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RING TRANSFORMATIONS OF SOME 4-AMINOPTERIDINE 3-OXIDES AND DERIVATIVES

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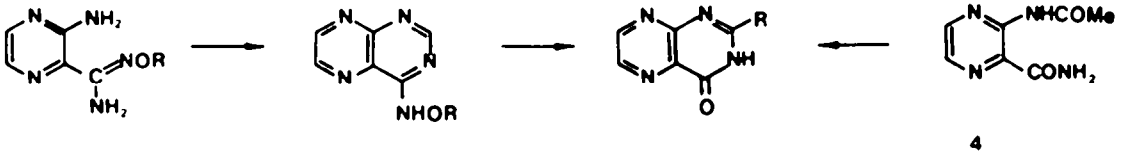
Abstract—Syntheses of 4-aminopteridine 3-oxides are described. The pyrimidine part undergoes transformations with various reagents to give 4-hydroxyaminopteridines, substituted pyrazines, or substituted 1,2,4-oxadiazolylpyrazines. s-Triazolo(1,5-a)pyrazines can be prepared from the 1,2,4-oxadiazolylpyrazines. The ring opening of the pyrimidine part of pteridines proceeds either by a C_7–N_1 or N_1–C_4 bond cleavage.

Heterocyclic compounds with a hydroxylamino, hydroxyimino or amidoxime function are useful synthons for the preparation of various heterocyclic systems[1-3] and therefore we decided to investigate in more detail the application of such functionality for syntheses in the pteridine series. We describe now some new results concerning the synthéses and transformations of some pteridine 3-oxides, in particular 4-amino-2-phenylpteridine 3-oxide.

As starting material, we used the appropriate pyrazinecarboxamide oximes with an unsubstituted (**5**), acylated (**1a**, **1b**) or alkylated (**1c**) amidoxime group. The O-substituted amidoximes were transformed upon heating with triethyl orthoformate into the corresponding O-substituted 4-hydroxyaminopteridines (**2a**, **2b** and **2c**), thus demonstrating a new and simple way for the preparation of pteridines with a hydroxyamino function. The acetoxy group in **2a** can be removed in the presence of aqueous hydrochloric acid at room temperature to give 4-hydroxyaminopteridine (**2d**) in a moderate yield. Upon heating, however, compound **2d** is transformed with the same reagent into 4(3H)-pteridinone (**3a**). Its 2-methyl analog (**3b**) was conveniently prepared by thermal cyclization of **4**.

4-Amino-2-phenylpteridine 3-oxide (**6b**) was prepared from 2-benzoylaminopyrazine-3-carboxamide oxime (**5**) either in the presence of sulfuric or polyphosphoric acid. This is a simple route for the preparation of the practically unknown pteridine 3-oxides.[4] This new compound undergoes a variety of transformations and most of them involve the primary attack at the pyrimidine part of the molecule. It is well known that pteridines react with numerous nucleophiles either by addition or substitution, leading in many cases to ring opened products.[5,6] In the presence of hydrazine hydrate at room temperature a cleavage of the C_7–N_2 bond of **6b** occurs giving the corresponding hydrazone (**7b**). This demonstrates that substitution at position 2 of the pteridine ring does not prevent the reaction. As anticipated, 4-aminopteridine 3-oxide (**6a**) undergoes the same reaction to give the corresponding hydrazone (**7a**). In addition to the spectroscopic evidence, the structure of compounds **7a** and **7b** follows from their conversion to other pyrazine derivatives. Alkaline hydrolysis of **7a** gave **14a** and acid hydrolysis converted **7b** to **5**.

4-Aminopteridine 3-oxide (**6a**) when heated in water, is transformed in good yield into 4-hydroxyaminopteridine (**8a**). This transformation was also accompanied by ring opening to give small amounts of pyrazine derivatives (**10a** and **14a**). The same reaction with the 2-phenyl analog (**6b**) gave the product **8b** in a lower yield and the oxadiazolyl derivative (**9**) was observed as a by-product. On the other hand, when compound **5** was treated with alkali, **8b** was formed only in small amount, the major product being the oxadiazolyl derivative (**9**). Since we anticipated that compound **9** may be not formed directly in this reaction, but presumably via the pteridine 3-oxide (**6b**) or from **8b**, we performed a separate experiment with **6b**. This compound, when heated for 1 min in dilute aqueous NaOH solution, was transformed into a mixture of compound **9**(20%), the hydroxyaminopteridine (**8b**) (5%) and acid **11a** (27%), the amount of the later product being raised when the alkali treatment was prolonged to 10 min. The structure of the acid (**11a**) is in accord with the spectroscopic data and it has been further substantiated by its transformation into an ester with a simultaneous alkylation of the oxime part (**11b**). Moreover, the acid is converted thermally into 2-phenyl-3-hydroxy-4(3H)pteridinone (**12**) which readily undergoes ring opening under the influence of alkali to give back the

