146. *West African Timbers. Part V.* The Structure of Khivorin, a Constituent of* Khaya ivorensis.

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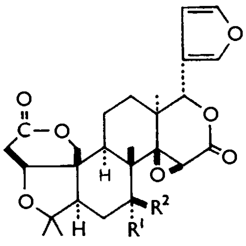
Khivorin, $C_{32}H_{42}O_{10}$, a new furanoid lactone, has been isolated from the timber of *Khaya ivorensis*. Its reactions indicate that it belongs to the limonin group of compounds, and structure (VIII) is assigned to it. Only the configurations of the 1- and 3-hydroxyl groups remain to be assigned.

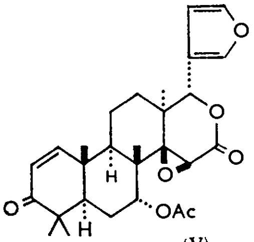
In continuation [1,2] of a systematic survey of the heartwoods of the Meliaceae we have examined *Khaya ivorensis*, the commonest species of the genus *Khaya*. Its timber is known in the trade as Lagos wood. An authentic specimen was obtained by courtesy of the Forestry Research Department, Ibadan (Forest Herbarium, Ibadan No. 42796).

Extraction of the heartwood with light petroleum gave an oil which afforded khivorin, $C_{32}H_{42}O_{10}$. Its ultraviolet and infrared spectra indicate (cf. refs. 1 and 2) the presence of a furan ring. The infrared spectrum showed no band indicative of a hydroxyl group but there was very strong ester and/or lactone absorption. Hydrolysis with alkali gave furan-3-aldehyde and a δ-lactone, khivol, $C_{21}H_{32}O_5$, containing hydroxyl groups ($\nu_{max.}$ 3300 and 1765 cm.$^{-1}$). If khivorin contains three acetoxy-groups we can account for all its carbon atoms: khivorin ($C_{32}H_{42}O_{10}$) + $3H_2O \longrightarrow$ furan-3-aldehyde (C_5H_4O) + khivol ($C_{21}H_{32}O_5$) + $3CH_3{\cdot}CO_2H$.

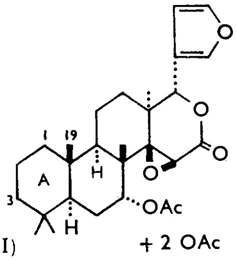
This hydrolysis is analogous to that of limonol [3-5] (I), which on treatment with alkali gives [6] furan-3-aldehyde and merolimonol (IV), and of gedunin (V) which gives [2] furan-3-aldehyde. It is a reasonable hypothesis that the same structural element is responsible for the production of furan-3-aldehyde in each case, *viz.* rings C and D, the furan ring, and the 7α-hydroxyl group found in limonol (I). Further, khivol should be related to khivorin in the same way as merolimonol (IV) is to limonol (I).



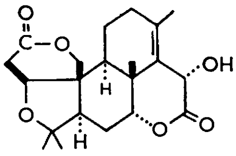
(I ; R¹ = OH ; R² = H)
(II ; R¹ = H ; R² = OH)
(III ; R¹R² = O)



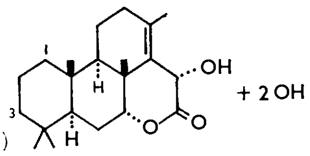
(V)



(VI)



(IV)



(VII)

If we allow for three acetoxy-groups, a furan ring, an epoxy-group, and a δ-lactone grouping in khivorin its formula is consistent with the presence of three carbocyclic rings. A partial structure fitting these facts is (VI), structure (VII) following for khivol. (The physical properties of the hydrolysis product of khivorin suggest that khivol may be

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* Part IV, *J.*, 1961, 3705.

[1] Akisanya, Bevan, Hirst, Halsall, and Taylor, *J.*, 1960, 3827.

[2] Akisanya, Bevan, Halsall, Powell, and Taylor, *J.*, 1961, 3705.

[3] Arigoni, Barton, Corey, Jeger, *et al.*, *Experientia*, 1960, **16**, 41.

[4] Arnott, Davie, Robertson, Sim, and Watson, *Experientia*, 1960, **16**, 49.

[5] Barton, Pradhan, Sternhill, and Templeton, *J.*, 1961, 255.

