THE SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF 2,3 "SECO" FENTANYL

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Abstract: A structurally novel, 2,3 "seco" analogue of fentanyl has been synthesized by a short and efficient procedure. Central-analgesic activity was found to be ca. 30 times lower than fentanyl but still several times higher than morphine.

Keywords: Fentanyl, open-chained analogues, central analgesics

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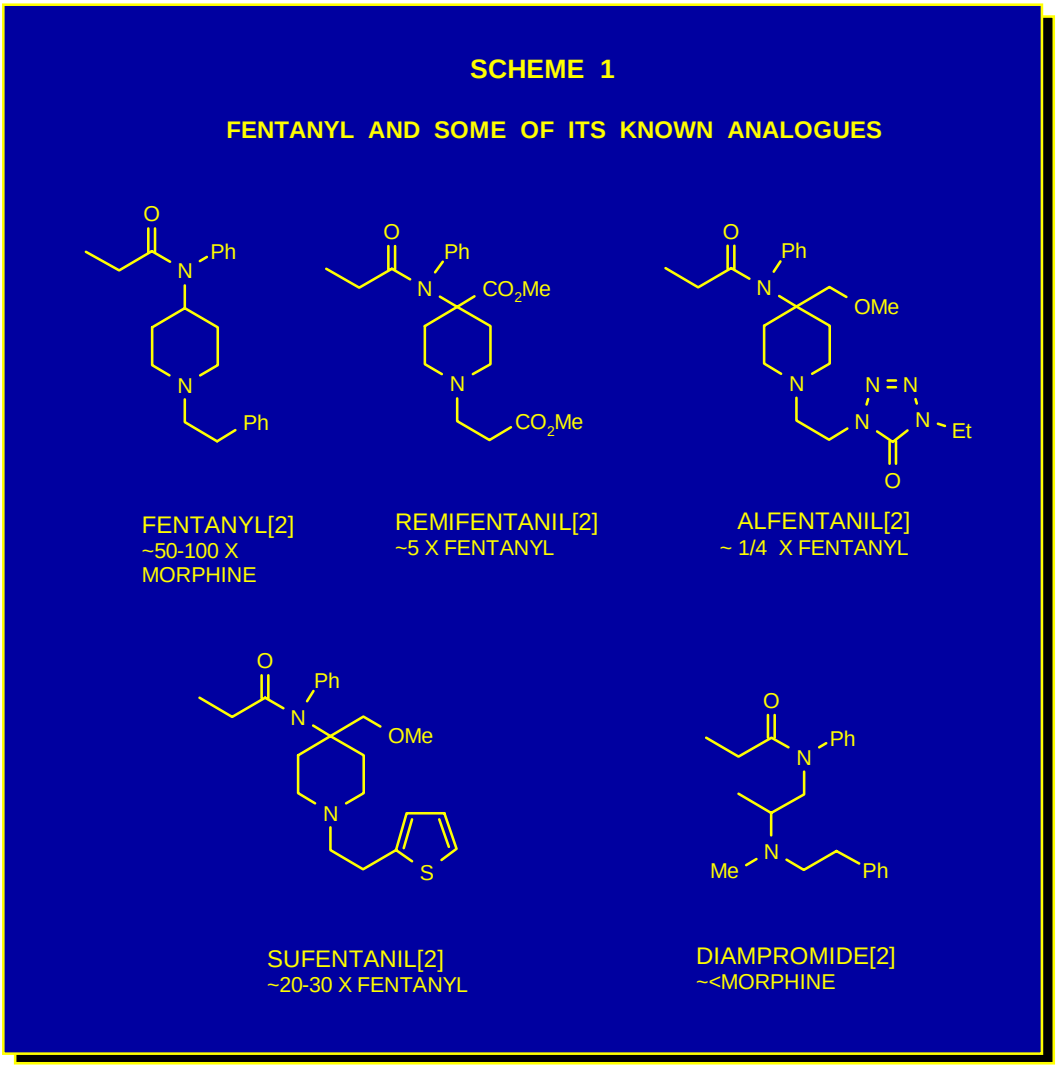
I Introduction
II Results and Discussion
III References

I Introduction

Fentanyl [1,2] is a highly potent (50-100 X morphine) and clinically widely used narcotic analgesic, Scheme 1. Although a large number of its analogues has been prepared so far[1,3], including acyclic compounds like diampromide[2], to our knowledge an exact open-chained analogues has not been synthesized yet. A significance of this compound is to probe the steric requirements of μ opioid receptors and to provide better insight into the structure-activity relationship (SAR) for fentanyl analogues.



