636. *Experiments in the* cyclo*Butane Series. Part IV.* The Interaction of Diethyl* cis-cyclo*Butane*-1 : 2-*dicarboxylate with Phenylmagnesium Bromide.*

By F. B. Kipping and J. J. Wren.

A detailed study of the reaction given in the title is described.

The hydroxy-ketone (II) was obtained [1] in only 12% yield from diethyl *cis-cyclo*butane-1 : 2-dicarboxylate (I) and phenylmagnesium bromide, and the reaction has now been investigated in detail in order, if possible, to obtain this substance in larger yield, as it was required for a subsequent investigation. Four of the numerous experiments are described in the Experimental section and the reaction scheme and the Table show the nature of the

Compounds isolated from the reaction of phenylmagnesium bromide with diethyl cis-cyclo*butane*-1 : 2-*dicarboxylate* (% *yields*).

Experiment No.	1	2	3	4
Conditions:	Diester into reagent (3 mol.)	Reagent (3 mol.) into diester	As expt. 1, on 16-fold scale	Diester into stirred reagent (6 mol.)
Diene (V)	*ca.* 10	—	Some	30
Hydroxy-ketone (II)	20	0	18·4	9
Olefinic ketone (III)	—	14	*ca.* 3	—
Ketal (X)	—	—	—	30
Lactone (IX)	—	11	3·6	—
Diketone (VII)	—	—	12	—

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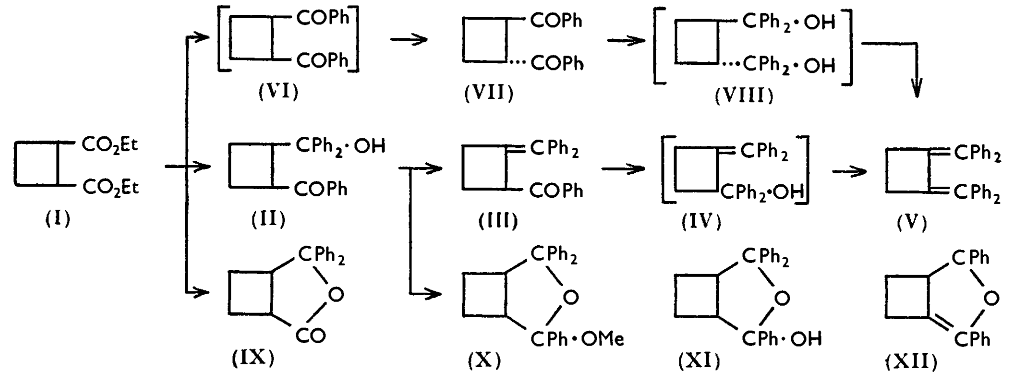
* Part III, preceding paper.

[1] Alberman and Kipping, *J.*, 1951, 779.

products and the yields : in the scheme, assumed intermediate products which were not actually isolated are in brackets. A maximum yield of 20% only was obtained of the hydroxy-ketone.

The hydroxy-ketone (II) may be formed either directly from the ester (I) or from the diketone (VI) or lactone (IX) and it is not clear whether the olefinic ketone (III) is formed in the reaction or during working up of the product.



The lactone (IX) of (±)-*cis*-2-(α-hydroxydiphenylmethyl)*cyclo*butanecarboxylic acid was obtained by Ellingboe and Fuson[2] from the reaction of *cis*-*cyclo*butane-1 : 2-dicarboxylic anhydride with two molecular equivalents of phenylmagnesium bromide. The present experiments gave at first a form (α), m. p. 102·5—103·5°, but later a more stable form (β), m. p. 117—118°, which appears identical with Ellingboe and Fuson's material. Chromatography of lactones on alumina is known to involve considerable loss of material,[3] and the 11% yield of the lactone obtained by this means in experiment 2 is probably considerably less than was produced in the reaction.

