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1,3-DIACETYL-11,19-DEOXA-11-OXO-MELIACARPIN, A POSSIBLE PRECURSOR OF AZADIRACHTIN, FROM *AZADIRACHTA INDICA* A. JUSS (MELIACEAE)

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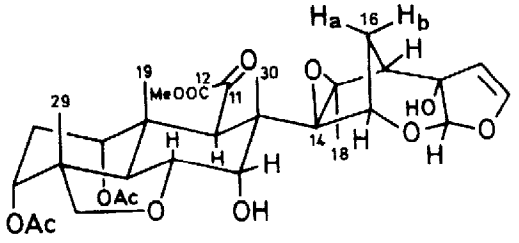
Summary: 1,3-Diacetyl-11,19-deoxa-11-oxo-meliacarpin (1), a possible intermediate in the biosynthesis of azadirachtin, was isolated from methanolic extracts of *Azadirachta indica* seeds. Structure 1 is proposed on the basis of ^{1}H and ^{13}C NMR data.

4ß-Methyl azadirachtin analogues such as 1-cinnamoyl-3-feruloyl-11-hydroxy-meliacarpin (2) and related systems[1-3] or 1-cinnamoylmelianolone[4] have been found up to now only in extracts of *Melia azedarach*.[1-4] We report on the isolation from *Azadirachta indica* A. Juss of the first compound of this type, 1,3-diacetyl-11,19-deoxa-11-oxo-meliacarpin (1), which may be considered a possible intermediate in the biosynthesis of azadirachtin (3).



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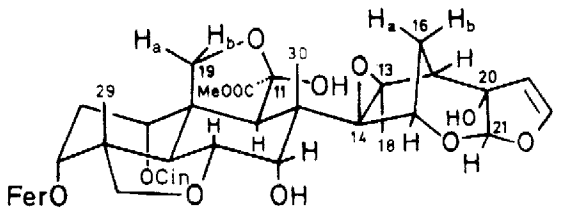

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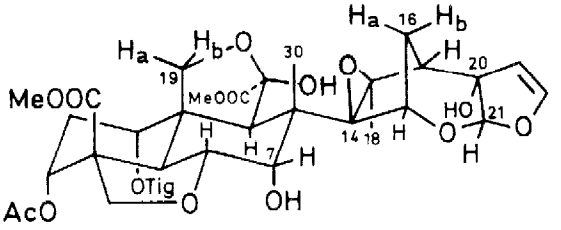

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Isolation: 4 mg of keto ester 1 were isolated from the methanol extract of 5 kg finely grounded neem seeds collected from Togo after solvent partition between petrol ether and water (1:1) and ethyl acetate and water (1:1) followed by repeated column chromatography over silica gel with methylene chloride and reversed phase chromatography (RP 18, methanol/water).

Structure determination: $C_{31}H_{40}O_{13}$ (620); amorphous; ^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] 1.15 (3H, s, 19-H); 1.26 (3H, s, 29-H); 1.68 (3H, s, 30-H); 2.17 (3H, s, 18-H), 2.08 (3H, s, CH_3CO); 3.76 (3H, s, 12-OCH_3); 2.14 (3H, s, CH_3CO); 2.76 (1H, s, 7-OH); 3.14 (1H, s, 20-OH); 4.93 (1H, t, $^{3}J_{1,2\alpha}$ = 3.0, $^{3}J_{1,2\beta}$ = 3.0, 1-H); 2.17 (1H, dt, $^{2}J_{2\alpha,\beta}$ = 17.0, $^{3}J_{2\beta,1}$ = 3.0, $^{3}J_{2\beta,3}$ = 3.0, 2-H$_\beta$); 2.25 (1H, dt, $^{2}J_{2\alpha,\beta}$ = 17.0, $^{3}J_{2\alpha,1}$ = 3.0, $^{3}J_{2\alpha,3}$ = 3.0, 2-H$_\alpha$); 4.30 (1H, t, $^{3}J_{3,2\alpha}$ = 3.0, $^{3}J_{3,2\beta}$ = 3.0, 3-H); 2.76 (1H, d, $^{3}J_{5,6}$ = 12.5, 5-H); 4.16 (dd, $^{3}J_{6,5}$ = 12.5, $^{3}J_{6,7}$ = 3.2,

