

**271. The Resolution of cis- and trans-Norcaryophyllenic Acid.**

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Synthetic *cis*- and *trans*-norcaryophyllenic (3 : 3-dimethylcyclobutane-1 : 2-dicarboxylic) acids have been resolved into their optical isomerides. The synthetic *d-trans*-acid has been shown, by mixed m. p., to be identical with the *d*-norcaryophyllenic acid obtained by oxidation of caryophyllene. The bearing of this identity on the stereochemistry of caryophyllene is discussed and it is pointed out that the widespread assumption that natural products necessarily possess the most stable configuration is without experimental foundation.

As a complement to the synthesis of the *dl*-norcaryophyllenic acids (J., 1936, 593) it was necessary to undertake the resolution of both the *cis*- and the *trans*-acid in order to establish the stereochemical configuration of the *d*-norcaryophyllenic acid obtained as a primary product in the oxidation of caryophyllene (Evans, Ramage, and Simonsen, J., 1934, 1806).

Synthetic *dl-cis*-norcaryophyllenic acid was resolved by means of its neutral cinchonidine salt. In this way *d*- and *l-cis-norcaryophyllenic acids* were obtained as plates, m. p. 165°,  $[\alpha]_{5461}^{20} + 4.9^\circ$  and  $- 5.9^\circ$ , respectively; they differed very considerably in appearance from the active acid derived from caryophyllene.

Synthetic *dl-trans*-norcaryophyllenic acid was resolved by means of its neutral brucine salt. The *d*- and *l-trans-norcaryophyllenic acids* so obtained had m. p. 123—126° and 126°, and  $[\alpha]_{5461}^{18} + 122.2^\circ$  and  $- 129.0^\circ$ , respectively. They crystallised from water in aggregates of prisms, very similar in appearance to the *d*-norcaryophyllenic acid of Evans, Ramage, and Simonsen (*loc. cit.*), which had m. p. 125—127°,  $[\alpha]_{5461} + 137^\circ$ . A mixture of the synthetic *d-trans*-acid with an authentic specimen of this material (m. p. 125—126°) melted at 123—126°. (This mixed m. p. has been independently confirmed by Professor Simonsen.) It is therefore to be concluded that the active norcaryophyllenic acid isolated from the oxidation experiments is a *trans*-acid and not a *cis*-acid as was formerly supposed.

Whether this conclusion may be regarded as indicating that the 0 : 2 : 4-bicyclooctane system in caryophyllene has the *trans*-configuration must remain an open question. It seems likely that inversion during the oxidation process would give rise to some *dl*-acid, whereas none was isolated from the oxidation product; for this reason inversion may be considered unlikely. This, however, is not a conclusive argument, since  $\Delta^3$ -carene gives, on oxidation, acids having both the *cis*- and the *trans*-configuration (for references

see Simonsen, "The Terpenes," 1932, Vol. II, p. 56 *et seq.*). It is noteworthy, however, that in systems of this type, in which a *cyclohexane* ring is fused in the 1 : 2-position to a smaller ring, the strain in the *trans*-modification may be considerably relieved by the adoption of the *Z*-configuration by the *cyclohexane* ring. Furthermore, it is desirable to point out that the widespread tacit assumption that natural products necessarily, or even probably, possess the least strained or most stable configuration seems to be unsupported by any experimental evidence; indeed, the synthetic work of Ruzicka, Koolhaas, and Wind (*Helv. Chim. Acta*, 1931, 14, 1151, 1171) shows that the sesquiterpenes of the selinene class belong to the *cis*-decalin series, which has been shown by measurement of heats of combustion (Roth and Lassé, *Annalen*, 1925, 441, 48) to be the less stable form.

## EXPERIMENTAL.

$\beta\beta$ -Dimethyl- $\delta$ -valerolactone (J., 1936, 594) was converted into  $\beta\beta$ -dimethyladipic acid by the following improvement of Blanc's method (*Bull. Soc. chim.*, 1908, 3, 291) :

*Ethyl  $\delta$ -bromo- $\beta\beta$ -dimethylvalerate.* 100 G. of  $\beta\beta$ -dimethyl- $\delta$ -valerolactone were dissolved in 500 c.c. of absolute alcohol, and the ice-cooled solution saturated with dry hydrogen bromide. The solution was kept overnight, poured into 2 l. of water, and extracted with ether. The extract was washed with sodium carbonate solution and water, dried, and distilled, yielding 173 g. (93%) of the pure bromo-ester, b. p. 89—90°/1.8 mm.

