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SYNTHESIS OF PRECURSORS OF NOVEL MORPHINAN ANALOGUES

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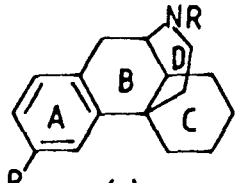
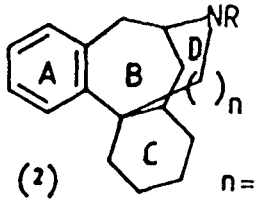
Since the discovery that the morphinans (1), compounds containing the carbon-nitrogen skeleton of morphine, exhibited analgesic activity (Grewe & Mondon 1948) there has been considerable interest in preparing many analogues of these compounds in order to produce an analgesic with a more acceptable pharmacological profile than that of morphine. The work described here is based on synthetic approaches to B and D ring expanded morphinans (2).

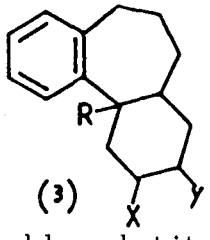


(1)

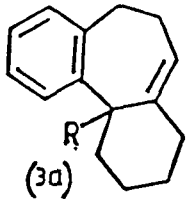


(2) n=1 or 2

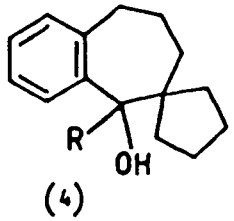
Two approaches to the preparation of tricyclic precursors (3) have been utilised. The first involves a [4+2] cycloaddition reaction (Fieser & Holmes 1936), the second the Wagner-Meerwein rearrangement of spiro-derivatives (4) (Belleau et al, 1975).



(3)



(3a)



(4)

(i) A suitably substituted dieneophile was prepared from benzosuberone by hydrolysis and esterification of its cyanotrimethylsilyl ether. Reaction of this dieneophile with 2,3-dimethyl-1,3-butadiene followed by hydrogenation gave the tricyclic adduct (3, R=CO_2Et, X=Y=Me).

(ii)

[a] The spiroketone prepared from benzosuberone and 1,4-dibromobutane was converted to the cyanohydrin (4, R=CN) which underwent an acid catalysed Wagner-Meerwein rearrangement to give the tricyclic precursor (3a, R=CN).

[b] Cyanomethylation of the spiroketone with lithium-acetonitrile gave a spiro-derivative (4- R=CH_2CN) which failed to undergo rearrangement giving instead a unsaturated cyano compound. Work with model compounds has offered an alternative route to the tricyclic morphinan precursor (3, R=CH_2CN, X=Y=H). The compounds synthesised all gave the requisite elemental and spectral analyses.

Future work will involve the investigation of synthetic routes to the novel morphinan analogues (2) from the tricyclic precursors (3).

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Grewe and Mondon, (1948) Chem. Ber., 81:279
Fieser and Holmes, (1936) J. Am. Chem. Soc., 48:2319
Belleau et al (1973) Ibid. 95:7910.
Belleau et al (1975) Can. J. Chem., 53:237