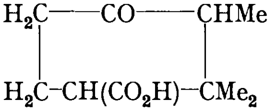
103. *The Bromination of Camphorquinone.*

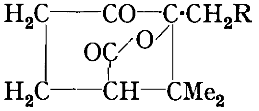
By W. C. Evans, J. L. Simonsen, and (in part) M. B. Bhagvat.

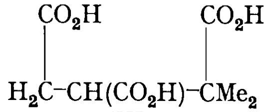
It was shown some years ago (Gibson and Simonsen, J., 1925, **127**, 1295; Bhagvat and Simonsen, J., 1927, 77; compare Bredt-Savelsberg, Zaubrecher, and Knieke, *Ber.*, 1927, **60**, 1801) that the acid formed by the action of sulphuric acid on camphorquinone (Manasse and Samuel, *Ber.*, 1897, **30**, 3157; 1902, **35**, 3831) was 2 : 2 : 3-trimethyl*cyclo*hexan-4-one-1-carboxylic acid (I), the somewhat unusual Meerwein–Wagner rearrangement involved being commented on by Ingold (*Ann. Reports*, 1927, 122). At the time experiments were initiated with the object of determining the structure of the two substances, $C_{10}H_{11}O_3Br_3$ and $C_{10}H_{12}O_3Br_2$, prepared by Manasse and Samuel (*loc. cit.*) by the action of bromine on the diketone, but were discontinued owing to the poor yields obtained. Since camphorquinone can now readily be prepared in quantity (this vol., p. 137), the investigation of these bromo-derivatives has been resumed. It was thought at first that they were derivatives of camphoric anhydride, since it was observed that when camphorquinone was treated with bromine in acetic acid solution this anhydride was formed, but a study of their reactions has shown them to be derivatives of the acid (I).

When the tribromide is reduced in acetic acid solution with zinc dust at room temperature or in ethyl acetate with aluminium amalgam, a *monobromide*, $C_{10}H_{13}O_3Br$, m. p. 144—145°, is obtained; if, however, the reduction with zinc dust is completed on the water-bath, 2 : 2 : 3-trimethyl*cyclo*hexan-4-one-1-carboxylic acid (I) is formed. This suggested that the tribromide was the lactone of a hydroxy-derivative of this acid, and this view received support from the preparation of the tribromide by the direct action of bromine on the ketonic acid. It remained, therefore, only to determine the positions of the hydroxy-group and of the bromine atoms.

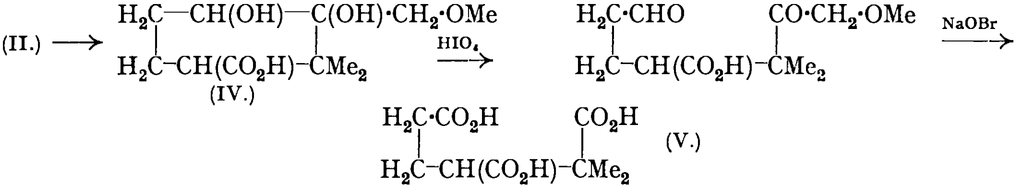
By the action of sodium methoxide on the monobromide a *methoxy*-compound, $C_{11}H_{16}O_4$, m. p. 81—82°, was obtained, which gave on oxidation with nitric acid αα-dimethyltricarballylic acid (III). The formation of this acid proved that the hydroxy- and the methoxy-group could not be attached to any of the carbon atoms 1, 2, and 6, and, of the possible isomerides, (II) has been shown to represent the monobromide and the methoxy-compound.


(I.)

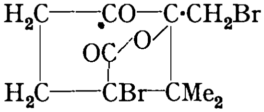

(II.) R = Br or OMe.

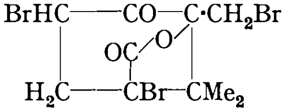

(III.)

By catalytic hydrogenation of the methoxy-lactone the *lactone* of 3-*hydroxy*-3-*methoxymethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*ol*-1-*carboxylic acid*, m. p. 48—49°, was prepared, which after conversion into the dihydroxy-acid (IV) by alkali, was oxidised successively with periodic acid (*inter al.*, Karrer and Hirohata, *Helv. Chim. Acta*, 1933, **16**, 959) in acetic acid and with sodium hypobromite in alkaline solution, β-methylpentane-βγε-tricarboxylic acid (V) being obtained in excellent yield. The oxidation of the cyclic dihydroxy-acid proceeds evidently in accordance with the following scheme and thus affords a rigid proof of the positions of the methoxy-group and of the lactone ring in the parent keto-lactone.



