312. *The Chemistry of the Caryophyllene Series. Part IV. Clovene and Clovenic Acid.*

By Robert David Blair.

Clovenic acid, obtained from clovene by oxidation with chromic anhydride (Ruzicka, Gibson, and, in part, Blair, *Helv. Chim. Acta*, 1931, **14**, 570), was primarily considered for degradation experiments on the clovene molecule. In agreement with the results of Ruzicka and others (*loc. cit.*) the acid showed exceptional stability. Any formula proposed for clovene must take this into account.

Clovene was prepared from caryophyllene by the method of Asahina and Tsukamoto (*J. Pharm. Soc. Japan*, 1922, **484**, 1). It was oxidised to clovenic acid ($C_{15}H_{24}O_4$) by Ruzicka and Gibson's method (*loc. cit.*), an oily neutral product also being obtained which on further oxidation with chromic anhydride gave clovenic acid. Methylmagnesium iodide reacted with clovenic anhydride in the same manner as the ethyl compound (*loc. cit.*), yielding an *acid* ($C_{16}H_{26}O_3$), m. p. 195°, from which clovenic acid was obtained by the action of chromic anhydride. From phenylmagnesium bromide and clovenic anhydride, a lactone ($C_{27}H_{32}O_2$), m. p. 212°, was obtained in very good yield, along with a crystalline keto-acid ($C_{21}H_{28}O_3$), m. p. 270°.

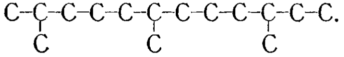
Oxidation of the lactone with chromic anhydride gave a crystalline neutral product ($C_{27}H_{28}O_3$), m. p. 244°, besides an unsaturated crystalline acid substance ($C_{23}H_{27}O_2$), m. p. 185—186°, in very small amount.

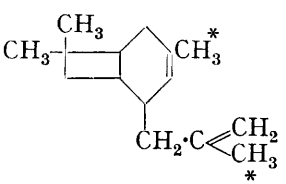
The acid product also was oxidised with chromic anhydride and gave a few crystals of a substance, m. p. 240°, which was not investigated further. Work with the Grignard reagent was now abandoned, since oxidation of the products did not lead to degradation.

Clovenic acid was not attacked by alkaline permanganate solution, permanganate in aqueous acetone at 0°, 30% hydrogen peroxide in glacial acetic acid, or boiling concentrated nitric acid. Distillation of the calcium and thorium salts, and of the acid with soda lime and copper powder, did not yield any positive results. Moreover, although clovene, caryophyllene, and β-caryophyllene alcohol all reduce selenium dioxide with liberation of selenium, no crystalline constituent or derivative could be isolated. Ozonisation of clovene resulted in a 30% yield of clovenic acid; the nature of the neutral product has not been investigated.

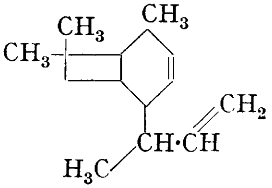
The formation of an amine being considered advantageous for degradation, clovenic acid was treated with hydrazoic acid in the hope of obtaining the diamine. A quantitative yield of clovenic anhydride was obtained! By the action of gaseous ammonia on clovenic acid and also on the anhydride, the *di-ammonium* salt was formed, m. p. 168—170° (decomp.) (Found: N, 9·0. $C_{15}H_{30}O_4N_2$ requires N, 9·3%). It was not possible to obtain the imide, since the ammonium salt decomposed on heating, giving clovenic anhydride with evolution of ammonia.

In an attempt to prepare the monomethyl ester of clovenic acid, partial esterification, and also partial saponification of the di-ester, were tried in vain. It was finally prepared from sodium methoxide and clovenic anhydride, but was unstable, decomposing to give clovenic anhydride and methyl alcohol on heating.

