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Synthesis of (−)-Brevioxime

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Abstract—The synthesis of (−)-Brevioxime and related JH biosynthesis inhibitor **1** was accomplished in nine steps from 3-hydroxypyrrolidine.

Brevioxime is a natural product isolated from *Penicillium brevicompactum* Dierckx growing on corn by Primo-Yufera and co-workers.[1] It was shown to display in vitro inhibition of juvenile hormone biosynthesis and was isolated by assay guided fractionation from a supernatant that displayed growth regulation effects on the Milkweed bug *Oncopeltus fasciatus.* The use of effective insecticides is typically plagued by non-target toxicity and a major goal of pesticide research is to find safer, more selective products. Since the molecular target of Brevioxime is confined to insect species, it represents a potentially selective method of control. It's synthesis was therefore undertaken with a view to preparing analogs that would be commercially attractive. Two racemic syntheses have recently appeared,[2] which differ slightly in their strategy to the one presented here (Fig. 1).

The target was initially envisioned to be prepared by an epoxidation of the acyl enamine **1** with concomitant cyclization to the alcohol, a strategy that appeared readily adaptable to an enantioselective synthesis via a Jacobsen epoxidation.[3] Furthermore, **1** is itself a natural product, reported by the same group who described it's occurrence, isolation and synthetic preparation.[4] This compound was claimed to have similar in vivo and in vitro activity on the Milkweed bug as does Brevioxime. It was prepared by a strategy that relied on an electrochemical oxidation of an acyl pyrrole and subsequent acid catalyzed dehydration at elevated temperature (Fig. 2). Further analysis of the enamine **1** leads to a protected acylpyrrolidine and the known ester **2**.[5]

3-Hydroxypyrrolidine appeared to be an attractive starting material as the hydroxyl function could be later eliminated to establish the enamine. Silylation followed by acylation gave the propionamide **5**, the enolate of which was reacted with 0.5 equiv. of the ester **2** to give the *beta*-ketoamide **6** in 80% yield based on **2**. At this point the silyl ether was exchanged for a mesylate and the resulting compound **8** was treated with potassium *tert*-butoxide in DMSO to give the requisite acylenamine **1** with a trace of the 3-pyrroline isomer (Scheme 1). The spectroscopic data for **1** was in agreement with that of the natural material.[4]

Exploratory chemistry performed on a series of analogs indicated that despite a number of attempts to effect a one-pot epoxidation/cyclization, the reactivity of the epoxy amide always resulted in the addition of a nucleophile (OH, 3-$ClPhCO_2$) if one was present and decomposition otherwise. The oxidation was therefore performed in methanol with Oxone® and CF_3COMe[6] in order to generate the aminal **9** and cyclization was performed in a separate

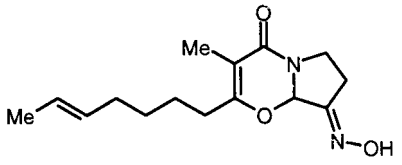

Figure 1. Structure of Brevioxime.

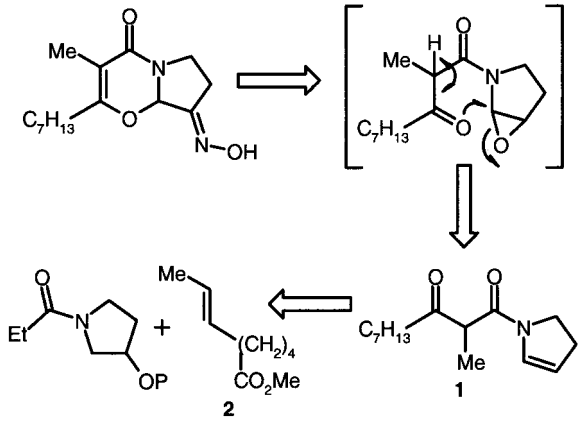

Figure 2. Retrosynthetic analysis of Brevioxime.

Keywords: insecticides; pyrrolines.

