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LETTERS TO THE EDITOR

SYNTHESIS OF 1-METHOXY-4-(2-MORPHOLINOETHYL)-3,3-DIPHENYLPYRROLIDIN-2-ONE

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Doxapram has long been used as an intravenously-administered drug for treatment of acute respiratory insufficiency [1]. As a part of our research program toward development of novel respiratory stimulants, we were interested in the synthesis of more potent doxapram analogs. Herein we report a concise synthesis of *N*-methoxypyrrolidinone **1**.

The key step in the synthesis is transformation of lactone **4** into *N*-OMe lactam **7**, which was elaborated to the target compound **1** in a straightforward three-step sequence.

The prerequisite lactone **4** was prepared in an iodotetraphenyl-λ^5-stibane-catalyzed cycloaddition reaction between oxirane **3** and diphenyl ketene, generated from acid chloride **2** [2] prior to the cycloaddition [3]. Transformation of lactone **4** into lactam **7** was achieved in a two-step sequence. Initially, lactone **4** was converted to *O*-methylhydroxamic acid **5** in the Me_3Al-mediated [4] reaction with $H_2NOMe \cdot HCl$. Because the hydroxamic acid **5** was unstable and readily cyclized back to lactone **4**, it was used in the next step without purification. Cyclization of compound **5** under Mitsunobu conditions [5] afforded the desired lactam **7** together with the isomeric *O*-methyl oxime **6** (ratio **7**:**6** = 1:3). The ratio of *N*- *vs*. *O*-cyclization products was improved to 1:1 by substitution of THF and CH_2Cl_2 by more polar DMF or NMP. Gratifyingly, the isomers could be separated by chromatography on silica gel. Furthermore, the undesired oxime **6** could be smoothly hydrolyzed back to the lactone **4** under acidic conditions [6] (81% yield) and reused in the synthesis of lactam **7**.

Lactam **7** was elaborated to the target compound **1** in a three-step sequence comprising hydroboration–oxidation [7] to alcohol **8**, followed by conversion to chloride **9** and, finally, alkylation of morpholine [8, 9].

IR spectra were recorded on a Shimadzu IR Prestige21 FTIR spectrometer in thin film. ^1H and ^{13}C NMR spectra were registered on a Varian Mercury 400 instrument (400 and 100 MHz, respectively) in $CDCl_3$, using the residual solvent peak as an internal reference (7.26 ppm for ^1H nuclei, 77.0 ppm for ^{13}C nuclei). High-resolution mass spectra (ESI) were obtained on a micromass micrOTOF-Q Mass Spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 Analyzer. Melting points were determined by using an OptimMelt automated melting point system and are uncorrected.

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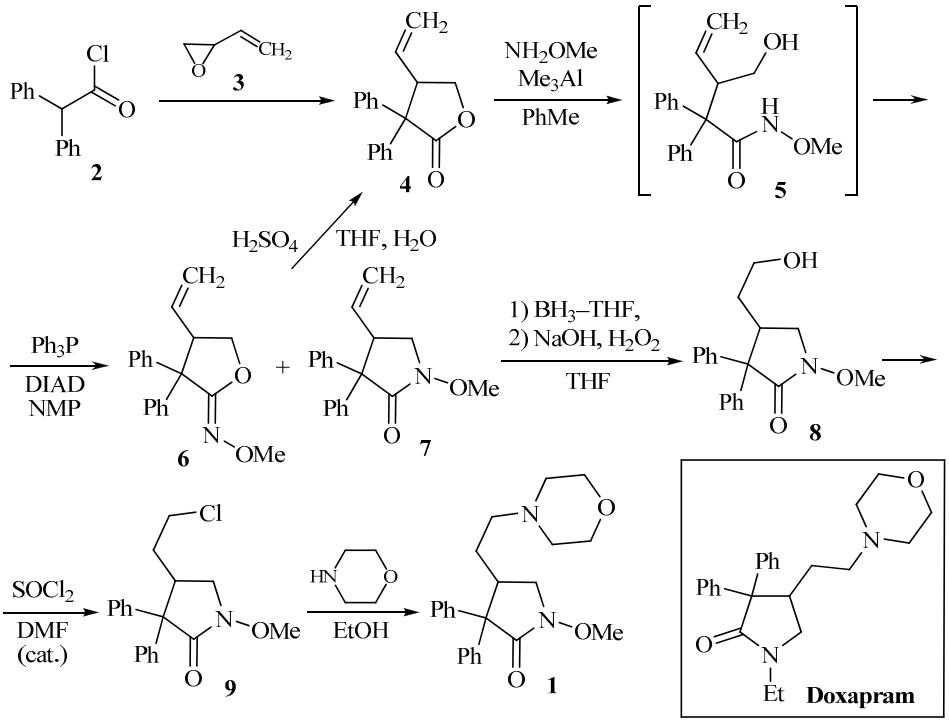

