703. *The Direct Formation of* cyclo*Pentanones by the Action of Mineral Acids on Carboxy-adipic Acids and Related Compounds.*

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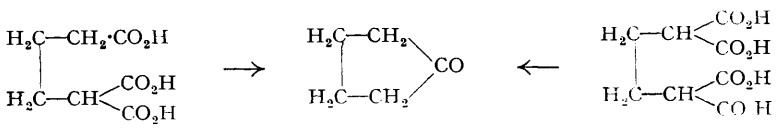
α-Carboxy- and α-cyano-adipic acids are found to yield *cyclo*pentanones when heated with hydrobromic acid : the reaction is largely specific for the formation of a five-membered ring. Its structural requirements are examined and a mechanism suggested. This leads to the rationalisation of certain previously unexplained observations in the literature.

Some features of interest are summarised concerning the preparation of compounds required in the investigation.

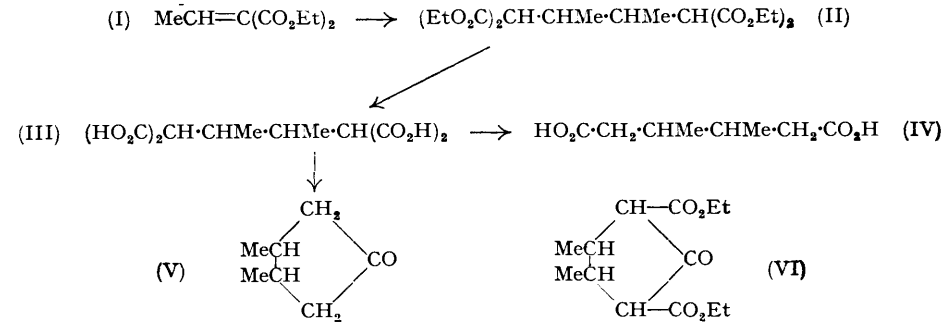
The formation of *cyclo*pentanone and its derivatives from the corresponding adipic acids or esters, by such methods as those of Blanc and of Dieckmann, are among the classical reactions of organic chemistry. We now find that mono- and di-α-carboxyadipic acids give substantial yields of *cyclo*pentanone when boiled with mineral acid.



This reaction has been generalised and its structural requirements and a possible mechanism have been established. It occurs under very much milder conditions than those prevailing in the usual pyrolytic formation of cyclic ketones from adipic acids.

The occurrence of the reaction was first established during the preparation of βγ-dimethyladipic acid (IV). The synthetical route was the bimolecular reduction of ethylidenemalonic ester (I) with aluminium amalgam and moist ether to the tetracarboxylic

ester (II) (Vogel, *J.*, 1927, 1985; Ställberg-Stenhagen, *Arkiv Kemi*, 1951, **3**, 256), followed by hydrolysis to the tetra-acid (III) and decarboxylation to (IV):

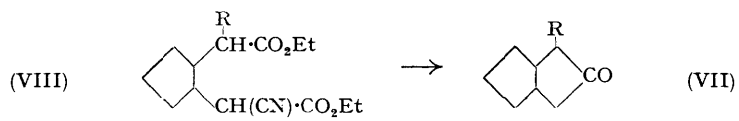


The last two stages were carried out by the usual procedure with boiling concentrated hydrochloric acid. This gave, however, not only the acid (IV) but a 30% yield of the corresponding 3 : 4-dimethyl*cyclo*pentanone (V). Both these were mixtures of the two possible stereoisomerides. The acid yielded the pure *meso*-isomeride after many crystallisations; the ketone (which was characterised by the preparation of its 2 : 4-dinitrophenylhydrazone, oxime, semicarbazone, and dibenzylidene derivative) is estimated from thermal analysis to contain about 80% of the *trans*-form.

A plausible explanation for the unexpected appearance of the cyclic ketone was that it had come from the hydrolysis of cyclic material, such as the keto-diester (VI), already formed during the bimolecular reduction. Indeed, when this reaction was carried out by the usual technique, so that the ether used as reaction medium boiled, the tetra-ester fraction gave a pronounced ferric chloride colour. However, this explanation was insufficient, for, when the reduction was conducted by two successive treatments at 0—5°, a pure tetra-ester was obtained. This gave no ferric chloride colour but, when boiled with hydrochloric acid, yielded no less than 45% of the cyclic ketone (V) together with 52% of the acid (IV).

The hydrolysis of cyano- and carbethoxy-derivatives of adipic esters has been for years a standard method of obtaining the corresponding dicarboxylic acids, and the formation of volatile ketones in this way is a factor leading to appreciable losses in yield. The Table on page 3498 shows that when no cyclisation occurs the yield of dicarboxylic acid is nearly quantitative.

A few indications of this type of cyclisation can be found in the literature. Barrett and Linstead (*J.*, 1935, 436) observed the formation of small amounts of *cis*-*bicyclo*[3 : 3 : 0]-octan-3-one (VII; R = H) by the hydrolysis of (VIII; R = H).



