The Structure and Chemistry of Leucodrin

By G. W. Perold and K. G. R. Pachler

A novel oxidation procedure for cleaving glycol groups has been applied to leucodrin aryl methyl ether, to yield norleucodrinic acid aryl methyl ether. The study of derivatives of this product allows the derivation of the structure of leucodrin; the stability of the nor-derivative towards alkaline hydrogen peroxide is demonstrated. The cleavage of an intermediate α-keto-acid with periodic acid is substantiated.

LEUCODRIN, $C_{15}H_{16}O_8$, from various *Leucadendron* spp., was previously studied by Rapson,[1] who showed that it is a phenolic dilactone containing three alcoholic hydroxyl groups. He finally proposed two alternative structures (I) and (II) for it. Both (I) and (II) were, however, suspect; thus, the degradation of the hydrated form of leucodrin aryl methyl ether with periodic acid gave *p*-methoxyphenylsuccinic acid, whereas β-(*p*-methoxyphenyl)-α-oxoglutaric acid would be expected from (I); on the other hand, the same reaction yielded no glyoxylic acid, which is an expected product from (II).

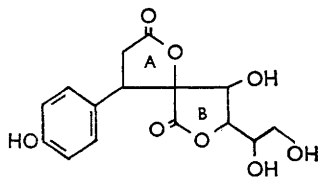
We now present chemical evidence [2] for structure (I)

[1] W. S. Rapson, *J. Chem. Soc.*, (*a*) 1938, 282; (*b*) 1939, 1085; (*c*) 1940, 1271.

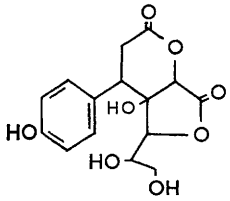
[2] G. W. Perold and K. G. R. Pachler, *Proc. Chem. Soc.*, 1964, 62.

for leucodrin * and demonstrate its unusual chemical behaviour.†

The lactonic carbonyl groups of leucodrin give rise to two strong peaks at 1800 cm.$^{-1}$ (a γ-lactone ring carrying



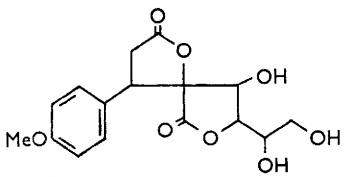
(I)



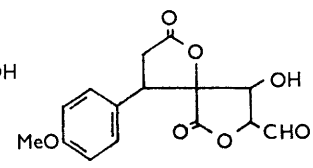
(II)

an electronegative substituent in the γ-position [4,5a] [(I), ring A] and 1770 cm.$^{-1}$ (the normal γ-lactone ring) [(I), ring B]. This agrees with the dilactone situation of structure (I) and negates the dilactonic structure (II). The peak at 840 cm.$^{-1}$ confirms [5b] the 1,4-substitution pattern of the aromatic ring, while the bathochromic and hyperchromic shifts of the ultraviolet absorption peak in alkaline solution demonstrate the presence of the *p*-hydroxyphenyl unit.

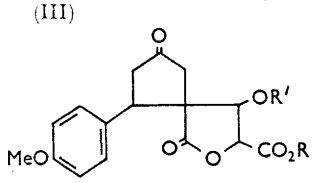
The presence of a glycol side-chain was demonstrated by Rapson [1c] who obtained 1 mol. of formaldehyde on reaction of periodic acid with leucodrin in either the lactonic or the hydrated form. The glycol hence contains a terminal primary hydroxyl group; as the major reaction product of this oxidation could not be characterised (also in our hands), this left the nature of the other hydroxyl group of the glycol undefined. The glycol cleavage of leucodrin aryl methyl ether (III) with periodic acid in the presence of chromic acid has now yielded a fully characterised norleucodrinic acid aryl methyl ether (V; R = R′ = H), thus demonstrating



(III)



(IV)



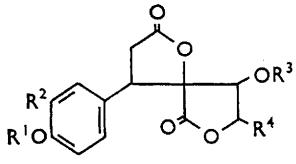
(V: R = H, Me, Et; R′ = H, Ac)

the secondary–primary nature of the glycol group. This mixture of oxidants is used in dilute solution under mild conditions; the more powerful ‡ oxidant, periodic acid, specifically cleaves the glycol ethane bond, and also regenerates the chromic acid as it in turn is consumed in specifically oxidising the intermediate aldehyde (IV) to the carboxylic acid (V).

