Research on Nitrogen and Sulfur Heterocyclic Compounds: Synthesis of 10*H*-Pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]-diazepin-5(4*H*)-one and some Derivatives

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The synthesis of 10*H*-pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]diazepin-5(4*H*)-one (**16**) and some derivatives are described from methyl 3-bromomethylthiophene-4-carboxylate (**5**). The key step of these sequences is the intramolecular cyclization of the carbonylazides **12** and **13**.

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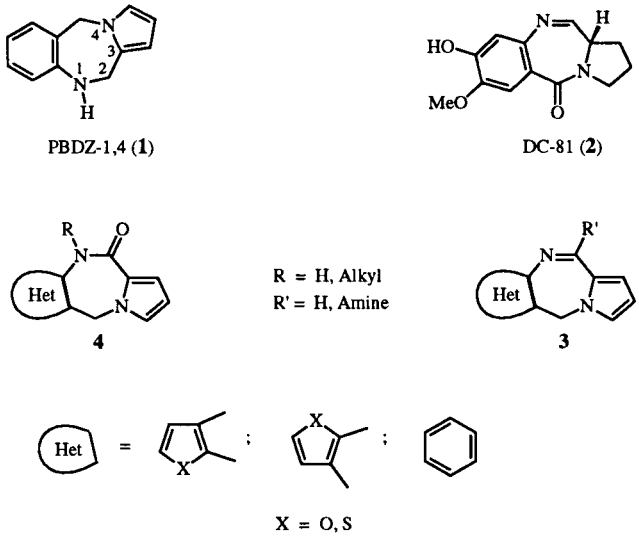
The various reported tricyclic ring systems containing a common 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine moiety **1** are potential antitumor antibiotics based on their structural similarity to anthramycin. DC-81 **2** [1] is a new synthetic tricyclic compound belongs to this class.

We previously reported [2,3,4,5] the synthesis of some pyrrolo[1,2-*a*][1,4]diazepines **3** and diazepinones **4** annelated to a thiophene or a furan ring (2,3- or 3,2-junction). The closure reaction was carried out by intramolecular cyclization of carbonyl azides in warm acetic acid. In a similar manner we prepared the known pyrrolo[1,2-*a*][1,4]-benzodiazepin-11-one [3] in 62% yield. Recently, we described [6] a facile procedure to obtain the pyrrolo[1,2-*a*]-thieno[2,3-*e*][1,4]diazepine (**3**) (R' = H) starting from 3-bromomethyl-2-nitrothiophene. Because, compounds containing a 3,4-fused thiophene ring are few expanded, we wish to report herein the synthesis of some pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]diazepines derivatives.

