Some Aspects of the Chemistry of Pyrimido[1,2-*b*]pyridazinones

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On reacting the 3-aminopyridazines **1a,d,e** with dimethyl acetylenedicarboxylate (DMAD), the pyrimido[1,2-*b*]pyridazin-2-(2*H*)-ones **2e-g**, whereas starting from **1f**, the 4(4*H*)-ones **5a** and **3b,d** were prepared. In the 2(2*H*)-one series, the reactions of **2b** with various amino compounds resulted in various types of products. The reaction of *N*-methylaminopyridazines **1g,h** with DMAD led to the *endo*-*N*-substituted derivatives **8a,b**, whereas **1h** with diethyl ethoxymethylenemalonate (DEM) gave the *exo*-*N*-substituted compound **1k**. The constitution of the compounds was proved by spectroscopic and chemical evidences.

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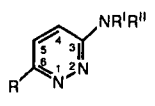
We recently reported [1] that the reaction of 3-aminopyridazines **1b,c** with DMAD or diethyl propiolate led to the pyrimido[1,2-*b*]pyridazin-2(2*H*)-one derivatives **2a-d**, whereas pyrimido[1,2-*b*]pyridazin-4(4*H*)-ones **3e,a** were obtained from **1a,b** with isopropylidene ethoxymethylenemalonate (IPEM).The constitution of some related compounds erronously described by others were corrected by us on the basis of spectroscopic investigations.

We have also made quantum chemical calculations for an interpretation of these results [2].

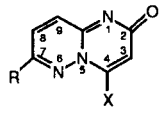
Some members of this family of compounds showed a positive inotropic effect in an *in vivo* pharmacological study [3], thus we decided to prepare other derivatives. Simultaneously, a general method was searched for the preparation of 2(2*H*)- and 4(4*H*)-one derivatives.

On reacting the 6-substituted 3-aminopyridazines **1a,-d,e** with DMAD in methanol, the expected pyrimido-[1,2-*b*]pyridazin-2(2*H*)-ones **2e-g** were obtained. However, under similar conditions, only **4** could be separated from 6-amino-3(2*H*)-pyridazinone (**1f**) as a result of nucleophilic addition to the triple bond. The intramolecular cyclization of **4** to the pyrimido[1,2-*b*]pyridazin-4(4*H*)-one derivative **5a** could be achieved in hot acetic acid. Starting from **5a**, **3b** and **3d**, *i.e.* the 4(4*H*)-one isomers of the 2(2*H*)-ones **2b**, **d**, were obtained (Scheme 1).

In agreement with our previous results [1] as well as with other literature data [4-6], the compounds **1d-f** with DEM gave the novel 3-pyridazinylaminomethylenemalonates **6a-c** in a high yield. The thermal cyclization of **6c** led to



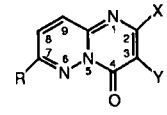
1



2

a (R = R' = R'' = H)
b (R = Cl, R' = R'' = H)
c (R = Mph, R' = R'' = H)
d (R = Me, R' = R'' = H)
e (R = $CONH_2$, R' = R'' = H)
f (R = OH, R' = R'' = H)
g (R = Cl, R' = Me, R'' = H)
h (R = Mph, R' = Me, R'' = H)
i (R = Cl, R' = Me, R'' = Ac)
j (R = Mph, R' = Me, R'' = Ac)
k [R = Mph, R' = Me, R'' = CH=C(COOEt)$_2$]

a (R = Cl, X = H)
b (R = Cl, X = COOMe)
c (R = Mph, X = H)
d (R = Mph, X = COOMe)
e (R = H, X = COOMe)
f (R = Me, X = COOMe)
g (R = $CONH_2$, X = COOMe)
h (R = Cl, X = $CONH_2$)
i [R = Cl, X = $CONH(CH_2)_2OH$]
j [R = $NH(CH_2)_2OH$, X = $CONH(CH_2)_2OH$]

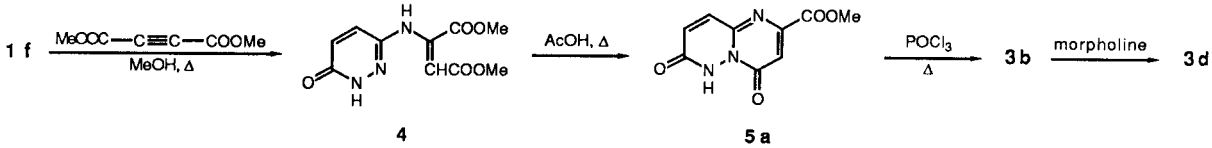


3

a (R = Cl, X = Y = H)
b (R = Cl, X = COOMe, Y = H)
c (R = Mph, X = Y = H)
d (R = Mph, X = COOMe, Y = H)
e (R = H, X = Y = H)
f (R = Cl, X = H, Y = COOEt)

Mph = morpholino

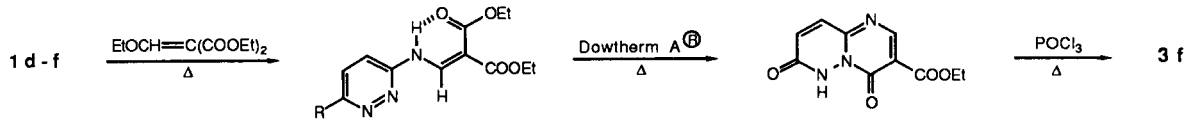
Scheme 1



4

5 a

Scheme 2



6

a R = Me
b R = $CONH_2$
c R = OH

5b which upon treating with phosphorus oxychloride resulted in ethyl [7-chloro-4(3*H*)-oxopirimido[1,2-*b*]pyridazine-3-carboxylate] (**3f**) (Scheme 2) also obtained by Tišler *et al.* in another way [5]. Compound **3c**, *i.e.* the 4(4*H*)-one isomer of **2c**, was prepared in two different ways, either by thermal cyclization of isopropylidene [(6-morpholino-3-pyridazinyl)aminomethylenemalonate] obtained from **1b** with IPEM [6] or by nucleophilic substitution of the 7-chloro compound **3a** with morpholine.

