A New Approach for the Synthesis of Pteridines: The Synthesis of 3-substituted-2-thioxo-1,2-dihydro-4(3*H*)-pteridinones

Uroš Urleb*[#], Richard Neidlein and Walter Kramer

Pharmazeutisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 364, D-6900 Heidelberg, Federal Republic of Germany

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Dedicated to Professor Gerhard Fritz, Karlsruhe, on the occasion of his 70th birthday

3-Substituted-2-thioxo-1,2-dihydro-4(3*H*)-pteridinones can be conveniently prepared by the reaction of methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** with *N*-nucleophiles. The scope and limitations of the method are presented. The tautomeric form of 2-thioxo-1,2-dihydro-4(3*H*)-pteridinones was determined on the basis of a ^{13}C-{^1H}-NOE experiment.

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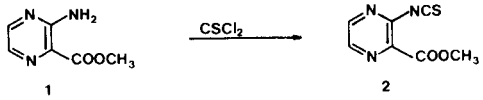
Aromatic and heteroaromatic compounds bearing an *ortho* amino and ester groups are useful synthons for the preparation of various condensed heterocyclic systems [1]. Although the chemistry of methyl 2-isothiocyanatobenzoate has been investigated intensively [2-5], heterocyclic analogues have not attracted any attention. Our previous research on heterocyclic isothiocyanates [6] and the fact, that the number of publications on the synthesis and reactivity of heterocyclic isothiocyanates is very limited [7], prompted us to start this investigation. We report a new approach for the synthesis of pteridines from pyrazine, which enables 3-substituted-2-thioxo-1,2-dihydro-4(3*H*)-pteridinones or 3-substituted-2-thiolumazines to be prepared.

Although several methods are available for the syntheses of pteridines [8,9], the methodology whereby the pyrazine intermediate requiring the addition of N-3 to complete the pteridine ring has not been widely used [9]. Our method represents a facile and short way to 3-substituted pteridinones.

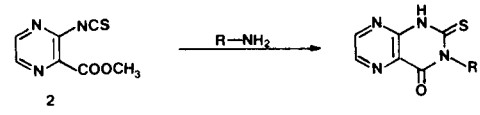
Scheme 1



1 2

Treatment of methyl 3-amino-2-pyrazinecarboxylate **1** with thiophosgene afforded methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (Scheme 1). Methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** is stable at room temperature and displays in its ir spectrum an intensive absorption at 2060 cm^{-1}, which is assigned to the N=C=S stretching vibration. The subsequent reaction of isothiocyanate **2** with primary alkylamines, arylalkylamines, aminoalcohols, aminoacids or aminoacid ester and hydrazine hydrate led to 3-substituted 2-thiolumazines **3a-k** (Scheme 2). The reaction could be performed in a short time under mild reaction conditions at room or slightly elevated temperature in ethanolic solution, or in the case of aminoacids in dioxane-water mixture at alkaline *p*H value (*p*H = 9).

Scheme 2

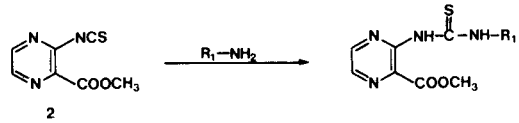


2

3a, R=CH_3
3b, R= n-Pr
3c, R= CH_2—CH=CH_2
3d, R=CH_2CH_2Ph
3e, R=CH_2CH_2OH
3f, R=$CH_2CH_2OCH_2CH_2OH$
3g, R=NH_2
3h, R=CH_2COOH
3i, R=$CH(CH_3)COOH$
3j, R=CH_2CH_2COOH
3k, R=CH_2COOEt

An analogous treatment of isothiocyanate **2** with sterically hindered amines, such as adamantylamine, *t*-butylamine and D,L(±)-α-methylbenzylamine led only to the methyl 3-(*N*-substituted-thioureido)-2-pyrazinecarboxylate **4a-c** (Scheme 3). Under more drastic reaction conditions, *e.g.* in refluxing pyridine, the expected pteridine derivatives were not formed. When isothiocyanate **2** was treated with aniline in refluxing ethanol, methyl 3-(3-anilinothioureido)-2-pyrazinecarboxylate **4d** was formed and no cyclized product could be isolated, because of low nucleophilicity of the aniline amino group (Scheme 3).

