Derivatives of Benzo[5,6]cyclohepta[1,2-*b*]thiophene. Synthesis of 2,3,7,8-Tetrahydro-3-oxothieno[1,2-*b*]cyclohepta[5,6,7-*de*]isoquinoline and 1,2,3,7,8,11b-Hexahydro-3-oxothieno[1,2-*b*]cyclohepta[5,6,7-*de*]isoquinoline

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The synthesis of the title compounds was carried out by cyclization *via* isocyanate of *(E)*-4,5-dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylideneacetic acid and 4,5-dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]-thiophene-10-ylacetic acid respectively, which were obtained by the Wadsworth-Emmons modification of the Wittig reaction of 4,5-dihydro-10*H*-10-oxobenzo[5,6]cyclohepta[1,2-*b*]thiophene and triethyl phosphonacetate. The structures of these new compounds are described.

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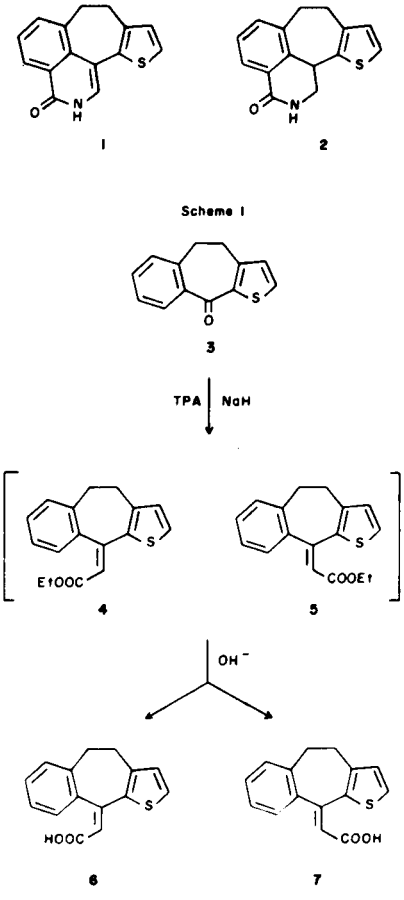
In our continuous efforts towards the search for novel psychotropic agents, we have recently described the synthesis of several new heterocyclic systems incorporating in their molecules the structure of benzo[4,5]cyclohepta-[1,2-*b*]thiophene [1,2,3]. Some of the reported compounds have been shown to possess useful pharmacological properties in laboratory animals [4].

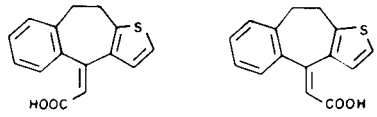
In order to extend our investigations to other heterocycles with the isomeric structure of benzo[5,6]cyclohepta-[1,2-*b*]thiophene, we have synthesized the title compounds **1** and **2** which constitute the first instance of the new 3-oxothieno[1,2-*b*]cyclohepta[5,6,7-*de*]isoquinoline ring system.

For our initial synthetic approach, we selected 4,5-dihydro-10*H*-10-oxobenzo[5,6]cyclohepta[1,2-*b*]thiophene (**3**) [5] (Scheme I) as starting material. The Wadsworth-Emmons condensation of this compound with triethyl phosphonacetate, using sodium hydride as the base and tetrahydrofuran as the solvent, afforded a mixture of the two isomeric *E*- and *Z*-10-ylideneacetic esters **4** and **5** in a total yield of 87% and an approximate *E* to *Z* ratio of 1:1, as deduced from the analysis of the signal intensities of the ^{1}H-nmr spectrum of the mixture.

Because of the difficulties encountered in the separation of these esters, the mixture was directly hydrolyzed in 10% sodium hydroxide and ethanol. In this reaction a mixture of the corresponding 10-ylideneacetic isomeric acids **6** and **7** was formed in an overall yield of 76% and an *E* to *Z* ratio of 2:3 respectively. These could not be separated by fractional crystallization or chromatographic techniques. However, it was observed that when the mixture was treated with 15% sodium hydroxide in ethanol, the sodium salt of one of the components precipitated, giving, after filtration and acidification with 10% hydrochloric acid, a pure white solid which was identified as the *E* isomer compound **6** (see later).