Table 1

Some Characteristic IR (potassium bromide, cm^{-1}), ^1H NMR (DMSO-d_6), δ ppm and UV (96% Ethanol) Data of Isomeric Pairs **2a-d** and **3a-d**

Compound	IR amide-I	ν C = O (ester)	^1H NMR 3-H (J, Hz)	UV ϵ_c/ϵ_b
2a	1640	–	6.40 d (7.5)	0.18
2b	1645	1745	6.80 s	0.23
2c	1630	–	6.30 d (8.0)	0.10
2d	1645	1749	6.57 s	0.11
3a	1709	–	6.70 d (6.5)	0.81
3b	1726	1755	7.12 s	0.88
3c	1686	–	6.42 d (6.4)	1.67
3d	1693	1734	6.93 s	0.72

Table 2

Some ^1H and ^{13}C NMR Chemical Shifts of Compounds **1i, j** and **8a, b** in Different Solvents

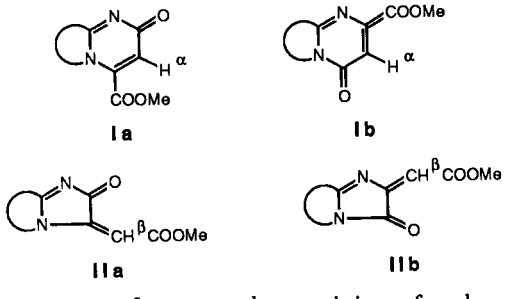
Assignment	Solvent	**1i**	**1j**	**8a**	**8b**
	[a]	3.61	3.42 d	–	3.56
NCH_3	[b]	–	–	–	3.47
	[c]	3.58	3.36	3.90	3.80
	[a]	8.01 d	7.4 d	–	7.26
4-*H*	[b]	–	–	–	7.66
	[c]	8.22	8.06	7.65	7.86
	[a]	7.50	7.01	–	6.49
5-*H*	[b]	–	–	–	6.88
	[c]	8.14	7.62	8.10	7.38
	[a]	35.3	35.1	–	29.0
NCH_3	[b]	–	–	–	–
	[c]	–	–	28.7	28.8

[a] Deuteriochloroform. [b] Dimethyl sulfoxide-d_6. [c] Trifluoroacetic acid. [d] Broadened signals due to the hindered amide rotation.

The constitution of these compounds was proved by the spectroscopic methods (see Tables 1 and 3).

In the cases of products obtained in the reaction of the 3-aminopyridazines **1a-e** with DMAD, the theoretically also possible constitutions of type **II** (Scheme 3) were excluded on the basis of the ^{13}C nmr data. The structure types **I** and **II** can well be distinguished by the coupling constant between the carbon of the ring carbonyl and the α- or β-hydrogen, respectively: $^2J[C(O),H^{\alpha}] \leq 1.4$ Hz (**I**), while $^3J[C(O), H^{\beta}] \geq 5.3$ Hz (**II**) [7,8]. In our compounds, type **I** was proven by the value of *ca.* 2 Hz for J. It was earlier shown that in the ir spectra of the pyrimido[1,2-*b*]-pyridazin-2(2*H*)-one and -4(4*H*)-one isomers, the amide-I band can be expected at 1650 and 1700 cm^{-1}, respectively [1] in a good agreement with the calculated carbonyl π-bond order values [5]. This important difference can also be observed for the novel compounds.

Scheme 3



Ia **Ib**

IIa **IIb**

The uv spectra of compounds containing a fused pyrimidinone ring can usually be divided in to three λ-regions (a, b and c) characterized each by one extinction maximum. According to the 2- or 4-position of the carbonyl group, the ratios of the extinction coefficients belonging to the b and c regions, (ϵ_c/ϵ_b) is 0.3 or *ca.* 1, respectively [9,10]. In the case of pyrimido[1,2-*b*]pyridazin-2(2*H*)-one compounds this value is *ca.* 0.2, while 0.7 for the 4(4*H*)-ones. Important differences can also be observed in the ^1H and ^{13}C nmr spectra of 2(2*H*)- and 4(4*H*)-one isomers. In the ^1H nmr spectra the 3-H signal of 4(4*H*)-ones is shifted downfield as compared to the corresponding signal of the 2(2*H*)-one isomers. In the ^{13}C nmr spectra the carbonyl line of the ring in the case of 4(4*H*)-one is shifted upfield by about 10 ppm.