Norleucodrinic acid aryl methyl ether (V; R = R′ = H) crystallised as the monohydrate, m. p. 120°. It consumed no lead tetra-acetate in acetic acid solution in 24 hr., so that an α-hydroxy-acid structure is here not involved. The high acid strength (pK_a ~3·1) is therefore in accord with the electronegative lactone closure in the α-position to the newly formed carboxyl group. Esters and their acetates were readily obtained from this product, and their infrared spectra confirmed this substitution pattern. Thus, the lower-frequency absorption of lactone ring B of leucodrin is in this series of derivatives increased and coincides with the higher-frequency absorption of lactone ring A (Table 1).

TABLE 1

Infrared carbonyl absorption in potassium bromide medium * for



R^1	R^2	R^3	R^4	$\nu_{max.}$ (cm.$^{-1}$) (with rel. peak area)	
H	H	H	CH(OH)·CH$_2$·OH	1791(1)	1765(1)
Me	H	H	CO$_2$H	1795(2)	1730(1)
Me	H	H	CO$_2$Me	1802(2)	1768(1)
Me	H	Ac	CO$_2$Me	1805(2)	1760(2)
Me	H	H	CO$_2$Et	1800(2)	1757(1)
Me	H	Ac	CO$_2$Et	1805(2)	1751(1)
Me	Cl	H	CO$_2$Me	1801(2)	1765(1)
Me	Cl	Ac	CO$_2$Me	1801(2)	1760(2)
Me	Cl	H	CO$_2$Et	1801(2)	1754(1)

* Samples of ~0·5 mg. in 300 mg. of KBr were scanned on the Perkin-Elmer model 521 spectrophotometer to locate the maxima for the purpose of this comparison.

The acetates of these methyl and ethyl esters (V) proved on the whole to be sufficiently soluble in deuteriochloroform to afford satisfactory nuclear magnetic resonance (n.m.r.) spectra. Where pyridine had to be used as solvent the chemical shifts are subject to specific solvent–solute interactions, and these spectra are therefore not specifically referred to in the following discussion. The n.m.r. results are in Table 2.

The τ-values observed for the aromatic protons are as expected from known substituent effects,[6] the A_2B_2 (and ABC) type spectra obtained confirming the known substitution pattern of the aromatic rings. Chemical shifts for acetyl, methyl, and ethyl groups (and for the side-chain protons of leucodrin tetra-acetate) are in accord with other reported data on proton resonances in

* The structure of dibromoleucodrin has been shown [3] to correspond to (I) by *X*-ray diffraction analysis.

† Presented in part at the (I.U.P.A.C.) Third International Symposium on the Chemistry of Natural Products, Kyoto, April 1964.

‡ The following values are from W. M. Latimer, "Oxidation Potentials," 2nd edn., Prentice-Hall, Englewood Cliffs, New Jersey, 1961, pp. 69 and 249.

$H_5IO_6 + H^+ + 2e^- \longrightarrow IO_3^- + 3H_2O$; $E°$, 1·6 v.

$Cr_2O_7^{2-} + 14H^+ + 6e^- \longrightarrow 2Cr^{3+} + 7H_2O$; $E°$, 1·3 v.

[3] R. D. Diamand and D. Rogers, *Proc. Chem. Soc.*, 1964, 63.

[4] W. Brügel, G. Stengel, F. Reicheneder, and H. Suter, *Angew. Chem.*, 1957, **68**, 441.

[5] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd edn., Methuen, London, 1959, (*a*) p. 187; (*b*) p. 65.

[6] G. W. Smith, *J. Mol. Spectroscopy*, 1964, **12**, 146, and references cited there.

similar chemical environments.[7] The τ-values for the protons situated on the two lactone rings do, however, deviate considerably from the values expected from the γ-butyrolactone spectrum [8] allowing for the appropriate substituent effects.[9] These protons experience unusual shielding–deshielding effects due to the variety of centres of magnetic anisotropy present (phenyl, carboxyl, carbonyl groups) and to the rigid and compact nature of the molecule.

