Tetrahedron Letters No. 18, pp. 787-794, 1962. Pergamon Press Ltd. Printed in Great Britain.

STRUCTURE OF CYANOMACLURIN, A COMPONENT OF JACKWOOD

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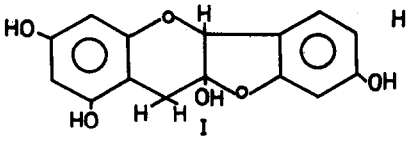
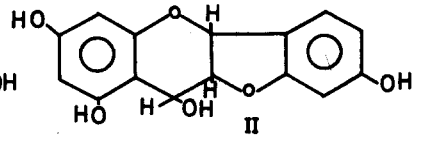
(Received 20 June 1962)

CYANOMACLURIN is a water soluble colourless component of the heartwood of Artocarpus integrifolia (Jackwood). Structure (I) was proposed for it by Appel and Robinson[1]. On the suggestion of Sir Robert Robinson, work was undertaken in this laboratory for its synthesis. At a later stage he felt that the original structure may require revision and in view of the recent developments in the chemistry of lucoanthocyanidins, which are found to be flavan-3:4-diols, the alternative structure (II) should also be considered. We have therefore dealt with this matter first.



I



II

Extraction. In the method of Perkin[2] the heartwood was extracted with hot water, morin removed by precipitation with lead acetate and cyanomaclurin crystallized from acetic acid. Freudenberg and Weinges[3] also adopted the same method but they were able to separate out a small quantity of racemic cyanomaclurin by counter-current distribution between ether and water. From the light petroleum and benzene extracts of the heartwood, obtained from different places, Dave et al.[4], isolated four related compounds

[1] H. Appel and R. Robinson, J. Chem. Soc. 752 (1935).

[2] A.G. Perkin, J. Chem. Soc. 715 (1905).

[3] K. Freudenberg and K. Weinges, Liebigs Ann. 613, 61 (1958).

[4] K.G. Dave, S.A. Telang and K. Venkataraman, Tetrahedron Letters 9 (1962).

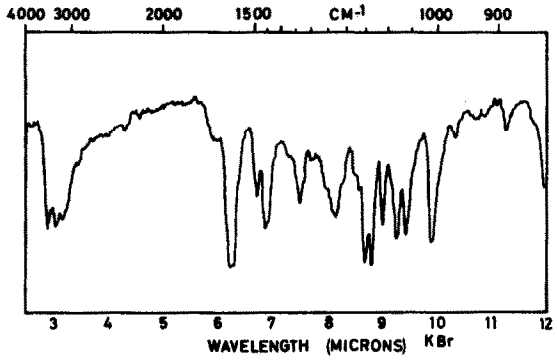


FIG. 1

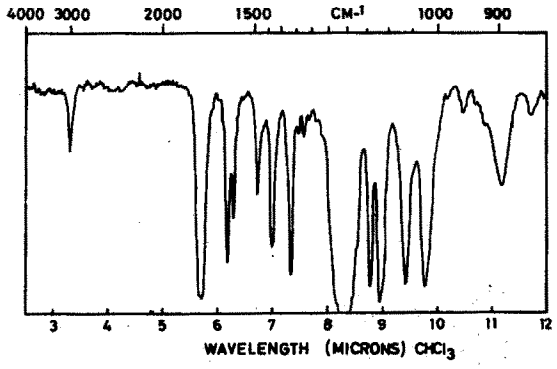


FIG. 2

artocarpin, artocarpetin, artocarpanone, and iso-artocarpin and established their constitutions. We find that by using fresh heartwood and fractional extraction with organic solvents it is more easy to separate the various components of the heartwood. Initial extractions with hot light petroleum and with benzene removed fatty matter and artocarpin. Later extraction could be done with cold alcohol or acetone. The concentrate was treated with water whereby most of the morin and the residual artocarpin were thrown out. The last traces of morin were precipitated as neutral lead salt. The deleaded filtrate was extracted exhaustively with ethyl acetate.

