166. *Alicyclic Compounds. Part II.* The Preparation of* cyclo*Hexane*-1 : 3-*diones and Their Enol Ethers.*

By Eric G. Meek, J. H. Turnbull, and Walter Wilson.

4-Methyl*cyclo*hexane-1 : 3-dione, previously imperfectly characterised, has been made by three methods. Monoenol ethers are prepared from several *cyclo*hexane-1 : 3-diones and (*a*) ethanol in presence of toluene-*p*-sulphonic acid, (*b*) ethyl iodide and sodium ethoxide, or (*c*) ethyl orthoformate and an acid catalyst. Method (*a*) is not applicable to 2-methyl-diones, and (*b*) is useful only with 2-methyl-diones. Method (*c*) is generally applicable, but under certain conditions gives complex compounds formed by the coupling of three dione molecules through a CH group.

During experiments directed towards the synthesis of steroids and other natural products (cf. Birch, *J.*, 1951, 3027; *Ann. Reports*, 1951, 204; Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645), we have examined the preparation of certain *cyclo*hexane-1 : 3-diones (3-hydroxy*cyclo*hex-2-enones) and their enol ethers.

*cyclo*Hexane-1 : 3-dione was most easily made by hydrogenation of resorcinol in alkaline solution, but conditions milder than those hitherto recommended were necessary to prevent further reduction. With methyl iodide and methanolic sodium methoxide it afforded the 2-methyl compound, but the maximum yield was only 58% (cf. Friedman and Robinson, *Chem. and Ind.*, 1951, 777); and this was not improved by methylation in aqueous sodium hydroxide with a large excess of methyl iodide, partial ring scission to 5-ketohexanoic acid also occurring. Further methylation of 2-methyl*cyclo*hexane-1 : 3-dione (in methanol) gave the enol ether; the 2 : 2-dimethyl compound could not be isolated. In contrast, 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione always gave a mixture of the 2-methyl and the 2 : 2-dimethyl derivative, as reported by Desai (*J.*, 1932, 1079) and Hirsjarvi (*Chem. Abs.*, 1948, **42**, 2936).

Gilling (*J.*, 1913, 2029) described the reduction of 4-methylresorcinol; the product was believed to be 4-methyl*cyclo*hexane-1 : 3-dione, but was not satisfactorily characterised. We confirmed the formation of the 4-methyl-dione, a syrup, which rapidly oxidised in air to (crystalline) α-methylglutaric acid. The dione was characterised as the methylenebis-derivative, and was synthesised by two further, interdependent methods. Methyl 4-carbethoxy-5-keto-2-methylhexanoate (from ethyl acetoacetate, methyl α-methylacrylate, and sodium ethoxide) on successive treatment with sodium ethoxide and alcoholic potassium hydroxide yielded a separable mixture of α-methylgutaric acid and the 4-methyl-dione, in proportions which varied widely in different experiments (Table 1).

Table 1. *Cyclisation of methyl 4-carbethoxy-5-keto-2-methylhexanoate.*

Diester	Na	EtOH	Reflux	KOH	H_2O	Reflux	Products ‡		
(g.)	(g.)	(c.c.)	(hr.)	(g.)	(c.c.)	(hr.)	A (%)	B (%)	C (%)
30	3	140	3	16·5	80	6½	0	26	26
30	3	110	3	7·5	80	6½	55	0	16
5	0	50	0	8	40	6	27	0	32
30	3·5	110 †	2½	20	80	6	0	51	47
30	3·5	120 †	3 *	20	70	4 *	0	20	74

* Under nitrogen. † Methanol.

‡ A, Diester recovered; B, 4-methyl*cyclo*hexane-1 : 3-dione; C, α-methylglutaric acid.

