Pyridazines 93 [1]. An Unexpected Reaction Behaviour of 3-Aminopyridazine Towards 2-Methylphenylisocyanate

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Reaction of 3-aminopyridazine (**1**) with 2-methylphenylisocyante (**4**) affords not only the desired urea derivative (**5**) but also an unexpected side-product (**6**), which could be identified as the corresponding biuret derivative by means of elemental and spectroscopic data as well as crystal structure determination.

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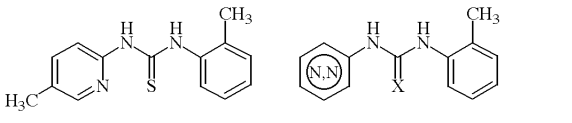
Introduction.

Previously, we reported on the antiviral [2] and anticonvulsant [3] activities of *N*-aryl-*N'*-diazinyl-substituted urea and thiourea derivatives. In an extension of our investigations directed toward the exploitation of the bioisosteric potential of the pyridazine, pyrimidine, and pyrazine system we now became interested in the synthesis of diazine analogues (**B**) [4] of the potent antineoplastic agent 5-MTUoT (**A,** Scheme 1) [5].

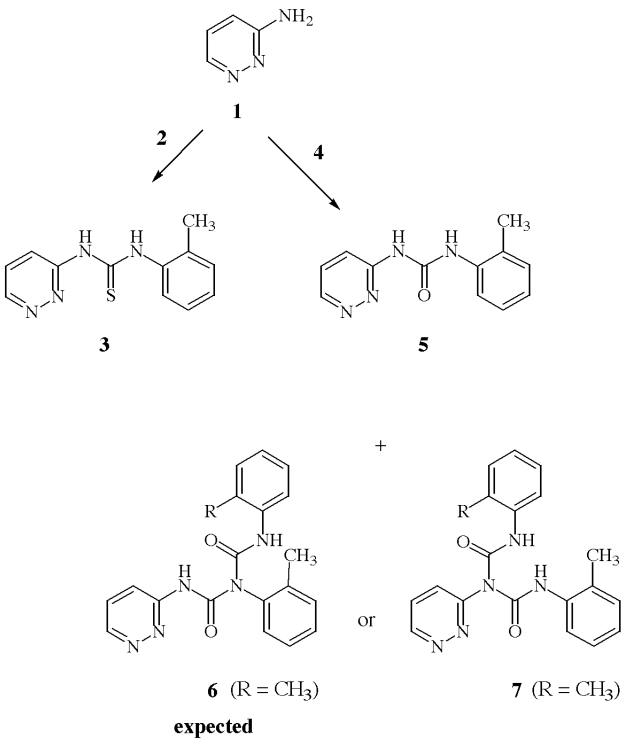
Scheme 1



The preparation of (thio)ureas usually can be achieved by reaction of an amine with the appropriate iso(thio)cyanate [6]. By contrast, aminodiazines do not react with iso(thio)cyanates under standard conditions obviously due to the poor nucleophilicity of the amino function. Recently we have reported an efficient procedure [7] for the synthesis of such target compounds, which are readily accessible by reacting the aminodiazine with the iso(thio)cyanate in dry *N*,*N*-dimethylformamide in the presence of sodium hydride.

Under the same reaction conditions as described above, treatment of 3-aminopyridazine (**1**) with 2-methylphenylisothiocyanate (**2**) led to the desired thiourea **3**. On the contrary, reaction of **1** with 2-methylphenylisocyanate (**4**) surprisingly yielded two products, which could be separated and identified as the urea derivate (**5**) and an ureido compound as indicated by spectroscopic data and elemental analyses. This additional attack of **4** on compound **5** can lead to the formation of either compound

Scheme 2



6 or **7**, but considering the poor nucleophilicity of the amino group of aminodiazines we expected an attack of another isocyanate molecule on the NH-group adjacent to the phenyl moiety (Scheme 2).

