# SYNTHESIS OF (1,6aβ,10aβ)-DECAHYDRO-5-METHYL-1-PHENYL-1H-2,5-BENZOXACINE

John H. Musser[1*], Philip F. VonVoightlander, and Jacob Szmuszkovicz

CNS Research, The Upjohn Company
Kalamazoo, Michigan 49001, U.S.A.

Abstract- The synthesis of epimeric (1,6aβ,10aβ)-decahydro-5-methyl-1-phenyl-1H-2,5-benzoxazines is described.

Tetrahydro-5-methyl-1-phenyl-1H-2,5-benzoxazine (nefopam) is reported to be an analgesic agent.[2] Nefopam is of interest because its analgesic effects are not reversed by the opioid antagonist naloxone.[3] We wanted to determine whether compounds related to nefopam but with the fused benzene ring replaced by cyclohexane would retain analgesic activity.

**Results and Discussion**

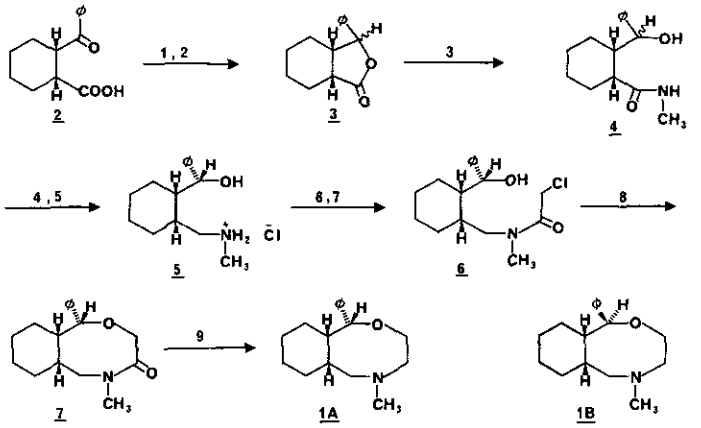
Epimeric (1,6aβ,10aβ)-decahydro-5-methyl-1-phenyl-1H-2,5-benzoxazines 1A and 1B were synthesized by the route shown in the Scheme. The synthesis of ketoacid 2 is based on a procedure by Fieser et al.[4] and the stereochemistry was established as cis.[5] Reduction of 2 with sodium borohydride gave lactones 3A and 3B in a 2:1 ratio. The ratio was determined by integration of the relative intensities of the benzyl methines in the PMR spectrum. From Dreiding models it is clear that lactone 3A would predominate upon reduction for steric reasons. Based on preparative considerations, we decided to carry the diastereomeric mixture along the synthesis until the carbinolamine 5 stage. At this point, we were able to preferentially crystallize the predominant epimer (5A) from the mixture as the HCl salt. The minor epimer 5B remains in the mother liquor and was obtained as an amorphous solid upon removal of solvent.

In generating chloroacetamidocarbinol 6A, excess chloroacetyl chloride was used followed by ester hydrolysis with base. Use of 1 eq of acid chloride gives a mixture of 6A, chloroacetyl ester, the diacetylated adduct and starting material. Note, however, that the hydrolysis must be done at 0°C since higher temperatures bring about displacement of chlorine by methoxide giving a methoxyacetamidocarbinol instead of the desired product 6A.

Although cyclization of chloroacetamidocarbinol 6A to give 7A can be effected with dimsylanion in dimethylsulfoxide, experimentally it was more advantageous, both in yield and ease of procedure, to use sodium hydride in tetrahydrofuran (THF). This latter method is interesting in that cyclization is retarded under complete anhydrous conditions, whereas, the reaction goes to completion at reflux

upon addition of a catalytic amount of water. Reduction of 7A with lithium aluminum hydride (LAH) in THF at reflux gave the target compound 1A. Compound 1B was prepared by the same sequence of steps as for 1A.

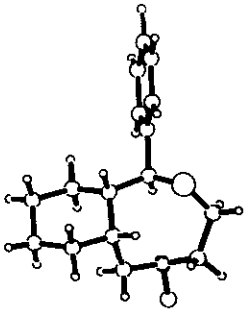
**Scheme**




Reaction conditons: 1) $NaBH_4$/EtOH; 2) HCl/Ether; 3) 40% $CH_3NH_2$/THF; 4) LAH/THF; 5) HCl/Ether, fractional crystallization; 6. Chloroacetyl chloride, Pyridine/THF; 7) NaOH/MeOH, 0°C; 8)NaH/THF, catalytic amount $H_2O$; 9) LAH/THF.

