Derivatives of Benzo[4,5]cyclohepta[1,2-*b*]thiophene. 4. Synthesis of 1-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-yl)-3-alkylaminoazetidines

Amelia Jiménez and Salvador Vega*

Instituto de Química Médica, C. S. I. C., Juan de la Cierva, 3,
Madrid-28002, Spain

Received February 10, 1986

Thirteen 1-(9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-yl)-3-alkylaminoazetidines **11** have been synthesized in three steps from 4-amino-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (**6**), which was obtained from the reduction of either 4-azido **4** or 4-hydroxyimino **5** derivatives. All the compounds have been evaluated as potential antidepressive agents.

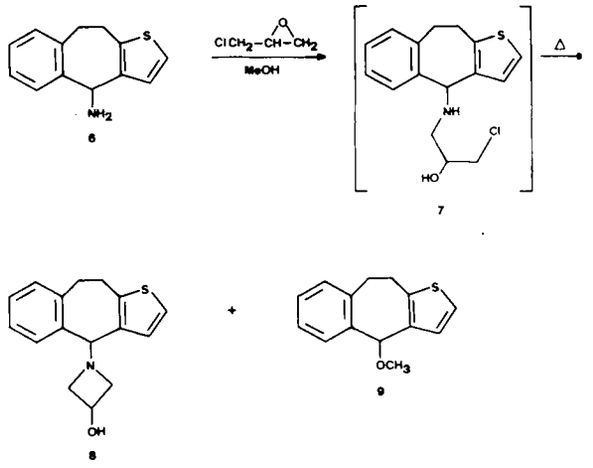
J. Heterocyclic Chem., **23**, 1503 (1986).

It has recently been described that the coupling of the azetidine ring with the benzo[*a,d*]cycloheptene structure leads to compounds which were found to have antidepressant activity in pharmacological screening [1]. The active series had the tricyclic ring attached to position 1 and a basic group in position 3 of the azetidine moiety. On the other hand, mono- [2] and dithiophene analogues [3] of the tricyclic antidepressive agents amitriptyline and nortriptyline have been synthesized and shown to have activity.

These observations, and our interest in the development of new psychoactive drugs derived of benzo[4,5]cyclohepta[1,2-*b*]thiophene [4], prompted us to achieve the synthesis of an, as yet, unreported series of 1-(9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-yl)-3-alkylaminoazetidines **11** with possible antidepressant properties.

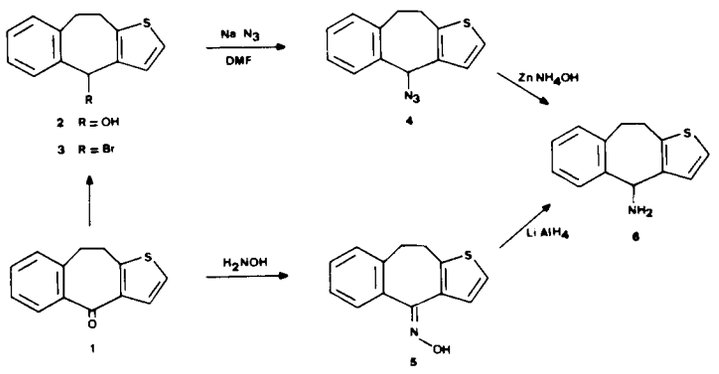
In our synthetic approach, we started from the amine **6** (Scheme I) which was prepared by two different methods. Thus, reaction of 4-bromo-9,10-dihydro-4*H*-benzo[4,5]-cyclohepta[1,2-*b*]thiophene (**3**) [5] with sodium azide in refluxing *N,N*-dimethylformamide gave the azide **4** which was transformed into amine **6** using lithium aluminum hydride in ether. Alternatively, **6** was also prepared in a two step process involving initial reaction of ketone **1** with hydroxilamine hydrochloride in ethanol-pyridine to generate the oxime **5** [6] followed by reduction with zinc and ammonium hydroxide in ethanol-water.

