63. *The Active Principles of Leguminous Fish-poison Plants. Part IV. The Isolation of Malaccol from* Derris malaccensis.

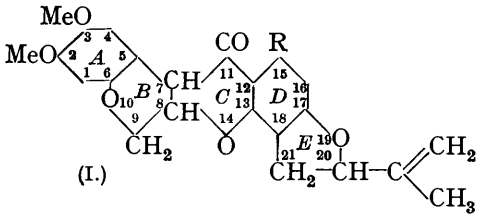
By Stanley H. Harper.

An optically active phenol, *malaccol*, isolated from an ethereal extract of the root of *Derris malaccensis* (Kinta type), is shown to have the formula $C_{20}H_{16}O_7$. From a study of its reactions and by comparison of these with the reactions of sumatrol and of elliptone, structure (II, R = OH), *i.e.*, 15-hydroxyelliptone, is suggested for malaccol.

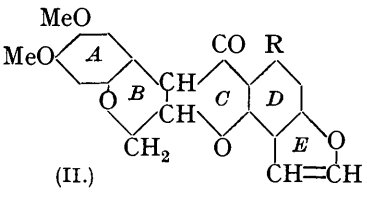
In Part I (J., 1939, 812) the isolation of *l*-α-toxicarol from *Derris malaccensis* (Kinta type) root was described. During the ether extraction a gelatinous precipitate had separated, which was filtered off before the solution was concentrated to obtain the crystalline toxicarol. This gelatinous precipitate (1·5%, calc. on the root) has now been examined in detail. No crystalline solid was deposited on standing in ether, but on warming a solution in acetone separation of bright yellow crystals commenced which was completed by refluxing. It follows that in the root this substance is present in some stabilised non-crystalline form, either as a colloid or in some form of combination, broken down by the solvent. This substance, though sparingly soluble in most solvents, was readily purified by crystallisation from benzene or ethyl acetate and obtained as bright yellow prisms or needles, m. p. 225°, solidifying to star-shaped clusters of needles and remelting at 244° (this was at first thought to be due to dimorphism; see, however, p. 311), $[\alpha]_D^{18°}$ + 190° in chloroform and + 67° in benzene. Recently Meyer and Koolhaas (*Rec. Trav. chim.*, 1939, **58**, 207) have described a greenish-yellow crystalline substance, m. p. 244°, $[\alpha]_D$ + 107° in benzene, isolated from Sumatra type *Derris* root. Although the differences of physical constants are considerable, examination of a specimen kindly sent by Dr. Meyer revealed that his substance, to which he has given the name *malaccol*, also had a second melting point at 225°, and their identity was shown by non-depression of melting point on admixture. These properties clearly distinguish this substance from the known constituents of *Derris* root and the name malaccol has therefore been adopted. Owing to the very sparing solubility (*ca.* 0·3% at 20°) no great weight is attached to the numerical values of the specific rotations in benzene, although qualitatively these are in agreement.

Malaccol gives a positive Durham test and a strong ferric chloride colour suggesting a close relationship with toxicarol and sumatrol. The analytical results obtained for malaccol, together with those of derivatives discussed subsequently, clearly establish the formula $C_{20}H_{16}O_7$, as suggested by Meyer and Koolhaas. This formula bears the same relationship to that of elliptone ($C_{20}H_{16}O_6$) as does the formula of sumatrol ($C_{23}H_{22}O_7$) to that of rotenone ($C_{23}H_{22}O_6$), and malaccol is thus isomeric with elliptolone (J., 1939, 1424). The positive Durham test given by malaccol indicates that rings *A*, *B*, and *C* are the same as in rotenone (I, R = H). This, with the fact that there are two methoxyl groups and a keto-group, accounts for five of the seven oxygen atoms; the remaining two are therefore probably attached to ring *D*. The presence of an active carbonyl group, established by the formation of an *oxime*, in conjunction with the strong ferric chloride reaction, indicates that there is a phenolic hydroxyl group in the *o*-position to the carbonyl group; in agree-

ment with this conclusion it has been observed that malaccol, like sumatrol, is almost insoluble in aqueous potassium hydroxide. Acetylation gives rise to a product, which has not yet been obtained pure, giving a negative ferric chloride reaction; it is therefore probably a mixture of the monoacetate and the diacetate derived from the enolic form.

