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Pyrrolo[1,4]diazepines, *via* Thermolyse of Carbonylazides, and [3,2,2]Cyclazines, *via* Diels-Alder Reaction of [f]Indolizines, Annelated to [1]Benzothiophene.

Philippe OHIER, Adam DAÏCH* and Bernard DECROIX.

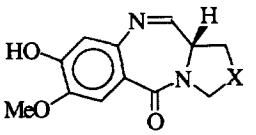
Laboratoire de Chimie, Université du Havre, 30 rue Gabriel Pèri, 76600, Le Havre, France.

Abstract: Easy access to fused tricyclic pyrrolo[1,2-a][1]benzothieno[2,3-e][1,4]diazepines from the corresponding carbonyl azides by thermolysis in acetic acid is described. Moreover, new [1]benzothieno[2,3(3,2)-f]indolizines were synthesized in one-pot from 2(3)-(2-formylpyrrol-1-ylmethyl)-[1]benzothiophene and with diethyl acetylenedicarboxylate (DEAD) they led regiospecifically to [3,2,2] cyclazines fused to a [1]benzothiophene ring by 1,3-dipolar cycloaddition reaction rather than Diels-Alder adducts. Copyright © 1996 Elsevier Science Ltd

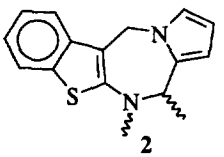
During the past few years much attention has been paid to the development of benzo[1,4]diazepines and derivatives annelated to a heterocyclic ring which have remarkable tranquilizing, hypnotic, and central nervous system (CNS) activities like the Neothramycin (DC-81) and derivatives **1**.[1] In connection with our work on new thieno-fused N-heterocycles with potential pharmacological activity, we have recently described some [1]benzothieno[1,3]diazepinones fused to a piperidine,[2,3] pyrrolidine,[3] and pyrrolidone ring.[3,4] Now, we wish to report herein the first synthesis of [1]benzothienodiazepin(on)es annelated to a pyrrole ring as in **2** and which incorporate the pyrrolo[1,4]diazepine skeleton of compounds **1**. Our attention was first directed towards the synthesis of the carbonyl azide derivatives **8c,d** as key intermediates in this synthetic sequence. Examination of the reactivity of formyl compounds **6b** and **17**, in particular their cyclization in polyphosphoric acid (PPA) led to [1]benzothieno[2,3(3,2)-f]indolizines. Such **f** fused [1]benzothiophenes were previously unknown, and to our knowledge only one indolizine fused to [1]benzothiophene at junction **e** is reported in the literature.[5] In addition, these indolizines have synthetic potential because they contain the reactive [1]benzothiophene-2,3-quinodimethane (**3**)[6,7] moiety which as in the better known 2,3-dimethylene-2,3-dihydrothiophene (**4**)[8,9] containing analogues might lead to react in Diels-Alder reactions. In our case, the diene moiety **3** in [1]benzothieno[f]indolizines structures **11** and **18** generated from the formyl derivatives **6b** and **17** by cyclization, reacted regiospecifically with DEAD to give the [3,2,2]cyclazines annelated to a [1]benzothiophene ring via 1,3-dipolar addition rather than the classical [4+2]π Diels-Alder adducts.

Fax: +33 35 21 22 08

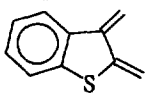
Scheme 1.