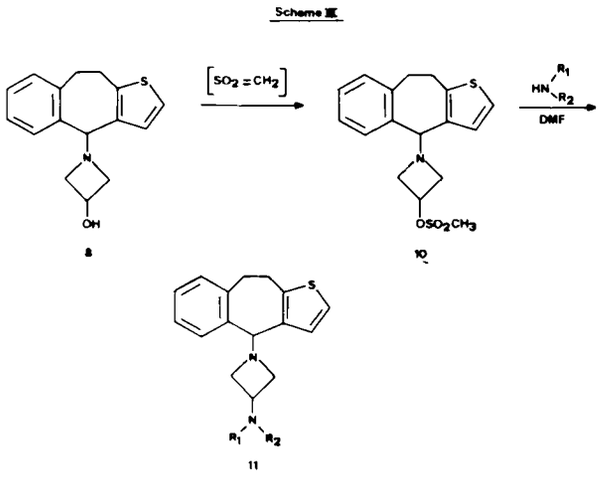
Scheme II



The preparation of compound **8** (Scheme II) was carried out by the general method described by Gaertner [7,8] for the synthesis of 1-alkyl-3-azetidinols. This method is based on the spontaneous cyclization of the unstable 1-alkylamino-3-chloro-2-propanols, obtained from primary

Scheme I





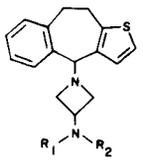
amines and epichlorhydrin.

In our case, the amine **6** was condensed with an equimolecular amount of epichlorhydrin in methanol for two days at room temperature and without isolation of the intermediate **7**, this was cyclized *in situ* to the azetidinol **8** by refluxing the reaction mixture for three days. In this reaction, together with compound **8** which was isolated as the hydrochloride salt in 41% yield, a 10% of 4-methoxy-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (**9**) was also obtained. The formation of **9** can be explained through a cation of the tropylium type which evidently interacts with the solvent in the course of the reaction. Change of methanol by dimethylsulfoxide or attempts to isolate the intermediate **7** to perform the cyclization in basic conditions were unsuccessful.

Mesylate **10** (Scheme 3) was first prepared in 50% yield by reaction of azetidinol **8**, with methane sulfonyl chloride in pyridine, according to the method described by Anderson [9]. However, a better yield of **10** could be obtained by the method of Crossland [10] in which triethylamine in dry benzene is used and involves the addition of the alcohol to the sulfene intermediate derived from methyl chloride by E_2 elimination of hydrogen chloride.

Table 1

Physical and Analytical Data of Compounds **11**



	R_1	R_2	Yield (%)	Mp (°C) Solvent Ethanol	Formula	Maleate	Analysis Calcd./Found (%)		
						C	H	N	S
11a	H	Methyl	90	112-113 [a]	$C_{21}H_{24}N_2O_4S$	63.00	9.52	11.11	12.69
						62.87	9.68	10.95	12.98
11b	H	Ethyl	92	125-127	$C_{22}H_{26}N_2O_4S$	63.76	6.28	6.76	7.72
						63.92	6.16	6.82	7.56
11c	H	*iso*-Propyl	78	246-248	$C_{23}H_{28}N_2O_4S$	64.48	6.54	6.54	7.47
						64.14	6.36	6.27	7.18
11d	H	*t*-Butyl	75	192-194	$C_{24}H_{30}N_2O_4S$	65.15	6.78	6.33	7.23
						65.05	6.84	6.18	7.59
11e	H	Cyclohexyl	72	182-184	$C_{26}H_{32}N_2O_4S$	66.66	6.83	5.98	6.83
						66.63	6.98	5.80	7.24
11f	H	β-Hydroxyethyl	62	156-158	$C_{22}H_{26}N_2O_5S$	61.39	6.04	6.04	7.44
						61.58	6.22	6.29	7.12
11g	H	Benzyl	68	162-164	$C_{27}H_{28}N_2O_4S$	68.06	5.88	5.88	10.05
						68.42	5.96	5.90	10.02
11h	H	β-Phenylethyl	62	164-166	$C_{29}H_{30}N_2O_4S$	69.32	5.97	5.57	6.37
						69.09	5.63	5.39	6.48
11i	H	Pyrrolidinoethyl	64	166-168	$C_{26}H_{33}N_3O_4S$	64.59	6.83	8.69	6.62
						64.63	6.56	8.43	6.33
11j	H	Morpholinoethyl	65	152-154 [b]	$C_{30}H_{37}N_3O_9S$	58.53	6.12	6.68	5.20
						58.70	6.41	6.51	5.21
11k	H	*N,N*-Diethylaminoethyl	66	130-132	$C_{26}H_{35}N_3O_4S$	64.32	7.21	8.65	6.59
						64.51	7.18	8.72	6.40
11l	H	*N,N*-Diethylaminopropyl	65	164-166 [c]	$C_{35}H_{45}N_3O_{12}S$	58.45	6.15	5.74	5.33
						58.43	5.88	5.51	5.67
11m	Methyl	Methyl	35	170-172 [d]	$C_{40}H_{48}N_4O_4S_2$	58.02	5.75	5.92	7.22
						57.99	5.66	5.87	7.59

