Derivatives of Benzo[4,5]cyclohepta[1,2-*b*]thiophene. 1. Synthesis and Cyclization of *N*-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta-[1,2-*b*]thiophene-4-ylmethyl)amides [1]

Enrique Arribas and Salvador Vega* [2]

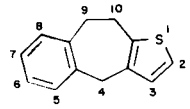
Instituto de Química Médica, C.S.I.C.,
Juan de la Cierva, 3, Madrid-6, Spain

Received May 24, 1983

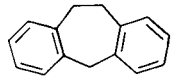
Starting from ketone III several acyl derivatives of 4-aminomethyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta-[1,2-*b*]thiophene (VII) have been synthesized. The intramolecular cyclization of some of these new amides through the Bischler-Napieralski reaction is described.

J. Heterocyclic Chem., **21**, 161 (1984).

As it is known, several compounds with interesting biological properties posses in their molecules the 9,10-dihydrobenzo[4,5]cyclohepta[1,2-*b*]thiophene skeleton (I) which is a thiophene isostere structure of the also biologically important 10,11-dihydrobenzo[a,d]cycloheptane ring system (II). Examples of these compounds are Ketotifen and Pizotifen synthesized by a group at Sandoz [3,4].



I

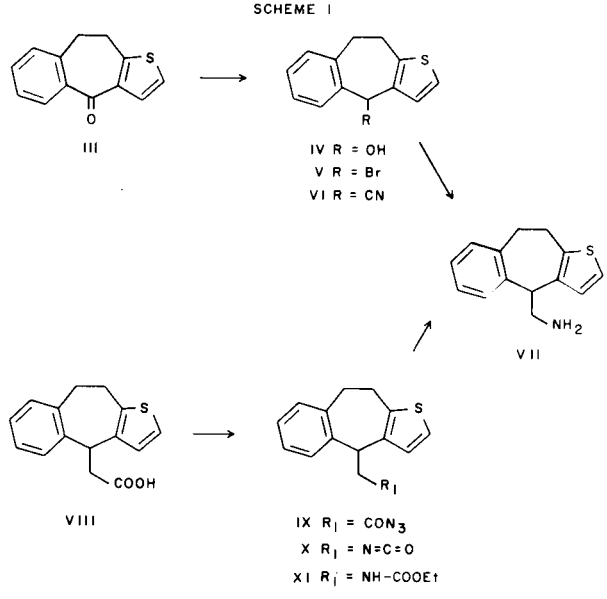


II

Bearing in mind the potential pharmaceutical activity of this heterocyclic ring, we have studied the feasibility to elaborate it into other systems by fusing an additional ring, *e.g.*, between positions 3 and 4. Our expectation was that this could be made by the Bischler-Napieralski cyclization of suitable amides of type XVI-XVII. This report describes the preparation of some of these amides and their cyclization to the new 1,6,7,11b-tetrahydrobenzo-[1,2]cyclohepta[3,4,5-*hi*]thieno[3,4-*c*]pyridine ring system.

The key compound in this synthesis was amine VII (Scheme 1) which was prepared in two ways both starting from ketone III [5]. In the first, alcohol IV obtained from III by reduction with sodium borohydride, was halogenated with phosphorus tribromide to the 4-bromo-derivative V which in turn was transformed into nitrile VI using silver cyanide. Reduction of VI with lithium aluminum hydride-aluminum chloride gave 4-aminomethyl-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (VII) in 70% yield. V was obtained as a white crystalline solid which turned out to be somewhat unstable. Because of this instability it could not be obtained in pure form and had to be directly used as such in the following step. All attempts to prepare the 4-chloro analog of V by thionyl chloride [6] or hydrogen chloride halogenation [7] or by means of the combinations triphenyl phosphine-carbon tetrachloride or triphenyl phosphite-chloro [8,9], resulted in tar formation or starting material recovery. Attempted preparations of VI with cuprous cyanide in pyridine [10], dimethylsulfoxide [11] or *N*-methyl pyrrolidone [7], or heating the free alcohol with a mixture of sodium cyanide, glacial acetic acid and sulfuric acid [12], gave nothing of the desired product. On the other hand, a direct conversion of ketone III to carbonitrile VI using tosymethyl isocyanide (Tos MIC) [13] was also unsuccessful.

