Synthesis of 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-11b-methyl[1,4]thiazino[3,4-*a*]isoquinoline Derivatives

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Alkylation of the 2-mercaptoacetamide **4a** with chloropropanone afforded the ketoamide **10** which on direct acid-catalyzed cyclization furnished **12**. The cyclization can be arrested at the stage of the enamide **11**. Periodate oxidation of **12** gave the equatorial sulfoxide **14**. Reduction of **12** with diborane led to **13** which was oxidized to yield a mixture of sulfoxides **17** and **18**. The configuration of **12**, **14**, **17**, and **18** was established on the basis of nmr data. Compounds **12**, **14**, and **18** showed an interesting degree of antihypertensive activity.

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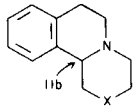
The hexahydrobenzo[*a*]quinolizine molecule **1** is a valuable template which has provided a variety of compounds with diverse biological activities. In contrast to the rather extensive literature on a number of related aza-, oxa-, and thia-systems, it is surprising to find that the hexahydro[1,4]thiazino[3,4-*a*]isoquinoline **2** received little attention (1).



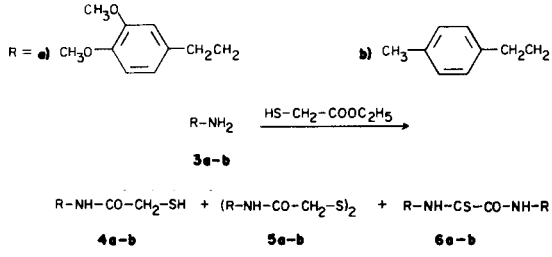
1 X = CH_2

2 X = S

Therefore, as a part of our program designed to develop novel antihypertensive agents it was deemed worthwhile to examine derivatives of the latter system **2** from both the chemical and pharmacological point of view. We felt that such derivatives should have an angular methyl substituent (position 11b), since it has been observed in the tetrahydroisoquinoline series that further increase of the antihypertensive activity may be achieved by the introduction of 1-methyl or 1,1-dimethyl groups (2-3). Furthermore, this angular methyl could protect the compounds against metabolic changes.

We now wish to report the preparation of the heretofore unknown 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-11b-methyl[1,4]thiazino[3,4-*a*]isoquinolines *via* the route shown in Scheme 3. The key precursor in this synthesis was the 2-mercaptoacetamide **4a**.

Scheme I



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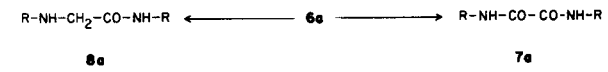
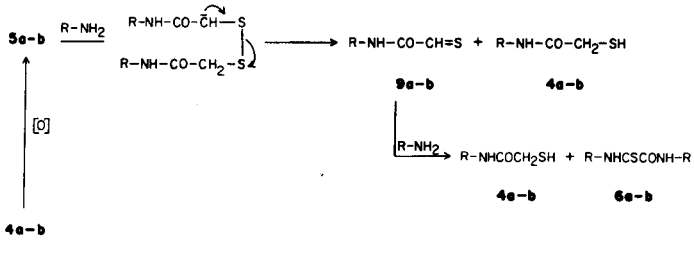