1 Neothramycin (DC-81)
X= CH_2, S, CHOH.



2



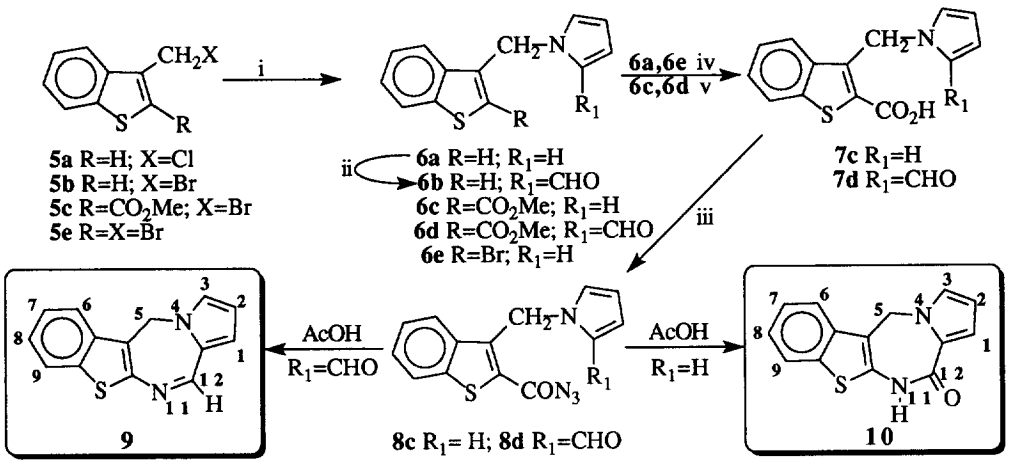
3

4

The requisite carbonyl azides compounds **8c** and **8d** were obtained in 3 steps starting from suitable 3-halogenomethyl[1]benzothiophene **5a-e** as shown in Scheme 2. Condensation of the potassium salt of pyrrole or pyrrole-2-carboxaldehyde, prepared *in situ* from potassium metal and pyrrole or pyrrole-2-carboxaldehyde in anhydrous THF,[10] with halides **5a-c**, gave the N-alkylated products **6a-e** (yields of 48 to 65%). The formyl derivative **6b** was also prepared by functionalization of pyrrole ring of **6a** by Vilsmeier-Haack formylation with an improved yield of 75% compared to the direct N-alkylation process. Classical saponification of esters **6c,d** with potassium hydroxide in methanol followed by Weinstock reaction[11] (treatment of carboxylic acids **7c,d** with dry triethylamine, ethyl chloroformate and finally sodium azide) led to carbonyl azides **8c,d** in satisfactory yields of 87 and 61% respectively. The acid **7c** could be prepared alternatively treatment of **6a** or **6e** with butyllithium at room temperature, then at reflux in diethyl ether, followed by carbonatation with carbon dioxide. This gave the expected acid **7c** in a yield of 61 and 23% respectively; in the latter case, a large amount of compound **6a** (55%) resulting from decarboxylation reaction was recovered in organic layer. Heating these carbonyl azides **8c,d** in a large excess of acetic acid gave directly 5*H*-pyrrolo[1,2-a][1]benzothieno[2,3-e]-[1,4]diazepine (**9**) and 5*H*-pyrrolo[1,2-a][1]benzothieno[2,3-e][1,4]diazepin-12(11*H*)-one (**10**) in yields of 61 and 55% respectively. These spontaneous intramolecular cyclizations took place via the intermediate mixed carboxylic carbamic acid anhydride which is sufficiently stable to not decompose with loss of carbon dioxide to give the acetylated product. In the case of **8c**, only the higher reactivity of the α position of pyrrole ring towards the electrophilic substrate is observed. When a formyl group is present, **8d**, only nucleophilic attack on this group was occured, as we have previously noticed for similar structures in preceding papers.[10,12-14] Structures of these triheterocyclic diazepines **9** and **10** were supported by their IR, ^{1}H NMR, ^{13}C NMR and Mass specta as well as by their elemental analysis and details of spectroscopic data are given in experimental section.

On the other hand, according to the process described by us to generate *in situ* species containing the 2,3-dimethylene-2,3-dihydrothiophene (**4**) moiety the formyl derivative **6b** constitutes an important precursor for the [1]benzothiophene-2,3-quinodimethane (**3**) analogues.

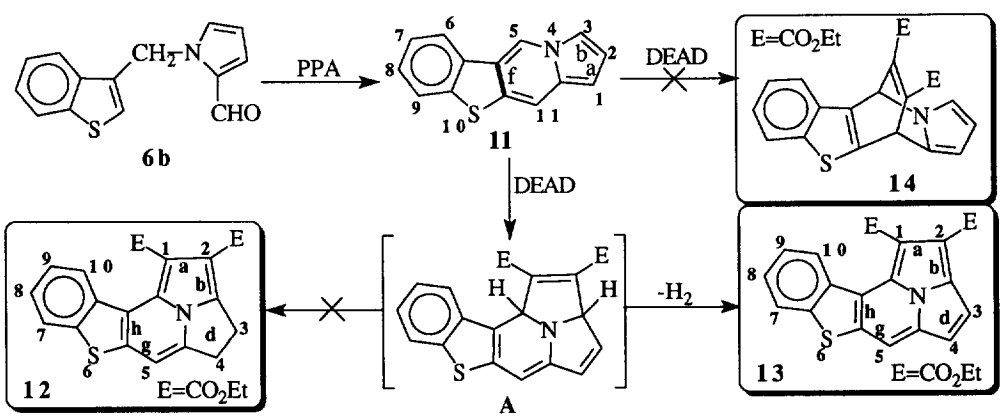
Scheme 2.



