New Synthesis of 5,6,7,8-Tetrahydro-4*H*-thieno[2,3-*d*]azepine

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This paper describes two new access routes to 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine from 2-(2-thienyl)ethylamine or its *N*-(2-chlorobenzyl) derivative. One of these two syntheses involves a new ring expansion from a 6,7-dihydro[3,2-*c*]pyridinium derivative, chloromethylated in position 4.

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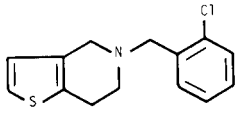
The remarkable platelet antiaggregating and antithrombotic activities [2] of ticlopidine [3] or 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**1**) led us to synthesize the more effective derivative of ticlopidine, 6-(2-chlorobenzyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**2**) (X = Cl).



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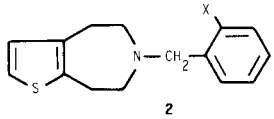

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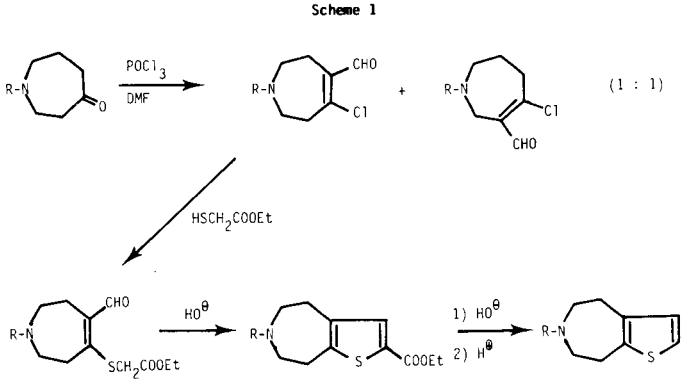
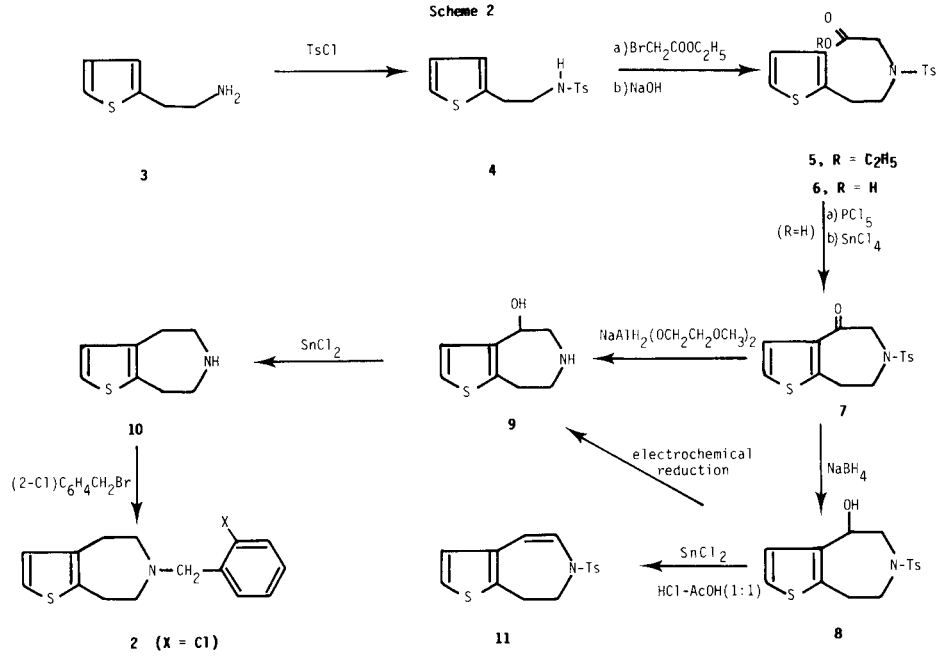
Scheme 1



The 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine heterocycle was mentioned recently in a patent [4] and antithrombotic activities are claimed for the *N*-benzylated derivative **2** (X = H). The synthesis described [4] uses *N*-alkylhexahydroazepin-4-one as the starting material (Scheme 1).

