Tetrahedron. Vol. 26, pp. 1637 to 1645. Pergamon Press 1970. Printed in Great Britain

ANDIROBIN

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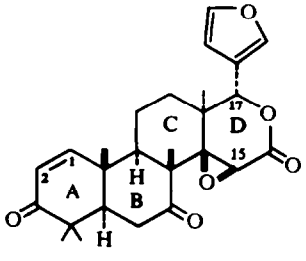
(*Received in the UK* 25 *September* 1969; *Accepted for publication* 1 *November* 1969)

Abstract—The seeds of the tree *Carapa guianensis* (*Meliaceae*) have yielded two compounds of the tetranortriterpenoid type. They have been identified as the known limonoid, 7-deacetoxy-7-oxogedunin (I), and a new member of this class, andirobin (XIV), whose biosynthesis probably involves an oxidative ring B cleavage.

THE tree *Carapa guianensis* Aubl., of the *Meliaceae* family, is widely distributed in the Amazonas State of Brasil and the wood is extensively used as commercial timber.[1] The seeds have also been used as a source of vegetable oils, but this is limited due to the occurrence in the seeds of bitter principles; this is probably to be associated with the use of the seeds in indigenous medicine.[2] Examination of the seeds of *Carapa guianensis*, for which the local name is "Andiroba", has yielded two compounds of the limonoid type. The limonoids[3, 4] are phytochemically characteristic of the *Meliaceae* family[5] and the two substances isolated in the present study were recognized as the known compound[6] 7-deacetoxy-7-oxogedunin (I) and a new natural product which was named andirobin.[7]

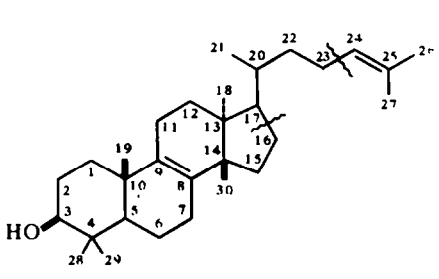
The compound, m.p. 260–264°, was recognized as the known natural product,[6] 7-deacetoxy-7-oxogedunin (I), on the basis of the following facts. Its molecular formula was shown to be $C_{26}H_{30}O_6$, and its spectroscopic properties pointed directly towards the following groupings: a cyclohexanone (ν_{CO}1720 cm^{-1}), an αβ-epoxylactone (ν_{CO}1745 cm^{-1}; τ 6·10s, 15-*H*; τ 4·52s, 17-*H*), a β-monosubstituted furan (τ 2·57m, two α-furan-*H*; τ 3·62m, β-furan-*H*), an αβ-unsaturated cyclohexenone (ν_{CO}1685 cm^{-1}; τ_A2·87d, τ_B4·07d, J_{AB} = 11 Hz with no additional coupling), and five tertiary Me groups (τ 8·63s, 8·78s, 8·87s, 8·87s, 8·87s). Direct comparison of this compound with authentic[6] 7-deacetoxy-7-oxogedunin (I), kindly supplied by Professor D. A. H. Taylor, University of Ibadan, Nigeria, confirmed its identification.

Andirobin, $C_{27}H_{32}O_7$, showed several points of spectroscopic similarity to 7-