Koelsch and Stratton (*J. Amer. Chem. Soc.*, 1944, **66**, 1881) and Birch and Johnson (*J.*, 1951, 1493) have also obtained cyclic ketonic products from similar series of reactions which involved both reductions with aluminium amalgam and acid hydrolysis, but in no case was it definitely established at which stage the cyclisation occurred. In the light of the new results there is little doubt that the formation of the *bicyclo*octanone occurs during the hydrolytic stage, and this would agree with the recent work of Šorm, Šormova, and Sedivy on the corresponding methylated compounds (VII and VIII; R = Me) (*Coll. Czech. Chem. Comm.*, 1947, **12**, 554).

We have investigated the effect of structural variation and of experimental procedure on the yield of ketone. The highest yields (up to nearly 80%) are given when aqueous hydrobromic acid is used in the hydrolysis. The use of toluene-*p*-sulphonic acid in benzene or of trifluoroacetic anhydride gave no detectable ketone.

For the examination of structural variations twenty poly-acids or -esters were used, with the results summarised in the Table.

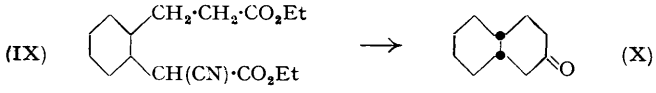
Products resulting from the treatment of polycarboxylic compounds with mineral acids.

	Acid [f]	Time for homogeneity, min.	Yield of ketone, % *	Yield of diacid, %	Material accounted for, %
$CHEt(CO_2Et)_2$	HBr	—	0	—	—
$(EtO_2C)_2CH\cdot[CH_2]_3\cdot CO_2Et$	HCl	23	10	83	93
$(EtO_2C)_2CH\cdot[CH_2]_3\cdot CO_2Et$	HBr	3	48	50	98
$(HO_2C)_2CH\cdot[CH_2]_3\cdot CO_2H$	HBr	1	42	50	92
$(EtO_2C)_2CH\cdot[CH_2]_2\cdot CH(CO_2Et)_2$	HCl	1·25 hr.	27	67	94
$(EtO_2C)_2CH\cdot[CH_2]_2\cdot CH(CO_2Et)_2$	HBr	18	78	21	99
$(HO_2C)_2CH\cdot[CH_2]_2\cdot CH(CO_2H)_2$	HBr	4	79	19	98
$(EtO_2C)_2CMe\cdot[CH_2]_2\cdot CMe(CO_2Et)_2$ [a]	HBr	—	—	—	—
$(HO_2C)_2CMe\cdot[CH_2]_2\cdot CMe(CO_2H)_2$	HBr	8 hr.	0	90	90
$(MeO_2C)_2CH\cdot[CHMe]_2\cdot CH(CO_2Me)_2$ [b]	HCl	1·5 hr.	21	76	97
$(EtO_2C)_2CH\cdot[CHMe]_2\cdot CH(CO_2Et)_2$ [c]	HCl	7·75 hr.	45	52	97
$(EtO_2C)_2CH\cdot[CHMe]_2\cdot CH(CO_2Et)_2$ [c]	HBr	—	73	15	98
$MeO_2C\cdot[CH_2]_4\cdot CO_2Me$	HCl	2	0	100	100
$EtO_2C\cdot[CH_2]_4\cdot CO_2Et$	HBr	—	0	100	100
$HO_2C\cdot CH_2\cdot[CHMe]_2\cdot CH_2\cdot CO_2H$ [d]	HCl	—	0	100	100
$(EtO_2C)_2CH\cdot[CH_2]_3\cdot CH(CO_2Et)_2$	HBr	22	0	96	96
$(HO_2C)_2CH\cdot[CH_2]_3\cdot CH(CO_2H)_2$	HBr	—	0	99	99
$(EtO_2C)_2CH\cdot CH_2\cdot CH(CO_2Et)_2$	HBr	15	0	100	100
$(EtO_2C)_2CH\cdot[CH_2]_5\cdot CH(CO_2Et)_2$	HBr	25	0	100	100
$(EtO_2C)_2CH\cdot[CH_2]_6\cdot CH(CO_2Et)_2$	HBr	25	0	100	100
$EtO_2C\cdot CH(CN)\cdot[CH_2]_3\cdot CO_2Et$	HBr	—	35	69 [e]	—
$EtO_2C\cdot CH(CN)\cdot[CH_2]_4\cdot CO_2Et$	HBr	—	0	99 [e]	—
(VIII; R = H)	HBr	2	20	—	—

* As 2 : 4-dinitrophenylhydrazone.

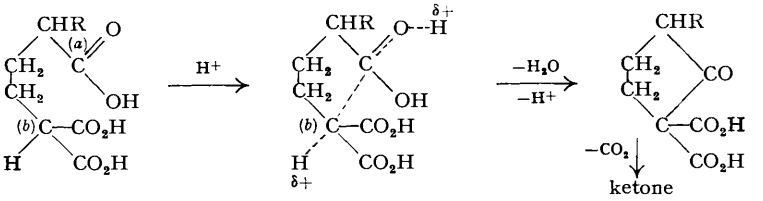
[a] Discontinued as the precipitation of tetra-acid caused experimental difficulty : no ketone was detected. [b] *meso*-. The 2 : 4-dinitrophenylhydrazone had m. p. 148—148·5° and the *meso*-dimethyladipic acid, m. p. 132—133°. [c] Mixture of stereoisomers obtained from the low-temperature bimolecular reduction. [d] This was not carried out in the special apparatus, but a 12 hr. reaction period yielded no ketone. [e] Adipic acid contaminated with ammonium bromide. [f] HBr indicates constant-boiling acid and HCl a 1 : 1-mixture of acid and water.

