483. *Photochemical Transformations. Part XV.*[1] *Synthetic Studies on Geigerin and its Derivatives.*[2,3]

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The partial syntheses of anhydrogeigerin, deoxygeigerin, and, in radiochemical yield, of geigerin itself have been accomplished starting with artemisin. Full stereochemical control was exercised at every step, including the critical photochemical rearrangement of the eudesmanolide to the guaianolide skeleton. 2-Bromolumisantonin has been prepared, and subjected to *X*-ray analysis.

In the first Paper of this series[4] we showed that irradiation of santonin (I; R = R′ = H, 6βH) in aqueous acetic acid gave isophotosantonic acid lactone (II; R = R′ = H, 6βH). The general nature of this rearrangement was demonstrated in a later Paper.[1] In particular, we reported the conversion of artemisin acetate (I; R = H, R′ = OAc, 6βH), 8-epiartemisin acetate (I; R = OAc, R′ = H, 6βH), and 6-epi-8-epiartemisin acetate (I; R = OAc, R′ = H, 6αH) into the respective guanianolides (II). These substances are potentially useful for the partial synthesis of naturally occurring guaianolides, and in the present Paper we report the preparation of anhydrogeigerin (III; R = H, 11αMe), deoxygeigerin (IV; R = H) and, in radiochemical yield, geigerin itself (IV; R = OH).

[1] Part XIV, Barton, Levisalles, and Pinhey, *J.*, 1962, 3472.
[2] Preliminary communication, Barton and Pinhey, *Proc. Chem. Soc.*, 1960, 279.
[3] Preliminary communication, Barton, Pinhey, and Wells, *Proc. Chem. Soc.*, 1962, 112.
[4] Barton, de Mayo, and Shafiq, *J.*, 1957, 929.

The constitution and partial stereochemistry of geigerin were defined in an earlier Paper.[5] The full stereochemistry was determined by *X*-ray crystallography [6] of 1-bromogeigerin acetate (V; R = Br, R′ = OAc), the product of bromination of geigerin acetate with *N*-bromosuccinimide.[2] Although the *X*-ray work does not define the configuration at C-1, this is established as β by chemical considerations [5] as well as by the synthetic work outlined below. Two further examples of the general photochemical rearrangement are described. Irradiation of artemisin ethyl carbonate (I; R = H, R′ = O·CO_2Et, 6βH) and of artemisin methanesulphonate (I; R = H, R′ = O·SO_2Me, 6βH) gave the corresponding lactones.

The configuration at C-11 in α-santonin was until recently [3,7] regarded as 11αH.[8] This erroneous assignment was very confusing, and, for simplicity, we give here only the correct C-11 configurations. Since artemisin and santonin have been rigidly correlated,[9,10] the C-11 configuration in artemisin is also defined. The revised C-11 configuration of α-santonin was confirmed by Asher and Sim [11] using 2-bromosantonin. In collaboration with Dr. R. A. Silva we prepared this compound for Dr. Sim by a known method,[12] and confirmed that there was no epimerisation at C-11 during its synthesis (see Experimental section).

Anhydrogeigerin (III; R = H, 11αMe) had been prepared [5] by dehydrating geigerin (IV; R = OH) under acid conditions, or by treating geigerin methanesulphonate (IV; R = O·SO_2Me) with collidine. It was therefore assigned formula (VI). However, we found that heating of 1-bromogeigerin acetate (V; R = Br, R′ = OAc) with dimethylformamide gave a dienone which clearly had structure (III; R = OAc, 11αMe). Chromous chloride reduction of this new dienone afforded anhydrogeigerin which must, therefore, be (III; R = H, 11αMe). The nuclear magnetic resonance spectrum of anhydrogeigerin showed one doublet (τ 8·59 and 8·72), corresponding to the 11-methyl group coupled with a single proton, and two sharp singlets (τ 8·07 and 8·19) corresponding in position and intensity to two vinylic methyl groups. There were no vinyl protons. The revised constitution (III; R = H, 11αMe) of anhydrogeigerin was thus confirmed.

In Part XIV [1] we described the synthesis of 6-deoxyisophotoartemisic acid acetate (VII; R = H, R′ = OAc) and of its 8-epimer (VII; R = OAc, R′ = H) by chromous chloride reduction of the lactones (II; R = H, R′ = OAc, 6βH) and (II; R = OAc, R′ = H, 6βH), respectively. The latter acid was also obtained by hydrogenolysis of 6-epi-8-epi-isophotoartemisic acid lactone (II; R = OAc, R′ = H, 6αH). Treatment of either acid with perchloric–acetic acid at 70° gave the lactone (III; R = H, 11βMe) which was smoothly transformed into anhydrogeigerin (III; R = H, 11αMe) on treatment with cold dilute ethanolic potassium hydroxide. The more complicated interpretation [2] of this reaction sequence is no longer required now that the C-11 configuration in artemisin has been revised (see above). This synthesis provided the first connection between the natural guaianolides and the eudesmanolides, and afforded proof of the absolute configuration of geigerin.[2]

Dehydration with thionyl chloride and pyridine [4] of 8-epi-isophotoartemisic lactone acetate (II; R = OAc, R′ = H, 6βH) gave the non-conjugated anhydro-compound (VIII) in high yield. Selective hydrogenation of this compound afforded stereospecifically the lactone (IX; R = Ac). Mild alkaline hydrolysis furnished the corresponding alcohol which gave the parent acetate on acetylation. For comparison the hydrogenolysis of 1-bromogeigerin acetate (V; R = Br, R′ = OAc) was examined. This furnished, in

