Syntheses and Transformations of Some 1,2,4-Oxadiazolylpyrazines

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Cyanopyrazines with an *ortho*-amino, oxo and other groups are transformed into the corresponding amidoximes. From these the corresponding 1,2,4-oxadiazolyl derivatives can be prepared and interconversions to the corresponding pteridine 3-oxides are described.

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Our interest in the chemistry of heterocyclic hydroxylamines, hydroxyimino derivatives or amidoximes which are useful synthons for the preparation of different heterocyclic systems (1-3), prompted us to investigate further the reactivity of such compounds. In this paper we report on reactions leading to pyrazinyloxadiazoles and in part also to pteridine 3-oxides. Transformations of the latter will be published in a separate publication.

The cyano group of several substituted cyanopyrazines reacts readily with free hydroxylamine to give the corresponding amidoximes. However, if an adjacent amino group is first converted into an amidine with *N,N*-dimethylformamide dialkyl acetal, hydroxylamine reacts with both functional groups and, for example, compound **1** (R = N=CHNMe$_2$) is transformed into **2** (R = NHCH=NOH, R$_1$ = H). Alternatively, this compound can be obtained by ring opening of the pyrimidine part of 4-aminopteridine 3-oxide under the influence of free hydroxylamine. If in the above reaction between the amidine (**1**, R = N=CHNMe$_2$) instead of the free base hydroxylamine hydrochloride is used, 4-aminopteridine 3-oxide (**5**, R = H) is obtained as the main product (80%), accompanied with some 2-aminopyrazine-3-carboxamide oxime (**2**, R = NH$_2$, R$_1$ = H) (11%) and traces of 2-amino-3-cyanopyrazine and 2-aminopyrazine-3-carboxamide. On the other hand, 4-aminopteridine 3-oxide is formed in good yield from the amidoxime **2** (R = NH$_2$, R$_1$ = H) with either triethyl orthoformate or diethoxymethyl acetate.

The amidoxime **2** (R = NH$_2$, R$_1$ = H) is amenable to several other transformations. The amino group of the amidoxime function can be converted into the chloro substituted derivative (**4**) and the hydroxyimino part of the same functional group can be alkylated (**2**, R = NH$_2$, R$_1$ = Me), acylated (**2**, R = NH$_2$, R$_1$ = COMe or COPh) or carbethoxylated (**2**, R = NH$_2$, R$_1$ = COOEt). It is well established that acylation of hydroxylamines usually leads to the thermodynamically more stable *N*-acyl compounds (hydroxamic acids), whereas amidoximes are generally *O*-acylated (4-6). With triethyl orthoacetate under reflux the corresponding carboxamide *O*-(1,1-diethoxy)ethyloxime (**2**, R = NH$_2$, R$_1$ = CMe(OEt)$_2$) is obtained and this is further transformed in hot glacial acetic acid into a mixture of 4-amino-2-methylpteridine 3-oxide (**5**, R = Me), the starting amidoxime (**2**, R = NH$_2$, R$_1$ = H) and the oxadi-

