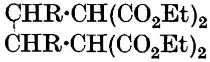
CCLXXVI.—*Syntheses of Cyclic Compounds. Part VII. The Stereoisomeric βγ-Diphenyladipic Acids.*

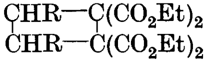
By Mariam P. Oommen and Arthur Israel Vogel.

It has been shown (Part I, J., 1927, 1985) that ethyl βγ-dimethylbutane-ααδδ-tetracarboxylate (I; R = Me), a mixture of two

(I.)



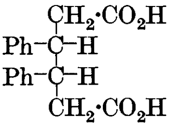
$$\begin{array}{l} CHR\cdot CH(CO_2Et)_2 \\ | \\ CHR\cdot CH(CO_2Et)_2 \end{array}$$



(II.)

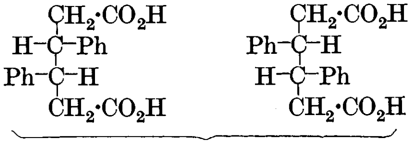
stereoisomerides, gives an almost quantitative yield of the *cyclo*butane compound (II; R = Me) when treated with sodium methoxide and bromine. The corresponding phenyl compound (I; R = Ph), which was separated into a solid form, m. p. 88°, and a liquid form, behaved differently, for whereas only a *cyclo*butane compound

(II; R = Ph) could be isolated from the latter, the former gave a quantitative yield of ethyl αδ-dibromo-βγ-diphenylbutanetetracarboxylate, no trace of cyclic compound being isolated (Part II, J., 1928, 1013). Similar results were later obtained independently by Bachér for the methyl esters (I; R = Ph) (*J. pr. Chem.*, 1928, **120**, 131). This remarkable difference in behaviour towards cyclisation is attributed to the inhibition of free rotation by the bulky phenyl groups, and we have sought to obtain further experimental support for this view by the attempted resolution of the two closely related βγ-diphenyladipic acids, which we can now prepare readily.



$$\begin{array}{c} CH_2\cdot CO_2H \\ Ph-C-H \\ Ph-C-H \\ CH_2\cdot CO_2H \end{array}$$

(III.)



$$\underbrace{\begin{array}{c} CH_2\cdot CO_2H \\ H-C-Ph \\ Ph-C-H \\ CH_2\cdot CO_2H \end{array} \qquad \begin{array}{c} CH_2\cdot CO_2H \\ Ph-C-H \\ H-C-Ph \\ CH_2\cdot CO_2H \end{array}}$$

(IV.)

According to ordinary stereochemical principles, one of these acids (III) is of the *meso*-type, and the other (IV) is resolvable into optically active components. If, in addition, free rotation is appreciably inhibited by the bulky phenyl groups it would be expected that the *meso*-form (III) would be capable of optical resolution but the rotation would be less than that of the ordinary racemic compound.

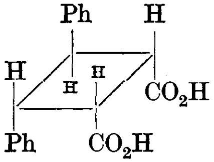
Although Wislicenus (*J. pr. Chem.*, 1896, **54**, 59) stated that "cinnamic ester is unaffected by treatment with moist aluminium amalgam," yet Henle (*Annalen*, 1906, **384**, 16) isolated two acids, m. p. *ca.* 270° and 169—170°, respectively, by the separation and hydrolysis of the reduction products of methyl cinnamate with aluminium amalgam. By reducing this ester with moist aluminium amalgam under the conditions previously described (J., 1927, 594), we have prepared two βγ-diphenyladipic acids of m. p.'s (sharp) 270—271° and 185—186°, respectively. The latter has been resolved with brucine in aqueous solution, the normal brucine salt of the *d*-acid separating out first. From this salt d-βγ-*diphenyladipic acid*, m. p. 200—201°, $[\alpha]_D^{20^\circ} + 14{\cdot}4^\circ$ in absolute alcohol, was obtained by decomposition with dilute hydrochloric acid. The mother-liquors yielded l-βγ-*diphenyladipic acid*, m. p. 200—201°, $[\alpha]_D^{20^\circ}$ $-14{\cdot}3^\circ$ in absolute alcohol.

