A New Synthesis of Kigelin. Conversion of Elemicin into Kigelin

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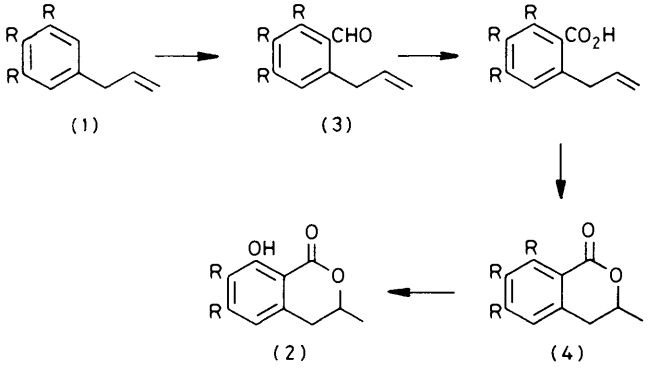
The natural product elemicin has been transformed into the methyl ether of kigelin, a naturally occurring dihydroisocoumarin from *Kigelia pinnata*.

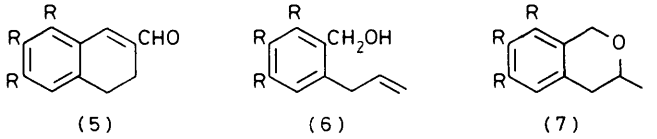
KIGELIN (2) is a naturally occurring dihydroisocoumarin, isolated from *Kigelia pinnata DC* by Govindachari and his co-workers,[1] who also determined its structure. Three syntheses are reported for the compound. One is by Govindachari *et al.*,[2] another is by Chatterjea and his co-workers.[3] The third synthesis is by Narasimhan *et al.*[4] who used an aromatic lithiation reaction as a crucial step in the synthesis and obtained the compound in fewer steps and in better overall yield than in the previous methods.

Comparison of kigelin (2) with another natural product elemicin (1)[5] suggested that the latter could be transformed into kigelin (2) by a sequence shown in Scheme 1.



SCHEME 1 R = OMe

Hence compound (1) was treated with the Vilsmeier–Haack complex prepared from *N*-methylformanilide (MFA) and phosphorus trichloride oxide. The reaction, however, provided only compound (5), presumably

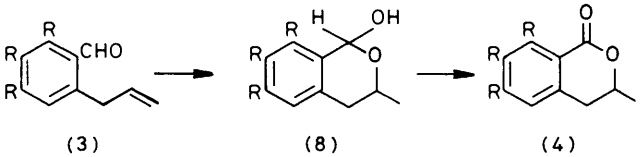


R = OMe

formed by diformylation and reduction (this reaction has been discussed in an earlier paper[6]). Attempts to obtain monoformylation by a variety of modifications [*e.g.* 1 mol equiv. of MFA–$POCl_3$; *N*,*N*-dimethylformamide(DMF)–$POCl_3$; use of solvents such as chloroform, *etc.*] failed and in each case only compound (5) was obtained in lower yield (with 1 mol equiv. MFA) with recovery of the starting compound. However, when dichloromethane was used as the solvent and the Vilsmeier–Haack complex was prepared from DMF and $POCl_3$, the monoformylation product (3) was also obtained. It is not clear why the reactivity is altered by the use of dichloromethane.

Thus, having compound (3) to hand, we tried to perform the reactions in Scheme 1. However, oxidation of the formyl group to the acid group could not be achieved under a variety of conditions ($AgNO_3$–NaOH; CrO_3–H_2SO_4; Jones' reagent; H_2O_2–NaOH–dioxan; α,α'-bipyridyl–CrO_3 complex[7]; storage under oxygen). An alternative approach, involving reduction of the formyl group of compound (3) to give the alcohol (6), then cyclization to the isochroman (7), and finally oxidation[3] of the isochroman to the desired dihydroisocoumarin (4) was then attempted. Here, although the formyl group could be reduced by $NaBH_4$ to give the desired alcohol in 94% yield, its further cyclisation to the isochroman (7) could not be achieved [PPA; H_2SO_4; HBr–AcOH; $HClO_4$–H_2O–benzene; $PdCl_2(CH_3CN)_2$–NaH].

