Synthesis of New Thienocyclopenta[3,2-*d*]-oxazole and Thiazole Derivatives

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Synthesis of thieno[2',3':5,4]cyclopenta[3,2-*d*]oxazole and thiazole derivatives are achieved by insertion of carbon dioxide and disulfide into 4-amino-5-chloro-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-one.

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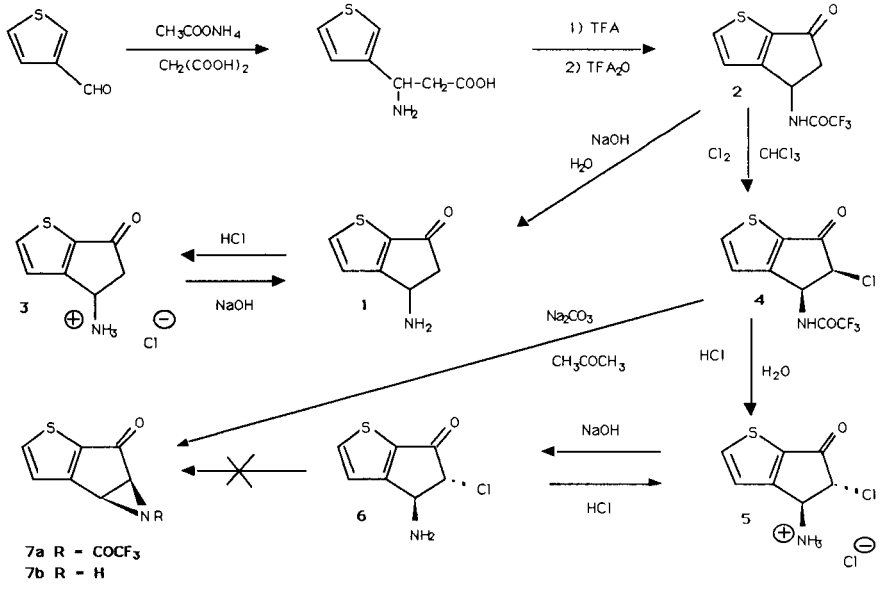
Insertion of carbon dioxide and carbon disulfide into organic compounds is of a great interest in chemistry and particularly allows the synthesis of new heterocyclic derivatives with potential therapeutic properties [1,2,3]. Accordingly, we wish herein to report the reactivity of the 4-amino-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-one (**1**) which synthesis we recently described, towards carbon dioxide and disulfide and its ability to form carbamates and dithiocarbamates. The properties have been applied to some halo derivatives of **1** and have led to the synthesis of new thieno[2',3':5,4]cyclopenta[3,2-*d*]oxazole and thiazole derivatives.

The synthesis of the 4-amino-5,6-dihydro-4*H*-cyclopenta-[*b*]thiophen-6-one (**1**) was achieved in 3 steps starting from thiophene-3-carboxaldehyde and *via* its trifluoroacetyl derivative **2** as previously described [4] (Scheme 1). Compound **1** was an unstable oil which could be salified by hydrochloric acid to give the ammonium chloride **3**. In alkaline medium, **3** regenerated **1**. Compound **2** has been submitted to various halogenation reactions and, particularly the *cis* chloro compound **4** has conducted to the formation of the aziridine **7a** [5]. The hydrolysis of the trifluoroacetyl group of **4**, under acidic conditions, led to the *trans* ammonium chloride **5** which gave the free base **6** in alkaline medium. All synthesis attempts of the aziridine base **7b** from **6** failed and we have also demonstrated that hydrolysis of the trifluoroacetyl group of **7a** occurred always with the simultaneous cleavage of the aziridine ring [6].