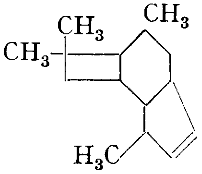
The formula recently proposed by Ruzicka (*Chem. and Ind.*, 1935, 509) for caryophyllene, and the older formula of Henderson, McCrone, and Robertson (J., 1929, 1370) fail, in that they suggest a formula for clovene which could not yield a C_{15} dicarboxylic acid on oxidation. It was pointed out by Ingold (*Ann. Reports*, 1924, 103) that the sesquiterpene skeleton is not merely composed of three isoprene nuclei, but is, so to speak, a folded farnesol chain,  $C{-}\underset{\substack{|\\ C}}{C}{-}C{-}C{-}C{-}\underset{\substack{|\\ C}}{C}{-}C{-}C{-}C{-}\underset{\substack{|\\ C}}{C}{-}C{-}C.$ Now, although Ruzicka's formula can be divided into three isoprene units, it cannot be represented as a folded farnesol chain unless the positions of the methyl groups marked * in (I) are altered to the positions shown in (II). It will be seen that such a formula for caryophyllene can give rise to two different formulæ for clovene (III and IV), either of which on oxidation could give a dicarboxylic acid *without loss of carbon*. Either acid would, moreover, be expected to possess exceptional stability. Formula (I) on cyclisation would give the symmetrical structure (V).



(I.)

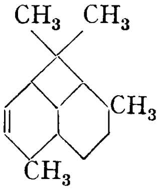


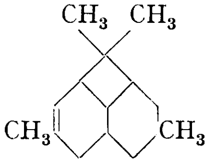
(II.)



(III.)

(IV.)





(V.)

EXPERIMENTAL.

Action of Methylmagnesium Iodide on Clovenic Anhydride.—Clovenic anhydride (10 g.) in absolute ether (30 c.c.) was added to a Grignard solution consisting of magnesium (3 g.) and methyl iodide (9 c.c.) in absolute ether (30 c.c.) and refluxed (10 hrs.). An acid *product*, m. p. 195°, was obtained (Found: C, 71·7; H, 10·0; equiv., 269·8; *M*, 261. $C_{16}H_{26}O_3$ requires C, 72·0; H, 10·0%; *M*, 267), along with an oily neutral product. Both substances on oxidation with chromic anhydride gave clovenic acid (m. p. and mixed m. p.).

Reduction. The acid product gave on treatment with sodium and *n*-amyl alcohol at 170° an acid substance, m. p. 137—138°. The m. p. of a mixture with the ethyl Grignard compound (*loc. cit.*) suffered a depression of 30°.

Clovenic Anhydride and Phenylmagnesium Bromide.—Clovenic anhydride (10 g.) in absolute ether (30 c.c.) was added to a Grignard solution consisting of magnesium (2·7 g.) and bromobenzene (17·3 g.) in absolute ether (80 c.c.), and refluxed (3 hrs.). Worked up in the usual manner, a neutral crystalline *product* (7·5 g.), m. p. 212° (Found: C, 83·35; H, 8·5; *M*, 350. $C_{27}H_{32}O_2$ requires C, 83·5; H, 8·2%; *M*, 388), and a crystalline acid *product* (1·5 g.), m. p. 269° (Found: C, 76·9; H, 8·6; *M*, 306. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·5%; *M*, 327), were obtained. The neutral substance, which was saturated to bromine and permanganate, did not give a *p*-nitrobenzoate or semicarbazone. It also resisted attempts at dehydration, reduction, and saponification.

Oxidation. The neutral product (2·5 g.) in glacial acetic acid (20 c.c.) was heated on the water-bath with a solution of chromic anhydride (10 g.) in water (8 c.c.) to which was added glacial acetic acid (100 c.c.). After 6 hours' heating, the acetic acid was distilled off, and on separation into neutral and acid products, a *substance*, m. p. 244°, was obtained from the ethereal extract (Found: C, 80·7; H, 7·15; *M*, 356, 365. $C_{27}H_{28}O_3$ requires C, 81·0; H, 7·0%; *M*, 400). The alkaline extract gave on acidification an unsaturated *acid*, m. p. 185—186° (Found: C, 82·2; H, 8·0; *M*, 342, 352. $C_{23}H_{27}O_2$ requires C, 82·4; H, 8·1%; *M*, 335).

The neutral oxidation product was recovered unchanged after being heated (3 hrs.) on a boiling water-bath with a mixture of glacial acetic acid (6·5 c.c.) and formic acid (98%; 4 c.c.). No crystalline derivative of either semicarbazide or 2 : 4-dinitrophenylhydrazine was obtained.

I take this opportunity of expressing my thanks to Professor Dr. L. Ruzicka, in whose laboratory the work was commenced, and also to Professor G. G. Henderson, M.A., F.R.S., for his interest in the investigation. I am grateful to the Carnegie Trust for a Teaching Fellowship.

THE UNIVERSITY, GLASGOW. [*Received, June* 13*th*, 1935.]