785. *The Synthesis of (±)-Angustione and Related Compounds.**

By G. R. ENSOR and W. WILSON.

4 : 4-Dimethyl- and 4 : 4 : 6-trimethyl-*cyclo*hexane-1 : 3-diones have been synthesised. Synthetic (±)-2-acetyl-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione is identical with (±)-angustione.

THE *cyclo*hexane-1 : 3-dione derivatives (—)-angustione and dehydroangustione, isolated from *Backhousia angustifolia*, were investigated several years ago in Simonsen's laboratory.[1, 2] The revised structure (IX) recently proposed by Birch [3] has now been confirmed by the total synthesis of (±)-angustione. Soon after the publication [4] of a preliminary account of this work, Chan and Hassall [5] independently described the synthesis of (±)-angustione by a different method.

In model experiments, dimethyl αα-dimethylglutarate (II; R = H) was selectively hydrolysed by alkali to the half-ester (III; R = H), the second methoxycarbonyl group

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* Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] Gibson, Penfold, and Simonsen, *J.*, 1930, 1184.

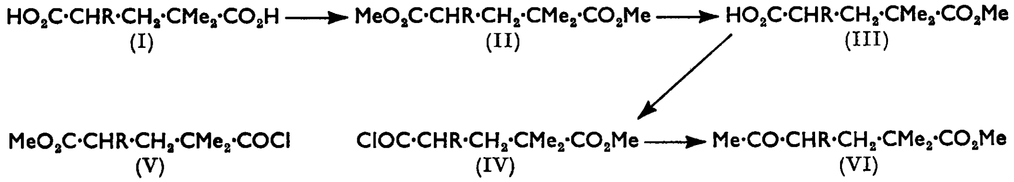
[2] Cahn, Gibson, Penfold, and Simonsen, *J.*, 1931, 286.

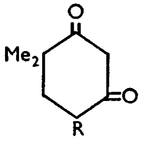
[3] Birch, *J.*, 1951, 3026.

[4] Ensor and Wilson, *Chem. and Ind.*, 1955, 2860.

[5] Chan and Hassall, *J.*, 1955, 2860.

being sterically hindered. The corresponding ester chloride (IV; R = H) with dimethylcadmium afforded the oxo-ester (VI; R = H), which was cyclised by sodium methoxide (cf. ref. 6) to 4 : 4-dimethyl*cyclo*hexane-1 : 3-dione (VII; R = H) which had the expected physical characteristics (Table 1; cf. ref. 7). A by-product from the dimethylcadmium reaction was a crystalline lactone $C_9H_{16}O_2$; this is formulated as (VIII), which could arise by a simple sequence of reactions. Although ester acid chlorides of type (IV) often partially isomerise [8] to (V), the ester chlorides (IV; R = H and Me) obtained in the present work gave homogeneous *p*-bromoanilides, and it is therefore assumed that rearrangement





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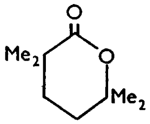
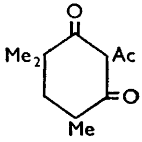


(VIII)



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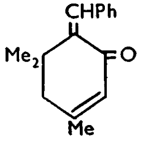

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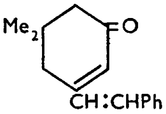

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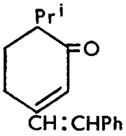

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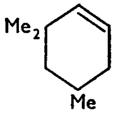

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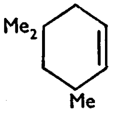

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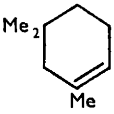
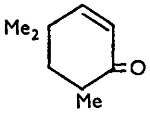
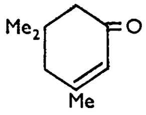


(XV)



(XVI)



(XVII)

did not occur. Isomerisation would not invalidate the synthesis, as each member of a pair of isomeric ester chlorides would yield the same *cyclo*hexane-1 : 3-dione.