Structure elucidation could be achieved by X-Ray analysis. Thus, the structure of a 3,5-di(2-methylphenyl)-1-(3-pyridazinyl) biuret (**6**) has to be assigned to the new compound (Figure 1).

In order to gain insight into structural features influencing the formation of the biuret derivative, the following experiments were carried out: On one hand, we

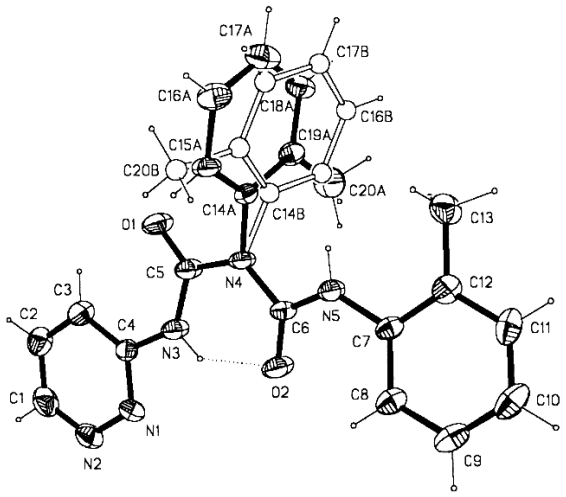


Figure 1. Molecular structure of **6** in crystalline state with 2-methylphenyl group C(14)-C(20) in both A and B orientations (A full bonds, B open bonds; 20% ellipsoids). Selected bond lengths (Å): N(1)-N(2) = 1.346(5), N(1)-C(4) = 1.321(5), N(2)-C(1) = 1.318(7), N(3)-C(4) = 1.397(5), N(3)-C(5) = 1.344(5), N(4)-C(5) = 1.413(5), N(4)-C(6) = 1.398(5), N(5)-C(6) = 1.345(5), N(5)-C(7) = 1.413(5), C(5)-O(1) = 1.206(5), C(6)-O(2) = 1.205(4), N(3)···O(2) = 2.589(4).

Table 1

Atomic Coordinates and Equivalent Isotropic Displacement Parameters of the Non-hydrogen Atoms of $C_{20}H_{19}N_5O_2$ (**6**). C(#A) and C(#B) Sites are from an Orientation-disordered 2-Methylphenyl Group with Refined Site Occupancies of 0.515(4) for A- and 0.485(4) for B-sites