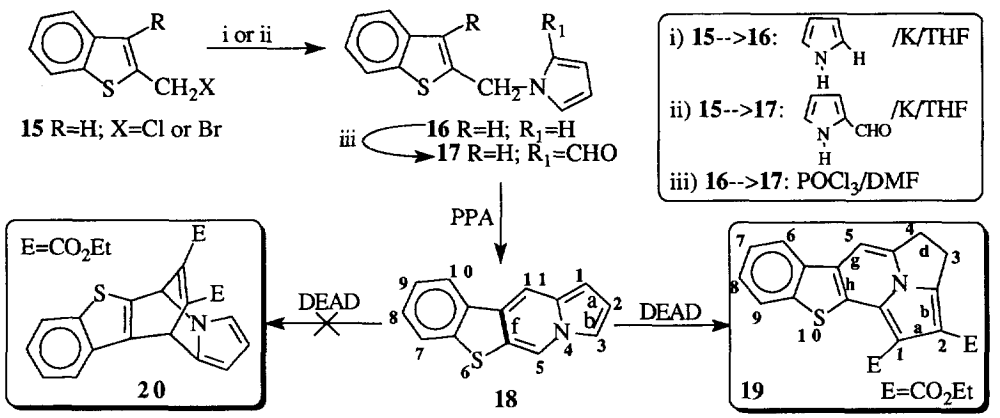
i) N-alkylation process: K/THF/pyrrole or pyrrole-2-carboxaldehyde; ii) Vilsmeier & Haack: $POCl_3$/DMF; iii) Weinstock: 1° NEt_3/Me_2CO, 2° $ClCO_2Et$, 3° NaN_3/H_2O; iv) BuLi/CO_2; v) 1° KOH/MeOH, 2° HCl.

Thus, the aldehyde derivative **6b** treated with polyphosphoric acid (PPA) at 90°C for 4 hours led, after an alkaline treatment at low temperature, to the [1]benzothieno[3,2-f]indolizine **11** in 59% yield as colorless crystals. This indolizine, when heated with diethyl acetylenedicarboxylate (DEAD) in toluene, gave preferentially via the intermediate **A** after dehydrogenation, the 1,3-dipolar cycloaddition adduct **13** in 61% yield. No trace of compound **14** resulting from [4+2]π Diels-Alder reaction was detected, Scheme 3. It is interesting to note that comparable results were observed in the thiophene series except that thieno[2,3(3,2)-f]-indolizines led to the corresponding hydrogenated thieno[3,2,2]cyclazines[9] analogous to **12** rather than the dehydrogenated products obtained in the [1]benzothiophene series. This difference prompted us to investigate the same reactions with the positional isomer (**17**) namely 2-(2-formylpyrrol-1-ylmethyl)[1]benzothiophene.

Scheme 3.



Scheme 4.



According to Scheme 4, the formyl product **17** was obtained in two pathways by direct alkylation of pyrrole-2-carboxaldehyde with 2-bromo(or chloro)methyl[1]benzothiophene (**15**) (57%) or by formylation of **16** under Vilsmeier-Haack conditions (62%). In all our cases, the formylation reaction generally gave better yields. When the formyl derivative **17** was submitted to hot polyphosphoric acid in a similar manner as the isomer **6b**, the cyclodehydration occured and the indolizine **18** was isolated in 61% yield. Allowing this to react with DEAD in hot toluene, led to cyclazine **19** in 63% yield. The product results from 1,3-dipolar cycloaddition but in this case, only the hydrogenated compound was isolated. The structure of **19** was supported by NMR analysis, thus, the ^1H NMR spectrum displays H_3, H_4 and H_5 as multiplets at δ = 4.26-4.33, 3.52-3.62 and 5.60-5.63 ppm respectively whereas the ^{13}C NMR spectrum shows the C_3 and C_4 at δ = 24.5 and 33.1 ppm. These values were in agreement to these observed for the all analogous thieno[3,2,2]cyclazines reported earlier.[9] As for cyclazine **13**, we observed an important deshielding of about +2.8 ppm of H_5 proton (δ = 8.28-8.38 ppm) compared to the same proton of the hydrogenated thieno[3,2,2]-cyclazines and product **19** cited above but they were in accordance with those reported for various non hydrogenated substituted [3,2,2]cyclazines (δ = 8.23 to 8.94 ppm).[19] Furthermore the chemical shift of protons H_3 and H_4 which appear as multiplets at δ = 8.28-8.38 ppm and 7.42-7.58 ppm respectively, were also identical to values reported by the same authors.[19]