[a] Free base mp 87-88° (Hexane). [b] Dimaleate. [c] Trimaleate. [d] Hemimaleate.

The tricyclic aminoazetidines **11** were synthesized by nucleophilic displacement of the sulfonate group of compound **10** by amines. The reaction was carried out by heating at 50-60° a solution of mesylate **10** and an excess of the required amine in *N,N*-dimethylformamide. Under these conditions, the possible nucleophilic attack by other species present in solution was not produced.

All of the amines used in this reaction were sufficiently basic to avoid the azetidine ring opening [11]. Primary amines reacted particularly well giving the corresponding azetidines in good yield (Table 1). In the case of secondary amines, however, only the 3-dimethylamino derivative could be obtained in acceptable yield.

Except for **11a**, which was a solid, all the azetidine derivatives were oily compounds in their free base form. Compounds **11a-l** exhibited in their intrared spectra a band at 3300-3200 cm^{-1} characteristic of the stretching frequencies of NH bond. The ^{1}H-nmr spectra in deuteriochloroform solution of these compounds showed the NH proton signals at δ 1.25-1.45. Azetidines **11a-m** exhibited the signals of the CH proton attached to position 4 of the tricyclic ring as a singlet at δ 4.10-4.25, and the signals corresponding to the CH proton on position 3 of the azetidine moiety as a multiplet at δ 4.30-4.55.

The salts of these derivatives with strong acids resulted highly hygroscopic. For this reason, they were converted to their respective maleate salts which proved to be stable in aqueous solution. In this form, they were tested for their ability to block the cortical imipramine receptors *in vitro*. Some of these compounds were found to be active — less than 10 times as potent as desipramine — which suggests a relative antidepressant profile for them.

EXPERIMENTAL

All melting points (uncorrected) were determined using a Gallenkamp capillary apparatus. The ir spectra were recorded with a Perkin-Elmer Model 257 instrument. The ^{1}H-nmr spectra were measured with a Varian EM-390 spectrometer using TMS as internal standard. Chemical shifts are given in δ units.

4-Azido-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (**4**).

To a solution of 4-bromo-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]-thiophene (**3**) (4.0 g, 0.014 mole) in ethanol (64 ml) sodium azide (0.96 g, 0.014 mole) was added. The mixture was heated at reflux for 3 hours. After cooling, the ethanol was evaporated *in vacuo* at room temperature and the residue was taken up in ether. After removal of the ether, the residue was purified by column chromatography (ethyl acetate 1:cyclohexane 1) to give 2.8 g (70%) of **4** as a yellowish oil; ir (film): 2100 cm^{-1} (N_3); ^{1}H nmr (deuteriochloroform): 3.1 (m, 2, CH_2), 3.8 (m, 2, CH_2), 5.7 (s, 1, CH), 7.1 (s, 2, thiophene protons), 7.3 (s, 4, benzene protons).

Anal. Calcd. for $C_{13}H_{11}N_3S$: C, 64.73; H, 4.56; N, 17.42; S, 13.27. Found: C, 64.48; H, 4.56; N, 17.52; S, 13.48.