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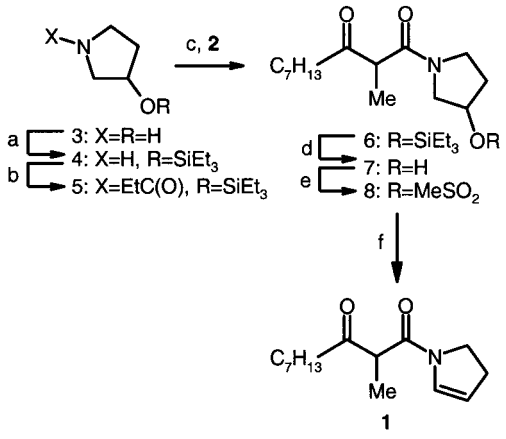
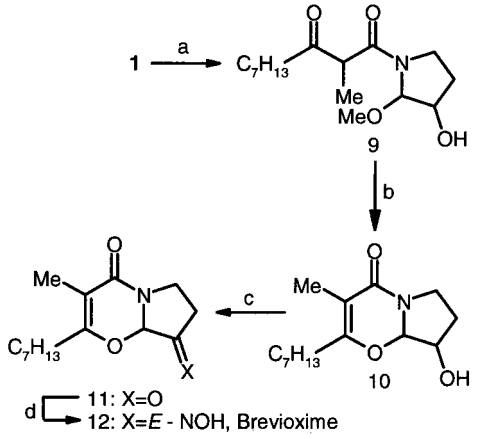


Scheme 1. Reagents and conditions: (a) 1.05 equiv. Et_3SiCl, pyridine, rt, 16 h. (b) 1.1 equiv. EtC(O)Cl, pyridine, rt, 16 h, 71% for two steps. (c) 1.05 equiv. *n*-BuLi, 1.1 equiv. *i*-Pr_2NH, 0.5 equiv. **2**, THF, −78°C, 4 h, 80%. (d) 1 equiv. TBAF, 1 equiv. HOAc, THF, rt, 1 h, 80% (e) 1.1 equiv. $MeSO_2Cl$, 1.3 equiv. NEt_3, CH_2Cl_2, rt, 16 h, 97% (f) 2.1 equiv. KO-*t*-Bu, DMSO, rt, 1 h, 76%.

step to yield a 3:2 mixture of the *syn* and *anti* isomers of **10**, which were readily separable by chromatography. This constitutes a formal synthesis of (+/−) Brevioxime and the synthesis was completed in a similar manner to that already described.[2] Thus, oxidation with the Dess–Martin periodinane yielded the ketone **11**. This compound, which appeared somewhat unstable, was immediately condensed with hydroxylamine to give a 7:1 mixture of oxime isomers as judged by ^{1}H NMR of the crude product (Scheme 2). The more polar (undesired) product eluded isolation, presumably due to isomerization to the more stable *E*-isomer.[2b] The spectroscopic data for the target compound was in agreement with that published.[1,2b]

An enantioselective synthesis was next examined. Treatment of acylenamine **1** with Jacobsen's catalyst *S*,*S*-Mn-(salen) with sodium periodate as the oxidant in methanol in the presence of imidazole gave crude aminal **9** which was immediately cyclized to a mixture of the alcohols **10** albeit in very low yield. Isolation of the less polar isomer by flash



Scheme 2. Reagents and conditions: (a) 1 equiv. Oxone®, 1.5 equiv. $NaHCO_3$, MeOH/$CF_3C(O)Me$ (10:1), rt, 16 h; (b) 0.1 equiv. PPTS, toluene, reflux, 1 h, 41% for two steps; (c) 1.1 equiv. Dess–Martin periodinane, CH_2Cl_2, rt, 16 h; (d) 1.2 equiv. $HONH_2$·HCl, 1.2 equiv. NEt_3, MeOH, rt, 16 h, 56% for two steps.

column chromatography gave the optically active material. Conversion of this to Brevioxime as already described gave material with an absolute optical rotation of −24° (cf. that of the natural material −39°). Crystallization of this material (ca. 35 mg) gave 5 mg of white needles with $[\alpha]_D$ of −126°. This suggests that the natural product as isolated is not optically pure and that the current synthesis provides only 19% ee. Efforts are currently underway to determine the absolute configuration of this material.

