1003. *Diterpenoid Bitter Principles. Part III.* The Constitution of Clerodin.*[1]

By D. H. R. Barton, H. T. Cheung, A. D. Cross, L. M. Jackman, and M. Martin-Smith.

The bitter principle clerodin (from *Clerodendron infortunatum*) has two acetate residues attached to primary and secondary hydroxyl groups in 1,3-relationship, a vinyl ether system contained in a five-membered ring, a 1,2-epoxide grouping of the type (), and an ethereal oxygen atom which is relatively inert. The last is attached to a secondary position and also to the same carbon atom as that to which the oxygen of the cyclic vinyl ether is connected. A relationship between the 1,2-epoxide grouping and the 1,3-glycol system has been demonstrated. Dehydrogenation of clerodin affords 1,2,5-trimethylnaphthalene.

Nuclear magnetic resonance studies are in full agreement with the above facts and, in addition, define further the nature of the cyclic vinyl ether group and the presence of tertiary and secondary methyl groups.

From this evidence the constitution for clerodin determined earlier by *X*-ray crystallography [2] receives strong support. The *X*-ray technique gives the complete relative stereochemistry of the molecule and when this is combined with optical rotatory dispersion measurements reported here the absolute stereochemistry can also be deduced.

Clerodin, the bitter principle of the Indian bhat tree, *Clerodendron infortunatum*, was first isolated by Banerjee,[3] who made a preliminary investigation of the compound and favoured the molecular formula $C_{13}H_{18}O_3$. Chaudhury and Dutta,[4] as a result of further preliminary work, supported a larger molecular formula, $C_{28}H_{40}O_8$.

The constitution and stereochemistry of clerodin have been established as (I; R = Ac) by Sim, Hamor, Paul, and Robertson,[2] using *X*-ray crystallography. The molecular formula, $C_{24}H_{34}O_7$, follows from this work, whilst the molecular weight has been fully confirmed by a mass spectrometric determination kindly carried out by Dr. R. I. Reed at the University of Glasgow. The chemical and nuclear magnetic resonance data that we outline in the sequel provide strong support for the assigned constitution.

Extraction of the ground leaves and twigs of *Clerodendron infortunatum* gave a crude solid from which three crystalline compounds were isolated. All were shown to be closely related. One of the compounds, present in major amount, was clerodin. Preliminary investigation showed that clerodin had two acetate residues, two *C*-methyl groups (Kuhn–Roth), and no methoxyl group. It was readily hydrogenated to a saturated (tetranitromethane test) derivative, which we designate dihydroclerodin-I (II; R = Ac, R′ = R″ = H).† This compound, like clerodin, had no hydroxyl group (infrared), a point about which there had been some confusion earlier.[3,4]

Mild alkaline hydrolysis of clerodin furnished deacetylclerodin (I; R = H), reconverted into clerodin on acetylation. Hydrogenation of deacetylclerodin afforded a saturated dihydro-derivative (II; R = R′ = R″ = H), also available by hydrolysis of dihydroclerodin-I (II; R = Ac, R′ = R″ = H) and reconverted into this by acetylation.

Reduction of dihydroclerodin-I (II; R = Ac, R′ = R″ = H) by lithium aluminium

* The papers by Barton and Elad, *J.*, 1956, 2085, 2090, are regarded as Parts I and II in this series.

† Dihydro-compounds are indicated as series I if the vinyl ether grouping is reduced and as series II if the 1,2-epoxide has been opened.

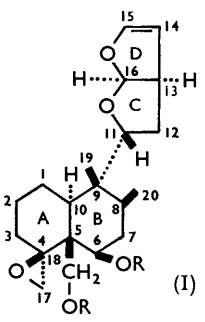
[1] For a preliminary account see *Proc. Chem. Soc.*, 1961, 76.

[2] Sim, Hamor, Paul, and Robertson, *Proc. Chem. Soc.*, 1961, 75.

[3] Banerjee, *Science and Culture*, 1936, **2**, 163; *J. Indian Chem. Soc.*, 1937, **14**, 51; *Trans. Bose Res. Inst.*, 1935—1936, **11**, 71; 1936—1937, **12**, 75.

[4] Chaudhury and Dutta, *J. Indian Chem. Soc.*, 1951, **28**, 295; 1954, **31**, 8.

hydride gave a triol (III; R = R′ = H) which could be reacetylated to a diacetate [tetrahydroclerodin (III; R = R′ = Ac)]. The latter acetate showed hydroxyl absorption in the infrared spectrum but could not be acylated easily and was not oxidised by chromic acid. The new hydroxyl group produced by reduction must, therefore, be tertiary. Similar reduction of clerodin itself gave deacetyldihydroclerodin-II (IV; R = H) which could be readily acetylated to a diacetate (IV; R = Ac), designated dihydroclerodin-II and this, on catalytic hydrogenation, furnished tetrahydroclerodin (III; R = R′ = Ac).



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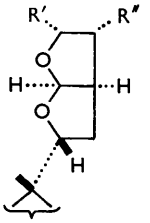

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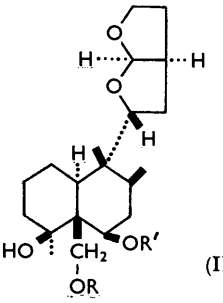

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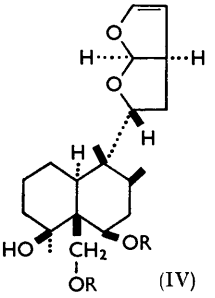

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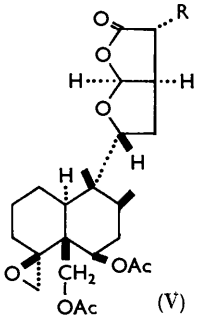

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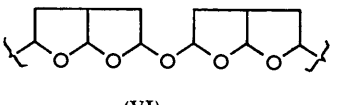


(VI)

Clearly these reduction products are formed by cleavage of an ethereal ring. A 1,2-epoxide always seemed most likely, although a trimethylene oxide ring could not be entirely excluded.[5] Dihydroclerodin-I showed (in CS_2) a C–H stretching band at 3045 cm.$^{-1}$ which would support [6] the presence of a 1,2-epoxide. The assignment was confirmed by nuclear magnetic resonance considerations presented below.

Clerodin is very sensitive to acidic conditions and undoubtedly this accounts for some of the difficulties in earlier work. Dissolution in acetic or propionic acid at room temperature converted clerodin into the corresponding hemiacetal esters (II; R = Ac, R′ = OAc or O·CO·Et, R″ = H). Dihydroclerodin-I (II; R = Ac, R′ = R″ = H) itself was inert under these conditions. Treatment of the acetic acid adduct with aqueous acetic acid at room temperature then afforded the hemiacetal (II; R = Ac, R′ = OH, R″ = H), which is the second major crystalline compound from *Clerodendron infortunatum* (see above). The hemiacetal was oxidised smoothly by chromic acid to the γ-lactone (V; R = H) which showed a lactone band at 1795 cm.$^{-1}$. The presence of a five-membered vinyl ether system is thus proved. The acetylated clerodin, m. p. 205°, prepared by Chaudhury and Dutta [4] by the use of acetic anhydride and sodium acetate, is very probably our clerodin hemiacetal acetate (II; R = Ac, R′ = OAc, R″ = H). The configuration at $C_{(15)}$ in all clerodin derivatives is almost certainly α as indicated, for this is the much less hindered orientation.

[5] See Cross, *Proc. Chem. Soc.*, 1960, 344.

[6] Henbest, Meakins, Nicholls, and Taylor, *J.*, 1957, 1459; for tabulated correlations see A. D. Cross, " An Introduction to Practical Infrared Spectroscopy," Butterworths, London, 1960.

