Synthesis of 2-Phenyl-3,4-dihydro-2*H*- and -3,4,5,6-tetrahydro-2*H*-1,6-benzothiazocine Derivatives

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The resynthesis of 2-phenyl-3,4-dihydro-2*H*-benzothiazocin-5(6*H*)-one (**1**) was investigated in order to prepare derivatives with potential CNS activity. Lactam **1** could be converted to amidine derivatives **6a-e** *via* the intermediacy of the thioether **5a**. Reduction of **1** with lithium aluminum hydride gave amine **8a**. Reductive alkylation of **8a** gave **9a** and **9b** while acylation of **8a** gave derivatives **10a-d**. No interesting biological properties were found for these compounds.

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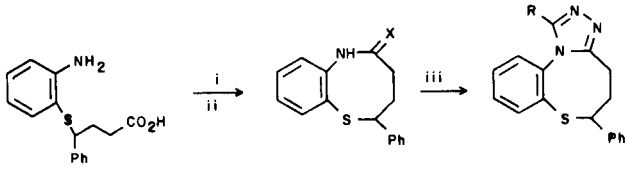
Discussion.

The chemistry of 2-phenyl-3,4-dihydro-2*H*-1,6-benzothiazocin-5(6*H*)-one (**1**) has not been reported in spite of the fact that **1** was prepared twenty years ago [1]. As a result of the CNS activity of related compounds [2] as well as our continuing interest in benzo-fused heterocycles with potential biological activity, we decided to prepare several derivatives of **1**.

Lactam **1** was prepared using essentially the literature procedure [1]. However, ring closure of amino acid **2** was achieved in much greater yield using dicyclohexylcarbodiimide rather than thionyl chloride which was used previously (59% *vs* 31%). Preparative hplc was the most effective method to purify **1** (Scheme 1). Lactam **1** could be activated for further reactions by conversion to thiolactam **3** by means of phosphorus pentasulfide. Reaction of **3** with formic acid hydrazide produced the novel triazole derivative **4a**. Interestingly, attempts to prepare the methyl analogue **4b** using acetic acid hydrazide failed to give a characterizable product.

Scheme 1

i. $C_6H_{11}N{=}C{=}NC_6H_{11}/CH_2Cl_2$/room temperature. ii. P_2S_5/pyridine/-heat. iii. $HCONHNH_2$/Ethanol/heat.

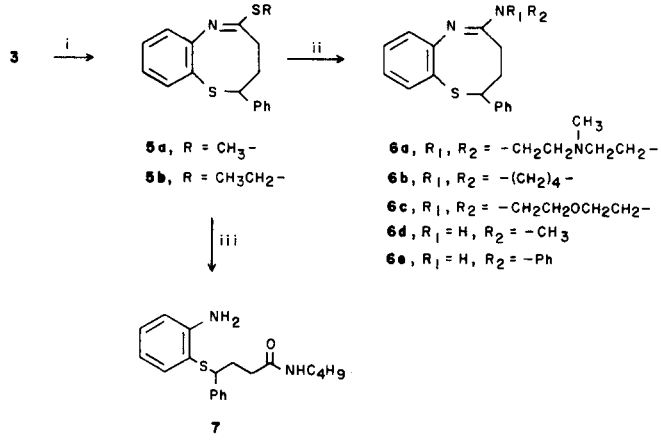


2 — **1**, X = O; **3**, X = S — **4a**, R = H; **4b**, R = CH_3

We were interested in preparing amidine derivatives of **1**. In this regard, **3** was converted to thiomethyl ether **5a** or, less preferably, thioethyl ether **5b** which were reacted with amines to give the desired derivatives **6a-e** (Scheme 2). *N*-Methylpiperazinyl derivative **6a** and methylamino derivative **6d** were characterized as fumarate salts whereas **6b, c** and **e** did not form crystalline derivatives. When **5a** was heated with butylamine under identical conditions as used to form **6d** only amino amide **7** formed; no trace of the butylamine analogue of **6d** was found. Attempts to cyclize **7** failed to give the desired derivative of **6**.