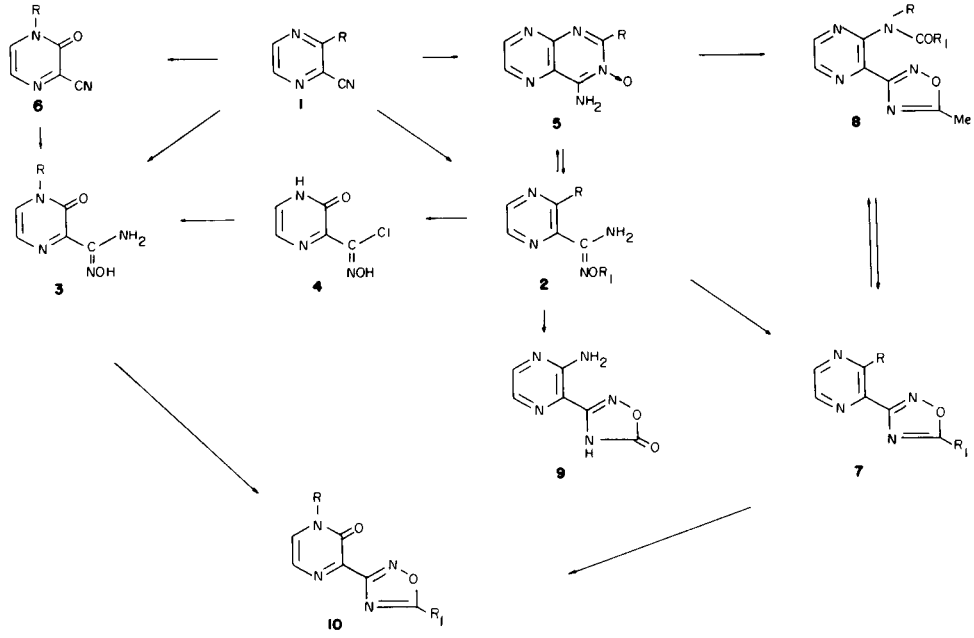

Table I

Compound No.	R	R_1	Mp °C	crystallized from	Yield %	Formula	Analysis % Calcd.(Found) C	H	N	MS M⁺	Solvent	NMR Data (chemical shifts, δ, coupling constants (J, Hz) H_5 and H_6	H_2' and H_6'	H_3' and H_4' and H_5'	$J_{5,6}$	Other signals
2	NH_2	H	185-187	methanol	85	$C_7H_5N_5O$	39.21 (39.35)	4.61 (4.96)	45.73 (45.84)	153	DMSO-d_6	7.40 and 7.58 (d)			2.4	9.4 (s, OH), 7.02 and 5.62 (broad s, two NH_2)
2	NHCOPh	H	196-198	ethanol	74	$C_{12}H_{11}N_5O$	56.02 (55.75)	4.31 (4.19)	27.23 (26.98)	257	DMSO-d_6	8.48 and 8.59 (d)	7.98-8.23 (m)	7.70 (m)	2.4	12.60 and 10.77 (broad s, NH, OH), 6.40 (broad s, NH_2)
3	Me	H	220-222	water	82	$C_6H_6N_4O_2$	42.85 (43.00)	4.80 (4.85)	33.32 (33.29)	168	DMSO-d_6 (125°)	7.37 and 7.61 (d)			4.2	3.46 (s, Me)
2	OMe	H	226-229	ethanol-DMF	65 (a)	$C_6H_6N_4O_2$	42.85 (42.82)	4.80 (5.00)	33.32 (33.21)	168	DMSO-d_6	8.20 (s)			—	3.90 (s, Me), 10.02 (s, OH), 5.70 (broad s, NH_2)
2	Cl	H	185-187	methanol	89 (b)	$C_5H_4ClN_4O$	34.80 (35.02)	2.92 (3.11)	32.47 (32.12)	172	DMSO-d_6	8.47 and 8.63 (d)			2.3	10.03 (s, OH), 5.87 (broad s, NH_2)
2	Cl	COMe	125-127	ethanol	60 (c)	$C_7H_7ClN_4O_2$	39.18 (39.25)	3.29 (3.45)	26.11 (26.27)	214	DMSO-d_6	8.60 and 8.70 (d)			2.4	2.12 (s, Me)
3	Me	COMe	169-170	ethanol	64	$C_8H_{10}N_4O_3$	45.71 (45.90)	4.80 (5.01)	26.66 (26.82)	210	DMSO-d_6	7.32 and 7.79 (d)			4.2	3.47 (s, NMe), 2.09 (s, COMe)
2	OMe	COMe	132-134	ethanol	45	$C_8H_{10}N_4O_3$	45.71 (45.49)	4.80 (5.01)	26.66 (26.39)	210	DMSO-d_6	8.17 and 8.28 (d)			2.7	3.89 (s, OMe), 2.10 (s, COMe)

(a) From 2-methoxy-3-cyanopyrazine (9). (b) From 2-chloro-3-cyanopyrazine (8,9). (c) After 4 hours reaction time.

azolylpyrazine (**7**, R = NH_2, R_1 = Me). The latter compound can be prepared in good yield also in several other ways. The simplest one is to treat the amidoxime (**2**, R = NH_2, R_1 = H) with hot *N,N*-dimethylacetamide dimethyl acetal or by heating the *O*-acetyl oxime (**2**, R = NH_2, R_1 = COMe) in glacial acetic acid. It can be also prepared from **8** (R = R_1 = H or COMe, R_1 = Me) in the presence of hydrochloric acid at room temperature or from the *O*-(1,1-diethoxy)ethyloxime and polyphosphoric acid. For the formation of 4-amino-2-methylpteridine 3-oxide from the *O*-(1,1-diethoxy)ethyloxime (**2**, R = NH_2, R_1 = $CMe(OEt)_2$) we have no firm mechanistic interpretation or evidence, although an intermediate fused oxadiazepine can be postulated. We could only establish that the above pteridine 3-oxide is not formed from either the oxadiazolyl derivative **7** (R = NH_2, R_1 = Me) or the amidoxime **2** (R = NH_2, R_1 = H) since both compounds remain unchanged under the applied reaction conditions.

The oxadiazolylpyrazines **8** are obtained from the corresponding 4-aminopteridine 3-oxides (**5**, R = H or Me) in the presence of acetic anhydride at room temperature. On the other hand, 4-amino-2-methylpteridine 3-oxide (**5**, R = Me) could be prepared either from 2-acetylaminopyrazine-3-carboxamide oxime (**2**, R = NHCOMe, R_1 = H) when heated in glacial acetic acid or in the presence of polyphosphoric acid.

All above mentioned alkylated or acylated amidoximes are *O*-substituted compounds as evident from fruther chemical transformations and nmr spectral correlations. The starting amidoxime (**2**, R = NH_2, R_1 = H) reveals in its nmr spectrum besides the two ring protons a singlet at δ 9.64, corresponding to one proton (OH group) and two broadened singlets at δ 7.02 and 5.62, each corresponding to two protons (two NH_2 groups). In the case of *O*-substituted compounds, in addition to the pyrazine ring protons, there are only two slightly broadened singlets, each integrating for two protons and appearing at about the same field as in the case of the unsubstituted amidoxime. The nmr spectra of 2-acylamino derivatives (**2**, R = MeCONH or PhCONH, R_1 = H) are different and signals corresponding to the functional groups (OH, NH) appear at a relative low field (over 9 δ) and a broad singlet at 5.76 (compound **2**, R = NHCOMe, R_1 = H) or 6.40 (compound **2**, R = NHCOPh, R_1 = H) corresponding to the NH_2 group.