From the concentrated extract crude cyanomaclurin separated out and addition of petroleum ether completed the separation. This was subjected to counter-current distribution between water and ether. The aqueous fractions and the last ether fractions contained cyanomaclurin and the early ether fractions a small amount of morin. The middle fractions yielded a different product which on crystallization from ethyl acetate-light petroleum melted at 228°C. It gave the colour reactions of dihydroflavonols and the ferric reaction was brown-red. In circular paper chromatography it gave a single ring, R_f 0.6 at 26°C, using 15 per cent aqueous acetic acid as solvent; U.V. absorption: λ_{min} 260 mμ and λ_{max} 285 mμ*. It yielded an acetate melting at 190-194°C. All these data and analysis agreed with those recorded for dihydromorin, earlier isolated from the wood of East African Mulbery (Morus lactea Mildber) by Carruthers et al.[5] The heartwood therefore contains besides cyanomaclurin and morin, dihydromorin also as a water soluble component. The collected aqueous layers of the counter-current distribution were extracted exhaustively with ethyl acetate. From the concentrated extract cyanomaclurin could be obtained as colourless prisms turning brown at about 260°C and not melting below 360°C; U.V. absorption: λ_{min} 255 mμ, λ_{max} 281 mμ*; I.R. in KBr is given in Fig. 1

Derivatives of cyanomaclurin. When acetylated using acetic anhydride and pyridine at room temperature or at the boiling point of acetic anhydride, it yielded the same acetate; U.V. absorption: λ_{min} 255 mμ, λ_{max} 274 mμ*. It gave the same I.R. spectrum (Fig. 2) as the sample of the acetate originally made by Prof. A.G. Perkin and kindly provided by Dr. K. Aghoramurthy. The methylation of cyanomaclurin can be effected by means of dimethyl sulphate, anhydrous potassium carbonate and dry acetone or using diazo-

* U.V. absorptions were taken in absolute methanol.

[5] W.R. Carruthers, R.H. Farmer and R.A. Laidlaw, J. Chem. Soc. 4440 (1957).

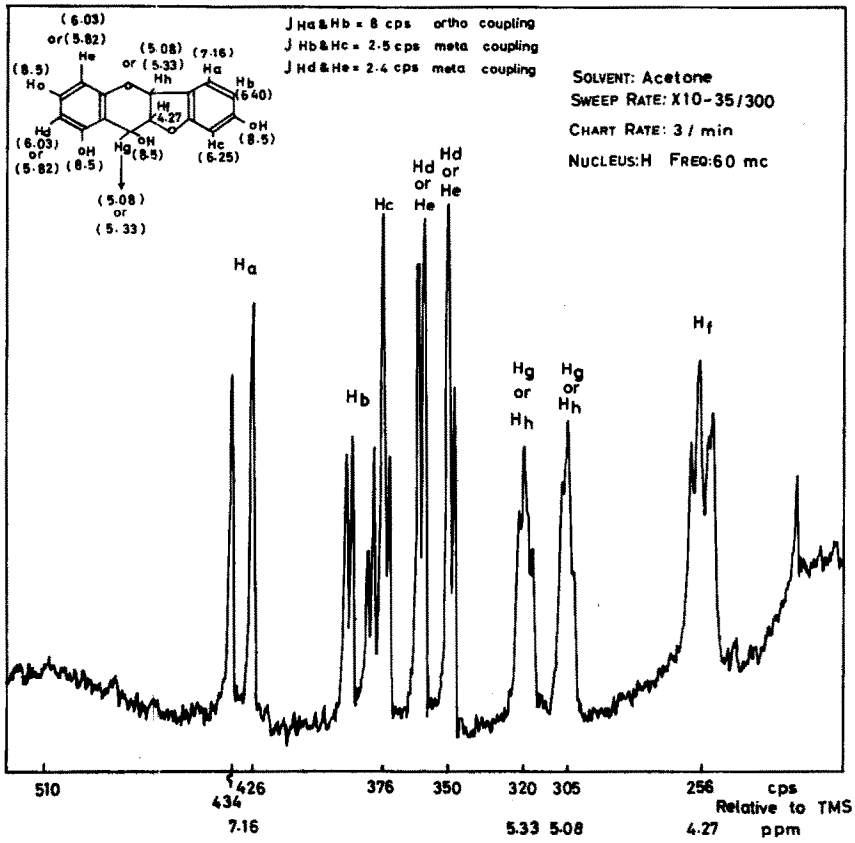


FIG. 3

methane in methanol-ether mixture. The methyl ether had a marked range in melting point. By fractional crystallization using ethyl acetate-light petroleum it could be separated into two fractions. The less soluble minor fraction melted at 145°C and was optically inactive whereas the more soluble major fraction melted at 75°C and was dextrorotatory: $[\alpha]_D^{19}$, +135°, ethylacetate, 1.15 per cent. Otherwise the two fractions agreed in composition, properties and in spectra. Therefore the first was the racemic trimethyl ether and the second (+) trimethyl ether. The elemental analysis of cyanomaclurin and its derivatives, the methoxyl value for the trimethyl

