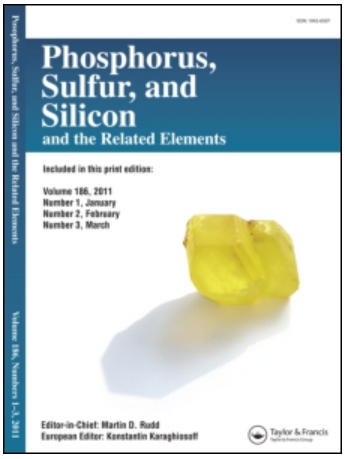

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M. M. Ghorab[a]; H. I. Heiba[a]; Mona A. El-gawish[b]
[a] Department of Drug Radiation Research, National Center for Radiation Research and Technology, Cairo, Egypt [b] Department of Radiation Biology, National Center for Radiation Research and Technology, Cairo, Egypt

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REACTIONS WITH ETHYL-4,5,6,7-TETRAHYDRO-2-ISOTHIOCYANATO-1-BENZOTHIOPHENE-3-CARBOXYLATE. SYNTHESIS OF SOME NOVEL HETEROCYCLIC COMPOUNDS WITH POTENTIAL HYPNOTIC ACTIVITY

M. M. GHORAB,† H. I. HEIBA† and MONA A. EL-GAWISH‡

†Department of Drug Radiation Research; ‡Department of Radiation Biology, National Center for Radiation Research and Technology, Nasr City, P.O. Box 29, Cairo, Egypt

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Ethyl-4,5,6,7-tetrahydro-2-isothiocyanato-1-benzothiophene-3-carboxylate (**2**), prepared from ethyl-4,5,6,7-tetrahydro-2-amino-1-benzothiophene-3-carboxylate (**1**) by the thiophosgene method, was converted with nucleophiles into benzothieno[2,3-d]pyrimidine derivatives (**3–5**) and (**7**) either directly or through thiourethane (**6a**). The tricyclic, benzothienopyrimidine systems (**8**) and (**9**) were obtained either from the isothiocyanate (**2**) or the thiourethane (**6a**), while the tetracyclic systems, triazolothienopyrimidines (**10, 11**); tetrazolothienopyrimidines (**12, 13**) and tetrazepino derivative (**14**), were obtained from 2,3,5,6,7,8-hexahydro-3-amino-2-hydrazino-1-benzothieno[2,3-d]pyrimidine-4(3H)-one (**9**). Preliminary pharmacological screening revealed that some of the new compounds exhibited hypnotic activity.