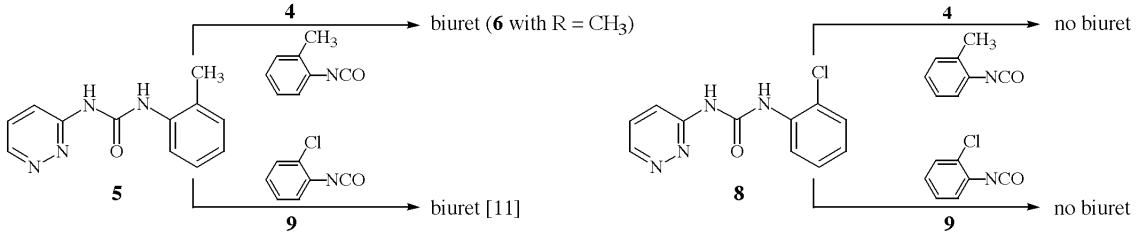
	x/a	*y/b*	*z/c*	U_{eq} [Å^2 x 10^3]
O(1)	0.4024(7)	0.3489(2)	0.6520(1)	91(1)
O(2)	0.3747(6)	0.2336(2)	0.4661(1)	87(1)
N(1)	0.3678(5)	0.0194(3)	0.6107(2)	73(1)
N(2)	0.3712(5)	-0.0683(3)	0.6497(3)	88(1)
N(3)	0.3889(6)	0.1972(2)	0.5904(2)	67(1)
N(4)	0.4008(6)	0.3679(2)	0.5421(1)	65(1)
N(5)	0.4241(6)	0.4039(2)	0.4320(2)	63(1)
C(1)	0.3933(6)	-0.0548(4)	0.7130(3)	96(2)
C(2)	0.4136(7)	0.0441(4)	0.7418(2)	83(2)
C(3)	0.4098(7)	0.1335(4)	0.7035(2)	76(1)
C(4)	0.3882(6)	0.1158(3)	0.6377(2)	57(1)
C(5)	0.3921(8)	0.3049(3)	0.5996(2)	65(1)
C(6)	0.3987(7)	0.3280(3)	0.4782(2)	55(1)
C(7)	0.4096(5)	0.3942(3)	0.3636(2)	58(1)
C(8)	0.4179(5)	0.2948(4)	0.3321(2)	72(1)
C(9)	0.4060(6)	0.2923(5)	0.2651(2)	84(2)
C(10)	0.3865(7)	0.3861(5)	0.2297(2)	97(2)
C(11)	0.3789(7)	0.4832(5)	0.2613(2)	90(2)
C(12)	0.3886(6)	0.4898(4)	0.3293(2)	67(1)
C(13)	0.3739(9)	0.5979(4)	0.3636(2)	86(2)
C(14A)	0.4512(7)	0.4804(3)	0.5530(3)	48(2)
C(15A)	0.6277(6)	0.5190(4)	0.5633(3)	63(2)
C(16A)	0.6566(8)	0.6286(4)	0.5746(4)	82(2)
C(17A)	0.5091(10)	0.6997(3)	0.5757(4)	90(3)
C(18A)	0.3326(9)	0.6612(4)	0.5654(4)	72(3)
C(19A)	0.3037(6)	0.5515(4)	0.5541(3)	60(2)
C(20A)	0.1124(11)	0.5097(7)	0.5430(8)	98(4)
C(14B)	0.3521(8)	0.4832(3)	0.5516(4)	48(2)
C(15B)	0.1800(7)	0.5278(5)	0.5407(4)	63(2)
C(16B)	0.1547(9)	0.6390(5)	0.5456(4)	82(2)
C(17B)	0.3015(11)	0.7057(4)	0.5615(4)	90(3)
C(18B)	0.4735(9)	0.6611(4)	0.5724(4)	72(3)
C(19B)	0.4988(7)	0.5499(4)	0.5674(4)	60(2)
C(20B)	0.6848(12)	0.5014(7)	0.5800(8)	98(4)

investigated the reactivity of the urea derivative **5** with 2-methylphenylisocyanate (**4**) and the corresponding 2-chlorophenylisocyanate (**9**), respectively. On the other hand, the *N*-(2-chlorophenyl)-*N'*-(3-pyridazinyl)urea (**8**) [4] was treated with both isocyanates **4** and **9**.

The results obtained show that reaction of *N*-(methylphenyl)-*N'*-pyridazinylurea (**5**) with the isocyanates **4** or **9**, respectively, resulted in the formation of the corresponding biuret derivatives. However, the urea derivative **8** in which the methyl group in compound **5** is replaced by an electron-withdrawing chloro atom was not acylated under these reaction conditions (see Scheme 3).

In summary, the results obtained show that there is an influence on the substituent at the phenyl moiety in the urea derivative on the formation of a biuret. Whereas **5** can be acylated with both **4** and **9**, replacement of the methyl group by an electron-withdrawing chloro atom (compound **8**) prevents the formation of the by-product possibly due to the reduced nucleophilicity of the N-atom adjacent to the phenyl ring. Moreover, we could observe that reaction of the isothiocyanate **2** with **1** does not result in the formation of a biuret analogue. It should be noted that not only the 3-aminopyridazine derivative **5** can be transformed into the diacylated derivative but also other aminodiazines do undergo this unexpected reaction [8,9]. The synthesis of these (thio)urea compounds and biuret analogues will be published together with their biological activities [4].