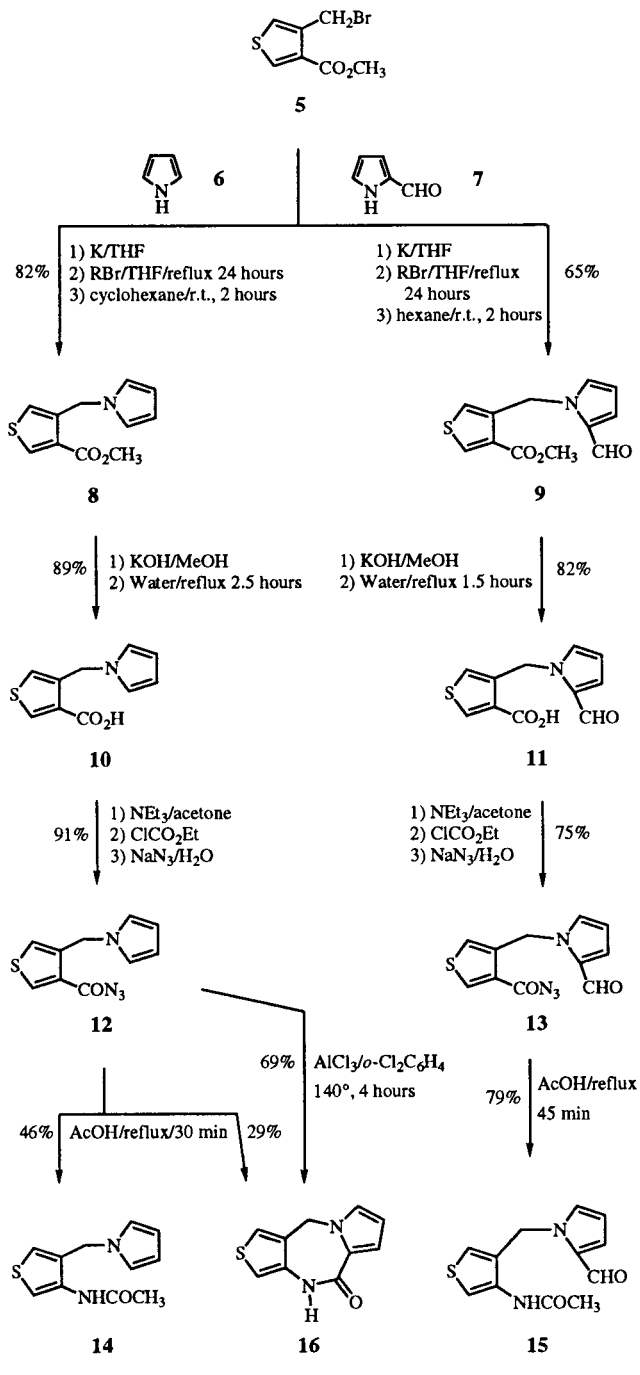
Scheme 1



Thus the methyl 3-bromomethylthiophene-4-carboxylate (**5**) [7] treated with the potassium salt of pyrrole (**6**) or pyrrole-2-carboxaldehyde (**7**) furnished the ester **8** and the ester-aldehyde **9** in 82% and 65% yield respectively (Scheme 1). Saponification of these esters with aqueous alcoholic potassium hydroxide produced the acids **10** (89%) and **11** (92%). These carboxylic acids were converted *via* the Weinstock reaction [8] to the corresponding azides **12** (91%) and **13** (75%). Heated with benzene they gave the intermediates isocyanates characterized by their strong N=C=O band absorption at ν = 2250 cm^{-1} in the ir spectrum, and they were used without isolation for the next step. Submitted to boiling acetic acid the azide-aldehyde **13** gave only the acetamide-aldehyde **15** in 79% yield. We did not obtain the expected cyclized product **17** in contrast to our previous cited works with 2,3- or 3,2-substituted thiophene [2,3,4] or furan [5].

On the other hand, the carbonyl azide **12** treated with acetic acid under the same conditions gave a mixture of the acetamide **14** (62%) and a cyclic lactam (38%) namely 10*H*-pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]diazepin-5(4*H*)-one (**16**). The ratio of these compounds were determined by ^{1}H nmr analysis of the crude product and were easily separated by chromatography on a silica gel column using ligroin-benzene as the eluent. Both results show that the intermediate which is almost certainly the mixed carboxylic carbamic acid anhydride [9,10] is not reactive enough to produce either the azomethine link or the lactam link but it decomposes with loss of carbon dioxide to the acetamide **14** or **15** as the single product or the major product. Nevertheless, treatment of the carbonyl azide **12** under Friedel-Crafts conditions [11] using *o*-dichlorobenzene as the solvent and aluminium trichloride (99.9%) as the catalyst at 140° furnished the expected tricyclic lactam **16** in satisfactory yield (69%) (Scheme 2). Furthermore, the acetamide-aldehyde **15** in warm hydrochloric acid solution (4*N*) according to the literature [12], afforded, by intramolecular condensation of the supposed intermediate amine with the adjacent formyl group, diazepine **17** in 67% yield (Scheme 3). This compound treated with methyl iodide in dry benzene at room temperature gave the corresponding iminium salt **18** in good yield (89%).

Scheme 2

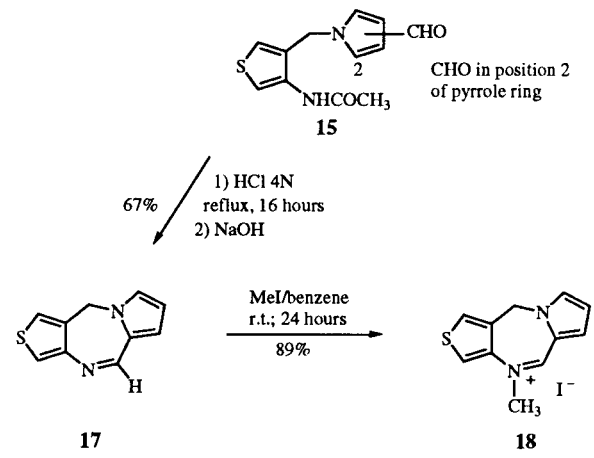


The microanalysis and spectroscopic data (ir, ^{1}H nmr and ^{13}C nmr) confirm the structures assigned for the various compounds obtained (details are reported in the Experimental). Further studies of these tricyclic systems and biological screening are under investigations.