The conversion of the hemiacetal of clerodin (II; R = Ac, R′ = OH, R″ = H) into dihydroclerodin-I (II; R = Ac, R′ = R″ = H) was desirable because the former had been isolated in such large quantity (see above) from the plant. We reasoned that toluene-*p*-sulphonation of the hemiacetal should give a derivative (II; R = Ac, R′ = $C_6H_4Me{\cdot}SO_2$, R″ = H) which would at once dissociate to the corresponding oxonium ion. Reduction of the latter *in situ* by sodium borohydride would furnish the desired dihydroclerodin-I (II; R = Ac, R′ = R″ = H). In the event, treatment of the hemiacetal with toluene-*p*-sulphonyl chloride in triethylamine–diethylene glycol dimethyl ether at 0°, followed by addition of the borohydride at −25° to −35°, gave a moderate, but useful, yield of dihydroclerodin-I (II; R = Ac, R′ = R″ = H).

In order to prepare a clerodin derivative containing a " heavy " atom suitable for *X*-ray crystallographic studies the addition of bromine to the vinyl ether system was investigated. Treatment with bromine in acetic acid containing sodium acetate gave smoothly a bromo-acetate (II; R = Ac, R′ = OAc, R″ = Br). Similar reaction with bromine water furnished a bromohydrin (II; R = Ac, R′ = OH, R″ = Br), which was oxidised by chromic acid to the bromo-lactone (V; R = Br) with infrared lactone absorption at 1785 cm.$^{-1}$. It is this compound which was used for the *X*-ray crystallographic study referred to above.

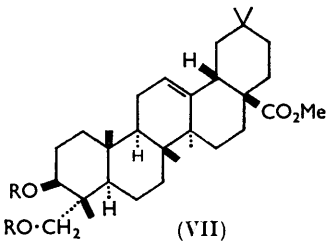
The minor crystalline constituent of *Clerodendron infortunatum* (see above) was found to be the anhydride (VI) of clerodin hemiacetal. The evidence for this unusual structure is briefly as follows. Analysis and molecular-weight determinations suggest a C_{48} formula. Dissolution in aqueous acetic acid gave a high yield (>85%) of clerodin hemiacetal (II; R = Ac, R′ = OH, R″ = H), showing that the two halves of the molecule are identical. Oxidation with chromic acid gave the known γ-lactone (V; R = H) (see above). Reduction with lithium aluminium hydride furnished the corresponding hexaol. Finally the constituent was synthesised by acid-catalysed dehydration of clerodin hemiacetal under mild conditions. We have tried to establish if clerodin hemiacetal and its anhydride are formed from clerodin during storage or in processing. A control experiment with clerodin itself gave no indication of change during our processing procedure. We conclude, therefore, that clerodin hemiacetal and its anhydride may well be true natural products. However, we cannot exclude that they are produced from clerodin during storage in the plant (a period of at least two months) or that some of the other non-crystalline constituents are capable of catalysing the conversion of clerodin into these derivatives.

We now present proof that the acetate residues of clerodin are attached to a 1,3-glycol system. First, heating deacetyltetrahydroclerodin (III; R = R′ = H) with copper bronze gave formaldehyde, isolated as the dimedone derivative, in yield comparable with that obtained from hederagenin methyl ester (VII; R = H) under the same conditions. Secondly, treatment of deacetyltetrahydroclerodin (III; R = R′ = H) with ethyl chloroformate in pyridine solution furnished a cyclic carbonate (III; R,R′ = CO). The infrared carbonyl frequency (1735 cm.$^{-1}$) of this compound indicated a six-membered ring and hence derivation from a 1,3-glycol. An analogous carbonate (II; R,R = CO, R′ = R″ = H) was formed in the same way from deacetyldihydroclerodin-I (II; R = R′ = R″ = H). Hederagenin methyl ester, on the other hand, gave only a diethoxycarbonyl derivative [7] (VII; R = CO_2Et) under identical conditions. The OH and $CH_2{\cdot}OH$ groups of hederagenin methyl ester are both equatorial but *trans* in configuration. It seems reasonable to assign carbonate formation then to the presence of these two groups (when in 1,3-relationship) in a *cis*-configuration as, in fact, is written into the clerodin formulæ already presented.

The selective reactivity of the two hydroxyl groups of deacetylclerodin derivatives was next investigated with results which eventually determined the relationship between the 1,3-glycol system and the 1,2-epoxide grouping. Deacetyldihydroclerodin-I (II;

[7] Fieser, Herz, Klohs, Romero, and Utne, *J. Amer. Chem. Soc.*, 1952, **74**, 3309.

R = R′ = R″ = H) on treatment with toluene-*p*-sulphonyl chloride in pyridine readily afforded a monotoluene-*p*-sulphonate (VIII; R = *p*-$C_6H_4Me{\cdot}SO_2$, R′ = H) oxidised by chromic acid to a stable ketone (IX) with a cyclohexanone-type carbonyl band in its infrared spectrum. Deacetyltetrahydroclerodin (III; R = R′ = H), submitted to the same reaction sequence, gave first a monotoluene-*p*-sulphonate (III; R = *p*-$C_6H_4Me{\cdot}SO_2$, R′ = H) and then a ketone (X) which was too unstable to be isolated. On chromatography over alumina, or treatment with very mild base, this compound was rapidly transformed into a diketone shown by further experiment to have structure (XII; R = Me). We consider that the latter is formed from (X; see arrows) by fission of the 4,5-carbon bond to give a methylene-ketone (XI) which at once adds the anion from the methyl ketone grouping (XI: see arrows) to give the product (XII; R = Me). The evidence for the constitution (XII; R = Me) is briefly as follows. The compound formed a dioxime and a bis-2,4-dinitrophenylhydrazone of the correct composition. It gave



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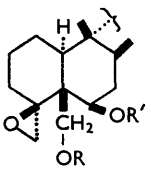

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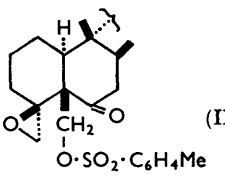

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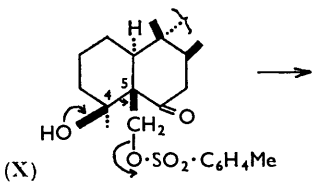

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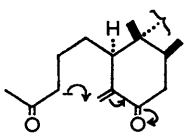

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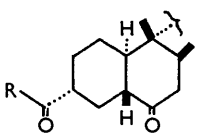

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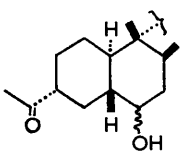

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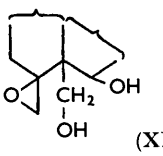

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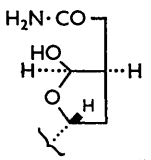

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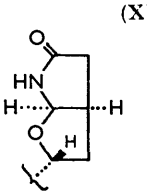


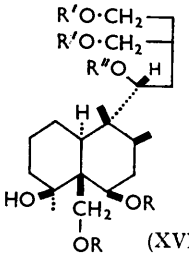
(XVI)

positive iodoform and Zimmermann tests and showed a clear methyl ketone band in its nuclear magnetic resonance spectrum. Controlled hypochlorite oxidation afforded a keto-acid (XII; R = OH). All these compounds had the expected infrared spectra and analytical compositions. Reduction of the diketone with sodium borohydride in excess gave a diol, but reduction under controlled conditions furnished a ketol (XIII). The latter showed a methyl ketone band in its nuclear magnetic resonance spectrum.

The formation of the diketone (XII; R = Me) is important because it not only proves the presence of the grouping () in clerodin but, on the basis of mechanistic considerations (see above), requires the presence of the partial structure (XIV) (probably contained in two six-membered rings).