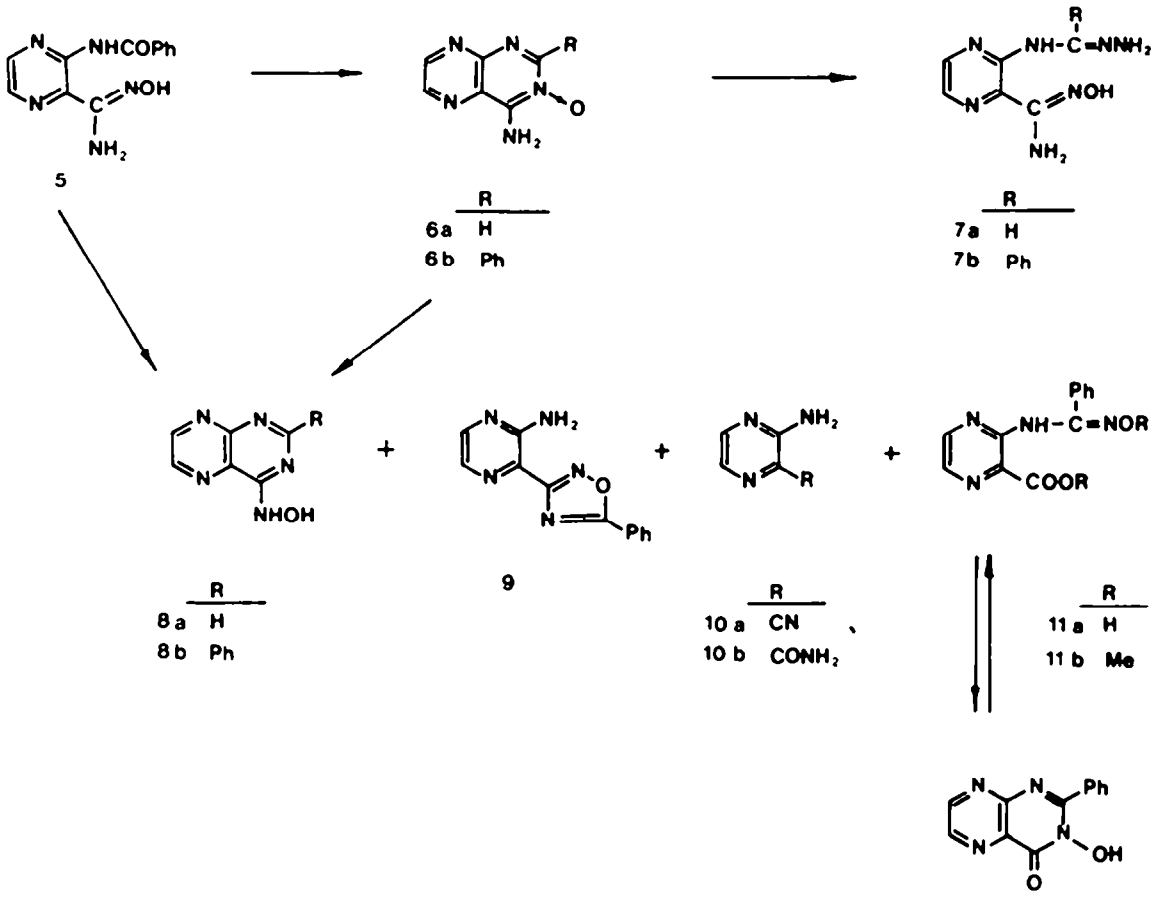


4

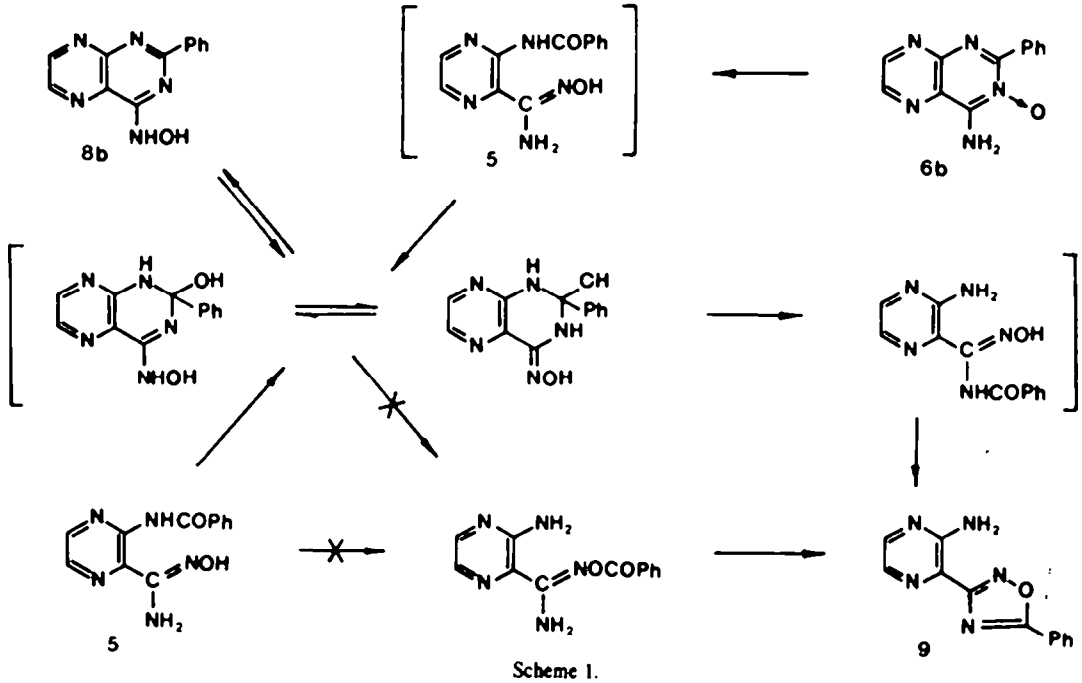
	R
1a	COMe
1b	COPh
1c	Me

	R
2a	COMe
2b	COPh
2c	Me
2d	H

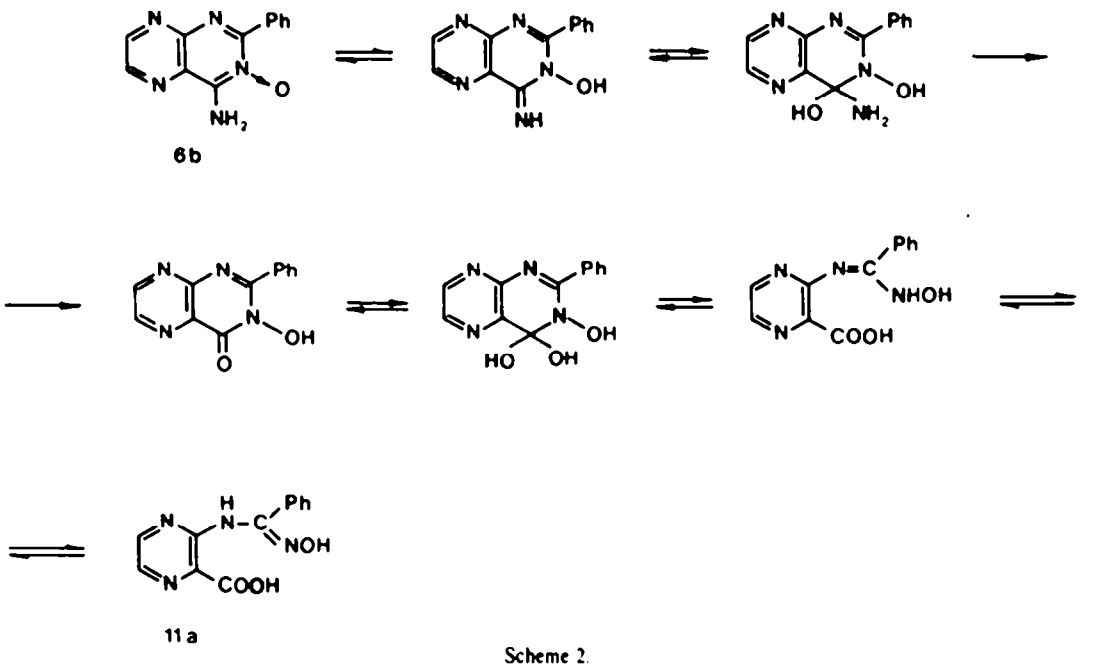
	R
3a	H
3b	Me



acid (**11a**). An alternative structure of this product, represented as 2-benzoylaminopyrazine-3-carbohydroxamic acid, is improbable, based also on the NMR spectroscopic data. The signal for the phenyl group appears as a singlet (δ 7.35), whereas in the case of the alternative structure two separated multiplets in a ratio of 2 : 3 would be expected. It was also of interest to investigate the stability of the hydroxyaminopteridine **8b** in alkaline solution. After a short treatment with aqueous alkali the compound remained unchanged, but longer treatment resulted in conversion of **8b** into the oxadiazolyl derivative (**9**).



Scheme 1.



Scheme 2.

A mechanistic interpretation of all these transformations involves the cleavage of the C_7–N_1 bond as represented in Scheme 1. Scheme 1 also shows other plausible conversions, but we have shown by separate experiments that these reactions do not take place. Conversion of compound **6b** into **8b** occurs most probably via **5** and is thus another example of Dimroth rearragement. Intermediates, as shown in parentheses, could not be isolated in the course of these transformations. For the formation of acid **11**, another mechanistic interpretation must be given, taking into account the N_1–C_4 bond cleavage and the process is represented in Scheme 2.