The protons of lactone ring B give rise to an AB system with a vicinal coupling constant of ~8·5 c./sec., in good agreement with the couplings observed in βγ-dicarboxy-γ-butyrolactone.[10] In the spectrum of leucodrin tetra-acetate, proton B is further split by a spin–spin interaction with a side-chain proton. The downfield shift of proton A on acetylation (τ_{CHOH}, 5·06 to τ_{CHOAc}, 4·06) observed for the ethyl ester of compound

TABLE 2

N.m.r. data on derivatives of norleucodrinic acid aryl methyl ether (V)

Assignment	Spectral type	(V; R = Me, R′ = H) *	(V; R = Et, R′ = H)	(V; R = Me, R′ = Ac)	(V; R = Et, R′ = Ac)
Aromatic protons	A_2B_2 †	Obscured by solvent	$\tau_A \sim 3{\cdot}0$ ‡ $\tau_B \sim 2{\cdot}6$	$\tau_A \sim 3{\cdot}0$ ‡ $\tau_B \sim 2{\cdot}7$	$\tau_A \sim 3{\cdot}0$ ‡ $\tau_B \sim 2{\cdot}7$
Lactone ring A CH–CH_2	ABC	τ_A 5·15, $^3J_{AB}$ 13·0 τ_B 6·48, $^3J_{AC}$ 8·7 τ_C 6·96, $^2J_{BC}$ −17·4	τ_A 5·50, $^3J_{AB}$ 13·6 τ_B 6·71, $^3J_{AC}$ 8·2 τ_C 7·03, $^2J_{BC}$ −17·4	τ_A 5·77, $^3J_{AB}$ 13·5 τ_B 6·72, $^3J_{AC}$ 8·6 τ_C 7·13, $^2J_{BC}$ −17·6	τ_A 5·77, $^3J_{AB}$ 13·3 τ_B 6·71, $^3J_{AC}$ 8·8 τ_C 7·13, $^2J_{BC}$ −17·3
Lactone ring B CH–CH	AB	τ_A 4·64, $^3J_{AB}$ 8·6 τ_B 5·56	τ_A 5·06, $^3J_{AB}$ 8·8 τ_B 6·00	τ_A 4·09, $^3J_{AB}$ 8·7 τ_B 6·04	τ_A 4·06, $^3J_{AB}$ 8·6 τ_B 6·08
Ar–OMe	Singlet	τ 6·30	τ 6·16	τ 6·17	τ 6·16
CO_2 Me	Singlet	τ 6·40	—	τ 6·23	—
CO_2Et	A_3X_2	—	τ_X 5·70, $^3J_{AX}$ 7·3 τ_A 8·71	—	τ_X 5·76, $^3J_{AX}$ 7·1 τ_A 8·74
OAc	Singlet	—	—	τ 7·68	τ 7·67

N.m.r. data on derivatives of *m*-chloro-norleucodrinic acid aryl methyl ether (IX)

Assignment	Spectral type	(IX; R = Me, R′ = H) *	(IX; R = Et, R′ = H) *	(IX; R = Me, R′ = Ac)
Aromatic protons	ABC	Obscured by solvent	Obscured by solvent	$\tau_A \sim 3{\cdot}0$ ‡ $\tau_B \sim 2{\cdot}7$ $\tau_C \sim 2{\cdot}6$
Lactone ring A CH–CH_2	ABC	τ_A 5·14, $^3J_{AB}$ 12·8 τ_B 6·44, $^3J_{AC}$ 8·3 τ_C 6·85, $^2J_{BC}$ −17·4	τ_A 5·14, $^3J_{AB}$ 12·8 τ_B 6·44, $^3J_{AC}$ 8·4 τ_C 6·86, $^2J_{BC}$ −17·2	τ_A 5·80, $^3J_{AB}$ 13·2 τ_B 6·74, $^3J_{AC}$ 8·2 τ_C 7·10, $^2J_{BC}$ −17·3
Lactone ring B CH–CH	AB	τ_A 4·60, $^3J_{AB}$ 8·7 τ_B 5·47	τ_A 4·59, $^3J_{AB}$ 8·6 τ_B 5·47	τ_A 4·08, $^3J_{AB}$ 8·4 τ_B 5·99
Ar–OMe	Singlet	τ 6·24	τ 6·26	τ 6·06
CO_2Me	Singlet	τ 6·39	—	τ 6·21
CO_2Et	A_3X_2	—	τ_X 5·90, $^3J_{AX}$ 7·1 τ_A 9·00	—
OAc	Singlet	—	—	τ 7·66

N.m.r. data on leucodrin tetra-acetate

Assignment	Spectral type	Tetra-acetate of compound (I)
Aromatic protons	A_2B_2	$\tau_A \sim 2{\cdot}8$ ‡ $\tau_B \sim 2{\cdot}6$
Lactone ring A CH–CH_2	ABC	τ_A 5·80, $^3J_{AB}$ 12·4 τ_B 6·72, $^3J_{AC}$ 7·8 τ_C7·13, $^2J_{BC}$ −17·2
Lactone ring B CH–CH	AB	τ_A 4·18, $^3J_{AB}$ 8·3 τ_B 6·23 Proton B is further split by proton X in the side-chain; $^3J_{BX}$ 2·4
Side-chain CH_2–CH	A_2X	τ_A 5·95, $^3J_{AX}$ 6·4 τ_X 4·90
OAc	Singlet	τ_1 7·71 (2 OAc), τ_2 7·89, τ_3 8·06

* Solution in pyridine. † Nomenclature according to Pople, Schneider, and Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill, London, 1959, ch. 5.2. ‡ ~Indicates less accurate values (±0·1 p.p.m.).

