

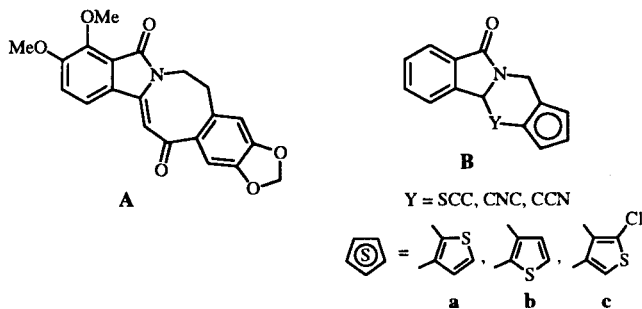
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Cyclization of thioglycolic acids derivatives **3a-d** gave isoindolo[1,2-*b*]thieno[2,3(3,2 or 3,4)-*e*][1,3]-thiazocines **4a-d**. Isoindolo[2,1-*a*]thieno[2,3(3,2 or 3,4)-*f*][1,4] or [1,5]diazocines **10b** or **11a-c** were synthesized from Beckmann or Schmidt rearrangement of the ketones **7a-c**.

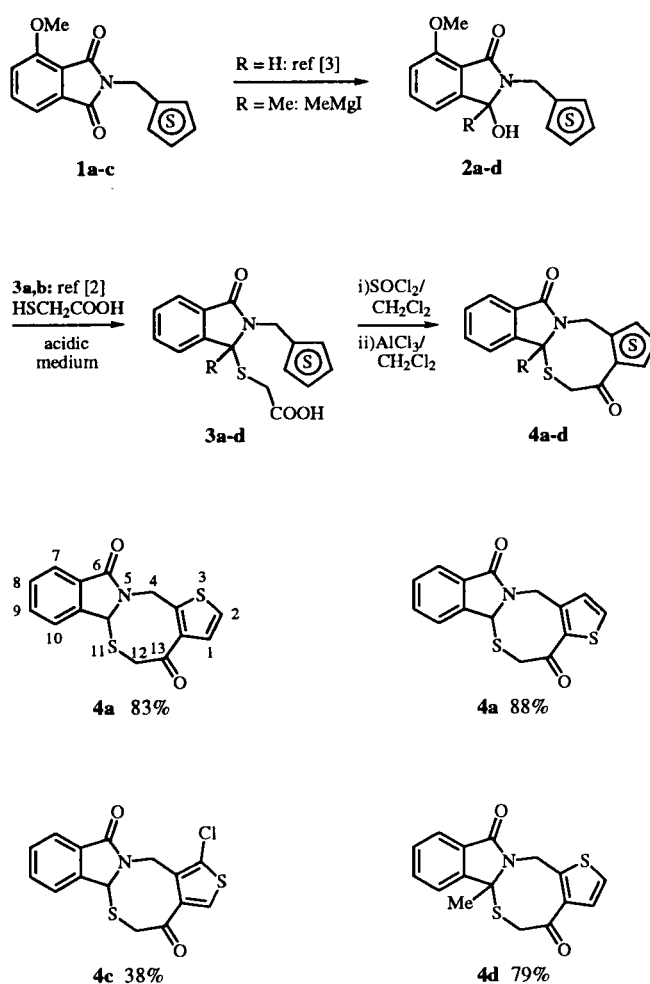
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Many tetracyclic natural products and bioactive compounds have an isoindole moiety and magallanesine **A** [1] is one example. During the course of a project directed towards the synthesis of potential polycyclic systems we wish to report herein the synthesis of new tetracyclic systems as **B** incorporating the isoindole moiety and a thiophene ring both annelated to an eight membered ring as thiazocine (Y = S-C-C) and diazocine (Y = C-N-C or C-C-N). The previously reported 3-carboxymethylthio-2-thienylmethylisoindol-1-ones **3a-c** [2] and the unknown starting acid **3d** (prepared from phthalimide **1a** through the action of methylmagnesium bromide followed by the action of thioglycolic acid in an overall yield of 81%) and thienoazepinoisoindoleiones **7a-c** [3] could to be excellent precursors for this purpose.