SCHEME I

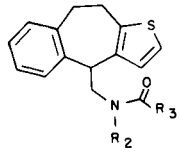


In the second way amine VII was accomplished through the Curtius reaction of acid VIII. Thus, VIII was converted to its mixed anhydride with triethyl amine and ethyl chloroformate and treated with sodium azide, and the intermediate acyl azide IX was heated in the presence of ethanol to give urethane XI in 85% yield. This urethane was subsequently hydrolized in hot concentrated hydrochloric acid.

Compound VIII was not described in the literature and had to be synthesized. The two synthetic pathways developed for this purpose are shown in Scheme 2. In one of them, alkylation of diethyl malonate with 4-bromo-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (V) using sodium hydride in an aprotic solvent (benzene) led to the malonic ester XII. Its alkaline hydrolysis afforded the cor-

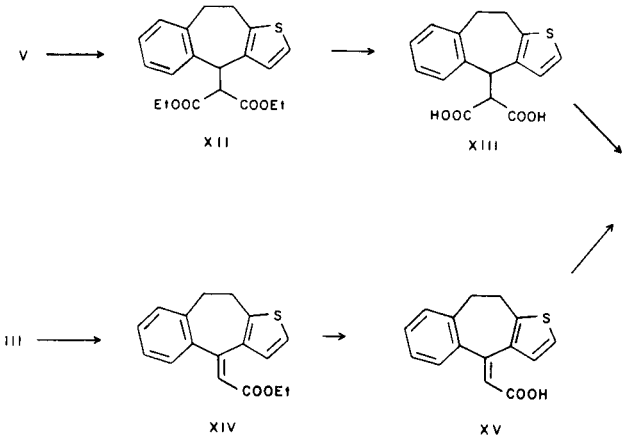
Table 1

N-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylmethyl)amides

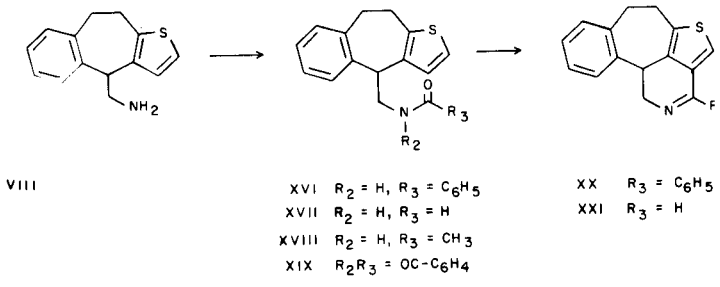


N°	R_2	R_3	Reactant	Yield %	Mp°C	Molecular Formula	Analysis % Calcd./Found C	H	N	S
XVI	H	C_6H_5	Benzoyl Chloride	90	178-179	$C_{21}H_{19}NOS$	75.68	5.70	4.20	9.61
							75.90	5.66	4.30	970
XVII	H	H	Formic Acid-Acetic Anhydride	65	109-110	$C_{15}H_{15}NOS$	70.02	5.87	5.44	12.43
							69.98	5.87	5.43	12.67
XVIII	H	CH_3	Acetic Anhydride	73	139-140	$C_{16}H_{17}NOS$	70.84	6.27	5.16	—
							70.70	6.32	5.14	—
XIX		$OC\text{-}C_6H_4$	Phthalic Anhydride	88	196-197	$C_{22}H_{17}NO_2S$	73.53	4.73	3.89	8.91
							73.53	4.70	4.11	9.03
XI	H	OC_2H_5	Ethyl Chlorocarbonate	73	oil	$C_{17}H_{19}NO_2S$	67.77	6.31	4.65	—
							67.96	6.30	4.48	—

SCHEME 2



SCHEME 3

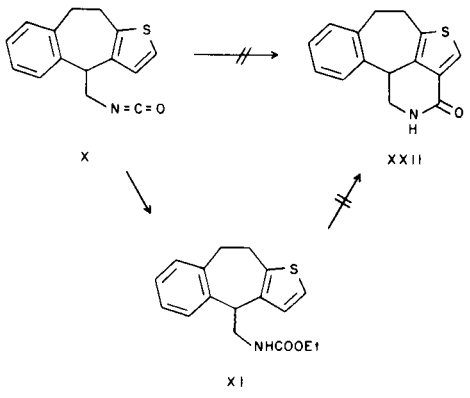


responding malonic acid XIII which was decarboxylated in pyridine in the presence of piperidine to acid VIII. On the other one, ketone III was subjected to the Wittig-Horner reaction with triethylphosphonoacetate followed by hydrolysis in alkaline medium and sodium amalgam reduction of the 4-ylidenacetic acid XV to give the saturated acetic acid VIII identical with that described above.