By a similar sequence of reactions, ααγ-trimethylglutaric acid (I; R = Me) was converted into (±)-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (VII; R = Me), which had the characteristic properties of a *cyclo*hexane-1 : 3-dione (cf. refs. 6, 7). The same dione was originally obtained in the early degradative studies on angustione.[2] A crystalline by-product was obtained from the reaction between dimethylcadmium and the ester chloride (IV; R = Me); this product was found to be 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (VII; R = Me). Presumably, dimethylcadmium cyclised some of the oxo-ester (VI; R = Me), for dimethylcadmium catalyses the condensation of benzaldehyde with acetophenone,[9] and ethylmagnesium bromide effects certain Claisen condensations.[10]

[6] Meek, Turnbull, and Wilson, *J.*, 1953, 811.
[7] *Idem*, *J.*, 1953, 2891.
[8] Cason, *J. Org. Chem.*, 1948, **13**, 227.
[9] Gilman and Nelson, *Rec. Trav. chim.*, 1936, **55**, 518.
[10] Hauser, Swamer, and Adams, *Org. Reactions*, 1954, **8**, 137.

It is well established [11,12] that *cyclo*hexane-1 : 3-diones undergo *C*-acylation at $C_{(2)}$. Treatment of (±)-4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione with acetic anhydride–sodium acetate gave the liquid 2-acetyl compound (IX) which was characterised as the crystalline imine and copper salt. These derivatives were identical with those reported for (±)-angustione, obtained by hydrogenation of natural dehydroangustione. 2-Acetyl*cyclo*hexane-1 : 3-diones have two characteristic ultraviolet absorption bands; [3,12] it was found that the copper salts of the 2-acetyl-diones, including synthetic angustione, when dissolved in acidified ethanol exhibit the same characteristic absorption (Table 2).

TABLE 1. *Light absorption and* p*K's of* cyclo*hexane*-1 : 3-*diones.*

	Ethanol		50% Ethanol					pK_a in 50% ethanol	
						Isosbestic point		Spectroscopic	Electrometric
	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	pH	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	λ (mμ)	$10^3\varepsilon$		
4 : 4-Dimethyl ...	255	18·4	2·45	257	18·3	266	13	6·18	6·20
			9·55	282	26·9				
4 : 4 : 6-Trimethyl	257	18·9	1·9	258	21	268	15·4	6·44	6·37
			12·3	284·5	31				

TABLE 2. *Light absorption of 2-acetyl*cyclo*hexane-1 : 3-diones in acidified ethanol.*

	Acetyl-dione				Copper salt			
	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$	$\lambda_{max.}$ (mμ)	$10^3\varepsilon$
Unsubstituted [a]	233	15	272	11·5	233	15	272	13·5
5 : 5-Dimethyl [b]	234	12	274	12	234	12	274	12
4 : 4 : 6-Trimethyl	—	—	—	—	235	10·5	275	10

[a] Copper salt, m. p. 271—272° (decomp.); Smith [12] gives m. p. 263—265°. [b] Copper salt, m. p. 260° (decomp.); Dieckmann and Stein [11] give m. p. 260°.

Published methods [13] for the preparation of αα'γ-trimethylglutaric acid did not appear to be wholly satisfactory, and alternative routes were sought, but with only limited success. In model experiments, it was shown that 2 : 6-dibenzylidene*cyclo*hexanone gave glutaric acid when oxidised with permanganate. Unfortunately, 3 : 3 : 5-trimethyl*cyclo*hexanone (dihydro*iso*phorone) did not form a benzylidene derivative. This was unexpected, in view of the ease with which *iso*phorone (XVII) forms a benzylidene derivative, usually formulated as (X).[14] It is more likely that benzylidene*iso*phorone is (XI); the presence of an absorption band at 323·5 mμ is consistent with this view, as benzylidenepiperitone has a similar band at 323 mμ, and the structure (XII) of benzylidenepiperitone has been established by oxidative degradation.[15] Dehydration of *trans*-3 : 3 : 5-trimethyl*cyclo*hexanol gave a mixture of isomeric trimethyl*cyclo*hexenes, probably (XIII), (XIV), and (XV); earlier workers [16] have established the presence of large amounts of *cyclo*geraniolene (XV) in the dehydration products; but it is now clear that at least one of the other isomers mentioned is present. Chromic acid oxidation of the trimethyl*cyclo*hexene mixture gave a mixture of trimethyl*cyclo*hexenones. Some *iso*phorone [XVII; derived from (XV)] was present in the mixture, as shown by the isolation of *iso*phorone 2 : 4-dinitrophenylhydrazone. Permanganate oxidation of the ketone mixture afforded useful amounts of αα'γ-trimethylglutaric acid; this indicates the presence of the trimethyl*cyclo*hexenone (XVI), derived from (XIII), or of an isomeric ketone derived from (XIV).