In conclusion, a route has been developed to natural products **1** and Brevioxime, both of which are inhibitors of juvenile hormone biosynthesis. This method is short, efficient (nine steps and 7.7% overall yield from 3-hydroxypyrrolidine to (+/−)-Brevioxime) and amenable to the synthesis of analogs and which may therefore find application in the development of more selective methods of insect control.

Experimental

General techniques

Reactions were carried out under an atmosphere of dry nitrogen using anhydrous solvents purchased from the Aldrich Chemical Company Inc. where appropriate. Amine bases were dried and stored over potassium hydroxide. Glassware was oven dried before use. Reactions were monitored by TLC on E. Merck silica gel plates (0.25 mm) and visualised under UV light (254 nm) and/or heating with phosphomolybdic acid ethanol solution. Reaction temperatures were measured internally. Solvents used for work-up and chromatography were reagent grade from E. Merck or VWR Scientific. Flash chromatography was performed on E. Merck silica gel (60, particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure materials.

NMR spectra were recorded on a Varian 300 MHz instrument at 25°C. Chemical shifts are reported relative to residual solvent peak. Multiplicities are designated singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) or broad singlet/multiplet (bs/bm). IR samples were prepared by evaporation of a solution of the compound from $CDCl_3$ onto a NaCl plate under a stream of nitrogen. IR spectra were recorded on a Perkin–Elmer 1600 series spectrometer. Mass spectra were recorded on a Micromass spectrometer under FAB conditions. Melting points were recorded on a Thomas Hoover Unimelt apparatus and are uncorrected. Microanalyses were performed at Quantitative Technologies Inc., Salem, NJ.

Propionamide 5. To a solution of 3-hydroxypyrrolidine hydrochloride (46.8 g, 379 mmol) in pyridine (400 mL) at 0°C was added chlorotriethylsilane (59.9 g, 1.05 equiv.). The mixture was allowed to warm to an ambient temperature and was stirred overnight. Pyridine (200 mL) was added and with ice bath cooling, propionyl chloride (36.2 mL, 1.1 equiv.) was added. The mixture was again stirred overnight at ambient temperature before being diluted with ethyl ether and washed twice with water. The aqueous phase was extracted with ethyl ether which was

washed with water and the combined organic extracts were dried ($MgSO_4$). The residue was concentrated, diluted with toluene and again concentrated. The residue was then filtered through a pad of silica gel, washing with toluene, methylene chloride and ethyl ether. The methylene chloride and ethyl ether washings were combined and concentrated to give amide **5** (69 g, 71%) as a yellow oil. R_f 0.28 (silica, ethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.5–4.3 (m, 1H), 3.6–3.2 (2×m, 4H), 2.4–2.2 (m, 2H), 2.0–1.8 (m, 2H), 1.15 (m, 3H), 1.0–0.9 (m, 9H), 0.6 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.9, 69.8, 68.3, 53.3, 52.6, 42.9, 42.0, 33.6, 32.0, 26.4, 26.0, 7.4, 5.2, 3.1; IR (film) ν_{max} 2955, 2877, 1651, 1434, 1236, 1110, 1033, 745 cm^{-1}; MS (M+H$^+$) 258.3. Anal. Calcd for $C_{21}H_{39}NO_3Si$: C, 60.65; H, 10.57; N, 5.44; Si, 10.91. Found: C, 59.66; H, 10.52; N, 5.38; Si, 10.10.