The amides of Table 1 were synthesized by acylation of the aminomethyl compound VII (Scheme 3). The methods were those commonly used in organic chemistry and all of them are conveniently described in the Experimental. In the case of phthalic anhydride the second hydrogen atom was also displaced giving rise to phthalimide XIX. Ethyl chloroformiate did react with the amine VII producing urethane XI which had already been described before by Curtius rearrangement of acyl azide IX and subsequent treatment with ethanol. Formamide XVII could also be prepared in 70% yield by sodium borohydride reduction of isocyanate X. In this reaction an 8% of *N,N*-di-(9,10-dihydro-4*H*-benzo[4,5-]cyclohepta[1,2-*b*]thiophene-4-ylmethyl) urea was also obtained.

The cyclization of compounds XVI-XVIII (Scheme 3) by the Bischler-Napieralski reaction was first attempted by the method employed by Humber *et al.* [14] for the synthesis of the benzo[1,2]cyclohepta[3,4,5-*de*]isoquinoline which uses polyphosphoric acid as the condensing agent. However, under numerous sets of conditions no cyclized product could be obtained. Identical results were obtained by the use of other condensing agents as phosphorus pentachloride, phosphorus oxychloride, *etc.* In contrast, treatment of XVI with polyphosphoric ester at 80° afforded the desired product XX in 45% yield. The structure of XX was assigned from its analytical and spectral data. Thus, the mass spectrum showed a m/e, 315 (M^+) and the ir spectrum revealed the presence of a C=N (1610 cm^{-1}) band and the absence of bands in the 3400-3300 and 1700-1640 cm^{-1} region characteristic of stretching frequencies of NH and CO bonds respectively. Its nmr spectrum in deuterated chloroform showed the disappearance of the signal due to the proton in position 3 of the thiophene ring, confirming the formation of the expected thieno pyridine XX. The extension of these experimental conditions to the formamide XVII led to an impure mixture from which, by column chromatography, only a 5% yield of the tetracyclic base XXI was isolated. Compound XVIII afforded under the same conditions a very complex mixture which was not

SCHEME 4



further examined

Finally, in order to open a new route for the synthesis of XX and XXI, the intramolecular cyclization of isocyanate X to lactam XXII both directly and *via* urethane XI (Scheme 4) was attempted. However, when compound X was refluxed in diphenyl-ether [15] or in *o*-dichlorobenzene in the presence of aluminum chloride [16], nothing of the desired product was formed, all the starting material being recovered. Likewise, heating of urethane XI with polyphosphoric acid [14] also failed to give lactam XXII.

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 Perkin-Elmer R-12 and Varian XL-100-15 spectrometers using TMS as internal reference. Mass spectra were obtained on a Varian MAT-711 spectrometer.

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

Ketone III [5] (43 g, 0.2 mole) was dissolved in ethanol (500 ml) and the solution heated at 60°. Sodium borohydride (15.2 g, 0.4 mole) was added in portions and the mixture was refluxed for 2 hours. The reaction mixture was poured into cold water (2.5 l) and the resultant white solid filtered and recrystallized from cyclohexane (40 g, 92%), mp 106-107°; ir (nujol): 3200 cm^{-1} (OH); ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 1, OH), 3.1 (m, 4, CH_2-CH_2), 5.86 (s, 1, CH), 7.1 (s, 2, thiophene), 7.3 (s, 4, benzene).

Anal. Calcd. for $C_{13}H_{12}OS$: C, 72.20; H, 5.59; S, 14.78. Found: C, 72.19; H, 5.61; S, 15.06.

