912. *Sesquiterpenoids. Part XI.* The Constitution of Geigerin.*

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The earlier work on the constitution of geigerin has been extended. Geigerin contains a secondary hydroxyl group placed in the vinylogous α-position with respect to the ketone group. The relation between this hydroxyl group and the lactone system has been firmly established and the constitution of geigerin shown to be (III; R = H). The nature of the so-called *allo*geigeric acid has been elucidated. On the basis of the constitution of this acid and of other facts the stereochemistry of geigerin has been partially defined.

The sesquiterpenoid lactone, geigerin, was first isolated by Rimington and Roets [1] from *Geigeria aspera* Harv. These authors showed that geigerin, $C_{15}H_{20}O_4$, was a ketonic lactone and made a preliminary study of its chemistry. Our attention was first directed to this compound by Professor C. Rimington, F.R.S., who very kindly made available to us his original specimens. Preliminary investigations carried out in 1954 in collaboration with Dr. E. W. Warnhoff revealed that geigerin was an αβ-unsaturated derivative of *cyclo*pentanone, but the work could not be pursued to completion owing to lack of material.

In the meantime important contributions to the chemistry of geigerin have been made by Perold [2,3] who has shown, by dehydrogenation of suitable derivatives to, *inter al.*, guaiazulene (I), that the compound is a guianolide.[4] On mild treatment with alkali the lactone ring of geigerin is opened with formation of *allo*geigeric acid, $C_{15}H_{22}O_5$.[1-3] This acid is no longer an αβ-unsaturated ketone and does not relactonise spontaneously. On the basis of these and other observations Perold [3] proposed the constitution (II) for geigerin.

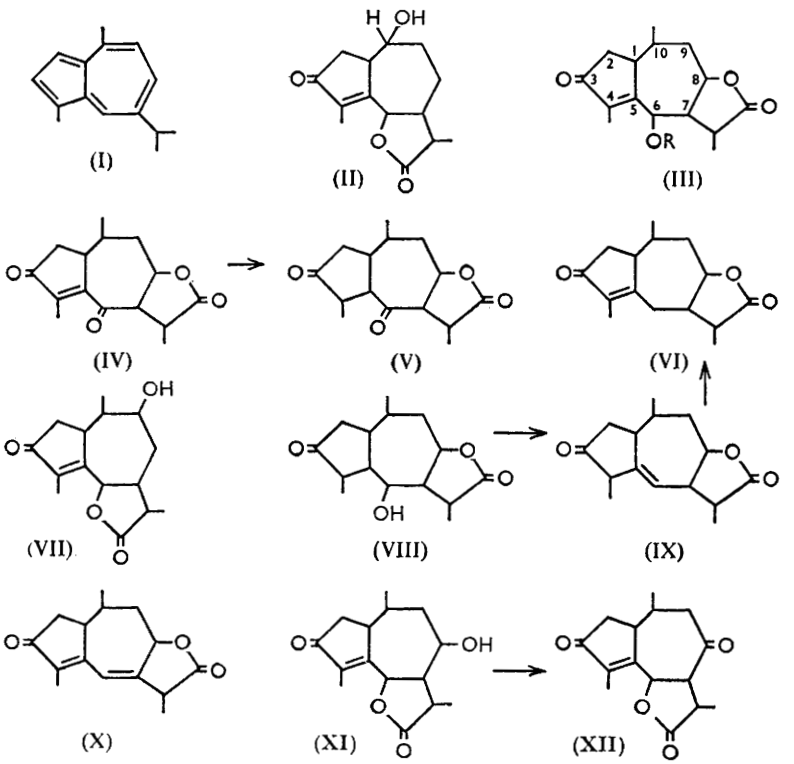
Through the generosity of Dr. G. W. Perold and of Dr. J. P. de Villiers (National Chemical Research Laboratory, C.S.I.R., South Africa), both of whom very kindly provided us with geigerin, we have been able to investigate further the interesting chemistry of this lactone. We have been able to show conclusively that geigerin is represented by formula (III; R = H).

Ozonolysis of geigerin gave acetic acid, confirming the placing of the αβ-unsaturated ketone grouping. Contrary to earlier reports,[1-3] geigerin was readily acetylated to a

* Part X, *J.*, 1958, 963.

