Reactivity of 7-(2-Dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines: Synthesis of Pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine Derivatives as Potential Benzodiazepine Receptor Ligands. 1

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A series of 7-methylpyrazolo[1,5-*a*]pyrimidines were reacted with dimethylformamide dimethylacetal to give the corresponding dimethylaminovinyl derivatives. These were reacted with ammonium acetate affording, through a ring closure, a number of 6-methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidines bearing various substituents on the pyrazole ring. The 6-acetyl-2-hydroxy-7-methylpyrazolo[1,5-*a*]pyrimidine was used as starting material for obtaining some *O*-alkyl derivatives. Catalytic transfer hydrogenation of 2-benzyloxy-6-methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine led to the 2-hydroxy derivative.

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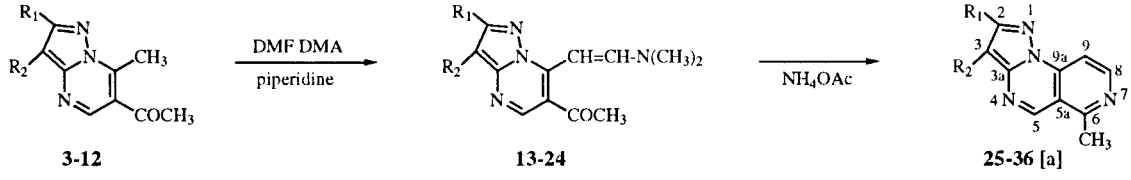
During recent years several research groups have focused on the development of compounds showing affinity for the benzodiazepine (BDZ) receptor. A number of these compounds differ widely in their chemical structure, molecular size, and physiochemical properties. They comprise structures of semirigid cyclic systems like pyrazolopyridine (ethazolate, cartazolate, tracazolate), quinolines (PK8165), β-carbolines (β-CCE, β-CCM), and pyrazoloquinolines (CGS) [1-2].

Many authors [3-6] have tried to define the common structural features among this large variety of agents. With these structures as precedents, it was felt that compounds belonging to the pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine series, being related with the pyrazoloquinolines of CGS series, would posses structural features necessary to elicit interaction with the BDZ receptor. The synthesis and the evaluation of the BDZ receptor affinity of a preliminary series of pyrazolo[1,5-*a*]pyrido[3,4-*e*]-pyrimidines has already been the subject of one of our papers [7]. In that report, compounds bearing an ethoxycarbonyl group at the 3-position and a functionalized side chain at the N-7 were studied. Although the reported compounds bind poorly with the BDZ receptor, the prospect that proper structural modifications on the pyrazolo-[1,5-*a*]pyrido[3,4-*e*]pyrimidine system might generate a series of more active molecules, was felt to warrant further investigation.

As outlined in Scheme 1 preparation of pyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine derivatives **25-36** was achieved by reaction of 7-dimethylaminovinyl derivatives **13-24** with ammonium acetate. These latter compounds, in turn, were obtained upon treatment of 6-acetyl-7-methylpyra-

Scheme 1



3-12 **13-24** **25-36** [a]

3	$R_1 = OH$	$R_2 = H$
4	$R_1 = OCH_3$	$R_2 = H$
5	$R_1 = OC_2H_5$	$R_2 = H$
6	$R_1 = O(CH_2)_2OH$	$R_2 = H$
7	$R_1 = OCH_2COOC_2H_5$	$R_2 = H$
8	$R_1 = OCH(CH_3)COOC_2H_5$	$R_2 = H$
9	$R_1 = OCH_2C_6H_5$	$R_2 = H$
10	$R_1 = CH(CH_3)_2$	$R_2 = H$
11	$R_1 = CH(CH_3)_2$	$R_2 = CH_3$
12	$R_1 = C(CH_3)_3$	$R_2 = CH_3$
13	$R_1 = OCH_3$	$R_2 = H$
14	$R_1 = OC_2H_5$	$R_2 = H$
15	$R_1 = O(CH_2)_2OH$	$R_2 = H$
16	$R_1 = OCH_2COOC_2H_5$	$R_2 = H$
17	$R_1 = OCH(CH_3)COOC_2H_5$	$R_2 = H$
18	$R_1 = OCH_2C_6H_5$	$R_2 = H$
19	$R_1 = CH(CH_3)_2$	$R_2 = H$
20	$R_1 = CH(CH_3)_2$	$R_2 = CH_3$
21	$R_1 = C(CH_3)_3$	$R_2 = CH_3$
22	$R_1 = CH_3$	$R_2 = NO_2$
23	$R_1 = C_6H_5$	$R_2 = H$
24	$R_1 =$ 	$R_2 = H$

[a] For compounds **25-36** R_1, R_2 are specified in Table I.

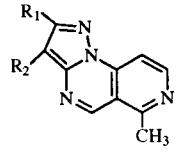
zolo[1,5-*a*]pyrimidines **3-12** with dimethylformamide dimethylacetal (DMF.DMA).