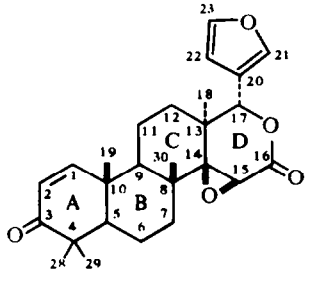


I 7-Deacetoxy-7-oxogedunin

deacetoxy-7-oxogedunin (I) (see Table), but there were also some differences which were highly informative. The similarities indicated the presence in andirobin of an αβ-epoxylacetone (ν_{CO}1760 cm^{-1}; τ 5·92s, 15-*H*; τ 4·47s, 17-*H*), a β-monosubstituted furan (τ 2·54m, two α-furan-*H*; τ 3·62m, one β-furan-*H*), and an αβ-unsaturated cyclohexenone (ν_{CO} 1680 cm^{-1}; τ_A 2·80d, τ_B 3·88d, J_{AB} = 11 Hz with no additional coupling). In addition, the NMR spectrum of andirobin indicated the presence of only four tertiary methyl groups (τ 8·88s, 8·88s, 9·01s, 9·05s), an olefinic methylene group, which showed no evidence of additional coupling (τ 4·55s, 4·67s), and a methoxycarbonyl group (ν_{CO} 1745 cm^{-1}; τ 6·25s, OCH_3). The presence of a methyl ester group in andirobin was established by its alkaline hydrolysis which yielded andirobinic acid, $C_{26}H_{30}O_7$, which on treatment with diazomethane gave back andirobin. Thus, andirobin could be regarded as having a C_{26}-skeleton and the presence of a β-monosubstituted furan and an αβ-epoxylactone strongly suggested that andirobin belonged to the limonoid class[8] of natural products with the tetranortriterpenoid C_{26}-skeleton.[3, 4] The bio-oxidative transformation of euphol-type precursors via the C_{30}-protolimonoids leading eventually to the oxygenated C_{26}-skeleton of the limonoids is now widely appreciated[3, 4, 9, 10] and this type of biogenetic analysis was first applied[8, 11, 12] to account for the structural complexities of limonin and its congeners. These processes may be formally represented by the transformation (II → III) and include the migration of the C-30 Me group from C-14 to C-8.



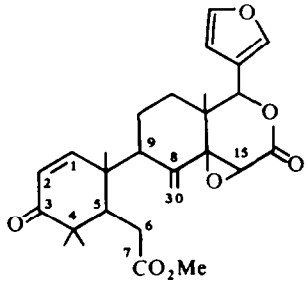
II



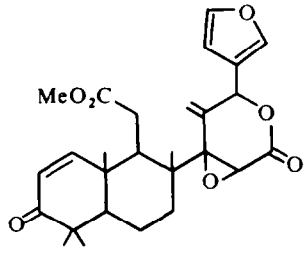
III

Thus, the seven O atoms of the andirobin molecule could be assigned to a furan residue, an αβ-epoxy-δ-lactone, a methoxycarbonyl group, and an αβ-unsaturated ketone of the cyclohexenone type with H atoms located on the α- and β-C atoms. It may be noted in relation to the C_{26} skeleton of (III) that, if this skeleton were indeed associated with andirobin, the αβ-unsaturated ketone had to be located in ring A, either as (i) $\overset{1}{CH}{=}\overset{2}{CH}{-}\overset{3}{CO}$ or (ii) $\overset{3}{CH}{=}\overset{2}{CH}{-}\overset{1}{CO}$. The situation (i) which is indicated in formula (III) is favoured by the congeneric association of andirobin with the compound I and the similarity (see Table) between the relevant NMR signals for andirobin and 7-deacetoxy-7-oxo-gedunin (I). It was clear that the presence in andirobin of an olefinic methylene group and a methoxycarbonyl group could be a consequence of further oxidative cleavage of a carbocyclic ring. At the time[7] when the structural study of andirobin was in progress, a number of such oxidative ring cleavages had been proposed in order to correlate the constitutions of various natural products with terpenoid precursors. Dammarenolic acid,[13] nyctanthic acid,[13, 14]

limonin,[8, 11] and canaric acid[15] exemplify the ring A cleavage process and the formation of nimbin was considered as an example of ring C cleavage.[16] Since 1964, many other examples have been recognized. These cases have been well reviewed by Dreyer[3] and more recent examples include lansic acid,[17] zapoterin[18] and spathelin.[19] It may be noted that recently mahoganin[20] has been described[21] as a mixture of methyl angolensate and methyl 6-hydroxy-angolensate. These oxidative ring cleavages lead to products containing a carboxyl and an olefinic group or their equivalent, so two possible constitutions (IV, ring B cleavage) or (V, ring C cleavage) could be considered for andirobin, and the constitution (IV) was eventually established.