[1] Rimington and Roets, *Onderstepoort J. Vet. Sci.*, 1936, **7**, 485.
[2] Perold, *J. S. African Chem. Inst.*, 1955, **8**, 12.
[3] Perold, *J.*, 1957, 47.
[4] See Cekan, Herout, and Šorm, *Chem. and Ind.*, 1954, 604.

monoacetate (III; R = Ac) and oxidised to dehydrogeigerin (IV). Since the latter was stable to chromic acid and since geigerin contains 3 *C*-Me groups, it follows that geigerin cannot be a primary alcohol, but must be secondary. On the basis of this and other considerations we at first favoured [5] the constitution (VII) for geigerin. This was shown to be incorrect by the following experiments. Reduction of geigerin with zinc dust and acetic acid gave in good yield a deoxygeigerin (VI). The usual mechanistic considerations [6] suggest that this ready removal of the secondary hydroxyl group requires the presence either of an α-ketol or of a vinylogous α-ketol. The properties of dehydrogeigerin (IV) (see further below) exclude the former possibility. It was still conceivable, however, that the lactone ring terminated in the vinylogous α-position and that a different lactone ring was formed by relactonisation on to the (original) secondary hydroxyl group. This was excluded by the following experiments. Geigerin was converted into its methanesulphonate (III; R = $Me{\cdot}SO_2$) in the usual way. Treatment of this with sodium iodide [7] and reduction of the resulting iodide with zinc under mild conditions gave the same deoxygeigerin. Similarly dihydrogeigerin,[3] now represented as (VIII), gave a methanesulphonate. When this was refluxed with collidiue, the product contained deoxygeigerin, isolated as its 2 : 4-dinitrophenylhydrazone. Clearly the methanesulphonate group must be eliminated to give, at least partly, the βγ-unsaturated ketone (IX), readily isomerised to (VI).



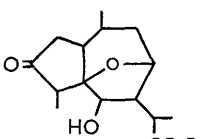
The properties of dehydrogeigerin are fully in accord with its formulation as (IV). Thus it was readily reduced by zinc dust, even at room temperature, to give dehydrodihydrogeigerin (V), a reaction characteristic of an ene-1 : 4-dione.

[5] See Barton and de Mayo, *Quart. Rev.*, 1957, **11**, 189.
[6] See Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.
[7] For example, Prelog, Norymberski, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 360.

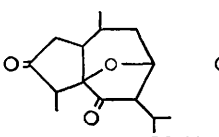
On treatment with perchloric acid in acetic acid geigerin was dehydrated to anhydrogeigerin. On the basis of its ultraviolet spectrum ($\lambda_{max.}$ 297 mμ) and infrared bands at 1759 (γ-lactone), 1685 (*cyclo*pentenone), and 1649 and 1596 cm.$^{-1}$ (conjugated ethylenic linkages) this is formulated as (X).

The infrared spectrum of geigerin [2,3] shows that it is a γ-lactone. Deoxygeigerin (VI) has infrared bands at 1762 (γ-lactone), 1693 (*cyclo*pentenone), and 1644 cm.$^{-1}$ (conjugated ethylenic linkage) and thus retains the same γ-lactone grouping. We have now obtained additional evidence in support of the placing of this γ-lactone grouping in the geigerin molecule as in (III; R = H). Treatment of geigerin methanesulphonate with base gave a mixture of two products: with aqueous sodium hydroxide at room temperature the ester afforded mainly 6-*epi*geigerin (as III; R = H), the constitution of which was shown by chromic acid oxidation to dehydrogeigerin (IV); treatment with ethanolic potassium hydroxide under similar conditions furnished, besides some 6-*epi*geigerin, a further isomeric γ-lactone, showing infrared bands at 1768 (γ-lactone), 1695 (*cyclo*pentenone), and 1637 cm.$^{-1}$ (conjugated ethylenic linkage). This must be formulated as 6-*epiallo*geigerin * (XI) because on chromic acid oxidation it gave a new diketone, dehydro-6-*epiallo*geigerin (XII). The chromophore of the latter compound was stable to zinc dust reduction in agreement with its formulation. A compound obtained earlier [9] from *neo*tenulin and formulated identically shows the same resistance (of the chromophore) to zinc dust reduction. These results, therefore, not only confirm the position of the lactone ring in geigerin but also support the earlier structural proposals for tenulin.[8]