[7] N.M.R. Spectra Catalogue, Varian Associates, Palo Alto, California.

[8] Ref. 7, spectrum No. 63.

[9] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959.

[10] Ref. 7, spectrum No. 456.

(V) proves that this alcoholic hydroxyl group is secondary.

The part of the n.m.r. spectrum assigned to the remaining protons of lactone ring A constitute a strongly coupled three-spin system (ABC) due to the magnetic non-equivalence of the methylene protons. The magnitude of the geminal coupling, assumed to be of negative sign, can only be explained by the hyperconjugative effect of an adjacent π-bond centre. The increase in magnitude of ~5 c./sec. as compared to the coupling constant in methane (−12·4 c./sec.) [11] suggests a five-membered ring with a dihedral angle of ~30° between the π-electron and the methylene protons.[12] The π-electron enhancement in a six-membered ring would be expected to be much smaller (≤2 c./sec.).

Information on the conformation of the lactone ring A may be obtained from the vicinal coupling constants. The $\cos^2\phi$ relationship between vicinal coupling constants and dihedral angle of the coupling protons calculated theoretically by Karplus [13] for an ethane fragment has been applied successfully in some instances [14] to determine the conformation of five-membered rings. Although recent investigations indicate that the Karplus equation should not be used on a quantitative basis, qualitative conclusions may be drawn from experimentally determined parameters; in this case the values of the vicinal coupling constants for the lactone ring A protons show that the dihedral angles between the methine CH bond and the methylene CH bonds must be ~30° and ~150°, thus indicating a considerable buckling of this lactone ring.

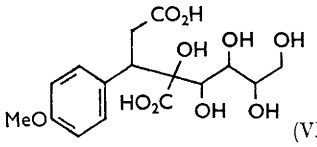
On this basis we assign the methylene proton exhibiting the larger vicinal coupling (B) to the proton *trans* to the methine proton A. This assignment is supported by the chemical shift data; the lower τ-value (6·7) observed for proton B as compared to proton C is attributed to the deshielding effect of the aromatic ring, which is *cis* to proton B and would thus affect this proton to a greater extent. Further support for this assignment is obtained by comparing the τ-values of proton C of (V; R = Et, R′ = H) and of (V; R = Et, R′ = Ac). The *X*-ray data [3] show that the secondary hydroxyl group of lactone ring B is close to proton A on lactone ring A which is *cis* to proton C. Acetylation of this hydroxyl group causes an upfield shift of the resonance of protons A (+0·27 p.p.m.) and B (+0·10 p.p.m.), but does not affect the resonance position of proton C, which is on the other side of lactone ring A.

Rapson [1b] degraded leucodrin aryl methyl ether with hydrogen peroxide in alkaline solution to racemic *p*-methoxyphenylsuccinic acid. We have confirmed this by direct comparison of the product with a synthetic sample,[15] and also observed that this product was only partly racemised (see Experimental section).

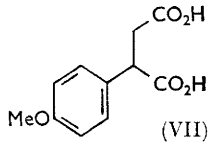
* The reported [16] value is $[\alpha]_D^{29}$ −122° (in ethanol).

[11] M. Karplus, D. H. Anderson, T. C. Farrar, and H. S. Gutowsky, *J. Chem. Phys.*, 1957, **27**, 597.
[12] M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, 1963, **85**, 1899.
[13] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

On applying this reaction to norleucodrinic acid aryl methyl ether (V; R = R′ = H), this oxidative cleavage of the polyhydroxy side-chain was shown to be quite specific. Leucodrin aryl methyl ether (III) in the hydrated form (VI) presents a regularly hydroxylated side-chain to this oxidant, and it is readily cleaved to the corresponding succinic acid derivative (VII). The hydrated form (VIII) of the norleucodrinic acid ether



(VI)



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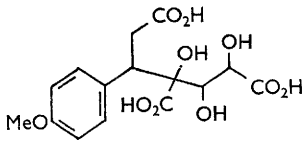
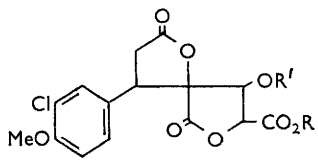


(VIII)



(IX: R = H, Me, Et; R′ = H, Ac)

(V; R = R′ = H), however, possesses a polyhydroxy carboxylate side-chain which is so resistant to this reagent that very little of the hydrogen peroxide is consumed. On finally acidifying with hydrochloric acid, free chlorine is therefore produced and *m*-chloronorleucodrinic acid aryl methyl ether (IX; R = R′ = H) is formed in high yield in the ring-closed dilactonic form.