Support for the assignment of all cis relative configuration to 1A is found in the PMR spectrum. The benzylmethine appears as a singlet and an analogous system[6] also has a singlet for the all cis stereochemistry. In contrast the benzylmethine of epimer 1B appears as doublet (J=10Hz). However, it is not possible using Dreiding models to predict the dihedral angle between the benzylmethine and the adjacent cyclohexylmethine for 1B because of the flexibility of the eight membered ring. Therefore, an X-ray analysis was employed to provide an unambiguous stereochemistry for 1B. The investigation demonstrated that the relative configuration assumed for 1B is correct.[7] The Figure contains a ball and stick three dimensional representation for 1B.

**Figure**



Analgesic testing of both 1A and 1B was carried out in rats by the warm plate test.[8] Although 1B is inactive, 1A is about as potent ($ED_{50}$ 9 mg/kg) as nefopam ($ED_{50}$ 7 mg/kg).

**EXPERIMENTAL**

Lactones 3. To an ice cold solution of sodium borohydride (7.6 g, 0.2 mol) in 95% ethanol (1 L) was added a solution of ketoacid 2.[4] After stirring 2 h at room temperature, 10% aq HCl and ether were added. The resulting biphase solution was gently refluxed overnight to effect lactonization. The ethereal phase was separated, washed with brine, dried ($Na_2SO_4$) and concentrated to give 20.4 g (94% yield) of epimeric lactones 3 as an oil. IR (neat): 1780 (C=O); 1175, 1130 (C-O-C); and 690-770 $cm^{-1}$ (Ar C-H). PMR ($CDCl_3$): 7.30 (s, 5H); benzylmethines (1H) in a 2:1 ratio, 5.47 (d, J=5Hz) and 5.18 (d, J=3Hz); and 3.0 to 1.0 ppm (m, 10H).

Carbinolamides 4. A mixture of lactones 3 (19.1 g, 88.4 mmol), 40% aq methylamine and THF was stirred at room temperature overnight. Chloroform was added and the organic phase was washed with 10% aq HCl, saturated aq $NaHCO_3$, dried ($Na_2SO_4$) and concentrated to give 21.6 g (99% yield) of epimeric carbinolamides 4. IR (neat): 3350, 3400 (N-H, O-H); 1650 (C=O); and 690-770 $cm_{-1}$ (Ar C-H). PMR ($CDCl_3$): 7.27 (s, 5H); benzylmethines (1H) in a 2:1 ratio, 4.67 (d, J=2Hz) and 4.48 (d, J=8Hz); aminemethyls (3H) in a 2:1 ratio, 2.68 (s) and 2.61 (s); and 2.5 to 1.0 ppm (m, 10H).

Carbinolamines 5A and 5B. To a slurry of LAH (5.7 g, 150 mmol) in THF (200ml) was added a solution of carbinolamides 4 (18.5 g, 74.9 mmol) in THF (200 ml). The reaction was refluxed for 3 h, then cooled. The excess LAH was decomposed in succession with water (5.7 ml), 15% aq NaOH (5.7 ml) and water (17.1 ml). After stirring for 30 min the resulting suspension was filtered through a pad of $MgSO_4$ and concentrated to give 16.6 g (95% yield) of epimeric carbinolamines 5 as an oil. Ethereal HCl (excess) was added to the oil dissolved in ether. The resulting precipitate was filtered, washed with ether and dissolved in a methanol-ether solution. Carbinolamine HCl 5A (6.3 g, 33% yield) was the major epimer, mp 218-221°C. IR (KBr): 3380 (O-H); 2800, 2750, 2460, 2410 ($^+NH_2$); 1605, 1494, 1480 ($^+NH_2$, C=C); 1075, 1060, 1000, 975 (C-O, C-N); and 755, 750, 700 $cm^{-1}$ (Ar C-H). PMR ($D_2O$): 7.50 (m, 5H); 4.68 (d, 1H, J=8Hz); 3.20 (m, 2H); 2.65 (s, 3H); and 2.2 to 1.0 ppm (m, 10H). MS m/e (rel. intensity): 233 ($P^+$, 21) and 44 (100). Anal. calcd. for $C_{15}H_{23}NO \cdot HCl$: C, 66.79; H, 8.91; N, 5.19; Cl, 13.17. Found: C, 66.98; H, 9.09; N, 5.17; Cl, 13.24.