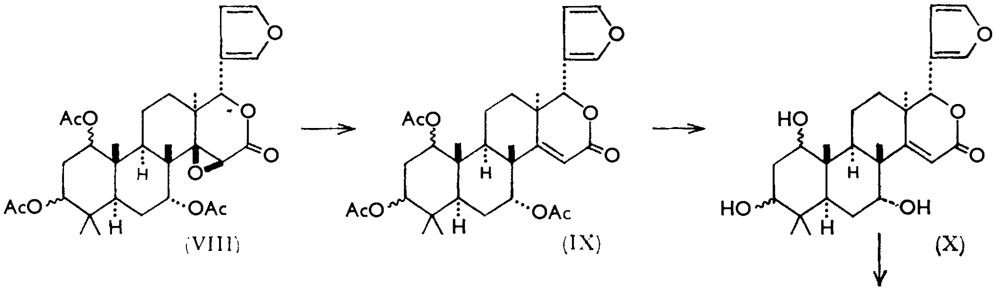
[6] Melera, Schaffner, Arigoni, and Jeger, *Helv. Chim. Acta*, 1957, **40**, 1420.

accompanied by some of the isomeric αβ-unsaturated lactone.) Khivorin then falls into the limonin group but with ring A intact, as in gedunin (V).[2]

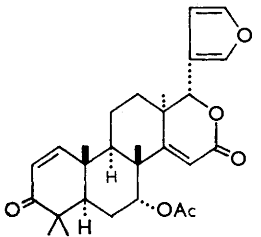
Chromous chloride reduction (cf. ref. 3) of khivorin (VIII) gave deoxykhivorin whose ultraviolet spectrum was in keeping with the presence of both a furan ring and an αβ-unsaturated δ-lactone. Similar reduction of gedunin (V) and dihydrogedunin (V; double bond in ring-A reduced) afforded the corresponding deoxy-compounds (XII) and (XII; double bond in ring-A reduced). The molecular-rotation changes on formation of the deoxy-compounds are: khivorin (VIII), +337°; gedunin (V), +278°; dihydrogedunin, +262°; limonin (III), +421°;[5,7] tetrahydrolimonin, +374°;[5] and epilimonol (II), +236°.[5] These values indicate that the absolute configurations of khivorin and gedunin are the same as that of limonin.

Ozonolysis of deoxykhivorin led to attack at the furan ring and formation of the acid (XIII). The change in molecular rotation on formation of the acid is −121°; the corresponding value in the case of the acid formed on ozonolysis of dihydrogedunin (V; double bond in ring-A reduced) is −113°.[2]

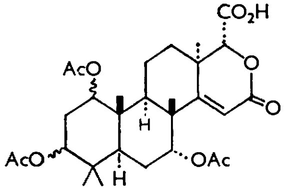
In partial structure (VI) two acetoxy-groups have still to be placed. On biogenetic grounds one would expect one to be at $C_{(3)}$. Possible sites for the other, bearing in mind the sites of oxidation in limonin (III),[3] are $C_{(1)}$ and $C_{(19)}$. The following evidence indicates that they are at $C_{(1)}$ and $C_{(3)}$, structure (VIII) following for khivorin, only their configurations remaining to be assigned. Hydrolysis of deoxykhivorin (IX) removed the acetyl groups without transformation of rings C and D, the trisdeacetyl derivative (X), $C_{26}H_{36}O_6$, and acetic acid being produced. Oxidation of the trisdeacetyl compound gave an enolic triketone (XI), $C_{26}H_{30}O_6$, with $\lambda_{max.}$ 2530 Å (ε 16,100) in ethanol and 2850 Å (ε 24,100) in ethanol containing alkali. These data are consistent with the presence of an enolic 1,3-diketone [cf. dimedone,[8] $\lambda_{max.}$ 2550 Å (ε 16,900) in ethanol and 2820 Å (ε 27,700) in alkaline ethanol]. The possibility of a 1,2-enolic diketone is excluded by the lack of reaction of khivol with periodic acid and by the ultraviolet absorption data.



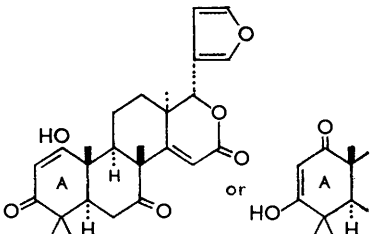
(VIII) (IX) (X)



(XII)



(XIII)



(XI)

A typical 1,2-enolic grouping such as that found in α-elaterin (cucurbitacin E) absorbs[9] at 2680 Å (ε 8300) in ethanol and at 3110 Å (ε 5500) in alkaline ethanol.

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[7] Geissman and Tulagin, *J. Org. Chem.*, 1946, **11**, 760.
[8] Eistert, Merkel, and Reiss, *Chem. Ber.*, 1954, **87**, 1513.
[9] Gilbert and Mathieson, *Tetrahedron*, 1958, **4**, 302.

