Metallation of Diazines. V. Synthesis of Analogues of Biologically Active Molecules

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2-Chloro-4-methoxypyrimidine was lithiated by lithium 2,2,6,6-tetramethylpiperidide. The resulting lithio derivative was reacted with carbonyl derivatives and iodine. Synthesis of analogues of biologically active molecules is reported.

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Introduction.

The regiospecific preparation and modification of polysubstituted aromatic molecules constitute engaging fundamental problems is synthetic chemistry. The *ortho*-directed lithiation of aromatics is a powerful synthetic tool due to its high regioselectivity to have access to new molecules. Particularly, in the pyrimidine system which is present in many pharmaceutical and agrochemical molecules, the *ortho*-directed lithiation reaction is a valuable and efficient method to afford new pyrimidine derivatives and analogues of biologically active molecules.

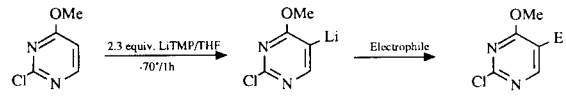
While this reaction has been throughly studied with some heterocycles such as pyridine, very few *ortho*-lithiations of pyrazines [1,2], pyridazines [3] and pyrimidines [4,7] have been reported.

As a continuation of our studies on direct metallation of diazines [1,2,3,7], we report the direct lithiation and functionalization of 2-chloro-4-methoxypyrimidine and the synthesis of analogues of biologically active pyrimidine derivatives.

Results.

Treatment of 2-chloro-4-methoxypyrimidine **1** in anhydrous tetrahydrofuran (THF) with 2.3 equivalents of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as the metallating agent at −70° for 1 hour gave the *ortho*-lithio derivative **2**, which was submitted to the reaction of various electrophiles (Scheme I).

Scheme I



1 2 3(a-g)

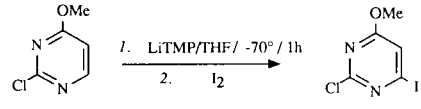
3a	E = D	85%	**3e**	E = 2(OMe)PhCH(OH)-	64%
3b	E = $SiMe_3$	49%	**3f**	E = 3,4,5(OMe)$_3$Ph-CH(OH)-	62%
3c	E = CH(OH)-CH_3	62%	**3g**	E = CHO	30%
3d	E = CH(OH)-Ph	66%			

In order to determine the most effective conditions of access to the *ortho*-lithiated intermediate, we varied expermental conditions: reaction temperature, solvent, amount of LiTMP and time of metallation. The lithio-derivative **2** was quenched with deuteriomethanol/deuterium chloride and the resultant mixture was analysed by ^{1}H nmr spectroscopy. The best result (85%) was obtained using 2.3 equivalents of LiTMP in THF as the solvent at −70° and for a 1 hour as the metallation time. The reactivity of the lithio-derivative **2** with various electrophiles such as trimethylsilyl chloride, acetaldehyde, benzaldehyde, *O*-anisaldehyde, 3,4,5-trimethoxybenzaldehyde, ethyl formate was investigated and compounds **3b-g** were obtained in moderated yields. Compounds **3b** and **3d** have been recently described by Wada *et al.* [5b] in lower yields and with some different experimental data: 1.2 equivalents of LiTMP in THF at 0° and 10 minutes as the metallation time.

We observed that the yield of the lithio derivative was dramatically affected by the ratio between LiTMP and pyrimidine when the directed metallation group is a methoxy group.

With iodine as the electrophile the unexpected 2-chloro-4-methoxy-6-iodopyrimidine **4** was obtained in good yield (85%), Scheme II.

Scheme II

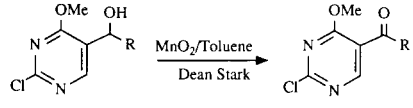


1 4

This surprising regioselectivity at C_6 is exclusively observed with iodine as an electrophile. This result has urged us to examine various experimental conditions able to induce a regioselectivity. This study is in progress, and we hope to rationalize the difference of regioselectivity observed with the nature of the electrophile.

