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THE SYNTHESIS OF SOME CYCLIC DIKETONES ISOLATED FROM COFFEE

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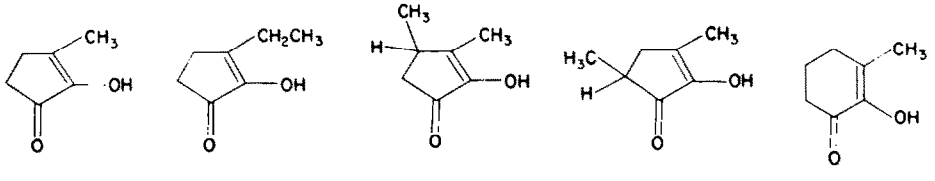
Abstract—The syntheses of several alkylated derivatives of cyclopentane-1, 2-dione (cyclopent-2-en-2-ol-1-one), four of which have been previously identified in roasted coffee[2], are described.

The elucidation of the structure of five cyclic diketones (I–V) isolated from coffee has been recently reported.[2] These structures had to be postulated on the sole basis of spectroscopic data (IR, UV and mass spectrometry), since any degradative approach was precluded by the paucity of the material avaliable.[3] Consequently, the correctness of the interpretation of the spectral data could be proven only by synthesis and more specifically, compounds I and V having been previously described in the literature,[4,5] by the synthesis of compound II and of at least one of the dimethyl diketones III and IV.[6]

It is the purpose of this publication to describe the synthetic work which led to the preparation of the isomeric compounds II, III and IV and of three other substituted cyclopentane-1,2-diones that were isolated, as important by-products, from one of the synthetic routes which led to compound IV.



I II III IV V

The preparation of compounds II and III presented no difficulty and was achieved by decarboxylative hydrolysis of the appropriate diketodiesters VIc and VId, which in turn resulted from the alkylation of VIa and VIb. The diketodiesters VIa and VIb have been previously reported in the literature[4,7] and were prepared by condensation of the appropriate glutarate with diethyl oxalate. The only peculiarity observed

[1] To whom inquiries concerning this paper should be addressed.

[2] M. A. Gianturco, A. S. Giammarino and R. G. Pitcher, *Tetrahedron* **19**, 2051 (1963) following paper.

[3] The concentrations of the 5 compounds in the roasted coffee used (a commercial blend) varied from $4 \cdot 10^{-5}\%$ (III) to $2 \cdot 10^{-4}\%$ (I).

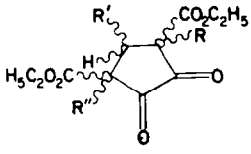
[4] G. Hesse and K. W. F. Boeckmann, *Liebigs. Ann.* **563**, 37 (1949).

[5] K. Wallach, *Ber*, **414**, 314; **437**, 180 (1900).

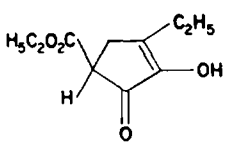
[6] Actually, as indicated by the arguments presented in the previous paper,[2] the proof of the structures of any two of the three isomers II-IV would have permitted an unequivocal structural assignment for the third isomer.

[7] G. Hesse and E. Buecking, *Liebigs Ann.* **563**, 31 (1949).

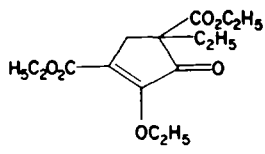
in the alkylation of VIa and VIb consisted in the fact that better yields of the products of C-alkylation are obtained when the reactions are conducted, in presence of an excess of alkylating agent, with two equivalents of base per equivalent of substrate.[8] Some O-alkylation probably occurred concomitantly with the prevalent C-alkylation when either VIa or VIb was treated with the alkylating agent in presence of sodium alkoxide; this was specifically proven in the case of the ethyl compound, since alkaline extraction of an ether solution of the crude alkylation mixture of compound VIa led to the isolation of two products, whose analysis and IR spectra agreed with structure VII, for the alkali-soluble compound,[9] and with VIII for the alkali-insoluble material.



VI



VII



VIII

VIa: R=R′=R″=H
VIb: R=R″=H; R′=CH_3
VIc: R=C_6H_5; R′=R″=H

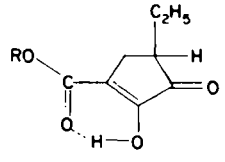
VId: R=R′=CH_3; R″=H
VIe: R=CH_3; R′=R″=H
VIf: R=R″=CH_3; R=H

While both VII and VIII can be converted into 3-ethylcyclopentane-1,2-dione (II) by treatment with acids, the ordinary conditions (reflux in 20–30% H_2SO_4) are adequate for the hydrolysis of VII, but not for the hydrolysis of VIII; for the latter, refluxing with hydriodic acid was found to be necessary.

It should be pointed out that Nazarov and Akhrem have reported[10] the isolation of a substance analyzing only approximately for $C_7H_{10}O_2$, which they described as "presumably" being 3,4-dimethylcyclopentane-1,2-dione (III) from the acid hydrolysis of the epoxidation product of 2,4-dimethylcyclopent-2-en-1-one. However, since the melting point of the material isolated by the Russian workers is almost twenty

[8] A similar phenomenon has been previously reported[4] for an analogous reaction.

[9] Considerable evolution of CO_2 occurred upon acidification of the alkaline solution; obviously, the carbethoxy group on the t-carbon atom of VIc is easily removed by alkali. The resulting product was assigned structure VII, rather than the isomeric structure VIIa, on the basis of its I.R. spectrum;



VIIa

inter alia (See experimental for data on the C=O and C=C absorptions of VII), the absorption due to the —OH stretching vibrations is identical with that typical of the cyclic diketones I-IV [2·82 μ (sharp) and 2·97 μ (relatively broad)][3], which is very different from the extremely broad and diffuse —OH absorption characteristic of enolized β-ketoesters.