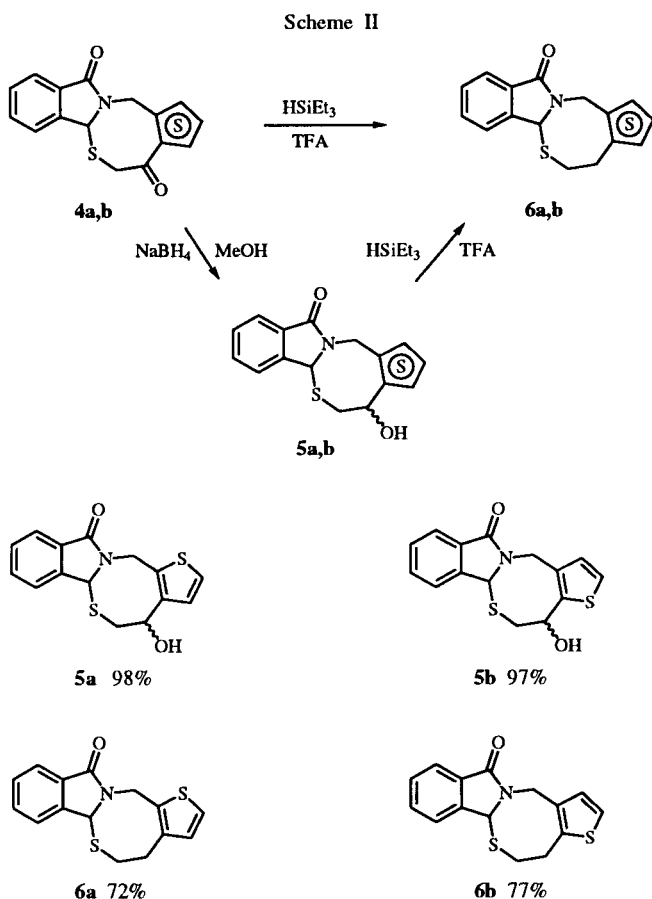
Actually (Scheme I), the acids **3a-d** treated with thionyl chloride in dichloromethane gave the acid chlorides, which under Friedel-Crafts cyclization conditions [4] using aluminium trichloride as a catalyst afforded the expected ketones **4a-d** in good yields. The lower yield was observed for **4c** (38%) due to the difficulty encountered when the cyclization occurs on the 3,4 position of the thiophene ring [4]. The ketone **4a** exhibit a S-CH₂ methylene ¹H nmr signal as a singlet at 3.90 ppm and a AB system for the N-CH₂ methylene with chemical shifts of 4.80 and 5.38 ppm with a coupling constant of J = 16.2 Hz. The ketones **4b,c** exhibit a S-CH₂ methylene ¹H nmr signal as an AB system (J = 15.4 Hz) similar to the N-CH₂ methylene signal (J = 16.4 Hz).

Scheme I



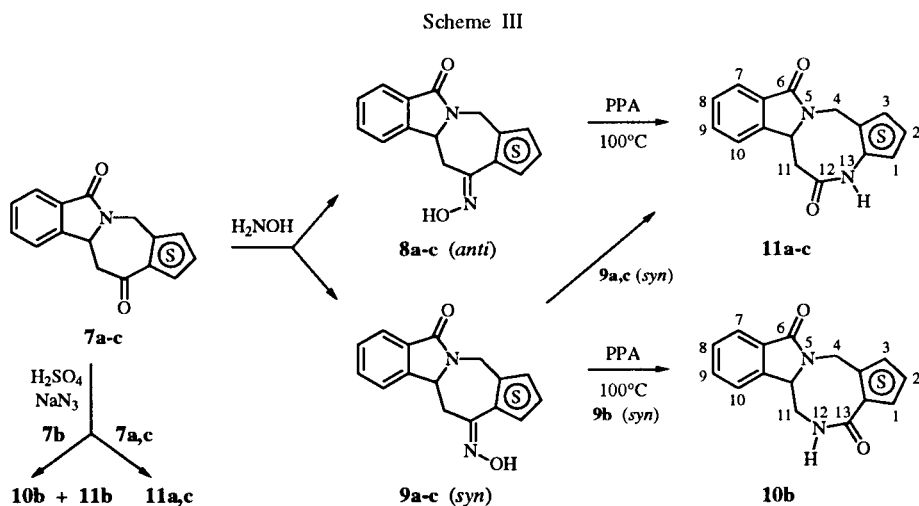
To confirm our attribution a regioselective reduction of the ketones **4a,b** using sodium borohydride in methanol gave a mixture of the two diastereomer alcohols **5a,b**. The ratio depends of the temperature, the reaction time and the position of the fused thiophene (3,2 or 2,3). This mixture treated with triethylsilane in trifluoroacetic acid led to the thienothiazocines **6a,b** in a 70-74% overall yield calculated from the starting ketone. A direct reduction of ketones **4a,b**

to thiazocines **6a,b** was possible using triethylsilane in trifluoroacetic acid but did not improve the yields. Compounds **5a** or **6a** exhibit a N-CH₂ methylene ¹H nmr signal as a AB system (J = 14 Hz) with chemical shifts of about 4.6 and 5.5 ppm similar to those observed for the equivalent protons in the ketone **4a**. Analogous remarks can be made for compounds **4b**, **5b**, **6b**.






In an other hand the [1,4] or [1,5] diazocines **B** (Y = C-N-C, C-C-N) have been prepared from the suitable thienoazepinoisindoliones **7a-c** [3] *via* a Beckmann rearrangement of the corresponding oximes or *via* the Schmidt rearrangement. Thus, ketones **7a-c** heated with hydroxylamine hydrochloride in the presence of sodium acetate afforded the corresponding oximes in a mixture of *syn* (**8a-c**) and *anti* (**9a-c**) forms. The *anti* isomer is the major product in all cases (see Table 1). The geometry of the seven membered ring seem to favour that form since, even when the sulfur atom of the thiophene ring is near the ketone group the *anti* isomer is the major product in contrast to our previously reported papers for related compounds [4-6]. When these oximes were treated with polyphosphoric acid at 100° under nitrogen we formed from oximes **8b** (74%) + **9b** (26%) the expected rearrangement leading to the [1,5] diazocines **11b** (74%) and [1,4] diazocine **10b** (26%) respectively. Interestingly was the reaction of the mixture **8a** + **9a** or **8c** + **9c** under the same conditions because only the corresponding [1,5] diazocines **11a** or **11c** was obtained. The excellent yields for both (95 and 96%) show that an isomerization of the *syn* oxime to the *anti* oxime in acidic medium occurs before the Beckmann rearrangement. This type of isomerization has been previously reported elsewhere [7, 8].