Another set of experiments showed the interesting transformations of the amidines (**13**) which were prepared from the corresponding 4-aminopteridine 3-oxides (**6**) and N,N-dimethylformamide dimethyl acetal. Amidine **13a** is slowly converted back to **6a** in methanol at room temperature, but it is decomposed into pyrazine derivatives **10a** and **10b** in the presence of dilute alkali at room temperature. In a methanolic solution of hydroxylamine, the amidine underwent ring opening at the pyrimidine part with simultaneous formation of amidoxime and hydroxyiminomethylamino functions (**14b**), a minute amount of **14a** being formed as by-product. In the presence of hydrochloric acid (1 : 1), amidine **13a** is transformed at room temperature in good yield into the oxadiazolylpyrazine (**15a**), which is also formed from the 2-methyl analog (**13b**), from **15c** or from **17a**. This latter reaction indicates that after ring opening resulting from cleavage of the C_7–N_1 bond, the substituted amino function, regardless its complexity, is converted into a free amino group. In boiling water or with dilute alkali at room temperature, the oxadiazolylpyrazine (**15a**) is decomposed into the pyrazine derivatives **10a** and **10b**. The 2-phenyl analog (**13c**) is also transformed under the influence of hydrochloric acid (1 : 1) and at room temperature into **15b**, the benzoylamino group being resistant to hydrolysis under these