SYNTHESIS OF (±)-GADAIN, A NEW LIGNAN FROM JATROPHA GOSSYPIFOLIA LINN (EUPHORBIACEAE)

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Abstract -(±)-Gadain, a new lignan isolated from Jatropha gossypifolia, has been synthesised by the condensation of 3-(3, 4 - methylenedioxybenzyl) - butyrolactone with piperonal in the presence of sodium methoxide in methanol. The key intermediate lactone was prepared by the Stobbe condensation of piperonal with dimethyl succinate followed by hydrogenation to the butanoic acid derivative and the reduction of the potassium salt of butanoic acid with calcium borohydride.

We have recently isolated a new lignan (+) - gadain (1)[1], from the petrol extract of Jatropha gossypifolia Linn (Euphorbiaceae). An interesting cis-trans isomerisation had been observed[1] while studying the ^{1}H-NMR spectrum of gadain in $CDCl_3$. Two species were found to be present, the cis (Z) and its trans (E) isomer in a ratio of 2:1. This conversion is possibly catalysed by the usual trace of hydrochloric acid in $CDCl_3$. The reaction is not reversible and with time the ratio of intensities reversed. On keeping gadain in 1N HCl for 72 h it changed completely to the trans (E) isomer. We now like to report the synthesis of (±)- gadain. The key intermediate lactone (2) was obtained according to the procedure reported by Brown et al[2]. Stobbe condensation of piperonal (3) with dimethyl succinate (4) followed by hydrogenation to the butanoic acid derivative (6) and subsequent reduction of the potassium salt of the latter with calcium borohydride gave the lactone (2).

Piperonal (3) on treatment with dimethyl succinate (4) in methanol in the presence of sodium methoxide underwent Stobbe condensation to give 4-(3,4- methylenedioxyphenyl)-3-methoxycarbonylbut-3-enoic acid (5), $C_{13}H_{12}O_6$ (M^+264),mp 140°C (methanol), yield 45%. The ^{1}H-NMR spectrum in $CDCl_3$ revealed the presence of three aromatic protons in the region δ6.99-6.67, one vinyl proton (s at δ7.77)

and one carboxylic acid group (br s at δ 8.01, D_2O exchangeable). The spectrum also showed the presence of one methylenedioxy (2H, s, δ 5.95) and one carbomethoxy group (3H, s, δ 3.79). On catalytic hydrogenation with 10% Pd-C in methanol at atmospheric pressure 4-(3, 4 - methylenedioxyphenyl)-3-methoxycarbonylbut-3-enoic acid (5) afforded the butanoic acid derivative (6), $C_{13}H_{14}O_6$ (M^+266), mp 91°C (ether), yield 79%. The ^{1}H-NMR spectrum in $CDCl_3$ clearly indicated the absence of vinyl proton which was originally present in the butenoic acid (5). The spectrum showed a five proton multiplet in the region δ 3.92-2.50 for C_2, C_3 and C_4 protons. The butanoic acid (6) was converted to its potassium salt by adding dropwise aqueous 40% ethanolic potassium hydroxide to a solution of (6) in ethanol until the solution just became basic. The solution was concentrated and on vacuum drying a white solid was obtained. The potassium salt in ethanol was reduced with calcium borohydride [3] to 3-(3, 4 -methylenedioxybenzyl)-butyrolactone, bp 191-194°C/1 mm, $C_{12}H_{12}O_4$ (M^+220), yield 42%. The infrared absorption spectrum showed an intense peak at 1775 cm^{-1} indicating the presence of a γ-lactone moiety in it. The ^{1}H-NMR spectrum revealed the presence of methylenedioxy group (s, 2H, δ 5.97) and three aromatic protons (m, δ 7.01 - 6.65). It showed two multiplets in the region δ 4.50-4.00 (2H, C_4-H_2) and δ 3.29-2.42 (5H, C_2-H_2, C_3-H and two benzylic protons). This lactone had been earlier prepared[4] from safrol oxide by condensation with ethyl sodioacetoacetate followed by hydrolysis with potassium hydroxide. Condensation of the butyrolactone (2) with piperonal (3) in methanol in the presence of sodium methoxide afforded (±)-gadain, $C_{20}H_{16}O_6$ (M^+ 352), mp 154°C (benzene), $[\alpha]_D^{25}$ 0° (chloroform), yield 11%. The compound was purified by preparative TLC (vide experimental) and its structure established from UV, IR and ^{1}H-NMR spectral analysis. An intense band at 1725 cm^{-1} in its IR spectrum indicated the presence of an α,β -unsaturated γ-lactone moiety. The disposition of the olefinic double bond in (±)-gadain was confirmed from the chemical shift values of the olefinic proton at C_6 and the aromatic proton at C_2,. The authors had made a detailed ^{1}H-NMR study of the naturally occurring gadain and its hydrochloric acid transformation product[1]. The aromatic C_2,-H and the olefinic C_6-H were used as markers in confirming the disposition of the olefinic proton. The appearance of the highly deshielded aromatic proton (C_2, at δ 7.72) in (±)-gadain confirmed its proximity to the carbonyl group. The C_6-olefinic proton appeared in the region δ 6.80-6.56 which

