BENZOMORPHAN RELATED COMPOUNDS. XXIII.[1] A NEW SYNTHESIS OF 7,8-BENZOMORPHANS[2]

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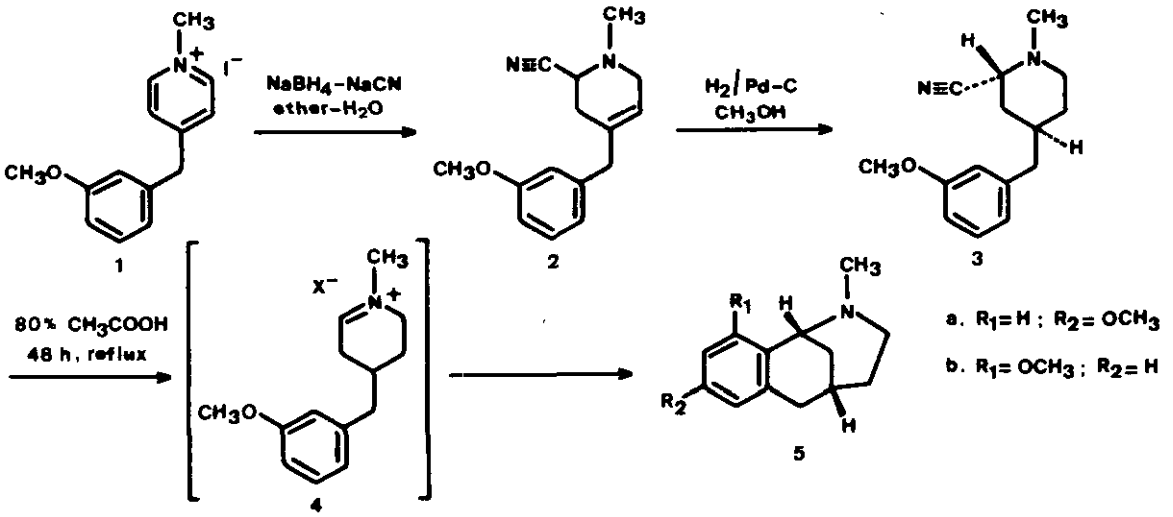
Abstract- A new synthesis of 7,8-benzomorphans based on the acid catalyzed cyclization of 4-benzyl-2-cyanopiperidines is described.

The 7,8-benzomorphans are structural analogues of the well known analgesics 6,7-benzomorphans, in which the aromatic ring is fused to the C_7-C_8 side of the bridged 2-azabicyclo[3.3.1]nonane system.

In previous papers[3-5] we have reported the synthesis of several compounds of this group and reviewed earlier synthetic approaches to the 7,8-benzomorphan ring system[5] and heteroaromatic analogues.[4] The key step in two of these syntheses was the closure of the carbocyclic B ring by cyclization upon the benzene ring of a 2,3,4,5-tetrahydropyridinium salt, generated either by base-promoted isomerization of a 1,2,3,6-tetrahydropyridine followed by acid treatment[3] or by mercuric acetate oxidation of a 4-benzylpiperidine.[4]

We report here the use of 2-cyanopiperidines as an alternative way to generate the tetrahydropyridinium salt required for the cyclization step. 2-Cyanopiperidines[6] and 2-cyanotetrahydropyridines[7] are versatile synthetic intermediates since they can be considered as latent forms of iminium salts which are able to react with activated aromatic ring such as indole.[8] However, to our knowledge there are no precedents



about the use of these kind of α-amino nitriles to promote cyclizations upon the benzene ring.

The reaction sequence used for the synthesis of 7,8-benzomorphans 5 is depicted in the preceding scheme.

The required 2-cyanopiperidine 3 was prepared in three steps from 4-(3-methoxybenzyl) pyridine ,[9] by quaternization with methyl iodide, reductive cyanation[10] of the resulting pyridinium salt, and finally, catalytic hydrogenation of the tetrahydropyridine double bond. The most significant spectroscopic data of 2-cyanopiperidine 3 were an ir absorption at 2210 cm^{-1} due to the cyano group and a doublet of doublets, with J=4.2 and 1.2 Hz, in the ^{1}H-nmr spectrum, corresponding to the equatorial C-2 methine proton.[11] The axial disposition of the cyano group fits[12] with the negative upfield γ-effect shift of C-6 (δ 50.6) as compared with 4-(3-methoxybenzyl)-1-methylpiperidine (δ 55.9).[4]

As expected, treatment of 3 with refluxing acetic acid afforded a mixture of 7,8-benzomorphans 5a and 5b, which were separated by column chromatography and identified by comparison with samples previously obtained by oxidative cyclization of 4-(3-methoxybenzyl)-1-methylpiperidine.[4]

Although the yield of the cyclization step is only moderate, it is slightly higher than that obtained by the mercuric acetate method. On the other hand, the higher yields of similar cyclizations from 2-cyano-4-(indolylmethyl)piperidines[6,13] simply reflect the greater reactivity of the indole ring.