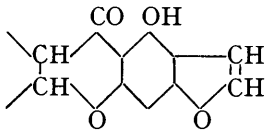


(I.)

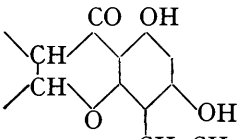


(II.)

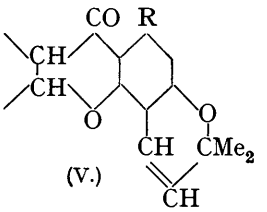
That ring *D* is a phloroglucinol residue is shown by the close similarity of the ferric chloride colours given by malaccol and its dehydro- and tetrahydro-derivatives with those of the corresponding derivatives of sumatrol (Robertson and Rusby, J., 1937, 497), in which the presence of a phloroglucinol residue has recently been confirmed by synthesis (Kenny, Robertson, and George, J., 1939, 1601). The remaining oxygen is therefore attached to ring *D* in position 17. By analogy with elliptone (II, R = H) (for a proof of its structure, see J., 1939, 1424) and in conformity with the formula $C_{20}H_{16}O_7$, this oxygen atom will form part of a furan ring. Malaccol therefore possesses either structure (II, R = OH), *i.e.*, 15-hydroxyelliptone, or the linear structure (III). Inasmuch as the other members of this group have been shown to possess the angular structure, excepting sumatrol, for which the evidence is inconclusive, formula (II, R = OH) is preferred to (III). Further experiments, now described, support this formulation, but do not distinguish between the angular and the linear formula.



(III.)



(IV.)



(V.)

On the basis of either formula catalytic hydrogenation should lead to the taking up of four atoms of hydrogen with the fission of ring *E* to give the dihydric phenol (IV). Hydrogenation over Adams's catalyst in ethyl acetate confirmed this view, approximately four atoms being taken up. Absorption was slow, which is in accord with the furan structure for ring *E* (cf. the reduction of elliptone; J., 1939, 1099). The product, *tetrahydromalaccol*, was separated from unchanged malaccol by its ready solubility in 2% aqueous potassium hydroxide. The presence of an additional phenolic group was shown by the formation of a *triacetate* with acetic anhydride, giving a negative ferric chloride reaction.

Treatment of malaccol with sodium acetate in boiling alcohol, a process which is known only to racemise C_7—C_8 (Cahn, Phipers, and Boam, J., 1938, 513), yielded inactive *dl*-malaccol, m. p. 244°. C_7—C_8 are thus the only asymmetric centres in the molecule.

Malaccol differs from the other members of this group in giving a positive rotation in benzene solution. The other members all give a negative rotation and it has been customary to assign them a lævo-configuration (cf. Cahn, Phipers, and Boam, *loc. cit.*). It would be strange, therefore, if malaccol, occurring along with toxicarol, sumatrol, rotenone, and deguelin (?) in this root, were to have the opposite configuration as suggested by the sign of the rotation in benzene solution. A study of the values of these rotations (Table I), however, discloses that the introduction of a phenolic hydroxyl in position 15 in each case gives a positive increment to the specific rotation. Malaccol fits in the series as 15-hydroxyelliptone and it would appear probable that these substances all belong to

the same stereochemical series, which for convenience can be designated the *l*-series. Hence optically active malaccol will be designated *l*-malaccol where necessary to distinguish it from the racemic compound.

TABLE I.

$[\alpha]_D$ in benzene.

Rotenone (I, R = H) [1]	− 225°	Sumatrol (I, R = OH) [4]	− 184°
Deguelin (V, R = H) [2]	− 101	Toxicarol (V, R = OH) [5]	− 66
Elliptone (II, R = H) [3]	− 18	Malaccol (II, R = OH)	+ 67

[1] Jones and Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 2554.

