Synthesis of Some Fused Thiomorpholine Azaheterocycles

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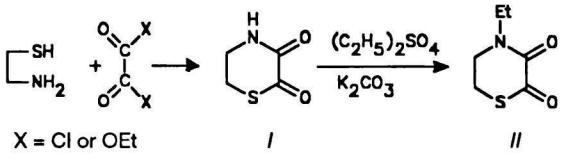
4-Ethylthiomorpholine-2,3-dione (*II*) reacted with thiosemicarbazide and yielded the 1,2,4-triazine derivative. This product when reacted with 2-chloro-3-aminopyridine gave the azine compound. Reaction of *II* with thiourea gave 4-ethylthiomorpholinoimidazole-2-thione.

The number of publications on the chemistry of 1,2,4-triazines and 1,2,4-triazoles [1—4] has increased tremendously during last years due to their herbicidal [5—7] and biological activities [7—12]. These compounds are aza analogue of pyrimidine nucleobase and a number of natural antibiotics (Reumycin) are considered to be pyrimido[5,4-*e*]-[1,2,4]-triazines [13, 14].

In the hope of obtaining more potent biologically active products, the author replaced thiomorpholine moiety by pyrimidine and could synthesize some fused thiomorpholine azaheterocycles. 4-Ethylthiomorpholine-2,3-dione (*II*) is a suitable substrate for these preparations.

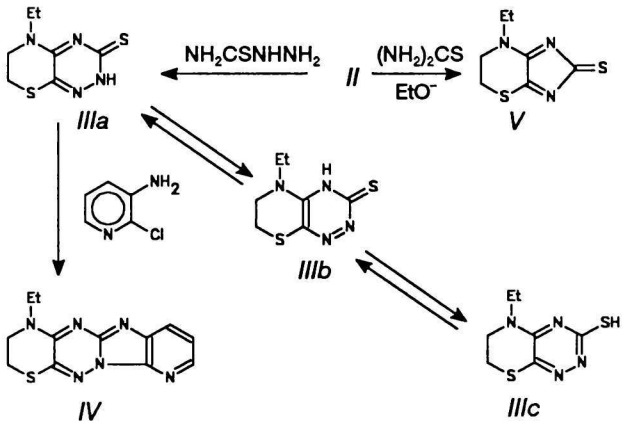
Thiomorpholine-2,3-dione (*I*) was prepared by the reaction of 1-aminoethane-2-thiol with diethyl oxalate or oxalyl chloride. This product was reacted with diethyl sulfate in acetone and in the presence of anhydrous potassium carbonate to give *II* (Scheme 1).



I *II*

Scheme 1

Reaction of *II* with thiosemicarbazide gave 5-ethyl-2,3,6,7-tetrahydro-1,4-thiazino[3,2-*e*]-[1,2,4]-triazine-3-thione (*IIIa*). This product is suggested to be formed *via* losing of two molecules of water, product *III* could be existing in the forms *IIIb* and *IIIc* (Scheme 2). Treatment of *IIIa* with 2-chloro-3-aminopyridine gave the fused system 4-ethyl-2,3-dihydro-pyrido[2″,3″:4′,5′]imidazo[2′,3′:2,3]triazino-[5,6-*b*]-[1,4]-thiazine (*IV*). Formation of *IIIa* is suggested to proceed *via* the attack of hydrazine



Scheme 2

moiety in thiosemicarbazide on the oxo group in the position 3 of dione *II* followed by formation of the unisolable intermediate 2-amino-5-ethyl-1,4-thiazino[2,3-*b*]-[1,3,4]-thiadiazine and under Dimroth rearrangement the more thermodynamically stable forms of *III* were obtained. Compound *IV* is suggested to be formed *via* the hydrogen sulfide and hydrogen chloride loss. As the same time treatment of *II* with thiourea in ethanolic sodium ethoxide gave 4-ethyl-2,3-dihydro-6*H*-1,4-thiazino[3,2-*e*]imidazole-6-thione (*V*). It is believed that these reactions take place *via* the attacks of nucleophiles on the position 3 followed by the position 2 in compound *II*.

EXPERIMENTAL

Melting points are measured on an electrothermal apparatus. IR spectra (KBr) were determined on a Pye—Unicam instrument and ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer (90 MHz). Microanalytical data were determined at the Cairo University, Egypt.

Thiomorpholine-2,3-dione (*I*)

Method A. An equimolar ratio of 1-aminoethane-2-thiol and diethyl oxalate (0.02 mol) in ethanol (100 cm^3) was heated under reflux for 6 h. Evaporation of excess ethanol left a viscous oil which on purification from benzene gave brown crystals, m.p. = 202 °C (76 % yield).