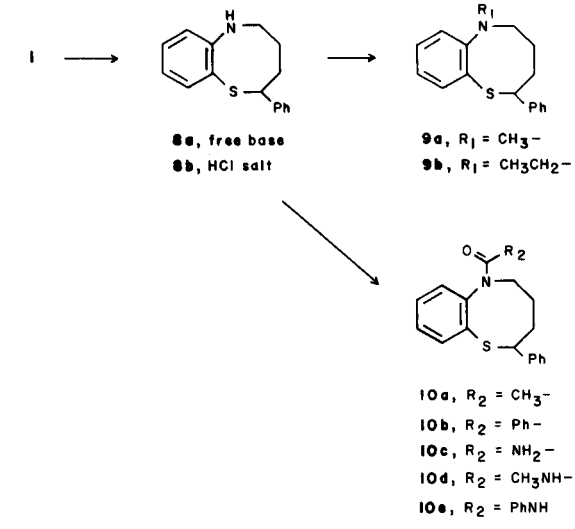
Scheme 2

i. NaH/RI/DMF. ii. R_1R_2NH/heat. iii. $C_4H_9NH_2$/heat.



Scheme 3

i. $LiAlH_4$/ether/heat. ii. $RCO_2H/NaBH_4$/0°.



Lactam **1** was reduced to amine **8a** by lithium aluminum hydride in quantitative yield and the product was storable for extended periods of time at room temperature as the hydrochloride salt **8b**. Alkylation of **8a** to methyl and ethyl derivatives **9a** and **9b**, respectively, was accomplished using the reductive alkylation procedure of Gribble [3]. Acyl derivatives **10a-10e** were prepared using standard methods.

Unfortunately, the derivatives prepared in this study were inactive in our biological assays [4] and no further work on this class of compounds is planned.

EXPERIMENTAL

Melting points were determined on a Mel-Temp capillary block melting point apparatus and are uncorrected. All compounds are homogeneous by thin layer chromatographic analysis using Whatman K5F or K65 (5 × 10 cm) silica gel analytical plates ^{1}H nmr measurements were obtained on a Varian Associates CFT-20 spectrometer with tetramethylsilane as the internal standard; shifts are reported in δ units in deuteriochloroform solvent unless otherwise noted.

3,4-Dihydro-2-phenyl-2*H*-1,6-benzothiazocin-5(6*H*)-one (**1**).

4-(*o*-Aminophenylthio)-4-phenylbutyric acid (17.1 g, 0.0595 mole) and *N,N'*-dicyclohexylcarbodiimide (13.55 g, 0.0658 mole) were combined in methylene chloride (175 ml) and stirred at room temperature for 18 hours. The reaction mixture was concentrated and the residue was purified on a Waters LC 500 hplc using 50% ethyl acetate in hexanes as the eluant. The pure product (10.30 g, 59%) mp 234-235° (lit [1] mp 228-230°).

Anal. Calcd. for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20; S, 11.90. Found: C, 71.09; H, 5.69; N, 5.25; S, 11.66.

3,4-Dihydro-2-phenyl-2*H*-1,6-benzothiazocin-5(6*H*)-thione (**3**).

Lactam **1** (14.42 g, 0.049 mole), phosphorus pentasulfide (3.1 g, 0.030 mole) and pyridine (250 ml) were refluxed for 24 hours. The solvent was removed *in vacuo* and the residue was triturated with 5% aqueous sodium carbonate (250 ml) for 1 hour. The solid was collected by filtration, washed with water and air dried. The product was purified by elution through a short column of magnesium silicate (12.9 g, 93%) and the analytical sample prepared by recrystallization from methylene chloride/hexanes, mp 198-199.5°; ms: m/z 285 (M^+); ^{1}H nmr: δ 7.30 (brs, 9H, aromatic *H*), 3.90 (m, 1H, s-C*H*), 2.7 (m, 4H, CH_2); uv (methanol): 293 nm.