[2] Haller and LaForge, *ibid.*, 1934, **56**, 2415. This value is for a "deguelin concentrate"; the author in unpublished work has obtained a similar figure.

[3] Harper, J., 1939, 1099.

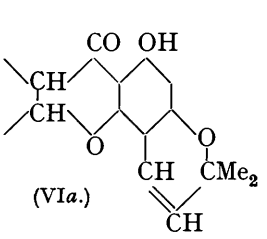
[4] Robertson and Rusby, *loc. cit.*

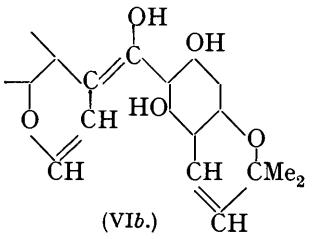
[5] Harper, J., 1939, 812.

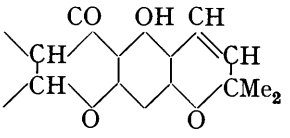
The identity of the second melting point of *l*-malaccol (244°) with that of *dl*-malaccol suggested that the double melting point was in reality due to racemisation in the fused state and not due to dimorphism. On maintaining *l*-malaccol just above the lower melting point (226°) a rapid loss of optical activity was observed, $[\alpha]_D$ falling from + 190° to + 10° (chloroform) in 2 minutes. Admixture of this resolidified material with *dl*-malaccol led to no depression of melting point of the latter, confirming that racemisation occurs on fusion and the double melting point is due to this cause. A similar instability of the optically active form was observed in the vapour phase. *l*-Malaccol readily sublimed at 195° in a high vacuum, but the product was pale yellow and 75% racemised. Resublimation of this material sufficed to give optically inactive *dl*-malaccol, m. p. 249°, unchanged by crystallisation from chloroform–ethyl alcohol. The difference of melting point of *dl*-malaccol prepared by alcoholic sodium acetate and by sublimation (there was no depression on admixture) recalls that of *dl*-elliptone (176°) prepared by alcoholic sodium acetate and that of Buckley's substance (181°) (J., 1939, 1099); as yet no explanation can be offered for these differences.

l- and *dl*-Malaccol, on refluxing in alcoholic sodium acetate, were oxidised by iodine to a soluble iodo-compound, obtained by precipitation of the reaction mixture with water. Removal of iodine by means of zinc dust and acetic acid gave in both cases *dehydromalaccol* ($C_{20}H_{14}O_7$), m. p. 257°. As with the dehydro-compounds from sumatrol and toxicarol, the Durham test was negative. When racemising *l*-malaccol with alcoholic sodium acetate it had been noticed that there was an induction period of several minutes before *dl*-malaccol started to separate. When oxidation with iodine was carried out during this period, the reaction took a different course. A bright yellow iodo-compound was precipitated, which on treatment with zinc dust and acetic acid gave, as did the material obtained by pouring the alcoholic mother-liquor into water, a yellow crystalline *substance*, m. p. 257°. This, however, was not the dehydro-compound obtained above, as a mixture gave a marked depression of m. p. Acetylation with acetic anhydride in pyridine gave a *monoacetyl* derivative, m. p. 227°. Analyses of these do not distinguish between the formulæ $C_{20}H_{14}O_8$ and $C_{20}H_{14}O_7$ for the parent substance. If the former is correct, the additional oxygen atom may be in the form of a bridge between C_7 and C_8, as acetylation indicates but one hydroxyl group and the substance gives a negative Durham test. This would be in accord with the known substitution of iodine atoms on these carbon atoms in this reaction. If, however, the substance has the second formula, it would be a dehydro-compound isomeric with that obtained above. An explanation of this possible isomerism can be found in the work of Cahn, Phipers, and Boam (*loc. cit.*) on the interconversion of α- and β-toxicarol. They showed that racemisation of *l*-toxicarol by alkali took place through the intermediate open-chain phenol (VI*b*), which is the precursor of both *dl*-α- (VI*a*) and *dl*-β-toxicarol (VI*c*) by rotation around the single linkage C_{11}—C_{12}. Both α- and β-toxicarol give distinct but isomeric dehydro-compounds by elimination of the hydrogen atoms attached to C_7 and C_8. By analogy substances with the angular (II, R = OH) and the linear formula (III) should be interconvertible in the presence of alkali. Cahn,

