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SYNTHESIS OF 1,3- AND OF 1,5-BENZOXAZOCINE DERIVATIVES

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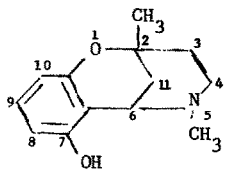
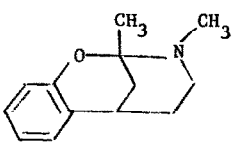
We wish to report the synthesis of 2,5-dimethyl-3,4,5,6-tetrahydro-2,6-methano-2H-1,5-benzoxazocine-7-ol 1 and of 2,3-dimethyl-3,4,5,6-tetrahydro-2,6-methano-2H-1,3-benzoxazocine 2, which represent two new heterocyclic ring systems. We were prompted to synthesize benzoxazocine derivatives because of their relationship to benzomorphans 3,[1] a series of potent analgesics† which includes phenazocine[2] and pentazocine.[3]



1



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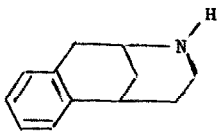


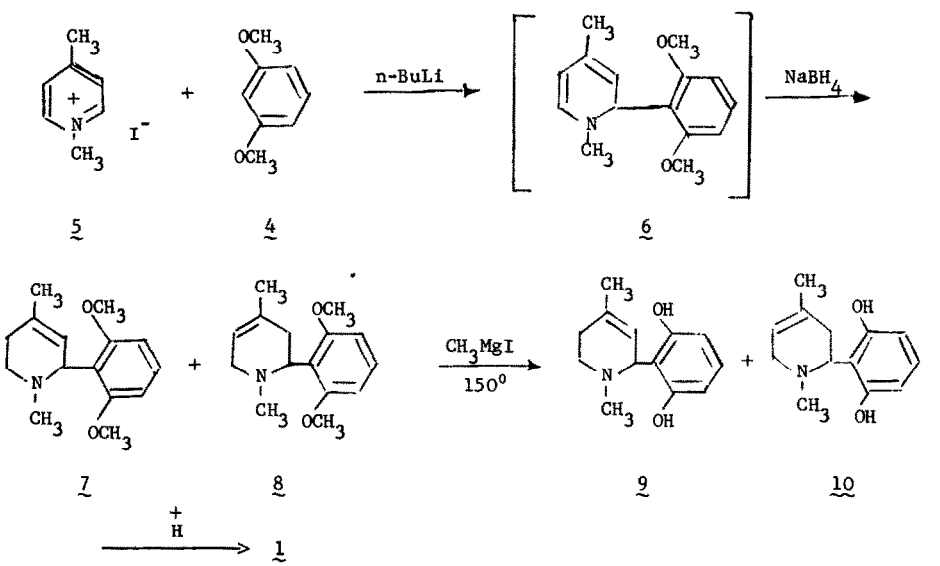
3

The synthesis of 1 was accomplished as shown in Scheme I. A solution of 4 was smoothly transformed into its lithio salt at -5 to -10° with n-butyl lithium. This was stirred at room temperature for 18 hr with 1,4-dimethylpyridinium iodide 5 in ether. Isolation produced in high yields crude 1,2-dihydropyridine derivative 6, which was reduced with sodium borohydride[4] in methanol containing 2N sodium hydroxide to a mixture of tetrahydropyridines 7 and 8.[5] Fusion of this mixture with methylmagnesium iodide[6] at 150° for 2 hr gave the demethylated products 9 and 10. Treatment of the phenolic mixture with concentrated hydrochloric acid gave 1 (22% overall yield from 4) as a liquid (after elution on silica gel with methanol), which was homogeneous on tlc and glc; nmr ($CDCl_3$)δ 1·30(3H, s, $O-C-CH_3$), 1·5-2·85(6H, m, methylene protons), 2·36(3H, s, $N-CH_3$), 4·4(1H, m, benzylic proton), 6·35(2H, d, aromatic 2H), 7·02(1H, m, aromatic H); mass spectrum m/e 219(M^+), 204(M^+-15), 176(M^+-43), 161(base peak); ultraviolet absorption λ_{max}^{EtOH} 280 mμ, (ε 2000). The data clearly support structure 1. During

† Compound 1 was active at 20 mg/kg/sc in mice in the tail flick test.

the acid catalyzed cyclization no product derived from the secondary carbonium ion was detected.