Anal. Calcd. for $C_{16}H_{15}NS_2$: C, 67.33; H, 5.30; N, 4.91; S, 22.47. Found: C, 67.10; H, 5.35; N, 5.19; S, 22.86.

5,6-Dihydro-6-phenyl-4*H*-*s*-triazolo[3,4-*e*][1,6]benzothiazocine (**4**).

Thiolactam **3** (2.9 g, 0.010 mole) and formic acid hydrazide (0.71 g, 0.118 mole) were refluxed in xylenes (50 ml) for 18 days with *p*-toluenesulfonic acid (0.05 g) as a catalyst. The reaction mixture was concentrated and triturated with hexanes and then with water. The solid was dissolved in methylene chloride and the solution was dried with sodium sulfate and concentrated to give a dark yellow solid (2.80 g, 94%). The analytical sample was prepared from methylene chloride-ether, mp 163-165°; ms: m/z 293 (M^+); ^{1}H nmr: δ 8.25 (s, 1H, N-C*H*=N), 8.10 (m, 1H), 7.50 (m, 3H), 7.30 (s, 5H, all aromatic *H*), 3.80 (t, 1H, SC*H*), 3.6 (m, 2H, N=CCH_2), 2.45 (m, 2H, CH_2).

Anal. Calcd. for $C_{17}H_{14}N_3S$: C, 69.59; H, 5.15; N, 14.32; S, 10.93. Found: C, 69.25; H, 5.27; N, 14.36; S, 10.96.

3,4-Dihydro-5-(methylthio)-2-phenyl-2*H*-1,6-benzothiazocine (**5a**).

Thiolactam **3** (5.70 g, 0.020 mole) in dimethylformamide (25 ml) was treated with sodium hydride (1.2 g, 0.050 mole; prewashed with petroleum ether) and stirred for 0.5 hour. The resulting deep red solution was treated with methyl iodide (6.2 ml, 0.10 mole) dropwise (exothermic) and the mixture was stirred for 30 minutes. After cooling to 0°, the reaction was quenched with water (10 ml) and the mixture was concentrated. The residue was triturated with water and the resultant solid collected by filtration, purified by elution through magnesium silicate (chloroform eluant) and crystallized (4.55 g, 76%). The analytical sample was prepared from methanol, mp 91-92°; ms: m/z 299 (M^+); ir (potassium bromide): 1625 cm^{-1}; uv (methanol): 231, 295 nm; ^{1}H nmr: δ 7.77 (dd, 1H), 7.32 (brs, 6H), 7.04 (m, 2H, all aromatic *H*), 3.60 (m, 1H, SC*H*), 2.52 (s, 3H, SCH_3). 2.3 (m, 4H, CH_2).

Anal. Calcd. for $C_{17}H_{17}NS_2$: C, 68.18; H, 5.72; N, 4.68; S, 21.41. Found: C, 68.18; H, 5.64; N, 4.55; S, 21.55.

Compound **5a** could also be prepared in 50% yield by the action of potassium hydroxide and dimethylsulfate on **3**.

3,4-Dihydro-5-(ethylthio)-2-phenyl-2*H*-1,6-benzothiazocine (**5b**).

In a similar manner as for **5a**, **3** (0.57 g, 0.0020 mole) was treated with sodium hydride (0.12 g, 0.0050 mole) and then with ethyl iodide (0.83 ml, 0.010 mole) to give **5b** (0.34 g, 54%) upon work-up, mp 95-96°; ms: m/z 313 (M^+); uv (methanol): 232 sh, 265; ir (potassium bromide): 1640 cm^{-1}; ^{1}H nmr: δ 7.76 (d, 1H), 7.34 (brs, 6H), 7.0 (m, 2H, all aromatic *H*), 3.60 (m, 1H, SC*H*), 3.12 (q, 2H, SCH_2), 2.2 (m, 4H, CH_2), 1.42 (t, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{19}NS$: C, 68.97; H, 6.11; N, 4.47; S, 20.46. Found: C, 69.23; H, 6.15; N, 4.32; S, 20.41.