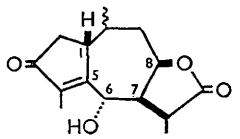
We now turn to the structure of *allo*geigeric acid.† We formulate this compound as (XIII; R = H) on the basis of the following experiments. Oxidation of methyl *allo*geigerate [3] (XIII; R = Me) with chromic acid afforded methyl dehydro*allo*geigerate (XIV). From its infrared spectrum the latter contained no hydroxyl group. If methyl dehydro-*allo*geigerate contains one methoxycarbonyl and two ketone groups it is clear that the fifth oxygen must be either ethereal or a further ketone group. The latter was made improbable by the observation that reduction of *allo*geigeric acid with zinc dust and acetic acid gave deoxygeigerin (VI). It was then found that treatment of either *allo*geigeric acid or its methyl ester with the 2 : 4-dinitrophenylhydrazine reagent furnished the 2 : 4-dinitrophenylhydrazone of geigerin. It thus seemed that the conversion of geigerin into *allo*geigeric acid must be reversible. In the event refluxing *allo*geigeric acid with acetic acid gave back geigerin. Also it was found that, from ultraviolet absorption spectra, the true geigeric acid and *allo*geigeric acid must be in equilibrium in alkaline



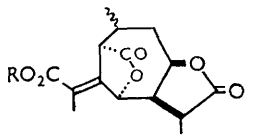
(XIII)



(XIV)



(XV)



(XVI)

solution, the position of equilibrium being approximately 90% on the side of *allo*geigeric acid. Acidification of such a mixture gave back some geigerin (from the true geigeric acid). The addition of the secondary hydroxyl, revealed by opening the lactone ring of geigerin, to the β-position of the αβ-unsaturated ketone function explains these facts in a unique manner.

* We use the prefix *allo* for this compound in the same sense as it has been employed by Braun, Herz, and Rabindran.[8]

† We gratefully acknowledge helpful discussions with Mr. S. K. Pradhan in connection with the chemistry of this compound.

[8] See Braun, Herz, and Rabindran, *J. Amer. Chem. Soc.*, 1956, **78**, 4423.
[9] Barton and de Mayo, *J.*, 1956, 142.

The properties of *allo*geigeric acid throw some light on the stereochemistry of geigerin. *allo*Geigeric acid does not lactonise, even on sublimation at 200°. The hydroxyl and the carboxyl group bearing side chain must, therefore, be *trans* to each other. Since *allo*-geigeric acid always reverts to geigerin, rather than to the isomeric (*trans*) lactone engaging the 6-hydroxyl group, it is reasonable to accept the lactone ring of geigerin as *cis*. If we place the 7-side chain in the customary β-configuration, then geigerin can be represented (at $C_{(6)}$, $C_{(7)}$, and $C_{(8)}$) as in (XV). 6-*epi*Geigerin (see above) does *not* undergo an *allo*-geigeric acid-type change with alkali. If one has the 6-, 7-, and 8-substituents all *cis* to each other, then this lack of $C_{(8)} \longrightarrow C_{(5)}$ bridging is understandable. It has also been argued from rotatory-dispersion studies [10] that the hydrogen at $C_{(1)}$ in geigerin is β (see XV).

We may now consider the dilactone-acid obtained by de Waal [11] on oxidation of geigerin with nitric acid. We formulate this substance as (XVI; R = H) on the basis of the following evidence. The ultraviolet absorption spectra of the acid and of its methyl ester (XVI; R = Me) indicated the presence of an αβ-unsaturated CO_2H (CO_2Me) function. The infrared spectrum of the acid showed bands at 1782 (γ-lactone; strength equivalent to two groups) and 1720 $cm.^{-1}$ (carboxyl). The ester gave bands at 1781 with a shoulder at 1800 (two γ-lactones), 1726 (αβ-unsaturated methoxycarbonyl), and 1670 $cm.^{-1}$ (conjugated ethylenic linkage). Ozonolysis of the acid gave acetic acid, confirming the presence of the system $CO_2H{\cdot}CMe{:}C<$. It will be seen that the formation of the additional γ-lactone ring in (XVI; R = H) is consistent with the stereochemistry summarised in the expression (XV).

Experimental

M. p.s were taken on the Kofler block. Unless specified to the contrary, $[\alpha]_D$ refer to $CHCl_3$, ultraviolet absorption spectra to EtOH, and infrared absorption spectra to $CHCl_3$ solutions. Microanalyses were carried out by Mr. J. M. L. Cameron (Glasgow) and Miss J. Cuckney (Imperial College) and their respective associates. Light petroleum refers to the fraction of b. p. 60—80°.