Similar treatment of ethyl 4-carbethoxy-5-ketohexanoate had given glutaric acid but no *cyclo*hexanedione (Vorländer, *Annalen*, 1897, **294**, 318). It is believed that glutaric acids arise in these experiments by alkaline scission of the uncyclised β-keto-esters. The best preparative method for 4-methyl*cyclo*hexanedione involved acid hydrolysis of methyl 4-carbethoxy-5-keto-2-methylhexanoate, esterification of the product to methyl 5-keto-2-

---

* Part I, *J.*, 1952, 4686.

methylhexanoate, and cyclisation (sodium methoxide) (cf. Vorländer, *Annalen*, 1897, **294**, 269; von Schilling and Vorländer, *ibid.*, 1899, **308**, 190).

*cyclo*Hexanediones usually deteriorate on exposure to air, but are stable in the absence of oxygen; 4-methyl*cyclo*hexane-1 : 3-dione is particularly susceptible to aerial oxidation. The stabilities of diones in air follow the irregular sequence: 5 : 5-dimethyl $\gg$ unsubstituted compound $>$ 2-methyl $>$ 2 : 5 : 5-trimethyl $>$ 4-methyl.

Three methods for the conversion of *cyclo*hexanediones into monoenol ethers have been compared. (*a*) The "esterification" method (alcohol and an acid catalyst; Stollé, Diss., Bonn, 1893; Vorländer, *ibid.*, 1897, **294**, 253; Crossley and Renouf, *J.*, 1908, 629; Gilling, *loc. cit.*; Frank and Hall, *loc. cit.*) gave good yields with 2-unsubstituted diones; 2-methyl-diones did not react. (*b*) Ethyl iodide and alkoxide were used for making enol ethers from 2-methyl- and 2 : 5 : 5-trimethyl-*cyclo*hexanedione. *C*-Substitution usually predominates in alkylations of 2-unsubstituted diones, particularly with methyl iodide (cf. Desai, *loc. cit.*; Woods and Tucker, *J. Amer. Chem. Soc.*, 1948, **70**, 2174; Crossley, *J.*, 1901, 138; Hewett, *J.*, 1936, 50; Frank and Hall, *loc. cit.*; Stetter and Dierichs, *Chem. Ber.*, 1952, **85**, 61). (*c*) The "acetalisation" method (ethyl orthoformate and sulphuric acid) was practicable for conversion of all the diones into enol ethers; yields of 46—85% were obtained in small-scale experiments, and the reaction was not hindered by 2-methyl substituents (Table 2). The method appeared to be less satisfactory with methyl orthoformate.

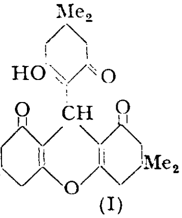
TABLE 2. *Enol ethers obtained by the orthoformate method* (c).

Dione	Wt. (g.)	$HC(OEt)_3$ (c.c.)	EtOH (c.c.)	Reflux (hr.)	Product	Yield (%)
*cyclo*Hexane-1 : 3-dione	10	15	6	18	Et ether, b. p. 104—108°/4 mm., m. p. 3—4° [a]	67
Dimedone	14	21·4	8	138	"Anhydride" (I), m. p. 222—223°	79
Dimedone	2	3	1·5	4	Et ether, b. p. 58—64°/0·001 mm., m. p. 57—59° [a]	46 [c]
2-Methyl*cyclo*hexane-1 : 3-dione	6·8	10·2	4	25½	Et ether, b. p. 76—78°/0·01 mm., m. p. 44—46° [b]	41 [d]
2 : 5 : 5-Trimethyl*cyclo*hexane-1 : 3-dione	2·5	3·8	1·5	17	Et ether, b. p. 70—73°/0·05 mm., m. p. 50° [b]	69 [e]
4-Methyl*cyclo*hexane-1 : 3-dione	1	1·2	1	17	Et ether, b. p. 60—62°/0·08 mm.[a]	88

[a] Also obtained by method (*a*). [b] Also obtained by method (*b*). [c] +5% of unchanged dione. [d] +48% of unchanged dione. [e] Product distilled directly from reaction mixture.

