

9. The Structure of Geigerin.

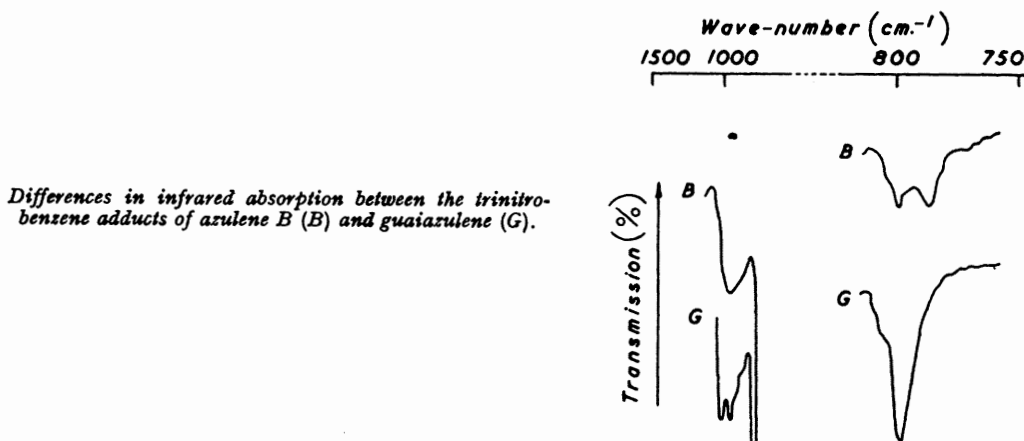
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The bitter principle geigerin, $C_{15}H_{20}O_4$, has previously¹ been shown to contain a hindered hydroxyl group, an $\alpha\beta$ -unsaturated ketone, and a lactone group in a chamazulene-based framework. A structure for the molecule is now presented, on the basis of chemical changes of derived products and dehydrogenation to various azulenes, as the 13 \rightarrow 8-lactone of a 1:9-unsaturated 13-carboxypolyhydro-4:8-dihydroxy-2-oxochamazulene.

THE bitter principle geigerin occurs² in the "vermeerbos" (vomiting bush), represented by various *Geigeria* spp. which grow abundantly in various areas of South Africa³ and cause heavy annual losses of sheep through "vermeersiekte" (vomiting disease). It has been reported to be associated in the plant with the suspected poisonous principle, vermeeric acid, with which it is apparently closely related chemically.⁴

Anhydrous geigerin, $C_{15}H_{20}O_4$, contains a hindered hydroxyl,¹ an $\alpha\beta$ -unsaturated¹ ketone,² and a lactone² group. Catalytic hydrogenation over platinum followed by dehydrogenation over palladium-charcoal yielded an azulene, tentatively identified as chamazulene;¹ this finding is confirmed in the present study.

Reduction of geigerin with lithium aluminium hydride, followed by dehydrogenation as above, yielded¹ as main product an azulene (azulene B), giving a trinitrobenzene adduct, m. p. 135–137°. In order to avoid the possibility of intramolecular changes



during dehydrogenation of the intermediate hydroxymethyl derivative, the hydroxymethyl group was now converted into a methyl group by known procedure and the product dehydrogenated as before. The final product was again azulene B (trinitrobenzene adduct, m. p. 135.5–137°). Satisfactory analytical data have now* been obtained for this adduct, indicating the composition $C_{15}H_{18}$ for azulene B. The identity of azulene B with guaiazulene was demonstrated† by the identity of their ultraviolet absorption and by a mixed melting point of their trinitrobenzene adducts. The low melting point of the adduct of azulene B may therefore be attributed to the presence of a small but persistent

* Cf. ref. 1.

† The author is grateful to Professor D. H. R. Barton for helpful comment on this point.

¹ Perold, *J. S. African Chem. Inst.*, 1955, 8, 12.

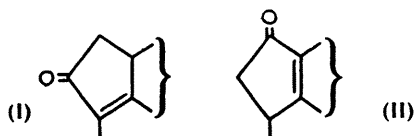
² Rimington and Roets, *Onderstepoort J. Vet. Sci.*, 1936, 7, 485.

³ Steyn, *Farming in S. Africa*, 1943, 18, 747.