The main conclusions which we draw are as follows: (1) Tri- and tetra-carboxylic acids (and esters) of the adipic series all give the corresponding *cyclo*pentanones when boiled with aqueous hydrogen bromide. (2) The species responsible for cyclisation are the acids not the esters; no ketone can be detected when tetramethyl butane-1 : 1 : 4 : 4-tetracarboxylate is boiled with hydrogen bromide until the mixture becomes homogeneous; on the other hand the formation of ketone from the corresponding acid is immediate. (3) Acids of the adipic series containing no additional carboxyl or similar groups yield no *cyclo*pentanones under these conditions. If one additional carboxyl or cyano-group is present the yield of *cyclo*pentanone is about 40%. If two such groups are present the yield rises to about 70%. The highest yield observed was that of *cyclo*pentanone itself from butane-1 : 1 : 4 : 4-tetracarboxylic acid (79%). (4) The formation of cyclic ketones is prevented if both α-carbon atoms are alkylated. (5) *cyclo*Hexanones are not formed from carboxyl, carbalkoxyl, or cyano-derivatives of pimelic acid, which give quantitative yields of pimelic acid when boiled with hydrobromic or hydrochloric acids. The single known exception to this rule is provided by the conversion of (IX) into the *cis*-β-decalone (X) by boiling hydrochloric acid (Barrett,



Cook, and Linstead, *J.*, 1935, 1065). The yield is however quite small. Steric conditions may be presumed to be unusually favourable for cyclisation in this case. (6) It is not surprising that no *cyclo*butanone, *cyclo*heptanone, or *cyclo*octanone is formed by the treatment of the appropriate tetracarboxylic ester with boiling hydrogen bromide. (7) Dipropyl ketone is not formed by an analogous intermolecular reaction from ethylmalonic acid. In another case diethyl malonate gave no acetone.

This acid-catalysed cyclisation of carboxy-adipic acids is assigned the following mechanism :



If R = CO_2H, there will be an additional decarboxylation in the final stage. Attack is initiated by a proton at the carbonyl group of one carboxyl (*a*); a cyclic transition state is formed in which the bond (*b*) attaching the hydrogen to the malonic acid residue is weakened; the cyclisation is completed by the elimination of water from the potential carbonyl, formation of a carbon–carbon bond, and elimination of the " malonic " hydrogen. Decarboxylation completes the reaction. This mechanism explains why no cyclisation of αα′-dimethyl-acids is possible and why at least one end of the chain must carry two activating groups. We attribute the increase in yield from the cyclisation of the tetracarboxylic acids to a statistical effect.

The clear-cut distinction between the adipic and pimelic series is surprising, for they are usually very similar in their capacity for cyclisation. The difference is attributed to the fact that ketonisation always competes with direct decarboxylation. Unless the system is very favourable for the formation of the cyclic intermediate (which is true for the carboxy-derivatives of adipic acids) then the malonic residues are decarboxylated, after which no cyclisation is possible.

Preparation and Purification of Materials.—It was clearly essential that the materials used in this work should be free from alicyclic products. The methods are described in the experimental section. A few incidental features of interest are summarised below.

(a) *Butane*-1 : 1 : 4 : 4-*tetracarboxylic ester.* This intermediate was used by Perkin in some classical syntheses of alicyclic compounds. His methods (*J.*, 1885, **47**, 807; 1887, **51**, 19; 1894, **65**, 578; 1895, **67**, 108; *Ber.*, 1886, **19**, 2038) have been improved by Noyes and Kyriakides (*J. Amer. Chem. Soc.*, 1910, **32**, 1057), who allowed ethyl magnesiomalonate to react with ethylene dibromide. The product, however, contains *cyclo*hexane-1 : 1 : 4 : 4-tetracarboxylic ester (Meincke, Cox, and McElvain, *ibid.*, 1935, **57**, 1133; Feofilaktov and Ivanov, *J. Gen. Chem. U.S.S.R.*, 1935, **5**, 1558), and enolic *cyclo*pentanone-carboxylic esters are also present. By employing a large excess of magnesiomalonate under controlled conditions, we have obtained tetraethyl butanetetracarboxylate for the first time as a crystalline solid, m. p. 17°. There is no doubt as to its homogeneity. The melting point is unchanged by regeneration from the sodio-compound; the ester yields an αα′-dimethyl derivative, and gives pure adipic acid on acid hydrolysis.