The structures of the [1,4] diazocine **10b** and the [1,5] diazocine **11b** are supported by their ir and nmr spectra as well as their microanalyses. Details are reported in the Experimental. The stronger difference between the [1,4] or [1,5] diazocine is the chemical shift of the protons attached to the C₁₁ carbon. The former are shifted down field 3.57 ppm compared to the latter 2.31 ppm and 2.92 ppm. In addition the signal is a multiplet for the two equivalent protons of the [1,4] diazocine due to the proximity of the N-H proton. The signal located at 2.31 ppm is a doublet of a doublet in the [1,5] diazocine with coupling constants of



$J = 12.4$ Hz (*gem* coupling) and $J = 10.5$ Hz (with the close proton H_{10b} of the isoindole system). Furthermore the signal located at 2.92 ppm is a doublet ($J = 12.4$ Hz, *gem* coupling) since no coupling was observed with the proton H_{10b} . Finally, the methylene located between the nitrogen atom and the thiophene ring appears as an AB system with chemical shift of 4.60 and 5.29 ppm and a coupling constant of $J = 17.5$ Hz for the [1,4] diazocine and 3.87 and 5.36 ppm with a coupling constant of $J = 14.7$ Hz for the [1,5] diazocine. The two other [1,5] diazocines **11a,c** reveal spectra similar to those of **11b**.

Table 1

	% of oximes		% of diazocines (yield)			
	9 (<i>syn</i>)	8 (<i>anti</i>)	Beckmann		Schmidt	
			10	11	10	11
	20	80	0	100 (96)	0	100 (81)
	26	74	26 (21)	74 (59)	44 (32)	56 (42)
	20	80	0	100 (95)	0	100 (76)

To confirm our results the Schmidt rearrangement of ketones **7a-c** afforded a successful route to tetracyclic diazocines. As expected, under the usual conditions of the reaction (ketone in solution of dichloromethane, sodium azide, concentrated sulfuric acid, room temperature) ketones **7a,c** gave the [1,5] diazocines **11a,c** and ketone **7b** gave a mixture of [1,4] diazocine **10b** (44%) and [1,5] diazocine **11b** (56%). The yields are lower than those observed during the Beckmann reaction and the aryl rearrangement is preferred in all cases (56 to 100%).

In summary, we have shown that *N*-methylthienylisoindol-3-ylthioglycolic acids **3a-d** and thienoazepinoisoindoles **7a-c** were excellent precursors for the synthesis of tetracyclic systems containing an eight membered ring as [1,3]thiazocine and [1,4] or [1,5]diazocine.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrometer. The 1H and ^{13}C nmr spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform solution and chemical shift (δ) are expressed in ppm relative to internal TMS. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60 F (70-300 mesh) was

used for column chromatography. The elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 Mt. St. Aignan, France.

2,3-Dihydro-3-hydroxy-3-methyl-2-(thien-2'-ylmethyl)-1*H*-isoindol-1-one (**2d**).

In a stirred solution of phthalimide **1a** (2.43 g, 10 mmoles) in dry dichloromethane (100 ml) was slowly added 2 equivalents of methylmagnesium bromide with stirring. After 3 hours the mixture was poured into an aqueous solution of ammonium chloride. The organic layer was decanted and the aqueous layer was extracted with dichloromethane. The combination of organic layers was dried and evaporated. The solid is a little instable (dehydration) and is pure enough to be used without further purification. Compound **2d** was obtained in a yield of 95%; ir: 3308 (OH), 1678 (C=O) cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.60 (s, 3H, CH_3), 3.37 (s, 1H, OH), 4.56 (d, 1H, CH_2 , $J = 15.7$ Hz), 4.68 (d, 1H, CH_2 , $J = 15.7$ Hz), 6.87 (dd, 1H, H_4 , $J = 5.1$, 3.3 Hz), 7.00 (d, 1H, H_3 , $J = 3.3$ Hz), 7.13 (d, 1H, H_5 , $J = 5.1$ Hz), 7.37- 7.70 (m, 4H, H_{arom})

2,3-Dihydro-2-(2'-chlorothiien-3'-ylmethyl)-1*H*-isoindol-1-one-3-thioglycolic Acid (**3c**).

Hydroxylactams **2c** (3.35 g, 10 mmoles) and thioglycolic acid (0.83 ml, 12 mmoles) were refluxed over night in acetic acid. The mixture was concentrated to dryness and the residue was triturated with ether, filtered, then recrystallized from acetone. Compound **3c** was obtained in a yield of 85%, mp 154°; ir: 3102 (OH), 1733 (C=O), 1668 (C=O) cm^{-1} ; 1H nmr (DMSO- d_6): δ ppm 2.52 (d, 1H, SCH_2 , $J = 15.6$ Hz), 2.79 (d, 1H, SCH_2 , $J = 15.6$ Hz), 4.46 (d, 1H, NCH_2 , $J = 15.6$ Hz), 4.88 (d, 1H, NCH_2 , $J = 15.6$ Hz), 5.71 (s, 1H, CH), 6.90 (d, 1H, H_4 , $J = 5.6$ Hz), 7.39 (d, 1H, H_5 , $J = 5.6$ Hz), 7.45-7.80 (m, 4H, H_{arom})

2,3-Dihydro-3-methyl-2-(thien-2'-ylmethyl)-1*H*-isoindol-1-one-3-thioglycolic Acid (**3d**).