⁴ Rimington, Roets, and Steyn, *Onderstepoort J. Vet. Sci.*, 1936, 7, 507; de Waal, *ibid.*, 1938, 10,

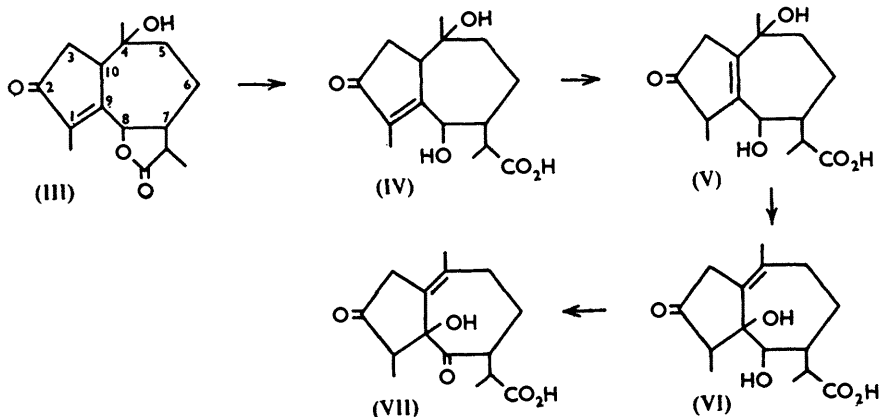
impurity. This is supported by the infrared spectra of the two adducts, which show identity at all points, excepting a modification of the twinned *isopropyl* peaks at 1393 and 1381 cm^{-1} shown by guaiazulene and the appearance of a small additional peak at 783 cm^{-1} in the spectrum of the adduct of azulene B (see Figure). The lactonic carbonyl group in geigerin therefore occupies position 15 of the guaiazulene skeleton.

Hydrogenation of geigerin over palladium on calcium carbonate readily afforded a sharply melting dihydrogeigerin, λ_{max} 290 $\text{m}\mu$ ($\log \epsilon$ 1.45). Ketone absorption in the infrared occurs at 1740 cm^{-1} (*cyclopentanone*⁵); this corresponds to infrared peaks observed for geigerin itself at 1705 and 1647 cm^{-1} (ketone group⁶ and double bond for *cyclopentenone*). The *K* band shown¹ by geigerin at 239 $\text{m}\mu$ ($\log \epsilon$ 4.19 in EtOH) therefore demonstrates that the double bond is fully substituted,⁷ thus permitting the alternative partial structures (I) and (II).



Lactone-carbonyl infrared absorption for geigerin and dihydrogeigerin occurs at 1779 and 1773 cm^{-1} respectively (saturated γ -lactone⁸). With the lactonic-carbonyl group in position 15, the lactonised hydroxyl group is therefore in either position 6 or position 8. The latter is indicated as follows.

Rimington and Roets² hydrolysed geigerin to geigeric acid, $\text{C}_{15}\text{H}_{22}\text{O}_5$, m. p. 201–203°, $[\alpha]_{\text{D}} +105^\circ$, by treatment with alcoholic potassium hydroxide and to an oily acid (methyl ester, $\text{C}_{16}\text{H}_{24}\text{O}_5$, m. p. 98.5°) with boiling hydrochloric acid. In our hands, hydrolysis of geigerin in aqueous-alcoholic potassium hydroxide invariably yielded a hydroxy-acid, $\text{C}_{15}\text{H}_{22}\text{O}_5$, m. p. 177°, $[\alpha]_{\text{D}} +182^\circ$ (methyl ester, $\text{C}_{16}\text{H}_{24}\text{O}_5$, m. p. 101.5°, $[\alpha]_{\text{D}} +168^\circ$),



hereinafter designated as *allogeigeric acid*. Its absorption at λ_{max} 292 $\text{m}\mu$ ($\log \epsilon$ 1.45) (isolated ketone) and at 1736 cm^{-1} (*cyclopentanone*), together with a very small peak (in high concentration) at 1603 cm^{-1} (ethylenic double bond), shows that the double bond

⁵ Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1954, p. 114; Meyer, Jeger, Prelog, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 747.

⁶ Jones, Humphries, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 960.

⁷ Dorfman, *Chem. Rev.*, 1953, **53**, 62.

⁸ Bellamy, *op. cit.*, p. 153.

has moved out of conjugation. The negative colour reaction with tetranitromethane indicates⁹ an allyl alcohol structure, so that the lactonised * hydroxyl group must in geigerin occupy an allyl position with respect to the original double bond, *i.e.*, position 8, whichever of the partial structures (I) or (II) is being considered.†

Chromic acid oxidation of *allogeigeric* acid readily afforded a dehydro*allogeigeric* acid, $C_{15}H_{20}O_5$. Its absorption at λ_{max} , 296 $m\mu$ ($\log \epsilon$ 1.73), (two non-conjugated ketone groups) and (in potassium bromide dispersion) at 1686 (carboxyl), 1721 (*cyclopentanone*), and 1757 cm^{-1} ($\beta\gamma$ -unsaturated ketone¹¹), together with the absence of noticeable ethylenic absorption (fully substituted double bond) and the negative colour reaction with tetranitromethane, demonstrates that a further allyl shift is involved. This allyl change can concern only the originally free hydroxyl group of geigerin, which is therefore placed at position 4.