On the other hand, acidification of the above alkaline filtrate did not yield the acid **7** but a mixture of both isomers **6** and **7** in approximately equal proportions. This indicated that a part of the *Z* isomer **7** was converted to the *E* form **6** by an isomerization process probably catalyzed by the basic and acidic media used in the work-up of the mixture and facilitated by the extended conjugated nature



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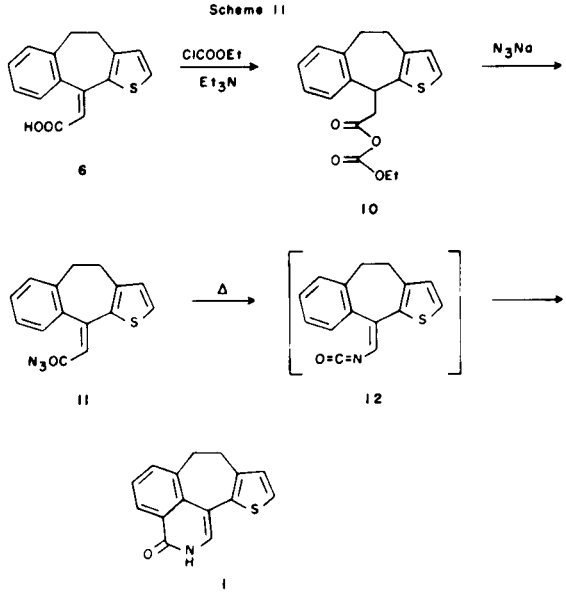
of the systems **6** and **7**. Consecutive similar treatments of the mixture led to the entire transformation of the carboxylic acid **7** into isomer **6**. For this reason **7** could not be isolated and described.

The identification of **6** as the *E* isomer was determined from its ^{1}H-nmr spectrum (deuteriochloroform) by comparison with those of the original mixture of **6** and **7** and of compounds **8** and **9**, the structure of which had been demonstrated in a previous paper [3]. Thus, taking as a comparison reference the olefinic protons signals, easily visible as singlets in the spectra of all these acids (Figure I), it was concluded that the signal at δ 6.30 belonged to the *E* compound **6** while the signal at δ 5.92 corresponded to its *Z* isomer **7**.

The acid **6** was subsequently converted to the acylazide **11** (Scheme II) through its mixed anhydride **10** according to the method of Kaiser and Weinstock [6], and the azide cyclized *via* a Curtius type rearrangement to the lactam **1** followed the procedure employed for the synthesis of 2,3,6,7-tetrahydro-3-oxobenzo[1,2]cyclohepta[3,4,5-*hi*]thieno[3,4-*c*]pyridine and 2,3,7,8-tetrahydro-3-oxothieno-[2,1-*b*]cyclohepta[5,6,7-*de*]isoquinoline [3].

Scheme II



Structural assignments for this compound were based on its elemental and spectral analysis. Thus, **1** exhibited in its infrared spectrum bands at 3300 and 1640 cm^{-1} characteristic of stretching frequencies of NH and CO bonds respectively. Its ^{1}H-nmr spectrum (DMSO-d_6) showed, be-

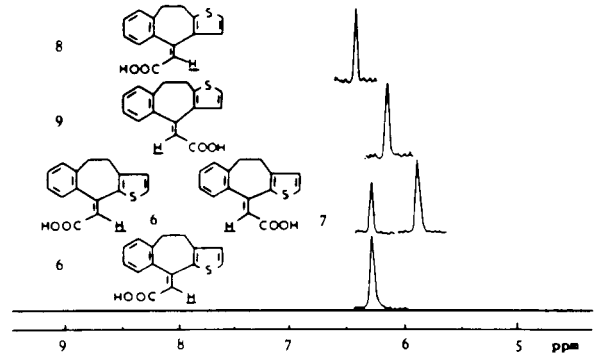
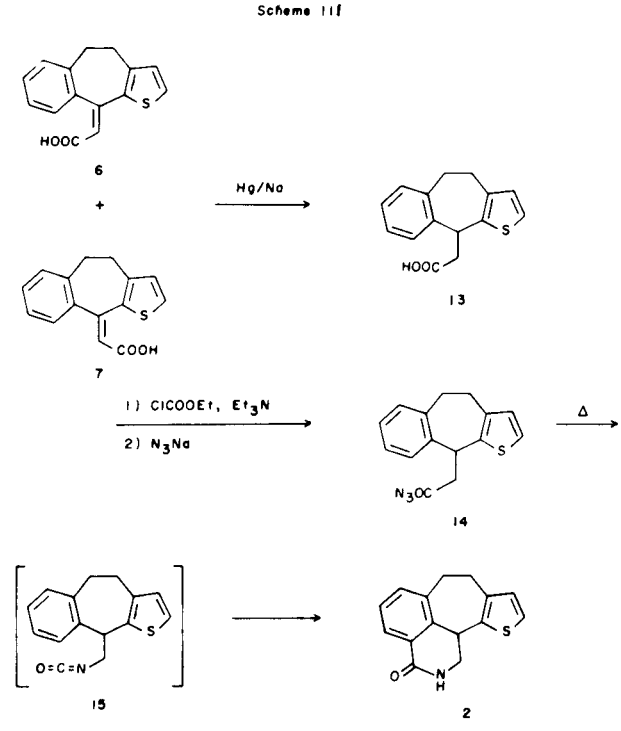


Figure I. Chemical shifts of the olefinic protons.

sides the multiplet at δ 2.9 due to the protons of the dimethylenic bridge, two doublets centered at δ 6.73 and δ 7.10 (J = 5.4 Hz) corresponding to the AB system formed by the thiophene protons. The signal of the olefinic proton was overlapped by the multiplet of the benzene protons. The identification of this compound confirmed the *E* configuration previously assigned to the acid **6**.