3,3-Diphenyl-4-vinyldihydrofuran-2(3*H*)-one *O*-Methyloxime (6) and 1-Methoxy-3,3-diphenyl-4-vinylpyrrolidin-2-one (7). A 2 M solution of Me_3Al in PhMe (7.77 ml, 15.55 mmol) was added dropwise to a cooled (0°C) solution of *O*-methylhydroxylamine hydrochloride (1.30 g, 15.55 mmol) in dry PhMe (18 ml) under Ar atmosphere. 3,3-Diphenyl-4-vinyldihydrofuran-2(3*H*)-one (**4**) (1.37 g. 5.18 mmol) was added, and the reaction mixture was stirred at 55°C for 20 h. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 (15 ml) and cooled to 0°C, and saturated aq. $NaHCO_3$ (15 ml) was added. The resulting suspension is stirred at 0°C for 10 min, filtered through Celite, and the Celite pad was washed with CH_2Cl_2 (10 ml). The layers were separated, and the water phase was extracted with CH_2Cl_2 (2×15 ml). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (40 ml) and dried over Na_2SO_4. The solvents were evaporated to give 3-hydroxy-*N*-methoxy-2,2-diphenylpent-4-enamide (**5**), which was used in the next step without purification.

Compound **5** was dissolved in NMP (20 ml), cooled to 0°C, and DIAD (0.98 g, 4.85 mmol) and Ph_3P (1.27 g, 4.85 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. Water (20 ml) is added to the reaction mixture, and the resulting suspension was extracted with *t*-BuOMe (3×15 ml). Volatiles were removed under reduced pressure. Purification of the crude mixture by column chromatography (10 to 50% EtOAc–petroleum ether) afforded pure compounds **6** and **7**.

Compound 6. Yield 400 mg (26%), white powder, mp 165-167°C (MeOH), R_f 0.48 (EtOAc–petroleum ether, 1:3). IR spectrum, ν, cm^{-1}: 1666 (C=N). ^{1}H NMR spectrum, δ, ppm: 3.81 (3H, s, OCH_3); 3.94-4.02 (2H, m, 5-CH_A, 4-CH); 4.35-4.43 (1H, m, 5-CH_B); 5.13-5.18 (1H, m) and 5.26-5.34 (2H, m, CH=CH_2); 7.05-7.10 (2H, m, H Ph); 7.21-7.36 (6H, m, H Ph); 7.46-7.51 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 49.8; 59.2; 62.5; 71.5; 119.6; 127.0; 127.2; 127.7; 127.8; 128.8; 129.3; 132.7; 140.3; 141.2; 161.1. Found, %: C 77.55; H 6.58; N 4.72. $C_{19}H_{19}NO_2$. Calculated, %: C 77.79; H 6.53; N 4.77.