The experiments outlined above define the function of six of the seven oxygen atoms in clerodin. The relationship of the seventh atom to the vinyl ether system was defined in a simple manner. The γ-lactone (V; R = H) from clerodin gave an amide (XV) on treatment with ammonia. Dissolution of this amide in acetic acid at room temperature

afforded a γ-lactam (XVI). Such remarkably ready lactamisation can only be explained if the carbon bearing the " alkyl "-oxygen of the γ-lactone grouping in (V; R = H) is also " acetalic " in character and thus has ethereal oxygen attached to it. The normal fate of the amide (XV) in acetic acid would have been reversion to its lactonic progenitor (V; R = H). This defined one point of attachment for the seventh (ethereal) oxygen atom of clerodin. The other was partially characterised by the following experiments. Prolonged reduction of clerodin hemiacetal (II; R = Ac, R′ = OH, R″ = H) with an excess of lithium aluminium hydride furnished a nicely crystalline hexaol (XVII; R = R′ = R″ = H) which gave a penta-acetate (XVII; R = R′ = R″ = Ac) on acetylation. This derivative retained one hydroxyl group (infrared spectrum) which must be tertiary, because it resisted oxidation by chromic acid. Since the tertiary hydroxyl group formed by opening the 1,2-epoxide group of clerodin has these properties it follows that the two hydroxyl groups resulting from the fission of ring C [see (I)] must both be primary or secondary. With ethyl chloroformate the hexaol gave, first a tetra-acylated derivative (XVII; R,R = CO, R′ = CO_2Et, R″ = H) and, on further reaction, a penta-acylated derivative (XVII; R,R = CO, R′ = R″ = CO_2Et). The former consumed one atom of oxygen on chromic acid titration, the latter none. The formulæ given explain these facts.



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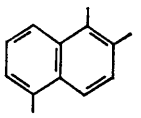
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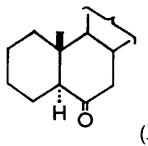


(XIX)

Evidence for the carbon skeleton of clerodin was obtained by dehydrogenation. This gave 1,2,5-trimethylnaphthalene (XVIII), the derivation of which from structure (I; R = Ac) is obvious.

The relative configurations of clerodin and its derivatives, as written into the formulæ in this paper, are defined by *X*-ray crystallography.[2] The only centre where the assignment is doubtful is $C_{(4)}$. We favour a β-configuration for the oxygen atom of the 1,2-epoxide because tetrahydroclerodin (III: R = R′ = Ac), on dehydration with thionyl chloride or phosphorus oxychloride in pyridine, affords an oily product which shows infrared absorption indicative of $>C=CH_2$. Such a direction of elimination would favour an equatorial hydroxyl group in tetrahydroclerodin [8] and thus a β-configuration. The point is, however, not settled decisively by our experiments.

The absolute configuration which we tentatively favour for clerodin is already written into (I; R = Ac) and derived formulæ. It is based on the following considerations. The ketone toluene-*p*-sulphonate (IX) shows an optical rotatory dispersion curve which, although of enhanced amplitude, is enantiomeric with respect to that of a 6-keto-*trans*-A/B-steroid (as XIX). The same type of curve, but of more normal amplitude, was shown by the keto-acid (XII; R = OH) described above. We thank Professor W. Klyne (Westfield College, University of London) for his kindness in determining these curves.

The biogenesis of clerodin does not call for extended comment. Since the carbon skeleton is the same as that in columbin [9] we can consider that the biogenesis follows the same path as there proposed and thus involves two 1,2-methyl migrations from a diterpenoid skeleton of normal type.

[8] See Barton, Campos-Neves, and Cookson, *J.*, 1956, 3500.
[9] Barton and Elad, *J.*, 1956, 2085, 2090.

Throughout this investigation we have made extensive use of nuclear magnetic resonance spectroscopy. Conclusions reached on chemical grounds have frequently been anticipated by measurements of this kind and, in addition, further conclusions about the constitution of clerodin can be derived which are not available from our chemical work. Table 1 lists the absorption data for clerodin and a number of its derivatives and the following paragraphs summarise briefly the conclusions reached.

The presence in clerodin of two *C*-methyl groups, in addition to those of the two acetyl residues, follows directly from the integrated intensities of the absorption near 9·0 in all spectra examined. In the spectrum (4) (for numbering see Table 1) of dihydroclerodin-II (IV; R = Ac) the two methyl groups are separately resolved as a singlet and an asymmetric doublet (an AB_3 system), thus establishing their attachment to quaternary and tertiary carbon atoms, respectively.

TABLE 1.

Chemical shifts (τ values) and coupling constants (in parentheses in c./sec.) of protons in clerodin and its derivatives.

		Position of Protons				
	Compound	19	20	O·CO·CH_3	6	11
1	(I; R = Ac)	9·05	9·05	8·14, 7·98	*a*	*ca.* 6·1 [a]
2	(II; R = Ac, R′ = R″ = H)	9·07	9·07	8·14, 7·98	5·5 [a]	*ca.* 5·8 [a]
3	(II; R = R′ = R″ = H)	9·13	9·13	— —	6·84	*ca.* 5·8 [a]
4	(IV; R = Ac)	8·96	9·08 [c]	7·98, 7·90	*ca.* 5·5	6·10
5	(IV; R = H)	9·04	9·04	— —	6·2	*ca.* 6·1 [a]
6	(III; R = R′ = Ac)	8·97	8·97	7·98, 7·91	*ca.* 5·2 [a]	*ca.* 5·8 [a]
7	(III; R = R′ = H)	9·07	9·07	— —	*ca.* 6·2 [a]	*ca.* 5·8 [a]
8	(V; R = H)	9·05	9·05	8·07, 7·91	*ca.* 5·5 [a]	5·88
9	(XII; R = Me)	8·87	9·09 (7·8)	— —	—	5·78 [c]

		Position of Protons				
	Compound	14	15	16	17	18
1	(I; R = Ac)	*a*	3·61 (*ca.* 2·5)	4·09 (6·0)	7·14 [b]	5·80, 5·18 (12·8)
2	(II; R = Ac, R′ = R″ = H)	*a*	6·15 [c]	4·51 (4·8)	7·12 [b]	5·77, 5·17 (12·4)
3	(II; R = R′ = R″ = H)	*a*	6·15 [c]	4·37 (5·0)	7·58 [b]	5·95, 5·67 (12·5)
4	(IV; R = Ac)	5·16 (2·5)	3·53 (2·5)	4·00 (6·1)	8·69	5·49, 5·13 (12·8)
5	(IV; R = H)	5·19 (2·5)	3·56 (2·5)	4·01 (6·4)	8·55	5·56
6	(III; R = R′ = Ac)	*a*	6·15 [c]	4·39 (5·0)	8·69	5·42, 5·05 (12·8)
7	(III; R = R′ = H)	*a*	6·15 [c]	4·41 (5·0)	8·58	5·62
8	(V; R = H)	*a*	—	3·96 (5·6)	*a*	5·64, 5·14 (12·4)
9	(XII; R = Me)	*a*	6·15 [c]	4·34 (5·0)	7·86	—

a Overlapping other absorption. *b* Partially resolved AB system. *c* Complex multiplet.

Clerodin (1) and those of its derivatives (2, 3) containing the epoxide ring exhibit absorption in the region 7·2—7·6, typical of the protons of an epoxide. This absorption is absent in compounds (4—7) in which the epoxide ring is reduced, which however exhibit singlets near 8·6, characteristic of a *C*-methyl group in a tertiary alcoholic system. These observations are only explicable in terms of the reduction of a primary epoxide to a tertiary alcohol.[10]

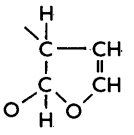
In many spectra (1—7) an unequivocal assignment of lines arising from the absorption of the methylenic protons of the groups CH_2·OAc or CH_2·OH was possible. In the acetylated compounds the two protons are non-equivalent and the resulting absorptions are AB patterns [11] with the coupling constant, *J*, equal to 12—13 c./sec., a value characteristic of the coupling in an acyclic methylene group. In certain of the free alcohols (5, 7) the methylenic protons attain accidental equivalence, and give rise to a single absorption line. These results prove that the primary acetate group in clerodin is attached to a fully substituted carbon atom.

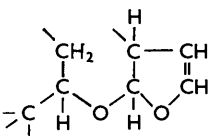
[10] Cf. Tarbell, Carman, Chapman, Huffman, and McCorkindale, *J. Amer. Chem. Soc.*, 1960, **82**, 1005.

[11] L. M. Jackman, " Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon London, 1959, p. 89.

