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THE CHEMISTRY OF THE GENUS *ENTANDROPHRAGMA*

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Abstract—The results of previous investigations of the heartwood of species of the genus *Entandrophragma* are discussed, and the investigation of three further species is described. A new compound, candollein, has been isolated.

THE genus *Entandrophragma*, which is confirmed to the African mainland south of the Sahara, consists of ten species which are generally recognized as distinct, together with some four varieties that are probably not of specific rank. The timber of all these has now been examined in this laboratory by thin-layer chromatography, and by the large-scale extraction of adequate samples to isolate the characteristic oxidized triterpenes of the limonoid group. The results, some of which have previously been reported in detail, form an interesting study in chemical taxonomy, and are collected here for comparison. Although the seeds certainly contain limonoids, we have not so far succeeded in obtaining any of these crystalline.

The timber extractives which we have obtained are shown in Table 1.

TABLE 1

Species	Total yield of petrol-soluble extract (%)	Yield of crystalline limonoids (%)	Compounds isolated
E. angolense[1]	0·1	—	—
E. bussei[1]	3·0	0·6	Entandrophragmin and bussein
E. caudatum[1]	2·0	0·15	Entandrophragmin
E. candollei[2]	0·2	0·00005	Candollein
E. congoense	0·4	0·2	Gedunin
E. cylindricum[2]	2·5	0·2	Entandrophragmin
E. deiningeri	0·1	—	—
E. delevoyi[1]	1·0	0·02	Gedunin
E. excelsum[1]	0·2	—	—
E. macrophyllum[2]	0·35	0·15	Gedunin and/or methyl angolensate
E. palustre	0·05	—	—
E. spicatum	3·0	0·2	Entandrophragmin
E. stolzii[1]	0·1	—	—
E. utile[2]	0·5	0·1	Utilin

All the species also contain crystalline phytosterols which can be isolated from most timber.

On the basis of the timber chemistry, the species fall into two groups. One of these, Group I, contains the simpler limonoid triterpenes gedunin and methyl angolensate, which are not

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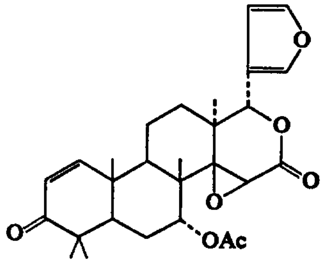
[1] D. A. H. TAYLOR, *J. Chem. Soc.* 3495 (1965).

[2] A. AKISANYA, C. W. L. BEVAN, J. HIRST, T. G. HALSALL and D. A. H. TAYLOR, *J. Chem. Soc.* 3827 (1960).

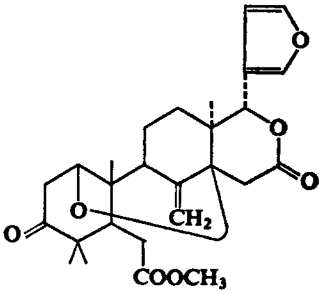
acylated, or contain only acetyl groups. The others, Group II, contain more complex compounds derived by further hydroxylation and C and O alkylation of the triterpene nucleus in numerous positions. These groups consist of the following species.

Group I

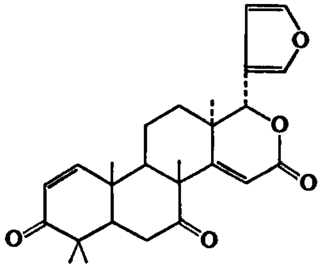
Entandrophragma macrophyllum *A. Chev*. This is a West Coast variety, which is generally included in *E. angolense*. As it is chemically distinct, it is convenient to maintain the name here. Chemically, this is a variable species, which we find to contain gedunin (I) or methyl angolensate (II); some 70–80 per cent of the Nigerian population appear to contain mainly gedunin, while the remainder contain methyl angolensate or a mixture of the two.[3] The occurrence of gedunin, one of the simplest of the limonoids, is consistent with what we know



