SYNTHESIS AND REACTIVITY OF SOME MANNICH BASES. VII. SYNTHESIS OF 3-(2-DIALKYLAMINOETHYL)-1,2-BENZISOXAZOLES

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Abstract -3-(2-Dialkylaminoethyl)-1,2-benzisoxazoles (**2**) are accessible by direct cyclization of the corresponding Mannich bases oxime acetates (**11**) in refluxing benzene in the presence of anhydrous potassium carbonate. The previously known methods for ring closure to 1,2-benzisoxazole were ineffective for this class of pharmacologically relevant compounds.

INTRODUCTION

The synthesis of 1,2-benzisoxazoles substituted in the 3 position with various pharmacophores is an area of intensive research driven by potential applications in the pharmaceutical field. Thus, the biological activity of these derivatives has been recently investigated as inhibitors of LTB_4 binding to human neutrophiles,[1] affinity ligands for serotonergic and dopaminergic receptors,[2] potential atypical antipsychotic activity[3] and selective inhibitors of acetylcholinesterase.[4] In the latter case it is hoped that memory impairment in patients with Alzheimer disease can be attenuated if the cholinergic neurotransmission is enhanced by blocking the enzyme responsible for the metabolic breakdown of acetylcholine. Based on the X-Ray structure of the acetylcholinesterase from *Torpedo californica*,[5] a model binding mode of 1,2-benzisoxazoles inhibitors in the active site of the enzyme has been proposed. The essential interactions are illustrated in Figure 1 for the lead compound (**1**), reported by scientists at Pfizer Inc.[4] The hydrogen bonds between the protonated piperidine and the negatively charged

carboxylate side chain on Asp-72 as well as the backbone NH of Phe-288 and the benzisoxazole are the major contributors to the strong binding of this inhibitor. Other nonspecific hydrophobic interactions within the hydrophobic pocket of the enzyme seem to provide further stabilization of the complex. An equally promising structure for this class[6] would be the 3-(2-dialkylaminoethyl)-1,2-benzisoxazole (**2**) whereby the crucial hydrogen bonding to Asp-72 is found equally favorable as in compound (**1**). All the other elements perceived essential to the binding are preserved, including the two carbon optimal spacer between the heterocycle and the pharmacophore.

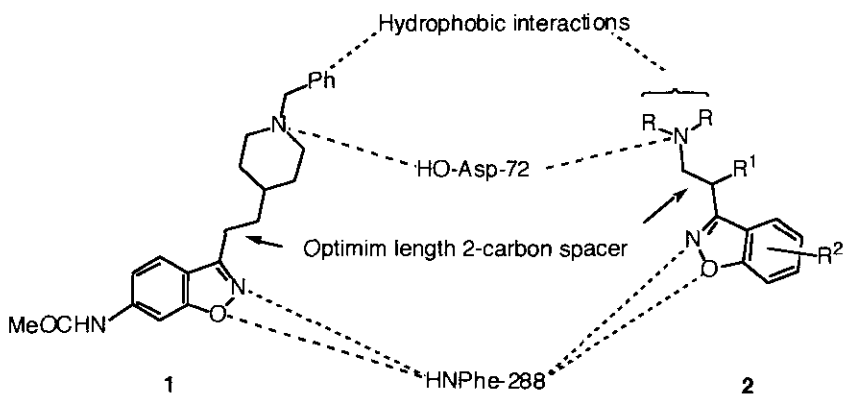


Figure 1. Possible binding model for benzisoxazoles (**2**).

The retrosynthesis of the target compound suggested a few reasonable precursors as shown in Figure 2. Disconnection **a** has been previously investigated[7] while disconnections **b** and **c** present stability problems reported for carbanions (**5**),[8] (**8**),[9] and (**9**).[10] Due to our continuos interest in the synthesis and pharmacological properties of new Mannich bases[11] we chose the use of the retron (**11**) for the generation of 3-(β-dialkylaminoethyl)-1,2-benzisoxazoles. The present paper reports our preliminary results on the successful synthesis of various compounds of type (**2**), bearing a 2-dialkylaminoethyl substituent in the 3 position of the 1,2-benzisoxazole *via* this route.