Following a sequence used previously in our laboratory, compounds **10-12** were synthesized by reacting ethoxymethylenacetylacetone with 3-, or 4-substituted-5-aminopyrazoles. Among these compounds, 5-amino-4-methyl-3-methylethylpyrazole (**1**) and 5-amino-3-(1,1-dimethylethyl)-4-methylpyrazole (**2**) were hitherto unreported and were prepared starting from the β-oxonitriles described in the Experimental. Compounds **1** and **2** were used without purification; analytical and spectral data are referred to the corresponding diacetyl derivatives.

beliefs, alkylation takes place on the oxygen atom of the hydroxy group and not on N-1, as it was erroneously referred in a preliminary communication [9]. The conclusive and definitive proof for the proposed structures was furnished by a more thorough ^1H and ^{13}C-nmr study. Not only the values of the chemical shifts of the proton linked to the carbon attached to the heteroatom was in accordance with the substitution on the oxygen, but also the presence of one carbonyl signal. This led us to rule out the previously reported structures. When compound **3** was reacted with DMF.DMA, red tars were obtained. Working up the reaction mixture yielded, in low yield, a

Table 1

Physical Data of 6-Methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidines **25-37**



Compound	R_1	R_2	Molecular Formula (% yield)	Mp (°C)	Crystallization solvent	Elemental Analysis (Calcd./Found) C	H	N
25	OCH_3	H	$C_{11}H_{10}N_4O$ (55)	215-216	water	61.67/61.46	4.70/4.92	26.15/26.38
26	OC_2H_5	H	$C_{12}H_{12}N_4O$ (52)	123-124	water	63.14/62.92	5.30/5.44	24.54/24.23
27	$O(CH_2)_2OH$	H	$C_{12}H_{12}N_4O_2$ (46)	158-160	water	59.00/59.18	4.95/5.11	22.93/23.10
28	$OCH_2COOC_2H_5$	H	$C_{14}H_{14}N_4O_3$ (61)	138-139	ethanol	58.73/58.51	4.92/4.75	19.57/19.85
29	$OCH(CH_3)COOC_2H_5$	H	$C_{15}H_{16}N_4O_3$ (44)	95-96	cyclohexane	59.99/60.11	5.37/5.16	18.65/18.32
30	$OCH_2C_6H_5$	H	$C_{17}H_{14}N_4O$ (73)	174-175	ethanol	70.33/70.57	4.86/4.61	19.29/18.93
31	$CH(CH_3)_2$	H	$C_{13}H_{14}N_4$ (70)	89-90	ethanol	69.00/69.16	6.23/6.12	24.76/24.52
32	$CH(CH_3)_2$	CH_3	$C_{14}H_{16}N_4$ (66)	144-145	ethanol	69.97/69.66	6.71/6.59	23.31/23.57
33	$C(CH_3)_3$	CH_3	$C_{15}H_{18}N_4$ (68)	123-124	ethanol	70.83/71.05	7.13/6.89	22.03/21.67
34	CH_3	NO_2	$C_{11}H_9N_5O_2$ (45)	284-285	ethanol	54.31/54.48	3.73/3.62	28.79/28.95
35	C_6H_5	H	$C_{16}H_{12}N_4$ (64)	180-181	ethanol	73.82/73.64	4.64/4.85	21.52/21.33
36		H	$C_{14}H_{10}N_4S$ (59)	202-203	ethanol	63.13/63.34	3.78/3.94	21.03/21.22
37	OH	H	$C_9H_8N_4O$ (35)	>320	ethanol	57.43/57.29	4.28/4.46	29.77/29.99

Among various modifications in the pyrazolo[1,5-*a*]-pyrido[3,4-*e*]pyrimidine parent structures, the introduction of a hydroxy group at the 2-position seemed worthwhile because it would produce compounds with a closer resemblance with pyrazoloquinolines of the CGS series. Thus 6-acetyl-2-hydroxy-7-methylpyrazolo[1,5-*a*]pyrimidine (**3**) was synthesized according to a reported method [8]. It appeared interesting, before reacting this compound with DMF.DMA, to introduce simple or functionalized alkyl side chains on the starting compound through classical alkylation procedures. Therefore, compound **3** was reacted with methyl and ethyl iodides, ethyl chloroacetate, ethyl α-bromopropionate and chloroethanol to give compounds **4-8** as described in the Experimental. Surprisingly, and contrary to our earlier

substance to which the structure of 6-acetyl-2-methoxy-7-dimethylaminovinylpyrazolo[1,5-*a*]pyrimidine was attributed, being identical by chromatographic, analytical and spectral comparison with **13** previously prepared.

