PYRROLO[2,1-*c*][1,4]BENZODIAZEPINES : SYNTHESIS OF *N*-SUBSTITUTED AMIDINES

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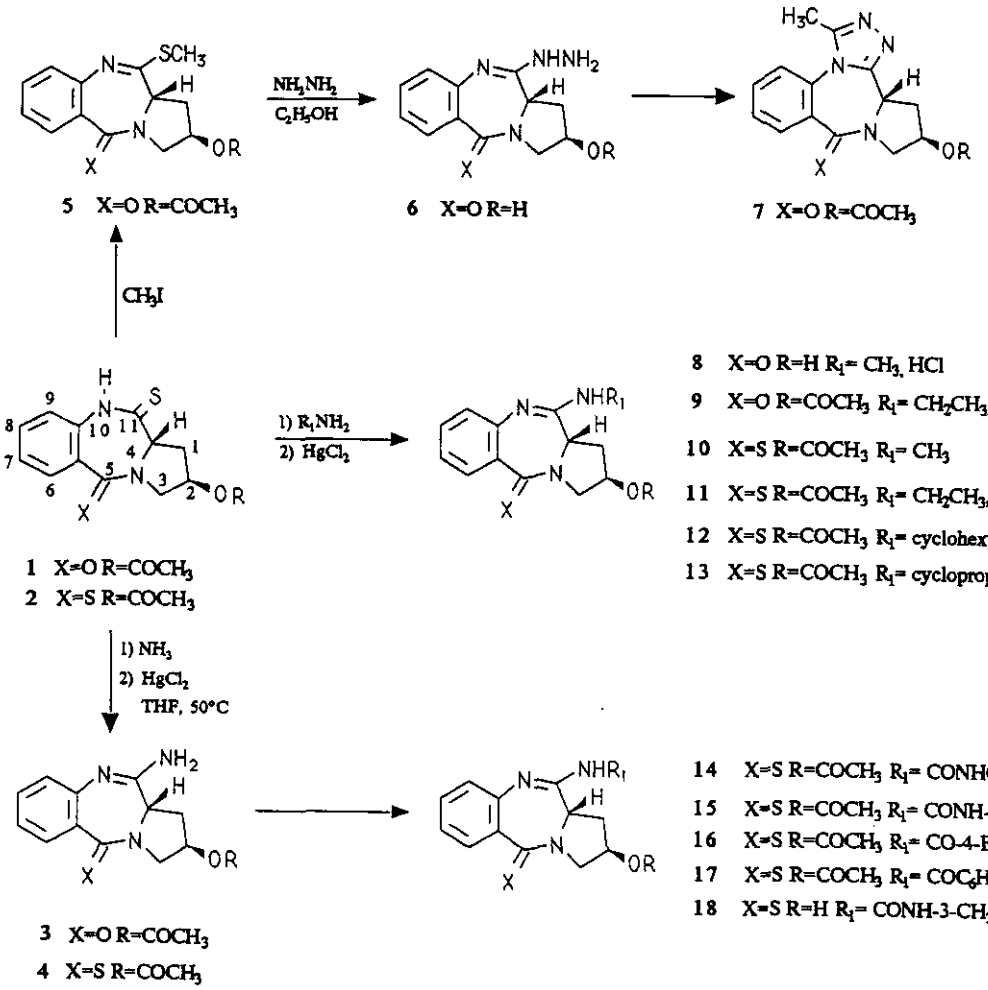
Abstract-Synthesis of *N*-substituted amidines derived from pyrrolo[2,1-*c*][1,4]-benzodiazepines is described.

