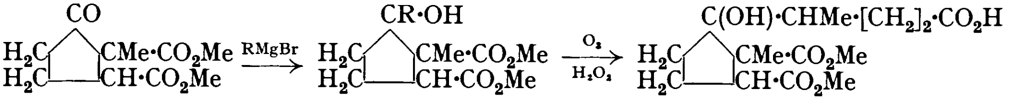
199. *Synthesis of Substances Analogous to Bile Acid Degradation Products. Part III. The Attempted Use of Diallyl as an Agent to introduce the Requisite Side Chain in the Synthesis of the Acid* $C_{13}H_{20}O_6$.

By John W. Baker and Harold Burton.

The difficulties encountered in the introduction of the carboxylated side chain $CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ into the appropriately substituted *cyclo*pentanone esters have already been noticed (preceding paper) and it was thought that the desired result might be attained by use of the Grignard reaction with a bromo-unsaturated hydrocarbon of the type $CHMeBr{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CR_2$, the requisite carboxyl group being subsequently obtained by oxidative fission at the double linking. A suitable bromohydrocarbon appeared to be the monohydrobromide of diallyl, since the corresponding monohydriodide has the structure $CHMeI{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CH_2$ (Griner, *Ann. Chim.*, 1892, **26**, 331). Addition of hydrogen bromide (less than 1 mol.) to diallyl in acetic acid proceeds smoothly to give a mixture containing 47% of the *monohydrobromide* and 53% of the *dihydrobromide*, which are readily separated by fractional distillation. The former derivative was condensed, under various conditions, with magnesium and *methyl 2-methyl*cyclo*pentanone-2 : 3-dicarboxylate* (prepared by the method used by Kay and Perkin for the corresponding ethyl ester; J., 1906, 89, 1642), and the product subjected, without purification, to ozonolysis and subsequent oxidation with cold alkaline hydrogen peroxide, in an attempt to realise the synthesis,



(R = $\cdot CHMe\cdot[CH_2]_2\cdot CH{:}CH_2$).

but neither the hydroxy-acid ester nor the corresponding unsaturated derivative could be isolated.

During the decomposition of the ozonide the unexpected production of acetaldehyde (along with the anticipated formaldehyde) led to a reinvestigation of the structure of the monobromo-compound and, subsequently, that of diallyl itself.

The formation of formaldehyde and succindialdehyde by ozonolysis of diallyl (Harries and Türk, *Annalen*, 1905, **343**, 360) definitely shows that the hydrocarbon is, at least mainly, $\Delta^{\alpha\epsilon}$-*n*-hexadiene (I), but repetition of the ozonolysis on a sample prepared in the usual manner from allyl bromide (Lespieu, *Ann. Chim.*, 1912, **27**, 149) afforded some acetaldehyde (identified as its *p*-nitrophenylhydrazone), indicating the presence of at least traces of the isomeric hydrocarbons (II) and/or (III), which may account for the frequently observed occurrence of acetic acid amongst the products of oxidation of diallyl (Sorokin, *J. pr. Chem.*, 1881, **23**, 1). Oxidation of the non-volatile product with hydrogen peroxide,

$CH_2{:}CH\cdot CH_2\cdot CH_2\cdot CH{:}CH_2$ (I.) $CH_3\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH_2$ (II.) $CH_3\cdot CH{:}CH\cdot CH{:}CH\cdot CH_3$ (III.)

however, gave almost pure succinic acid in which no trace of malonic and only the smallest trace of oxalic acid could be detected. Hence it would appear probable that the amount of the isomeric hydrocarbon (II) or (III) present in diallyl is small.