Table 3

^{13}C NMR Data of Compounds **2a-d**, **3a-d** and **5a**

Compound	δ, ppm (J, Hz) in DMSO-d_6 solution										
	C-2	C-3	C-4	C-7	C-8	C-9	C-9a	C=O (ester)	OCH_3	NCH_2 [a]	OCH_2[a]
2a	168.8 d (8)	117.0 dd (171, 2.5)	143.6 dd (191.5, 4.5)	147.4 d (9)	136.7 d (179)	132.2 d (181)	149.6 dt (8, 4, 4)	–	–	–	–
2b	167.8 s	115.8 d (178.5)	144.5 d (3)	147.5 dd (4.6, 8)	137.0 d (180)	132.7 d (182)	149.8 dd (7, 4.5)	161.8 qi (4)	55.3 qa (149.5)	–	–
2c	169.3 d (8)	116.2 dd (170, 2.5)	143.3 dd (188, 4.5)	154.4 d (9.5)	123.7 d (173)	134.0 d (176)	148.1 ddd (9, 4, 2.5)	–	–	46.9 t (140)	67.1 tt (145, 4)
2d	168.3 s	114.0 d (172)	145.1 d (4)	153.9 d (9)	124.5 d (170)	134.2 dd (177, 2)	148.2 dd (9, 2.5)	162.8 qi (4)	50.0 qa (148.5)	–	–
3a	154.8 d (180.5)	112.0 dd (170.5, 7)	157.6 dd (8, 2.0)	150.3 d (12.5)	139.0 d (179)	131.9 d (182)	150.7 ddd (14, 6, 2)	–	–	–	–
3b	151.9 s	112.8 d (173)	158.0 s	151.2 d (12.5)	139.4 d (180)	132.3 d (183)	150.6 dd (9, 2.5)	165.6 qi (3.5)	54.5 qa (148.5)	–	–
3c	153.1 d (184.5)	110.5 dd (168.5, 7.5)	158.3 dd (9, 1.5)	155.2 dd (5, 4)	122.8 d (172.5)	135.9 d (175)	149.4 ddd (13.5, 6, 4.5)	–	–	46.9 t (139)	67.3 tt (144.5, 4)
3d	150.3 s	110.9 d (171)	158.5 s	155.5 dd (9, 2)	123.5 d (173)	136.1 d (176)	148.9 dd (8, 3)	166.2 qi (3.5)	54.3 qa (148)	46.7 t (136.5)	67.2 tt (144.5, 4)
5a	151.0 s	111.3 d (172)	158.7 t (1.5)	161.9 d (10.5)	127.4 d (176)	138.9 d (177)	149.8 dd (9, 3)	166.1 qi (4)	54.5 qa (148)	–	–

[a] In morpholine ring. [b] Measured in deuteriochloroform solution.

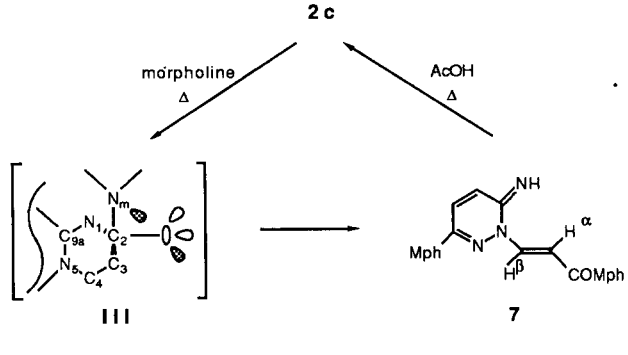
For the decision of the carbonyl isomerism, useful informations are also afforded by mass spectroscopy [11].

The reaction of pyrimido[1,2-*b*]pyridazinones with nucleophiles had already been studied in a few models. Thus, the chlorine atom of 7-chloro-3-phenylpyrimido[1,2-*b*]-pyridazin-2(2*H*)-one, containing no carboxylic function was substituted by methylamine to give the 7-methylamino derivative [12], whereas the reaction of 4-phenylpyrimido-[1,2-*b*]pyridazin-2(2*H*)-one with potassium *t*-butoxide gave the appropriate pyrimidinone derivative by *N-N* bond fission [13].

We studied the reaction of methyl [7-chloro-2(2*H*)-oxo-pyrimido-[1,2-*b*]pyridazine-4-carboxylate (**2b**) with several amino compounds as nucleophilic participants. Different types of products could be separated depending on the amine used. With morpholine the 7-morpholino derivative **2c**, with ammonia the amide **2h** and with 2-aminoethanol the compounds **2i** and **2j** were obtained.

The reaction of **2c** with morpholine at elevated temperature led to the opening of the lactam-ring to give the acrylic acid morpholide derivative **7** (Scheme 4). This reaction may involve the formation of the tetrahedral intermediate **III** as a result of nucleophilic attack of the morpholine nitrogen on the carbonyl group of **2c** and the subsequent cleavage of the N_1-C_2 bond. In **III**, the lone pair of the morpholine nitrogen and one of the electron pairs of the carbonyl oxygen are in an antiperiplanar position to the N_1-C_2 bond, thus the stereoelectronic requirements are satisfied.

Scheme 4



Mph = morpholino

In **7**, the *E* configuration of the HC=CH group is supported by the value of the olefinic proton-proton coupling constant (^3J = 12.8 Hz). For the *E* geometry, the calculated [14] and measured chemical shifts are much closer than in the case of *Z* geometry. The *E* configuration (and the *endo-N*-position) is also proved by the results of DNOE measurements. Namely, on saturation of the *H*-β signal, the intensity enhancements of the N-C*H*$_2$ triplet of the acylmorpholine ring (and the *H*-α doublet) could be

Table 4

Physical and Analytical Data of Compounds **1i-k**, **2e-j**, **3b-d**, **f**, **4**, **5a**, **b**, **6a-c**, **7**, **8a**, **b**