Some of the enol ethers were difficult to purify, as also found by previous workers. The ethers were stable in dry nitrogen, but in air hydrolysis to the diones and then oxidation occurred. 3-Ethoxy*cyclo*hexenone was rapidly hydrolysed to the parent dione, even by cold dilute sodium hydrogen carbonate solution, or more slowly by distilled water. The remaining ethers were hydrolysed easily in dilute sodium hydroxide (cf. Frank and Hall, also Gilling, *locc. cit.*). Although simple enol ethers are stable to alkalis, the present compounds are vinylogues of carboxylic esters, and abnormal alkali-sensitivity might be expected; the 2-methyl compounds are hydrolysed more slowly.

In the reaction between dimedone and ethyl orthoformate (catalyst, sulphuric acid), prolongation of the reaction time gave a high-melting solid, instead of the enol ether. This solid was identical with the compound obtained by Vorländer and Guthke (*Ber.*, 1929, **62**, 549) from dimedone and formic acid, or from dimedone, chloroform, and alkali, and formulated by them as the anhydride (I). Acetic anhydride was a more effective catalyst than sulphuric acid in promoting the formation of (I) (cf. Post, "Chemistry of Aliphatic Orthoesters," Reinhold Publ. Corp., New York, 1943, pp. 69 *et seq.*). *cyclo*Hexane-1 : 3-dione afforded products similar to (I), which require further investigation.



(I)

The enol ethers exhibit the intense light absorption expected for a modified αβ-unsaturated ketone system. The main band at 2490—2500 Å is shifted to 2650—2680 Å by a 2-methyl substituent. Methyl groups in other positions have almost no effect on the absorption.

EXPERIMENTAL

Ultra-violet spectrographs were determined on a Unicam SP 500 Spectrophotometer, with 1-cm. quartz cells; unless otherwise stated the concentration was 0·001%, in commercial absolute ethanol.

cyclo*Hexane*-1 : 3-*dione*.—A mixture of Raney nickel (6 c.c. of thick slurry) (Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471), resorcinol (42 g.), and sodium hydroxide (9 g., 0·6 equiv.) in water (90 c.c.) was hydrogenated at 20°/90 atm. for 8 hours in a horizontal rocker-type bomb (Chas. W. Cook and Sons Ltd., Birmingham), and worked up by King and Felton's method (*J.*, 1948, 1371), to give the dione (25·7 g., 61%), m. p. 107—109°, and unchanged resorcinol (11·8 g., 28%) (cf. Thompson, *Org. Synth.*, 1947, **27**, 21).

When alkali (1·16 equiv.) and hydrogen at 30°/110 atm. (10 hours) were used, the yield of dione was only 42·5%. *cyclo*Hexane-1 : 3-diol (mixed isomers; 19%), b. p. 138°/10·5 mm., was extracted by ethanol from the evaporated aqueous phase; no resorcinol was recovered (cf. Rigby, *J.*, 1949, 1586; Clarke and Owen, *J.*, 1950, 2103).

2-*Methyl*cyclo*hexane*-1 : 3-*dione*.—*cyclo*Hexane-1 : 3-dione (28 g.) was added to an ice-cold solution of sodium (11·6 g., 2 equiv.) in methanol (100 c.c.). After the addition of methyl iodide (33 c.c., 2 equiv.) the mixture was refluxed for 2½ hours, the solvent removed in a vacuum, and the residue dissolved in water (50 c.c.). Acidification (to pH 3) with concentrated hydrochloric acid precipitated the product (18·4 g., 58%), m. p. 208—210° (from aqueous ethanol). Blaise and Maire, *Bull. Soc. chim.*, 1908, **3**, 421, give m. p. 210°.

*cyclo*Hexane-1 : 3-dione (15 g.), sodium hydroxide (32 g., 6 equiv.), 50% aqueous ethanol (120 c.c.), and methyl iodide (95 g.) were stirred at room temperature for 8 days (by which time the mixture was homogeneous), then evaporated under reduced pressure, and the residue was dissolved in water (100 c.c.). Acidification, as above, gave 2-methyl*cyclo*hexane-1 : 3-dione (7 g., 41·5%). Extraction of the aqueous liquors with ether and chloroform gave 5-keto-hexanoic acid (46% yield in one experiment). The dione was stable indefinitely in a sealed tube, but soon decomposed in air.

