NOVEL TYPE OF ANALGESIC —— SYNTHESIS AND ANALGESIC ACTIVITY

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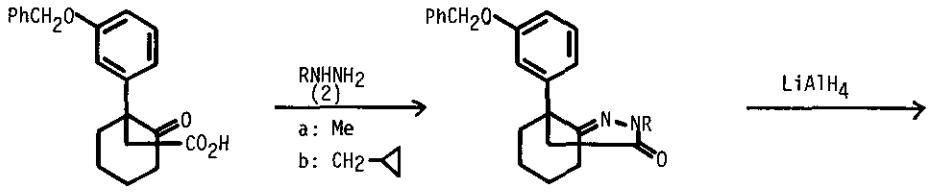
Abstract —— Two 4a-(3-hydroxyphenyl)decahydrocinnolines (7 and 9) have been synthesised from 2-(3-benzyloxyphenyl)-2-hydroxycarbonyl-methylcyclohexanone (1), and both showed stronger analgesic activity than morphine.

Previously we have reported the synthesis of many azamorphinan derivatives, some of which showed stronger analgesic activity than morphine.[1-4] In a continuation of this study we have achieved the synthesis of new analgesic compounds having the 4a-(3-hydroxyphenyl)decahydrocinnoline system as the basic skeleton and here we wish to describe this work.

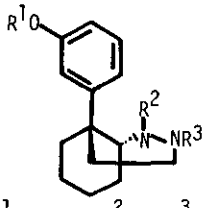
Condensation of 2-(3-benzyloxyphenyl)-2-hydroxycarbonylmethylcyclohexanone (1)[3] with methylhydrazine (2a) in boiling benzene gave, in 61 % yield, the 2,3,4,4a,5,6,7,8-octahydro-3-cinnolinone (3a) [mp 111 - 112°C; ν_{max} 1650 cm^{-1}; δ ($CDCl_3$) 3.33 (3H, s, NMe)], which was reduced by lithium aluminium hydride to the decahydrocinnoline (4) [mp 114 - 116°; δ (DMXO-d_6) 2.83 (3H, s, NMe)] in 50 % yield. The stereochemistry[1] of the decahydrocinnoline ring system was shown to be trans by X-ray analysis.[5] Treatment of the hydrochloride of 4 with acetic anhydride in the presence of sodium acetate, followed by reduction of the resulting amide (5) [mp 120 - 121°; ν_{max} 1640 cm^{-1}; δ (CCl_4) 2.03 (3H, s, OMe)] with lithium aluminium hydride afforded the 1-ethyl-2-methyldecahydrocinnoline (6), in 75 % yield, characterised as its hydrochloride [mp 156 - 158°; δ (DMSO-d_6) 1.31 (3H, t, J 7 Hz, $CH_2\underline{CH_3}$)]. Finally, debenzylation of the hydrochloride of 6 was carried out in a current of hydrogen in the presence of 30 % palladium-carbon in ethanol to give, in 52 % yield, the 4a-(3-hydroxyphenyl)decahydrocinnoline (7), which was also isolated as

the corresponding hydrochloride, mp 142 - 144°.

Chart 1



(1) (3)



(4) R^1=CH_2Ph, R^2=H, R^3=Me
(5) R^1=CH_2Ph, R^2=Ac, R^3=Me
(6) R^1=CH_2Ph, R^2=Et, R^3=Me
(7) R^1=h, R^2=Et, R^3=Me
(8) R^1=CH_2Ph, R^2=H, R^3=CH_2-cyclopropyl
(9) R^1=R^2=H, R^3=CH_2-cyclopropyl

Similary, the 2-cyclopropylmethyldecahydrocinnoline (8),[4] prepared from 2 and cyclopropylmethylhydrazine (2b) through 3b, was debenzylated as above to produce the 4a-(3-hydroxyphenyl)decahydrocinnoline (9), characterised as its hydrochloride, mp 246 - 249°; δ(MDSO-d_6) 0.36 - 0.90 (5H, m, cyclopropane protons).

Pharmacology

The following table shows the results of screening the decahydrocinnoline derivatives for analgesic activity by a hot plate method. Male mice ddY-strain (20 - 24 g) were used. Both compounds were administered subscutaneously to mice and ED_{50} was calculated by the Lichfield-Wilcoxone method.[6]

Table ED_{50} by Lichfield-Wilcoxone method

Compd.	ED_{50}, mean value mg/kg	95 % fiducial limit mg/kg
7	0.07	0.03 ∿ 0.17
9	0.2	0.16 ∿ 0.25

The cinnolines 7 and 9 were thus demonstrated to be about 27 times and 10 times respectively, more potent than morphine.

References

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