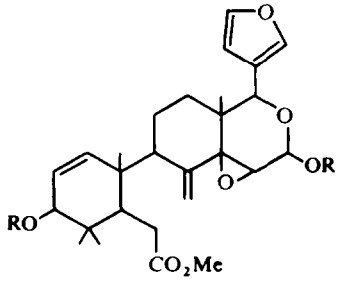


IV

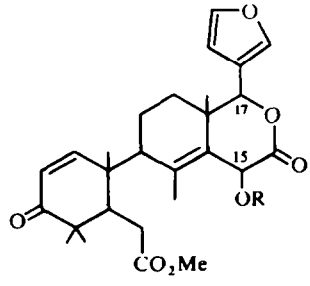


V

Reduction of andirobin (IV) with potassium borohydride gives andirobindiol (VI), characterized as its diacetate (VII). The NMR spectrum of andirobindiol diacetate showed that borohydride reduction of andirobin had resulted in the reduction of the ketonic and the lactonic carbonyl groups; the transformation of a lactone to a hemiacetal is rather unusual, but it has been observed previously.[22, 23] The NMR spectrum of andirobindiol diacetate (VII) showed an ABC system (τ_A 4·53d, τ_B 3·83q, τ_C 4·73d; J_{AB} = 10 Hz, J_{BC} = 2 Hz, J_{AC} = 0 Hz), which could be assigned to the allylic acetate system, $>C-CH_C(OAc)-CH_B=CH_A-C<$, and an AB system ($\tau_A$ 6·23d, τ_B 3·58d, J_{AB} = 3 Hz) associated with the epoxyhemiacetal grouping $>C(-O-)-CH_A-CH_B(OAc)-O-$. The UV spectrum of andirobindiol diacetate (VII) (λ_{max} 209 mm, ε_{max} 9100) is typical of a furan residue. Subtraction[24] of the UV spectrum of andirobindiol diacetate (VII) from that of andirobin (V) gave a difference curve (λ_{max} 235 nm, ε_{max} 9500) which is chromophorically characteristic of the enone grouping,



VI: R = H
VII: R = Ac

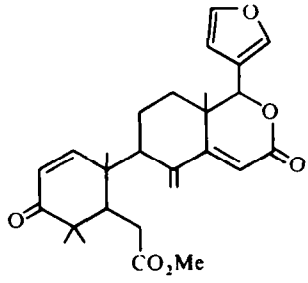


VIII: R = H
IX: R = Ac

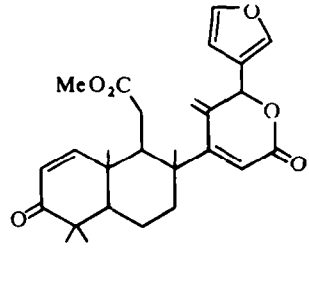
—CH=CH—CO—, present in many steroids and terpenoids. For example, cholest-1-en-3-one shows λ_{max} 230 nm (ε_{max} 10,700).[25]

Controlled catalytic hydrogenation of andirobin gave dihydroandirobin and it was clear that this reduction was associated with the simultaneous alteration of the olefinic methylene and the epoxy groupings of andirobin. Thus, the NMR spectrum of dihydroandirobin monoacetate (IX) shows the presence of one olefinic Me group (τ 8·13s) and a highly deshielded hydrogen (τ 3·58s) which is located at C-15; the corresponding C-15 H atom of andirobin has a chemical shift of τ 5·92. It follows that the formation of dihydroandirobin (VIII) from andirobin (V) involves the 1,4-addition of hydrogen, which results in the following transformation:

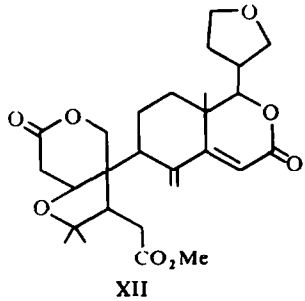
A reaction characteristic of the αβ-epoxy-δ-lactone grouping is its reduction with chromous chloride[8, 26] to an αβ-unsaturated-δ-lactone. This reaction has been extensively used[3] in the structural investigation of the limonoids, and treatment of andirobin with chromous chloride gave deoxyandirobin (X). Comparison of the NMR spectra (Table) of andirobin (V) and deoxyandirobin (X) shows obvious similarities except that the C_{15}-H in andirobin (τ 5·92s) has shifted downfield to τ 3·90 in the NMR spectrum of deoxyandirobin (X). Comparison of the UV spectra of deoxyandirobin (X) [λ_{max} 220 sh (ε 14,400), 237 nm (ε 16,300), 270 infl (ε 720)] with model αβ-unsaturated δ-lactones ($\lambda_{max} \sim 220$ nm)[12] clearly indicates that a conjugative interaction is required between the C=C of the exocyclic methylene group and the αβ-unsaturated lactone of deoxyandirobin (X).