In order to synthesize the simple member of this series, 2-hydroxy-6-methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine (**37**), compound **3** was alkylated with benzyl chloride giving the corresponding 2-benzyloxy derivative **9**. The latter compound underwent the usual reaction sequence, leading eventually to 2-benzyloxy-6-methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine (**30**), which was debenzylated by treatment with ammonium formate in the presence of 10% palladium on charcoal, according to a reported procedure [10]. When debenzylation was carried out by means of catalytic hydrogenation, overreduction occurs, and 4,5-

Table II

Spectral Data of 6-Methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidines (**25-37**)

Compound	R_1	R_2	^{1}H-nmr Spectrum [a] [b] [c] [d].
25	OCH_3	H	3.32 (s, 3H, 6-CH_3), 4.26 (s, 3H, OCH_3), 6.75 (s, 1H, H-3), 8.52 (d, J = 5.8 Hz, 1H, H-9), 8.80 (d, 1H, H-8), 9.50 (s, 1H, H-5). [c]
26	OC_2H_5	H	1.47 (t, 3H, OCH_2CH_3), 2.96 (s, 3H, 6-CH_3), 4.39 (q, 2H, OCH_2CH_3), 6.22 (s, 1H, H-3), 7.93 (d, J = 6.0 Hz, 1H, H-9), 8.66 (d, J = 6.0 Hz, 1H, H-8), 9.05 (s, 1H, H-5). [a]
27	$O(CH_2)_2OH$	H	2.99 (s, 3H, 6-CH_3), 3.78 (t, 2H, OCH_2CH_2OH), 4.35 (t, 2H, OCH_2CH_2OH), 4.99 (t, 1H, OH, exchangeable), 6.43 (s, 1H, H-3), 7.75 (d, J = 5.9 Hz, 1H, H-9), 8.69 (d, J = 5.9 Hz, 1H, H-8), 9.25 (s, 1H, H-5). [b]
28	$OCH_2COOC_2H_5$	H	1.31, (t, 3H, OCH_2CH_3), 3.03 (s, 3H, 6-CH_3), 4.30 (q, 2H, OCH_2CH_3), 4.90 (s, 2H, OCH_2), 6.40 (s, 1H, H-3), 7.82 (d, 6.0 Hz, 1H, H-9), 8.68 (d, J = 6.0 Hz, 1H, H-8), 9.12 (s, 1H, H-5). [a]
29	$OCH(CH_3)COOC_2H_5$	H	1.25 (t, 3H, OCH_2CH_3), 1.70 (d, 3H, CH-CH_3), 3.10 (s, 1H, 6-CH_3), 4.30 (q, 2H, OCH_2CH_3), 5.30 (q, 1H, $OCHCH_2$) 6.35 (s, 1H, H-3), 7.90 (d, J = 5.9 Hz, 1H, H-9), 8.60 (d, J = 5.9 Hz, 1H, H-8), 9.10 (s, 1H, H-5). [a]
30	$OCH_2C_6H_5$	H	2.98 (s, 3H, 6-CH_3), 5.43 (s, 2H, OCH_2), 6.29 (s, 1H, H-3), 7.37-7.51 (m, 5H, ArH_5), 7.95 (d, J = 5.9 Hz, 1H, H-9), 8.70 (d, J = 5.9 Hz, 1H, H-8), 9.08 (s, 1H, H-5). [a]
31	$CH(CH_3)_2$	H	1.41, (d, J = 6.95 Hz, 6H, $CH(CH_3)_2$), 3.01 (s, 3H, 6-CH_3), 3.19-3.28 (m, 1H, $CH(CH_3)_2$), 6.68 (s, 1H, H-3), 8.11 (d, J = 5.9 Hz, 1H, H-9), 8.74 (d, J = 5.9 Hz, 1H, H-8), 9.08 (s, 1H, H-5). [a]
32	$CH(CH_3)_2$	CH_3	1.39, (d, J = 6.96 Hz, 6H, $CH(CH_3)_2$), 2.38 (s, 3H, 3-CH_3), 2.98 (s, 3H, 6-CH_3), 3.20-3.30 (m, 1H, $CH(CH_3)_2$), 8.05 (d, J = 5.8 Hz, 1H, H-9), 8.69 (d, J = 5.8 Hz, 1H, H-8), 8.99 (s, 1H, H-5). [a]
33	$C(CH_3)_3$	CH_3	1.48 (s, 9H, $C(CH_3)_3$), 2.50 (s, 3H, 3-CH_3), 2.97 (s, 3H, 6-CH_3), 8.05 (d, J = 6.0 Hz, 1H, H-9), 8.67 (d, J = 6.0 Hz, 1H, H-8), 8.97 (s, 1H, H-5). [a]
34	CH_3	NO_2	2.87 (s, 3H, 2-CH_3), 3.12 (s, 1H, 6-CH_3), 8.22 (d, J = 6.0 Hz, 1H, H-9), 8.93 (d, J = 6.0 Hz, 1H, H-8), 9.57 (s, 1H, H-5). [a]
35	C_6H_5	H	3.02 (s, 3H, 6-CH_3), 7.14 (s, 1H, H-3), 7.46-7.51 (m, 3H, ArH_3), 8.02-8.07 (m, 2H, ArH_2), 8.22 (d, J = 5.8 Hz, 1H, H-9), 8.80 (d, J = 5.8 Hz, 1H, H-8), 9.12 (s, 1H, H-5). [a]
36		H	3.12 (s, 3H, 6-CH_3), 7.10 (s, 1H, H-3), 7.15 (dd, H4'-H3' = 4.8 Hz, J = 3.7 Hz, 1H, H4'), 7.40 (dd, JH5'-H4' = 4.8 Hz, J = H5'-H3' = 1.0 Hz, 1H, H-5'), 7.55 (dd, J = H3'-H4' = 3.7 Hz, J = H3'-H5' = 1.0 Hz, 1H, H3'), 8.20 (d, J = 5.9 Hz, 1H, H-9), 8.75 (d, J = 5.9 Hz, 1H, H-8), 9.12 (s, 1H, H-5). [a]
37	OH	H	2.99 (s, 3H, 6-CH_3), 6.20 (s, 1H, H-3), 7.75 (d, J= 5.9 Hz, 1H, H-9), 8.68 (d, J = 5.9 Hz, 1H, H-8), 9.22 (s, 1H, H-5), 11.25 (bs, 1H, OH, exchangeable). [b]