*$\beta\beta$ -Dimethyladipic acid.* 667 G. of the above bromo-ester were added to a suspension of 398 g. of AnalaR potassium cyanide in 450 c.c. of water containing 66 c.c. of acetic acid and 66 g. of sodium iodide. 1700 C.c. of rectified spirit were added, and the whole refluxed on the water-bath for 7 hours; 1325 c.c. of 40% aqueous potassium hydroxide were then added, and the refluxing continued overnight, after which the alcohol was distilled off and the residue boiled under reflux for a further 30 hours.

The dark product was boiled with norit, acidified, diluted to 5 l. with water, and filtered from the insoluble tar. The filtrate was thoroughly extracted with ether, and the residue from evaporation of the dried extract was treated with an excess of sodium carbonate solution. Extraction with ether, followed by drying and distillation, gave 70 g. of recovered  $\beta\beta$ -dimethyl- $\delta$ -valerolactone, b. p. 90—91°/1.5 mm. The residual sodium carbonate solution was then acidified, and extracted with ether, evaporation of the dried extract yielding a hard cake of the crude acid (253 g.). This was crystallised from chloroform (300 c.c.) and light petroleum (b. p. 60—80°; 500 c.c.), yielding 233 g. (48%) of almost pure  $\beta\beta$ -dimethyladipic acid, m. p. 86—87°.

*Ethyl cyanonorcaryophyllenate.* Despite many variations in the experimental procedure it was not found possible to devise conditions for obtaining this substance in a pure state. The bulk of the material used was obtained by the following modification of the procedure previously described. 205 G. of ethyl  $\alpha\alpha'$ -dibromo- $\beta\beta$ -dimethyladipate were stirred overnight under reflux on the water-bath with 95 g. of pure sodium cyanide in 200 c.c. of absolute ethyl alcohol. The dark brown product was poured into ether, the solution filtered, washed with calcium chloride solution, dried over calcium chloride, and distilled. The product (143 g.; b. p. 143—160°/3.5 mm.) gave a strongly positive reaction for bromine, and was similarly treated once more with 55 g. of sodium cyanide in 150 c.c. of absolute alcohol. On working up in the above manner, 77 g. of *cyano-ester*, b. p. 133—136°/1.5 mm., were obtained; although giving only a weakly positive test for bromine, the product was far from pure (Found : C, 52.3; H, 7.1; N, 3.0.  $C_{13}H_{19}O_4N$  requires C, 61.7; H, 7.5; N, 5.5%).

*Carboxynorcaryophyllenic acid.* 18 G. of the impure cyanonorcaryophyllenic ester were refluxed for 72 hours with 36 g. of potassium hydroxide in 180 c.c. of water. The product was acidified, and extracted with ether. After drying and removal of ether, the product solidified in a vacuum desiccator (10.5 g.; m. p. 163—165°). It was dissolved in 30 c.c. of water, and crystallised by saturating the solution with hydrogen chloride while cooling it in ice; yield, 6.9 g. of almost pure acid, m. p. 170—171° (decomp.). A further crystallisation by the same method yielded pure 3 : 3-dimethylcyclobutane-1 : 2 : 2(1 : 1 : 2)-tricarboxylic acid in prisms, m. p. 176° (decomp.) (Found : C, 49.7; H, 5.8.  $C_9H_{12}O_6$  requires C, 50.0; H, 5.6%).

*Norcaryophyllenic acid.* (i) 9.7 G. of carboxynorcaryophyllenic acid were heated to 175—180° for 15 minutes, the evolution of carbon dioxide having then ceased. The cooled residue was taken up in water, and the solution evaporated to dryness. The resulting semi-solid mass (7.8 g.) was dissolved in 50 c.c. of hot water and made just alkaline with ammonia. An excess of 25% calcium chloride solution was added to the boiling solution, and the copious precipitate filtered off hot and washed with hot water. It was then dissolved in hydrochloric acid, and the

solution extracted with ether. Evaporation of the dried extract left 3.52 g. of crude acid, m. p. 134—139°; one crystallisation from water yielded 2.50 g. of almost pure *cis*-norcaryophyllenic acid, m. p. 147—150°. The filtrate from the calcium salt was acidified and extracted with ether. Evaporation of the dried extract yielded 3.95 g. of crude acid, m. p. 110—120°; one crystallisation from water afforded 2.14 g. of somewhat impure *trans*-norcaryophyllenic acid, m. p. 140—145°.