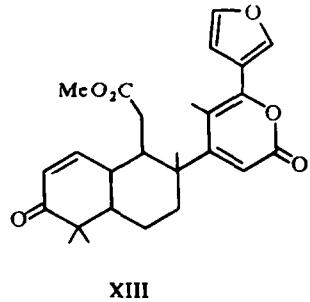
X



XI

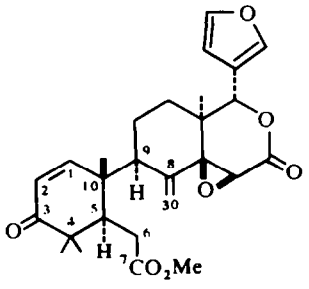


XII

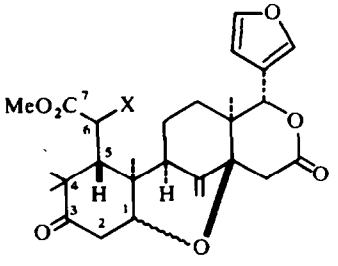


XIII

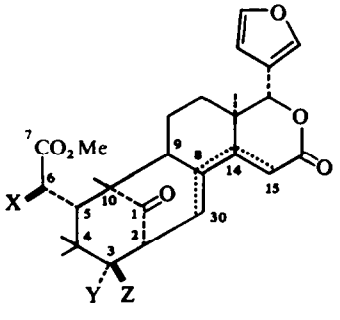
Either of the constitutions (IV or V) account for all the structural features of andirobin discussed up to this point, but it was now possible to distinguish between these two possibilities on the basis of the two corresponding constitutions (X or XI) of deoxyandirobin. Subtraction of the UV spectrum of andirobin from that of deoxyandirobin gave a difference curve [λ_{max} 257 nm (ε 8300)] clearly associated with the cisoid–diene lactone chromophore shown in formula X. This chromophore had already been encountered in the constitutional investigation of limonin and one of the limonin degradation products (XII) has the UV spectral max[11,12] [λ_{max} 255 nm (ε 7800)]. If deoxyandirobin had the alternative constitution (XI), then it would be expected to undergo a very easy isomerization to the conjugated α-pyrone (XIII). An exceptionally easy transformation of this general type has been discovered in the withanolide series[27] in which an analogous formation of an α-pyrone took place during chromatography on silica gel. Deoxyandirobin was recovered unchanged



XIV: Andirobin



XV: Methyl angolensate, X = H[29]
XVI: Methyl 6 hydroxyangolensate, X = OH[30]
XVII: Methyl 6 acetoxyangolensate, X = OAc[30]



XVIII: Mexicanolide, X = H, YZ = O[31]
XIX: Fissinolide, X = Y = H, Z = OAc[32]
XX: Khayasin, X = Y = H, Z = OCOCHMe$_2$[33]
XXI: Dihydromexicanolide, X = Y = H, Z = OH[31]
XXII: Swietenolide, X = Z = OH, Y = H[34]
} Double bond at C_8—C_{14}

XXIII: Carapin, X = H, YZ = O[35]
XXIV: 6-Hydroxycarapin, X = OH, YZ = O[36]
XXV: Swietenine, X = OH, Y = H, Z = O-Tigloyl[37]
} Double bond at C_{14}—C_{15}

XXVI: X = Y = H, Z = OAc[38]
XXVII: X = Y = H, Z = OAc, 12β-OAc[3,38]
} Double bond at C_8—C_{30}; αC_{14}—H

after heating with glacial acetic acid–50% sulphuric acid. This evidence certainly establishes the constitution of deoxyandirobin as X and of andirobin as IV.

Biogenetic analogy and correlation with 7-deacetoxy-7-oxogedunin (I) suggested that andirobin had the configurational formula XIV. This was subsequently established by Ekong and Olagbemi,[28] who carried out an elegant direct chemical correlation between 7-deacetoxy-7-oxogedunin (I) and deoxyandirobin (X).