Geigerin and its Derivatives.—Geigerin gave 16·25% of *C*-Me (Calc. for 3 *C*-Me, 17·05%). Geigerin, left overnight with pyridine–acetic anhydride, gave *geigerin acetate* (III; R = Ac) as colourless needles (from chloroform–ether–hexane), m. p. 130—131°, $[\alpha]_D$ −102° (*c* 0·92), $\lambda_{max.}$ 237 mμ (ε 16,000), $\nu_{max.}$ 1776 (γ-lactone), 1751 (acetate), 1712 (*cyclo*pentanone) and 1658 $cm.^{-1}$ (conjugated ethylenic linkage) (Found: C, 66·85; H, 7·15. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%).

Geigerin (320 mg.) was left overnight with methanesulphonyl chloride (6 ml.) and pyridine (30 ml.). The neutral product was filtered in methylene dichloride solution through alumina (Grade III). Crystallisation from benzene–ether afforded geigerin methanesulphonate (III; R = Me·SO_2), m. p. 143—145°, $[\alpha]_D$ −124° (*c* 1·42), $\lambda_{max.}$ 236 mμ (ε 15,300), $\nu_{max.}$ 1770 (γ-lactone), 1703 (*cyclo*pentenone), and 1647 $cm.^{-1}$ (conjugated ethylenic linkage).

Ozonolysis of Geigerin.—Geigerin (100 mg.) in ethanol-free chloroform (40 ml.) was ozonised at room temperature until the maximum at 238 mμ had disappeared. The chloroform solution was shaken with water, left for 2 hr., and then steam-distilled until no more volatile acid was evolved. The combined distillate was neutralised with sodium hydroxide solution, concentrated *in vacuo*, and then, after adjustment of the pH to 7, treated with *p*-bromophenacyl bromide (330 mg.) in ethanol (10 ml.) in the usual way. Chromatography of the product gave *p*-bromophenacyl acetate (67 mg.), identified by m. p., mixed m. p., and infrared spectrum.

allo*Geigeric Acid* (XIII; R = H) *and its Derivatives.*—Geigerin (520 mg.) was treated at room temperature with 0·1N-ethanolic potassium hydroxide (100 ml.). After 15 hr. ε had reached 1700, and after 40 hr. 1400, unchanged on further standing. Separation into neutral and acid fractions gave geigerin (51 mg.) and *allo*geigeric acid (167 mg.) respectively. Treatment of *allo*geigeric acid with the same concentration of ethanolic potassium hydroxide gave (at equilibrium) the same value for $\varepsilon_{max.}$.

Methyl *allo*geigerate (93 mg.) was treated with excess of chromium trioxide in acetic acid

[10] Djerassi, Osiecki, and Herz, *J. Org. Chem.*, 1957, **22**, 1361.
[11] de Waal, *Onderstepoort J. Vet. Sci.*, 1938, **10**, 395.

at room temperature in the usual way. Chromatography over silica gel and sublimation of the fractions eluted with ether gave needles of *methyl dehydro*allo*geigerate* (XIV), m. p. 125—128°, $[\alpha]_D$ +79° (*c* 1·23), $\lambda_{max.}$ 287 mμ (ε 77), $\nu_{max.}$ 1741 and 1721 cm.$^{-1}$ (in CCl_4) (Found: C, 65·45; H, 7·25. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·55%).

Treatment of either *allo*geigeric acid or its methyl ester with methanolic hydrochloric acid containing 2 : 4-dinitrophenylhydrazine at room temperature gave, in one day, geigerin 2 : 4-dinitrophenylhydrazone identified, after chromatography over bentonite–Celite and crystallisation from chloroform–methanol, by m. p., mixed m. p., and ultraviolet and infrared spectra. *allo*-Geigeric acid (36·5 mg.) in acetic acid (14 ml.) was refluxed for 23 hr. Separation into acid and neutral fractions gave neutral material. This was chromatographed over alumina (Grade III) to furnish geigerin (15 mg.), identified by m. p., mixed m. p., and infrared spectrum.