proved that in (±)-gadain the olefinic proton must be trans to the carbonyl.

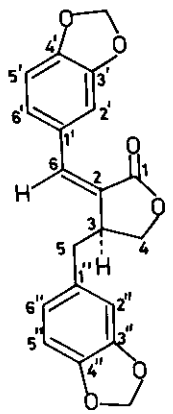

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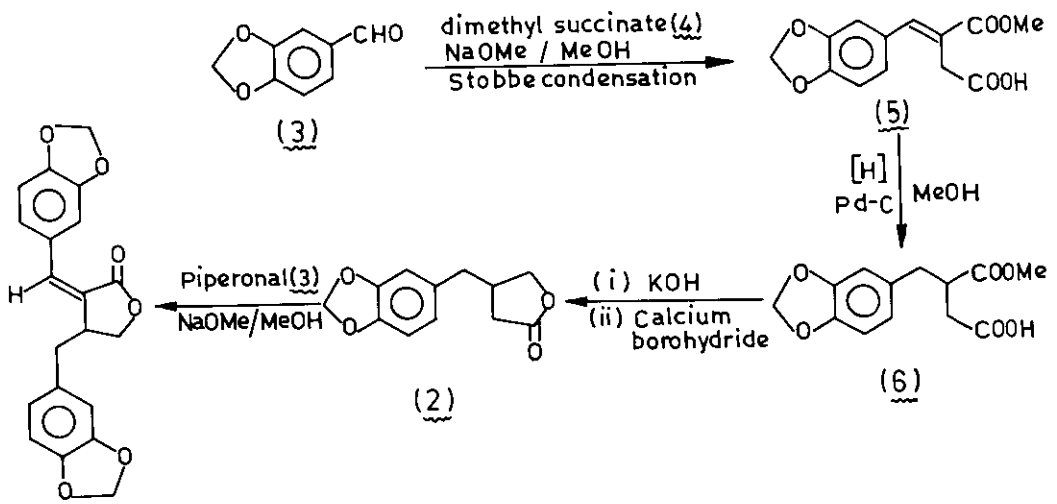
CHART 1



EXPERIMENTAL

Melting points have been recorded in a Kofler block apparatus and are uncorrected. The UV spectra (in 95% aldehyde free ethanol)were recorded in a Varian 634 spectrophotometer, the IR spectra (KBr) in a Perkin-Elmer spectrophotometer, the

80 MHz ^{1}H-NMR spectra (in $CDCl_3$, tetramethylsilane being used as internal standard) in a Varian CFT-20 spectrometer and the mass spectra using 70 e.v. Atlas AEI mass spectrometer (Model No. MS-30).

