

NIESHOUTOL, A STERNUTATORY HYDROXYCOUMARIN FROM SNEEZEWOOD

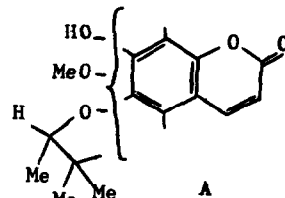
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Recently there has been considerable interest in the coumarins¹⁻³ and chromones^{1,4} of Ptaeroxylon utile (sneezewood) but as yet the nature of the active principle has not been resolved. One sternutatory factor is nieshoutol¹, C₁₅H₁₆O₅, m.p. 143-144° which can now be firmly allocated structure (1) on the following evidence.

Nieshoutol is an optically inactive hydroxycoumarin
($\nu_{\text{max}}^{\text{CCl}_4}$ 3569, 1736, 1620, and 1578 cm⁻¹; $\lambda_{\text{max}}^{\text{EtOH}}$ 230, 251, 258 and 340 nm (log ϵ 4.18, 3.64, 3.55, 4.08); $\lambda_{\text{max}}^{1\% \text{NaOH-EtOH}}$ 255, 340, 400 nm (log ϵ 4.26, 3.98, 3.79) which was deduced¹ from the n.m.r. (see Table) to have the partial structure A.

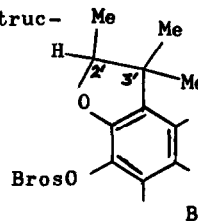


The 2,3,3-trimethyldihydrofuran system, which is present in nieshoutin (2), a coumarin also isolated from sneezewood, might from the similarity of the chemical shift values be fused similarly in both compounds.

Nieshoutol readily affords an acetate, m.p. 126-128° [$\nu_{\text{max}}^{\text{CHCl}_3}$ 1770 cm⁻¹ (OAc)] and a methyl ether, m.p. 99-100°, but its hydroxyl group which is intramolecularly hydrogen bonded can not be at C-7 from its u.v. behaviour. In simpler systems a 7-hydroxycoumarin can be characterised from the change in u.v. on addition of base and the data⁵ on isofraxidin (6,8-dimethoxy-7-hydroxycoumarin) suggests that in trioxygenated coumarins the presence of a 7-hydroxyl group can be determined in this way.

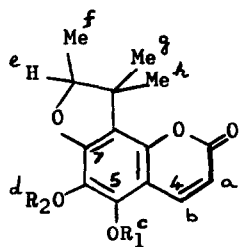
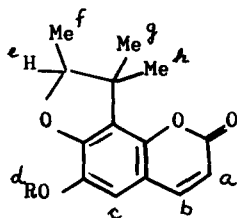
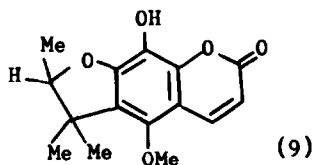
A number of heavy atom phenolic derivatives of (1) were prepared⁶, including the brosylate (3), m.p. 175-176°, but these in each case proved unsuitable for x-ray studies. Most interestingly however, the n.m.r. of this brosylate when compared with that of nieshoutol, shows shielding of both the C-2' hydrogen (0.28 ppm) and the C-2' methyl (0.21 ppm). The reason for this shielding is

not yet clear since nieshoutol p-bromobenzoate, m.p. 213-215°, benzyl ether, m.p. 119-121°, and mesylate, m.p. 118-120° all give spectra very similar to that of the parent phenol, only the tosylate, m.p. 153-155° showing a comparable amount of shielding of the secondary methyl system. From a study of models it seemed likely that, for the observed effect, the partial structure B was required (and therefore two likely structures, (1) or (9), for nieshoutol) since only in this environment might the brosylate be expected to exert such a specific effect on the C-2' substituents. To test this hypothesis, the phenol (4), m.p. 157-159° was prepared (by Claisen rearrangement of 7-O-(3,3-dimethylallyl)aesculetin² at 170° which proceeded with attendant cyclisation²) and converted to the brosylate (5), m.p. 128-129.5°. From the n.m.r. spectra of (4) and (5) it can be seen that there is a marked shielding of the secondary methyl system (0.36 and 0.25 ppm for the hydrogen and methyl respectively). The downfield shift (0.43 ppm) of the aromatic proton in (5) was as expected for a strong electron withdrawing group in the ortho position. In the spectrum of the corresponding mesylate, m.p. 128-130°, a similar effect was observed, but unlike the brosylate the remainder of the spectrum was unaffected.