RESULTS AND DISCUSSION

The synthesis of the starting oximes (**12**) (Scheme 1) was based on the Mannich reaction of the corresponding *o*-hydroxyaryl alkyl ketones and was reported previously.[11] The chemoselective acetylation of **12** was carried out with excess acetic anhydride at room temperature to yield the corresponding *o*-hydroxyaryl alkyl ketoxime acetates (**11**) as slightly yellow oils. Alternatively, treatment of the oximes with an equivalent amount of acetyl chloride in THF provided the desired compounds (**11**)

as hydrochlorides. These ionic compounds precipitated out of the solution thus preventing further esterification of the phenolic hydroxyl group. Neutralization by treatment with base provided the desired compounds in a more expedient way and with improved yields. The oxime acetates obtained under these conditions displayed in their ^{13}C NMR spectrum a diagnostic peak at around 20 ppm, that is characteristic for the α-methylene of the *E* (*syn*-alkyl) geometrical isomer of the oxime double bond.[12] The preservation of the *E* configuration around the oxime carbon nitrogen double bond was crucial for the anticipated cyclization step to benzisoxazoles (**2**). The *Z*-isomer (*anti*-alkyl) has a nonplanar

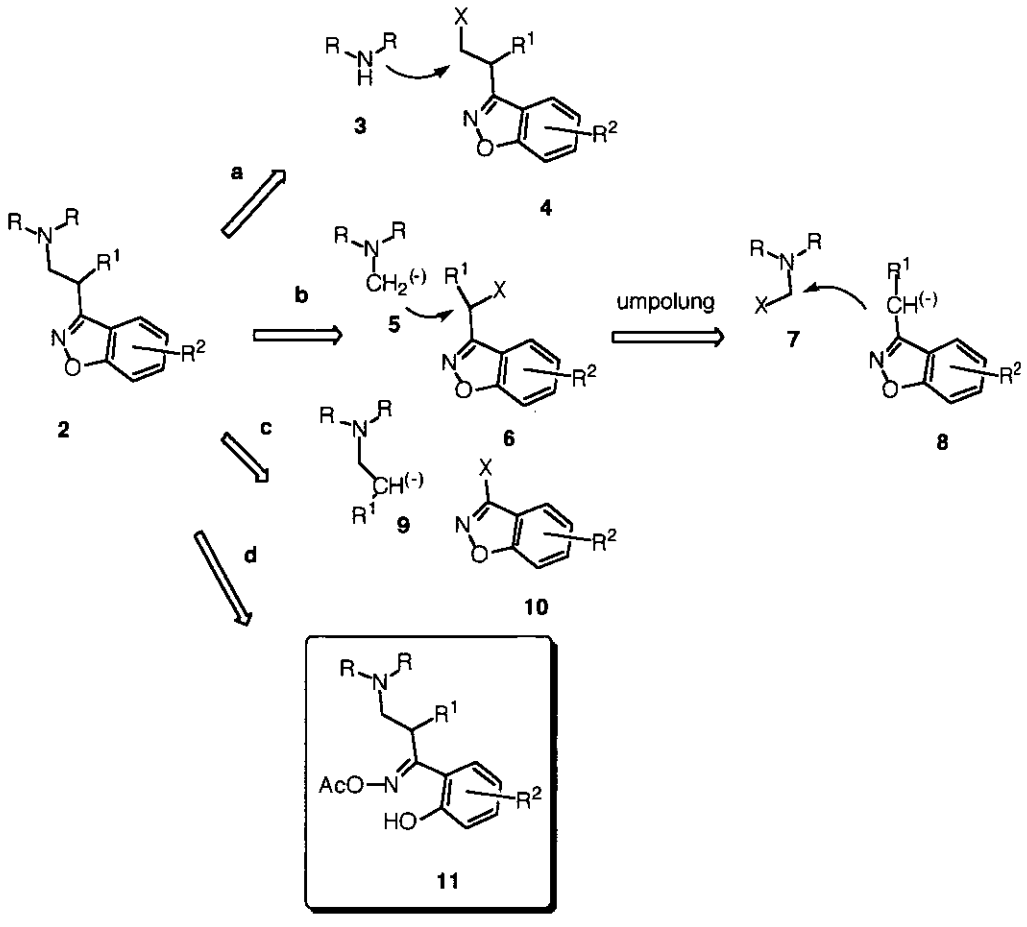
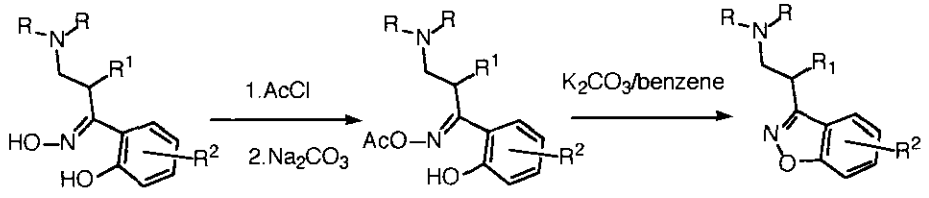