(b) *Butane*-1 : 1 : 4-*tricarboxylic ester.* This was prepared by treatment of diethyl adipate with dimethyl oxalate (Wislicenus and Schwanhäusser, *Annalen*, 1897, **297**, 111) and pyrolysis of the product. Another route was also employed—condensation of ethyl γ-bromobutyrate with sodiomalonic ester (cf. Montemartini, *Gazzetta*, 1896, **26**, II, 261; Boorman, Linstead, and Rydon, *J.*, 1933, 568). The bromo-ester was prepared in 82% yield by treatment of γ-butyrolactone with ethanolic hydrogen bromide at 0°; this is more convenient than previously described methods.

(c) 1-*Cyanobutane*-1 : 4-*dicarboxylic ester and* 1-*cyanopentane*-1 : 5-*dicarboxylic ester.* These were prepared by condensation of ethyl sodiocyanoacetate with the appropriate bromo-ester. Ethyl δ-bromovalerate was conveniently made from the corresponding δ-hydroxy-ester, formed by oxidising *cyclo*pentanone with persulphuric acid in ethanol (*cf.* Büchi and Jeger, *Helv. Chim. Acta*, 1949, **32**, 540).

(d) When diethyl ethylidenemalonate is reduced with aluminium amalgam, a low-boiling substance is formed as well as the bimolecular reduction product. Vogel (*loc. cit.*) assumed this to be diethyl malonate, but it is in fact diethyl ethylmalonate [$CHEt(CO_2Et)_2$].

Experimental

Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

Diethyl Ethylidenemalonate.—This was prepared according to Vogel's method (*loc. cit.*; cf. Ställberg-Stenhagen, *loc. cit.*), in a crude yield of 82%. It was fractionated through a Stedman column before use, and then had $n_D^{26\cdot5}$ 1·4385 (Found: C, 57·5; H, 7·65. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%. Microhydrogenation: 1·00 double bond). Light absorption: $\lambda_{max.}$ 225 mμ, ε 5,600. Attempts to determine a saponification equivalent led to brown colours which masked the end-point (cf. Komnenos, *Annalen*, **1883**, **218**, 162).

"Bimolecular" Reduction of Diethyl Ethylidenemalonate.—(a) *At reflux temperature.* Aluminium foil (90 g.), amalgamated according to Vogel's directions (*J.*, 1927, 594), was covered with ether, and diethyl ethylidenemalonate (240 g.) was added with stirring during 30 min. When the vigorous reaction had subsided, water was added (3 × 10 ml. and 1 × 30 ml.), and the product was stirred overnight. The sludge was filtered off and continuously extracted with ether.

After drying ($MgSO_4$), the combined ethereal solutions were evaporated and distilled. A low-boiling material (52·4 g.), b. p. 52—54°/0·5 mm., n_D^{20} 1·4161, was removed, and then tetraethyl 2 : 3-dimethylbutane-1 : 1 : 4 : 4-tetracarboxylate (196 g., 81%), n_D^{22} 1·4455—1·4462, distilled at *ca.* 146°/0·1 mm.

The low-boiling material was identified as diethyl ethylmalonate by further purification; it had n_D^{26} 1·4135 (Found: C, 57·25; H, 8·7. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·55%). On hydrolysis ethylmalonic acid, m. p. 112·5—114·5°, was isolated (lit., m. p. 112°), which decarboxylated at 160° to butyric acid. Vogel (*loc. cit.*) had assumed this by-product to be recovered diethyl malonate.

(b) *At low temperature.* Aluminium foil was prepared and amalgamated by Vogel's method except that the final washings with ethanol and ether were omitted. The amalgam (from 63 g. of Al) was covered with ether and stirred at 0°. Diethyl ethylidenemalonate (68·5 g.; $n_D^{26\cdot5}$ 1·4403) was added during 4 min. and the mixture stirred overnight at 0°. The solution was filtered, the solid washed with ether, and the united ethereal solutions dried and evaporated to yield a crude product (63·9 g.) which instantly decolorised permanganate. Reduction of this material was repeated with aluminium (49·5 g.) at 0°. After 35 min., water (5 ml.) was added and then further portions at hourly intervals (7 × 5 ml.). The temperature was kept below 10° and the mixture stirred overnight at 0° and worked up as described above. The crude product (49·6 g.) did not immediately reduce cold permanganate or give a colour with ferric chloride. Distillation gave diethyl ethylmalonate (16·8 g.), b. p. 48°/0·1 mm., $n_D^{21\cdot5}$ 1·4154, and tetraethyl 2 : 3-dimethylbutane-1 : 1 : 4 : 4-tetracarboxylate (31·5 g.), b. p. 70—80°/10^{-4} mm. (bath temp.), n_D^{20} 1·4452 (Found: C, 58·25; H, 8·25; OEt, 48·55. Calc. for $C_{18}H_{30}O_8$: C, 57·75; H, 8·1; OEt, 48·1%). Though it gave no ferric chloride colour, it still yielded a *cyclo*pentanone on treatment with acid (see Table).