In summary, we report the first synthesis of [1]benzothienopyrrolo[1,4]diazepines (**9** and **10**) by thermal reaction and [1]benzothieno[f]indolizines (**11**, **18**) which under Diels-Alder reaction conditions gave regiospecifically [3,2,2]cyclazines annelated to the [1]benzothiophene heterocycle (**13** and **19**). Since the observed results are different in the two series of thiophene and [1]benzothiophene, the potential of systems incorporating diene **3** toward some dienophiles is currently under investigation in our laboratory.

EXPERIMENTAL SECTION.

All melting points were determined using a Leitz heat plate apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The nuclear magnetic resonance spectra (^1H and ^{13}C) were taken on a Bruker AC-200 (200 MHz) instrument in the indicated solvent. Chemical shifts values are reported in ppm from TMS as an internal reference and are given in δ units and the following abbreviations are used: s for singlet, d for doublet, dd for doublet of doublet, t for triplet, br for broad, m for multiplet and finally BT for [1]benzothiophene. Elemental analyses were obtained in the microanalysis laboratory of the I.N.S.A at Rouen, F 76130 Mt-St-Aignan, France. Mass spectral measurements were recorded on a AEI MS 902 S Spectrometer. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60F (70-300 mesh) was used for column chromatography. The starting halogenomethyl[1]-benzothiophene **5a-e** and **15** were prepared according to known procedures.[15-18] Commercially available reagents and solvents were purified when necessary by standard literature methods.

General procedure for N-alkylation of halides 5a-e and 15.

To a well stirred suspension of the potassium salt of the pyrrole ring, prepared *in situ* from pyrrole (4.5 g, 65 mmol) or pyrrole-2-carboxaldehyde (6.19 g, 65 mmol) and potassium metal (2.6 g, 66 mg-atom) in dry THF (70 ml), was added dropwise under nitrogen atmosphere and at room temprature, a solution of halides **5a-e** or **15** (60 mmol) in 80 ml of the same solvent. The mixture was heated under reflux for 4 hours. After cooling, cyclohexane (100 ml) was added to the reaction mixture and allowed to stand for 2 hours at room temperature. The mixture was filtered on celite, evaporated and finally purified as indicated in table 1 by recrystallization. All the physical and chemical constants of these products are summarized in the same table.

Vilsmeier-Haack formylation of 2(3)-(1-pyrrolylmethyl)[1]benzothiophene (6a and 16).

To 0.8 g (11 mmol) of dry DMF cooled at 5-10°C, $POCl_3$ (1.69 g, 11 mmol) was added dropwise with stirring. After the addition was complete the mixture was allowed to react at room temperature for 15 minutes. 1,2-dichloroethane (10 ml) was added and then the solution (2.13 g, 10 mmol) of 1-([1]benzothien-2(3)-ylmethyl)pyrrole (**6a**) or (**16**) in 10 ml of the same solvent. After an additional 30 minutes at room temperature, the reaction mixture was refluxed for 3 hours under a low stream of nitrogen. The solution was then cooled and a solution of 7.5 g (55 mmol) of sodium acetate trihydrate in 20 ml of water was added. The biphasic mixture was stirred vigorously for 15 minutes, then refluxed for 1/2 hour. After cooling, the reaction mixture was extracted with diethyl ether and the combined extracts were washed twice with saturated Na_2CO_3, brine and dried over $MgSO_4$. Removal of the solvent afforded a brown oil which solidified on cooling. Recrystallization from a mixture of hexane-ligroin gave the aldehyde **6b** (75%) or the aldehyde **17** (62%). Physical and chemical characteristics of these compounds are identical with those observed for products **6b** and **17** obtained by the direct N-alkylation process and are summarized in table 1 and table 2.

General procedure for the synthesis of carboxylic acids 7c,d.

Method A: Hydrolysis of esters **6c,d**. A mixture of ester **6c** or **6d** (10 mmol) and potassium hydroxide pellets (1.5 g, 30 mmol) in a mixture of methanol (20 ml) and water (5 ml) was refluxed for 2.5 hours. After cooling, the reaction mixture was concentrated *in vacuo*, diluted with 40 ml of water, extracted with diethyl ether (2x25 ml). The aqueous layer was cooled and acidified cautiously with an hydrochloric solution (1/1) to pH = 1.5≈2. The precipitate formed was collected by filtration, washed with diethyl ether and finally recrystallized.