***B*-ketoamide 6.** To a solution of diisopropylamine (5.1 mL) in THF (150 mL) at −25°C was added *n*-BuLi (14.0 mL, 2.5 M solution in hexanes) dropwise. The cooling bath was removed and the mixture was stirred for an additional 30 min before being cooled to −70°C. Amide **5** (8.6 g, 33.5 mmol) in tetrahydrofuran (20 mL) was then added dropwise and the resulting mixture was stirred at this temperature for an additional 1 h. Ester **2** (2.6 g, 16.7 mmol) in tetrahydrofuran (15 mL) was then added and the resulting mixture was stirred at −78°C for 4 h. The reaction was then quenched by the addition of a saturated solution of ammonium chloride, warmed to ambient temperature and extracted with ethyl ether. The organic phase was dried ($MgSO_4$) and purified by flash column chromatography (silica gel, ethyl ether/hexanes 4:6 then 6:4) to give *B*-ketoamide **6** (5.1 g, 80%) as a pale yellow oil. R_f 0.33 (silica gel, ethyl ether/hexanes 8:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.4 (m, 2H), 4.4 (m, 1H), 3.7–3.3 (m, 5H), 2.6–2.4 (m, 2H), 2.0–1.8 (m, 4H), 1.7–1.5 (m, 5H), 1.4–1.2 (m, 5H), 0.94 (m, 9H), 0.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 207.4, 207.1, 207.0, 168.0, 168.7, 130.9, 125.0, 71.1, 69.6, 55.3, 54.7, 53.3, 53.0, 44.9, 44.7, 44.1, 39.2, 35.1, 33.3, 32.2, 28.9, 23.0, 17.8, 13.3, 13.2, 6.6, 4.6; IR (film) ν_{max} 2954, 2876, 1722, 1644, 1427 cm^{-1}; MS (M+H$^+$) 382; Anal. Calcd for $C_{21}H_{39}NO_3Si$: C, 66.09; H, 10.30; N, 3.67; Si, 7.36. Found: C, 65.79; H, 10.48; N, 3.73; Si, 7.44.

Alcohol 7. To a solution of silyl ether **6** (4.9 g, 12.9 mmol) in tetrahydrofuran (43 mL) was added acetic acid (736 μL) and tetra-butylammonium fluoride (12.9 mL, 1.0 M solution in tetrahydrofuran). The mixture was stirred at ambient temperature before being diluted with ethyl acetate, washed with water and then a saturated solution of sodium bicarbonate. The aqueous phase was re-extracted twice with methylene chloride and the combined organic phases were dried ($MgSO_4$). Purification by flash column chromatography (silica gel, ethyl ether then ethyl acetate) gave alcohol **7** (2.75 g, 80%) as a colorless oil. R_f 0.20 (silica gel, ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.4–5.3 (m, 2H), 4.5 (bs, 1H), 3.7–3.4 (m, 5H), 3.3–3.0 (bm, 1H); 2.5 (m, 2H), 2.1–1.9 (m, 4H), 1.64 and 1.62 (2×s, 3H), 1.6–1.5 (m, 2H), 1.4–1.2 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 207.5, 207.4, 207.2, 169.3, 169.2, 169.1, 168.0, 130.8, 125.0, 70.8, 69.1, 55.0, 54.6, 53.1, 53.0, 52.9, 52.7, 44.9, 44.7, 44.1, 39.7, 39.5, 39.4, 34.2, 32.7, 32.2, 28.9, 23.0, 17.8, 13.3, 13.2; IR (film) ν_{max} 3403, 2936, 1714, 1633, 1434 cm^{-1}; MS (M+H$^+$) 268; Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 8.29; N, 5.24. Found: C, 66.71; H, 9.27; N, 5.27.