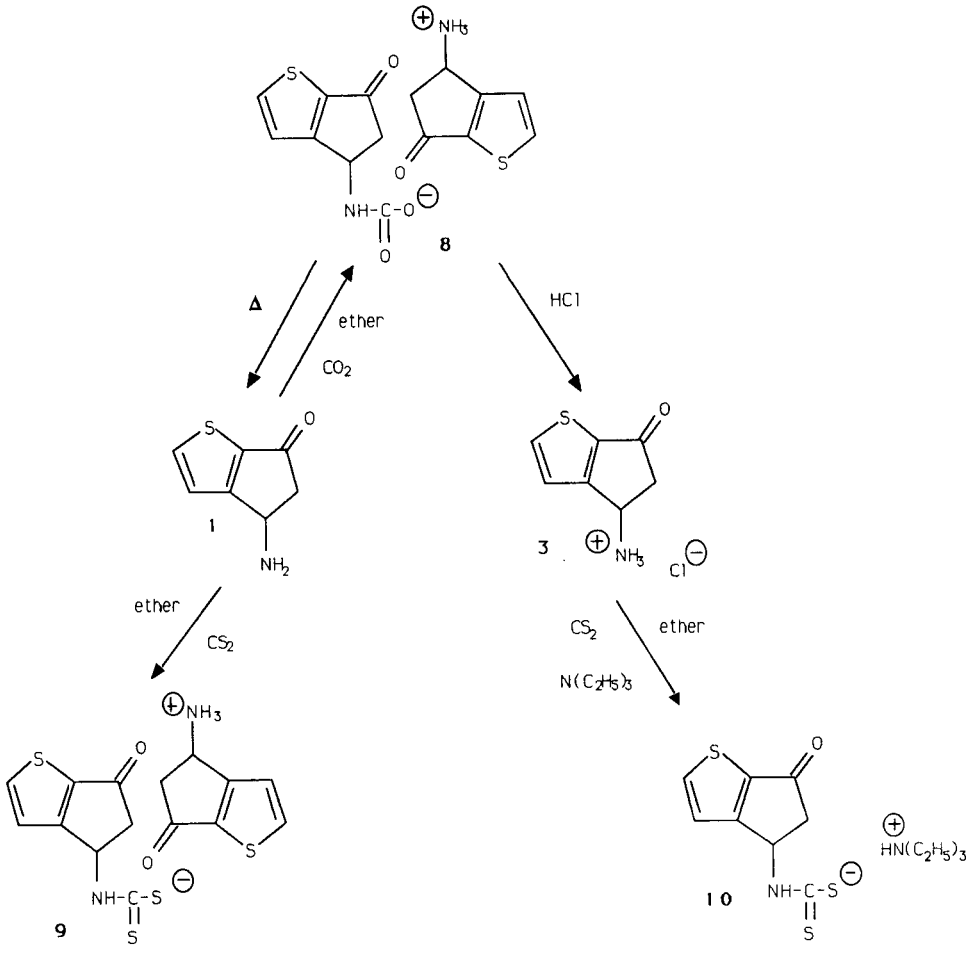
When **1**, in an etheral solution, was treated at room temperature with gaseous carbon dioxide, it gave a solid which precipitated from the reaction mixture. The spectrometric ir and nmr data of the latter were in favor of the carbamate structure **8** (Scheme 2). Its chemical behaviour confirmed this latter. In fact, the oil obtained by fusion of **8** at 55° was identified as **1**. Further, in solution, conversion of **8** to **1** take place in 2 hours, as it was observed with the nmr sample. At least, treatment of **8** by refluxing 6*N* aqueous solution of hydrochloric acid gave quantitatively the ammonium chloride **3**. However the instability of **8** could not allow its elemental microanalysis.

In a similar manner, treatment at room temperature, of

Scheme 1



Scheme 2



an etheral solution of **1** with carbon disulfide led also to a precipitate which was identified as the dithiocarbamate **9**. However, when the reaction was also run in ether, starting from the ammonium chloride **3** in the presence of an excess of triethylamine, the precipitate that appeared within a few minutes was identified as the triethylammonium dithiocarbamate **10**. Compounds **9** and **10** proved to be stable under the usual conditions.

On the other hand the solid, which precipitated when **3** was treated under the same conditions with carbon dioxide, could not be analysed and regenerated immediately into **1** by exposure to air.