Scheme 3



EXPERIMENTAL

Melting points were determined with a Kofler hot-stage microscope (Reichert) and are uncorrected. Infrared spectra (potassium bromide pellets) were recorded on a Mattson Galaxy Series FTIR 3000 spectrophotometer. Mass spectra were obtained on a Finnigan MAT SSQ 7000 spectrometer (EI, 70 eV). All NMR spectra were recorded in deuteriodimethyl sulfoxide solution in 5 mm tubes at 30 °C on a Varian Gemini 200 spectrometer (199.98 MHz for ^{1}H, 50.29 MHz for ^{13}C) with the deuterium signal of the solvent as the lock. The centre of the solvent multiplet was used as internal standard. Chemical shifts are expressed in parts per million (ppm). DEPT spectra were run in a standard manner using only the $\theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. Reactions were monitored by thin layer chromatography using Polygram® SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness) and visualised using an UV lamp. Column chromatography was conducted on Merck silica gel 60 (230-400 mesh). Elemental analyses were performed by Mag. J. Theiner, Institute of Physical Chemistry, University of Vienna, Austria. All reagents with the exception of 3-aminopyridazine, which was prepared in analogy to [10] were commercially available and used without further purification. Light petroleum refers to the fraction of bp 40-60 °C.

General Procedure for the Reaction of 3-Aminopyridazine (**1**) with 2-Methylphenyliso(thio)cyanate.

A solution of 250 mg (2.63 mmol) of 3-aminopyridazine (**1**) in 4 mL of dry *N*,*N*-dimethylformamide was added *via* a syringe to a stirred suspension of sodium hydride (105 mg, 2.63 mmol, 60 % dispersion in mineral oil) in 2 mL of ice-cooled dry *N*,*N*-dimethylformamide. To the stirred reaction mixture a solution of 2.89 mmol (1.1 equivalents) of 2-methylphenyliso(thio)-cyanate in 1 mL of dry *N*,*N*-dimethylformamide was added slowly at 0 °C. The mixture was then allowed to warm up to room temperature. After stirring for additional 3 hours, the mixture was poured into water/2*N* HCl, whereupon compounds **3** and **5** precipitated from their aqueous layers. The colourless crystals were collected by filtration, washed with cooled light petroleum and recrystallised. Compound **6** was consequently recovered from the acid mother liquor by evaporation of the solvent. The residue thus obtained was subjected to column chromatography (silica gel, ethyl acetate) followed by recrystallisation from diisopropyl ether/ethyl acetate.

N-(2-Methylphenyl)-*N'*-(3-pyridazinyl)thiourea (**3**).

This compound was obtained as light yellow needles (ethyl acetate/methanol), 282 mg (40 %), mp 183-185 °C; ir: NH 3212 cm^{-1}; ^{1}H nmr: δ 13.26 (br s, 1H, NH), 11.08 (br s, 1H, N'H), 8.92 (dd, 1H, J_{46} = 1.3 Hz, J_{56} = 4.5 Hz, pyridazine H-6), 7.74 (dd, 1H, J_{45} = 9.1 Hz, J_{56} = 4.5 Hz, pyridazine H-5), 7.69-7.58 (m, 2H, phenyl H-6, pyridazine H-4), 7.31-7.16 (m, 3H, phenyl H-3, H-4, H-5), 2.28 (s, 3H, CH_3); ^{13}C-nmr: δ 179.1 (C=S), 156.7 (pyridazine C-3), 147.6 (pyridazine C-6), 137.3 (phenyl C-1), 133.1 (phenyl C-2), 130.3, 129.8, 126.6, 126.5, 126.0 (phenyl C-3, C-4, C-5, C-6, pyridazine C-5), 118.6 (pyridazine C-4), 17.8 (CH_3); ms: m/z 244.1 (64 %, M^+).

Anal. Calcd. for $C_{12}H_{12}N_4S$: C, 58.99; H, 4.95; N, 22.93. Found: C, 59.20; H, 4.87; N, 22.89.