(±)-*trans*-1 : 2-Dibenzoyl*cyclo*butane (VII) was obviously obtained *via* its *cis*-isomer (VI) : the latter isomerises rapidly in ethanolic sodium hydroxide at room temperature,[4] presumably *via* an enol intermediate, and Grignard reagents are known to facilitate enolisation; only the *trans*-isomer, therefore, would be isolable in these experiments. Such *trans*-diketone formed in the reaction mixture could react with Grignard reagent to give the diol (VIII) [in contrast to the *cis*-diketone (VI), which would give the hydroxy-ketone (II) owing to steric hindrance [1]] : dehydration of the diol would give the diene (V) which was conveniently isolated by chromatography. Alternatively, the diene might come from the olefinic alcohol (IV) formed by reaction of the olefinic ketone (III) with Grignard reagent.

The γ-hydroxy-ketone (II) should be tautomeric with the lactol (XI). That the tautomeric equilibrium favours the keto-form (as it does in the case of the simplest γ-hydroxyketone, 4-oxopentanol [5]) was shown by infrared spectroscopy : spectra of the crystals (in Nujol mull) and of a solution (in CCl_4) showed a prominent band in the region of C:O stretching frequencies, of intensity similar to that for the *trans*-isomer in which tautomerism is sterically impossible. The *trans*- was prepared from the *cis*-isomeride by the action of ethanolic sodium hydroxide and its structure confirmed by dehydration to the olefinic ketone (III). The tautomerism of the *cis*-isomer may explain the formation of the ketal, tetrahydro-2-methoxy-2 : 5 : 5-triphenyl-3 : 4-*cyclo*butanofuran (X) in experiment 4 (and in several others). This compound slowly crystallised from methanolic

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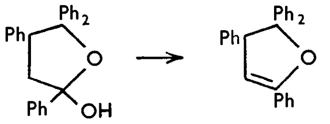
[2] Ellingboe and Fuson, *J. Amer. Chem. Soc.*, 1934, **56**, 1777.

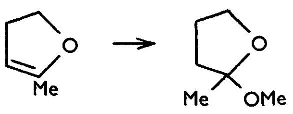
[3] Lederer and Lederer, " Chromatography," Elsevier, Amsterdam, 1954, p. 117.

[4] Ellingboe and Fuson, *J. Amer. Chem. Soc.*, 1934, **56**, 1774.

[5] Lüttke, *Chem. Ber.*, 1950, **83**, 571.

mother-liquors which had failed to yield more of the hydroxy-ketone when evaporated and seeded. It did not crystallise from a saturated solution of the pure hydroxy-ketone in methanol, and was obtained in high yield from experiment 4, which yielded relatively little of the hydroxy-ketone. It is therefore unlikely that the ketal is formed by interaction of the solvent with the lactol tautomer (XI). However, dehydration of the latter might occur *in situ*, giving the dihydrofuran (XII) which, by addition of methanol, could give the ketal: parallels for both stages are found in the literature, namely, the dehydration of tetrahydro-2-hydroxy-2 : 4 : 5 : 5-tetraphenylfuran with hydrochloric and acetic acid [6] and the reaction of 4 : 5-dihydro-2-methylfuran with methanol and a trace of acetic acid : [7]





Chemical proof of the tautomeric nature of the hydroxy-ketone was afforded by conversion into the ketal. The reagent usually employed for this type of methylation, 2% anhydrous methanolic hydrogen chloride at room temperature, merely dehydrated the keto-form to the olefinic ketone. However, toluene-*p*-sulphonic acid dehydrates this type of compound less readily than hydrochloric acid, and it proved a suitable catalyst for the methylation. An attempt to prepare the methyl ether of the keto-form, by using Purdie's reagent, gave only the dehydration product.

The above findings concerning the reaction of the diester with phenylmagnesium bromide bear many analogies to the known reactions with Grignard reagents of succinic anhydride [8] and of phthalic anhydride and esters.[9]

No adduct with maleic anhydride could be prepared from 1 : 2-bisdiphenylmethylene-*cyclo*butane. The parent compound, 1 : 2-dimethylene*cyclo*butane, is a particularly reactive diene [10] and, since essentially only two phenyl groups of the tetraphenyldiene are conjugated with the diene system,[11] electronic considerations suggested that the latter should be at least as reactive as 1 : 4-diphenylbuta-1 : 3-diene. Steric hindrance must therefore account for its failure to yield an adduct; this view is supported by the failure of 1 : 2-difluorenylidene-ethane [12] and 1 : 1 : 4 : 4-tetraphenylbuta-1 : 3-diene to yield adducts (experiments on the latter compound confirmed an earlier report [13]).