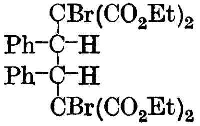
All attempts to resolve the other acid, m. p. 270—271°, by fractional crystallisation of its strychnine, brucine, or quinine salts were unsuccessful. The configuration (III) is therefore assigned to this acid, and (IV) to the resolvable acid. Work is in progress on the optical resolution of various βγ-substituted phenyladipic acids, the rotation of which would be expected to be greater.

It is very probable from the work of Stoermer, Stobbe, and others that ξ-truxinic acid, synthesised from the liquid form of ethyl βγ-diphenylbutane-ααδδ-tetracarboxylate (J., 1928, 1013), has the configuration (V), with the phenyl groups situated on opposite sides of the ring, which would indicate, if it be assumed that there is no change in configuration during ring formation, that the solid ester is the *meso*-form. This is supported by the production of the acid of m. p. 270—271° by hydrolysis of the solid ester with alcoholic potassium hydroxide and subsequent heating at 200°. The racemic configuration previously assigned to the ester of m. p. 88°, and to the dibromo-ester (formula VI, J., 1928, 1014), requires correction, the latter being more probably represented by VI (below).

The two lower homologues, αβ-diphenyl-succinic (Wren and Still, J., 1915, **107**, 444) and -glutaric (Avery and Maclay, *J. Amer. Chem. Soc.*, 1929, **51**, 2837) acids, have been previously resolved, and a summary of their properties is given in the table below. Both forms in the glutaric series are resolvable owing to the unsymmetrical disposition of the two asymmetric carbon atoms. The marked decrease in the optical rotation with increasing length of the polymethylene chain is noteworthy.

(V.)





$$\begin{array}{l} \mathrm{CBr(CO_2Et)_2} \\ \mathrm{Ph-C-H} \\ \mathrm{Ph-C-H} \\ \mathrm{CBr(CO_2Et)_2} \end{array}$$

(VI.)

		M. p. (active).		Rotation.		
Acid.	M. p.	*d.*	*l.*	*d.*	*l.*	Solvent.
αβ-Diphenyl-succinic	229—230°	Not resolved.				
	183	179—180°	176—177°	+369·7°	−368·9°	$C_2H_5{\cdot}OH$
αβ-Diphenyl-glutaric	226—228	224—226	*	+ 58·7	− 58·0	$CH_3{\cdot}CO{\cdot}CH_3$
	208—210	202	202	+140·6	−140·0	,,
βγ-Diphenyl-adipic	270—271	Not resolved.				
	185—186	200—201	200—201	+ 14·4	− 14·3	$C_2H_5{\cdot}OH$

* The m. p. of this *l*-form is given by Avery and Maclay (*loc. cit.*) as being "slightly lower" than that of the *d*-form.

EXPERIMENTAL.

Henle's method of reduction has been replaced by the following, which gives better yields of the bimolecular compounds.

Reduction of Methyl Cinnamate with Moist Aluminium Amalgam in Ether.—100 G. of recrystallised methyl cinnamate were reduced by 150—200 g. of moist aluminium amalgam (Vogel, J., 1927, 594) suspended in 2—2·5 litres of ether and contained in a 5-litre Pyrex flask. There was a period of induction of about 1 hour, and the reduction was considered complete after 6 hours. The ethereal solution was dried over anhydrous potassium carbonate, and the ether slowly distilled off. The residue solidified on cooling to 0° to a mass of crystals which were filtered off and washed with a little ether; yield, 7—8 grams, m. p. 170°, consisting mainly of methyl *meso*-βγ-diphenyladipate. The filtrate on distillation gave 30—35 g. of a colourless liquid, b. p. 115—130°/17 mm. (methyl β-phenylpropionate), and at 230°/17 mm. a very small quantity of liquid passed over. The pale yellow residue, which became very viscous but did not solidify on cooling, was dissolved in warm dry ether. The solution on cooling deposited 1—1·5 g. of the ester, m. p. 170°. The ether was evaporated from the filtrate, the residue dissolved in the minimum quantity of warm methyl alcohol, and then cooled to 0°, whereupon it solidified. The crystals were filtered off with suction and washed with small quantities of ice-cold methyl alcohol; yield 15—16 g., m. p. 70—71°, consisting chiefly of methyl *r*-βγ-diphenyladipate. The filtrate on evaporation yielded 15—20 g. of a viscous liquid, which could not be induced to crystallise.