Scheme 3



2

4a, R_1= tert.-Butyl
4b, R_1= Adamantyl
4c, R_1= $CH(CH_3)Ph$
4d, R_1= Ph

The common type of prototropic tautomerism in heterocyclic compounds involves the movement of a proton between a ring nitrogen atom and a substituent atom connected to the ring [10]. In case of 2-thiolumazines the tautomeric equilibrium between thioamide- and imine-thiol-form seems to be widely shifted towards the thioamide-form [11] (Scheme 4) as indicated by the uv spectra [11-14]. Some applications of ^{13}C-nmr spectroscopy to heteroaromatic tautomerism have also been made [15-17].

Scheme 4

For analysis of the tautomerism in our pteridine system we used the technique of selective heteronuclear $^{13}C\{^1H\}$-NOE difference spectroscopy [18] as a tool to determine the neighboured carbon atoms to the tautomeric proton. Compound **3k** was investigated as an example.

For complete and unequivocal ^{13}C chemical shift assignments of **3k** the $^{13}C\{^1H\}$-NOE difference technique was applied in combination with two dimensional heteronuclear correlation spectroscopy (^{1}H, ^{13}C-COSY) and J-coupling patterns in the proton-coupled carbon nmr spectrum.

Selective low power irradiation of the CH_2-9 protons provides signal enhancements of C-2, C-4 and C-9 and due to weak irradiation of the ^{13}C-satellite lines of H-9 a small NOE of C-9 itself (Figure 1c). In the proton-coupled ^{13}C nmr spectrum (Figure 2) the most downfield shifted signal is split into a triplet by coupling with CH_2-9 (^3J = 5 Hz) and must be assigned therefore to C-2. The next of the three quarternary downfield carbon signals displays a septet (couplings with the CH_2-9 and CH_2-11 protons, ^3J = 3.1 Hz, ^2J = 6.2 Hz) and corresponds to the ethoxycarbonyl group. The third signal (C-4) appears as a double triplet owing to long-range couplings to the CH_2-9 and H-6 protons (^3J = 3.1 Hz, ^4J = 0.8 Hz).

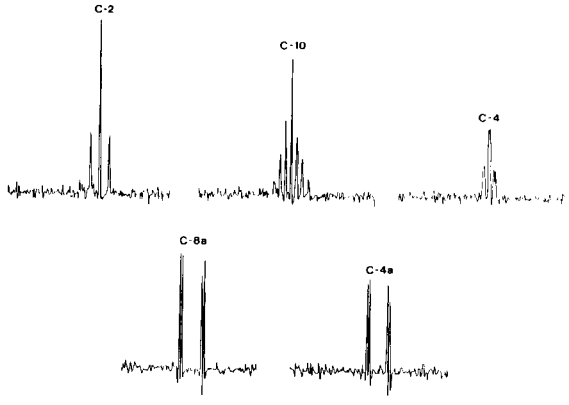


Figure 2. 62.89 MHz ^{13}C nmr spectrum of **3k** in DMSO-d_6 recorded with gated decoupling (non-protonated carbon atoms).

Selective low power irradiation of the exchangeable proton at 13.9 ppm produces only two NOEs at quarternary carbon atoms (Figure 1b). As one of these signals has already been assigned to carbon C-2 the other signal has to be assigned to carbon C-8a. So it can be assumed that the thio-amide-form must predominate or exclusively exist as the only tautomer of **3k**, because no enhancement of the C-8a signal can occur if the proton would be bound to the sulfur in the imine-thiol-form. Furthermore, no NOE was detected for C-9 which one could expect for the imine-thiol-tautomer on irradiation of the SH-proton.

With the known identity of C-8a the assignment of the protonated carbon and hydrogen atoms is now possible by long range and one bond heteronuclear chemical shift correlation spectroscopy (Figure 3). Both, proton and carbon chemical shifts of C-7/H-7 appear at lower field than C-6/H-6 which is in accordance with the assignments in similar systems by H. Günther and coworkers [19].