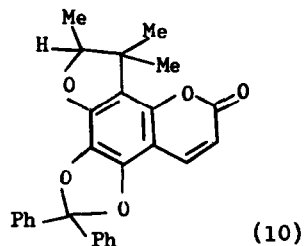


Since the hydroxyl and methoxyl functions of nieshoutol must be either ortho or para related, it was realised that conclusive information might be gained if nieshoutol could be converted to the corresponding diol. Treatment of (1) with freshly prepared 40% HBr/HOAc for 3 hr. at gentle reflux gave, after separation on t.l.c. (i) nieshoutol acetate (5%); (ii) unreacted (1) (22%); (iii) a diol monoacetate (6), m.p. 176-178° (22%), which gave nieshoutol acetate on diazomethylation; and (iv) a diol (7), m.p. 122-126° (40%) which with diazomethane afforded nieshoutol methyl ether. From these interconversions it can be seen that no skeletal rearrangement has accompanied demethylation

In the monoacetate (6) ($\nu_{\max}^{\text{CCl}_4}$ 3570 cm^{-1} ; $\lambda_{\max}^{\text{EtOH}}$ 226, 252, 260 and 335 nm) (log ϵ 4.03, 3.67, 3.70, 3.95), the intramolecularly hydrogen bonded hydroxyl can be placed at C-5 since the n.m.r. of the derived brosylate (8), m.p. 209-211°, shows a significant shielding (0.35 ppm) of the C-4 proton. A similar

(1) $R_1 = \text{Me}, R_2 = \text{H}$ (3) $R_1 = \text{Me}, R_2 = \text{Bros}$ (6) $R_1 = \text{H}, R_2 = \text{Ac}$ (7) $R_1 = R_2 = \text{H}$ (8) $R_1 = \text{Bros}, R_2 = \text{Ac}$ (2) $R = \text{Me}$ (4) $R = \text{H}$ (5) $R = \text{Bros}$ 

(9)



(10)

TABLE

Chemical shifts (τ) at 60 MHz for coumarins (1)-(8) (in CDCl_3)

	Ha	Hb	Hc	Hd	He	Hf	Hg	Hh*
	1H,d J=9.5 Hz	1H,d J = 9.5Hz	s	s	1H,q J=6.5 Hz	3H,d J=6.5 Hz	3H,s	3H,s
1	3.81	2.13	6.03, 3H	4.83, 1H [†]	5.43	8.59	8.46	8.72
2	3.81	2.44	3.27, 1H	6.10, 3H	5.43	8.55	8.42	8.70
3	3.80	2.16	6.05, 3H	-	5.71	8.80	8.52	8.82
4	3.80	2.47	3.18, 1H	4.50, 1H [†]	5.44	8.59	8.43	8.71
5	3.75	2.43	2.75, 1H	-	5.80	8.84	8.52	8.84
6	3.85	2.02	3.93, 1H [†]	7.60, 3H	5.45	8.62	8.48	8.73
7	3.85	2.02	4.0, broad, 2H [†]	-	5.47	8.62	8.48	8.76
8	3.78	2.41	-	7.93, 3H	5.39	8.60	8.42	8.67

*The high field methyl may be that which is cis to the C-2' methyl.⁸[†]Disappears on addition of D_2O .

shielding (0.25 ppm) of a C-4 proton by a tosylate at C-5 has been recorded⁷ without comment for clausenin tosylate. Further, in (8), the acetate signal has been shifted upfield by 0.33 ppm which requires an ortho relationship of the two functionalities. It was found, in confirmation, that the diol (7) afforded a cyclic ketal (10), m.p. 194-195° when kept with dichlorodiphenylmethane in pyridine.

Since the methoxyl group of nieshoutol has been shown to be at C-5, the hydroxyl group in (1) must now be placed at C-6. From n.m.r. evidence, the dihydrofuran ring must be placed with its oxygen at C-7, as it is in nieshoutin (2), thus confirming the close relationship between these two co-occurring coumarins.

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