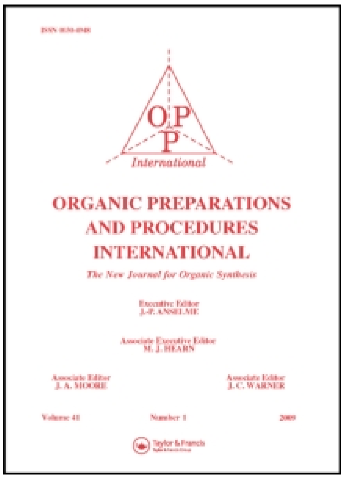

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SYNTHESIS OF OCIMIN

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SYNTHESIS OF OCIMIN

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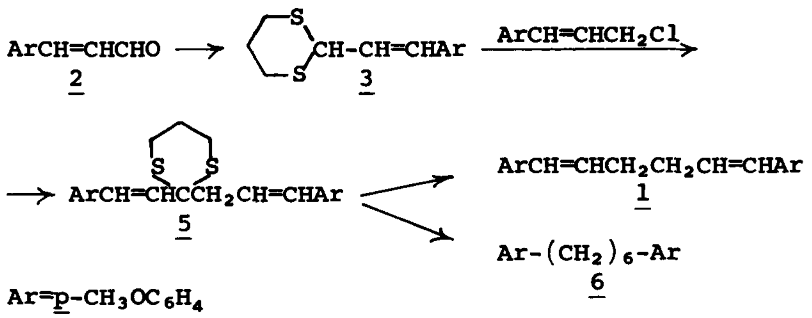
From the essential oil of Ocimum americanum L., there was recently isolated a product $C_{20}H_{22}O_2$ for which the name ocimin and the structure 1,6-bis(4′-methoxyphenyl)hexa-1(E), 5(E)-diene (1) were proposed.[1] Although the appellation, neolignan, has been applied to this unusual Ar-C_6-Ar product,[2] no experimental justification has been provided.[3] We report here a brief synthesis of this compound from p-anisaldehyde.



4-Methoxycinnamaldehyde (2), readily obtained by Claisen-Schmidt condensation of p-anisaldehyde and acetaldehyde,[4] condensed with propane-1,3-dithiol to yield 2-(4′-methoxystyryl)-1,3-dithiane (3). Alkylation of the anion of 3 derived by treatment with n-butyllithium, with the readily available 4′-methoxycinnamyl chloride (4),[5] gave the required intermediate, 2-(4′-methoxycinnamyl)-2-(4′-methoxystyryl)-1,3-dithiane (5).

An initial attempt to convert (5) to ocimin (1) directly by heating with Raney nickel in ethanol solution was unsuccessful, desulphurisation being accompanied by double bond reduction, yielding 1,6-bis-(4′-methoxyphenyl)hexane (6). Alternative procedures to obviate this difficulty were accordingly sought and two proved successful. Thus, reduction of the dithiane (5) with the cupric chloride-zinc chloride-lithium aluminium hydride reagent[6,7] yielded ocimin (1). It has been noted that dimethylsulphoxide deactivates Raney nickel catalyst toward C=C reduction.[8] When the dithiane (5) was stirred with the catalyst in this solvent at room temperature, ocimin again could be isolated, albeit in lower yield.

EXPERIMENTAL

Pmr spectra are reported for $CDCl_3$ solutions using TMS as internal standard at 60 MHz and melting points (capillary) were determined using a Gallenkamp apparatus.

4-Methoxycinnamyl Chloride (4) prepared as described[5] had mp 72-73°, lit.[5] mp 71.5-73°, δ 3.80 (s, OMe), 4.23 (d, J=6.5 Hz, $-CH_2-$), 5.9-6.4 (m, $=CH-CH_2$), 6.67 (d, J=16 Hz, ArCH=), 6.88 (d, J=9 Hz, H-3 and -5) and 7.36 (d, J=9 Hz, H-2 and -6); 4-methoxycinnamaldehyde (2) prepared as described[4] had mp 57-59°, δ 3.85 (s, OMe), 6.61 (dd, J=16, 7.5 Hz, -CH-CHO, 6.97 (d, J=9 Hz, H-3 and -5), 7.47 (d, J=16 Hz, ArCH-), 7.56 (d, J=9 Hz, H-2 and -6) and 9.71 (d, J=7.5 Hz, -CHO).