The absorption arising from the α-proton of the secondary acetate (or alcohol) in most compounds overlaps other absorptions, but in the spectra of a number of compounds its approximate position could be inferred from intensity measurements. In deacetyldihydroclerodin-I (II; R = R′ = R″ = H) (3) this proton absorbs at 6·8 compared with *ca.* 6·2 in deacetyltetrahydroclerodin (III; R = R′ = H) (7), suggesting a close steric relation between it and the tertiary alcoholic oxygen atom in the latter compound.

The spectra of clerodin (1) and those derivatives (4, 5) containing the dihydrofuran ring exhibit a triplet (J ~2·5 c./sec.) near 3·6 which can be assigned to the α-olofinic proton since in the spectra (2, 3, 6, 7, 9) of saturated derivatives the band is replaced by another, equivalent to two protons, in the region 6·0—6·3. In the spectra of dihydroclerodin-II (IV; R = Ac) (4) and its deacetyl derivative (5) an identical triplet was also observed at 5·2 and can be assigned to the β-olefinic proton. Convincing evidence for the correctness of these assignments is provided by the proton spectrum of 2,3-dihydrofuran in which the α- and β-olefinic proton absorptions appear as quartets (J = 3·1 c./sec.) at 3·77 and 5·14, respectively. Evidently all coupling constants between the α-, β-, and γ-protons are equal. The spectra (1, 4, 5) of all compounds containing the dihydrofuran ring exhibit a doublet (J = 6·0 — 6·4 c./sec.), equivalent to one proton, at 4·00—4·10. This band is found at 4·30—4·50 with a reduced coupling constant (J = 4·8—5·0 c./sec.) in the spectra (2, 3, 6, 7) of the corresponding dihydro-derivatives, and at 3·96 (J = 5·6 c./sec.) in that of clerodin γ-lactone (V; R = H) (8). Clearly this absorption must be due to the proton at position 16, the paramagnetic shifts associated with the double bond and particularly the carbonyl group being attributable to electron withdrawal from the oxygen atom.[12] The very low τ-values found for this proton require the presence of a second oxygen substituent at position 16 [cf. 3·9—4·6 for the anomeric protons in aldopyranosides [13]], leading to the partial structure (XX). Unequivocal confirmation of

(XX) 



(XXI)

structure (XX) was provided by double irradiation experiments * which established that the proton coupled to that at position 16 absorbed at 7·4 (allylic methine) in clerodin and 8·1 (aliphatic methine) in tetrahydroclerodin (III; R = R′ = Ac). The spectrum (9) of the diketone exhibits, in addition to the absorptions of the protons at positions 15 and 16, a double doublet, equivalent to one proton at 5·78. This band must therefore arise from a single proton at position 11. The separations of the inner and outer pairs of lines of this multiplet were field-dependent (determined at 40 and 56·4 Mc./sec.) which identifies it as the X-band of an ABX system. Accordingly, $C_{(11)}$ must be attached to a methylene group and a quaternary carbon atom and the partial structure (XX) can be extended to (XXI).

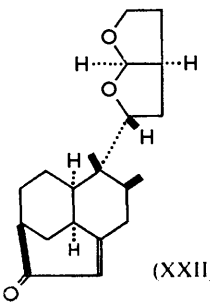
Several interesting aspects of the chemistry of clerodin did not immediately shed light on its constitution. However, now that the latter is known their significance can be properly evaluated. Treatment of the diketone (XII; R = Me) with potassium t-butoxide in t-butyl alcohol gave, with loss of one molecule of water, an αβ-unsaturated ketone having an ultraviolet maximum at 249 mμ (ε 10,400) and infrared bands indicative of a cyclohexenone. The nuclear magnetic resonance spectrum showed a single peak (τ 3·93) for one vinyl hydrogen atom and the band of the methyl ketone group of (XII; R = Me) had disappeared. For these, and sequential, reasons this enone must be

* The technique employed was developed by Dr. D. W. Turner who kindly made the necessary measurements.

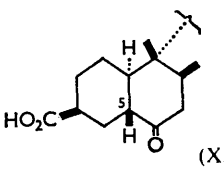
[12] Ref. 11, p. 55.

[13] Lemieux, Kullnig, Bernstein, and Schneider, *J. Amer. Chem. Soc.*, 1958, **80**, 6098.

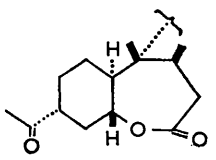
formulated as (XXII). Hydrogenation afforded a cyclohexanone (XXII; double bond reduced) with an infrared carbonyl band at 1710 cm.$^{-1}$. The main proof of constitution was as follows. Ozonolysis of the enone (XXII) gave a crystalline keto-acid in good yield. This was stable to various alkaline treatments and is therefore formulated as the *trans*-derivative (XXIII), epimerisation at $C_{(5)}$ having taken place during the working up.



(XXII)



(XXIII)



(XXIV)

The keto-acid (XXIII) afforded a methyl ester which, when warmed with potassium t-butoxide and then hydrolysed, gave the known keto-acid (XII; R = OH). A *cis*-fusion of rings in (XXII) is, of course, obligatory. Another reaction of the diketone (XII; R = Me) which proceeded in an initially unexpected manner was its behaviour with perphthalic acid. This furnished in a good yield a keto-lactone. This compound is formulated as (XXIV) since it gave a positive iodoform test and showed a methyl ketone band in its nuclear magnetic resonance spectrum. The selective attack of per-acid at the 6-carbonyl group of the diketone (XII; R = Me) parallels the selective reduction by sodium borohydride referred to above (see XIII).

Dr. A. K. Banerjee has kindly informed us [14] that he has also obtained 1,2,5-trimethylnaphthalene by dehydrogenation of clerodin.

Experimental

M. p.s were taken on the Kofler block. Unless specified to the contrary, $[\alpha]_D$ refer to $CHCl_3$, ultraviolet absorption to EtOH solutions. Nuclear magnetic resonance spectral measurements were made at 21° on approx. 10% w/v solutions in $CDCl_3$ with tetramethylsilane as an internal standard. Spectra were calibrated by the side-band technique with a Muirhead–Wigan decade oscillator model D-695-A. Compounds containing free hydroxyl groups were equilibrated with D_2O before measurements were made. Light petroleum refers to the fraction of b. p. 60—80°, unless stated otherwise. Microanalyses were carried out by Mr. J. M. L. Cameron (Glasgow) and Miss J. Cuckney (Imperial College) and their respective associates.

Extraction of Clerodendron infortunatum.—Dry ground leaves and twigs of the shrub (3·5 kg.) were left in ether (14 l.) for 5 days at room temperature with occasional stirring. The filtered ethereal extract was treated twice with charcoal to remove chlorophyll, and the resultant yellow solution concentrated *in vacuo* at <40° to approx. 300 ml. Light petroleum (b. p. 40—60°) (150 ml.) was added cautiously and the solution left at 0°. Crude solid was collected at intervals. The residual solution was again concentrated and the process repeated until no more solid separated (11—20 g. total).

This solid (120 g.) in benzene (250 ml.) was chromatographed over alumina (2·5 kg.; Brockmann grade III). Elution with benzene and with benzene–chloroform mixtures afforded successively a wax (5 g.), clerodin (I; R = Ac) (25 g.), an oil (10 g.), clerodin hemiacetal anhydride (VI) (800 mg.), an oil (40 g.), and clerodin hemiacetal (II; R = Ac, R′ = OH, R″ = H) (30 g.). The non-crystalline products were not investigated further.

Clerodin crystallised from ether–light petroleum (b. p. 40—60°) as needles, m. p. 164—165°, $[\alpha]_D$ −47° (*c* 1·66), ε 4550 at 208 mμ, $\nu_{max.}$ (in Nujol) 1727 and 1252 (acetates), 1615 and 738 (vinyl ether) cm.$^{-1}$, $\nu_{max.}$ (in CCl_4) 3025 (olefinic C–H stretch) and 3045 (epoxide) cm.$^{-1}$ (Found:

[14] See Bose, *J. Indian Chem. Soc.*, 1960, **37**, 653.

