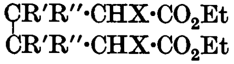
CCLX.—*Syntheses of Cyclic Compounds. Part I. Ethyl βγ-Dimethylbutane-ααδδ-tetracarboxylate and some* cyclo*Butane Compounds derived therefrom.*

By Israel Vogel.

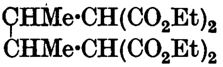
In extending his investigations on the reduction of unsaturated compounds by moist aluminium amalgam (this vol., p. 594), the author has been led to examine the reduction of esters of the type CR′R″:CX·CO_2Et (I), where X may be CO_2Et, COMe, or CN, and R′,R″ may be Me,H; Ph,H; Me,Me; or the *cyclo*pentane or *cyclo*hexane ring. Coupling would presumably take place in the β-positions (compare Vogel, *loc. cit.*), resulting in the formation of compounds

II) which (if $X = CO_2Et$) are homologues, symmetrically substituted in the β- and γ-positions, of ethyl butanetetracarboxylate, a

(II.)



$$\begin{array}{l} CR'R''\cdot CHX\cdot CO_2Et \\ | \\ CR'R''\cdot CHX\cdot CO_2Et \end{array}$$



$$\begin{array}{l} CHMe\cdot CH(CO_2Et)_2 \\ | \\ CHMe\cdot CH(CO_2Et)_2 \end{array}$$

(III.)

substance which has found wide application as a synthetic agent in the hands of Professor Perkin and his collaborators (see numerous papers in J., 1884—1900). This series of researches has therefore been instituted with the following objects: (1) to synthesise compounds of the type (II); (2) to study the influence of groups and rings in the β- and γ-positions on (*a*) the relative ease of formation and stability of four-, five-, six-, and higher-membered rings by condensation with the appropriate reagents, and (*b*) the stability of the *cis*- and *trans*-anhydrides of the cyclic dibasic acids; (3) to synthesise substituted adipic acids from compounds of the type (II) and to employ them in the investigation of the stability of the *cis*- and *trans*-anhydrides as well as of their simpler cyclic derivatives.

The present communication is concerned with the reduction of ethyl ethylidenemalonate by moist aluminium amalgam.* This substance has been previously reduced by means of moist sodium amalgam by Higginbotham and Lapworth (J., 1923, **123**, 1618), who state that " products of at least two distinct types," a volatile β-ketonic ester and a bimolecular compound (III), are formed. No conclusive evidence as to the presence of the β-ketonic ester was given, nor was the dimethylbutanetetracarboxylate isolated, its presence in the primary reduction product being inferred from the production of two isomeric ββ'-dimethyladipic acids by hydrolysis, heating at 160°, and subsequent distillation under low pressure. The author, by employing moist aluminium amalgam as the reducing agent, has found no difficulty in preparing *ethyl dimethylbutanetetracarboxylate* (III) in quantity. On hydrolysis with alcoholic potassium hydroxide, it readily yields a mixture of two stereoisomeric *βγ-dimethylbutane-ααδδ-tetracarboxylic acids*, which can be separated into two forms (*meso* and racemic) melting at 152—154° (decomp.) and 185—185·5° (decomp.), respectively. The racemic configuration is provisionally assigned to the less fusible form. On heating the mixture of the two tetracarboxylic acids at 200°, carbon dioxide was eliminated and a mixture of the two corresponding ββ'-dimethyladipic acids was obtained melting over the range 105—120°, which on esterification and hydrolysis

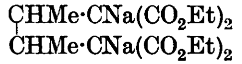
---

* A description of the application of moist aluminium amalgam in the separation of mixtures of unsaturated compounds, especially those exhibiting three-carbon tautomerism, is reserved for a future communication.

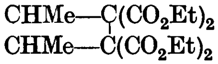
yielded chiefly a mixture of acids, m. p. 113—117° (compare Higginbotham and Lapworth, *loc. cit.*, who found the upper limit of m. p. range was 75° or 128°, according as acetic acid or sodium bicarbonate was used to minimise alkalinity in the sodium amalgam reduction). The description of the separation of the two isomeric ββ′-dimethyladipic acids as well as that of some of their derivatives is reserved for a future paper.