[a] deuteriochloroform, [b] dimethyl sulphoxide-d_6, [c] trifluoroacetic acid; [d] Chemical shifts are given in ppm (δ), relative to internal tetramethylsilane; Coupling constants (J) are given in Hz; b = broad

Table III

^{13}C-nmr Spectral Data for Compounds **25-26-29** [a]

Carbon	Compound **25**	Compound **26**	Compound **29**
C_2	166.76 (m)	168.77	167.33
C_3	85.13 (d, $^1J_{C3-H3}$ = 182.9)	87.71 (d, $^1J_{C3-H3}$ = 182.4)	88.29 (d, $^1J_{C3\,H3}$ = 183.9)
C_{3a}	146.28 (m) [b]	148.79 (m) [b]	148.00 (m) [b]
C_5	148.96 (d, $^1J_{C5-H5}$ = 184.0)	151.50 (d, $^1J_{C5-H5}$ = 184.0)	151.73 (d, $^1J_{C5-H5}$ = 184.0)
C_{5a}	111.43 (m)	114.06 (m)	114.08 (m)
C_6	158.87 (m)	161.53 (m)	161.58 (m)
C_8	150.41 (dd, $^1J_{C8-H8}$ = 180.3, $^2J_{C8-H9}$ = 2.0)	153.25 (dd, $^1J_{C8-H8}$ = 180.1, $^2J_{C8-H9}$ = 2.5)	153.28 (dd, $^1J_{C8-H8}$ = 178.3, $^2J_{C8-H9}$ = 2.5)
C_9	105.99 (dd, $^1J_{C9-H9}$ = 172.0, $^2J_{C9-H8}$ = 8.5)	108.52 (dd, $^1J_{C9-H9}$ = 172.2, $^2J_{C9-H8}$ = 8.5)	108.45 (dd, $^1J_{C9-H9}$ = 173.0, $^2J_{C9-H8}$ = 8.1)
C_{9a}	139.80 (m) [b]	142.00 (m) [b]	142.32 (m) [b]
Others	55.95 (q, OCH_3)	67.27 (tq, OCH_2)	173.64 (m, CO)
	20.99 (q, 6-CH_3)	23.72 (q, 6-CH_3)	75.07 (dq, $CHCH_3$)
		16.73 (qt, OCH_2CH_3)	63.28 (tq, OCH_2)
			23.71 (q, 6-CH_3)
			20.01 (dq, $CHCH_3$)
			16.24 (qt, OCH_2CH_3)

[a] Chemical shifts (δ, ppm) and selected ^{n}J (C-H) values (Hz). [b] Assignments may be reversed.

dihydro-2-hydroxy-6-methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]-pyrimidine (**38**) was isolated from the reaction mixture.

The BDZ receptor binding study of compounds **25-37** is in progress.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were measured for nujol mulls with a Perkin Elmer 681 spectrophotometer. ^1H and ^{13}C nmr spectra were recorded with a Varian Gemini 200 instrument; chemical shifts are reported in ppm with tetramethylsilane as the 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.

General Procedure for Preparing Compounds **1-2.**

Hydrazine hydrate (17 ml, 337 mmoles) was added to a solution of 2,4-dimethyl-3-oxopentanenitrile (28.27 g, 225 mmoles) [11], or of 2,4,4-trimethyl-3-oxopentanenitrile (bp 89-90° P =17 mbar)(prepared according to the same procedure), dissolved in ethanol (100 ml) with magnetic stirring. The solution was refluxed for 8 hours. Removal of the solvent at reduced pressure left a viscous oil, a small amount of which (2 g, 14.36 mmoles) was treated with acetic anhydride (2 ml) yielding a diacetyl derivative.

3-Methylethyl-4-methyl-5-aminopyrazole (**1**).

This compound was obtained as light yellow oil, 36 g (72%).

1-Acetyl-5-aminoacetyl-3-methylethyl-4-methylpyrazole.

This compound was obtained as white crystals from ethanol/water, mp 74-75°; ^1H nmr (deuteriochloroform): δ 1.23 (d, J = 9.24, 6H, $CH(CH_3)_2$), 1.94 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 2.59 (s, 3H, 4-CH_3), 2.90 (dq, appears as quintet, 1H, $CH(CH_3)_2$), 8.96 (bs, 1H, NH, exchangeable).

Anal. Calcd. for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.81. Found: C, 59.45; H, 7.85; N, 19.11.

