74. *Experiments on the Synthesis of the Pyrethrins. Part I. Synthesis of Chrysanthemum Monocarboxylic Acid.*

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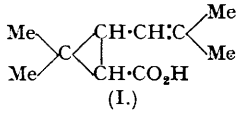
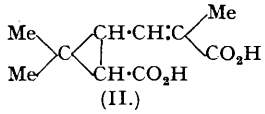
Addition of ethyl diazoacetate to βε-dimethyl-$\Delta^{\beta\delta}$-hexadiene gave the ethyl esters of *dl-cis-* and *dl-trans*-2 : 2-dimethyl-3-*iso*butenyl*cyclo*propane-1-carboxylic acids. Resolution of the crystalline dl-trans-*acid* by means of the *quinine* salt gave the *l-trans*-acid ($[\alpha]_D$ − 14·0°) in a state of optical purity. This acid is the optical enantiomorph of chrysanthemum monocarboxylic acid ($[\alpha]_D$ + 14·2°), the acidic component of pyrethrin I, which is therefore *d-trans*-2 : 2-dimethyl-3-*iso*butenyl*cyclo*propane-1-carboxylic acid. The *quinine* salt of the *d-trans*-acid could not be obtained pure. However, by fractional crystallisation of the *p*-phenylphenacyl ester of the recovered acid ($[\alpha]_D$ + 8·0°), the p-*phenylphenacyl* ester of the *d-trans*-acid was obtained optically pure and identical with that prepared from the natural acid.

During 1910—1916 Staudinger and Ruzicka elucidated the main structural features of pyrethrins I and II, the active principles of Dalmatian pyrethrum flowers, *Chrysanthemum cinerariifolium*. These were shown to be esters of the keto-alcohol, pyrethrolone, with chrysanthemum mono- and di-carboxylic acids respectively. Chrysanthemum monocarboxylic acid, separated by reason of its volatility in steam, was an optically active liquid acid, $C_{10}H_{16}O_2$. On ozonisation the acid gave *l-trans*-caronic acid and acetone, establishing its structure as (I). Likewise the dicarboxylic acid, an optically active crystalline acid, $C_{10}H_{14}O_4$, gave on ozonisation *l-trans*-caronic acid and pyruvic acid, establishing its structure as (II).


(I.)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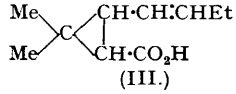
(III.)

In the interval preceding the publication of Staudinger and Ruzicka's work (*Helv. Chim. Acta*, 1924, **7**, 177, 201) Yamamoto (*J. Tokyo Chem. Soc.*, 1919, **40**, 126; *J. Chem. Soc. Japan*, 1923, **44**, 311, 1070) independently isolated from Japanese pyrethrum flowers, *C. cinerariifolium*, an optically inactive liquid acid, pyrethronic acid, $C_{10}H_{16}O_2$. On ozonisation the acid gave *dl-trans*-caronic acid and propaldehyde, establishing its structure as (III). The difference in properties and structure of pyrethronic and chrysanthemum monocarboxylic acids could be explained if Japanese and Dalmatian pyrethrum contained different active principles This has, however, been disproved by Gnadinger and Corl (*J. Amer. Chem. Soc.*, 1929, **51**, 3054), who isolated pyrethrins I and II from Japanese pyrethrum.

In view of the uncertainty of the identity of chrysanthemum monocarboxylic acid and pyrethronic acid, the differing structures put forward for each, and the fact that these structures depend solely on degradative evidence, an attempt has been made to clarify the problem by synthetic methods. In view of the internal self-consistency of Staudinger and Ruzicka's structures for the mono- and the di-carboxylic acids attention has been directed in the first place to the synthesis and resolution of chrysanthemum monocarboxylic acid.

Staudinger, Muntwyler, Ruzicka, and Seibt (*Helv. Chim. Acta*, 1924, **7**, 390) attempted to synthesise chrysanthemum monocarboxylic acid by the addition of ethyl diazoacetate to βε-dimethyl-$\Delta^{\beta\delta}$-hexadiene. This hexadiene was prepared by distilling βε-dichloro-βε-dimethylhexane with soda–lime, but by modern standards the hydrocarbon was very impure. From the products of addition, followed by hydrolysis, *dl-cis*-2 : 2-dimethyl-3-*iso*butenyl*cyclo*propane-1-carboxylic acid was isolated in crystalline form in 1% yield. The *dl-trans*-acid was not isolated, but was shown to be present in the oily mother-liquor from the *dl-cis*-acid,

since ozonisation gave *dl-trans*-caronic acid. No comparison was therefore possible between the natural optically active acid and the synthetic product.

