238. *Constituents of the Leaves of Certain* Leucadendron *Species. Part III. Oxidations of Leucodrin Derivatives with Periodic Acid and Lead Tetra-acetate.*

By William Sage Rapson.

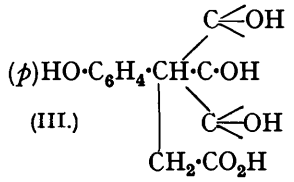
Quantitative oxidations of both the hydrated and the unhydrated forms of leucodrin methyl ether and leucodrin tetramethyl ether with periodic acid and lead tetra-acetate have been carried out. Although interpretation of the results in terms of a full structure for leucodrin has not been possible, it seems certain that leucodrin has the partial structure (II), and possibilities with regard to the finer details of its structure are discussed in the light of this, and the other new data obtained.

In Part II (J., 1939, 1085) two alternative formulations were suggested for leucodrin, namely, (I) and (II). These were based on the isolation of anisylsuccinic acid as a product of the action of alkaline hydrogen peroxide on leucodrin methyl ether, and on a demonstration of the close proximity of the three alcoholic hydroxyl groups present in its structure. The anisylsuccinic acid was isolated in these experiments in its racemic modification. It has now been isolated in an optically active form by treatment of hydrated leucodrin methyl ether with periodic acid, and has been shown to racemise with ease in alkaline media. The facts that epimerisation phenomena have not been observed in a study of leucodrin and of its derivatives, and that this optically active modification could be obtained from leucodrin methyl ether after prolonged heating with alkalis, seem definitely to exclude structures of type (I).

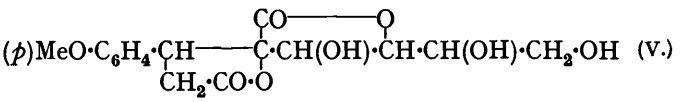
(I.) $(p)HO\cdot C_6H_4\cdot \underset{CO\cdot O\cdot}{CH}\cdot CH_2\cdot C_5H_8O_3\cdot CO\cdot O\cdot$ $\qquad$ $(p)HO\cdot C_6H_4\cdot \underset{CH_2\cdot CO\cdot O\cdot}{CH}\cdot C_5H_8O_3\cdot CO\cdot O\cdot$ (II.)

In the $C_5H_8O_3$ residue of (II) there are to be accommodated three alcoholic hydroxyl groups, and points of ring closure for the two lactone groups, so that all the five carbon atoms are oxygenated. Both lactone ring systems have been established as being fairly stable, since mutarotation has not been observed on solution of leucodrin in aqueous or aqueous-alcoholic media; and on acidification of alkaline solutions of leucodrin and of leucodrin methyl ether, the optical rotatory powers of the solutions reverted during 80—100 hours to those recorded for solutions of the corresponding lactonic forms. The slowness with which the lactone ring systems are re-formed after acidification of alkaline solutions of leucodrin and its derivatives has allowed oxidations to be effected in two different ways. In acid media it has been found possible to effect oxidations without hydration of the lactone groups occurring, and, for example, both lead tetra-acetate and periodic acid reacted stoicheiometrically with leucodrin methyl ether, giving up two equivalents of oxygen and generating one mol. of formaldehyde. On the other hand, when leucodrin or its methyl ether was dissolved in alkali, and the solution acidified with excess of periodic acid, eight equivalents of oxygen were absorbed. At the same time still the one mol. of formaldehyde was formed, and the other identified product of the reaction was anisylsuccinic acid in an

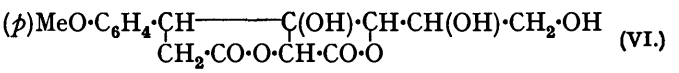
optically active form. Lead tetra-acetate reacted slightly differently when its acetic acid solutions were added to alkaline solutions of leucodrin methyl ether. Approximately 15 equivalents of oxygen were absorbed, but still the one mol. of formaldehyde was produced. It is probable, from the amount of formaldehyde generated in this reaction, and from the amount of oxygen absorbed, that but the one $CH_2{\cdot}O$ group is present in the $C_5H_8O_3$ residue, and that this therefore contains but the one branch in its carbon skeleton; and from the formation of anisylsuccinic acid and not one of its half-aldehydes in the periodic acid oxidation, this branch must occur as in (III) in the hydrated form of the leucodrin structure.