Compounds **9** and **10** were obtained in a similar manner from the amidoximes **2** or **3** as well as the chloro analog (**7**, R = Cl, R_1 = Me). In an attempt to convert the amino group in **7** (R = NH_2, R_1 = Me) into an oxo group, besides the anticipated product (**10**, R = H, R_1 = Me) also the chloro analog (**7**, R = Cl, R_1 = Me) was obtained in a small amount. Finally, the reaction between the amidoxime **2** (R = NH_2, R_1 = H) and ethyl acetoacetate should be mentioned. Here, as the sole product the acetonyl derivative **7** (R = NH_2, R_1 = CH_2COMe) was obtained. This

contrasts the reaction of arylhydroxylamines which affords a mixture of indoles, pyrroles and azooxybenzenes (7). The above results show a high reactivity of the corresponding amidoximes and oxadiazolylpyrazines and the possibilities of their interconversions as well as further formation and susceptibility to ring opening of the corresponding pteridine 3-oxides.

EXPERIMENTAL

Melting points were determined on a Kofler hot plate apparatus. The nmr spectral measurements were performed on a JEOL JNM C-60 HL spectrometer with TMS as internal standard. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L spectrometer.

General Method for the Preparation of Substituted Pyrazinecarboxamide Oximes.

To an ice-cold solution of hydroxylamine, prepared from its hydrochloride (174 mg) and methanolic sodium methoxide (46 mg Na/5 ml), the corresponding cyano compound (1 mmole) was added. The suspension was stirred at room temperature for 1 hour, the solvent evaporated *in vacuo* and the residue was suspended in water (3-4 ml). If necessary, the *p*H was set to about 5 by addition acetic acid. The product was filtered and crystallized from the appropriate solvent. Compounds are listed in Table 1.

2-Benzoylamino-3-cyanopyrazine (**1**, R = NHCOPh).

A mixture of 2-amino-3-cyanopyrazine (**1**, R = NH_2) (1.2 g), benzoyl chloride (1.9 g) and pyridine (25 ml) was heated under reflux for 3 hours. Upon evaporation *in vacuo* the oily residue was treated with water (18 ml) and the separated product was crystallized from ethanol (1.6 g, 71%), mp 177-178°; ms: M^+ = 224; nmr (DMSO-d_6): δ 8.63 and 8.81 (d, H_5 and H_6), 7.85-8.07 (m, $H_{2'}$and $H_{6'}$), 7.55 (m, $H_{3'}$ and $H_{4'}$ and $H_{5'}$), $J_{5,6}$ = 2.5 Hz.

Anal. Calcd. for $C_{12}H_8N_4O$: C, 64.29; H, 3.60; N, 24.99. Found: C, 64.37; H, 3.53; N, 25.24.

3-Cyano-2(1*H*)-pyrazinone (**6**, R = H).

To an ice-cold mixture of 2-amino-3-cyanopyrazine (**1**, R = NH_2) (0.6 g), water (6 ml) and concentrated sulfuric acid (1 ml) an aqueous solution of sodium nitrite (0.6 g in 3 ml of water) was added dropwise during 10 minutes. The mixture was left at 0° for 1 hour and then 3 hours at room temperature. Upon cooling on ice, the product was filtered and crystallized from ethanol (0.35 g, 58%), mp 192-194°; ms: M^+ = 121; nmr (DMSO-d_6): δ 7.58 and 7.89 (d, H_5 and H_6), $J_{5,6}$ = 3.6 Hz.

Anal. Calcd. for $C_5H_3N_3O$: C, 49.59; H, 2.50; N, 34.70. Found: C, 49.60; H, 2.68; N, 34.85.

2-Oxo-1,2-dihydropyrazine-3-carboxamide Oxime (**3**, R = R_1 = H).

(a) The compound was obtained in 86% yield by the general procedure from 3-cyano-2(1*H*)-pyrazinone.

(b) A solution of the carbohydroxymoyl chloride (**4**) (0.11 g) in ethanol (2 ml) was treated dropwise with concentrated aqueous ammonia (0.5 ml) and the mixture was left at room temperature for 2.5 hours. The solution was evaporated to dryness, water (1 ml) was added and the product filtered (58 mg, 59%), mp 228-230°; ms: M^+ 154; nmr (DMSO-d_6): δ 8.08 (s, H_5 and H_6), 6.42 (broad s, NH_2), 11.30 (broad s, NH, OH).

Anal. Calcd. for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 39.25; H, 3.94; N, 36.11.

3-Cyano-1-methyl-2(1*H*)-pyrazinone (**6**, R = Me).

(a) A solution of 3-cyano-2(1*H*)-pyrazinone (**6**, R = H) (0.6 g) in chloroform (12 ml) was treated with *N,N*-dimethylformamide dimethyl acetal (0.8 g) and left at room temperature for 2 hours. The mixture was then heated under reflux for 5 minutes and evaporated to dryness. The residue was suspended in chloroform (5 ml), filtered and crystallized from ethanol (0.48 g, 72%), mp 173-175°; ms: M^+ = 135; nmr (DMSO-d_6): δ 7.59 and 8.20 (d, H_5 and H_6), 3.55 (s, Me), $J_{5,6}$ = 4.0 Hz.

Anal. Calcd. for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.52; H, 4.00; N, 31.17.

(b) A solution of sodium methoxide, prepared from sodium (26 mg) and methanol (4 ml) was evaporated to dryness and dry *N,N*-dimethylformamide (4 ml) and 3-cyano-2(1*H*)-pyrazinone (**6**, R = H) (0.13 g) were added. Upon treatment with methyl iodide (0.25 g) the mixture was left at room temperature for 45 minutes and evaporated *in vacuo* to dryness. The residue was suspended in water (3 ml) and filtered to give the product (80 mg, 55%), which was identical in all respects with the compound obtained as described under (a).