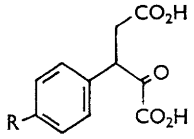
The spectral characteristics of (IX) and its ester and acetate derivatives clearly support its relationship to the chlorine-free analogue (V). The three aromatic protons now seen for (IX) show the expected pattern, whereas the lactonic protons show no change. These data are included in Tables 1 and 2 and furthermore confirm the conclusions drawn above.

Periodic acid cleaved the hydrated form of leucodrin aryl methyl ether to yield [1c] *p*-methoxyphenylsuccinic acid in an optically active form with $[\alpha]_D$ −100°. This cleavage applied to the hydrated form of (V; R = R′ = H) now gave an optically purer form of (−)-*p*-methoxyphenylsuccinic acid with $[\alpha]_D$ −126° (in 50% ethanol).*

While some α-keto-acids are now known [17] to be cleaved with periodic acid, this cleavage is fairly slow. In the present context the α-keto-acid here concerned, β-(*p*-methoxyphenyl)-α-oxoglutaric acid (XI), and its methoxyl-free analogue (X) were therefore synthesised [18] and their reaction with periodic acid studied. In aqueous acetic acid solution ("acid start") both (X)

[14] R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *J. Chem. Soc.*, 1962, 3699; R. J. Abraham and K. A. McLauchlan, *J. Mol. Phys.*, 1962, **5**, 513; R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 1964, 3739; R. J. Abraham, *ibid.*, 1965, 256.
[15] V. Askam and W. H. Linnell, *J. Chem. Soc.*, 1954, 2436.
[16] M. Naps and I. B. Johns, *J. Amer. Chem. Soc.*, 1940, **62**, 2450.
[17] D. B. Sprinson and E. Chargaff, *J. Biol. Chem.*, 1946, **164**, 433.
[18] G. W. Perold and H. K. L. Hundt, following Paper.

and (XI) slowly consumed periodic acid (see Experimental section), the presence of the electron-releasing *para*-substituent in (XI) increasing the rate of reaction to almost twice that of (X).



(X: R = H)

(XI: R = MeO)

When the keto-acids were initially dissolved in aqueous alkali and then acidified with periodic acid ("alkaline start"), thus simulating the reaction conditions employed in the degradation of the hydrated form of leucodrin to *p*-methoxyphenylsuccinic acid, this relationship between reaction rates for (X) and (XI) was roughly maintained, with both rates increased about ten-fold (Table 3). In preparative experiments

TABLE 3

Moles of periodic acid consumed per mole of aryloxoglutaric acids (X) and (XI)

"Acid start"			"Alkaline start"		
Time (hr.)	(X)	(XI)	Time (hr.)	(X)	(XI)
1	0·06	0·11	0·5	0·09	0·18
5	0·08	0·18	1·5	0·19	0·31
20	0·22	0·35	4	0·32	0·55
40	0·32	0·55			
Approx. rate of change	0·007	0·012	Approx. rate of change	0·07	0·11

the same relationship was found. After a reaction time of 105 mins. the product from (X) was only chromatographically shown to contain phenylsuccinic acid; in the case of (XI) the same conditions gave a product from which *p*-methoxyphenylsuccinic acid could be isolated in pure form in 16% yield.

EXPERIMENTAL

Melting points are corrected. Some of the infrared spectra were taken on the Perkin-Elmer model 21 instrument,* others as noted. Ultraviolet absorptions were measured on the Unicam S.P. 500 spectrophotometer. Specific rotations were measured at room temperature in 50% ethanol solutions. N.m.r. spectra were recorded on a Varian A60 spectrometer (probe temperature ~35°) of dilute solutions (≤5 mole %) in deuteriochloroform or pyridine solution with tetramethylsilane as internal reference. Explicit analyses of n.m.r. spectra were performed for the lactone ring protons only, using a computer programme for the direct analysis of three-spin systems as described by Brügel *et al.*[19] for the ABC analyses; the accuracy is estimated to be ±0·01 p.p.m. for the chemical shifts and ±0·2 c./sec. for the coupling constants.