[5] Barton and Levisalles, *J.*, 1958, 4518.
[6] Hamilton, McPhail, and Sim, *Proc. Chem. Soc.*, 1960, 278.
[7] Asher and Sim, *Proc. Chem. Soc.*, 1962, 111.
[8] See Cocker and McMurry, *Tetrahedron*, 1960, **8**, 181.
[9] Sumi, *J. Amer. Chem. Soc.*, 1958, **80**, 4869.
[10] Bolt, Cocker, and McMurry, *J.*, 1963, 5235; we thank Professor Cocker for sending us a copy of this Paper prior to publication.
[11] Asher and Sim, *Proc. Chem. Soc.*, 1962, 335.
[12] Klein, *Ber.*, 1907, **40**, 939; Wedekind, *ibid.*, 1908, **41**, 359.

good yield, 1-epigeigerin acetate (V; R = H, R′ = OAc) which was hydrolysed by alkali to the corresponding alcohol, which, in turn, was reactylated to the parent acetate. On the basis of the earlier C-11 configuration in santonin and artemisin [8] the compounds (IX; R = H) and (V; R = H, R′ = OH) should have given identical products when the lactone ring was opened. Since this was not so, our first suspicions as to the need for a revision of the C-11 configuration were aroused. At the time, however, we did not exclude a more complicated and unknown explanation for this difference.

On reduction with chromous chloride, and spontaneous lactonisation of the derived acid, the lactone (IX; R = H) gave 1-epi-11-epideoxygeigerin (X) ($[\alpha]_D$ +190°). On treatment of the latter with dilute sulphuric acid at 90° a second epimer (XI) ($[\alpha]_D$ −59°) of deoxygeigerin was obtained. Chromous chloride reduction of the acetate (IX; R = Ac) and treatment of the non-crystalline acidic product with dilute sulphuric acid in the same way also gave this epimer. Under mild alkaline conditions 11-epideoxygeigerin (XI) afforded deoxygeigerin (IV; R = H) ($[\alpha]_D$ −20°), and the partial synthesis was thus accomplished.

A further epimer of deoxygeigerin was obtained by reduction of the methanesulphonate (V; R = H, R′ = O·SO_2Me) of 1-epigeigerin (see above). This fourth epimer (V; R = R′ = H) had $[\alpha]_D$ +130°. It was also prepared by mild alkaline treatment of 1-epi-11-epideoxygeigerin (X). On digestion with dilute sulphuric acid 1-epigeigerin (V; R = R′ = H) gave deoxygeigerin (IV; R = H). If the configuration of 1-epigeigerin be accepted, then the inversion of C-1 by acid and of C-11 by alkali will explain all the results cited.

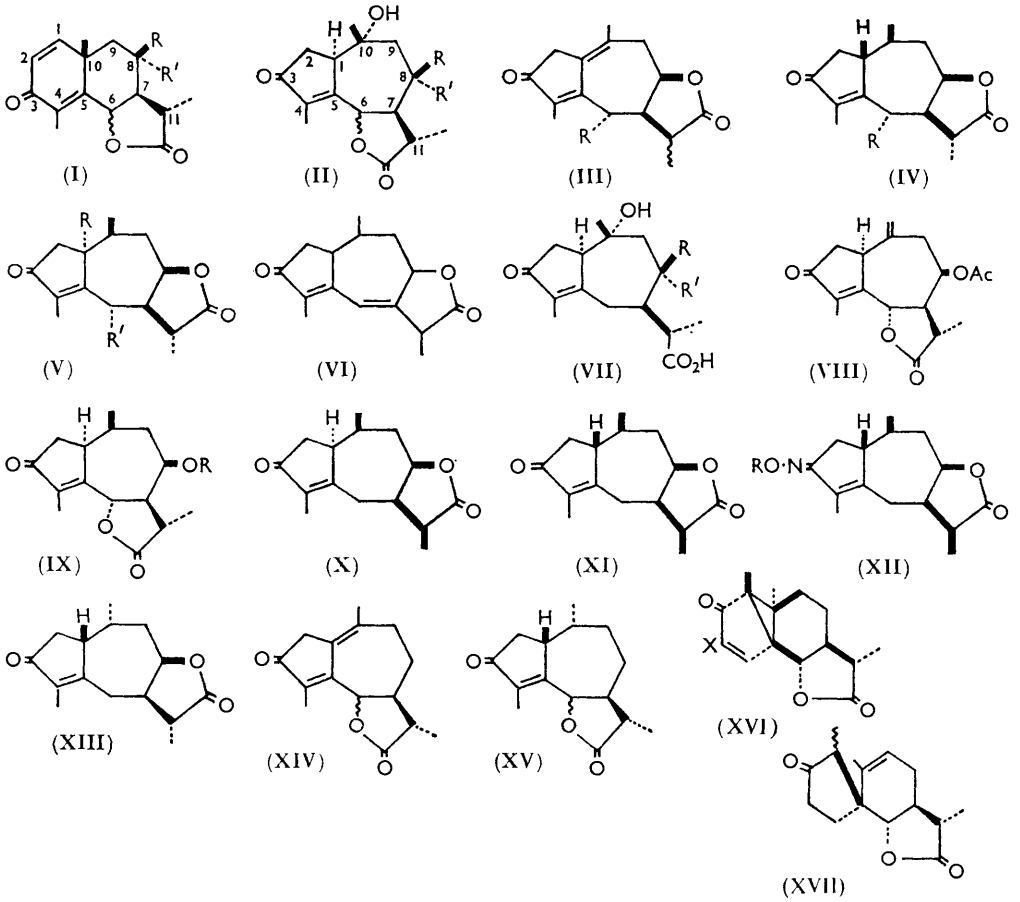
Further evidence about the above stereochemical assignments was obtained when 11-epideoxygeigerin (XI) was converted into its oxime (XII; R = H) and treated with alkali under the usual conditions. The oxime was recovered unchanged, and we at first argued [3] that this implied that alkali was inverting C-1, and acid C-11. However, the methoxyimino-compound (XII; R = Me), prepared using methoxyamine, inverted at C-11 under the usual alkaline conditions, giving deoxygeigerin *O*-methyl oxime. It appears that the oxime anion from (XII; R = H) precludes electrostatically the formation of the second anion required for inversion at C-11.