4-Amino-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (**6**). Method A.

The azide **4** (24.1 g, 0.1 mole) dissolved in dry ether (200 ml) was added over 1 hour to a stirred suspension of lithium aluminum hydride (5.7 g, 0.15 mole) in dry ether (400 ml) at 0°. The mixture was refluxed for 3 hours then cooled to -10°, and a solution of dry ether-ethyl acetate (1:1) was slowly added. Cold hydrochloric acid was added and the aqueous layer was separated, neutralized with ammonium hydroxide and extracted with ether. The combined organic extracts were washed with 5% sodium carbonate and water, dried (magnesium sulfate) and evaporated yielding the amine **6** (8.6 g, 38%) as a solid, mp 80-82° (hexane); ir (nujol): 3300 cm^{-1} (NH_2); ^{1}H-nmr (deuteriochloroform): 1.65 (s, 2, NH_2), 3.05 (m, 2, CH_2), 3.70 (m, 2, CH_2), 5.25 (s, 1, CH), 7 (s, 2, thiophene protons), 7.25 (s, 4, benzene protons).

Anal. Calcd. for $C_{13}H_{13}NS$: C, 72.55; H, 6.04; N, 6.61; S, 14.88. Found: C, 72.72; H, 6.12; N, 6.48; S, 14.66.

The hydrochloride salt of **6** had mp 204-205° (ethanol).

Method B.

To a solution of the oxime **5** (3.2 g, 0.014 mole) in ethanol (16 ml), ammonium chloride (0.64 g, 0.012 mole), zinc powder (4.8 g, 0.07 mole) and 25% ammonium hydroxide (80 ml) was added. The mixture was refluxed for 3 hours, cooled and filtered. The solution was made alkaline with 33% sodium hydroxide (9 ml) and extracted with a mixture of benzene-ether (1:1). The extracts were washed with brine, dried (magnesium sulfate) and evaporated to give the compound **6** (2.4 g, 82%) identical with that described above.

1-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-yl)-3-azetidinol (**8**).

To a solution of the amine **6** (2.4 g, 0.012 mole) in methanol (15 ml), epichlorhydrin (0.95 g, 0.012 mole) was added. After 2 days in the dark at room temperature, the solution was refluxed for 3 days and evaporated to dryness. The residue was dissolved in acetone (75 ml). On cooling, the hydrochloride salt of the azetidinol **8** crystallized and was collected by filtration. The liquid phase was evaporated, and the residue was dissolved in methanol and refluxed overnight. It was concentrated to dryness, taken up in acetone, and cooled, yielding a second batch of the product (1.37 g, 41%), mp 174-175° (acetone).

The hydrochloride salt when treated with 20% sodium hydroxide gave the free base of azetidinol **8** as a white solid which was filtered, washed with water and dried, mp 138-140° (acetone); ir (nujol): 3350 cm^{-1} (OH); ^{1}H-nmr (deuteriochloroform): 2.95 (s, 1, OH), 2.65 (m, 4, CH_2-CH_2), 3.30 (m, 4, CH_2-CH_2), 6.80 (d, 1, thiophene proton); 7.03 (s, 4, benzene protons), 7.10 (d, 1, thiophene proton).

Anal. Calcd. for $C_{16}H_{17}NOS$: C, 70.84; H, 6.27; N, 5.16; S, 11.81. Found: C, 71.02; H, 6.43; N, 4.92; S, 11.62.

Finally, the residual acetone solution was concentrated to dryness and the residue was chromatographed on silica gel. Elution with cyclohexane-ethyl acetate (1:1) gave a white solid (0.12 g, 10%) which resulted to be 4-methoxy-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (**9**), mp 60° (hexane); ^{1}H-nmr (deuteriochloroform): 3.30 (s, 3, CH_3), 3.40 (m, 4, CH_2-CH_2), 5.20 (s, 1, CH), 7.03 (s, 2, thiophene), 7.25 (s, 4, benzene protons).

Anal. Calcd. for $C_{14}H_{14}OS$: C, 73.04; H, 6.09; S, 13.91. Found: C, 72.87; H, 5.92; S, 14.25.