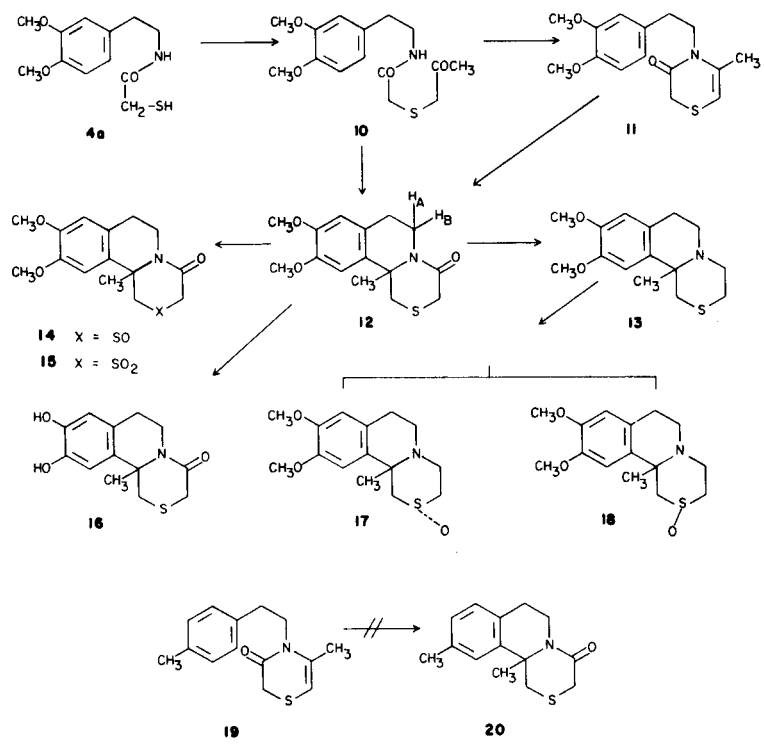
The condensation of 3,4-dimethoxybenzeneethanamine **3a** with ethyl 2-mercaptoacetate at 160-170° produced a mixture of three products (Scheme 1) which were readily separated by column chromatography and identified as the 2-mercaptoacetamide **4a** (48%), the corresponding disulfide **5a** (5.6%), and the ethanemonothiodiamide **6a** (23%). An analogous reaction of **3b** with ethyl 2-mercaptoacetate led to a mixture of **4b** (40%), **5b** (traces), and **6b** (23%). To confirm the structure of **6a**, this compound was exposed to sodium hydroxide in aqueous ethanol, and the reaction product **7a** was compared with an authentic sample (4). Upon desulfurization with Raney nickel, **6a** yielded the *N,N'*-bis-substituted glycinamide **8a**.

Scheme 2



A reasonable mechanistic pathway which explains the formation of **6a-b** is outlined in Scheme 2. The cleavage of the S-S bond has been observed with a number of nucleophiles (5,6), however, the primary amines have not been mentioned in this context. We suggest that the interaction of disulfides **5a-b** with R-NH_2 results in the abstraction of the α-proton, and the sulfur atom accepts the surplus of electrons to generate 2-mercaptoacetamides **4a-b** and thioxoacetamides **9a-b**. The latter compounds may undergo the Canizzaro reaction, and in the presence of amines R-NH_2 form directly ethanemonothiodiamides **6a-b**. This scheme also accounts for the product distribution: the disulfides **5a-b** are being constantly consumed whereas **4a-b** accumulate.

Scheme 3



The reaction of the 2-mercaptoacetamide **4a** with chloropropanone proceeded smoothly to give **10** (Scheme 3). Intramolecular cyclodehydration (7) of this ketoamide was effected by refluxing in benzene for 2 hours in the presence of 0.1 molar equivalent of *p*-toluenesulfonic acid and the resultant thiazinone **11** was isolated in a quantitative yield. When using more vigorous conditions (0.2 molar equivalent of *p*-toluenesulfonic acid, 4 hours reflux in benzene), **10** was converted into the tricyclic compound **12**. Periodic tlc monitoring of the reaction mixture proved the expected intermediacy of **11**. In a separate experiment, **11** underwent the ring closure-isomerization under similar conditions to furnish **12**.

The formation of **12** is closely related to the Friedel-Crafts-type reaction of α-amido alcohols (8). This method has been used extensively in the syntheses of polycyclic lactams from open-chain ketoamides (8-14), however, most of the workers did not isolate (15) the intermediate enamide (a dehydrated form of the corresponding α-amido alcohol). In this paper we report the cyclization of the ketoamide **10** which provides an entry into substituted hexahydro[1,4]thiazino[3,4-*a*]isoquinolines and can be readily arrested at the stage of the enamide **11**. The presence of activating methoxy groups appears to be critical for the electrophilic aromatic substitution **11**→**12** since an analogous enamide **19** was refractory to ring-closure even under forcing conditions (Scheme 3).