EXPERIMENTAL

Ir spectra were registered with a Perkin-Elmer 1430 spectrophotometer. ^{1}H-Nmr spectra were measured on a Perkin-Elmer R-24B (60 MHz) instrument or, when indicated, on a Varian XL-200 spectrometer (200 MHz). ^{13}C-Nmr spectra were recorded with a Varian XL-200 spectrometer (50.3 MHz). All nmr spectra were measured in $CDCl_3$ and chemical shift values are expressed in ppm (δ) relative to internal Me_4Si. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate. Tlc and column chromatography were carried out on SiO_2 (silica gel 60, Merck 63-200 μm), and the tlc spots were located with uv light or iodoplatinate reagent. Microanalyses were performed on a Carlo Erba 1106 analyzer by Institut de Química Bioorgànica, Barcelona.

4-(3-Methoxybenzyl)-1-methyl-1,2,3,6-tetrahydropyridine-2-carbonitrile (4)

6N Hydrochloric acid (3.4 ml) was added dropwise to a stirred solution of sodium cyanide (2.45 g, 50 mmol) in water (36 ml) layered with ether (65 ml), keeping the temperature below 15 °C. Pyridinium iodide 1[9] (4 g, 11.7 mmol) and sodium borohydride (0.51 g, 13.6 mmol) were added portionwise to the resulting two-phase solution. The mixture was stirred at room temperature for 4 h, the organic phase was decanted, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with aqueous 5% hydrochloric acid, dried, and evaporated to give 0.35 g of 4-(3-methoxybenzyl)-1-methyl-1,2,3,6-tetrahydropyridine-borane: ir (NaCl) 2380-2280 (borane); ^{1}H-nmr 1.7-2.2 (m, 2H, 3-H), 2.43 (s, 3H, NCH_3), 2.80 (t, J=6 Hz, 2H, 2-H), 3.0-3.5 (m, 2H, 6-H), 3.20 (br s, 2H, Ar-CH_2), 3.66 (s, 3H, OCH_3), 5.23 (br s, 1H, 5-H), 6.5-7.3 (m, 4H, Ar-H). This complex (0.27 g, 1.17 mmol) was

refluxed in ethanol (60 ml) for 24 h. The residue after evaporation was dissolved in water and extracted with ether to afford 4-(3-methoxybenzyl)-1-methyl-1,2,3,6-tetrahydropyridine[9] (230 mg, 90%): ir (NaCl) 1600 and 1585 (C=C); ^{1}H-nmr 2.23 (s, 3H, NCH_3), 2.83 (br s, 2H, 6-H), 3.15 (s, 2H, $ArCH_2$), 3.66 (s, 3H, OCH_3), 5.23 (br s, 1H, =CH), 6.4-6.7 (m, 3H, Ar-H), 7.0-7.2 (m, 1H, Ar-H). The picrate melted at 95-96 °C (ethanol). Anal. Calcd. for $C_{20}H_{22}N_4O_8$: C, 53.81; H, 4.97; N, 12.55. Found: C, 53.89; H, 4.96; N, 12.29; ^{1}H-nmr 2.9 (s, 3H, N^+CH_3), 3.25 (s, 2H, Ar-CH_2), 3.65 (s, 3H, OCH_3), 5.35 (br s, 1H, =CH), 6.4-6.7 (m, 3H, Ar-H), 6.9-7.1 (m, 1H, Ar-H). The aqueous acidic extracts were basified with sodium carbonate and extracted with ether to give the unstable cyanotetrahydropyridine 2[9] (2.63 g, 90%): ir (NaCl) 2210 (CN), 1610 (C=C); ^{1}H-nmr (200 MHz) 2.10 (br d, J=16 Hz, 1H, 3-H), 2.39 (s, 3H, NCH_3), 2.52 (br d, J=16 Hz, 1H, 3-H), 2.91 (br d, J=16 Hz, 1H, 6-H), 3.24 (br d, J=16 Hz, 1H, 6-H), 3.29 (s, 2H, Ar-CH_2), 3.75 (dd, J=5, 1.6 Hz, 1H, 2-H), 3.77 (s, 3H, OCH_3), 5.51 (m, 1H, 5-H), 6.7-6.9 (m, 2H, Ar-H), 7.1-7.2 (m, 2H, Ar-H); ^{13}C-nmr 32.0 (C-3), 43.0 (Ar-CH_2), 43.3 (NCH_3), 50.3 (C-6), 51.8 (C-2), 55.1 (OCH_3), 112.0 (C-4′), 114.3 (C-2′), 116.5 (CN), 121.1 (C-5), 121.3 (C-6′), 129.4 (C-5′), 131.6 (C-4), 140.0 (C-1′), 159.8 (C-3′).