3-(1,1-Dimethylethyl) 4-methyl-5-aminopyrazole (**2**).

Removal of the solvent in this case left a white waxy solid, 36 g (68%).

1-Acetyl-5-aminoacetyl-3-(1,1-dimethylethyl) 4-methylpyrazole.

This compound was obtained as white crystals from ethanol/water, mp 170-172°; ^1H nmr (deuteriochloroform): δ 1.32 (s, 9H, $CH(CH_3)_3$, 2.04 (s, 3H, $COCH_3$), 2.14 (s, 3H, $COCH_3$), 2.59 (s, 3H, 4-CH_3), 8.65 (bs, 1H, NH, exchangeable).

Anal. Calcd. for $C_{12}H_{19}N_3O_2$: C, 60.73; H, 8.07; N, 17.70. Found: C, 60.51; H, 7.97; N, 17.39.

General Procedure for the Synthesis of **4-5** and **8**.

6-Acetyl-2-hydroxy-7-methylpyrazolo[1,5-*a*]pyrimidine (**3**), [8] (1.33 g, 7.0 mmoles) was dissolved in anhydrous *N,N*-dimethylformamide (20 ml), anhydrous potassium carbonate (0.9 g, 7.0 mmoles) and methyl or ethyl iodide or 2-bromopropionate (14.0 mmoles) were added. Exclusion of external moisture was achieved by insertion of a calcium chloride guard tube at the top of the condenser. The mixture was heated at 50° with magnetic stirring for 5 hours. Compound **8** required also a catalytic amount of natrium iodide (0.05 g). The course of reaction was monitored by thin layer chromatography (chloroform /methanol 10/1). The inorganic residue was filtered off and the solvent was removed *in vacuo* leaving a solid substance.

6-Acetyl-2-methoxy-7-methylpyrazolo[1,5-*a*]pyrimidine (**4**).

This compound was obtained as yellow crystals from water, 0.9 g (72%), mp 146-147°; ^1H nmr (deuteriochloroform): δ 2.62 (s, 3H, $COCH_3$), 3.10 (s, 3H, 7-CH_3), 4.10 (s, 3H, OCH_3), 6.10 (s, 1H, H-3), 8.80 (s, 1H, H-5).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.52; H, 5.40; N, 20.47. Found: C, 58.30; H, 5.35; N, 20.17.

6-Acetyl-2-ethoxy-7-methylpyrazolo[1,5-*a*]pyrimidine (**5**).

This compound was obtained as yellow crystals from water, 10 g (77%), mp 98-99°; ^1H nmr (deuteriochloroform): δ 1.46 (t, 3H, OCH_2CH_3), 2.59 (s, 3H, $COCH_3$), 3.10 (s, 3H, 7-CH_3), 4.32 (q, 2H, OCH_2CH_3), 6.10 (s, 1H, H-3), 8.75 (s, 1H, H-5).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.97; N, 19.16. Found: C, 60.35; H, 6.16; N, 19.29.

Ethyl 6-Acetyl-7-methylpyrazolo[1,5-*a*]pyrimidin-2-yl-2-oxypropanoate (**8**).

This compound was obtained as ivory crystals from water, 0.63 g (49%), mp 93-94°; ^1H nmr (deuteriochloroform): δ 1.15 (t, 3H, OCH_2CH_3), 1.70 (d, 3H, $CHCH_3$), 2.60 (s, 3H, $COCH_3$), 3.05 (s, 3H, 7-CH_3), 4.15 (q, 2H, OCH_2CH_3), 5.20 (q, 1H, $CHCH_3$), 6.15 (s, 1H, H-3), 8.82 (s, 1H, H-5).

Anal. Calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.80; H, 6.09; N, 14.72.

Preparation of Compounds **6** and **7**.

6-Acetyl-2-hydroxy-7-methylpyrazole[1,5-*a*]pyrimidine (**3**) (1.46 g, 7.6 mmoles) was suspended in toluene (100 ml) to which powdered potassium hydroxide (1.46 g), anhydrous potassium carbonate (1.66 g) and 18-crown ether (0.52 g) were added. The suspension was heated to reflux under magnetic stirring for 2 hours, then 2-bromoethanol or ethyl 2-bromopropionate was added and the mixture was refluxed for an additional 20 hours. The solvent was distilled off at reduced pressure and a solid substance was obtained.

6-Acetyl-2-(2-hydroxy)ethoxy-7-methylpyrazolo[1,5-*a*]pyrimidine (**6**).

This compound was obtained as yellow crystals from water, 0.9 g (50%), mp 160-162°; ^1H nmr (deuteriochloroform): δ 2.63 (s, 3H, $COCH_3$), 3.04 (s, 3H, 7-CH_3), 3.99 (t, 2H, OCH_2CH_2OH), 4.48 (t, 2H, OCH_2CH_2OH), 6.11 (s, 1H, H-3), 8.76 (s, 1H, H-5).

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.56; N, 17.86. Found: C, 56.02; H, 5.76; N, 17.72.

Ethyl 6-Acetyl-7-methylpyrazolo[1,5-*a*]pyrimidin-2-yl-2-oxyacetate (**7**).