The mass spectral data fully support the assignment of isomeric structures **11** and **12**. The spectrum of **11** displays a molecular ion peak at m/e 293 and a base peak arising from dimethoxystyrene at m/e 164. In contrast, compound **12** yields a base peak at m/e 205 (*cf.* reference 16) which is typical for all derivatives of **12**. The molecular ion peak is followed by the M-15 ion, and this loss of the angular methyl is confirmed by the presence of a metastable peak.

The nmr spectrum of **12** has one notable feature which reflects the configuration of the ring junction: a doublet of perturbed triplets centered at δ 5.01 (J_{gem} = 8.5 Hz, J = 3 Hz) assignable to H_A or H_B (Scheme 3). As expected, the anisotropy of the lactam carbonyl causes a remarkable difference in chemical shifts of these geminal protons, one of them being in the deshielding area of the carbonyl group. Winterfeldt, *et al.*, (14,17) have demonstrated in a series of indoloquinolizine alkaloids that this effect can be utilized to distinguish between *trans*- and *cis*-fused lactams with an angular substituent. Following their arguments we have concluded that the deshielded proton in the spectrum of **12** is equatorial ($J_{ee} \sim J_{ae} \ll J_{gem}$), and hence, we assign *trans* stereochemistry to the ring junction (18). It is likely that the initial product of the cyclization **11**→**12** is the *cis*-isomer which stems from a kinetically controlled process, and the formation of the thermodynamically stable trans-isomer

occurs subsequently (11,14).

Reduction of **12** with diborane gave **13** whose ir spectrum showed prominent Bohlmann bands at 2760 and 2810 cm^{-1}, indicative of *trans*-fused rings (10,11,13). Complete *O*-demethylation of **12** was achieved by the action of boron tribromide to afford compound **16**.

Periodate oxidation of **12** produced stereospecifically the equatorial sulfoxide **14**. It has been postulated (19) that the axial preference in the conformation of thiane 1-oxides is due to attractive interactions of the S-O bond with the *syn*-axial protons. Such a preference is clearly reversed in the presence of substituents (20). In our case, the axial oxygenation of **12** appears to be hindered by both the lactam carbonyl and the axial methyl group (20,22). The assignment of an equatorial sulfinyl oxygen in **14** is supported by the nmr data: the chemical shifts for angular methyl in **12** and **14** are practically identical and the spectrum of **14** reveals a considerable nonequivalence of the geminal CH_2-SO protons (21,22). This indicates that the lone electron pair on the sulfur is axial and causes a selective shielding of the *trans* co-axial α-proton. Treatment of **14** with *m*-chloroperbenzoic acid yielded the sulfone **15**.

Oxidation of **13** with sodium meta-periodate produced a mixture of the equatorial sulfoxide **17** and the axial sulfoxide **18** in the ratio 55:45. While the nmr spectrum of **17** showed a singlet at δ 1.49 for the angular methyl, the corresponding resonance for **18** was observed at δ 1.76. Thus, the angular methyl protons signal of **18** occurs 12 Hz downfield (23) of its position in the spectrum of **13** which is due to the "syn-axial effect" of the S-O bond (23,24). Apparently, the angular methyl group of **18** lies in a deshielding cone. In the spectrum of **17**, the angular methyl protons signal is 4 Hz upfield of its position in **13** and appears to be shielded by the *syn*-axial lone electron pair on sulfur. To confirm the stereochemistry of the sulfoxides **17** and **18**, their nmr spectra was run in deuteriochloroform containing 0.5 equivalent of tris-(dipivaloylmethanato)europium. As expected (25), the addition of the lanthanide reagent resulted in a downfield shift (58 Hz) of the methyl resonance in the spectrum of **18** whereas the corresponding signal of **17** remained practically unaffected (1 Hz downfield). Although the question of the preferred site of complexation with shift reagents is complicated in polyfunctional molecules (26), it is believed that the strong dipolar nature of the S-O bond makes sulfoxides a favored site for complex formation (21,27).

Compounds **12**, **14**, and **18** produced appreciable antihypertensive effects in spontaneously hypertensive rats at 25-100 mg./kg. and showed very low acute toxicity. Interestingly, the sulfoxide **17** was found inactive, in contrast to its stereoisomer **18**.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded with a Perkin-Elmer 225 spectrometer. Using a Varian A-60A instrument, nmr spectra were determined in deuteriochloroform (unless otherwise stated) with tetramethylsilane as internal standard. The chemical shifts and coupling constants are expressed in δ and Hz, respectively. Mass spectra were obtained with an LKB 9000 S spectrometer.