C, 66·15; H, 7·75; *C*-Me, 15·35; *O*-Me, 0. Calc. for $C_{24}H_{34}O_7$: C, 66·35; H, 7·9; 4*C*-Me, 13·85%).

Clerodin gave a strong yellow colour with tetranitromethane. It was not acetylated by pyridine–acetic anhydride even on the steam bath.

Further reference to clerodin hemiacetal anhydride is made below. Clerodin hemiacetal, recrystallised from ether, proved identical by all criteria with authentic material (see below).

Deacetylclerodin.—Clerodin (420 mg.) in methanol (30 ml.) and water (40 ml.) was treated with potassium hydroxide (600 mg.) on the steam bath for 70 min. The saponified product which crystallised was filtered off. Recrystallisation from ethanol gave *deacetylclerodin* (I; R = H) (280 mg.) as prisms, m. p. 230—242°, $[\alpha]_D$ −45° (*c* 0·81 in pyridine), ε 3500 at 209 mμ, $\nu_{max.}$ (in Fluorolube) 1375 cm.$^{-1}$ (singlet only) (Found: C, 69·15; H, 9·05; *C*-Me, 9·2. $C_{20}H_{30}O_5$ requires C, 68·55, H, 8·65; 2*C*-Me, 8·55%). Treatment with pyridine–acetic anhydride for 3 days at room temperature gave back clerodin (m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum).

Dihydroclerodin-I.—Clerodin (4·91 g.) in ethyl acetate (100 ml.) was hydrogenated over 5% palladised charcoal (500 mg.) (1 mol. uptake). Crystallisation of the product from ether gave *dihydroclerodin-I* (II; R = Ac, R′ = R″ = H) (4·70 g.) as prisms, m. p. 169—170°, $[\alpha]_D$ −20° (*c* 1·44), no end absorption, $\nu_{max.}$ (in Nujol) 1730 and 1258 and 1224 (acetates) cm.$^{-1}$, $\nu_{max.}$ (in CCl_4) 3045 (epoxide) cm.$^{-1}$ (Found: C, 66·25; H, 8·2. $C_{24}H_{36}O_7$ requires C, 66·05; H, 8·3%).

Dihydroclerodin-I (700 mg.) in methanol (20 ml.) was refluxed with potassium hydroxide (1·1 g.) in water (20 ml.) for 2 hr. Chromatography of the oily product over alumina (Grade V) and elution with benzene furnished *deacetyldihydroclerodin-I* (II; R = R′ = R″ = H) as needles (from ether) (190 mg.), m. p. 188—195°, $[\alpha]_D$ −5° (*c* 1·65) (Found: C, 68·45; H, 9·2. $C_{20}H_{32}O_5$ requires C, 68·15; H, 9·15%). The same product (7·1 mg.; m. p., mixed m. p., and infrared spectrum) was formed on hydrogenation of deacetylclerodin (10·1 mg.) in ethyl acetate (10 ml.) over 5% palladised charcoal (25 mg.). Treatment of deacetyldihydroclerodin-I with pyridine–acetic anhydride gave back dihydroclerodin-I (m. p., mixed m. p., and infrared spectrum).

Clerodin Hemiacetal and its Derivatives.—Clerodin (400 mg.) in glacial acetic acid (4 ml.) was kept at room temperature until $[\alpha]_D$ was constant (72 hr.). Removal of the solvent *in vacuo* and crystallisation from ether furnished *clerodin hemiacetal acetate* (II; R = Ac, R′ = OAc, R″ = H) (315 mg.) as prisms, m. p. 208—210°, $[\alpha]_D$ +32° (*c* 2·22), no ultraviolet absorption (Found: C, 63·15; H, 7·7; Ac, 26·15. $C_{26}H_{38}O_9$ requires C, 63·15; H, 7·75; 3Ac, 26·1%). The same compound was obtained by acetylation of clerodin with sodium acetate and acetic anhydride according to the directions of Chaudhury and Dutta.[4]

Clerodin (100 mg.) in propionic acid (1 ml.) was kept at room temperature for 72 hr. (constant $[\alpha]_D$). Removal of the solvent *in vacuo* and crystallisation from ether afforded *clerodin hemiacetal propionate* (II; R = Ac, R′ = O·CO·Et, R″ = H) as cubes, m. p. 183—185°, $[\alpha]_D$ 0° (*c* 2·11) (Found: C, 63·7; H, 8·3. $C_{27}H_{40}O_9$ requires C, 63·75; H, 7·95%).

Clerodin hemiacetal acetate (60 mg.) in glacial acetic acid (0·75 ml.) and water (10 ml.) was kept at room temperature for 12 hr. Addition of an excess of sodium hydrogen carbonate, extraction with chloroform, and crystallisation of the product from ether gave *clerodin hemiacetal* (II; R = Ac, R′ = OH, R″ = H) as prisms (32 mg.), m. p. 179—181°, $[\alpha]_D$ −34° (*c* 2·35) (the rotation of −17° given in our preliminary communication is in error), no ultraviolet absorption, $\nu_{max.}$ (in CS_2) 3045 (epoxide) cm.$^{-1}$ (Found: C, 63·65; H, 8·2. $C_{24}H_{36}O_8$ requires C, 63·7; H, 8·0%). This hemiacetal (600 mg.) in glacial acetic acid (10 ml.) was treated with sodium dichromate (300 mg.) in the same solvent (10 ml.) overnight. Crystallisation of the product from acetone–light petroleum furnished the *γ-lactone* (V; R = H) (510 mg.) as prisms, m. p. 192—193°, $[\alpha]_D$ −23° (*c* 1·04), no ultraviolet absorption, $\nu_{max.}$ (in CCl_4) 1795 (γ-lactone) and 1720 (acetates) cm.$^{-1}$ (Found: C, 63·75; H, 7·85. $C_{24}H_{34}O_8$ requires C, 64·0; H, 7·6%).

Clerodin hemiacetal (II; R = Ac, R′ = OH, R″ = H) (20 g.) and toluene-*p*-sulphonyl chloride (10 g.) in triethylamine (100 ml.) and diethylene glycol dimethyl ether (150 ml.) was kept at 0° for 45 min., then cooled to −25° to −35°. Sodium borohydride (4·17 g.) in the same ether (50 ml.) (at room temperature) was added, and the resulting suspension shaken at −25° to −35° for 2 hr. After addition of water and acidification with cooling, the mixture was extracted with chloroform. The chloroform solution was washed with aqueous alkali and water and then gave a gum which on chromatography over alumina (grade III) gave dihydroclerodin-I (II; R = Ac, R′ = R″ = H) (3·80 g.) and recovered hemiacetal (4·32 g.).

Clerodin Bromohydrin and its Derivatives.—Clerodin (515 mg.) in ether (50 ml.) was shaken

with bromine water added in small portions until the latter was in slight excess. The ethereal solution was washed with sodium hydrogen carbonate solution and worked up in the usual way. Crystallisation of the product from benzene–light petroleum afforded *clerodin bromohydrin* (II; R = Ac, R′ = OH, R″ = Br) as needles (480 mg.), m. p. 186—187° (decomp.), $[\alpha]_D$ −13° (*c* 1·16) (Found: C, 53·6; H, 6·3. $C_{24}H_{35}BrO_8$ requires C, 54·25; H, 6·65%). This bromohydrin (103 mg.) in glacial acetic acid (5 ml.) was treated with sodium dichromate (49 mg.) at room temperature for 90 min. (uptake 1O). Crystallisation of the product from benzene–light petroleum furnished the *bromo-γ-lactone* (V; R = Br) as prisms (82 mg.), m. p. 168—169°, $[\alpha]_D$ −37° (*c* 0·48), no ultraviolet absorption, $\nu_{max.}$ (in Nujol) 1780 (γ-lactone), 1745 (OAc) and 1710 (OAc) cm.$^{-1}$ (Found: C, 54·5; H, 6·3. $C_{24}H_{33}BrO_8$ requires C, 54·45; H, 6·3%).