3,4-Dihydro-5-(4-methyl-1-piperazinyl)-2-phenyl-2*H*-1,6-benzothiazocine Difumarate (**6a**).

Methylthio ether **5a** (1.00 g, 0.0033 mole), *N*-methylpiperidine (15 ml) and glacial acetic acid (4 drops) were combined and refluxed 48 hours. The reaction mixture was concentrated and the residue dissolved in 2*N* acetic acid. The solution was filtered through diatomaceous earth, cooled to 0° and basified with ammonium hydroxide. The aqueous layer was extracted with methylene chloride (3x) and the combined organic extracts were dried with sodium sulfate, filtered through magnesium silicate and concentrated to give **6a** (0.43 g, 37%). This material was dissolved in ethanol (hot 2.5 ml) and the solution was treated with fumaric acid (0.29 g, 0.0025 mole) dissolved in hot ethanol (2.5 ml). Ether was added to the hot ethanol solution and the mixture was cooled to −10°. The product was collected by filtration and recrystallized from ethanol:ether (1:2), 0.40 g (56%), mp 198-199°; ms: m/z 351 (M^+); ^{1}H nmr: δ 7.65 (dd, 1H), 7.27 (s, 5H), 7.20 (d, 1H), 6.90 (dd, 2H, all aromatic *H*), 6.65 (s, 4H, fumaric acid C*H*), 3.70 (m, 4H, =CNCH_2), 2.70 (m, 4H, CH_3NCH_2), 2.43 (s, 3H, NCH_3).

Anal. Calcd. for $C_{21}H_{25}N_3S{\cdot}2C_4H_4O_4$: C, 59.68; H, 5.70; N, 7.20; S, 5.49. Found: C, 59.85; H, 5.81; N, 7.67; S, 5.42.

3,4-Dihydro-2-phenyl-5-(1-pyrrolidinyl)-2*H*-1,6-benzothiazocine (**6b**).

In a manner similar to above, **5a** (0.5 g, 0.0017 mole) was treated with pyrrolidine (15 ml) and glacial acetic acid (4 drops) dissolved in xylenes (15 ml) and refluxed for 4 days. The product precipitated from the 2*N* acetic acid solution upon basifying with ammonium hydroxide and was collected by filtration (0.409 g, 76%). Purification was effected by filtration through magnesium silicate (methylene chloride eluant) and crystallization from methylene chloride-hexanes to give pure **6b**, mp 163-164°; ms: m/z 322 (M^+); uv (methanol); 255 sh, 262 nm; ir (potassium bromide): 1640 cm^{-1}; ^{1}H nmr: δ 7.74 (dd, 1H), 7.34 (brs, 6H), 7.0 (m, 2H, all aromatic *H*), 3.62 (m, 5H, SC*H* and NCH_2), 2.01 (m, 8H, CH_2).

Anal. Calcd. for $C_{20}H_{22}N_2S$: C, 74.44; H, 6.88; N, 8.69; S, 9.94. Found: C, 74.03; H, 6.88; N, 8.46; S, 9.64.

3,4-Dihydro-5-(1-morpholino)-2-phenyl-2*H*-1,6-benzothiazocine (**6c**).

Thioether **5a** (0.50 g, 0.0017 mole) was treated with morpholine (15 ml) and glacial acetic acid (0.1 ml) using the above procedures. The product was isolated as an oil (0.50 g, 89%) after basification with ammonium hydroxide; ms: m/z 338 (M^+); ir (potassium bromide): 1625 cm^{-1}; uv (methanol): 222 sh, 266 nm; ^{1}H nmr: δ 7.70 (dd, 1H), 7.45 (brs, 6H), 7.0 (m, 2H, all aromatic *H*), 3.75 (m, 9H, SC*H*, CH_2N, CH_2O), 2.25 (m, 4H, CH_2).