2-(Hydroxyiminomethyleneamino)pyrazine-3-carboxamide Oxime (**2**, R = NHCH=NOH, R_1 = H).

(a) A solution of free hydroxylamine was prepared from hydroxylamine hydrochloride (0.3 g) and methanolic sodium methylate (from 90 mg of sodium and 5 ml of methanol). Upon cooling to 0°, the pyrazine derivative **1** (R = N=CHNMe$_2$) (0.3 g) was added and after standing at room temperature for 15 minutes, the mixture was heated to boil. Upon evaporation the solid residue was suspended in water (3 ml) and the product was filtered and crystallized from methanol (0.3 g, 89% yield), mp 230-233° (with conversion into 4-aminopteridine 3-oxide); ms: M^+ = 196; nmr (DMSO-d_6): δ 7.77 and 7.86 (d, H_5 and H_6), 7.60 (d, CH), 5.77 (broad s, NH_2), 10.59 (d, NH), 10.05 (s, OH), $J_{5,6}$ = 2.4, J_{NHCH} = 9.5 Hz.

Anal. Calcd. for $C_6H_8N_6O_2$: C, 36.73; H, 4.11; N, 42.84. Found: C, 36.90; H, 4.32; N, 45.52.

(b) 4-Aminopteridine 3-oxide (**5**, R = H) (0.15 g) and hydroxylamine hydrochloride (0.15 g) were treated with a methanolic solution of sodium methylate (from 46 mg of sodium and 3 ml of methanol) and the mixture was stirred at room temperature for 70 minutes. Upon evaporation to dryness the residue was suspended in water (2 ml), the product filtered and washed with water to give the carboxamide oxime, mp 230-233°, identical in all respects with the product as described under (a).

Reaction Between 3-Cyano-2-(*N,N*-dimethylaminomethyleneamino)pyrazine (**1**, R = =CHNMe$_2$) and Hydroxylamine Hydrochloride. 4-Aminopteridine 3-Oxide (**5**, R = H).

(a) A mixture of the *N,N*-dimethylaminomethyleneamino compound (**1**, R = N=CHNMe$_2$) (3) (0.175 g), hydroxylamine hydrochloride (0.14 g) and methanol (4 ml) was heated under reflux for 40 minutes and upon cooling the separated product was filtered and crystallized from water (0.13 g, 80%) to give 4-aminopteridine 3-oxide (**5**, R = H), mp 275-278° dec; ms: M^+ = 163; nmr (deuterium oxide, 95°): δ 8.52 and 8.62 (d, H_6 and H_7), 8.49 (s, H_2), $J_{6,7}$ = 2 Hz.

Anal. Calcd. for $C_6H_5N_5O$: C, 44.17; H, 3.09; N, 42.93. Found: C, 44.20; H, 3.27; N, 42.96.

The above filtrate was evaporated to dryness, the residue was suspended in water (1.5 ml) and the product filtered. It was identified as 2-aminopyrazine-3-carboxamide oxime (**2**, R = NH_2, R_1 = H) (15 mg, 11%). TLC examination of the filtrate showed the presence of 2-amino-3-cyanopyrazine (**1**, R = NH_2) and 2-aminpyrazine-3-carboxamide.

(b) 4-Aminopteridine 3-oxide (**5**, R = H) could be obtained in an alternative manner if the corresponding amidoxime (**2**, R = NH_2, R_1 = H) (0.2 g) and triethyl orthoformate (4 ml) were heated under reflux for 1 hour. It was obtained in 80% yield (0.172 g).

(c) If a mixture of the amidoxime (**2**, R = NH_2, R_1 = H) (0.153 g) diethoxymethyl acetate (0.4 g) and toluene (5 ml) was heated under reflux for 1 hour 4-aminopteridine 3-oxide (**5**, R = H) was obtained in 74% yield (0.12 g). From the filtrate a mixture (17 mg) of compound **1** (R = NH_2) and 2-ethoxymethyleneamino-3-cyanopyrazine (**1**, R = ETOCH=N) could be isolated.

2-Oxo-1,2-dihydropyrazine-3-carbohydroxymoyl Chloride (**4**).

A mixture of the carboxamide oxime (**2**, R = NH_2, R_1 = H) (0.153 g), water (3 ml) and concentrated hydrochloric acid (1 ml) was cooled to 0° and treated dropwise with an aqueous solution of sodium nitrite (0.13 g

in 1 ml of water) during 5 minutes. The mixture was left at 0° for 30 minutes and neutralized with solid sodium bicarbonate to pH = 4. The separated product was filtered and crystallized from a mixture of methanol and *N,N*-dimethylformamide (0.1 g, 58%), mp 225-228° (dec); ms: M^+ = 173; nmr (DMSO-d_6): δ 7.24 and 7.10 (d, H_5 and H_6), 7.70 (broad s, NH), 11.97 (broad s, NOH), $J_{5,6}$ = 3.6 Hz.

Anal. Calcd. for $C_5H_4ClN_3O_3$: C, 34.60; H, 2.32; N, 24.21. Found: C, 34.60; H, 2.65; N, 24.60.

2-Aminopyrazine-3-carboxamide *O*-Methyloxime (**2**, R = NH_2, R_1 = Me).