The use of ethyl dimethylbutanetetracarboxylate (III) in synthetical work depends on the fact that it readily yields a *disodium* compound (IV) on treatment with sodium ethoxide or preferably

(IV.)



$$\begin{array}{l}\text{CHMe}\cdot\text{CNa(CO}_2\text{Et)}_2\\ \text{CHMe}\cdot\text{CNa(CO}_2\text{Et)}_2\end{array}$$

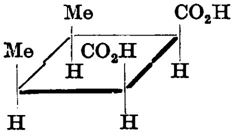


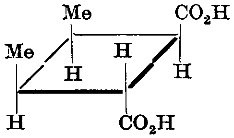
$$\begin{array}{l}\text{CHMe—C(CO}_2\text{Et)}_2\\ \text{CHMe—C(CO}_2\text{Et)}_2\end{array}$$

(V.)

sodium methoxide, the latter being very much more reactive than the former. By bromine, (IV) is quantitatively converted into *ethyl* 2 : 3-*dimethyl*cyclo*butane*-1 : 1 : 4 : 4-*tetracarboxylate* (V). The latter on hydrolysis with alcoholic potash yields the corresponding tetracarboxylic acid, which, on heating to 180°, esterification, and subsequent hydrolysis with alcoholic potassium hydroxide, gives rise to a mixture of the two cyclo*butanedicarboxylic acids* (VI) and (VII), melting respectively at 87—88° and 200·5—201·5°. They may be separated by treatment with acetyl chloride (compare Auwers and Thorpe, *Ber.*, 1895, **28**, 623; Komppa, *Annalen*, 1909, **368**, 152; 1909, **370**, 209; Perkin and Scarborough, J., 1921, **119**, 1405); the *trans*-acid remains unaffected whilst the *cis*-acid is converted into the anhydride.

(VI.)





(VII.)

Further evidence in support of ring closure is provided by comparison of the physical properties of the esters (Table I).

TABLE I.

Substance.	B. p.	*d.*	*n.*	[R_L] obs.	[R_L] calc.
MeCH·CH(CO$_2$Et)$_2$ MeCH·CH(CO$_2$Et)$_2$	225—226°/16 mm.	1·0887	1·44873	92·16	91·93
MeCH–C(CO$_2$Et)$_2$ * MeCH–C(CO$_2$Et)$_2$	208—210°/16 mm.	1·1216	1·45573	90·16	89·73
MeCH·CH$_2$·CO$_2$Et MeCH·CH$_2$·CO$_2$Et	139—141°/15 mm.	0·98777	1·43447	60·74	60·92
MeCH–CH·CO$_2$Et MeCH–CH·CO$_2$Et	138—139°/14 mm.	1·00955	1·43888	59·43	58·72

* Slightly impure. See p. 1991.

No details as to temperature, etc., are included, as they are given in full in the experimental section. It is evident that whilst there is no great difference in the boiling points, there are marked differences in the densities and the refractivities, those of the cyclic being greater than those of the corresponding open-chain compounds. The exaltations of the molecular refractivity for the D line of the two *cyclo*butane compounds (0·43 and 0·71) are comparable with those previously observed by other workers for the *cyclo*butane ring (compare Oestling, J., 1912, **101**, 457, mean value 0·48; Eisenlohr, "Spektrochemie organische Verbindungen," 1912, mean value 0·46; Lebedev, *J. Russ. Phys. Chem. Soc.*, 1913, **45**, 1388, mean value 0·60; Zelinsky, *Ber.*, 1913, **46**, 1093; 1927, **60**, 711, mean value 0·45; Kon, J., 1922, **121**, 513, from *cyclo*hexane*spirocyclo*butanone, 0·77).

The analogous unsubstituted open-chain and *cyclo*butane compounds were prepared many years ago by Perkin (J., 1887, **51**, 1; 1894, **65**, 572). Whilst speculations as to the effect of groups are at present premature—it is hoped to discuss the question fully when a larger number of substituted derivatives have been studied—it may be added that the properties of the βγ-dimethyl homologues are very similar to those of the corresponding unsubstituted compounds, a result which would be expected from the modified strain theory of Thorpe and Ingold, since the normal tetrahedral angle of 115·3° has been altered only to 112·5° (compare Ingold, Sako, and Thorpe, J., 1922, **121**, 1177; Ingold, *ibid.*, p. 2676) by the substitution of CHMe for CH_2. It is a curious fact that the only *cyclo*butanedicarboxylic acid directly isolated by Perkin (*loc. cit.*) was the *cis*-acid, the *trans*-acid being prepared by heating the *cis*-acid with hydrochloric acid at 190°, whereas in the case of the corresponding *cyclo*pentanedicarboxylic acids the *trans*-acid was the only form directly isolated. In the present research, both forms were directly isolated.