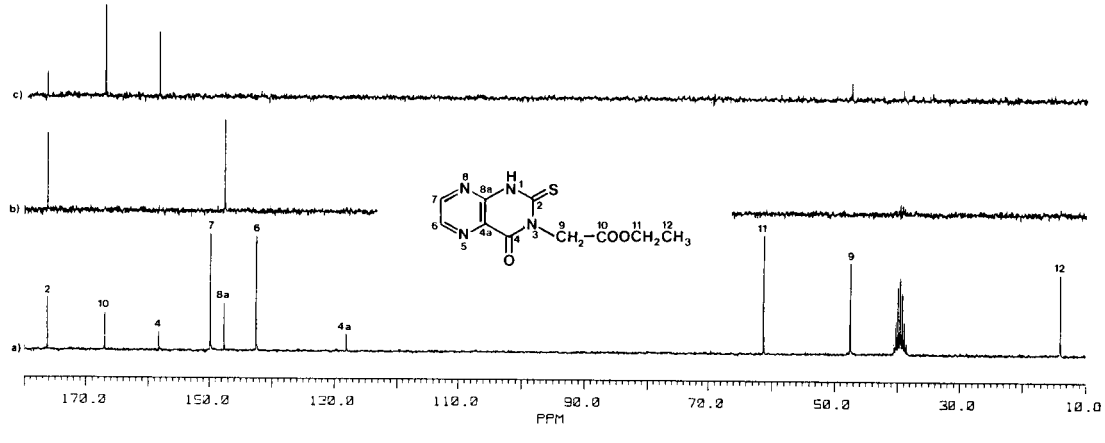


Figure 1. (a) Proton noise-decoupled 62.89 MHz ^{13}C nmr spectrum of **3k** in DMSO-d_6; NOE difference spectra resulting from irradiation of (b) NH and (c) 9-CH_2).

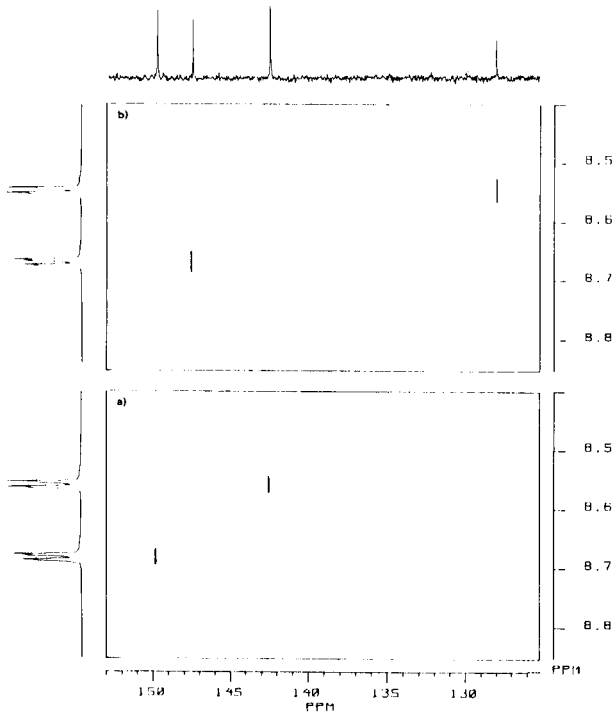


Figure 3. One bond (a) and long range (b) heteronuclear shift correlation spectra of **3k** recorded in DMSO-d_6 at observation frequencies of 250.13/62.89 MHz for ^1H and ^{13}C, respectively.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Microanalyses were performed on a Heraeus CHN-O Rapid analyzer. Electron impact mass spectra were measured at 100 eV on a Varian MAT 311 A mass spectrometer. The nmr spectra were recorded on a Bruker HX-90E (^1H, 90 MHz) and Bruker WM-250 spectrometer (^{13}C, 62.89 MHz). Tetramethylsilane was used as internal standard. The ^{13}C chemical shifts in DMSO-d_6 are referred to the solvent chemical shift (39.5 ppm). Experimental details for the $^{13}C\{^1H\}$-NOE difference technique were similar as described in lit [18]. The ^{13}C, ^1H-shift correlated spectra of **3k** were acquired and processed with Bruker standard software; relaxation delay: 3s; delays for polarisation and refocussing (0.5/J) were optimized for $^1J_{C,H}$ = 188 Hz (2.66 ms) and $^3J_{C,H}$ = 11 Hz (45.45 ms) respectively; spectral widths: 3401 Hz in F_2, 250 Hz in f_1; initial matrix: 256 x 2K real data points, zero-filled to 512 x 2K data points; window functions: Lorentz-Gauss lineshape transformation in f_1 and exponential multiplication in f_2. The ir spectra were recorded on a Perkin-Elmer model 325 instrument as potassium bromide pellets.