This compound was obtained as yellow crystals from water, 11 g (52%), mp 105-106°; ^1H nmr (deuteriochloroform): δ 1.30 (s, 3H, OCH_2CH_3), 3.00 (s, 3H, $COCH_3$), 3.30 (s, 3H, 7-CH_3), 4.20 (q, 2H, OCH_2CH_3), 5.05 (s, 2H, CH_2), 6.30 (s, 1H, H-3), 8.92 (s, 1H, H-5).

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.14; H, 5.23; N, 15.02.

Preparation of 6-Acetyl-2-benzyloxy-7-methylpyrazolo[1,5-*a*]-pyrimidine (**9**).

Compound **3** (3.23 g, 20 mmoles) was suspended in anhydrous *N,N*-dimethylformamide (25 ml) to which potassium carbonate (3.0 g, 23 mmoles) and benzyl chloride (3.5 ml, 30 mmoles) were added. The suspension was heated at 50° under magnetic stirring for 4 hours. On cooling a white precipitate was obtained which was filtered and washed with water to eliminate the inor-

ganic residue. White crystals were obtained from ethanol, 4.32 g (76%), mp 149-150°; ^{1}H nmr (deuteriochloroform): δ 2.66 (s, 3H, $COCH_3$), 3.10 (s, 3H, 7-CH_3), 5.42 (s, 2H, OCH_2), 6.15 (s, 1H, H-3), 7.36-7.48 (m, 5H, ArH), 8.77 (s, 1H, H-5).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.93. Found: C, 68.04; H, 5.45; N, 14.65.

Preparation of Compounds **10-12.**

3-Ethoxymethylenpentane-2,4-dione [12] (3.74 g, 24 mmoles) was added to a solution of 5-amino-3-methylethylpyrazole [13] or of compounds **1** or **2** in ethanol (100 ml). The mixture was refluxed under magnetic stirring for 2 hours. On cooling a yellow precipitate separates out.

6-Acetyl-7-methyl-2-methylethylpyrazolo[1,5-*a*]pyrimidine (**10**).

This compound was obtained from 5-amino-3-methylethylpyrazole as yellow crystals from ethanol, 4.36 g (82%), mp 68-70°; ^{1}H nmr (deuteriochloroform): δ 1.40 (d, Jgem = 6.93 Hz, 6H, $CH(CH_3)_2$), 2.68 ($COCH_3$), 3.15 (s, 3H, 7-CH_3), 3.18-3.25 (m, 1H, CH), 6.56 (s, 1H, H-3), 8.92 (s, 1H, H-5).

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.36; H, 6.96; N, 19.34. Found: C, 66.25; H, 6.93; N, 19.20.

6-Acetyl-3,7-dimethyl-2-methylethylpyrazolo[1,5-*a*]pyrimidine (**11**).

From compound **1**, following the above procedure, yellow crystals from ethanol were obtained, 4.84 g (88%), mp 136-137°; ^{1}H nmr (deuteriochloroform): δ 1.40 (d, Jgem = 6.93 Hz, 6H, $CH(CH_3)_2$), 2.30 (s, 3H, 3-CH_3), 2.62 (s, 3H, $COCH_3$), 3.15 (s, 3H, 7-CH_3), 3.18-3.27 (m, 1H, CH), 8.70 (s, 1H, H-5).

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.41; N, 18.16. Found: C, 67.78; H, 7.53; N, 18.47.

6-Acetyl-3,7-dimethyl-2-(1,1-dimethylethyl)pyrazolo[1,5-*a*]-pyrimidine (**12**).

From compound **2**, following the above procedure, yellow crystals from ethanol were obtained, 4.64 g (79%), mp 107-108°; ^{1}H nmr (deuteriochloroform): δ 1.45 (s, 9H, $C(CH_3)_3$), 2.45 (s, 3H, 3-CH_3), 2.65 (s, 3H, $COCH_3$), 3.11 (s, 3H, 7-CH_3), 8.72 (s, 1H, H-5).

Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.80; N, 17.12. Found: C, 68.64; H, 7.76; N, 17.23.

6-Acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines **13-21**.

Compounds **13-21** were prepared according to a reported procedure [14].

6-Acetyl-7-(2-dimethylaminovinyl)-2-methoxypyrazolo[1,5-*a*]-pyrimidine (**13**).

According to the above method either starting from compound **3** or from **4**, yellow crystals were obtained from ethanol/water, 3.33 g (64% from compound **4**) (48% from compound **3**), mp 150-151°; ^{1}H nmr (deuteriochloroform): δ 2.62 (s, 3H, $COCH_3$), 3.18 (s, 6H, $N(CH_3)_2$), 5.95 (s, 1H, H-3), 7.22 (d, J_{trans} = 12.6 Hz, 1H, $CHCHN(CH_3)_2$), 8.70 (s, 1H, H-5), 9.65 (d, J_{trans} = 12.6 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 59.98; H, 6.19; N, 21.52. Found C, 60.07; H, 6.31; N, 21.41.

6-Acetyl-7-(2-dimethylaminovinyl)-2-ethoxypyrazolo[1,5-*a*]-pyrimidine (**14**).