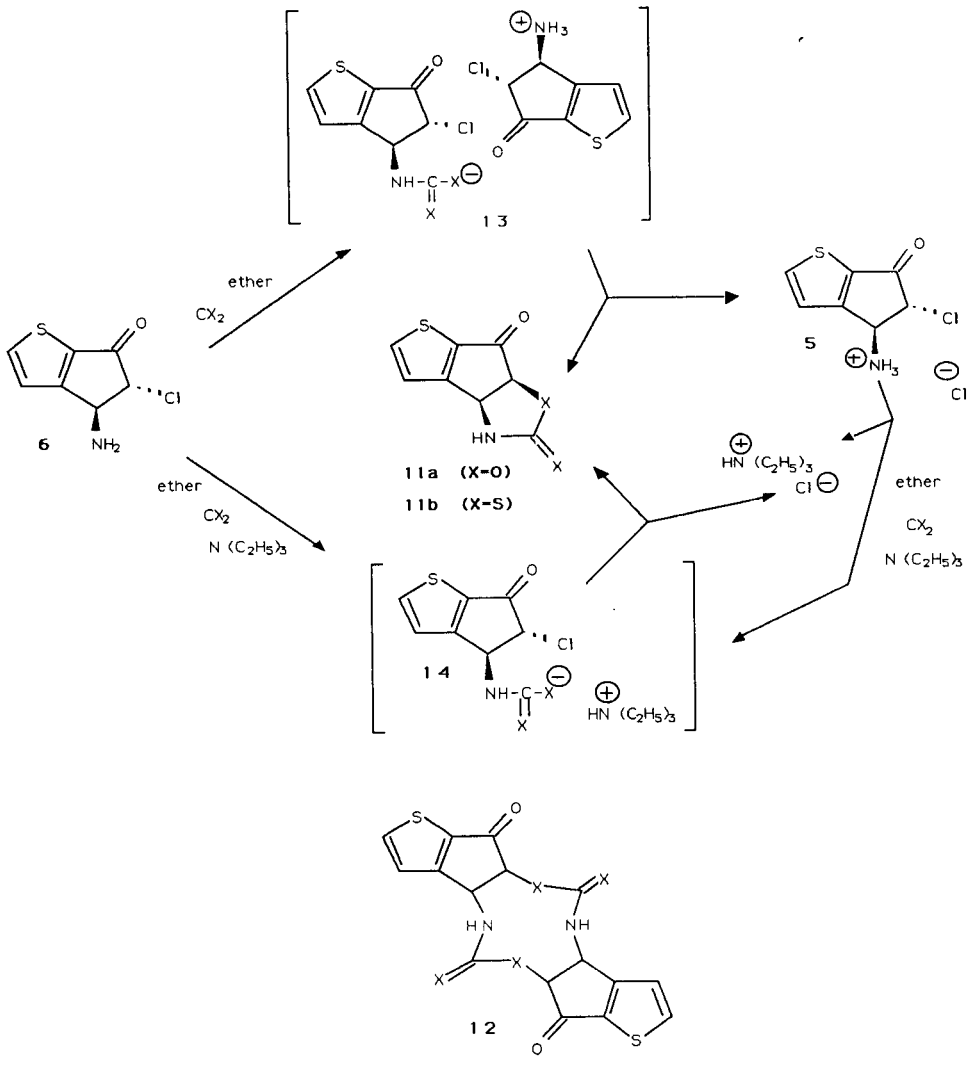
This ability to form carbamates and dithiocarbamates prompted us to apply these reactions to the chloro derivatives **5** and **6** (Scheme 3). Treatment of the free base **6**, in an etheral solution with carbon dioxide or disulfide, led to solids which precipitated within a few minutes from the reaction mixture. Their nmr spectrometric data indicated, in the two cases, the presence, in equal parts, of two compounds: the *trans* ammonium chloride **5** and a *cis* disubstituted unknown derivative which could be isolated by washing with water.

The derivative, obtained in the reaction with carbon dioxide was identified to as oxazolidinone structure **11a** and the compound, resulting from the reaction with carbon disulfide, the thiazolidinethione **11b**. The spectrometric mass data ruled out in both cases the probable dimeric structure **12**.