The simplest way of completing the partial synthesis of geigerin would be by acetoxylation of deoxygeigerin (IV; R = H). In experiments carried out initially in collaboration with Dr. T. Miki, treatment of deoxygeigerin with lead tetra-acetate and boron trifluoride [13] gave, in good yield, an isomer of geigerin acetate. This compound could be reduced back to deoxygeigerin with chromous chloride, and had strong reducing properties. The obvious structure, 2-acetoxydeoxygeigerin, was confirmed by the nuclear magnetic resonance spectrum which showed a doublet (τ 4·34 and 4·45) attributable to a single C-2 proton coupled with the proton at C-1.[14] In order to establish if any geigerin acetate (IV; R = OAc) was formed, the reaction was repeated using lead tetra-[1-^{14}C]acetate and, after separation of the crystalline 2-acetoxygeigerin, the residue was diluted with inactive geigerin acetate. Recovery of the geigerin acetate showed that the acetoxylation gave, in two separate experiments, 0·3 and 0·1%. The yields were confirmed by conversion into geigerin acetate 2,4-dinitrophenylhydrazone and repeat counting. (In a preliminary experiment [2] a yield of 0·6% was found. The two lower figures represent experiments on a larger scale, and should be more reliable.)

Insofar as a radiochemical yield can be accepted as evidence of a chemical synthesis we have completed the partial synthesis of geigerin from artemisin. The hydrolysis of geigerin acetate to geigerin had, of course, been carried out earlier.[5]

We also studied the selective hydrogenation of anhydrogeigerin (III; R = H), since it was conceivable that this would provide a simple alternative route from artemisin to deoxygeigerin. In fact, a fifth stereoisomer of deoxygeigerin resulted. This must have

[13] Henbest, Jones, and Slater, *J.*, 1961, 4472.
[14] Williamson and Johnson, *J. Amer. Chem. Soc.*, 1961, **83**, 4623; *J. Org. Chem.*, 1961, **26**, 4563.



(see above) a 10α-methyl group, and, assuming *cis*-hydrogenation, we formulate the product as (XIII). The recent work of Büchi and Loewenthal [15] provides a close analogy for this formulation. Selective hydrogenation of anhydroisophoto-α-santonic lactone (XIV) [1,4] gave a comparable dihydro-derivative which we formulate as (XV). Selective hydrogenation of anhydroisophoto-β-santonic lactone [1] proceeded similarly, to give a dihydro-derivative (11-epimer of XV).

In recent work [16] we established the stereochemistry (XVI; X = H) of lumisantonin.* In collaboration with Dr. R. A. Silva we converted lumisantonin into 2-bromolumisantonin (XVI; X = Br). The constitution of the latter was established by its spectroscopic properties, by an alternative synthesis by photoisomerisation of 2-bromosantonin, and by hydrogenation over platinum in the presence of triethylamine to the known dihydrolumisantonin.[17–19] Hydrogenation in the absence of triethylamine gave the compound (XVII).[18,19] 2-Bromolumisantonin was examined using *X*-ray crystallography by Professor Dorothy Crowfoot Hodgkin and her collaborators; she has kindly informed us that the stereochemistry assigned to lumisantonin is confirmed in every detail.

* The configuration at C-11 has been inverted in accordance with later studies already referred to in the present text.

[15] Büchi and Lowenthal, *Proc. Chem. Soc.*, 1962, 280.
[16] Barton and Gilham, *Proc. Chem. Soc.*, 1959, 391; *J.*, 1960, 4596.
[17] Cocker, Crowley, Edward, McMurry, and Stuart, *J.*, 1957, 3416.
[18] Arigoni, Bosshard, Bruderer, Büchi, Jeger, and Krebaum, *Helv. Chim. Acta*, 1957, **40**, 1732.
[19] Barton, de Mayo, and Shafiq, *Proc. Chem. Soc.*, 1957, 205; *J.*, 1958, 140.

Experimental

Melting points were taken on a Kofler hot-stage apparatus. Unless specified to the contrary, ultraviolet spectra refer to ethanolic solutions and optical rotations and infrared spectra to chloroform solutions. Irradiations were carried out over a bare mercury-arc lamp in Pyrex apparatus.[4] Nuclear magnetic resonance spectra were determined on a Varian Associates A60 spectrometer on permanent loan from the Wellcome Trust, and were taken in deuterochloroform unless specified to the contrary. Light petroleum refers to the fraction of b. p. 60—80°, unless otherwise indicated.

Irradiation of Artemisin Ethyl Carbonate (I; R = H, R′ = O·CO_2Et, 6βH).—The carbonate [9] (2·0 g.) in 45% aqueous acetic acid (200 ml.) was irradiated at reflux under nitrogen (infrared control). The solvent was removed *in vacuo* and the residue taken up in methylene dichloride and further processed in the usual way. Crystallisation from ethyl acetate–light petroleum afforded *isophotoartemisic lactone ethyl carbonate* (II; R = H, R′ = O·CO_2Et, 6βH) (170 mg.), m. p. 213—221°, $[\alpha]_D$ +111° (*c* 1·04), $\lambda_{max.}$ 238 mμ (ε 14,500), $\nu_{max.}$ 3650, 1784, 1740, 1705, and 1640 cm.$^{-1}$ (Found: C, 61·05; H, 6·95. $C_{18}H_{24}O_7$ requires C, 61·35; H, 6·85%).