This compound was obtained from compound **5** as yellow crystals from cyclohexane/ethyl acetate, 3.78 g (69%), mp 181-183°; ^{1}H nmr (deuteriochloroform): δ 1.46 (t, 3H, OCH_2CH_3), 2.59 (s, 3H, OCH_3), 3.09 (s, 3H, $N(CH_3)_2$), 4.32 (q, 2H, OCH_2CH_3), 5.89 (s, 1H, H-3), 7.20 (d, J_{trans} = 12.5 Hz, 1H, $CHCHN(CH_3)_2$), 8.63 (s, 1H, H-5), 9.60 (d, J_{trans} = 12.5 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.29; H, 6.61; N, 20.42. Found: C, 61.49; H, 6.44; N, 20.50.

6-Acetyl-7-(2-dimethylaminovinyl)-2-(2-hydroxy)ethoxypyrazolo[1,5-*a*]pyrimidine (**15**).

This compound was obtained from compound **6** as yellow crystals from cyclohexane/ethyl acetate, 3.02 g (52%), m.p. 181-182°; ^{1}H nmr (deuteriochloroform): δ 2.62 (s, 3H, OCH_3), 3.05 (s, 3H, $N(CH_3)_2$), 3.99 (t, 2H, OCH_2CH_2OH), 5.94 (s, 1H, H-3), 7.20 (d, J_{trans} = 12.7 Hz, 1H, $CHCHN(CH_3)_2$), 8.66 (s, 1H, H-5), 9.60 (d, J_{trans} = 12.7 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{14}H_{18}N_4O_3$: C, 57.91; H, 6.24; N, 19.29. Found: C, 57.69; H, 6.42; N, 19.18.

Ethyl 6-Acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidin-2-yl-2-oxyacetate (**16**).

This compound was obtained from compound **7** as yellow crystals from cyclohexane/ethyl acetate, 5.32 g (80%), mp 159-160°; ^{1}H nmr (deuteriochloroform): δ 1.20 (t, 3H, OCH_2CH_3), 2.61 (s, 3H, $COCH_3$), 3.05 (s, 3H, $N(CH_3)_2$), 3.25 (s, 3H, $N(CH_3)_2$), 4.15 (q, 2H, OCH_2CH_3), 4.84 (s, 2H, OCH_2), 6.00 (s, 1H, H-3), 7.22 (d, J_{trans} = 12.6 Hz, 1H, $CHCHN(CH_3)_2$), 8.64 (s, 1H, H-5), 9.45 (d, J_{trans} = 12.6 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.06; N, 16.84. Found: C, 57.82; H, 6.14; N, 16.97.

Ethyl 6-Acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidin-2-yl-2-oxypropanoate (**17**).

This compound was obtained from compound **8** as yellow crystals from ethyl acetate, 4.08 g (59%), mp 162-163°; ^{1}H nmr (deuteriochloroform): δ 1.15 (t, 3H, OCH_2CH_3), 1.70 (d, 3H, $CHCH_3$), 2.50 (s, 3H, $COCH_3$), 3.05 (s, 3H, $N(CH_3)_2$), 3.30 (s, 3H, $N(CH_3)_2$), 4.15 (q, 2H, OCH_2CH_3), 5.20 (q, 1H, $CHCH_3$), 5.95 (s, 1H, H-3), 7.20 (d, J_{trans} = 12.7 Hz, 1H, $CHCHN(CH_3)_2$), 8.60 (s, 1H, H-5), 9.45 (d, J_{trans} = 12.7 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40; N, 16.17. Found: C, 58.90; H, 6.39; N, 16.17.

6-Acetyl-2-benzyloxy-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]-pyrimidine (**18**).

This compound was obtained from compound **9** as yellow crystals from ethanol, 4.3 g (64%), mp 155-157°; ^{1}H nmr (deuteriochloroform): δ 1.61 (s, 3H, $COCH_3$), 3.07 (s, 3H, $N(CH_3)_2$), 3.20 (s, 3H, $N(CH_3)_2$), 5.37 (s, 2H, OCH_2), 5.92 (s, 1H, H-3), 7.21-7.47 (m, 6H, 1H, $CHCHN(CH_3)_2$, 5H, ArH), 8.67 (s, 1H, H-5), 9.56 (d, J_{trans} = 12.82 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{19}H_{20}N_4O_2$: C, 67.83; H, 5.99; N, 16.65. Found: C, 67.60; H, 6.12; N, 16.35.

6-Acetyl-7-(2-dimethylaminovinyl)-2-methylethylpyrazolo[1,5-*a*]-pyrimidine (**19**).

This compound was obtained from compound **10** as yellow crystals from cyclohexane/ethyl acetate, 2.99 g (55%), mp 151-152°; ^{1}H nmr (deuteriochloroform): δ 1.38 (d, J_{gem} = 6.96 Hz, 6H, $CH(CH_3)_2$), 2.64 (s, 3H, $COCH_3$), 3.08-3.27 (m, 7H, 1H,

$CH(CH_3)_2$, 6H, $N(CH_3)_2$), 6.34 (s, 1H, H-3), 7.28 (d, J_{trans} = 12.5 Hz, 1H, $CHCHN(CH_3)_2$), 8.69 (s, 1H, H-5), 9.87 (d, J_{trans} = 12.5 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 66.35; H, 7.52; N, 20.29.