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

To a stirred solution of alcohol IV (4.3 g, 0.02 mole) in anhydrous ether, phosphorus tribromide (1.8 g, 0.0066 mole) was added. The white precipitate obtained was immediately filtered and washed with ether to afford the bromo derivative V (4.5 g, 83%), mp 90-92° (cyclohexane). This compound was shown to be somewhat unstable, therefore it was not further characterized and used as such in the following step.

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

4-Bromo-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (V) (14 g, 0.05 mole) was added to a stirred suspension of silver cyanide (9 g, 0.068 mole) in benzene (160 ml) and the mixture was heated under reflux for 12 hours. The inorganic material was filtered off, washed with benzene, and the combined solutions were treated with charcoal and evaporated. Trituration of the residual oil with benzene and hexane afforded nitrile VI (7 g, 70%) as white needles, mp 113-114° (benzene-hexane); ir (nujol): 2250 cm^{-1} (C≡N); ^{1}H-nmr (deuteriochloroform): δ 3.0-3.5 (m, 4, CH_2-CH_2), 5.4 (s, 1, CH), 7.15 (s, 2, CH, thiophene), 7.2-7.6 (m, 4, benzene).

Anal. Calcd. for $C_{14}H_{11}NS$: C, 74.65; H, 4.92; N, 6.21. Found: C, 74.60; H, 5.11; N, 6.16.

Diethyl (9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl)-malonate (XII).

A solution of diethyl malonate (20 g, 0.127 mole) in anhydrous benzene (70 ml) was added dropwise to a stirred suspension of sodium hydride (6 g, 0.127 mole) in anhydrous benzene (350 ml). The mixture was stirred for 30 minutes at 50° and then treated dropwise with a solution of 4-bromo-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (V) (28 g, 0.1 mole) in dry benzene (300 ml). The mixture was refluxed for 5 hours, allowed to stand overnight, washed with water, dried (magnesium sulfate) and evaporated *in vacuo*. The residual oil was distilled under reduced pressure, (27 g, 76%), bp 160-165°/0.1 mm; ir (film): 1730-1750 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.0 and 1.5 (2t, 6, $2CH_3$), 3.1 (m, 4, CH_2-CH_2), 4.1 (m, 5, CH_2-CH_3 and CH-COOEt), 4.95 (d, J = 9.5 Hz, 1, CH-C), 6.95 (d, J = 5.4 Hz, 1, S-C=CH), 7.08 (d, J = 5.4 Hz, 1, S-CH=C), 7.27 (s, 4, benzene).

Anal. Calcd. for $C_{20}H_{22}O_4S$: C, 67.04; H, 6.14; S, 8.93. Found: C, 66.98; H, 6.14; S, 9.00.

(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl)malonic Acid (XIII).

A solution of the above diester XII (12 g, 0.0335 mole) in ethanol (100 ml) was mixed with s solution of potassium hydroxide (48.6 g) in water (50 ml) and the mixture was refluxed for 5 hours. Ethanol was distilled off, the residue diluted with water (400 ml) and the solution was acidified with hydrochloric acid. After standing overnight, the precipitated product was filtered, washed with water and dried *in vacuo*, (8 g, 79%), mp 175-178° (ethanol); ir (nujol) 1720 cm^{-1} (C=O); ^{1}H-nmr (sodium deuteroxide): δ 3.1 (m, 4, CH_2-CH_2), 4.05 (d, J = 12 Hz, 1, HC-COOH), 4.85 (d, 1, CH-C), 6.95 (d, J = 5.4 Hz, 1, S-C=CH), 7.13 (d, J = 5.4, 1, S-CH=C), 7.25 (s, 4, benzene).

Anal. Calcd. for $C_{16}N_{14}O_4S$: C, 63.57; H, 4.63; S, 10.59. Found: C, 63.61; H, 4.62; S, 10.48.

Ethyl (*Z*) and (*E*)-9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]-4-ylidenacetate (XIV).