EXPERIMENTAL

Ultraviolet absorption and pK_a measurements (Tables) were carried out as described previously.[6, 7]

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[11] Dieckmann and Stein, *Ber.*, 1904, **37**, 3370; Crossley and Renouf, *J.*, 1912, 1524; Rogers and Smith, *J.*, 1955, 341.

[12] Smith, *J.*, 1953, 803.

[13] Perkin and Smith, *J.*, 1903, 771; Hoch and Karrer, *Helv. Chim. Acta*, 1954, **37**, 397.

[14] Cornubert and Borrel, *Compt. rend.*, 1926, **183**, 296; *Bull. Soc. chim. France*, 1929, **45**, 1158.

[15] Earl and Read, *J.*, 1926, 2072; cf. Bardhan and Adhya, *J.*, 1956, 260.

[16] Knoevenagel, *Annalen*, 1897, **297**, 199; Wallach and Franke, *ibid.*, 1902, **324**, 114; Wallach and Schennert, *ibid.*, p. 102.

Dimethyl αα-Dimethylglutarate.—Camphoric anhydride (177 g.) was converted[17] into *iso*lauronolic acid (94 g.; m. p. 132—134°). Oxidation[18] with nitric acid then afforded crude αα-dimethylglutaric acid, which was converted into the dimethyl ester (52 g.; b. p. 99—107°/12 mm.; Blaise[19] gives b. p. 215—216°) by boiling methanol and sulphuric acid. The light-absorption properties of *iso*lauronolic acid ($\lambda_{\max.}$ 229 mμ; ε 9000) are consistent with an αβ-unsaturated acid structure.

γ-Methoxycarbonyl-γ-methylvaleric Acid (III; R = H).—Dimethyl αα-dimethylglutarate (10 g.), absolute ethanol (50 c.c.), and N-ethanolic potassium hydroxide (56 c.c.) were stirred at 20° for 24 hr., alcohol distilled off at 15 mm., and water (50 c.c.) added. A small amount of oil was removed by ether-extraction; acidification of the aqueous layer and ether-extraction afforded *γ-methoxycarbonyl-γ-methylvaleric acid* (5·8 g.), b. p. 135—140°/12 mm., n_{D}^{19} 1·4382 (Found: C, 55·6; H, 7·9%; equiv., 176. $C_7H_{13}O_2{\cdot}CO_2H$ requires C, 55·2; H, 8·1%; equiv., 174).

γ-Methoxycarbonyl-γ-methylvaleroyl Chloride (IV; R = H).—The above acid (5·8 g.) and thionyl chloride (8·1 g.) were heated at 30—40° for 4 hr., yielding the chloride (5·5 g.), b. p. 68—71°/2 mm., n_{D}^{18} 1·4475, characterised by the formation of a p-*bromoanilide* (76%), m. p. 72—74° (Found: N, 4·2. $C_{14}H_{18}O_3NBr$ requires 4·3%).