Phipers, and Boam found that alcoholic sodium acetate gave α-toxicarol, and potassium carbonate in acetone preferentially β-toxicarol. *l*-Malaccol, however, gave the same *dl*-compound by both these methods, and no second substance could be isolated. If dehydromalaccol and this second oxidation product are isomeric, *dl*-malaccol will have the opposite configuration to *l*-malaccol, *i.e.*, if *l*-malaccol is (II, R = OH), *dl*-malaccol will be (III) (or vice versa). Dehydromalaccol will then be derived from *dl*-malaccol by


(VI*a*.)


(VI*b*.)


(VI*c*.)

removal of the hydrogen atoms attached to C_7—C_8, and this second oxidation product will similarly correspond to *l*-malaccol. To the author the facts that only one *dl*-compound can be isolated and particularly that it is formed in the absence of alkali (*i.e.*, by fusion and sublimation), when it is unlikely that racemisation proceeds through the open-chain mechanism, suggest that both *l*- and *dl*-malaccol have the same configuration (preferably II, R = OH) and that the second oxidation product has the formula $C_{20}H_{14}O_8$.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. Acetyl determinations were unsatisfactory, so reliance is placed instead on methoxyl content. These determinations are by the author, using Clark's semimicro-method (*J. Assoc. Off. Agric. Chem.*, **1932**, **15**, 136). Melting points, as in previous papers of this series, were observed in Mason's apparatus (*Chem. and Ind.*, **1925**, 577) and are uncorrected.

The finely ground air-dried root (1000 g.) of *Derris malaccensis* (Kinta type) as used in Part I (*loc. cit.*) was extracted to completion with ether in a large Soxhlet apparatus. The extract (1·5 l.), on cooling, deposited a gelatinous precipitate (A), which, after standing overnight, was filtered off, washed with ether, and air-dried (15 g.). The ethereal filtrate on concentration and refrigeration rapidly deposited hard crystalline masses of crude *l*-α-toxicarol, but was not further examined. Precipitate A was completely soluble in acetone (100 c.c.) in the cold, but on warming, the separation of yellow crystals commenced, which was completed by refluxing for 30 minutes. The liquid was filtered hot, to give nearly pure *malaccol* (1·01 g.; *i.e.*, 0·1%, calc. on the root). On keeping, the filtrate slowly deposited crude sumatrol. Final purification was effected by crystallisation from chloroform–ethyl alcohol, ethyl acetate, or benzene, from which malaccol separated as bright yellow, irregular prisms or needles, m. p. 225°, solidifying to star-shaped clusters of needles and remelting at 244°. $[\alpha]_D^{18°}$ + 190° in chloroform (c = 1·02); malaccol was not soluble at this concentration in benzene or acetone (cf. Meyer and Koolhaas, *loc. cit.*). The mother-liquor from a benzene crystallisation (by evaporation: 30 mg./10 c.c.) gave $[\alpha]_D$ + 67° (c = 0·3), but this can only be approximate [Found: (*ex* benzene) C, 65·4; H, 4·6; (*ex* chloroform–ethyl alcohol) C, 65·3; H, 4·6; OMe, 16·9. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4; 2OMe, 16·9%]. An attempt to determine the molecular weight by the Rast method was unsuccessful. In the Durham test malaccol gave an intense blue colour changing to green and with alcoholic ferric chloride a green colour. In the Goodhue test (*J. Assoc. Off. Agric. Chem.*, **1936**, **19**, 118) it gave only a pale red colour at 1 mg./c.c., which was nearly the limit of solubility. It was insoluble in 2% aqueous potassium hydroxide.