Methylation of 5 : 5-*Dimethyl*cyclo*hexane*-1 : 3-*dione* (*Dimedone*).—Dimedone was methylated by Desai's procedure. Steam-distillation of the residues, after extraction of the 2-methyl compound (36·9%), gave 2 : 2-dimethyldimedone (10%), m. p. 99°, which was filtered off from the distillate. (Desai gives m. p. 95°.)

In a similar experiment, sodium (1·25 equiv.) and methyl iodide (1·8 equiv.) in methanol yielded the 2-methyl compound (54·5%), the 2 : 2-dimethyl compound (3·6%), and dimedone (14%), which was recovered as its methylenebis-derivative.

Sodium (1·01 equiv.) and methyl iodide (1·66 equiv.) gave 2-methyldimedone (65%), dimethyldimedone (1·8%), and unchanged dimedone (28%).

Methyl 4-*Carbethoxy*-5-*keto*-2-*methylhexanoate* (cf. Ruzicka, *Helv. Chim. Acta*, 1919, **2**, 144).—A mixture of methyl α-methylacrylate (85 c.c.) (which contained 0·2% of quinol), ethyl aceto-acetate (105 g.), and cold sodium ethoxide solution [from ethanol (320 c.c.) and sodium (18·6 g.)] was kept for 44 hours at room temperature. Excess of glacial acetic acid (final pH 4) was added, and the solvents were removed in a vacuum. Water (200 c.c.) was added to the residue and the oil isolated with ether. Fractionation gave *methyl* 4-*carbethoxy*-5-*keto*-2-*methylhexanoate* (59·1 g., 30%), b. p. 103—105°/0·05 mm., n_D^{22} 1·4472 (Found: C, 58·1; H, 8·2. $C_{11}H_{18}O_5$ requires C, 57·4; H, 7·85%), which gave no precipitate with formaldehyde in cold 50% aqueous ethanol.

Use of two mols. of ethyl acetoacetate (some of which was recovered) as above (44 hours) gave an increased yield (57%); but after 62 hours the yield was 44% (cf. Albertson, *J. Amer. Chem. Soc.*, 1948, **70**, 669).

4-*Methyl*cyclo*hexane*-1 : 3-*dione*.—(a) *By cyclisation of the above diester.* Several runs are summarised in Table 1. The diester was stirred with sodium ethoxide solution first at 0°, then under reflux. Aqueous potassium hydroxide was added and the refluxing continued. After addition of concentrated hydrochloric acid (to pH 7), ethanol was removed in a vacuum; further acidification (to pH 2), extraction with ether, and fractionation of the extract gave 4-*methyl*cyclo*hexane*-1 : 3-*dione*, b. p. 111°/0·025 mm., $n_D^{22\cdot5}$ 1·5213, $\lambda_{max.}$ 2550 Å (log ε 4·10) (Found: C, 65·0, 64·65; H, 7·8, 8·0. $C_7H_{10}O_2$ requires C, 66·7; H, 7·95%. Both analyses were performed on the same day as the final distillation; even poorer analyses were obtained after a longer period), and α-methylglutaric acid, b. p. 150—160°/0·022 mm., m. p. 77—78° (from benzene) (Found: C, 48·95; H, 6·6%; equiv., 73·6. Calc. for $C_6H_{10}O_4$: C, 49·3; H, 7·6%; equiv., 73·1), which formed an anil, m. p. 175—176°. α-Methylglutaric acid has m. p. 77—78°, and forms an anil, m. p. 178—179°. After 16 hours' exposure to the air, 50—60% of the dione was oxidised to α-methylglutaric acid.

