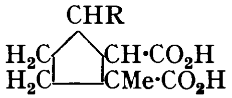
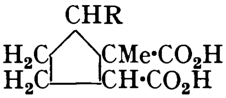
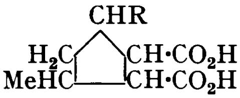
198. *Synthesis of Substances Analogous to Bile Acid Degradation Products. Part II. Synthesis of some Straight-chain Polycarboxylic Esters.*

By John W. Baker.

The rapid advances in the elucidation of the cholane skeleton which have occurred since the publication of Part I (J., 1931, 1546) have confirmed the view that ring IV (D) is a five-membered one, and an important consequence of the new cholane constitution is that the structure of the acid $C_{13}H_{20}O_6$ obtained by Wieland and Vocke (*Z. physiol. Chem.*, 1928, **177**, 68) is now limited to two (I or II) or, at the most, three (III) possibilities.


(I.)


(II.)

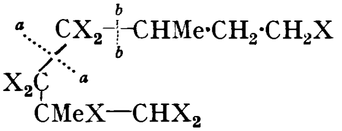

(III.)

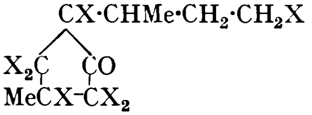
($R = CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$)

The synthesis of appropriate *cyclo*pentanone esters containing a carbonyl group at the desired point of attachment of the side chain R presents comparatively little difficulty (compare Part I, *loc. cit.*), but the earlier suspicion that the attachment of the required side chain could not be effected by the more usual condensation reactions has, unfortunately, been confirmed. No appreciable yields of condensation products could be obtained by application of either the Reformatsky (using zinc or magnesium) or Grignard (see following paper) reaction to such *cyclo*pentanone esters, nor did the preliminary reduction of the carbonyl group or Knoevenagel condensations appear hopeful. The experience gained in such attempts suggests that there is but small prospect of success along these lines.

An alternative method, which from preliminary experiments appears to be more hopeful, is referred to in the following communication.

Meanwhile another line of attack has been developed, namely, the synthesis of a straight-chain ester of type (IV) which should, by application of the Dieckmann reaction, afford only the appropriately substituted *cyclo*pentanone ester (V). Complete hydrolysis of (V) and reduction of the carbonyl to a methylene group would give an acid of structure (I).


(IV.)


(V.)

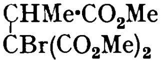
$CHX_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2X$
(VI.)

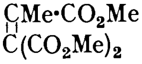
($X = CO_2Me$)

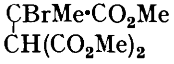
The synthesis of the two component esters (represented by scission at *aa*) of such a straight-chain ester has been achieved, although the best method of uniting them (either at *aa* and/or at *bb*) has yet to be worked out.

Condensation of methyl sodiomalonate with methyl γ-bromovalerate gives a 20—25% yield of *methyl* β-*methyl*-n-*butane*-ααδ-*tricarboxylate* (VI).

The synthesis of esters of the type $CHX_2{\cdot}CMeX{\cdot}CHX_2$ ($X = CO_2Me$, Ac, $CH_2{\cdot}CO_2Et$, or CN) (VII) presents more difficulty, due partly to the readiness with which the product undergoes a reverse Michael reaction causing fission into CH_2X_2 and $CMeX{:}CX_2$. Thus even in dry toluene the main product of the condensation of ethyl sodioethanetricarboxylate with ethyl β-bromo-*n*-propane-αβ-dicarboxylate appears to be ethyl citraconate. The polar and steric effect of the β-methyl substituent in promoting fission (compare Cooper, Ingold, and Ingold, J., 1926, 1868) is striking, since a similar condensation using ethyl α-bromosuccinate readily afforded ethyl *n*-butane-αβγγδ-pentacarboxylate. Condensation of ethyl sodiomalonate with ethyl αβ-dibromo-*n*-propane-αβ-dicarboxylate gave ethyl ethanetetracarboxylate as the main product. Cyano-esters of the required type have been prepared by Hope by addition of hydrogen cyanide to β-methylglutaconic esters, but the corresponding carbethoxy-derivatives could not be obtained from these, since hydrolysis of ethyl αβ-dicyano-β-methylglutarate (Hope and Sheldon, J., 1922, **121**, 2223) gave only nitrogen-containing products which appear to be pyridine derivatives (compare Kon and Nanji, J., 1932, **2426**). A synthesis of the required ester of type (VII) was finally effected starting from *methyl* n-*propane*-ααβ-*tricarboxylate*,* which was prepared in the same manner as the corresponding ethyl ester (Bischoff, *Ber.*, 1880, **13**, 2164; 1881, **14**, 614). This was readily converted into the α-*bromo-ester* (VIII), from which, by treatment with pyridine, *methyl* Δ^{α}-*propene*-ααβ-*tricarboxylate* (IX) was obtained.


