8*H*-PYRAZOLO[5',1':2,3]PYRIMIDO[5,4-*d*][1,2]DIAZEPINE: A NEW TRICYCLIC SYSTEM

Fabrizio Bruni,* Barbara Cosimelli,[a] Annarella Costanzo, Gabriella Guerrini, and Silvia Selleri

Universita' di Firenze, Dipartimento di Scienze Farmaceutiche, Via Gino Capponi 9, 50121 Firenze and [a]Dipartimento di Chimica Organica e centro CNR sulla chimica e la struttura dei composti eterociclici e loro applicazioni, Via Gino Capponi 9, 50121 Firenze, Italy

Abstract- Starting from a series of 6-acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines (**2a-g**), several derivatives of the pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine system (**3a-g**) were obtained by reaction with hydrazine hydrate. Some compounds were finally alkylated at *N* -8 position.

Continuing our investigations on heterocyclic systems containing a pyrazole moiety, we recently synthesized some pyrazolo[1,5-*a*][1,3]diazepines and studied their action on the Central Nervous System (CNS).[1] We hereby report the synthesis of a series of 8*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepines.

This heterocyclic system contains a pyrazolo[1,5-*a*]pyrimidine moiety, some derivatives of which have been found to exert an interesting action on the CNS.[2] Moreover, the condensation of a 1,2-diazepine ring on the above structure led to a heterocyclic system which may be correlated to a series of 2,3- and 3,4-benzodiazepine derivatives.[3-6] We therefore thought it interesting to study the benzodiazepine (BDZ) receptor affinity of a number of derivatives of this tricyclic system and this report is part of an effort to define more precisely the structural requirements for BDZ binding specificity.[7]

A number of 2- or 3-substituted 6-acetyl-7-methylpyrazolo[1,5-*a*]pyrimidines (**1a-d**),[8] (**1e**),[9] (**1f-g**) (see experimental section) were used as starting materials. Their 7-methyl group is acidic enough to react with dimethylformamide dimethylacetal (DMF·DMA) to give a series of 7-dimethylaminovinyl derivatives (**2a-g**) in

moderate yield, following a procedure which has already been described.[8]

The resulting enamines (**2a-g**), which are useful intermediates in the synthesis of more complex systems, [8,10] react with hydrazine hydrate in acetic acid solution, undergoing an intramolecular cyclization. Analytical and spectral (ir and ^{1}H-nmr) data for all target molecules were in fact consistent with the structures of 2- or 3-substituted 6-methylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepines (**3a-g**).

Ir spectra exhibit a single band at 3400-3300 cm^{-1}, attributed to the NH stretching vibration ; the ^{1}H-nmr data of compounds (**3a-g**) are in good agreement with those reported for similar compounds. [8,10] In particular the ^{1}H-nmr spectrum of **3a** exhibits seven signals: the singlet of 6-CH_3 at δ 2.98, a broad singlet at δ 10.83 which exchanges with D_2O attributable to an NH group, a singlet at δ 8.67 due to H-5 and four doublets the assignements of which required a more detailed study. In fact the chemical shifts of H-3, H-10 and H-2, H-9 in $CDCl_3$ are very close as are their respective coupling constants. A homonuclear COSY experiment allowed us to put into relationship the doublet at δ 6.73 with that at δ 8.16 and the doublet at δ 6.56 with that at δ 7.72, but not to attribute the signals respectively. For this purpose we examined the C-H signals in the ^{13}C coupled spectrum, where, apart the only simple doublet attributable to the carbon atom in position five (C-5, δ 149.91), two of the remaining methine ring carbons appear as doublets of doublets and the other two as doublets of doublets of doublets. These latter (δ 105.39 and δ 130.03) change into doublets of doublets on treatment with D_2O, thus confirming a long range coupling with the NH proton.