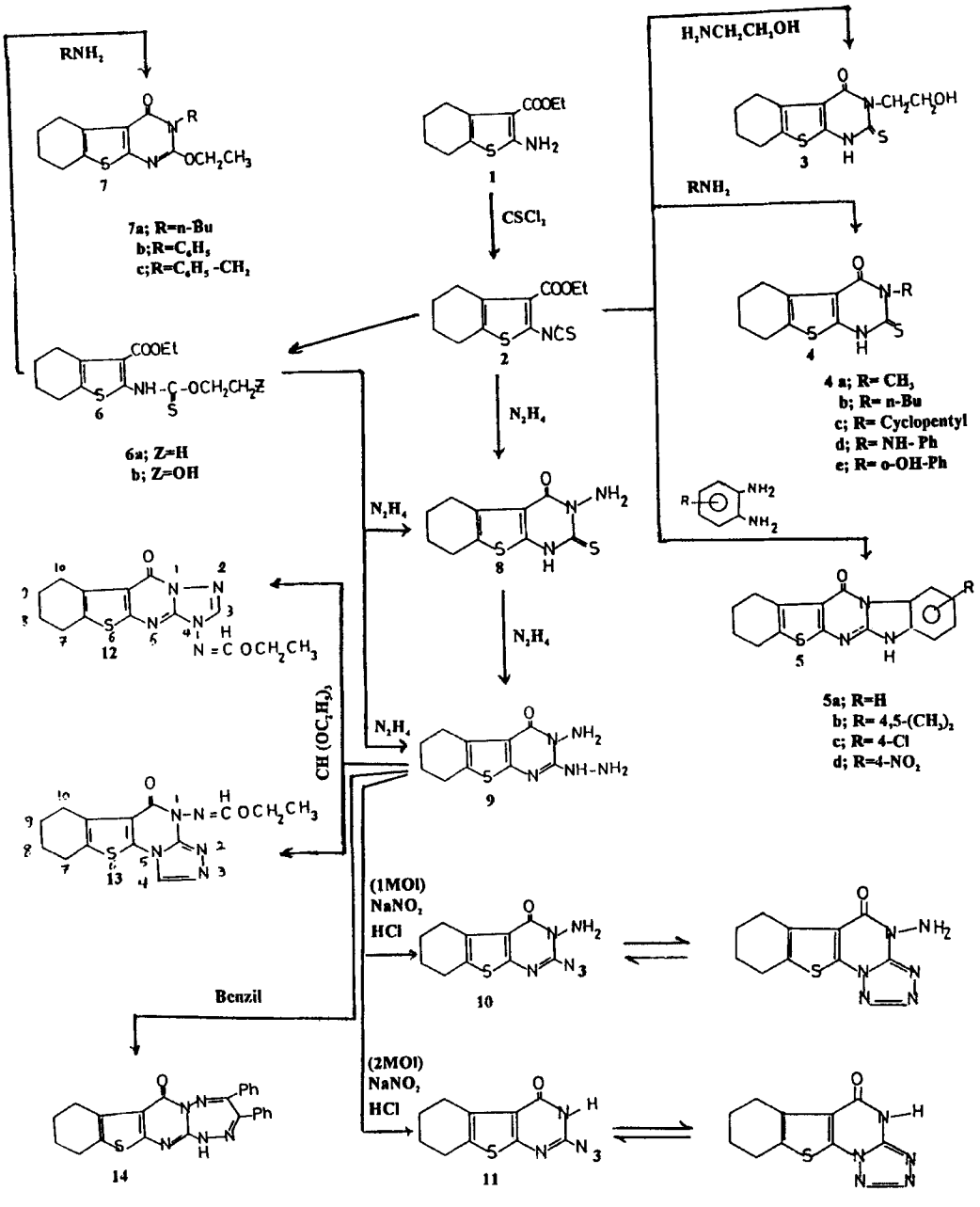
Key words: Thienopyrimidines, hypnotic activity.

INTRODUCTION

Aromatic and heterocyclic *o*-aminoester derivatives are strategic intermediates for the preparation of various condensed heterocyclic systems.[1] Although the chemistry of methyl-2-isothiocyanatobenzoate has been investigated intensively,[2–5] the number of publications on the synthesis and reactivity of heterocyclic isothiocyanates is very limited.[6] This prompted the authors to undertake the synthesis of (**2**) from (**1**)[7] and thiophosgene. Compound (**2**) since it contains two reactive groups at ortho positions is a versatile intermediate, which through reactions with some nucleophiles and alcohols, furnished a series of heterocyclic systems analogous to methaqualone, known with its potential hypnotic activity.[8,9] The sequence of reactions leading to the formation of the title compounds is depicted in (Scheme I).

RESULTS AND DISCUSSION

Condensation of (**2**) with aminoethanol resulted in the formation of 3-(2-hydroxyethyl)-2-thiooxo-benzothieno[2,3-d]pyrimidine-4(3H)one (**3**), while interaction of (**2**) with aliphatic or aromatic amines yielded the corresponding 2-thiooxo-3-substituted benzothieno[2,3-d]pyrimidine-4(3H)one (**4a–e**).



SCHEME I

The reaction of (**2**) with substituted 1,2-phenylenediamines resulted in the formation of the corresponding benzimidazopyrimidines (**5a–d**).

Interaction of (**2**) with anhydrous ethanol gave the corresponding thiourethane (**6a**), while treatment of (**2**) with ethylene glycol gave (**6b**).

Condensation of the thiourethane (**6a**) with aliphatic or aromatic amines in anhydrous ethanol yielded the anticipated 2,3,5,6,7,8-hexahydro-3-substituted-2-ethoxy[1]benzothieno[2,3-d]pyrimidine-4(3H)one (**7a–c**).

Treatment of the thiourethane (**6a**) with hydrazine hydrate in ethanol at room temperature afforded 3-amino-2-thiooxobenzothieno[2,3-d]pyrimidine-4(3H)one (**8**). The same product (**8**) was also obtained by reaction of (**2**) with hydrazine hydrate in dichloromethane at room temperature. On repeating the above reaction in boiling ethanol 2,3,5,6,7,8-hexahydro-3-amino-2-hydrazino[1]benzothieno[2,3-d]pyrimidine-4(3H)one (**9**) was formed. The same product (**9**) was also obtained by heating (**8**) with hydrazine hydrate.