Mesylate 8. To a solution of alcohol **7** (2.6 g, 9.7 mmol) in methylene chloride (50 mL) was added triethylamine (1.76 mL, 1.3 equiv.) followed by methane sulfonyl chloride (830 μL, 1.1 equiv.) and the mixture was stirred at ambient temperature overnight. The mixture was then diluted with 1 N hydrochloric acid and extracted twice with methylene chloride. The organic phase was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, ethyl acetate/hexanes 7:3) to give mesylate **8** (3.26 g, 97%) as a colorless oil. R_f 0.35 (silica gel, ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.4 (m, 2H), 5.3 (m, 1H), 3.9 (m, 1H), 3.8–3.4 (m, 4H), 3.07 and 3.06 (2×s, 3H), 2.6–2.4 (m, 2H), 2.4–2.1 (m, 2H), 2.0–1.9 (m, 2H), 1.64 and 1.63 (2×s, 3H), 1.6 (m, 2H), 1.5–1.3 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.3, 207.1, 207.0, 206.7, 169.0, 168.8, 168.7, 130.8, 125.1, 79.3, 79.1, 78.5, 78.3, 53.2, 53.1, 53.0, 52.9, 52.6, 52.2, 44.4, 44.1, 43.8, 43.7, 39.4, 39.3, 39.2, 38.8, 38.7, 33.0, 32.2, 30.9, 28.9, 22.9, 17.9, 13.4, 13.3; IR (film) ν_{max} 2937, 1714, 1651, 1634, 1434, 1360, 1173, 965, 902 cm^{-1}; MS (M+H$^+$) 346; Anal. Calcd for $C_{16}H_{27}NO_5S$: C, 55.63; H, 7.88; N, 4.05; S, 9.28. Found: C, 55.30; H, 8.06; N, 3.97; S, 9.30.

Acyl enamine 1. To a solution of mesylate **8** (0.73 g, 2.1 mmol) in dimethylsulfoxide (21 mL) was added potassium *tert*-butoxide (498 mg, 2.1 equiv.) and the mixture was stirred at ambient temperature for 1 h. Ice was then added followed by a saturated solution of ammonium chloride. The mixture was extracted twice with ethyl ether and the combined organic phase was washed with water and dried ($MgSO_4$). The material (400 mg 76%), was sufficiently pure by ^{1}H NMR to be used in the next step without further purification. Purification of a small sample by flash column chromatography (silica gel, ethyl ether/hexanes 4:6 then 6:4 then 8:2) gave an analytical sample of acyl enamine **1**. R_f 0.22 (silica gel, ethyl ether/hexanes 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0–6.9 and 6.6–6.5 (2×m, 1H), 5.4 (m, 2H), 5.3 (m, 1H), 3.86 (m, 2H), 3.6 and 3.5 (2×q, 1H), 2.8 and 2.7–2.6 (2×m, 2H), 2.6–2.4 (m, 2H), 2.0 (m, 2H), 1.63 (m, 3H), 1.6 (m, 2H), 1.4 (m, 3H), 1.4–1.3 (m, 2H).H), 1.4–1.3 (m, 2H)H ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.9, 165.9, 165.6, 130.8, 129.3, 128.2, 125.0, 113.0, 111.6, 53.2, 53.1, 45.8, 45.4, 39.2, 32.2, 30.1, 28.9, 28.1, 23.0, 17.8, 13.3, 13.1; IR (film) ν_{max} 3105, 2936, 2858, 1722, 1643, 1614, 1425 cm^{-1}; MS (M+H$^+$) 250.2.

Alcohols 10. To a solution of acyl enamine **1** (169 mg, 0.68 mmol) in methanol (7 mL) was added 1,1,1-trifluoroacetone (0.7 mL), sodium bicarbonate (86 mg, 1.5 equiv.) and Oxone® (417 mg, 1 equiv.) and the resulting mixture was stirred overnight at ambient temperature. The mixture was diluted with water and twice extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and concentrated to yield an inseparable mixture of isomers. The material was not further purified but a ^{1}H NMR spectrum showed the presence of four methoxy signals. The oil was dried azeotropically with toluene and toluene (30 mL) then