Following the synthetic approach used in the preparation of the tetracyclic compound **1** it was also possible to obtain 1,2,3,7,8,11b-hexahydro-3-oxothieno[1,2-*b*]cyclohepta[5,6,7-*de*]isoquinoline (**2**). Thus, sodium amalgam reduction of the mixture of 10-ylideneacetic acids **6** and **7** in ethanol (Scheme III) generated the saturated acid **13** in 92% yield which, in turn, was converted to the lactam **2** by the foregoing sequence of reactions.

Scheme III



The lower yield (45%) of this lactam in the rearrangement-cyclization step fo the azide **14** can be explained by the absence of the double bond at position 10 of the molecule, which abolishes the conjugation and permits the free rotation of the isocyanate group around the carbon-carbon bond of **15**.

As in the case of lactam **1**, the infrared spectrum of **2** exhibited the characteristic bands at 3260 and 1650 cm^{-1} of the NH and CO groups respectively. However, its ^{1}H-nmr spectrum (deuteriochloroform) showed significant differences mainly in the appearance of a multiplet centered at δ 3.90, assigned to the protons of the methylene next to the NH group, a triplet centered at δ 4.83 corresponding to the proton on the carbon atom adjacent to the methylene group and a broad signal at δ 5.30 due to the amidic proton.

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.

Ethyl *(E)* and *(Z)*-4,5-Dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylidenacetate (**4** and **5**).

To a stirred suspension of sodium hydride (2.3 g, 0.1 mole, 4.2 g of a 55% dispersion oil) in tetrahydrofuran (62 ml) triethyl phosphonacetate (24.7 g, 0.11 moles) 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 4,5-dihydro-10*H*-10-oxobenzo[5,6]cyclohepta[1,2-*b*]thiophene (**3**) [6] (11 g, 0.05 moles) in tetrahydrofuran (62 ml) was added during 30 minutes. The mixture was refluxed for 68 hours and poured into ice-water. The resultant oil was extracted with ether. The extracts were washed with water, dried (magnesium sulfate) and evaporated. The residue was distilled at reduced pressure to give 12.9 g (87%) of an oil of bp 184-188° at 1 mm which was a mixture of ethyl *(E)* and *(Z)*-4,5-dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylidenacetate (**4** and **5**), *E*-*Z* ratio 1:1, nmr; ir (film): 1720 cm^{-1} (CO).

Anal. Calcd. for $C_{17}H_{16}O_2S$: C, 71.83; H, 5.63; S, 11.26. Found: C, 71.59; H, 5.74; S, 11.41.

(E) and *(Z)*-4,5-Dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylidenacetic Acid (**6** and **7**).

A mixture of ethyl *(E)* and *(Z)*-4,5-dihydro-10*H*-benzo[5,6]cyclohepta-[1,2-*b*]thiophene-10-ylidenacetate (**4** and **5**) (14.6 g, 0.051 moles), ethanol (146 ml) and 10% aqueous sodium hydroxide (146 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 yellow solid was filtered, washed with water and dried, yielding 9.9 g (76%) of a mixture of the *E* and *Z* isomeric 10-ylidenacetic acids **6** and **7** in an approximate *E* to *Z* ratio of 2:3; nmr; mp 182-184° (benzene-heptane); ir (nujol): 1690 cm^{-1} (CO).

Anal. Calcd. for $C_{15}H_{12}O_2S$: C, 70.31; H, 4.68; S, 12.50. Found: C, 70.20; H, 4.80; S, 12.39.

(E)-4,5-Dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylidenacetic Acid (**6**).

The mixture of *(E)* and *(Z)*-4,5-dihydro-10*H*-benzo[5,6]cyclohepta-[1,2-*b*]thiophene-10-ylidenacetic acids (**6** and **7**) (2.1 g, 7.5 mmoles) was treated with ethanol (10 ml) and 10% aqueous sodium hydroxide (15 ml). The mixture was stirred at 22° for 15 minutes. The precipitated sodium salt was dissolved in water and the solution treated with 10% hydrochloric acid. The new precipitate was collected by filtration, washed with water and dried to give 1.05 g of *(E)*-4,5-dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylidenacetic acid (**6**), mp 209-210° (benzene-hexane); ir (nujol): 1690 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 2.95 (s, 4, CH_2-CH_2), 6.28 (s, 1, CH), 6.68 (d, J = 5.4 Hz, 1, S-C=CH), 7.06 (d, J = 5.4 Hz, 1, S-CH=C), 7.20 (s, 4, benzene).