3-(1-Pyrrolylmethyl)[1]benzothiophene-2-carboxylic acid (7c). This compound was isolated after recystallization from ethanol-water as a white solid in 87% yield, mp 195°C; IR(KBr): ν 3350-2910 (br O-H), 1680 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 5.72 (s, 2H, CH_2-N), 5.9-5.96 (m, 2H, H_3 and H_4 pyrrole), 6.82-6.85 (m, 2H, H_2 and H_5 pyrrole), 7.44-7.48 (m, 2H, 2H BT), 8.0-8.08 (m, 2H, 2H BT), 10.12 (br, 1H, OH). Anal. Calcd. for $C_{14}H_{11}NO_2S$ (257.31): C, 65.35; H, 4.31; N, 5.44. Found: C, 65.29; H, 4.19; N, 5.36.

3-(1-(2-Formyl)pyrrolylmethyl)[1]benzothiophene-2-carboxylic acid (7d). This product was obtained after recystallization from ethanol-water as white-yellow needles in a yield of 67%, mp 244°C; IR (KBr): ν 3365-2956 (br O-H), 1680 (C=O), 1635 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.94 (s, 2H, CH_2-N), 6.15-6.18 (m, 1H, H_4 pyrrole), 6.31-6.35 (m, 1H, H_3 pyrrole), 6.89-6.93 (m, 1H, H_5 pyrrole), 7.41-7.43 (m, 2H, 2H BT), 7.81-7.85 (m, 2H, 2H BT), 9.69 (s, 1H, CHO), 10.05 (br, 1H, OH). Anal. Calcd. for $C_{15}H_{11}NO_3S$ (285.31): C, 63.15; H, 3.89; N, 4.91. Found: C, 63.19; H, 3.88; N, 4.80.

Table 1: Physical characteristics and elemental analyses of N-alkylated products **6a-e**, **16** and **17**.

N°	R	R_1	mp°C	Yield%	Recrystallization (a)	Formula (M.W)	Analyses Calcd / Found C%	H%	N%
6a	H	H	51-52	61	A-B (3 / 7)	$C_{13}H_{11}NS$ (213.29)	73.20 / 72.96	5.20 / 5.05	6.57 / 6.22
6b	H	CHO	62-64	65	B-D (4 / 1)	$C_{14}H_{11}NOS$ (241.31)	69.68 / 69.41	4.59 / 4.48	5.80 / 5.62
6c	CO_2Me	H	91-92	60	C-E (3 / 2)	$C_{15}H_{13}NO_2S$ (271.33)	66.40 / 66.27	4.83 / 4.79	5.16 / 5.09
6d	CO_2Me	CHO	127-9	48	F-G (3 / 2)	$C_{16}H_{13}NO_3S$ (299.34)	64.20 / 64.08	4.38 / 4.21	4.68 / 4.38
6e	Br	H	68-70	53	C-D (1 / 1)	$C_{13}H_{10}BrNS$ (292.19)	53.44 / 53.08	3.45 / 3.37	4.79 / 4.55
16	H	H	53-54	58	A-B (2 / 3)	$C_{13}H_{11}NS$ (213.29)	73.20 / 72.89	5.20 / 5.07	6.57 / 6.21
17	H	CHO	65-66	57	B-D (3 / 2)	$C_{14}H_{11}NOS$ (241.31)	69.68 / 69.39	4.59 / 4.62	5.80 / 5.69

(a) A: Toluene, B: Hexane, C: Diethyl ether, D: Ligroin, E: Benzene, F: Methanol, G: Water.

Table 2: IR spectral Data and NMR chemical shifts of N-alkylated products **6a-e**, **16** and **17**.