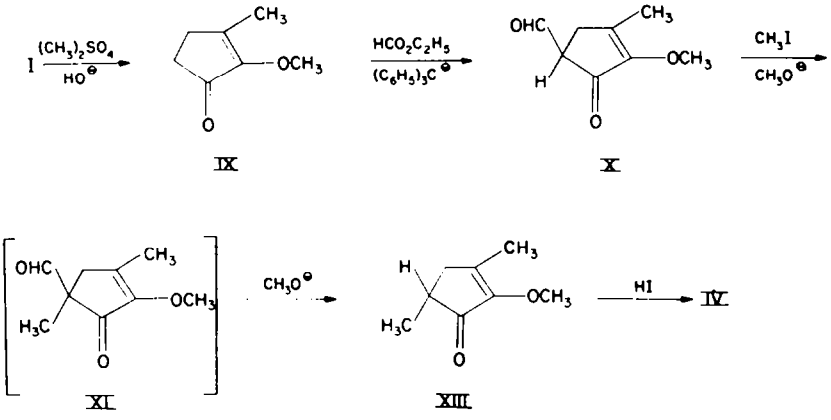
[10] I. N. Nazarov and A. A. Akhrem, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk.* 1383 (1956) (C.A. **51**, 8021).

degrees higher than that of compound III prepared in this laboratory by an unequivocal method, it was found necessary to conclude[11] that the product isolated by Nazarov and Akhrem could not be III. It might perhaps be 3,5-dimethylcyclopentane-1,2-dione (IV) in view of the reportedly facile isomerization[12] of 2,4-dimethylcyclopent-2-en-1-one into 3,5-dimethylcyclopent-2-en-1-one.

The synthesis of IV could also be accomplished by the decarboxylative hydrolysis of the appropriate diketodiester (VIf), which in turn was obtained by the monoalkylation of VIe or by dialkylation of VIa. However, it was found that a more direct (and preferred) approach to the synthesis of IV can be based upon the alkylation of the methyl ether, IX, of compound I.

The only precaution which must be observed in the first synthetic route to IV consists in the adoption of a two-step procedure for the introduction of two methyl groups in the molecule of VIa. Attempts to introduce both methyl groups in one step resulted only in the isolation of the monomethyl derivative (VIe)

However, the second synthetic approach to compound IV (alkylation of IX) is more direct and practical, since the starting material (I) for the synthetic sequence is commercially available.[13] The successful outcome of this procedure depends, however, upon the blocking of one of the 5 positions of IX prior to the alkylation step. If this precaution is observed, 3,5-dimethylcyclopentane-1,2-dione is obtained



in satisfactory yield (50% overall). The intermediate 2-methoxy-3-methyl-5-formylcyclopent-2-en-1-one (X), is considerably stable towards alkali; in fact, a sample of this compound was recovered unchanged after refluxing for one hour in a 0·4N solution of sodium methoxide in methanol. The corresponding methylated derivative XI, in the same conditions of basicity, is instead deformylated in the cold, practically as rapidly as it is formed from X. On the other hand, both X and XI have considerable thermal stability and can be purified by vapor-liquid chromatography.

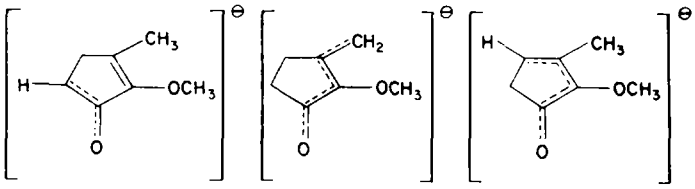
When direct methylation of IX was attempted, without prior formylation, a complex mixture resulted, independently of whether sodium amide or triphenylmethyl sodium were used as the base and methyl iodide or methyl chloride as the alkylating agent. Vapor-liquid chromatography of the reaction mixture, after

[11] Attempts to obtain a sample for a direct comparison resulted in failure.

[12] I. N. Nazarov and A. N. Elizarova, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk.* 295 (1951) (C.A. **46**, 914).

[13] K & K Laboratories, Inc., Jamaica, N.Y., New York.

cleavage of the ether function, revealed in fact the presence of seven compounds (six peaks, A–F, see below). Comparisons of retention times, IR and mass spectra led to the identification of peak C as 3,5-dimethylcyclopentane-1,2-dione (IV, from anion XIII), peak D as 3-methylcyclopentane-1,2-dione (I, corresponding to the starting material IX) and peak F as 3-ethylcyclopentane-1,2-dione (II, from anion anion XIV). The presence of a small amount of 3,4-dimethylcyclopentane-1,2-dione (III, corresponding to the improbable anion XV) was only indicated by the presence of a small peak (peak E, whose area was less than 3% of the total area of peaks A–F) having the appropriate retention time. However, the identity of this peak was not conclusively proven. The structures of the other three alkylation products represented by peaks A and B is discussed below. Peak A, trapped from a polar



