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THE SYNTHESIS OF 2,3,5,6-TETRAHYDROIMIDAZO [2, 1-b] THIAZOLES UTILISING α-BROMO-MICHAEL ACCEPTORS

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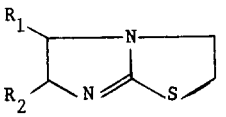
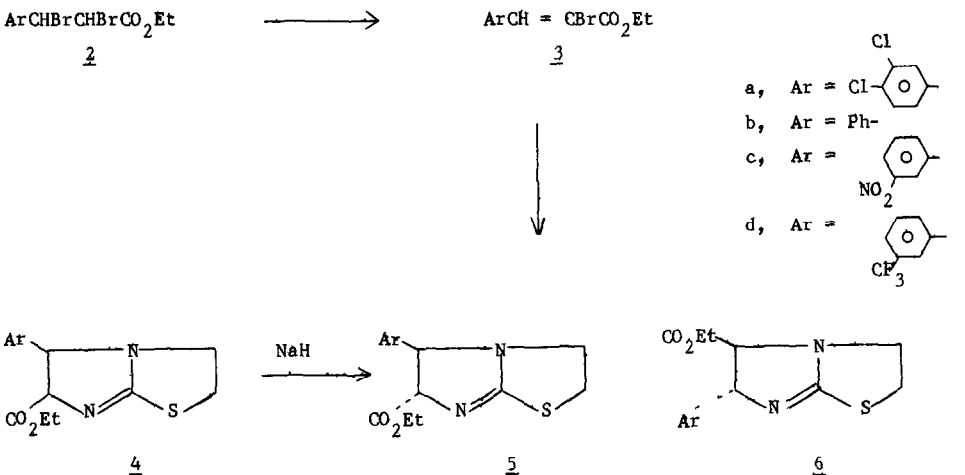
6-Phenyl 2,3,5,6-tetrahydroimidazo (2, 1-b) thiazole (1a) is a potent anthelmintic[1] for which immune response potentiation[2], and antinflammatory properties[3] have been claimed. A facile synthesis of the isomeric 5-aryl substituted and 5-aryl-6-alkyl-disubstituted-tetrahydroimidazo (2, 1-b) thiazoles (1b) and (1c) was required in order to explore their biological properties. The cis and trans esters (4) and (5) were selected as ideal starting materials for the study and this preliminary report describes their facile formation from the ambident nucleophile, 2-aminothiazoline and the α-bromo Michael acceptors (3).



1 a R_1 = H, R_2 = Ph
b R_1 = Ar, R_2 = H
c R_1 = Ar, R_2 = alkyl
d R_1 = Ph, R_2 = $(Et)_2COH$

The α-bromo cinnamates were conveniently generated in situ as a mixture of geometrical isomers by treatment of an ethyl acetate solution of the substituted cinnamate ester dibromides (2) with one equivalent of triethylamine. This solution was then reacted with 2-aminothiazoline (one equivalent) and a further equivalent of triethylamine. In a typical example utilising (2a) as the starting material, the solution was refluxed for 12 hours and from the reaction mixture was obtained the cis-ester, (4a) in 20% yield, m.p. 128-130° (acetone/petroleum ether), I.R.γ (nujol) 1750 cm^{-1} (C = O), N.M.R.δ ($CDCl_3$), 7.42 (d, 1H), 7.30 (d, 1H), 7.15 (d.d, 1H), 5.22 (d, 1H, -CH benzylic), 4.68 (d, 1H, -CH-CO_2Et), 3.9-2.9 (m. 6H, $-CH_2-CH_2-$, $-CH_2-O-$), 0.90 (t, 3H, $-CH_3$), the trans-ester (5a) in 27% yield, m.p. 84-85° (acetone/petroleum ether), I.R.γ (nujol) 1720 cm^{-1} (C = O), N.M.R.δ ($CDCl_3$) 7.55 (d, 1H), 7.44 (d, 1H), 7.25 (d.d, 1H), 4.72 (d, 1H, -CH benzylic) 4.60 (d, 1H, -$CHCO_2Et$), 4.22 (q, 2H, $-CH_2-O-$), 3.55 (m, 4H,