In the present investigation 2-hydrazino-3-amino derivative (**9**) was used as starting material for the synthesis of the tetracyclic systems tetrazolobenzothienopyrimidine (**10**) and (**11**), thus, treatment of (**9**) with nitrous acid in a molar ratio (1:1) gave rise to the amino tetrazolobenzothienopyrimidine derivative (**10**). However upon treatment of (**9**) with nitrous acid in a molar ratio (1:2), deamination of the amino group at position 3 takes place resulting in the formation of (**11**).

Reaction of (**9**) with triethyl orthoformate gave two isomeric products, (**12**) and (**13**) depending on the cyclization took place either to the nitrogen at position 1 or at position 3. The structure determination of both systems is based on the ^{1}H-NMR spectra.[10] Namely, $4CH_2$ cyclo in (**13**) is shifted approximately for $\Delta\delta = 0.6$ ppm to lower field in comparison to the $4CH_2$ cyclo in the isomeric (**12**). This is further supported by the chemical shift of H_4; since H_4 in compound (**13**) appears at lower field than H_3 in compound (**12**).

Again reaction of (**9**) with benzil in xylene furnished the tetrazepino derivative (**14**).

EXPERIMENTAL

Mps are uncorrected. Elemental analyses were carried out in the microanalytical laboratories of the Faculty of Science, Cairo University. Ultra-violet and visible absorption spectra were examined using Beckman double beam spectrophotometer model 24, ranging from 190–700 nm. IR spectra (KBr) were measured on a Pye Unicam SP-1200 spectrophotometer, ^{1}H-NMR spectra recorded on a VARIAN GEMINI 200 (200 MHz, ^{1}H-NMR) using DMSO-d_6 as a solvent and TMS as an internal reference. Mass spectra were obtained using HP MODEL:MS-5988.

3-(2-Hydroxyethyl)-2-thiooxo-benzothieno[2,3-d]pyrimidine-4(3H)one (**3**): A mixture of **2**[11] (0.01 mol) and aminoethanol (0.01 mol) in tetrahydrofurane (10 ml) was stirred at room temperature for 24 h. The precipitate was filtered and recrystallized from ethanol to give (**3**), (82% yield) (Table I), ν_{max}/cm^{-1} 3500 (OH), 3250 (NH), 2900 (CH) aliphatic and 1680 (C=O), δH [$^2H_6$] DMSO) 14.0 (1H, s, OH), 5.0 (1H, s, NH), 4.8 (2H, t, CH_2—O), 4.00 (2H, t, N—CH_2), 2.0, 2.8 (8H, 2s, $4CH_2$ cyclo). UV spectrum of (**3**) in dimethylsulfoxide showed λ_{max} at 258, 293, 355 nm and logε at 3.63, 3.88, 4.17.

2-Thiooxo-3-methyl-benzothieno[2,3-d]pyrimidine-4(3H)one (**4a**): A mixture of **2** (0.01 mol) and methylamine (33% solution) in anhydrous ethanol (10 ml) was stirred at room temperature for 1 h. The precipitate was collected by filtration and recrystallized from ethanol to give (**4a**) (72% yield) (Table I), ν_{max}/cm^{-1} 3250 (NH), 1700 (C=O), δH ([$^2H_6$] DMSO) 7.5 (1H, s, NH), 2.0, 2.8 (8H, 2s, $4CH_2$ cyclo), 1.3 (3H, s, CH_3); m/z 252 (M^+, 1.20%); 179 (100); 151 (50.28), 125 (9.92); 91 (18.01), 71 (7.71).