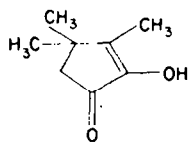
XIII XIV XV

column, yielded only one peak when reinjected onto a nonpolar column and proved to be homogeneous substance, analyzing correctly for $C_8H_{12}O_2$ [m.w. 140 (mass spectrometry)]. Peak B, instead, upon reinjection onto a nonpolar column, yielded two peaks, B_1 and B_2; the analysis of B_1, coupled with the mass spectrum (m.w. 154), led to the molecular formula $C_9H_{14}O_2$. Compound B_2 was not obtained in an amount sufficient for an elemental analysis, but its IR and UV spectra confirmed that it was a substituted cyclopentane-1,2-dione and the mass spectrum gave the molecular weight of 168; consequently, the molecular formula of B_2 must be $C_{10}H_{16}O_2$. Moreover, the comparison of the 7·0–7·4 μ region of the IR spectra of I–IV, cyclopentane-1,2-dione, 4-methylcyclopentane-1,2-dione, 4,4-dimethylcyclopentane-1,2-dione, peaks A, B_1 and B_2 (Fig. 1) strongly suggested that: (1) In compound A, the substituent on C-3—the carbon atom adjacent to the enolized carbonyl—is a methyl group; (2) In compounds B_1 and B_2, the substituent on C-3 is *not* a methyl group. With these limitations and keeping into account the plausible anionic precursors, four structures could be considered for peak A and five for peak B_1.[14] However, considerations on the relative retention times of peaks A and B_1 and of compounds I–IV permitted limiting the choice of structures possible for A and B_1 to the pairs XVI–XVII and XVIII–XIX, respectively.[15]

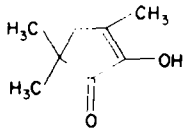
Finally, intensity measurements on the peaks corresponding to the loss of a methyl group (M-15) relative to the peaks corresponding to the molecular ion (M) in the mass spectra of many substituted cyclopentane-1,2-diones and, more particularly, in those of 4,4-dimethylcyclopentane-1,2-dione, compound A and compound B_1,

[14] These structures are as follows. For peak A: 3,4,5-, 3,4,4-, and 3,5,5-trimethylcyclopentane-1,2-dione and, possibly, 3-methyl-5-ethylcyclopentane-1,2-dione; for peak B_1: 3-ethyl-4,4-dimethyl-, 3-ethyl-5,5-dimethyl- or 3-ethyl-4,5-dimethylcyclopentane-1,2-dione, 3-isopropyl-4-methyl- or 3-isopropyl-5-methylcyclopentane-1,2-dione.

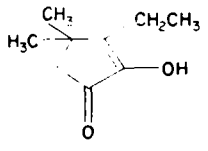
[15] An N.M.R. det., performed through the courtesy of Mr. E. A. Pier of Varian Associates, Palo Alto, California, confirmed the presence of an ethyl group in compound B_1.



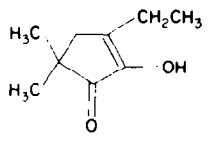
XVI



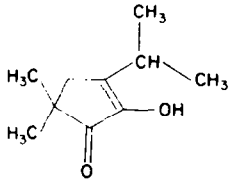
XVII



XVIII



XIX



XX

led to the conclusion that neither A nor B_1 could possibly have a gem-dimethyl group in the (allylic) C-4 position. In fact, the values of $\frac{M-15}{M} \times 100$ are 230 for 4,4-dimethylcyclopentane-1,2-dione and approximately 100 for both compound A and compound B_1; consequently, the only plausible structures for A and B_1 seemed to be XVII and XIX.[16] The correctness of this postulation was proven for compound A by synthesis of 3,5,5-trimethylcyclopentane-1,2-dione (selenium dioxide oxidation of 2,4,4-trimethylcyclopentanone).[17] With regard to the minor component corresponding

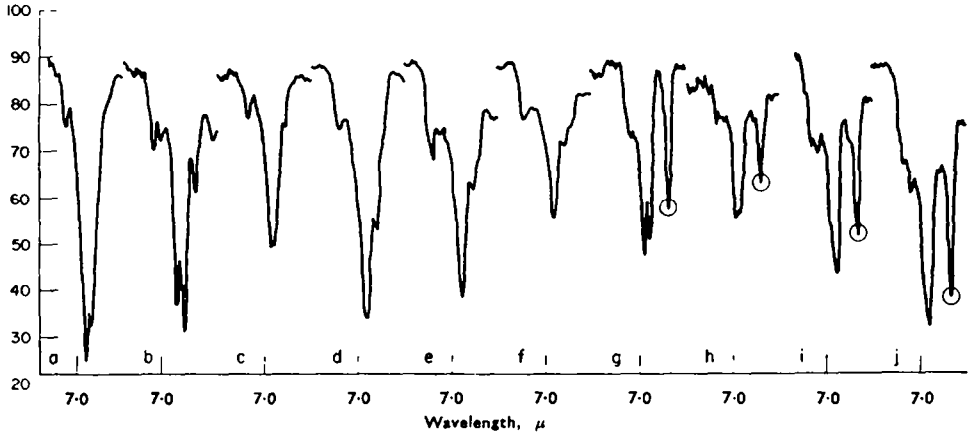


FIG. 1. Infra red spectra (6·5–7·5u, $CHCl_3$) of: Cyclopentane-1.2-Dione (a); 3-Ethylcyclo-pentane-1,2-Dione (b); 4-Methylcyclopentane-1.2-Dione (c); 4,4-Dimethylcyclopentane-1,2-Dione (d); Peak B_1(e); Peak B_2 (f); 3-Methylcyclopentane-1,2-Dione (g); 3,4-Dimethylcyclopentane-1,2-Dione (h); 3,5-Dimethylcyclopentane-1,2-Dione (i); Peak A (j).

[16] For the validity of such an approach in problems of structural determinations, see: *Mass Spectrometry* by K. Biemann, McGraw-Hill, N.Y. (New York). We extend our thanks to Mr. E. Emery of the Colgate-Palmolive Company, New Brunswick, N.J. for having suggested this approach to us.

[17] It should be noted that the m.ps of XVII and of the previously known[18] XVI are not very different from each other.