4-(3,4- Methylenedioxyphenyl)-3-methoxycarbonylbut-3-enoic acid (5)

To a solution of sodium methoxide (1g) in methanol (50 ml) piperonal (2g) and dimethyl succinate (20 ml, d, 1.4g/ml) were added and the reaction mixture was heated to reflux for 2 h. The mixture was cooled, acidified with dilute hydochloric acid (1N) and extracted with ether (3 x 100 ml). The ethereal fraction was then re-extracted with aqueous sodium bicarbonate (3 x 50 ml). On acidification of the aqueous sodium bicarbonate layer with concentrated hydrochloric acid (12N) an oil separated out. This was extracted into chloroform. The latter layer was washed with water, dried and concentrated to furnish (5) as a yellow solid which was crystallised from methanol, mp 140°C, yield 45%; ν_{max}(KBr): 2940, 1720, 935 cm^{-1}, m/z 264(M^+), 246, 236, 215, 185.

4-(3, 4-Methylenedioxyphenyl)-3-methoxycarbonylbutanoic acid (6)

To a solution of (5) (1.2g) in methanol (50 ml) 10% Pd-C (0.5g) was added. The mixture was stirred under hydrogen at atmospheric pressure for 6 h. It was filtered and evaporated to a white solid (6) which was crystallised from ether, mp 91°C, yield 79%; ν_{max}(KBr) : 2950, 1740, 1725, 940 cm^{-1}; $\delta(CDCl_3)$: 8.16, 7.14-6.65, 6.00, 3.77, 3.32-2.50; m/z : 266 (M^+), 248, 238, 207, 187.

The potassium salt of the acid (6) was prepared by adding aqueous ethanolic potassium hydroxide (40%) to a solution of (6) (500 mg) in ethanol (50 ml) until the solution just became basic. The solution was concentrated and finally on vacuum drying a white solid (540 mg) was obtained.

3-(3, 4 - Methylenedioxybenzyl)-butyrolactone (2)

To a solution of calcium chloride (300 mg) in anhydrous ethanol (20 ml) cooled to -5°C a solution of sodium borohydride (250 mg) in the same solvent (20 ml) was added with stirring over 15 min. The solution was stirred for a further 30 min. A solution of the potassium salt of (6) (500 mg) in ethanol (20 ml) was added over 30 min. The mixture was then stirred for 2 h at -5°C and for a further 4 h at room temperature. It was diluted with water (50 ml), acidified with hydrochloric acid (6N) and extracted with ether (3 x 100 ml). Concentration of the organic layer afforded (2) as a yellowish oil, bp 191-94°C/1 mm; yield 42%; ν_{max}(KBr) : 1775 cm^{-1}; m/z 220 (M^+), 192, 164, 162.

(±)-Gadain

A mixture of (2) (125 mg), piperonal (75 mg) and sodium methoxide (50 mg) in benzene (10 ml) was kept in a stoppered flask at room temperature for 96 h with occasional stirring. The mixture was acidified with dilute hydrochloric acid (1N) and extracted with benzene (3 x 50 ml.) The organic layer was washed with aqueous sodium bicarbonate solution (3 x 20 ml) and then with water (3 x 50 ml). (±)-Gadain was isolated by preparative TLC, [R_f 0.53, benzene : ethyl acetate, 9:1] from the reaction mixture and crystallised from benzene, mp 154°C, yield 11%, ν_{max} (KBr) : 1725, 1620, 915 cm^{-1}; λ_{max} (EtOH) : 337, 293, 235 nm (logϵ :4.20, 4.05, 4.12 respectively); δ($CDCl_3$) : 7.72 (d, 1H, J =1.5 Hz, C_2'-H), 7.14 (dd, 1H, J = 8 and 1.5 Hz, C_6'-H), 6.80-6.56 (m, 5H, C_5'-H, C_2''-H, C_5'' -H, C_6-H and C_6''-H), 5.96 (s, 2H, -OCH_2O-), 5.92 (s, 2H, -OCH_2O-), 4.35-4.0 (m, 2H, C_4-H_2), 3.24 (m, 1H, C_3-H), 2.88-2.74 (m, 2H, C_3-H_2) ; m/z : 352 (M^+), 201, 151, 173, 77, 28.

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