TABLE I

Characterization data for newly synthesized compounds

Compd. no.	M.p (T/°C)	Formula	Analyses Required(found)(%)		
			C	H	N
3	238	$C_{12}H_{14}N_2O_2S_2$	51.06(51.10)	4.96(4.90)	9.92(9.80)
4a	301	$C_{11}H_{12}N_2O\ S_2$	52.38(52.50)	4.76(4.80)	11.11(11.20)
4b	208	$C_{14}H_{18}N_2O\ S_2$	57.14(57.30)	6.12(6.00)	9.52(9.60)
4c	164	$C_{15}H_{18}N_2O\ S_2$	58.82(58.90)	5.88(5.90)	9.15(9.10)
4d	226	$C_{16}H_{15}N_3O\ S_2$	58.35(58.50)	4.55(4.60)	12.76(12.70)
4e	199	$C_{16}H_{14}N_2O_2S_2$	58.18(58.30)	4.24(4.10)	8.48(8.40)
5a	194	$C_{16}H_{13}N_3O\ S$	65.08(65.20)	4.40(4.30)	14.23(14.30)
5b	253	$C_{18}H_{17}N_3O\ S$	66.87(66.80)	5.26(5.20)	13.00(13.10)
5c	248	$C_{16}H_{12}ClN_3OS$	58.27(58.20)	3.64(3.70)	12.74(12.80)
5d	238	$C_{16}H_{12}N_4O_3S$	56.47(56.60)	3.52(3.60)	16.47(16.60)
6a	125	$C_{14}H_{19}N\ O_3S_2$	53.67(53.80)	6.07(6.20)	4.47(4.40)
6b	117	$C_{14}H_{19}N\ O_4S_2$	51.06(51.00)	5.77(5.70)	4.25(4.20)
7a	81	$C_{16}H_{22}N_2O_2S$	62.74(62.60)	7.18(7.10)	9.15(9.20)
7b	221	$C_{18}H_{18}N_2O_2S$	66.25(66.10)	5.52(5.60)	8.58(8.50)
7c	228	$C_{19}H_{20}N_2O_2S$	67.05(67.10)	5.88(5.80)	8.23(8.10)
8	267	$C_{10}H_{11}N_3O\ S_2$	47.43(47.60)	4.34(4.20)	16.60(16.50)
9	232	$C_{10}H_{13}N_5O\ S$	47.80(47.60)	5.17(5.10)	27.88(27.90)
10	137	$C_{10}H_{10}N_6O\ S$	45.80(45.90)	3.81(3.70)	32.06(32.20)
11	182	$C_{10}H_9\ N_5O\ S$	48.58(48.70)	3.64(3.50)	28.34(28.40)
12	189	$C_{14}H_{15}N_5O_2S$	52.99(52.90)	4.73(4.80)	22.08(22.00)
13	208	$C_{14}H_{15}N_5O_2S$	52.99(53.10)	4.73(4.60)	22.08(22.20)
14	172	$C_{24}H_{19}N_5O\ S$	67.76(67.60)	4.47(4.60)	16.47(16.40)

Formation of (**4b–d**): A mixture of **2** (0.01 mol) and required amines (0.01 mol) in dichloromethane (10 ml) was stirred at room temperature for 24 h. The precipitate was filtered, washed with methanol and recrystallized from ethanol to give (**4b**) (63% yield), (**4c**) (62% yield) and (**4d**) (31% yield) (Table I). **4b–d**; ν_{max}/cm^{-1} 3200 (NH). UV spectrum of (**4d**) in dimethylsulfoxide showed λ_{max} at 258, 355, 395 nm and logε at 3.57, 3.68, 3.72.

3-(2-Hydroxyphenyl)-2-thiooxo-benzothieno[2,3-d]pyrimidine-4(3H)one (**4e**): A mixture of **2** (0.01 mol) and *o*-aminophenol (0.01 mol) in tetrahydrofuran (10 ml) was heated under reflux for 5 h. The reaction mixture was cooled, filtered and recrystallized from ethanol to give (**4e**) (65% yield) (Table I), ν_{max}/cm^{-1} 3500 (OH).

Formation of benzimidazothienopyrimidines (**5a–d**): A mixture of **2** (0.01 mol) and the required 1,2-phenylenediamine (0.01 mol) in chloroform (10 ml) was heated under reflux for 6 h. The reaction mixture was cooled, filtered and recrystallized to give (**5a–d**) (64% yield) (Table I), ν_{max}/cm^{-1} 3350 (NH), 1680 (C=O) and 3100 (CH) aromatic; **5a** m/z 295 (M^+, 6.53%); 179 (100), 151 (69.83); 118 (24.53); 108 (41.81); 65 (24.96), **5b** δH ([$^2H_6$] DMSO) 12.8 (1H, s, NH), 7.2–7.7 (2H, d, arom.), 1.8, 2.6 (8H, 2s, $4CH_2$ cyclo) and 2.3 ppm (6H, s, $2CH_3$).