EXPERIMENTAL

Melting points were determined on a Leitz hot-plate apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-20 spectrometer. The ^{1}H nmr and ^{13}C nmr spectra were obtained on a varian EM 360 spectrometer and a Bruker AC 200. Chemical shifts are reported in ppm from TMS as the internal reference and are given in δ units. Elemental analyses were performed by laboratoire de microanalyse de l'INSA de Rouen, place Emile Blondel, 76130 Mont-Saint-Aignan, France.

Scheme 3



All organic reagents are available commercially, and were used without further purification. Solvents were freshly distilled and degassed. All reaction were performed in dry glasswares in an atmosphere of dry nitrogen. Dry THF was prepared by distillation over sodium metal and benzophenone. Reactions were monitored by analytical tlc performed on DC-Alufolien silica gel plates and products were visualized by uv light. Column chromatography was carried out with silca gel 60 (70-230 mesh ASTM, Merck).

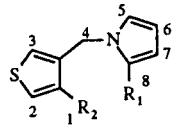
Methyl 4-(1-Pyrrolymethyl)thiophene-3-carboxylate (**8**) and Methyl 4-[1-(Formyl)pyrrolylmethyl]thiophene-3-carboxylate (**9**).

To a well stirred suspension of the potassium salt of the pyrrole ring [prepared from pyrrole (4.50 g, 65 mmoles) and potassium metal (2.60 g, 66 mg-atom) or pyrrole-2-carboxaldehyde (6.19 g, 65 mmoles) and potassium metal (2.54 g, 65 mg-atom)] in dry tetrahydrofuran (80 ml), kept under nitrogen, a solution of (14.56 g, 62 mmoles) of methyl 4-bromomethylthiophene-3-carboxylate (**5**) in the same solvent (100 ml) was added slowly dropwise at room temperature. The mixture was heated under reflux for 4 hours. After cooling to room temperature, cyclohexane or hexane (150 ml) was added to the reaction mixture and was allowed to stand at room temperature for 2 hours. The mixture was filtered, evaporated and purified by distillation under reduced pressure (**8**: $bp_{0.3}$, 140-142°, **9**: $bp_{0.2}$, 143-146°). An analytical sample of **8** and **9** was obtained as colorless prisms by recrystallization from hexane. All the physical an chemical constants of these products are summarized in Tables 1 and 2.

4-(1-Pyrrolylmethyl)thiophene-3-carboxylic Acid (**10**) and 4-[1-(2-Formyl)pyrrolylmethyl]thiophene-3-carboxylic Acid (**11**).

A mixture of the above ester **8** or **9** (10 mmoles) and potassium hydroxide pallets (3 g, 60 mmoles) in a mixture of methanol (25 ml) and water (10 ml) was refluxed for 2.5 hours (1.5 hours in the case of ester **9**). After cooling, the reaction mixture was extracted with diethyl ether (2 x 25 ml). The water layer was saturated with sodium chloride, extracted twice with diethyl ether and decanted. The aqueous phase was treated with charcoal, filtered and acidi-

Table 1
Yields and Physical Data of Compounds **8-15**



Product No.	R_1	R_2	Mp°	Yield (%) [a]	Formula	Analyses Calcd./Found C%	H%	N%
8	H	CO_2Me	69	82 (A)	$C_{11}H_{11}NO_2S$ (221.28)	59.71 59.62	5.01 4.99	6.33 6.23
9	CHO	CO_2Me	49	65 (A)	$C_{12}H_{11}NO_3S$ (249.29)	57.82 57.61	4.45 4.31	5.62 5.59
10	H	CO_2H	153	89 (B/C)	$C_{10}H_9NO_2S$ (207.25)	57.95 57.89	4.38 4.18	6.76 6.52
11	CHO	CO_2H	135	82 (B/C)	$C_{11}H_9NO_3S$ (234.25)	56.16 56.01	3.86 3.79	5.95 5.69
12	H	CON_3	liq [b]	91	$C_{10}H_8N_4OS$ (232.26)	----- -----	----- -----	----- -----
13	CHO	CON_3	liq [b]	75	$C_{11}H_8N_4O_2S$ (260.27)	----- -----	----- -----	----- -----
14	H	NHCOMe	108	46 (A/D)	$C_{11}H_{12}N_2OS$ (220.29)	59.97 59.69	5.49 5.31	12.71 12.40
15	CHO	NHCOMe	164	79 (E/D)	$C_{12}H_{12}N_2O_2S$ (248.30)	58.05 58.39	4.87 5.09	11.28 11.30

[a] Recrystallization: A, Hexane; B, Ethanol; C, Water; D, Diethyl ether; E, Benzene. [b] These Compounds were used for the next step without further purification.

