *4*). The crystals obtained were recrystallized from ethanol-water (3:2) to yield *7* (901 mg, 90 %) as colorless prisms, m.p. 222—223°C, λ_{max} in acidic solution 262 nm (ε 21 000), λ_{max} in basic solution 291 nm (ε 42 600), ν_{max} 3180(br), 1600, 1380, 1250 cm^{-1}, mass spectrum $M^+ = 334$ m.u. (Found: C 71.8; H 9.02. $C_{20}H_{30}O_4$ (334.46) requires C 71.8; H 9.04).

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