EXPERIMENTAL

M. p.s are corrected, b. p.s uncorrected. Mol. wt. determinations were made by the cryoscopic method with ethylene dibromide as solvent, infrared spectra were examined in Nujol mull, and ultraviolet spectra on Unicam S.P. 500 spectrophotometers.

Diethyl cis-cyclo*Butane*-1 : 2-*dicarboxylate* (I).—Using anhydrous ethanol in the preparation previously described [1] gave an improved yield (84%) of material of b. p. 78·5°/0·4 mm.

Reaction of the cis-*Diester* (I) *with Phenylmagnesium Bromide.*—(1) The diester (5·0 g.) in ether (20 ml.) was added during ½ hr. to Grignard reagent prepared from magnesium (2·0 g.) and bromobenzene (12·6 g.) in ether (100 ml.); a viscous yellow oil was deposited and refluxing was maintained during a further 1 hr. After hydrolysis, using ice and ammonium chloride, and

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[6] Scholtis, *Annalen*, 1945, **557**, 82.

[7] Schniepp, Geller, and Von Korff, *J. Amer. Chem. Soc.*, 1947, **69**, 672.

[8] Baddar, Lanson, El-Assal, and Habashi, *J.*, 1955, 456.

[9] Runge, " Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft m.b.H., Stuttgart, 1944, p. 452.

[10] Blomquist and Verdol, *J. Amer. Chem. Soc.*, 1955, **77**, 1806; 1956, **78**, 109; Cunov, *Diss Abs.*, 1955, **15**, 981.

[11] Alberman, Haszeldine, and Kipping, *J.*, 1952, 3284.

[12] Wagner-Jauregg, *Annalen*, 1931, **491**, 1.

[13] Alder and Schumacher, *ibid.*, 1950, **570**, 178.

steam-distillation (1½ hr.) the plastic product was crystallised from ethanol; 1·7 g. (20%) of the hydroxy-ketone (II) were thus obtained, having m. p. and mixed m. p. 164—165°; recrystallisation from ethanol gave needles, m. p. 166·5—167° (Found : *M*, 351, 356. Calc. for $C_{24}H_{22}O_2$: *M*, 342). Its infrared spectrum showed characteristic bands at 3390 (OH str.), 1656 (C:O str.), and 915 cm.$^{-1}$ (*cyclo*butane ?). The original ethanolic mother-liquor was evaporated and the residue subjected to the usual dehydration conditions; [1] after several weeks, yellow fluorescent crystals separated, which by chromatography afforded about 10% of diene (V).

(2) The same quantities being used as in experiment 1, the Grignard reagent was added to the well-stirred diester solution during 20 min., and refluxing was continued during a further 20 min. First a yellow precipitate was formed, then this was replaced by light brown oil on the vessel walls. Worked up as above, the crude product (5·7 g.) was dissolved in boiling methanol (100 ml.); the filtered solution on cooling gave no crystals of the desired hydroxy-ketone, even when seeded. Olefinic ketone (III) (1·2 g.) crystallised from the more concentrated solution. Solvent was then removed from the mother-liquor in a stream of dry nitrogen at 100°, and the residual oil chromatographed in benzene solution on alumina. The benzene eluate on evaporation yielded a pale yellow oil which did not crystallise even when seeded with various possible compounds. A colourless oil was washed off the column with 95% ethanol and it began to crystallise after 4 days. Ether was then used to crystallise rectangular plates of the α-form of 2-(*α-hydroxydiphenylmethyl*)cyclo*butanecarboxylic lactone* (IX) (11%), which, after recrystallisation and vacuum-sublimation, had m. p. 102·5—103·5° (Found : C, 81·7; H, 6·4%; *M*, 253, 268. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%; *M*, 264). Its infrared spectrum showed bands at 1773 (s.; C:O str. in γ-lactone) and 913 cm.$^{-1}$ (*cyclo*butane ?), and was closely similar to that of the *cyclo*hexane analogue. Dissolution of the lactone in alcoholic potassium hydroxide followed by precipitation with aqueous acid slowly yielded prisms of the β-form, m. p. 117—118° (from ethanol) (Found : C, 82·1; H, 6·0%). The lactone (IX) was previously reported as having m. p. 116—117°.[2] The infrared spectra of the α- and the β-form showed minor differences, consistent with dimorphism. A mixture of the two melted sharply at 117—118°, and the β-form was obtained by seeding solutions of the α with the β, but not *vice versa* : the β-form is thus the more stable.