6-Acetyl-7-(2-dimethylaminovinyl)-2-methylethyl-3-methylpyrazolo[1,5-*a*]pyrimidine (**20**).

This compound was obtained from compound **11** as yellow crystals from cyclohexane, 3.6 g (63%), mp 156-157°; ^1H nmr (deuteriochloroform): δ 1.38 (d, J_{gem} = 6.95 Hz, 6H, $CH(CH_3)_2$), 2.28 (s, 3H, 3-CH_3), 2.60 (s, 3H, $COCH_3$), 3.15-3.28 (m, 7H, 1H, $CH(CH_3)_2$, 6H, $N(CH_3)_2$), 7.30 (d, J_{trans} = 12.6 Hz, 1H, $CHCHN(CH_3)_2$), 8.68 (s, 1H, H-5), 9.90 (d, J_{trans} = 12.6 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{16}H_{22}N_4O$: C, 67.10; H, 7.74; N, 19.56. Found: C, 67.01; H, 7.71; N, 19.48.

6-Acetyl-7-(2-dimethylaminovinyl)-2-(1,1-dimethylethyl)-3-methylpyrazolo[1,5-*a*]pyrimidine (**21**).

This compound was obtained from compound **12** as yellow crystals from cyclohexane, 3.66 g (61%), mp 130-131°; ^1H nmr (deuteriochloroform): δ 1.46 (s, 9H, $C(CH_3)_3$), 2.42 (s, 3H, 3-CH_3), 2.62 (s, 3H, $COCH_3$), 3.06 (s, 3H, $N(CH_3)$), 3.24 (s, 3H, $N(CH_3)$), 7.30 (d, J_{trans} = 12.5 Hz, 1H, $CHCHN(CH_3)_2$), 8.68 (s, 1H, H-5), 9.95 (d, J_{trans} = 12.5 Hz, 1H, $CHCHN(CH_3)_2$).

Anal. Calcd. for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found: C, 67.81; H, 8.00; N, 18.87.

6-Acetyl-7-(2-dimethylaminovinyl)-2-methyl-3-nitropyrazolo[1,5-*a*]pyrimidine (**22**).

This compound was prepared according to a reported method [15].

6-Acetyl-7-(2-dimethylaminovinyl)-2-phenylpyrazolo[1,5-*a*]-pyrimidine (**23**).

This compound was prepared according to a reported method [15].

6-Acetyl-7-(2-dimethylaminovinyl)-2,2'-thienylpyrazolo[1,5-*a*]-pyrimidine (**24**).

This compound was prepared according to a reported method [15].

General Procedure for Preparing 6-Methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidines **25-36.**

The dimethylaminovinyl derivatives **13-24** (10 mmoles) were refluxed in acetic acid (30 ml), ammonium acetate (20 g) for 2 hours. After cooling, the mixture was diluted with water (50 ml) and the precipitate was filtered off, washed with water and dried to yield compounds **25-36**. Analytical and spectroscopic data are reported in Tables I, II and III.

2-Hydroxy-6-methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidines (**37**).

A suspension of **30** (0.87 g, 3 mmoles) in ethanol (70 ml) was heated at 50°, then ammonium formate (0.93 g, 15 mmoles) and 1.8 g of 10% palladium on charcoal were added. The solution was refluxed for 20 minutes. The course of reaction was monitored by tlc (chloroform/methanol 7/3). The solvent was evaporated to dryness under reduced pressure; the residue was washed with water and filtered. Yellow crystals were obtained from ethanol, 0.29 g (52%) mp >320°.

4,5-Dihydro-2-hydroxy-6-methylpyrazolo[1,5-*a*]pyrido[3,4-*e*]-pyrimidine (**38**).

A suspension of **30** (0.58 g, 2 mmoles) in ethanol (200 ml) and *N,N*-dimethylformamide (40 ml) was hydrogenated in a Parr apparatus at room temperature and 3 atmospheres for 3 hours, in the presence of 0.12 g of 10% palladium on charcoal. The obtained solution was filtered and the solvent was evaporated to dryness under reduced pressure. The light brown residue was recrystallized from ethanol and obtained as cream crystals, 0.25 g (63%) mp 279-280°; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.31 (d, $J_{CH_2\text{-}NH}$ = 1.5 Hz, 2H, 5-CH_2 appears as singlet after set decoupling at 7.15 ppm), 4.64 (s, 3H, H-3), 6.95 (d, $J_{H9\text{-}H8}$ = 5.3 Hz, 1H, H-9), 7.15 (bd, 1H, N4-H exchangeable), 8.23 (d, $J_{H8\text{-}H9}$ = 5.3 Hz, 1H, H-8), 10.12 (bs, 1H, OH, exchangeable).

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.94; N, 27.70. Found: C, 59.47; H, 4.92; N, 27.91.

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