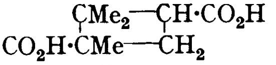
132. *The Synthesis of* cis- *and* trans-dl-*Norcaryophyllenic Acids and of Dehydronorcaryophyllenic Acid.*

By H. N. Rydon.

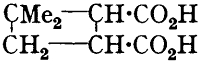
A LIQUID dibasic acid, $C_9H_{14}O_4$, was isolated by Semmler and Mayer (*Ber.*, 1911, **44**, 3157) from the product of ozonolysis of the mixture of sesquiterpenes known as caryophyllene. They named it " caryophyllenic acid " and assigned to it the structure (I) which represents it as a methylnorpinic acid. Deussen and Hacker (*J. pr. Chem.*, 1929, **122**, 261) threw a certain amount of doubt on this formula by the isolation of a " dibromocaryophyllenic acid." The position was further complicated by the work of Ruzicka, Bardhan, and Wind (*Helv. Chim. Acta*, 1931, **14**, 423), who not only separated Semmler's acid into two fractions —an acid, $C_9H_{14}O_4$, m. p. 66—75°, and a homologue, $C_8H_{12}O_4$, m. p. 145—150°—but showed that the glycols obtained from the former by the action of phenylmagnesium bromide and of methylmagnesium iodide gave different products on oxidation.

Experiments were undertaken to synthesise an acid of structure (I) in order to compare it with the product from natural sources. While the work was in progress Evans, Ramage, and Simonsen (J., 1934, 1806) isolated caryophyllenic acid, $C_9H_{14}O_4$, m. p. 80—81°, and *d*-norcaryophyllenic acid, $C_8H_{12}O_4$, m. p. 125—127°, in a pure condition; they also converted the latter into dehydronorcaryophyllenic acid, $C_8H_{10}O_4$, m. p. 193°. Ruzicka and Zimmermann (*Helv. Chim. Acta*, 1935, **18**, 219) confirmed these results and tentatively assigned the structure (II) to norcaryophyllenic acid. Ramage and Simonsen (*Chem. and Ind.*, 1935, **54**, 151) then showed, by oxidative experiments, that this structure must be the correct one and also that dehydronorcaryophyllenic acid must be (III). Further work (Ramage and Simonsen, J., 1935, 532) proved conclusively that caryophyllenic and norcaryophyllenic acids were directly related, a point that had previously been assumed.



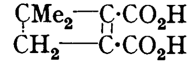
$$\begin{array}{l}\mathrm{CMe_2{-}CH{\cdot}CO_2H}\\ \mathrm{CO_2H{\cdot}CMe{-}CH_2}\end{array}$$

(I.)



$$\begin{array}{l}\mathrm{CMe_2{-}CH{\cdot}CO_2H}\\ \mathrm{CH_2{-}CH{\cdot}CO_2H}\end{array}$$

(II.)

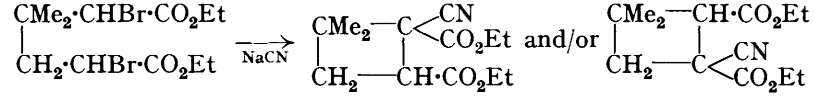


$$\begin{array}{l}\mathrm{CMe_2{-}C{\cdot}CO_2H}\\ \mathrm{CH_2{-}C{\cdot}CO_2H}\end{array}$$

(III.)

In view of these results it was decided to abandon the attempts to synthesise (I) and to direct attention to the synthesis of (II) and (III); it is with this work that the present paper is chiefly concerned.