The dione and formaldehyde in 50% aqueous ethanol gave the *methylenebis*-compound, m. p. 131—133° (from aqueous ethanol), $\lambda_{max.}$ 2550 Å (log ε 4·47) (Found: C, 68·8; H, 7·9. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

(b) *Through methyl* 5-*keto*-2-*methylhexanoate*. Methyl 4-carbethoxy-5-keto-2-methylhexanoate (32 g.) was heated with water (80 c.c.) and concentrated hydrochloric acid (45 c.c.) at 100° for 3 hours. After being kept at room temperature overnight the mixture was extracted with ether, and the aqueous layers were evaporated to 70 c.c. under reduced pressure and extracted with ether and chloroform. The combined extracts were dried ($MgSO_4$), the solvents were evaporated, and the residue was distilled, to give an oil, b. p. 120—166°/15 mm. (23·5 g.). This was separated into a neutral and an acidic fraction. The neutral fraction gave *methyl* 5-*keto*-2-*methylhexanoate* (7·6 g., 35%), b. p. 110—111°/18 mm. $n_D^{20\cdot5}$ 1·4329 (Found: C, 60·45; H, 8·95. $C_8H_{14}O_3$ requires C, 60·8; H, 8·8%). The acidic fraction yielded 5-keto-2-methylhexanoic acid (12·75 g., 63%), b. p. 160—163°/20 mm., which was refluxed for 6 hours with methanol (100 c.c.) and concentrated sulphuric acid (0·5 c.c.), to give a further amount of the ester (10·75 g., 79%), b. p. 114—120°/30 mm., n_D^{20} 1·4290, and unchanged acid (2·4 g., 19%), b. p. 168—171°/30 mm.

Anhydrous sodium methoxide [prepared by adding methanol (13 c.c.) to "powdered" sodium (2·1 g.) in toluene (30 c.c.) and distilling off the toluene and excess of methanol] was suspended in ether (35 c.c.) and methyl 5-keto-2-methylhexanoate (5·25 g.) in ether (20 c.c.) dropped in with cooling. After the mixture had been kept overnight and stirred for 2 hours, water (35 c.c.) was added. Ether-extraction removed no material and showed that no ester remained. Acidification of the aqueous layers and extraction yielded the 4-methyl-dione (2·73 g., 65%), b. p. 82—92°/0·01 mm., characterised as the methylenebis-compound, m. p. 131—132°.

(c) *By sodium amalgam reduction of* 4-*methylresorcinol*. Gilling's instructions being followed, this reaction gave the 4-methyl-dione (37%), identical with the material obtained as in (a) and (b), and unreduced 4-methylresorcinol (23%).

Preparation of Enol Ethers.—The less stable enol ethers were purified by distillation in a special molecular still (Meek, *Chem. and Ind.*, in the press).

(a) *Frank and Hall's method.* The dione, ethanol, benzene, and a little toluene-*p*-sulphonic acid were refluxed under a continuous water-separator for the times stated below. The solvents were removed and the enol ether distilled; any unchanged dione could be recovered by crystallisation from the residue. 2-Methyl- (90%) and 2 : 5 : 5-trimethyl-*cyclo*hexane-1 : 3-dione (78%) were recovered unchanged after 156 and 190 hours respectively. *cyclo*Hexane-1 : 3-dione gave (119 hours) 3-ethoxy*cyclo*hexenone (76%), b. p. 80—90°/0·2 mm., $\lambda_{max.}$ 2490 Å (log ε 4·27) which could not be obtained pure (Found: C, 63·7, 63·5; H, 8·5, 8·5. Calc. for $C_8H_{12}O_2$: C, 68·6; H, 8·6%) (Woods and Tucker give b. p. 95—105°/1 mm.). Almost complete reversion to the dione occurred after 3 weeks' exposure to the air; hydrolysis to the dione occurred on shaking with distilled water for 2 hours, and even more rapidly with cold 5% sodium hydrogen carbonate solution. Dimedone yielded 3-ethoxy-5 : 5-dimethyl*cyclo*hexenone (76%; 119 hours), b. p. 92°/1·8 mm., m. p. 59—60°, $\lambda_{max.}$ 2500 Å (log ε 4·28) (Frank and Hall give b. p. 93°/1 mm., m. p. 57—58°; Desai, m. p. 60°; Crossley and Renouf, m. p. 60°; Beringer and Kuntz, *J. Amer. Chem. Soc.*, 1951, **73**, 364, m. p. 58·5—59·5°). After 7 hours' refluxing 60% of the dimedone was recovered unchanged.