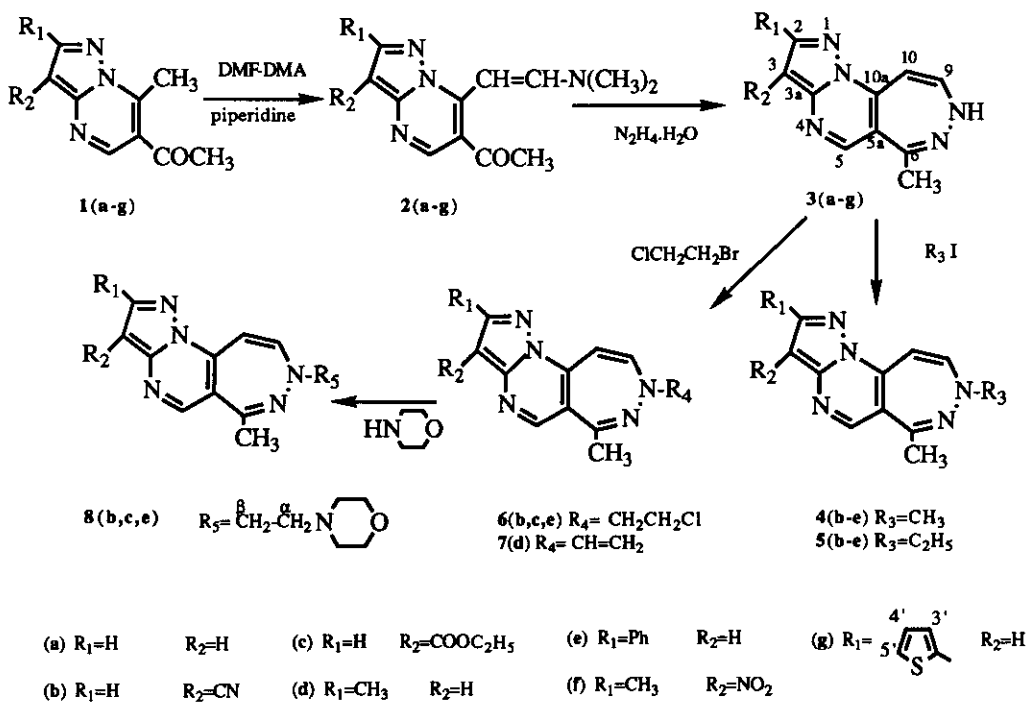
Therefore, on the basis of chemical shifts C-10 (δ 105.39) and C-9 (δ 130.03) have been identified. In a similar way the signals at δ 96.81 and δ 144.67 were attributed to C-3 and C-2, respectively. Finally, once the carbon resonances have been established the HETCOR spectrum allowed an unambiguous assignement of H-10, H-9 and H-3, H-2 signals.

To better correlate this new series of compounds with some 2,3-benzodiazepine derivatives,[11,12] we thought it interesting to introduce the analougous alkyl chains at *N* -8 position of pyrazolo [5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine system. The reaction was performed in anhydrous DMF solution and in the presence of K_2CO_3 (Method a) following a well-known procedure.[13] However, in some cases, this reaction proceeded too sluggishly; the substrates were therefore treated with alkyl iodides in the presence of NaH dispersion in anhydrous THF (Method b). Although the above alkylations gave moderate to low yields, no attempts at

optimization were made.

N -morpholinoethyl derivatives (**8b,c,e**) were prepared in a two-step procedure. First, compounds (**3b,c,e**) were alkylated with chlorobromoethane according to Method a, to give **6b,c,e**. In the same conditions **3d** reacted too slowly giving **7d** instead of the expected 8-(2-chloroethyl) derivative. The chloroethyl derivatives (**6b,c,e**) were in turn reacted with an excess of morpholine in methyl isobutyl ketone at reflux in the presence of KI to give the desired compound (**8b,c,e**).

Scheme



EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ir spectra were measured for nujol mulls with a Perkin Elmer 681 spectrophotometer. ^{1}H and ^{13}C nmr spectra were recorded with a Varian Gemini 200 instrument; chemical shifts are reported in ppm high frequency from tetramethylsilane as secondary reference standard and coupling constants in Hz. Silica gel plates (Merck F_{254}) were used for analytical tlc. Solvents were removed under reduced pressure. Compounds (**1a-d**) and (**2a-d**) were obtained as

reported in Ref. 8.

6-Acetyl-2,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (**1f**).

3-Ethoxymethylenepentane-2,4-dione[14] (3.74 g; 24 mmol) was added to a solution of 3-methyl-4-nitro-5-aminopyrazole[15] (2.84 g; 20 mmol) in ethanol (100 ml) . The mixture was refluxed under magnetic stirring for 1 h. On cooling a yellow precipitate separates out (3.95 g, 71%).

Yellow crystals (EtOH), mp 204-205 °C. Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.30; H, 4.31; N, 24.02. Ir ν_{max}: 1690 (CO) cm^{-1}. ^1H Nmr ($CDCl_3$) δ ppm: 2.75 (s, 3H, $COCH_3$), 2.84 (s, 3H, 2-CH_3), 3.18 (s, 3H, 7-CH_3), 9.20 (s, 1H, H-5).

6-Acetyl-2-thienylpyrazolo[1,5-*a*]pyrimidine (**1g**).

Operating as above, 3-(2-thienyl)-5-aminopyrazole[16] (4.95 g; 30 mmol) and 3-ethoxymethylenepentane-2,4-dione[11] (5.6 g; 48 mmol) in ethanol (100 ml), afforded compound (**1g**) as yellow solid (2.74 g, 32%).

Yellow crystals (EtOH), mp 221-222 °C. Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.30; N, 16.33. Found: C, 60.69; H, 4.50; N, 16.44. Ir ν_{max}: 1670 (CO) cm^{-1}. ^1H Nmr ($CDCl_3$) δ ppm: 2.69 (s, 3H, $COCH_3$), 3.19 (s, 3H, 7-CH_3), 6.92 (s, 1H, H-3), 7.16 (dd, $J_{H4'-H5'}$= 4.9 Hz and $J_{H4'-H3'}$= 3.5 Hz, 1H, H-4'), 7.43 (dd, $J_{H5'-H4'}$= 4.9 Hz and $J_{H5'-H3'}$= 1.1 Hz, 1H, H-5'), 7.63 (dd, $J_{H4'-H3'}$= 3.5 Hz and $J_{H5'-H3'}$= 1.1 Hz, 1H, H-3'), 8.82(s, 1H, H-5).