Treatment of Tetraethyl 2 : 3-Dimethylbutane-1 : 1 : 4 : 4-tetracarboxylate with Acid.—The ester (196 g.) was refluxed with hydrochloric acid (165 ml.) and water (165 ml.), and the ethanol formed removed continuously through a small column during 8 hr. Finally it was refluxed overnight to complete decarboxylation. The liquid was then steam-distilled until the odour of ketone was no longer detectable (*ca.* 500 ml. of distillate). After decolorisation with charcoal, the solution of steam-involatile material was set aside at 0° for 2 days; a mixture of the stereoisomers of βγ-dimethyladipic acid (28 g., 31%; m. p. 124—130°) crystallised. The mother-liquors yielded a further 3·7 g. of crude material. Four recrystallisations of the main crop from ethyl acetate gave *meso*-βγ-dimethyladipic acid (14·2 g.), m. p. 131—133·3° (Ställberg-Stenhagen, *Arkiv Kemi*, **1951**, **3**, 256, records m. p. 133—134°).

The steam-volatile ketonic material yielded 3 : 4-*dimethyl*cyclo*pentanone* 2 : 4-*dinitrophenylhydrazone* which, after five recrystallisations from ethanol, separated in yellow needles, m. p. 149·2—150° (Found: C, 54·0; H, 5·45; N, 19·15. $C_{13}H_{16}O_4N_4$ requires C, 53·45; H, 5·5; N, 19·5%). In a second experiment the crude derivative was chromatographed on alumina from benzene solution and ten fractions collected, the melting points of which lay between 140° and 147°.

The semicarbazone of the ketone (sodium acetate–semicarbazide hydrochloride method), after four crystallisations from methanol, had m. p. 205—207·5° (bath pre-heated to 196°). In a bath pre-heated to 209°, and with a temperature rise of 3·6°/min., the m. p. was 209·5—212°. Reference to a standard m. p. curve of mixtures of semicarbazones of *cis*- and *trans*-3 : 4-dimethyl*cyclo*pentanones indicated that the original ketone contained *ca.* 80% of *trans*-

isomer. It is interesting that Koelsch and Stratton (*J. Amer. Chem. Soc.*, 1944, **66**, 1882) obtained 3 : 4-diethyl*cyclo*pentanone, containing 90% of the *trans*-isomer, by acid hydrolysis of tetraethyl 2 : 3-diethylbutane-1 : 1 : 4 : 4-tetracarboxylate (obtained from a bimolecular reduction). Since the proportion of *meso*- and racemic forms in the starting material was not known, the possibility of preferential cyclisation of one of these cannot be discussed.

The *oxime* melted at 99·8—100·5° after 7 recrystallisations from aqueous ethanol (Found : N, 10·65. $C_7H_{13}ON$ requires N, 10·3%).

A *dibenzylidene* derivative had m. p. 113—114° (Found : C, 87·6; H, 7·05. $C_{21}H_{20}O$ requires C, 87·5; H, 7·0%). Light absorption ($CHCl_3$) : λ_{max} 349 mμ; ε 34,600 : $\lambda_{inf.}$ 353 mμ; ε 33,000. The 2 : 4-*dinitrophenylhydrazone* of the dibenzylidene derivative crystallised from ethanol in dark red needles, m. p. 220° (decomp.) (Found : C, 69·8; H, 5·0; N, 11·75. $C_{27}H_{24}O_4N_4$ requires C, 69·2; H, 5·15; N, 11·95%). Light absorption ($CHCl_3$) : $\lambda_{max.}$ 410, 600 mμ; ε 19,200, 28,200.

Tetraethyl meso-2 : 3-*Dimethylbutane*-1 : 1 : 4 : 4-*tetracarboxylate*.—*meso*-Acid (1·30 g.; m. p. 179°) was treated with ethereal diazomethane and yielded the *tetramethyl* ester. This crystallised from ethyl acetate–light petroleum (b. p. 60—80°) and then methanol in rhombohedra, m. p. 102·5—103·5° (Found: C, 52·9; H, 7·05; OMe, 39·3. $C_{14}H_{22}O_8$ requires C, 52·85; H, 6·95; OMe, 39·0%).

Tetramethyl Butane-1 : 1 : 4 : 4-*tetracarboxylate*.—Condensation of ethylene dibromide (slightly more than 1 mol.) with ethyl magnesiomalonate (2 mol.) gave, in a number of experiments, the required product contaminated with tetraethyl *cyclo*hexane-1 : 1 : 4 : 4-tetracarboxylate (m. p. 77°) which proved very difficult to remove. The following conditions were employed.

Magnesium turnings (20 g.) were treated with dry ethanol (45 ml.), and carbon tetrachloride (0·4 ml.) was added. Reaction commenced on slight warming and diethyl malonate (200 g.) in dry ethanol (200 ml.) was added with stirring and cooling. A few drops of mercury were introduced, and the mixture heated on a steam-bath for 90 min. and then cooled. Ethylene dibromide (58 g.) was added dropwise during 30 min. and the mixture heated and stirred for 12 hr. Volatile matter was removed under reduced pressure, ether (200 ml.) added, and the cooled mass decomposed with hydrochloric acid. The ether solution was washed with dilute acid, sodium hydrogen carbonate solution, and water. On drying, evaporation, and distillation, diethyl malonate (125·5 g.) was recovered (b. p. 53°/0·7 mm.; n_D^{18} 1·4151—1·4168).