A mixture of sodium propoxide (prepared from 80 mg of sodium and 12 ml of propanol), 2-aminopyrazine-3-carboxamide oxime (**2**, R = NH_2, R_1 = H) (0.46 g) and methyl iodide (0.8 g) was heated under reflux for 5 hours. Upon evaporation to dryness, the residue was crystallized from water to give the product (0.24 g, 48%), mp 108-110°; ms: M^+ = 167; nmr (DMSO-d_6): δ 7.23 and 7.43 (d, H_5 and H_6), 3.52 (s, Me), 5.67 and 6.80 (broad s, NH_2), $J_{5,6}$ = 2.4 Hz.

Anal. Calcd. for $C_6H_9N_5O$: C, 43.11; H, 5.43; N, 41.90. Found: C, 43.25; H, 5.30; N, 42.00.

2-Aminopyrazine-3-carboxamide *O*-Acetyloxime (**2**, R = NH_2, R_1 = COMe).

The amidoxime (**2**, R = NH_2, R_1 = H) (0.153 g) was treated with acetic anhydride (1 ml) and upon standing at room temperature for 15 minutes the mixture was cooled on ice. The separated product was filtered and the filtrate was evaporated to dryness to give some more of the product (total yield 0.19 g, 97%), mp 170-171.5° (from ethanol); ms: M^+ = 195; nmr (DMSO-d_6): δ 7.50 and 7.76 (d, H_5 and H_6), 2.08 (s, Me), 6. 57 and 7.16 (broad s, NH_2), $J_{5,6}$ = 2.4 Hz.

Anal. Calcd. for $C_7H_9N_5O_2$: C, 43.07; H, 4.65; N, 35.89. Found: C, 43.40; H, 4.24; N, 35.80.

In a similar manner were prepared some other acetylated oximes, listed in Table 1.

2-Aminopyrazine-3-carboxamide *O*-Ethoxycarbonyloxime (**2**, R = NH_2, R_1 = COOEt).

A mixture of the amidoxime (**2**, R = NH_2, R_1 = H) (0.14 g), triethylamine (0.15 g) and chloroform (5 ml) was treated with ethyl chloroformate (0.14 g) and after standing at room temperature for 1 hour the mixture was evaporated to dryness. The residue was suspended in water (3 ml), the product was filtered and crystallized from ethanol (0.19 g, 92%), mp 157-158°; ms: M^+ = 225; nmr (DMSO-d_6): δ 7.30 and 7.54 (d, H_5 and H_6), 3.95 (q, OCH_2Me), 1.21 (t, OCH_2Me), 6.35 (broad s, NH_2), 6.92 (broad s, NH_2), $J_{5,6}$ = 2.2, J_{Et} = 6.6 Hz.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.66; H, 4.92; N, 31.10. Found: C, 42.77; H, 4.83; N, 30.92.

2-Aminopyrazine-3-carboxamide *O*-(1,1-Diethoxy)ethyloxime (**2**, R = NH_2, R_1 = $CMe(OEt)_2$).

A mixture of the amidoxime (**2**, R = NH_2, R_1 = H) (0.35 g) and triethyl orthoacetate was heated under reflux for 30 minutes. Upon evaporation to dryness, the residue was crystallized from ethanol (0.325 g, 53%), mp 118-120°; ms: M^+ = 269; nmr (DMSO-d_6): δ 7.68 and 7.92 (d, H_5 and H_6), 3.52 (q, OCH_2Me), 1.52 (s, Me), 1.10 (t, OCH_2Me), 6.08 and 7.33 (broad s, NH_2), $J_{5,6}$ = 2.55, J_{Et} = 7 Hz.

Anal. Calcd. for $C_{11}H_{19}N_5O_3$: C, 49.06; H, 7.11; N, 26.01. Found: C, 48.84; H, 7.05; N, 26.12.

2-Amino-3-(5'-methyl-1',2',4'-oxadiazolyl-3')pyrazine (**7**, R = NH_2, R_1 = Me).

(a) A mixture of the amidoxime (**2**, R = NH_2, R_1 = H) (0.1 g) and *N,N*-dimethylacetamide dimethyl acetal (0.3 g) was heated at 100° for 5 minutes (or, alternatively, in 5 ml of chloroform 30 minutes under reflux). The solid residue, obtained after evaporation, was crystallized from ethanol (70 mg, 60% yield), mp 217-219°; ms: M^+ = 177; nmr (DMSO-d_6): δ 7.64 and 7.84 (d, H_5 and H_6), 2.57 (s, Me), 6.70 (broad s, NH_2), $J_{5,6}$ = 2.2 Hz.

Anal. Calcd. for $C_7H_7N_5O$: C, 47.45; H, 3.98; N, 39.53. Found: C, 47.33; H, 4.17; N, 39.34.

(b) A solution of the *O*-acetyloxime (**2**, R = NH_2, R_1 = COMe) (0.23 g) in glacial acetic acid (5 ml) was heated under reflux for 1.5 hour and upon evaporation to dryness and crystallization from ethanol the pure product was obtained in 72% yield (0.15 g), identical in all respects with that as described under (a).

(c) A mixture of 2-formylamino-3-(5'-methyl-1',2',4'-oxadiazolyl-3')pyrazine (**8**, R = R_1 = H) (45 mg) and hydrochloric acid (2 ml of 1:1) was stirred at room temperature for 70 minutes. Upon neutralization with solid sodium bicarbonate the product was filtered and crystallized from ethanol (35 m g, 90% yield). The product is identical with the compound as described under (a).