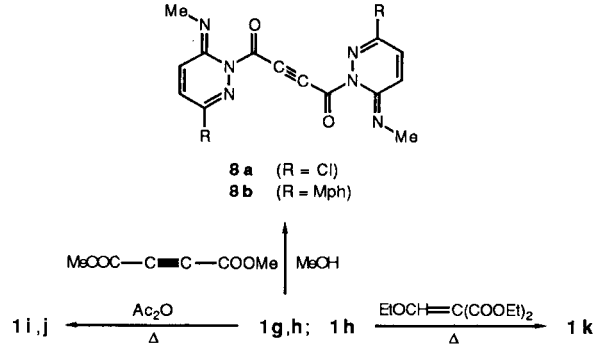
Compound	mp (°C) (Crystallized from)	Yield (%)	Molecular Formula	Analysis (%) (Found/Calcd.) C	H	N
1i	123-124 [a] (ethanol)	64				
1j	96-98 (ethanol)	67	$C_{11}H_{16}N_4O_2$ (236.27)	55.77 55.91	6.83 6.82	23.75 23.71
1k	92-94 (ethanol)	54	$C_{17}H_{24}N_4O_5$ (364.36)	56.07 56.03	6.84 6.64	15.31 15.38
2e	198-200 (2-propanol)	15	$C_9H_7N_3O_3$ (205.17)	52.47 52.69	3.59 3.44	20.35 20.48
2f	188-190 (2-propanol)	33	$N_{10}H_9N_3O_3$ (219.19)	54.91 54.79	4.18 4.14	19.02 19.17
2g	224-226 (ethanol)	48	$C_{10}H_8N_4O_4$ (248.19)	48.30 48.39	3.40 3.25	22.15 22.58
2h	297-298 (70% ethanol)	54	$C_8H_5ClN_4O_2$ (224.63)	42.53 42.77	2.42 2.24	24.74 24.94
2i	235-236 (50% ethanol)	21	$C_{10}H_9ClN_4O_3$ (268.66)	44.73 44.70	3.63 3.38	20.52 20.85
2j	271-272 (80% ethanol)	10	$C_{12}H_{15}N_5O_4$ (293.28)	48.75 49.14	5.00 5.12	23.41 23.88
3b	253-255 (methanol)	54	$C_9H_6ClN_3O_3$ (239.64)	45.32 45.11	2.47 2.52	17.48 17.53
3c	188-190 (ethanol)	68	$C_{11}H_{12}N_4O_2$ (232.24)	56.81 56.89	5.28 5.21	24.01 24.13
3d	234-236	75	$C_{13}H_{14}N_4O_4$ (290.28)	53.65 53.79	5.01 4.86	19.02 19.30
3f	152-154 [b] (ethanol)	50				
4a	217-218 (ethanol)	55	$C_{10}H_{11}N_3O_5$ (253.21)	47.51 47.43	4.30 4.38	16.39 16.59
5a	290-292 (ethanol)	70	$C_9H_7N_3O_4$ (221.17)	48.77 48.87	3.29 3.19	18.70 19.00
5b	269-271 [c]	32	$C_{10}H_9N_3O_4$ (235.19)	50.99 51.06	3.81 3.86	18.02 17.87
6a	140-142 (ethanol)	72	$C_{13}H_{17}N_3O_4$ (279.29)	55.79 55.90	6.32 6.14	14.96 15.04
6b	198-201 (ethanol)	71	$C_{13}H_{16}N_4O_5$ (308.29)	50.53 50.64	5.50 5.23	18.25 18.17
6c	188-190 (ethanol)	72	$C_{12}H_{15}N_3O_5$ (281.26)	51.36 51.24	5.41 5.38	14.99 14.98
7	224-226 (2-propanol)	53	$C_{15}H_{21}N_5O_3$ (319.36)	56.62 56.41	6.58 6.63	21.78 21.93
8a	> 300	12	$C_{14}H_{10}Cl_2N_6O_2$ (365.18)	46.18 46.04	2.68 2.76	22.90 23.02
8b	> 300	17	$C_{22}H_{26}N_8O_4$ (466.50)	56.14 56.64	5.94 5.62	23.56 24.02

[a] Reported value 121-123° [15]. [b] Reported value 154-155° [5]. [c] Dimethyl formamide-ethanol 1:1.

observed, while the intensity of the 4-*H* signal of the pyridazine ring was not altered. (In the case of *exo-N* substitution the intensity of the 4-*H* doublet should have been indentical). A similar result was obtained from the opposite experiment. The intensity of the *H-β* signal was not altered by irradiation of the 4-*H* signal. Otherwise, the cyclization of **7** in hot acetic acid gave **2c**.

On reacting the *exo-N*-methyl analogues of the compounds **1b,c**, *i.e.* **1g,h**, with DMAD in methanol the red-coloured **8a** and **8b** *endo-N*-acyl derivatives could only be separated in low yields, respectively (Scheme 5). On the other hand, the reaction of **1g** and **1h** with acetic anhydride gave the white *exo-N*-acyl derivatives **1i** [15] and **1j**, respectively, Similarly, the reaction of **1h** with DEM afforded the *exo-N* substituted product (**1k**).

Scheme 5



The substitution of the *exo* or *endo*-nitrogen was proved by ir, ^{1}H and ^{13}C nmr investigations (see Table 2).

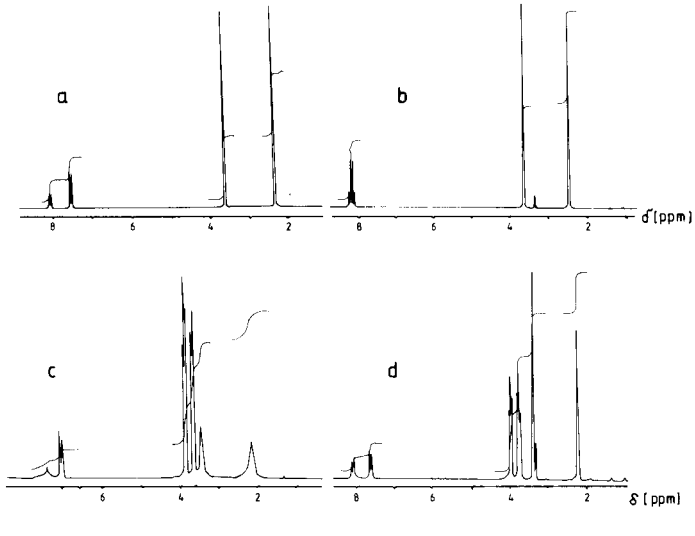
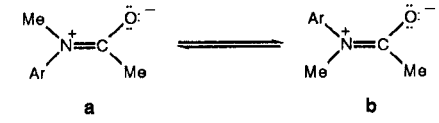


Figure 1 ^{1}H nmr spectra of **1i** (a,b) and **1j** (c,d) in deuteriochloroform (a, c) and trifluoroacetic acid (b,d)

The constitutions of **1i** and **1j** are supported by the relatively low amide-I frequency (1674 and 1657 cm^{-1}), respectively. In the case of the alternatively possible *endo-N* substitution the dipolar resonance form of the amide group should be unfavourable because of the participation of the more electron poor ring-nitrogen, thus causing an increase in this frequency.