(III.)



(V.)



(VI.)

Support for this comes from similar oxidation experiments with leucodrin methyl ether. This substance was unattacked when its alkaline solutions were acidified with periodic acid, indicating that the alcoholic groups of the hydrated material are not on adjacent carbon atoms. When its alkaline solutions were acidified with acetic acid solutions of lead tetra-acetate, however, two equivalents of oxygen were absorbed, and a monobasic *acid* $C_{18}H_{26}O_8$ (IV) formed. This corresponds to the oxidation of a $>C(OH){\cdot}CO_2H$ group in hydrated leucodrin tetramethyl ether to $>CO$. Two alternative structures (V) and (VI) appear possible for leucodrin methyl ether according as to whether the hydroxyl group involved in this oxidation is in the γ- or the δ-position with respect to the other carboxyl group.

Neither of these is completely satisfactory. The oxidation of the hydrated form of (V) with periodic acid would be expected to yield 1-keto-2-anisylglutaric acid, and not anisylsuccinic acid. On the other hand, structure (VI), while explaining the production of three equivalents of acid (as yet unidentified in character) in the periodic acid oxidation of hydrated leucodrin methyl ether, fails in one important respect. Such a structure should yield glyoxylic acid as one product of such oxidation. The elegant method of Fosse and Hieulle (*Compt. rend.*, 1925, **181**, 286) has, however, repeatedly failed to show the presence of this acid among the products of this oxidation.

Other modes of degradation have not thrown any further light on this structural problem. Unsuccessful attempts have been made to determine the nature (aldehydic or ketonic) of the carbonyl group which must be present in (IV). But (IV) has proved unreactive towards ketonic reagents, and has given intractable products with even the mildest oxidising agents. Similar results were experienced when working with its bromo-derivative, prepared by the oxidation of bromoleucodrin tetramethyl ether with lead tetra-acetate. In further experiments unsuccessful attempts were made to reduce leucodrin tetramethyl ether by the action of sodium and absolute alcohol, and similar failure attended attempts to reduce the lactone groups of this substance by the action of sodium amalgam in acid media (cf. Wolff, *Annalen*, 1881, **208**, 109). Oxidation experiments with the leucodrin dimethyl ether already described (Part II, *loc. cit.*) gave no significant results, and attempts to prepare other partially methylated leucodrins have failed. Reductions of leucodrin with phosphorus and hydriodic acid have been carried out, but have yielded only intractable products.

Experimental.

Mutarotation Experiments.—(a) *Leucodrin.* The value $[\alpha]_D^{17°} - 19{\cdot}2°$ (*c*, 3·5 in 40% alcohol) remained unaltered after 100 hours. In order to follow the closure of the lactone rings of leucodrin polarimetrically, the solution used for the above determination (25 c.c.) was treated with N-alkali (10 c.c.), kept for 10 minutes, and then acidified with dilute sulphuric acid and made up to 50 c.c. Found immediately: $[\alpha]_D^{16°} + 25{\cdot}7°$ (*c*, 1·75); after 17 hours $[\alpha]_D^{15°}$ 0°;

after 100 hours $[\alpha]_D^{15°}$ −18·5°. (b) *Leucodrin methyl ether.* The value $[\alpha]_D^{15°}$ −19·9° (*c*, 3 in 40% alcohol) also was unaltered by standing. The solution used for the determination (25 c.c.) was treated with alkali, and the solution acidified and made up to 50 c.c. as described above. Found immediately: $[\alpha]_D^{15°}$ + 21·9° (*c*, 1·5); after 18 hours, $[\alpha]_D^{16°}$ 0°; after 80 hours $[\alpha]_D^{16°}$ − 16·2°. At this stage leucodrin methyl ether crystallised from the solution, and no more observations were possible.

Oxidations of Leucodrin Methyl Ether in the Lactonic Form.—(a) *With periodic acid.* The leucodrin methyl ether (*ca.* 20 mg.) was dissolved in water (20 c.c.), and a measured excess of 2% periodic acid solution added. After 2 hours reaction was complete, and the decrease in the oxidising power of the solution was determined iodometrically (Found: oxygen absorbed, 1·98 equivs.).