Decomposition of the ozonide of the monohydrobromide also gave some acetaldehyde (together with formaldehyde) and a lachrymatory bromo-aldehyde which could not be definitely characterised, since it lost hydrogen bromide on distillation even under reduced pressure. All attempts to obtain a crystalline bromine-containing product failed, but oxidation of the non-volatile, neutral and acid products of ozonolysis with perhydrol gave small amounts of succinic acid, and a trace of oxalic acid could be detected as its calcium salt. On the basis of modern orientation theory (Lucas, *et al.*, *J. Amer. Chem. Soc.*, 1924, **46**, 2475; 1925, **47**, 1459, 1462; Burton and Ingold, J., 1928, 904), the most probable structure of the isomeric monobromo-derivative which gives rise to acetaldehyde on ozonolysis is $CH_3\cdot CHBr\cdot CH_2\cdot CH{:}CH\cdot CH_3$ (IV), which should afford β-bromo-*n*-butaldehyde as the second product of ozone fission. An attempt to synthesise this aldehyde by addition of hydrogen bromide to crotonaldehyde led to the isolation of its trimolecular *polymeride*, $(C_4H_7OBr)_3$, as a crystalline solid. Since no trace of this polymeride could be obtained from the products of ozonolysis of the monohydrobromide, it would again appear that the amount of (IV) present is small.

Although admittedly incomplete (since the object of this investigation was not to determine the structure of the small quantities of isomerides present), it would seem that the evidence obtained justifies the belief that the *main* constituent of diallyl is $\Delta^{\alpha\epsilon}$-hexadiene, its monohydrobromide consisting largely of ε-bromo-Δ^{α}-hexene (V) (which would afford γ-bromo-*n*-valeraldehyde as the second product of ozone fission), so that this bromohydrocarbon should be of value as a reagent to introduce the requisite side chain in the synthesis of the $C_{13}H_{20}O_6$ acid obtained in the degradation of the cholic acid molecule. Bouveault and Locquin (*Bull. Soc. chim.*, 1908, **3**, 442) found that 5-alkyl*cyclo*pentanone-2-carboxylic esters could be readily obtained by alkylation of ethyl sodio*cyclo*pentanone-2-carboxylate, fission to the α-alkyladipic ester, and reclosure of the ring in a new direction by the Dieckmann reaction. By use of a bromo-unsaturated hydrocarbon of type (V), attachment of the appropriate side chain should be effected, the carbonyl group being subsequently introduced by oxidation at the ethylenic linking. A preliminary experiment in which the monohydrobromide was condensed with the sodio-derivative of methyl *cyclo*pentanone-2-

carboxylate under conditions in which ring fission of the alkylated *cyclo*pentanone ester might be expected to occur gave a small yield of an ester which seems to be methyl α-(α-methyl-Δ^{α}-pentenyl)adipate, and this method is being further explored.

EXPERIMENTAL.

Addition of Hydrogen Bromide to Diallyl.—110 G. of diallyl (Lespieu, *loc. cit.*) in 400 c.c. of acetic acid were treated with 160 c.c. of 55% (wt./vol.) hydrogen bromide in acetic acid and left at room temperature for 18 hours. The mixture was poured into water, the oil separated, and the remaining traces extracted with ether. The combined extracts were washed with aqueous sodium hydrogen carbonate and dried over calcium chloride. Fractionation of the residue after evaporation of the ether gave 47 g. of the *monohydrobromide*, b. p. 41—43°/13 mm. (Found : C, 44·7; H, 6·9; Br, 48·0. $C_6H_{11}Br$ requires C, 44·2; H, 6·8; Br, 49·1%), 9 g. of intermediate fraction, and 63 g. of the *dihydrobromide*, b. p. 82—84°/5 mm. (Found : Br, 62·3. $C_6H_{12}Br_2$ requires Br, 65·6%). The analytical data indicate that separation of the two products from each other and from the unbrominated hydrocarbon is not quite complete.

Ozonolysis of Diallyl.—5 G. of diallyl were ozonised in chloroform solution for 36 hours, initially with efficient ice-cooling, and the ozonide, after evaporation of the chloroform in a vacuum at room temperature, decomposed by boiling with water under reflux. The escaping volatile matter was bubbled through a solution of *p*-nitrophenylhydrazine in dilute hydrochloric acid, and gave acetaldehyde-*p*-nitrophenylhydrazone, m. p. and mixed m. p. 128°. Formaldehyde was detected in a distillate of the aqueous liquor by its odour and the usual characteristic tests.