The ^{1}H nmr data are also in full agreement with the proposed constitutions. The broadening of the 4-*H* signal of **1i** and especially of **1j** as well as that of the *N*-methyl and acetyl singlets of **1j** (Figure 1) can be interpreted by the *slow* interconversion of the rotamers **a** and **b** (Scheme 6).

Scheme 6



Ar = 6-morpholino-3-pyridazinyl

Comparing the chemical shifts measured in deuteriochloroform and trifluoroacetic acid also indicates the *exo* position of the acetyl group (Table 2). In the latter solvent the *N*-methyl signal is slightly upfield shifted, while the 4-*H* and 5-*H* signals are downfield shifted at a much higher extent. This fact proves that the *exo*-nitrogen is *not* protonated, *i.e.* this is the amide-nitrogen.

In the ^{1}H nmr spectrum of the *endo-N*-acyl derivative **8b** a similar broadening of signals cannot be observed. Moreover, the shift difference of the *N*-methyl singulets (measured also in the same solvents) has an opposite sing and is much higher as compared to **1j**. Because of poor solubility of **8a** in deuteriochloroform, the nmr measurements could only be carried out in trifluoroacetic acid. Nevertheless, an analogous constitution for **8a** could also be deduced from the ^{1}H nmr spectrum. The N-CH_3 signal appears at 3.90 ppm (for **8b** this value is 3.80 ppm) and in its ^{13}C nmr spectrum the shift of the N-CH_3 line (28.7 ppm) is practically identical as compared to that of **8b** (28.8 ppm). On the other hand, significantly different data were obtained for **1i** and **1j**.

These facts prove the different positions of the acyl groups in **8a,b** and **1i,j** respectively.

The *exo-N*-disubstituted constitution of **1k** is supported by the chemical shift of the N-CH_3 signal (37.6 ppm) and was proved unambiguously by its proton-coupled ^{13}C nmr spectrum. Namely, each line of the *N*-methyl quartet is further split to a doublet due to the coupling with the olefinic hydrogen, ^{3}J(C,H) = 6 Hz. Moreover, both lines of the doublet of the N-C*H*= group at 144.0 ppm show a further quartet splitting of 3 Hz, which similarly arises from a ^{3}J(C,H) type interaction between the olefinic C*H*= carbon and the hydrogens of the N-CH_3 group. In the case of an

endo-N-substitution, the analogous $^5J(C,H)$ coupling would not cause any significant splitting.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. The ir spectra were recorded in potassium bromide pellets on a Bruker IFS-113v FT-spectrometer equipped with an ASPECT 2000 computer. The ^1H and ^{13}C nmr spectra were recorded on Bruker WM-250 (^1H, ^{13}C) and WP-80-SY (^{13}C) FT spectrometers (controlled by an ASPECT 2000 computer at 250.13 (^1H) and 62.89 or 20.14 (^{13}C) MHz, respectively, at ambient temperature, using the ^2H signal of the solvent as the lock and TMS as internal reference. Typical parameters for ^1H measurments were as follows: pulse width: 1 μs (~20° flip angle): acquisition time 1.64 s for 16 or 32 K data points. Lorentzian exponential multiplication was used for signal-to-noise enhancement (line width 0.7 Hz). Data processing parameters for the ^{13}C spectra at 62.89 or 20.14 MHz, respectively were pulse width 7 or 3.5 μs (~30° flip angle); BB decoupling with 3 or 1.5 W; number of scans: 1-40 K; acquisition time, 1.02 or 1.64 s.

DNOE experiments of compound **7** were performed with the Bruker microprogramme. To generate NOE, gated decoupling was used with a delay time of 30 s and a decoupling power of 40 mW; number of scans, 32; relaxation delay, 0.1 s; dummy scans, 2. The uv spectra were recorded on a Cary 118 spectrometer in 96% ethanol.

Syntheses of compounds **1a** [16], **1b** [17], **1c** [6], **1d** [18], **1e** [19], **1f** [20], **1g** [21] and **1h** [22] were performed according to the quoted literature. The syntheses of **2a-d**, **3a** and **e** were reported earlier by us [1].

General Method for the Preparation of Pyrimido[1,2-*b*]pyridazin-2(2*H*)-ones **2e-g**.

Dimethyl acetylenedicarboxylate (10 mmoles) was added to a stirred solution of the appropriate 3-aminopyridazine (10 mmoles) in methanol either at reflux, for **2e** and **2g**, or at room temperature, for **2f**, under nitrogen. After stirring for several hours (monitored by tlc) under these conditions, the product was isolated either by suction and recrystallisation, **2g**, or by work up as follows for **2e,f**. The solvent was evaporated *in vacuo* and water was added to the oily residue. The solution was extracted with dichloromethane and the crude product obtained was chromatographed on silica gel using benzene-methanol (9:1) as eluent and recrystallized.

Methyl [2(2*H*)-Oxopyrimido[1,2-*b*]pyridazine-4-carboxylate] (**2e**).

This compound had uv: λ max (ε) 230 (28730), 257-265 sh (7040), 316 (1830); ir: ν C=O 1753 (ester), 1659 (amide-I) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.93 (s, 3H, OCH_3), 6.70 (s, 1H, 3-CH), 7.63 (m, 2H, 8- and 9-CH), 8.53 (m, 1H, 7-CH).

Methyl [7-Methyl-2(2*H*)-oxopyrimido[1,2-*b*]pyridazine-4-carboxylate] (**2f**).