Methyl 3-Isothiocyanato-2-pyrazinecarboxylate (**2**).

A suspension of methyl 3-amino-2-pyrazinecarboxylate **1** [20] (1.76 g, 11.5 mmoles) in dichloromethane (10 ml) was added to a stirred suspension of calcium carbonate (2.9 g, 72.5 mmoles) in water (40 ml) and dichloromethane (80 ml) at room temperature. To the stirred mixture with ice-bath cooling was slowly added thiophosgene (1 ml, 13 mmoles). The temperature of the reaction mixture was left to reach room temperature and stirring was continued for 48 hours. Inorganic salts were removed by filtration, the organic phase was separated and washed with water (20 ml) and 5% aqueous sodium bicarbonate (20 ml). After drying over magnesium sulfate, the dichloromethane was removed under reduced pressure and the residue purified using column chromatography (silica gel, chloroform:acetone = 30:1) to give 1.19 g (53%) of **2**, mp 20-23°; ir: 3450, 2060, 1730 cm^{-1}; ms: (30°) m/e 195 (M^+, 100); ^1H-nmr (deuteriochloroform): δ 4.07 (s, 3H, OCH_3), 8.59 (s, 2H, H_5 and H_6); ^{13}C-nmr (deuteriochloroform): δ 53.5 (CH_3), 138.8 (dd, ^3J = 10.9 Hz, ^4J = 2.1 Hz, C-3), 141.4 (dd, ^1J = 188.4 Hz, ^2J = 10.6 Hz), 142.3 (m, ^3J = 12 Hz, C-2), 143.8 (br, NCS), 146.5 (dd, ^1J = 186.5 Hz, ^2J = 11.6 Hz, C-6), 163.0 (dq, ^3J = 3.9 Hz, ^4J = 0.8 Hz, CO).

Anal. Calcd. for $C_7H_5N_3O_2S$ (195.20): C, 43.07; H, 2.58; N, 21.53. Found: C, 43.05; H, 2.56; N, 21.15.

General Procedure for the Synthesis of 3-Alkyl-2-thioxo-1,2-dihydro-4(3*H*)-pteridinones **3a-c**.

A mixture of methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (0.22 g, 1.2 mmoles) and the alkylamine (1.2 mmoles) in absolute ethanol (3 ml) was stirred at room temperature for 5 hours. The separated product was filtered off and recrystallized from appropriate solvent.

3-Methyl-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3a**).

This compound was obtained as yellow solid, 309-311° (315° [14]); ir: 3080, 1655, 1570 cm^{-1}; ms: (122°) m/e 194 (M^+, 100); ^1H-nmr (DMSO-d_6): δ 3.69 (s, 3H, CH_3), 8.33 and 8.64 (2d, J = 1.95 Hz, 1H each, H_6 and H_7).

3-Propyl-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3b**).

This compound was obtained as pale yellow crystals (methanol-chloroform), mp 265-268°; ir: 2960, 1715, 1570 cm^{-1}; ms: (122°) m/e 222 (M^+, 100); ^1H-nmr (DMSO-d_6): δ 0.93 (t, J = 7 Hz, 3H, CH_3), 1.60-1.76 (m, 2H, CH_2), 4.3 (t, J = 7 Hz, 2H, CH_2), 8.63 and 8.75 (2s, 1H each, H_6 and H_7), ^{13}C-nmr (DMSO-d_6): δ 11.1 ($CH_2CH_2CH_3$), 19.3 ($CH_2CH_2CH_3$), 47.7 ($CH_2CH_2CH_3$), 128.7 (C-4a), 141.8 (C-6), 147.3 (C-8a), 149.0 (C-7), 158.4 (C-4), 176.2 (C-2).

Anal. Calcd. for $C_9H_{10}N_4OS$ (222.27): C, 48.43; H, 4.54; N, 25.21. Found: C, 48.81; H, 4.64; N, 25.38.

3-Allyl-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3c**).