Carbinolamine·HCl 5B was separated from the epimeric solution by exhaustive recrystallization. After concentrating the mother liquor, 5B was obtained as an amorphous solid, mp 170-178°C. IR (KBr): 3400 (O-H); 2800, 2480, 2420 ($^+NH_2$); 1605, 1495 ($^+NH_2$, C=C); 1025 (C-O); and 755, 700 $cm^{-1}$ (Ar C-H). PMR ($D_2O$): 7.55 (s, 5H); 4.57 (d, 1H, J=12Hz); 3.34 (d, 2H, J=6Hz); 2.85 (s, 3H); and 2.2 to 1.0 ppm (m, 10H). MS m/e (rel intensity): 233 ($P^+$, 9) and 44 (100).

Chloroacetamidocarbinol 6A. To a cold suspension of 5A (6.06 g, 22.5 mmol), pyridine (12 ml) and

THF (200 ml) was added chloroacetyl chloride (3.76 ml, 47.25 mmol) in THF (50 ml). The reaction was stirred for 6 h at room temperature and the solvent was removed in vacuo giving a dark oil. The oil was carefully dissolved in ice cold methanolic NaOH (3.5 g in 100 ml) and stirred at 0°C for 2 h. Most of the methanol was then removed in vacuo at 0°C. Methylene chloride and ice were added and the organic phase was washed with brine, dried ($MgSO_4$) and concentrated to an oil. The oil was purified by HPLC using gradient elution starting with a 1:1 mixture of ethyl acetate/cyclohexane and increasing the ethyl acetate content of the eluent. The desired product eluted first to give 4.2 g (60% yield) of oil. IR (neat): 3450, 2550 (O-H); 1650 (C=O); and 690-770 $cm^{-1}$ (Ar C-H, C-Cl). PMR ($CDCl_3$): 7.3 (s, 5H); 4.34 (d, 1H, J=8Hz); 3.86 (s, 2H); 2.7 to 4.2 (m, 2H); and 2.1 to 1.0 ppm (m, 10H).

Bicycloamide 7A. To a degreased suspension of sodium hydride (3.9 g 50% dispersion in oil, 81 mmol) in THF (400 ml) was added chloroacetamidocarbinol 6A (12.1 g, 39.1 mmol) in THF (100 ml). The reaction mixture was brought to reflux and a catalytic amount of water (2 drops) was added. After stirring overnight at reflux the mixture was cooled and the excess sodium hydride was decomposed with saturated aq ammonium chloride. Chloroform was added and the organic phase was washed with 10% aq HCl, 15% aq NaOH, brine, dried ($MgSO_4$) and concentrated to give a yellow oil. The oil was crystallized from a 40:60 mixture of ethyl acetate/cyclohexane to give 5.9 g (55% yield) of 7A, mp 130-133°C. IR (KBr): 1635 (C=O); 1595, 1585, 1495 (C=C); 1130 (C-O-C); 1400, 1350, 1230 (C-N); and 745, 710 $cm^{-1}$ (Ar C-H). PMR ($CDCl_3$): 7.34 (s, 5H); 4.56 (s, 1H); 5.00 (q, 1H, J=7Hz); 2.75 (d, 1H, J=0.5Hz); 2.18 (m, 1H); 4.39 (q, 2H, J=9Hz); 3.08 (s, 3H); and 2.0 to 1.0 ppm (m, 9H). CMR ($CDCl_3$) (off resonance): 170.06 (s, C=O); 141.35 (s, Ar); 128.04, 126.93, 125.66 (d, Ar); 83.83 (d, benzyl); 71.26 (t, $OCH_2$); 51.83 (t, $NCH_2$); 36.40 (q, $NCH_3$); 44.30, 40.13 (d, angular); and 34.47, 25.76, 22.08, 19.71 ppm (t, ring). MS m/e (rel. intensity): 273 ($P^+$, 31) and 168 (100). Anal. calcd. for $C_{17}H_{23}NO_2$: C, 74.73: H, 8.42; N, 5.13. Found: C, 74.82; H, 8.60; N, 5.26.