Condensation of Amines **3a-b** with Ethyl 2-Mercaptoacetate.

An intimate mixture of 3,4-dimethoxybenzeneethanamine **3a** (9 g.) and ethyl 2-mercaptoacetate (6 g.) was heated at reflux for 5 hours. The reaction mixture was chromatographed over a silica gel column eluted with chloroform, and three tlc homogeneous fractions were obtained:

N,N'-Bis-[2-(3,4-dimethoxyphenyl)ethyl]ethanemonothiodiamide (**6a**).

Two g. (23%) of **6a** was obtained, R_f 0.76, m.p. 112-114° (benzene-ether); nmr: 2.92 (m, 4H, CH_2), 3.49 (t, J = 7, 2H, CH_2-N-CO), 3.85 (s, 12H, CH_3O), 3.90 (m, 2H, CH_2-N-CS), 6.79 (m, 6H, Ar-H), 8.3 and 9.6 (br, 1H + 1H, NH); ms: m/e 432 (42%, M^+), 399 (11%, loss of • SH), *368.53 for 432→399, 164 (100%), 151 (35%).

Anal. Calcd. for $C_{22}H_{28}N_2O_5S$: C, 61.08; H, 6.53; N, 6.48. Found: C, 61.19; H, 6.45; N, 6.49.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-mercaptoacetamide (**4a**).

Six g. (48%) of **4a** was obtained R_f 0.55, m.p. 90-91° (benzene); nmr: 1.82 (t, J = 8.5, 1H, SH, exchangeable), 2.75 (t, J = 6.5, 2H, CH_2), 3.15 (d, J = 8.5, 2H, CH_2-S, singlet upon exchange), 3.50 (m, 2H, CH_2-N), 3.82 (s, 6H, CH_3O), 6.70 (br, 1H, NH), 6.75 (m, 3H, Ar-H).

Anal. Calcd. for $C_{12}H_{17}NO_3S$: C, 56.44; H, 6.71; N, 5.49. Found: C, 56.55; H, 6.71; N, 5.27.

N,N'-Bis-[2-(3,4-dimethoxyphenyl)ethyl]-2,2'-dithio-bis-acetamide (**5a**).

Seven tenths g. (5.6%) of **5a** was obtained, R_f 0.35, yellowish oil; nmr: 2.82 (t, J = 6.5, 4H, CH_2), 3.39 (s, 4H, CH_2-S), 3.15 and 3.55 (m, 2H + 2H, CH_2-N), 3.84 (s, 12H, CH_3O), 6.70 (m, 6H, Ar-H), 7.10 (br, 2H, NH); ms: m/e 508 (M^+).

A similar condensation of 4-methylbenzeneethanamine **3b** (7 g.) with ethyl 2-mercaptoacetate (6.2 g.) yielded two major products:

N-[2-(4-Methylphenyl)ethyl]-2-mercaptoacetamide (**4b**).

Four and four tenths g. (40%) of colorless oil (**4b**) was obtained; nmr: 1.83 (t, J = 8.5, 1H, SH), 2.32 (s, 3H, CH_3), 2.81 (t, J = 6.5, 2H, CH_2), 3.17 (d, J = 8.5, 2H, CH_2-S), 3.55 (q, J = 6.5, 2H, CH_2-N), 6.60 (br, 1H, NH), 7.09 (m, 4H, Ar-H).

Anal. Calcd. for $C_{11}H_{15}NOS$: C, 63.12; H, 7.23; N, 6.69. Found: C, 63.10; H, 7.31; N, 6.63.

N,N'-Bis-[2-(4-methylphenyl)ethyl]ethanemonothiodiamide (**6b**).

Two g. (23%)of **6b** was obtained m.p. 145-147° (benzene); nmr: 2.32 (s, 6H, CH_3), 2.80 and 3.02 (overlapping triplets, 4H, CH_2), 3.58 and 3.92 (overlapping quartets, 4H, CH_2-N), 7.12 (m, 8H, Ar-H), 8.3 and 9.6 (br, 1H + 1H, NH); ms: m/e 340 (32%, M^+), 307 (16%, loss of •SH), 235 (5%), 118 (100%).

