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# A NEW AND FACILE STEREOSELECTIVE SYNTHESIS OF CIS-4a-ARYL-1,2,3,4,4a,5,6,8a-OCTAHYDROISOQUINOLINE DERIVATIVES

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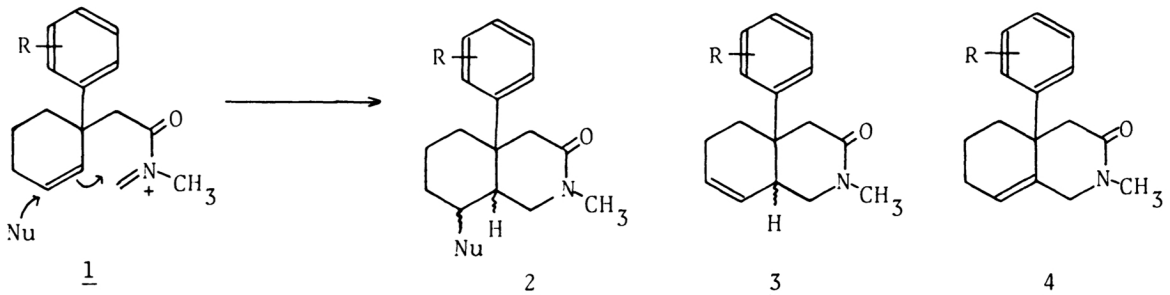
Cis-1,2,3,4,4a,5,6,8a-octahydro-2-methyl-4a-phenylisoquinolin-3-one was obtained by cyclization of the acyliminium ion intermediate, derived from the corresponding amide. Reduction of this cyclization product with $LiAlH_4$ in THF afforded cis-1,2,3,4,4a,5,6,8a-octahydro-2-methyl-4a-phenylisoquinoline. In a similar way, the octahydro-4a-(2-methoxyphenyl)-isoquinolin-3-one was also prepared from the corresponding amide.

Although many synthetic strategies for morphine-based substructural analogs have been reported,[1-6] the new structural variants in this field are still required in the hope of finding significant analgesics with fewer undesirable side effects. We investigated a new and facile synthesis of 4a-arylisoquinolin-3-ones such as 2-4, which would be considerably difficult to prepare, though they should be treated as key structural variants of morphine molecule.[5] For the synthesis of these compounds, we examined a cyclization of acyliminium ion intermediates (1), which might exhibit high stereoselectivity.[7] The results of our studies are described in this paper.



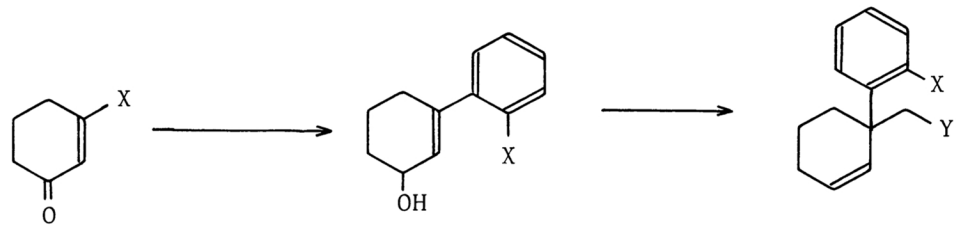

1 2 3 4

The amide (10), the key intermediate for the formation of the acyliminium ion intermediate, was prepared as follows. Phenylation of ethoxycyclohexenone (5)[8] with phenyllithium by the method of Keck,[9] followed by hydrolysis of the reaction

mixture with 10 % hydrochloric acid yielded the phenylcyclohexenone (6). Reduction of 6 with $NaBH_4$ in EtOH at 0 °C gave the enol (7). Claisen rearrangement[10,11] of 7 was effected by the use of triethyl orthoacetate (4 mol. equiv.) at 145 °C for 14 h in the presence of phenol as a catalyst to give the ester (8).[12] Hydrolysis of 8 with 10 % EtOH-NaOH gave the acid (9)[12] in 55 % yield from 5, mp 88-90 °C. The acid (9) was easily converted to the amide (10) [1.2 equiv. $SOCl_2$, benzene, reflux, 2 h, then $CH_3NH_2 \cdot HCl$, $Na_2CO_3$, $H_2O$, 0 °C ⟶ room temperature, 10 h], mp 113-115 °C; MS m/e 229 ($M^+$); $^1H$ NMR ($CDCl_3$) δ 2.56 (2H, s, $CH_2CON$), 2.60 (3H, s, $NCH_3$), and 6.04 (2H, s, olefinic H). Treatment of 10 with parafromaldehyde (5 mol. equiv.) in the presence of p-toluenesulfonic acid (1 mol. equiv.) in chloroform under reflux for 14 h resulted in formation of cis-1,2,3,4,4a,5,6,8a-octahydro-2-methyl-4a-phenylisoquinolin-3-one (11) in 52 % yield, mp 120-122 °C; MS m/e 241 ($M^+$); $^1H$ NMR ($CDCl_3$) δ 2.76 (3H, s, $NCH_3$), and 5.74 (2H, braod s, olefinic H). In this reaction, the 1,2,3,4,4a,5,6,8-octahydro type compound (4, R=H) was not observed. Formation of the alternative expected product (2; R=H, Nu=p-TosO)[13] would be retarded by the steric hindrance of phenyl group. It can be considered that formation of the cis-octahydro-4a-phenylisoquinolin-3-one is kinetically more favorable than that of the trans-isomer. In fact, the stereochemistry of the ring-juncture of 11 was determined as cis by the subsequent transformation. Hydrogenation of 11 over Pd-C catalyst gave the decahydro-4a-phenylisoquinolin-3-one (12) as an oil; MS m/e 243 ($M^+$); $^1H$ NMR ($CDCl_3$) δ 2.75 (3H, s, $NCH_3$). Reduction of 12 with $LiAlH_4$ in THF yielded the cis-decahydro-4a-phenylisoquinoline (13),[5,14,15] the spectral and physical data of which were identical with those in the literature in all respects, picrate, mp 142-144 °C (lit.[14] 144-146 °C). Furthermore, reduction of 11 with $LiAlH_4$ gave the corresponding octahydro-2-methyl-4a-phenylisoquinoline (14) as an oil; MS m/e 227 ($M^+$); $^1H$ NMR ($CDCl_3$) δ 2.26 (3H, s, $NCH_3$), and 5.74 (2H, broad s, olefinic H).