PPTS (17 mg, 0.1 equiv.) were then added and the mixture was heated at reflux for 1 h. The mixture was then cooled and purified by flash column chromatography (silica gel, ethyl ether/hexanes 6:4 then 8:2 then ethyl ether then ethyl acetate) to give the less polar isomer (41 mg) and the more polar isomer (32 mg, 41% for two steps). Less polar isomer: R_f 0.31 (silica gel, ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.4 (m, 2H), 5.03 (d, 1H), 4.5 (m, 1H), 3.7–3.6 (m, 2H), 2.4 (d, 1H), 2.4–2.2 (m, 3H), 2.1–1.9 (m, 3H), 1.79 (s, 3H), 1.64 (m, 3H), 1.6–1.5 (m, 2H), 1.4–1.3 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 130.7, 125.2, 106.4, 92.2, 75.3, 41.7, 31.2, 30.5, 30.0, 29.1, 26.2, 17.9, 10.0; IR (film) ν_{max} 3377, 2931, 2857, 1649, 1454 cm^{-1}; MS (M+H$^+$) 266.0. More polar isomer: R_f 0.22 (silica gel, ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.4 (m, 2H), 5.21 (d, 1H), 4.5 (bs, 1H), 3.8–3.5 (m, 2H), 2.4 (bs, 1H), 2.4–2.2 (m, 3H), 2.1–1.9 (m, 3H), 1.80 (s, 3H), 1.65 (m, 3H), 1.6–1.5 (m, 2H), 1.4 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 162.4, 130.8, 125.2, 106.7, 87.7, 70.6, 41.9, 32.2, 30.5, 29.3, 29.1, 26.2, 17.9, 10.0; IR (film) ν_{max} 3386, 2931, 2857, 1650, 1454 cm^{-1}; MS (M+H$^+$) 266.0.

Enantioselective epoxidation. To a solution of acyl enamine **1** (3.0 g, 10 mmol) in methanol (50 mL) was added (*S,S*)-(+)-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (300 mg, 0.05 equiv.), imidazole (1.52 g, 2 equiv.) and sodium periodate (5.90 g, 2.5 equiv.). The mixture was stirred at ambient temperature for 14 h before being diluted with ethyl ether and washed twice with water and once with sodium bicarbonate solution. The organic phase was dried ($MgSO_4$), concentrated and treated in a manner similar to that described above to yield 0.3 g of alcohols **10.**

Brevioxime. To a solution of alcohols **10** (73 mg, 0.27 mmol) in methylene chloride (5 mL) was added Dess–Martin periodinane (128 mg, 1.1 equiv.) and the mixture was stirred at ambient temperature overnight. The mixture was then concentrated and extracted with ethyl ether. The ethyl ether was concentrated and the crude ketone was re-dissolved in methanol (5 mL). Hydroxylamine hydrochloride (23 mg, 1.2 equiv.) was added followed by triethylamine (45 μL, 1.2 equiv.) and the mixture was stirred overnight. The mixture was then diluted with ethyl acetate, washed with water and dried ($MgSO_4$). Purification by flash column chromatography (silica gel, ethyl ether/hexanes 4:6 then 6:4 then 8:2) gave brevioxime (43 mg, 56% over two steps). White solid. mp (browns before melting) 133–140 °C (dec).R_f 0.32 (silica gel, ethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3 (bs, 1H), 5.56 (d, J=XX Hz, 1H), 5.4 (m, 2H), 4.1 (m, 1H), 3.5 (m, 1H), 3.0–2.8 (m, 2H), 2.4–2.2 (m, 2H), 2.0 (m, 2H), 1.83 (s, 3H), 1.63 (d, 3H), 1.6–1.5 (m, 2H), 1.4 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 163.3, 158.0, 130.8, 125.2, 107.0, 84.1, 41.6, 32.2, 30.6, 29.2, 26.3, 23.7, 17.9, 10.1; IR (film) ν_{max} 3241, 2926, 1641, 1450 cm^{-1}; MS (M+H$^+$) 279.1; Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 65.20; H, 8.16; N, 8.95.

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