The structure of geigerin may therefore be formulated as (III), the changes discussed thus occurring by way of a double allyl shift hinging on the freeing of the lactonised 8-hydroxy-group. In the initially formed hydroxy-acid (IV), the double bond shifts to the alternative allyl position (9 : 10) to give (V), the driving force for this change being the formation of a double allyl structure involving both the 4- and the 8-hydroxyl group. The tertiary 4-hydroxyl group then finally undergoes a preferred allyl shift to give *allogeigeric* acid (VI). Dehydro*allogeigeric* acid is then formulated as (VII).

Further data in support of the above formulations are the relevant values for active hydrogen given in the Experimental section, the positive Raymond reaction afforded by geigerin (methylene group adjacent to ketone group¹²), the theoretical consumption of active oxygen in glycol group determinations on *allogeigeric* acid (see Experimental section),‡ and the absence of coloration with 2 : 3 : 5-triphenyltetrazolium chloride in an alkaline solution¹² of dehydro*allogeigeric* acid (tertiary α -ketol).§

The retention in *allogeigeric* acid of the skeletal structure of geigerin was confirmed by dehydrogenation of catalytically hydrogenated *allogeigeric* acid to chamazulene, isolated as its trinitrobenzene adduct, which was identical (mixed m. p., identical ultraviolet and infrared absorption) with the authentic derivative.

EXPERIMENTAL

M. p.s are corrected. Infrared spectra were taken on the Perkin-Elmer Model 21 instrument, in $CHCl_3$ except where otherwise indicated. Ultraviolet absorptions were measured in EtOH (except where otherwise indicated) on the Zeiss Opton M4Q ultraviolet spectrophotometer. Specific rotations were measured at room temperature in $CHCl_3$.

Geigerin.—Geigerin was obtained from *G. aspera* Harv. as previously¹ described. Supplementary amounts of crude geigerin were obtained from Mr. F. J. le Roux and from Dr. J. P. de Villiers, Veterinary Research Laboratory, Onderstepoort, who are both thanked for their kind assistance. Anhydrous geigerin was readily obtained by boiling the hydrate in chloroform until a clear solution resulted and then adding light petroleum (b. p. 60—80°), to give colourless

* That the allyl shift here discussed does not in the first place involve the free hydroxyl group of geigerin is also indicated by the relative stability of geigerin to aqueous acids.¹⁰

† Incidental support for this location of functions is provided by the alkaline saponification of dihydrogeigerin. On working up after acidification spontaneous re-lactonisation to the starting product occurred, as expected for a (saturated) γ -hydroxy-acid which is not subject to any particular environmental directive influence.

‡ The consumption of smaller amounts of active oxygen by geigerin itself under the same conditions indicates the partial formation of *allogeigeric* acid.

§ Consideration of the reactions described now rules out the alternative 9 : 10-en-3-one partial structure (II), as this would not permit of a non-conjugated allyl tertiary ketol structure for dehydro*allogeigeric* acid. Location of the free hydroxyl group at position 10 in the case of the accepted 1 : 9-en-2-one structure is excluded similarly, while its location at the alternative "double allyl" position 7 is rendered improbable by the ready formation of dehydro*allogeigeric* acid.

⁹ Heilbronner, *Helv. Chim. Acta*, 1953, **36**, 1124.

¹⁰ Ref. 2, pp. 497, 499.

¹¹ Jones, Williams, Whalen, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2027.

¹² Axelrod, *Analyt. Chem.*, 1955, **27**, 1308.

prisms, m. p. and mixed m. p. 192° (Found: C, 67.9; H, 7.7; active H, 0.39. Calc. for $C_{15}H_{20}O_4$: C, 68.2; H, 7.6; 1H, 0.38%). The Raymond reaction, carried out¹³ at 100° for 2 min., was strongly positive for 100 μ g. of geigerin.

Dihydrogeigerin.—Geigerin monohydrate (150 mg.) was hydrogenated in the presence of 2 g. of palladium oxide-calcium carbonate (1% of palladium) in ethanol at 35°, uptake of hydrogen ceasing after slightly more than 1 mol. had been absorbed. The semicrystalline product from aqueous ethanol gave *dihydrogeigerin* (60 mg.), colourless prisms, m. p. 184–187°, raised to 188° on further crystallisation (Found: C, 67.75; H, 8.0; active H, 0.42. $C_{16}H_{22}O_4$ requires C, 67.6; H, 8.3; 1H, 0.38%), $[\alpha]_D + 134^\circ$ (*c*, 0.752), λ_{max} , 290 $m\mu$ ($\log \epsilon$ 1.45).