The question of the existence of two anhydrides of a *cyclo*butane-1 : 2-dicarboxylic acid is of great interest. Baeyer (*Annalen*, 1890, **258**, 145) predicted from his strain theory that *trans*-anhydride formation should not take place in the *cyclo*propane and should occur in the *cyclo*pentane series, but he was doubtful whether it would be possible in the corresponding 1 : 2-*cyclo*butane-compounds. Perkin (J., 1894, **65**, 572), in testing this prediction experimentally for the unsubstituted *cyclo*butanedicarboxylic acids, found that the *trans*-acid was practically unaffected by heating with acetyl chloride, but on heating with acetic anhydride it was converted into the *cis*-anhydride. The author has found that *trans*-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid behaves similarly; on heating it with acetic anhydride for 2 hours, the *cis*-anhydride is produced. It appears that the strain in the *trans*-anhydride is so great that the compound is incapable of isolation under the experimental conditions employed (compare Windaus, Hückel, and Reverey, *Ber.*, 1923, **56**, 91, who have isolated the *trans*-anhydride of hexahydrohomophthalic acid and find that an equilibrium mixture of the *cis*- and *trans*-anhydrides is formed on heating it with acetic anhydride). The question whether the *cis*-anhydride is formed *via* the *cis*-acid or the *trans*-anhydride must still be regarded as an open one.

The ethyl dimethylbutanetetracarboxylate used in this research was obtained by the reduction of ethyl ethylidenemalonate (Goss, Ingold, and Thorpe, J., 1923, **123**, 3353) by moist aluminium amalgam; the yield averaged 45%, the remainder of the product consisting of unchanged malonic ester, which was readily separated by fractional distillation in a vacuum. This yield is surprising, since, under the conditions employed, reduction takes place quantitatively (mesityl oxide, benzylideneacetone) or not at all (ethyl ββ-dimethylacrylate). Two explanations are possible: (*a*) ethyl ethylidenemalonate decomposes under the influence of the moist aluminium amalgam, and (*b*) the ethylidenemalonate contains a considerable quantity of malonic ester which cannot be removed by fractionation in a vacuum. The latter explanation is probably the correct one and receives support from the analytical results as well as from a comparison of the molecular refractivities of Goss, Ingold, and Thorpe's ethyl ethylidenemalonate and that prepared directly from the acid, only the latter exhibiting the expected exaltation due to the presence of conjugated double bonds.

EXPERIMENTAL.

The yield of ethyl ethylidenemalonate, b. p. 113—135°/20 mm., prepared by Goss, Ingold, and Thorpe's method averaged 85 g. from 100 g. of malonic ester [Found: C, 54·5; H, 7·5. Calc. for $CH_3{\cdot}CH{:}C(CO_2Et)_2$: C, 58·1; H, 7·5%. Calc. for $CH_2(CO_2Et)_2$: C, 52·5; H, 7·5%]. On redistillation in a vacuum, a fraction was obtained having b. p. 111—112°/12 mm., $d_{4^\circ}^{17\cdot2^\circ}$ 1·05237, $n_D^{17\cdot2}$ 1·42567, $[R_L]_D$ 45·29.

Ethylidenemalonic acid was obtained by adding 50 g. of acetaldehyde to 75 g. of malonic acid in 100 g. of pyridine at —5°, followed by 2·5 c.c. of piperidine during 1 hour, the whole being vigorously stirred. The reaction mixture was kept at 0° overnight, the orange-coloured solid mass cooled to —5° and decomposed with a slight excess of ice-cold dilute sulphuric acid, and the pale yellow ethylidenemalonic acid, m. p. 82° (Komnenos, *Annalen*, 1883, **218**, 165, gives m. p. 84), *quickly* separated. The acid, on esterification with absolute ethyl alcohol and sulphuric acid, yielded ethyl ethylidenemalonate, which was obtained pure after two fractionations in a vacuum. It had b. p. 115—117°/15 mm., $d_{4^\circ}^{17\cdot4^\circ}$ 1·01938, $n_{\mathrm{D}}^{17\cdot4^\circ}$ 1·43007, $[R_L]_{\mathrm{D}}$ 47·17 (calc., 46·60) (compare Komnenos, *loc. cit.*; d^{15° 1·0435) (Found : C, 57·8; H, 7·6. Calc. for $C_9H_{14}O_4$: C, 58·1; H, 7·5%).