To a stirred suspension of sodium hydride (7.4 g, 0.33 mole, 13.5 g of a 55% dispersion oil) in tetrahydrofuran (190 ml) triethyl phosphonacetate (75 g, 0.33 mole) under nitrogen was added at a rate such that the reaction temperature was maintained at 30-35°. The mixture was stirred at 22° for 1 hour and a solution of 9,10-dihydro-4*H*-4-oxobenzo[4,5]cyclohepta[1,2-*b*]thiophene (III) (32.6 g, 0.15 mole) in tetrahydrofuran (200 ml) was added during 30 minutes. The mixture was refluxed for 70 hours and poured into ice-water. The resultant solid was filtered, washed with water and hexane and dried to yield 30.0 g (76%) of ethyl *Z* and *E*-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylidenacetate (XIV), (*Z*-*E* ratio 4:1, nmr). The analytical sample was recrystallized from hexane, mp 106-107°; ir (nujol): 1720 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{16}O_2S$: C, 71.83; H, 5.63; S, 11.26. Found: C, 71.69; H, 5.64; S, 11.31.

9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl-acetic Acid (VIII).

Method A.

The foregoing mixture of *Z* and *E* isomeric esters XIV (34 g, 0.12 mole) was hydrolyzed by refluxing for 5 hours in a mixture of ethanol (340 ml) and 10% aqueous sodium hydroxide (340 ml). The ethanol was evaporated and the residue was acidified with 2*N* aqueous hydrochloric acid. The precipitated white solid, which was a mixture of the corresponding *Z* and *E* isomeric acids XV, was filtered, washed with water and dried, yielding 28 g (90%). This solid in hot ethanol (280 ml) was added

to a flask containing 5% sodium amalgam (280 g). The mixture was stirred for 3 hours at 60-70°, the ethanol layer was decanted and the residue was washed with ethanol. The combined ethanol solutions were diluted with and equal volume of water and acidified with hydrochloric acid. The resultant solid was filtered, washed with water and dried. Recrystallization from benzene-heptane afforded the product VIII (24.9 g, 95%), mp 168-169°; ir (nujol): 1690 cm^{-1} (C=O); ^{1}H-nmr (acetone-d_6): δ 3.15 (m, 6, $3CH_2$), 4.8 (t, J = 8 Hz, 1, CH), 7.02 (d, J = 5.4 Hz, 1, S-C=CH), 7.3 (br s, benzene and S-CH=C).

Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.76; H, 5.42; S, 12.40. Found: C, 69.58; H, 5.39; S, 12.51.

Method B.

A mixture of 9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl-malonic acid (XIII) (5 g, 0.016 mole), pyridine (10 ml) and piperidine (0.6 ml) was refluxed for 3 hours and the solution was poured into 5*N* hydrochloric acid (50 ml) at 90° under stirring. After standing overnight, the precipitated product was filtered, washed with water and dried *in vacuo*, yielding 3.9 g (95%) of the compound (VIII) identical with that described above.

9,10-Dihydro-4*H*-[4,5]cyclohepta[1,2-*b*]thiophene-4-yl-acetylazide (IX).

To a solution of 4-yl-acetic acid VIII (30 g, 0.116 mole) in dry tetrahydrofuran (730 ml) was added triethylamine (31 ml, 0.218 mole) and then ethyl chloroformate (16 ml, 0.16 mole) at 0° under nitrogen. The mixture was kept at 0° for 1 hour and then cooled to -10°, and a solution of sodium azide (10.4 g, 0.16 mole) in water (75 ml) was added and the organic phase was separated, dried, and evaporated at 22° to give the acetyl azide IX as an orange oil (32.8 g, 91%); ir (film): 2150 cm^{-1} (N_3).

9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl-methylisocyanate (X).

The above azide IX was dissolved in dry benzene (400 ml) and the solution was refluxed for 5 hours. The benzene was evaporated to leave the methyl isocyanate X as an orange oil which was distilled at reduced pressure (23 g, 78%): bp 150°/0.05 mm; ir (film) 2270 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.1 (m, 4, CH_2-CH_2), 3.6 (q, 2, CH_2), 4.2 (t, J = 8.4 Hz, 1, CH), 6.8 (d, J = 5.7 Hz, 1, S-C=CH), 7.02 (d, J = 5.7 Hz, 1, S-CH=C), 7.2 (s, 4, benzene).

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.57; H. 5.13; N, 5.48. Found: C, 70.37; H, 5.30; N, 5.33.

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

Method A.

