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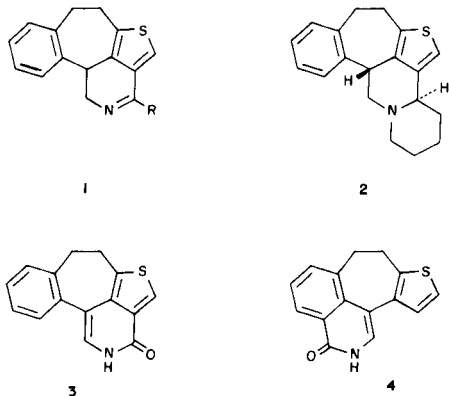
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The title compounds **3** and **4** were synthesized by cyclization *via* isocyanate of the *Z* and *E*-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylidenacetic acids **8** and **9**, which in turn were prepared by the Wadsworth-Emmons reaction of ketone **5** with triethyl phosphonacetate followed by separation and independent hydrolysis of the corresponding esters **6** and **7**. The structures of these new compounds as well as the configurations of their isomeric precursors are described.

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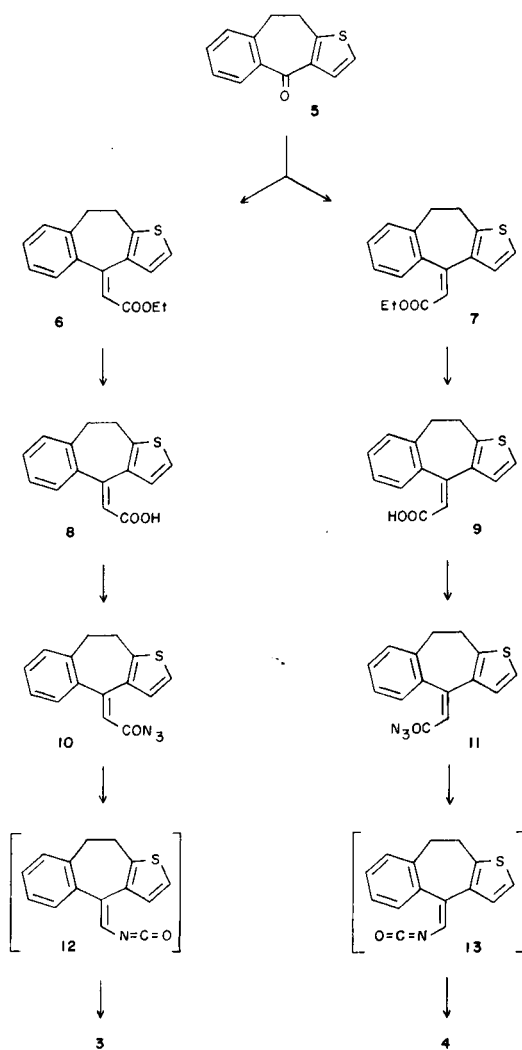
In connection with a program directed towards the search of derivatives of benzo[4,5]cyclohepta[1,2-*b*]thiophene with potential antipsychotic properties, we have already described in preceding papers [2,3], the preparation of *N*-(9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylmethyl)amides and their cyclization to the novel heterocyclic compounds **1**, as well as the synthesis of (\pm)-6,8-*b*,9,10,11,12,13,13a-octahydro-5*H*-7-thia-12a-azabenzof[naph[1,2,3-*cd*]azulene (QM-7184) (**2**), a new neuroleptic drug with potent α -adrenoceptor blocking activity [4].

In continuation of this research program, we now wish to report the synthesis of the title compounds **3** and **4** which are the first examples of the hitherto unknown 3-oxobenzo[1,2]cyclohepta[3,4,5-*hi*]thieno[3,4-*c*]pyridine and 3-oxothieno[2,1-*b*]cyclohepta[5,6,7-*de*]isoquinoline ring systems.