Anal. Calcd. for $C_{20}H_{22}N_2S$: S, 9.47; Found: S, 9.56.

3,4-Dihydro-5-methylamino-2-phenyl-2*H*-1,6-benzothiazocine Fumarate (**6d**).

Thioether **5a** (1.0 g, 0.0033 mole), methylamine (25 ml) and several crystals of *p*-toluenesulfonic acid were heated to 170-180° in a sealed tube for 2 days. The reaction mixture was concentrated to a thick oil and the residue dissolved in warm 2*N* acetic acid. The aqueous solution was filtered, basified with ammonium hydroxide and extracted with methylene chloride (3x). After drying the organic layers over sodium sulfate, concentration yielded 0.71 g (75%) of an oil which was converted to its fumarate salt as above, 0.21 g (21%), mp 199-200°; ms: m/z 282 (M^+); ^1H nmr (DMSO-d_6): δ 7.90 (m, 1H), 7.30 (brs, 8H, all aromatic *H*), 6.75 (s, 2H, fumarate C*H*), 3.80 (m, 3H, SCH_3), 3.10 (brs, 3H, NCH_3), 2.50 (m, 4H, CH_2).

Anal. Calcd. for $C_{17}H_{18}N_2S{\cdot}C_4H_4O_4$: C, 63.29; H, 5.57; N, 7.03; S, 8.05. Found: C, 63.35; H, 5.69; N, 7.00; S, 8.01.

5-Anilino-3,4-dihydro-2-phenyl-2*H*-1,6-benzothiazocine (**6e**).

Thioether **5a** (0.50 g, 0.0017 mole) was reacted with aniline in a manner similar to the above to give the product as an oil, 0.40 g (70%); ms: Calcd. for $C_{22}H_{23}N_2S$: 344.1347 (M^+). Found: 344.1348; uv (methanol): 276 nm; ir (neat) 1645, 1625 cm^{-1}; ^1H nmr: δ 7.3 (m, 14H, aromatic *H*), 4.22 (brs, 1H, N*H*), 3.69 (m, 1H, SC*H*), 2.3 (m, 4H, CH_2).

4-(*o*-Aminophenylthio)-*N*-butyl-4-phenylbutyramide (**7**).

Thioether **5a** (1.0 g, 0.0033 mole) was treated with butylamine (2 ml) in a sealed tube as above. Work-up gave the crude product as an oil (0.95 g, 100%). Filtration through magnesium silicate (chloroform eluant) and recrystallization from methylene chloride-hexanes gave the product as white crystals, 0.55 g (68%); mp 88-89°; ms: m/z 342 (M^+); uv (methanol): 304 nm; ir (potassium bromide): 1652 cm^{-1}; ^1H nmr: δ 7.25 (brs, 5H, phenyl *H*), 7.20 (m, 2H), 6.60 (m, 2H, both aromatic *H*), 5.39 (brs, 1H, N*H*), 4.22 (brs, 2H, CONH_2), 4.01 (m, 1H, SC*H*), 3.20 (q, 2H, NCH_2), 2.10 (m, 4H, ring CH_2), 1.2 (m, 4H, chain CH_2), 0.92 (t, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{26}N_2OS$: C, 70.13; H, 7.65; N, 8.18; S, 9.36. Found: C, 69.91; H, 7.60; N, 8.24; S, 9.30.

3,4,5,6-Tetrahydro-2-phenyl-2*H*-1,6-benzothiazocine (**8a**).