Figure 2. Retrosynthetic analysis of 3-(2-dialkylaminoethyl)-1,2-benzisoxazoles (**2**).

conformation due to the steric hindrance with the hydroxyl group in the *ortho* position and does not cyclize. On the contrary, the *E* isomer (**11**) is stabilized by intramolecular hydrogen bonding with the hydroxyl in *ortho* and the cyclization reaction is highly favourable.[13] The cyclization to the desired 1,2-benzisoxazoles was attempted according to the popular method of Thakar *et al.*[14] with unsatisfactory



12 11 2

Scheme 1. Reaction conditions: a)AcCl, 0°C, THF; b) K_2CO_3, refluxing benzene.

results. Refluxing of **11** in pyridine was accompanied by an intense reddish coloring of the solution and a resinous crude was obtained after the work up. Treatment with hydrochloric acid in ethanol followed by cooling provided the desired cyclized hydrochloride in low yield.

	R^1	R^2	R	Yield 2[a]	mp (°C) 2	Elemental analysis[b] C	H	N
a	H	6-CH_3	CH_2-CH_2-O-CH_2-CH_2	39	186-187	59.29 (59.46)	6.81 (6.78)	9.74 (9.91)
b	H	5-CH_3	CH_2-CH_2-O-CH_2-CH_2	61	212-213	59.27 (59.46)	6.95 (6.78)	10.08 (9.91)
c	CH_3	5-CH_3	CH_2-CH_2-O-CH_2-CH_2	38	184-185	60.59 (60.70)	7.19 (7.13)	9.30 (9.44)
d	H	5-CH_3	CH_2-CH_2-CH_2-CH_2-CH_2	53	210-211	63.90 (64.17)	7.66 (7.48)	9.79 (9.98)
e	H	H	CH_3	53	206-208	58.19 (58.28)	6.73 (6.67)	12.41 (12.35)
f	CH_3	5-CH_3	CH_3	43	196-197	61.48 (61.29)	7.58 (7.46)	10.81 (11.00)
g	H	5-CH_3	CH_3	48	198-199	59.69 (59.87)	7.24 (7.11)	11.41 (11.64)

Table 1. Benzisoxazoles (**2**). a) Yield for isolated hydrochlorides. b) Theoretical values are given in brackets.

Since the cyclization on other oxime acetates that did not have the amino group in the β position worked very well under similar conditions we assume that a retro Michael reaction might occur followed by subsequent polymerization of the resulting azadiene. The use of aqueous NaOH or Na_2CO_3 effected only the hydrolysis of the acetate and returned some starting oxime. Eventually it was found that K_2CO_3 in benzene accomplished the desired cyclization in synthetically useful yields (Table 1). No 1,3-benzoxazole resulting through a Beckmann rearrangement process could be detected under these conditions.[15]

In conclusion, we have demonstrated that the acquisition of 3-(2-dialkylaminoethyl)-1,2-benzisoxazoles (**2**) can be achieved *via* the direct cyclization of the corresponding *o*-hydroxyaryl β-dialkylaminoethyl ketoxime acetates (**11**). This should provide an alternative approach to the synthesis of these interesting candidates for the inhibition of the acetylcholinesterase.