The constitution (XIV) of andirobin is of considerable interest in that it or its equivalent could well have a role as the biosynthetic precursor of the B-secolimonoids.[3] This group now includes methyl angolensate (XV) and its derivatives (XVI and XVII) as well as the interesting class of bicyclo-[3.3.1]-nonanolides (XVIII–XXVII). The structural inter-relations between all these natural products has been attractively interpreted[31, 37] in terms of acceptable mechanisms of the β-addition and Michael types involving, as precursors, compounds which have the andirobin skeleton. Andirobin (XIV) has also been isolated[39] from the seeds of *Cedrela odorata* L. (*Meliaceae*) and deoxyandirobin (X) has been extracted from the bark of *Khaya grandifolia* C.DC (*Meliaceae*).[40] The heartwood of *Carapa guianensis* Aubl. has also been examined[41] and the extractives include 11β-acetoxygedunin and 6α,11β-diacetoxygedunin.

EXPERIMENTAL

UV spectra were measured in 95% EtOH and NMR spectra were determined on $CDCl_3$ solns using TMS as the internal standard. Only significant bands from IR spectra and assignable signals from NMR spectra are given. The multiplicities of NMR signals are quoted as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

M.ps were determined using a Kofler hot stage microscope and are uncorrected.

Separations by column chromatography were carried out using Hopkins and Williams MFC grade silica. Merck Kieselgel G was used for thick and thin layer chromatography (TLC). During isolation processes, the combination of appropriate fractions was determined by examination of their IR spectra and TLC behaviour.

All evaporations were carried out under diminished press.

Extraction of the seeds of Carapa guianensis (Aubl.)

Isolation of andirobin (XIV) *and 7-deacetoxy-7-oxogedunin* (I). The peeled seeds (8200 g) were cut into small pieces and defatted by extraction with cold light petroleum (b.p. 40–60°; 13 × 5 l). The defatted material was then powdered, further extracted with light petroleum (b.p. 40–60°; 3 × 5 l) to remove residual fats, and finally extracted with boiling MeOH (12 × 5 l). The combined MeOH extracts were concentrated (6 l), cooled, and the white solid (8·2 g), m.p. 176–183°, collected. This solid was fractionated by column chromatography and elution with benzene–$CHCl_3$ (1:3) yielded fraction A (6·4 g). Further elution with $CHCl_3$ followed by MeOH gave fraction B (1·2 g).

Recrystallization of fraction A from MeOH gave *andirobin* as colourless crystals, m.p. 195–197°. [Found: C, 68·6; H, 6·7; M (mass spectrum), 468. $C_{27}H_{32}O_7$ requires: C, 69·2; H, 6·9%; M, 468]; λ_{max} 218 nm (ε 10,000), 233 nm (ε 10,200); ν_{max} (Nujol) 1760, 1745, 1680 cm^{-1}; NMR spectrum τ 2·54m (two α-furan-*H*); τ 3·62m (β-furan-*H*); τ_A 2·80d, τ_B 3·88d (AB system, J_{AB} = 11 Hz, 1-*H*, 2-*H*); τ 4·47s (17-*H*); τ 4·55s, τ 4·67s ($C{=}CH_2$): τ 5·92s (15-*H*); τ 6·25s (CO_2CH_3); *J* 8·88s, τ 8·88s, τ 9·01s, τ 9·05s (four CH_3). $[\alpha]_D^{22}$ 38·5 ($CHCl_3$, *c* 1·015).

Further chromatography of fraction B, followed by recrystallization from MeOH, gave 7-deacetoxy-7-oxogedunin as colourless plates, m.p. 260–264° (lit. m.p. 262–265°),[6] $[\alpha]_D^{22}$ −57·5° ($CHCl_3$, *c* 1·015) (lit. $[\alpha]_D$ −50°).[6] (Found: C, 70·9; H, 7·0. Calc. for $C_{26}H_{30}O_6$: C, 71·2; H, 6·9%); ν_{max} ($CHCl_3$) 1745, 1720, 1685 cm^{-1}; NMR spectrum τ 2·57m (two α-furan-*H*); τ 3·62m (β-furan-*H*); τ_A 2·87d, τ_B 4·07d (AB system, J_{AB} = 11 Hz, 1-*H*, 2-*H*); τ 4·52s (17-*H*); τ 6·10s (15-*H*); τ 8·63s, 8·78s, 8·87s, 8·87s, 8·87s (five CH_3). This material was identical (m.p., IR, and NMR) with an authentic sample.[6]