Finally, the desired conversion of compound (3) into compound (4) was achieved according to Scheme 2. Treatment of the aldehyde (3) with mercury(II) acetate in aqueous THF gave the alcohol (8) in 82% yield. Compound (8) on oxidation with pyridinium chlorochromate furnished kigelin methyl ether (4) in 77% yield. Kigelin methyl ether (4) has already been demethylated to kigelin (2) by aluminium chloride in diethyl ether.[2]



SCHEME 2 R = OMe

EXPERIMENTAL

All m.p.s and b.p.s are uncorrected. Silica gel used for flash chromatography was t.l.c. silica gel (>200 mesh) without binder. I.r. spectra were recorded on a Perkin-Elmer 337 spectrophotometer, and ^1H n.m.r. spectra on a Perkin-Elmer R32 (90 MHz) spectrometer using Me_4Si as internal standard.

6-Allyl-2,3,4-trimethoxybenzaldehyde (3).—To the Vilsmeier–Haack complex prepared by mixing DMF (12.7 ml) and $POCl_3$ (15 ml) at 0—5 °C was added a solution of elemicin (1) (10 g) in dry dichloromethane (30 ml). The mixture, protected from moisture, was left at room temperature for five days. It was then poured over crushed ice and stirred well. The cold solution was extracted with dichloromethane (3 × 25 ml) and then with diethyl ether (2 × 30 ml). The combined organic extracts were washed

in turn with water, aqueous sodium hydrogen carbonate, and saturated brine and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave an oil (6.35 g) which, on distillation under reduced pressure (b.p. 115—118 °C/1.5 mmHg), gave the starting compound (1) (5.1 g, 51% recovery).

The aqueous layer was treated with sodium acetate trihydrate (20 g) and the mixture was heated on a water-bath for 20—25 min. Extraction with diethyl ether, followed by washing of the extract with water, aqueous sodium hydrogen carbonate and water, drying (Na_2SO_4) and removal of the solvent under reduced pressure gave an oil (4.350 g) which, on flash chromatography (1—3% ethyl acetate–hexane as eluant) gave the *aldehyde* (3) as a pale yellow liquid (1.9 g, 16.7%), b.p. 150—155 °C (bath temperature) at 0.7 mmHg (Found: C, 66.1; H, 6.75. $C_{13}H_{16}O_4$ requires C, 66.08; H, 6.83%); $\nu_{max.}$ (neat) 1 680, 990, and 910 cm^{-1}; δ (CCl_4) 3.68br (2 H, d, *J* 7 Hz, ArCH_2), 3.80 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.96 (3 H, s, OMe), 4.84—5.17 (2 H, m, CH=CH_2), 5.67—6.14 (1 H, m, CH_2CH=CH_2), 6.47 (1 H, s, ArH), and 10.26 (1 H, s, CHO).

Further elution (with 5% ethyl acetate–hexane) gave compound (5) (2.0 g, 17%), m.p. 85 °C (hexane), identical with an authentic sample.[6]

1-*Hydroxy*-6,7,8-*trimethoxy*-3-*methylisochroman* (8).—Mercury(II) acetate (638 mg) was dissolved in water (2 ml) with stirring. Tetrahydrofuran (THF) (2 ml) was then introduced, when a yellow precipitate was obtained. To the vigorously stirred mixture at room temperature was added a solution of compound (3) (425 mg) in THF (2 ml) over 2 min, by which time the yellow colour was completely discharged. Stirring was continued for further 20 min and then 3M aqueous sodium hydroxide (2 ml) was added rapidly, followed by a solution of sodium borohydride (19 mg) in 3M aqueous sodium hydroxide (2 ml). The mixture was stirred until most of the mercury had coagulated. The supernatant THF layer was separated and the aqueous layer was saturated with sodium chloride and extracted first with THF (2 × 3 ml) and then with diethyl ether (2 × 15 ml). The combined organic extracts were evaporated to dryness under reduced pressure, the residue was redissolved in THF and the solution was passed through a short pad of neutral alumina. Removal of the solvent under reduced pressure gave the required *alcohol* (8) (375 mg, 82%), m.p. 129—130 °C (ethyl acetate–hexane) (Found: C, 61.6; H, 7.1. $C_{13}H_{18}O_5$ requires C, 61.40; H, 7.14%); $\nu_{max.}$ (Nujol) 3 410 cm^{-1}; δ ($CDCl_3$) 1.31 (3 H, d, *J* 6 Hz, CH*Me*), 2.56br (2 H, d, *J* 7 Hz, ArCH_2), 3.5—3.64 (1 H, exchanges with D_2O, OH), 3.81 (6 H, s, 2 × OMe), 3.91 (3 H, s, OMe), 4.26—4.54 (1 H, m, C*H*Me), 6.01—6.2br (1 H, s, collapses to sharp singlet after D_2O exchange, C*H*OH), and 6.39 (1 H, s, ArH).