Compound 7. Yield 410 mg (27%), white powder, mp 115-117°C (MeOH), R_f 0.27 (EtOAc–petroleum ether, 1:3). IR spectrum, ν, cm^{-1}: 1717 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.31-3.40 (1H, m) and 3.75 (1H, dd, J = 7.2, J = 8.2, 5-CH_2); 3.79-3.90 (1H, m, 4-CH); 3.87 (3H, s, OCH_3); 5.07 (1H, dd, J = 1.4, J = 10.0) and 5.24 (1H, dd, J = 1.4, J = 17.2, CH=C<u>H</u>$_2$); 5.36 (1H, ddd, J = 8.0, J = 10.0, J = 17.2, C<u>H</u>=CH_2); 6.92-6.98 (2H, m, H Ph); 7.18-7.39 (6H, m, H Ph); 7.63-7.78 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 43.6; 47.8; 58.1; 62.4; 118.2; 127.0; 127.2; 128.0; 128.1; 128.3; 128.9; 134.9; 140.2; 141.0; 172.0. Found, %: C 77.43; H 6.52; N 4.73. $C_{19}H_{19}NO_2$.

Calculated, %: C 77.79; H 6.53; N 4.77.

4-(2-Hydroxyethyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (8). A 1 M solution of BH_3 in THF (2.81 ml) was added to a solution of 1-methoxy-3,3-diphenyl-4-vinyl-pyrrolidin-2-one (**7**) (0.41 g, 1.40 mmol) in dry THF (10 ml) at 0°C under Ar atmosphere. The reaction mixture was stirred at room temperature for 4 h, then cooled to 0°C, and 1 N NaOH (3 ml) and 35% H_2O_2 (3 ml) were added. The mixture was stirred at room temperature for 2 h, and then saturated aq. NH_4Cl (10 ml) was added. The resulting suspension was extracted with CH_2Cl_2 (3×15 ml). The combined organic extracts were washed with saturated aq. NH_4Cl (20 ml) and dried over Na_2SO_4. Volatiles were evaporated. Purification of the crude product by column chromatography (20 to 90% EtOAc–petroleum ether) afforded product **8**. Yield 180 mg (41%), white foam, R_f 0.23 (EtOAc–petroleum ether, 1:1). IR spectrum, ν, cm^{-1}: 1696 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79-0.90 (1H, m) and 1.67 (1H, dddd, *J* = 3.2, *J* = 5.7, *J* = 8.3, *J* = 14.4, C$\underline{H}_2$CH$_2$OH); 1.40-1.50 (1H, m, OH); 3.15-3.21 (1H, m) and 3.81 (1H, dd, *J* = 7.0, *J* = 8.2, 5-CH$_2$); 3.32-3.42 (1H, m, C$\underline{H}_A$OH); 3.54-3.70 (2H, m, C$\underline{H}_B$OH, 4-CH); 3.78 (3H, s, OCH$_3$); 6.79-6.87 (2H, m, H Ph), 7.11-7.32 (6H, m, H Ph); 7.48-7.54 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 32.6; 35.2; 48.1; 57.8; 60.4; 62.3; 126.9; 127.3; 128.0; 128.1; 128.5; 128.7; 140.4; 140.8; 172.3. Found, *m*/*z*: 312.1592 $[M+H]^+$. $C_{19}H_{21}NO_3$. Calculated, *m*/*z*: 312.1594.

4-(2-Chloroethyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (9). A mixture of 4-(2-hydroxyethyl)-1-meth-oxy-3,3-diphenylpyrrolidin-2-one (**8**) (0.24 g, 0.76 mmol), $SOCl_2$ (3 ml), and DMF (50 μl) was stirred at room temperature for 20 h. The excess of $SOCl_2$ was removed under reduced pressure. The mixture was cooled to 0°C and treated with sat. $NaHCO_3$ (15 ml), then extracted with *t*-BuOMe (3×10 ml). The combined organic extracts were washed with water (20 ml) and brine (20 ml) and dried over Na_2SO_4. Volatiles were evaporated. Purification of the crude product by column chromatography (10 to 35% EtOAc–petroleum ether) afforded product **9**. Yield 210 mg (84%), white powder, mp 123-125°C (MeOH), R_f 0.23 (EtOAc–petroleum ether, 1:3). IR spectrum, ν, cm^{-1}: 1710 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.11-1.21 (1H, m) and 1.95 (1H, dddd, *J* = 3.4, *J* = 5.3, *J* = 10.3, *J* = 14.9, C$\underline{H}_2$CH$_2$Cl); 3.19-3.25 (1H, m) and 3.88 (1H, dd, *J* = 7.1, *J* = 8.1, 5-CH$_2$); 3.45 (1H, ddd, *J* = 4.3, *J* = 10.3, *J* = 11.3, CH$_A$Cl); 3.51-3.64 (2H, m, CH$_B$Cl, 4-CH); 3.87 (3H, s, OCH$_3$); 6.87-6.91 (2H, m, H Ph); 7.20-7.41 (6H, m, H Ph); 7.57-7.61 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 32.6; 35.3; 42.7; 47.5; 57.6; 62.4; 127.2; 127.4; 128.2; 128.3; 128.4; 128.6; 140.1; 140.7; 172.2. Found, %: C 68.99; H 6.07; N 4.21. $C_{19}H_{20}ClNO_2$. Calculated, %: C 69.19; H 6.11; N 4.25.