TABLE. CHEMICAL SHIFTS (τ) FOR THE INDICATED PROTONS IN THE NMR SPECTRA OF ANDIROBIN (XIV) AND RELATED COMPOUNDS

Location of protons or substituents	1-H	2-H	3-H	7-CO_2Me	$C{=}CH_2$	15-H	16-H	17-H	Two α-furan	One β-furan	Olefinic methyl	Tertiary methyl	Acetate
7-Deacetoxy-7-oxogedunin (I)	2·87* d	4·07* d				6·10		4·52	2·57 m	3·62 m		8·63 8·78 8·87 8·87 8·87	
Andirobin (XIV)	2·80* d	3·88* d		6·25	4·55 4·67	5·92		4·47	2·54 m	3·62 m		8·88 8·88 9·01 9·05	
Andirobindiol diacetate (VII)	4·53† d	3·83† q	4·73† d	6·30	4·82 4·92	6·23‡ d	3·58‡ d	5·05	2·67 m	3·68 m		9·08 9·08 9·17 9·22	7·67 7·87
Dihydroandirobin monoacetate (IX)	3·21* d	3·99* d		6·27		3·58		4·92	2·52 m	3·58 m	8·13	8·68 8·83 8·87 8·93	7·78
Deoxyandirobin (X)	3·28* d	4·02* d		6·25	4·77 4·82	3·90		4·42 d	2·48 m	3·53 m		8·85 8·87 8·87 8·97	

Proton counts. All signals have the appropriate integrated intensities.

Multiplicity of signals. Unless otherwise indicated, all signals are singlets. For other cases, d = doublet, q = quartet, and m = multiplet.

* AB systems, J_{AB} = 11 Hz.

† ABX system, J_{AB} = 10 Hz, J_{BC} = 2 Hz, J_{AC} = 0 Hz.

‡ AB system, J_{AB} = 3 Hz.

Andirobinic acid. Andirobin (300 mg) was heated (10 hr) under reflux with KOH (150 mg) in MeOH (20 ml). Addition of water, evaporation of the MeOH, and acidification gave a ppt which was collected. Chromatography (silica-$CHCl_3$) followed by crystallization from ether–cyclohexane gave *andirobinic acid* as colourless plates, m.p. 152–154°. (Found: C, 65·9; H, 6·8. $C_{26}H_{30}O_7.H_2O$ requires: C, 66·1; H, 6·8%).

Treatment of a methanolic soln of andirobinic acid with ethereal diazomethane gave andirobin.

Andirobindiol (VI). A soln of andirobin (155 mg) in MeOH (30 ml) was added to a suspension of KBH_4 (300 mg) in water (0·5 ml) and the mixture was stirred at room temp (20 hr). Acidification with AcOH (0·4 ml), dilution with water, and evaporation of the MeOH gave a crystalline solid which was collected. Crystallization from aqueous acetone and recrystallization from ether gave *andirobindiol* (153 mg) as colourless plates, m.p. 201–203°. (Found: C, 68·2; H, 7·9; OMe, 5·8. $C_{26}H_{33}O_6(OMe)$ requires: C, 68·6; H, 7·7; OMe, 6·6%); $[\alpha]_D^{17}$ 68·7°.