Anal. Calcd. for $C_{20}H_{24}N_2OS$: C, 70.53; H, 7.11; N, 8.23. Found: C, 70.80; H, 7.09; N, 8.05.

N,N'-bis-[2-(3,4-dimethoxyphenyl)ethyl]ethanediamide (**7a**).

A mixture of **6a** (0.4 g.), ethanol (15 ml.), and 5% aqueous sodium hydroxide (12.5 ml.) was kept under mild reflux for 2 hours. Ethanol was removed *in vacuo*, and the aqueous residue was extracted with chloroform. The extracts were concentrated and chromatographed on a column of silica gel using chloroform to elute 0.23 g. (60%) of compound **7a**, m.p. 173-175° (acetic acid-ethanol) in accordance with lit. (4); nmr: 2.83 (t, J = 7, 4H, CH_2), 3.59 (q, J = 7, 4H, CH_2-N), 3.87 (s, 12H, CH_3O), 6.81 (m, 6H, Ar-H), 7.69 (t, J = 7, 2H, NH); ms: m/e 416 (M^+).

Anal. Calcd. for $C_{22}H_{28}N_2O_6$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.27; H, 6.76; N, 6.69.

N,N'-Bis-[2-(3,4-dimethoxyphenyl)ethyl]glycinamide (**8a**).

A mixture of **6a** (0.3 g.), ethanol (70 ml.), and Raney nickel (5 g.) was stirred and refluxed for 72 hours. After cooling, the resultant slurry was filtered, the filtrate evaporated, and the residual material was chromatographed on silica gel. Elution with chloroform afforded **8a** (0.17 g., 61%) as colorless oil; nmr: 2.02 (br, 1H, NH, exchangeable), 2.70 (m, 6H, CH_2 and CH_2-N), 3.23 (s, 2H, N-CH_2-CO), 3.50 (q, J = 7, 2H, CH_2-N-CO), 3.87 (s, 12H, CH_3O), 6.77 (m, 6H, Ar-H), 7.22 (br, 1H, NH-CO); ms: m/e 402 (<1%, M⁺), 251 (100%, loss of dimethoxytropylium), 238 (26%), 194 (64%), 165 (72%), 164 (42%), 151 (36%). The corresponding hydrochloride salt was purified for elemental analyses, m.p. 179-181° (2-propanol).

Anal. Calcd. for $C_{22}H_{30}N_2O_5$·HCl: C, 60.19; H, 7.12; N, 6.38. Found: C, 60.29; H, 7.12; N, 6.43.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-2-[(2-oxopropyl)thio]acetamide (**10**).

To a stirred solution of **4a** (4.2 g.) and triethylamine (1.67 g.) in absolute ethanol (50 ml.) was added dropwise a solution of chloropropanone (1.67 g.) in dry ether (20 ml.) at 5°. The reaction mixture was stirred for 2 hours at ambient temperature, evaporated to dryness, and the residue was triturated with dry acetone. The resulting slurry was filtered, and the filtrate was stripped on a rotavapor to give **10** (3.5 g., 68%) which was suitable for use in the next step; ir (chloroform): 3350, 1700, 1680 and 1650 cm^{-1}; nmr: 2.20 (s, 3H, CH_3CO), 2.77 (t, J = 6.5, 2H, CH_2), 3.10 and 3.23 (singlets, 2H + 2H, CH_2-S-CH_2), 3.50 (m, 2H, CH_2-N), 3.82 (s, 6H, CH_3O), 6.63 (br, 1H, NH), 6.70 (m, 3H, Ar-H); ms: m/e 311 (M⁺).

4-[2-(3,4-Dimethoxyphenyl)ethyl]-5-methyl-2*H*-1,4-thiazin-3(4*H*)one (**11**).