(3) On sixteen times the scale of experiment 1, addition of the diester took ¾ hr., and refluxing was continued during ½ hr. Crystallisation of the crude product from methanol gave 25·2 g. (18·4%) of the hydroxy-ketone (II). The mother-liquor yielded colourless inhomogeneous crystals (4·2 g.) which on dehydration gave yellow, mildly fluorescent material, which probably consisted of diene (V) and olefinic ketone (III). After evaporation, the same mother-liquor then slowly yielded 3·1 g. (2·4%) of the olefinic ketone, m. p. and mixed m. p. 94—95·5°. Fractional distillation of the mother-liquor at 1·1 mm. then yielded three main fractions : (i) diphenyl, b. p. 93°, (ii) a viscous yellow oil, b. p. 182—200°, and (iii) a very viscous, deep orange oil, b. p. 210—255°, with a strong odour. Fraction (ii) began to crystallise after several weeks, and cubes of the pure diketone (VII) were obtained by recrystallisation from ether (m. p. 97·5—98·5°; cf. needles, m. p. 97°; [14] 96—97·5° [4]) (Found : C, 82·1; H, 5·8%; *M*, 284, 263. Calc. for $C_{18}H_{16}O_2$: C, 81·8; H, 6·1%; *M*, 264). Its infrared spectrum (C:O str., 1675 cm.$^{-1}$) bore close resemblances to that of acetophenone. An alcoholic solution of the diketone gave a precipitate with Brady's reagent after 2 min. Its dioxime, even after repeated recrystallisation, tended to decompose near the m. p.; when heating was started at 167·5° it melted at 168—170° (cf. no mention of decomposition, m. p. 169—170° [4]). 1·3 g. of the lactone (IX; α-form) later crystallised from fraction (ii) of the distillate. Fraction (iii) was not investigated : it did not crystallise, even after being seeded with various possible compounds.

(4) Experiment 1 was repeated, except that half the quantity of diester was used and the reagent was stirred vigorously. No oil separated during the addition (¾ hr.) and continued refluxing (½ hr.). The crude product was a cream-coloured solid which yielded 0·38 g. of the slightly impure hydroxy-ketone from methanol (200 ml.). The mother-liquor was evaporated to *ca.* 40 ml. and left for 1 day : it deposited dense crystals (1·33 g.), m. p. 115·5—118·5°, of the ketal (X; see below). [Complete evaporation of the mother-liquor left a brownish oil (2·4 g.), which was dehydrated as usual : diene (1·42 g.) was then isolated from it by crystallisation and chromatography.]

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[14] Kao and Fuson, *J. Amer. Chem. Soc.*, 1932, **54**, 1120.