Method B. To 1-aminoethane-2-thiol (0.02 mol; 1.26 g) in dry benzene (50 cm^3), oxalyl chloride (0.023 mol; 0.3 g) in dry benzene (50 cm^3) was added in portions with stirring. After complete addition, stirring was continued for further 3 h at room temperature, then the reaction mixture was left aside overnight. Distillation of benzene gave brown crystals, m.p. = 201—203 °C (62 % yield).

For $C_4H_5NO_2S$ (M_r = 131.07) w_i(calc.): 36.65 % C, 3.84 % H, 24.41 % S; w_i(found): 36.5 % C, 4.0 % H, 24.5 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1420 ν(C—S—C), 1680 ν(S—C=O), 1760 ν(N—C=O), 3250 ν(NH). ^1H NMR spectrum ($CDCl_3$), δ: 3.1 (t, 2H, CH_2N), J = 1.0 Hz, 2.6 (t, 2H, CH_2S), J = 1.0 Hz, 5.8 (s, 1H, NH).

4-Ethylthiomorpholine-2,3-dione (*II*)

To *I* (0.01 mol) in acetone (50 cm^3), diethyl sulfate (0.012 mol) in acetone (50 cm^3) was added followed by anhydrous potassium carbonate (3 g). Heating the reaction mixture under reflux for 3 h and pouring into cold water while stirring gave a white precipitation which on recrystallization from ethanol gave *II* (77 % yield), m.p. = 184 °C.

For $C_6H_9NO_2S$ (M_r = 159.124) w_i(calc.): 45.28 % C, 5.65 % H, 20.11 % S; w_i(found): 45.3 % C, 5.7 % H, 20.2 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 1685 ν(C=O), 1735 ν(C=O, amide). ^1H NMR spectrum (DMSO), δ: 3.0 (t, 2H, CH_2N), J = 1.0 Hz, 2.7 (t, 2H, CH_2S), J = 1.0 Hz, 1.8 (t, 3H, CH_3), J = 1.0 Hz, 4.1 (q, 2H, CH_2), J = 1.1 Hz.

5-Ethyl-2,3,6,7-tetrahydro-1,4-thiazino[3,2-*e*]-[1,2,4]-triazine-3-thione (*IIIa*)

An equimolar ratio of *II* (1.6 g; 0.01 mol) and thiosemicarbazide (0.91 g; 0.01 mol) in absolute ethanol (100 cm^3) and triethylamine (1 cm^3) was heated under reflux for 7 h. After cooling the separated solid product was collected and recrystallized from benzene to give *IIIa* in the form of yellowish white needles (86 % yield), m.p. = 285 °C.

For $C_7H_{10}N_4S_2$ (M_r = 214.18) w_i(calc.): 39.25 % C, 4.66 % H, 26.1 % N, 29.88 % S; w_i(found): 39.3 % C, 4.7 % H, 26.0 % N, 30.0 % S. IR spectrum, $\tilde{\nu}/cm^{-1}$: 3320 ν(NH). ^1H NMR spectrum (DMSO), δ: 3.2 (t, 2H, CH_2N), J = 1.1 Hz, 2.2 (t, 2H, CH_2—S), J = 0.9 Hz, 1.6 (t, 3H, CH_3), J = 1.0 Hz, 4.1 (q, 2H, CH_2), J = 1.2 Hz, 5.2 (s, 1H, NH).

4-Ethyl-2,3-dihydro-pyrido[2″,3″:4′,5′]imidazo-[2′,3′:2,3]triazino[5,6-*b*]-[1,4]-thiazine (*IV*)

To *II* (0.01 mol; 2.14 g) in ethanol (100 cm^3) a catalytic amount of triethylamine (1 cm^3) was added followed by 2-chloro-3-aminopyridine (0.01 mol; 1.3 g). Then the reaction mixture was heated under reflux for 6 h. After cooling, the separated solid product was filtered and recrystallized from dimethylformamide to give *IV* in the form of white crystals (62 % yield), m.p. = 302—303 °C.