To determine the amount of formaldehyde generated in this reaction, leucodrin methyl ether (*ca.* 250 mg.) was dissolved in water, excess of periodic acid solution added, and the mixture kept in a stoppered bottle for 2 hours. Saturated sodium acetate solution (30 c.c.) was added, followed by a 70% solution of dimedon in alcohol (6 c.c.). The solution was shaken at frequent intervals during 3 hours, and the crystalline precipitate then collected (Found: CH_2O formed, 0·96 mol.).

In an attempt to isolate the other product of the reaction, the mixture after oxidation had been effected was shaken with barium carbonate for 2 hours, and the liquid filtered from insoluble salts and evaporated in a vacuum (bath temperature 50°). The residue was sticky and contained enmeshed crystals of inorganic matter. Efforts to purify and characterise it failed.

(b) *With lead tetra-acetate.* A weighed amount of leucodrin methyl ether was treated with an excess of standard N/10-lead tetra-acetate (McClenahan and Hockett, *J. Amer. Chem. Soc.*, 1938, **60**, 2061) and kept for 4 hours, and the decrease in the oxidising power of the solution determined by adding solutions of sodium acetate and potassium iodide and titrating the liberated iodine with thiosulphate (Found: oxygen absorbed, 2·00 equivs.).

Oxidations of Leucodrin Methyl Ether in the Hydrated Form.—(a) *With periodic acid.* The leucodrin methyl ether (*ca.* 10 mg.) was dissolved in N/10-sodium hydroxide (10 c.c.), and an excess (10 c.c.) of a standardised solution of potassium periodate in dilute sulphuric acid added. After 2 hours the oxidising power of the solution was determined iodometrically and compared with that in a suitably conducted blank experiment (Found: oxygen absorbed, 8·04 equivs.).

To determine the formaldehyde formed in this reaction, leucodrin methyl ether (*ca.* 250 mg.) was oxidised as above, and the formaldehyde–dimedon condensation product then precipitated as described in the case of the oxidation in the lactonic form (Found: CH_2O formed, 1·01 mols.).

The determination of the acidity developed in the reaction was complicated by the fact that acidimetric estimations with phenolphthalein as indicator were impossible in the presence of periodic acid. In practice it was found feasible to reduce all the periodic acid to iodic acid with ethylene glycol before carrying out the titrations. Leucodrin methyl ether (*ca.* 300 mg.) was dissolved in an excess of N/10-alkali, and the solution made neutral to phenolphthalein with acid. An excess of a periodic acid–sulphuric acid solution was added, and the mixture kept for 2 hours. The excess of periodic acid was then reduced by the addition of a few drops of ethylene glycol, and after 2 hours the acidity of the solution was determined by titration with N/10-baryta solution and compared with that obtained in an analogously conducted blank experiment (Found: acidity generated in the reaction, 2·95 equivs.).

In a further experiment leucodrin methyl ether (2 g.) was dissolved in N-alkali (15 c.c.), and a solution of potassium periodate in excess of dilute sulphuric acid solution added. After 2·5 hours, the solution was saturated with ammonium sulphate and extracted with ether. The ethereal extracts were washed with sodium thiosulphate solution and dried, and the ether evaporated. The residue was acidic and was recrystallised from water, from which it separated in prismatic needles. It sintered in the m. p. tube at 188·5—190° and formed a meniscus at 196—198°. This behaviour was not altered by repeated crystallisation [Found: equiv., 112·5. Calc. for $C_{11}H_{12}O_5$ (dibasic): equiv., 112]. Its m. p. was raised by admixture with the anisylsuccinic acid obtained from leucodrin methyl ether by the action of alkaline hydrogen peroxide (J., 1939, 1088). After heating in 20% sodium hydroxide solution for 8 hours, however, its crystal form altered and its m. p. rose to that of this material. At the same time its optical activity, $[\alpha]_D^{17°}$ approx. −100° (*c*, 1 in 50% alcohol), disappeared. This same product, presumably *l*-anisylsuccinic acid, was also isolated when leucodrin methyl ether was oxidised as above, after 12 hours' previous heating on the water-bath with 20% potassium hydroxide solution.