II Results and Discussion

Herein we report the synthesis of 2,3 “seco” fentanyl, *4*, as outlined in Scheme 2. Methy-phenethyl amine was condensed [4-7] with methyl acetoacetate at ~170^{o} to yield keto-amide *1*. This intermediate was reductively aminated [8] with aniline using Zn dust in acetic acid, to afford anilino-amide *2*. Reductive deoxygenation of the amide function [9] with diborane generated *in situ* ($NaBH_4$, $BF_3{\cdot}Et_2O$) cleanly furnished diamine *3*. The synthesis was completed by acylation of the secondary amine function with propionyl chloride, followed by the precipitation of monooxalate salt.

Pharmacological testing of *4*, as monooxalate salt, (rat tail withdrawal test) shown that the central analgesic activity was ca. 30 times lower then fentanyl, but 5-10 times higher then morphine. Effective dose (ED_{50}) was found to be 0.35mg/Kg (confidence limits 0.22 - 0.57), compared to 0.011 mg/Kg for fentanyl citrate and 3.15 mg/Kg for morphine sulphate[10]. This finding strongly suggests the influence of the steric factor upon the central-analgesic activity and in particular, the importance of the piperidine ring as a key pharmacophore. Nevertheless, the open chained analogue (which has the structure of 1,3 diamines) can still coordinate effectively with μ receptors, causing a high level of analgesia.

Selected spectroscopic data are presented in the Table.

A more general method for the synthesis of 2,3 “seco” analogues of fentanyl is currently being investigated and will be published in a due course.

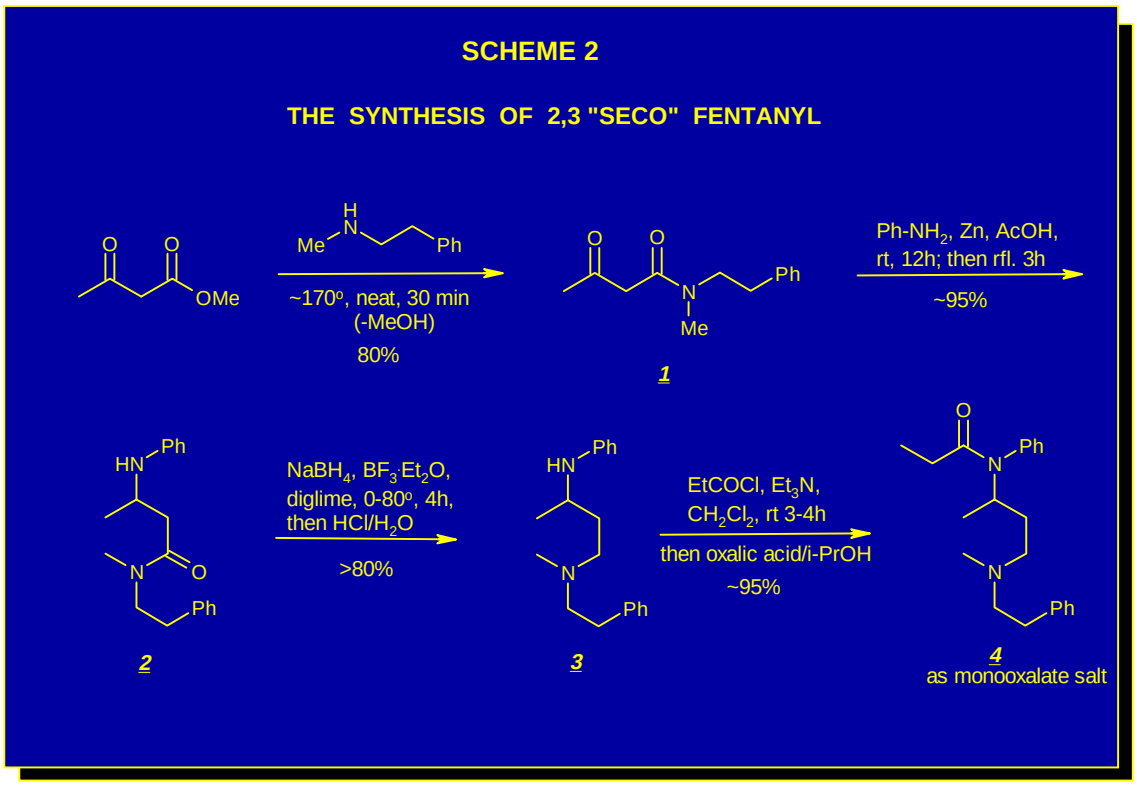
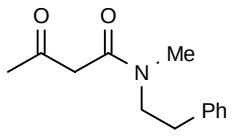
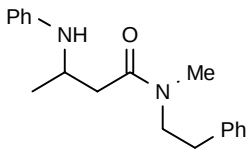
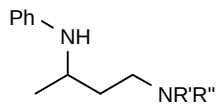
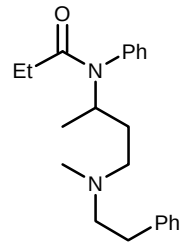