N-(2-Methylphenyl)-*N'*-(3-pyridazinyl)urea (**5**).

This compound was obtained as colourless needles (ethyl acetate), 234 mg (39 %), mp 188-192 °C; ir: NH 3281, CO 1708 cm^{-1}; ^{1}H nmr: δ 10.04 (br s, 1H, N'H), 9.93 (br s, 1H, NH), 8.84 (dd, 1H, J_{46} = 1.4 Hz, J_{56} = 4.6 Hz, pyridazine H-6), 7.92 ("d", 1H, J = 7.4 Hz, phenyl H-6), 7.82 (dd, 1H, J_{45} = 9.0 Hz, J_{46} = 1.4 Hz, pyridazine H-4), 7.62 (dd, 1H, J_{45} = 9.0 Hz, J_{56} = 4.6 Hz, pyridazine H-5), 7.21-7.12 (m, 2H, phenyl H-3, H-4), 7.01-6.93 (m, 1H, phenyl H-5), 2.28 (s, 3H, CH_3); ^{13}C nmr: δ 156.1 (pyridazine C-3), 152.1 (C=O), 147.1 (pyridazine C-6), 136.1 (phenyl C-1), 130.3, 128.9, 126.3, 123.3, 120.9 (phenyl C-3, C-4, C-5, C-6, pyridazine C-5), 127.6 (phenyl C-2), 117.2 (pyridazine C-4), 17.9 (CH_3); ms: m/z 228.1 (25 %, M^+).

Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.44; H, 5.19; N, 24.66.

3,5-Di(2-methylphenyl)-1-(3-pyridazinyl)biuret (**6**).

This compound was obtained as colourless needles (diisopropyl ether/ethyl acetate), 76 mg (8 %), mp 178-189 °C; ir: NH 3165, CO 1716, 1675 cm^{-1}; ^{1}H nmr: δ 10.26 (br s, 1H, NH), 8.92 (dd, 1H, J_{46} = 1.4 Hz, J_{56} = 4.7 Hz, pyridazine H-6), 8.50 (br s, 1H, NH), 8.36 (dd, 1H, J_{45} = 9.1 Hz, J_{46} = 1.4 Hz, pyridazine H-4), 7.92 (d, 1H, J = 7.8 Hz, phenyl H), 7.49-7.38 (m, 5H, 4x phenyl H, pyridazine H-5), 7.22-7.02 (m, 3H, 3x phenyl H), 2.36 (s, 3H, CH_3), 2.10 (s, 3H, CH_3); ^{13}C nmr: δ 155.2, 153.1, 152.2 (pyridazine C-3, 2x C=O), 148.4 (pyridazine C-6), 137.5, 135.4, 134.9, 128.6 (phenyl C-1, C-1', C-2, C-2'), 132.2, 130.5, 130.4, 129.6, 128.3, 128.0, 126.9, 125.0, 122.0 (phenyl C-3, C-3', C-4, C-4', C-5, C-5', C-6, C-6', pyridazine C-5), 118.4 (pyridazine C-4), 17.5 (CH_3), 17.4 (CH_3); ms: m/z 361.1 (<5 %, M^+).

Anal. Calcd. for $C_{20}H_{19}N_5O_2$: C, 66.47; H, 5.30; N, 19.38. Found: C, 66.19; H, 5.28; N, 19.12.

X-Ray Structure Determination of **6**.

Crystal data: $C_{20}H_{19}N_5O_2$, M_r = 361.40, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 7.304(4) Å, b = 12.348(6) Å, c = 20.497(12) Å, V = 1848.6(17) Å^3, Z = 4, D_x = 1.299 Mg/m^{-3}, λ = 0.71073 Å, μ = 0.088 mm^{-1}, T = 298(2) K.