Attempts to characterise glyoxylic acid as a product of this reaction were made as follows:

Leucodrin methyl ether (*ca.* 300 mg.) was dissolved in N/10-alkali (25 c.c.), and an excess of periodic acid–sulphuric acid mixture added. After 2 hours the excess of periodic acid and the iodic acid formed in the reaction were removed by pouring the further acidified mixture into a slight excess of sodium sulphide solution. Sodium acetate was then added, followed by hydrazine hydrate (5—6 drops). On addition of a solution of xanthydrol (1 g.) in acetic acid (110 c.c.), and subsequent dilution of the reaction mixture to 500 c.c., turbidity developed and a precipitate formed on shaking. This was collected, but no acidic material could be extracted from it with alcoholic sodium hydroxide solution (cf. Fosse and Hieulle, *Compt. rend.*, 1925, **181**, 286). The fact that the acidic condensation product of glyoxylic acid could be isolated if tartaric acid was added to the initial reaction mixture established the correctness of the procedure.

(b) *With lead tetra-acetate.* Leucodrin methyl ether (*ca.* 50 mg.) was dissolved in an excess of N/10-alkali, and into the solution was run an excess of N/10-lead tetra-acetate solution in acetic acid. After 4 hours the remaining lead tetra-acetate was estimated iodometrically (Found : oxygen absorbed, 14·95 equivs.).

To determine the amount of formaldehyde generated in this reaction, the leucodrin methyl ether (*ca.* 70 mg.) was dissolved in alkali, and just a few drops less than the calculated amount of lead tetra-acetate solution run in. When the oxidising agent had disappeared, the reaction mixture was cooled in ice, a 6% alcoholic solution of dimedon (5 c.c.) added, and the acetic acid almost neutralised by the careful addition of 50% potassium hydroxide solution. As the neutral point was approached, the solution became turbid and crystals separated. The solution was diluted with water, and after 4 hours the condensation product was collected, and its purity established by a mixed m. p. determination (Found : CH_2O formed, 0·99 mol.). The general application of lead tetra-acetate for oxidations in aqueous acetic acid media was described by Baer, Grosheintz, and Fischer (*J. Amer. Chem. Soc.*, 1939, **61**, 2607) after the above experiments had been effected.

Oxidation of Leucodrin Tetramethyl Ether in the Hydrated Form with Lead Tetra-acetate.—Quantitative experiments were carried out as already described for leucodrin methyl ether (Found : oxygen absorbed, 2·06 equivs.). In order to isolate the product of the oxidation, leucodrin tetramethyl ether (2 g.) was dissolved in an excess of N/10-alkali, and to the solution was added just more than the calculated amount of lead tetra-acetate solution. After 4 hours the excess of the oxidising agent was destroyed by the addition of a drop of lactic acid, and the reaction mixture was evaporated in a vacuum (bath temperature 55°). Water was added to the residue, and the organic matter extracted with ether. Evaporation of the washed and dried extracts gave a clear viscous residue, which crystallised in contact with water. It was purified by repeated separation from alcohol with water, separation in a crystalline condition (plates) occurring only after considerable dilution. The material melted indefinitely at 73—76·5° and this, and its peculiar behaviour during recrystallisation, were established as due to the presence of water of crystallisation—the anhydrous compound being a viscous substance which could not be induced to crystallise [Found (crystalline material) : C, 55·8; H, 7·1; H_2O lost at 100°, 4·5; equiv. (approx.), 380. $C_{18}H_{26}O_8,H_2O$ (monobasic) requires C, 55·7; H, 7·2; H_2O, 4·6%; equiv., 388]. It gave no semicarbazone or 2 : 4-dinitrophenylhydrazone, and although it reduced silver oxide in suspension in dilute sodium hydroxide solution, no crystalline product of the reaction could be isolated. Acetylation experiments yielded similar intractable products, and after being left in acetone containing hydrogen chloride (0·5%) for 24 hours the substance was recovered unchanged. With nitric acid extensive oxidation occurred.

Oxidation of Bromoleucodrin Tetramethyl Ether in the Hydrated Form with Lead Tetra-acetate.—This was effected as already described for leucodrin tetramethyl ether. The product was recrystallised from dilute acetic acid, separating in radiating clusters of prisms, m. p. 178° (decomp.) (Found : equiv., 450. Calc. for $C_{18}H_{25}O_8Br$: equiv., 449). No characterisable product was obtained from it by the action of a suspension of strontium carbonate in bromine water.

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