Malaccol (100 mg.) and hydroxylamine hydrochloride (100 mg.) were heated at 100° for 6 hours in pyridine (3 c.c.). On dilution with water the *oxime* (62 mg.) separated in needles. Recrystallised from methyl alcohol, it formed feathery needles, decomp. 240° (Found: N, 4·0. $C_{20}H_{17}O_7N$ requires N, 3·7%).

Attempts to acetylate malaccol were unsuccessful: (a) Malaccol (100 mg.) and acetic anhydride (0·1 c.c.) in pyridine (2 c.c.) were kept at room temperature for 2 hours. Dilution with water gave a gum, which, after 24 hours, during which the excess of acetic anhydride

decomposed, was dissolved in alcohol and reprecipitated with water. This solid gave no colour with ferric chloride, but could not be obtained crystalline. (b) Malaccol (200 mg.) and sodium acetate (50 mg.) were refluxed for 30 minutes in acetic anhydride (1 c.c.), and the mixture poured into water and kept overnight. The gum, on standing in alcohol, slowly deposited a small crop of colourless prisms, m. p. 225—235° (decomp.). It gave no colour with ferric chloride and was probably the diacetate, but there was insufficient for further purification.

Tetrahydromalaccol.—Malaccol (500 mg.) in ethyl acetate suspension (100 c.c.) was reduced catalytically in the presence of Adams's catalyst (100 mg.). Absorption was complete in 18 hours, the malaccol having gone into solution and a volume (63 c.c. at N.T.P.) corresponding to 4 atoms of hydrogen (62 c.c.) being taken up. The filtered solution was concentrated to small bulk, diluted with ether, and extracted with 2% potassium hydroxide solution. The ethereal layer on evaporation gave a trace of unreduced malaccol. The alkaline layer was acidified; the precipitated phenol (485 mg.) crystallised from a small volume of ethyl alcohol to give *tetrahydromalaccol* in colourless needles, m.p. 222°, giving a brownish-green colour with ferric chloride (Found: C, 64·4; H, 5·3; OMe, 16·7. $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·4; OMe, 16·7%). Acetylation with sodium acetate–acetic anhydride gave a small yield of the *triacetyl* derivative, which crystallised from alcohol in fern-like clusters, m. p. 195°, and gave no colour with ferric chloride [Found: OMe, 12·8. $C_{20}H_{17}O_7(CO{\cdot}CH_3)_3$ requires OMe, 12·5%].

dl-*Malaccol.*—(a) A suspension of malaccol (250 mg.) and sodium acetate (500 mg.) was refluxed in alcohol (50 c.c.), partial solution taking place. After 10 minutes a sudden precipitation of pale yellow needles occurred; after a further 2 hours' refluxing, these were filtered off. Crystallisation from chloroform–ethyl alcohol (1 : 3) gave dl-*malaccol* in very pale yellow needles, m. p. 244°, $[\alpha]_D \pm 0°$ in chloroform (Found: C, 64·3; H, 4·4; OMe, 16·9. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4; OMe, 16·9%); yield, variable, 150—200 mg. In the Durham test *dl*-malaccol gave an intense green colour and in the Goodhue test at 1 mg./c.c. (the limit of solubility) a pale red of approximately the same intensity as that given by *l*-malaccol. With alcoholic ferric chloride it gave a blue-green colour.

(b) A suspension of malaccol (250 mg.) and potassium carbonate (500 mg.) was refluxed in "AnalaR" acetone (10 c.c.). After 2 hours the suspension was poured into water and acidified; the precipitate crystallised from chloroform–ethyl alcohol (1 : 3) to give *dl*-malaccol, m. p. 249°, $[\alpha]_D \pm 0°$ in chloroform (Found: C, 64·9; H, 4·3%). There was no depression of m. p. on admixture with preparation (a) above.