Hydrogenation of this carbonate (103 mg.) in ethanol (8 ml.) over 10% palladised charcoal (77 mg.) (1·1 mol. uptake) gave, after chromatography on alumina (grade III) and crystallisation from ethyl acetate–light petroleum, a *dihydro-derivative* (65 mg.), m. p. 159—160°, $[\alpha]_D$ −5° (*c* 0·71), $\nu_{max.}$ 3650, 1773, 1738, and 1276 cm.$^{-1}$ (Found: C, 61·0; H, 7·5. $C_{18}H_{26}O_7$ requires C, 61·0; H, 7·4%). This compound is the analogue of dihydroisophotosantonic lactone.[1]

Neither isophotoartemisic lactone ethyl carbonate nor its dihydro-derivative could be converted into a cyclic carbonate by pyrolysis, with or without pyridine, or by the action of sodium hydride in dry benzene.

Irradiation of Artemisin Methanesulphonate (I; R = H, R′ = O·SO_2Me, 6βH).—The sulphonate [1] (2·0 g.) in 45% aqueous acetic acid (200 ml.) was irradiated at reflux under nitrogen (infrared control). Chromatography of the product on alumina (grade III) gave, on eluting with benzene–acetone (20 : 1), starting material. Further elution with benzene–acetone (1 : 1) afforded *isophotoartemisic lactone methanesulphonate* (II; R = H, R′ = O·SO_2Me, 6βH) (140 mg.), m. p. 164—166° (decomp.) (from ethyl acetate), $[\alpha]_D$ +113° (*c* 0·93, in acetone), $\lambda_{max.}$ 238 mμ (ε 15,200), $\nu_{max.}$ 3600, 1783, 1710, 1645, 1350, and 1180 cm.$^{-1}$ (Found: C, 53·85; H, 6·25; S, 9·1. $C_{16}H_{22}O_7S$ requires C, 53·65; H, 6·2; S, 8·95%).

Hydrogenation of 2-Bromosantonin (with R. A. Silva).—2-Bromosantonin [12] (910 mg.) in methanol (200 ml.) was hydrogenated over platinum oxide (54 mg.). Crystallisation of the product from ethanol gave α-tetrahydrosantonin (384 mg.) (m. p., mixed m. p., $[\alpha]_D$, and ultraviolet and infrared spectra).

1-*Bromogeigerin Acetate* (V; R = Br, R′ = Ac) *and its Reactions*.—Geigerin acetate (680 mg.), *N*-bromosuccinimide (450 mg.), and one crystal of benzoyl peroxide were refluxed for 2½ hr. in carbon tetrachloride (10 ml.). Removal of the solvent *in vacuo*, addition of water and extraction into methylene dichloride gave, on evaporation, 1-*bromogeigerin acetate* as prisms (490 mg.), m. p. 147—153° (decomp.) (from methylene dichloride–benzene), $[\alpha]_D$ −101° (*c* 0·89), $\lambda_{max.}$ 234 mμ (ε 11,000), $\nu_{max.}$ 1778, 1748, 1723, 1640, and 1270 cm.$^{-1}$ (Found: C, 53·2; H, 5·55. $C_{17}H_{21}BrO_5$ requires C, 53·0; H, 5·5%).

1-Bromogeigerin acetate (116 mg.) in dimethylformamide (8 mg.) was refluxed for 1½ hr. (ultraviolet control). The solvent was removed under reduced pressure, and the residue chromatographed on alumina (grade III; 1·5 g.). Elution with benzene gave the conjugated *dienone* (III; R = OAc, 11αMe) needles, m. p. 133—135° (from ether), $[\alpha]_D$ −219° (*c* 0·97), $\lambda_{max.}$ 303 mμ (ε 13,600), $\nu_{max.}$ 1770, 1747, 1695, and 1603 cm.$^{-1}$ (Found: C, 67·15; H, 6·6. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

1-Bromogeigerin acetate (134 mg.) in ethyl acetate (10 ml.) was hydrogenated over Raney nickel (100 mg.). Crystallisation of the product from ethyl acetate–light petroleum gave 1-*epigeigerin acetate* (V; R = H, R′ = OAc) as prisms, m. p. 166—168°, $[\alpha]_D$ +127° (*c* 0·90), $\lambda_{max.}$ 235 mμ (ε 14,300), $\nu_{max.}$ 1778, 1747, 1707, and 1646 cm.$^{-1}$ (Found: C, 66·4; H, 7·3. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%). The yield of 1-epigeigerin acetate was erratic, but using 5% palladised calcium carbonate in ethyl acetate gave a reproducible yield (70%).

1-Epigeigerin acetate (230 mg.) in distilled water (9 ml.) and saturated aqueous sodium hydrogen carbonate (7 ml.) was heated on a steam-bath for 20 hr. The solution was acidified (2N-hydrochloric acid) and left at room temperature for 24 hr. Extraction into chloroform

gave 1-*epigeigerin* (V; R = H, R′ = OH) (55 mg.), needles, m. p. 203—204° (from ethyl acetate–light petroleum), $[\alpha]_D$ +143° (*c* 0·90), $\lambda_{max.}$ 238 mμ (ε 13,500), $\nu_{max.}$ 3350, 1770, 1702, and 1640 cm.$^{-1}$ (Found: C, 68·3; H, 7·7. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%). Alternatively, the acetate (160 mg.) was heated with 5% sulphuric acid (16 ml.) on a steam-bath for 6 hr. Extraction into chloroform and crystallisation as above gave 1-epigeigerin (82 mg.). Acetylation with pyridine–acetic anhydride overnight at room temperature gave the parent acetate.

Anhydrogeigerin and its Hydrogenation.—The conjugated dienone (III; R = OAc, 11αMe) (42 mg.), in acetone (1·5 ml.) and acetic acid (1·5 ml.), was treated with M-chromous chloride in N-hydrochloric acid [20] (2 ml.) overnight at room temperature under nitrogen. Crystallisation of the product from methanol gave anhydrogeigerin [5] (III; R = H, 11αMe), identified by m. p., mixed m. p., and ultraviolet and infrared spectra.