This compound had uv: λ max (ε) 229 (31130), 265 (8240), 320 (2170); ir: νC=O 1736 (ester), 1645 (amide-I) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.53 (s, 3H, 7-CH_3), 4.00 (s, 3H, OCH_3), 6.61 (s, 1H, 8-CH), 7.26 (d, J = 9 Hz, 1H, 8-CH), 7.53 (d, 1H, 9-CH).

Methyl [7-Carbamoyl-2(2*H*)-oxopyrimido[1,2-*b*]pyridazine-4-carboxylate] (**2g**).

This compound had ir: νC=O 1750 (ester), 1710 (amide-I of carbamoyl group), 1650 (amide-I of ring) cm^{-1}; ^1H nmr (DMSO-d_6 + deuteriochloroform): δ 4.00 (s, 3H, OCH_3), 6.73 (s, 1H, 3-CH), 7.63 and 8.07 (2 x 1H, NH_2), 7.77 (d, 9, 1H, 9-CH), 8.03 (d, 1H, 8-CH).

Dimethyl [*N*-[3(2*H*)-Oxo-6-pyridazinyl]aminobutenedioate] (**4**).

Dimethyl acetylenedicarboxylate (1.42 g, 10 mmoles) was added to a stirred suspension of **1f** (1.11 g, 10 mmoles) in methanol (15 ml). The reaction mixture was refluxed for 10 hours and the precipitate was filtered off and recrystallized.

This compound had uv: λ max (ε) 300 (14325); ir: νNH 3350-2750, νC=O 1750, 1710 (ester), 1695 (amide-I) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.71 (s, 6H, OCH_3) 5.41 (s, 1H, *H*CCOOMe), 6.90 (d, 9, 1H, 5-CH), 7.55 (d, 1H, 4-CH), 9.71 (s, 1H, NH-amine), 12.42 (s, 1H, NH-amide); ^{13}C nmr (DMSO-d_6): δ 53.2 and 54.7 (OCH_3) 99.5 (=CH), 131.1 (C-4), 133.4 (C-5), 143.9 (=C, quaternary), 146.8 (C-6), 161.3 (C-3), 166.4 and 169.4 (ester C=O).

Methyl [4,7(4*H*,6*H*)-Dioxopyrimido[1,2-*b*]pyridazine-2-carboxylate] (**5a**).

A suspension of **4** (0.85 g, 3.3 mmoles) in acetic acid (8 ml) was stirred under reflux for 8 hours. After cooling at room temperature, the precipitate was filtered off and recrystallized. This compound had ir: νC=O 1750 (ester), 1715, 1680 (amide-I) cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.01 (s, 3H, OCH_3), 6.98 (s, 1H, 3-CH), 7.45, d (9.2, 1H, 9-CH), 8.05 (d, 1H, 8-CH); ^{13}C nmr: see Table 3.

Methyl [7-Chloro-4(4*H*)-oxopyrimido[1,2-*b*]pyridazine-2-carboxylate] (**3b**).

Compound **5a** (0.70 g, 3.2 mmoles) was added to phosphorus oxychloride (10 ml) and the mixture was stirred under reflux for 4 hours. The excess of phosphorus oxychloride was removed *in vacuo*, then cold water was added to the residue. After all solid had dissolved, the solution was neutralized with sodium carbonate. The product was extracted with dichloromethane and recrystallized. This compound had uv: λ max (ε) 246 (8640), 337 (7600); ^1H nmr (DMSO-d_6): δ 3.91 (s, 3H, OCH_3), 7.12 (s, 1H, 3-CH), 7.94 (d, 9.5, 1H, 8-CH), 8.20 (d, 1H, 9-CH); ^{13}C nmr: see Table 3.

Methyl [7-Morpholino-4(4*H*)-oxopyrimido[1,2-*b*]pyridazine-2-carboxylate] (**3d**).

A solution of **3b** (0.20 g, 0.8 mmole) and morpholine (0.20 g, 2.2 mmoles) in ethanol (4 ml) was stirred at room temperature for 3 days. The precipitate was filtered off and recrystallized. This compound had uv: λ max (ε) 226 (17130), 274 (15850), 313 (11410); ^1H nmr (DMSO-d_6): δ 3.64 (t, 4.6, 4H, NCH_2), 3.75 (t, 4H, OCH_2), 3.88 (s, 3H, OCH_3), 6.93 (s, 1H, 3-CH), 7.84 (d, 10.1, 1H, 8-CH), 7.90 (d, 1H, 9-CH); ^{13}C nmr: see Table 3.

7-Morpholinopyrimido[1,2-*b*]pyridazin-4(4*H*)-one (**3c**).

Method A.

A suspension of isopropylidene[(6-morpholino-3-pyridazinyl)aminomethylenemalonate] [6] (2.00 g, 6.0 mmoles) in Dowtherm A® (10 ml) was stirred at 220° (bath temperature) for 20 minutes. After cooling at room temperature, the solution was added dropwise to petroleum ether (30 ml). The precipitate was filtered off and purified by column chromatography on silica gel using benzene-methanol (8:2) as eluent. The crude product was recrystallized. This compound had uv: λ max (ε) 220 (15790), 254 (9990), 298 (16720); ^1H nmr (DMSO-d_6): δ 3.61 (m, 4H, NCH_2), 3.74 (m, 4H, OCH_2), 6.42 (d, 6.3, 1H, 3-CH), 7.78 (s, 2H, 8- and 9-CH), 8.09 (d, 1H, 2-CH); ^{13}C nmr: see Table 3.

Method B.

The same procedure was followed as described for **3d**, yield 68%. The products obtained by methods A and B were identical in all respects.

General Procedure for the Preparation of Diethyl [*N*-(6-Substituted-3-pyridazinyl)aminomethylenemalonates] **6a-c** and **1k**.