It was shown that when an artificial mixture of acetaldehyde and formaldehyde (containing excess of the latter) is boiled with water under an air-cooled reflux condenser, and the escaping volatile matter is passed into *p*-nitrophenylhydrazine in dilute hydrochloric acid, *only* acetaldehyde-*p*-nitrophenylhydrazone is obtained, and this method constitutes a convenient means of detecting acetaldehyde in the presence of excess of formaldehyde.

The residual aqueous liquor after decomposition of the ozonide was cooled, 20 c.c. of perhydrol added, and the whole left for 24 hours. Evaporation on the steam-bath with repeated addition of water to remove hydrogen peroxide gave a clean crystalline acid, which, after recrystallisation from water had m. p. 183° either alone or mixed with authentic succinic acid, gave all the characteristic tests of this acid, and was converted into the anhydride, m. p. 119—120°. The absence of malonic acid was shown by gently heating a portion of the original acid product, no odour of acetic acid being detected and no ethyl acetate being formed on warming with alcohol and sulphuric acid. Addition of aqueous calcium chloride to an ammoniacal solution of the original acid product acidified with dilute acetic acid gave only a trace of turbidity, indicating the presence of only a very small amount of oxalic acid.

In order to ensure that the acetaldehyde did not originate from any ethyl alcohol in the chloroform used as solvent, the ozonolysis was repeated in dry hexane (distilled over sodium) with identical results.

Ozonolysis of the Monohydrobromide.—8 G. of the monohydrobromide were similarly ozonised in chloroform solution. A very faint yellow colour indicated the slight liberation of bromine in the early stages. Decomposition of the ozonide and the detection of formaldehyde and acetaldehyde were effected as described above. The aqueous liquor was extracted repeatedly with ether, and the extract separated by aqueous sodium hydrogen carbonate into neutral (A) and acid (B) portions, leaving a residual aqueous liquor (C).

The residue from A was a lachrymatory bromine-containing oil which could not be distilled without much decomposition and loss of hydrogen bromide (Found for the first few drops of the distillate : C, 46·05; H, 6·85; Br, 22·01. C_5H_9OBr requires C, 36·4; H, 5·45; Br, 48·5%. C_5H_8O requires C, 71·5; H, 9·5%). With semicarbazide acetate and *p*-nitrophenylhydrazine, only small amounts of insoluble products, which could not be purified, were obtained. No trace of $(C_4H_7OBr)_3$ (below) could be isolated.

The bicarbonate extract (B) was evaporated to small bulk on the steam-bath, acidified with concentrated hydrochloric acid at 0°, and repeatedly extracted with ether. The residue from the dried ethereal solution was a brown syrup containing bromine. When it was treated with *N*-potassium hydroxide under conditions under which β-bromobutyric acid affords crotonic acid, no trace of this acid could be detected. From the product obtained by oxidation of the aqueous liquor (C) with nitric acid (*d* 1·52) were isolated succinic acid, m.p. 182° (alone and mixed), and a trace of a bromine-containing substance, m. p. 251° (decomp.), not obtained in quantity sufficient for identification. The ozonolysis was also repeated in hexane solution with similar results.

Addition of Hydrogen Bromide to Crotonaldehyde.—After a few hours a mixture of 35 g. of freshly distilled crotonaldehyde and 75 c.c. of 55% (wt./vol.) hydrogen bromide in acetic acid separated into 2 layers and was at once poured into ice and sodium hydrogen carbonate solution and extracted with ether [on prolonged standing (18 hours), the reaction mixture turns black and the product is then a thick black tarry oil]. After repeated washing with aqueous bicarbonate, the residue from the dried ethereal extract was distilled, with much decomposition, and afforded a mobile yellow oil, b. p. 65—75°/10 mm., which was not homogeneous and rapidly darkened and became viscous on keeping. The distillate was again washed with aqueous bicarbonate and, on cooling in ice, partly crystallised. The crystalline material was drained on porous porcelain, and washed with a small quantity of ligroin (b. p. 40—60°) at 0°. The *trimeride* of β-bromo-*n*-butaldehyde crystallises from a concentrated solution of ligroin at 0° in stellate clusters of fine needles, m. p. 98° [Found : C, 32·0; H, 4·8; Br, 52·6; *M*, 404, 423. $(C_4H_7OBr)_3$ requires C, 31·8; H, 4·6; Br, 53·0%; *M*, 453]. The aldehyde is very soluble in ligroin and gives a purple colour after prolonged keeping with Schiff's reagent. An attempt to prepare a semicarbazone from the original distillate resulted only in the slow crystallisation of the solid trimeride.