Clerodin (70 mg.) in glacial acetic acid (4 ml.) was treated with sodium acetate (500 mg.) and bromine (120 mg.) for 90 min. at room temperature. Crystallisation of the product from acetone–light petroleum gave *clerodin bromohydrin acetate* (II; R = Ac, R′ = OAc, R″ = Br) as prisms (75 mg.), m. p. 186—187°, $[\alpha]_D$ +9° (*c* 0·69), $\nu_{max.}$ (in Nujol) 1750 (hemiacetal acetate) and 1730 (acetates) cm.$^{-1}$ (Found: C, 54·6; H, 6·85. $C_{26}H_{37}O_9Br$ requires C, 54·45; H, 6·5%).

The γ-Lactam (XVI; R = Ac) *from Clerodin.*—The γ-lactone (V; R = H) (1·04 g.) in methanol (75 ml.) was added to liquid ammonia (50 ml.) at −70° and left for 1 hr. with occasional stirring before being allowed to warm to room temperature. Removal of the solvent *in vacuo* at <50° and crystallisation from ether furnished the amide (XV; R = Ac) as prisms, m. p. up to 280°, $\nu_{max.}$ (in Nujol) 3535 (OH), 3235 (NH), 1740 and 1715 (acetates) and 1690 (amide-I) cm.$^{-1}$ This amide (100 mg.) in glacial acetic acid (5 ml.) was kept at room temperature for 30 min. before the solvent was removed *in vacuo* at room temperature. Crystallisation of the residue from chloroform–light petroleum (b. p. 40—60°) gave the *γ-lactam* (XVI; R = Ac) as prisms (quantitative yield), m. p. 265—280° (decomp.), $[\alpha]_D$ −6° (*c* 0·81), $\nu_{max.}$ (in Nujol) 3340 (NH), 1740 (acetates), and 1710 (γ-lactam) cm.$^{-1}$ (Found: C, 64·4; H, 8·1; N, 3·15. $C_{24}H_{35}NO_7$ requires C, 64·1; H, 7·85; N, 3·1%).

Dihydroclerodin-II (IV; R = Ac).—Clerodin (120 mg.) in dry ether (20 ml.) was refluxed with lithium aluminium hydride (200 mg.) for 16 hr. The product, crystallised from benzene, gave *deacetyldihydroclerodin-II* (IV; R = H) as prisms (62 mg.), m. p. 218—225°, $[\alpha]_D$ −56° (*c* 0·78 in pyridine) (Found: C, 68·9; H, 9·35. $C_{20}H_{32}O_5$ requires C, 68·15; H, 9·15%). Treatment with pyridine–acetic anhydride overnight at room temperature and crystallisation of the product from ether–light petroleum (b. p. 40—60°), furnished *dihydroclerodin-II* (IV; R = Ac) as prisms, m. p. 153—155°, $[\alpha]_D$ −32° (*c* 0·69), $\nu_{max.}$ (in CCl_4) 3540 (OH), 1742 (acetates), and 1621 (vinyl ether) cm.$^{-1}$ (Found: C, 66·2; H, 8·4. $C_{24}H_{36}O_7$ requires C, 66·05; H, 8·3%).

Tetrahydroclerodin (III; R = R′ = Ac).—Dihydroclerodin-I (700 mg.) in dry ether (50 ml.) was added slowly to lithium aluminium hydride (350 mg.) suspended in the same solvent (20 ml.) under reflux, and refluxing continued for 24 hr. The product, worked up by the potassium hydrogen tartrate method with continuous extraction with chloroform, crystallised from benzene–light petroleum to furnish *deacetyltetrahydroclerodin* (III; R = R′ = H) as prisms (490 mg.), m. p. 172—173°, $[\alpha]_D$ −15° (*c* 1·16) (Found: C, 68·15; H, 9·4. $C_{20}H_{34}O_5$ requires C, 67·75; H, 9·65%). The same compound (m. p., mixed m. p., and infrared spectrum) was obtained by catalytic hydrogenation of deacetyldihydroclerodin-II (IV; R = H) in ethyl acetate over palladised charcoal.

Treatment of deacetyltetrahydroclerodin with pyridine–acetic anhydride overnight at room temperature gave *tetrahydroclerodin* (III; R = R′ = Ac) as prisms (from ether), m. p. 142—147°, $[\alpha]_D$ −6° (*c* 1·10), $\nu_{max.}$ (in CCl_4) 3530 (OH) cm.$^{-1}$ (Found: C, 65·7; H, 8·7. $C_{24}H_{38}O_7$ requires C, 65·75; H, 8·75%). The same compound (m. p., mixed m. p., and infrared spectrum) was formed when dihydroclerodin-II (IV; R = Ac) (see above) was hydrogenated in ethyl acetate over palladised charcoal.

Tetrahydroclerodin was recovered unchanged after treatment with sodium dichromate (excess) in glacial acetic acid at room temperature for 24 hr.

Dehydrogenation of Clerodin.—Clerodin (750 mg.) was mixed with selenium powder (1·7 g.) and kept at 285—315° under oxygen-free nitrogen for 24 hr. The product, ground to a powder, was exhaustively extracted with ether and then with light petroleum (b. p. 40—60°). The extract, taken up in light petroleum (b. p. 40—60°), was filtered through alumina (grade V) and then extracted with syrupy phosphoric acid to remove azulenic materials. The residual product was then sublimed *in vacuo*, to give a pale yellow oil with an infrared spectrum almost identical with that of authentic 1,2,5-trimethylnaphthalene. The identity was established

by conversion into the 1,3,5-trinitrobenzene adduct and into the picrate and comparison (m. p., mixed m. p., and infrared spectrum) with authentic specimens obtained earlier from onocerin.[15]

Reduction of Clerodin Hemiacetal (II; R = Ac, R′ = OH, R″ = H) *with Lithium Aluminium Hydride.*—Clerodin hemiacetal (6·0 g.) in dry dioxan (50 ml.) was added dropwise to a boiling suspension of lithium aluminium hydride (4·5 g.) in the same solvent (50 ml.), and the refluxing continued for 5 days. Ethyl acetate (excess) and water (100 ml.) were added and the organic solvents removed *in vacuo*. Filtration, extraction of the filtrate continuously with chloroform for 48 hr., and crystallisation of the product from acetone–methanol, gave the *hexaol* (XVII; R = R′ = R″ = H) (4·2 g.), prisms, m. p. 146—148°, $[\alpha]_D$ −21° (*c* 0·72 in pyridine), $\nu_{max.}$ (in Nujol) 3300 (OH) cm.$^{-1}$ (Found: C, 64·0; H, 10·05. $C_{20}H_{38}O_6$ requires C, 64·15, H, 10·25%). The hexaol consumed no periodate, but with pyridine–acetic anhydride overnight at room temperature it gave a *penta-acetate* (XVII; R = R′ = R″ = Ac). This did not crystallise even after repeated chromatography; it had b. p. 154—166°/1 × 10^{-5} mm., $[\alpha]_D$ −22° (*c* 0·49), $\nu_{max.}$ (in $CHCl_3$) 3570 (OH) and 1742—1727 (5 acetates) cm.$^{-1}$ (Found: C, 61·95; H, 8·3; Ac, 34·35. $C_{30}H_{48}O_{11}$ requires C, 61·65; H, 8·3; 5Ac, 36·8%). The penta-acetate consumed no chromic acid on treatment with sodium dichromate in acetic acid for 20 hr. at room temperature.