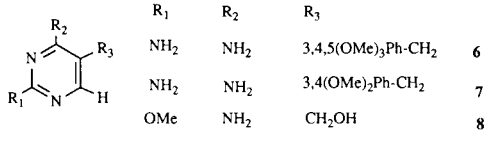
The secondary alcohols **3e** and **3f** are readily oxidized with manganese(IV) oxide to give ketones **5e** and **5f** in good yields (Scheme III).

Scheme III



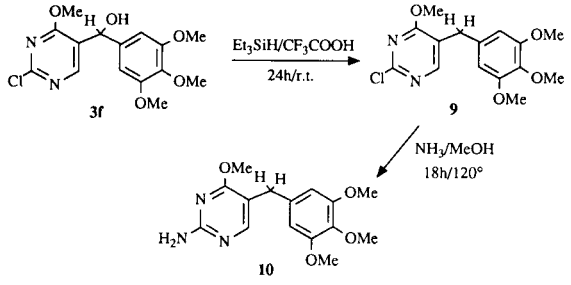
3e	R = 2(OMe)Ph	**5e**	88%
3f	R = 3,4,5(OMe)$_3$Ph	**5f**	92%

Interposition of a methylene group between the phenyl ring and the 2,4-diaminopyrimidine leads to benzyldiaminopyrimidines, a class of compounds well known for their antibacterial activity [8-11]. We can mention trimethoprim **6** and diaveridin **7**. Bacimethrin **8** is another biologically active molecule.



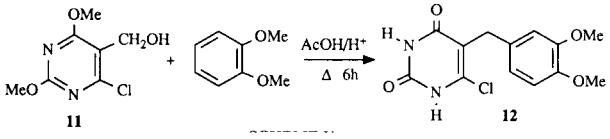
Hydrogenolysis of compound **3f** to 3,4,5-trimethoxyphenyl-2-chloro-4-methoxypyrimidylmethane **9** (Scheme IV) was performed by triethylsilane in trifluoroacetic acid at room temperature [12]. The methylenic hydrocarbon **9** was obtained in good yield (88%). A further nucleophilic substitution of chlorine by an amino group with ammonia under high pressure led to **10** (analogue of the trimethoprim **6**) in a moderated yield (30%) (Scheme IV).

Scheme IV



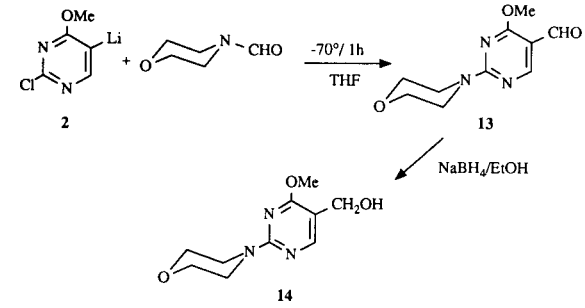
An analogue **12** of diaveridin **7** is obtained by action of veratrol in acidic medium (Scheme V) [9] on the primary alcohol **11**, this compound has been described in a previous paper [7] and was obtained by metallation of 4-chloro-2,6-dimethoxypyrimidine, followed by action of ethyl formate and further reduction with sodium borohydride in ethanol.

Scheme V



Action of 4-formylmorpholine on the *ortho*-lithiated derivative **2** led to a formylpyrimidine derivative **13** in moderate yield (33%). Under these conditions we observed nucleophilic substitution of the chlorine atom by morpholine. A further reduction of **13** by sodium borohydride in ethanol gave a primary alcohol **14** (Scheme VI) in good yield (85%). Compound **14** is an analogue of bacimethrin **8**.

Scheme VI



Conclusion.