The residue (60 g.) gave a strong colour reaction with ferric chloride : it was dissolved in ether (200 ml.) and the solution washed with N-potassium hydroxide and water : working up and distillation yielded material, b. p. 150—166°/1·8 mm., n_D^{26} 1·4378—1·4405 (46·1 g.). It still gave a red-purple ferric chloride reaction, and the above treatment with alkali was repeated. A series of fractions (total 40·0 g., 38%) was isolated by distillation (b. p. 154—165°/0·1 mm.; $n_D^{18\cdot5}$ 1·4410—1·4413) : all gave only yellow or orange colours with ferric chloride.

The disodium derivative of one of these fractions (b. p. 154—160°/0·1 mm.; $n_D^{18\cdot5}$ 1·4410; 15·6 g.) was prepared in dry ether (30 ml.) by adding sodium ethoxide, prepared from sodium (2·2 g.), dry ethanol (33 ml.), and ether (40 ml.). The salt was precipitated by the addition of more ether (230 ml.), filtered off, and washed with ether. Regeneration, by shaking it with hydrochloric acid (12 ml.) in water (24 ml.) and distillation, gave a sample (b. p. 130—146°/0·2 mm.) which crystallised (m. p. 13—17°) on the addition of a trace of impure tetraethyl *cyclo*hexane-1 : 1 : 4 : 4-tetracarboxylate. The material thus obtained was used to seed another of the fractions (b. p. 160—165°/0·1 mm.; $n_D^{18\cdot5}$ 1·4410; 7·09 g.) which could then be crystallised as prisms (5·96 g.) (from ethanol at low temperature), m. p. 15—17°, b. p. 120—130°/0·2 mm. (bath temp.), n_D^{17} 1·4408 (Found : C, 55·5; H, 7·45; OEt, 52·2%; Sap. equiv., 86·0. Calc. for $C_{16}H_{26}O_8$: C, 55·5; H, 7·55; OEt 52·0%; Sap. equiv., 86·6).

It is likely that the enolic material which was removed during purification was diethyl 2-keto*cyclo*pentane-1 : 3-dicarboxylate or the triethyl 1 : 1 : 3-tricarboxylate. The extracted material gave intense purple colours with ferric chloride, and a copper enolate was isolated. The material may arise from the action of magnesium ethoxide on tetraethyl butane-1 : 1 : 4 : 4-tetracarboxylate. In support of this view, the ready cyclisation of the latter to diethyl 2-keto-*cyclo*pentane-1 : 3-dicarboxylate by hot sodium ethoxide (diethyl carbonate is eliminated) may be cited (Meincke, Cox, and McElvain, *loc. cit.*).

Butane-1 : 1 : 4 : 4-*tetracarboxylic Acid*.—The tetraethyl ester (m. p. 16—17°; 2·22 g.) was shaken with potassium hydroxide (1·84 g.) in water (8 ml.) for 12 hr. The product was concentrated under reduced pressure, acidified with hydrochloric acid (*ca.* 7 ml.), and then evaporated to dryness *in vacuo* at >40°. Continuous ether extraction (2 days) gave the tetra-acid (1·42

g., 95%) which was recrystallised from acetone–petroleum–ethyl acetate and then had m. p. 179° (with decarboxylation) (Found : C, 41·5; H, 4·45%; equiv., 61·3. Calc. for $C_8H_{10}O_8$: C, 41·05; H, 4·3%; equiv., 58·5). Decarboxylation gave adipic acid, m. p. 152°. Its *tetramethyl* ester, prepared with diazomethane like the others described below, crystallised from aqueous methanol or petroleum in long needles, m. p. 73·5—75·5° (Found : C, 49·75; H, 6·5; OMe, 42·65. $C_{12}H_{18}O_8$ requires C, 49·65; H, 6·25; OMe, 42·8%).

Tetraethyl Hexane-2 : 2 : 5 : 5-*tetracarboxylate*.—A mixture of tetraethyl butane-1 : 1 : 4 : 4-tetracarboxylate (3·5 g.; m. p. 14—17°) and methyl iodide (3·6 g.) was added to ice-cold sodium ethoxide, prepared from sodium (0·5 g.) and dry ethanol (10 ml.). The mixture was set aside (1½ hr.), refluxed (2 hr.), and evaporated. Water was added, the mixture extracted with ether, and the extract washed with dilute sodium thiosulphate solution, dried, and evaporated to give tetraethyl hexane-2 : 2 : 5 : 5-tetracarboxylate (3·44 g., 91%). On recrystallisation from light petroleum (b. p. 60—80°) this had m. p. 52·5—53·5° (3·17 g.).

The ester was hydrolysed at 25° as described under butane-1 : 1 : 4 : 4-tetracarboxylic acid except that a little ethanol was added and a longer reaction time allowed. Extraction of the residue after careful evaporation, anhydrous acetone being used, gave the tetra-acid (1·51 g.), m. p. 207° (with decarboxylation; bath pre-heated to 170° and heated rapidly). The m. p. after decarboxylation was 110—114° (mixture of stereoisomers). *Tetramethyl hexane*-2 : 2 : 5 : 5-*tetracarboxylate*, m. p. 93—94°, crystallised from aqueous methanol or petroleum (Found : C, 53·05; H, 7·15; OMe, 39·05. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·0; OMe, 39·0%).