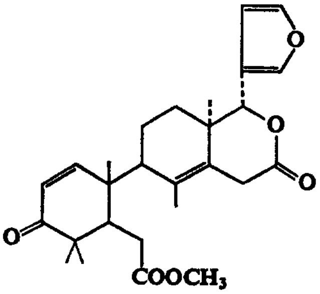
(I)



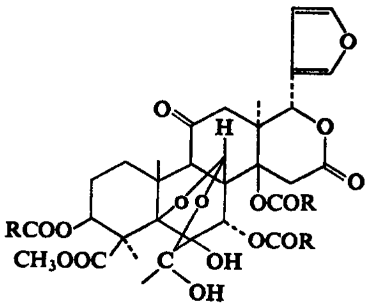
(II)



(III)



(IV)



(V)

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[3] C. W. L. Bevan, D. E. U. Ekong and D. A. H. Taylor, *Nature* **206**, 1323 (1965).

of the chemistry of the rest of the genus, and may possibly suggest that *E. macrophyllum* is biochemically less evolved than the other species. The occurrence of methyl angolensate is of more interest. This results from a fission of ring B, which has been brought about in the laboratory by alkaline hydrolysis of 7-deacetyl-7-oxo deoxygedunin (III).[4] This gives the unsaturated lactone (IV), whereas methyl angolensate and the several known related compounds are all at a higher state of oxidation corresponding to a di-unsaturated lactone. This suggests that biochemically, methyl angolensate may arise by a Bayer–Villiger type peroxide oxidation of a 7-oxo compound such as (III) or an earlier intermediate in the biosynthesis. The ring D lactone itself is generally considered to arise by a similar peroxide oxidation of a 16-oxo compound, and evidence that this is in fact the case has recently been produced by Overton and his colleagues.[5] Methyl angolensate therefore seems to arise by a process which branches from that leading to gedunin at an intermediate stage, possibly fairly early in the synthesis, in a way that has not yet been found in other species of the genus. This alternative pathway leading to ring B fission is more characteristic of genera such as *Khaya*, *Cedrela*, and *Swietenia* in which methyl angolensate and other ring B cleaved compounds are of common occurrence.

E. angolense (*Welw.*) *C.DC.* This species in its strict sense occurs across Africa from Angola, through the Congo to East Africa. We have examined 5-kg samples of several East African specimens[1] and found them to give oily extracts. No crystalline limonoids have yet been isolated and thin-layer chromatography suggests the presence of gedunin and possibly methyl angolensate in small amount. A number of specimens from Angola and the Congo have been examined by thin-layer chromatography; the results are not conclusive but suggest similarity to East African material, although some appear to contain more highly oxidized compounds. A larger scale extraction of Angolan material would be interesting.

E. congoense: *A. Chev.* This species, which grows in Kasai,[6] has mostly been considered a synonym of *E. angolense*. Two specimens which we have examined have contained amounts of gedunin comparable to that found in *E. macrophyllum.*

E. excelsum (*Dawe et Sprague*) *Sprague*, E. deiningeri *Harms*, *and* E. stolzii *Harms*. These grow in East Africa, and are almost certainly synonyms. We have examined 5-kg batches of all three, and obtained no crystalline products, chromatographically they appear similar to East African *E. angolense*.

E. delevoyi *De Wild.* This botanically very distinctive species grows in Zambia and Katanga. We have isolated gedunin from it in fair yield, the thin-layer chromatogram shows the presence of another substance in major amount, but this has not yet been isolated.

Group II

E. cylindricum *Sprague*. This species, like most of those in Group II, gives a much more copious extract, from which entandrophragmin crystallizes in about 0·2 per cent yield. This is a very complex high molecular weight compound for which we have recently proposed the provisional structure (V).[7] It contains three different *O*-acyl groups, isobutyryl; 2-methyl butyryl, and 2:3-epoxy-2-methylbutyryl, and also a *C*-acetyl group which is concealed in a ketal linkage, as in tenulin.[8] Entandrophragmin occurs in several species of *Entandrophragma* but has not so far been found in any other genus.