Lithiation in the pyrimidine system with a methoxy group as the *ortho*-activating group afforded various substituted pyrimidines. This methodology is a powerful synthetic tool to access to *ortho*-functionalized 5-substituted pyrimidines. These compounds are of general interest to synthesize derivatives of biological interest and further investigations in this area are currently in progress.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ^{1}H nmr spectra were recorded in deuteriochloroform with tetramethylsilane as the internal standard or in deuterated dimethyl sulfoxide with hexamethyldisiloxane as the internal standard on a Varian EM 360 L, Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus. The ir spectra were obtained as potassium bromide pellets with a Perkin Elmer R12 spectrophotometer.

Tetrahydrofuran was distilled from benzophenone-sodium and used immediately. Water content of the solvent was estimated by the modified Karl-Fischer method (THF less than 50 ppm water).

Metallations were performed under an argon atmosphere whose water content was regularly checked. Reagents were handled with syringes through septa.

General Procedure for Metallation.

A solution of butyllithium (1.6 *M* in hexane, 2.9 ml, 4.6 mmoles) was added to cold (−30°), stirred, anhydrous tetrahydrofuran (40 ml) under an atmosphere of dry argon. The mixture was warmed to 0° and 2,2,6,6-tetramethylpiperidine (0.88 ml, 5.2 mmoles) was added, the solution was kept at 0° for 45 minutes, it was then cooled to −70°. A solution of 0.29 g of 2-chloro-4-methoxypyrimidine (2.0 moles) in 5 ml of tetrahydrofuran was added and the mixture was stirred for 1 hour at −70°. The electrophile was added and stirring was continued for 1 hour at −70°. Hydrolysis was then carried out at −70° using a mixture of 35% aqueous hydrochloric acid (2 ml), ethanol (2 ml) and tetrahydrofuran (8 ml). The solution gently warmed to room temperature, made slightly basic with a saturated sodium hydrogenocarbonate solution (10 ml) and evaporated under vacuum nearly to dryness. The residue was extracted with dichloromethane (4 x 40 ml). The organic extract was dried (magnesium sulphate) and evaporated. The crude product was purified by column chromatography on silica gel or by sublimation.

2-Chloro-5-deutero-4-methoxypyrimidine **3a**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with 1 ml of mixture deuteriomethanol, deuterium chloride 1:1 gave 0.247 g (85%) of **3a**. The crude product was purified by sublimation, mp 57°; ^{1}H nmr (deuteriochloroform): δ 3.93 (s, 3H, OCH_3), 8.00 (s, 1H, H_6) ppm.

2-Chloro-4-methoxy-5-trimethylsilylpyrimidine **3b**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with trimethylsilyl chloride (1.25 ml, 10 mmoles) gave 0.21 g (49%) of a colorless liquid of **3b**; ^{1}H nmr (deuteriochloroform): δ 0.40 (s, 9H, $Si(CH_3)_3$), 4.07 (s, 3H, OCH_3), 8.5 (s, 1H, H_6); ir ν 2970, 1570, 1460, 1355, 1120 cm^{-1}.

Anal. Calcd. for $C_8H_{13}N_2OClSi$: C, 44.32; N, 12.93; H, 6.00. Found: C, 43.9; N, 12.9; H, 5.9.

(2-Chloro-4-methoxy-5-pyrimidinyl)ethanol **3c**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with acetaldehyde (1 ml, 18 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate (8.5:1.5) as an eluent 0.23 g (62%) of **3c**, mp 109-110°; ^{1}H nmr (deuteriochloroform): δ 1.47 (d, 3H, CH_3), 2.63 (s, 1H, OH), 4.00 (s, 3H, OCH_3), 5.03 (q, 1H, CH(OH), 8.43 (s, 1H, H_6); ir: ν 3380, 2970, 1585, 1560 cm^{-1}.

Anal. Calcd. for $C_7H_9N_2O_2Cl$: C, 44.56; N, 14.85; H, 4.78. Found: C, 44.2; N, 14.7; H, 4.6.