Reduction with Moist Aluminium Amalgam. Preparation of Ethyl βγ-Dimethylbutane-ααδδ-tetracarboxylate (III).—Ethyl ethylidenemalonate (b. p. 113—135°/20 mm.; 150 g.) was reduced by 200 g. of aluminium amalgam prepared by the author's method (this vol., p. 594). The product was worked up in the usual manner and fractionated in a vacuum. Ethyl malonate was recovered below 140°/16 mm.; the temperature then rose rapidly to 210° and *ethyl βγ-dimethylbutane-ααδδ-tetracarboxylate* distilled at 210—240°/16 mm. (yield, 68 g. or 45%). On refractionation, the pure ester was obtained; it had b. p. 225—226°/16 mm., $d_{4^\circ}^{17\cdot0^\circ}$ 1·0887, $n_{\mathrm{D}}^{17\cdot0^\circ}$ 1·44873, $[R_L]_{\mathrm{D}}$ 92·16 (calc., 91·93) (Found : C, 57·6; H, 8·0. $C_{18}H_{30}O_8$ requires C, 57·8; H, 8·0%). It is a viscid, colourless liquid having a faint odour and on exposure to the atmosphere it slowly becomes pale yellow. The *disodio*-compound (IV) is best prepared from the pure ester and anhydrous sodium methoxide (see below). After being washed with a mixture of pure dry ethyl alcohol and pure dry ether (1 : 3), it is obtained as a pale yellow solid (Found : Na, 11·0. $C_{18}H_{28}O_8Na_2$ requires Na, 11·0%). It decomposes on exposure to the atmosphere.

Hydrolysis of the ester (III). Solutions of the ester (30 g.) in ethyl alcohol (60 g.) and of potassium hydroxide (30 g.) in water (60 g.) were mixed, heated on the steam-bath for 6 hours, and evaporated to dryness. The residue was dissolved in a little water, the solution was extracted with ether to remove any unchanged ester if present and acidified with dilute sulphuric acid, the small quantity of resinous matter which separated was removed by filtration, and the pale yellowish-brown filtrate was saturated with ammonium sulphate and extracted seven times with ether. After *slow* evaporation of the ether, a yellow oil remained which immediately solidified to an almost colourless, crystalline solid (yield, 16 g.), m. p. 155—162° (decomp.). On addition of pure dry ether, the major portion dissolved and a crystalline solid, m. p. 177—179° (decomp.), remained. This was almost pure r-*βγ-dimethylbutane-ααδδ-tetracarboxylic acid* (Found: C, 45·6; H, 5·5; equiv., by titration, 66. $C_{10}H_{14}O_8$ requires C, 45·8; H, 5·3%; equiv., 65·5).

Separation of the Two βγ-Dimethylbutane-ααδδ-tetracarboxylic Acids.—The *r*-acid could be readily isolated from the mixture,

m. p. 155—162° (decomp.) (Found: C, 45·5; H, 5·5%; equiv., by titration, 66), by fractional crystallisation from concentrated hydrochloric acid, in which it was only moderately easily soluble. It was thus obtained in small, hard prisms, m. p. 185—185·5° (decomp.) (Found: C, 45·7; H, 5·4%; equiv., by titration, 66). Other solvents which may be used for the separation are acetone, benzene–alcohol, and ethyl acetate. The *meso*-acid, which is much more soluble than the *r*-acid, can be isolated from the mother-liquors and has m. p. 152—154° (decomp.).