EXPERIMENTAL

All melting points were determined on a Boëtius apparatus and are uncorrected. IR spectra were recorded on a Specord M80 spectrophotometer. NMR analysis were performed on a Varian Inova or a Gemini 200 instrument. All chemical shifts are reported in ppm downfield from tetramethylsilane; the coupling constants (*J*) are given in Hz. Elemental analysis were performed by the Microanalysis Center of the Asachi Technical University. All reagents were obtained commercially and used without further purification. Final purification of all products for the elemental analysis was done by recrystallization from ethanol. All the reported compounds were isolated and gave correct elemental analysis results and displayed the expected spectral characteristics. Intermediates (**11**) were used in the cyclization step without prior purification with the exception of compound (**11b**).

General procedure for the synthesis of *o*-hydroxyaryl 2-dialkylaminoethyl ketoxime acetates (11):

The oxime (**12**) (15 mmol) was dissolved in THF (45 mL), cooled to 0°C and treated dropwise with acetyl chloride (15 mmol, 0.6 mL) solution in the same solvent (15 mL). The formation of the corresponding hydrochloride was observed shortly. The reaction was stirred for 30 min at 0°C and the reaction flask was placed in the freezer overnight. The solution was then filtered to yield a white crystalline product that was washed with ether and then recrystallized from ethanol. Brief stirring with $NaHCO_3$ in ether followed by filtration through a plug of Flourisil® provided the oxime acetate (**11**) as a free amine in 80-90% yield.

1-(2-Hydroxy-5-methylphenyl)-3-(4-morpholinyl)-1-propanone oxime acetate (11b). ^1H NMR ($CDCl_3$) δ 11.00 (br s,1H), 7.18 (s, 1H), 7.08 (dd, ^3J=8.2 Hz, ^4J=1.8 Hz, 1H), 6.86 (d, ^3J=8.2 Hz, 1H), 3.66 (t, ^3J=4.6 Hz, 4H), 2.81 (m, 4H), 2.50 (t, ^3J=4.6 Hz, 4H), 2.24 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.6, 165.6, 156.2, 133.1, 128.8, 128.7, 118, 116.1, 66.6, 53.3, 24.8, 20.5, 19.2; MS m/z 246 (M^+); IR (KBr, cm^{-1}): 1780 ($\nu_{C=O}$).

General procedure for the synthesis of 3-(2-dialkylaminoethyl)-1,2-benzisoxazoles (2):

The oxime acetate (**11**) (10 mmol) was dissolved in benzene (30 mL) and treated with K_2CO_3 (10 mmol, 1.38 g) under refluxing conditions for 2 to 3 h. The suspension was cooled to rt and partitioned between ether and an aqueous 10% KOH solution. The organic phase was subsequently extracted with water, dried on Na_2SO_4 and concentrated under vacuum to yield an oily crude product. Treatment with concentrated hydrochloric acid of its ethanol solution provided the corresponding hydrochloride as a white precipitate. The crystals were separated by filtration, washed with acetone and recrystallized from ethanol. Brief stirring with $NaHCO_3$ in ether followed by filtration through a plug of Flourisil® provided the benzisoxazoles (**2**) as a free amine.

6-Methyl-3-[2-(4-morpholinyl)ethyl]-1,2-benzisoxazole hydrochloride (2a). ^{1}H NMR (D_2O) δ 7.26 (d, ^3J=8 Hz, 1H), 6.88 (m, 2H), 3.83 (br s, 4H), 3.44 (m, 2H), 3.28 (br s, 4H), 3.19 (m, 2H), 2.15 (s, 3H); ^{13}CNMR (D_2O) δ 165.3, 157.1, 145.1, 128.3, 123.0, 120.2, 111.7, 66.2, 56.3, 54.4, 23.5, 22.2. IR (KBr, cm^{-1}): 1635 ($\nu_{C=N}$).