2-(4′-Methoxystyryl)-1,3-dithiane (3) - A mixture of 4-methoxycinnamaldehyde (2.0 g), propane-1,3-dithiol (1.44 g) and *p*-toluenesulphonic acid monohydrate (*ca* 150 mg) in chloroform solution (25 ml) was stirred at room temperature for 4 hr, then washed with 20% aqueous sodium hydroxide solution (25 ml) and water. Evaporation of the dried (Na_2SO_4) organic layer gave a solid residue, which was recrystallized from chloroform-methanol to give the *dithiane* (**3**) as needles (2.04 g), mp 104°, δ 1.8-2.2 (m, $C\underline{H}_2(CH_2S-)_2$), 2.8-3.0 (m, $-SCH_2$), 3.80 (s, OMe), 4.81 (d, J=7.5 Hz, -SCHS-), 6.11 (dd, J=16, 7.5 Hz, $=C\underline{H}-C\underline{H}\langle^{S}_{S}$), 6.76 (d, J=16 Hz, ArC$\underline{H}$=), 6.85 (d, J=9 Hz, H-3 and -5) and 7.36 (d, J=9 Hz, H-2 and -6).

Anal. Calcd. for $C_{13}H_{16}OS_2$: C, 61.86; H, 6.39

Found: C, 61.91; H, 6.42%

2-(4′-Methoxycinnamyl)-2-(4′-methoxystyryl)-1,3-dithiane (**5**).- *n*-Butyllithium (1.0 ml, 2.5 M solution in hexane) was added to a solution of the dithiane (**3**)(504 mg) in tetrahydrofuran (15 ml) over 1 min, then stirred at -30° for 40 min. A solution of 4-methoxycinnamyl chloride (456 mg) in tetrahydrofuran (5 ml) was then added at -78° with stirring at this temperature for 1 hr and for a further 1 hr while the temperature rose to 0°. The mixture was then poured on to crushed ice, extracted with ether and worked up in the usual way to yield a viscous brown oil which was dissolved in benzene and chromatographed on silica gel. Elution with benzene gave the dithiane (**5**) as a yellowish oily solid (750 mg), δ 1.8-2.2 (m, $C\underline{H}_2(CH_2S-)_2$), 2.55-3.05 (m, $-SCH_2$ and CH_2), 3.78 (s, OMe), 3.82 (s, OMe), 5.95-6.37 (m, 2H, vinyl-H) and 6.6-7.5 (m, 10 H, ArH and vinyl H). This material was used in this state of purity; on standing, it formed a dark resin.

1,6-Bis(4'-methoxyphenyl)hexa-1(E),5(E)-diene. (1). - Lithium aluminium hydride (365 mg) was added in small batches to a suspension of anhydrous cupric chloride (162 mg) and anhydrous zinc chloride (326 mg) in tetrahydrofuran (20 ml) under nitrogen, and the mixture stirred at room temperature for 45 min. A solution of the dithiane (5)(238 mg) in tetrahydrofuran (5 ml) was then added and the mixture heated under reflux for 1 hr. Water (2 ml) was then added cautiously to the cooled reaction mixture, and the resultant black slurry diluted with dichloromethane (20 ml) and filtered. The insoluble residue was washed with boiling dichloromethane (2 x 20 ml), and the combined filtrates washed with a solution of mercuric acetate (480 mg) in water (15 ml), then water and dried (Na_2SO_4). Evaporation of the solvent gave a residual yellow oil, which crystallized from ethyl acetate to give the diene, ocimin (1)[9] as plates (36 mg), mp 169-172°, lit[1] mp 168-171°, δ 2.4 (br.t, $-CH_2-$), 3.80 (s, OMe), 5.95-6.30 (m, $=C\underline{H}CH_2$), 6.42 (d, J=16 Hz, ArCH=), 6.86 (d, J=9 Hz, H-3' and 5') and 7.32 (d, J=9 Hz, H-2' and 6').

Action of Raney Nickel on Dithiane (5)

a) In ethanol solution. - Raney nickel W-2 (ca 6 g) was added to a solution of the dithiane (230 mg) in ethanol (170 ml) and the mixture refluxed for 17 hr, filtered and evaporated.

Crystallization of the residual solid from light petroleum gave 1,6-di-p-anisylhexane as needles (140 mg), mp 70-71°, lit[10] mp 71.5°, δ 1.40 (m, C-2,3,4,5-H), 2.52 (t, $ArCH_2$), 3.71 (s, OMe) and 6.72-7.33 (m, ArH).

b) In dimethylsulphoxide solution. - Raney nickel (ca 3 g) was added to a solution of the dithiane (120 mg) in dimethylsulphoxide (60 ml) and the mixture stirred at room temperature for 20 hr. It was then filtered, the filtrate diluted with water and extracted with ether. Evaporation of the dried extract gave a brown oil, which crystallized from ethyl acetate to give ocimin (9 mg), mp 169-172°.

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