234. *Constituents of the Leaves of Certain* Leucadendron *Species. Part II. Degradation Experiments with Leucodrin.*

By William Sage Rapson.

Dibromoleucodrin has been shown to be analogous in structure to leucodrin itself, its acidity being due to the enhanced reactivity of the phenolic hydroxyl group. The degradation of leucodrin with a variety of reagents has been studied, and conclusions are drawn with regard to its structure.

In a preliminary study (J., 1938, 282) leucodrin ($C_{15}H_{16}O_8$) was characterised as containing two lactone groups and one phenolic and three alcoholic hydroxyl groups. From the results of potash fusion experiments the phenolic hydroxyl was deduced as being present in a *p*-hydroxyphenylethyl group. Dichloroleucodrin and dibromoleucodrin, however, differed from the parent substance in behaving like monoacidic dilactones. It has now been found that dibromoleucodrin gives a series of derivatives completely analogous to those of leucodrin itself, and it appears as if its acidity, as well as that of its chlorine analogue, has its origin in the increased acidity of the phenolic group resulting from the presence of the halogen atoms in the *o*-positions. Apart from the studies of Bennett, Brooks, and Glasstone (J., 1935, 1821), scanty data are available as to the effects of halogen substituents on the acidity of phenols, and it has been difficult to find simple analogies to the present case. Dibromo-*p*-cresol, which Zincke and Wiederhold (*Annalen*, 1902, **320**, 204) state to be soluble in warm sodium bicarbonate solution, gave only a very indistinct end-point in titrations with phenolphthalein as indicator. 3 : 5-Dibromo-4-hydroxybenzoic acid and its ethyl ester, however, were accurately titratable with alkalis.

Formaldehyde has been identified as one product of the action of lead tetra-acetate on leucodrin and various derivatives. In no case, however, has it been possible to characterise any other product of the oxidation. Leucodrin, dibromoleucodrin, leucodrin methyl ether, and bromoleucodrin methyl ether all yielded intractable oils as the major products of the reaction. These are probably mixtures. In an attempt to overcome this difficulty, *acetyliso-propylideneleucodrin methyl ether* was hydrolysed and a *monoacetyl-leucodrin methyl ether* obtained. This, however, was not attacked by lead tetra-acetate. The same result was obtained when a *leucodrin dimethyl ether*, formed by the hydrolysis of iso*propylidene-leucodrin dimethyl ether*, was submitted to this reagent. It is unlikely, therefore, that the hydroxyl groups which react with acetone in the formation of *iso*propylideneleucodrin are the two in the group $C(OH)\cdot CH_2\cdot OH$ which gives rise to the formaldehyde in the oxidations with lead tetra-acetate. The third alcoholic hydroxyl group must be involved, and the close proximity of all three alcoholic groups therefore seems certain. An attempt to protect the $CH_2\cdot OH$ group during degradation with lead tetra-acetate failed because leucodrin methyl ether did not give a triphenylmethyl ether with triphenylchloromethane.

As already described (*loc. cit.*), anisic acid has been obtained by the oxidation of leucodrin methyl ether. It has not been possible to moderate this reaction so as to give intermediate products. On the other hand, *leucodrin tetramethyl ether*, when subjected to the action of potassium permanganate, was so inert that under mild conditions no oxidation occurred at all. With more vigorous conditions, anisic acid and unchanged initial material could be isolated from the reaction mixture, but no remnant of the aliphatic side chain. From the amount of potassium permanganate consumed, it appears as if this is completely oxidised once attack begins.

With nitric acid, leucodrin tetramethyl ether readily yielded *nitroleucodrin tetramethyl ether*, but this was attacked only very slowly by hot concentrated nitric acid. The substance formed has been characterised as a dilactonic acid, $C_{18}H_{19}O_{11}N$, and it is apparently derived by the oxidation of $CH_2\cdot OMe \longrightarrow CO\cdot OH$. The carboxyl group can be esterified by the catalytic method with ease, and since it is not eliminated when the acid is heated above 150°, it is unlikely that the $CH_2\cdot OH$ group from which it is derived is attached to the same carbon atom as either of the lactonic carboxyl groups. Indications have been obtained also that the free hydroxyl groups generated when leucodrin tetramethyl ether is dissolved in alkali are not on adjacent carbon atoms, since, when such solutions were acidified with periodic acid, no reduction of the periodic acid was observed.