5-Methyl-3-[2-(4-morpholinyl)ethyl]-1,2-benzisoxazole hydrochloride (2b) ^{13}C NMR (D_2O) δ 162.5, 156.0, 135.8, 134.1, 121.7, 110.8, 110.7, 65.2, 55.3, 53.4, 21.6, 21.3. IR (KBr, cm^{-1}): 1635 ($\nu_{C=N}$). FABMS (deuterated hydrochloride) 248.1 (MW-Cl).

5-Methyl-3-[2-(4-morpholinyl)ethyl]-1,2-benzisoxazole (2b') ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 3H), 3.69 (t, ^3J=4.7 Hz, 4H), 3.12 (m, 2H), 2.84 (m, 2H), 2.53 (t, ^3J=4.7 Hz, 4H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.5, 156.5, 132.8, 131.3, 121.7, 120.4, 109.4, 66.8, 56.3, 53.4, 23.1, 21.0. MS m/z 246 (M^+), HRMS calcd for $C_{14}H_{18}N_2O_2$ 246.13682, found 246.13858.

5-Methyl-3-[1-methyl-2-(4-morpholinyl)ethyl]-1,2-benzisoxazole hydrochloride (2c). ^{1}H NMR (D_2O) δ 7.03 (dd, ^3J=8 Hz, ^4J=1.8 Hz, 1H), 6.79 (d, ^4J=1.8 Hz, 1H), 6.75 (d, ^3J=8 Hz, 1H), 3.83 (br s, 4H), 3.42 (m, H) and 3.23 (m) overlap for 7H, 2.14 (s, 3H), 0.98 (d, ^3J=7 Hz, 3H). ^{13}C NMR (D_2O) δ 161.2, 152.1, 133.9, 132.9, 131.4, 121.7, 118.4, 66.0, 62.0, 36.6, 21.9, 18.0. IR (KBr, cm^{-1}): 1635 ($\nu_{C=N}$).

5-Methyl-3-[2-(1-piperidinyl)ethyl]-1,2-benzisoxazole hydrochloride (2d). ^{1}H NMR (D_2O) δ 7.33 (m, 3H), 2.80-4.00 (m, 8H), 2.34 (3H, s), 1.40-2.00 (m, 6H). ^{13}C NMR (D_2O) δ 162.4, 156.2, 135.7, 134.0, 121.7, 110.6, 54.9, 24.2, 22.5, 21.6, 21.5. FABMS (deuterated hydrochloride) 246.1 (MW-Cl). IR (KBr, cm^{-1}): 1635 ($\nu_{C=N}$)

5-Methyl-3-[2-(1-piperidinyl)ethyl]-1,2-benzisoxazole (2d'). ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1H), 7.33

(m, 2H), 3.10 (m, 2H), 2.78 (m, 2H), 2.48 (t, ^3J=5.3 Hz, 4H), 2.43 (s, 3H), 1.58 (m, 4H), 1.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.5, 156.9, 132.7, 131.21, 121.8, 120.6, 109.3, 56.8, 54.3, 25.9, 24.2, 23.3, 21.0. MS m/z 244 (M^+), HRMS calcd for $C_{15}H_{20}N_2O$ 244.15755, found 244.15860.

3-(2-Dimethylaminoethyl)-1,2-benzisoxazole hydrochloride (2e). ^{1}H NMR (D_2O) δ 7.22 (m, 2H), 6.83 (m, 2H) 3.21 (m, 2H), 3.12 (m, 2H), 2.75 (s, 6H). ^{13}C NMR (D_2O) δ 157.0, 155.7, 131.4, 128.3, 120.2, 118.9, 116.8, 53.9, 42.9, 21.9.

3-(2-Dimethylamino-1-methylethyl)-5-methyl-1,2-benzisoxazole hydrochloride (2f). ^{1}H NMR (D_2O) δ 7.40 (s, 1H), 7.18 (s, 2H), 3.66 (m, 1H), 3.59 (m, 1H), 3.38 (m, 1H), 2.74 (s, 6H), 2.19 (s, 3H), 1.26 (d, ^3J=6.6 Hz, 3H). ^{13}C NMR (D_2O) δ 164.0, 161.3, 136.9, 135.2, 123.0, 121.9, 111.9, 62.7, 45.8, 30.5, 22.6, 19.3. IR (KBr, cm^{-1}): 1635 ($\nu_{C=N}$).