Lactam **1** (0.98 g, 0.00364 mole) and lithium aluminum hydride (0.55 g, 0.0145 mole) were refluxed in ether (50 ml) for 18 hours. The reaction was cooled and quenched by the sequential addition of 0.5 ml water, 0.5 ml 15% sodium hydroxide solution and 0.5 ml water. The reaction mixture was filtered, the solid washed with methylene chloride and the combined organic layers were treated with charcoal and sodium sulfate. Concentration and distillation gave the pure product (0.73 g, 79%), bp 152° (0.06 mm Hg); ms: m/z 255 (M^+); ir (neat): 3389, 3278 cm^{-1}; ^1H nmr: δ 7.50 (dd, 1H), 7.24 (brs, 5H), 7.2 (m, 1H), 6.9 (m, 2H, all aromatic *H*), 4.48 (brs, 1H, N*H*), 3.86 (m, 2H, NCH_2), 3.40 (m, 1H, SC*H*), 2.0 (m, 4H, CH_2).

Anal. Calcd. for $C_{16}H_{17}NS$: C, 75.25; H, 6.71; N, 5.48; S, 12.56. Found: C, 75.24; H, 7.04; N, 5.64; S, 12.39.

The hydrochloride salt **8b** formed quantitatively by the addition of ethanolic hydrogen chloride to an ethereal solution of **8a**; mp 234-235°.

Anal. Calcd. for $C_{16}H_{17}NS{\cdot}HCl$: C, 65.85; H, 6.22; N, 4.80; S, 10.99; Cl, 12.15. Found: C, 66.00; H, 6.38; N, 4.67; S, 10.67; Cl, 12.13.

3,4,5,6-Tetrahydro-6-methyl-2-phenyl-2*H*-1,6-benzothiazocine (**9a**).

Amine **8a** (0.50 g, 0.002 mole) was dissolved in formic acid (7 ml) and sodium borohydride (0.80 g, 0.021 mole) was added in portions at 0°. When addition was complete, the reaction was allowed to warm to room temperature. After stirring 18 hours, the reaction mixture was treated with an additional 0.5 g sodium borohydride and stirred for 6 hours. The mixture was quenched with water, basified with 10*N* sodium hydroxide and extracted wth chloroform. The organic layer was dried over sodium sulfate and concentrated to a yellow oil (0.488 g, 92%). The analytical sample was prepared using silica gel tlc (15% ethyl acetate-hexanes eluant); ms: m/z 269 (M^+); ^1H nmr: δ 7.25 (brs, 5H, phenyl *H*), 7.10 (m, 4H, aromatic *H*), 4.90 (dd, 1H, SC*H*), 3.50 (t, 2H, CH_2N), 2.90 (s, 3H, CH_3), 1.75 (m, 4H, CH_2).

Anal. Calcd. for $C_{17}H_{19}NS$: C, 75.79; H, 7.11; N, 5.20; S, 11.90. Found: C, 75.41; H, 7.10; N, 4.92; S, 11.65.

3,4,5,6-Tetrahydro-6-ethyl-2-phenyl-2*H*-1,6-benzothiazocine (**9b**).

Amine **8a** (0.55 g, 0.0021 mole) was treated in glacial acetic acid (7.5 ml) with sodium borohydride. Work-up as above and purification by silica gel tlc gave the product as a yellow oil, 0.57 g (92%); ms: m/z 283 (M^+).

Anal. Calcd. for $C_{18}H_{21}NS$: C, 76.27; H, 7.47; N, 4.94; S, 11.31. Found: C, 76.24; H, 7.58; N, 4.55; S, 11.31.

6-Acetyl-3,4,5,6-tetrahydro-2-phenyl-2*H*-1,6-benzothiazocine (**10a**).

Amine **8a** (0.51 g, 0.002 mole) was treated with acetic anhydride/pyridine (2:1 ratio, 9 ml) for 18 hours. The solvents were removed *in vacuo* and the residue was dissolved in methylene chloride. Concentration gave the product as an oil (0.45 g, 76%) which was crystallized from ether, mp 108-110°; ms: m/z 297 (M^+); ir (potassium bromide): 1650 cm^{-1}; ^1H nmr: δ 7.30 (m, 9H, aromatic *H*), 4.96 (m, 2H, NCH_2); 4.40 (m, 1H, SC*H*), 2.0 (m, 7H, CH_2, CH_3).