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[4] D. E. U. Ekong and E. O. Olagbemi, *J. Chem. Soc.* (C) 944 (1966).

[5] J. D. Conolly, K. L. Handa, R. McCrindle and K. H. Overton, *Chem. Commun.* 867 (1966).

[6] L. Liben and R. Dechamps, *Bull. Jard. Botanique Bruxelles* **36**, 415 (1966).

[7] D. A. H. Taylor and K. Wragg, *Chem. Commun.* 81 (1967).

[8] W. Merz, W. A. Rohde, K. Rabindran, P. Jayaraman and N. Viswanathan, *J. Am. Chem. Soc.* **84**, 3857 (1962).

E. utile (*Dawe et Sprague*) *Sprague*. *E. utile* gives a much smaller amount of extract than *E. cylindricum*, and the major extractive is utilin. This is very closely related indeed to entandrophragmin, but contains an *O*-acetyl group instead of the *O*-isobutyryl group of the latter.

E. candollei *Harms*. We originally reported[2] that *E. candollei* contained only β-sitosterol, which is present in unusually large amount. Thin-layer chromatography indicated the presence of a limonoid and as *E. candollei* is locally common a search was made. A substance candollein, further described in the Experimental section, has now been isolated in small yield. This compound was at first thought to be entandrophragmin, as it has the same i.r. spectrum and m.p., and gives no depression on mixed m.p. The NMR spectrum is however different, and there is no doubt that the two compounds, though similar, are distinct.

E. bussei *Harms ex Engler*. This Tanganyikan species gives an unusually large amount of extractive, from which bussein crystallizes readily. Chromatography of the mother liquors gives a similar amount of entandrophragmin. Bussein is a similar compound to entandrophragmin, but contains more *C*-acyl groups, and is an enolizable β-diketone. Such compounds, recognizable by the ferric chloride colour, have been found in several other genera.

E. caudatum *Sprague*. This botanically distinct Rhodesian species is chemically very similar to *E. bussei*, and cannot easily be distinguished from it by thin-layer chromatography. On extraction however it gives mainly entandrophragmin, together with only small amounts of bussein.

E. spicatum (*C.DC.*) *Sprague and* E. ekebergiodes (*Harms*) *Sprague*. These two species, the first from S. W. Africa and the second from Angola, are probably synonyms and are botanically very similar to *E. bussei*. From *E. spicatum* we have obtained only entandrophragmin, though the thin-layer chromatogram showed the presence of bussein or a very similar compound. A small sample of *E. ekebergiodes* from Angola was indistinguishable from *E. bussei* by thin-layer chromatography.

E. palustre *Staner*. This species was also not distinguishable qualitatively from *E. bussei* by thin-layer chromatography; quantitatively however it gives a very small amount of extract from which nothing crystalline was obtained. The spectrum of the crude extract suggested that a larger scale extraction would give entandrophragmin or a very similar compound.

The relationships of these species extend outside the genus throughout the family Meliaceae; although so far the only similar compounds obtained outside the Meliaceae are limonin itself and its congeners, from *Citrus* and allied species in the Rutaceae.[9] Gedunin has been found in several other genera, in *Xylocarpus*,[1] *Cedrela*[10] and *Guarea*,[10, 11] methyl angolensate, as mentioned previously, in *Khaya*,[12] *Cedrela*,[13] *Swietenia* and *Guarea*.[11] The more complex compounds entandrophragmin and bussein have not so far been found outside the genus, although somewhat similar compounds to entandrophragmin have been found in *Ekebergia*[14] and compounds similar to bussein in *Pseudocedrela*[14] and *Chukrasia*.[15]

The new compound, candollein, mentioned above, gives analytical data corresponding to the formula $C_{42}H_{54}O_{16}$. The NMR spectra of both candollein and entandrophragmin are very similar, the main differences being that the two singlets at δ6·12 and 5·74 in entandro-

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[9] G. Ourisson, P. Crabbe and O. R. Rodig, *Tetracyclic Triterpenes*, p. 170. Hermann, Paris (1964).