reaction conditions. Also with dimethylamine hydrochloride, the amidine **13a** is transformed at room temperature into the corresponding oxadiazolyl derivative (**16a**). The structure of the latter compound is supported by the fact that the same product is obtained when the amine **15a** is treated with N,N-dimethylformamide dimethyl acetal. The amidine function in **16a** is easily transformed under the action of hydroxylamine into a hydroxyiminomethylamino function (**17a**) and this compound is also obtained directly from the pteridine 3-oxide (**13a**) with hydroxylamine hydrochloride at room temperature. The methyl analog **17b** is obtained in a similar manner from **16b** and the oxime function can be acetylated in the usual manner to give **17c**. All oxadiazolylpyrazines, except compound **17a**, show negative color reaction with ferric chloride.

Another interesting transformation occurs if the oxadiazolyl derivatives **17a** and **17b** are treated with hot polyphosphoric acid. In this case, the hydroxyiminomethylamino side chain is cyclized to a fused triazolo ring and the s-triazolo(1,5-a) pyrazine derivatives **18a** and **18b** are formed. The cyclization is amenable also with the acylated derivative **17c** in the presence of hot glacial acetic acid or water to give **18b** in lower yield. The unsubstituted oxadiazolyl derivative **18a**, however, is decomposed under these reaction conditions to yield 8-cyano-s-triazolo(1,5-a) pyrazine (**19**).