(2-Chloro-4-methoxy-5-pyrimidinyl)phenylmethanol **3d**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with benzaldehyde (0.25 ml, 2.4 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate (8:2) as an eluent 0.33 g (66%) of **3d**, mp 107-109°; ^{1}H nmr (deuteriochloroform): δ 3.63 (s, 1H, OH), 3.93 (s, 3H, OCH_3), 5.80 (s, 1H, CH(OH), 7.25 (s, 5H, phenyl), 8.30 (s, 1H, H_6); ir: ν 3360, 3060, 1580, 1550 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_2O_2Cl$: C, 57.48; N, 11.18; H, 4.39. Found: C, 57.6; N, 10.8; H, 4.3.

(2-Chloro-4-methoxy-5-pyrimidinyl)-2-methoxyphenylmethanol **3e**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with 2-methoxybenzaldehyde (0.29 ml, 2.4 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate (9:1) as an eluent 0.36 g (64%) of **3e**, mp 115-116°; ^{1}H nmr (deuteriochloroform): δ 3.63 (s, 1H, OH), 3.80 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 6.06 (s, 1H, CH(OH), 6.7-7.4 (m, 4H, phenyl), 8.30 (s, 1H, H_6); ir: ν 3280, 2920, 1600, 1580, 1550 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}N_2O_3Cl$: C, 55.61; N, 9.98; H, 4.63. Found: C, 55.5; N, 9.7; H, 4.8.

(2-Chloro-4-methoxy-5-pyrimidinyl)-3,4,5-trimethoxyphenylmethanol **3f**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with 3,4,5-trimethoxybenzaldehyde (0.45 g, 2.3 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate (8:2) as an eluent 0.44 g (62%) of **3f**, mp 121-123°; ^{1}H nm r (deuteriochloroform): δ 3.57 (s, 1H, OH), 3.77 (s, 9H, OCH_3), 4.00 (s, 3H, OCH_3), 5.83 (s, 1H, CH(OH), 6.6 (s, 2H, phenyl), 8.40 (s, 1H, H_6); ir: ν 3400, 3000, 2940, 1580, 1550 cm^{-1}.

Anal. Calcd. for $C_{15}H_{17}N_2O_5Cl$: C, 52.86; N, 8.22; H, 5.00. Found: C, 52.6; N, 8.0; H, 5.2.

2-Chloro-4-methoxy-5-formylpyrimidine **3g**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with ethyl formate (0.19 ml, 2.3 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate (8.5:1.5) as an eluent 0.11 g (30%) of **3g**, mp 94-95°; ^{1}H nmr (deuteriochloroform): δ 4.20 (s, 3H, OCH_3), 8.80 (s, 1H, H_6); 10.3 (s, 1H, CHO); ir: ν 2920, 1700, 1580, 1550 cm^{-1}.

Anal. Calcd. for $C_6H_5N_2O_2Cl$: C, 41.74; N, 16.23; H, 2.90. Found: C, 41.5; N, 15.9; H, 2.6.

2-Chloro-4-methoxy-6-iodopyrimidine **4**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with a solution of 0.56 g (2.2 mmoles) of iodine in 5 ml of tetrahydrofuran gave after purification by column chromatography on silica gel with a mixture of hexane, ethyl acetate (8.5:1.5) as an eluent 0.46 g (85%) of **4**, mp 109-111°; ^{1}H nmr (deuteriochloroform): δ 4.10 (s, 3H, OCH_3), 7.20 (s, 1H, H_5); ir: ν 2920, 1550, 1515 cm^{-1}.

Anal. Calcd. for $C_5H_4N_2OClI$: C, 22.19; N, 10.35; H, 1.48. Found: C, 22.1; N, 10.0; H, 1.2.

General Procedure for the Oxidation of Alcohols into Ketones.