Despite the lack of success of Staudinger and his collaborators it was felt that this method could be improved to become a practical route to the *dl-cis*- and *dl-trans*-acids. Through the work of Henne and his students (Henne, Chanan, and Turk, *J. Amer. Chem. Soc.*, 1941, **63**, 3474; Henne and Turk, *ibid.*, 1942, **64**, 826; Henne and Chanan, *ibid.*, 1944, **66**, 395) βε-dimethyl-$\Delta^{\beta\delta}$-hexadiene has become available in good yield and high purity by a two-step synthesis from β-methylallyl chloride. Addition of ethyl diazoacetate to the hydrocarbon at 100—125° caused immediate and vigorous reaction with evolution of nitrogen, the heat of reaction being dissipated by refluxing of excess of the hydrocarbon used as a diluent. From the product the mixed ethyl esters of *dl-cis*- and *dl-trans*-2 : 2-dimethyl-3-*iso*butenyl*cyclo*propane-1-carboxylic acids were obtained in 64% yield. This procedure has the advantage over the sealed tube method of Staudinger and his collaborators in that the yield and purity of the product were greatly improved and the preparation could be carried out with rapidity on a much larger scale. Saponification of the mixed esters gave a solid mixture of the *dl-cis*- and *dl-trans*-acids. The *dl-cis*-acid had the higher melting point (116°) and was the less soluble. It was separated from the *dl-trans*-acid by low-temperature crystallisation from ethyl acetate. The dl-trans-*acid* recovered by distillation was crystallised with difficulty from ethyl acetate owing to its high solubility and had m. p. 54°. Each acid was characterised by the preparation of derivatives, and the configurations confirmed by ozonolysis. Ozonisation of the *dl-cis*-acid gave *dl-cis*-caronic acid. Ozonisation of the *dl-trans*-acid likewise gave *dl-trans*-caronic acid; the *methyl* ester gave *monomethyl* dl-trans-*caronate*, and the *ethyl* ester gave *monoethyl* dl-trans-*caronate*.

Quinine was selected for the resolution and by fractional crystallisation from aqueous alcohol, the *quinine* salt of the *l-trans*-acid ($[\alpha]_D$ — 115·3°) was obtained pure. Decomposition with hydrochloric acid gave the *l-trans*-acid in a state of optical purity ($[\alpha]_D$ — 14·0°). It is therefore the enantiomorph of natural chrysanthemum monocarboxylic acid ($[\alpha]_D$ + 14·2°). Further proof of this was obtained by comparison of the melting points and specific rotations of the *amide*, *anilide*, and p-*phenylphenacyl* ester. The *l-trans*-acid, first obtained as a liquid, was ultimately crystallised. Although the natural acid has previously been obtained only as a liquid, on cooling and seeding with the *l-trans*-acid, the natural acid readily crystallised, m. p. 17—21°. Further crystallisation of the more soluble fractions from the salt of the *l-trans*-acid failed to give the *quinine* salt of the *d-trans*-acid in a state of purity; although a pure sample was prepared from the natural acid for comparison ($[\alpha]_D$ — 109·3°). Acid recovered from the salt of lowest rotation had ($[\alpha]_D$ + 8·0°). This was converted into the *p*-phenylphenacyl ester and fractionally crystallised from light petroleum. The less soluble fraction was the *dl*-ester, m. p. 115°; from the more soluble fraction the *d*-ester, m. p. 67°, was obtained in a state of optical purity and identical with the *p*-phenylphenacyl ester prepared from the natural acid.

Experimental.

All rotations were observed in absolute alcohol at room temperature. M. p.'s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