A solution of hydroxylactam **2d** (2.59 g, 10 mmoles), thioglycolic acid (0.83 ml, 12 mmoles), paratoluenesulfonic acid (catalytic amount) in dichloromethane was stirred over night. The organic layer was extracted with 10% aqueous sodium hydroxide solution. The aqueous layer was washed with dichloromethane, acidified with 10% aqueous hydrochloride acid solution then was extracted twice with dichloromethane. The combination of organic layers was dried and evaporated to give **3d** as an oil (85%), 1H nmr (deuteriochloroform): δ 1.62 (s, 3H, CH_3), 2.41 (d, 1H, SCH_2 , $J = 15.7$ Hz), 2.59 (d, 1H, SCH_2 , $J = 15.7$ Hz), 4.77 (d, 1H, NCH_2 , $J = 15.9$ Hz), 5.05 (d, 1H, NCH_2 , $J = 15.9$ Hz), 6.85 (dd, 1H, H_4 , $J = 4.7$, 3.5 Hz), 7.04 (d, 1H, H_3 , $J = 3.5$ Hz), 7.13 (d, 1H, H_5 , $J = 4.7$ Hz), 7.35-7.63 (m, 3H, H_{arom}), 7.80 (d, 1H, H_{arom} , $J = 7.0$ Hz).

Isoindolothienothiazocinediones **4a-d**.

General Procedure.

A mixture of compound **3a-d** (3.5 mmoles), in dry dichloromethane (20 ml) and thionyl chloride (0.4 ml) was stirred under reflux until all solid has disappeared (2-3 hours). After another 30 minutes of reflux, the solution was evaporated under reduced pressure. The residue was dissolved into dry dichloromethane (20 ml) to furnish a solution of the corresponding acyl chloride. This solution was added drop by drop to a stirred mixture of aluminium trichloride (99.99%, 1.5 g, 11 mmoles) and

dry dichloromethane (50 ml). Stirring was continued for 1 hour. The solution was poured into cold water, decanted and extracted with dichloromethane. The combined organic layer was washed with water, dried (magnesium sulfate), and evaporated. The resulting solid **4a-d** was recrystallized from ethanol.

4,10_b-Dihydroisoidolo[1,2-*b*]thieno[2,3-*e*]thiazocine-6,13-(12*H*)-dione (4a).

This compound was obtained in a yield of 83%, mp 248°; ir: 1708 (C=O), 1671 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.90 (s, 2H, H₁₂), 4.80 (d, 1H, H₄, J = 16.2 Hz), 5.38 (d, 1H, H₄, J = 16.2 Hz), 5.87 (s, 1H, H_{10b}), 7.16 (d, 1H, H₃, J = 5.4 Hz), 7.42 (d, 1H, H₂, J = 5.4 Hz), 7.45-7.62 (m, 3H, H_{8,9,10}), 7.83 (d, 1H, H₇, J = 7.3 Hz); ¹³C nmr: δ 38.9 (CH₂), 39.9 (CH₂), 65.4 (CH), 123.3 (CH), 124.0 (CH), 124.3 (CH), 129.8 (CH), 130.4 (CH), 131.4 (C), 132.5 (CH), 137.3 (C), 141.1 (C), 141.8 (C), 166.5 (CO), 191.0 (CO).

Anal. Calcd. for C₁₅H₁₁NO₂S₂: C, 59.78; H, 3.68; N, 4.65. Found: C, 59.52; H, 3.76; N, 4.48.

4,10_b-Dihydroisoidolo[1,2-*b*]thieno[3,2-*e*]thiazocine-6,13(12*H*)-dione (4b).

This compound was obtained in a yield of 88%, mp 219°; ir: 1702 (C=O), 1654 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.89 (d, 1H, H₁₂, J = 15.1 Hz), 4.00 (d, 1H, H₁₂, J = 15.1 Hz), 4.62 (d, 1H, H₄, J = 15.4 Hz), 5.28 (d, 1H, H₄, J = 15.4 Hz), 5.88 (s, 1H, H_{10b}), 7.31 (d, 1H, H₃, J = 4.8 Hz), 7.45-7.63 (m, 4H, H_{2,8,9,10}), 7.80 (d, 1H, H₇, J = 7.3 Hz); ¹³C nmr: δ 38.8 (CH₂), 40.3 (CH₂), 65.5 (CH), 123.2 (CH), 123.8 (CH), 129.8 (CH), 131.4 (C), 132.4 (CH), 133.3 (CH), 133.4 (CH), 139.1 (C), 140.5 (C), 141.0 (C), 166.7 (CO), 188.5 (CO).

3-Chloro-4,10_b-dihydroisoidolo[1,2-*b*]thieno[3,4-*e*]thiazocine-6,13(12*H*)-dione (4c).