This result and particularly the secondary formation of the ammonium chloride **5** was clearly in favor of an intermediate of a carbamate or dithiocarbamate structure **13**.

In order to increase the yields of the reactions, they were run starting either from the free base **6** or from the ammonium chloride **5** in ether and in the presence of an excess of triethylamine. Under these conditions, treatment with carbon dioxide or disulfide led quantitatively to the oxazolidinone **11a** or to the thiazolidinethione **11b** which, in all cases, precipitated from the etheral solution with triethylammonium chloride. The presence of the latter, which was eliminated by washing with water, assigned the

Scheme 3



triethylammonium carbamate structure to the intermediate **14**.

This pathway, which seems an efficient method to form oxazole and thiazole fused rings, will be applied to the numerous chlorethylamino sequences that we previously described especially in the indane series [7].

EXPERIMENTAL

General Methods.

Melting points were taken on a Köfler bank and are uncorrected. Infrared spectra were recorded on a Philips PU 9716 apparatus and only noteworthy absorptions (reciprocal centimeters) are listed. Nmr spectra were recorded on a Jeol FX 200 in DMSO-d_6 solution using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. Mass spectra were determined on a Jeol D300 mass spectrometer.

trans 5-Chloro-6-oxo-5,6-dihydro-4*H*-cyclopenta[*b*]thien-4-ylammonium Chloride (**5**).

A mixture of *cis* chlorotrifluoroacetylaminocyclopentanone (**4**) (5 g, 0.017 mole) in a 6*N* aqueous hydrochloric acid solution (100 ml) was refluxed for 30 minutes. The solution was cooled, filtered and the filtrate was evaporated to dryness under reduced pressure. The solid residue was recrystallized to give **5** as white crystals (3.7 g, 98%), mp >260° (2-propanol); ir (potassium bromide): 3200-2640 (NH_3), 1715 (CO); ^{1}H-nmr: 9.3 (br, NH_3), 8.56 (d, $J_{H\text{-}2\ H\text{-}3}$ = 5 Hz, H-2), 7.61 (d, $J_{H\text{-}3\ H\text{-}2}$ = 5 Hz, H-3), 5.23 (d, $J_{H\text{-}5\ H\text{-}4}$ = 2.4 Hz, H-5), 5.00 (d, $J_{H\text{-}4\ H\text{-}5}$ = 2.4 Hz, H-4); ^{13}C-nmr: 184.89 (C-6), 160.13 (C-6a), 144.83 (C-2), 125.44 (C-3a), 124.80 (C-3), 62.72 (C-5), 54.66 (C-4).

Anal. Calcd. for $C_7H_7NOCl_2S$: C, 37.52; H, 3.15; N, 6.25; S, 14.31. Found: C, 37.38; H, 3.09; N, 6.29; S, 14.25.

trans 4-Amino-5-chloro-5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-6-one (**6**).

A solution of ammonium chloride **5** (3.7 g, 0.017 mole) in water (50 ml) was adjusted to *p*H = 14 with sodium hydroxide and extracted with chloroform (150 ml). The organic layer was separated, dried over calcium chloride and the solvent was removed under reduced pressure. The solid residue was recrystal-

lized to give **6** (2.5 g, 80%), mp 117° (ether/petroleum ether); ir (potassium bromide): 3370 and 3300 (NH_2), 1700 (CO); ^{1}H-nmr: 8.40 (d, $J_{H\text{-}2\ H\text{-}3}$ = 5 Hz, H-2), 7.33 (d, $J_{H\text{-}3\ H\text{-}2}$ = 5 Hz, H-3), 4.69 (d, $J_{H\text{-}5\ H\text{-}4}$ = 2.4 Hz, H-5), 4.32 (d, $J_{H\text{-}4\ H\text{-}2}$ = 2.4 Hz, H-4), 2.5 (br, NH_2); ^{13}C-nmr: 187.52 (C-6), 168.83 (C-6a), 143.60 (C-2), 124.68 (C-3a), 124.15 (C-3), 58.87 (C-5), 50.86 (C-4).