1-Methoxy-4-(2-morpholinoethyl)-3,3-diphenylpyrrolidin-2-one (1). The reaction mixture of 4-(2-chloroethyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (**9**) (118 mg, 0.36 mmol) and morpholine (0.20 ml, 2.27 mmol) in EtOH (5 ml) was heated in a closed vial at 105°C for 48 h. Volatiles were evaporated, and water (10 ml) was added. The resulting suspension is extracted with EtOAc (3×12 ml). The combined organic extracts were washed with water (30 ml) and brine (20 ml) and dried over Na_2SO_4. Purification of the crude product by column chromatography (50 to 100% EtOAc–petroleum ether) afforded product **1**. Yield 100 mg (76%), white foam, R_f 0.33 (MeOH-CH_2Cl_2, 1:9). IR spectrum, ν, cm^{-1}: 1706 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.78-0.90 (1H, m) and 1.57-1.68 (1H, m, CHC$\underline{H}_2$CH$_2$N); 2.27-2.46 (6H, m, CH$_2$N(CH$_2$)$_2$); 3.19-3.26 (1H, m) and 3.84 (1H, dd, *J* = 7.0, *J* = 8.0, 5-CH$_2$); 3.27-3.38 (1H, m, 4-CH); 3.66-3.75 (4H, m, CH$_2$OCH$_2$); 3.86 (3H, s, OCH$_3$); 6.87-6.93 (2H, m, H Ph); 7.18-7.38 (6H, m, H Ph); 7.54-7.59 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 26.8; 36.4; 48.3; 53.9; 56.8; 58.0; 62.3; 66.9; 127.0; 127.3; 128.1 (2C); 128.5; 128.7; 140.5; 140.8; 172.3. Found, %: C 72.29; H 7.51; N 7.23. $C_{23}H_{28}N_2O_3$. Calculated, %: C 72.61; H 7.42; N 7.36.

REFERENCES

1. C. S. Yost, *CNS Drug Rev.*, **12**, 236 (2006).
2. E. A. Lund, I. A. Kennedy, and A. G. Fallis, *Can. J. Chem.*, **74**, 2401 (1996).
3. M. Fujiwara, M. Imada, A. Baba, and H. Matsuda, *J. Org. Chem.*, **53**, 5974 (1988).
4. I. M. Bell, D. C. Beshore, S. N. Gallicchio, and T. M. Williams, *Tetrahedron. Lett.*, **41**, 1141 (2000).

5. M. J. Genin, W. H. Ojala, W. B. Gleason, and R. L. Johnson, *J. Org. Chem.*, **58**, 2334 (1993).
6. S. R. Schow, J. D. Bloom, A. S. Thompson, K. N. Winzenberg, and A. B. Smith, *J. Am. Chem. Soc*., **108**, 2662 (1986).
7. S. Danishefsky, K. Vaughan, R. C. Gadwood, and K. Tsuzuki, *J. Am. Chem. Soc*., **102**, 4262 (1980).
8. C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B. V. Franko, and H. Jenkins, *J. Med. Chem.*, **7**, 302 (1964).
9. A. D. Cale, H. Jenkins, B. V. Franko, J. W. Ward, and C. D. Lunsford, *J. Med. Chem.*, **10**, 214 (1967).