$$\begin{array}{l} CHMe{\cdot}CO_2Me \\ | \\ CBr(CO_2Me)_2 \end{array}$$
(VIII.)


$$\begin{array}{l} CMe{\cdot}CO_2Me \\ \| \\ C(CO_2Me)_2 \end{array}$$
(IX.)


$$\begin{array}{l} CBrMe{\cdot}CO_2Me \\ | \\ CH(CO_2Me)_2 \end{array}$$
(X.)

Application of the Michael reaction to this ester under various conditions did not give an ester of the required type. Thus, using excess of methyl acetoacetate and methyl-alcoholic sodium methoxide, the only crystalline product isolated appears to be methyl 3 : 5-

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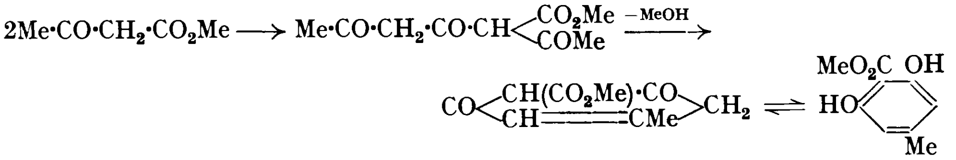
* The use of methyl esters in this work has been found to be essential in order to increase the probability of obtaining crystalline reaction products.

dihydroxy-*p*-toluate (methyl paraorsellinate) (XI) resulting from self-condensation of the acetoacetic ester.



$2Me{\cdot}CO{\cdot}CH_2{\cdot}CO_2Me \longrightarrow Me{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH{<}^{CO_2Me}_{COMe} \xrightarrow{-MeOH}$

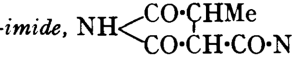
(XI.)

$CH(COMe)_2{\cdot}CMe(CO_2Me){\cdot}CMe(CO_2Me){\cdot}CH(CO_2Me)_2$ (XII.)

Addition of hydrogen bromide to (IX), however, occurs in the expected direction to give *methyl* β-*bromo*-n-*propane*-ααβ-*tricarboxylate* (X), which is isomeric with (VIII) and condenses with methyl sodiomalonate to give *methyl* β-*methyl*-n-*propane*-ααβγγ-*pentacarboxylate*, an ester of the required type (VII, X = CO_2Me). An attempt to condense (X) directly with the sodio-derivative of (VI) resulted only in the formation of *methyl* βγ-*dimethyl*-n-*butane*-ααβγδδ-*hexacarboxylate* (XII) derived from two molecules of the bromo-ester.

EXPERIMENTAL.

Methyl β-*Methyl*-n-*butane*-ααδ-*tricarboxylate* (VI).—To a solution of 1·15 g. of sodium in 20 c.c. of dry methyl alcohol were added 6·6 g. of methyl malonate and, after cooling, 10·3 g. of methyl γ-bromovalerate. The mixture was heated under reflux on a steam-bath for 3 hours, poured into a large volume of water, and extracted with ether, and the extract washed with water and with saturated aqueous calcium chloride. By fractional distillation, the residue from the dried ethereal extract gave the *ester*, b. p. 145°/3 mm. (Found: C, 53·8; H, 7·4. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·3%).