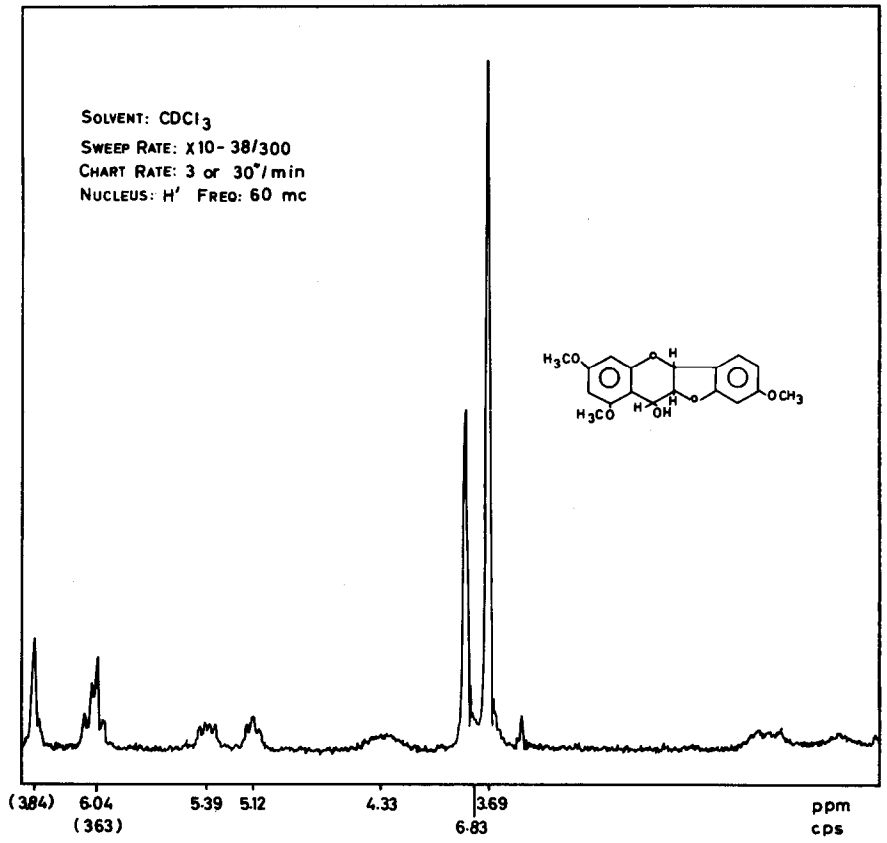


FIG. 4

ether and acetyl value for the tetraacetate agreed with those recorded by Appel and Robinson. The conversion of cyanomaclurin into morinidin also proceeded as described by them.

Constitution of cyanomaclurin. Positive chemical proof which will conclusively support I or II has not been available. The reactions mentioned above do not distinguish between the two structures. Freudenberg[6] has more recently favoured structure (I) for cyanomaclurin and stated in

[6] K. Freudenberg, Experientia XVI/3, 101 (1960).