A solution of the acetylazide IX (1 g, 0.0035 mole) in ethanol (30 ml) was refluxed for 24 hours. The hot mixture was filtered and the filtrate evaporated to give an oil which was chromatographed on silica gel. Elution with benzene-methanol (5:1) gave the urethane XI as an oil (0.9 g, (85%); ir (film): 3345 cm^{-1} (NH), 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{19}NO_2S$: C, 67.77; H, 6.31; N, 4.65. Found: C, 67.96; H, 6.30; N, 4.48.

Method B.

The amine VII (2 g, 0.009 mole) was added to a mixture of ethylene dichloride (24 ml) and 1*N* sodium hydroxide (9 ml). Ethyl chloroformate (1 g, 0.0096 mole) was added over 10 minutes with vigorous stirring at 0°. The reaction mixture was kept at 22° for 13 hours, the organic phase was separated, washed with water and dried (magnesium sulfate). Evaporation of the solvent gave the compound XI (2 g, 73%) identical with that described above.

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

Method A.

The carbonitrile VI (11.5 g, 0.05 mole) dissolved in dry ether (350 ml) was added over 1 hour to a suspension of lithium aluminum hydride (2.1 g, 0.055 mole) and aluminum chloride (7.4 g, 0.055 mole) in ether (115 ml). The mixture was refluxed for 2 hours then allowed to remain at room temperature for 60 hours. Concentrated hydrochloric acid (21 ml) and water (160 ml) were added and the ether was removed by distillation. The remaining aqueous mixture was heated until all solids were dissolved, filtered and cooled to yield the hydrochloride salt of compound VII (9 g, 70%) as white needles, mp 300° (methanol-ethyl acetate).

Anal. Calcd. for $C_{14}H_{16}ClNS$: C, 63.30; H, 6.02; N, 5.27; Cl, 13.33. Found: C, 63.13; H, 6.15; N, 5.26; Cl, 13.65.

The hydrochloride salt when treated with 20% sodium hydroxide and ether gave, after washing with water, drying and evaporation of the solvent, the free base as an oil; ir (nujol): 3400 cm^{-1} (NH_2); ^{1}H-nmr (deuteriochloroform): δ 1.4 (s, 2, NH_2), 3.1 (m, 4, CH_2-CH_2), 3.2 (d, J = 7.4 Hz, 2, CH_2N), 4.05 (t, J = 7.4 Hz, 1, CH), 6.9 (J = 5.4 Hz, 1, S-C=CH), 7.12 (d, J = 5.4 Hz, 1, S-CH=C), 7.27 (s, 4, benzene).

The picrate had mp 218° (ethanol).

Method B.

A mixture of urethane XI (0.8 g, 0.0026 mole) and concentrated hydrochloric acid (40 ml) was refluxed for 24 hours. The hot mixture was filtered and the filtrate evaporated. The white solid residue was washed with cold water and dried *in vacuo* yielding 0.15 g (20%) of the hydrochloride salt of VII identical with that described above.

N-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl-methyl)-benzamide (XVI).

To a suspension of the 4-aminomethyl derivative VII (2.3 g, 0.01 mole) in 10% sodium hydroxide (12 ml) benzoyl chloride (2.2 g, 0.016 mole) was added at 22°. The mixture was stirred for 3 hours and the white precipitate was filtered, washed with water and dried (3.0 g, 90%), mp 178-179° (ethanol); ir (nujol): 3340 cm^{-1} (NH), 1635 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.1 (m, 4, CH_2-CH_2), 3.9 (m, 2, CH_2N),4.5 (m, 1, CH), 6.1 (m, 1, NH), 7.0 (d, J = 5.4 Hz, 1, S-C=CH), 7.15 (d, J = 5.4 Hz, 1, S-CH=C), 7.3 (s, 4, benzene), 7.6 (m, 5, C_6H_5-C=O).

Anal. Calcd. for $C_{21}H_{19}NOS$: C, 75.68; H, 5.70; N, 4.20; S, 9.61. Found: C, 75.80; H, 5.66; N, 4.30; S, 9.70.

N-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl-methyl)-formamide (XVII).

Method A.