The pyrrolo[2,1-*c*][1,4]benzodiazepines (PBD) such as anthramycin, tomaymycin, neothramycins A and B are thought to exert their antitumor activity[1] through a covalent binding via an aminal linkage from the electrophilic carbinolamine-bearing C-11-position to an N-2 of guanine within the minor grove of DNA.[2] Although several groups have demonstrated the lack of reactivity of the N-10-C-11 lactam moiety of PBD[3] it can be easily converted into thiolactam which appears to be more reactive.[4] We have recently demonstrated that in mild conditions the thiolactam (**1**) and dithiolactam (**2**) react with ammonia in the presence of mercuric chloride to give respectively the amidines (**3**) and (**4**).[5] This easy conversion prompted us to extend this reaction to hydrazine and primary amines. The thiolactam (**1**), dithiolactam (**2**) and iminothioether (**5**) are unreactive towards primary amines at boiling temperature. Nevertheless, hydrazine in boiling ethanol affords the hydrazidine (**6**). This reaction also resulted in the hydrolysis of the acetoxy protecting group in the C-2 position. Treatment of (**6**) with acetic anhydride conducts to the triazolopyrrolobenzodiazepine (**7**). The presence of mercuric chloride is required to enhance the reactivity of thiolactams (**1**) and (**2**) with primary aliphatic amines such as methyl-, ethyl-, cyclohexyl-, cyclopropylamines in dry THF to give *N*-substituted amidines. The typical experiment is as follows. A solution of thiolactam (**1**) or dithiolactam (**2**) in dry THF was warmed to 55°C, an excess of corresponding amines was added in the solution and 1.5 equivalent of mercuric chloride was incorporated in one portion. After the addition, the reaction mixture became black and was stirred for one hour. Mercuric sulfide was filtered off, THF was evaporated to dryness and the residue was extracted with ethyl acetate and the organic layer was washed with saturated aqueous solution of sodium thiosulfate to give the corresponding amidines (**8**, **9**, **10**, **11**, **12**, **13**) which may be transformed into their hydrochlorides by treatment with hydrochloric acid in 2-propanol at room temperature. In boiling 2-propanol this reaction resulted in the hydrolysis of the acetoxy protecting group (compound **8**). The amidines (**3**) and (**4**) are stable and react with isocyanate in boiling toluene to give ureas like (**14**) and (**15**) or with acid chloride in dry THF in the presence of TEA at room temperature to give amides like (**16**) and (**17**).

All the first attempts made with aromatic primary amines or secondary amines using the conditions described above are unsuccessfull. Biological evaluation of these amidines and related derivatives are in progress.

Scheme 1



5 X=O R=$COCH_3$

6 X=O R=H

7 X=O R=$COCH_3$

1 X=O R=$COCH_3$

2 X=S R=$COCH_3$

3 X=O R=$COCH_3$

4 X=S R=$COCH_3$

8 X=O R=H R_1= CH_3, HCl

9 X=O R=$COCH_3$ R_1= CH_2CH_3, HCl

10 X=S R=$COCH_3$ R_1= CH_3

11 X=S R=$COCH_3$ R_1= CH_2CH_3, HCl

12 X=S R=$COCH_3$ R_1= cyclohexyl

13 X=S R=$COCH_3$ R_1= cyclopropyl

14 X=S R=$COCH_3$ R_1= $CONHC_6H_5$

15 X=S R=$COCH_3$ R_1= CONH-3-CH_3-C_6H_4

16 X=S R=$COCH_3$ R_1= CO-4-F-C_6H_4

17 X=S R=$COCH_3$ R_1= COC_6H_5

18 X=S R=H R_1= CONH-3-CH_3-C_6H_4

Table 1 Spectroscopic and microanalytical data of compounds (6-18).