This compound was obtained as white crystals (methanol-*N*,*N*-dimethylformamide), mp 223-226°; ir: 3080, 1720, 1580 cm^{-1}; ms: (132°) m/e 220 (M^+, 41), 205 (100); ^1H-nmr (DMSO-d_6): δ 5.01-5.13 (m, 2H, allyl H), 5.26 (dd, J = 1.7 Hz, 9.3 Hz, allyl H), 5.71-6.07 (m, 1H, allyl H), 8.65 and 8.77 (2d, J = 2.4 Hz, 1H each, H_6 and H_7); ^{13}C-nmr (DMSO-d_6): δ 48.2 ($CH_2CH=CH_2$), 117.2 ($CH_2CH=CH_2$), 128.7 (C-4a), 131.3 ($CH_2CH=CH_2$), 141.9 (C-6), 147.5 (C-8a), 149.1 (C-7), 158.2 (C-4), 176.2 (C-2).

Anal. Calcd. for $C_9H_8N_4OS$ (220.25): C, 49.08; H, 3.66; N, 25.44. Found: C, 49.32; H, 3.75; N, 25.65.

3-(2-Phenylethyl)-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3d**).

This compound was obtained as colourless crystals in 88% yield, mp 263-264°; ir: 2940, 1710, 1560 cm^{-1}: ms: (154°) m/e 284 (M^+, 26), 104 (100); ^1H-nmr (DMSO-d_6): δ 2.98 (t, 2H, NCH_2CH_2), 4.59 (t, 2H, NCH_2CH_2), 7.32 (s, $5H_{arom}$), 8.66 and 8.77 (2d, J = 1.95 Hz, 1H each, H_6 and H_7), 13.63 (broad, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 31.9 (NCH_2CH_2), 47.6 (NCH_2CH_2), 126.4 (C-4'), 128.5 (C-2',3',5',6'), 128.7 (C-4a), 138.4 (C-1'), 141.9 (C-6), 147.4

(C-8a), 149.1 (C-7), 158.3 (C-4), 176.1 (C-2).

Anal. Calcd. for $C_{14}H_{12}N_4OS$ (284.34): C, 59.14; H, 4.25; N, 19.70. Found: C, 59.29; H, 4.25; N, 19.49.

3-(2-Hydroxyethyl)-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3e**).

A solution of methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (0.12 g, 0.6 mmole) and 2-aminoethanol (0.38 g, 0.6 mmole) in 5 ml of absolute ethanol was stirred at room temperature for 1 hour and the separated product was filtered off. Recrystallization from methanol-*N,N*-dimethylformamide (1:1) gave 0.1 g (73%) of a pale yellow solid, mp 235-236°; ir: 3300, 3220, 3080, 1670 cm^{-1}; ms: (160°) m/e 224 (M^+,3), 181 (100); ^{1}H-nmr (DMSO-d_6): δ 2.90 (t, 1H, OH), 3.66 (t, J = 6.6 Hz, 2H, NCH_2CH_2), 4.54 (t, J = 6.6 Hz, 2H, NCH_2CH_2), 8.55 and 8.72 (2d, J = 1.95 Hz, 1H each, H_6 and H_7); ^{13}C-nmr (DMSO-d_6): δ 47.7 (NCH_2CH_2), 56.6 (NCH_2CH_2), 128.8 (C-4a), 141.5 (C-6), 147.9 (C-8a), 149.1 (C-7), 158.9 (C-4), 176.8 (C-2).

Anal. Calcd. for $C_8H_8N_4O_3S$ (224.24): C, 42.85; H, 3.60; N, 24.98. Found: C, 42.73; H, 3.74; N, 24.69.

3-(2-(2-Hydroxyethoxy)ethyl)-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3f**).

A solution of methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (0.14 g, 0.7 mmole) and 2-(2-aminoethoxy)ethanol (0.07 g, 0.7 mmole) in absolute ethanol (3 ml) was heated at reflux for 3 hours, the precipitated product was filtered off and recrystallized from ethanol to give 0.10 g (52%) of pale yellow solid, mp 217-220°; ir: 3420, 1720, 1580, 1190 cm^{-1}; ms: (142°) m/e 268 (M^+, 3), 181 (100); ^{1}H-nmr (DMSO-d_6): δ 3.49-3.68 (m, 7H, OH, $3CH_2$), 4.60 (t, J = 6.8 Hz, 2H, CH_2), 8.65 and 8.72 (2d, J = 1.95 Hz, 1H each, H_6 and H_7); ^{13}C-nmr (DMSO-d_6): δ 44.9 (NCH_2CH_2O), 60.2 (OCH_2CH_2OH), 65.5 (NCH_2CH_2O), 72.3 (OCH_2CH_2OH), 128.6 (C-4a), 141.9 (C-6), 147.4 (C-8a), 149.1 (C-7), 158.5 (C-4), 176.4 (C-2).