Chloroformylation of this aminoketone using the Vilsmeier reagent gave a mixture of two isomeric α-chloroaldehydes. This was followed by ethyl 2-mercaptoacetate *S*-alkylation by the α,β-unsaturated α-chloroaldehyde, cyclization of dicarbonyl compound according to the Dieckmann method, saponification of ester and decarboxylation. This paper presents two other access routes to this 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine heterocyclic system. The azepinic heterocycle is built on the suitably substituted thiophenic one to avoid the formation of isomers as described in the literature.

Scheme 2



The first access route (Scheme 2) uses *N*-tosyl-2-(2-thienyl)ethylamine (**4**) obtained by tosylation of 2-(2-thienyl)ethylamine [5] (**3**), using a heterogeneous chloroform biphasic system according to the Schotten-Baumann procedure. Condensation of this tosylamine **4** with ethyl bromoacetate gave ethyl *N,N*-[2-(2-thienyl)ethyl]tosylglycinate (**5**) which was saponified to give glycine derivative **6**. The acid chloride, obtained by chlorination of acid **6**, using phosphorus pentachloride, was converted into 6-tosyl-5,6,7,8-tetrahydrothieno[2,3-*d*]azepin-4-one (**7**), according to an intramolecular Friedel-Crafts reaction, using stannic chloride as a Lewis catalyst. Reduction of this ketone **7** with sodium borohydride in an ethanolic medium gave 4-hydroxy-6-tosyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**8**). Hydrogenolysis of the secondary alcohol function with stannous chloride in an acidic medium [6] was unsuccessful; the only product obtained was 6-tosyl-7,8-dihydro-6*H*-thieno-[2,3-*d*]azepine (**11**) resulting from dehydratation of alcohol **8**. Refluxing ketone **7** in toluene with sodium bis(2-methoxyethoxy)aluminum hydride [7] as the reducing agent caused simultaneous reduction of the carbonyl function and cleavage of the tosyl group to give 4-hydroxy-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**9**). This aminoalcohol **9** can also be obtained using electrochemical reduction [8] of the tosyl group from alcohol **8**. Cathodic cleavage of the N-S bond was successful using indirect reduction: pyrene anion radical as the reducing agent [9], dimethylformamide as the solvent and tetrabutylammonium perchlorate as the electrolytic support. We maintaned an electrolytic potential at −2.52V. At a redox potential of pyrene (−1.80V) no reduction of compound **8** was obtained. Reduction was stopped as soon as the red colour of the pyrene anion radical [10] appeared. Hydrogenolysis of the secondary alcohol function of the aminoalcohol **9** [6] gave 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**10**). We obtained the upper homologous derivative of ticlopidine **2** (X = Cl) by *N*-alkylation of amine **10** with 2-chlorobenzyl bromide.