We have been unable to establish with an equal degree of certainty the position of the other bromine atoms in the dibromo- and the tribromo-lactone. Both yield dimethylmalonic acid on oxidation with potassium permanganate in alkaline solution, no trace of either oxalic or *as.*-dimethylsuccinic acid being formed. This result receives its simplest explanation if the lactones are represented by (VI) and (VII) respectively.

(VI.)



(VII.)

Although these lactones contain a carbonyl group, they show no tendency to react with the ordinary ketonic reagents. The methoxy-lactone (II) yields with semicarbazide acetate a crystalline *derivative*, $C_{12}H_{17}O_3N_3$, containing one molecule of water less than the true semicarbazone.

It appears to us unlikely that the tribromo-lactone is a direct bromination product of camphorquinone; the diketone is probably first converted by hydrogen bromide into the *cyclo*hexanone acid, which then undergoes bromination. Support is lent to this view by the fact that, whilst bromination proceeds rapidly in the presence of water, with dry bromine the reaction is very slow and the yield of tribromide poor and variable. The positions in which the bromine atoms enter the *cyclo*hexanone nucleus are also of interest. It was observed previously (*loc. cit.*, p. 78) that the methyl ester of the acid gave on bromination methyl 5 : 5-dibromo-2 : 2 : 3-trimethyl*cyclo*hexan-4-one-1-carboxylate, whereas with the acid itself carbon atom 5 is only monobrominated, other bromine atoms entering the 1- and 3-positions in the ring, the latter being eliminated with formation of the lactone. The position of the bromine atom in the 3-methyl group is similar in all respects to that in β(10)-bromocamphor, but, unlike this bromine atom, it appears to be stabilised. It would, however, seem to activate the adjacent carbon atom, since it is unusual for a lactone to be reduced with zinc and acetic acid.

EXPERIMENTAL.

Lactone of 1 : 5-*Dibromo*-3-*hydroxy*-3-*bromomethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*one*-1-*carboxylic Acid.*—The following method for the preparation of the tribromo-lactone was found to be more convenient than that adopted by Manasse and Samuel, although the yield by this method can be much improved if moist bromine is used. To finely divided camphorquinone (5 g.), moist bromine (20 g.) was added gradually; after a short induction period the mixture became warm and liquefied and hydrogen bromide was evolved. The yellowish-white product was warmed on the water-bath to remove hydrogen bromide and extracted with ether, which eliminated resinous impurities. The pure lactone (8 g.) separated from alcohol in prisms m. p. 199—200°; in chloroform (*c*, 4), $[\alpha]_D$ −34·0°.

For the preparation of the lactone from 2 : 2 : 3-trimethyl*cyclo*hexan-4-one-1-carboxylic acid, the acid (2·5 g.) was placed in a desiccator, fitted with a Bunsen valve, together with bromine (10 g.), water, and calcium carbonate. After some days, when the absorption of bromine was complete, the dark brown solid was ground with ether, and the residue (m. p. 193°) recrystallised from alcohol; the lactone had m. p. 199—200° (Found : Br, 57·4. Calc. for $C_{10}H_{11}O_3Br_3$: Br, 57·3%). The lactone was stable to potassium permanganate in acetone or in suspension in cold sodium carbonate solution. It was, however, attacked by permanganate in warm alkaline solution, the oxidation being complete after the addition of permanganate corresponding to 12—13 atoms of oxygen. The product, isolated in the usual manner, consisted solely of dimethylmalonic acid, decomp. 190°, both alone and after admixture with an authentic specimen. When the lactone was shaken in acetic acid with hydrogen in the presence of platinum-black, partial reduction to the dibromo-lactone occurred.