Leucodrin.—Milled air-dried leaves of *Leucadendron adscendens* (1·1 kg.) were left overnight with 4 l. of 96% ethanol, the extract recovered using a basket centrifuge, and the extraction repeated once. The combined extracts were reduced to 1 l. *in vacuo*, diluted with 1 l. of water, and basic lead acetate (200 g.) in 3 l. of water added. The filtered light yellow solution was concentrated to 300 ml. *in vacuo*; leucodrin crystallised (80 g.), m. p. 202—206°. Pure leucodrin was obtained from water (45 g.), m. p. 216° (Found: C, 55·5; H, 5·0. Calc. for $C_{15}H_{16}O_8$: C, 55·6; H, 5·0%), $[\alpha]_D$ −21° (*c* 1·7), $\lambda_{max.}$ (in water) 222, 269 mμ (ε 8540, 1150), (in 0·1N-NaOH) 237, 284 mμ (ε11,500, 1860), $\nu_{max.}$ 3520, 3465, 3295, 3135 (OH); 1800, 1770 (C=O); 840 (1,4-substituted benzene ring). Leucodrin tetra-acetate (from leucodrin dissolved in acetic anhydride and pyridine [1a]) had m. p. 192·5—193·5° (Found: C, 55·8, 55·8; H, 4·9, 4·9. Calc. for $C_{23}H_{24}O_{12}$: C, 56·1; H, 4·9%).

Leucodrin Aryl Methyl Ether (III).—To a stirred mixture of leucodrin (15 g.), water (25 ml.), and dimethyl sulphate (10 ml.), was gradually added 13·5N-potassium hydroxide solution (14 ml.), followed by two further 10-ml. additions of dimethyl sulphate and altogether 21 ml. of 13·5N-potassium hydroxide solution. After adding 20 ml. of 9N-hydrochloric acid and heating at 95° for 10 min., the solution was cooled, to give (after two crystallisations from water) 10 g. of the monohydrate of (III), m. p. 174·5° after loss of water through 100° and resolidification (Found: C, 57·0; H, 5·4. Calc. for $C_{16}H_{18}O_8,H_2O$: C, 56·8; H, 5·4%). This simplified preparation of (III) confirms the stereochemical stability of the spiro-dilactone configuration of leucodrin, as the same compound is now obtained when passing through an intermediate alkaline stage as previously with diazomethane in ether.[1a] Dreiding models of leucodrin clearly show the steric interference between the *ortho* hydrogen atoms of the benzene ring and the secondary hydroxyl group of lactone ring B when the aromatic ring is in the enantiomeric situation on lactone ring A.

In 0·1N-lead tetra-acetate solution in acetic acid the consumption of reagent [g.-atom of O/mole of (III) at room temperature] was: 0·5 hr., 0·22; 1 hr., 0·34; 2 hr., 0·57. In acetic acid containing 20% of water, 1·0 g.-atom of O/mole of (III) was taken up after 4 hr.

Norleucodrinic Acid Aryl Methyl Ether (V; R = R′ = H).—Leucodrin aryl methyl ether (III) (1 g., 3 mmoles) was stirred for 1 hr. at 35° with 1 l. of an aqueous solution containing 14 mmoles of chromium trioxide and 28 mmoles of periodic acid. The clear yellow solution was treated with excess of sulphur dioxide and the green solution extracted continuously with ether for 46 hr., to yield 843 mg. of a glassy residue which crystallised readily from hot water to give (V; R = R′ = H) as the *hydrate*, m. p. ~120°, pK_a ~3·1 [Found: C, 53·0, 52·8; H, 4·7, 4·7%; Equiv. (by dissolution in alkali and back-titration with acid), 115, 115; (by direct potentiometric titration with alkali), 338. $C_{15}H_{14}O_8,H_2O$ requires C, 53·0; H, 4·7%; Equiv. (dilactonic carboxylic acid), 113; (as monocarboxylic acid), 340]. No reaction occurred during 24 hr. at room temperature in 0·1N-lead tetra-acetate solution in acetic acid.