Table I

60 MHz ^{1}H NMR Spectral Data

Compound No.	Solvent	NMR Chemical Shift (ppm)
4	$CDCl_3$	2.33 (s, 3H, ArC*H*$_3$), 2.72-3.27 (m, 4H, NC*H*$_2$C*H*$_2$), 6.58-7.12 (m, 3H, thiophene), 7.13 and 7.60 (2d, J = 8, 4H, *Ar*CH$_3$)
5	$CDCl_3$	1.13 (t, J = 7, 3H, CH$_2$C*H*$_3$), 2.35 (s, 3H ArC*H*$_3$), 2.72-3.30 (m, 2H, NCH$_2$C*H*$_2$), 3.35-3.60 (m, 2H, NC*H*$_2$CH$_2$), 3.93 (s, 2H, NC*H*$_2$CO), 3.98 (q, J = 7, 2H, OC*H*$_2$CH$_3$), 7.02-7.20 (m, 3H, thiophene), 7.35 and 7.62 (2d, J = 8, 4H, *Ar*CH$_3$)
6	$CDCl_3$	2.37 (s, 3H, *Ar*CH$_3$), 2.88-3.25 (m, 2H, NCH$_2$C*H*$_2$), 3.25-3.60 (m, 2H, NC*H*$_2$CH$_2$), 3.95 (s, 2H, NC*H*$_2$CO), 6.60-7.25 (m, 3H, thiophene), 7.28 and 7.63 (2d, J = 8, 4H, *Ar*CH$_3$)
11	$CDCl_3$	2.36 (s, 3H, ArC*H*$_3$), 2.78-3.05 (m, 2H NCH$_2$C*H*$_2$), 3.60-3.85 (m, 2H, NC*H*$_2$CH$_2$), 5.70 (d, J = 9, 1H NCH=C*H*), 6.73 (d, J = 9, 1H, NC*H*=CH), 6.75-7.10 (m, 2H, thiophene), 7.27 and 7.67 (2d, J = 8, 4H, *Ar*CH$_3$)
13 (2 rotamers)	$CDCl_3$	2.90-3.27 (m, 2H, NCH$_2$C*H*$_2$), 3.42-3.78 (m, 2H, NC*H*$_2$CH$_2$), 3.80 and 4.03 (2s, 2H, NC*H*$_2$Ar), 4.50 and 4.78 (2s, 2H, NCOC*H*$_2$Cl), 6.78-7.33 (m, 7H, thiophene and aromatic)
	DMSO-d_6	2.76-3.27 (m, 2H, NCH$_2$C*H*$_2$), 3.27-3.77 (m, 2H, NC*H*$_2$CH$_2$), 4.35 (s, 2H, NC*H*$_2$Ar), 4.65 (s, 2H, NCOC*H*$_2$Cl), 6.70-7.53 (m, 7H, thiophene and aromatic)
14	CF_3COOD	3.17-3.55 (m, 2H, NCH$_2$C*H*$_2$), 3.92-4.30 (m, 2H, NC*H*$_2$CH$_2$), 5.03 (s, 2H, C*H*$_2$Cl), 5.48 (s, 2H, NC*H*$_2$Ar), 7.28-7.68 (m, 6H, thiophene and aromatic)
18 (2 stereoisomers)	$CDCl_3$	2.66-3.48 (m, 4H, NC*H*$_2$C*H*$_2$), 4.40 and 4.48 (2s, 2H, NC*H*$_2$Ar), 5.06 and 5.88 (2s, 1H, C=C*H*Cl), 7.18-8.21 (m, 6H, thiophene and aromatic)

Scheme 3

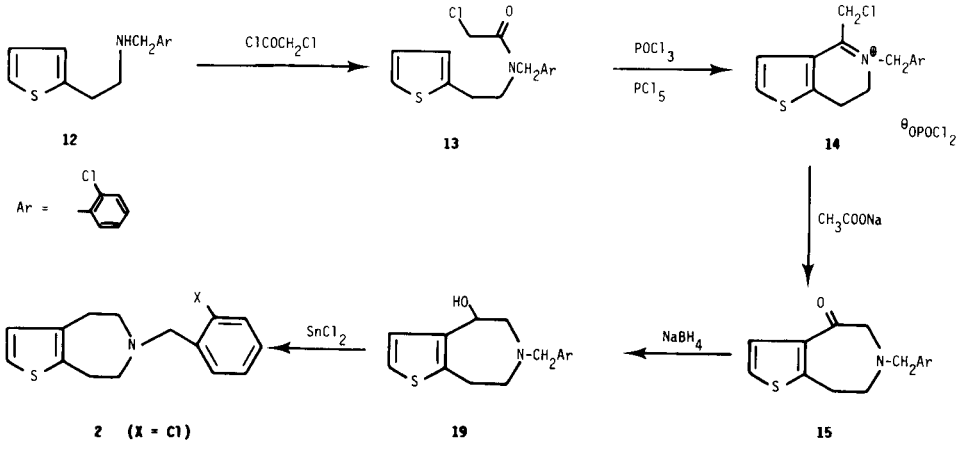
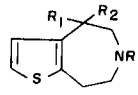


Table III

Carbon-13 NMR Chemical Shift Data [a] of Compound **13** Rotamers

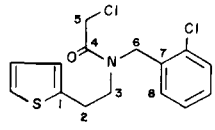


Solvent	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
$CDCl_3$	139.66	27.63	45.53	167.27	40.80	49.05	133.59	139.66
	140.87	28.78	49.42		41.42	50.33	136.26	140.87
DMSO-d_6	140.33	27.09	46.33	166.85	42.21	48.21	132.63	134.63
	140.94	28.31				49.31	134.14	

[a] All shifts assignments are reported relative to tetramethylsilane as internal reference.