Andirobindiol diacetate (VII). Andirobindiol (106 mg), Ac_2O (2·5 ml), and pyridine (2 ml) were set aside at room temp (18 hr). Addition of iced water, extraction with $CHCl_3$, chromatography and crystallization from cyclohexane–ether gave *andirobindiol diacetate* as colourless needles, m.p. 118–120°. (Found: C, 66·9; H, 7·6. $C_{31}H_{40}O_9$ requires: C, 66·9; H, 7·2%); λ_{max} 209 nm (ε 9100). ν_{max} 1730 cm^{-1}; NMR spectrum τ 2·67m (two α-furan-*H*); τ 3·68m (β-furan-*H*); τ_A 4·53d, τ_B 3·83q, τ_C 4·73 (ABC system, J_{AB} = 10 Hz, J_{BC} = 2 Hz, J_{AC} = O Hz, 1-*H*, 2-*H*, 3-*H*); τ 5·05s (17-*H*); τ 4·82s, τ 4·92s ($C{=}CH_2$); τ_A 6·23d, τ_B 3·58d (AB system, J_{AB} = 3 Hz, 15-*H* and 16-*H*); τ 6·30s (CO_2CH_3); τ 7·67s, τ 7·87s (two $OCOCH_3$); τ 9·08s, τ 9·08s, τ 9·17s, τ 9·22s (four CH_3).

Dihydroandirobin monoacetate (IX). The hydrogenation of andirobin (210 mg) in AcOH (10 ml) with Pd–C catalyst was allowed to proceed until the uptake volume of H_2 corresponded to one molecular equiv. The catalyst was then removed and evaporation of the AcOH gave a residue which was chromatographed ($CHCl_3$–MeOH, 9:1). Acetylation of the major fraction with Ac_2O–pyridine and recrystallization of the product from acetone–ether–cyclohexane gave *dihydroandirobin monoacetate* as colourless plates, m.p. 163–167°. (Found: C, 68·4; H, 7·1. $C_{29}H_{36}O_8$ requires: C, 68·0; H, 7·1%); λ_{max} 213 nm (ε 15,400), 230 nm (sh) (ε 12,000); NMR spectrum τ 2·52m (two α-furan-*H*); τ 3·58m (one β-furan-*H*); τ_A 3·21d, τ_B 3·99d (AB system, J_{AB} = 11 Hz, 1-*H*, 2-*H*); τ 4·92s (17-*H*); τ 3·58s (15-*H*); τ 6·27s (CO_2CH_3); τ 7·78s ($OCOCH_3$); τ 8·13s ($C{=}C{-}CH_3$); τ 8·68s, τ 8·83s, τ 8·87s, τ 8·93s (four CH_3). $[\alpha]_D^{17}$ −0·2° (*c*, 1·017).

Deoxyandirobin (X). Chromous chloride[42] soln was added dropwise at room temp under N_2 to a soln of andirobin (89 mg) in AcOH (20 ml) until a blue colour persisted. After standing under N_2 overnight, the soln was diluted with water and extracted with $CHCl_3$. This extract was shaken with $NaHCO_3$ aq, dried, and evaporated. Crystallization from aqueous EtOH gave *deoxyandirobin*, m.p. 172–173°. (Found: C, 71·5; H, 7·0. $C_{27}H_{32}O_6$ requires: C, 71·7; H, 7·1%); λ_{max} 220 nm (sh) (ε 14,400), 237 nm (ε 16,300), 270 nm (infl) (ε 720); NMR spectrum τ 2·48m (two α-furan-*H*); τ 3·53m (one β-furan-*H*); τ_A 3·28d, τ_B 4·02d (AB system, J_{AB} = 11 Hz, 1-*H*, 2-*H*); τ 4·42d (*J* = 1·5 Hz, 17-*H* coupled to furan-H); τ 4·77s, τ 4·82s ($C{=}CH_2$); τ 3·90s (15-*H*); τ 6·25s (CO_2CH_3); τ 8·85s, τ 8·87s, τ 8·87s, τ 8·97s (four CH_3 groups).

A mixture of deoxyandirobin (48 mg), AcOH (10 ml), and H_2SO_4 (50%; 0·5 ml) was heated at 100° for 90 min. Addition of water and $CHCl_3$ extraction gave deoxyandirobinic acid, which by treatment with ethereal diazomethane followed by crystallization from aqueous EtOH gave deoxyandirobin (15 mg).

Acknowledgement—The seeds of *Carapa guianensis* used in this investigation were obtained from the Jardim Botânico, Rio de Janeiro, through the kind courtesy of Professor Walter B. Mors, Instituto de Tecnologia Agrícola e Alimentar, Ministério da Agricultura, Rio de Janeiro, Brasil. We thank Professor D. A. H. Taylor for the gift of an authentic sample of 7-deacetoxy-7-oxogedunin.

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