[10] C. W. L. Bevan, J. W. Powell and D. A. H. Taylor, *J. Chem. Soc.* 980 (1963).

[11] J. R. Housley, F. E. King, T. J. King and P. R. Taylor, *J. Chem. Soc.* 5095 (1962).

[12] E. K. Adesogan, C. W. L. Bevan, J. W. Powell and D. A. H. Taylor, *J. Chem. Soc.* (C) 2127 (1966).

[13] W. R. Chan and K. E. Magnus, *Chem. Ind. London* 1751 (1964).

[14] D. E. U. Ekong, Unpublished work.

[15] D. A. H. Taylor, Unpublished work.

phragmin are combined into one broad two-proton singlet at δ5·98, that the methyl region is different, and that the quartet at δ3·68 and the singlet methyl group at δ1·48, both due to the 2:3-epoxy-2-methylbutyryl residue in entandrophragmin, are missing. Hydrolysis of candollein, like entandrophragmin, gave 6 mol. of total acid and 3 of volatile acid, NMR spectroscopic examination of the volatile acids[16] showed the presence of acetic, 2-methyl butyric, and isobutyric acids. The results indicate that candollein probably has the same nucleus as entandrophragmin, with the epoxymethylbutyric acid residue replaced by another.

EXPERIMENTAL

E. spicatum. A specimen of this timber obtained from the Forest Officer at Ondangua, S.W. Africa, was a branch of a large tree. The powdered heart wood (2 kg) was extracted with light petroleum (b.p. 60–80°), the extract was concentrated, the crystalline product filtered off and recrystallized from methanol, giving entandrophragmin (3·5 g) as prisms, m.p. 253–254°; identical in NMR spectrum with an authentic sample. The mother liquors gave i.r. spectra indicating the presence of β-diketones similar to bussein, but no crystalline compound was isolated.

E. palustre. The finely powdered timber (0·75 kg, herbarium number Louis 11859, supplied by Monsieur R. Dechamps of the Musee Royale de l'Afrique Centrale, Tervuren) was extracted with light petroleum. Evaporation of the extract gave a small residue (less than 100 mg) from which no crystals were obtained. The i.r. spectrum and TLC suggested the presence of entandrophragmin or a similar compound.

E. deiningerii. A sample of this timber was provided by the Regional Forest Officer, Lushoto, Tanganyika. Extraction gave an oil from which no crystalline products were obtained.

E. candollei. Powdered timber (200 kg, herbarium reference F.H.I. 060684) was extracted with light petroleum (b.p. 60–80°), and the extract evaporated. The residue (*ca.* 400 g) which largely crystallized, was chromatographed several times on alumina; following the progress of separation by thin-layer chromatography. Large amounts of "β" sitosterol were obtained, together with a fraction (350 mg) which partly melted at 137°, and then finally melted at 250°. This was rechromatographed, giving more "β" sitosterol and candollein (98 mg), m.p. 254–256°. (Found: C, 61·7, 61·65; H, 6·7, 6·7. $C_{42}H_{54}O_{16}$ required: C, 61·9; H, 6·7%.)

Hydrolysis of candollein. Candollein (22·6 mg) was refluxed in methanol (5 ml) and 1·62 N NaOH (1 ml) for 15 min. After cooling titration showed the equivalent of 5·5 mol. of acid from a molecular weight of 814. The solution was then treated with extra acid, the volatile acids distilled, which by titration were equivalent to 2·3 mol. The titration solution was evaporated and the residue dissolved in deuterium oxide and analysed by NMR spectroscopy;[16] showing equivalent amounts of acetic, isobutyric and 2-methyl butyric acids.

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[16] D. H. Calam and D. A. H. Taylor, *J. Chem. Soc.* (C) 949 (1966).