Deoxygeigerin.—(a) *From geigerin.* Geigerin (76 mg.), zinc dust (500 mg.), and acetic acid (4·0 ml.) were refluxed for 18 hr. The neutral product (69 mg.), crystallised from ethyl acetate–hexane, gave *deoxygeigerin* (VI), m. p. (needles) 131—135°, $[\alpha]_D$ −17° (*c* 1·12), $\lambda_{max.}$ 238 mμ (ε 14,000) (Found: C, 72·65; H, 8·0. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%). The derived 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as red needles, m. p. 271—173°, $\lambda_{max.}$ (in $CHCl_3$) 387 mμ (ε 28,900) (Found: C, 58·6; H, 5·65; N, 12·5. $C_{21}H_{24}O_6N_4$ requires C, 58·85; H, 5·65; N, 13·1%).

(b) *From geigerin methanesulphonate.* The ester (112 mg.) and anhydrous sodium iodide (1·24 g.) were refluxed in acetone (9 ml.) for 24 hr. The product was shaken with zinc dust (550 mg.) in acetic acid (5 ml.) at room temperature overnight. The resultant halogen-free oil was chromatographed over alumina (Grade III), to give deoxygeigerin (VI) (17 mg.), identified by m. p., mixed m. p., and infrared spectrum.

(c) *From* allo*geigeric acid.* The acid (48 mg.), in acetic acid (3·5 ml.), was refluxed with zinc dust (400 mg.) for 19 hr. Chromatography of the product over alumina gave deoxygeigerin (15 mg.), identified by m. p., mixed m. p., and infrared spectrum.

(d) *From dihydrogeigerin.*[3] Dihydrogeigerin (136 mg.) was left with methanesulphonyl chloride (1·5 ml.) in pyridine (13 ml.) at room temperature for 21 hr. The product was refluxed with collidine (10 ml.) for 2 hr. to give, on conversion into the 2 : 4-dinitrophenylhydrazone, the derivative of deoxygeigerin. This was identified by m. p., mixed m. p., and ultraviolet and infrared spectra.

Dehydrogeigerin.—Geigerin (300 mg.) in " AnalaR " acetic acid (30 ml.) was treated with chromium trioxide (225 mg.) in the same solvent (150 ml.). The neutral product, crystallised from benzene–hexane, gave *dehydrogeigerin* (IV) (243 mg.), m. p. (prisms) either 108° and then 132—136°, or 132—136°, $[\alpha]_D$ +3° (*c* 0·73), +5° (*c* 1·58), $\lambda_{max.}$ 234 mμ (ε 10,150) (Found: C, 68·4; H, 6·7. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

Dehydrodihydrogeigerin (V).—(*a*) Dehydrogeigerin (IV) (150 mg.) and zinc dust (600 mg.) were heated with acetic acid (10 ml.) at 100° for 20 hr. The neutral product (140 mg.) was crystallised from benzene, to give *dehydrodihydrogeigerin* (V), m. p. (plates) 237—238°, $[\alpha]_D$ +135° (*c* 0·89), $\lambda_{max.}$ 285 mμ (ε 80) (Found: C, 68·35; H, 7·85. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%).

(*b*) Dehydrogeigerin (35·4 mg.), zinc dust (200 mg.), and acetic acid (10 ml.) were shaken at room temperature for two days. Crystallisation from benzene gave the same dehydrodihydrogeigerin as described above.

Anhydrogeigerin (X).—(*a*) Geigerin (264 mg.) was heated with 72% aqueous perchloric acid (2 ml.) and " AnalaR " acetic acid (18 ml.) on the steam-bath for 8 hr., the reaction being followed by the development of an ultraviolet maximum at 297 mμ. The neutral fraction (223 mg.) was chromatographed over alumina (Grade III) to give, on elution with benzene, *anhydrogeigerin* (X). Recrystallised from ethyl acetate–hexane and then from aqueous methanol, this had m. p. 160—162°, $[\alpha]_D$ −203° (*c* 0·69), $\lambda_{max.}$ 211 and 297 mμ (ε 9000 and 16,100 respectively) (Found: C, 73·4; H, 7·35. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35%). The derived 2 : 4-*dinitrophenylhydrazone* (dark red needles from chloroform–methanol) had m. p. 275—280°, $\lambda_{max.}$ (in $CHCl_3$) 403 mμ (ε 31,200) (Found: C, 58·9; H, 5·25; N, 13·25. $C_{21}H_{22}O_6N_4$ requires C, 59·15; H, 5·2; N, 13·15%).