The hexaol (700 mg.) in dry pyridine (8 ml.) containing redistilled ethyl chloroformate (3 ml.) was left at 0° for 45 min. Chromatography of the product over alumina (grade V) gave two compounds. Elution with chloroform and crystallisation from benzene–ether afforded the *hexaol carbonate diethoxycarbonyl derivative* (XVII; R,R = CO, R′ = CO_2Et, R″ = H) as prisms (390 mg.), m. p. 141—142°, $[\alpha]_D$ −33° (*c* 0·91), $\nu_{max.}$ (in $CHCl_3$) 3350 (OH) and 1745 (carbonate and O·CO_2Et) cm.$^{-1}$ (Found: C, 59·45; H, 8·05. $C_{27}H_{44}O_{11}$ requires C, 59·55; H, 8·15%). The earlier fractions from the chromatogram were combined with the mother liquors from the above crystallisation and treated again with ethyl chloroformate. Chromatography of this product gave, besides the derivative reported above, the *carbonate triethoxycarbonyl derivative* (XVII; R,R = CO, R′ = R″ = CO_2Et). Crystallised from benzene–ether as needles (60 mg.), this had m. p. 129—130°, $[\alpha]_D$ −38° (*c* 1·04) (Found: C, 58·5; H, 8·0. $C_{30}H_{48}O_{13}$ requires C, 58·4; H, 7·85%). The di- and tri-ethoxycarbonyl derivatives gave a marked m. p. depression on admixture. The former consumed 1O on titration with chromic acid at room temperature, the latter none.

Characterisation of the 1,3-*Glycol System in Deacetylclerodin Derivatives.*—(a) *Copper bronze reactions.* Hederagenin methyl ester (80 mg.), mixed with copper bronze (160 mg.), was heated for 2 hr. at 270—300° (metal bath) in a stream of oxygen-free nitrogen which was then passed through saturated aqueous dimedone. After being left for 12 hr. at 0° the formaldehyde dimedone derivative was removed (5·7 mg.) and identified by m. p. and mixed m. p. Under the same conditions deacetyltetrahydroclerodin (85 mg.) gave the formaldehyde dimedone derivative (5·4 mg.), identified by m. p., mixed m. p., and infrared spectrum.

(b) *Reactions with ethyl chloroformate.* Deacetyltetrahydroclerodin (III; R = R′ = H) (50 mg.) in pyridine, when left with an excess of ethyl chlorocarbonate at 0° for 45 min., gave, after chromatography over alumina (grade V) and crystallisation from benzene–light petroleum (b. p. 80—100°), *deacetyltetrahydroclerodin carbonate* (III; R,R′ = CO), prisms, m. p. 226—228°, $[\alpha]_D$ −49° (*c* 0·78), $\nu_{max.}$ (in $CHCl_3$) 3580 and 3400 (OH) and 1735 (carbonate) cm.$^{-1}$ (Found: C, 66·6; H, 8·4. $C_{21}H_{32}O_6$ requires C, 66·3; H, 8·5%).

Deacetyldihydroclerodin-I (70 mg.) was similarly converted into its *carbonate* (II; R,R = CO, R′ = R″ = H). After chromatography over alumina (grade V) and crystallisation from benzene–light petroleum, this formed prisms (32 mg.), m. p. 276—281°, $[\alpha]_D$ −49° (*c* 0·67), $\nu_{max.}$ (in $CHCl_3$) 1739 (carbonate) cm.$^{-1}$, no OH absorption (Found: C, 67·1; H, 8·05. $C_{21}H_{30}O_6$ requires C, 66·65; H, 8·0%).

Hederagenin methyl ester (150 mg.) in the same way gave *di*-O-*ethoxycarbonylhederagenin methyl ester* (VII; R = CO_2Et) as prisms (from benzene–methanol), m. p. 172—176°, $[\alpha]_D$ +73° (*c* 1·10), $\nu_{max.}$ (in $CHCl_3$) 1740 (O·CO_2Et and Me ester) cm.$^{-1}$ (Found: C, 70·05; H, 9·15. $C_{36}H_{56}O_8$ requires C, 70·1; H, 9·15%).

Toluene-p-*sulphonation of Deacetylclerodin Derivatives.*—Deacetyltetrahydroclerodin (1·445 g.), left with toluene-*p*-sulphonyl chloride (5 mol.) in pyridine (20 ml.) overnight at 0°, gave *deacetyltetrahydroclerodin monotoluene*-p-*sulphonate* (III; R = *p*-C_6H_4Me·SO_2, R′ = H).

[15] Barton and Overton, *J.*, 1955, 2639.

Recrystallised from benzene–light petroleum, this formed needles (1·94 g.), m. p. 152—153°, $[\alpha]_D$ −8° (*c* 1·06), $\lambda_{max.}$ 225 mμ (ε 13,000), $\nu_{max.}$ (in Nujol) 3300 (OH), 1600, and 1500 (benzene) cm.$^{-1}$ (Found: C, 63·85; H, 7·95. $C_{27}H_{40}O_7S$ requires C, 63·75; H, 7·95%).

Deacetyldihydroclerodin-I monotoluene-p-*sulphonate* (VIII; R = *p*-$C_6H_4Me{\cdot}SO_2$, R′ = H), prepared in the same way and crystallised from benzene–light petroleum, had m. p. 149—151°, $[\alpha]_D$ +35° (*c* 1·41) (Found: C, 63·75; H, 7·75. $C_{27}H_{38}O_7S$ requires C, 64·0; H, 7·55%). This monotoluene-*p*-sulphonate (370 mg.) in glacial acetic acid (30 ml.) was treated with sodium dichromate (357 mg.) at room temperature for 38 hr. The product, after chromatography over alumina (grade III) and elution with benzene, afforded the *monoketone ester* (IX). Crystallised from benzene–light petroleum, this formed prisms (120 mg.), m. p. 152—153°, $[\alpha]_D$ +75° (*c* 0·63), $\nu_{max.}$ (in Nujol) 1715 (CO) cm.$^{-1}$ (Found: C, 64·55; H, 7·65. $C_{27}H_{36}O_7S$ requires C, 64·25; H, 7·2%).

Oxidation of Deacetyltetrahydroclerodin Monotoluene-p-*sulphonate and Reactions Sequential thereto.*—The monotoluene-*p*-sulphonate (3·01 g.) was treated at room temperature with a four-fold excess of oxidant (sodium dichromate in acetic acid) until one O had been consumed (titrimetric control). The product was worked up at less than 40° and formed a colourless gum with $\lambda_{max.}$ 225 mμ (ε 10,000) and infrared absorption at 3380 (OH) and 1701 (cyclohexanone) cm.$^{-1}$. Chromatography over alumina (grade III) (or treatment with aqueous-ethanolic 2% sodium hydroxide for 1 hr. at room temperature) gave the *diketone* (XII; R = Me). After crystallisation from ether this formed prisms (1·41 g.), m. p. 183—186°, $[\alpha]_D$ +9° (*c* 0·95), $\lambda_{max.}$ 275 mμ (ε 120), $\nu_{max.}$ (in Nujol) 1702 (ketones) cm.$^{-1}$ (Found: C, 71·9; H, 9·35. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·05%). It gave a negative tetranitromethane test but strongly positive Zimmermann and iodoform reactions.

The diketone furnished a yellow *bis*-2,4-*dinitrophenylhydrazone* as prisms (from acetic acid), m. p. 169—171°, $\lambda_{max.}$ 366 mμ (ε 46,300) (Found: C, 54·95; H, 5·45. $C_{32}H_{38}N_8O_{10}$ requires C, 55·3; H, 5·5%). It also gave a *dioxime*, m. p. 249—251° (from aqueous ethanol), $[\alpha]_D$ −63° (*c* 1·07) (Found: C, 66·35; H, 9·15; N, 7·8. $C_{20}H_{32}N_2O_4$ requires C, 65·9; H, 8·85; N, 7·7%).

Reduction of the diketone (XII; R = Me) (80 mg.) in methanol (4 ml.) at 0° with sodium borohydride (3·0 mg.) in methanol (3 ml.) for 20 min. afforded a product which was separated by chromatography over alumina (grade III) into a diol (7 mg.) (see below) and the *ketol* (XIII) (41 mg.). Crystallised from ether–light petroleum this had m. p. 131—134°, $[\alpha]_D$ +16° (*c* 0·52), $\nu_{max.}$ (in Nujol) 3485 (OH) and 1705 (CO) cm.$^{-1}$ (Found: C, 71·7; H, 9·85. $C_{20}H_{32}O_4$ requires C, 71·4; H, 9·6%).