βε-Dimethyl-$\Delta^{\alpha\epsilon}$-hexadiene (cf. Henne, Chanan, and Turk, *J. Amer. Chem. Soc.*, 1941, **63**, 3474).—In a 5-l. three-necked flask fitted with two double-surface condensers, a 1-l. dropping funnel, and a mercury-sealed Hershberg wire stirrer, fine magnesium turnings (48 g.; 2 atoms) were covered with dry ether (500 c.c.), and bromine (1 c.c.) added. β-Methylallyl chloride (360 g.; 4 mols.) in dry ether (750 c.c.) was then run in during 1 hour, reaction usually starting immediately, at such a rate that the refluxing ether was under control. Stirring finally became difficult owing to the separation of magnesium chloride. In one run in which the separation of the magnesium chloride was delayed, the yield of product was 20% greater than usual, but it was not found possible to control the separation of halide. After standing overnight, the reaction mass was decomposed with water (750 c.c.) and sufficient acetic acid (about 100 c.c.) to render the solution acid. The ethereal layer was separated, washed with water and sodium carbonate solution, and dried over calcium chloride. The ether was removed through a Dufton column, and the residue fractionated to give a cut, b. p. 107—116° (yield, 61—86% of the theoretical). This crude βε-dimethyl-$\Delta^{\alpha\epsilon}$-hexadiene, containing traces of halogen, was distilled over sodium; b. p. 112·0—113·5, the main fraction having b. p. 113·5° (Henne, Chanan, and Turk, *loc. cit.*, record b. p. 114·3°).

βε-Dimethyl-$\Delta^{\beta\delta}$-hexadiene (cf. Henne and Chanan, *ibid.*, 1944, **66**, 395).—6—8 Mesh activated alumina (500 g., Peter Spence and Sons) was shaken with chromic acid (50 g.) in water (250 c.c.) until absorption was complete. After the impregnated alumina had been dried at 100°, a portion was packed into a combustion tube to give a 50 × 2 cm. filling. The air was displaced with hydrogen, and reduction carried out at 425° until the catalyst had become uniformly green. For isomerisation to the conjugated diene βε-dimethyl-$\Delta^{\alpha\epsilon}$-hexadiene (515 g.) was added during 12 hours from a Hershberg funnel while the catalyst was maintained at 250—275°. The distillate, after drying over calcium chloride, was distilled over sodium through the Dufton column and a cut, b. p. 130—135°, taken. On keeping at 0° the conjugated diene crystallised in large prisms, from which the liquid impurities were decanted. βε-Dimethyl-$\Delta^{\beta\delta}$-hexadiene had b. p. 134·0° and m. p. 13° (381 g.; 75%) (Henne and Turk, *ibid.*, 1942, **64**, 826, give b. p. 134·5° and m. p. 13·94°).

Addition of Ethyl Diazoacetate to βε-Dimethyl-$\Delta^{\beta\delta}$-hexadiene (cf. Staudinger, Muntwyler, Ruzicka, and Seibt, *Helv. Chim. Acta*, 1924, **7**, 390).—βε-Dimethyl-$\Delta^{\beta\delta}$-hexadiene (88 g.; 0·80 mol.) and copper bronze (2 g.) were placed in a 500 c.c. three-necked flask, fitted with a reflux condenser, dropping funnel, and thermometer with the bulb dipping into the liquid. About 1 c.c. of ethyl diazoacetate was added, and the mixture heated until reaction commenced as shown by a steady evolution of nitrogen (temperature 100—125°). The remainder of the ethyl diazoacetate (46 g. in all; 0·40 mol.) was then added at such a rate as to maintain steady refluxing without external heating (15—20 minutes, temperature 125—130°).

The products from five such runs were bulked and fractionated by vacuum distillation. After two distillations the required ester fraction of ethyl *dl-cis*- and *dl-trans*-2 : 2-dimethyl-3-*iso*butenyl*cyclo*propane-1-carboxylates was obtained, b. p. 95—115°/12 mm. (250 g.; 64%, calculated on the ethyl diazoacetate). From the fraction, b. p. up to

75°/12 mm., βε-dimethyl-$\Delta^{\beta\delta}$-hexadiene (195 g.) was recovered by crystallisation and used for further condensations. The ester mixture (250 g.) was refluxed with potassium hydroxide (100 g.) in alcohol (1 l.) for 2 hours; insufficient potassium *cyclo*butanetetracarboxylate had then separated to warrant filtration (cf. Owen and Simonsen, J., 1932, 1424; 1933, 1225). Alcohol was distilled off, and the residue diluted with water and extracted with ether. From the aqueous layer the mixed acids separated on acidification and were taken out in ether. After removal of the ether the residue was distilled in a vacuum to give a mixture of *dl-cis-* and *dl-trans*-2 : 2-dimethyl-3-*iso*butenyl*cyclo*propane-1-carboxylic acids as a viscous oil which rapidly and completely crystallised, b. p. 143°/12 mm., 109°/1 mm. (195 g.; 91%).