Methyl 2 : 2-*Dimethyl*-5-*oxohexanoate* (VI; R = H).—A Grignard solution was made from methyl bromide (11·4 g.), magnesium (2·89 g.), and ether (60 c.c.). Anhydrous finely powdered cadmium chloride (11 g.) was added with stirring and stirring continued at 30° until the Gilman test was negative. Dry benzene (70 c.c.) was added, and about 20 c.c. of this distilled off to remove the ether. γ-Methoxycarbonyl-γ-methylvaleroyl chloride (8·5 g.) in dry benzene (20 c.c.) was added dropwise with cooling, and the reaction completed by stirring at 80° for 40 min. After decomposition with ice and dilute hydrochloric acid, the benzene solution was distilled, to give an oil, b. p. 98—103°/12 mm. Crystals were gradually deposited, trituration with light petroleum (b. p. 40—60°), and recrystallisation from the same solvent gave αα*δδ-tetramethyl-δ-valerolactone* (VIII) (0·9 g.), m. p. 80·5—81·5° (Found: C, 69·7; H, 10·45. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%). The lactone gave a negative iodoform reaction, did not form a 2 : 4-dinitrophenylhydrazone, and had no absorption bands between 220 and 310 mμ; it slowly dissolved in aqueous alkali and was regenerated on acidification, and with concentrated aqueous ammonia gave 5-*hydroxy*-2 : 2 : 5-*trimethylhexanoamide*, m. p. 123—124° (from ethyl acetate) (Found: N, 7·7. $C_9H_{19}O_2N$ requires N, 8·1%). The light petroleum liquors were distilled, to give methyl 2 : 2-dimethyl-5-oxohexanoate (VI; R = H) (4 g.), b. p. 100—102°/12 mm., n_{D}^{20} 1·4371 (Found: C, 62·8; H, 9·4. $C_9H_{16}O_3$ requires C, 62·7; H, 9·8%) [2 : 4-*dinitrophenylhydrazone*, m. p. 100—100·5° (Found: N, 15·65. $C_{15}H_{20}O_6N_4$ requires N, 15·9%)]; this ester gave a positive iodoform reaction.

4 : 4-*Dimethyl*cyclo*hexane*-1 : 3-*dione* (VII; R = H).—Solvent-free sodium methoxide (from 2·1 g. of sodium) was suspended in dry ether (40 c.c.) and methyl 2 : 2-dimethyl-5-oxohexanoate (3·8 g.) in dry ether (30 c.c.) added slowly with stirring at 5°. The mixture was stirred for 16 hr. at 20°, then iced water added. The ether layer was removed; the aqueous layer was acidified with hydrochloric acid and extracted with ether (4 × 60 c.c.); recrystallisation of the extract from ethyl acetate gave the *dione* (1·4 g.), m. p. 103—105° (Found: C, 68·4; H, 8·8. $C_8H_{12}O_2$ requires C, 68·6; H, 8·65%); other physical properties are given in Table 1. The dione gave a reddish colour with ferric chloride in aqueous ethanol, and with formaldehyde in aqueous ethanol and a trace of piperidine gave *methylenebis*-4 : 4-*dimethyl*cyclo*hexane*-1 : 3-*dione*, m. p. 98—99°, $\lambda_{\max.}$ 256 mμ (ε 26,300) (Found: C, 69·6; H, 8·2. $C_{17}H_{24}O_2$ requires C, 69·8; H, 8·3%).

3 : 3 : 5-*Trimethyl*cyclo*hexanone*.—*trans*-3 : 3 : 5-Trimethyl*cyclo*hexanol (45 g.) was added slowly with stirring to a mixture of sodium dichromate (60 g.), water (300 c.c.), and concentrated sulphuric acid (50 g.). The mixture was left for 20 hr., then extracted with ether, to give the ketone (36 g.), b. p. 71—73°/15 mm. The 2 : 4-dinitrophenylhydrazone was obtained in two forms: orange-yellow prisms (from glacial acetic acid), m. p. 147—148° (Found: N, 17·15. Calc. for $C_{15}H_{20}O_4N_4$: N, 17·5%); and yellow needles, m. p. 110°, from ethanol. Recrystallisation of the second form gave a mixture of the two and eventually transformation into the first was complete. The low-melting form appears to have been isolated by Braude and Evans[20] (m. p. 115—16°), and the high-melting form by Morgan and Hardy[21] (m. p. 145—147°).

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[17] Bardhan, Banerji, and Bose, *J.*, 1935, 1127.

[18] Perkin, *J.*, 1902, 246.

[19] Blaise, *Bull. Soc. chim. France*, 1899, **21**, 626.

[20] Braude and Evans, *J.*, 1954, 613.

[21] Morgan and Hardy, *Chem. and Ind.*, 1933, 518.