N°	R	R_1	IR (KBr) ν in cm^{-1} CH=O	C=O	^1H NMR [$CDCl_3$/TMS (internal)] δ in ppm. (b) BT : [1]benzothiophene
6a	H	H	-	-	5.04 (s, 2H, CH_2-N), 6.32-6.36 (m, 2H, H_3 and H_4 pyrrole), 6.8 -6.91 (m, 2H, H_2 and H_5 pyrrole), 7.35-7.51 (m, 3H, 3H BT), 7.75-7.96 (m, 1H, 1H BT), 7.98-8.08 (m, 1H, 1H BT).
6b	H	CHO	1655	-	5.88 (s, 2H, CH_2-N), 6.27-6.30 (m, 2H, H_3 and H_4 pyrrole), 7.01 -7.06 (m, 2H, H_5 pyrrole and 1H BT), 7.40-7.45 (m, 3H, 3H BT), 7.73-7.78 (m, 1H, 1H BT), 9.67 (s, 1H, CHO).
6c	CO_2Me	H	-	1702	3.94 (s, 3H, OCH_3), 5.72 (s, 2H, CH_2-N), 6.08-6.12 (t, 2H, H_3 and H_4 pyrrole), 6.76-6.78 (t, 2H, H_2 and H_5 pyrrole), 7.37-7.44 (m, 2H, 2H BT), 7.72-7.80 (m, 2H, 2H BT).
6d	CO_2Me	CHO	1650	1690	3.84 (s, 3H, OCH_3), 6.12-6.15 (m, 1H, H_4 pyrrole), 6.33 (s, 2H, CH_2-N), 6.82-6.83 (m, 1H, H_3 pyrrole), 6.85-6.87 (m, 1H, H_5 pyrrole), 7.32-7.38 (m, 2H, 2H BT), 7.74-7.78 (m, 2H, 2H BT), 9.39 (s, 1H, CHO).
6e	Br	H	-	-	5.26 (s, 2H, CH_2-N), 6.11-6.13 (m, 2H, H_3 and H_4 pyrrole), 6.7-6.76 (m, 2H, H_2 and H_5 pyrrole), 7.28-7.32 (m, 2H, 2H BT), 7.5 -7.54 (m, 1H, 1H BT), 7.68-7.7 (m, 1H, 1H BT).
16	H	H	-	-	5.29 (s, 2H, CH_2-N), 6.21-6.25 (m, 2H, H_3 and H_4 pyrrole), 6.7 -6.78 (m, 2H, H_2 and H_5 pyrrole), 7.08 (s, 1H, 1H BT), 7.26-7.4 (m, 2H, 2H BT), 7.66-7.76 (m, 2H, 2H BT).
17	H	CHO	1650	-	5.84 (s, 2H, CH_2-N), 6 (dd, 2H, H_4 pyrrole), 6.98-7.09 (m, 2H, H_3 and H_5 pyrrole), 7.39-7.51 (m, 3H, 3H BT), 7.72-7.81 (m, 1 H, 1H BT), 7.8-7.95 (m, 1H, 1H BT), 9.7 (s, 1H, CHO).

Method B: Carbonatation of compounds **6a** and **6e**. To a solution of 47 mmol of 3-(1-pyrrolylmethyl) [1]benzothiophene α brominated or not (**6a** or **6e**) in anhydrous diethyl ether (100 ml) under stirring, was added cautiously dropwise 50 mmol of butyllithium (1.65 N solution in hexane) at room temperature. After 2 hours of reflux, the mixture was cooled at -30°C and a carbon dioxide gas was bubbled slowly over a period of about 10 minutes until saturation of the solution. The mixture was hydrolyzed by 50 ml of crushed ice and separated. The aqueous solution was then cooled again and acidified with an hydrochloric solution (10%). The precipitate formed was collected and worked up as indicated above in method **A**. After recystallization, the expected acids were obtained in a yield of 61 and 23% respectively from **6a** and **6e**. In the case of the bromoderivative **6e**, the organic phase after an usual treatment, furnished an oily residue which was purified by chromatography on silicagel column eluting with a mixture of diethyl ether-hexane (4/1) to give a white solid in 55% yield. Physical characteristics of this product were identical to those given for **6a** (tables 1 and 2).

Weinstock reaction: Synthesis of carbonylazides 8c and 8d.