The mixed acids (65 g.) were dissolved in ethyl acetate (200 c.c.) and kept at 0° to give a crop A (7 g.), m. p. 110—112°. The filtrate was cooled to − 80° to give a crop B (14 g.), m. p. 95—105°. Crops A and B after crystallisation several times from ethyl acetate (5 vols.) at room temperature gave the *dl-cis*-acid as fine cubic prisms, m. p. 113—116° (Staudinger, Muntwyler, Ruzicka, and Seibt, *loc. cit.*, give m. p. 115—116°) (Found : C, 71·4; H, 9·35; equiv., by titration, 169·2. Calc. for $C_{10}H_{16}O_2$: C, 71·4; H, 9·6%; equiv., 168·2). The dl-trans-*acid* in the filtrate from B was recovered by distillation, the viscous oil rapidly crystallising, m. p. 47—52°. The acid was very soluble but crystallised slowly from a very concentrated solution in ethyl acetate as elongated prisms up to 5 cm. in length, m. p. 54° (Found : C, 71·35; H, 9·5%; equiv. by titration, 169·2, 169·5). The *dl-trans*-acid had a marked negative heat of solution in ethyl acetate and methyl alcohol.

In later preparations the separation of the *dl-cis*-acid could not be effected so readily, prolonged fractional crystallisation from concentrated solutions in ethyl acetate at room temperature being necessary. This was facilitated by the characteristic crystalline forms of the *dl-cis-* and *dl-trans*-acids, enabling hand separation to be carried out.

The *dl-cis*-acid was characterised by the preparation of the following derivatives by standard methods : *amide*, fine needles, m. p. 93°, from light petroleum (Found : C, 71·5; H, 9·9. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·2%); N-*xanthylamide* (cf. Phillips and Pitt, *J. Amer. Chem. Soc.*, 1943, **65**, 1355), plates, m. p. 142°, from dioxan–water (2 : 1) (Found : C, 79·5; H, 7·25. $C_{23}H_{25}O_2N$ requires C, 79·5; H, 7·25%); *anilide*, needles, m. p. 125°, from light petroleum (Found : C, 78·95; H, 8·6. $C_{16}H_{21}ON$ requires C, 78·95; H, 8·7%); p-*phenylphenacyl* ester, clumps of prisms, m. p. 91°, from alcohol (Found : C, 79·3; H, 7·3. $C_{24}H_{28}O_3$ requires C, 79·5; H, 7·2%); *p*-bromophenacyl ester, obtained as an oil which only slowly solidified and could not be satisfactorily recrystallised; *p*-nitrobenzyl ester, obtained as an oil which only slowly solidified. This ester was very soluble in light petroleum, crystallising on evaporation as plates, m. p. 44—45°.

Ozonisation. The *dl-cis*-acid (1 g.) in chloroform (50 c.c.) was treated with excess of ozone at 0°. The solvent was removed at room temperature in a vacuum, and the oily ozonide decomposed by warming on the steam-bath with water for 15 minutes. The solution was concentrated and allowed to crystallise. *dl-cis*-Caronic acid (368 mg.) separated slowly as brownish prisms, m. p. 174—175° with evolution of water (Perkin and Thorpe, J., 1899, **75**, 48, record 176°).

The *dl-trans*-acid was characterised by the preparation of the following derivatives by standard methods : *amide*, silky needles, m. p. 126°, from light petroleum (Found : C, 71·0; H, 10·0%), less soluble than the *dl-cis*-amide; *anilide*, needles, m. p. 111°, from light petroleum (Found : C, 78·5; H, 8·5%), more soluble than the *dl-cis*-anilide; p-*phenylphenacyl* ester, plates, m. p. 115°, from alcohol (Found : C, 79·4; H, 7·15%); *ethyl* ester (ethyl alcohol–sulphuric acid), b. p. 117—121°/20 mm. (Found : C, 72·6; H, 10·5. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·3%); *methyl* ester, prepared by means of methyl alcohol–sulphuric acid, b. p. 95°/13 mm., 108°/20 mm., $d_4^{25°}$ 0·9274, $n_D^{25°}$ 1·4614, $[R_L]_D$ 53·97 (calc., 51·99) (Found : C, 72·6; H, 9·7. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·95%). When the ester was prepared by the action of excess of ethereal diazomethane, the distilled ester contained a crystalline solid, separated by decantation and rinsing with ether. The substance crystallised as needles and decomposed at 128—130° with vigorous evolution of nitrogen; after resolidification the melt had m. p. 100°. The substance was evidently the pyrazoline formed by addition of diazomethane to the double bond of the ester.