Synthesis of Esters of the Type $CHX_2{\cdot}CMeX{\cdot}CHX_2$ (see p. 812).—*Methyl* n-*propane*-ααβ-*tricarboxylate*. A mixture of 132 g. of methyl malonate and 23 g. of sodium dissolved in 400 c.c. of dry methyl alcohol was gently heated for 10 minutes and cooled slightly, and 167 g. of methyl α-bromopropionate added in small successive portions, sodium bromide separating. The whole was refluxed for 1—2 hours and poured into water, and the neutral fraction isolated by ether extraction. The residue (203 g.) obtained from the dried extract crystallised, and gave 145 g. of nearly pure ester and 47 g. of liquid. The *ester* crystallised from ether–ligroin (b. p. 40—60°) in rhombic prisms, m. p. 48—49° (Found: C, 49·7; H, 6·5. $C_9H_{14}O_6$ requires C, 49·5; H, 6·4%). Distillation of the liquid portion gave a further quantity of the ester, b. p. 135°/12 mm. Saturated with ammonia in methyl-alcoholic solution, the ester afforded the *triamide*, m. p. 249° (decomp.), as a crystalline powder (from dilute ethyl alcohol) (Found: C, 41·6; H, 6·4; N, 23·9. $C_6H_{11}O_3N_3$ requires C, 41·6; H, 6·4; N, 24·3%), and the more soluble *amide-imide*,  which crystallised from dilute alcohol in burr-like clusters of fine needles, m. p. 162° (Found: C, 46·0; H, 5·4; N, 18·2. $C_6H_8O_3N_2$ requires C, 46·2; H, 5·1; N, 18·0%).

Methyl α-*bromo*-n-*propane*-ααβ-*tricarboxylate* (VIII) was prepared by gradual addition of 24 g. of bromine to 32 g. of the above ester, gentle heat being applied to initiate the reaction. After hydrogen bromide ceased to be evolved, the product was largely diluted with ether, washed with water and sodium carbonate solution, and dried with sodium sulphate. Distillation of the residue from the ethereal solution gave 33 g. of the bromo-ester, b. p. 150°/7 mm., which seemed to contain a little unbrominated ester (Found: Br, 24·1. $C_9H_{13}O_6Br$ requires Br, 26·9%).

Attempted condensation of this bromo-ester with methyl malonate in methyl-alcoholic sodium methoxide gave the saturated ester, m. p. 48—49° (alone or mixed), the bromine being replaced by hydrogen. The reduction is effected by the methyl-alcoholic sodium methoxide, the bromo-ester being similarly converted by simple refluxing with this reagent for 1·5 hours.

Methyl Δ^{α}-*Propene*-ααβ-*tricarboxylate* (IX).—The bromo-ester (33 g.) was poured into 15 g. of pyridine, and left for 24 hours. Some evolution of heat and darkening occurred, pyridine hydrobromide separating. After isolation of the product by pouring into water, extraction with ether, and washing with water, dilute hydrochloric acid and sodium hydrogen carbonate solution, it was found still to contain bromine and two further treatments with pyridine were necessary before a bromine-free product was obtained. Distillation of the dried ethereal extract gave the unsaturated *ester*, b. p. 178°/53 mm. (Found: C, 49·8; H, 5·8.

$C_9H_{12}O_6$ requires C, 50·0; H, 5·6%). The *amide* crystallised from dilute alcohol in hard nodules, m. p. 198° (decomp.) (Found : C, 42·6; H, 5·6. $C_6H_9O_3N_3$ requires C, 42·1; H, 5·3%). Mesaconic acid, m. p. 202° (alone or mixed with a genuine specimen), was obtained by hydrolysis of the ester.

Attempted condensation of (IX) *with methyl acetoacetate.* The condensation with 1 mol. of the latter in presence of methyl-alcoholic sodium methoxide gave mainly acid products. When a large excess of the acetoacetate was used, and the mixture refluxed on the steam-bath for 65 hours, a neutral fraction was obtained from which a small amount of a crystalline substance, m. p. 250—251° (decomp.), separated. Distillation of the liquid portion gave two fractions : (1) b. p. 120—140°/3—4 mm.; and (2) b. p. 140—150°/3 mm., which partly crystallised. Recrystallisation of this solid material from ether–ligroin (b. p. 40—60°) gave methyl paraorsellinate, m. p. 97° (Found : C, 59·3; H, 5·6. Calc. : C, 59·3; H, 5·5%).