For $C_{12}H_{12}N_6S$ (M_r = 272.264) w_i(calc.): 52.93 % C, 4.44 % H, 30.86 % N, 11.75 % S; w_i(found): 53.9 % C, 4.5 % H, 31.0 % N, 12.0 % S. ^1H NMR spectrum (DMSO), δ: 3.1 (t, 2H, CH_2N), J = 1.1 Hz, 2.6 (t, 2H, CH_2S), J = 1.0 Hz, 1.6 (t, 3H, CH_3), J = 1.1 Hz, 4.1 (q, 2H, CH_2), J = 1.2 Hz, 6.6—6.8 (dd, 3H, pyridine), $J_{4,6}$ = 1.3 Hz, $J_{5,6}$ = 5.1 Hz.

4-Ethyl-2,3-dihydro-6*H*-1,4-thiazino[3,2-*e*]imidazole-6-thione (*V*)

Compound *II* (0.01 mol; 1.6 g) and thiourea (0.01 mol; 0.76 g) in ethanolic sodium ethoxide (0.011 mol; 0.75 g/100 cm^3) were heated under reflux for 3 h. After cooling and neutralization with cold dilute hydrochloric acid, the separated solid product was filtered, washed with water and recrystallized from dimethylformamide to give *V* in the form of pale yellow crystals (76 % yield), m.p. = 226 °C.

For $C_7H_9N_3S_2$ (M_r = 199.167) w_i(calc.): 42.21 % C, 4.518 % H, 21.09 % N, 32.13 % S; w_i(found): 42.2 % C, 4.5 % H, 21.2 % N, 32.3 % S. ^1H NMR spectrum (DMSO), δ: 2.0 (t, 3H, CH_3), J = 1.1 Hz, 3.5 (q, 2H, CH_2), J = 1.0 Hz, 3.1 (t, 2H, CH_2—N), J = 0.9 Hz, 2.6 (t, 2H, CH_2—S), J = 1.2 Hz.

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5*H*-Isoindolo[1,2-*b*][3]benzazepines IX.* The ^{1}H and ^{13}C NMR Spectra of 5*H*-Isoindolo-[1,2-*b*][3]benzazepin-5-ones

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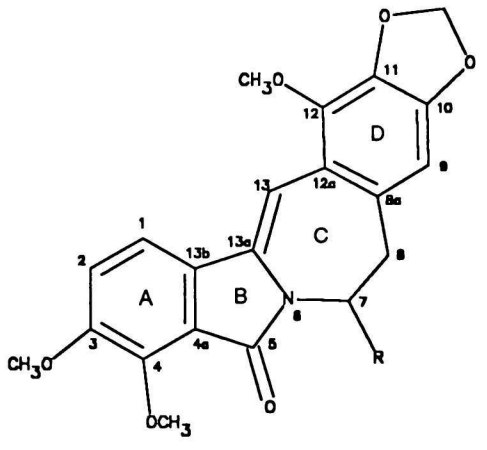
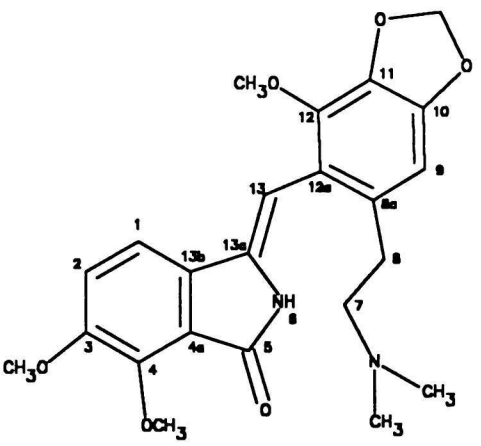
One- and two-dimensional NMR methods were employed for constitutional studies of 7,8-dihydro-5*H*-isoindolo[1,2-*b*][3]benzazepin-5-one derivatives synthesized from the unnatural alkaloid narceine imide. Their chemical shifts were compared with those of geometric isomers of substituted 1-benzylideneisoindolin-3-ones — synthetic precursors of the above-mentioned group of compounds.

Chilenine and lennoxamine, plant metabolites with an isoindolo[1,2-*b*][3]benzazepine ring system, isolated from species of the *Berberidaceae* family, constitute a new group of alkaloids [1]. Several synthetic procedures were developed for their preparation [2—4]; the secophthalideisoquinoline alkaloid narceine imide was the starting material for preparation of a series of derivatives and analogues of lennoxamine [5—7]. This paper presents the NMR study of 7,8-dihydro-5*H*-isoindolo[1,2-*b*][3]benzazepin-5-ones *I—III*, their model substances and their isomers *IV—VIII*.



I—III

	R
I	$N(CH_3)_2$
II	$OCOCH_3$
III	H



IV

* For Part *VIII* see *Chem. Papers 45,* 567 (1991).