A mixture of **10** (31.1 g.), *p*-toluenesulfonic acid (1.9 g.), and benzene (600 ml.) was refluxed under water separator for 2 hours. After cooling, the reaction mixture was washed successively with 10% sodium bicarbonate, water, and brine solution. Benzene was removed in a rotavapor and the semi-solid product was recrystallized from 2-propanol-hexane, m.p. 81-83°, yield 29 g. (99%); ir (chloroform): 1660 cm^{-1}; nmr: 1.92 (d, J = 1.5, 3H, CH_3), 2.80 (t, J = 7.5, 2H, CH_2), 3.22 (d, J = 1.5, 2H, CH_2-S), 3.85 and 3.87 (multiplet and a narrow doublet, 8H, CH_2-N and CH_3-O), 5.45 (q, J = 1.5, 1H, =CH), 6.80 (s, 3H, Ar-H); ms: m/e 293 (35%, M⁺), 164 (100%), 151 (36%).

Anal. Calcd. for $C_{15}H_{19}NO_3S$: C, 61.40; H, 6.52; N, 4.77. Found: C, 61.50; H, 6.68; N, 4.75.

1,6,7,11b-Tetrahydro-9,10-dimethoxy-11b-methyl[1,4]thiazino[3,4-*a*]isoquinolin-4(3*H*)one (**12**).

A mixture of **10** (15.5 g.), *p*-toluenesulfonic acid (1.9 g.), and benzene (500 ml.) was refluxed under water separator for 4 hours. After cooling, the reaction mixture was washed successively with 10% sodium bicarbonate, water, and brine solution. Benzene was removed in a rotavapor, and the crude product was filtered through a column of silica gel packed in chloroform. Usual work-up of the main fraction gave 12.5 g. (85%) of **12**, m.p. 150-152° (2-propanol-ether); ir (chloroform): 2840, 2830, and 1620 cm^{-1}; nmr: 1.85 (s, 3H, CH_3), 2.68 and 2.81 (multiplets, 3H, CH_2 and CH_A-), 3.03 and 3.40 (multiplets, 2H + 2H, CH_2-S-CH_2), 3.68 (s, 6H, CH_3O), 5.01 (doublet of perturbed triplets J_{gem} = 8.5, J = 3, 1H, CH_B-N), 6.62 (s, 2H, Ar-H); ms: m/e 293 (40%, M⁺), 278 (45%, M-CH_3), *263.8 for 293→278, 247 (74%, M-CH_2S), 205 (100%), 247 -CH_2CO), *170.1 for 247→205.

Anal. Calcd. for $C_{15}H_{19}NO_3S$: C, 61.40; H, 6.52; N, 4.77. Found: C, 61.32; H, 6.59; N, 4.65.

1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-11b-methyl[1,4]thiazino[3,4-*a*]isoquinoline (**13**).

To a solution of **12** (7 g.) in dry tetrahydrofuran (100 ml.) was added dropwise 1*M* solution of diborane in tetrahydrofuran (30 ml.) at 0°. The reaction mixture was stirred 3 hours at room temperature, decomposed with 10 ml. of water, and filtered with anhydrous magnesium sulfate. The filtrate was evaporated and the crude product was chromatographed on a column of neutral alumina. Elution with a chloroform-methanol mixture (35:1) afforded 5 g.(75%) of the title base; ir (chloroform): 2840, 2810, 2760 cm^{-1}; nmr: 1.56 (s, 3H, CH_3), 2.1-3.6 (multiplets, 10H, CH_2), 3.82 (s, 6H, CH_3-O), 6.57 and 6.63 (singlets, 1H + 1H, Ar-H); ms: m/e 279 (M⁺). The corresponding hydrochloride salt was precipitated in ether and recrystallized from 2-propanol, m.p. 170-172°.

Anal. Calcd. for $C_{15}H_{21}NO_2S$·HCl: C, 57.03; H, 7.02; N, 4.43. Found: C, 56.83; H, 7.31; N, 4.18.

1,6,7,11b-Tetrahydro-9,10-dimethoxy-11b-methyl[1,4]thiazino[3,4-*a*]isoquinolin-4(3*H*)one 2-Oxide (**14**).