Lactone of 1-*Bromo*-3-*hydroxy*-3-*bromomethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*one*-1-*carboxylic Acid.*—We were unable to prepare this substance by Manasse and Samuel's method, but the following modification was found satisfactory, although the yield varied considerably. To well-cooled camphorquinone (10 g.), moist bromine (30 g.) was added slowly with constant stirring, it being found necessary in some experiments to warm the mixture slightly to start the reaction. If the addition of bromine is too rapid, a mixture consisting mainly of the tribromo-lactone is obtained. After warming on the water-bath to remove hydrogen bromide the viscid yellow gum was dissolved in alcohol; on cooling, the nearly pure dibromo-lactone m. p. 120°, was deposited and a further crystallisation from alcohol gave lustrous needles m. p. 137—138°; in chloroform (*c*, 5), $[\alpha]_{5461}$ + 40·0°. Like the tribromo-lactone, the dibromide was stable to potassium permanganate in acetone, but it was slowly attacked in warm sodium carbonate solution, dimethylmalonic acid forming the sole product of the oxidation.

Reduction of the Lactone of 1 : 5-*Dibromo*-3-*hydroxy*-3-*bromomethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*one*-1-*carboxylic Acid.*—(1) 2 : 2 : 3-*Trimethyl*cyclo*hexan*-4-*one*-1-*carboxylic acid.* To a solution of the tribromo-lactone (12 g.) in acetic acid (300 c.c.), zinc dust (50 g.) was added gradually After 12 hours the mixture was heated on the water-bath for 2 hours, the filtered solution nearly neutralised with sodium carbonate and extracted with ether, and the dried ethereal solution evaporated. The residual oil crystallised when kept over sodium hydroxide in a vacuum and it was identified as the *cyclo*hexanone acid by the preparation of the oxime, m. p. 163—164° and the semicarbazone, m. p. 228—229° (Found : C, 55·1; H, 7·8. Calc. for $C_{11}H_{19}O_3N_3$: C, 54·8; H, 7·9%), the melting points in each case being unaltered in admixture with authentic specimens.

(2) *Lactone of* 3-*hydroxy*-3-*bromomethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*one*-1-*carboxylic acid.* To a solution of the tribromo-lactone (5 g.) in ethyl acetate (80 c.c.), an excess of aluminium amalgam was added. The reduction proceeded with considerable evolution of heat and after 12 hours the mixture was heated on the water-bath for 1 hour. The ethyl acetate was removed from the filtered solution, and the solid residue (1·4 g.) crystallised from methyl alcohol, the *bromo-lactone* forming small needles, m. p. 144—145°; in chloroform (*c*, 4), $[\alpha]_D$ + 72·25° (Found : C, 46·1; H, 5·1; Br, 30·7. $C_{10}H_{13}O_3Br$ requires C, 46·0; H, 5·0; Br, 30·6%). A much improved yield (80%) of the bromo-lactone is obtained if the reduction is effected with zinc and acetic acid at room temperature, but owing to the large volume of liquid involved the above method is much more rapid and convenient. The lactone is stable to potassium permanganate in acetone, but is rapidly attacked in the presence of alkali. It cannot be reduced catalytically, but when warmed with zinc and acetic acid it yields 2 : 2 : 3-trimethyl*cyclo*hexanon-4-one-1-carboxylic acid.

Lactone of 3-*Hydroxy*-3-*methoxymethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*one*-1-*carboxylic Acid.*—To a solution of the monobromo-lactone (5 g.) in the minimum quantity of methyl alcohol, sodium methoxide (MeOH, 10 c.c.; Na, 0·45 g.) was added gradually, the temperature being maintained at 40—50°. After the solution had become neutral the methyl alcohol was removed in a vacuum, the residue dissolved in ether, and the filtered ethereal extract evaporated. The oil obtained solidified and after draining on porous porcelain was recrystallised from dry ether, from which it separated in large prisms, m. p. 81—82°, b. p. 173°/18 mm.; in chloroform (*c*, 5), $[\alpha]_{5461}$ + 64·6° [Found: C, 62·1, 62·5; H, 7·1, 7·5; OMe, 15·8. $C_{10}H_{13}O_3(OMe)$ requires C, 62·3; H, 7·5; OMe, 14·6%]. If the above conditions were not closely adhered to, the *methoxy-lactone* was contaminated with a considerable quantity of an oil which gave an intense purple colour with ferric chloride. The lactone was readily soluble in the ordinary organic solvents with the exception of ligroin and it crystallised well from hot water. It was insoluble in sodium carbonate solution, but dissolved readily in warm aqueous sodium hydroxide, a gummy acid being precipitated on acidification. It was unstable to potassium permanganate in alkaline solution. The lactone reacted readily with phenyl-, *p*-nitrophenyl-, and 2 : 4-dinitro-phenylhydrazines to give sparingly soluble gums, and the oxime was an oil. With semicarbazide acetate in alcoholic solution a *substance* was deposited which crystallised from methyl alcohol in leaflets, m. p. 183—184° (Found: C, 57·2; H, 6·4; N, 16·8. $C_{12}H_{17}O_3N_3$ requires C, 57·4; H, 6·8; N, 16·7%).