Anal. Calcd. for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71; S, 10.78. Found: C, 72.81; H, 6.55; N, 4.67; S, 10.98.

6-Benzoyl-3,4,5,6-tetrahydro-2-phenyl-2*H*-1,6-benzothiazocine (**10b**).

Amine **8a** (0.51 g, 0.002 mole) was treated with benzoyl chloride (0.5 ml, 0.0043 mole) in pyridine (5 ml) for 18 hours. Work-up as above gave the product which was purified on silica gel tlc to a white solid, 0.41 g (57%). The analytical sample was crystallized from methylene chloride-hexanes, mp 122-123°; ms: m/z 359 (M^+); ir (potassium bromide): 1639 cm^{-1}.

Anal. Calcd. for $C_{23}H_{21}NOS$: C, 76.84; H, 5.89; N, 3.90; S, 8.92. Found: C, 76.72; H, 6.04; N, 3.85; S, 9.14.

3,4,5,6-Tetrahydro-2-phenyl-6*H*-1,6-benzothiazocine-6-carboxamide (**10c**).

Amide hydrochloride **8b** (0.36 g, 0.0012 mole) was dissolved in glacial acetic acid (10 ml) and treated with potassium cyanate (0.10 g, 0.0012 mole). The mixture was warmed, poured into water (150 ml) and the aqueous solution extracted with methylene chloride (3x). The organic layer was washed with saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated to dryness, 0.30 g (82%). The analytical sample was recrystallized from ether, mp 135-137°; ms: m/z 298 (M^+); ir (potassium bromide): 1667 cm^{-1}; uv (methanol): 226 sh, 266 nm.

Anal. Calcd. for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39; S, 10.75. Found: C, 68.32; H, 6.10; N, 9.30; S, 11.04.

3,4,5,6-Tetrahydro-*N*-methyl-2-phenyl-6*H*-1,6-benzothiazocine-6-carboxamide (**10d**).

Amine **8a** (0.53 g, 0.0021 mole) in ether (3 ml) was added to methyl isocyanate (0.14 g, 0.0021 mole) in ether (2 ml) and the solution was stirred for 3 days. The precipitate was collected by filtration and washed with ether, 0.38 g (57%). The analytical sample was prepared by silica gel tlc (ethyl acetate eluant), 0.35 g (53%), mp 144-144.5°; ms: m/z 312 (M^+); uv (methanol): 224 sh, 260 nm; ir (potassium bromide): 1652 cm^{-1}; ^1H nmr: δ 7.29 (brs, 9H, aromatic *H*), 4.33 (brs, 1H, N*H*), 3.88 (m, 3H, SC*H*, NCH_2), 2.8 (d, 3H, NCH_3), 2.15 (m, 4H, CH_2).

Anal. Calcd. for $C_{18}H_{20}N_2OS$: C, 69.20; H, 6.45; N, 8.97; S, 10.26. Found: C, 69.48; H, 6.46; N, 8.93; S, 10.57.

3,4,5,6-Tetrahydro-2-phenyl-6*H*-1,6-benzothiazocine-6-carboxanilide (**10e**).

Amine **8a** (0.53 g, 0.0021 mole) in ether was treated as above with phenylisocyanate (0.44 g, 0.0044 mole) in ether to give the product **10e** as white crystals, 0.49 g (63%). The analytical sample was prepared from ether, 0.25 g (32%), mp 120-122°; ms: m/z 374 (M^+).

Anal. Calcd. for $C_{23}H_{22}N_2OS$: C, 73.76; H, 5.92; N, 7.48; S, 8.56. Found: C, 73.80; H, 6.19; N, 7.74; S, 8.49.

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