Table II

60 MHz ^1H NMR Spectral Data



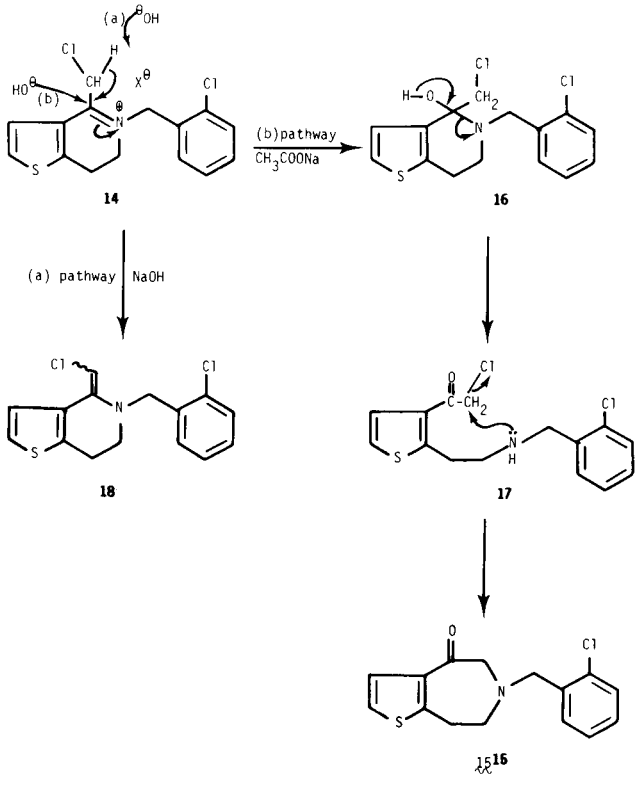
Compound No.	R_1, R_2	R	Solvent	NMR Chemical Shift (ppm)
2	H, H	(2-Cl)$C_6H_4CH_2$	C_6D_6	2.35-2.80 (m, 8H,N(CH_2,CH_2)$_2$, 3.62 (s, 2H, NCH_2Ar), 6.47 and 6.67 (2d, J = 6, 2H, thiophene), 6.70-7.55 (m, 4H, aromatic)
7	O	(4-CH_3)$C_6H_4SO_2$	$CDCl_3$	2.33 (s, 3H, ArCH_3), 3.20 (t, J = 6, 2H, NCH{CH_2), 3.62 (t, J ^{5} 6, 2H, NCH_2CH_2), 4.11 (s, 2H, NCH_2CO), 6.87-7.56 (m, 6H, thiophene and aromatic)
8	H, OH	(4-CH_3)$C_6H_4SO_2$	$CDCl_3$	2.38 (s, 3H, ArCH_3), 2.87-3.20 (m, 2H, NCH$_2$$CH_2$), 3.25-3.73 (m, 2H N$CH_2CH_2$), 4.70-4.95 (m, 1H, C*H*OH), 6.90 (s, 4H, *Ar*CH_3), 7.23 and 7.67 (2d, J = 6, 2H, thiophene)
9	H, OH	H	$CDCl_3$	2.65-3.45 (m, 6H, CH_2NCH_2CH_2), 4.60-4.80 (m, 1H, C*H*OH), 6.80 (s, 2H, thiophene)
10	H, H	H	$CDCl_3$	2.67-3.02 (m, 8H, N(CH_2CH_2)$_2$), 6.65 and 6.83 (2d, J = 6, 2H, thiophene)
15	O	(2-Cl)$C_6H_4CH_2$	$CDCl_3$	3.08 (s, 4H, NCH_2CH_2), 3.58 (s, 2H, NCH_2Ar), 3.72 (s, 2H, NCH_2CO), 6.88 and 7.27 (2d, J = 6, 2H, thiophene), 7.10-7.23 (m, 4H, aromatic)
19	H, OH	(2-Cl)$C_6H_4CH_2$	$CDCl_3$	2.43-3.27 (m, 6H, CH_2NCH_2CH_2), 3.80 (s, 2H, NCH_2Ar), 4.45-4.70 (m, 4, 1H, C*H*OH), 6.85 (s, 2H, thiophene), 7.08-7.50 (m, 4H, aromatic)