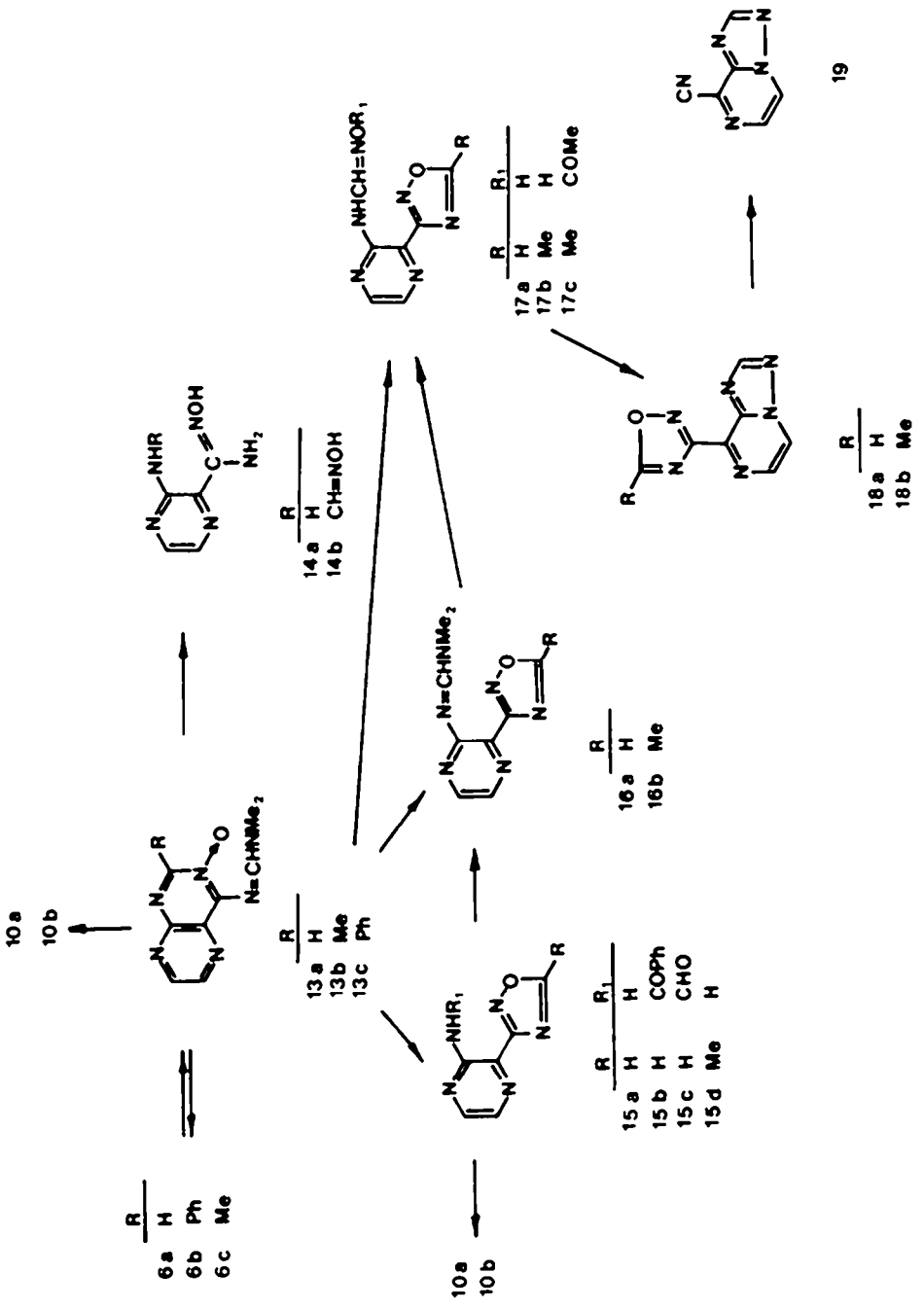
All these reactions reveal the great reactivity of pteridine 3-oxides and the possibility of forming various heterocycles by participation of either the amidine and N-oxide function, the amino and N-oxide function, or the hydroxyiminomethylamino function.