6-H); 4.55 (d, $^3J_{7,6}$ = 3.2, 7-H); 4.22 (s, 9-H); 4.49 (d, $^3J_{15,16a}$ = 3.5, 15-H); 1.60 (ddd, $^2J_{16a,b}$ = 13.0, $^3J_{16a,17}$ = 5.2, $^3J_{16a,15}$ = 3.5, 16-H_a); 1.26 (d, $^2J_{16a,b}$ = 13.0, 16-H_b); 2.34 (d, $^3J_{17,16a}$ = 5.2, 17-H); 5.68 (s, 21-H); 5.05 (d, $^3J_{22,23}$ = 2.9, 22-H); 6.44 (s, $^3J_{23,22}$ = 2.9, 23-H); 3.59 (d, $^2J_{28\alpha,\beta}$ = 7.7, 28-H_α); 3.62 (d, $^2J_{28\alpha,\beta}$ = 7.7, 28-H_β). ^{13}C NMR (62.89 MHz, $CDCl_3$): δ [ppm] 72.72 (d, C-1), 26.94 (t, C-2), 71.60 (d, C-3), 42.83 (s, C-4), 37.71 (d, C-5), 73.16 (d, C-6), 74.41 (d, C-7), 41.34 (s, C-8), 44.71 (d, C-9), 49.19 (s, C-10), 193.35 (s, C-11), 161.50 (s, C-12), 67.89 (s, C-13), 69.43 (s, C-14), 76.04 (d, C-15), 25.02 (t, C-16), 16.23 (q, C-19), 48.55 (d, C-17), 20.11 (q, C-18), 83.77 (s, C-20), 107.60 (d, C-21), 108.99 (d, C-22), 147.06 (d, C-23), 78.53 (t, C-28), 17.17 (q, C-29), 21.55 (q, C-30), 170.59 (s, CH_3COO), 170.00 (s, CH_3COO), 21.09 (q, CH_3COO), 20.95 (q, CH_3COO), 52.96 (q, $COOCH_3$).

The ^{1}H NMR spectrum of 1 is very similar to the spectra of 2^{1-3} and $3^{1-3,5}$ in the following signals: *i)* Two olefinic protons 22-H, 23-H (δ 5.05 and 6.44) of the dihydrofuran ring and a low field singlet for 21-H at δ 5.68; *ii)* the four spin system 15-H, 16-$H_{a,b}$, 17-H (δ 4.49, 1.60, 1.26 and 2.34); *iii)* the four spin system 1-H, 2-$H_{\alpha,\beta}$, 3-H (δ 4.93, 2.25, 2.17, 4.30); *iv)* the AB system of 28-$H_{\alpha,\beta}$ at δ 3.59 and 3.62; *v)* the three spin system 5-H, 6-H, 7-H (δ 2.76, 4.16 and 4.55); *vi)* two methyl signals (18-H, 30-H) at δ 2.17 and 1.68, respectively.

Unlike the NMR of azadirachtin (3) the spectrum of 1 exhibits, as found for 2, four methyl groups instead of two as in azadirachtin, and only one methoxycarbonyl group. The additional methyl groups were assigned to be C-19 and C-29 by n.O.e. experiments: Saturation of 19-H (δ 1.15) gives enhancement of 30-H, 2-H_β, 6-H, and 1-H. Enhancement of 19-H, 28-H_β, 6-H, and 3-H is observed upon irradiation of 29-H (δ 1.26). 19-H, 6-H, 15-H, and 7-H are enhanced upon saturation of 30-H (δ 1.68).

9-H (δ 4.22) which can be assigned by the strong n.O.e. with 18-H (δ 2.17) is shifted downfield by nearly 1 ppm as compared to 2 (δ 3.45) and 3 (δ 3.34). Two hydroxyl groups showing chemical shifts very similiar to 20-OH and 7-OH in 2 and 3 were found by D_2O exchange. The strong n.O.e. between 18-H and 9-H, 7-OH, and 20-OH shows that the configuration at C-20 and C-13 is like that in 2 and 3.

These data suggest that the structure of the new compound 1 is similiar to that of 1-cinnamoyl-3-feruloyl-11-hydroxy-meliacarpin (2).

The ^{13}C NMR spectrum is consistent with structure 1. The singlets at δ 193.35 and 161.5 were assigned to a carbonyl group (C-11) and a methoxycarbonyl group (C-12), resp., which is shifted to higher field because of the conjugation to the carbonyl group C-11. Such shifts are common for α-keto esters.

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