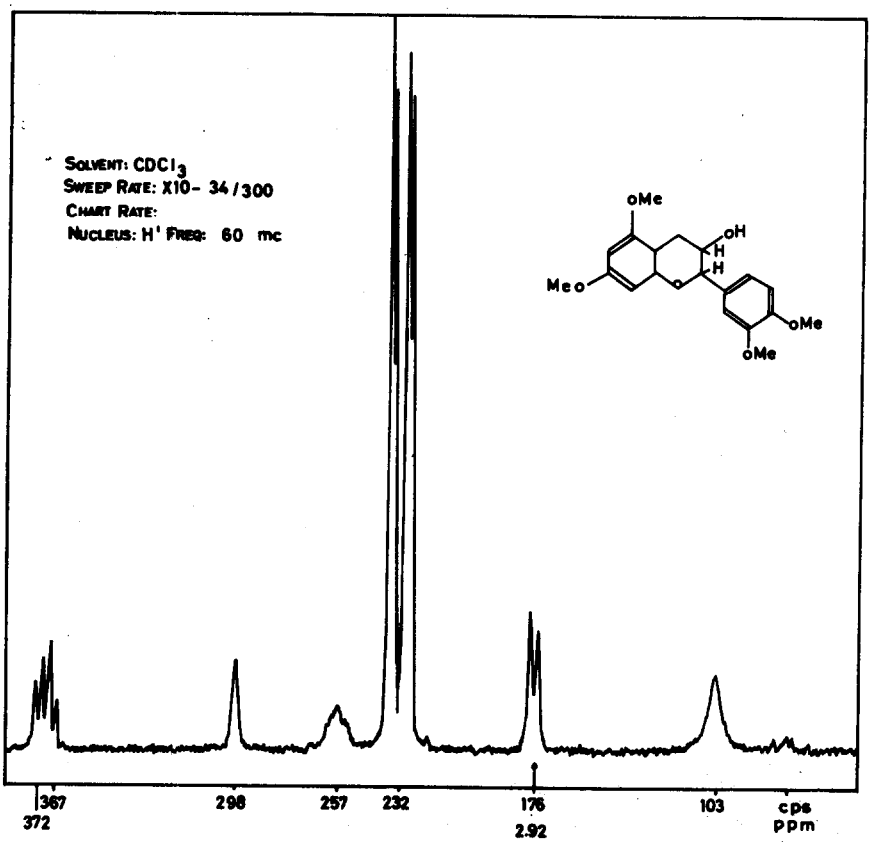


FIG. 5

support that catalytic reduction has not removed a hydroxyl group, showing absence of a >CHOH group in the 4 position and that the NMR spectrum does not indicate the presence of three CH groups in neighbouring positions.

On the other hand, we find that cyanomaclurin acetate does not react with N-bromosuccinimide, a reaction characteristic of catechin acetates[7] which have the reactive benzylic $>CH_2$ group. Further cyanomaclurin has high optical rotation, $[\alpha]_D^{26}$, $+204^\circ$, ethylacetate 0.8 per cent, a property

[7] A.K. Ganguly, T.R. Seshadri and P. Subramanian, Proc. Indian Acad. Sci. 46A, 25 (1957).

in which it differs markedly from the catechins and resembles peltogynol[8] having the flavan-4-ol structure. However, the oxidation of the >CHOH group, which was successful in the case of peltogynol methyl ether, does not proceed with cyanomaclurin methyl ether. Similar difficulty has been met with in other 5-methoxy flavan diols also, e.g. leucocyanidin tetramethyl ether. This could not be attributed entirely to the presence of a 5-methoxy group because besides simple flavan-4-ol, 5-methoxy flavan-4-ol also has now been found to undergo the oxidation with manganese dioxide under the same conditions.

We have, therefore, used the NMR spectrum for studying the problem. The marked difference between the two formulae is the presence of a $>CH_2$ in I and its absence in II. We have examined NMR spectra of cyanomaclurin and its derivatives for the indication of $>CH_2$ group. As standard of comparison the closely related catechins and their derivatives have been employed. Preliminary studies were made with the hydroxy compounds using heavy water as solvent. Whereas (+) catechin and (-) epicatechin showed the presence of a $>CH_2$ group, cyanomaclurin did not. Further confirmation was obtained from the spectra of methyl ethers in deuteroacetone. There was definite absence of the $>CH_2$ peak in the spectrum of cyanomaclurin methyl ether, whereas (+) catechin methyl ether showed the characteristic peak at 2.92 p.p.m. Finally detailed studies have been made using samples of cyanomaclurin (acetone solution), its methyl ether and acetate and also (+) catechin methyl ether (deuterochloroform). Trimethylsilane was used as internal reference and in all the cases measurement was taken in a A-60 spectrometer of Varian-Associates at 60 mc. Figure 3 contains the data pertaining to cyanomaclurin and they agree definitely with the requirements of formula (II) and exclude formula (I). The chemical shifts due to the

[8] W.R. Chan, W.G.C. Forsyth and C.H. Hassal, J. Chem. Soc. 3174 (1958).

three adjacent protons in the structure (II) are in good accord with their environmental positions. This structure is also supported by the spin-spin decoupling experiment. Figures 4 and 5 give the comparison of the methyl ether of cyanomaclurin with that of (+) catechin in deuterochloroform; the absence of the $>CH_2$ group in cyanomaclurin methyl ether is clear and the spectrum further confirms the structure (II).

We convey our grateful thanks to Sir Robert Robinson for entrusting us with this work, to Dr. S.S. Dharmatti of the Atomic Energy Laboratory, Bombay and Dr. Andre Gagneux of Harvard University for the preliminary comparison of the NMR spectra of cyanomaclurin and catechin and their derivatives and to Dr. Norman S. Bhacca of Varian Associates, California, for the detailed NMR spectra presented in this note.