(c) By subliming twice at 195° in a high vacuum, malaccol was completely racemised. Crystallisation as above gave *dl*-malaccol, m. p. 249°. There was no depression of m. p. on admixture with either of the above preparations.

Oximation of *dl*-malaccol (100 mg.) as described above (p. 312) gave the *oxime* (70 mg.), decomposing at 270°, in needles insoluble in boiling methyl alcohol. It separated, however, from boiling butyl alcohol in microcrystalline plates containing solvent of crystallisation, decomposing at 260° (Found: N, 2·3. $C_{20}H_{17}O_7N{,}3C_4H_9{\cdot}OH$ requires N, 2·3%).

Dehydromalaccol.—(a) *l*-Malaccol (250 mg.) and sodium acetate (500 mg.) were refluxed in alcohol (25 c.c.) until separation of *dl*-malaccol occurred. Iodine (500 mg.) in alcohol (10 c.c.) was then added gradually, and the resultant solution refluxed for 1 hour. The iodo-compound (350 mg.), obtained by pouring the solution into water, was reduced with zinc dust (250 mg.) in boiling acetic acid (5 c.c.). After 1·5 hours, when the iodo-compound had gone into solution, a further quantity of zinc dust (125 mg.) was added. After 2 hours the solution was filtered hot and cooled; the *dehydromalaccol* so obtained was recrystallised from chloroform–ethyl alcohol (1 : 3) and obtained in bright yellow plates (90 mg.), m. p. 257° (Found: C, 65·0; H, 3·7; OMe, 16·9. $C_{20}H_{14}O_7$ requires C, 65·6; H, 3·8; OMe, 16·9%), giving a negative Durham test and a green colour with ferric chloride.

(b) *dl*-Malaccol (250 mg.), oxidised as in (a), gave the same dehydro-compound (105 mg.), a mixture showing no depression of m. p.

Acetylation with acetic anhydride in pyridine was unsuccessful, only a small yield of impure material being obtained, which, however, gave a positive ferric chloride reaction.

(c) A boiling suspension of *l*-malaccol (250 mg.) and sodium acetate (500 mg.) in alcohol (25 c.c.) was treated in the course of 10 minutes (*i.e.*, before racemisation had commenced) with iodine (500 mg.) in alcohol (10 c.c.). The malaccol went into solution with deposition of a yellow iodo-compound (150 mg.). After 1 hour this was filtered off and reduced with zinc dust as described in (a) above. The *substance* (54 mg.) crystallised from chloroform–ethyl alcohol (1 : 3) in bright yellow plates, m. p. 257°. The original alcoholic filtrate, when poured

into water, gave a further quantity of material which on reduction gave the same substance. A mixed m. p. determination with dehydromalaccol from (a) above gave a depression to 230° (Found : C, 63·3, 63·4; H, 3·9, 3·6; OMe, 16·9, 17·0. $C_{20}H_{14}O_8$ requires C, 62·9; H, 3·7; OMe, 16·3. $C_{20}H_{14}O_7$ requires C, 65·6; H, 3·8; OMe, 16·9%). The substance gave a negative Durham test and a green colour with ferric chloride. It was recovered unchanged after refluxing both with alcoholic sodium acetate and with alcoholic sulphuric acid for 8 hours.

Acetylation of this substance (100 mg.) with acetic anhydride (1 c.c.) in pyridine (0·5 c.c.) at 100° for 2 hours gave the *monoacetyl* derivative (88 mg.), which crystallised from chloroform–ethyl alcohol (1 : 3) in brownish-yellow flakes, m. p. 227°, and gave no colour with ferric chloride [Found : C, 62·8; H, 4·0; OMe, 14·8. $C_{20}H_{13}O_8(CO{\cdot}CH_3)$ requires C, 62·3; H, 3·8; OMe, 14·7. $C_{20}H_{13}O_7(CO{\cdot}CH_3)$ requires C, 64·7; H, 4·0; OMe, 15·2%].

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