(*b*) Geigerin methanesulphonate (50 mg.) and collidine (6 ml.) were refluxed for 2 hr. The product gave, on conversion into the 2 : 4-dinitrophenylhydrazone, the derivative of anhydrogeigerin mentioned above (m. p. and mixed m. p.).

Treatment of Geigerin Methanesulphonate with Alkali.—(a) *With aqueous sodium hydroxide.*

The ester (680 mg.) was shaken overnight with 0·1N-aqueous sodium hydroxide (100 ml.). Extraction of the alkaline solution with ether gave a fraction (38 mg.) which crystallised from ether, then having m. p. 180—181°. Acidification with 6N-hydrochloric acid and further extraction gave a neutral gum which was chromatographed over alumina (grade III). Elution with benzene–ether gave crystalline material, m. p. 180°, not depressed on admixture with the substance obtained from the neutral fraction (see above). Elution with ether gave material of m. p. 175°. The combined fractions were crystallised from chloroform–hexane, to give 6-epi*geigerin* (as III; R = H) (53 mg.), m. p. 177—179°, $[\alpha]_D$ −51° (*c* 1·01), $\lambda_{max.}$ 238 mμ (ε 15,100) (Found: C, 68·15; H, 7·8. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%). There was a marked depression in m. p. on admixture with geigerin. Elution with acetone gave a further fraction (36 mg.), m. p. 213—230° (see below).

(b) Geigerin methanesulphonate (750 mg.) was treated overnight with 0·1N-ethanolic potassium hydroxide (120 ml.). Dilution with water, acidification with 6N-hydrochloric acid, and chromatography as above gave, as the more easily eluted compound, 6-*epi*geigerin (25 mg.), identical with the lactone described above and, as the less easily eluted substance, 6-epiallo-*geigerin* (XI). Recrystallised from chloroform–ethyl acetate, this (50 mg.) had m. p. 245—248°, $[\alpha]_D$ −83° (*c* 1·32), $\lambda_{max.}$ 237 mμ (ε 15,400) (Found: C, 68·4; H, 7·75%). 6-*epiallo*Geigerin was not depressed in m. p. on admixture with the more difficult fraction to elute, m. p. 213—230°, referred to under (a) above.

Oxidation of 6-*epi*geigerin (18 mg.) with chromium trioxide as for the oxidation of geigerin (see above) gave dehydrogeigerin, identified by m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum.

Oxidation of 6-*epiallo*geigerin (56 mg.) under the same conditions gave a product (52 mg.) which, on crystallisation from benzene, furnished *dehydro*-6-epiallo*geigerin* (XII), m. p. 149—153°, $[\alpha]_D$ +31° (*c* 1·12), $\lambda_{max.}$ (in dioxan) 235 mμ (ε 7700) (Found: C, 68·85; H, 7·15. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%). In EtOH the ultraviolet spectrum had initially $\lambda_{max.}$ 213 and 239 mμ (ε 6400 and 7800 respectively), $\lambda_{inflex.}$ 263 and 305 mμ (ε 4600 and 1000 respectively).

Dehydro-6-*epiallo*geigerin (47 mg.) and zinc dust (100 mg.) were refluxed in acetic acid (10 ml.) for 26 hr. (spectrophotometric control). There was no reduction in $\varepsilon_{max.}$.

The Dilactone-acid (XVI; R = H) *of de Waal.*[11]—Recrystallised from ethyl acetate this acid had m. p. 278—282°, $\lambda_{max.}$ 213 mμ (ε 6300), and $\nu_{max.}$ 3190—2610 (carboxylic acid), 1782 (bis-γ-lactone), and 1720 cm.$^{-1}$ (carboxyl). The derived methyl ester (XVI; R = Me), after crystallisation from benzene–light petroleum, had m. p. 185—190°, $[\alpha]_D$ +182° (*c* 1·52), $\lambda_{max.}$ 220 mμ (ε 10,100), $\nu_{max.}$ 1800 and 1781 (γ-lactones), 1726 (methoxycarbonyl) and 1670 cm.$^{-1}$ (conjugated ethylenic linkage).

The dilactone-acid (40 mg.) in chloroform (30 ml.) was ozonised until the absorption maximum at 218 mμ had disappeared. The volatile acid produced was isolated as in the ozonolysis of geigerin (see above) and identified as acetic acid.

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