The occurrence of khivorin in *Khaya ivorensis*, and gedunin in *Entandrophragma angolense*, both of the Meliaceae, suggests that compounds related to limonin may occur commonly in this family. It has already been suggested (cf. ref. 10) that swietenolide and swietenine, from *Swietenia macrophylla* (also one of the Meliaceae), are related to limonin, and nimbin which occurs in *Melia azadirachta* and contains (cf. ref. 11) a β-monosubstituted furan, two methoxycarbonyl groups, an acetoxy-group, and an αβ-unsaturated-ketone, may be of the same group. If so, it appears that the currently accepted formula $C_{29}H_{36}O_9$ is incorrect and that $C_{30}H_{38}O_9$ may be more likely. This would permit the usual C_{26} carbon skeleton after allowance for the acetoxy-group and the two methoxycarbonyl groups it is known to contain.

Other compounds which we have obtained[1] from related plants, including methyl angolensate, utilin, and entandrophragmin, are apparently of the same group.

EXPERIMENTAL

M. p.s were determined on a Köfler block and are corrected. Rotations were determined for chloroform solutions at room temperature. Unless otherwise stated, ultraviolet spectra were determined on ethanol solutions. The alumina used for chromatography was of activity I—II, and was deactivated as indicated.

Isolation of Khivorin (VIII).—Powdered heartwood of *Khaya ivorensis* was continuously extracted with boiling light petroleum (b. p. 60—80°). The extract was macerated with ether and the solid crystallised from methanol, giving *khivorin* as prisms, m. p. 256—263°, $[\alpha]_D$ −42° (*c* 1·04) (Found: C, 65·35, 65·25; H, 7·25, 7·2. $C_{32}H_{42}O_{10}$ requires C, 65·5; H, 7·2%), $\lambda_{max.}$ 2090 Å (ε 6285), $\nu_{max.}$ (in dichloromethane) 1500 and 875 (furan), 1720—1750, and 1235 (lactone and acetate) cm.$^{-1}$. The yield of khivorin was *ca.* 0·05% of the weight of timber used.

Hydrolysis of Khivorin.—Khivorin (3·09 g.) in 95% ethanol (90 c.c.) was treated with potassium hydroxide (2·09 g.), and the mixture was steam-distilled for 40 min. into a solution of 2,4-dinitrophenylhydrazine in methanol–perchloric acid. The product (16%) was furan-3-aldehyde 2,4-dinitrophenylhydrazone, dark-red crystals (from acetic acid), m. p. and mixed m. p. 230—234°.

When the reaction mixture was acidified and concentrated a precipitate was formed. It was taken up in methanol and treated with charcoal: crystallisation afforded *khivol* (VII; OH at $C_{(1)}$ and $C_{(3)}$) as prisms, m. p. 234—236°, $[\alpha]_D$ +27° (*c* 0·92) [Found: C, 68·8; H, 8·9; active H, 0·89. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·85; active H (3OH), 0·83%], $\lambda_{max.}$ 2260 Å (ε 2860), $\nu_{max.}$ (in Nujol) 3300, 1765, 1149, and 1072 cm.$^{-1}$.

Three samples of khivol (*ca.* 30 mg.) were treated in methanol (20 c.c.) with 0·135N-periodic acid solution (5 c.c.). After 25 hr. only 0·02 mol. of acid had been consumed.

Reduction of Khivorin (VIII) *with Chromous Chloride.*—Khivorin (0·5 g.) in acetone (25 c.c.) and acetic acid (25 c.c.) was treated under nitrogen with chromous chloride solution (approx. 0·6N) until the mixture had a bluish tint. Nitrogen was then bubbled through the solution for 18 hr. The acetone and part of the acetic acid were removed under reduced pressure and the residual solution was poured into hot water. The precipitate was collected and washed; *deoxykhivorin* (IX) formed prisms (from methanol), m. p. 243—245°, $[\alpha]_D$ +16° (*c* 0·99) (Found: C, 67·1, 67·5, 67·15; H, 7·4, 7·35, 7·2. $C_{32}H_{42}O_9$ requires C, 67·35; H, 7·4%), $\lambda_{max.}$ 2130 Å (ε 14,030), $\nu_{max.}$ (in dichloromethane) 1710—1750s, 1615, 1497, and 874 (furan), and 1040—1053 cm.$^{-1}$.