A solution of sodium meta-periodate (2.6 g.) in water (70 ml.) was added to a solution of **12** (2.4 g.) in methanol (150 ml.), and the mixture was stirred for 20 hours at room temperature. The resulting suspension was filtered, the filtrate was concentrated and extracted with chloroform. The combined extracts were washed with water, dried over magnesium sulfate, filtered, and evaporated to yield 2 g. (79%) of **14**, m.p. 215-217° (2-propanol-benzene); ir (chloroform): 1630, 1145, 1065 and 1040 cm^{-1}; nmr: 1.80 (s, 3H, CH_3), 2.82 (m, 2H, CH_2), 3.11 and 3.65 (broad singlets, 1H + 1H, CH_2-SO), 3.32 (double multiplet, J = 8, 1H, CH_A-N), 3.89 (s, 6H, CH_3-O), 4.01 and 4.51 (doublets, J = 3.5, 1H + 1H, CO-CH_2-SO), 4.95 (double multiplet, J = 8, 1H, CH_B-N), 6.63 and 6.71 (singlets, 2H, Ar-H); ms: m/e 309 (93%, M⁺), 294 (85%, M-CH_3), 277 (20%), 261 (20%), 246 (27%), 205 (100%).

Anal. Calcd. for $C_{15}H_{19}NO_4S$: C, 58.22; H, 6.19; N, 4.53. Found: C, 58.32; H, 6.14; N, 4.44.

1,6,7,11b-Tetrahydro-9,10-dimethoxy-11b-methyl[1,4]thiazino[3,4-*a*]isoquinolin-4(3*H*)one 2,2-Dioxide (**15**).

A solution of **14** (0.62 g.) and *m*-chloroperbenzoic acid (0.35 g.) in chloroform (10 ml.) was stirred at room temperature for 2 hours and then heated shortly under reflux. The solvent was removed *in vacuo*, the residue was triturated with ethanol, and the crystalline product was collected by filtration. Recrystallization from methanol afforded 0.5 g. (77%) of **15**, m.p. 217-219°; nmr: 1.97 (s, 3H, CH_3), 2.82 (m, 2H, CH_2), 3.20 (double multiplet, J = 9, 1H, CH_A-N), 3.52 and 3.77 (broad singlets, 1H + 1H, CH_2-SO_2), 3.87 (s, 6H, CH_3-O), 4.12 (broad singlet, 2H, SO_2-CH_2-CO), 5.00 (doublet multiplet, J = 9, 1H, CH_B-N), 6.63 (s, 2H, Ar-H); ms: m/e 325 (50%, M⁺), 310 (100, M-CH_3), *295.7 for 325→310.

Anal. Calcd. for $C_{15}H_{19}NO_5S$: C, 55.38; H, 5.88; N, 4.30. Found: C, 55.55; H, 5.94; N, 4.09.

1,6,7,11b-Tetrahydro-9,10-dihydroxy-11b-methyl[1,4]thiazino[3,4-*a*]isoquinolin-4(3*H*)one (**16**).

A solution of boron tribromide (4 g.) in methylene chloride (20 ml.) was added to a solution of **12** (0.5 g.) in 20 ml. of the same solvent at 0°. The reaction mixture was stirred for 3 hours, evaporated under reduced pressure, and the residue was triturated with water. The amorphous precipitate (28) formed was collected by filtration and dried; yield 325 mg. (72%); homogeneous by tlc; ir (nujol): 3320, 3140, and 1585 cm^{-1}; nmr (DMSO-d_6): 1.73 (s, 3H, CH_3), 2.60 (m, 3H, CH_2 and CH_A-N), 2.98, 3.23 and 3.42 (broad singlet, multiplet, and broad singlet, respectively, totally integrating for 4H, CH_2-S-CH_2), 4.76 (double multiplet, J = 9.5, 1H, CH_B-N), 6.54 and 6.75 (singlets, 1H + 1H, Ar-H), 8.6 (broad, 2H, OH); ms: m/e 265 (41%, M⁺), 250 (39%, M-CH_3), 219 (71%, M-CH_2S), 177 (100, 219-CH_2CO).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.84; H, 5.70; N, 5.28. Found: C, 58.50; H, 5.44; N, 5.01.