Norleucodrinic Acid Aryl Methyl Ether Ethyl Ester (V; R = Et, R′ = H).—When the glassy extract [863 mg.; from 1 g. of (III) as above] was heated in ethanolic solution for a few minutes, the ethyl ester (V; R = Et, R′ = H) crystallised on cooling (756 mg.), m. p. 170° (from ethanol) [Found: C, 58·4, 58·2; H, 5·2, 5·2; "MeO," 17·8, 17·5%; Equiv. (by dissolution in alkali and back-titration with acid), 117, 115. Calc. for $C_{17}H_{18}O_8$: C, 58·3; H, 5·2; (1 MeO) + (1 EtO) as "MeO," 17·7%; Equiv. (dilactonic ester), 117].

The acetate (V; R = Et, R′ = Ac) of this hydroxy-ester was obtained by leaving it (330 mg.) in 1·5 ml. of acetic anhydride and 1·1 ml. of pyridine for 17 hr.; crystals from

* Dr. J. Morris and the S.A. Iron and Steel Industrial Corporation, Ltd., Pretoria, are particularly thanked for this assistance.

[19] W. Brügel, T. Ankel, and F. Krückeberg, *Z. Elektrochem.*, 1960, **64**, 1121.

acetic acid (330 mg.; m. p. 159°) [Found: C, 58·0; H, 5·2; "MeO," 15·3. Calc. for $C_{19}H_{20}O_9$: C, 58·2; H, 5·1; (1 MeO) + (1 EtO), as "MeO," 15·8%].

The methyl ester (V; R = Me, R′ = H) of the hydroxy-acid was obtained from it (100 mg.) by direct heating in methanol (35 mg. of product; m. p. 216°). Alternatively, the solution of the acid (390 mg.) in 20 g. of methanol containing 0·6 g. of dry hydrogen chloride was refluxed for 1 hr. and dried, to give 394 mg. of product; this was recrystallised from methanol (m. p. 216°) (Found: C, 56·9; H, 4·8; O, 37·5. Calc. for $C_{16}H_{16}O_8$: C, 57·2; H, 4·8; O, 38·1%).

The acetate (V; R = Me, R′ = Ac) of the foregoing methyl ester was prepared from it (202 mg.) in acetic anhydride and pyridine as before and crystallised from acetic acid (174 mg.; m. p. 134·5°) (Found: C, 57·4; H, 5·0; MeO, 15·6. Calc. for $C_{18}H_{18}O_9$: C, 57·2; H, 4·8; 2 MeO, 16·4%).

Partially Racemised p-*Methoxyphenylsuccinic Acid* (VII) *from* (III).—Leucodrin aryl methyl ether (III) (1 g.) in 10 ml. of 5N-sodium hydroxide was treated with two 10-ml. portions of 30% hydrogen peroxide solution as described.[1b] On adding 10 ml. of 9N-hydrochloric acid, effervescence occurred and needles separated (152 mg.), m. p. 197—198°. Two crystallisations from acetic acid gave (VII) (90 mg.), $[\alpha]_D$ −75°(*c* 1·2), m. p. 202·5°, and no depression of the m. p. on admixture with the synthetic[15] compound [Found: C, 59·2; H, 5·6; MeO, 14·0%; Equiv., 112. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4; MeO, 13·8%; Equiv. (dicarboxylic acid), 112]. The synthetic compound was obtained as described[15] and had m. p. 202·5—203° [Found: Equiv., 112, 113. $C_{11}H_{12}O_5$ requires Equiv. (dicarboxylic acid), 112].

(−)-p-*Methoxyphenylsuccinic Acid* (VII) *from Norleucodrinic Acid Aryl Methyl Ether* (V; R = R′ = H).—A solution of (V; R = R′ = H) (342 mg., 1 mmole) in 5 ml. of N-potassium hydroxide was heated for 15 min., cooled, and acidified with a solution of 1·17 g. (5 mmoles) of para-periodic acid and 5 ml. of 2N-sulphuric acid in 10 ml. of water, and kept for 90 min. at 32°. The colourless solution was treated with an excess of sulphur dioxide, cooled, and extracted continuously with ether for 16 hr., to yield an extract (246 mg.) which crystallised from hot water to give finally 64 mg. of *prisms*, m. p. 190·3—191°, $[\alpha]_D$ −126° (*c* 1·02) [Found: C, 59·3; H, 5·7%; Equiv., 111. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%; Equiv. (dicarboxylic acid), 112].

m-*Chloro-norleucodrinic Acid Aryl Methyl Ether* (IX; R = R′ = H).—Norleucodrinic acid aryl methyl ether (V; R = R′ = H) (501 mg.) in 5 ml. of 5N-sodium hydroxide was treated with two 5-ml. portions of 30% hydrogen peroxide as before; on acidifying with 5 ml. of 9N-hydrochloric acid, only very slight effervescence occurred. The product was 328 mg. of needles, m. p. ~145° (essentially unchanged on recrystallisation from water and from acetic acid) [Found: C, 48·4; H, 4·3; Cl, 11·2; * MeO, 10·5%; Equiv. (by dissolution in alkali and back-titration with acid), 128; (by direct potentiometric titration), 369. $C_{15}H_{13}ClO_8,H_2O$ requires C, 48·1; H, 4·0; Cl, 9·5; 1 MeO, 8·3%; Equiv. (dilactonic carboxylic acid), 125; (as monocarboxylic acid), 375].