[18] G. L. Blanc and J. F. Thorpe, *J. Chem. Soc.* **99**, 2010 (1900).

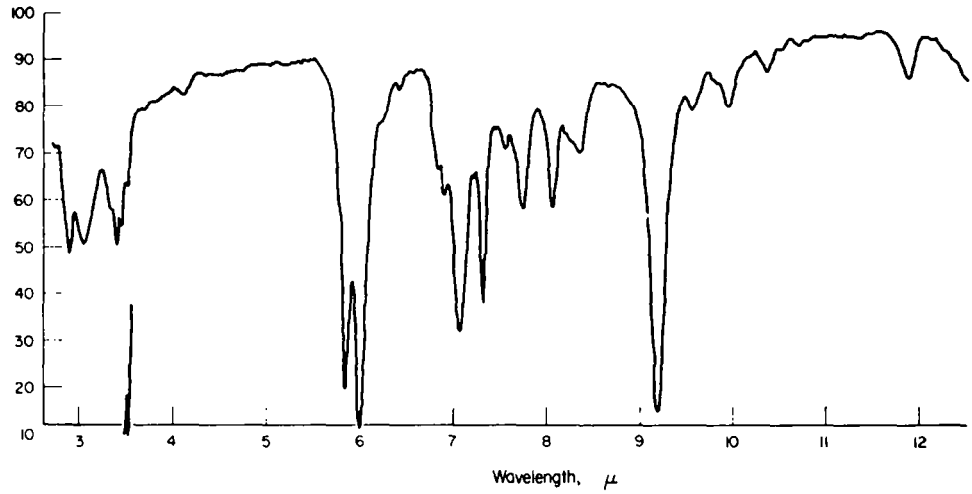


FIG. 2. Infrared spectrum ($CHCl_3$) of Peak A.

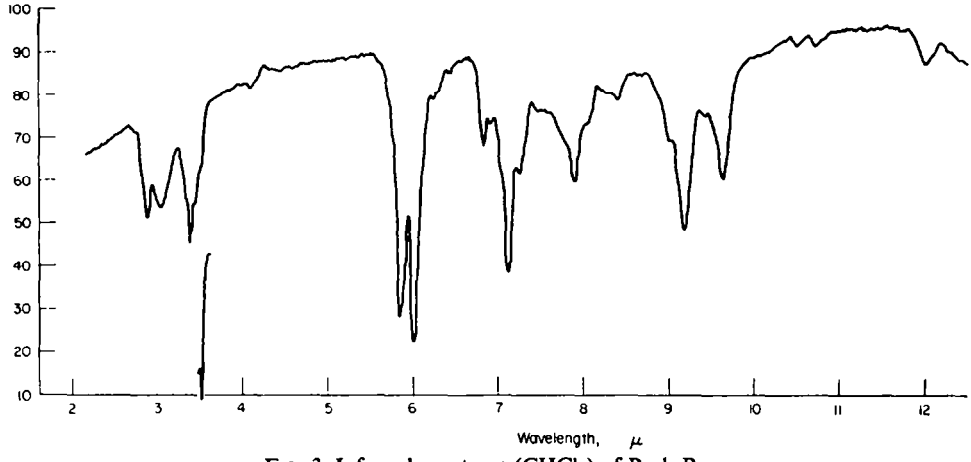


FIG. 3. Infrared spectrum ($CHCl_3$) of Peak B_1.

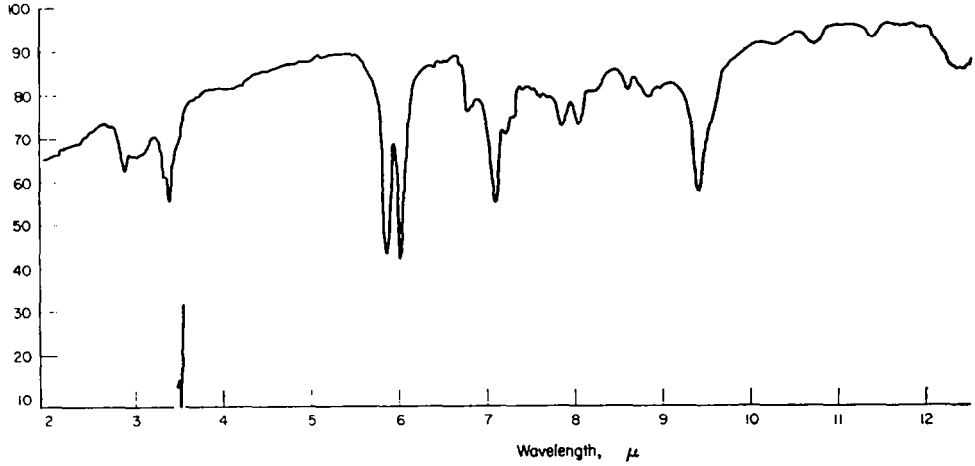


FIG. 4. Infrared spectrum ($CHCl_3$) of Peak B_2.

to peak B_2, it seems safe to assume that the most likely structure for it is that of 3-isopropyl-5,5-dimethylcyclopentane-1,2-dione, XX, in view of its formula, IR spectrum (no methyl group on C-3), UV spectrum [substituent on C-3, as indicated by λ_{max}^{EtOH} 259 μ (see Ref. 2 for UV data of various cyclopentane-1,2-diones)], mass spectrum $\left(\frac{M-15}{M} \times 100 = 100\right)$ and possible mode of formation (alkylation of the resonance-stabilized ion resulting from equilibration of the methyl ether of compound XIX with any of the many anions present in the alkylation mixture of IX after the inception of the alkylation[19]).