The second access route (Scheme 3) used *N*-(2-chlorobenzyl)-2-(2-thienyl)ethylamine (**12**) [11] as the starting material. Chloroacetylation of this amine **12** with chloroacetyl chloride gave *N,N*-(chloroacetyl)(2-chlorobenzyl)-2-(2-thienyl)ethylamine (**13**). This amine **13** occurs as two rotamers [12] confirmed by ^1H (Table I) and ^{13}C (Table II) nmr spectroscopy [13].

Such rotamers are classical in *N*-alkylated and *N,N*-dialkylated benzamides [14] and *N*-alkylated formamides [15]. This amide **13** was converted into a 6,7-dihydrothieno[3,2-*c*]pyridinium derivative **14** according to the Bischler-Napieralski reaction [16]. We present in Scheme 4 a proposed mechanism for the conversion of compound **14** into 6-(2-chlorobenzyl)-5,6,7,8-tetrahydrothieno[2,3-*d*]-azepin-4-one (**15**).

By refluxing in weakly alkaline medium, nucleophilic addition of an hydroxylic anion on an iminium derivative **14** gave amine **16**, the cleavage of which gave chloroketone **17**. Intramolecular *N*-alkylation gave β-aminoketone **15**. To our knowledge, this pattern of ring expansion has never been described in literature. In stronger alkaline medium at room temperature, compound **14** isomerized

Scheme 4



into β-chloroenamine **18** which we isolated.

Reduction of β-aminoketone **15** gave 6-(2-chlorobenzyl)-4-hydroxy-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**19**), which was hydrogenolized [6] to get 6-(2-chlorobenzyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**2**) (X = Cl) (Scheme 3). The ^1H nmr spectral data of the new compounds are presented in Tables I and II.

New 5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepines did not reveal in animal models, the platelet antiaggregating activities of ticlopidine.

EXPERIMENTAL

Melting points were determined on a Köfler hot-stage and are uncorrected. The ^1H nmr spectra were obtained on a Hitachi-Perkin-Elmer R-24A nmr spectrometer using tetramethylsilane as the internal standard in the solvents indicated. Elemental analysis were performed by Microanalytical Laboratory in Sanofi-Recherche (Toulouse-France).

N-Tosyl-2-(2-thienyl)ethylamine (**4**).

To a mixture of 80 g (0.629 mole) of 2-(2-thienyl)ethylamine (**3**), 86.8 g (0.629 mole) of potassium carbonate, 200 ml of water and 300 ml of chloroform was added dropwise with stirring at room temperature a solution of 120 g (0.629 mole) of tosyl chloride in 300 ml of chloroform. The reaction mixture was stirred at room temperature for 4 hours. The organic layer was separated, dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The solid residue was recrystallized from diisopropyl ether to give 150 g (85%) of colorless crystals, mp 65°.

Anal. Calcd. for $C_{13}H_{15}NO_2S_2$: C, 55.48; H, 5.37; N, 4.98; S, 22.79. Found: C, 55.40; H, 5.32; N, 4.92; S, 22.59.

Ethyl *N,N*-[2-(2-Thienyl)ethyl]tosylglycinate (**5**).

To a solution of 18 g (0.072 mole) of compound **4** in 150 ml of dimethylformamide were added 12.06 g (0.072 mole) of ethyl bromoacetate and 9.96 g (0.072 mole) of potassium carbonate. The reaction mixture was gently heated at 90° for 4 hours. After cooling the mineral salts were filtered off and the organic solvent was evaporated *in vacuo* to dryness. The resulting oil was taken up with diethyl ether, washed with water, dried over anhydrous sodium sulfate and concentrated to an oily residue (21.05 g, 95%) which was directly used in the subsequent reaction without further purification.