This compound was obtained in a yield of 38%, mp 208°; ir: 1663 (C=O, C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.27 (d, 1H, H₁₂, J = 15.4 Hz), 3.38 (d, 1H, H₁₂, J = 15.4 Hz), 4.53 (d, 1H, H₄, J = 16.4 Hz), 5.26 (d, 1H, H₄, J = 16.4 Hz), 5.71 (s, 1H, H_{10b}), 7.40-7.70 (m, 4H, H_{1,8,9,10}), 7.81 (d, 1H, H₇, J = 7.0 Hz); ¹³C nmr: δ 37.9 (CH₂), 39.2 (CH₂), 65.1 (CH), 123.2 (CH), 123.9 (CH), 127.6 (CH), 128.8 (C), 129.7 (CH), 131.5 (C), 132.3 (C), 132.7 (CH), 139.4 (C), 141.4 (C), 166.8 (CO), 193.8 (CO).

Anal. Calcd. for C₁₅H₁₀ClNO₂S₂: C, 53.65; H, 3.00; N, 4.17. Found: C, 53.70; H, 2.98; N, 4.19.

4,10_b-Dihydro-10_b-methylisoidolo[1,2-*b*]thieno[2,3-*e*]thiazocine-6,13(12*H*)-dione (4d).

This compound was obtained in a yield of 79%, mp 192°; ir: 1708 (C=O), 1650 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.89 (s, 3H, CH₃), 2.97 (d, 1H, H₁₂, J = 15.3 Hz), 3.48 (1H, H₁₂, J = 15.3 Hz), 4.66 (d, 1H, H₄, J = 16.5 Hz), 5.15 (d, 1H, H₄, J = 16.5 Hz), 7.09 (d, 1H, H₃, J = 5.1 Hz), 7.20 (d, 1H, H₂, J = 5.1 Hz), 7.40-7.66 (m, 3H, H_{8,9,10}), 7.78 (d, 1H, H₁₀, J = 7.5 Hz); ¹³C nmr: δ 24.9 (CH₃), 36.9 (CH₂), 38.2 (CH₂), 70.3 (C), 122.1 (CH), 123.4 (CH), 123.6 (CH), 129.5 (CH), 130.0 (CH), 130.1 (C), 132.9 (CH), 136.6 (C), 142.0 (C), 147.2 (C), 166.2 (CO), 192.6 (CO); ms: (IE, 70 ev) m/z 315 (M⁺), 240, 169, 159, 146, 137, 124, 97, 96.

Anal. Calcd. for C₁₆H₁₃NO₂S₂: C, 60.93; H, 4.15; N, 4.44. Found: C, 60.70; H, 4.30; N, 4.36.

Reduction of Thiazocinones 4a,b into Alcohols 5a,b.

To a stirred solution of thiazocine **4a,b** (10 mmoles) in methanol (100 ml) was slowly added sodium borohydride (0.8 g, 21 mmoles). One hour after, 10% hydrochloric acid was added and the solvent was evaporated. The residue was triturated with water then filtered. The solid was washed with water, dried and recrystallized in acetone. Two diastereomers were obtained with evolving ratio with the time of reaction.

4,10_b-Dihydro-13-hydroxyisoidolo[1,2-*b*]thieno[2,3-*e*]thiazocin-6(12*H*)one (5a).

This compound was obtained in a yield of 98%.

Isomer 1 had ¹H nmr (DMSO-d₆): δ 2.92-3.11 (m, 2H, H₁₂), 4.75-5.00 (m, 1H, H₄), 5.15-5.50 (m, 3H, H₄+OH+H₁₃), 5.72-5.82 (m, 1H, H_{10b}), 7.01 (d, 1H, H₃, J = 5.1 Hz), 7.40 (d, 1H, H₂, J = 5.1 Hz), 7.43-7.74 (m, 4H, H_{7,8,9,10}).

Isomer 2: ¹H nmr (DMSO-d₆): δ 2.90-3.10 (m, 2H, H₁₂), 4.59 (d, 1H, H₄, J = 15.1 Hz), 4.95-5.10 (m, 1H, H₁₃), 5.18 (d, 1H, H₄, J = 15.1 Hz), 5.20 (s, 1H, H_{10b}), 7.16 (d, 1H, H₃, J = 5.4 Hz), 7.47 (d, 1H, H₂, J = 5.4 Hz), 7.40-7.75 (m, 4H, H_{7,8,9,10}).

Anal. Calcd. for C₁₅H₁₃NO₂S₂: C, 59.38; H, 4.32; N, 4.62. Found: C, 58.98; H, 4.19; N, 4.30.

4,10_b-Dihydro-13-hydroxyisoidolo[1,2-*b*]thieno[3,2-*e*]thiazocin-6(12*H*)-one (5b).

This compound was obtained in a yield of 97%.

Isomer 1: ¹H nmr (DMSO-d₆): δ 2.70-3.70 (m, 2H, H₁₂), 4.59 (d, 1H, H₄, J = 14 Hz), 5.05 (d, 1H, H₄, J = 14 Hz), 5.43-5.55 (m, 1H, H₁₃), 5.80 (s, 1H, OH), 6.10 (s, 1H, H_{10b}), 6.94 (d, 1H, H₃, J = 5.1 Hz), 7.34 (d, 1H, H₂, J = 5.1 Hz), 7.43-7.75 (m, 4H, H_{7,8,9,10}).