Anal. Calcd. for $C_{10}H_{12}N_4O_3S$ (268.30): C, 44.77; H, 4.51; N, 20.88. Found: C, 44.94; H, 4.60; N, 20.76,

3-Amino-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3g**).

To a solution of methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (0.4 g, 2.1 mmoles) in ethanol (6 ml), 99% hydrazine hydrate (1 ml) was added, the reaction mixture was stirred for 5 minutes and precipitated product was filtered off to give 0.46 g (97%) of dark yellow solid, mp over 310°; ir: 3310, 3205, 3080, 2970, 1705, 1580 cm^{-1}; ms: (135°) m/e 195 (M^+, 100); ^{1}H-nmr (DMSO-d_6): δ 8.56 and 8.70 (2s, 1H each, H_6 and H_7); hrms Calcd. for $C_6H_5N_5OS$: 195.0215. Found: 195.0222 (peak matching).

General Procedure for the Synthesis of 3-(Carboxyalkyl)-2-thioxo-1,2-dihydro-4(3*H*)-pteridinones **3h-j**.

To a stirred solution of aminoacid (2.6 mmoles) in water (3 ml, dioxane (3 ml) and 1*M* sodium hydroxide (2.6 ml), methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (0.5 g, 2.6 mmoles) was added. The reaction mixture was stirred at 60° for 7 hours and then evaporated under reduced pressure. The residue was suspended in water (10 ml) and acidified with 1*M* hydrochloric acid until *p*H of 3 was obtained. The precipitated solid was isolated by suction filtration.

3-(Carboxymethyl)-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3h**).

This compound was obtained in 75% yield (methanol), mp 260-263°; ir: 3440, 2980, 1715, 1570 cm^{-1}; ms: (190°) m/e 238 (M^+, 100); ^{1}H-nmr (DMSO-d_6): δ 5.13 (s, 2H, CH_2), 8.66 and 8.78 (2d, J = 1.95 Hz, 1H each, H_6 and H_7), 13.86 (broad, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 47.4 (CH_2), 128.1 (dd, ^3J = 10.8 Hz, ^4J = 1.5 Hz, C-4a), 142.5 (dd, ^1J = 189.6 Hz, ^2J = 10.4 Hz, C-6), 147.6 (dd, ^3J = 11.2 Hz, ^4J = 1.5 Hz, C-8a), 149.8 (dd, ^1J = 187.5 Hz, ^2J = 11.8 Hz, C-7), 158.3 (dt, ^3J = 3.1 Hz, ^4J = 0.8 Hz, C-4), 168.4 (t, ^2J = 6 Hz, COOH), 176.4 (t, ^3J = 5.4 Hz, C-2).

Anal. Calcd. for $C_8H_6N_4O_3S$ (238.23): C, 40.34; H, 2.54; N, 23.52. Found: C, 40.24; H, 2.56; N, 23.50.

3-(1-Carboxyethyl)-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3i**).

This compound was obtained as pale yellow crystals in 93% yield (water), mp 180° dec; ir: 3580, 2960, 1715, 1680, 1570 cm^{-1}; ms: (169°) m/e 252 (M^+, 100); ^{1}H-nmr (DMSO-d_6): δ 1.52 (d, J = 6.9 Hz, 3H, CH_3), 6.34 (q, J = 6.9 Hz, 1H, CH), 8.66 and 8.78 (2d, J = 2.1 Hz, 1H each, H_6 and H_7), 12.78 and 13.87 (2s, 1H each, NH); ^{13}C-nmr (DMSO-d_6): δ 13.1 (CH_3), 56.1 (CH), 128.4 (C-4a), 142.4 (C-6), 147.3 (C-8a), 149.6 (C-7), 157.7 (C-4), 170.3 (COOH), 176.3 (C-2).

Anal. Calcd. for $C_9H_8N_4O_3S$ (252.25): C, 42.85; H, 3.20; N, 22.21. Found: C, 43.10; H, 3.29; N, 22.35.

3-(2-Carboxyethyl)-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3j**).

