# NEW DI-ISOPRENYLATED INDOLE DERIVATIVES FROM HEXALOBUS CRISPIFLORUS

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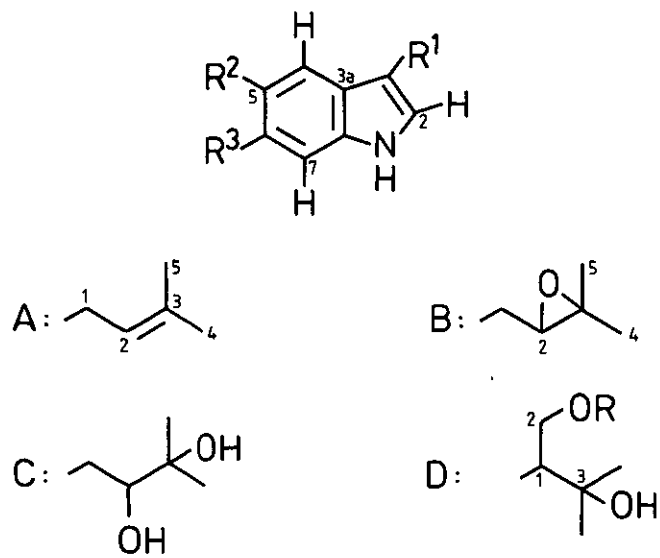
Abstract ———— From the stem bark of H.crispiflorus twelve new isoprenylated indoles were isolated and their structures determined; some of these compounds exhibit antifungal activity.

From the petrol ether extract of the stem bark of Hexalobus crispiflorus A.Rich. (Annonaceae) the di-isoprenylated indoles 1 - 13 were isolated (Table 1).

| | $R^1$ | $R^2$ | $R^3$ | $[\alpha]_D^{20}$ | mp |
|---|---|---|---|---|---|
| 1 | A | H | A | - | 36/7 |
| 2 | B | H | A | + 9° | 72/3 |
| 3 | B | H | B | +26° | - |
| 4 | C | H | A | -35° | - |
| 5 | $D^1$ | H | A | -16° | - |
| 6 | $D^2$ | H | A | -18° | - |
| 7 | $D^3$ | H | A | -20° | - |
| 8 | $D^4$ | H | A | -20° | - |
| 9 | A | A | H | - | 78/9 |
| 10 | B | B | H | + 6° | - |
| 11 | $D^2$ | B | H | +30° | - |
| 12 | $D^3$ | B | H | +25° | - |
| 13 | $D^4$ | B | H | +27° | - |




| | R |
|---|---|
| $D^1$ | H |
| $D^2$ | hexadecanoyl |
| $D^3$ | 9(Z)-octadecenoyl |
| $D^4$ | 9,12(Z,Z)-octadecadienoyl |

Table 1: Compounds isolated from Hexalobus crispiflorus ($[\alpha]_D^{20}$: measured in $CHCl_3$; mp: °C).

Separation was achieved by successive chromatography of the crude extract on alumina and silica gel. Components 6 - 8 and 11 - 13 finally had to be separated by HPLC on RP-18.

The presented structures are the result of comprehensive spectroscopic studies in combination with chemical conversions[1].

All isolated compounds exhibit the structural feature of an indole substituted by two $C_5$-units, which biogenetically derive from isoprene.

In compounds 6 - 8 and 11 - 13 one of the $C_5$-units is esterified by fatty acids. The structures of the seven different substituents A to C and $D^1$ to $D^4$ were deduced from the ms- and nmr-spectra. The fatty acid residues were determined by comparison of the $^{13}$C-nmr data of the isolated compounds 6 - 8 and 11 - 13 with the spectra of authentic methyl esters from palmitic, oleic and (Z,Z)-linoleic acid. In addition, these esters were obtained by methanolytic cleavage of the original compounds and identified by gc-ms.

The positions of the substituents at the indole ring system were established from the nmr data. Since the shift increments on ortho-carbons caused by alkylation of comparable aromatic systems are in the range of ± 1 ppm [2], the doublets at 110 - 111 and 118 - 119 ppm (Table 2) can be attributed to C-7 and C-4 of the indole[2-4]. Irradiation experiments allow unambiguous recognition of the corresponding proton signals and corroborate the fact that the $^1$H-nmr signal at lowest field (7.6 - 7.4 ppm) belongs to H-4. Multiplicity and coupling constants of H-4 and H-7 served to distinguish the 6-substituted indoles 1 to 8 from the 5-substituted 9 to 13 ones.

A singlet between 112 and 116 ppm is observed in the off-resonance $^{13}$C-nmr of all isolated compounds (Table 2). This signal must be attributed to the characteristically high field resonance of C-3, which appears at 101.8 ppm in unsubstituted indole[3] and is shifted to lower field upon C-3-alkylation[4].