EXPERIMENTAL[20]

Vapour-liquid chromatography (stainless steel columns) was carried out in the following conditions: (a) [R_T'] 4m × 0·25″ DEGA packed column (15% on chromosorb) operated at 175° with a flow of 110 ml He/min; (b) [R_T'] 2m × 0·25″ silicone gum packed column (15% on chromosorb) operated at 125° with a flow of 70 ml He/min.

The IR spectra were determined on a Beckman IR4 spectrophotometer, employing a beam condensor and an ultramicrocell (path length 0·115 mm); slit opening: 0·55 mm at 10 μ; gain: 3%; period: 2; scanning speed: 1 μ/min.

The m.ps were determined on a Kofler apparatus on samples purified by VPC and deposited from the gas stream by rapid cooling. Samples obtained in this fashion (microcrystallites) may melt 2-3° lower than samples of the same purity obtained by conventional crystallization.

Materials

3,5-Dicarbethoxycyclopentane-1,2-dione (VIa). This was prepared in 70% yield by condensation of diethyl glutarate with diethyl oxalate, according to Hesse and Buecking[7]; m.p. 116–118° (lit.[7] 118°).

3,5-Dicarbethoxy-4-methylcyclopentane-1,2-dione (VIb). This was prepared in 72% yield by condensation of diethyl 3-methylglutarate with diethyl oxalate, according to Hesse and Boeckmann[4]; m.p. 106–108° (lit.[4] 108°).

3-Methylcyclopentane-1,2-dione (I). This was prepared by decarboxylative hydrolysis of VIe, according to Hesse and Boeckmann,[4] and had the following physical properties: m.p. 102–104° (lit.[4] 106°); R_T' = 20 min; λ_{max}^{EtOH} 258 mu; lg ε = 4·05.

The alkylation product (VIe) of 3,5-dicarbethoxycyclopentane-1,2-dione (VIa), which upon hydrolysis yielded I, was isolated as a complex analyzing correctly (C, H) for $C_{12}H_{15}O_6Na \cdot C_{12}H_{16}O_6$, m.p. 172–174° (lit.[4] 179°). (Found: C, 53·79; H, 5·90. Calcd. for $C_{12}H_{15}O_6Na \cdot C_{12}H_{16}O_6$: C, 53·91; H, 5·84%).

The same complex had been isolated previously by Hesse and Boeckmann, but the analytical values reported by these authors were not entirely satisfactory.[4] Stirring for 3 hr a suspension of the complex in an excess of cold 20% H_2SO_4, effected its quantitative conversion into 3,5-dicarbethoxy-3-methylcyclopentane-1,2-dione (VIe), which was isolated by ether extraction and distillation; b.p. 148–150°/0·009 mm (lit.[4] 142°/0·002 mm); n_D^{19} 1·4920. (Found: C, 56·03; H, 6·28. Calcd. for $C_{12}H_{16}O_6$: C, 56·22; H, 6·30%).

3,4-Dimethylcyclopentane-1,2-dione (III). A hot solution of 25·6 g (0·1 mole) VIb in 100 ml abs. ethanol was added with stirring to a solution of 4·6 g (0·2 mole) Na in 100 ml ethanol. The resulting mixture was cooled to room temp, treated with 30 g (0·21 mole) methyl iodide, stirred overnight at room temp. and then refluxed for 8 hr (until neutral). After cooling, the pH was adjusted to 5·5 and the solution left in the refrigerator overnight; the white precipitate (9 g) which formed was separated and, after crystallization from ethanol, analyzed correctly for $C_{13}H_{17}O_6Na \cdot C_{13}H_{16}O_6$;

[19] It may be worthwhile to remark that the products of polyalkylation can be made to clearly predominate in the mixture resulting from direct methylation of IX by carrying out the reaction in presence of an excess of base (see experimental).

[20] Microanalyses by Mr. Joseph Nemeth of the Department of Chemistry and Chemical Engineering of the University of Illinois, Urbana, Ill.

m.p. 190–192°. This complex is probably analogous to the one isolated by Hesse and Boeckmann[4] and by us during the preparation of compound I (see above). (Found: C, 55·58; H, 6·34. $C_{13}H_{17}O_6Na \cdot C_{13}H_{18}O_6$ requires: C, 55·51; H, 6·27%).

The alcoholic mother liquor was concentrated (red. press.) and the residue dissolved in 100 ml water was decolorized with SO_2, brought to pH 2 with H_2SO_4 and then filtered. The resulting wet cake was dissolved in ether, the aqueous layer extracted with the same solvent and the combined organic layers, after the usual work-up, left 16 g of oily material. Since both this oily material and the solid complex mentioned above yielded compound III upon hydrolysis, as could be verified in a small-scale experiment followed by VPC analysis, the two were combined and refluxed with 200 ml 20% H_4SO_4. After 30 hr the mixture, which was still somewhat turbid, was decolorized with Norite, filtered, saturated [$(NH_4)_2SO_4$] and extracted with ether. Removal of the solvent, after drying (Na_2SO_4), left an oily residue; this, upon distillation, yielded 6 g crude 3,4-dimethylcyclopentane-1,2-dione (III), b.p. 86–89°/4 mm, which immediately solidified, and 4 g of oil, b.p. 160–175°/0·1 mm, which was not further investigated.[21] The crude III was purified by preparative VPC. The yield of pure material was 5·2 g (40%) ; even lower yields (average of two preparations: 30%) were obtained when equivalent amounts of VIb, sodium ethoxide and methyl iodide were employed. The pure III had the following physical properties: m.p. 71–72°; R_T': 21 min; λ_{max}^{EtOH} 259 mu; lg ε = 4·06. (Found: C, 66·50: H, 8·05. $C_7H_{10}O_2$ requires: C, 66·64; H, 7·99%).