Table. Selected spectroscopic data for the synthesized compounds.

No	COMPOUND	IR	^{1}H NMR	^{13}C NMR	MS
1	 **1**	3028; 2934; 1722; 1642; 1593; 1496; 1454; 1434; 1403; 1383; 1360; 1309; 1238; 1212; 1157; 1032; 751; 703	[the mixture of rotatory isomers]	[the mixture of rotatory isomers] 21.89, 30.03, 33.34, 33.47, 34.43, 36.49, 49.22, 49.76, 50.27, 52.09, 126.34, 126.85, 128.14, 128.45, 128.76, 137.90, 138.74, 166.43, 166.65, 202.44, 202.70	220 (M+1, 100)
2	 **2**	3342; 3086; 3051; 3026; 2926; 1632; 1602; 1498; 1454; 1434; 1404; 1364; 1319; 1259; 1180; 1155; 1123; 1095; 1075; 1030; 750; 698	[the mixture of rotatory isomers] 1.13 (d, J= 5.8, CH_3), 1.26 (d, 6.0, CH_3), 2.05- 2.16 (m), 2.30- 2.41 (m), 2.59 (dd, J_1= 4.2, J_2= 15.8), 2.75- 2.86 (m), 2.81 (s, CH_3), 2.93 (s, CH_3), 3.46 (t, 7.4), 3.58 (td, J_d= 2, J_t= 7.2), 3.82- 4.12 (m), 6.55- 6.72 (m, 3H_{Ar}), 7.05- 7.37 (m, 7H_{Ar})	[smesa rotacionih izomera] 20.63, 20.72, 33.25, 33.56, 34.61, 36.09, 38.18, 38.97, 45.87, 49.02, 51.36, 113.39, 117.18, 126.23, 126.70, 128.40, 128.71, 129.22, 138.01, 138.97, 147.00, 170.93, 171.13	297 (M+1, 100) 311 (M+14, 10) 353 (M+57, 5)
3	 **3**	3393, 3295, 3085, 3052, 3026, 2961, 2930, 2843, 1602, 1505, 1454, 1431, 1374, 1319, 1265, 1181, 1155, 1075, 1058, 1031, 994, 748, 696	1.15 (d, J= 6.4, CH_3), 1.63 (q, J= 6.4, CH_2), 2.27 (s, N-CH_3), 2.48 (t, J= 6.8, CH_2), 2.53- 2.62 (m, 1H), 2.70- 2.80 (m, 3H), 3.49 (pr. s., 1H), 4.03 (pr. s., 1H), 6.53 (d, J= 7.6, 2 ***o***-H_{Ar}), 6.63 (t, J= 7.2, 1 ***p***-H_{Ar})	20.67, 33.74, 34.03, 42.01, 47.43, 54.66, 58.58, 112.94, 116.54, 125.85, 128.25, 128.58, 129.11, 140.30, 147.71	191 (M-91, 25) 283 (M+1, 100)
4	 **4**	3062, 3027, 2953, 2941, 2863, 2799, 1657, 1595, 1496, 1454, 1395, 1377, 1253, 1131, 1092, 1077, 1060, 1032, 769, 748, , 702	1.02 (t, J= 7.4, CH_3), ~1.02 (CH_3), 1.38- 1.52 (m, 1H), 1.63- 1.82 (m, 1H), 1.93 (q, J= 7.6, CH_2), 2.29 (s, N-CH_3), 2.42- 2.65 (m, 4H), 2.72- 2.82 (m, 2H), 4.92 (quint, J= 7.0, CH), 7.07- 7.44 (m, 10H_{Ar})	9.29 (CH_3); 18.90 (CH_3); 28.12(CH_2); 32.42(CH_2); 33.34(CH_2); 41.73(CH_3); 48.38(CH); 54.41(CH_2); 59.31(CH_2); [125.47; 127.74; 127.87; 128.00; 128.24; 128.84; CH_{Ar}]; 138.58(C_{Ar}); 140.00 (C_{Ar}); 173.04(C=O)	339 (M+1, 100)