Isomer 2: ¹H nmr (DMSO-d₆): δ 2.90 (dd, 1H, H₁₂, J = 14.1, 10 Hz), 3.06 (dd, 1H, H₁₂, J = 14.1, 2.4 Hz), 4.33 (d, 1H, H₄, J = 14.3 Hz), 5.05 (d, 1H, H₄, J = 14.3 Hz), 5.10-5.20 (m, 1H, H₁₃), 5.24 (s, 1H, H_{10b}), 6.40 (d, 1H, OH, J = 4 Hz), 6.89 (d, 1H, H₃, J = 5.1 Hz), 7.39 (d, 1H, H₂, J = 5.1 Hz), 7.42-7.72 (m, 4H, H_{7,8,9,10}).

Anal. Calcd. for C₁₅H₁₃NO₂S₂: C, 59.38; H, 4.32; N, 4.62. Found: C, 58.88; H, 4.01; N, 4.39.

Reduction of Thiazocinones 4a,b into Thiazocines 6a,b.

Thiazocinone **4a,b** (0.30 g, 1 mmole) was stirred overnight with triethylsilane (0.5 ml, 3 equivalents) and trifluoroacetic acid (2 ml). The solvent was evaporated and the residue was dissolved in dichloromethane. The organic layer was washed with a solution of sodium hydrogen carbonate, dried and evaporated. The residue was chromatographed on silicagel eluting with dichloromethane, and finally recrystallized from ethanol.

4,10_b-Dihydroisoidolo[1,2-*b*]thieno[2,3-*e*]thiazocine-6(12*H*)-one (6a).

This compound was obtained in a yield of 72%, mp 159°; ir: 1694 (C=O) cm⁻¹, ¹H nmr (deuteriochloroform): δ 2.70-3.45 (m, 4H, H_{12,13}), 4.58 (d, 1H, H₄, J = 14.8 Hz), 5.06 (s, 1H, H_{10b}), 5.41 (d, 1H, H₄, J = 14.8 Hz), 6.81 (d, 1H, H₃, J = 5.1 Hz), 7.19 (d, 1H, H₂, J = 5.1 Hz), 7.35-7.60 (m, 3H, H_{8,9,10}), 7.80 (d, 1H, H₇, J = 7.0 Hz); ¹³C nmr: δ 32.3 (CH₂), 35.1 (CH₂), 35.3 (CH₂), 65.1 (CH), 122.9 (CH), 123.9 (CH), 125.3 (CH), 128.7 (CH), 129.0 (CH), 131.2 (C), 131.5 (CH+C), 139.8 (C), 142.3 (C), 165.2 (CO).

Anal. Calcd. for C₁₅H₁₃NOS₂: C, 62.69; H, 4.56; N, 4.87. Found: C, 62.51; H, 4.67; N, 4.85.

4,10_b-Dihydroisoindolo[1,2-*b*]thieno[3,2-*e*]thiazocin-6(12*H*)-one (**6b**).

This compound was obtained in a yield of 77%, mp 164°; ir: 1691 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.75-3.50 (m, 4H, H_{12,13}), 4.31 (d, 1H, H₄, J = 14.1 Hz), 5.02 (s, 1H, H_{10b}), 5.31 (d, 1H, H₄, J = 14.1 Hz), 6.90 (d, 1H, H₃, J = 5.1 Hz), 7.06 (d, 1H, H₂, J = 5.1 Hz), 7.30-7.55 (m, 3H, H_{8,9,10}), 7.76 (d, 1H, H₇, J = 7.00 Hz); ¹³C nmr: δ 31.2 (CH₂), 35.7 (CH₂), 36.1 (CH₂), 65.6 (CH), 123.1 (CH), 123.2 (CH), 124.0 (CH), 128.8 (CH), 129.4 (CH), 131.4 (C), 131.7 (CH), 132.4 (C), 139.8 (C), 142.5 (C), 165.7 (CO).

Formation of Oximes **8a-c** and **9a-c**.

A mixture of azepinone **7a-c** (3.7 mmoles), hydroxylamine hydrochloride (0.28 g, 4.1 mmoles), sodium acetate (0.33 g, 4.1 mmoles), ethanol (24 ml) and water (6 ml) was stirred under reflux for 2 hours. After cooling, water was added and the precipitate was filtered then dried. The mixture of isomers was used without further purification.

4,10_b-Dihydro-11*H*-12-oximiniothieno[3',2':5,6]azepino[2,1-*a*]isoindol-6-ones **8a** and **9a**.

The mixture of *syn* (20%) + *anti* (80%) isomers was obtained in a yield of 100%; ir: 3233 (OH), 1665 (C=O) cm⁻¹.

The **8a** *anti* oxime had ¹H nmr (deuteriochloroform): δ 3.04 (dd, 1H, H₁₁, J = 16.5, 8.6 Hz), 3.63 (dd, 1H, H₁₁, J = 16.5, 3.5 Hz), 4.83 (d, 1H, H₄, J = 16.4 Hz), 4.86 (dd, 1H, H_{10b}, J = 8.6, 3.5 Hz), 5.14 (d, 1H, H₄, J = 16.4 Hz), 7.12 (d, 1H, H₃, J = 5.4 Hz), 7.18 (d, 1H, H₂, J = 5.4 Hz), 7.38-7.65 (m, 3H, H_{8,9,10}), 7.82 (d, 1H, H₇, J = 7.3 Hz).