In a flask equipped with a Dean-Stark trap, a mixture of the secondary alcohol (1.0 mmole), anhydrous toluene (50 ml) and freshly prepared manganese(IV) oxide (2 g, 23 mmoles) was heated to boiling for 1 hour. The mixture was then filtered and the precipitate was extracted with tetrahydrofuran (3 x 20 ml). The combined filtrate and extracts were dried (magnesium sulfate) and evaporated. The crude product was purified by column chromatography on silica gel or by sublimation.

(2-Chloro-4-methoxy-5-pyrimidinyl)-2-methoxyphenyl Ketone **5e**.

Oxidation of **3e** according to the general procedure gave after purification by column chromatography on silica gel with a mixture dichloromethane, ethyl acetate 9.5:0.5 as an eluent 245 mg (88%) of **5e**, mp 127-129°; ^{1}H nmr (deuteriochloroform): δ 3.83 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.8-8.0 (m, 4H, phenyl), 8.43 (s, 1H, H_6); ir: ν 3000, 2940, 1670, 1550 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}N_2O_3Cl$: C, 56.01; N, 10.05; H, 3.94. Found: C, 56.3; N, 9.8; H, 4.2.

(2-Chloro-4-methoxy-5-pyrimidinyl)-3,4,5-trimethoxyphenyl Ketone **5f**.

Oxidation of **3f** according to the general procedure gave after purification by column chromatography on silica gel with a mixture dichloromethane, ethyl acetate 9.5:0.5 as an eluent 310 mg (92%) of **5f**, mp 115-116°; ^{1}H nmr (deuteriochloroform): δ 3.83 (s, 3H, OCH_3), 3.93 (s, 6H, OCH_3), 4.08 (s, 3H, OCH_3), 7.05 (s, 2H, phenyl), 8.43 (s, 1H, H_6); ir: ν 2980, 2940, 1670, 1550 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}N_2O_5Cl$: C, 53.17; N, 8.27; H, 4.43. Found: C, 53.5; N, 8.1; H, 4.1.

(2-Chloro-4-methoxy-5-pyrimidinyl)-3,4,5-trimethoxyphenylmethane **9**.

A mixture of secondary alcohol **3f** (0.341 g, 1 mmole), trifluoroacetic acid (2 ml, 26 mmoles), and triethylsilane (0.25 ml, 1.5 mmoles) was stirred at room temperature for 24 hours. After elimination of trifluoroacetic acid under reduced pressure, water was added (10 ml) and the solution was adjusted to *p*H = 8 by

ammonia. The aqueous solution was extracted with dichloromethane (4 x 40 ml). The extract was dried (magnesium sulfate) and evaporated under reduced pressure, the crude product was purified by column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate 9.5:0.5 as an eluent to give 286 mg (88%) of **9**, mp 95-96°; ^{1}H nmr (deuteriochloroform): δ 3.77 (s, 2H, CH_2), 3.83 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.40 (s, 2H, phenyl), 8.07 (s, 1H, H_6); ir: ν 2920, 1600, 1590, 1560 cm^{-1}.

Anal. Calcd. for $C_{15}H_{17}N_2O_4Cl$: C, 55.47; N, 8.63; H, 5.24. Found: C, 55.3; N, 8.4; H, 5.4.

(2-Amino-4-methoxy-5-pyrimidinyl)-3,4,5-trimethoxyphenylmethane **10**.

The reaction was performed in a pressure vessel. (2-Chloro-4-methoxy-5-pyrimidinyl)-3,4,5-trimethoxyphenylmethane **9** (0.25 g, 0.77 mmole) was added to a saturated solution of ammonia in ethanol (25 ml), and the pressure vessel was heated at 120-130° for 18 hours. The solvent was removed under reduced pressure and the residue was extracted with dichloromethane (4 x 25 ml). The extract was dried (magnesium sulfate) and evaporated under reduced pressure, the crude product was purified by column chromatography on alumina with a mixture of dichloromethane, methanol 9.6:0.4 as an eluent and by a second column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate 1:1 as an eluent to give 71 mg (31%) of **10**, mp 147-149°; ^{1}H nmr (deuteriochloroform): δ 3.66 (s, 2H, CH_2), 3.80 (s, 9H, OCH_3), 3.88 (s, 3H, OCH_3), 5.08 (m, 2H, NH_2), 6.42 (s, 2H, phenyl), 7.81 (s, 1H, H_6); ir: ν 3300, 2920, 1590, 1560 cm^{-1}.