Compd No	Yield (%)	mp (°C) (Solvt of cryst.)	Ir (KBr) $\upsilon_{max}(cm^{-1})$	^{1}H Nmr (DMSO-d_6) δ ppm / TMS J (Hz)	Molecular Formula	Elemental analysis Found (%) (Required) C	H	N
6	72	158 (ethanol)	3460-3240 (OH,NH)	7.12-6.98 (m, Ar) 6.03 (NH) 5.04 (s, OH) 4.32 (s, H-2, H-11a) 3.66 (d, J=12.21, H-3a) 3.40 (dd, J=8.30 and 4.40, H-3b) 2.76 (m, H-1a) 1.87 (m, H1-b)				
7	80	200 (ether)	1730(C=O) 1630(C=O)	7.95-7.58 (m, Ar) 5.38 (s, H-2) 4.94 (m, H-11a) 3.75 (d, J=14.40, H-3a) 3.70 (dd, J=8.78 and 4.40, H-3b) 3.24 (m, H-1a) 2.50 (m, H-1b) 2.50 (s, CH_3) 2.02 (s, $OCOCH_3$)	$C_{16}H_{16}N_4O_3$	61.44 (61.53	5.16 5.16	17.71 17.93)
8	63	>260 (2-propanol)	3300-2860 (OH,NH) 1640(C=O)	11.62 (s, NH) 10.30 (s, NH) 7.84-7.51 (m,Ar) 4.58 (br s, H-2) 4.44 (br s, H-11a) 3.55 (m, H-3) 3.18 (s, CH_3) 2.88 (m, H-1a) 2.10 (m, H-1b)	$C_{13}H_{16}N_3O_2Cl$	55.61 (55.42	5.75 5.72	14.59 14.91)
9	60	216 (2-propanol)	3050(NH) 1740,1645(C=O)	11.72 (s, NH) 10.18 (s, NH) 7.87-7.46 (m, Ar) 5.31 (br s, H-2) 4.68 (br s, H-11a) 3.73 (m, H-3) 3.73 (m, CH_2) 3.10 (m, H-1) 2.02 (s, $OCOCH_3$) 1.26 (m, CH_3)	$C_{16}H_{20}N_3O_3Cl$	56.59 (56.88	6.10 5.96	12.12 12.43)
10	63	190 (ether/ petroleum ether)	3340(NH)	7.35 (s, NH) 8.04-6.96 (m, Ar) 5.37 (br s, H-2) 4.32 (m, H-11a) 4.16 (dd, J=14.40 and 6.60, H-3a) 3.86 (dd, J=14.40 and 5.15, H-3b) 3.31 (m, H-1a); 2.76(s, CH_3) 2.50 (m, H-1b) 2.05 (s, $OCOCH_3$)	$C_{15}H_{17}N_3O_2S$	59.53 (59.58	5.21 5.33	13.67 13.89)

11	67	178 (2-propanol)	3380-2730 (NH) 1730(C=O)	11.86(s, NH) 10.21 (s, NH) 8.12-7.40 (m, Ar) 5.43 (br s, H-2) 4.95 (m, H-11a) 4.30 (dd, J=15.21 and 6.84, H-3a) 3.85 (dd, J=14.15 and 5.37, H-3b) 3.70 (m, CH_2) 3.19 (m, H-1a) 2.60 (m, H-1b) 2.07 (s, $OCOCH_3$) 1.05 (t, J=6.84, CH_3)	$C_{16}H_{20}N_3O_2ClS$	54.05 (54.30	5.62 5.69	12.00 11.87)
12	61	180 (ether)	3400(NH) 1740(C=O)	8.04-6.95 (m, Ar) 6.77 (d, J=8.59, NH) 5.35 (br s, H-2) 4.33 (m, H-11a) 4.10 (dd, J=14.65 and 6.35, H-3a) 3.93 (dd, J=14.65 and 4.88, H-3b) 3.03 (m, H-1a) 2.50 (m, H-1b) 2.05 (s, $OCOCH_3$) 1.73-1.08 (m, cyclohexyl)	$C_{20}H_{25}N_3O_2S$	64.55 (64.66	6.76 6.78	11.20 11.31)
13	72	220 (2-propanol)	3380(NH) 1740(C=O)	8.08-6.96 (m, Ar) 7.20 (d, NH) 5.28 (m, H-2) 4.32 (d, J=28, H-11a) 4.12 (dd, J=12.60 and 6.84, H-3a) 3.90 (dd, J=14.40 and 5.37, H-3b) 2.83 (m, H-1a) 2.48 (m, H-1b) 2.00 (s, $OCOCH_3$) 0.76-0.5 (m,cyclopropyl)	$C_{17}H_{19}N_3O_2S$	62.20 (61.98	5.79 5.81	12.79 12.75)
14	40	226 (2-propanol)	3280(NH),1740 1640(C=O)	11.60 (s, NH) 9.80 (s, NH) 8.10-7.00 (m, Ar) 5.43 (br s, H-2) 4.80 (m, H-11a) 4.18 (dd, J=14.65 and 5.86, H-3a) 4.08 (dd, J=14.60 and 5.40, H-3b) 3.40 (m, H-1a) 2.30 (m, H-1b) 2.07 (s, $OCOCH_3$)	$C_{21}H_{20}N_4O_3S$	61.60 (61.74	5.00 4.93	13.70 13.71)
15	55	202 (2-propanol)	3280(NH),1740 1630(C=O)	11.60 (s, NH) 9.74 (s, NH) 8.10-6.80 (m, Ar) 5.40 (br s, H-2) 4.80 (m, H-11a) 4.21 (dd, J=14.40 and 6.84, H-3a) 4.03 (dd, J=14.35 and 5.85, H-3b) 3.33 (m, H-1a) 2.25 (m, H-1b) 2.28 (s, CH_3) 2.07 (s, $OCOCH_3$)	$C_{22}H_{22}N_4O_3S$	62.78 (62.54	5.25 5.24	13.09 13.26)