General procedure for the preparation of compounds (**2e-g**).

Dimethylformamide dimethylacetal (1.43 g; 12 mmol) was added at 80-90 °C to a suspension of (**1e**)[10] or (**1f-g**) (10 mmol) in anhydrous toluene (100 ml). A small amount of piperidine (0.5 ml) was added as a catalyst. The mixture was heated and magnetically stirred for 4 h. Evaporation *in vacuo* left a residue which was recovered with a little ethanol and filtered.

i) 6-Acetyl-7-(2-dimethylaminovinyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (**2e**)

Yellow crystals (EtOAc/cyclohexane), (2.61 g, 66%), mp 183-184 °C. Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.56;

H, 5.92; N, 18.28. Found: C,70.51; H, 5.99; N, 18.41.^{1}H Nmr ($CDCl_3$) δ ppm: 2.67 (s, 3H, $COCH_3$), 3.12 (s, 3H, N-CH_3), 3.34 (s, 3H, N-CH_3), 6.83 (s, 1H, H-3), 7.27-7.48 (m, 4H: 3H, ArH_3 and 1H, C<u>H</u>CHN$(CH_3)_2$), 7.96-8.01 (m, 2H, ArH_2), 8.74 (s, 1H, H-5), 10.01 (d, J_{trans}= 12.4 Hz, 1H, CHC<u>H</u>N$(CH_3)_2$). ^{1}H Nmr (DMSO-d_6) δ ppm: 2.67 (s, 3H, $COCH_3$), 3.12 (s, 3H, NCH_3), 3.34 (s, 3H, NCH_3), 6.65 (s, 1H, H-3), 6.93 (d, J_{trans}=12.5 Hz, 1H, C<u>H</u>CHN$(CH_3)_2$), 7.15-7.35 (m, 3H, ArH_3), 7.65-7.75 (m, 2H, ArH_2), 8.45 (s, 1H, H-5), 9.56 (d, J_{trans}=12.5 Hz, 1H, CHC<u>H</u>N$(CH_3)_2$).

ii) <u>6-Acetyl-7-(2-dimethylaminovinyl)-2-methyl-3-nitropyrazolo[1,5-*a*]pyrimidine</u> (**2f**).

Yellow crystals (EtOH), (2.49 g, 86.4%), mp 246-247 °C. Anal. Calcd for $C_{13}H_{15}N_5O_3$: C, 53.97; H, 5.22; N, 24.21. Found: C, 53.91; H, 5.25; N, 24.39. ^{1}H Nmr ($CDCl_3$) δ ppm: 2.67 (s, 3H, $COCH_3$), 2.78 (s, 3H, 2-CH_3), 3.17 (s, 3H, N-CH_3), 3.38 (s, 3H, N-CH_3), 7.27 (d, J_{trans}=12.4 Hz, 1H, C<u>H</u>CHN$(CH_3)_2$), 9.01(s, 1H, H-5), 9.90 (d, J_{trans}=12.4 Hz, 1H, CHC<u>H</u>N$(CH_3)_2$).

iii) <u>6-Acetyl-7-(2-dimethylaminovinyl)-2-thienylpyrazolo[1,5-*a*]pyrimidine (2g)</u>.

Yellow crystals (EtOH), (2.12 g, 52%), mp 164-165 °C . Anal. Calcd for $C_{16}H_{16}N_4OS$: C, 61.51; H, 5.16; N, 17.93. Found: C, 61.43; H, 5.28; N, 18.07. ^{1}H Nmr ($CDCl_3$) δ ppm: 2.65 (s, 3H, $COCH_3$), 3.10 (s, 3H, N-CH_3), 3.33 (s, 3H, N-CH_3), 6.70 (s, 1H, H-3), 7.13 (dd, $J_{H4'-H5'}$= 4.8 Hz and $J_{H4'-H3'}$= 3.7 Hz, 1H, H-4'), 7.31 (d, J_{trans}=10.9 Hz, 1H, C<u>H</u>CHN$(CH_3)_2$), 7.36 (dd, $J_{H5'-H4'}$= 4.8 Hz and $J_{H5'-H3'}$= 1.1 Hz, 1H, H-5'), 7.53 (dd, $J_{H3'-H4'}$ = 3.7 Hz and $J_{H3'-H5'}$= 1.1 Hz, 1H, H-3'), 8.71 (s, 1H, H-5), 9.93 (d, J_{trans}= 10.9 Hz, 1H, CHC<u>H</u>N$(CH_3)_2$).

<u>General procedure for the preparation of compounds</u> (**3a-g**).

Hydrazine hydrate (0.60 g; 12 mmol) was added to a solution of 6-acetyl-7-dimethylaminovinylpyrazolo[1,5-*a*]pyrimidine (**2a-g**) (10 mmol) dissolved in glacial acetic acid (200 ml). The solution was magnetically stirred and refluxed for 2 h. At this time the reaction was judged completed by monitoring the disappearance of starting materials by tlc analysis ($CHCl_3$-MeOH 5:1 v/v as eluant). The new materials were coloured and very impure. Several recrystallizations using charcoal for clarification were needed to obtain pure samples.

i) 6-Methyl-8*H*-pyrazolo[5',1' :2,3]pyrimido[5,4-*d*][1,2]diazepine (**3a**).