The $^{13}$C-shifts of the substituted indole carbon atoms induced by the substituents depend typically on their structures. Changing from the $\gamma,\gamma$-dimethylallyl group to the epoxidized substituent ($A \rightarrow B$) causes a shift difference of 3.6 to 4 ppm on the substituted carbon atom regardless of its position (Table 2). This effect enables the assignment of the different substituents to their individual positions. The information is complemented by the fact that in the $^{13}$C-resonances, the $CH_2$-carbons of substituents A or B exhibit a shift difference of 10 ppm if located at the benzene ring (C-5 or C-6) in comparison to substitution at C-3.

| C | m | 1 | 2 | 3 | 4 | 5 | 6 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 | d | 120.7[a] | 121.2[a] | 121.6[a] | 122.5[a] | 121.8[a] | 121.8[a] | 121.3[a] | 122.1[a] | 122.7[a] |
| 3 | s | 116.0 | 112.2 | 112.4 | 112.1 | 113.6 | 113.7 | 115.8 | 112.1 | 113.6 |
| 3a | s | 125.7 | 125.6 | 126.3 | 125.6 | 126.3 | 126.5 | 127.7 | 127.7 | 128.7 |
| 4 | d | 118.8 | 118.7 | 119.0 | 118.5 | 119.1 | 119.4 | 118.0 | 118.4 | 119.2 |
| 5 | d(s)* | 120.2[a] | 120.6[a] | 120.7[a] | 120.5[a] | 120.8[a] | 120.8[a] | 132.5 | 128.9 | 129.3 |
| 6 | s(d)* | 135.8 | 136.1 | 132.1 | 136.1 | 136.3 | 136.1 | 122.8[a] | 123.2[a] | 123.3[a] |
| 7 | d | 110.3 | 110.3 | 111.0 | 110.6 | 110.4 | 110.3 | 110.9 | 111.1 | 111.2 |
| 7a | s | 137.0 | 136.7 | 136.8 | 137.0 | 136.3 | 136.5 | 135.0 | 135.1 | 134.9 |
| 1' | t(d)* | 24.2 | 24.9 | 25.3 | 27.8 | 48.1 | 46.6 | 24.1 | 25.1 | 46.4 |
| 2' | d(t)* | 123.3[b] | 64.3 | 64.2[b] | 77.5 | 64.3 | 65.1 | 123.2[b] | 64.1[b] | 65.1 |
| 3' | s | 131.7[c] | 58.7 | 58.6 | 72.6 | 74.3 | 72.6 | 131.5[c] | 58.7 | 72.7 |
| 4' | q | 25.7[d] | 25.2 | 24.8[c] | 26.4[b] | 29.2[b] | 28.3[b] | 25.7[d] | 24.9 | 28.4[b] |
| 5' | q | 17.8 | 18.9 | 18.9[d] | 23.7[b] | 27.2[b] | 28.1[b] | 17.8 | 18.9 | 28.2[b] |
| 1" | t | 34.6 | 34.6 | 35.7 | 34.5 | 34.5 | 34.5 | 34.5 | 35.5 | 35.6 |
| 2" | d | 124.2[b] | 123.9 | 65.0[b] | 124.0 | 123.8 | 123.9 | 124.6[b] | 65.2[b] | 65.1 |
| 3" | s | 131.8[c] | 132.0 | 58.6 | 132.0 | 132.1 | 132.0 | 131.7[c] | 58.7 | 58.6 |
| 4" | q | 25.8[d] | 25.8 | 24.9[c] | 25.7 | 25.8 | 25.7 | 25.8[d] | 24.9 | 24.9 |
| 5" | q | 17.8 | 17.8 | 19.0[d] | 17.7 | 17.8 | 17.8 | 17.8 | 18.9 | 19.1 |

Table 2: $^{13}$C-nmr data of basic carbon skeletons (recorded in $CDCl_3$; δ(ppm) downfield from TMS; a,b,c,d: assignments may be interchanged; *:multiplicity depends on individual structure; $R^1$s are numbered x'; $R^2$s and $R^3$s are numbered x").

Treatment with acid (aqueous acetic acid (10%)/acetone, room temperature, 20h) converts 2 into a mixture of 4 and 5 in an approximately 2:1 ratio. Since the products exhibit optical activity, this reaction must proceed stereospecifically.
The isolated di-isoprenylated indoles are present in the dried plant material in quantities ranging from about 0.01% (1 and 10) to 0.001% (3 and 9); thus they occur

in concentrations similar to the other alkaloids of H.crispiflorus, which are mainly of the noraporphine type[5].

In regard to the easy conversion of 2 into 4 and 5, the latter substances might probably be artefacts, though all separations and purifications were performed in absence of acidic or basic media. However, the occurence of the esters 6 - 8 and 11 - 13 suggests, that 5 is a genuine natural compound.

From a critical point of view, it cannot be excluded that the compounds having chiral centres in both substituents (3, 10 - 13) might be (partial) mixtures of diastereomers, in spite of the fact that all spectra and the HPLC look like those of completely pure compounds.

Indoles substituted by only two separate isoprenoid units are very rare natural products. 1 had only recently be isolated from Uvaria elliotiana[6], which belongs to the same plant family. Therefore, this type of structure might be of chemotaxonomic significance for the Annonaceae.

In biological tests some of the isolated compounds exhibit antifungal activity against Saprolegnia asterophor.

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