N,N-[2-(2-Thienyl)ethyl]tosylglycine (**6**).

To a solution of 349.5 g (0.951 mole) of compound **5** in 1000 ml of ethanol was added 750 ml of aqueous 2*N* sodium hydroxide. The reaction mixture was stirred at room temperature overnight. Solvents were evaporated *in vacuo* to dryness and residue was dissolved in water. The aqueous basic solution was washed with diethyl ether and acidified with 6*N* hydrochloric acid. The aqueous acidic solution was extracted with methylene chloride. The organic extracts were evaporated *in vacuo* to dryness and the solid residue recrystallized from diisopropyl ether to give 290.5 g (90%) of colorless crystals, mp 150°.

Anal. Calcd. for $C_{15}H_{17}NO_4S_2$: C, 53.07; H, 5.05; N, 4.13; S, 18.89. Found: C, 52.97; H, 5.01; N, 4.08; S, 18.79.

6-Tosyl-5,6,7,8-tetrahydrothieno[2,3-*d*]azepin-4-one (**7**).

To a solution of 88.6 g (0.261 mole) of compound **6** in 400 ml of 1,2-dichloroethane were added quickly 57.06 g (0.274 mole) of phosphorus pentachloride. The reaction mixture was gently heated at 60° for 30 minutes. After cooling to −10°, a solution of 39.8 ml (0.339 mole) of stannic chloride in 150 ml of 1,2-dichloroethane was added. After addition the mixture was maintained at −10° for 2 hours then acidified wth 2*N* hydrochloric acid. The organic layer was separated, washed with *N* hydrochloric acid then water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The solid residue was recrystallized from ethyl acetate to give 27.6 g (33%) of yellow crystals, mp 130°.

Anal. Calcd. for $C_{15}H_{15}NO_3S_2$: C, 56.05; H, 4.70; N, 4.36; S, 19.96. Found: C, 55.96; H, 4.69; N, 4.29; S, 19.85.

4-Hydroxy-6-tosyl-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**8**).

To a suspension of 10 g (0.031 mole) of compound **7** in 100 ml of ethanol was added portionwise with stirring 0.6 g (0.0155 mole) of sodium borohydride and stirred at room temperature for 1 hour. The reaction mixture was evaporated *in vaco* to dryness. The oily residue was taken up with *N* hydrochloric acid and extracted with methylene chloride. The organic extracts were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The solid residue was recrystallized from 2-propanol to give 8.55 g (85%) of colorless crystals, mp 148°.

Anal. Calcd. for $C_{15}H_{17}NO_3S_2$: C, 55.70; H, 5.30; N, 4.33; S, 19.83. Found: C, 55.68; H, 5.25; N, 4.30; S, 19.79.

4-Hydroxy-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**9**).

Method 1: Chemical Reduction.

To a solution of 14 g (0.043 mole) of compound **7** in 140 ml of dry toluene was added 44 g (0.218 mole) of a 70% toluene solution of sodium bis-(2-methoxyethoxy)aluminum hydride. The reaction mixture was heated at 120° for 18 hours under an inert atmosphere. After cooling the reaction mixture was poured into 2*N* hydrochloric acid. The acidic solution, washed with methylene chloride, was alkalinized with aqueous concentrated potassium hydroxide and extracted wth methylene chloride. The organic extracts were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The oily residue was taken up with ethanol and maleic acid (1 equivalent) was added. Maleate was filtered off, dried and recrystallized from ethanol to give 7.1 g (57%) of colorless crystals, mp 195°.

Anal. Calcd. for $C_8H_{11}NOS{\cdot}C_4H_4O_4$: C, 50.51; H, 5.30; N, 4.91; S, 11.24. Found: C, 50.42; H, 5.28; N, 4.85; S, 11.05.

Method 2: Controlled-Potential Indirect Electrochemical Reduction.