Anal. Calcd. for C_7H_6NOClS: C, 44.80; H, 3.20; N, 7.47; S, 17.07. Found: C, 44.71; H, 3.23; N, 7.51; S, 17.28.

6-Oxo-4,5-dihydro-4*H*-cyclopenta[*b*]thien-4-ylammonium-*N*-[6-oxo-4,5-dihydro-4*H*-cyclopenta[*b*]thien-4-yl]carbamate (**8**).

A solution of amine **1** (1.5 g, 0.01 mole) in ether (100 ml) was bubbled for 5 minutes at room temperature, with a gaseous carbon dioxide flow. The precipitate that appeared was filtered and washed with ether to give **8** as white crystals (1.5 g, 43%), mp 55°; ir (potassium bromide): 3600-2600 ($^+NH_3$ CO_2^-), 3300 (NH), 1670 (CO); ^{1}H-nmr: 8.21 (d, $J_{H\text{-}2\ H\text{-}3}$ = 5 Hz, H-2), 7.30 (d, $J_{H\text{-}3\ H\text{-}2}$ = 5 Hz, H-3), 7.2 (br, NH), 5.09 (m, H-4$_{(NH3)}$), 4.38 (m, H-4$_{(NH)}$), 3.20 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}4}$ = 9 Hz, H-5a), 2.5 (br, NH_3), 2.74 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}4}$ = 3 Hz, H-5b).

6-Oxo-4,5-dihydro-4*H*-cyclopenta[*b*]thien-4-ylammonium-*N*-[6-oxo-4,5-dihydro-4*H*-cyclopenta[*b*]thien-4-yl]dithiocarbamate (**9**).

Carbon disulfide (1.2 ml, 0.02 mole) was added, at room temperature, to a stirred solution of amine **1** (1.5 g, 0.01 mole) in ether (100 ml). The precipitate that appeared was filtered, washed with ether and recrystallized to give **9** as white crystals (1.6 g, 42%), mp 70° (2-propanol); ir (potassium bromide): 3600-2600 ($^+NH_3$ CS_2^-), 3290 (NH), 1670 (CO); ^{1}H-nmr: 8.7 (br, NH), 8.31 and 8.14 (d, $J_{H\text{-}2\ H\text{-}3}$ = 5 Hz, H-2), 7.43 and 7.29 (d, $J_{H\text{-}3\ H\text{-}2}$ = 5 Hz, H-3), 6.14 (m, H-4$_{(NH3)}$), 4.83 (m, H-4$_{(NH)}$), 3.37 and 3.23 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H5a\ H\text{-}4}$ = 9 Hz, H-5a), 2.94 and 2.86 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}4}$ = 3 Hz, H-5b), 2.5 (br, NH_3).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S_4$: C, 47.10; H, 3.69; N, 7.32; S, 33.52. Found: C, 47.14; H, 3.57; N, 7.19; S, 33.58.

Triethylammonium-*N*-[6-oxo-4,5-dihydro-4*H*-cyclopenta[*b*]thien-4-yl]dithiocarbamate (**10**).

Triethylamine (7 ml, 0.05 mole) was added, at room temperature, to a stirred suspension of ammonium chloride **3** (1.9 g, 0.01 mole) in ether (100 ml). The insoluble was filtered and carbon disulfide (1.2 ml, 0.02 mole) was added to the filtrate. The precipitate that appeared was filtered, washed with ether and recrystallized to give **10** as white crystals (2.7 g, 82%), mp 160° (2-propanol); ir (potassium bromide): 3110 (NH), 3000-2500 ($^+$NH CS_2^-), 3290 (NH), 1675 (CO); ^{1}H-nmr 8.72 (d, $J_{NH\ H\text{-}4}$ = 8 Hz, NH), 8.18 (d, $J_{H\text{-}2\ H\text{-}3}$ = 5 Hz, H-2), 7.33 (d, $J_{H\text{-}3\ H\text{-}2}$ = 5 Hz, H-3), 6.16 (m, H-4), 3.4 (br, $^+$NH), 3.22 (dd, $J_{H\text{-}5a\ H\text{-}5b}$ = 19 Hz, $J_{H\text{-}5a\ H\text{-}4}$ = 9 Hz, H-5a), 2.91 (dd, $J_{H\text{-}5b\ H\text{-}5a}$ = 19 Hz, $J_{H\text{-}5b\ H\text{-}4}$ = 3 Hz, H-5b).