Formic acid (1 ml) and acetic anhydride (2 ml) were heated together for 2 hours at 60°. To this mixture was added at 22° amine VII (2.2 g, 0.01 mole) over 1 hour with stirring. After standing at 22° for 16 hours the mixture was poured into cracked ice and the resultant precipitate extracted with chloroform. The combined organic extracts were washed with water, dried (magnesium sulfate) and evaporated to yield compound XVII (1.6 g, 65%) as an oil which crystallizes at 0°, mp 109-110° (benzene-heptane); ir (nujol): 3370 cm^{-1} (NH), 1660 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 2.8-4.4 (m, 7, CH_2-CH_2 and CH-CH_2N), 5.6 (br s, 1, NH), 6.87 (d, J = 5.4 Hz, 1, S-C=CH), 7.04 (d, J = 5.4 Hz, 1, S-CH=C), 7.1-7.4 (m, 4, benzene), 8.1 (s, 1, CH=O).

Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.02; H, 5.87; N, 5.44; S, 12.43. Found: C, 69.98; H, 5.87; N, 5.43; S, 12.67.

Method B.

Isocyanate X (19.2 g, 0.075 mole) was dissolved in 1,2-dimethoxyethane (192 ml) and added during 15 minutes at 0° to a stirred suspension of sodium borohydride (10.8 g, 0.28 mole) in 1,2-dimethoxyethane (100 ml) under a nitrogen atmosphere. The mixture was stirred at 0° for 2 hours, then heated at 60° for 1 hour and finally concentrated *in vacuo*. Chloroform was added to the residue and 2*N* hydrochloric acid was added while cooling to 0°. The organic phase was separated, dried (magnesium sulfate) and evaporated. The residue was chromatographed on silica gel. Elution with cyclohexane-ethyl acetate (1:1) gave firstly the *N*,*N*-di(9,10-di-

hydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-yl-methyl)urea (3.0 g, 8%), mp 243-244° (ethanol); ir (nujol): 3300 cm^{-1} (NH), 1635 cm^{-1} (C=O).

Anal. Calcd. for $C_{29}H_{28}N_2OS_2$: C, 71.90; H, 5.78; N, 5.78; S, 13.22. Found: C, 71.99; H, 5.63; N, 5.65; S, 13.15.

Continued elution with the same solvent mixture gave formamide XVII (13.5 g, 70%) identical with that described above.

N-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylmethyl)-acetamide (XVIII).

To a solution of the amino derivative VII (1.14 g, 0.005 mole) in ethanol (10 ml), anhydride acetic (0.85 g, 0.008 mole) was added at 22°. The mixture was stirred for 4 hours and then was extracted with benzene. The extracts were washed with water, dried (magnesium sulfate) and evaporated yielding acetamide XVIII (1.0 g, 73%), mp 139-140° (benzene-hexane); ir (nujol): 3280 cm^{-1} (NH), 1640 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.9 (s, 3, CH_3), 3.1 (m, 4, CH_2-CH_2), 3.75 (m, 2, CH_2-N), 4.35 (t, J = 5.2 Hz, 1, CH), 5.5 (br s, 1, NH), 6.95 (d, J = 5.4 Hz, S-C=CH), 7.15 (d, J = 5.4 Hz, 1, S-CH=C), 7.27 (s, 4, benzene).

Anal. Calcd. for $C_{16}H_{17}NOS$: C, 70.84; H, 6.27; N, 5.16. Found: C, 70.70; H, 6.32; N, 5.14.

N-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylmethyl)-phthalimide (XIX).

A mixture of amine VII (0.7 g, 0.003 mole) and phthalic anhydride (0.5 g, 0.0033 mole) was heated at 135° with stirring. In a few minutes the reaction was finished, giving a solid which was filtered, washed with water and dried (1 g, 88%), mp 196-197° (benzene-hexane); ir (nujol): 1705 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): δ 3.1 (m, 4, CH_2-CH_2), 3.8 (m, 2, CH_2-N), 4.5 (t, J = 7.4 Hz, 1, CH), 7.1 (m, 6, benzene and thiophene), 7.75 (s, 4, C_6H_4-CO).

Anal. Calcd. for $C_{22}H_{17}NO_2S$: C, 73.53; H, 4.73; N, 3.89; S, 8.91. Found: C, 73.53; H, 4.70; N, 4.11; S, 9.03.

1,6,7,11b-Tetrahydro-3-phenylbenzo[1,2]cyclohepta[3,4,5-*hi*]thieno[3,4-*c*]-pyridine (XX).