Scheme I



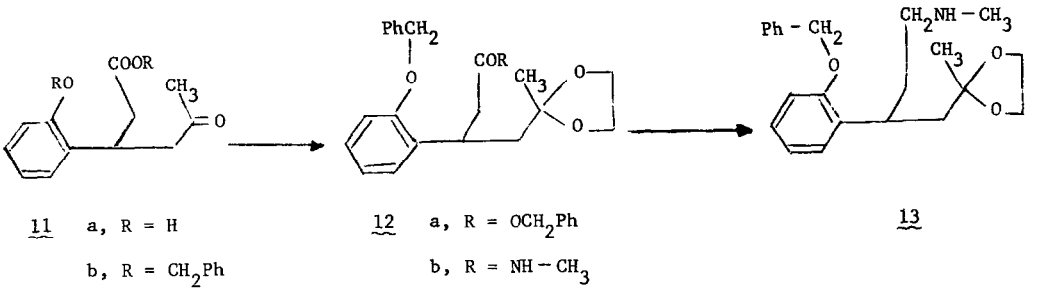
5 4 6

7 8 9 10

1

The synthesis of the 1,3-benzoxazocine derivative 2 is shown in Scheme II. The acid 11a[7] on treatment with benzyl bromide and potassium carbonate in refluxing acetone gave 11b in 90% yield. Reaction of 11b in refluxing benzene with ethylene glycol and p-toluenesulfonic acid gave the ketal 12a, which on treatment with methylamine in ethylene glycol[8] gave the amide 12b, mp 98-99° (53%). Reduction of 12b with lithium aluminum hydride in ether afforded the amine 13 (75%). On heating 13 with a mixture of concentrated hydrochloric acid and acetic acid (1:2) at 85° for 6 hr, the benzoxazocine 2 was formed and purified (80% yield) by preparative tlc (silica gel G 5% methanol/chloroform); nmr ($CDCl_3$) δ 1.51 (3H, s, O-C-CH_3), 2.0 (4H, m, 4 methylene protons), 2.35 (2H, m, N-CH_2-), 2.43 (3H, s, N-CH_3), 3.04 (1H, m, benzylic proton), 6.87 (4H, m, aromatic); mass spectrum m/e 203 (M^+), 188 (M^+-CH_3). One possible mechanism for the conversion of 13 to 2 is outlined in Scheme II.

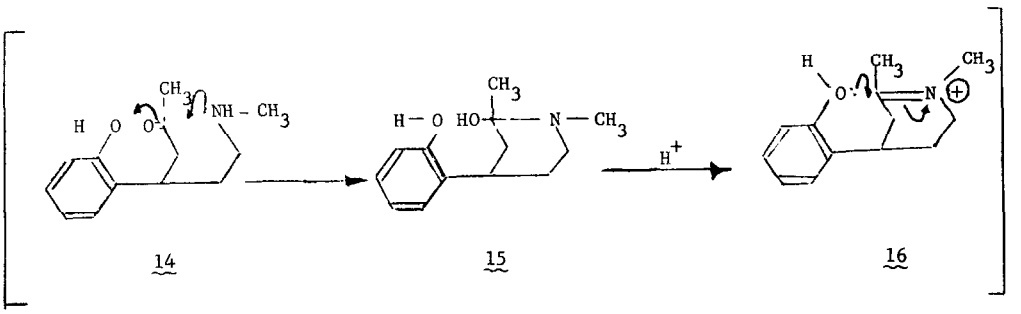
Scheme II



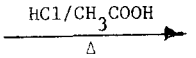
11 a, R = H
b, R = CH_2Ph

12 a, R = OCH_2Ph
b, R = $NH-CH_3$

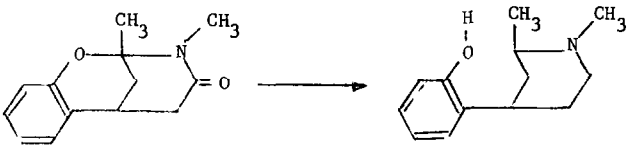
13



14 15 16



2



17 18

It is interesting to note that the treatment of the lactam 17[7,9] with a wide variety of reducing agents, including lithium aluminum hydride, aluminum hydride,[10] and diborane[11] only gave the ring cleavage product 18;[12] nmr(DMSO)δ 1.05 (3H, d, J = 6Hz, C-CH_3), 2.24 (3H, s, N-CH_3), 1.5-3.0 (8H, m), 6.9 (4H, m, aromatic); ir ($CHCl_3$) 3600 cm^{-1} (OH). We attribute this to the complexing of the metal to the pyranyl oxygen thereby weakening the C-O bond.

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