Attempted Grignard Condensations on cyclo*Pentanone Esters.*—*Methyl* cyclo*pentanone*-2 : 3-*dicarboxylate*, b. p. 162°/15 mm. (Found : C, 53·9; H, 6·2. $C_9H_{12}O_5$ requires C, 54·0; H, 6·0%), was prepared by the Dieckmann reaction from *methyl* n-*butanetricarboxylate*, b. p. 168°/16 mm. (Found : C, 51·6; H, 6·8. $C_{10}H_{16}O_6$ requires C, 51·7; H, 6·9%), in a manner similar to that used by Kay and Perkin (*loc. cit.*) for the corresponding ethyl esters. The *cyclo*pentanone ester gives a *semicarbazone*, m. p. 188—189° after crystallisation from methyl alcohol (Found : C, 46·6; H, 5·9. $C_{10}H_{15}O_5N_3$ requires C, 46·7; H, 5·8%).

Methylation of the *cyclo*pentanone ester (Kay and Perkin, *loc. cit.*) afforded *methyl 2-methyl*-cyclo*pentanone*-2 : 3-*dicarboxylate*, b. p. 146°/4 mm. (Found : C, 53·9, 54·2; H, 7·1, 7·0. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·5%). The low values for carbon may be due to the production of methane during combustion, since the ester gives no colour with ferric chloride and yields a *semicarbazone*, m. p. 234° (decomp.), which gives the required analytical values (Found : C, 48·8; H, 6·3. $C_{11}H_{17}O_5N_3$ requires C, 48·75; H, 6·3%).

Essentially the same results were obtained when an attempt was made to condense this ester with the magnesium compound of $CHMeBr{\cdot}[CH_2]_2{\cdot}CH{:}CH_2$ (from diallyl) either by addition of the ester to the previously prepared Grignard reagent or by the preparation of the latter *in situ*, and only the latter process need be described. The bromo-compound was added dropwise to 1·5 g. of magnesium in 50 c.c. of dry ether and after formation of the Grignard compound had commenced the remainder of the bromo-compound and 10 g. of the *cyclo*pentanone ester were added together in small successive portions with mechanical stirring. The mixture was gently refluxed on the steam-bath for 36 hours, decomposed with ice and ammonium chloride, and the dried ethereal solution slowly evaporated at the ordinary temperature. The residue was dissolved in dry chloroform and ozonised for 48 hours, the chloroform evaporated, and the syrupy ozonide decomposed by boiling with water. The volatile products consisted of formaldehyde and acetaldehyde and the residual cooled aqueous liquor was oxidised with hydrogen peroxide and sodium hydrogen carbonate at room temperature for 24 hours. The liquid was extracted with ether and separated into neutral (A) and acid (B) fractions by sodium hydrogen carbonate. (A) gave an aldehyde reaction with Schiff's reagent, but distillation proved it to consist mainly of unchanged ketonic ester, b. p. 144°/4 mm.; semicarbazone (Found : C, 48·4; H, 6·2%), m. p. 234° either alone or mixed with a genuine specimen. Hydrolysis of (B) with boiling concentrated hydrochloric acid for 5 hours gave *n*-pentane-αγδ-tricarboxylic acid, m. p. 177° (Found : C, 47·1; H, 5·8. Calc. : C, 47·1; H, 5·9%), similarly obtained by Haworth and Perkin (J., 1908, **93**, 579) from the *cyclo*pentanone ester, as the sole crystalline product. Esterification of another portion of (B) with methyl alcohol and sulphuric acid gave a neutral ester which again seemed to consist mainly of the original cyclic ester.

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