(d) A mixture of 2-diacetylamino-3-(5'-methyl-1',2',4'-oxadiazolyl-3')pyrazine (**8**, R = COMe, R_1 = Me) (0.1 g) and hydrochloric acid (1.5 ml of 1:1) was stirred at room temperature for 2 hours, after neutralization the oxadiazolyl derivative **7** (R = NH_2, R_1 = Me) was obtained in 86% yield (58 mg), identical with the above products.

(e) A solution of 2-aminopyrazine-3-carboxamide *O*-(1,1-diethoxy)-ethyl oxime (**2**, R = NH_2, R_1 = $CMe(OEt)_2$) (0.2 g) in glacial acetic acid (4 ml) was heated under reflux for 50 minutes. The solvent was evaporated and the residue was crystallized from methanol to give 4-amino-2-methylpteridine-3-oxide (**5**, R = Me) (60 mg, 40%). Evaporation of the filtrate and sublimation of the residue *in vacuo* at 190° afforded a mixture (10 mg) of 2-aminopyrazine-3-carboxamide oxime (**2**, R = NH_2, R_1 = H) and the oxadiazolylpyrazine (**7**, R = NH_2, R_1 = Me).

(f) A mixture of the *O*-(1,1-diethoxy)ethyl oxime (**2**, R = NH_2, R_1 = $CMe(OEt)_2$) (0.13 g) and polyphosphoric acid (0.67 g) was heated at 85° for 5 minutes. Upon dilution with water (3-4 ml), the solution was neutralized with sodium bicarbonate and extracted several times with chloroform (10 × 5 ml). There were obtained 21 mg of the oxadiazolylpyrazine (**7**, R = NH_2, R_1 = Me) and by tlc the presence of a small amount of the amidoxime (**2**, R = NH_2, R_1 = H) and the pteridine oxide (**5**, R = Me) was detected.

2-Aminopyrazine-3-carboxamide *O*-Benzoyloxime (**2**, R = NH_2, R_1 = COPh).

To a stirred mixture of the amidoxime (**2**, R = NH_2, R_1 = H) (0.153 g), triethylamine (0.125 g) and chloroform (4 ml) benzoyl chloride (0.165 g) was added dropwise and the mixture was stirred at room temperature for 1 hour. Upon evaporation to dryness the residue was suspended in water (4 ml), the product was filtered (0.25 g, 97%) and crystallized from ethanol, mp 216-218°; ms: M^+ = 257; nmr (DMSO-d_6): δ 7.35 and 7.59 (d, H_5 and H_6), 7.55-7.80 (m, $H_{2'}$ and $H_{6'}$), 7.10 (m, $H_{3'}$ and $H_{4'}$ and $H_{5'}$ and NH_2), 6.62 (broad s, NH_2), $J_{5,6}$ = 2.3 Hz.

Anal. Calcd. for $C_{12}H_{11}N_5O_2$: C, 56.02; H, 4.31; N, 27.23. Found: C, 56.04; H, 4.60; N, 27.40.

2-Amino-3-(5'-phenyl-1',2',4'-oxadiazolyl-3')pyrazine (**7**, R = NH_2, R_1 = Ph).

(a) A mixture of the benzoyloxime (**2**, R = NH_2, R_1 = COPh) (0.1 g) and polyphosphoric acid (0.9 g) was heated at 70° for 1 hour, cooled and diluted with water (3 ml). The separated product was filtered, suspended in water (3 ml), the suspension was neutralized with solid sodium bicarbonate and the obtained product was crystallized from a mixture of ethanol and *N,N*-dimethylformamide (80 mg, 86% yield), mp 220-223°; ms: M^+ = 239; nmr (DMSO-d_6, 75°): δ 7.47 and 7.64 (d, H_5 and H_6), 7.53-7.72 (m, H_2 and H_6 of Ph), 7.15 (m, H_3, H_4 and H_5 of Ph), 6.50 (broad s, NH_2), $J_{5,6}$ = 2.2 Hz.

Anal. Calcd. for $C_{12}H_9N_5O$: C, 60.24; H, 3.79; N, 29.28. Found: C, 60.32; H, 3.80; N, 29.35.

(b) If the above benzoyloxime (**2**, R = NH_2, R_1 = COPh) (0.1 g) was heated in a solution of dilute sodium hydroxide (2 ml of 5%) for 35 minutes, upon acidification the oxadiazolylpyrazine (**7**, R = NH_2, R_1 = Ph) was obtained (72 mg) together with a minimum amount of **2** (R = NH_2, R_1 = H) as detected by tlc.

4-Amino-2-methylpteridine 3-Oxide (**5**, R = Me).

(a) A solution of 2-acetylaminopyrazine-3-carboxamide oxime (3) (0.475 g) (**2**, R = NHCOMe, R_1 = H) in glacial acetic acid (8 ml) was heated under reflux for 1 hour. Upon evaporation of the solvent, the residue was suspended in ethanol (5 ml), filtered and crystallized from ethanol (yield 0.34 g, 79%), mp 278-280° dec; ms: M^+ = 177; nmr (deuterium oxide, 78°): δ 8.19 and 8.32 (d, H_6 and H_7), 2.60 (s, Me), $J_{6,7}$ = 1.8 Hz.

Anal. Calcd. for $C_7H_7N_5O$: C, 47.45; H, 3.98; N, 39.53. Found: C, 47.62; H, 3.85; N, 39.60.