Evaporation of the red solution left a residue which was recovered with ether and filtered.

Yellow crystals (H_2O), (0.74 g, 40%), mp 183-184 °C. Anal. Calcd for $C_{10}H_9N_5$: C, 60.28; H, 4.55; N, 35.15. Found: C, 60.40; H, 4.62; N, 34.98. ^{1}H Nmr (DMSO-d$_6$) δ ppm: 2.95 (s, 3H, 6-CH_3), 6.73 (d, J_{H10-H9}= 2.2 Hz, lH, H-10), 6.77 (d, J_{H3-H2}= 2.2 Hz, 1H, H-3), 7.90 (d, J_{H2-H3}=2.2 Hz, lH, H-2), 8.26 (d, J_{H9-H10}= 2.2 Hz, lH, H-9), 8.73 (s, 1H, H-5), 13.25 (br s, exch., 1H, NH). ^{1}H Nmr ($CDCl_3$) δ ppm: 2.98 (s, 3H, 6-CH_3), 6.56 (d, J_{H10-H9}= 2.3 Hz, lH, H-10), 6.73 (d, J_{H3-H2}= 2.2 Hz, lH, H-3), 7.72 (d, J_{H9-H10}= 2.3 Hz, lH, H-9), 8.16 (d, J_{H2-H3}=2.2 Hz, lH, H-2), 8.67 (s, lH, H-5), 10.83 (br s, exch., 1H, NH). ^{13}C Nmr (DMSO-d$_6$) δ ppm: 15.00 (q, ^{1}J= 131 Hz, 6-CH_3), 96.81 (dd, ^{1}J= 181 Hz, $^2J_{C3-H2}$= 10.0 Hz, C-3), 105.39 (ddd, ^{1}J= 175 Hz, $^2J_{C10-H9}$= 9.0 Hz, $^3J_{C10-NH}$= 4.0 Hz, C-10), 114.38 (m, C-5a), 130.03 (ddd, appears as doublet of pseudo triplet, ^{1}J= 187 Hz, $^2J_{C9-H10}$= 8.6 Hz, $^2J_{C9-NH}$= 8.5 Hz, C-9), 143.23 (m, C-10a*), 144.67 (dd, ^{1}J= 185 Hz, $^2J_{C2-H3}$= 5.4 Hz, C-2), 145.44 (m, C-3a*), 147.32 (dq, appears as quintet, $^2J_{C6-CH3}$= 6.9 Hz, $^3J_{C6-H5}$= 6.9 Hz, C-6), 149.91 (d, ^{1}J= 184 Hz, C-5)

* Attribution may be reversed.

ii) 6-Methyl-8*H*-pyrazolo[5',1' :2,3]pyrimido[5,4-*d*][1,2]diazepine-3-carbonitrile (**3b**).

This substance crystallized from the mother liquors. Purification was accomplished by several recrystallizations from acetic acid, affording light pink crystals.

Pink crystals (AcOH), (1.79 g, 75%), mp 240-241 °C. Anal. calcd for $C_{11}H_8N_6$: C, 58.92; H, 3.59; N, 37.46. Found: C, 58.95; H, 3.52; N, 37.49. ^{1}H Nmr (DMSO-d$_6$) δ ppm: 3.03 (s, 3H, 6-CH_3), 6.82 (d, J_{H10-H9}= 2.5 Hz, lH, H-10), 7.96 (d, J_{H9-H10}= 2.5 Hz, lH, H-9), 8.85 (s, 1H, H-2), 9.06 (s, lH, H-5), 13.30 (br s, exch., 1H, NH).

iii) Ethyl 6-methyl-8*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine-3-carboxylate (**3c**).

Evaporation of the reaction solvent left a residue, which was purified by several recrystallizations, using charcoal for clarification.

White crystals (EtOH), (1.51 g, 57%), mp 237-238 °C. Anal. Calcd for $C_{13}H_{13}N_5O_2$: C, 57.55; H, 4.82; N,

25.81. Found: C, 57.52; H, 4.88; N, 25.82. ^{1}H Nmr ($CDCl_3$) δ ppm: 1.44 (t, J= 7.1 Hz, 3H, OCH_2CH_3), 3.04 (s, 3H, 6-CH_3), 4.47 (q, J= 7.1 Hz, 2H, OCH_2CH_3), 6.61 (d, J_{H10-H9}= 2.3 Hz, 1H, H-10), 7.76 (d, J_{H9-H10}= 2.3 Hz, 1H, H-9), 8.62 (s, 1H, H-2), 8.97 (s, 1H, H-5).

iv) 2,6-Dimethyl-8*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine (**3d**).

The residue from evaporation of the mother liquor was treated with water and evaporated again *in vacuo* to a small volume. A red crystalline precipitate separated out. The filtered solid was air-dried and dissolved in $CHCl_3$ (300 ml), then treated with silica gel until a yellow solution was obtained. Evaporation of $CHCl_3$ afforded a solid which was purified by recrystallization from 70% EtOH.