16	52	188 (ether)	3450(NH) 1730(C=O)	11.96 (s, NH) 8.30-7.28 (m, Ar) 5.54 (br s, H-2) 4.90 (m, H-11a) 4.26 (dd, J=14.40 and 6.58, H-3a) 4.00 (dd, J=14.40 and 5.86, H-3b) 3.30 (m, H-1a) 2.35 (m, H-1b) 2.07 (s, $OCOCH_3$)	$C_{21}H_{18}N_3O_3FS$	61.25 (61.30	4.22 4.09	10.23 10.21)
17	88	278 (ether / petroleum ether)	1735(C=0)	11.95 (s, NH) 8.23-7.30 (m, Ar) 5.55 (br s, H-2) 4.88 (d, J=7.31, H-11a) 4.25 (dd, J=14.16 and 6.35, H-3a) 3.99 (dd, J=14.20 and 5.86, H-3b) 3.39 (m, H-1a) 2.40 (m, H-1b) 2.07 (s, $OCOCH_3$)	$C_{21}H_{19}N_3O_3S$	64.26 (64.10	4.96 4.86	10.44 10.67)
18	92	206 (ether)	3320(NH) 1700(C=0)	11.80 (s, NH) 9.78 (s, NH) 8.18-6.85 (m, Ar) 4.54 (br s, H-2) 4.54 (br s, H-11a) 3.38 (m, H-3) 3.30 (m, H-1a) 2.54 (m, H-1c) 2.28 (s, CH_3)	$C_{20}H_{20}N_4O_2S$	63.19 (63.13	5.40 5.29	14.64 14.72)

EXPERIMENTAL

All melting points were measured by using a Köfler bank apparatus and were uncorrected. Infrared spectra were recorded on a Philips PU 9716 spectrophotometer. ^{1}H Nmr spectra were taken on a JEOL JNM-FX 200 in DMSO-d_6 solution using TMS as an internal standard.

(2R, 11aS)-2-Acetoxy-1,2,3,11a-tetrahydro-11-methylthio-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**5**)
To a stirred solution of the thiolactam (**1**) (2 g , 0.0069 mol) in tetrahydrofuran (50 ml) was added K_2CO_3 (2 g, 0.014 mol) and methyl iodide (1.84 g, 0.013 mol). The reaction mixture was stirred for 17 h at room temperature. The mixture was filtered and the filtrate was evaporated in vacuo. The resultant yellow oil was triturated with petroleum ether and the precipitate separated by filtration. The yellow solid was recrystallized from diethyl ether to give **5** (1.55 g, 75%).

(2R, 11aS)-11-Hydrazino-1,2,3,11a-tetrahydro-2-hydroxy-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**6**)
Hydrazine (5 ml, 0.10 mol) was added to a solution of the iminothioether (**5**) (1 g , 0.0032 mol) in ethanol (70 ml) and the reaction mixture was heated under reflux for 4 h. The solvent was then evaporated in vacuo and water (100 ml) was added to the residue. The white precipitate was filtered and recrystallized from ethanol to give **6** (0.58 g, 72%).