To the well stirred and cooled solution of carboxylic acid **7c** or **7d** (25 mmol), dry acetone (75 ml) and dry triethylamine (2.73 g, 27 mmol) was added under an atmosphere of nitrogen, a solution of ethyl chloroformate (3.8 g, 35 mmol) in dry acetone (10 ml) over a period of 15 minutes. The reaction was allowed to react at 0-5°C for 20 minutes and a solution of sodium azide (2.92 g, 45 mmol) in 10 ml of cool water was added dropwise. After reaction at 0°C for 1 hour, the mixture was poured on crushed ice and extracted with carbon tetrachloride (3x50 ml). The combined organic layers were washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the oily orange residue was used for the next reaction without other purifications. The carbonyl azide **8c** was obtained in a yield of 65% and was characterized by IR absorption (IR (neat): ν 2170 (CON_3), 1710 (C=O) cm^{-1}). In the case of **8d**, the residue was recrystallized from hexane-diethyl ether (7/3) and gave a white-yellow solid in a yield of 61%, mp 68-70°C; IR (KBr): ν 2160 (CON_3), 1700 (C=O), 1650 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.08-6.12 (m, 2H, H_4 pyrrole), 6.28 (s, 2H, CH_2-N), 6.79-6.81 (m, 1H, H_3 pyrrole), 6.89-6.95 (m, 1H, H_5 pyrrole), 7.33-7.39 (m, 2H, 2H BT), 7.74-7.78 (m, 2H, 2H BT), 9.62 (s, 1H, CHO). Anal. Calcd. for $C_{15}H_{10}N_4O_2S$ (310.33): C, 58.06; H, 3.25; N, 18.05. Found: C, 57.98; H, 3.22; N, 18.01.

5*H*-Pyrrolo[1,2-a][1]benzothieno[2,3-e][1,4]diazepine (9) and 5*H*-Pyrrolo[1,2-a][1]benzothieno[2,3-e][1,4]diazepin-12(11*H*)-one (10).

A solution of 1g of carbonyl azide **8c** or **8d** in 70 ml of glacial acetic acid was refluxed vigorously during 1 hour and concentrated *in vacuo*. The residue after trituration with diethyl ether was collected by filtration and recrystallized with the appropriated solvent.

5*H*-Pyrrolo[1,2-a][1]benzothieno[2,3-e][1,4]diazepine (9). This compound was isolated after recystallization from dichloromethane-hexane (1/4) as yellow crystals in a yield of 61%, mp 136°C; IR (KBr): ν 1615 (CH=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.05-6.09 (m, 1H, H_2), 6.28 (s, 2H, CH_2-N), 6.77-6.80 (m, 1H, H_1), 6.86-6.91 (m, 1H, H_3), 7.33-7.36 (m, 2H, 2H BT), 7.71-7.76 (m, 2H, 2H BT), 8.35 (s, 1H, CH=N); MS: *m/z* 238 (M^+). Anal. Calcd. for $C_{14}H_{10}N_2S$ (238.30): C, 70.56; H, 4.23; N, 11.75. Found: C, 70.37; H, 3.98; N, 11.49.

5*H*-Pyrrolo[1,2-a][1]benzothieno[2,3-e][1,4]diazepin-12(11*H*)-one (10). This compound was obtained after recystallization from ethyl acetate-diethyl ether as brown needles in a yield of 55%, mp 228°C; IR (KBr): ν 3300-2885 (br CONH), 1700 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ: 5.41 (s, 2H, CH_2-N), 5.91-5.94 (m, 1H, H_2), 6.11-6.15 (m, 1H, H_1), 6.72-6.74 (m, 1H, H_3), 7.61-7.66 (m, 2H, 2H BT), 7.80-7.86 (m, 2H, 2H BT), 10.51 (br, 1H, OH); MS: *m/z* 254 (M^+). Anal. Calcd. for $C_{14}H_{10}N_2OS$ (254.31): C, 66.12; H, 3.96; N, 11.02. Found: C, 66.07; H, 3.84; N, 10.85.

[1]Benzothieno[2,3(3,2)-f]indolizines (11) and (18). General Procedure.

A suspension of carboxaldehyde **6b** or **17** (1.3 g, 5.38 mmol) in polyphosphoric acid (15 g) was stirred under nitrogen at 90°C for 4 hours. After cooling, the solution was poured slowly into 100 ml of ice-water and the pH was adjusted to 5≈6 with 20% aqueous sodium hydroxide. The mixture was extracted with dichloromethane (3x40 ml) and the organic phase was worked up in the usual manner to give a green-brown solid. Recrystallization of the resulting solid from diethyl ether-hexane afforded indolizines **11** and **18**.

[1]Benzothieno[3,2-f]indolizine (11). This compound was obtained in a yield of 59%, mp 151°C (decomp); ^{1}H NMR ($CDCl_3$) δ: 6.38 (dd, 1H, J=1.8 and 3.6 Hz, H_1 pyrrole), 6.84 (dd, 1H, J=1.8 and 3.6 Hz, H_2 pyrrole), 7.22-7.26 (m, 2H, 2H BT (H_7 and H_8)), 7.38-7.41 (m, 1H, H_3 pyrrole), 7.47-7.56 (m, 2H, 1H BT (H_6) and H_{11}), 7.71-7.78 (m, 1H, 1H BT (H_9)), 8.58 (s, 1H, H_5). Anal. Calcd. for $C_{14}H_9NS$ (223.29): C, 75.31; H, 4.06; N, 6.27. Found: C, 75.07; H, 3.94; N, 6.09.