Yellow crystals ($EtOH/H_2O$), (0.8 g, 40%), mp 219-220 °C. Anal. Calcd for $C_{11}H_{11}N_5$: C, 61.90; H, 5.20; N, 32.84. Found: C, 61.77; H, 5.25; N, 32.81. ^{1}H Nmr ($CDCl_3$) δ ppm: 2.56 (d, J_{CH3-H3}= 0.5 Hz, 3H, 2-CH_3), 2.95 (s, 3H, 6-CH_3), 6.52 (d, J_{H3-CH3}= 0.5 Hz, 1H, H-3), 6.55 (d, J_{H10-H9}= 2.4 Hz, 1H, H-10), 7.71 (d, J_{H9-H10}= 2.4 Hz, 1H, H-9), 8.59 (s, 1H, H-5).

v) 6-Methyl-2-phenyl-8*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*] [1,2]diazepine (**3e**).

The reaction solvent was concentrated *in vacuo* and water was added. The precipitate formed was purified by several recrystallizations, using charcoal for clarification.

Pink crystals ($EtOH/H_2O$), (1.86 g, 68%), mp 265-266 °C. Anal. Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.75; N, 25.43. Found: C, 69.78; H, 4.88; N, 25.27. ^{1}H Nmr ($CDCl_3$) δ ppm: 3.04 (s, 3H, 6-CH_3), 6.59 (d, J_{H10-H9}= 2.4 Hz, 1H, H-10), 7.02 (s, 1H, H-3), 7.38-7.50 (m, 3H, ArH_3), 7.72 (d, J_{H9-H10}= 2.4 Hz, 1H, H-9), 8.02-8.07 (m, 2H, ArH_2), 8.65 (s, 1H, H-5).

vi) 2,6-Dimethyl-3-nitro-8*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine (**3f**) .

Bright red crystals ($EtOH/H_2O$), (1.23 g, 48%), mp 274-275 °C. Anal. Calcd for $C_{11}H_{10}N_6O_2$: C, 51.16; H, 3.90; N, 32.54. Found: C, 51.08; H, 3.92; N, 32.33. ^{1}H Nmr (DMSO-d_6) δ ppm: 2.70 (s, 3H, 2-CH_3), 3.05 (s, 3H, 6-CH_3), 6.81 (d, J_{H10-H9}= 2.6 Hz, 1H, H-10), 7.95 (d, J_{H9-H10}= 2.6 Hz, 1H, H-9), 9.18 (s, 1H, H-5), 13.40 (br s, exch., 1H, NH).

vii) 6-Methyl-2-thienyl-8*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine (3g).

The reaction solvent was concentrated *in vacuo* and a filtrable solid was obtained, which was purified by recrystallization from ethanol.

White crystals (EtOH), (1.47 g, 52.7%), mp 262-263 °C. Anal. Calcd for $C_{14}H_{11}N_5S$: C, 59.76; H, 3.94; N, 24.89. Found: C, 59.84; H, 4.03; N, 24.77. ^{1}H Nmr ($CDCl_3$) δ ppm: 3.02 (s, 3H, 6-CH_3), 6.58 (d, J= 2.3 Hz, 1H, H-10), 6.91 (s, 1H, H-3), 7.13 (dd, $J_{H4'-H3'}$= 3.6 Hz, $J_{H4'-H5'}$= 5.0 Hz, 1H, H-4'), 7.38 (dd, $J_{H5'-H4'}$= 5.0 Hz, $J_{H5'-H3'}$= 1.1 Hz 1H, H-5'), 7.60 (dd, $J_{H3'-H4'}$= 3.6 Hz, $J_{H3'-H5'}$= 1.1 Hz, 1H, H-3'), 7.78 (d, J= 2.3 Hz, 1H, H-9), 8.64 (s, 1H, H-5), 15.07 (s, exch., 1H, NH).

Alkylation of 8*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepines.

Method a: A solution of the diazepine (10 mmol) in anhydrous DMF (30 ml) was treated with methyl or ethyl iodide or with 1-bromo-2-chloroethane, in the presence of anhydrous K_2CO_3 (molecular ratio 1:1:1). The course of the reaction was monitored by tlc analysis up to disappearance of the starting material ($CHCl_3$-MeOH 5:1 v/v as eluant). The solvent was removed *in vacuo* and the residue recovered with $CHCl_3$ (250 ml) and treated with silica gel up to clarification of the dark solution. After filtration the chloroform was evaporated leaving a solid residue.

Method b: A suspension of 50% NaH in mineral oil was magnetically stirred in anhydrous THF (20 ml) and heated at 55°C. After 15 min the diazepine (2 mmol) and methyl or ethyl iodides were added in one portion. The molecular ratio of diazepine: alkyl iodide: NaH was 1: 1.5:1.8.

The course of the reaction was monitored by tlc analysis and the alkylation often lasted about 8 h. Evaporation of the solvent left a gummy residue which was triturated with a little ethanol and filtered.

i) 6,8-Dimethylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine-3-carbonitrile (**4b**) .