The **9a** *syn* oxime had ¹H nmr (deuteriochloroform): δ 2.59 (dd, 1H, H₁₁, J = 13.4, 8.9 Hz), 3.31 (dd, 1H, H₁₁, J = 13.4, 3.9 Hz), 4.44 (d, 1H, H₄, J = 16.2 Hz), 4.86 (dd, 1H, H_{10b}, J = 8.9, 3.9 Hz), 5.59 (d, 1H, H₄, J = 16.2 Hz), 7.13 (d, 1H, H₃, J = 5.1 Hz), 7.18 (d, 1H, H₂, J = 5.1 Hz), 7.37-7.60 (m, 3H, H_{8,9,10}), 7.84 (d, 1H, H₇, J = 7.5 Hz).

Anal. Calcd. for C₁₅H₁₂N₂O₂S: C, 63.36; H, 4.26; N, 9.85. Found: C, 63.35; H, 3.94; N, 9.60.

4,10_b-Dihydro-11*H*-12-oximiniothieno[2',3':5,6]azepino[2,1-*a*]isoindol-6-ones **8b** and **9b**.

The mixture of *syn* (26%) + *anti* (74%) isomers was obtained in a yield of 99%; ir: 3198 (OH), 1661 (C=O) cm⁻¹.

The **8b** *anti* oxime had ¹H nmr (deuteriochloroform): δ 3.02 (dd, 1H, H₁₁, J = 16.1, 7.5 Hz), 3.41 (dd, 1H, H₁₁, J = 16.1, 4.3 Hz), 4.46 (d, 1H, H₄, J = 16.4 Hz), 4.71 (dd, 1H, H_{10b}, J = 7.5, 4.3 Hz), 4.94 (d, 1H, H₄, J = 16.4 Hz), 6.80 (d, 1H, H₃, J = 5.2 Hz), 6.98 (d, 1H, H₂, J = 5.2 Hz), 7.15-7.45 (m, 3H, H_{8,9,10}), 7.55 (d, 1H, H₇, J = 7.5 Hz).

The **9b** *syn* oxime had ¹H nmr (deuteriochloroform): δ 2.97 (dd, 1H, H₁₁, J = 13.7, 4.3 Hz), 3.30 (dd, 1H, H₁₁, J = 13.7, 5.5 Hz), 4.33 (d, 1H, H₄, J = 16.7 Hz), 4.81 (dd, 1H, H_{10b}, J = 5.5, 4.3 Hz), 5.17 (d, 1H, H₄, J = 16.7 Hz), 6.83 (d, 1H, H₃, J = 5.1 Hz), 7.20 (d, 1H, H₂, J = 5.1 Hz), 7.21-7.42 (m, 3H, H_{8,9,10}), 7.52 (d, 1H, H₇, J = 7.5 Hz).

3-Chloro-4,10_b-dihydro-11*H*-12-oximiniothieno[3',4':5,6]azepino[2,1-*a*]isoindol-6-ones **8c** and **9c**.

The mixture of *syn* (20%) + *anti* (80%) isomers was obtained in a yield of 99%; ir: 3220 (OH), 1664 (C=O) cm⁻¹.

The **8c** *anti* oxime had ¹H nmr (deuteriochloroform): δ 3.18 (dd, 1H, H₁₁, J = 14.5, 5.6 Hz), 3.48 (dd, 1H, H₁₁, J = 14.5, 4.6 Hz), 4.50 (d, 1H, H₄, J = 16.4 Hz), 4.90-5.05 (m, 2H, H₄+H_{10b}), 7.38 (s, 1H, H₁), 7.35-7.75 (m, 4H, H_{7,8,9,10}).

The **9c** *syn* oxime had ¹H nmr (deuteriochloroform): δ 2.92 (dd, 1H, H₁₁, J = 13.9, 2.7 Hz), 3.33 (dd, 1H, H₁₁, J = 13.9, 6.5 Hz), 4.38 (d, 1H, H₄, J = 16.4 Hz), 4.90-5.05 (m, 1H, H_{10b}), 5.15 (d, 1H, H₄, J = 16.4 Hz), 7.35-7.75 (m, 5H, H_{1,7,8,9,10}).

Beckmann Rearrangement of Oximes **8a-c** and **9a-c**.

A mixture of oxime **8a-c** + **9a-c** (3.52 mmoles) and polyphosphoric acid (15 g) was heated at 100° for 45 minutes, then cooled. Water (150 ml) and ice were added and the mixture was basified with a 50% aqueous sodium hydroxide solution. Diazocines were extracted several times with dichloromethane. The combination of organic layers was dried, evaporated, and the residue was chromatographed on silicagel eluting with dichloromethane/acetone 90/10. Recrystallization from chloroform afforded pure amides **10** and **11**. The yields are reported in Table 1.

Schmidt Rearrangement of Ketones **7a-c**.

A solution of azepinone **7a-c** (5 mmoles) in dry dichloromethane (20 ml) was cooled with stirring and concentrated sulfuric acid (2.4 ml) was slowly added. Sodium azide (0.95 g, 15 mmoles) was added by portions during 30 minutes. Stirring was continued at room temperature for 24 hours. The mixture was poured on ice and was basified with a 50% aqueous sodium hydroxide solution. The aqueous solution was extracted several times with dichloromethane. The combination of organic layers was dried and concentrated. Purification of the residue was accomplished in a similar manner as above. The yields are reported in Table 1.

10_b,11-Dihydro-4*H*-isoindolo[2,1-*a*]thieno[3,2-*f*][1,5]diazocine-6,12(13*H*)-dione (**11a**).