This compound was recrystallized from *N,N*-dimethylformamide to give pale yellow solid in 85% yield, mp 271-274°; ir: 3280, 2840, 1740, 1695, 1580 cm^{-1}; ms: (160°) m/e 252 (M^+, 100); ^{1}H-nmr (DMSO-d_6): δ 2.66 (t, J = 7.9 Hz, 2H, CH_2), 4.60 (t, J = 7.9 Hz, 2H, CH_2), 8.65 and 8.77 (2d, J = 1.95 Hz, 1H each, H_6 and H_7); ^{13}C-nmr (DMSO-d_6): δ 30.5 (NCH_2CH_2), 42.1 (NCH_2CH_2), 128.7 (C-4a), 141.9 (C-6), 147.4 (C-8a), 149.1 (C-7), 158.4 (C-4), 172.3 (COOH), 176.1 (C-2).

Anal. Calcd. for $C_9H_8N_4O_3S$ (252.25: C, 42.85; H, 3.20; N, 22.21. Found: C, 43.00; H, 3.27; N, 22.12.

3-(2-Ethoxycarbonylmethyl)-2-thioxo-1,2-dihydro-4(3*H*)-pteridinone (**3k**).

To a solution of ethyl glycinate hydrochloride (0.52 g, 3.7 mmoles) in water (5 ml), dioxane (5 ml) and 1*M* sodium hydroxide (3.7 ml), methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (0.72 g, 3.7 mmoles) was added, and the reaction mixture was stirring at 50° for 4 hours. The precipitated solid was filtered off and recrystallized from methanol-*N,N*-dimethylformamide (1:1) to give 0.40 g (41%) of white or pale red crystals, mp 238-241°; ir: 3460, 2980, 1730, 1580 cm^{-1}; ms: (124°) m/e 266 (M^+, 100); ^{1}H-nmr (DMSO-d_6): δ 1.22 (t, J = 7.1 Hz, 3H, CH_3), 4.17 (q, J = 7.1 Hz, 2H, CH_2), 5.18 (s, 2H, CH_2), 8.70 and 8.82 (2d, J = 2.44 Hz, 1H each, H_6 and H_7), 13.9 (b s, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 14.0 ($COOCH_2CH_3$), 47.5 (CH_2), 61.2 ($COOCH_2CH_3$), 128.0 (dd, ^3J = 10.8 Hz, ^4J = 1.5 Hz, C-4a), 142.5 (dd, ^1J = 189.8 Hz, ^2J = 10.4 Hz, C-6), 147.6 (dd, ^3J = 12.0 Hz, ^4J = 1.5 Hz, C-8a), 149.8 (dd, ^1J = 187.3 Hz, ^2J = 11.6 Hz, C-7), 158.2 (dt, ^3J = 3.1 Hz, ^4J = 0.8 Hz, C-4), 167.0 (tt, ^3J = 3.1 Hz, ^2J = 6.2 Hz, COOH, *cf.* **3h**), 176.3 (t, ^3J = 5.2 Hz, C-2).

Anal. Calcd. for $C_{10}H_{10}N_4O_3S$ (266.28): C, 45.11; H, 3.79; N, 21.04. Found: C, 45.27; H, 3.90; N, 21.08.

General Procedure for the Synthesis of Methyl 3-(3-Alkylthioureido)-2-pyrazinecarboxylates **4a-c**.

To a solution of methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (0.33 g, 1.7 mmoles) in absolute ethanol (5 ml), primary alkylamine (1.7 mmoles) was added, stirred at room temperature for 5 hours and the precipitated product was filtered off.

Methyl 3-(3-*t*-Butylthioureido)-2-pyrazinecarboxylate (**4a**).

Recrystallization from ethanol gave pale yellow product in 49% yield, mp 180-183°; ir: 3280, 3080, 2990, 1700, 1590, 1515 cm^{-1}; ms: (100°) m/e 268 (M^+, 60), 153 (100); ^{1}H-nmr (DMSO-d_6): δ 1.56 (s, 9H, CH_3), 3.93 (s, 3H, OCH_3), 8.39 and 8.53 (2d, J = 2.44 Hz, 1H each, H_5 and H_6), 10.92 and 11.27 (2 broad s, 1H each, NH); ^{13}C-nmr (deuteriochloroform): δ 28.2 ($C(CH_3)_3$), 53.7 ($COOCH_3$), 54.6 ($C(CH_3)_3$), 127.3 (C-2), 136.1 (C-6), 143.6 (C-5), 149.7 (C-3), 165.5 (C=O), 178.1 (C=S); hrms: Calcd. for $C_{11}H_{16}N_4O_2S$: 268.0994. Found: 268.0993 (peak matching).