1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-11b-methyl[1,4]thiazino[3,4-*a*]isoquinoline 2-Oxides (**17** and **18**).

To a solution of the hydrochloride of **13** (7 g.) in methanol (180 ml.) was added a solution of sodium meta-periodate (6.1 g.) in water (100 ml.) and the mixture was stirred overnight at room temperature. The resulting suspension was filtered, the filtrate was concentrated *in vacuo*,

rendered basic with 10% sodium hydroxide, and extracted with chloroform. The extracts were evaporated and the residue was chromatographed on silica gel eluting with chloroform-methanol (20:1). Usual work-up of the fractions afforded 3 g. (46%) of **17** and 2.45 g. (37%) of the more polar isomer **18**.

Compound **17** had m.p. 106-108°; nmr: 1.49 (s, 3H, CH_3), 2.6-3.7 (multiplets, 10H, CH_2), 3.89 (s, 6H, CH_3-O), 6.64 and 6.76 (singlets, 1H + 1H, Ar-H); ms: m/e 295 (M^+). The corresponding hydrochloride salt melted at 248-250° (methanol).

Anal. Calcd. for $C_{15}H_{21}NO_3S \cdot HCl$: C, 54.29; H, 6.68; N, 4.22. Found: C, 53.99; H, 6.58; N, 4.08.

Compound **18** had m.p. 146-148°; nmr: 1.76 (s, 3H, CH_3), 2.7-3.5 (multiplets, 10H, CH_2), 3.88 (s, 6H, CH_3-O), 6.63 and 6.77 (singlets, 1H + 1H, Ar-H); ms: m/e 295 (M^+). The corresponding hydrochloride salt melted at 255-257° (ethanol).

Anal. Calcd. for $C_{15}H_{21}NO_3S \cdot HCl$: C, 54.29; H, 6.68; N, 4.22. Found: C, 54.21; H, 6.58; N, 4.06.

5-Methyl-4-[2-(4-methylphenyl)ethyl]-2*H*-1,4-thiazin-3(4*H*)one (**19**).

To a stirred solution of **4b** (4.2 g.) and triethylamine (2.18 g.) in absolute ethanol (65 ml.) was added dropwise a solution of chloropropanone (2.18 g.) in dry ether (20 ml.) at 5°. The mixture was stirred for 2 hours at ambient temperature, solvents were removed *in vacuo*, and the residue was triturated with dry acetone. The resulting slurry was filtered, and the filtrate was evaporated to give 4 g. (70%) of *N*-[2-(4-methylphenyl)ethyl]-2-[(2-oxopropyl)thio]acetamide; ir (chloroform): 3370, 1705, and 1660 cm^{-1}; nmr: 2.22 and 2.31 (singlets, 6H, CH_3), 2.83 (t, J = 7, 2H, CH_2), 3.13 and 3.27 (singlets, 2H + 2H, CH_2-S-CH_2), 3.57 (q, J = 7, 2H, CH_2-N), 6.78 (broad, 1H, NH), 7.12 (m, 4H, Ar-H); ms: m/e 265 (M^+). This compound (3.9 g.) was heated with *p*-toluenesulfonic acid (0.29 g.) in boiling benzene (80 ml.) for 2 hours upon using a water separator. After cooling, the mixture was washed successively with 10% sodium bicarbonate, water, and brine solution. Benzene was removed *in vacuo* and the residue was chromatographed on silica gel. Elution with chloroform afforded 2.7 g. (74%) of **19**, pale oil; ir (chloroform): 1655 cm^{-1}; nmr: 1.95 (d, J = 1, 3H, CH_3), 2.31 (s, 3H, aromatic CH_3), 3.25 (d, J = 1, 2H, CH_2-S), 5.52 (q, J = 1, 1H, =CH), 7.12 (m, 4H, Ar-H), and deceptively simple signals for CH_2-CH_2-N centered at 3.34, pair of doublets (J = 10) at 2.76 and 3.93 and pair of doublets at 2.85 and 3.83; ms: m/e 247 (M^+).

Anal. Calcd. for $C_{14}H_{17}NOS$: C, 67.97; H, 6.93; N, 5.66. Found: C, 67.67; H, 7.00; N, 5.46.

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