(ii) The bulk of the acids used in this work were obtained from the cyano-ester by the methods described previously (J., 1936, 595).

*Resolution of dl-cis-Norcaryophyllenic Acid.*—5.0 G. of *dl-cis*-norcaryophyllenic acid, m. p. 150—151°, were dissolved in 375 c.c. of hot water, and 8.55 g. of cinchonidine stirred in. The filtered solution, on standing, deposited 4.29 g. of salt as flattened needles. Systematic fractional crystallisation from water yielded finally 3.49 g. of the neutral cinchonidine salt of the *d*-acid in transparent prisms, m. p. 215° (decomp.),  $[\alpha]_{5461}^{20} - 138.0^\circ$  ( $l = 2$ ;  $c = 0.8772$  in ethyl alcohol). This was dissolved in 350 c.c. of hot water containing a little alcohol and decomposed with ammonia. The precipitated cinchonidine was filtered off, and the acidified filtrate extracted with ether. Evaporation of the dried extract yielded 1.07 g. of active acid, m. p. 160—162°. Crystallisation from water (in which the active acid was less soluble than the *dl*-acid) yielded *d-cis-norcaryophyllenic acid* in plates, m. p. 163—165°,  $[\alpha]_{5461}^{20} + 4.9^\circ$  ( $l = 2$ ;  $c = 1.8496$  in chloroform) (Found: C, 55.6; H, 7.0.  $C_8H_{12}O_4$  requires C, 55.8; H, 7.0%).

The more soluble cinchonidine salt crystallised in silky needles which were too highly coloured to allow of the determination of its rotation. Decomposition of the most soluble fraction from a long series of crystallisations yielded 1.15 g. of crude active acid, m. p. 165°. One crystallisation from water afforded *l-cis-norcaryophyllenic acid* as plates, m. p. 165°,  $[\alpha]_{5461}^{20} - 5.9^\circ$  ( $l = 2$ ;  $c = 1.0984$  in chloroform) (Found: C, 55.9; H, 7.2%). An intimate mixture of approximately equal weights of the *d*- and the *l*-acid melted at 150°.

*Resolution of dl-trans-Norcaryophyllenic Acid.*—8.22 G. of *dl-trans*-norcaryophyllenic acid, m. p. 148—149°, were dissolved in 300 c.c. of hot water and 37.64 g. of anhydrous brucine added with stirring. The filtered solution deposited, on standing, 25.44 g. of thin, hair-like needles. Two recrystallisations from water gave 13.76 g. (29.3%) of the neutral brucine salt of the *l*-acid in silky needles,  $[\alpha]_{5461}^{18.6} - 81.46^\circ$  ( $l = 2$ ;  $c = 1.6992$  in acetone). These were dissolved in 150 c.c. of hot water and decomposed with ammonia. The filtrate from the precipitated brucine was acidified and extracted with ether. Evaporation of the dried extract left 2.32 g. of crude active acid; three crystallisations from water (in which the active acid is more soluble than the *dl*-acid) gave 0.93 g. of *l-trans-norcaryophyllenic acid* in transparent aggregates of prisms, m. p. 126°,  $[\alpha]_{5461}^{18} - 129.0^\circ$  ( $l = 2$ ;  $c = 2.0000$  in chloroform) (Found: C, 56.2; H, 7.1.  $C_8H_{12}O_4$  requires C, 55.8; H, 7.0%).

As with the *cis*-acid, the most soluble salts were too highly coloured to permit of the determination of rotation; decomposition of the most soluble fraction with ammonia yielded 3.54 g. of crude *l*-acid. Three crystallisations from water afforded *d-trans-norcaryophyllenic acid* in transparent aggregates of prisms, m. p. 123—125°,  $[\alpha]_{5461}^{18} + 122.3^\circ$  ( $l = 2$ ;  $c = 1.9960$  in chloroform) (Found: C, 55.9; H, 6.9%).

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