A mixture of benzamida XVI (0.7 g, 0.002 mole) and polyphosphoric ester was heated in an oil bath at 80° for 12 hours. The mixture was then poured into ammonium hydroxide and extracted with ether. The combined organic extracts, washed with water and dried (magnesium sulfate), were evaporated to yield the product XX (0.3 g, 45%), mp 135-136° (ethyl acetate-hexane); ir (nujol): 1615 cm^{-1} (C=N); ^{1}H-nmr (deuteriochloroform): δ 3.1 (m, 4, CH_2-CH_2), 4.0 (m, 2, CH_2N), 4.7 (m, 1, CH), 7.35 (m, 5, benzene and thiophene), 7.6 (m, 5, benzene); ms: 315 (M^+).

Anal. Calcd. for $C_{21}H_{17}NS$: C, 80.00; H, 5.39; H, 4.44. Found: C, 80.12; H, 5.36; N, 4.51.

1,6,7,11b-Tetrahydrobenzo[1,2]cyclohepta[3,4,5-*hi*]thieno[3,4-*c*]pyridine (XXI).

This compound was obtained from the formamide XVII (0.72 g, 0.003 mole) and polyphosphoric ester (20 g) by the procedure described above. A mixture of benzene-ether (1:1) was used for the extraction and the residue was chromatographed on silica gel. Elution with ethyl acetate-methanol (12:1) gave the pyridine XXI (65 mg, 5%), ir (nujol): 1635 cm^{-1} (C=N); ^{1}H-nmr (deuteriochloroform): δ 2.5-3.2 (m, 4, CH_2-CH_2), 4.1-4.9 (m, 3, CH-CH_2), 6.7-7.7 (m, 6, CH, benzene and thiophene); ms: 239 (M^+). The base was transformed in its corresponding picrate salt, mp 202-203° (ethanol).

Anal. Calcd. for $C_{21}H_{16}N_4O_7S$: C, 53.84; H, 3.44; N, 11.96; S, 6.82. Found: C, 53.95; H, 3.46; N, 11.90; S, 6.69.

Acknowledgement.

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

REFERENCES AND NOTES

[1] Presented, in part, at the Eighth International Congress of Heterocyclic Chemistry, Graz, Austria, August, 1981.

[2] To whom correspondence should be addressed.

[3] J. P. Bourquin, P. Jean, G. Schwarb and E. Waldvogel, Ger. Patent 2,302,970 (1973); *Chem. Abstr.*, **79**, P105090p (1973).

[4] E. Jucker, A. Ebnoether and A. Stoll, Belgian Patent 636,717 (1964); *Chem. Abstr.*, **61**, P14644 (1964).

[5] J. M. Bastian, A. Ebnoether, E. Sucker, E. Rissi and A. Stoll, *Helv. Chim. Acta*, **49**, 214 (1966).

[6] C. R. Ellefson and J. W. Casie, *J. Med. Chem.*, **19**, 1161 (1976).

[7] J. Gootjes, A. B. Funcke and W. T. Nauta, *Arzneim.-Forsch.*, **19**, 1936 (1969).

[8] J. P. Verheyden and J. G. Moffat, *J. Org. Chem.*, **37**, 2289 (1972).

[9] J. P. Verheyden and J. G. Moffat, *ibid.*, **35**, 2319 (1970).

[10] R. C. Fuson and A. J. Rachlin, *J. Am. Chem. Soc.*, **64**, 1567 (1942).

[11] M. S. Newman and H. Boden, *J. Org. Chem.*, **26**, 2525 (1961).

[12] R. Baltzly and E. Lorz, US Patent 2,956,063 (1960); *Chem. Abstr.*, **55**, p27331g (1961).

[13] O. H. Oldenzield, D. Vauleusen and A. M. Vanleusen, *J. Org. Chem.*, **42**, 3114 (1977).

[14] L. G. Humber, M. A. Davis, R. A. Thomas and J. R. Watson, *J. Heterocyclic Chem.*, **3**, 247 (1966).

[15] F. Eloy and A. Deryckere, *Chim. Ther.*, **6**, 469 (1969).

[16] C. Corral, R. Madroñero and S. Vega, *J. Heterocyclic Chem.*, **14**, 99 (1977).