The corresponding *methyl ester* (IX; R = Me, R′ = H) was obtained from the acid (439 mg.) by heating it for 7 hr. at 70° in 10 ml. of methanol containing 0·6 g. of dry hydrogen chloride. The product (331 mg.), m. p. 250—252°, was recrystallised from butanone, m. p. 255° [Found: C, 51·9; H, 4·1; Cl, 10·4; * O, 34·7; MeO, 16·6%; Equiv., 125. $C_{16}H_{15}ClO_8$ requires C, 51·9; H, 4·1; Cl, 9·6; O, 34·5; 2 MeO, 16·8%; Equiv. (dilactonic ester), 123].

Hydrolysis of this methyl ester (122 mg.) in 0·5N-sodium hydroxide in 50% ethanol for 2 hr. at 95° gave back the corresponding acid, m. p. ~140° and no depression on admixture with the original acid (Found: C, 48·2; H, 3·9. $C_{15}H_{13}ClO_8,H_2O$ requires C, 48·1; H, 4·0%).

The *acetate* (IX; R = Me, R′ = Ac) of m. p. 167—168° (139 mg.) was obtained by keeping the methyl ester (151 mg.) in acetic anhydride and pyridine as above (Found: C, 52·3; H, 4·5. Calc. for $C_{18}H_{17}ClO_9$: C, 52·4; H, 4·2%).

The *ethyl ester* (726 mg.) (IX; R = Et, R′ = H) was obtained by heating the acid (1·035 g.) in 50 g. of ethanol containing 1·5 g. of hydrogen chloride for 5 hr. and had m. p. 177·0—177·5° (from ethanol) (Found: C, 53·1; H, 4·6. Calc. for $C_{17}H_{17}ClO_8$: C, 53·1; H, 4·5%).

Periodic Acid Titrations of the β-*Aryl*-α-*oxoglutaric Acids* (X) *and* (XI) (Table 3).—"*Acid start.*" Samples (5—8 mg.) were kept in 2·8 ml. of 0·02M-periodic acid in aqueous acetic acid (60% water) at room temperature for the times given. Saturated aqueous sodium hydrogen carbonate solution (125 ml.), 10 ml. of 0·02N-sodium arsenite solution, and 0·5 ml. of 20% potassium iodide solution were then added, and the free iodine was titrated to a starch end-point after 10—15 min.

"*Alkaline start.*" Samples (5—8 mg.) were dissolved in 1·4 ml. of 0·036N-aqueous sodium hydroxide solution and acidified with 1·4 ml. of 0·042M-aqueous periodic acid; the further treatment was then as above.

Periodic Acid Oxidation of the β-*Aryl*-α-*oxoglutaric Acids* (X) *and* (XI).—(*a*) The phenyl-keto-acid[18] (X) (227 mg., 1·02 mmoles) was dissolved in 50 ml. of 0·1N-aqueous sodium hydroxide solution at room temperature and acidified with 25 ml. of 0·4N-sulphuric acid containing 2 mmoles of periodic acid. After 105 min. at 30°, the remaining oxidant was destroyed by passing an excess of sulphur dioxide. Continuous ether extraction (16 hr.) afforded a syrup (190 mg.) which only after months at room conditions started crystallising in part. Thin-layer chromatography of this product on silica gel with the solvent system benzene–n-butanol–acetic acid (45 : 8 : 4) showed two components in roughly equal proportions, *viz.*, unchanged keto-acid (X) (R_F 0·22) and phenylsuccinic acid (R_F 0·70), when run simultaneously with these two pure compounds.

(*b*) The p-methoxyphenyl-keto-acid[18] (XI) (259 mg., 1·03 mmoles) was treated as above, and yielded an ether extract (231 mg.) which, from acetic acid, finally gave 37 mg. (16%) of *p*-methoxyphenylsuccinic acid, m. p. and mixed m. p. 200° (Found: C, 59·1; H, 5·4. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%).

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* Analytical values for chlorine were high for both the acid and its methyl ester.