Leucodrin tetramethyl ether was unattacked by hydrogen peroxide in alkaline solution. Both the monomethyl and the dimethyl ether, however, gave rise to anisylsuccinic acid as a product of oxidation. The presence of the group (I) in leucodrin thus seems certain, and its partial structure can be written as (II) or (III). Other structures either are improbable or

(*p*)$HO\cdot C_6H_4\cdot$  $H\cdot CH_2\cdot C$
(I.)

(*p*)$HO\cdot C_6H_4\cdot$  $H\cdot CH_2\cdot C_6H_8O_5$
(II.)

(*p*)$HO\cdot C_6H_4\cdot$  $H\cdot C_6H_8O_5$
(III.)

do not allow of the close proximity of the three alcoholic hydroxyl groups. A limited number of structures of each type is possible in view of the degradations described above, and it should be possible to distinguish between these.

The effects of other oxidising agents on leucodrin have also been studied. Selenium dioxide under various conditions proved unreactive; the use of mercuric oxide led to no identifiable products, and an attempt to apply the Weerman reaction failed when it was found that *bromoleucodrin tetramethyl ether* did not yield a dihydroxydiamide with ammonia. Leucodrin methyl ether was recovered unchanged after treatment with the Oppenauer reagent, and failed to give characterisable products with chromic acid.

Experimental.

iso*Propylidenedibromoleucodrin.*—A solution of dibromoleucodrin in a large excess of acetone containing 0·5% of dry hydrogen chloride was kept for 48 hours. The acid was then neutralised with lead carbonate, and the filtered solution evaporated. The residue was crystallised from aqueous alcohol. It sintered at 249°, and formed a meniscus in the melting-point tube at 257° (Found : C, 42·0; H, 3·7; Br, 30·7. $C_{18}H_{18}O_8Br_2$ requires C, 41·4; H, 3·4; Br, 30·7%). It was insoluble in sodium bicarbonate solution.

*Diacetyl*iso*propylidenedibromoleucodrin*, obtained from the above substance by the action of cold acetic anhydride and pyridine, crystallised from alcohol in needles, m. p. 218—221° (Found : C, 43·6; H, 3·9; Br, 26·6. $C_{22}H_{22}O_{10}Br_2$ requires C, 43·6; H, 3·7; Br, 26·4%).

Dibromoleucodrin Tetramethyl Ether.—Methylation of dibromoleucodrin proceeded vigorously when it was mixed in acetone solution with methyl iodide and silver oxide. When the silver oxide was exhausted, the solids were removed, the filtrate evaporated, and the residue warmed with more silver oxide and methyl iodide. Four such treatments yielded a product which partially crystallised on treatment with alcohol. Recrystallised from this solvent, the product had m. p. 136·5—137·5° and was unaffected by treatment with acetic anhydride [Found : C, 42·4; H, 3·9; OMe, 22·9. $C_{15}H_{10}O_4Br_2(OMe)_4$ requires C, 42·4; H, 4·2; OMe, 23·3%].

iso*Propylidenedibromoleucodrin Methyl Ether.*—*iso*Propylidenedibromoleucodrin (1 g.) was dissolved in methyl alcohol, and an ethereal solution of diazomethane added until vigorous evolution of nitrogen no longer occurred and the solution had attained a slight permanent yellow coloration. It was kept for 10 minutes, the excess of diazomethane destroyed with acetic acid, and the solvents evaporated. The residue was a viscous oil which crystallised after several hours. The rhombic prisms obtained by repeated crystallisation from methyl alcohol sintered sharply at 175—176° but gave a clear melt and a meniscus only at 203° (Found : C, 42·3; H, 3·8; OMe, 6·2. $C_{19}H_{20}O_8Br_2$ requires C, 42·5; H, 3·8; OMe, 5·8%).