Reduction of the diketone (30 mg.) in methanol (3 ml.) with sodium borohydride (12 mg.) for 45 min. at room temperature gave the corresponding *diol*. This recrystallised from benzene–light petroleum as prisms (20 mg.), m. p. 163—165°, resolidifying and melting at 172—173°, $[\alpha]_D$ +20° (*c* 0·28), $\nu_{max.}$ (in CCl_4) 3310 (OH) cm.$^{-1}$ (Found: C, 70·85; H, 9·85. $C_{20}H_{34}O_4$ requires C, 70·95; H, 10·15%). This diol was identical with the material obtained as a by-product in the selective reduction described above.

The diketone (XII; R = Me) (83 mg.) in ether–chloroform (1 : 1; 10 ml.) containing monoperphthalic acid (4—5 times theor.) was kept at room temperature in the dark for 33 hr. (uptake of one equiv.). Crystallisation of the product from ether–light petroleum (b. p. 40—60°) gave the *keto-lactone* (XXIV) as needles (43 mg.), m. p. 143—145°, $[\alpha]_D$ −6° (*c* 0·47), $\nu_{max.}$ (in Nujol) 1715 (Me ketone and lactone) cm.$^{-1}$ (Found: C, 68·35; H, 9·2. $C_{20}H_{30}O_5$ requires C, 68·55; H, 8·65%). Treatment with aqueous-ethanolic alkali furnished a keto-acid which did not crystallise.

Treatment of the Diketone (XII; R = Me) *with Strong Base.*—The diketone (187 mg.) in t-butyl alcohol (11 ml.), made N with potassium t-butoxide, was heated at 50—60° for 1 hr. under oxygen-free nitrogen. Chromatography of the product over alumina (grade V) afforded the *cyclohexenone* (XXII) (140 mg.) as prisms (from benzene–light petroleum), m. p. 177—179°, $[\alpha]_D$ −206° (*c* 0·72), $\lambda_{max.}$ 249 mμ (ε 10,400), $\nu_{max.}$ (in Nujol) 1665 (conjugated ketone) and 1625 (conjugated C:C) cm.$^{-1}$ (Found: C, 75·95; H, 9·15. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%). Hydrogenation of this enone (49 mg.) in ethyl acetate (10 ml.) over 10% palladised charcoal (1 mol. uptake) gave the saturated *ketone* (XXII; saturated) (33 mg.) as plates (from benzene–light petroleum), m. p. 173—175°, $[\alpha]_D$ +57° (*c* 1·07), $\nu_{max.}$ (in CCl_4) 1710 (CO) cm.$^{-1}$ [Found: C, 75·6; H, 9·5%; *M* (Rast), 319. $C_{20}H_{30}O_3$ requires C, 75·45; H, 9·5%; *M*, 318].

The cyclohexenone (XXII) (530 mg.) in ethyl acetate (22·5 ml.) and glacial acetic acid (22·5 ml.) was ozonised at 0° for 40 min. (disappearance of ultraviolet band at 249 mμ). The

solvent was removed *in vacuo* and the residue was left in acetic acid (2 ml.) and water (20 ml.) containing 30% hydrogen peroxide (0·5 ml.) for 5 days at room temperature. Crystallisation of the product from chloroform–light petroleum (b. p. 40—60°) gave the *keto-acid* (XXIII) (340 mg.) as needles, m. p. 197—211° (decomp.), $[\alpha]_D$ +12° (*c* 0·30), $\nu_{max.}$ (in Nujol) 3535 (OH), 1740 (CO_2H), and 1710 (CO) cm.$^{-1}$ (Found: C, 67·55; H, 8·3. $C_{19}H_{28}O_5$ requires C, 67·85; H, 8·4%). The derived *methyl ester*, prepared with diazomethane in the usual way, crystallised from ether–light petroleum (b. p. 40—60°) as needles, m. p. 130—134°, $[\alpha]_D$ +14° (*c* 0·56), $\nu_{max.}$ (in Nujol) 1725 (ester) and 1700 (CO) cm.$^{-1}$ (Found: C, 68·05; H, 8·3. $C_{20}H_{30}O_5$ requires C, 68·55; H, 8·65%).

The keto-acid (XXIII) was recovered unchanged after treatment with (*a*) 2% sodium hydroxide in aqueous ethanol and (*b*) N-potassium t-butoxide at 55—60° in t-butyl alcohol. The derived methyl ester (25 mg.), kept in N-potassium t-butoxide in t-butyl alcohol (3 ml.) for 30 min. at 55—60° and then, after dilution with water (6 ml.), refluxed for 1½ hr., gave the keto-acid (XII; R = OH). After crystallisation from ether–light petroleum (b. p. 40—60°) the product (needles; 15 mg.) was identified by m. p., mixed m. p., and infrared spectrum.

Clerodin Hemiacetal Anhydride (VI).—When recrystallised from ether–light petroleum this *anhydride* (see above) formed prisms, m. p. 210—215°, $[\alpha]_D$ −67° (*c* 1·69), $\nu_{max.}$ (in Nujol) 1735, 1250, and 1225 (acetates) cm.$^{-1}$ (Found: C, 64·6; H, 7·7%; OMe, 0; *M*, 863. $C_{48}H_{70}O_{15}$ requires C, 65·0; H, 7·95%; *M*, 887). From benzene–light petroleum, it formed a *benzene solvate*, m. p. 136—142°, resolidifying and melting at 218—228°, $\lambda_{max.}$ (benzene absorption) 250, 255, and 260 mμ (ε 270, 300, and 240 mμ respectively), $\nu_{max.}$ (in Nujol) 1730, 1255, and 1230 (acetates), 690 (benzene) cm.$^{-1}$ (Found: C, 66·95; H, 7·85. $C_{48}H_{70}O_{15},C_6H_6$ requires C, 67·2; H, 7·95%). Treatment of the anhydride (45 mg.) in acetic acid—water (1 : 1; 1·2 ml.) for 18 hr. at room temperature gave, on crystallisation of the product from ether–light petroleum, clerodin hemiacetal (II; R = Ac, R′ = OH, R″ = H) (39 mg.), identified by m. p., mixed m. p., rotation, and infrared spectrum. Similarly, oxidation of the anhydride (45 mg.) with sodium dichromate dihydrate (66·5 mg.) in glacial acetic acid (5 ml.) at room temperature for 5 hr. gave, after crystallisation from ether–light petroleum, the known γ-lactone, (V; R = H) (23 mg.), identified by m. p., mixed m. p., rotation, and infrared spectrum.

The anhydride (VI) (200 mg.) in ether (100 ml.) was refluxed with lithium aluminium hydride (800 mg.) for 18 hr. The product, crystallised from ethyl acetate–light petroleum (b. p. 40—60°), gave the corresponding *hexaol* (100 mg.) as needles, m. p. 201—209°, $[\alpha]_D$ −76° (*c* 0·45), $\nu_{max.}$ (in Nujol) 3355 (OH) cm.$^{-1}$ (Found: C, 66·1; H, 9·0. $C_{40}H_{66}O_{11}$ requires C, 66·45; H, 9·2%).

Clerodin hemiacetal (583 mg.), moistened with glacial acetic acid (0·3 ml.), was heated at 120° for 5 min.; it liquified. Acetic acid (plus any water formed) was then slowly distilled at 110—125° under gradually reduced pressure (10 mm. to 1 mm.) during 35 min. To the residue were added chloroform and aqueous sodium hydroxide (slight excess). From the chloroform solution there was obtained a gum which, on chromatography over alumina (grade III, neutral), afforded (in order of elution) clerodin (10 mg.), clerodin hemiacetal acetate (55 mg.), clerodin hemiacetal anhydride (VI) (43 mg.), and recovered clerodin hemiacetal (77 mg.). The hemiacetal anhydride obtained was identical (m. p. and mixed m. p. for the unsolvated form and for the benzene adduct; and infrared spectra) with the naturally occurring compound.

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