Ethyl αα'-dibromo-ββ-dimethyladipate (IV) was cyclised to the *cyano*-ester (V or VI) by the method of Fuson and Kao (*J. Amer. Chem. Soc.*, 1929, **51**, 1536); acid hydrolysis of the product afforded a gum, which on treatment with concentrated hydrochloric acid yielded *dl-trans*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid (II), m. p. 148—149°, not depressed * by the *dl*-norcaryophyllenic acid obtained as a by-product in the preparation of the dehydro-acid (Ramage and Simonsen, *loc. cit.*); furthermore, (II) was readily converted by the method of Evans, Ramage, and Simonsen (*loc. cit.*) into 3 : 3-dimethyl-Δ^1-*cyclo*butene-1 : 2-dicarboxylic acid (III), m. p. 195°, unchanged * by authentic dehydronorcaryophyllenic acid.



(IV.) (V.) (VI.)

Treatment of the crude hydrolysis product with acetic anhydride yielded a liquid anhydride, which on digestion with water afforded *dl-cis*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid (II), m. p. 149—150°, depressed to 118—120° by the *trans*-acid. This *cis*-acid was readily acted upon by acetyl chloride with the formation of *dl-cis*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic anhydride, m. p. 40—41°; a mixture of this anhydride with the norcaryophyllenic anhydride of Ruzicka and Zimmermann (*loc. cit.*) melted at 39—41°.

These experiments thus confirm the structures (II) and (III) for norcaryophyllenic and dehydronorcaryophyllenic acid, respectively, so affording a synthetic proof of the rather unexpected presence in caryophyllene of a *gem*-dimethyl*cyclo*butane ring linked to another ring by adjacent carbon atoms.

A few points in the stereochemistry of norcaryophyllenic acid seem worthy of note. Three norcaryophyllenic acids have been described, one *d*-acid and two *dl*-acids. From the work here described, it seems probable that the acid, m. p. 148—149°, described as "*dl-cis*-norcaryophyllenic acid" by Ramage and Simonsen (J., 1935, 533) is in reality the *dl-trans*-acid, although the facile formation of an anhydride is certainly surprising. The *dl*-acid, m. p. 149—150°, described by Ruzicka and Zimmermann (*loc. cit.*) is, owing to the identity of its anhydride with the *dl-cis*-anhydride here described, almost certainly the *dl-cis*-acid.

It cannot, perhaps, be concluded with so much certainty that the naturally occurring *d*-acid has the *cis*-configuration, although the action of acetyl chloride at low temperatures in yielding a liquid anhydride which regenerates the parent acid, whereas acetic anhydride at high temperatures leads to the *dl-cis*-anhydride here described, seems to be considerable evidence in favour of this view. The *cis*-configuration is only to be expected, since, in the parent sesquiterpene, the *cyclo*butane and the *cyclo*hexane ring are most likely to be locked in the considerably less strained *cis*-position. If these configurations be accepted, it is evident that inversion in the sense *cis* ⟶ *trans* occurs during bromination in the preparation of the dehydro-acid; this is not unlikely if bromination is assumed to proceed through an intermediate enolic phase (Lapworth, J., 1904, **85**, 30). These points can, however, only be settled by further work, in particular the resolution of both the *cis*- and the *trans*-acid and a more thorough study of their relationship to one another; this work is actively in hand.

Neither α-*iso*propyl- nor α-iso*butyl-glutaric acid* could be oxidised to a hydroxy- or a lactonic acid, although Lawrence (J., 1899, **75**, 529) was able to oxidise β-*iso*propylglutaric acid to terpenylic acid by means of chromic acid, and Linstead and Rydon (J., 1933, 585) readily obtained δ-*iso*heptolactone by the oxidation of *iso*heptoic acid with alkaline permanganate; neither of these methods was successful when applied to the above α-*iso*-alkylglutaric acids.

EXPERIMENTAL.

The preparation of ββ-dimethyladipic acid by the oxidation of 3 : 3-dimethyl*cyclo*hexanone was a matter of some difficulty, since, contrary to Crossley and Renouf (J., 1905, **87**, 1496), a mixture of acids was produced. The following method is an improvement of Blanc's process (*Bull. Soc. chim.*, 1905, **33**, 898). A warm solution of 136 g. of ββ-dimethylglutaric anhydride in 1100 c.c. of calcium-dried absolute alcohol was added as fast as possible (25 minutes) to 180 g.