Anhydrogeigerin (108 mg.) in ethanol (5 ml.) was hydrogenated over 5% palladised charcoal (50 mg.) (1 mol. uptake), to give *dihydroanhydrogeigerin* (XIII), needles, m. p. 139—141° (from methanol–ether–light petroleum), $[\alpha]_D$ +22° (*c* 0·80), $\lambda_{max.}$ 238 mμ (ε 16,500), $\nu_{max.}$ 1760, 1694, and 1645 cm.$^{-1}$ (Found: C, 72·45; H, 8·4. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·15%).

Dihydroanhydrogeigerin was unchanged on treatment with potassium t-butoxide in t-butyl alcohol–benzene (1 : 1) under nitrogen for 3 hr. at room temperature, or for 2½ hr. at reflux.

In an analogous experiment, anhydroisophoto-α-santonic lactone [1] (XIV) (56 mg.) in ethanol (5 ml.) was hydrogenated over 5% palladised charcoal (50 mg.) (1 mol. uptake), to give *dihydroanhydroisophoto-α-santonic lactone* (XV), prisms, m. p. 152—154° (from ethyl acetate–light petroleum), $[\alpha]_D$ −104° (*c* 1·00), $\lambda_{max.}$ 240 mμ (ε 16,200), $\nu_{max.}$ 1783, 1706, and 1653 cm.$^{-1}$ (Found: C, 72·55; H, 8·2. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%). This compound was recovered unchanged from treatment with 5% hydrogen chloride in dimethylformamide at 50°, with perchloric acid (70%)–acetic acid (1 : 9) at 70°, with 4% ethanolic sodium hydroxide at room temperature for 4 hr., or with potassium t-butoxide under the conditions given above.

Similarly, hydrogenation of anhydroisophoto-β-santonic lactone (11-epimer of XIV) gave a *dihydro-derivative* (11-epimer of XV), needles, m. p. 180—182° (from ethyl acetate), $[\alpha]_D$ +17° (*c* 0·55), $\lambda_{max.}$ 240 mμ (ε 14,600), $\nu_{max.}$ 1775, 1697, and 1632 cm.$^{-1}$ (Found: C, 73·1; H, 8·1%).

Partial Synthesis of Anhydrogeigerin (III; R = H, 11αMe).—6-Deoxyisophotoartemisic acid acetate [1] (VII; R = H, R′ = OAc) (202 mg.), in perchloric acid (70%)–acetic acid (1 : 9) (20 ml.), was heated at 70° for 5 hr. (ultraviolet control using maximum at 300 mμ). The solution was extracted with chloroform and the organic layer washed with saturated aqueous sodium hydrogen carbonate. Chromatography of the product on alumina (grade III; 2 g.) in benzene gave 11-*epianhydrogeigerin* (III; R = H, 11βMe), needles, m. p. 107—108° (from ethyl acetate), $[\alpha]_D$ +18° (*c* 0·99), $\lambda_{max.}$ 299 mμ (ε 15,500), $\nu_{max.}$ 1770, 1690, and 1600 cm.$^{-1}$ (Found: C, 73·05; H, 7·7. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·4%).

Similarly, 6-deoxy-8-epi-isophotoartemisic acid acetate (VII; R = OAc, R′ = H) (137 mg.), in perchloric acid (70%)–acetic acid (1 : 9) (10 ml.), was heated at 70° for 7 hr. (ultraviolet control). Processing as above also gave 11-epianhydrogeigerin (III; R = H, 11βMe), identified by m. p., mixed m. p., $[\alpha]_D$, and ultraviolet and infrared spectra.

11-Epianhydrogeigerin had $[\alpha]_D$ +79° (*c* 0·95, in 1% ethanolic potassium hydroxide). Under the same conditions anhydrogeigerin showed $[\alpha]_D$ +77° (*c* 1·05). Accordingly, 11-epianhydrogeigerin (III; R = H, 11βMe) (55 mg.) in 1% ethanolic potassium hydroxide (2 ml.) was kept under nitrogen at room temperature for 20 min. Acidification with 2N-aqueous sulphuric acid, extraction into chloroform, and crystallisation of the product from ether–methanol gave anhydrogeigerin, identified by m. p., mixed m. p., $[\alpha]_D$, and ultraviolet and infrared spectra.

Partial Synthesis of Deoxygeigerin (IV; R = H).—8-Epi-isophotoartemisic lactone acetate (II; R = OAc, R′ = H, 6βH) (500 mg.) in dry dioxan (1·5 ml.) was treated at −5° with purified thionyl chloride (2·5 ml.) in dry pyridine (2·5 ml.) and dry dioxan (1·0 ml.) for 10 min. and poured into ice–water. Extraction into methylene dichloride and crystallisation from ethyl acetate–light petroleum gave the *anhydro-derivative* (VIII) (360 mg.) as prisms, m. p. 131—132°, $[\alpha]_D$ +192° (*c* 1·09), $\lambda_{max.}$ 236 mμ (ε 13,200), $\nu_{max.}$ 1785, 1742, 1705, 1647, and 900 cm.$^{-1}$ (Found: C, 66·9; H, 6·7. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

The 10(14)-olefin (VIII) (650 mg.) in ethanol (100 ml.) was hydrogenated over 10% palladised strontium carbonate (1·5 g.) (1·1 mol. uptake). Crystallisation of the product

[20] Cole and Julian, *J. Org. Chem.*, 1954, **19**, 131.

from ethyl acetate–light petroleum gave the *dihydro-derivative* (IX; R = Ac) (600 mg.) as prisms, m. p. 161—164°, $[\alpha]_D$ +150° (*c* 1·18), $\lambda_{max.}$ 236 mμ (ε 15,600), $\nu_{max.}$ 1785, 1742, 1703, and 1645 cm.$^{-1}$ (Found: C, 66·45; H, 7·2. $C_{17}H_{22}O_5$ requires C, 66·65; H, 7·25%).