White crystals (EtOH), (1.07 g, 45%), mp 198-199 °C. Method a. Anal. Calcd for $C_{12}H_{10}N_6$: C, 60.56; H, 4.29; N, 34.61. Found: C, 60.49; H,4.23 ; N, 35.07 . ^{1}H Nmr ($CDCl_3$) δ ppm: 3.00 (s, 3H, 6-CH_3), 3.99 (s, 3H, N-CH_3), 6.49 (d, J_{H10-H9} = 2.5 Hz, lH, H-10), 7.50 (d, J_{H9-H10}= 2.5 Hz, lH, H-9), 8.40 (s, 1H, H-2), 8.85 (s, 1H, H-5).

ii) Ethyl 6,8-dimethylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1 ,2]diazepine-3-carboxylate (**4c**) .

White crystals (EtOH), (1.05 g, 37%), mp 163-164 °C. Method a. Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.90; H, 5.29 ; N, 24.54. Found: C, 58.87; H, 5.26; N, 24.38. ^{1}H Nmr ($CDCl_3$) δ ppm: 1.38 (t, J= 7.1 Hz, 3H, OCH_2CH_3), 3.00 (s, 3H, 6-CH_3), 3.98 (s, 3H, N-CH_3), 4.43 (q, J= 7.1 Hz, 2H, OCH_2CH_3), 6.46 (d, J_{H10-H9}= 2.3 Hz, l H, H-10), 7.48 (d, J_{H9-H10}= 2.3 Hz, lH, H-9), 8.58 (s, 1H, H-2), 8.90 (s, lH, H-5).

iii) 2,6,8-Trimethylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine (**4d**) .

White crystals (H_2O), (0.9 g, 40%), mp 164-165 °C. Method b. Anal. Calcd for $C_{12}H_{13}N_5$: C, 63.41; H, 5.76; N, 30.81. Found: C, 63.05; H, 5.71; N, 30.46. ^{1}H Nmr (DMSO-d_6) δ ppm: 2.41 (s, 3H, 2-CH_3), 2.90 (s, 3H, 6-CH_3), 3.90 (s, 3H, N-CH_3), 6.52 (s, lH, H-3), 6.69 (d, J_{H10-H9}= 2.5 Hz, lH, H-10), 7.88 (d, J_{H9-H10}= 2.5 Hz, lH, H-9), 8.65 (s, lH, H-5).

iv) 6,8-Dimethyl-2-phenylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine (**4e**) .

Pink crystals (EtOH/H_2O), (1.27 g, 44%), mp 149-150 °C. Method b. Anal. Calcd for $C_{17}H_{15}N_5$: C, 70.56; H, 5.22; N, 24.20. Found: C, 70.75; H, 5.25; N, 24.00. ^{1}H Nmr (DMSO-d_6) δ ppm: 3.05 (s, 3H, 6-CH_3), 3.98 (s, 3H, N-CH_3), 6.72 (d, J_{H10-H9}= 2.5 Hz, lH, H-10), 7.25 (s, lH, H-3), 7.42-7.60 (m, 3H, ArH_3), 7.90 (d, J_{H9-H10}= 2.5 Hz, lH, H-9), 8.10-8.19 (m, 2H, ArH_2), 8.78 (s, lH, H-5).

v) 8-Ethyl-6-methylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine-3-carbonitrile (**5b**) .

White crystals (cyclohexane), (1.71 g, 68%), mp 162-163 °C. Method b. Anal. Calcd for $C_{13}H_{12}N_6$: C, 61.89; H, 4.79; N, 33.31. Found: C, 61.79; H, 4.88; N, 33.48. ^{1}H Nmr (DMSO-d_6) δ ppm: 1.50 (t, J= 6.5 Hz, 3H, NCH_2CH_3), 3.10 (s, 3H, 6-CH_3), 4.28 (q, J= 6.5 Hz, 2H, NCH_2CH_3), 6.85 (d, J_{H10-H9}= 2.5 Hz, lH, H-10), 8.00 (d, J_{H9-H10}= 2.5 Hz, lH, H-9), 8.85 (s, 1H, H-2), 9.10 (s, 1H, H-5).

vi) Ethyl 8-ethyl-6-methylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine-3-carboxylate (**5c**) .

White crystals (cyclohexane), (1.19 g, 40%), mp 104-105 °C. Method a. Anal. Calcd for $C_{15}H_{17}N_5O_2$: C, 60.18; H, 5.72; N, 23.39. Found: C, 59.86; H, 5.60; N, 23.07. ^{1}H Nmr ($CDCl_3$) δ ppm: 1.43 (t, J= 7.1 Hz,

3H,OCH_2CH_3), 1.57 (t, J= 7.0 Hz, 3H, NCH_2CH_3), 3.05 (s, 3H, 6-CH_3), 4.27 (q, J= 7.0 Hz, 2H,NCH_2CH_3), 4.45 (q, J= 7.1 Hz, 2H, OCH_2CH_3), 6.49 (d, J_{H10-H9}= 2.3 Hz, lH, H-10), 7.53 (d, J_{H9-H10}= 2.3 Hz, lH, H-9), 8.59 (s, 1H, H-2), 8.94 (s, lH, H-5).

vii) 2,6-Dimethyl-8-ethylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine (**5d**) .