Ozonisation. (1) The procedure was exactly that described for the *dl-cis*-acid. *dl-trans*-Caronic acid (520 mg.; 55%) separated rapidly as colourless nodules, m. p. 213°, not depressed by an authentic specimen of the same m. p. prepared by Perkin and Thorpe's method (*loc. cit.*).

(2) The *dl-trans*-methyl ester (4·6 g.) in chloroform (50 c.c.) was treated with excess of ozone at 0°, the solvent removed at room temperature in a vacuum, and the ozonide decomposed by warming on the steam-bath with water (50 c.c.). Excess of solid sodium bicarbonate was added, and the alkaline solution extracted with ether. The aqueous layer was acidified; the solid acid separating (2·33 g.; 53%) crystallised from light petroleum to give *monomethyl* dl-trans-*caronate* as fine plates, m. p. 101—102·5° (Found : C, 55·65; H, 6·8; equiv., by titration, 171·0. $C_9H_{12}O_4$ requires C, 55·8; H, 7·0%; equiv., 172·2). The identity of this half-ester was established by addition of a second equivalent of alkali and warming on the steam-bath until saponification had occurred. Upon acidification and concentration to a small bulk *dl-trans*-caronic acid separated as prisms, m. p. 213°, not depressed by an authentic specimen. Evaporation of the neutral ethereal extract gave, after crystallisation of the volatile solid from light petroleum, bimolecular acetone peroxide, m. p. 132—133° (Found : C, 48·3; H, 8·2. Calc. for $C_6H_{12}O_4$: C, 48·6; H, 8·2%) (Baeyer and Villiger, *Ber.*, 1899, **32**, 3632, record 132—133°).

(3) The *dl-trans*-ethyl ester (4·7 g.), treated with ozone as in (2), gave *monoethyl* dl-trans-*caronate* (2·25 g.; 50%), crystallising from light petroleum in plates, m. p. 73° (Found : C, 57·9; H, 7·7. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%).

Resolution of the dl-trans-*Acid.*—Attempts to prepare alkaloidal salts with cinchonine, strychnine, and brucine resulted in the separation of the alkaloids. Quinine, cinchonidine, and *l*-α-phenylethylamine salts crystallised from alcoholic solution, though all three salts were very soluble. Fractional crystallisation of the *l*-α-phenylethylamine salt yielded fractions differing only slightly in specific rotation ($[\alpha]_D$ − 7·98° and − 7·10°), and the acid recovered from these fractions was inactive. The cinchonidine and the quinine salt gave evidence of resolution, in both cases the *l-trans*-acid salt separating as the less soluble fraction. Quinine was selected for the resolution.

(1) Quinine (16·2 g.; 0·05 mol.) in alcohol (30 c.c.) was added to the *dl-trans*-acid (8·4 g.; 0·05 mol.) in alcohol (30 c.c.). After 8 hours the first fraction (6·5 g.) was removed, $[\alpha]_D$ − 114·8° (*c*, 1·028). Addition of water (50 c.c.) to the warm mother-liquor gave the second fraction (14·05 g.) after 24 hours, $[\alpha]_D$ −111·6° (*c*, 1·032). A further addition of water (30 c.c.) to the warm mother-liquor gave a third fraction (2·15 g.), $[\alpha]_D$ − 109·7° (*c*, 1·016). The final fraction did not crystallise satisfactorily and the acid recovered from it was only slightly lævorotatory.

Two crystallisations of the first fraction from aqueous alcohol (1 : 1) gave the optically pure *quinine* salt of the *l-trans*-acid (4·4 g.), m. p. 159—161·5°, $[\alpha]_D$ − 115·3° (*c*, 1·023) (Found : C, 72·85; H, 7·9. $C_{10}H_{16}O_2$,$C_{20}H_{24}O_2N_2$ requires C, 73·1; H, 8·2%). Decomposition of this salt with dilute hydrochloric acid and extraction with ether gave, after evaporation and heating in a vacuum to 80° to remove traces of solvent, *l-trans*-2 : 2-dimethyl-3-*iso*butenyl*cyclo*propane-1-carboxylic acid (1·3 g.) as a viscous oil, $[\alpha]_D$ − 14·01° (*c*, 1·535). After chilling to − 80° and then warming to 0°, the acid crystallised in elongated prisms, m. p. 17—21°, though a trace of crystalline material lingered until 30°.

The natural *d-trans*-acid (chrysanthemum monocarboxylic acid) had $[\alpha]_D$ +14·16° (*c*, 1·554) (Staudinger and Ruzicka, *loc. cit.*, give α_D + 20·1°. No rotations in solution have been recorded). At 0°, on introduction of a crystal of the *l-trans*-acid, the natural acid, previously only known as a liquid, crystallised in elongated prisms, m. p. 17—21°.