This acetate (660 mg.), in distilled water (40 ml.) and saturated aqueous sodium hydrogen carbonate (20 ml.), was heated on a steam-bath for 24 hr., acidified with 2N-aqueous sulphuric acid, left at room temperature overnight, and saturated with sodium chloride. Extraction into chloroform and crystallisation of the product from ethyl acetate–light petroleum gave the *hydroxy-lactone* (IX; R = H) (300 mg.) as prisms m. p. 212—215°, $[\alpha]_D$ +184° (*c* 0·86), $\lambda_{max.}$ 238 mμ (ε 14,000), $\nu_{max.}$ 3400, 1777, 1700, and 1645 cm.$^{-1}$ (Found: C, 68·05; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·15; H, 7·65%). Treatment of this alcohol with pyridine–acetic anhydride overnight at room temperature gave the parent acetate (IX; R = Ac).

The acetate (IX; R = Ac) (500 mg.) in acetone (30 ml.) was treated with M-chromous chloride in N-hydrochloric acid (30 ml.) under nitrogen at room temperature for 3 days. Dilution with water, extraction into chloroform, and separation (sodium hydrogen carbonate) gave an acid fraction (80%) which could not be crystallised, although it had the expected ultraviolet and infrared spectra. This acid (400 mg.) in 5% aqueous sulphuric acid (48 ml.) was heated on a steam-bath for 6 hr. Chromatography of the neutral product on alumina (grade III) and crystallisation from ethyl acetate–light petroleum gave 11-*epideoxygeigerin* (XI) as long needles, m. p. 126—128°, $[\alpha]_D$ −59° (*c* 1·03), $\lambda_{max.}$ 237 mμ (ε 17,100), $\nu_{max.}$ 1770, 1696, and 1643 cm.$^{-1}$ (Found: C, 72·75; H, 8·35. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%).

11-Epideoxygeigerin (XI) (300 mg.) in 2% ethanolic potassium hydroxide (10 ml.) was left at room temperature for 30 min. Acidification with 2N-aqueous sulphuric acid, extraction into chloroform, and crystallisation of the product from ethyl acetate–light petroleum gave deoxygeigerin (IV; R = H) (150 mg.), identified by m. p., mixed m. p., $[\alpha]_D$, and ultraviolet and infrared spectra.

The hydroxy-lactone (IX; R = H) (112 mg.) in acetone (5 ml.) was treated with M-chromous chloride in N-hydrochloric acid (5 ml.) at room temperature under nitrogen for 3 days. Crystallisation of the product from ethyl acetate–light petroleum gave 1-*epi*-11-*epideoxygeigerin* (X) (90 mg.), m. p. 127—128°, $[\alpha]_D$ +190° (*c* 1·01), $\lambda_{max.}$ 239 mμ (ε 16,700), $\nu_{max.}$ 1770, 1695, and 1642 cm.$^{-1}$ (Found: C, 72·45; H, 8·15%).

1-Epi-11-epideoxygeigerin (X) (30 mg.) in 5% aqueous sulphuric acid (3 ml.) was heated on a steam-bath for 4 hr. Crystallisation of the product from ethyl acetate–light petroleum gave 11-epideoxygeigerin, identified by m. p., mixed m. p., $[\alpha]_D$, and ultraviolet and infrared spectra.

1-Epi-11-epideoxygeigerin (X) (75 mg.) in ethanol (8 ml.) was hydrogenated over 10% palladised charcoal (50 mg.) (1·1 mol. uptake), to give *dihydro-1-epi-11-epideoxygeigerin*, m. p. 135—137° (from ethyl acetate–light petroleum), $[\alpha]_D$ −103° (*c* 1·06), $\nu_{max.}$ 1765 and 1735 cm.$^{-1}$ (Found: C, 71·85; H, 9·1. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%).

Preparation of 1-*Epideoxygeigerin* (V; R = R′ = H).—1-Epigeigerin (V; R = H, R′ = OH) (see above) (51 mg.) in dry pyridine (1 ml.) was treated with methanesulphonyl chloride (redistilled; 1 ml.) at 0° for 15 hr. Filtration of the product in methylene dichloride through alumina (grade III), and crystallisation from ether–benzene, gave 1-*epigeigerin methanesulphonate* (V; R = H, R′ = O·SO_2Me) of uncertain purity (35 mg.), m. p. 127—130° (decomp.), $[\alpha]_D$ +77° (*c* 0·80), $\lambda_{max.}$ 236 mμ (ε 13,000), $\nu_{max.}$ 1775, 1710, 1648, 1358, and 1180 cm.$^{-1}$ (Found: S, 8·8. $C_{16}H_{22}O_6S$ requires S, 9·45%).

The methanesulphonate (35 mg.) in acetone (2 ml.) and acetic acid (1 ml.) was treated with M-chromous chloride in N-hydrochloric acid (3 ml.) at room temperature under nitrogen for 15 hr. Crystallisation of the product from ethyl acetate–light petroleum gave 1-*epideoxygeigerin* (V; R = R′ = H) (18 mg.), m. p. 128—130°, $[\alpha]_D$ +130° (*c* 0·65), $\lambda_{max.}$ 238 mμ (ε 14,000), $\nu_{max.}$ 1760, 1696, and 1645 cm.$^{-1}$ (Found: C, 72·8; H, 8·5. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%).

Alternatively, 1-epi-11-epideoxygeigerin (X) (104 mg.), in ethanol (6 ml.) and 4% ethanolic potassium hydroxide (6 ml.), was left at room temperature for 4 hr., acidified with 2N-aqueous sulphuric acid, and left for 4 hr. Extraction into methylene dichloride and crystallisation of the product from ether gave 1-epideoxygeigerin (V; R = R′ = H) (49 mg.).