Methyl β-*bromo*-n-*propane*-ααβ-*tricarboxylate* (X) was obtained when 21 g. of the unsaturated ester (IX) were treated with 18 c.c. of 55% (wt./vol.) hydrogen bromide in acetic acid for 48 hours. The product was poured into water at 0° and extracted with ether, and the extract washed successively with water and sodium carbonate solution, and dried over calcium chloride. The crude product tends to lose hydrogen bromide but can be distilled if an oil pump is employed. The *bromo-ester*, b. p. 158—165°/5 mm., crystallises; m. p. 68° after recrystallisation from ether–ligroin (b. p. 40—60°) (Found : Br, 26·1. $C_9H_{13}O_6Br$ requires Br, 26·9%).

When the bromo-ester is refluxed with sodium iodide in ethyl alcohol for a while, and the product worked up (Baker, this vol., p. 216), the corresponding *iodo-ester*, b. p. 165—175°/10 mm., crystallising from ether–ligroin in feathery clusters of needles, m. p. 72°, is obtained (Found : I, 36·3. $C_9H_{13}O_6I$ requires I, 36·6%).

Methyl β-*Methyl*-n-*propane*-ααβγγ-*pentacarboxylate*.—To a solution of 0·76 g. of sodium in 20 c.c. of dry methyl alcohol, 5·7 g. of methyl malonate were added, followed, after thorough cooling, by 9·9 g. of the bromo-ester (X). After being kept at room temperature for 18 hours, the mixture was refluxed on the steam-bath for 5 hours and poured into water, and the slightly alkaline solution extracted with ether. Fractional distillation of the colourless residue from the dried extract gave fractions, b. p. 160—170°/1·5 mm. and 170° and over /1—1·5 mm., both of which partly crystallised after addition of ether and rubbing in ice. The *ester* crystallised from ice-cold ether in rosette clusters of minute prisms, m. p. 58° (Found : C, 48·4; H, 5·75. $C_{14}H_{20}O_{10}$ requires C, 48·3; H, 5·75%).

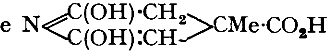
Methyl βγ-*Dimethyl*-n-*butane*-ααβγδδ-*hexacarboxylate* (XII).—This ester was obtained in an attempt to condense 3 g. of the bromo-ester (X) with 2·46 g. of methyl β-methyl-*n*-butane-ααδ-tricarboxylate (VI) in a cold solution of 0·23 g. of sodium in 2 c.c. of dry methyl alcohol. After being kept at room temperature for 18 hours, the mixture was refluxed on the steam-bath for 2—3 hours, diluted with ether, and poured into water, and the ethereal solution washed with aqueous sodium carbonate. The pale straw-coloured gum obtained by evaporation of the dried ethereal solution partly crystallised after being kept for 48 hours in a vacuum desiccator. After trituration with cold ether–ligroin, the *ester*, m. p. 179°, was crystallised from methyl alcohol (Found : C, 49·9; H, 5·7. $C_{18}H_{26}O_{12}$ requires C, 49·8; H, 5·9%).

Methyl β-*Keto*-n-*pentane*-γδ-*dicarboxylate*.—To a cold solution prepared from 38·7 g. of methyl acetoacetate and 7·7 g. of sodium dissolved in 120 c.c. of dry methyl alcohol, 55·7 g. of methyl α-bromopropionate were added. Sodium bromide began to separate almost immediately, and, after heating on the steam-bath for 1 hour, the product was poured into water, and the neutral fraction isolated in the usual manner. Fractional distillation gave the *keto-ester*, b. p. 146°/30 mm., which gives a faint purple colour with ferric chloride (Found : C, 53·5; H, 6·9. $C_9H_{14}O_5$ requires C, 53·5; H, 6·9%). The *semicarbazone* crystallised from dilute alcohol in clusters of small needles, m. p. 159° (Found : C, 46·6; H, 6·6. $C_{10}H_{17}O_5N_3$ requires C, 46·4; H, 6·6%). The crude bromo-ester obtained by the action of bromine on the above ester could not be distilled without decomposition, and direct treatment of the crude product with pyridine gave no pure bromine-free compound.