(3bS,5R)-5-Acetoxy-3b,4,5,6-tetrahydro-1-methyl-5*H*-[1,2,4]triazolo[4,3-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepin-8-one (**7**).

The hydrazino (**6**) (0.2 g , 0.87 mmol) in acetic anhydride (6 ml) was heated under reflux for 30 min. The solvent was removed by evaporation in vacuo and saturated aqueous solution of sodium hydrogen carbonate (20 ml) was added to the residue. The aqueous layer was extracted with chloroform (3x30 ml). The combined organic layers were dried ($CaCl_2$) and evaporated in vacuo to give a white solid which was recrystallized from diethyl ether to give **7** (0.2 g, 80%).

General procedure for the synthesis of the substituted amidines (**8**,**9**,**10**,**11**,**12** and **13**).

The corresponding thiolactam (**1**) (3.44 mmol) or dithiolactam (**2**) (3.26 mmol) was dissolved in dry tetrahydrofuran (50 ml) and warmed to 55°C. To this solution was added an excess of the corresponding amine (0.06 mol, 20 equivalents) followed by mercuric chloride (5.17 mmol, 1.5 equivalents). The reaction mixture became black and was stirred for 1 h and filtered and the filtrate was evaporated in vacuo. The residue was partitioned between ethyl acetate and saturated sodium thiosulfate solution. The organic layer was separated and washed successively with a saturated sodium thiosulfate solution and brine, dried (magnesium sulfate) and concentrated in vacuo. A solid was obtained for compounds (**10**,**12** and **13**) and were recrystallized from ether / petroleum ether, ether and 2-propanol respectively. For the others compounds an oil was obtained.For **9** and **11** , 2-propanol and hydrochloric acid were added at room temperature and the substituted amidine hydrochlorides were filtered and then recrystallized from 2-propanol. For the amidine (**8**), 2-propanol and aqueous hydrochloric acid were added and the solution heated under reflux for 30 min . After this time, the reaction mixture was cooled and the precipitate filtered and recrystallized from 2-propanol.

General procedure for the synthesis of the ureas (**14**, **15** and **18**).

To a suspension of the amidine (**4**) (3.45 mmol) in toluene (20 ml) was added the corresponding isocyanate (3.45 mmol, 1 equivalent). The reaction mixture was heated under reflux until a solution was obtained, the reflux was then continued for 30 min.

In the case of the phenylurea (**14**) a suspension was obtained towards the end of the reflux. The precipitate was filtered, washed with ether and recrystallized from 2-propanol to give **14** (40%). For the *m*-methylphenylurea (**15**), after 30 min of reflux the toluene was evaporated in vacuo and the solid residue washed with ether and recrystallized from 2-propanol (55%).

The urea (**15**) (0.71 mmol) was added to a solution of methanol (40 ml) with sodium (1.5 equivalents). The reaction mixture was stirred for 2 h at room temperature and the solvent evaporated in vacuo. The resultant solid was washed with water and recrystallized from ether to give the hydroxyurea (**18**) (92%).

General procedure for the synthesis of the amides (**16** and **17**).

To a cooled solution (0° C) of the amidine (**4**) (1.73 mmol) in tetrahydrofuran (15 ml) was added triethylamine (3.46 mmol, 2 equivalents) followed by a solution of the corresponding acid chloride (2.07 mmol,1.2 equivalents) in tetrahydrofuran (5 ml). The reaction mixture was allowed to attain room temperature and stirring was continued for 4 h. The reaction mixture was partitioned between dichloromethane and water and the organic layer separated. The aqueous layer was extracted twice more with dichloromethane and the combined organic layers were dried ($CaCl_2$), evaporation in vacuo gave a solid residue which was recrystallized from ether for the amide (**16**) (52%) and from ether / petroleum ether for the amide (**17**) (88%).

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Received, 5th June, 1992