As in the previous papers of this series, the starting material for the synthesis of **3** and **4** was ketone **5**, Scheme I, which was condensed through the Wadsworth-Emmons modification of the Wittig reaction with triethyl phosphonacetate in the presence of sodium hydride, to afford a mixture of the two isomeric *Z* and *E* 4-ylidenacetic esters **6**, and **7**. The global yield of the reaction was 76% and the *Z* to *E* ratio 4:1, as confirmed by the analysis of the signal

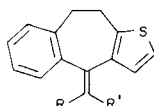
SCHEME I



intensities of the ^1H -nmr spectrum of the mixture.

The two esters were separated by fractional crystallization from petroleum ether and independently hydrolyzed in alkaline medium to the corresponding 4-ylidenacetic isomeric acids **8** and **9**.

Table I

(Z) and (E)-9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylidene Ethyl Esters and Acids

Compound number	R	R'	Mp °C solvent	Yield %	IR cm ⁻¹ C=O	solvent	1H-NMR δ values		
							HC=C	S-CH=C	S-C=CH
6	H	COOEt	106-107 Petroleum Ether	56	1720	Deuteriochloroform	6.08 (s)	7.08 (s)	7.08 (s)
7	COOEt	H	94-95 Petroleum ether	12	1720	Deuteriochloroform	6.37 (s)	7.11 (s)	7.11 (s)
8	H	COOH	193-194 Benzene	90	1690	DMSO-d ₆	6.03 (s)	7.30 (d) J = 5.4	7.02 (d) J = 5.4
9	COOH	H	235-236 Ethanol	86	1690	DMSO-d ₆	6.40 (s)	7.44 (d) J = 5.4	7.19 (d) J = 5.4

The forgoing acids were converted to the acylazides **10** and **11** by the method of the mixed anhydride of Kaiser and Weinstock [5] and these azides cyclized *via* a Curtius type rearrangement [6-8] to the lactams **3** and **4**, respectively.

In this reaction, which was carried out by heating the azides in refluxing benzene, the isocyanates **12** and **13** were not isolated and their cyclization took place spontaneously probably favored by the conjugation and the proper geometry of the reactants.

As expected, compounds **3** and **4** showed in their ir spectra absorption bands at 3300 and 1640 cm⁻¹ due to the stretching vibrations of the NH and CO amidic groups respectively.

The identification of **3** as 2,3,6,7-tetrahydro-3-oxobenzo[1,2]cyclohepta[3,4,5-*hi*]thieno[3,4-*c*]thieno[3,4-*c*]pyridine and **4** as 2,3,7,8-tetrahydro-3-oxothieno[2,1-*b*]cyclohepta[5,6,7-*de*]isoquinoline was made on the basis of the data obtained from their ¹H nmr spectra. Thus, the spectrum of **4** (DMSO-d₆), registered with a 250 MHz spectrometer, Figure I, showed the signals of an AB system in the form of two doublets centered at δ 6.82 and δ 7.18 (J = 5.4 Hz) corresponding to the protons of the positions 3 and 2 of the thiophenic ring. The presence of this AB system, unnoticed in the spectra of the compound obtained on instruments of lower resolution power, could be better observed by means of the double resonance technique, irradiating the proton at position 3 (δ 6.82). In these conditions, the spin-spin coupling was suppressed and the doublet due to the proton at position 2 (δ 7.18) was transformed into a singlet.

The nmr spectrum of compound **3** (DMSO-d₆) was also in agreement with the assigned structure. In this case, the signals of the thiophene and benzene protons were overlapped.

The identification of compounds **3** and **4** also permitted the determination of the *Z* or *E* configuration of the precedent isomeric esters and acids from which both lactams were prepared. The yields and the most important physical and spectral data of these esters and acids are listed in Table I.

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 ¹H nmr spectra were measured with Varian EM-390 and Cameca 250 spectrometer using TMS as internal standard. Chemical shifts are given in δ units.

Ethyl (*Z*) and (*E*)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetate (**6** and **7**).