Oxidation of the Lactone of 3-*Hydroxy*-3-*methoxymethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*one*-1-*carboxylic Acid.*—The methoxy-lactone was oxidised both with nitric acid and with potassium permanganate, but since the product was the same only the former oxidation is described. A mixture of the lactone (3 g.) and nitric acid (*d* 1·22; 80 c.c.) was heated on the water-bath for 4 hours and then boiled for 3 hours, the solution becoming colourless. After removal of the nitric acid the partially crystalline residue was mixed with acetyl chloride, heated for 1 hour, and distilled under diminished pressure; the viscid oil obtained crystallised after the addition of chloroform; m. p. 137—143°. This anhydride of αα-dimethyltricarballylic acid crystallised from ethyl acetate in prisms, m. p. 144—145° (Found: C, 51·7; H, 5·2. Calc. for $C_8H_{10}O_5$: C, 51·6; H, 5·4%). Digestion with water gave the tricarboxylic acid, which, crystallised from ethyl acetate–chloroform, had m. p. 155° (Found: C, 47·0; H, 5·7. Calc. for $C_8H_{12}O_6$: C, 47·1; H, 5·9%).

Lactone of 3-*Hydroxy*-3-*methoxymethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*ol*-1-*carboxylic Acid.*—A solution of the methoxyketo-lactone (1·4201 g.) in ethyl acetate (20 c.c.) containing palladium–norit (1 g.; 10%) was shaken with hydrogen until a volume corresponding to one molecule of hydrogen had been absorbed (16 hours). Evaporation of the filtered solution left a solid, which crystallised from ligroin (b. p. 40—60°) in needles, m. p. 48—49°; in methyl alcohol (*c*, 1·828), $[\alpha]_{5461}$ + 14·22° (Found: C, 61·7; H, 8·3. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·4%). The *hydroxy-lactone* was insoluble in cold alkali, but it dissolved readily on warming, the acidified solution depositing the dihydroxy-acid, which partly crystallised but could not be purified.

Oxidation of 3-*Hydroxy*-3-*methoxymethyl*-2 : 2-*dimethyl*cyclo*hexan*-4-*ol*-1-*carboxylic Acid.*—To a solution of the crude dihydroxy-acid (3 g.) in acetic acid, a solution of periodic acid (HIO_4, 2·7 g.) was added gradually, the mixture being cooled in ice. After 1 hour the reaction mixture was heated at 40—50° for 4 hours, cooled, and extracted with ether. The dried ethereal extract left on evaporation a brown oil (2·3 g.), which reduced Fehling's solution and reacted with the ordinary carbonyl reagents. This was dissolved in an excess of dilute sodium hydroxide solution, and sodium hypobromite (100 c.c.; 10%) added, bromoform being deposited. After 1 hour the filtered solution was treated with sulphur dioxide to remove the excess of hypobromite, acidified, and extracted with ether. Evaporation of the dried ethereal extract left a viscid oil (1·5 g.), which was dissolved in cold water and filtered from a little insoluble resin (charcoal). Evaporation of the water left a crystalline cake, from which, after three crystallisations from hydrochloric acid, the acid was obtained in cubes, decomp. about 150°, both alone and in admixture with β-methylpentane-βγε-tricarboxylic acid (Found: C, 49·7; H, 6·3. Calc. for $C_9H_{14}O_6$: C, 49·5; H, 6·4%).

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