Formation of thiourethane (**6a**): A solution of **2** (0.01 mol) in anhydrous ethanol (10 ml) was heated under reflux for 24 h. The solvent was evaporated in vacuo and the solid obtained was recrystallized from ethanol to give (**6a**) (85% yield), ν_{max}/cm^{-1} 3200 (NH); 2900 (CH) aliphatic and 1700 (C=O); δH ([$^2H_6$] DMSO) 12.5 (1H, s, NH), 4.5 (4H, 2q, $2CH_2$), 2.0, 2.8 (8H, 2s, $4CH_2$ cyclo), 1.5 (6H, 2t, $2CH_3$). UV spectrum of (**6a**) in dimethylsulfoxide showed λ_{max} at 262, 350 nm and logε at 3.80, 4.11.

Reaction of (**2**) *with ethylene glycol*: To a solution of **2** (0.01 mol) in benzene (10 ml) ethylene glycol (0.01 mol) was added and the mixture was heated under reflux for 10 h. The precipitate, formed after cooling, was collected by filtration and recrystallized from acetic acid to give (**6b**) (59% yield) (Table I), ν_{max}/cm^{-1} 3500 (OH), 3150 (NH), 2900 (CH) aliphatic and 1680 (C=O).

3-Substituted-2-ethoxy-benzothieno[2,3-d]pyrimidine-4(3H)one (**7a–c**): To a solution of **6a** (0.01 mol) in anhydrous ethanol (10 ml), the required amine (0.01 mol) was added and the mixture was refluxed

for 24 h. The solvent was evaporated in vacuo, and the separated solid was recrystallized from ethanol to give (**7a–c**) (30–60% yield) (Table I), **7c**; ν_{max}/cm^{-1} 2900 (CH) aliphatic, 1680 (C=O); δH ([$^2H_6$] DMSO) 7.5–8.8 (5H, m, arom.), 4.4 (2H, q, CH_2 ethyl), 4.0 (2H, s, N—CH_2), 2.0, 2.8 (8H, 2s, $4CH_2$ cyclo); 1.5 (3H, t, CH_3 ethyl).

3-Amino-2-thiooxo-benzothieno[2,3-d]pyrimidine-4(3H)one (**8**): Method A: To a solution of **2** (0.01 mol) in dichloromethane (10 ml), hydrazine hydrate (0.012 mol) was added and the mixture was stirred at room temperature for 2 h. The precipitate was collected by filtration and recrystallized from dioxan to give (**8**) (55% yield) (Table I), ν_{max}/cm^{-1} 3330, 3270, 3150 and 3100 (NH_2, NH); 1670 (C=O), m/z 253 (M^+, 36%).

Method B: The same compound was prepared from **6a** (0.01 mol) in ethanol (10 ml) and hydrazine hydrate (0.012 mol) by stirring at room temperature for 48 h in (65% yield).

3-Amino-2-hydrazino-benzothieno[2,3-d]pyrimidine-4(3H) one (**9**). *Method A*: A solution of (0.01 mol) **6a** and hydrazine hydrate (0.012 mol) in ethanol (10 ml) was heated under reflux for 2 h. The reaction mixture was cooled, filtered and recrystallized from ethanol to give (**9**) (89% yield) (Table I), ν_{max}/cm^{-1} 3400, 3350, 3200 and 3150 (NH_2, NH), 1690 (C=O). δH ([$^2H_6$] DMSO) 8.5 (1H, broad, NH), 4.5, 5.5 (4H, 2S, $2NH_2$) and 1.8, 2.8 ppm (8H, 2s, $4CH_2$ cyclo). UV spectrum of (**9**) in dimethylsulfoxide showed λ_{max} at 265, 273, 320 nm and logε at 3.74, 3.75, 3.69.

Method B: To a suspension of **8** (0.01 mol) in ethanol, (10 ml) hydrazine hydrate (0.012 mol) was added and the mixture was heated under reflux for 6 h. The precipitate was collected by filtration and recrystallized from ethanol to give (**9**) (75% yield).