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* The identity of these products has been independently confirmed by Prof. J. L. Simonsen, F.R.S.

of sodium. After being kept for 30 minutes at room temperature, the mixture was heated at 140—150° over-night and allowed to cool to 100°, and the alcohol distilled off while 1200 c.c. of water were slowly added; the residue was strongly acidified and steam-distilled. The distillate (2·5 l.) was saturated with ammonium sulphate and extracted with ether. Distillation of the dried extract from two such experiments yielded 187 g. (76%) of ββ-dimethyl-δ-valerolactone, b. p. 118—120°/20 mm., 89—90°/1·5 mm., m. p. 29°. ββ-Dimethyladipic acid was prepared from this lactone by Blanc's method (*Bull. Soc. chim.*, 1908, **3**, 291).

Ethyl αα′-*Dibromo*-ββ-*dimethyladipate*.—11 G. of ββ-dimethyladipic acid (m. p. 86—88°) were treated with 17·5 g. of thionyl chloride and heated on the steam-bath for 1 hour, 22 g. of bromine added drop by drop, and the whole heated over-night, poured into 80 c.c. of absolute ethyl alcohol, refluxed for 30 minutes, and poured into water. Extraction with ether, followed by drying and distillation, afforded 18 g. (75%) of *ethyl* αα′-*dibromo*-ββ-*dimethyladipate*, b. p. 178—182°/12 mm. (Found : Br, 41·6. $C_{12}H_{20}O_4Br_2$ requires Br, 41·2%).

3 : 3-*Dimethyl*cyclo*butane*-1 : 2-*dicarboxylic Acid*.—18 G. of ethyl dibromodimethyladipate were refluxed for 24 hours with 8 g. of sodium cyanide suspended in 15 c.c. of calcium-dried ethyl alcohol. The dark brown liquid was filtered and distilled. The product (11 g.), b. p. 135—137°/2 mm., was impure (Found : N, 2·7. Calc. for $C_{13}H_{19}O_4N$: N, 5·5%) and no successful method of purification has yet been devised. It was hydrolysed and decarboxylated by refluxing for 12 hours with 50 c.c. of concentrated hydrochloric acid. The cooled solution was exhaustively extracted with ether, evaporation of the dried extract affording 8 g. of a thick gum. 3 G. of this were heated with 15 c.c. of concentrated hydrochloric acid over-night at 180° in a sealed tube. The product (decolourised with charcoal) on evaporation yielded *dl-trans*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid, which crystallised from benzene (in which it was very sparingly soluble) in minute clusters of prisms, and from water in small needles, m. p. 148—149° (Found : C, 55·5; H, 6·9. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%).

A further 10 g. of the crude acid, prepared as described above, were heated at 220° in a sealed tube for 6 hours with 30 c.c. of acetic anhydride. On distillation 3 g. of anhydride were obtained as a thick oil, b. p. 98—100°/0·8 mm. This was digested with water and, on evaporation to dryness, followed by two recrystallisations from water, yielded 0·64 g. of *dl-cis*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic acid in prisms, m. p. 149—150° (Found: C, 55·6; H, 7·1. Calc. for $C_8H_{12}O_4$: C, 55·8; H, 7·0%).

0·45 G. of the *cis*-acid was treated with 4·5 c.c. of acetyl chloride. Reaction commenced in the cold and was completed by gentle refluxing for 1½ hours. Distillation afforded 0·24 g. of *dl-cis*-3 : 3-dimethyl*cyclo*butane-1 : 2-dicarboxylic anhydride as a colourless oil, b. p. 100—102°/1 mm., which solidified; m. p. 40—41° (Found : C, 62·3; H, 6·6. Calc. for $C_8H_{10}O_3$: C, 62·3; H, 6·5%).