Anal. Calcd. for $C_{15}H_{19}N_3O_4$: C, 59.02; N, 13.77; H, 6.23. Found: C, 58.8; N, 13.5; H, 6.4.

6-Chloro-5-(3,4-dimethoxyphenylmethyl)uracil **12**.

A mixture of 2,6-dimethoxy-4-chloro-5-hydroxymethylpyrimidine **11** (0.3 g, 1.47 mmoles), 1,2-dimethoxybenzene (0.2 ml, 1.54 mmoles), 30 ml of glacial acetic acid and 3 ml of concentrated hydrochloric acid (35 mmoles) was heated under reflux for 12 hours. The solvent was removed under reduced pressure and the residue was dissolved in water (5 ml). The product was extracted with dichloromethane (4 x 20 ml). The extract was dried (magnesium sulfate) and evaporated under reduced pressure, the crude product as purified by column chromatography on silca gel with a mixture of dichloromethane, methanol (9.6:0.4) as an eluent to give 87 mg (20%) of **12**, mp 251-253°; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 3.55 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 6.65 (d, 1H, J = 8 Hz, $H_{5'}$), 6.68 (d, 1H, $H_{6'}$), 6.79 (s, 1H, $H_{2'}$), 11.37 (s, 1H, NH), 11.91 (s, 1H, NH); ms: (m/z) 296 (M^+); ir: ν 3020, 2940, 1650, 1625, 1515 cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}N_2O_4Cl$: C, 52.61; N, 9.44; H, 4.38. Found: C, 52.3; N, 9.3; H, 4.0.

2-(4-Morpholino)-4-methoxy-5-formylpyrimidine **13**.

Metallation of **1** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with 4-formylmorpholine (0.53 g, 4.6 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate (9:1) as an eluent 0.133 g (30%) of **13**, mp 101-103°; ^{1}H nmr (deuteriochloroform): δ 3.6-4 (m, 8H, CH_2), 4.05 (s, 3H, OCH_3), 8.65 (s, 1H, H_6), 10.0 (s, 1H, CHO); ms: (m/z) 223 (M^+), 192 (M^+-OCH_3); ir: ν 2960, 2920, 2820, 1670, 1540, 1530 cm^{-1}.

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.81; N, 18.81; H, 5.81. Found: C, 53.9; N, 18.9; H, 5.6.

2-(4-Morpholino)-4-methoxy-5-pyrimidinyl)methanol **14**.

To a stirred solution of **13** (0.12 g, 0.5 mmoles) in methanol (10 ml) was added sodium borohydride. After 30 minutes methanol was distilled under reduced pressure. The residue was extracted with dichloromethane (2 x 10 ml). The organic extract was dried (magnesium sulfate) and evaporated. The crude product was purified by column chromatography on silica gel with a mixture of dichloromethane, ethyl acetate 9:1 as an eluent to give 102 mg (85%) of **14**, mp 157-159°; ^{1}H nmr (deuteriochloroform): δ 3.3 (s, 1H, OH), 3.6-3.9 (m, 8H, CH_2), 4.0 (s, 3H, OCH_3), 4.4 (s, 2H, CH_2(OH), 8.0 (s, 1H, H_6); ir: ν 3360, 3260, 2980, 2850, 1610, 1550 cm^{-1}.

Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.33; N, 18.67; H, 6.67. Found: C, 53.6; N, 18.3; H, 6.7.

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