A NEW SYNTHESIS OF 4-PHENYLPYRIDO(3,2-b)(1,4)BENZOTHIAZINES (1-AZAPHENOTHIAZINES)

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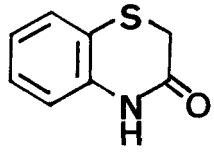
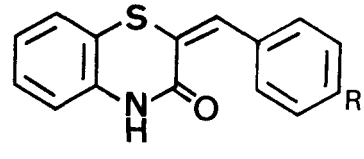
Phenothiazines such as chlorpromazine are used as major tranquillisers in the treatment of psychotic disorders. Many phenothiazines also possess sedative, antihistamine and antitussive activity. Due to the pharmacological importance of the phenothiazines, the synthesis of analogues containing a nitrogen atom in one of the benzenoid rings has also been investigated. Many 1-azaphenothiazines have been shown to be highly active as antitumour, CNS depressant, antihistamine and sedative agents. (Taneja et al 1984).

As part of a study of the preparation of pyridine containing heterocycles, the addition of malononitrile to the α,β- unsaturated ketone 2-benzylidene-2H-1, 4-benzothiazin-3(4H)-one was investigated as a possible route to the 1-azaphenothiazine structure. The formation of simple pyridines by reaction of α,β-unsaturated ketones with malononitrile in the presence of strong base had been reported (Otto 1979). 1,4-Benzothiazin-3(4H)-one (1) was prepared by reaction of 2-aminothiophenol with chloroacetic acid (Krapcho 1973). Condensation of (1) with benzaldehyde was carried out by reaction with sodium methoxide in DMF to give 2-benzylidene- 2H - 1,4-benzothiazin-3(4H)-one (2), R=H, in 26% yield. When the α,β- unsaturated ketone 2-benzylidene- 2H-1, 4-benzothiazin-3(4H)-one (2) was reacted with malononitrile in methanol containing sodium hydroxide, a yellow product was obtained in 24% yield. {IR ν max (KBr) 2210, 1600, 1500 cm^{-1}, ^1H n.m.r. δ[$(CD_3)_2$ SO] 3.90 (3H,s,OCH_3), 6.35-7.55 (9H, m,aromatic H), M^+ 331.1 (100%)} From the spectroscopic data, it is proposed that the structure of the product is the hitherto unreported 3-cyano-2-methoxy-4-phenylpyrido{3,2-b} {1,4}benzothiazine (3) R=H . Michael addition of malononitrile to the electron deficient β-carbon of (2) R=H followed by cyclization, Dimroth rearrangement and disproportionation afforded the 1-azaphenothiazine product (3) R=H.

This novel synthetic route provides a new method for the production of 1-azaphenothiazines. The use of substituted benzaldehydes in the reaction sequence afforded a series of 4'-substituted 1-azaphenothiazines {(3) R=OCH_3, OC_2H_5, NO_2, Br, Cl, F, CH_3,C_2H_5} Replacement of methanol as solvent by ethanol gave the 2-ethoxy products.



(1)



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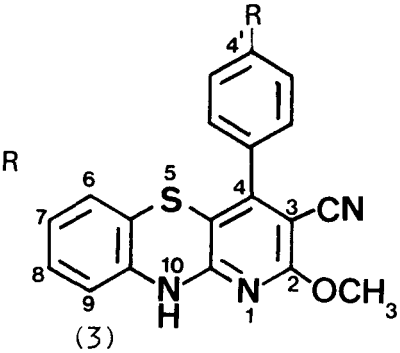

(3)

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