Dibromoleucodrin Methyl Ether.—This was best obtained by heating the above substance in methyl-alcoholic hydrochloric acid for 5—10 minutes. On dilution of the reaction mixture with water and cooling, a sticky material separated which crystallised after several hours. The same slowness in crystallisation was observed during purification, the *ether* separating gradually from aqueous methyl alcohol in needles, m. p. 179—180° after slight sintering. It was insoluble in sodium bicarbonate solution, and could be recovered unchanged after heating with strong alkali (Found : C, 38·8; H, 3·3. $C_{16}H_{16}O_8Br_2$ requires C, 38·7; H, 3·2%). Four attempts were made under different conditions to prepare this substance directly from dibromoleucodrin by the action of diazomethane. From only one of the products, however, was it obtained, and even then its purification was a long process.

Oxidation of Leucodrin Methyl Ether with Lead Tetra-acetate.—Leucodrin methyl ether (5 g.) was dissolved in pure acetic acid (75 c.c.), an excess of lead tetra-acetate (6 g.) added, and after 24 hours the mixture was warmed at 50° for ½ hour and an aqueous solution of sodium sulphate was added to destroy the excess of the tetra-acetate and to precipitate lead salts. The filtered solution was evaporated in a vacuum; on addition of Brady's reagent to the distillate, formaldehyde-2 : 4-dinitrophenylhydrazone was obtained, identified by a mixed m. p. test with an authentic specimen. The residue was viscous, and the organic material was extracted from it with ether. Evaporation of the dried extract, however, gave an oil, from which nothing crystalline could be obtained by the action of solvents, of ketonic reagents, or of acetic anhydride; with Brady's reagent it gave a non-crystalline product which was obviously a mixture. The same types of products were obtained from leucodrin itself, and from dibromoleucodrin, even when periodic acid was used in place of lead tetra-acetate.

Monoacetyl-leucodrin Methyl Ether.—Acetyl*iso*propylideneleucodrin methyl ether (6 g.) was

dissolved in acetic acid (45 c.c.), and concentrated hydrochloric acid (0·9 c.c.) added. The mixture was heated in a water-bath at 60° for 1 hour, and water then added. The *product* crystallised on scratching, and separated from dilute acid in colourless needles, m. p. 102—103° (Found : C, 54·4; H, 5·5. $C_{18}H_{20}O_9,H_2O$ requires C, 54·3; H, 5·5%). After treatment with lead tetra-acetate in acetic acid solution for 4 hours at 70°, it was recovered unchanged.

iso*Propylideneleucodrin Dimethyl Ether.*—After two treatments with silver oxide and methyl iodide in pure acetone solution, a product was obtained which crystallised from slightly aqueous alcohol in plates, m. p. 123·5—124·5° [Found : C, 61·4; H, 6·2; OMe, 16·0. $C_{18}H_{18}O_6(OMe)_2$ requires C, 61·2; H, 6·1; OMe, 15·8%]. On hydrolysis with hydrochloric acid in alcoholic solution, it gave a viscous oil. It is presumably an iso*propylideneleucodrin dimethyl ether.* On treatment with lead tetra-acetate in the usual way it was not attacked (the mixture failed to react with ketonic reagents). With hydrogen peroxide in alkaline solution it yielded anisylsuccinic acid. Left in contact with acetic anhydride and pyridine for 36 hours, it failed to give a crystalline acetyl derivative, behaving very much like leucodrin methyl ether in this respect.

Leucodrin Tetramethyl Ether.—After four successive treatments with methyl iodide and freshly prepared silver oxide, leucodrin gave a product which crystallised in contact with alcohol, separating from this solvent in prisms, m. p. 123—124° [Found : C, 59·7; H, 6·2; OMe, 32·4. $C_{15}H_{12}O_4(OMe)_4$ requires C, 60·0; H, 6·3; OMe, 32·6%]. In a typical attempt to degrade this substance with potassium permanganate, it was dissolved (5 g.) in aqueous alkali, and 4% permanganate solution [200 c.c. (9 O) and, after 20 hours, a further 100 c.c.] added; anisic acid was ultimately isolated, together with unchanged material (1—2 g.).