Anal. Calcd. for $C_{14}H_{22}N_2OS_3$: C, 50.88; H, 6.71; N, 8.48; S, 29.10. Found: C, 51.02; H, 6.77; N, 8.39; S, 29.08.

2,7-Dioxo-2,3,3a,7a-tetrahydrothieno[2′,3′:5,4]cyclopenta[3,2-*d*]-1,3-oxazole (**11a**).

Triethylamine (7 ml, 0.05 mole) was added to a stirred suspension of ammonium chloride **5** (2.2 g, 0.01 mole) in ether (100 ml). The insoluble was filtered and the filtrate was bubbled for 5 minutes at room temperature, with a gaseous carbon dioxide flow. The precipitate that appeared was filtered, washed with water and recrystallized to give **11a** as white crystals (1.8 g, 90%), mp 232° (water); ir (potassium bromide): 3250 (NH), 1765 and 1710 (CO); ^{1}H-nmr: 8.5 (br, NH), 8.45 (d, $J_{H\text{-}5\ H\text{-}4}$ = 5 Hz, H-5), 7.32 (d, $J_{H\text{-}4\ H\text{-}5}$ = 5 Hz, H-4), 5.30 (d, $J_{H\text{-}7a\ H\text{-}3a}$ = 6.8 Hz, H-7a), 5.19 (d, $J_{H\text{-}3a\ H\text{-}7a}$ = 6.8 Hz, H-7a); ^{13}C-nmr: 188.86 (C-7), 167.54 (C-6a), 156.68 (C-2), 145.12 (C-5), 140.69 (C-36), 124.27 (C-4), 81.76 (C-7a), 50.92 (C-3a); ms: (m/z, %) 195 (M^+, 28), 152 (31), 151 (24), 130 (24), 124 (28), 96 (27), 44 (64.

Anal. Calcd. for $C_8H_5NO_3S$: C, 49.23; H, 2.58; N, 7.18; S, 16.42. Found: C, 49.01; H, 2.62; N, 7.07; S, 16.17.

7-Oxo-2-thioxo-2,3,3a,7a-tetrahydrothieno[2′,3′:5,4]cyclopenta-[3,2-*d*]-1,3-thiazole (**11b**).

Triethylamine (7 ml, 0.05 mole) was added to a stirred suspension of ammonium chloride **5** (2.2 g, 0.01 mole) in ether (100 ml). The insoluble material was filtered and carbon disulfide (1.2 ml, 0.02 mole) was added, at room temperature, to the filtrate. The precipitate that appeared was filtered, washed with water and recrystallized to give **11b** as white crystals (2.1 g, 92%), mp 255° (water); ir (potassium bromide): 3300 (NH), 1685 (CO); ^{1}H-nmr: 11.0 (br, NH), 8.50 (d, $J_{H\text{-}5\ H\text{-}4}$ = 5 Hz, H-5), 7.33 (d, $J_{H\text{-}4\ H\text{-}5}$ = 5 Hz, H-4), 5.80 (d, $J_{H\text{-}7a\ H\text{-}3a}$ = 7.3 Hz, H-7a), 5.33 (d, $J_{H\text{-}3a\ H\text{-}7a}$ = 7.3 Hz, H-7a); ^{13}C-nmr: 194.99 (C-2), 189.91 (C-7), 165.15 (C-6a), 144.83 (C-5), 138.81 (C-3b), 123.81 (C-4), 63.60 (C-7a), 59.63 (C-3a); ms: (m/z, %) 229 (M^++2, 45), 228 (M^++1, 54), 227 (M^+, 100), 194 (60), 168 (54), 151 (49), 140 (76).

Anal. Calcd. for $C_8H_5NOS_3$: C, 42.27; H, 2.22; N, 6.16; S, 42.31. Found: C, 42.35; H, 2.08; N, 6.33; S, 42.25.

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