3-*Ethylcyclopentane*-1,2-*dione* (II). A solution of 24·2 g (0·1 mole) VIa in 250 ml ethanol was added with stirring to 400 ml of a solution of sodium ethoxide prepared from 4·6 g (0·2 mole) Na. The resulting slurry was treated with 31·2 g (0·2 mole) ethyl iodide and refluxed, with efficient stirring, for 12 hr (pH of the dark solution was neutral). The solvent was removed (red. press.), the oily residue dissolved in 200 ml water and the aqueous solution, after acidification (H_2SO_4) and saturation [$(NH_4)_2SO_4$], was extracted with ether. The usual work-up left an oily residue which, upon distillation, yielded 20 g colorless oil, boiling almost *in toto* at 146–150°/0·1 mm. This material was not homogeneous, but contained both VIc and VIII. This was indicated by the fact that when a solution of 13 g of this crude oil in 120 ml ether was shaken with 100 ml of 2N NaOH, 3 fractions could be isolated, an alkali-soluble one, an ether-soluble one and a solid precipitate. The ether-soluble fraction, 3·7 g, b.p. 136–137°/0·3 mm, gave no coloration ($FeCl_3$), analyzed correctly for VIII and its IR spectrum (CCl_4) showed carbonyl absorption at 5·70 μ, attributed to the unconjugated ester carbonyl, at 5·76 μ (shoulder), attributed to the second ester carbonyl, at 5·80 μ, attributed to the keto carbonyl and carbon-carbon double bond absorption at 6·11 μ. (Found: C, 60·22; H, 7.34. $C_{15}H_{22}O_6$ requires: C, 60·39; H, 7·43%).

After acidification of the alkaline fraction (vigorous evolution of CO_2), the alkali-soluble product could be isolated by ether extraction. The distilled oil, 1·9 g, b.p. 120–121°/0·4 mm, gave a strong brown coloration ($FeCl_3$), analyzed correctly for VII and its IR spectrum (CCl_4) showed O—H absorptions at 2·82 μ (sharp) and 2·97 μ (broader) and complex carbonyl and >C=C< absorption at 5.72 μ, 5·77 μ, (shoulder), 5·96 μ, and 6·10 μ. (Found: C, 60·39; H, 7·14. $C_{10}H_{14}O_4$ requires: C, 60·66; H, 7·08%).

The bulk of the material, however, was obtained as a slightly yellow precipitate, in the form of a sodium derivative (of either VII or VIc), which upon refluxing for 4 hr with an excess of 20% H_2SO_4 yielded II. In the same conditions, VII also yielded II, but VIII remained essentially unchanged. Compound VIII, however, could be conveniently transformed into II by refluxing with an excess of hydriodic acid for 1 hr.

In view of the results of these hydrolyses, the remaining crude oil (7 g) b.p. 146–150°/0·1 mm (see above) was refluxed for 6 hr with 20% H_2SO_4 (50 ml). The resulting yellow solution, after ether extraction and the usual work-up, yielded 3·5 g of an oil consisting (VPC) of 83% II and 17%, of higher boiling material, probably unreacted VIII. Distillation yielded 2·8 g pure II, b.p. 65–68°/1 mm (solidifying on cooling to ca. 20°); R_T': 24·6 min; λ_{max}^{EtOH} 259 mu, lg ε = 4·04. The over-all yield of pure II, based upon the amount of VIa employed, corresponds to 63%. (Found: C, 66·38; H,7·89. $C_7H_{10}O_2$ requires: C, 66·64; H, 7·99%).

[21] In view of the results obtained during the synthesis of 3-ethylcyclopentane-1,2-dione, (II) (see below) this higher boiling material might contain a product analogous to VIII, the hydrolysis of which requires the action of hot hydriodic acid. It is possible that the yield of III would be improved by using a shorter period of reflux with H_2SO_4.

2-Methoxy-3-methylcyclopent-2-en-1-one (IX). This compound was obtained in essentially quantitative yield by methylation of 3-methylcyclopentane-1,2-dione (I), with dimethyl sulfate in presence of sodium hydroxide; b.p. 91–92°/17 mm; $n_D^{24.5}$ 1·4880 (lit.[22] 85–92°/17 mm).

2-Methoxy-3-methyl-5-formylcyclopent-2-en-1-one (X). In a one-necked flask sealed by a rubber stopper, which in turn was fitted by means of a syringe needle with a Drierite tube, a solution of 3·15 g (0·025 mole) IX and 9·26 g (0·125 mole) Et formate in 30 ml dry ether was added and cooled to 5°. The air was completely replaced by N_2 and with stirring (magnetic stirrer) and using a syringe, 69 ml of approx. 0·36 N triphenylmethyl sodium in ether was added. The mixture was stirred for 2 hr at 5° then overnight at room temp., after which period it was essentially neutral. The resulting slurry was transferred under N_2 to sealed centrifuge tubes by means of a syringe and the supernatant ether (negative $FeCl_3$ test) was separated from the precipitate, which was washed with dry ether. The precipitate was dissolved in 20 ml water, the solution brought to pH 3 with 2N H_2SO_4, saturated $[(NH_4)_2SO_4]$ and extracted with ether. The usual work-up left 2·8 g crude X which, after crystallization from 2-propanol, gave 2·0 g essentially pure X (52% yield), m.p. 101–102°, R_T'': 38·4 min. This product, which gives an almost black coloration ($FeCl_3$), could be recovered essentially unchanged after 1 hr refluxing in 0·4 N sodium methoxide in methanol. (Found: C, 62·12; H, 6·65. $C_6H_{10}O_3$ requires: C, 62·33; H, 6·54%).