*Benzylidene*iso*phorone* (XI).—A mixture of freshly distilled *iso*phorone (30 g.), benzaldehyde (23 g.), ethanol (100 c.c.), and 45% aqueous sodium hydroxide (10 c.c.) was left for 7 days; the solution remained alkaline. Water was added, and the solid product (26 g.) was recrystallised from aqueous methanol. Benzylidene*iso*phorone had m. p. 81—82°, $\lambda_{max.}$ 323·5 (ε 27,300) and 235 mμ (ε 7800) (Cornubert and Borrel [14] give m. p. 78·5—79°).

Benzylidene-(±)*-piperitone* (XII).—(±)-Piperitone (12·5 g.; purified through the sodium bisulphite adduct) and benzaldehyde (8·75 g.), in ethanol (30 c.c.), were added to a cold solution of sodium (0·5 g.) in ethanol (25 c.c.). The mixture was poured into water and slightly acidified; ether-extraction and distillation gave a syrup, b. p. 135—141°/0·05 mm., which gave crystals, m. p. 59·5—60·5°, from methanol (Read and Smith [22] give m. p. 61°). Light-absorption max. in EtOH: 324 (ε 31,000) and 234·5 mμ (ε 7300).

*Trimethyl*cyclo*hexenone Mixture.*—*trans*-3 : 3 : 5-Trimethyl*cyclo*hexanol (284 g.) and concentrated sulphuric acid (8 c.c.) were heated together at 160—185° (bath), the hydrocarbon distilling off as it was formed. Redistillation gave a mixture of trimethyl*cyclo*hexenes (170 g.), b. p. 130—138°, n_D^{17} 1·4419. This product (150 g.) was diluted with glacial acetic acid (350 c.c.), and a solution of chromium trioxide (24 g.) in water (150 c.c.) and acetic acid (675 c.c.) was added with stirring at 18—28°. The mixture was left for 24 hr., 50% aqueous potassium hydroxide (200 c.c.) added, and the oily product isolated by ether-extraction. Unchanged trimethyl*cyclo*hexene (52 g.) was obtained, together with a mixture of trimethyl*cyclo*hexenones (26 g.), b. p. 95—105°/20 mm., n_D^{22} 1·4641 (Found: C, 77·9; H, 10·4. Calc. for $C_9H_{14}O$: C, 78·2; H, 10·2%). A resin was formed with 2 : 4-dinitrophenylhydrazine; repeated crystallisation from aqueous acetic acid gave a small amount of *iso*phorone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 143—144° (Found: N, 17·3. Calc. for $C_{15}H_{18}O_4N_4$: N, 17·6%).

Dimethyl ααγ*-Trimethylglutarate.*—The trimethyl*cyclo*hexenone mixture (10 g.), sodium hydroxide (4 g.), and water (500 c.c.) were stirred at 0°, and 5% aqueous potassium permanganate (500 c.c.) was added dropwise. The solid was removed and the filtrate continuously extracted with ether for 24 hr. The resulting syrup (10 g.) was extracted with hot light petroleum (b. p. 40—60°), to yield ααγ-trimethylglutaric acid (3 g.), m. p. 97—98° (Found: equiv., 87·8. Calc. for $C_8H_{14}O_4$: equiv., 87·1) (Perkin and Smith [13] give m. p. 97—98°). The fraction insoluble in light petroleum was a lactonic acid of equivalent weight 187; oxidation of this (7 g.) gave further quantities of trimethylglutaric acid (3 g.), m. p. 97—98°. The dimethyl ester, obtained by boiling the acid with methanol and concentrated sulphuric acid, had b. p. 115—120°/15 mm., $n_D^{21\cdot5}$ 1·4309.

γ*-Methoxycarbonyl-*αγ*-dimethylvaleric Acid* (III; R = Me).—Dimethyl ααγ-trimethylglutarate (7·5 g.) and 0·5N-ethanolic potassium hydroxide (75 c.c.) were stirred at 20° for 21 hr., a small amount of solid was filtered off, and the alcohol removed at 30—40° in a vacuum. The residue was dissolved in water, extracted with ether, and acidified. The liberated γ*-methoxycarbonyl-*αγ*-dimethylvaleric acid* (4·2 g.), b. p. 150—160°/13 mm., $n_D^{18\cdot5}$ 1·4428, was isolated by means of ether (Found: C, 57·6; H, 8·8%; equiv., 195. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%; equiv., 188).