Similar reduction of gedunin (V) and dihydrogedunin (V; double bond in ring A reduced) gave deoxygedunin (XII), as prisms (from methanol), m. p. 209—214°, $[\alpha]_D$ +105° (*c* 1·04) (Found: C, 71·8, 71·6; H, 7·25, 7·45. $C_{28}H_{34}O_6$ requires C, 72·1; H, 7·35%), and *deoxydihydrogedunin* (XII; double bond in ring A reduced), prisms (from methanol), m. p. 219—222°, $[\alpha]_D$ +64° (*c* 1·00) (Found: C, 71·85, 71·35; H, 7·9, 7·9. $C_{28}H_{36}O_6$ requires C, 71·8; H, 7·75%).

Ozonolysis of Deoxykhivorin.—Deoxykhivorin (1·05 g.) in ethyl acetate (100 c.c.) was treated with 6% ozonised oxygen for about 1 hr. The mixture was then heated under reflux with water for 45 min. The organic phase was washed and dried; evaporation gave a product (0·95 g.) which crystallised from methanol, giving the *acid* (XIII) as prisms, m. p. 299—304°,

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

[11] Sengupta, Sengupta, and Khastgir, *Tetrahedron*, 1960, **11**, 67.

$[\alpha]_D$ −5·5° (*c* 1·01) (Found: C, 63·4, 63·4; H, 7·4, 7·5. $C_{29}H_{40}O_{10}$ requires C, 63·5; H, 7·35%), $\lambda_{max.}$ 2230 Å (ε 9100).

Ethereal diazomethane formed the ***methyl ester***, m. p. 256—259° (from methanol), $[\alpha]_D$ −5·5° (*c* 0·96) (Found: C, 63·95, 64·05; H, 7·55, 7·75. $C_{30}H_{42}O_{10}$ requires C, 64·05; H, 7·5%).

Hydrolysis of Deoxykhivorin (IX).—Deoxykhivorin (5·01 g.) in ethanol (100 c.c.) containing potassium hydroxide (2·76 g.) was heated under reflux for 30 min. The solution was concentrated to half volume and poured into water at 90°. The precipitate was washed with water and dried (3·82 g., 98%). Crystallisation from methanol yielded ***trisdeacetyldeoxykhivorin*** (X) as prisms, m. p. 316—319°, $[\alpha]_D$ +34° (in pyridine) (*c* 1·02) (Found: C, 70·5; H, 8·1. $C_{26}H_{36}O_6$ requires C, 70·25; H, 8·15%), $\lambda_{max.}$ 2130 Å (ε 13,830), $\nu_{max.}$ (in Nujol) 3450 and 3340 (OH), 1720, 1650 (unsaturated δ-lactone), 1500 and 875 (furan) cm.$^{-1}$.

The filtrate was acidified with 2N-hydrochloric acid (24 c.c.), saturated with sodium chloride, and extracted with ether (5 × 200 c.c.). Sodium hydroxide (2·03 g.) in water (10 c.c.) was added to the ethereal extracts and the ether was distilled off. The residual solution was neutralised, and heated under reflux with 4-bromophenacyl bromide (6·0 g.) in ethanol (60 c.c.) for 3½ hr. and then set aside. Crystals (3·02 g.), m. p. 66—70°, separated overnight. More [1·03 g. (m. p. 56—79°) and 0·42 g. (m. p. 58—104°)] were obtained on evaporation of the mother-liquors.

The first and the second crop of crystals were purified by chromatography on alumina (deactivated with 5% of 10% acetic acid), and 4-bromophenacyl bromide (needles), m. p. 112—114°, and *p*-bromophenacyl acetate (plates), m. p. 83—85° (from methanol), were obtained.

Oxidation of Trisdeacetyldeoxykhivorin (X).—The hydrolysis product (3·81 g.) in acetone (750 c.c.) was oxidised with 8N-chromic acid solution [12] (8·85 c.c.) at room temperature. After 40 min. the excess of oxidant was destroyed by addition of methanol (10 c.c.). The product (2·89 g.) was isolated and purified by chromatography on alumina (deactivated with 10% of 10% acetic acid) to give the *enolic triketone* (XI), m. p. 275—282°, $[\alpha]_D$ +45° (*c* 0·95) (Found: C, 70·5; H, 7·05. $C_{26}H_{30}O_6$ requires C, 71·2; H, 6·90%), $\lambda_{max.}$ (in ethanol) 2530 Å (ε 16,100), $\lambda_{max.}$ (ethanol + 1% of 3N-potassium hydroxide) 2850 Å (ε 24,100).

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[12] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.