1-Epideoxygeigerin (25 mg.) in 5% aqueous sulphuric acid (2·5 ml.) was heated on a steam-bath for 12 hr. Crystallisation of the product from ethyl acetate–light petroleum gave deoxygeigerin.

Oximes of 11-*Epideoxygeigerin* (XI) *and Related Compounds*.—11-Epideoxygeigerin (42 mg.), in ethanol (0·5 ml.) containing hydroxylamine hydrochloride (55 mg.) and pyridine (3 drops), was left at room temperature for 15 hr. Crystallisation of the product from ethyl acetate–light petroleum gave 11-*epideoxygeigerin oxime* (XII; R = H) (40 mg.), m. p. 212—216°, $[\alpha]_D$ −97° (*c* 0·78), $\lambda_{max.}$ 211 mμ (ε 19,000), $\nu_{max.}$ 3600, 1765, and 1643 cm.$^{-1}$ (Found: C, 68·8; H, 7·7; N, 5·45. $C_{15}H_{21}NO_3$ requires C, 68·5; H, 8·0; N, 5·3%).

Deoxygeigerin oxime (11-epimer of XII, R = H) had m. p. 193—197° (from ethyl acetate–light petroleum), $[\alpha]_D$ −45° (*c* 0·68), $\lambda_{max.}$ 242 mμ (ε 19,000), $\nu_{max.}$ 3600, 1765, and 1642 cm.$^{-1}$ (Found: C, 68·25; H, 7·7; N, 5·25%).

Anhydrogeigerin oxime had m. p. 191—197° (from ethyl acetate), $[\alpha]_D$ −172° (*c* 0·71, in acetic acid), $\lambda_{max.}$ 288 mμ (ε 23,000), $\nu_{max.}$ 3620, 1763, 1640, and 1605 cm.$^{-1}$ (Found: C, 69·05; H, 7·9; N, 5·1. $C_{15}H_{19}NO_3$ requires C, 68·95; H, 7·35; N, 5·35%).

11-*Epianhydrogeigerin oxime* had m. p. 250° (decomp.) (from ethyl acetate), $[\alpha]_D$ +11° (*c* 0·74, in acetic acid), $\lambda_{max.}$ 289 mμ (ε 26,400), $\nu_{max.}$ 1752, 1642, and 1600 cm.$^{-1}$ (Found: C, 68·95; H, 7·1; N, 5·25%).

11-Epideoxygeigerin oxime and 11-epianhydrogeigerin oxime were recovered unchanged after treatment with 2—4% ethanolic potassium hydroxide at room temperature for up to 4 hr.

11-Epideoxygeigerin (XI) (79 mg.), in ethanol (1 ml.) containing methoxyamine hydrochloride (97 mg.) and pyridine (7 drops), was left at room temperature for 24 hr. Crystallisation of the product from methylene dichloride–light petroleum gave 11-*epideoxygeigerin* O-*methyl oxime* (XII; R = Me) (80 mg.), m. p. 162—163°, $[\alpha]_D$ −87° (*c* 0·90), $\lambda_{max.}$ 248 mμ (ε 20,000), $\nu_{max.}$ 1765 and 1625 cm.$^{-1}$ (Found: C, 69·1; H, 8·3. $C_{16}H_{23}NO_3$ requires C, 69·3; H, 8·35%).

Deoxygeigerin O-*methyl oxime* (11-epimer of XII, R = Me) had m. p. 107—109° [from methylene dichloride–light petroleum (b. p. 40—60°)], $[\alpha]_D$ −21° (*c* 1·12), $\lambda_{max.}$ 249 mμ (ε 20,000), $\nu_{max.}$ 1762 and 1622 cm.$^{-1}$ (Found: C, 69·5; H, 8·55%). 11-Epideoxygeigerin *O*-methyl oxime (XII; R = Me) (20 mg.) in ethanol (1 ml.) and 8% ethanolic potassium hydroxide (1 ml.) were kept at room temperature for 4 hr., acidified with aqueous acetic acid, set aside at room temperature for 4 hr., diluted with water, and extracted into chloroform. Crystallisation from methylene dichloride–light petroleum (b. p. 40—60°) gave deoxygeigerin *O*-methyl oxime.

Dihydroisophoto-α-santonic lactone (" unstable " epimer) [1] gave an *oxime*, m. p. 107—113° (from aqueous methanol), $[\alpha]_D$ +8° (*c* 1·00, in EtOH), $\nu_{max.}$ 3630, 1762, and 1603 cm.$^{-1}$ (Found: C, 60·2; H, 8·55; N, 4·85. $C_{15}H_{23}NO_4,H_2O$ requires C, 60·3; H, 8·35; N, 4·7%). The *oxime* from the corresponding " stable " epimer [1] had m. p. 107—113° (from aqueous methanol), $[\alpha]_D$ +31° (*c* 0·90, in EtOH), $\nu_{max.}$ 3640, 1762, and 1603 cm.$^{-1}$ (Found: C, 59·6; H, 8·25; N, 4·65%). The " unstable " epimer oxime was recovered unchanged {$[\alpha]_D$ +8° (*c* 0·77, in EtOH)} after treatment with 4% ethanolic potassium hydroxide at room temperature for 6 hr.

Acetoxylation of Deoxygeigerin (with T. Miki) (IV; R = H).—Deoxygeigerin (52 mg.) and lead tetra-acetate (400 mg.), in glacial acetic acid (6 ml.), acetic anhydride (1·0 ml.), and boron trifluoride etherate (1 ml.), were kept at room temperature for 18 hr. Addition of water and extraction into chloroform gave 2-*acetoxydeoxygeigerin* (44 mg.), m. p. 190—207° (from ethyl acetate), $[\alpha]_D$ +49° (*c* 0·70), $\lambda_{max.}$ 240 mμ (ε 14,000), $\nu_{max.}$ 1773, 1755, 1722, 1647, and 1245 cm.$^{-1}$ (Found: C, 66·75; H, 7·2. $C_{17}H_{22}O_5$ requires C, 66·7; H, 7·2%). 2-Acetoxydeoxygeigerin (50 mg.), in acetone (5 ml.) and acetic acid (1 ml.), was treated with M-chromous chloride in N-hydrochloric acid (3 ml.) at room temperature overnight, to give deoxygeigerin (35 mg.) (from ethyl acetate–light petroleum).