Table 2
IR and ^1H NMR Data of Compounds **8-15**

Product No.	IR(KBr) ν cm^{-1} CHO	C=O	Other	^1H NMR [$CDCl_3$/TMS (internal)] δ ppm [b] 1	2	3	4	5	6	7	8	N-H
8	–	1722	–	3.85	8.15	6.60	5.35	6.75	6.20	6.20	6.75	–
9	1658	1700	–	3.80	8.05	6.90	5.75	7.03	6.20	6.65	9.50	–
10 [a]	–	1678	2871	3.30	7.45	6.82	5.21	6.71	5.92	5.92	6.71	–
11 [a]	1590	1625	3160	4.25	8.30	7.40	5.30	7.10	6.32	6.55	9.54	–
12	–	1650	2160	–	7.75	6.90	5.20	6.70	6.18	6.18	6.70	–
13	1640	1670	2135	–	8.10	6.90	5.75	7.05	6.20	6.70	9.48	–
14	–	1692	3250	2.05	6.70	6.45	5.15	6.70	6.01	6.01	6.70	10.05
15	1641	1679	3297	2.40	7.75	7.15	5.30	7.02	6.15	6.70	9.40	9.20

[a] The ^1H nmr spectra of these compounds were enregistered in DMSO-d_6/TMS(internal). [b] Proton or proton of the group attached to carbons 1-8.

fied cautiously with an hydrochloric solution (1/1) to *p*H = 1.5 ~ 2. The precipitate formed was collected by filtration, washed with water and air dried. An analytical sample of acid **10** or **11** was obtained as white-yellow crystals by recrystallization from ethanol/water (1/1). The physical constants of these compounds are indicated in Tables 1 and 2.

4-(1-Pyrrolylmethyl)thiophene-3-carbonylazide (**12**) and 4-[1-(2-Formyl)pyrrolylmethyl]thiophene-3-carbonylazide (**13**).

A solution of carboxylic acid **10** or **11** (10 mmoles), dry acetone (75 ml) and dry triethylamine (2.73 g, 27 mmoles) was cooled in an ice-salt bath. To the well stirred and cooled solution, in an atmosphere of nitrogen, a solution of ethyl chloroformate (3.8 g, 35 mmoles) in dry acetone (7.5 ml) was added over a period of 30 minutes. When the addition was stopped, the reaction mixture was allowed to stir at 0° for 15 minutes and a solution of sodium azide (2.92 g, 45 mmoles) in cooled water was added dropwise over a period of 20 minutes. The mixture was allowed to stir at 0° for 30 minutes then poured onto crushed ice and extracted with carbon tetrachloride (3 x 50 ml). The combined organic layers were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure at 30-35° and the oily orange residue was used for the next reaction

without others purifications. The physical and chemical constants of these products **12** and **13** are summarized in Tables 1 and 2.

4-(1-Pyrrolylmethyl)thiophene-3-acetamide (**14**) and 10*H*-Pyrrolo-[1,2-*a*]thieno[3,4-*e*][1,4]diazepin-5(4*H*)-one (**16**).

A solution of (2 g, 8.62 mmoles) of 4-(1-pyrrolylmethyl)thiophene-3-carbonylazide (**12**) and glacial acetic acid (50 ml) was refluxed for 30 minutes. After cooling and evaporation of the solvent *in vacuo* the solid residue was filtered, washed with ethyl acetate (2 x 10 ml) and air dried. Recrystallization from chloroform gave 0.52 g (29%) of an analytical sample of the cyclic lactam **16** namely 10*H*-pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]diazepin-5(4*H*)-one, mp 242-243°; ir (potassium bromide): ν 3104-2920 (NH-CO), 1658 (C = O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.98 (s, 2H, CH_2-N), 5.95 (dd, 1H, H_4-pyrrole), 6.65 (dd, 1H, H_3-pyrrole), 6.72 (d, 1H, H_2-thiophene), 6.88 (m, 2H, H_5-pyrrole and H_5-thiophene), 7.47 (s, 1H, NH amidic); ^{13}C nmr (DMSO-d_6): δ 45.8, 108.0, 117.5, 118.0, 124.5, 126.0, 127.0, 127.8, 140.0, 160.5.

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.71. Found: C, 58.71; H, 3.91; N, 13.69.

