6-β-ARYLTROPAN-6-OLS - A NEW SERIES OF POTENTIAL ANALGESICS

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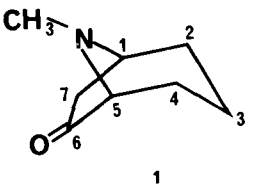
The chemistry and pharmacological properties of naturally occurring tropanes such as hyoscine, hyoscyamine and cocaine have undergone extensive investigation and as a consequence many synthetic antispasmodics and local anaesthetics have been developed. Analgesics related to pethidine, which owes its origins to atropine studies and based upon 3-substituted tropanes have also been synthesised and activities greater than pethidine have been reported (Casy 1978).

In contrast to 3-substituted tropanes, compounds with substituents in the 6-position are sterically constrained and there is a fixed spatial relationship between the tropane nitrogen and α- or β- 6 substituents. This offers a potential tool for the study of pharmacophore-receptor interactions in novel neurotransmitter mimics and antagonists. 6-Aryltropans exhibit structural similarities to 3-arylpiperidines (Iorio and Casy 1978) and 3-arylpyrrolidines (Bowman et al 1973), members of which groups show analgesic agonist and antagonist activities over a wide dose range.

Neglect of 6-substituted tropanes is a result of synthetic difficulties particularly on scale-up. The route to the key intermediate tropan-6-one(1) follows a classical Robinson reaction where hydroxysuccinaldehyde, prepared in situ is condensed with methylamine and acetonedicarboxylic acid in citrate buffer at pH5, to give 6β-hydroxytropan-3-one. The 3-carbonyl group is removed by Wolff-Kishner reduction and chromic acid oxidation affords tropan-6-one.



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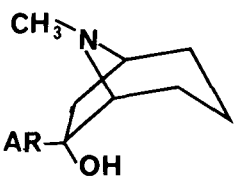

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Reaction of aryl Grignard reagents with tropan-6-one affords 6-aryltropan-6-ols(2) in good yield and a predominant 6β-aryl isomer. The orientation of the aryl ring may be predicted as occurring β- by a consideration of the Grignard/tropan-6-one transition complex. Confirmation of this came from 100MHz ^{1}H NMR studies of both the tertiary base of 6-phenyltropan-6-ol and its methiodide. From the spectra it is clear that one quaternary +N.$\underline{CH_3}$ signal occurs at the uncharacteristic high field resonance of δ2.67. The only reasonable explanation for this is that the equatorial +N.$\underline{CH_3}$ group experiences significant anisotropic shielding from the phenyl ring with a β-orientation.

N-Demethylation of 6β-phenyltropan-6-ol was affected by trichloroethylchloroformate and agonist and antagonist substituents inserted by standard techniques. Propionyloxy- and acetyloxy-esters bearing a structural resemblance to reversed esters of pethidine were prepared.

Tropane esters bearing nitrogen substituents characteristic of agonists were low potency morphine-like analgesics on the guinea-pig ileum; agents with antagonist substituents were inactive in tests of reversal of morphine response.

Bowman, R.E., Collier, H.O.J. Lockhard, I.M., Schneider, C., Webb, N.E., and Wright, M., J. Med. Chem. 16, 1181, (1973)
Casy, A.F., Progress in Drug Research 22, 149-227 (1978)
Iorio, M.A., and Casy, A.F., J. Med. Chem. 21, 812-815 (1978)