Sodium [1-^{14}C]acetate (0·1 mc; 0·55 mg.) and lead tetra-acetate (150 mg.), in acetic acid (1 ml.) and acetic anhydride (0·1 ml.), were kept for 6 hr. with occasional heating to maintain a homogeneous solution. Deoxygeigerin (20 mg.) and boron trifluoride etherate (0·3 ml.) were added and the solution was set aside at room temperature for 22 hr. Dilution with water, extraction into chloroform, and crystallisation from ethyl acetate gave 2-acetoxydeoxygeigerin (17,800 counts/min./mg.). The combined mother-liquors were diluted with inactive geigerin acetate (29 mg.). Chromatography in benzene on alumina (grade III), and crystallisation from ethyl acetate–light petroleum, gave material of constant activity (34 counts/min./mg.). Conversion into the 2,4-dinitrophenylhydrazone and crystallisation from ethyl acetate afforded material of constant activity (21 counts/min./mg.). These two figures are in agreement, and indicate a yield of geigerin acetate of 0·28%.

Sodium [1-^{14}C]acetate (see above; 1 mg.) and lead tetra-acetate (300 mg.), in glacial acetic acid (2 ml.) and acetic anhydride (0·2 ml.), were warmed occasionally during 3 hr., and left

at room temperature overnight. Deoxygeigerin (80 mg.) and boron trifluoride etherate (0·6 ml.) were added and the solution was left at room temperature for 7 hr. Processing as above gave geigerin acetate (0·11%), confirmed by conversion into the 2,4-dinitrophenylhydrazone as before.

The following " control " experiment was carried out to prove that the deoxygeigerin used in the above experiments was not contaminated with geigerin. Sodium [1-^{14}C]acetate (see above; 0·45 mg.), in glacial acetic acid (1 ml.) and acetic anhydride (0·1 ml.), was warmed on a steam-bath for 30 min. to allow exchange. Boron trifluoride etherate (0·3 ml.) and deoxygeigerin (19 mg.; same batch of compound used for all the radiochemical experiments) were added at room temperature, and the solution was kept for 15 hr. Dilution of the product with geigerin acetate (25 mg.) and recrystallisation from ethyl acetate–light petroleum gave inactive geigerin acetate (count equal to background).

Geigerin (50 mg.), in glacial acetic acid (2 ml.), acetic anhydride (0·2 ml.), and boron trifluoride etherate (0·6 ml.) containing sodium acetate (1 mg.), was left at room temperature for 15 hr. Dilution with water, extraction into chloroform, and crystallisation of the product gave geigerin acetate (45 mg.). Any geigerin present in the batch of deoxygeigerin would, therefore, have been acetylated under the conditions of the radiochemical experiments.

Preparation of 2-Bromolumisantonin (with R. A. Silva).—Lumisantonin (XVI; X = H) (425 mg.) in ethyl acetate (20 ml.) was titrated with bromine (1 ml.) in ethyl acetate (25 ml.) (1 mol. uptake) at room temperature, and left overnight at 0°. Lumisantonin dibromide crystallised (274 mg.), m. p. 105—120° (decomp.), $\lambda_{max.}$ 235 mμ (ε 3000), $\nu_{max.}$ (Nujol) 1778 and 1710 cm.$^{-1}$. Without further purification this material (272 mg.), in methylene dichloride (3 ml.) and dry triethylamine (15 ml.), was heated on a steam-bath for 30 min. Removal of the solvent *in vacuo* and crystallisation of the product from methylene dichloride–light petroleum gave *2-bromolumisantonin* (XVI; X = Br) (172 mg.) as hexagonal prisms, m. p. 179—181°, $[\alpha]_D$ −2° (*c* 2·53), $\lambda_{max.}$ 243 and 283 (ε 4500 and 2500), $\nu_{max.}$ 1785, 1710, and 1580 cm.$^{-1}$ (Found: C, 55·2; H, 5·5; Br, 24·75. $C_{15}H_{17}BrO_3$ requires C, 55·4; H, 5·25; Br, 24·55%).

Alternatively, 2-bromosantonin (see above) (906 mg.) in dioxan (140 ml.) was irradiated with a high-pressure mercury-arc lamp (infrared control). Removal of the solvent *in vacuo* and chromatography of the product on alumina (grade III) gave, on elution with benzene and crystallisation from ethyl acetate–light petroleum, 2-bromolumisantonin (163 mg.), identified by m. p., mixed m. p., $[\alpha]_D$, and ultraviolet and infrared spectra.

2-Bromolumisantonin (526 mg.), in methanol (100 ml.) and triethylamine (20 ml.), was hydrogenated over 5% palladised charcoal (448 mg.) (2 mol. uptake). Crystallisation of the product from ethyl acetate–light petroleum (b. p. 40—60°) gave dihydrolumisantonin [17-19] (262 mg.), identified by m. p., mixed m. p., $[\alpha]_D$, and ultraviolet and infrared spectra.

2-Bromolumisantonin (480 mg.) in methanol (100 ml.) was hydrogenated over 5% palladised charcoal (527 mg.) (2 mols. uptake). Crystallisation of the product from ethyl acetate–light petroleum gave the cyclopentanone (XVII) [18,19] (73 mg.) (Found: C, 72·3; H, 8·2. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·1%).

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