The filtrate was passed through a silica gel column, eluting with ligroin-benzene (15-85). The eluates are collected and evaporated to give 0.87 g (4 mmoles) of 4-(1-pyrrolylmethyl)thiophene-3-acetamide (**14**) (46% yield) which was recrystallized from hexane-diethyl ether. The physical and spectral data of this product are summarized in Table 1 and Table 2.

10*H*-Pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]diazepin-5(4*H*)-one (**16**).

A solution of (1 g, 4.31 mmoles) of 4-(1-pyrrolylmethyl)thiophene-3-carbonylazide (**12**) and dry *o*-dichlorobenzene (20 ml) wash heated at 100° for 30 minutes. After cooling, the reaction mixture was treated with anhydrous aluminium trichloride (1.7 g, 12.95 mmoles) (99.9%) and heated at 140° for 4 hours. After cooling at room temperature, the mixture was poured on cooled 4*N* potassium hydroxide solution. The organic layer was decanted, dried and concentrated. The crude residue was recrystallized from chloroform to give 0.61 g (69%) of yellow prisms which were identical to the cyclic lactam **16** described above.

4-[1-(2-Formyl)pyrrolylmethyl]thiophene-3-acetamide (**15**).

A solution of (2 g, 7.69 mmoles) of 4-[1-(2-formyl)pyrrolylmethyl]thiophene-3-carbonylazide (**13**) and glacial acetic acid (75 ml) was refluxed for 45 minutes. After cooling, the solvent was removed by evaporation and the crude residue was dissolved in dichloromethane. The organic layer was washed with sodium carbonate solution (2 x 40 ml), with water (2 x 50 ml), dried and concentrated to give the acetamide-aldehyde **15** as a yellow solid. All parameters of this product are summarized in Tables 1 and 2.

10*H*-Pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]diazepine (**17**).

A solution of (1 g, 4.03 mmoles) of 4-[1-(2-formyl)pyrrolylmethyl]thiophene-3-acetamide (**15**) in 4*N* hydrochloric acid solution (20 ml) was refluxed for 16 hours. After cooling and evaporation of the solvent *in vacuo*, the crude residue was dissolved in diethyl ether and washed twice with 2*N* potassium hydroxide solution. The organic solution was washed again with water, brine, dried and evaporated to give **17** (0.5 g, 67%) as a yellow solid. An analytical sample, mp 138-139°, was obtained by recrystallization from a mixture of diethyl ether and hexane; ir (potassium bromide): ν 3087 (C-H), 1593 (CH = N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.95 (s, 2H, CH_2-N), 6.12 (dd, 1H, H_4-pyrrole), 6.50 (dd, 1H, H_3-pyrrole), 6.73 (dd, 1H, H_5-pyrrole), 7.01 (d, 1H, H_2-thiophene), 7.22 (d, 1H, H_5-thiophene), 7.96 (s, 1H, N = CH); ^{13}C nmr (deuteriochloroform): δ 45.2, 107.3, 117.0, 119.3, 121.0, 124.0, 128.0, 128.5, 145.0, 146.0.

Anal. Calcd. for $C_{10}H_8N_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.52; H, 4.19; N, 14.85.

N-methyl-10*H*-pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]diazepinium Iodide (**18**).

A solution of (0.50 g, 2.66 mmoles) of 10*H*-pyrrolo[1,2-*a*]thieno[3,4-*e*][1,4]diazepine (**17**) and 3 ml of methyl iodide in dry benzene (15 ml) was stirred at room temperature for 24 hours. The precipitate formed was collected, washed with anhydrous diethyl ether and air dried to 0.78 g (89%) of the diazepinium salt **18** as white-yellow prisms. An analytical sample of mp = 286°, was obtained by recrystallization from dry methanol; ir (potassium bromide): ν 3077 (C-H aromatic), 2960 (C-H aliphatic), 1620 (CH = N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.05 (s, 3H, CH_3-N), 5.48 (s, 2H, CH_2-N), 6.62 (dd, 1H, H_4-pyrrole), 7.38 (dd, 1H, H_3-pyrrole), 7.55 (d, 1H, H_2-thiophene), 7.82 (dd, 1H, H_5-pyrrole), 8.12 (d, 1H, H_5-thiophene), 8.81 (s, 1H, CH = N-CH_3); ^{13}C nmr (DMSO-d_6): δ 46.5, 48.20, 115.0, 121.0, 124.0, 126.0, 129.0, 132.5, 138.5, 141.0, 149.5.

Anal. Calcd. for $C_{11}H_{11}N_2IS$: C, 40.01; H, 3.36; N, 8.48. Found: C, 39.71; H, 3.35; N, 8.46.

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