

NOVEL TYPE OF ANALGESIC — SYNTHESIS AND ANALGESIC ACTIVITY

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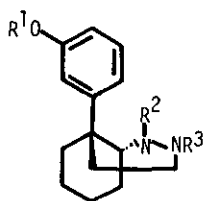
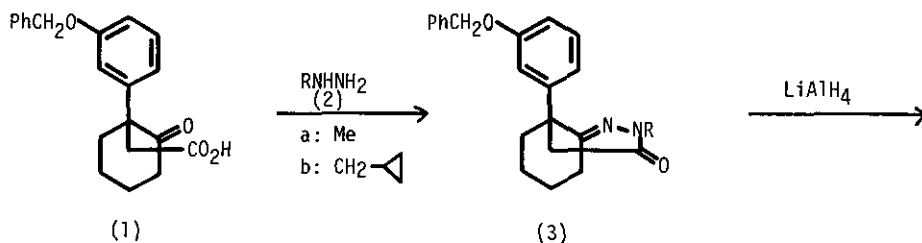
Abstract — Two 4a-(3-hydroxyphenyl)decahydrocinnolines (7 and 9) have been synthesised from 2-(3-benzyloxyphenyl)-2-hydroxycarbonylmethylcyclohexanone (1), and both showed stronger analgesic activity than morphine.

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 (CDCl₃) 3.33 (3H, s, NMe)], which was reduced by lithium aluminium hydride to the decahydrocinnoline (4) [mp 114 - 116°C; δ (DMXO-d₆) 2.83 (3H, s, NMe)] in 50 % yield. The stereochemistry¹ 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°C; ν_{\max} 1640 cm⁻¹; δ (CCl₄) 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°C; δ (DMSO-d₆) 1.31 (3H, t, J 7 Hz, CH₂CH₃)]. Finally, debenylation 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



- (4) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{Me}$
- (5) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Ac}$, $R^3 = \text{Me}$
- (6) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{Et}$, $R^3 = \text{Me}$
- (7) $R^1 = \text{H}$, $R^2 = \text{Et}$, $R^3 = \text{Me}$
- (8) $R^1 = \text{CH}_2\text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{CH}_2$ (cyclopropyl)
- (9) $R^1 = R^2 = \text{H}$, $R^3 = \text{CH}_2$ (cyclopropyl)

Similarly, 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 subcutaneously to mice and ED₅₀ was calculated by the Lichfield-Wilcoxon method.⁶

Table ED₅₀ by Lichfield-Wilcoxon 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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