This compound had a mp >270°; ir: 3080 (NH), 1701 (C=O), 1659 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.25 (dd, 1H, H₁₁, J = 9.9, 12.5 Hz), 2.94 (d, 1H, H₁₁, J = 12.5 Hz), 4.13 (d, 1H, H₄, J = 15.6 Hz), 4.85 (d, 1H, H_{10b}, J = 9.9 Hz), 5.42 (d, 1H, H₄, J = 15.6 Hz), 6.81 (d, 1H, H₃, J = 5.4 Hz), 7.20 (d, 1H, H₂, J = 5.4 Hz), 7.40-7.65 (m, 3H, H_{8,9,10}), 7.81 (d, 1H, H₇, J = 7.3 Hz); ¹³C nmr: δ 39.6 (CH₂), 44.8 (CH₂), 61.6 (CH), 126.8 (CH), 127.0 (CH), 128.6 (CH), 128.6 (CH), 132.6 (CH), 132.7 (C), 135.1 (C), 136.0 (CH), 139.7 (C), 148.4 (C), 169.6 (CO), 174.9 (CO).

Anal. Calcd. for C₁₅H₁₂N₂O₂S: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.46; H, 4.31; N, 9.89.

10_b,11-Dihydro-4*H*-isoindolo[2,1-*a*]thieno[3,2-*f*][1,4]diazocine-6,13(12*H*)-dione (**10b**).

This compound was the second eluted, mp 250°; ir: 3165 (NH), 1690 (C=O), 1633 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.57 (m, 2H, H₁₁), 4.60 (d, 1H, H₄, J = 17.5 Hz), 4.85 (s, 1H, H_{10b}), 5.29 (d, 1H, H₄, J = 17.5 Hz), 7.05 (d, 1H, H₃, J = 5.1 Hz), 7.40-7.84 (m, 6H, H_{2,7,8,9,10}+NH); ¹³C nmr: δ 41.6 (CH₂), 42.1 (CH₂), 61.7 (CH), 122.7 (CH), 123.6 (CH), 127.6 (CH), 128.5 (CH), 129.6 (CH), 131.7 (C), 131.8 (CH), 132.4 (C), 138.5 (C), 142.9 (C), 165.1 (CO), 167.1 (CO).

Anal. Calcd. for C₁₅H₁₂N₂O₂S: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.36; H, 4.28; N, 9.75.

10_b,11-Dihydro-4*H*-isoindolo[2,1-*a*]thieno[2,3-*f*][1,5]diazocine-6,12(13*H*)-dione (**11b**).

This compound was the first eluted, mp 233°; ir: 3073 (NH), 1708 (C=O), 1665 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.31 (dd, 1H, H₁₁, J = 12.4, 10.5 Hz), 2.92 (d, 1H, H₁₁, J = 12.4 Hz), 3.87 (d, 1H, H₄, J = 14.7 Hz), 4.80 (d, 1H, H_{10b}, J = 10.5 Hz), 5.36 (d, 1H, H₄, J = 14.7 Hz), 7.07 (d, 1H, H₃, J = 5.6 Hz), 7.15 (d, 1H, H₂, J = 5.6 Hz), 7.40-7.65 (m, 3H, H_{8,9,10}), 7.79 (d, 1H, H₇, J = 7.3 Hz); ¹³C nmr: δ 40.5 (CH₂), 44.4 (CH₂), 61.6 (CH), 126.8 (CH), 127.0 (CH), 126.4 (CH), 131.6 (CH), 132.6 (CH), 135.6 (C), 135.2 (C), 136.0 (CH), 142.1 (C), 148.4 (C), 169.7 (CO), 175.5 (CO).

Anal. Calcd. for C₁₅H₁₂N₂O₂S: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.29; H, 4.21; N, 9.51.

3-Chloro-10_b,11-dihydro-4*H*-isoindolo[2,1-*a*]thieno[3,4-*f*][1,5]-diazocine-6,12(13*H*)-dione (**11c**).

This compound had a mp >270°; ir: 3224 (NH), 1690 (C=O) cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.42 (dd, 1H, H₁₁, J = 13, 10.5 Hz), 2.91 (d, 1H, H₁₁, J = 13 Hz), 3.82 (d, 1H, H₄, J = 15 Hz), 4.81 (d, 1H, H_{10b}, J = 10.5 Hz), 5.62 (d, 1H, H₄, J = 15 Hz), 6.90 (s, 1H, H₁), 7.25-7.65 (m, 3H, H_{8,9,10}), 7.82 (d, 1H, H₇, J = 7.3 Hz); ¹³C nmr: δ 35.2 (CH₂), 39.8 (CH₂), 58.6 (CH),

116.3 (CH), 122.7 (CH), 122.8 (CH), 127.3 (C), 128.6 (CH), 131.0 (C), 132.1 (CH), 132.9 (C), 135.1 (C), 144.4 (C), 165.5 (CO), 171.5 (CO); ms: (EI, 70 ev) m/z 318 and 320 (M⁺), 319, 283, 275, 255, 172, 145, 132, 110, 77.

Anal. Calcd. for C₁₅H₁₁ClN₂O₂S: C, 56.52; H, 3.48; N, 8.79. Found: C, 56.45; H, 3.46; N, 8.67.

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