13—14 G. of crude methyl *meso*-βγ-diphenyladipate were obtained by dissolving the aluminium hydroxide sludge in hydrochloric acid (1 : 1) and filtering the solution through a filter cloth.

meso-βγ-*Diphenyladipic acid.* The crude ester, m. p. 170°, on recrystallisation from rectified spirit or from light petroleum (b. p. 100—120°), had m. p. 175°. Solutions of the ester (10 g.) in rectified spirit (20 g.) and of potassium hydroxide (12 g.) in dilute alcohol (25 c.c. of water and 25 c.c. of rectified spirit) were mixed and refluxed on the steam-bath for 4—5 hours. The resultant acid (nearly quantitative yield) separated from 96% alcohol in needles, which, after being dried at 100—105° to remove one molecule of alcohol of crystallisation, had m. p. 270—271°.

meso-βγ-*Diphenyladipyl chloride.* The acid (5 g.) was refluxed with 40 g. of redistilled thionyl chloride for 1 hour, the excess of thionyl chloride removed under reduced pressure, and the residue left in a vacuum desiccator over potassium hydroxide. The crude *chloride* (quantitative yield) melted at 187°, after recrystallisation from benzene (Found: Cl, 21·2. $C_{18}H_{16}O_2Cl_2$ requires Cl, 21·2%). The original acid, m. p. 270—271°, was produced on boiling with aqueous sodium carbonate, followed by acidification.

r-βγ-*Diphenyladipic acid.* The crude ester, m. p. 70—71°, after two or three recrystallisations from small quantities of methyl alcohol or from light petroleum (b. p. 40—60°), had m. p. 73—74°. Hydrolysis with alcoholic potassium hydroxide, exactly as described for the *meso*-acid, afforded the crude *r*-acid, m. p. 180—181°, in almost quantitative yield. It crystallised from hot water in needles, m. p. 185—186°.

Examination of the viscid residue. This was hydrolysed with alcoholic potassium hydroxide, and 15 g. of the resultant acid product, a viscid dark brown oil, were boiled with water; the decanted aqueous extract deposited 4—5 g. of a crystalline acid, m. p. 165—170°. The residue was repeatedly extracted with boiling water, and finally crystallised from rectified spirit, whereby 1 g. of the *meso*-acid, m. p. 270—271°, was obtained. Repeated recrystallisation of the other from hot water did not raise the m. p. above 170°; further repeated extraction with boiling benzene gave an acid of m. p. 182—183°, and the benzene extracts yielded a small quantity of β-phenylpropionic acid, m. p. 49°.

The total yields from 100 g. of methyl cinnamate are as follows, the figures in parentheses being those obtained by Henle's method (*loc. cit.*): methyl β-phenylpropionate, 30—35 g. (55 g.); methyl *meso*-βγ-diphenyladipate, 22—23 g. (8—9 g.); methyl *r*-βγ-diphenyladipate, 15—16 g. (4—5 g.).

Reduction of Ethyl Cinnamate with Moist Aluminium Amalgam in Ether.—This was carried out exactly as detailed for the methyl ester. The less fusible ester, *ethyl* meso-*βγ-diphenyladipate*, separated first and, after crystallisation from ethyl alcohol, had m. p. 116° (Found: C, 74·0; H, 7·7. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·4%). The other products of the reduction were not satisfactorily separated.

Action of Acetic Anhydride on the Acid of m. p. 270—271°.—The acid was heated under reflux with a large excess of acetic anhydride for 5 hours, and the excess of anhydride removed in a vacuum desiccator over potassium hydroxide. The solid residue crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 109—110°, solidifying at a slightly higher temperature and remelting at 235—245°. This substance contained 1 mol. of acetic anhydride (Found: C, 69·1; H, 5·9. Calc. for $C_{18}H_{16}O_3,C_4H_6O_3$: C, 69·1; H, 5·8%), which could not be completely removed by 2 hours' heating at 150°. The residue, after heating, melted at 235—245° (Found: C, 73·5; H, 5·7. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·8%), and was an amorphous powder insoluble in benzene, xylene, chloroform, or carbon tetrachloride. This is also the main product obtained by heating the acid with 2—3 times the calculated quantity of acetic anhydride. The compound of m. p. 109—110° yields the original acid on boiling with water: it is insoluble in cold aqueous sodium carbonate but dissolves on boiling. Henle (*loc. cit.*) has obtained a similar compound, m. p. 100—105°, solidifying and remelting at 235—240°, by the use of acetyl chloride.