Bicycloamine 1A. To a slurry of LAH (1.52 g, 40.0 mmol) in THF (200 ml) was added a solution of 7A (2.73 g, 10.0 mmol) in THF (100 ml). The mixture was refluxed for 3 h, then cooled. The excess LAH was decomposed in succession with water (1.5 ml), 15% aq NaOH (1.5 ml) and water (4.5 ml). After stirring for 20 min , the resulting suspension was filtered through $MgSO_4$ to give an oil. The oil was purified by first making the hexamic acid salt, crystallizing the salt (mp 165-168°C) from methanol/diisopropyl ether and neutralizing the salt with 15% aq NaOH. The resulting free amine crystallized on standing to give 2.07 g (80% yield) of 1A. IR (KBr): 2770 (N-C-H); 1600, 1490 (C=C); 1110 (C-O-C); 1070 (C-N-C); and 745, 705 $cm^{-1}$ (Ar C-H). PMR ($CDCl_3$): 7.28 (s, 5H); 4.85 (s, 1H); 3.52 (m, 2H); 2.34 (m, 1H); 4.16 (m, 2H); 2.42 (s, 3H); and 1.8 to 0.9 ppm (m, 10H). CMR ($CDCl_3$) (off resonance): 143.87 (s, Ar); 127.81, 126.28, 125.74, (d, Ar); 84.51 (d, benzyl); 70.87 (t, $OCH_2$); 59.53, 56.30 (t, $NCH_2$); 45.90 q, $NCH_3$); 46.69, 38.16 (d, angular); and 35.49, 26.57,

21.84, 19.81 ppm (t, cyclohexyl). MS m/e (rel. intensity): 259 ($P^+$, 13) and 44 (100). Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.76; H, 9.65; N, 5.41. Found: C, 78.85; H, 9.69; N, 5.35.

The experimental for the synthesis of bicycloamide 7B and bicycloamine 1B from carbinolamine HCl 5B is identical to the corresponding epimers 7A and 1A. Therefore, only the crystallization procedure and analytical data are recorded for 7B and 1B.

Bicycloamide 7B. The oil derived from cyclization of chloroacetamidocarbinol 6B was crystallized from ether, mp 109-111°C. IR (KBr) 1630 (C=O); 1490 (C=C); 1100, 1085 (C-O-C); and 760, 705 $cm^{-1}$ (Ar C-H). PMR ($CDCl_3$): 7.36 (s, 5H); 5.10 (d, 1H, J=12Hz); 4.01 (s, 2H); 3.03 (s, 3H); 2.60 to 1.95 (m, 2H) and 1.95 to 1.20 ppm (m, 10H). CMR ($CDCl_3$): 172.0 (C=O); 129.8 (Ar); 80.3 (benzyl); 65.1 ($OCH_2$); 53.8, 39.4 (angular); 37.6 ($NCH_2$); 33.0 ($NCH_3$); 28.7, 25.9, 24.8, 20.4 ppm (cyclohexyl). MS m/e (rel. intensity): 273 ($P^+$, 59) and 57 (100). Anal. calcd. for $C_{17}H_{23}NO_2$: C, 74.73; H, 8.42; N, 5.13. Found: C, 74.32; H, 8.84; N, 5.15.

Bicycloamine 1B. The oil obtained from the reduction of 7B was dissolved in a mixture of methanol and ether. After cooling overnight, 1B was obtained as a cystalline solid, mp 140-141°C. IR (KBr): 2780 (N-C-H); 1600, 1580, 1490 (C=C); 1110 (C-O); 1060 (C-N); and 760, 710, 700 $cm^{-1}$ (Ar C-H). PMR ($CDCl_3$): 7.25 (s, 5H); 4.92 (d, 1H, J=10Hz); 3.63 (m, 2H); 3.09 (q, 2H, J=12Hz); 2.47 (s, 3H); 2.34, 2.85, 1.83 (m, 3H); and 1.7 to 1.0 ppm (m, 9H). CMR ($CDCl_3$): 128.12, 127.28 (Ar); 84.85 (benzyl); 70.85 ($CH_2O$); 59.87, 57.31 ($CH_2N$); 47.35 ($NCH_3$); 47.65, 32.48 (angular); 31.01, 26.26, 23.40, 21.61 ppm (cyclohexyl). MS m/e (Rel. intensity): 259 ($P^+$, 3) and 111 (100). Anal. calcd. for $C_{17}H_{25}NO$: C, 78.76; H, 9.65; N, 5.41. Found: C, 78.67; H, 9.87; N, 5.17.

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