1-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-yl)-3-azetidinol mesylate (**10**). Method A.

To a stirred solution of azetidinol **8** (4.0 g, 0.015 mole) in anhydrous pyridine (30 ml) methanesulfonyl chloride (1.7 ml, 0.030 mole) was added at -20°. After standing for 1 hour at -20° and overnight at 0°, the solution was poured onto ice-water and extracted with ether. The extracts were washed with water, dried (magnesium sulfate), and evaporated *in vacuo* to give 2.6 g (50%) of **10** as an oil which crystallized slowly, mp 99-100° (benzene-hexane); ir (nujol): 1360 and 1180 cm^{-1} (SO_2); ^{1}H-nmr (deuteriochloroform): 2.90 (s, 3, CH_3), 3.10 (m, 7, CH_2-CH_2), 4.20 (s, 1, CH), 4.30 (m, 1, CH_2-CH_2), 4.85 (t, 1, CH-CH_2), 6.80 (d, J = 5.4 Hz, 1, S-C=CH), 7.03 (m, 4, benzene protons), 7.10 (d, J = 5.4 Hz, 1, S-CH=C).

Anal. Calcd. for $C_{17}H_{19}NO_3S_2$: C, 58.45; H, 5.44; N, 4.01; S, 18.33. Found: C, 58.36; H, 5.52; N, 4.21; S, 18.16.

Method B.

To a stirred solution of **8** (10 g, 0.037 mole) and triethylamine (3.7 g, 0.037 mole) in dry benzene (80 ml), was added dropwise methanesulfonyl chloride (4.2 g, 0.037 mole) under ice-cooling and with rigorous exclusion of moisture. The mixture was stirred at room temperature for an additional 3 hours. The precipitate formed was collected by filtration and the filtrate concentrated *in vacuo* to give 10 g (78%) of mesylate **10** identical with that described above.

1-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-yl)-3-alkylaminoazetidines **11a-m**. Table 1. General Method.

To a solution of mesylate **10** (0.01 mole) in *N,N*-dimethylformamide (20 ml), an excess (0.25 mole) of the corresponding amine was added. The mixture was heated in a stopped flask at 50-60° during 12 hours, poured onto 2*N* sodium hydroxide, and extracted with ether. The extracts were washed with water, dried (magnesium sulfate) and evaporated to dryness to yield, except for compound **11a**, a crude oil which was chromatographed on silica gel. Elution with ethyl acetate-cyclohexane (1:1) gave pure azetidines **11b-m**. All of them were converted to their respective maleate salts using maleic acid in ethanol.

Acknowledgements.

We are indebted to the Comisión Asesora de Investigación Científica y Técnica for the financial support of this work and our Department of Analysis for all analytical and spectral data.

REFERENCES AND NOTES

[1] P. Melloni, A. Della Torre, M. Meroni, A. Ambrosini and A. C. Rossi, *J. Med. Chem.*, **22**, 183 (1979).

[2] E. Vencovský, V. Sědicex, E. Peterova and B. Bandis, *Arzneim.-Forsch.*, **19**, 491 (1969).

[3] B. Yom-Tov, S. Gronowitz, S. B. Ross and N. E. Stjernström, *Acta Pharm. Suec.*, **11**, 149 (1974).

[4] E. Arribas, S. Vega, C. Benito, M. P. Fernández-Tomé and J. del Río, *Arzneim.-Forsch.*, **33**, 1417 (1983).

[5] E. Arribas and S. Vega, *J. Heterocyclic Chem.*, **21**, 161 (1984).

[6] J. M. Bastian, A. Ebnöther and E. Sucker, *Helv. Chim. Acta.*, **54**, 283 (1971).

[7] V. R. Gaertner, *Tetrahedron Letters*, 4691 (1966).

[8] V. R. Gaertner, *Tetrahedron Letters*, 141 (1964).

[9] A. G. Anderson, Jr. and R. Lok, *J. Org. Chem.*, **37**, 3953 (1972).

[10] R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

[11] V. R. Gaertner, *J. Heterocyclic Chem.*, **6**, 273 (1969).