Action of Acetic Anhydride on the Acid of m. p. 185—186°.—The acid was heated under reflux with 4—5 times the calculated quantity of acetic anhydride for 5 hours, and the excess of anhydride removed as above. The residue was a thick yellowish-brown oil which did not crystallise even after several months. It was insoluble in cold aqueous sodium carbonate but dissolved completely on boiling, regenerating the original acid, m. p. 185—186°. Treatment of the oil with aniline in dry benzene solution gave a sticky product which was not further investigated.

Resolution of βγ-Diphenyladipic Acid, m. p. 185—186°.—25 G. of the acid and 66·1 g. of brucine were finely powdered and stirred with 5·5 litres of boiling water until nearly complete solution had taken place. The filtered solution on cooling deposited crystalline plates of the brucine salt of the *d*-acid, the crystallisation being considerably accelerated by seeding with a little of the brucine *d*-acid salt from a previous resolution. After standing over-night, the crop of crystals was filtered off, and dried on a porous plate; yield, 48·5 g. The crude salt was recrystallised several times from the minimum quantity of boiling water. The course of the resolution was followed by determining the specific rotation in absolute alcohol in a 2-dcm. tube of the acid isolated from successive filtrates. The results are tabulated below.

Acid from	M. p.	Wt. in 25 c.c. of absolute alcohol.	Rotation observed.	$[\alpha_D]$.
1st filtrate	196°	Sparingly soluble.	Not determined.	—
2nd ,, ...	199—200	0·7490 g.	0·811°	+13·54°
3rd ,, ...	200—201	0·7100 g.	0·820	+14·43
4th ,, ...	200—201	0·6260 g.	0·717	+14·31
5th ,, ...	200—201	0·7720 g.	0·886	+14·34

The crop from which the last filtrate was obtained was decomposed with *N*-hydrochloric acid, extracted with ether, the ethereal solution dried with anhydrous sodium sulphate, and the residue, after evaporation of the ether, recrystallised from dilute alcohol containing a few drops of dilute acetic acid. Pure d-βγ-*diphenyladipic acid*, m. p. 200—201°, was thus obtained (Found : C, 72·5; H, 6·1; equiv., by titration, 147. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·4%; equiv., 149); $\alpha_D^{20^\circ}$ 0·888° ($l = 2$; $c = 3·09$ in absolute alcohol), whence $[\alpha]_D^{20^\circ}$ + 14·36°, unchanged after further recrystallisation.

The main filtrate from the first crop of brucine salt on standing for one week deposited long radiating clusters of needles; these were separated, the filtrate was concentrated under reduced pressure to half-bulk, and the crop of needles which separated after standing over-night was combined with the first crop; yield, after drying on porous porcelain, 29·0 g. This was recrystallised first from 2 l. and then from 1·5 l. of boiling water. The crystals of the *l*-acid brucine salt were needles, quite distinct from the plates of the *d*-acid salt. The acid isolated from the second recrystallisation had $[\alpha]_D$ — 13·5° in absolute alcohol. It was recrystallised six times from dilute alcohol containing a few drops of dilute acetic acid, and the rotation was then practically constant. l-βγ-*Diphenyladipic acid* had m. p. 200—201° (Found: C, 72·6; H, 6·0%; equiv., by titration, 147); $\alpha_D^{20^\circ}$ 1·035° (l = 2; *c* = 3·62 in absolute alcohol), whence $[\alpha]_D^{20^\circ}$ —14·30°.

The solubilities in various solvents of both the *d*- and the *l*-acid are greater than those of the *dl*-acid.

Racemisation of the Active Acids.—Equal quantities of *d*- and *l*-βγ-diphenyladipic acids were mixed and recrystallised from water. The resultant acid melted at 185—186° and was identical with the original *dl*-acid.

Attempts to resolve the Acid of m. p. 270—271°.—Fractional crystallisation of the normal salts of the acid with brucine in aqueous solution, and with strychnine and quinine in alcoholic solution, was carried out. In every case, the acid isolated from a small quantity of the salt was optically inactive and exhibited no change in m. p.

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