γ*-Methoxycarbonyl-*αγ*-dimethylvaleroyl Chloride* (IV; R = Me).—The above acid (3·7 g.) and thionyl chloride at 30—40° for 5 hr. gave the chloride (3 g.), b. p. 60—65°/2 mm., $n_D^{18\cdot5}$ 1·4451, which gave a p*-bromoanilide* (74%), m. p. 83—84° (Found: N, 4·0. $C_{15}H_{20}O_3NBr$ requires N, 4·1%).

Methyl 2 : 4 : 4*-Trimethyl-*5*-oxohexanoate* (VI; R = Me).—A Grignard solution from methyl bromide (7·0 g.), magnesium (1·7 g.), and ether (50 c.c.) was treated with anhydrous powdered cadmium chloride (7 g.). The ether was replaced with dry benzene (50 c.c.), and γ-methoxycarbonyl-αγ-dimethylvaleroyl chloride (2·8 g.) in benzene (20 c.c.) added with stirring. The mixture was stirred at 80° for 40 min., then ice and dilute hydrochloric acid added. Evaporation of the benzene gave an oil, which partly crystallised. Trituration with light petroleum (b. p. 40—60°) gave 4 : 4 : 6-trimethyl*cyclo*hexane-1 : 3-dione (0·3 g.), m. p. 130—131°, $\lambda_{max.}$ 258 mμ (ε 18,400) in EtOH, having an equivalent weight of 152 by electrometric titration; the m. p. was not depressed on admixture with the specimen described below. The light petroleum solution afforded *methyl* 2 : 4 : 4*-trimethyl-*5*-oxohexanoate* (1·4 g.), b. p. 95—105°/14 mm., n_D^{20} 1·4458 (Found: C, 64·35; H, 9·6. $C_{10}H_{18}O_3$ requires C, 64·5; H, 9·75%); the ester gave a positive iodoform test, and formed an oily 2 : 4-dinitrophenylhydrazine.

4 : 4 : 6*-Trimethyl*cyclo*hexane-*1 : 3*-dione* (VII; R = Me).—Sodium (1·0 g.) was converted into solvent-free sodium methoxide, which was suspended in dry ether (30 c.c.); methyl 2 : 4 : 4-trimethyl-5-oxohexanoate (0·9 g.) in dry ether (20 c.c.) was added, and the mixture stirred at

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[22] Read and Smith, *J.*, 1921, 785.

20° for 20 hr. Ice-water was added, the solution extracted with ether and acidified with hydrochloric acid, and the precipitated oil (0·6 g.) isolated by ether. Recrystallisation from light petroleum (b. p. 60—80°) gave the *dione*, m. p. 130—131° (Found: C, 69·85; H, 8·8. $C_9H_{14}O_2$ requires C, 70·1; H, 9·15%); the substance gave a greenish-brown colour with ferric chloride in 50% ethanol; piperonaldehyde in aqueous ethanol containing a little piperidine gave the derivative, m. p. 191—193° (Gibson, Penfold, and Simonsen[1] give m. p. 192—193°). Light absorption and pK_a values for the dione are given in Table 1.

(±)-*Angustione* (IX).—4 : 4 : 6-Trimethyl*cyclo*hexane-1 : 3-dione (0·5 g.), fused sodium acetate (0·2 g.), and acetic anhydride (5 c.c.) were refluxed for 7 hr. The acetic anhydride was removed at 15 mm., and the residue extracted with hot light petroleum (b. p. 60—80°). Distillation gave (±)-angustione, b. p. 130—140°/15 mm., characterised by the formation of an imine, m. p. 138—139° (from *cyclo*hexane) (Found: C, 67·75; H, 9·0. Calc. for $C_{11}H_{17}O_2N$: C, 67·65; H, 8·8%), and a greyish-blue copper salt, m. p. 201—202° (from light petroleum–benzene) (Cahn, Gibson, Penfold, and Simonsen[2] give m. p. 203—204°, and for the imine, m. p. 138—139°). The m. p. of the imine was not depressed on admixture with a specimen obtained from natural sources. The infrared spectra of the synthetic and the natural imine were practically identical.

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