2-Methoxy-3,5-dimethylcyclopent-2-en-1-one (XII). A mixture of 154 mg (0·001 mole) X and 312 mg (0·002 mole) methyl iodide was stirred overnight with 5 ml 0·4N sodium methoxide in methanol. At the end of this period, the solution had a (pH of 8 and work-up (see below) of a small sample, followed by analytical VPC), showed that it still contained, besides XII, small amounts of X and XI. Therefore, the main solution was treated with a second aliquot of sodium methoxide (5 ml of a 0·4 N solution) and methyl iodide (1·6 g) and again stirred overnight. Work-up of the mixture (acidification, saturation with $(NH_4)_2SO_4$, ether extraction, drying over Na_2SO_4 and removal of the solvent), left an oil consisting of essentially pure XII. However, this material (R_T'': 16·3 min)—even after purification by VPC on a polar and a non-polar column—repeatedly analyzed somewhat low for carbon (see below for typical analysis). Consequently, it was degraded, without further characterization, to the desired product IV (see below). (Found: C, 67·83; H, 8.·67. $C_8H_{12}O_2$ requires: C, 68·54; H, 8·63%).

In an earlier preparation, a solution of 154 mg (0·001 mole) X and 1·42 g (0·01 mole) methyl iodide in 2·5 ml methanol was stirred overnight at room temp. with 2·5 ml methanolic sodium methoxide prepared from 23 mg (0·001 mole) Na. The resulting neutral solution was worked up as indicated above and found (VPC) to contain approximately 79% XII, 17% X and 4% of a compound (not analyzed), R_T'' 31·0 min, the IR spectrum ($CHCl_3$) of which agreed with XI [absorption at 5·73 μ (aldehydic carbonyl), 5·83 μ (keto carbonyl) and 6·04 μ (carbon-carbon double bond in the ring). This material, upon treatment with methanolic sodium methoxide, was transformed instantaneously into XII (isolated by VPC and identified by IR)].

3,5-Dimethylcyclopentane-1,2-dione (IV). This was obtained by hydrolysis of XII or by decarboxylative hydrolysis of VIf.

(A). *From* XII. A solution of XII in an excess hydriodic acid was refluxed for 1 hr. Dilution with water, ether extraction and removal of the solvent yielded IV in essentially quantitative yield. A sample was purified for analysis by VPC; m.p. 91–92°, R_T': 16·6 min; λ_{max}^{EtOH} 259 mu; lg ε = 4·07. (Found: C, 66·76; H, 8·09. $C_7H_{10}O_2$ requires: C, 66·64: H, 7·99%).

(B). *From* VIa. A solution of 12·1 g (0·05 mole) 3,5-dicarbethoxycyclopentane-1,2-dione (VIa) in 50 ml abs, ethanol was added with stirring to 50 ml hot ethanolic sodium ethoxide prepared from 2·3 g (0·1 mole) Na. The resulting slurry was cooled to 20°, treated with 14·2 g (0·1 mole) methyl iodide and refluxed with stirring for 4 hr. The mixture was then treated with a solution of 1·63 g (0·075 mole) Na in 40 ml abs. ethanol, refluxed for 30 hr, treated with excess methyl iodide (80 g in 4 portions) and again refluxed for 26 hr (pH essentially neutral). Removal of the alcohol (red. press.), solution of the residue in 50 ml water, acidification, ether extraction and the usual work-up yielded 7·9 g of an oily residue. An aliquot of this oil (6.4 g) was refluxed with 60 ml 20% H_2SO_4 for 5 hr and after ether extraction and the usual work-up yielded 2 volatile fractions and some heavy residue. The first volatile fraction, 2·2 g, b.p. 100–102°/15 mm, which solidified immediately, was separated by preparative VPC into 3-methylcyclopentane-1,2-dione (I) identified by IR, and 3,5-dimethylcyclopentane-1,2-dione (IV), identical with another sample prepared by a different route (see above). The over-all

[22] C. A. Rojahn and F. Ruehl, *Arch. Pharm.* **264**, 311 (1926).

yield of IV, based upon the amount of VIa employed, was 35%. The second distillation fraction, 1·1 g b.p. 120–130°/0·1 mm, was not further investigated.[21]

(C). *From* VIe. When the preparation of 3,5-dimethylcyclopentane-1,2-dione was attempted via the monoalkylation of VIe followed by acid hydrolysis, IV was obtained (42% yield), but it was always accompanied by substantial amounts of I.[22]

Direct methylation of 2-methoxy-3-methylcyclopent-2-en-1-one (IX). 2-Methoxy-3-methylcyclopent 2-en-1-one (0·2 mole) was converted into the sodium derivative by using 0·2 moles finely divided sodium amide, with ether as a solvent at reflux under good stirring. Methyl iodide (0·2 mole) was then added and the mixture kept at reflux for 3 hr. Addition of water, acidification, extraction with ether and distillation yielded 18 g of a colorless oil, b.p. 84–86°/15 mm, which was a mixture of alkylation products of IX (see below). In addition, higher boiling fractions (8 g, b.p. 150–230/0·25 mm) were obtained but were not further investigated.

