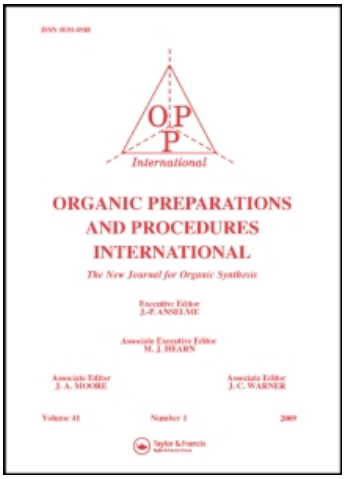

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FACILE SYNTHESIS AND AANTIMICROBIAL ACTIVITY OF SPIROBICYCLO[3.2.1]OCTANE-2',3-(4H)-[2H]-THIAZOLO[3,2-b]-s-TETRAZINES

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(10/14/91)

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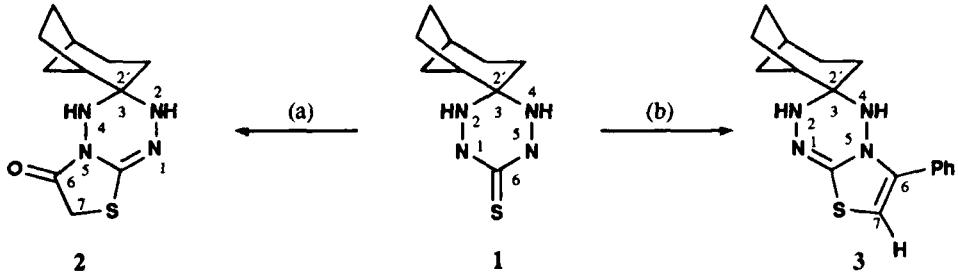
Thiazolo-s-tetrazines are of current interest because of their reported antimicrobial activity.[1] As a continuation of our earlier work on the synthesis of biologically active bridgehead nitrogen heterocyclic systems,[2] we now report the synthesis of novel bridgehead nitrogen spiro heterocyclic systems derived from spiro[bicyclo[3.2.1]octane-2',3-1,2,4,5-tetrahydro-s-tetrazine]-6-thione (**1**) and the biological activity associated with them.

Treatment of spiro[bicyclo[3.2.1]octane-2',3-1,2,4,5-tetrahydro-s-tetrazine]-6-thione (**1**), prepared from the reaction of bicyclo[3.2.1]octane-2-one with thiocarbohydrazide,[3] with chloroacetic acid or phenacyl chloride in anhydrous ethanol gave spiro[bicyclo[3.2.1]octane-2',3-(4H)-[2H]thiazolo[3,2-b]-s-tetrazine]-4"(5"H)-one (**2**) and spiro[bicyclo[3.2.1]octane-2',3-(4H)-[2H]-4"-phenylthiazolo[3,2-b]-s-tetrazine] (**3**). The structures of **2** and **3** were determined by elemental analysis, and IR and ^{1}H NMR spectral data. The presence of peak at 1725 cm^{-1} (C=O) in the IR spectrum of **2** and its absence in **3** supported the cyclic structures of **2** and **3**. This was confirmed by two proton and one proton singlets at δ 3.80 and 6.70 in the ^{1}H NMR spectra of **2** and **3** respectlvely. The molecular ion peaks at m/z 252 and m/z 348, respectively, in the mass spectra of **2** and **3** further confirmed their cyclic nature.

Compounds **2** and **3** were evaluated for their antimicrobial activity against gram-positive *Staphylococcus aureus*, gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* and the fungus *Candida albicans*. Neat samples and serial plate dilution method were used.[4] The minimum inhibitory concentration (M.I.C.) of compound **2** against *C. albicans* and *E. coli* were 500 μg/mL and 250 μg/mL, respectively. Compound **3** was active against *C. albicans* and *E. coli* when tested as a neat sample. It might, therefore, be used for local application in the form of powder or ointment provided further studies indicate an absence of toxicity following local application.



2 **1** **3**

a) $ClCH_2COOH$, NaOAc. b) $PhCOCH_2Cl$

EXPERIMENTAL SECTION

TLCs were run on silica-gel plates using acetone-benzene (1:3) as an eluting solvent. Melting points are uncorrected. IR and ^{1}H NMR spectra were recorded in $CDCl_3$ on Perkin-Elmer 722B and Burker AM-400 MHz spectrometers, respectively, and chemical shifts are referenced to TMS. Mass spectra were scanned on a Jeol JMSD-300 mass spectrometer operating at 70 eV.