Unsuccessful Attempts to prepare Esters of the Type $CHX_2\cdot CMeX\cdot CHX_2$.—*Ethyl* n-*butane*-αβγγδ-*pentacarboxylate*. 25 G. of ethyl ethane-ααβ-tricarboxylate were added to a solution of 2·4 g. of sodium in dry ethyl alcohol, and, after cooling, 27·5 g. of ethyl bromosuccinate were added. Separation of sodium bromide began at once with self-heating. After ½ hour's refluxing, the neutral product was isolated in the usual manner. Distillation gave 12 g. of the required *ester*, b. p. 210°/5 mm. (Found : C, 54·6; H, 7·2. $C_{19}H_{30}O_{10}$ requires C, 54·5; H, 7·2%).

Similar condensation using ethyl β-bromo-*n*-propane-αβ-dicarboxylate, b. p. 124°/25 mm. (prepared by saturating a solution of citraconic anhydride in dry methyl alcohol with dry hydrogen bromide), in place of ethyl bromosuccinate gave ethyl citraconate and ethanetricarboxylate as the main products. The condensation was repeated by dissolving 1·1 g. of " molecular " sodium in 12 g. of the tricarboxylate in dry toluene, removing any undissolved sodium, and dropping the dry filtrate slowly on 15 g. of the bromo-ester in the same solvent, care being taken to exclude water at all stages. The reaction mixture was kept at incipient ebullition for 1 hour, sodium bromide separating. The cooled reaction mixture was largely diluted with ether and poured into water and the residue from the dried ethereal extract was carefully fractionated (glycerol-bath and fractionating Claisen flask). The low fraction again seemed to consist of ethyl citraconate and practically the whole distilled below 160°/5 mm., indicating the absence of the required condensation product. Hydrolysis of the few drops, b. p. 210°/5 mm., gave only a trace of a solid acid, m. p. 182°, which seems to be succinic acid (Found : C, 41·2; H, 5·0. Calc. : C, 40·7; H, 5·1%).

Bromination of ethyl β-methyl-*n*-propane-αγγ-tricarboxylate (Michael, *Ber.*, 1900, **33**, 3748) with bromine without solvent gave the *γ-bromo-ester*, b. p. 184°/9 mm. (Found : Br, 22·5. $C_{13}H_{21}O_6Br$ requires Br, 22·7%). An attempt to condense this with the potassium derivative of ethyl αβ-dicyano-β-methylglutarate (Hope and Sheldon, *loc. cit.*) gave a very dark viscous oil from which, on hydrolysis with hydrochloric and sulphuric acids, β-methylglutaric acid, m. p. 82° (alone or mixed with a genuine specimen), was the only crystalline material isolated.

Hydrolysis of Ethyl αβ-Dicyano-β-methylglutarate.—This ester (25 g.) (*loc. cit.*) was refluxed for 18 hours with saturated ethyl-alcoholic hydrogen chloride and a few c.c. of concentrated sulphuric acid. When poured into aqueous sodium carbonate, the product was soluble, and from the solution a colourless viscous gum, b. p. 194—198°/1 mm., was extracted. After keeping and boiling with ether–ligroin, a crystalline *substance*, m. p. 109—110° after crystallisation from ether, was obtained (Found : C, 49·8; H, 5·6; N, 6·45%), which was further hydrolysed by boiling concentrated hydrochloric acid to an *acid*, m. p. 133° after crystallisation from ether containing a little acetone. The analytical data for the latter are those required by the pyridine derivative  $N{<}\begin{matrix}C(OH)\cdot CH_2\\ C(OH){:}CH\end{matrix}{>}CMe\cdot CO_2H$ (Found : C, 49·1; H, 5·4; N, 8·3. $C_7H_9O_4N$ requires C, 49·1; H, 5·3; N, 8·2%) (compare Kon and Nanji, *loc. cit.*), but the structure of the precursor, m. p. 109—110°, has not so far been correlated with this constitution.

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THE UNIVERSITY, LEEDS.

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