Conversion into a Mixture of ββ′*-Dimethyladipic Acids.*—Ten g. of the mixture of the tetracarboxylic acids were gradually heated to 200°; the evolution of carbon dioxide then ceased. The whole solidified on cooling to a yellowish-brown mixture (6 g.), m. p. 105—120°, of the two stereoisomeric ββ′-dimethyladipic acids (compare Higginbotham and Lapworth, *loc. cit.*). On esterification with absolute ethyl alcohol and sulphuric acid, the mixed esters, *ethyl* ββ′*-dimethyladipate*, were obtained. After two fractionations in a vacuum, the liquid had b. p. 139—141°/15 mm., $d_{4°}^{19.5°}$ 0·98777, $n_D^{19.5°}$ 1·43447, $[R_L]_D$ 60·74 (calc., 60·92) (Found: C, 62·4; H, 9·7. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·6%). It was a mobile liquid with a pleasant ethereal odour. The mixture of esters on hydrolysis with alcoholic potassium hydroxide yielded chiefly a crystalline solid, m. p. 113—117° (Found: equiv., by titration, 89. $C_8H_{14}O_4$ requires equiv., 87).

Synthesis of the cyclo*Butane Ring. Formation of Ethyl* 2 : 3-*Dimethyl*cyclo*butane*-1 : 1 : 4 : 4-*tetracarboxylate* (V).—To 5·3 g. of "molecular" sodium under 200 c.c. of pure dry ether, 15·0 c.c. of pure dry ethyl alcohol were added. When all the sodium had reacted (gentle warming was necessary), a solution of the pure ester (III) (40 g.) in pure dry ether (160 c.c.) was carefully added; the disodio-compound (IV) gradually separated. The mixture was stirred mechanically and dry bromine (5·7 g.) added during 1 hour. The stirring was continued for a further hour, and water then added to dissolve the precipitated sodium bromide. The solution was washed with dilute aqueous sodium bicarbonate and with water and dried with anhydrous sodium sulphate. On evaporation of the ether, a viscid reddish-brown oil (39 g.) was obtained: this was used in all the experiments described below. On fractionation in a vacuum, some carbonisation occurred (compare the corresponding open-chain ester, which distilled unchanged), but most of the liquid distilled as a colourless oil, b. p. 208—210°/16 mm.; this, however, darkened somewhat on exposure to the atmosphere. It had $d_{4°}^{16.7°}$ 1·1216, $n_D^{16.7°}$ 1·45573, $[R_L]_D$ 90·16 (calc., 89·73). Owing probably to the presence of a trace of bromine in the ester, the analytical results were unsatisfactory (Found : C, 56·4 ; H, 7·7. $C_{18}H_{28}O_8$ requires C, 58·1 ; H, 7·5%) (compare Perkin and Robinson, J., 1921, **119**, 1397, who obtained unsatisfactory analytical results for ethyl *cyclo*pentane-1 : 2 : 2 : 3-tetracarboxylate).

It was subsequently found that a much more convenient method of preparation was to use anhydrous sodium methoxide, prepared from " molecular " sodium and pure dry methyl alcohol ; the separation of the disodio-compound was then practically complete after 1 hour. The procedure was as described above, the quantities being 6·5 g. of sodium, 11·3 c.c. of methyl alcohol, 250 c.c. of ether ; 50 g. of ester in 200 c.c. of ether ; and 13·5 c.c. of bromine. The yield of crude *cyclo*butane ester was 49 g. It is not advisable to work with larger quantities, as the yield is thereby materially diminished.

Hydrolysis of the ester (V). Solutions of the ester (50 g.) in alcohol (100 g.) and of potassium hydroxide (50 g.) in water (100 g.) were used. The procedure was that described for the hydrolysis of the ester (III) (p. 1990). The dried ethereal extracts yielded 23 g. of a thick, pale yellow oil—this was employed in all the experiments described below. It slowly crystallised in a vacuum desiccator over concentrated sulphuric acid. The acid separated from ether–light petroleum (b. p. 40—60°) in star-shaped clusters or from benzene–light petroleum in needles, m. p. 138—139° (slight softening at 80°). Correct analytical results for the tetrabasic acid could not be obtained (compare Simonsen, J., 1908, **93**, 1785, who could not obtain correct analytical results for δ-methoxybutane-ααγγ-tetracarboxylic acid).