[1]Benzothieno[2,3-f]indolizine (18). This compound was obtained in a yield of 61%, mp 183°C (decomp); ^{1}H NMR ($CDCl_3$) δ: 6.35-6.41 (m, 1H, H_1 pyrrole), 6.86 (dd, 1H, J=1.4 and 2.8 Hz, H_2 pyrrole), 7.25-7.32 (m, 2H, 2H BT (H_8 and H_9)), 7.41-7.44 (m, 1H, H_3 pyrrole), 7.52-7.56 (m, 2H, 1H BT (H_{10}) and H_{11}), 7.58-7.61 (m, 1H, 1H BT (H_7)), 8.85 (s, 1H, H_5). Anal. Calcd. for $C_{14}H_9NS$ (223.29): C, 75.31; H, 4.06; N, 6.27. Found: C, 75.23; H, 3.89; N, 6.15.

General procedure for synthesis of [3,2,2]cyclazines 13 and 19.

To a solution of 1.2 g (5.37 mmol) of indolizine **11** or **18** in 20 ml of dry toluene was added 0.94 g (5.5 mmol) of diethyl acetylenedicarboxylate and the resulting mixture was refluxed for 6 hours. After cooling and concentration *in vacuo*, the yellow-brown residue was submitted to flash chromatography (silica gel; dichloromethane/hexane (2/3)) and led to cyclazines **13** and **19**.

1,2-Dicarbethoxy[1]benzothieno[2,3-h]cycl[3,2,2]azine (13). This product was obtained as a yellow powder after recystallization from dichloromethane/hexane (1/4) in a yield of 61%, mp 171°C (decomp); IR (KBr): ν 1708 and 1694 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.42-1.44 (m, 6H, $2CH_3$ (ester)), 4.44 (q, 2H, J=6.7 Hz, OCH_2 (ester)), 4.63 (q, 2H, J=6.7 Hz, OCH_2 (ester)), 7.15-7.38 (m, 2H, 2H BT (H_8 and H_9)), 7.42-7.58 (m, 1H, H_4), 7.68-7.95 (m, 2H, 2H BT (H_7 and H_{10})), 8.28-8.38 (m, 2H, H_3 and H_5). ^{13}C NMR ($CDCl_3$) δ: 14.2, 14.4, 61.1, 62.3, 110.5, 114.9, 116.4, 121.8, 121.9, 122.7, 125, 125.1, 125.3, 125.4, 127.1, 127.2, 130.7, 133.6, 136, 140.1, 163.8, 167.7; MS: *m/z* 391 (M^+). Anal. Calcd. for $C_{22}H_{17}NO_4S$ (391.44): C, 67.50; H, 4.38; N, 3.58. Found: C, 67.29; H, 4.31; N, 3.45.

1,2-Dicarbethoxy-3,4-dihydro[1]benzothieno[3,2-h]cycl[3,2,2]azine (19). This product was obtained as yellow crystals after recystallization from dichloromethane/hexane (1/6) in a yield of 63%, mp 177°C (decomp); IR (KBr): ν 1700 and 1693 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.37-1.40 (m, 6H, $2CH_3$ (ester)), 3.52-3.62 (m, 2H, $2H_4$), 4.26-4.33 (m, 4H, $2H_3$ and OCH_2), 4.51 (q, 2H, J=6.8 Hz, OCH_2 (ester)),

5.60-5.63 (m, 1H, H_5), 7.32-7.40 (m, 2H, 2H BT (H_7 and H_8)), 7.71-7.82 (m, 2H, 2H BT (H_6 and H_9)). ^{13}C NMR ($CDCl_3$) δ: 14.9, 15.3, 24.5, 33.1, 62.4, 63.8, 116.9 , 122.2, 122.9, 123.7, 124.3, 125, 125.8, 125.9, 127.9, 128.8, 130.1, 133.2, 136,8, 141.5, 161.9 , 165.2; MS: *m/z* 393 (M^+). Anal. Calcd. for $C_{22}H_{19}NO_4S$ (393.46): C, 67.16; H, 4.87; N, 3.56. Found: C, 67.08; H, 4.65; N, 3.33.

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