Solutions of the *tetramethyl ether* in alkali did not deposit this substance on acidification unless heated. The ether (accurately weighed) was therefore dissolved in the requisite amount of 0·2N-alkali, and the cooled solution acidified with a measured excess of a standard periodic acid solution. After 2 hours, the periodic acid was estimated iodometrically; none had been consumed.

Nitroleucodrin Tetramethyl Ether.—Leucodrin tetramethyl ether (0·2 g.) was heated on the water-bath for 20 minutes with a mixture of nitric acid (2·5 c.c.), water (1·5 c.c.), and acetic acid (1 c.c.). The *product*, precipitated from the mixture by the addition of water and cooling, crystallised from ethyl alcohol in rhombohedral prisms, m. p. 162—163° (Found : C, 53·3; H, 5·3; N, 3·3. $C_{19}H_{23}O_{10}N$ requires C, 53·6; H, 5·4; N, 3·3%). In an attempt to obtain degradation products from this substance, it was heated with concentrated nitric acid at 100° for 3 days. On dilution with water, solid material separated, which was separated into an acidic and a non-acidic fraction by the action of sodium bicarbonate solution. The neutral fraction predominated and was identified as the initial material. The *acid* fraction was recrystallised six times from aqueous methyl alcohol, its m. p. rising gradually to 139—140·5° [Found : C, 50·4; H, 4·8; N, 3·5; OMe, 21·3; equiv., 142. $C_{18}H_{19}O_{11}N$ (two lactone groups and one acidic group) requires C, 50·7; H, 4·7; N, 3·3; OMe, 21·3%; equiv., 142]. No other product could be isolated.

The *ethyl* ester of this acid crystallised from its solution in dry alcoholic hydrogen chloride when this was left overnight. It was not very soluble in alcohol, and was recrystallised from aqueous acetone, separating in rectangular prisms, m. p. 169·5—170·5° (Found : C, 52·8; H, 5·0. $C_{20}H_{23}O_{11}N$ requires C, 52·9; H, 5·3%).

Bromoleucodrin Tetramethyl Ether.—The ether (2 g.) was dissolved in methyl alcohol, and a solution of bromine (1 c.c.) in methyl alcohol added. The alcohol was then distilled off,and the solid residue recrystallised from ethyl alcohol. It separated in radiating clusters of prismatic crystals, m. p. 158·5—159·5° [Found : C, 49·1; H, 4·8. $C_{15}H_{11}BrO_4(OMe)_4$ requires C, 49·6; H, 5·0%]. It was dissolved in a dry alcoholic solution of ammonia and kept for 36 hours. On evaporation of the alcohol in a vacuum, a residue was obtained which would not crystallise. It dispersed in water to give an opaque solution, and when this was warmed with dilute acid the initial material was regenerated. The same type of product was obtained under similar conditions from leucodrin methyl ether.

Oxidation of Leucodrin Methyl Ether with Alkaline Hydrogen Peroxide.—The ether (3 g.) was dissolved in 20% sodium hydroxide solution (10 c.c.), and 30% hydrogen peroxide (11 c.c.) added. The temperature was kept at 30—35° for 2 hours, hydrogen peroxide (10 c.c. of 30%) added, and the temperature raised to 45° for 3 hours. On acidification there was a vigorous effervescence and crystals separated. These were recrystallised from slightly alcoholic water, separating in elongated rectangular plates, m. p. 199·5—200·5°, decomp. with evolution of gas above 205° [Found : C, 58·8; H, 5·3; OMe, 14·4; equiv., 112. Calc. for $C_{11}H_{12}O_5$ (dibasic) :

C, 58·9; H, 5·3; OMe, 13·9%; equiv., 112]. It gave a positive fluorescein reaction when treated with sulphuric acid and resorcinol, and with acetyl chloride gave an anhydride, m. p. 91°, from which the initial material could be regenerated with water. Anisylsuccinic acid has been reported (J., 1924, **127**, 560; *J. Amer. Chem. Soc.*, 1928, **50**, 2836) to give an anhydride, m. p. 91°, and to melt between 195° and 207° according to the rate of heating.

UNIVERSITY OF CAPE TOWN, SOUTH AFRICA. [*Received, April 5th,* 1939.]