White crystals (H_2O), (0.77 g, 32%), mp 120-121 °C. Method b. Anal. Calcd for $C_{13}H_{15}N_5$: C, 64.70; H, 6.22; N, 29.01. Found: C, 64.60; H, 6.24; N, 28.82. ^1H Nmr (DMSO-d_6) δ ppm: 1.44 (t, J= 6.9 Hz, 3H, NCH_2CH_3); 2.50 (s, 3H, 2-CH_3); 2.95 (s, 3H, 6-CH_3); 4.25 (q, J= 6.9 Hz, 2H, NCH_2CH_3); 6.56 (s, 1H, H-3); 6.70 (d, J_{H10-H9}= 2.5 Hz, lH, H-10); 7.92 (d, J_{H9-H10}= 2.5 Hz, lH, H-9); 8.68 (s, 1H, H-5).

viii) 8-Ethyl-6-methyl-2-phenylpyrazolo[5',1':2,3]pvrimido[5,4-*d*][1,2]diazepine (**5e**) .

White crystals (H_2O/iPrOH), (0.99 g, 33%), mp 98-99 °C. Method b. Anal. Calcd for $C_{18}H_{17}N_5$: C, 71.26; H, 5.64; N, 23.08. Found: C, 71.06; H, 5.65; N, 22.93. ^1H Nmr (DMSO-d_6) δ ppm: 1.45 (t, J= 6.9 Hz, 3H, NCH_2CH_3), 3.05 (s, 3H, 6-CH_3), 4.25 (q, J= 6.9 Hz, 2H, NCH_2CH_3), 6.71(d, J_{H10-H9}= 2.5 Hz, lH, H-10), 7.28 (s, 1H, H-3), 7.42-7.58 (m, 3H, ArH_3), 7.93 (d, J_{H9-H10}= 2.5 Hz, lH, H-9), 8.10-8.19 (m, 2H, ArH_2), 8.78 (s, 1H, H-5).

ix) 6-Methyl-8-(2-chloroethyl)pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine-3-carbonitrile (**6b**)

Light yellow crystals (EtOH), (1.51 g, 54%), mp 172-173 °C. Method a. Anal. Calcd for $C_{13}H_{11}N_6Cl$: C, 54.45; H, 3.86; N, 29.31. Found: C, 54.39; H, 3.87; N, 29.37. ^1H Nmr ($CDCl_3$) δ ppm: 3.06 (s, 3H, 6-CH_3), 3.95-3.97 (m, 2H, NCH_2CH_2Cl*), 4.45-4.55 (m, appears as doublet of triplet, 2H, NCH_2CH_2Cl*), 6.54 (d, J_{H10-H9} =2.5 Hz, lH, H-10), 7.64 (d, J_{H9-H10}= 2.5 Hz, lH, H-9), 8.41 (s, 1H, H-2), 8.91 (s, 1H, H-5).

*Attribution may be reversed.

x) Ethyl 6-methyl-8-(2-chloroethyl)pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine-3-carboxylate (**6c**)

Light yellow crystals (EtOH),(1.73 g, 52%), mp 159-160 °C. Method a. Anal. Calcd for $C_{15}H_{16}N_5O_2Cl$: C,

53.97; H, 4.83; N, 20.98. Found: C, 53.98; H, 4.86; N, 20.91. ^{1}H Nmr ($CDCl_3$) δ ppm: 1.43 (t, J= 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 3.10 (s, 3H, 6-CH_3), 3.96 (t, 2H, J= 5.2 Hz, $NC\underline{H}_2CH_2Cl$*), 4.39-4.54 (m, 4H: 2H, $OC\underline{H}_2CH_3$ and 2H, $NCH_2C\underline{H}_2Cl$*), 6.52 (d, $J_{H10\text{-}H9}$= 2.6 Hz, 1H, H-10), 7.62 (d, $J_{H9\text{-}H10}$= 2.6 Hz, 1H, H-9), 8.59 (s, 1H, H-2), 8.93 (s,1H, H-5).

*Attribution may be reversed.

xi) 6-Methyl-2-phenyl-8-(2-chloroethyl)pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine (**6e**)

White crystals (EtOH/H_2O), (0.87 g, 64%), mp 141-142 °C. Method a. Anal. Calcd for $C_{18}H_{16}N_5Cl$: C, 63.99; H, 4.77; N, 20.73. Found: C, 63.86; H, 4.85; N, 20.38. ^{1}H Nmr (DMSO-d_6) δ ppm: 3.05 (s, 3H, 6-CH_3), 3.95-4.13 (m, appears as doublet of triplet, 2H, $NC\underline{H}_2CH_2Cl$*), 4.56-4.67 (m, 2H, $NCH_2C\underline{H}_2Cl$*), 6.79 (d, $J_{H10\text{-}H9}$= 2.6 Hz, 1H, H-10), 7.31 (s, 1H, H-3), 7.48-7.53 (m, 3H, ArH_3), 8.01 (d, $J_{H9\text{-}H10}$= 2.6 Hz, 1H, H-9), 8.10-8.13 (m, 2H, ArH_2), 8.77 (s, 1H, H-5).