Formation of amino-tetrazolothienopyrimidine derivative (**10**): To a stirred suspension of **9** (0.01 mol) in a mixture of acetic acid (8 ml) and water (4 ml) a solution of sodium nitrite (0.01 mol) in water (6 ml) was added dropwise at 0°C. The mixture was left in the refrigerator for 12 h and the precipitate was collected by filtration and recrystallized from chloroform to give (**10**) (31% yield) (Table I), ν_{max}/cm^{-1} 2160 (N_3); 3320, 3200 (NH_2); m/z 262 (M^+, 2.73%); 57 (100); 246 (4.55); 219 (5.45); 193 (25.91); 179 (10.45); 151 (15.91), 105 (19.09); 83 (33.64).

Formation of (**11**): To a stirred suspension of **9** (0.01 mol) in a mixture of acetic acid (8 ml) and water (4 ml) a solution of sodium nitrite (0.02 mol) in water (6 ml) was added dropwise at 0°C. The reaction mixture was cooled, filtered and recrystallized from chloroform to give (**11**) (87% yield) (Table I), ν_{max}/cm^{-1} 2160 (N_3), 3250 (NH).

Formation of (**12**) *and* (**13**): A mixture of **9** (0.01 mol) and triethyl orthoformate (15 ml) was heated under reflux for 10 h. The reaction mixture was cooled and filtered. The solid obtained was dissolved in (3 ml) ethanol and separated by column chromatography (Kieselgel 60, 0.40–0.063 mm, E. Merck, and chloroform/methanol, 9:1, as solvent) into two fraction. The first fraction gave after evaporation

TABLE II

Effect of the test compounds (**3**), (**5b**), (**9**) and (**10**) on the righting reflex in adult rats

Compound and dose (mg/kg)		No.of rats out of that lost righting reflex	% Response
Diethylbarbituric acid sodium	250	3	75
	400	4	100
(3)	250	2	50
	400	3	75
(5b)	250	2	50
	400	4	100
(9)	250	2	50
	400	3	75
(10)	250	1	25
	400	4	100

of solvent in vacuo (12) (25% yield) (Table I), ν_{max}/cm^{-1} showed absence of (NH_2, NH), δH ($CDCl_3$) 8.7 (1H, s, H_3), 8.4 (1H, s, H_4), 4.6 (2H, q, OCH_2CH_3), 2.8, 3.2 (8H, 2s, $4CH_2$ cyclo); 1.5 (3H, t, OCH_2CH_3); m/z 317 (M^+, 96%), 245 (100), 218 (30.24); 161 (16.53); 135 (16.48); 111 (29.41); 55 (49.54).

The second fraction gave after evaporation of solvent in vacuo (**13**) (20% yield) (Table I); ν_{max}/cm^{-1} showed absence of (NH_2, NH), δH ($CDCl_3$) 9.2 (1H, s, H_4), 8.6 (1H, s, H_1), 4.9 (2H, q, OCH_2CH_3), 3.4, 3.7 (8H, 2s, $4CH_2$ cyclo), 1.8 (3H, t, OCH_2CH_3).

Formation of tetrazepine derivative (**14**): A mixture of **9** (0.01 mol) and benzil (0.01 mol) in xylene (20 ml) was heated under reflux for 7 h. The solvent was evaporated in vacuo and the solid obtained recrystallized from ethanol to give (**14**) (78% yield) (Table I), ν_{max}/cm^{-1} 3180 (NH), m/z 425 (M^+, 0.11%); 222 (100), 367 (68.81), 250 (90.96), 170 (66.73), 117 (6.92), 90 (1.84).

Testing for hypnotic activity: The criterion for the presence of hypnosis was the loss of righting reflex.[12] Adult albino rats (100–120 g) were used in this study. Diethylbarbituric acid sodium was used as the reference standard in addition to the test compounds (**3**), (**5b**), (**9**), and (**10**). The animals were divided into groups, each comprising 4 animals. One group was left as control and was injected (i.p) with 0.2 ml of isotonic saline. The other groups were injected with the tested compounds, suspended in water with few drops of tween-80, using doses of 250 and 400 mg/kg body weight. The animals were left in separate cages, and the onset and duration of hypnosis was recorded. The results obtained are represented in Table II. The tested compounds show certain hypnotic activity where compound (**5b**) is the most effective one. All the tested compounds are less effective than diethylbarbituric acid sodium.

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