Preparation of a Mixture of the cis- *and* trans-*Forms of* 2 : 3-*Dimethyl*cyclo*butane*-1 : 4-*dicarboxylic Acid*, (VI) *and* (VII).—The tetracarboxylic acid (V) (20 g.) was heated gradually to 180° ; the evolution of carbon dioxide then ceased. The gummy residue (compare the ββ′-dimethyladipic acids, which gave a crystalline solid) was esterified with absolute ethyl alcohol and sulphuric acid, and after two fractionations in a vacuum the mixed esters (9·5 g.), *ethyl* 2 : 3-*dimethyl*cyclo*butane*-1 : 4-*dicarboxylate*, were obtained as a fairly mobile liquid with a pleasant ethereal odour and having b. p. 138—139°/14 mm., $d_{4°}^{16·8°}$ 1·00955, $n_D^{16·8°}$ 1·43888, $[R_L]_D$ 59·43 (calc., 58·72) (Found : C, 63·5 ; H, 8·6. $C_{12}H_{20}O_4$ requires C, 63·2 ; H, 8·8%). The ester (10 g. in 20 g. of ethyl alcohol) was refluxed with potassium hydroxide (10 g. in 20 g. of water) on the steam-bath for 5 hours. The solution was then evaporated to dryness, the almost colourless residue dissolved in a little water, and the solution extracted with ether, carefully acidified with dilute sulphuric acid, and extracted seven times with ether. The ethereal solution, after being dried with anhydrous sodium sulphate and evaporated, yielded a colourless oil which immediately crystallised on agitation. On treatment with small quantities of pure dry ether, all the *cis*- and some *trans*-acid dissolved, leaving pure trans-2 : 3-*dimethyl*cyclo*butane*-1 : 4-*dicarboxylic acid*, m. p. 200—201·5°, as a crystalline solid (Found : C, 55·7; H, 7·1; equiv., by titration, 85. $C_8H_{12}O_4$ requires C, 55·9; H, 7·0%; equiv., 86). On evaporation of the ether, a mixture of the *cis*- and *trans*-acids was obtained.

Separation of the cis- *and* trans-*Forms of* 2 : 3-*Dimethyl*cyclo*butane*-1 : 4-*dicarboxylic Acid.*—The mixed acids (2 g.) were warmed to 50° with 4 g. of pure acetyl chloride; a vigorous reaction ensued and hydrogen chloride was evolved. After 1 hour, the liquid mass, containing some suspended crystalline solid (*trans*-acid), was placed in a vacuum desiccator over caustic potash; the excess acetyl chloride was almost wholly removed after 2 days. The semi-solid mass was treated with pure dry ether; some *trans*-acid remained undissolved which, after being washed with small quantities of ether, melted at 200·5—201·5°; the m. p. was unaffected by recrystallisation from acetone–petroleum (b. p. 40—60°). The ethereal solution was washed with dilute aqueous sodium carbonate then with water, and dried with anhydrous sodium sulphate, and the ethereal solution was allowed to evaporate spontaneously. The cis-*anhydride* of 2 : 3-*dimethyl*cyclo*butane*-1 : 4-*dicarboxylic acid* separated in needles, m. p. 50—51° (Found : C, 62·0; H, 6·5. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%). On acidifying the sodium carbonate washings and repeatedly extracting them with ether, more *trans*-acid was obtained. An aqueous solution of the *cis*-anhydride, on being allowed to concentrate over sulphuric acid, yielded the crystalline cis-*acid*, m. p. 87—88° (Found : C, 55·8; H, 7·0; equiv., by titration, 87. $C_8H_{12}O_4$ requires C, 55·9; H, 7·0%; equiv., 86).

By distilling the mixed acids in a vacuum, the *cis*-acid together with some anhydride, which passes over at a slightly lower temperature, is obtained; this provides the simplest method for the preparation of the pure *cis*-acid or of the *cis*-anhydride.

Attempt to Prepare the Anhydride of trans-2 : 3-*Dimethyl*cyclo*butane*-1 : 4-*dicarboxylic Acid.*—The pure *trans*-acid (1 g.) was gently boiled with an excess of pure redistilled acetic anhydride for 2 hours, and the excess of acetic anhydride removed over caustic potash in a vacuum desiccator. An ethereal solution of the oily residue was washed with dilute aqueous sodium carbonate and with water, dried with anhydrous sodium sulphate, and allowed to evaporate. The *cis*-anhydride, m. p. 50—51°, either alone or when mixed with a specimen prepared from the *cis*-acid, separated in needles.

In conclusion, I wish to thank Professor J. F. Thorpe, F.R.S., for his kind interest and advice. Some of the expenses of the research were met by a grant from the Chemical Society Research Fund.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON.

[*Received, May* 14*th*, 1927.]