Kigelin Methyl Ether (4).—To a well stirred suspension of pyridinium chlorochromate (324 mg) in dry dichloromethane (3 ml) was added a solution of compound (8) (230 mg) in dry dichloromethane (2 ml) in one portion. The mixture was stirred for 16 h then diluted with dry diethyl ether (10 ml). The organic phase was decanted and the precipitate was washed with dry diethyl ether (2 × 5 ml). The combined organic phases were washed in turn with 1M HCl (5 ml), water, and brine. Drying (Na_2SO_4) and evaporation of the solvent under reduced pressure gave a brown mass which was triturated with benzene and the extract was chromatographed over neutral alumina (benzene as eluant) to afford a solid which was crystallized from hexane to give the desired lactone (4) (175 mg, 77%), m.p. 104 °C (lit.,[2] m.p. 105 °C) (Found: C, 62.3; H, 6.45; Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39%); $\nu_{max.}$ (Nujol) 1 710 cm^{-1}; δ ($CDCl_3$) 1.43 (3 H, d, *J* 7 Hz, CH*Me*), 2.81 (2 H, d, *J* 6 Hz, ArCH_2), 3.85 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.32—4.73 (1 H, m, C*H*Me), and 6.5 (1 H, s, ArH).

6-*Allyl*-2,3,4-*trimethoxybenzyl Alcohol* (6).—To a solution of the aldehyde (3) (0.4 g) in THF (2 ml) was added a solution of sodium borohydride (200 mg) in water (0.4 ml). The mixture was stirred for 1 h and then decomposed with a saturated solution of ammonium chloride (2 ml). The usual work-up procedure gave a viscous liquid (380 mg, 94%) which could not be distilled. The product was, however, a single compound whose analytical and spectroscopic properties corresponded to those of the *alcohol* (6) (Found: C, 65.75; H, 7.7. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61%); $\nu_{max.}$ (Nujol) 3 500—3 300, 1 000, and 910 cm^{-1}; δ ($CDCl_3$) 1.8—2.0 (1 H, exchanges with D_2O, OH), 3.4br (2 H, d, *J* 7 Hz, ArCH_2CH), 3.78 and 3.8 (total 6 H, 2 × s, 2 × OMe), 3.88 (3 H, s, OMe), 4.52 (2 H, s, CH_2OH), 4.84—5.16 (2 H, m, CH=CH_2), 5.72—6.2 (1 H, m, C*H*=CH_2), and 6.43 (1 H, s, ArH).

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REFERENCES

[1] T. R. Govindachari, S. J. Patankar, and N. Viswanathan, *Phytochemistry*, 1971, **10**, 1603.
[2] T. R. Govindachari, S. J. Patankar, and N. Viswanathan, *Indian J. Chem.*, 1971, **9**, 507.
[3] J. N. Chatterjea, C. Bhakta, and N. D. Sinha, *J. Indian Chem. Soc.*, 1975, **52**, 158.
[4] B. H. Bhide, V. P. Gupta, N. S. Narasimhan, and R. S. Mali, *Chem. Ind. (London)*, 1975, 519.
[5] 'Rodd's Chemistry of Carbon Compounds,' Elsevier, 1974, 2nd edn., vol. IIIE, p. 172.
[6] N. S. Narasimhan and T. Mukhopadhyay, *Tetrahedron Lett.*, 1979, 1341.
[7] T. K. Chakroborty and S. Chandrasekaran, *Synth. Commun.*, 1980, **10**, 951.