Methyl 3-(3-Adamantylthioureido)-2-pyrazinecarboxylate (**4b**).

This compound was recrystallized from ethanol to give colourless crystals in 79% yield, mp 217-220°; ir: 3280, 3055, 2920, 1710, 1590, 1520 cm^{-1}; ms: (135°) m/e 346 (M^+, 51), 135 (100); ^{1}H-nmr (deuteriochloroform): δ 1.73 (s, 6H, adamantyl CH_2), 2.15 (s, 3H, adamantyl CH), 2.35 (s, 6H, adamantyl CH_2), 4.05 (s, 3H, OCH_3), 8.31 (s, 2H, H_5 and H_6), 11.09 (broad, 2H, NH); ^{13}C-nmr (deuteriochloroform): δ 29.6 (C-3', C-5', C-7'), 36.4 (C-4', C-6', C-10'), 40.7 (C-2', C-8', C-9'), 53.7 ($COOCH_3$), 55.3 (C-1'), 127.2 (C-2), 136.1 (C-6), 143.8 (C-5), 149.7 (C-3), 165.4 (C=O), 177.2 (C=S).

Anal. Calcd. for $C_{17}H_{22}N_4O_2S$ (346.46): C, 58.94; H, 6.40; N, 16.17. Found: C, 58.93; H, 6.42; N, 15.74.

Methyl 3-(3-(1-Phenylethyl)thioureido)-2-pyrazinecarboxylate (**4c**).

This compound was obtained in 71% yield (methanol), mp 156-159°; ir: 3290, 3060, 1690, 1585 cm^{-1}; ms: (113°) m/e 316 (M^+, 64), 120 (100); ^{1}H-nmr (DMSO-d_6): δ 1.56 (d, J = 6.8 Hz, 3H, CH_3), 3.94 (s, 3H, OCH_3), 5.50-5.66 (m, 1H, CH), 7.12-7.45 (m, 5H_{arom}), 8.43 and 8.58 (2d, J = 2.44 Hz, 1H each, H_5 and H_6), 10.95 (broad, 1H, NH), 11.43 (d, 1H, NH); ^{13}C-nmr (DMSO-d_6): δ 21.8 ($CH(CH_3)$), 53.0 ($COOCH_3$), 54.6 ($CH(CH_3)$), 126.1 (C-2', C-6'), 127.1 (C-4'), 127.6 (C-2), 128.5 (C-3',C-5'), 137.1 (C-6), 142.5 (C-1'), 144.3 (C-5), 148.9 (C-3), 165.7 (C=O), 178.1 (C=S).

Anal. Calcd. for $C_{15}H_{16}N_4O_2S$ (316.69): C, 56.95; H, 5.10; N, 17.71. Found: C, 57.11; H, 5.01; N, 17.76.

Methyl 3-(3-Anilinothioureido)-2-pyrazinecarboxylate (**4d**).

To a solution of methyl 3-isothiocyanato-2-pyrazinecarboxylate **2** (0.19 g, 1 mmole) in absolute ethanol (3 ml), aniline, (0.093 g, 1 mmole) was added, and reaction mixture was heated at reflux for 4 hours. The precipitated product was filtered off and recrystallized from *N,N*-dimethylformamide to give 0.20 g (74%) of colourless crystals, mp 197-200°; ir: 3450, 3280, 2830, 1695, 1645, 1580 cm^{-1}; ms: (131°) m/e 288 (M^+, 69), 229 (100); ^{1}H-nmr (DMSO-d_6): δ 3.97 (s, 3H, OCH_3), 7.25-7.74 (m, 5H_{arom}), 8.47 and 8.63 (2d, J = 2.4 Hz, 1H each, H_5 and H_6), 11.24 (s, 1H, NH), 12.93 (s, 1H, NH); hrms. Calcd. for $C_{13}H_{12}N_4O_2S$: 288.0681. Found: 288.0680 (peak matching).

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[#] Alexander von Humboldt Research Fellow 1989. Permanent address: Department of Pharmacy, E. Kardelj University of Ljubljana, Aškerčeva 9,61000 Ljubljana, Yugoslavia.

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