Spiro[bicyclo[3.2.1]octane-2',3-1,2,4,5-tetrahydro-s-tetrazine]-6-thione (1).- Bicyclo[3.2.1]octane-2-one (1.24 g, 0.01 mol) in ethanol (2 mL) was added dropwise with constant stirring to a solution of thiocarbohydrazide (1.06 g, 0.01 mol) in hot water (20 mL). The reaction mixture was allowed to stand for 24 hrs. The precipitated product was collected, washed well with water, and crystallized from ethanol as colorless needles (1.50 g, 70%), mp. 170°. IR: 1100 (C=S), 1540 (C-N stretching), 3250, 3475 (N-H stretching) cm^{-1}.

Anal. Calcd.for $C_9H_{16}N_4S$: C, 50.94; H, 7.54; N, 26.42; S, 15.10

Found: C, 50.78; H, 7.69; N, 26.28; S, 15.28

Spiro[bicyclo[3.2.1]octane-2',3-(4H)-[2H]-thiazolo[3,2-b]-s-tetrazine]-4"(5"H)-one (2).- A mixture of **1** (0.636 g, 0.003 mol), chloroacetic acid (0.285 g, 0.003 mol) in anhydrous ethanol (20 mL) was heated under reflux for 5 hrs, cooled and poured into water. The resulting solution was concentrated and kept overnight at room temperature. The precipitated solid was collected, washed with water, and crystallized from ethanol to give yellowish needles (0.32 g, 42%), mp. 135°. IR: 1520 (C-N stretching), 1595, 1630 (C=C and C=N), 1725 (C=O), 3350, 3480 (N-H stretching) cm^{-1}. ^{1}H NMR δ 1.5-3.3 (12 H, m, CH_2 and CH protons of bicyclooctane moiety); 3.8 (2 H, s, CH_2); 4.60 (2 H, brs, NH, exchangeable with D_2O). MS: m/z 252 $(M)^+$.

Anal. Calcd. for $C_{11}H_{16}N_4OS$: C, 52.38; H, 6.34; N, 22.22; S, 12.70

Found: C, 52.22; H, 6.12; N, 22.48; S, 12.98

Spiro[bicyclo[3.2.1]octane-2',3-(4H)-[2H]-4"-phenylthiazolo[3,2-b]-s-tetrazine]Hydrochloride (3).- A mixture of **1** (0.636 g, 0.003 mol) and phenacyl chloride (0.465 g, 0.003 mol) in dry ethanol (20 mL) was heated under reflux for 4 hrs. The brown colored solution was concentrated and kept overnight at room temperature. Hydrochloride **3** which separated was collected and crystallized from ethanol furnishing light brown crystals (0.48 g, 46%), mp. 140°. IR: 700, 765 (monosubstituted benzene ring), 1515 (C-N stretching), 1590, 1625 (C=C and C=N), 3475 (N-H stretching) cm^{-1}. ^{1}H NMR δ 1.0-3.9 (12 H, m, CH_2 and CH protons of bicyclooctane moiety); 4.75 (2 H, s, NH, exchangable with D_2O), 5.25 (1 H, s, $N^{\oplus}H$); 6.7 (1 H, s, C_7-H); 7.3-7.9 (5 H, m, Ph). MS: m/z 348 $[M]^+$.

Anal. Calcd.for $C_{17}H_{21}ClN_4S$: C, 58.54; H, 6.02; N, 16.07; S, 9.18

Found: C, 58.78, H, 5.89; N, 15.78; S, 9.32

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SYNTHESIS OF EVERNIPENTANONE BY ADDITION OF *n*-BUTYLLITHIUM ON ETHYL EVERNINATE

Submitted by (03/30/92)

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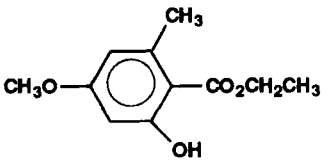
The preparation of tertiary alcohols by addition of organolithiums to esters has been suggested to proceed *via* the intermediate ketones from theoretical deductions and demonstrated by infrared spectroscopy of the Li-complexes in solution.[1] The present work describes the synthesis of 2-hydroxy-4-methoxy-6-methylvalerophenone (evernipentanone, **2**) by addition of *n*-butyllithium to ethyl everninate (**1**), thus adding a major argument to the theory.

When *n*-butyllithium was added to methyl 2,4,6-trimethylbenzoate, the starting material was



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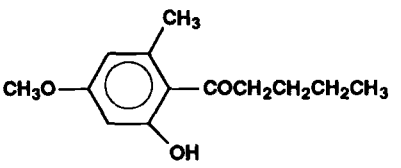

2

recovered quantitatively because of steric hindrance, whereas methyl 2-hydroxy-4-methoxybenzoate gave the expected tertiary alcohol. It therefore appeared that the formation of evernipentanone (**2**) is