Saponification of Dihydrogeigerin.—Dihydrogeigerin (252 mg.), dissolved at room temperature in 50% aqueous ethanol (30 ml.) containing potassium hydroxide (90 mg.), was kept for 7 days; dihydrogeigerin, m. p. and mixed m. p. 188°, $[\alpha]_D + 138^\circ$ (*c*, 0.713) (Found: C, 67.6; H, 8.2%), of unchanged infrared absorption, was recovered after acidification.

allogeigeric Acid.—Geigerin monohydrate (502 mg.) was stirred with 50% aqueous ethanol (50 ml.) containing potassium hydroxide (182 mg.) until a clear solution resulted (10 min.) and then kept at 30° for 46 hr. After dilution with water to 85 ml. and extraction with ether, the aqueous layer was acidified with hydrochloric acid, and the product recovered by means of ether-extraction as a colourless foam (466 mg.). Crystallisation from ethyl methyl ketone-toluene gave *allogeigeric acid* (388 mg.), m. p. 176–177°, raised to 177° on further crystallisation (Found: C, 63.95, 63.9; H, 7.7, 7.7; active H, 0.97% as highest value; neutr. equiv., 284. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.85; 3H, 1.08%; equiv., 282), $[\alpha]_D + 181^\circ$ (*c*, 0.949), $+182^\circ$ (*c*, 1.059), λ_{max} , 282 $m\mu$ ($\log \epsilon$ 1.45). No colour was obtained with tetranitromethane.

The *methyl ester* (obtained by use of ethereal diazomethane in quantitative yield), crystallised from benzene-light petroleum as colourless prisms, m. p. 101.5° (Found: C, 64.9; H, 8.0; active H, 0.70. $C_{16}H_{24}O_5$ requires C, 64.8; H, 8.2; 2H, 0.68%), $[\alpha]_D + 168^\circ$ (*c*, 1.079), λ_{max} , 290 $m\mu$ ($\log \epsilon$ 1.59).

Glycol Group Determinations.—After preliminary trials, determinations were carried out as follows, in all cases paired with blank determinations.

(a) *Lead tetra-acetate*. Samples (10 mg.) were kept in 0.1N-lead tetra-acetate in glacial acetic acid for 24 hr. at 60°, cooled, shaken with potassium iodide-sodium acetate solution¹⁴ until any precipitated lead dioxide had redissolved, and then titrated with sodium thiosulphate solution (Found for *allogeigeric acid*: 1.01, 1.04; for geigerin: 0.38, 0.39 g.-atom of oxygen consumed per mole).

(b) *Periodic acid*.¹⁵ Samples (10 mg.) were kept in 0.0264M-periodic acid in aqueous acetic acid for 120 hr. at room temperature and titrated with sodium thiosulphate solution after addition of potassium iodide solution (Found for *allogeigeric acid*: 0.94, 0.95; for geigerin: 0.52, 0.52 g.-atom of oxygen consumed per mole).

Dehydroallogeigeric Acid.—*alloGeigeric acid* (162 mg.) in acetic acid (5 ml.) was treated at room temperature with chromic anhydride (57 mg.) in water (0.2 ml.) and acetic acid (2 ml.). After 48 hr. excess of chromic acid was destroyed by brief heating with methanol (1 ml.) at 50°. The solution was evaporated *in vacuo* and the product recovered by ether-extraction as a colourless syrup (148 mg.) which gradually crystallised. Repeated crystallisation from toluene gave prisms of *dehydroallogeigeric acid*, m. p. 149–150° (Found: C, 64.2; H, 7.1; active H, 0.68%; equiv., 280. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2; 2H, 0.72%; equiv., 280), $[\alpha]_D + 101^\circ$ (*c*, 0.955), λ_{max} , 296 $m\mu$ ($\log \epsilon$ 1.73). No colour was formed with tetranitromethane.