4-Methyl*cyclo*hexane-1 : 3-dione was converted into the *ethyl* enol *ether* (? mixed isomers) (70·5%; 28 hours, in nitrogen atmosphere), b. p. 80—82°/0·3 mm., $n_D^{17\cdot5}$ 1·4950, $\lambda_{max.}$ 2490 Å (log ε 4·21) (Found: C, 69·8; H, 9·0. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%). When the reaction was conducted in dry air, oxidation occurred, and the product was impure diethyl α-methylglutarate, b. p. 48—53°/0·01 mm., 227°/735 mm., n_D^{19} 1·4423, hydrolysed by alkali to α-methylglutaric acid, m. p. 75—76° (Ingold, *J.*, 1921, 329, gives b. p. 238°/760 mm. for the ester).

(b) *Alkylation method.* The alkylation procedure was similar to that described for the preparation of 2-methyl*cyclo*hexanedione, but ethyl iodide was used. At the end of the reaction, water and sodium hydroxide were added (final pH 9—10). The neutral enol ether was immediately extracted with ether, and the aqueous phase acidified and extracted with chloroform to recover any unchanged dione. In this way, 2-methyl*cyclo*hexane-1 : 3-dione afforded 3-*ethoxy*-2-*methyl*cyclo*hexenone* (56%, with 6·5% of recovered dione), b. p. 78—86°/0·5 mm., n_D^{20} 1·4820, $\lambda_{max.}$ 2650 Å (log ε 4·32), which slowly crystallised and had m. p. 52° (Found: C, 69·5; H, 9·7. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%). 2 : 5 : 5-Trimethyl*cyclo*hexane-1 : 3-dione similarly gave 3-*ethoxy*-2 : 5 : 5-*trimethyl*cyclo*hexenone* (23%), b. p. 70—

78°/0·05 mm., m. p. 47—50°, $\lambda_{max.}$ 2680 Å (log ε 4·28) (Found : C, 71·6; H, 10·0. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9%).

(c) *Ethyl orthoformate method.* The dione, ethyl orthoformate, ethanol, and concentrated sulphuric acid (0·2 c.c.) were refluxed, water was added, sodium hydroxide solution added (pH 10), and the insoluble enol ether isolated with ether. The results are summarised in Table 2.

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-*Octahydro*-9-(2-*hydroxy*-6-*keto*-4 : 4-*dimethyl*cyclo*hex*-1-*enyl*)-1 : 8-*diketo*-3 : 3 : 6 : 6-*tetramethylxanthene* (I).—In the reaction between dimedone and ethyl orthoformate by the above method, an anomalous product of high m. p. was obtained when the time of reaction was prolonged. This product had m. p. 222—223° (from chloroform–ether), $\lambda_{max.}$ 2350 Å (log ε 4·17, in EtOH), (Found : C, 73·15; H, 8·0. Calc. for $C_{25}H_{32}O_5$: C, 72·8; H, 7·8%). The molecular weight was 460 (theor., 412), as determined by Bobranski and Sucharda's method (ebullioscopic, in benzene; see Belcher and Godbert, "Semi-micro Quantitative Organic Analysis," Longmans, London, 1947, p. 134). The same compound (1·4 g.; m. p. 229°) was obtained from dimedone (5·6 g.), acetic anhydride) (2·0 g.), and ethylorthoformate (9 g.) after 5½ hours' heating at 100°. The compound did not react with formaldehyde in cold 50% ethanol, 5N-hydrochloric acid, refluxing constant-boiling hydrobromic acid, 2 : 4-dinitrophenylhydrazine, or semicarbazide. It was identical (m. p. and mixed m. p., and acetate) with "methenyltris-dimedone anhydride," prepared from dimedone, chloroform, and aqueous sodium hydroxide (Vorländer and Guthke, *loc. cit.*).

The authors are grateful to Professor M. Stacey, F.R.S., for encouragement and facilities, and to Glaxo Laboratories Ltd., for financial assistance.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, October* 21*st*, 1952.]