4-(3-Methoxybenzyl)-1-methylpiperidine-2-carbonitrile (3)

A solution of 2-cyanotetrahydropyridine 2 (2.18 g, 9 mmol) in methanol (70 ml) was hydrogenated at room temperature under atmospheric pressure over 654 mg of 10% palladium on charcoal (Merck). When one equivalent of hydrogen was absorbed, the catalyst was filtered off and the filtrate was evaporated to give 3 (2.01 g, 85%). A pure sample was obtained by preparative tlc on elution with 85:15 acetone-ether; ir (NaCl) 2210 (CN); ^{1}H-nmr (200 MHz) 1.27 (qd, J=12.6, 4.2 Hz, 1H, 5-Ha), 1.54 (td, J=14, 4.2 Hz, 1H, 3-Ha), 1.66 (br d, J=12.6 Hz, 1H, 5-He), 1.92 (dt, J=12.6, 2.8 Hz, 1H, 3-He), 2.32 (td, J=12.6, 2.8 Hz, 1H, 6-Ha), 2.36 (s, 3H, NCH_3), 2.42 and 2.53 (2d, J=7.6 and 4.2 Hz, 1H each, Ar-CH_2), 2.71 (br d, J=12.6 Hz, 1H, 6-He), 3.80 (s, 3H, OCH_3), 3.83 (dd, J=4.2, 1.2 Hz, 1H, 2-He), 6.7-7.3 (m, 4H, Ar-H); ^{13}C-nmr 31.3 (C-3), 33.1 (C-4), 34.6 (C-5), 42.6 (Ar-CH_2), 43.9 (NCH_3), 50.6 (C-6), 54.7 (C-2), 55.1 (OCH_3), 111.4 (C-4′), 114.9 (C-2′), 116.3 (CN), 121.5 (C-6′), 129.3 (C-5′), 140.9 (C-1′), 159.7 (C-3′). Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.78; H, 8.19; N, 11.47. Found: C, 73.67; H, 8.35; N, 11.04.

8-Methoxy-2-methyl-1,5-methano-1,2,3,4,5,6-hexahydro-2-benzazocine (5a) and 10-Methoxy-2-methyl-1,5-methano-1,2,3,4,5,6-hexahydro-2-benzazocine (5b)

A solution of 2-cyanopiperidine 3 (1.67 g, 6.8 mmol) in aqueous 80% acetic acid (135 ml) was refluxed for 48 h under nitrogen atmosphere. The resulting solution was cooled, basified with concentrated ammonium hydroxide (pH 8-9), and extracted with chloroform. The extracts were dried and evaporated to leave an oil which was purified by column chromatography. On elution with chloroform-methanol (99:1), benzazocine 5b[4] (230 mg, 15%) was obtained; ^{1}H-nmr (200 MHz)[4] 2.15 (s, 3H, NCH_3), 2.67 (d, J=18 Hz, 1H, 6-H), 3.02 (dd, J=18, 6.6 Hz, 1H, 6-H), 3.77 (s, 3H, OCH_3), 4.32 (t, J=3 Hz, 1H, 1-He), 6.70 (d, J=8 Hz, 1H, Ar-H), 6.75 (d, J=8 Hz, 1H, Ar-H), 7.16 (d, J=8 Hz, 1H, Ar-H). On elution with chloroform-methanol (95:5) benzazocine 5a[4] (160 mg, 11%) was obtained; ^{1}H-nmr (200 MHz)[4] 2.15 (s, 3H, NCH_3), 2.43 (dd, J=12.6, 3

Hz, 1H, 3-He), 2.65 (d, J=18 Hz, 1H, 6-H), 3.05 (dd, J=18, 6.6 Hz, 1H, 6-H), 3.63 (t, J=3 Hz, 1H, 1-He), 3.79 (s, 3H, OCH_3), 6.6-6.9 (m, 2H, Ar-H), 7.10 (t, J=8 Hz, 1H, Ar-H).

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