The octahydro-4a-(2-methoxyphenyl)isoquinolin-3-one (20) was also prepared by the method as above. 2-Methoxyphenylation of 5 with 2-methoxyphenyllithium obtained from 2-bromoanisole,[9] followed by hydrolysis of the reaction mixture afforded the enone (15), which was led to the acid (18)[16] in 53 % yield from 5 through 16 and 17.[12] The amide (19),[17] obtained from 18 was treated with parafromaldehyde (5 mol. equiv.) in chloroform in the presence of p-toluenesulfonic acid (1 mol. equiv.) to give 20 in 45 % yield, mp 143-145 °C; MS m/e 271 ($M^+$); $^1H$ NMR ($CDCl_3$) δ 2.82 (3H, s, $NCH_3$), 3.82 (3H, s, $OCH_3$), and 5.71 (2H, s, olefinic

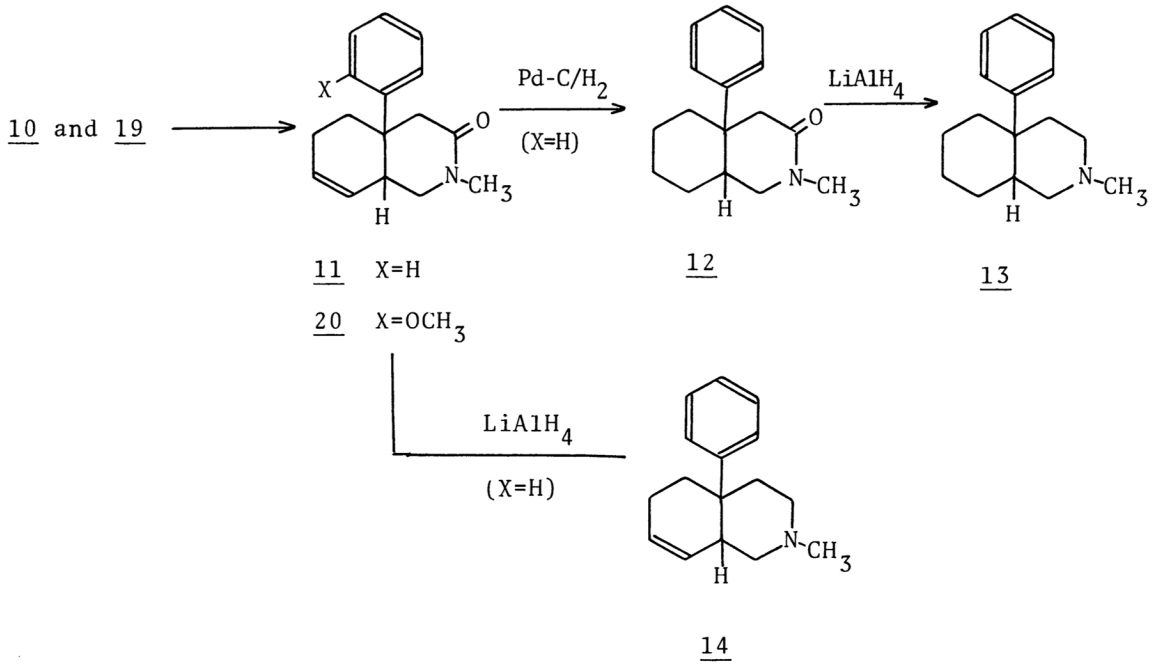
H). The yield of 20 increased to 50 % by using 1,2-dichloroethane instead of chloroform. Upon heating 10 and 19 with paraformaldehyde (5 mol. equiv.) in formic acid at 60 °C, the same results were obtained as above and yields of the corresponding cyclization products were not improved. Lewis acid such as $SnCl_4$ and $ZnCl_2$ in a variety of solvents were not effective in this cyclization reaction.



5 X=OEt
6 X=$C_6H_5$
15 X=2-($CH_3O$)-$C_6H_4$

7 X=H
16 X=$OCH_3$

8 X=H, Y=COOEt
9 X=H, Y=COOH
10 X=H, Y=$CONHCH_3$
17 X=$OCH_3$, Y=COOEt
18 X=$OCH_3$, Y=COOH
19 X=$OCH_3$, Y=$CONHCH_3$



11 X=H
20 X=$OCH_3$

12

13

14

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12) The compounds (6)-(8) and (15)-(17) were used for the next reaction without purification.

13) Although the formation of a trace amount of 2 (R=H, Nu=p-TosO) was detected by $^1$H NMR analysis of the crude product, it was not obtained in a pure form.

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16) mp 63-65 °C; MS m/e 246 ($M^+$).

17) mp 145-147 °C; MS m/e 259 ($M^+$); $^1$H NMR ($CDCl_3$) δ 2.54 (3H, d, J=4.5 Hz, $NCH_3$), 2.55, 3.12 (2H, each d, J=13 Hz, $CH_2CO$), 3.90 (3H, s, $OCH_3$), 5.80-6.25 (2H, m olefinic H).

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