Dehydrogenation of catalytically Reduced alloGeigeric Acid.—*alloGeigeric acid* (510 mg.) was hydrogenated over Adams platinum oxide (200 mg.) in glacial acetic acid in ambient conditions until the slow absorption of hydrogen ceased (1.08 moles) after 50 hr. The product was recovered as slightly yellowish, brittle foam (534 mg.). This (252 mg.) was heated with 128 mg. of palladium-charcoal (10% of palladium) in carbon dioxide at 300–340° during 5 min. and held at 340° for a further 6 min. The product was twice chromatographed over alumina,¹ to yield 13 mg. of deep blue liquid, which with *s*-trinitrobenzene (13 mg.) gave violet-black needles (16 mg.), m. p. 127.5–129°. Three crystallisations from ethanol raised the m. p. to 131.5–132.5°, with no depression on admixture with the similar adduct, m. p. 130–131°, of authentic

¹³ Schindler and Reichstein, *Helv. Chim. Acta*, 1951, **34**, 116.

¹⁴ Criegee, *Ber.*, 1931, **64**, 265.

¹⁵ Siggia, "Quantitative Analysis via Functional Groups," John Wiley and Sons, Inc., New York, 1949, p. 8.

chamazulene. Absorption in spectroscopic ligroin¹⁶ (λ_{\max} , $m\mu/\log \epsilon$): 244/4.34, 286/4.59, 305/3.98 (shoulder), 343/3.50 (shoulder), 350/3.63, 368/3.50. The infrared absorption in potassium bromide dispersion was identical with that similarly obtained for the authentic adduct of chamazulene.

Conversion of Geigerin into Azulene B.—Anhydrous geigerin (914 mg.) in dry tetrahydrofuran (15 ml.) was added to a stirred suspension of lithium aluminium hydride (2.5 g.) in tetrahydrofuran (40 ml.), the mixture stirred under reflux for 5 hr., and excess of reagent decomposed by ethyl acetate (20 ml.) with ice-cooling. The mixture was dried at 50°/30 mm., ether and saturated aqueous ammonium chloride solution (20 ml.) were added, and the precipitated salts were washed with ether. The product was recovered as a slightly yellowish glass (883 mg.), λ_{\max} , 280 $m\mu$ ($\log \epsilon$ 1.72) (shoulder) (ketone), infrared peaks at 3378 (hydroxyl), 1730 (ketone), and 1675 cm^{-1} (ethylenic double bond).

The crude product (880 mg.) was hydrogenated (0.6 mol. of H_2) over Adams platonic oxide (152 mg.) in acetic acid (30 ml.) and water (10 ml.) at 36°. The recovered syrup was kept in 50% aqueous methanol (20 ml.) containing potassium hydroxide (1 g.) at room temperature for 22 hr. Most of the solvent was then evaporated at 65°/40 mm. and the residual solution continuously extracted with ether for 10 hr., to yield a foam (754 mg.), infrared peak at 1733 cm^{-1} (ketone) and no ethylenic infrared absorption.

The foam (739 mg.) was warmed in anhydrous pyridine (15 ml.) containing toluene-*p*-sulphonyl chloride (4.43 g.) at 70° for 30 min., then kept at room temperature for 7 days. The product was obtained as a syrupy ester (672 mg.) showing diminished intensity of the hydroxyl absorption at 3378 cm^{-1} (Found: S, 6.3%).

The ester (660 mg.) in anhydrous tetrahydrofuran (15 ml.) was treated with lithium aluminium hydride (2.5 g.) as in the first stop, and refluxed for 10 hr. The neutral product was recovered as a viscous yellowish syrup (403 mg.) showing no specific absorption either in the ultraviolet or in the 6 μ region (Found: S, 0.18%).

This product (188 mg.) was dehydrogenated as before (102 mg. of 10% palladium-charcoal; 40 min. at 280°). Chromatography of the crude product (141 mg.) over alumina (20 g.) in 4:1 light petroleum (b. p. 30–60°)–benzene gave a pure blue frontal zone, followed by a slight, vaguely defined mauve zone. The lightly dried pure blue eluate (26 mg.) with *s*-trinitrobenzene (23 mg.) in warm ethanol gave a brownish-violet adduct (8 mg.), m. p. 131–133°. Recrystallisation from ethanol gave azulene B–trinitrobenzene adduct, m. p. and mixed m. p. 135.5–137° (Found: C, 61.3; H, 5.45. Calc. for $\text{C}_{21}\text{H}_{11}\text{O}_6\text{N}_3$: C, 61.3; H, 5.15%). The ultraviolet and the infrared (potassium bromide dispersion) absorption were respectively identical with the corresponding spectra of azulene B and its trinitrobenzene adduct. A mixture, in roughly equal proportions, of the adduct of azulene B and the similarly coloured adduct of guaiazulene (m. p. 150–151°) melted at 145–149°. The infrared spectra (potassium bromide dispersion) of these two adducts were essentially identical (see above).

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¹⁶ Pfau and Plattner, *Helv. Chim. Acta*, 1936, 19, 858.