Anal. Calcd. for $C_{15}H_{12}O_2S$: C, 70.31; H, 4.68; S, 12.50. Found: C, 70.15; H, 4.86; S, 12.42.

Acidification of the first alkaline filtrate with 10% hydrochloric acid gave a mixture of the original mixture of **6** and **7**. Consecutive similar treatments of this mixture led to the entire transformation of the carboxylic acid **7** into isomer **6** by an isomerization process.

(E)-4,5-Dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylidenacetylazide (**11**).

To a solution of *(E)*-10-ylidenacetic acid **6** (1 g, 5.3 mmoles) in dry tetrahydrofuran (25 ml) was added triethylamine (0.8 g, 7.6 mmoles) and then ethyl chloroformate (0.6 g, 5.3 mmoles) at 0° under nitrogen. The mixture was kept at 0° for 1 hour and then cooled to −10°, and a solution of sodium azide (0.34 g, 5.3 mmoles) in water (2 ml) was added dropwise in 10 minutes. After 2 hours at −10°, ether (15 ml) was added and the organic phase was separated, dried (magnesium sulfate) and evaporated at 22° to give the 10-ylidenacetylazide **11** as an orange viscous oil (1.1 g, 98%); ir (film): 2150 cm^{-1} (N_3). The compound was pure enough to be used as such in the following step.

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

A solution of *(E)*-4,5-dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylidenacetylazide (**11**) (1.1 g, 3.7 mmoles) in dry benzene (22 ml) was refluxed for 2 hours. The precipitated white solid was filtered, washed with benzene and dried, yielding 0.7 g (73%), mp 294-295° (dimethyl sulfoxide); ir (nujol) 3300 cm^{-1} (NH), 1640 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ 2.90 (m, 4, CH_2-CH_2), 6.73 (d, J = 5.4 Hz, 1, S-C=CH), 7.10 (m, 6, benzene, thiophene, =CH).

Anal. Calcd. for $C_{15}H_{11}NOS$: C, 71.15; H, 4.34; N, 5.53; S, 12.64. Found: C, 70.85; H, 4.12; N, 5.59; S, 12.43.

4,5-Dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylacetic Acid (**13**).

A mixture of *E* and *Z*-4,5-dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]-thiophene-10-ylideneacetic acids (**6** and **7**) (15 g, 0.058 moles) in hot ethanol (180 ml) was added to a flask containing 5% sodium amalgam (150 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 solutions were diluted with an equal volume of water and acidified with hydrochloric acid. The resultant solid was filtered, washed with water and dried to give 13.8 g (92%) of 10-ylacetic acid **13**, mp 198-199° (benzene-heptane); ir (nujol): 1695 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ 2.7-3.2 (m, 6H, $3CH_2$), 4.69 (t, J = 7.8 Hz, 1, CH), 6.66 (d, J = 5.4 Hz, 1, S-C=CH), 7.15 (m, 5, 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, 69.68; H, 5.49; S, 12.56.

4,5-Dihydro-10*H*-benzo[5,6]cyclohepta[1,2-*b*]thiophene-10-ylacetylazide (**14**).

This compound was obtained following the procedure described above for the preparation of **11** using the 10-ylacetic acid **13** (2.6 g, 0.01 mole) tetrahydrofuran (62 ml), triethylamine (1.9 g, 0.0187 moles), ethyl chloroformate (2.12 g, 0.014 moles) and sodium azide (0.9 g, 0.014 moles), yield 2.5 g (88%); ir (film): 2150 cm^{-1} (N_3). The compound was pure enough to be used as such in the following step.

1,2,3,7,8,11b-Hexahydro-3-oxothieno[1,2-*b*]cyclohepta[5,6,7-*de*]isoquinoline (**2**).

This compound was obtained by refluxing the azide **14** in dry benzene for 6 hours according to the procedure used for the preparation of lact-

am **1**, yield 45%, mp 194-195° (ethanol); ir (nujol): 3260 cm^{-1} (NH), 1650 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 2.7-3.3 (m, 4, CH_2-CH_2), 3.6-4.2 (m, 2, CH_2), 4.8 (t, J = 7.8 Hz, 1, CH), 6.62 (d, J = 5.4 Hz, 1, S-C=CH), 6.9-7.3 (m, 4, benzene and S-CH=C).

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.58; H, 5.09; N, 5.49; S, 12.54. Found; C, 70.65; H, 4.97; N, 5.56; S, 12.43.

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