A mixture of 4 g (0.0124 mole) of compound **8** and 0.65 g (0.0032 mole)

of pyrene in 150 ml of dimethylformamide containing 0.1*M* tetrabutylammonium perchlorate, used as supporting electrolyte, was placed in the cathodic compartment with a mercury electrode. Supporting electrolyte was placed in the anodic compartment with a graphite electrode. The anodic and cathodic compartments were separated by a membrane. The chosen fixed potential −2.52V was referred to silver −0.1*M* silver nitrate reference electrode for 30 minutes. The end of the reaction was determined by the appearance of the red coloured pyrene anion radical. The reaction mixture was poured into 6*N* hydrochloric acid and the acidic solution evaporated *in vacuo* to dryness. The residue was taken up with water and washed with methylene chloride. The aqueous solution was alkalinized with concentrated ammonium hydroxide and extracted with methylene chloride. This second organic extract dried over anhydrous sodium sulfate was evaporated *in vacuo* to dryness. The oily residue obtained was taken up with acetone and oxalic acid was added. Oxalate was filtered off, dried and recrystallized from ethanol to give 2.03 g (65%) of beige crystals, mp 117°.

Anal. Calcd. for $C_8H_{11}NOS \cdot C_2H_2O_4$: C, 46.32; H, 5.05; N, 5.40; S, 12.37. Found: C, 46.12; H, 5.00; N, 5.18; S, 12.21.

5,6,7,8-Tetrahydro-4*H*-thieno[2,3-*d*]azepine (**10**).

To a mixture of 6 ml of acetic acid and 3 ml of 12 *N* hydrochloric acid were added 0.6 g (0.00354 mole) of compound **9** and 2 g (0.0086 mole) of stannous chloride dihydrate. The reaction mixture was heated at 65° for 2 hours and evaporated *in vacuo* to dryness. The oily residue was taken up with ice water and alkalinized with aqueous concentrated potassium hydroxide. The basic solution was extracted with methylene chloride. The organic extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue obtained was taken up with diethyl ether ad a diethyl ether solution of hydrogen chloride was added. The hydrochloride was filtered off, dried and recrystallized from ethanol to give 0.5 g (75%) of beige crystals, mp 213°.

Anal. Calcd. for $C_8H_{11}NS \cdot HCl$: C, 50.65; H, 6.38; N, 7.38; S, 16.90. Found: C, 50.52; H, 6.29; N, 7.29; S, 16.84.

6-Tosyl-7,8-dihydro-6*H*-thieno[2,3-*d*]azepine (**11**).

To a mixture of 4 ml of acetic acid and 1 ml of 12*N* hydrochloric acid was added 0.15 g (0.000465 mole) of compound **8**. The reaction mixture was stirred at room temperature for 20 hours, then poured into water. The aqueous solution was extracted with methylene chloride. The organic extracts were washed with 5% aqueous sodium hydrogenocarbonate solution, dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was crystallized from ethanol to give 0.1 g (71%) of colorless crystals, mp 54°.

Anal. Calcd. for $C_{15}H_{15}NO_2S_2$: C, 65.91; H, 5.53; N, 5.12; S, 11.73. Found: C, 65.80; H, 5.49; N, 5.10; S, 11.65.

N,N-(Chloroacetyl)(2-chlorobenzyl)-2-(2-thienyl)ethylamine (**13**).

To a mixture of 105 g (0.417 mole) of *N*-(2-chlorobenzyl)-2-(2-thienyl)-ethylamine [10] (**12**), 57.54 g (0.417 mole) of potassium carbonate, 200 ml of water and 600 ml of methylene chloride was added dropwise a solution of 37.3 ml (0.458 mole) of chloroacetyl chloride in 150 ml of methylene chloride. The reaction mixture was stirred at room temperature for 4 hours. The organic layer was separated, dried over anhydrous sodium sulfate and evaporated *in vacuo* to dryness. The oily residue (130 g, 95%) was directly used in the subsequent reaction without further purification.

5-(2-Chlorobenzyl)-4-chloromethyl-6,7-dihydrothieno[3,2-*c*]pyridinium Dichlorophosphate (**14**).