The appropriate 3-aminopyridazine **1** (10 mmoles) was added to diethyl ethoxymethylenemalonate (6 ml) and the mixture was heated at 120° for 2-3 hours (monitored by tlc). Then, ethanol was added until a clear solution was obtained. After cooling the solution, the precipitate was filtered off and recrystallized.

Diethyl [*N*-(6-Methyl-3-pyridazinyl)aminomethylenemalonate] (**6a**).

This compound had ir: νC=O 1695-1680, 1653 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (t, 6.5, 3H, OCH_2CH_3), 1.40 (t, 6.5, 3H, OCH_2CH_3), 2.67 (s, 3H, 6-CH_3), 4.20 (qa, 2H, OCH_2), 4.28 (qa, 2H, OCH_2), 7.05 (d, 9, 1H, 4-CH), 7.37 (d, 1H, 5-CH), 9.25 (d, 13, 1H, =CHN), 11.13 (d, 1H, NH).

Diethyl [*N*-(6-Carbamoyl-3-pyridazinyl)aminomethylenemalonate] (**6b**).

This compound had ir: νC=O 1700, 1645 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.30 (t, 7, 3H, OCH_2CH_3), 1.33 (t, 7, 3H, OCH_2CH_3), 4.23 (qa, 2H, OCH_2),

4.27 (qa, 2H, OCH_2), 7.7 (br, 2H, NH_2), 7.83 (d, 10, 1H, 4-CH), 8.17 (d, 1H, 5-CH), 9.20 (d, 13, 1H, =CHN), 11.03 (d, 1H, NH).

Diethyl [*N*-(6(1*H*)-Oxo-3-pyridazinyl)aminomethylenemalonate] (**6c**).

This compound had ir: νC=O 1700, 1670 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.25 (t, 7, 3H, OCH_2CH_3), 1.29 (t, 7, 3H, OCH_2CH_3), 4.15 (qa, 2H, OCH_2), 4.24 (qa, 2H, OCH_2), 6.98 (d, 10, 1H, 5-CH), 7.70 (d, 1H, 4-CH), 8.54 (d, 13, 1H, =CHN), 10.51 (d, 1H, amine-NH), 12.7 (s, 1H, amide-NH).

Diethyl [*N*-Methyl-*N*-(6-morpholino-3-pyridazinyl)aminomethylenemalonate] (**1k**).

This compound had uv: λ max (ε) 309 (30865); ir: νC=O 1738 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.25 (t, 7, 6H, OCH_2CH_3), 3.38 (s, 3H, NCH_3), 3.54 (m, 4H, NCH_2) 3.76 (m, 4H, morpholino-OCH_2), 4.20 (qa, 4H, OCH_2CH_3), 7.44 (d, 9.9, 1H, 5-CH), 7.60 (d, 1H, 4-CH), 8.28 (s, 1H, =CHN); ^{13}C nmr (DMSO-d_6): δ 13.9 and 14.1 (OCH_2CH_3), 35.5 (NCH_3), 45.6 (NCH_2), 60.4 and 61.0 (OCH_2CH_3), 66.2 (morpholino-OCH_2), 101.5 (=C, quaternary), 115.5 (C-5), 118.8 (C-4), 144.0 (=CH), 152.2 (C-3), 157.9 (C-6), 166.2 and 166.8 (ester C=O).

Ethyl [4,7(4*H*,6*H*)-Dioxopyrimido[1,2-*b*]pyridazine-3-carboxylate] (**5b**).

A suspension of **6c** (1.35 g, 4.8 mmoles) in Dowtherm A® (15 ml) was stirred at 175° for 100 minutes. After cooling at room temperature, the precipitate was filtered off and washed with petroleum ether. The crude product was recrystallized. This compound had ir: νC=O 1750, 1700 (sh) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.28 (t, 7, 3H, CH_3), 4.23 (qa, 2H, CH_2), 7.35 (d, 9, 1H, 9-CH), 7.93 (d, 1H, 8-CH), 8.73 (s, 1H, 2-CH), 12.8 (br, 1H, NH).

Ethyl [7-Chloro-4(4*H*)-oxopyrimido[1,2-*b*]pyridazine-3-carboxylate] (**3f**).

A solution of **5b** (0.30 g, 1.3 mmoles) in phosporus oxychloride (5 ml) was stirred under reflux for 5 hours. The excess of phosporus oxychloride was removed *in vacuo* and the residue was treated with water (15 ml). The solution was neutralized with sodium carbonate, then extracted with dichloromethane.

7-Chloro-2(2*H*)-oxopyrimido[1,2-*b*]pyridazine-4-carboxamide (**2h**).

A stirred suspension of **2b** (1.50 g, 6.3 mmoles) in ethanol (15 ml) was treated with ammonia solution in water (d, 0.91, 12 ml) at room temperature. After stirring for 3 hours, the solid was filtered off an recrystallized. This compound had ir: νC=O 1700 (amide-I of carbamoyl group), 1640 (amide-I of ring) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.47 (s, 1H, 3-CH), 7.75 (s, 2H, 8- and 9-CH), 8.13 and 8.26 (2H, NH_2).

N-2-Hydroxyethyl[7-chloro-2(2*H*)-oxopyrimido[1,2-*b*]pyridazine-4-carboxamide] (**2i**) and *N*-2-Hydroxyethyl[7-*N*-(2-hydroxyethyl)-amino-2-(2*H*)-oxopyrimido[1,2-*b*]pyridazine-4-carboxamide] (**2j**).

A solution of **2b** (1.92 g, 8.0 mmoles) and 2-aminoethanol (1.10 g, 18.0 mmoles) in ethanol (45 ml) was stirred at room temperature for 24 hours. The precipitate was filtered off and recrystallized to give **2i**. This compound had ir: νC=O 1670, 1637 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.35 (m, 2H, NCH_2), 3.50 (m, 2H, CH_2OH), 4.82 (t, 4.5, 1H, OH), 6.50 (s, 1H, 3-CH), 7.73 (d, 9.6, 1H, 8-CH), 7.78 (d, 1H, 9-CH), 8.82 (t, 4.5, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 61.0 (CH_2OH), 114.6 (C-3), 132.4 (C-9), 136.8 (C-8), 147.0 (C-4), 148.5 (C-7), 149.4 (C-9a), 161.0 (amide C=O), 168.2 (C-2).