(b) A mixture of the oxime (**2**, R = NHCOMe, R_1 = H) (0.26 g) and polyphosphoric acid (1.5 g) was heated at 80° for 90 minutes. Upon dilution with water (5 ml) and neutralization with sodium bicarbonate the solution was repeatedly extracted with chloroform (10 times with 20 ml) to give 95 mg (40%) of the pteridine derivative, identical in all respect with the product obtained as described under (a).

2-Formylamino-3-(5'-methyl-1',2',4'-oxadiazolyl-3')pyrazine (**8**, R = R_1 = H).

A mixture of 4-aminopteridine 3-oxide (**5**, R = H) (0.1 g) and acetic anhydride (1 ml) was left at room temperature for 18 hours. Upon evaporation to dryness, the residue was crystallized from ethanol (yield 65 mg, 52%), mp 145-146.5°; ms: M^+ = 205; nmr (DMSO-d_6): δ 8.14 (s, H_5 and H_6), 2.61 (s, Me), 8.92 (s, CHO), 9.85 (broad s, NH).

Anal. Calcd. for $C_8H_7N_5O_2$: C, 46.83; H, 3.44; N, 34.12. Found: C, 46.99; H, 3.42; N, 33.85.

2-Diacetylamino-3-(5'-methyl-1',2',4'-oxadiazolyl-3')pyrazine (**8**, R = COMe, R_1 = Me).

(a) A mixture of 4-amino-2-methylpteridine 3-oxide (**5**, R = Me) (0.1 g) and acetic anhydride (1 ml) was stirred at room temperature for 8 hours. The oily residue, obtained after evaporation of the solvent, was crystallized from a mixture of ethyl acetate and cyclohexane (yield 55 mg, 37%), mp 129-131°; ms: M^+ = 261; nmr (deuteriochloroform): δ 8.44 and 8.57 (d, H_5 and H_6), 2.62 (s, Me), 2.22 (s, two COMe), $J_{5,6}$ = 2.4 Hz.

Anal. Calcd. for $C_{11}H_{11}N_5O_3$: C, 50.57; H, 4.24; N, 26.81. Found: C, 50.48; H, 4.35; N, 26.52.

(b) A mixture of the oxadiazolylpyrazine (**7**, R = NH_2, R_1 = Me) and acetic anhydride (2 ml) was heated under reflux for 2 hours. The oily residue, obtained after evaporation of the solvent, was treated with water (1.5 ml) and the product filtered (yield 175 mg, 79%). The compound was found to be identical in all respects with the product obtained as described under (a).

3-(2-Aminopyrazinyl-3')-1,2,4-oxadiazol-5(4*H*)-one (**9**).

A solution of 2-aminopyrazine-3-carboxamide *O*-ethoxycarbonyl oxime (**2**, R = NH_2, R_1 = COOEt) (0.2 g) in glacial acetic acid (4 ml) was heated under reflux for 5 hours. Upon evaporation to dryness, the residue was crystallized from *N,N*-dimethylformamide with addition of small amount of ethanol (yield 90 mg, 57%), mp 311-314° dec; ms: M^+ = 179; nmr (DMSO-d_6, 70°): δ 7.42 an d7.67 (d, H_5 and H_6), 6.48 (broad s, NH_2), $J_{5',6'}$ = 2.3 Hz.

Anal. Calcd. for $C_6H_5N_5O_2$: C, 40.23; H, 2.81; N, 39.10. Found: C, 40.32; H, 2.68; N, 39.10.

3-(1',2',4'-Oxadiazolyl-3')-2(1*H*)-pyrazinone (**10**, R = R_1 = H).

(a) A mixture of the amidoxime **3** (R = R_1 = H) (0.15 g) and triethyl orthoformate (2 ml) was heated under reflux for 8 hours and the solvent evaporated to dryness. The residue was suspended in methanol (3 ml), the product was filtered and crystallized from a mixture of *N,N*-dimethylformamide and ethanol (yield 88 mg, 55%), mp 194-196°; ms: M^+ = 164; nmr (trifluoroacetic acid): δ 9.12 (s, $H_{5'}$), 7.78 and 7.98 (d, H_5 and H_6), $J_{5,6}$ = 3.9 Hz.

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.91; H, 2.46; N, 34.14. Found: C, 44.05; H, 2.65; N, 34.03.

(b) The same product was obtained if the amidoxime **3** (R = R_1 = H) (0.154 g), diethoxymethyl acetate (0.4 g) and toluene (5 ml) were heated under reflux for 3 hours (yield 0.12 g, 73%).

(c) A mixture of the oxadiazolyl pyrazine (**7**, R = NH_2, R_1 = H) (22 mg), water (1 ml) and few drops of concentrated sulfuric acid was cooled to 5° and treated with aqueous sodium nitrite (22 mg in minimum amount of water). After 50 minutes at room temperature the separated product was filtered (yield 17 mg, 77%) and was found to be identical in all respects with the product obtained as described under (a).

2-Oxo-1,2-dihydropyrazine-3-carboxamide *O*-Acetyloxime (**3**, R = H, R_1 = COMe).

A mixture of the amidoxime **3** (R = R_1 = H) (0.4 g) and acetic anhydride (2.5 ml) was left at room temperature for 4 hours, evaporated to dryness and the residue was crystallized from ethanol (yield 355 mg, 70%), mp 132-135° (with cyclization into **10**, R = H, R_1 = Me); ms: M^+ = 196; nmr (DMSO-d_6): δ 7.87 and 8.01 (d, H_5 and H_6), 2.17 (s, Me), 12.5 (broad s, NH), 7.20 (broad s, NH_2), $J_{5,6}$ = 3.2 Hz.