3 : 3-*Dimethyl*-Δ^1-cyclo*butene*-1 : 2-*dicarboxylic Acid*.—0·5 G. of the synthetic *dl-trans*-acid was treated with 1·25 g. of phosphorus pentachloride and heated on the water-bath for 10 minutes. The product was heated over-night at 140° in a sealed tube with 0·5 g. of bromine, and the whole poured into 10 c.c. of methyl alcohol and refluxed for 1 hour; it was then treated with water, and the bromo-ester isolated with ether. Without distillation, this was refluxed with 1 g. of potassium hydroxide in 2 c.c. of ethyl alcohol for 2 hours. The product was diluted considerably with water, the alcohol driven off on the water-bath, the residue extracted with ether, and the product (after drying and removal of ether) triturated with concentrated hydrochloric acid; the insoluble portion (m. p. 140—150°), on crystallisation from water afforded leaflets of 3 : 3-dimethyl-Δ^1-*cyclo*butene-1 : 2-dicarboxylic acid, m. p. 195° (Found : C, 56·7; H, 6·35. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%).

Miscellaneous Experiments.—α-iso*Propylglutaric acid*. The following is an improvement of Heinke and Perkin's method (J., 1896, **69**, 1507). To a solution of 11·5 g. of sodium in 200 c.c. of absolute alcohol, 101 g. of ethyl *iso*propylmalonate were added followed by 69 g. of ethyl β-chloropropionate. The mixture was refluxed over-night and then worked up in the usual manner. Ethyl α-carbethoxy-α-*iso*propylglutarate (31 g.), b. p. 140—145°/2·5 mm., was refluxed for 3 days with 90 c.c. of formic acid, 25 c.c. of water, and 30 c.c. of concentrated sulphuric acid. α-*iso*Propylglutaric acid (15·5 g.; 89%) separated on cooling and was recrystallised from benzene–petroleum (b. p. 60—80°), forming clusters of prisms, m. p. 94—95°.

α-iso*Butylglutaric acid*. By the treatment described above, 108 g. of ethyl *iso*butylmalonate yielded 40 g. (26%) of ethyl α-carbethoxy-α-*iso*butylglutarate, b. p. 150—155°/2 mm., hydrolysis of which (24 hours) produced 21 g. (88%) of α-iso*butylglutaric acid*, m. p. 68° after crystallisation from light petroleum (Found : C, 57·4; H, 8·65. $C_9H_{16}O_4$ requires C, 57·4; H, 8·5%).

*Products from γ-carboxy-γ-*iso*heptolactone*. (1) Saturation of a solution of 12 g. of the lactonic acid in 100 c.c. of absolute alcohol with hydrogen bromide at 0° afforded only the bromine-free lactonic ester, b. p. 147—148°/12 mm., $n_D^{20^\circ}$ 1·4500, $d_{4^\circ}^{20^\circ}$ 1·0952, $[R_L]_D$ 49·08 (calc., 49·49). (2) 11 G. of the lactonic acid were mixed with 83 g. of phosphorus pentabromide and 20 g. of phosphorus tribromide; after 12 hours, the mixture was poured into alcohol. The product (23 g.), b. p. 145—150°/15 mm., deposited crystals; these, recrystallised from light petroleum (b. p. 60—80°), had m. p. 126—127° (Found: Br, 38·0. $C_7H_{11}O_2Br$ requires Br, 38·6%) and were not further investigated. Distillation of the filtrate yielded *ethyl* α-*bromo*-α-iso*propylglutarate*, b. p. 138—142°/11 mm. (Found: Br, 25·2. $C_{12}H_{21}O_4Br$ requires Br, 25·9%).

The author is indebted to Prof. L. Ruzicka for a specimen of norcaryophyllenic anhydride, to Prof. J. L. Simonsen, F.R.S., for a specimen of norcaryophyllenic acid and still more for his interest and encouragement, and to the Royal Society for a grant.

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[*Received, January 24th,* 1936.]