Preliminary X-ray investigations showed all crystals to scatter poorly with an upper resolution of about 0.90 Å^{-1}. A colourless prism of 0.10 x 0.18 x 0.35 mm was then used for X-ray data collection with a SIEMENS SMART CCD area detector three-circle diffractometer and graphite monochromatized Mo Kα radiation. The intensities of 16831 reflections with $\theta < 23°$ were measured by ω-scan frames (complete sphere, $\Delta\omega = 0.3°$, 20 sec per frame). The data were corrected for *LP* and absorption and were merged to 2538 unique reflections, R_{int} = 0.088, R_{sigma} = 0.051.

The structure was solved with direct methods and was refined on F^2 using program SHELXL97 [12]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted in calculated positions. One of the two 2-methylphenyl groups showed an orientation disorder with the methyl groups in a ratio of 0.515(4)/0.485(4) on either side of the molecular main plane as depicted in Figure 1. This disorder was modelled with rigid group and U_{ij} restraints. The final full matrix least-squares refinement varied 246 parameters and converged at $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.093$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.158$, and $S = 1.03$ for all 2538 unique reflections; $R1 = 0.062$ for the 1764 observed data [$I > 2\sigma(I)$]. Atomic coordinates are given in Table 1, further

crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 145894. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44 1223 336033, email: deposit@ccdc.cam.ac.uk).

The molecular structure of **6** in solid state is shown in Figure 1. The biuret moiety and the two terminal rings [N(1)-C(4), C(7)-C(13)] form an approximately planar system (0.114 Å r.m.s. deviation of the corresponding non-hydrogen atoms from best plane) that is stabilized by hybridization and by a short intramolecular hydrogen bond N(3)-H(3n)···O(2) with N(3)···O(2) = 2.589(4) Å and ∠N(3)-H(3n)-O(2) = 140°. Sterical hindrance by O(1) and N(5)-bonded H(5n) forces the third phenyl ring C(14A)-C(19A) [C(14B)-C(19B) for the alternative orientation] to be oriented approximately perpendicular to the molecular main plane. With these features the molecular structure of **6** corresponds closely to that of *N*,*N*',*N*''-triphenylbiuret [13], which crystallizes in a monoclinic lattice with a spatial arrangement of the molecules differing from that of **6**. The intramolecular hydrogen bond in triphenylbiuret measures N···O = 2.587 Å, very similar to **6**. Triphenylbiuret shows in addition a second intermolecular N-H···O hydrogen bond between the atoms corresponding in **6** to N(5) and O(1). Such hydrogen bond is missing in **6** because here the hydrogen H(5n) is buried so well between methyl C(17) and the third phenyl ring, that it is inaccessible for any H-bond acceptor other than the adjacent π-electrons of the phenyl ring C(14A)-C(19A)/C(14B)-C(19B). Although **6** does not contain an asymmetric C or N atom, it is evident from Figure 1 that the molecule has planar-chiral properties stemming from the asymmetry introduced by the 2-methylphenyl moiety C(14)-C(20) and the sterical hindrance against reorientation at suitable conditions of temperature and solvent. The chiral crystal lattice of **6** (space group $P2_12_12_1$) contains columnar arrangements of molecules π-stacked along 2_1-axes parallel to crystallographic **a**-axis. Within such columns the molecules fit only together if they have the same planar chirality, *i.e.* orientation of methyl C(20). However, because adjacent molecular columns obviously fit well together irrespective of the methyl C(20) orientations in neighbouring columns, the chiral crystal lattice can tolerate both planar-chiral enantiomers of **6**. Thus compound **6** is an example, where a chiral crystal lattice does not discriminate between enantiomers of the underlying molecules and cannot be used for enantiomer separation by crystallization.

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[11] The structure of the biuret resulting from the reaction of **5** with **9** was not confirmed by X-ray analysis. However, due to the poor nucleophilicity of the amino group of aminopyridazines and the structure of the methylphenyl biuret analogue **6** (with R = CH_3) we expect structure **6** (with R = Cl) for this product.

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