Tetraethyl Propane-1 : 1 : 3 : 3-*tetracarboxylate*.—This was prepared according to the method of Caunt, Crow, Haworth, and Vodoz (*J.*, 1950, 1632), and had $n_D^{20\cdot5}$ 1·4387.

Tetraethyl Pentane-1 : 1 : 5 : 5-*tetracarboxylate*.—Guha and Seshadriengar's method (*Ber.*, 1936, **69**, 1215) gave a yield of 42% (based on 1 : 3-dibromopropane) of *ester*, b. p. 172°/0·08 mm., n_D^{19} 1·4452. This gave no colour with ferric chloride (Found: C, 55·6; H, 7·8%; Sap. equiv., 89·9. $C_{17}H_{28}O_8$ requires C, 56·65; H, 7·85%; Sap. equiv., 90·1).

The ester (5·36 g.) was hydrolysed at 25°, by shaking it with potassium hydroxide (3·70 g.) in water (15 ml.) for 35 hr., and then filtered off, acidified, and evaporated *in vacuo*. The residue was continuously extracted with ether. Evaporation yielded crude tetra-acid (3·40 g., 92·2%) which was stirred with petroleum, filtered, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), to give pentane-1 : 1 : 5 : 5-tetracarboxylic acid (1·84 g.), m. p. 155° (with decarboxylation; bath preheated to 110°) (Perkin and Prentice, *J.*, 1891, **59**, 824, give m. p. 125—130°). The product was faintly yellow (Found : C, 43·7; H, 5·15%; Neut. equiv., 64·8. Calc. for $C_9H_{12}O_8$: C, 43·55; H, 4·85%; Neut. equiv., 62·1). The *tetramethyl* ester crystallised in prisms from light petroleum (b. p. 60—80°), m. p. 42—43·5° (Found : C, 51·45; H, 6·7; OMe, 40·5. $C_{13}H_{20}O_8$ requires C, 51·3; H, 6·65; OMe, 40·8%).

Triethyl Butane-1 : 1 : 4-*tricarboxylate*.—(a) *From γ-butyrolactone*. A solution of the lactone (60 g.) in dry ethanol (200 ml.), was saturated with dry hydrogen bromide gas at 0°, more gas being passed in intermittently over 3 days. The mixture was set aside (12 hr.) and then briefly warmed at 100°, the solvent removed *in vacuo*, and ether (500 ml.) together with an excess of sodium hydrogen carbonate slurry added with cooling. The ether solution was worked up to give ethyl γ-bromobutyrate (112 g., 82%), b. p. 83°/12 mm., n_D^{23} 1·4553—1·4558.

This bromo-ester (39 g.) was condensed with ethyl sodiomalonate [from sodium (4·6 g.) and diethyl malonate] according to the directions of Boorman, Linstead, and Rydon (*J.*, 1933, 568). Refluxing of the vigorously stirred mass for 20 hr. was required to cause the sodium to react with diethyl malonate in benzene. When the bromo-ester had been added, boiling and stirring were continued for 28 hr. After the addition of water and ether, triethyl butane-1 : 1 : 4-tricarboxylate (72%), b. p. *ca.* 115°/0·1 mm., n_D^{20} 1·4364, was isolated in the usual way. Mild alkaline hydrolysis gave the corresponding tricarboxylic acid (90%), m. p. 148° (Montemartini, *loc. cit.*, gives m. p. 130°; Wislicenus and Schwanhäusser, *loc. cit.*, and Dieckmann, *Annalen*, 1901, **317**, 62, each give 139—140°).

(b) *From diethyl adipate*. Sodium (3·45 g.) was dissolved in dry ethanol (55 ml.), the excess of solvent removed, and the residue baked at 100°/0·1 mm. for 1 hr. Benzene (20 ml.) and then diethyl oxalate (21·9 g.) were added. When all the solid had dissolved, diethyl adipate (30·3 g.) was introduced in portions and the mixture set aside for 48 hr. It was poured into ice (300 g.) and hydrochloric acid (15 ml.), and the product isolated with ether, washed, dried, and evaporated. Decomposition by heating under nitrogen at 160—180°/20 mm. in a Kon flask packed with glass wool (1·5 hr.) gave, on isolation with ether and distillation, three fractions : (i) b. p. 66—120°/0·2 mm., n_D^{21} 1·4278 (8·2 g.); (ii) b. p. 120—126°/0·25 mm., $n_D^{20\cdot5}$ 1·4373 (18·5 g.); (iii) b. p. 126—150°/0·3 mm., $n_D^{20\cdot5}$ 1·4440 (6·05 g.).

Fraction (ii), impure ethyl butane-1 : 1 : 4-tricarboxylate, was thrice redistilled and then had n_D^{20} 1·4352 (Found : C, 57·25; H, 8·05; OEt, 49·65. Calc. for $C_{13}H_{22}O_6$: C, 56·9; H, 8·1; OEt, 49·25%). Triebs and Meyer (*Chem. Ber.*, 1952, **85**, 615) have recently reported a similar reaction giving a yield of 70%.