The mother liquor of the recrystallization of **2i** was concentrated *in vacuo* and the residue was recrystallized several times to give **2j**. This compound had ir: νC=O 1670, 1625 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.3-3.6 (m, 8H, CH_2CH_2), 4.77 (m, 2H, OH), 6.23 (s, 1H, 3-CH), 7.43 (t, 4.5, 1H, NH), 7.20 (d, 10, 1H, 8-CH), 7.37 (d, 1H, 9-CH), 8.8 (t, 4.5, 1H amide-NH); ^{13}C nmr (DMSO-d_6: δ 43.8 (NCH_2), 45.5 (NCH_2), 60.5 (OCH_2), 61.4 (OCH_2), 113.3 (C-3), 127.2 (C-8), 133.8 (C-9), 148.6 (C-4), 149.4 (C-7), 153.4 (C-9a), 162.7 (amide C=O), 169.7 (C-2).

Methyl [7-Morpholino-2(2*H*)-oxopyrimido[1,2-*b*]pyridazine-4-carboxylate] (**2d**).

Starting from **2b** and morpholine, the same procedure was followed as described for **3d**, yield 71% of **2d**. The physical and spectroscopic data were identical with the published values [1].

4-[3-[3(2*H*)-Imino-6-morpholino-2-pyridazinyl]propenoyl]morpholine (**7**).

A solution of **2c** as monohydrate (2.20 g, 8.8 mmoles) in morpholine (7 ml) was stirred under reflux for 15 hours. After cooling at 5°, the precipitate was filtered off and recrystallized.

This compound had ir: νNH 3250, νC=O 1663 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.26 (t, 4.9, 4H, acylmorpholino-NCH_2), 3.51 (t, 4.8, 4H, 6-morpholino-NCH_2), 3.72 (t, 4H, acylmorpholino-OCH_2), 3.84 (t, 4H, 6-morpholino-OCH_2), 5.09 (d, 12.8, 1H, H-α), 7.03 (d, 9.8, 1H, 5-CH), 7.48 (d, 1H, H-β), 8.41 (d, 1H, 4-CH), 9.45 (br, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 46.3 (NCH_2), 48.9 (NCH_2), 66.2 and 66.6 (OCH_2), 89.3 (CH-α), 115.5 (C-4), 122.0 (C-5), 150.7 (CH-β), 150.9 (C-3), 158.2 (C-6), 167.5 (C=O).

The Reaction of **1g** and **1h** with Dimethyl Acetylenedicarboxalate.

A suspension of the appropriate 6-substituted-3-*N*-methylaminopyridazine (**1g** or **1h**) (5 mmoles) and DMAD (5 mmoles) in methanol (15 ml) was stirred under reflux for 5 hours. The precipitate was filtered off and resuspended in hot methanol, then filtered, to give **8a** or **8b**, respectively.

2,2'-Acetylenedicarbonyl-6,6'-dichloro-3,3'(2*H*,2'*H*')-*bis*(*N*-methylimino)-pyridazine (**8a**).

This compound had uv: λ max (ε) 422 (13475); ir: νC=O 1649 cm^{-1}; ^{13}C nmr (trifluoroacetic acid): δ 95.5 (≡C), 119.5 (C-4), 126.1 (C-5), 131.6 (C-6), 152.2 (C-3), 152.4 (C=O).

2,2'-Acetylenedicarbonyl-3,3'(2*H*,2'*H*)-bis(*N*-methylimino)-6,6'-dimorpholinopyridazine (**8b**).

This compound had uv: λ max (ε) 412 (9330); ir: νC=O 1657 cm^{-1}; ^{13}C nmr (trifluoroacetic acid): δ 47.3 (NCH_2), 67.3 (OCH_2), 110.0 (≡C), 118.7 (C-4), 124.2 (C-5), 157.6 (C=O), 159.1 (C-3), 160.9 (C-6).

Acetylation of **1g** and **1h**.

The 3-*N*-methylaminopyridazine derivative (**1g** or **1h**) was heated at 70° in acetic anhydride (10 fold by volume) for 4 hours. The mixture was concentrated *in vacuo* and the residue was treated with water. The solution was neutralized with 4% sodium hydroxide solution, then extracted with ethyl acetate. After drying and evaporation to dryness, the residue was suspended in diethyl ether filtered off and recrystallized to give **1i** or **1j**, respectively.

3-(*N*-Acetyl-*N*-methylamino)-6-chloropyridazine (**1i**).

This compound had ^1H nmr (deuteriochloroform): δ 2.35 (s, 3H, $COCH_3$); ^{13}C nmr (deuteriochloroform): δ 23.4 ($COCH_3$), 125.9 (C-4), 128.4 (C-5), 152.9 (C-3), 157.5 (C-6), 171.1 (C=O).

3-(*N*-Acetyl-*N*-methylamino)-6-morpholinopyridazine (**1j**).

This compound had ^1H nmr (deuteriochloroform): δ 2.11 (br s, 3H, $COCH_3$), 3.64 (m, 4H, NCH_2), 3.86 (m, 4H, OCH_2); ^{13}C nmr (deuteriochloroform): δ 22.4 ($COCH_3$), 44.9 (NCH_2), 65.8 (OCH_2), 113.8 (C-5), 125.5 (C-4), 152.0 (C-3), 158.2 (C-6), 170.1 (C=O). (For other ^1H and ^{13}C nmr data of **1i** and **1j** see Table 2.)

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