The *quinine* salt of the natural *d-trans*-acid had m. p. 97—110°, $[\alpha]_D$ — 109·3° (*c*, 1·010) (Found : C, 70·4; H, 8·15. $C_{10}H_{16}O_2,C_{20}H_{24}O_2N_2,H_2O$ requires C, 70·55; H, 8·3%).

Purification of the intermediate fractions of quinine salt was extremely slow, but a further fraction (1·5 g.) of the quinine salt of the *l-trans*-acid was obtained. The quinine salt of the *d-trans*-acid could not be obtained pure. Acid recovered from salt of the lowest rotation had $[\alpha]_D$ + 7·97° (*c*, 1·550). This acid (0·84 g.) was converted into the *p*-phenylphenacyl ester and fractionally crystallised from light petroleum. The first fraction (1·05 g.), m. p. 115°, consisted of the *dl-trans*-ester. The second fraction was purified by several crystallisations from light petroleum to give the *p*-phenylphenacyl ester of the *d*-trans-acid (0·1 g.), m. p. 66—67°, $[\alpha]_D$ + 32·33° (*c*, 0·402) (Found : C, 79·3; H, 7·0. Calc. for $C_{24}H_{26}O_3$: C, 79·5; H, 7·2%). The *p*-phenylphenacyl ester prepared from the natural *d-trans*-acid had m. p. 66—67°, undepressed on admixture with the above ester, $[\alpha]_D$ + 32·20° (*c*, 1·020) (Haller and La Forge, *J. Org. Chem.*, 1936, **1**, 50, give m. p. 65°).

(2) In another resolution, quinine (32·4 g.; 0·10 mol.) in alcohol (50 c.c.) was added to *dl-trans*-acid (16·9 g.; 0·10 mol.) in alcohol (30 c.c.). After standing overnight, the first fraction (16·7 g.) of salt was removed, $[\alpha]_D$ — 113·6° (*c*, 1·017). Two crystallisations of this fraction from alcohol–water (3 : 2) gave the quinine salt of the *l-trans*-acid (12·1 g.), m. p. 159·5—161°, $[\alpha]_D$ — 115·4° (*c*, 1·014). The *l-trans*-acid (4·0 g.) recovered from this salt had $[\alpha]_D$ — 14·07° (*c*, 1·920). Again it proved impossible to isolate the pure quinine salt of the *d-trans*-acid from the more soluble fractions of this resolution.

The *l-trans*-acid was characterised by the preparation of the following derivatives by standard methods (all crystallisations from light petroleum) : *amide*, needles, m. p. 122°, which solidified and remelted at 131—132°, $[\alpha]_D$ — 11·09° (*c*, 0·361) (Found : C, 71·55; H, 9·9. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·2%). The *d-trans*-amide made from the natural acid had m. p. 122°, which solidified and remelted at 131—132° (Staudinger and Ruzicka, *loc. cit.*, give m. p. 131°), $[\alpha]_D$ + 10·65° (*c*, 0·510) (Found : C, 71·8; H, 9·9%). The *dl-trans*-amide was prepared by recrystallising a mixture of 20 mg. of each of the active amides. It melted at 126—127°, alone or mixed with an authentic specimen.

Anilide, m. p. 101°, $[\alpha]_D$ + 2·60° (*c*, 1·540) (note the reversal of sign) (Found : C, 79·4; H, 8·6. $C_{16}H_{21}ON$ requires C, 79·0; H, 8·7%). The *d-trans*-anilide made from the natural acid had m. p. 101° (Staudinger and Ruzicka, *loc. cit.*, give m. p. 101°), $[\alpha]_D$ —2·60° (*c*, 1·540) (Found : C, 79·7; H, 8·6%). 30 Mg. of each of the above anilides were mixed and crystallised. The *dl-trans*-anilide had m. p. 111—112°, alone or mixed with an authentic specimen.

p-*Phenylphenacyl ester*, m. p. 66—67°, $[\alpha]_D$ — 32·11° (*c*, 1·012) (Found : C, 79·3; H, 7·0. $C_{24}H_{26}O_3$ requires C, 79·5; H, 7·2%). 30 Mg. of the *d-trans-p*-phenylphenacyl ester and the above ester were mixed and crystallised. The *dl-trans-p*-phenylphenacyl ester had m. p. 115°, alone or mixed with an authentic specimen.

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