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 (**5**) [9] (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-ylideneacetate (**6** and **7**), *Z*-*E* ratio 4:1, nmr.

The two esters were separated by fractional crystallization from petroleum ether. From the solution first 24 g of **6** were obtained, which crystallized as colourless needles, mp 106-107°; ir (nujol): 1720 cm⁻¹ (C=O); ¹H-nmr (deuteriochloroform): δ 7.25 (t, J = 7.4 Hz, 3, CH₃), 3.17 (s, 4, CH₂-CH₂), 4.25 (q, J = 7.4 Hz, 2, CH₂), 6.08 (s, 1, CH), 7.08 (s, 2, thiophene), 7.3 (s, 4, benzene).

Anal. Calcd. for C₁₇H₁₆O₂S: C, 71.83; H, 5.63; S, 11.26. Found: C, 71.69; H, 5.64; S, 11.31.

From the mother liquors 5 g of **7** was isolated in the form of prismatic crystals, mp 94-95°; ir (nujol): 1720 cm⁻¹ (C=O); ¹H-nmr (deuteriochloroform): δ 1.1 (t, J = 7.4 Hz, 3, CH₃), 3.12 (s, 4, CH₂-CH₂), 4.09 (q, J = 7.4 Hz, 2, CH₂), 6.37 (s, 1, CH), 7.11 (s, 2, thiophene), 7.3 (s, 4, benzene).

Anal. Calcd. for C₁₇H₁₆O₂S: C, 71.83; H, 5.63; S, 11.26. Found: C, 71.87; H, 5.59; S, 11.20.

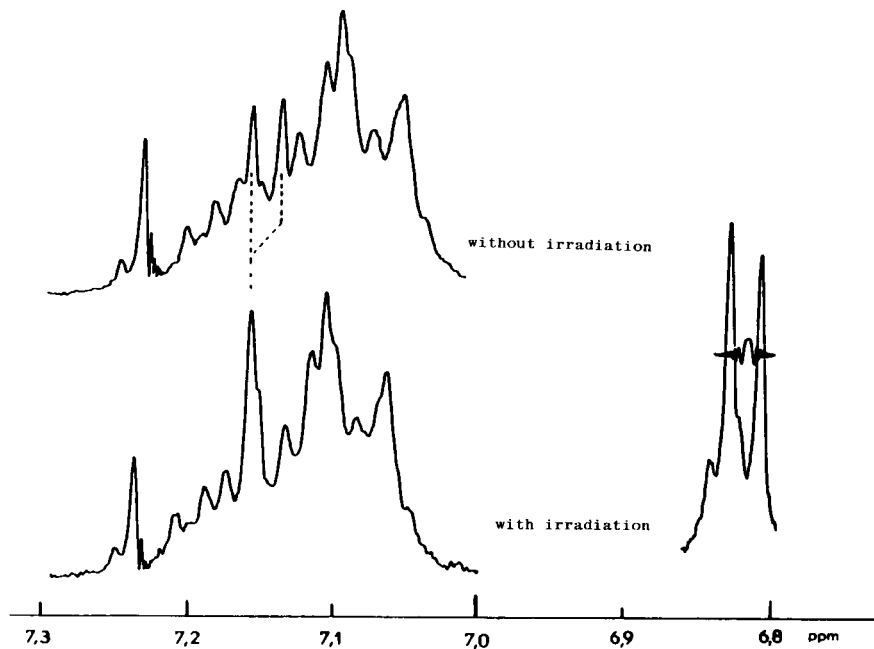


Figure 1. ^1H -nmr spectrum (250 MHz) of compound 4.

(*Z*)-9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetic Acid (**8**).