Anal. Calcd. for $C_8H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.75; H, 4.23; N, 28.84.

3-(5'-Methyl-1',2',4'-oxadiazolyl-3')-2(1*H*)-pyrazinone (**10**, R = H, R_1 = Me).

The above compound (**3**, R = H, R_1 = COMe) (0.2 g) and glacial acetic acid (4 ml) were heated under reflux for 2.5 hours. The residue, obtained after evaporation of the solvent, was crystallized from ethanol and thereafter from methanol (yield 0.13 g, 72%), mp 250-253° (dec; ms: M^+ = 178; nmr (DMSO-d_6): δ 7.42 and 7.57 (d, H_5 and H_6), 2.60 (s, Me), $J_{5,6}$ = 3.8 Hz.

Anal. Calcd. for $C_7H_6N_4O_3$: C, 47.19; H, 3.39; N, 31.45. Found: C, 46.99; H, 3.43; N, 31.19.

In a similar manner the following compounds were prepared.

2-Chloro-3-(5'-methyl-1',2',4'-oxadiazolyl-3')pyrazine (**7**, R = Cl, R_1 = Me) from **2** (R = Cl, R_1 = COMe).

This compound was obtained in 55% yield, mp 112-114° (from ethanol); ms: M^+ = 196; nmr (DMSO-d_6): δ 8.76 and 8.89 (d, H_5 and H_6), 2.72 (s, Me), $J_{5,6}$ = 2.4 Hz.

Anal. Calcd. for $C_7H_5ClN_4O$: C, 42.77; H, 2.56; N, 28.50. Found: C, 42.99; H, 2.63; N, 28.55.

3-(5'-Acetonyl-1',2',4'-oxadiazolyl-3')-2-aminopyrazine (**7**, R = NH_2, R_1 = CH_2COMe).

A mixture of the oxime **2** (R = NH_2, R_1 = H) (0.3 g), ethyl acetoacetate (0.6 g) and toluene (8 ml) was heated under reflux for 15 hours. Upon cooling, the product was filtered and crystallized from ethanol (yield 0.29 g, 68%), mp 186-188°; ms: M^+ = 219; nmr (DMSO-d_6): δ : δ 7.59 and 7.80 (d, H_5 and H_6), 4.28 (s, CH_2), 2.19 (s, Me), 6.75 (broad s, NH_2), $J_{5,6}$ = 2.3 Hz.

Anal. Calcd. for $C_9H_9N_5O_2$: C, 49.31; H, 4.14; N, 31.95. Found: C, 49.50; H, 4.26; N, 31.74.

1-Methyl-3-(5'-methyl-1',2',4'-oxadiazolyl-3')-2(1*H*)pyrazinone (**10**, R = R_1 = Me).

This compound was obtained in 49% yield from **3** (R = Me, R_1 = COMe), mp 158-160° (from ethanol); ms: M^+ = 192; nmr (DMSO-d_6): δ 7.46 and 7.90 (H_5 and H_6), 3.51 (s, NMe), 2.62 (s, Me), $J_{5,6}$ = 4.2 Hz.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 50.00; H, 4.62; N, 29.08.

2-Methoxy-3-(5'-methyl-1',2',4'-oxadiazolyl-3')-pyrazine (**7**, R = OMe, R_1 = Me).

The compound was prepared from **2** (R = OMe, R_1 = COMe). The oily product was sublimed at 70°/1.3 kPa (yield 36%), mp 75-78°; ms: M^+ = 192; nmr (DMSO-d_6): δ 8.39 (s, H_5 and H_6), 3.98 (s, OMe), 2.69 (s, Me).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 50.11; H, 4.45; N, 29.22.

Action of Nitrous Acid Upon 2-Amino-3-(5'-methyl-1',2',4'-oxadiazolyl-3')pyrazine.

A mixture of the oxadiazolyl pyrazine (**7**, R = NH_2, R_1 = Me) (0.1 g) and hydrochloric acid (9%, 2 ml) was cooled to 0°, treated with aqueous sodium nitrite (65 mg in 0.5 ml water) and left at 5° for 1 hour. The separated part was filtered and identified as oxadiazolylpyrazinone (**10**, R = H, R_1 = Me) (yield 63 mg, 63%). From the filtrate upon neutralization the chloro analog (**7**, R = Cl, R_1 = Me) was isolated (4 mg, 3.6%).

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REFERENCES AND NOTES

(1) A. Tomažič, M. Tišler and B. Stanovnik, *J. Heterocyclic Chem.*, **16**, 861 (1979).

(2) A. Tomažič, M. Tišler and B. Stanovnik, *Tetrahedron*, **37**, 1787 (1981).

(3) M. Kočevar, B. Stanovnik and M. Tišler, *Heterocycles*, **15**, 293 (1981).

(4) F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962).

(5) L. B. Clapp, *Adv. Heterocyclic Chem.*, **20**, 65 (1976).

(6) B. Verček, I. Leban, B. Stanovnik and M. Tišler, *J. Org. Chem.*, **44**, 1695 (1975).

(7) S. Saeki, M. Hayashida, T. Sukamoto and M. Hamana, *Heterocycles*, **2** 445 (1975).

(8) M. Asai, *Yakugaku Zasshi*, **81**, 1475 (1961); *Chem. Abstr.*, **56**, 8711 (1962).

(9) British Patent 928,152 (1963); *Chem. Abstr.*, **60**, 2971 (1964).