3-(2-Dimethylaminoethyl)-5-methyl-1,2-benzisoxazole hydrochloride (2g). ^{1}H-NMR (D_2O) 7.33 (br s, 3H), 3.56 (m, 2H), 3.33 (m, 2H), 2.92(br s, 6H), 2.34 (s, 3H); ^{13}C-NMR (D_2O) 156.6, 150.2, 130.0, 129.9, 128.2, 115.8, 104.8, 49.9, 38.4, 16.1, 15.6. IR (KBr, cm^{-1}): 1635 ($\nu_{C=N}$).

REFERENCES

1. H. Suh, S. Jeong, Y. N. Han, H. Lee, and J. Ryu, *Bioorganic & Medicinal Chemistry Letters*, 1997, **7**, 389.

2. A. Nuhrich, M. Varache-Lembège, J. Vercauteren, R. Dokhan, P. Renard, and G. Devaux, *Eur. J. Med. Chem.*, 1996, **31**, 957.

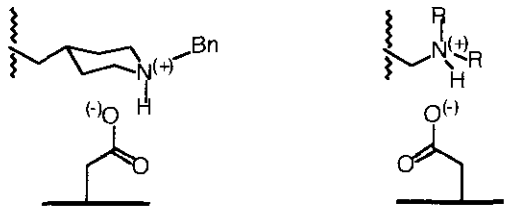
3. J. T. Strupczewski, K. J. Bordeau, Y. Chiang, E. J. Glamkowski, P. G. Conway, R. Corbett, H. B. Hartman, M. R. Szewczak, C.A. Wilmot, and G.C. Helsey, *J. Med. Chem.*, 1995, **38**, 1119; N. J. Hrib, J. G. Jurcak, K. L. Burgher, P. G. Conway, H. B. Hartman, L. L. Kerman, J. E. Roehr, and A. T. Woods, *J. Med. Chem.*, 1994, **37**, 2308.

4. A. Villalobos, J. F. Blake, C. K. Biggers, T. W. Butler, D. S. Chapin, Y. L. Chen, J. L. Ives, S. B. Jones, D. R. Liston, A. A. Nagel, D. M. Nason, J. A. Nielsen, I. A. Shalaby, and W.F. White, *J. Med. Chem.*, 1994, **37**, 2721.

5. J. L. Sussman, M. Harel, F. Frolow, C. Oefner, A. Goldman, L. Toker, and I. Silman, *Science*, 1991, **253**, 872.

6. Unpublished computational MM model. This model shows that conformational isomerism around the α,β-carbon-carbon single bond in the aspartate can lead to hydrogen bonding of the carboxylate to the

protonated amino group both in compounds (**1**) and (**2**) as shown below. As reported in ref. 4, minor changes in the backbone conformation of the protein are also observed.



7. H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato, and H. Nishima, *Chem. Pharm. Bull.*, 1976, **24**, 632.

8. J. March, "*Advanced Organic Chemistry*", Fourth Edition, John Wiley & Sons, 1992, p.198.

9. J.E.Oliver, R.M. Waters, and W.R. Lusby, *J. Org. Chem.*, 1989, **54**, 4970.

10. J. March, "*Advanced Organic Chemistry*", Fourth Edition, John Wiley & Sons, 1992, p. 991.

11. E. Comanita, I. Popovici, G. Roman, and B.Comanita, *Models in Chemistry*,1997, **134**, 3.

12. A. M. Silverstein, G. C. Basler, and C. M. Terrence, "*Spectrometric Identification of Organic Compounds*", Fourth Edition, John Wiley & Sons, 1981, p. 272.

13. D. M. Fink and B. A. Kurys, *Tetrahedron Lett.*, 1996, **37**, 995 and references cited therein.

14. K. A. Thakar, D. D. Goswami, and D. Bhawal, *Indian J. Chem.*, 1977, **15B**, 1058.

15. A. Nuhrich, M. Varache-Lembège, P. Renard, and G. Devaux, *Eur. J. Med. Chem.*, 1994, **29**, 75.

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