*Attribution may be reversed.

xii) 2,6-Dimethyl-8-vinylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepine (**7d**).

Colorless needles (cyclohexane), (0.26 g, 11%), mp 99-100 °C. Method a. Anal. Calcd for $C_{13}H_{15}N_5$: C, 65.25; H, 5.47; N, 29.27. Found: C, 65.27; H, 5.39; N, 28.96. ^{1}H Nmr (DMSO-d_6) δ ppm: 2.98 (s, 3H, 2-CH_3), 3.34 (s, 3H, 6-CH_3), 4.94 (d, J_{cis} =8.5 Hz, 1H,CH=$C\underline{H}_2$), 5.69 (d, J_{trans} =15.8 Hz, 1 H, CH=$C\underline{H}_2$), 6.58 (s, 1H, H-3), 6.92 (d, $J_{H10\text{-}H9}$= 2.5 Hz, 1 H, H-10), 7.34 (dd, 1H, J_{cis}= 8.5 Hz, J_{trans}= 15.8 Hz, $C\underline{H}$=CH_2), 8.24 (d, $J_{H9\text{-}H10}$= 2.5 Hz, 1H, H-9), 8.72 (s, 1H, H-5).

Reaction of **6b,c,e** with morpholine

Compounds (**6b,c,e**) (2 mmol) were dissolved in an excess of methyl isobutyl ketone (100 ml) and treated with morpholine (1.13 g; 13 mmol) and anhydrous K_2CO_3 (0.27 g; 2 mmol). A small amount (0.5 g; 3 mmol) of KI was also added. The mixture was refluxed under magnetic stirring for 72 h. When the reaction was over, as judged by the disappearance of starting materials by tlc analysis, the solvent was removed leaving a gum which crystallized upon standing to a yellowish product.

i) N-{2-[3-Cyano-6-methylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepin-8-yl]ethylen}morpholine (**8b**).

Light yellow crystals (EtOH), (0.33 g, 55 %), mp 132-133 °C. Anal. Calcd for $C_{17}H_{19}N_7O$: C, 60.52; H, 5.67; N, 29.05. Found: C, 60.32; H, 5.53; N, 28.76. ^{1}H Nmr ($CDCl_3$) δ ppm: 2.49 (m, 4H, CH_2NCH_2), 2.85 (t, J= 6.8 Hz, 2H, α-CH_2), 3.00 (s, 3H, 6-CH_3), 3.68 (m, 4H, CH_2OCH_2), 4.31 (t, J= 6.8 Hz, 2H, β-CH_2), 6.48 (d, J_{H10-H9} = 2.5 Hz, lH, H-10), 7.60 (d, J_{H9-H10} = 2.5 Hz, lH, H-9), 8.37 (s, 1H, H-2), 8.88 (s, 1H, H-5).

ii) N-{2-[3-Ethoxycarbonyl-6-methylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepin-8-yl]ethylen}morpholine (**8c**).

Light yellow crystals (EtOH), (0.31 g, 41%), mp 158-159 °C. Anal. Calcd for $C_{19}H_{24}N_6O_3$: C, 59.36; H, 6.29; N, 21.86. Found: C, 59.08; H, 6.35; N, 21.91. ^{1}H Nmr ($CDCl_3$) δ ppm: 1.42 (t, J =7.1 Hz, 3H, OCH_2CH_3), 2.52 (m, 4H, CH_2NCH_2), 2.87 (t, J= 6.5 Hz, 2H, α-CH_2), 3.04 (s, 3H, 6-CH_3), 3.71 (m, 4H, CH_2OCH_2), 4.33 (t, J= 6.5 Hz, 2H, β-CH_2), 4.45 (q,J =7.1 Hz, 2H, OCH_2CH_3), 6.49 (d, J_{H10-H9} = 2.4 Hz, lH, H-10), 7.61 (d, J_{H9-H10} = 2.4 Hz, lH, H-9), 8.58 (s, 1H, H-2), 8.92 (s, 1H, H-5).

iii) N-{2-[6-Methyl-2-phenylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepin-8-yl]ethylen}morpholine (**8e**).

White crystals (cyclohexane), (0.18 g, 23%), mp 147-148 °C. Anal. Calcd for $C_{22}H_{24}N_6O$: C, 68.02; H, 6.22; N, 21.63. Found: C, 68.05; H, 6.08; N, 21.49. ^{1}H Nmr ($CDCl_3$) δ ppm: 2.55 (m, 4H, CH_2NCH_2), 2.89 (t, J= 6.5 Hz, 2H, α-CH_2), 3.05 (s, 3H, 6-CH_3), 3.72 (m, 4H, CH_2OCH_2), 4.33 (t, J= 6.5 Hz, 2H, β-CH_2), 6.48 (d, J_{H10-H9}= 2.0 Hz, lH, H-10), 7.01 (s, 1H, H-3), 7.44-7.48 (m, 3H, ArH_3), 7.60 (d, J_{H9-H10}= 2.0 Hz, lH, H-9), 8.02-8.07 (m, 2H, ArH_2), 8.65 (s, 1H, H-5).

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