MS spectra were recorded with Finigan-Math instrument, model 8230, using chemical ionization (i-butane); ^{1}NMR and ^{13}C NMR spectra were recorded with Varian-Gemini instrument, at 200 and 50 MHz respectively, with TMS as internal standard and $CDCl_3$ as solvent. IR spectra were obtained with Perkin-Elmer FT IR 1725X (film). All the samples were homogeneous acc. to cap. GC (column DB-5).

REFERENCES

[1] I. V. Mićović, M. D. Ivanović, S. Vučković, D. Jovanović-Mićić, D. Beleslin, Lj. Došen-Mićović and V. D. Kiricojević; ***J. Serb. Chem. Soc.*** **1998** ***63*** (2) 93-112 and the references cited therein

[2] ***THE MERCK INDEX***, 12. Ed. MERCK & CO., Inc., N.Y., 1996

[3] a. A. F. Casy, R. T. Parfitt "***Opioid Analgesics***", Plenum Press, N.Y., USA, **1986**
b. A. F. Casy "***Opioid Receptors and Their Ligands***", pp.178-272 in ***Advances in Drug Research***, Ed. B. Testa, Vol 18, Academic Pres, London, **1989**

[4] J. Cossy, A. Thellend; ***Synthesis***; **1989**, 753 and the references cited therein

[5] M. Labelle, D. J. Gravel; ***J. Chem Soc. Chem. Comm***. **1985**, 105

[6] G. E. Utzinger; ***Hel. Chim. Acta*** **1952**, ***35***, 1359

[7] C. J. Kibler, A. Weissberger; ***Org. Synth., Coll. Vol. III,*** 108

[8] I. V. Mićović, M. D. Ivanović, D. M. Piatak, V. Đ. Bojić; ***Synthesis*** **1991**, 1043 see also: I. V. Mićović, M. D. Ivanović, G. M. Roglić, V. D. Kiricojević i J. B. Popović; ***J. Chem. Soc., Perkin Trans. 1***; **1996** 265

[9] a. H. C. Brown, P. Heim; ***J. Org. Chem***. **1973,** ***38***, 912

b. A. Pelter, K. Smith, H. C. Brown, ***Borane reagents***, Academic Press, **1988**, London

[10] All the ED_{50} values are calculated to free base.