Diethyl 1-*Cyanobutane*-1 : 4-*dicarboxylate*.—The method of Gagnon, Gaudry, and King (*J.*, 1944, 13) was used except that the ethyl γ-bromobutyrate was added to ethyl sodiocyanoacetate in benzene. The product (35%) had b. p. 120°/0·15 mm., n_D^{26} 1·4389 (Found : C, 57·95; H, 7·65; N, 6·25. Calc. for $C_{11}H_{17}O_4N$: C, 58·1; H, 7·55; N, 6·15%). Some starting material was recovered and a high-boiling material also isolated. Triebs and Meyer (*loc. cit.*) give b. p. 118°/0·15 mm., n_D^{22} 1·4408.

Diethyl 1-*Cyanopentane*-1 : 5-*dicarboxylate*.—Interaction of ethyl δ-bromovalerate with ethyl sodiocyanoacetate in benzene gave only an 8% yield of material, b. p. 120°/0·2 mm., n_D^{22} 1·4416 (Found : C, 60·25; H, 8·1. Calc. for $C_{12}H_{19}O_4N$: C, 59·75; H, 7·95%). The ethyl δ-bromovalerate was isolated in a 32% overall yield by employing a slight adaptation of Büchi and Jeger's method (*loc. cit.*).

Reduction of Diethyl cyclo*Pentylidenecyanoacetate*-2-*acetate*.—This diester was prepared according to Linstead and Meade's method (*J.*, 1934, 941 : cf. Barrett and Linstead, *ibid.*, 1935, 440) and had b. p. 125—135°/0·02 mm. (bath temp.), n_D^{19} 1·4895. Linstead and Meade give n_D^{20} 1·4883, and Roberts and Gorham (*J. Amer. Chem. Soc.*, 1952, **74**, 2278) give n_D^{25} 1·4831.

Considerable difficulty was experienced in hydrogenating this sample. In ethanol solution, with 10% palladium–charcoal, absorption of hydrogen at atmospheric pressure ceased prematurely and was continued under pressure (5 atm.), but the product on distillation still contained unsaturated material. Little further reduction was accomplished by treatment with aluminium amalgam but finally, after treatment with Raney nickel in ethanol for a week, further absorption was achieved with a palladium–charcoal catalyst. The diethyl *cyclo*pentyl-cyanoacetate-2-acetate distilled at 132—138°/0·1—0·2 mm., and had $n_D^{21\cdot5}$ 1·4672—1·4676 (Linstead and Meade, *loc. cit.*, give n_D^{20} 1·4623, and Roberts and Gorham, *loc. cit.*, record n_D^{25} 1·4599).

cis-bicyclo[3 : 3 : 0]*Octan*-3-*one* 2 : 4-*Dinitrophenylhydrazone*.—The above ester, when treated with hydrobromic acid according to the standard technique described below, blackened, but yielded a ketonic fraction which gave *cis-bicyclo*[3 : 3 : 0]octan-3-one 2 : 4-dinitrophenylhydrazone, m. p. 114—115°, in 21% yield (Found : C, 55·65; H, 5·5. Calc. for $C_{14}H_{16}O_4N_4$: C, 55·25; H, 5·3%). Roberts and Gorham (*loc. cit.*) give m. p. 115—116°.

General Technique for the Acid-catalysed Cyclisation Experiments.—These experiments were conducted in a standardised one-piece apparatus, comprising a small reaction-flask surmounted by a Vigreux column and equipped with a nitrogen inlet and a means of adding more reagent. The mixture of ester or polycarboxylic acid (1 g.) and cyclising agent (*e.g.*, 1 : 1 hydrochloric acid–water; 2—3 ml.) was placed in the flask, heated in an oil-bath by means of an electric hot-plate and stirred by a fine stream of nitrogen bubbles. Steam-volatile ketone was carried out continuously with the aid of the nitrogen stream and collected in an excess of a 2 : 4-dinitrophenylhydrazine reagent [2 : 4-dinitrophenylhydrazine (2 g.), concentrated sulphuric acid (8 ml.), methanol (30 ml.), and water (10 ml.)]. The acid mixture was replenished as required from a teat-pipette.

After precipitation of most of the ketonic derivative, the nitrogen stream was stopped and the residual acid heated overnight at 120° (for experiments with hydrochloric acid) or 130° (hydrobromic acid), to ensure complete decarboxylation. During this period the surface of the dinitrophenylhydrazine reagent was arranged just to touch the end of the gas-exit tube. Next day the nitrogen was turned on and any remaining ketone forced over by heating and stirring for 1 hr. The dinitrophenylhydrazine reagent was cooled to 0°, and the derivative filtered off, dried, and chromatographed on alumina (Spence type H) from benzene. The yields of ketones are reported in the Table.

Estimation of the diacid formed by decarboxylation was made by evaporating the contents of the flask, drying the residue *in vacuo* over sodium hydroxide pellets, and weighing it.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a maintenance grant (to J. E. H. H.).

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[*Received, July 12th*, 1953.]