To a solution of 104.3 g (0.318 mole) of compound **13** in 300 ml of phosphoryl chloride was added 132.3 g (0.636 mole) of phosphorus pentachloride. The reaction mixture was stirred at room temperature for 90 minutes and poured into diethyl ether. The precipitate was filtered off, washed with diethyl oxide and dried. The yellow crystals obtained (100 g, 76%) were very hygroscopic, mp 100°. This hygroscopic material was directly used in the subsequent reaction without further purification.

6-(2-Chlorobenzyl)-5,6,7,8-tetrahydrothieno[2,3-*d*]azepin-4-one (**15**).

A mixture of 98 g (0.237 mole) of compound **14**, 1500 ml of tetrahydrofuran and 600 ml of 2*N* aqueous sodium acetate solution was gently heated at reflux for 2 hours under inert atmosphere. After cooling the organic layer was separated and evaporated *in vacuo* to dryness. The oily residue was taken up with methylene chloride and washed with water. The organic solution was dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was taken up with diethyl ether and hydrogen chloride in diethyl ether was added. The hydrochloride was filtered off, dried and recrystallized from 2-propanol to give 21.75 g (28%) of colorless crystals, mp 170°.

Anal. Calcd. for $C_{15}H_{14}ClNOS \cdot HCl$: C, 54.88; H, 4.61; N, 4.27; S, 9.77. Found: C, 65.79; H, 4.59; N, 4.19; S, 9.66.

6-(2-Chlorobenzyl)-4-hydroxy-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**19**).

To a solution of 9.2 g (0.0315 mole) of compound **15** in 100 ml of ethanol was added portionwise 1.2 (0.0315 mole) of sodium borohydride. The reaction mixture was stirred at room temperature for 2 hours and evaporated *in vacuo* to dryness. The residue was taken up with water and extracted with diethyl oxide. The organic extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was taken up with ethanol and maleic acid was added. The precipitate was filtered off, dried and recrystallized from ethanol to give 9.2 g (71%) of colorless crystals, mp 158°.

Anal. Calcd. for $C_{15}H_{16}ClNOS \cdot C_4H_4O_4$: C, 55.67; H, 4.92; N, 3.42; S, 7.82. Found: C, 55.49; H, 4.85; N, 3.39; S, 7.63.

6-(2-Chlorobenzyl)-5,6,7,8-tetrahydro-4*H*-thieno[2,3-*d*]azepine (**2**).

Method: *N*-Alkylation of Compound **10**.

To a solution of 6.13 g (0.040 mole) of compound **10** in 60 ml of dimethylformamide were added 6.44 g (0.040 mole) of 2-chlorobenzyl chloride and 5.52 g (0.040 mole) of solid potassium carbonate. The reaction mixture was heated to 90° for 4 hours. After cooling the mineral salts were filtered off and the filtrate was evaporated *in vacuo* to dryness. The oily residue was taken up with water and extracted with diethyl ether. The organic extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was taken up in ethanol and methanesulfonic acid was added. The precipitate was filtered off, dried and recrystallized from ethanol to give 13.5 g (90%) of colourless crystals, mp 198°.

Anal. Calcd. for $C_{15}H_{16}ClNS \cdot CH_4O_3S$: C, 51.39; H, 5.39; N, 3.75; S, 17.15. Found: C, 51.20; H, 5.29; N, 3.69; S, 16.95.

Method: Hydrogenolysis of Compound **19**.

To a mixture of 160 ml of acetic acid and 80 ml of 12*N* hydrochloric acid were added 16.2 g (0.055 mole) of compound **19** and 26.13 g (0.138 mole) of anhydrous stannous chloride. The reaction mixture was heated at 65° for 2 hours. After cooling the crystals obtained were filtered off and washed with acetic acid diisopropyl ether. These crystals were taken up with 2 *N* aqueous sodium hydroxide. The basic solution was extracted with methylene chloride. The organic extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The oil residue was transformed into the maleate as in the preceding method to give 7.05 g (50%) of colorless crystals, mp 198°.

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[12] In deuteriochloroform (Table I), each methylene of benzylic acid chloroacetyl substituents appears as two singlets; in dimethylsulfoxide-d_6 (Table I) each methylene appears as one singlet.

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