Vapour-liquid chromatography showed that the main fraction, b.p. 84–86°/15 mm, consisted of at least 6 compounds. A sample of this material was refluxed for 1 hr in hydriodic acid (*d* 1·7) and worked up in the usual manner (dilution with water, decolorization with Na_2SO_3, ether extraction, drying over Na_2SO_4 and removal of the solvent). Vapor-liquid chromatography of this hydrolyzed mixture showed the presence of 6 peaks (peaks A–F), present in the following concentrations (expressed in parenthesis, as per cent of the total area of peaks A–F in the chromatogram): Peak A (20·32), R_T': 12 min, Peak B (4·17), R_T': 14 min, Peak C (18·50), R_T': 16·6 min, Peak D (46·61), R_T': 20 min, Peak E (3·37), R_T': 21 min, Peak F (7·03), R_T': 24·6 min. Trapping of the various peaks followed by IR and mass spectroscopic analysis led to the identification of peak C as 3,5-dimethylcyclopentane-1,2-dione (IV), peak D as 3-methylcyclopentane-1,2-dione (I) and peak F as 3-ethylcyclopentane-1,2-dione (II). Peak E had a retention time identical with that of an authentic sample of 3,4-dimethylcyclopentane-1,2-dione, but its identity was not definitely proven. Peak A, m.p. 87–88°, $\frac{M-15}{M} \times 100 = 102$ (see text) analyzed correctly for $C_8H_{12}O_2$ and it was proven to be 3,5,5-trimethylcyclopentane-1,2-dione by comparison with an authentic sample. The IR spectrum of peak A is given in Fig. 2. (Found: C, 68·60; H, 8·78. Calcd. for $C_8H_{12}O_2$: C, 68·54; H, 8·63%). Peak B, upon rechromatography on a non-polar column (silicone gum), yielded 2 compounds, B_1 and B_2. Compound B_1, m.p. 92–93°, $\frac{M-15}{M} \times 100 = 100$ (see text), R_T': 14 min, R_T'': 20 min, was definitely an alkylated cyclopentane-1,2-dione (IR, mass spectrum) and analyzed correctly for $C_9H_{14}O_2$; the most likely structure for it is 3-ethyl-5,5-dimethylcyclopentane-1,2-dione (XIX). The IR spectrum of peak B_1 is given in Fig. 3. (Found: C, 70·17; H, 9·25. $C_9H_{14}O_2$ requires: C, 70·10; H, 9·15%). Compound B_2 (16% of peak B or 0·67% of total peaks A–F) was obtained in too small an amount for a characterization by classical methods; however, its IR and UV spectrum permitted to definitely classify it as an alkylated cyclopentane-1,2-dione and the mass spectrum gave for it the molecular formula $C_{10}H_{16}O_2$; R_T': 14 min, R_T'': 26 min, $\frac{M-15}{M} \times 100 = 102$ (see text); λ_{max}^{EtOH} 259 mu. The IR spectrum of B_2 is given in Fig. 4.

The total yield of 3,5-dimethylcyclopentane-1,2-dione (IV) amounted to 12% (calc, on the basis of 2-methoxy-3-methylcyclopent-2-en-1-one employed) and was not improved when triphenylmethyl sodium, instead of sodium amide, was used as the base or when methyl chloride, rather than methyl iodide, was the alkylating agent. Moreover, when the reaction was carried out with 3 equivalents sodium amide per equivalent of IX, in presence of a 10-fold excess of methyl iodide, the areas of peaks A–F, as per cent of their total areas in the chromatogram, were as follows: Peak A: 67·22; Peak B (compounds B_1 and B_2): 29·85; Peak C: 1·65; Peak D: 0·64; Peak E: 0·35; Peak F: 0·29.

In view of the results above, the most convenient synthesis of 3,5-dimethylcyclopentane-1,2-dione

[22] When our experimental work was complete, Dr. Arend Noltes of Coca-Cola G.m.b.H., Essen, Germany, kindly informed us that he had described a preparation of compound IV in his doctoral thesis (Thesis, Utrecht, 1957), [by selenium dioxide oxidation of 2,4-dimethylcyclopentanone (12·5% yield)]. It must be pointed out that the same compound may have been obtained by I. N. Nazarov and I. W. Torgow [*Izvest. Akad. Nauk. S.S.S.R., Otdel, Khim. Nauk.* (1951), 417] but, while the original paper was unavailable to us, the compound is reported in *Chem. Abstr.* (C.A. **46**, 8021) as "probably being 3,5-dimethylcyclopentane-1,2-dione".

(IV) is the one based upon the alkylation of 2-methoxy-3-methyl-5-formylcyclopent-2-en-1-one (X) [50% over-all, see above].

Cyclopentane-1,2-*dione*. This was obtained by the procedure of Hesse and Buecing[4]; m.p. 50–52° (lit.[4] 56°); λ_{max}^{EtOH} 251 mu; lg ε = 3·94.

4-*Methylcyclopentane*-1,2-*dione*. This was prepared by the method of Hesse and Boeckmann[7] and purified by vapor-liquid chromatography; m.p. 60–62° (In the lit.,[7] it is reported that this compound has b.p. 96–97°/17 mm and solidifies on cooling); λ_{max}^{EtOH} 252 mu; lg ε = 3·90.

4,4-*Dimethylcyclopentane*-1,2-*dione*. This was prepared by the method of Komppa[24] and purified by vapor-liquid chromatography; m.p. 45–46° (lit.[24] 45°).

3,5,5-*Trimethylcyclopentane*-1,2-*dione* (XVII). This was obtained in 25% yield by selenium dioxide oxidation (4 hr at reflux in EtOH) of 2,4,4-trimethylcyclopentanone.[25] Its physical properties (m.p., R_f's, IR and mass spectrum) were identical with those of the sample (peak A) obtained by direct alkylation of IX (see above), which analyzed correctly for $C_8H_{10}O_2$.

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[24] G. Komppa, *Ann.* 370, 218 (1909).

[25] The preparation of 2,4,4-trimethylcyclopentanone by acid-catalyzed rearrangement of isophorone oxide is described in *Organic Synthesis* Vol. 39, p. 70. John Wiley, New York, N.Y.