$-CH_2CH_2-$), 1.30 (t, 3H, CH_3-) and the isomeric trans-ester (6a) in 1% yield, m.p. 98-100° (acetone), I.R.γ(nujol) 1740 cm^{-1} (C = O), N.M.R.$\delta(CDCl_3)$, 7.52 (d, 1H), 7.42 (d, 1H), 7.25 (d.d, 1H), 5.52 (d, 1H, -CH benzylic), 4.28 (q, 2H, $-CH_2-O-$), 3.50 (m, 5H, $-CH_2-CH_2-$, -CH CO_2 Et), 1.30 (t, 3H, CH_3-). The assignment of these structures to the 3 isomers isolated was made utilising N.M.R. spectral data and epimerisation studies. The cis-isomer (4a) was readily converted by a catalytic amount of sodium hydride in dioxan to its geometrical isomer (5a). The N.M.R. spectrum of the cis isomer showed the ester methylene and methyl proton signals at very high field owing to the shielding effect of the cis-aromatic ring. The trans-isomer (5a) showed a benzylic proton signal at 5.52 in its N.M.R. spectrum, compared with a figure of 5.40 for the benzylic proton in (1a), whereas its structural isomer (6a) displayed a benzylic doublet at 4.72 compared with a figure of 4.50 for the benzylic proton of 5-phenyl-2,3,5,6-tetrahydroimidazo (2, 1-b) thiazole[4], (1b Ar = Ph).

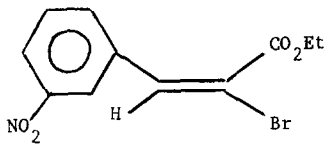


The 5-aryl-2,3,5,6-tetrahydroimidazo (2, 1-b) thiazoles, (4b-d) and (5b-d) shown in Table I were prepared in an analogous fashion. Attempts were not made to isolate the minor products (6 b-d).

Table 1

Compound	m.p.	Yield %	Reflux time
4b	99	10	20 hrs
5b	98 - 102	30	
4c	87 - 90	15	6 hrs
5c	129 - 131	18	
4d	121 - 122	33	9 hrs
5d	114 - 116	17	

The α-bromo cinnamate (3c) was separated by column chromatography (silica/elutant toluene) into the cis and trans isomers, (7) yellow oil, and (8), m.p. 69-71°(petroleum ether). The N.M.R. spectrum of the trans-isomer showed an olefin signal at δ 8.22 (calculated value 8.20)[5] whereas the cis-isomer displayed a singlet at 7.40 (calculated value 7.36).



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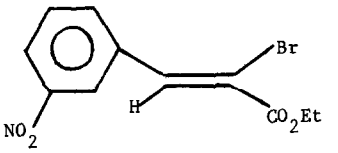

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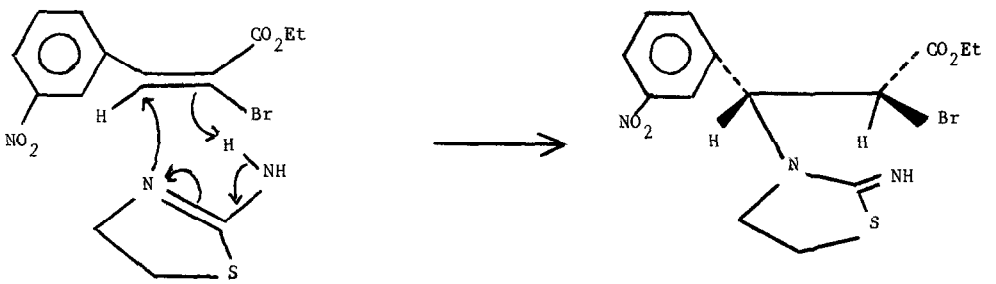

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The cis-isomer (7) reacted with one equivalent of 2-aminothiazoline and triethylamine at room temperature to give exclusively the cis ester (4c). In contrast the trans-isomer (8) reacted very slowly at ambient temperature, but on refluxing for 4 hours, the trans-ester (5c), together with a trace of (6c) was obtained. Similar stereoselective reactions have been observed recently[6], when cis- and trans-2-bromobut-2-enoate esters were treated with catechol to give the isomeric 1,4-benzodioxans. A cis Michael addition of 2-aminothiazoline (e.g. to 7) is postulated for these stereospecific reactions involving intramolecular hydrogen abstraction, followed by cyclisation of the resultant bromides (e.g. 9).

Confirmation of the structures assigned to the three isomeric esters (4), (5) and (6) was provided by an X-ray study[7] of the trans-isomer of the carbinol (1d), m.p. 115°-117° (petroleum ether), obtained by reaction of the ester (5b) with excess ethyl magnesium bromide. The trans-carbinol and related compounds exhibited high antidepressant activity and these results will be reported elsewhere.

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(7) X-ray studies carried out by Dr. A. F. Cameron, University of Glasgow.