A mixture of ethyl (*Z*)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetate (**6**) (34 g, 0.12 mole), ethanol (340 ml) and 10% aqueous sodium hydroxide (340 ml) was refluxed for 5 hours in an oil bath. The ethanol was evaporated and the residue was acidified with 2*N* aqueous hydrochloric acid. The precipitated white solid was filtered, washed with water and dried, yielding 28 g (90%), mp 193-194° (benzene); ir (nujol): 1690 cm^{-1} (C=O); ^1H -nmr (deuteriochloroform): δ 3.1 (s, 4, $\text{CH}_2\text{-CH}_2$), 6.03 (s, 1, CH), 7.02 (d, $J = 5.4$ Hz, 1, S-C=CH), 7.3 (m, 5, benzene and S-CH=C).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{S}$: C, 70.31; H, 4.68; S, 12.50. Found: C, 70.26; H, 4.75; S, 12.42.

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

This compound was obtained in a similar manner from ethyl (*E*)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetate (**7**), yield 86%, mp 235-236° (ethanol); ir (nujol): 1690 cm^{-1} (C=O); ^1H -nmr (deuteriochloroform): δ 3.08 (s, 4, $\text{CH}_2\text{-CH}_2$), 6.4 (s, 1, CH), 7.19 (d, $J = 5.4$ Hz, 1, S-C=CH), 7.3 (m, 4, benzene), 7.44 (d, $J = 5.4$ Hz, 1, S-CH=C).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{S}$: C, 70.31; H, 4.68; S, 12.50. Found: C, 70.46; H, 4.75; S, 12.38.

(*Z*)-9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetyl Azide (**10**).

To a solution of the (*Z*)-4-ylideneacetic acid **8** (8.2 g, 0.032 mole) in dry tetrahydrofuran (200 ml) was added triethylamine (6.2 g, 0.06 mole) and then ethyl-chloroformate (5.0 g, 0.044 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 (2.8 g, 0.044 mole) in water (20 ml) was added dropwise in ten minutes. After 2 hours at -10°, ether (90 ml) was added and the organic phase was separated, dried and evaporated at 22° to give the 4-ylideneacetyl azide **10** as a viscous oil (8.3 g, 92%), ir (film) 2145 cm^{-1} (N_3).

The compound was pure enough to be used as such in the following step. (*E*)-9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetyl Azide (**11**).

This compound was obtained from (*E*)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetic acid (**9**) in 95% yield by using the above method. The azide **11** consisted in an orange oil which was directly use in the following reaction: ir (film) 2145 cm^{-1} (N_3).

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

A solution of (*Z*)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetyl azide (**10**) (8.1 g, 0.029 mole) in dry benzene (160 ml) was refluxed for 2 hours. The precipitated white solid was filtered, washed with benzene and dried, yielding 4.0 g (54%); mp > 300° (*N,N*-dimethylformamide-water); ir (nujol): 3300 cm^{-1} (NH), 1640 cm^{-1} (C=O); ^1H -nmr (DMSO- d_6): 7.0°, δ 2.9 (m, 4, $\text{CH}_2\text{-CH}_2$), 7.1 (m, 6, benzene, thiophene and =CH), 8.5 (m, 1, NH).

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{NOS}$: C, 71.15; H, 4.35; N, 5.53. Found: C, 71.20; H, 4.62; N, 5.73.

2,3,7,8-Tetrahydro-3-oxothieno[2,1-*b*]cyclohepta[5,6,7-*de*]isoquinoline (**4**).

The title compound was obtained as described above for the preparation of the isomeric lactam **3** from (*E*)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylideneacetyl azide (**11**) in 62% yield, mp > 300° (*N,N*-dimethylformamide-water); ir (nujol): 3300 cm^{-1} (NH), 1640 cm^{-1} (C=O); ^1H -nmr (DMSO- d_6): 7.0°, δ 2.86 (broad s, 4, $\text{CH}_2\text{-CH}_2$), 6.82 (d, $J = 5.4$ Hz, 1, S-C=CH), 7.13 (broad s, 5, benzene, thiophene, =CH), 8.3 (m, 1, NH).

Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{NOS}$: C, 71.15; H, 4.35; N, 5.53. Found: C, 71.08; H, 4.46; N, 5.62.

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