Two recrystallisations of the *ketal* from methanol gave dense rectangular prisms, m. p. 120—121° : these had to be dried *in vacuo* at room temperature, since even at 45° decomposition took place; after 3 hr. at 95° they had become molten, and after 12 hr. crystallisation from methanol yielded the olefinic ketone (III), m. p. and mixed m. p. 95—95·5°. Several specimens were analysed, but all gave slightly low carbon values, even when crystallised from light petroleum (b. p. 40—60°) and carefully dried (Found: C, 83·8; H, 6·6; OMe, 8·3%; *M*, 328, 325. $C_{25}H_{24}O_2$ requires C, 84·2; H, 6·8; OMe, 8·7%; *M*, 356). Its infrared spectrum showed no bands at OH or C:O stretching frequencies; in the region of C·O·C stretching frequencies there were strong bands at 1192, 1166, 1133, and 1058 cm.$^{-1}$, and a very strong triplet, 1006, 999, 987 cm.$^{-1}$. According to Tschamler and Leutner,[15] acyclic 1 : 3-diethers have two strong bands in the region 1150—1080 cm.$^{-1}$, and cyclic 1 : 3-diethers two strong doublets, one 1160—1120 cm.$^{-1}$ and the other 1110—1050 cm.$^{-1}$.

The ketal was recovered unchanged from dilute ethanolic sodium hydroxide after ½ hr. at 20°. When a warm solution of it in glacial acetic acid was cooled, needles of the hydroxy-ketone (II) separated; with hydrochloric acid in glacial acetic acid it gave the olefinic ketone (III).

Dilute hydrochloric acid (3·5 ml.) and ketal (125 mg.) were heated together under a reflux condenser during 20 min., 1 ml. of the liquid was then distilled, and from the distillate, using the procedure described by Wild,[16] we isolated 4 mg. (5%) of almost colourless crystals, which recrystallised from 95% ethanol as parallelogrammic plates, m. p. (and mixed m. p. with methyl 3 : 5-dinitrobenzoate) 107·5—108·5°.

A control experiment, using methanol and hydroxy-ketone (II) instead of the ketal, gave a 10% yield of the ester, m. p. 108—108·5°.

Preparation of the Ketal (X) *from the Hydroxy-ketone* (II).—Anhydrous toluene-*p*-sulphonic acid (0·39 g.) was added to an ice-cold solution of the hydroxy-ketone (0·20 g.) in anhydrous methanol (100 ml.). After 45 hr. in a stoppered flask at room temperature the solution was shaken with ether and excess of dilute aqueous sodium hydroxide, and the ethereal layer washed with water and evaporated. Two crystallisations of the residue from methanol gave the pure ketal (0·10 g., 49%), m. p. and mixed m. p. 120—121°. Its infrared spectrum was identical with that of the compound obtained in experiment 4 above.

(±)-2-*Benzoyl*-1-*diphenylmethylene*cyclo*butane* (III).—This ketone was obtained by dehydration of the hydroxy-ketone (II) and crystallised from methanol as rods or slim hexagonal plates, m. p. 95—95·5°. Its infrared spectrum showed bands at 1670 (C:O str.) and 1642 cm.$^{-1}$ (C:C str.). Treatment with phenylmagnesium bromide, followed by working-up in the usual manner, gave an inhomogeneous product which probably consisted of the expected alcohol (IV) and the diene (V); dehydration converted it into the pure diene, identified by its ultraviolet spectrum and by mixed m. p.

(±)-trans-2-*Benzoyl*-1-(α-*hydroxydiphenylmethyl*)cyclo*butane*.—*cis*-Hydroxy-ketone (II) (0·8 g.), ethanol (40 ml.), and aqueous sodium hydroxide (2 ml.) were heated under reflux during 1 hr. The hot yellowish solution was then filtered and poured into water (150 ml.) : the crystalline precipitate which formed was collected and from ethanol gave colourless rods of the trans-*hydroxy-ketone*, m. p. 170·5—171·5° (mixed m. p. with starting material 146—155°) (Found: C, 83·9; H, 6·3. $C_{24}H_{22}O_2$ requires C, 84·2; H, 6·5%). Its infrared spectrum was similar to that of the *cis*-isomer (OH str., 3840; C:O str., 1667 cm.$^{-1}$). Under the usual dehydration conditions it was converted into the olefinic ketone (IV) identified by its ultraviolet spectrum and by mixed m. p.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

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[15] Tschamler and Leutner, *Monatsh.*, 1952, **83**, 1502.

[16] Wild, " Characterisation of Organic Compounds," Cambridge University Press, 1948, p. 53 (5).