EXPERIMENTAL

M.ps were determined on a Kofler hot plate m.p. 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.

4-Acetoxyaminopteridine (**2a**)

(a) A mixture of **1a**[1] (90 mg) and triethyl orthoformate (3 ml) was heated under reflux for 6 hr. The separated product was


R
6a H
6b Ph
6c Me
N=CHNMe2
10a
10b
NHR
C
NOH
NH2
R
14a H
14b CH=NOH
13a H
13b Me
13c Ph
N=CHNMe2
NHR1
R R1
15a H H
15b H COPh
15c H CHO
15d Me H
R
16a H
16b Me
NHCH=NOR1
R R1
17a H H
17b Me H
17c Me COMe
CN
19
R
18a H
18b Me

filtered off, crystallized from water and subsequently from a mixture of MeOH and DMF (yield 27 mg, 29%), m.p. 231–234°. ^{1}H NMR δ(DMSO-d_6) 8.15 and 8.30 (d, H_6 and H_7), 7.52 (s, H_2), 2.08 (s, Me), $J_{6,7}$ = 2.2 Hz. MS: 205 (M^+, 3%). (Found: C, 46.83; H, 3.25; N, 34.11. Calc. for $C_8H_7N_3O_2$: C, 46.83; H, 3.44; N, 34.12%).

(b) A mixture of **2d** (0.1 g) and Ac_2O (1 ml) was heated under reflux for 10 min, the mixture was evaporated to dryness and the residue was crystallized from water (yield 75 mg, 60%), m.p. underpressed with the product obtained as described under (a).

4-Benzoyloxyaminopteridine (**2b**)

(a) A mixture of **1b**[1] (0.34 g) and triethyl orthoformate (7 ml) was heated under reflux for 29 hr. Upon evaporation to dryness, the residue was suspended in MeOH (3 ml), filtered and crystallized from a mixture of MeOH and DMF (yield 0.12 g, 34%), m.p. 254–257° (dec). ^{1}H NMR δ(DMSO-d_6) 8.62 and 8.75 (d, H_6 and H_7), 8.00–8.22 (m, H_2, and H_6), 7.96 (s, H_2), 7.58 (m, H_3, and H_4, and H_5), $J_{6,7}$ = 2.25 Hz. MS: 267 (M^+, 2%). (Found: C, 58.72; H, 3.43; N, 26.03. Calc. for $C_{13}H_9N_4O_2$: C, 58.42; H, 3.39; N, 26.21%).

(b) A mixture of **2d** (12 mg) and benzoyl chloride (18 mg) in pyridine (0.5 ml) was heated at 80° for 45 min. Upon evaporation to dryness, water (1 ml) was added, the product was filtered off and crystallized from a mixture of MeOH and DMF (yield 8 mg, 41%). The compound was found to be identical in all respects with the product obtained as described under (a).

4-Methoxyaminopteridine (**2c**)

A mixture of **1c**[1] (70 mg) and triethyl orthoformate (2.5 ml) was heated under reflux for 8 hr, the mixture was evaporated to dryness and the residue was crystallized from EtOH (yield 40 mg, 54%), m.p. 263–266° (dec). ^{1}H NMR δ(DMSO-d_6) 7.86 and 8.01 (d, H_6 and H_7), 7.18 (s, H_2), 3.62 (s, Me), $J_{6,7}$ = 2.1 Hz. MS: 177 (M^+, 100%). (Found: C 47.62; H, 4.09; N, 39.65. Calc. for $C_5H_5N_4O$: C, 47.45; H, 3.98; N, 39.53%).

4(3H)-Pteridinone (**3a**)

Compound **2d** (80 mg) was suspended in dil HCl (1 ml of 1 : 1) and upon heating under reflux for 10 min the mixture was evaporated to dryness. The residue was dissolved in water (0.5 ml) and neutralized with solid $NaHCO_3$ to give the product (yield 20 mg, 28%), m.p. over 350° (Lit.[7] gives over 300°), identical with an authentic specimen.

2-Methyl-4(3H)-pteridinone (**3b**)

Compound **4** (0.16 g) was heated at 230–235° for 5 min and the product was crystallized from a mixture of EtOH and DMF (yield 75 mg, 52%), m.p. 210° (dec) (Lit.[8] gives m.p. about 210°). ^{1}H NMR δ(DMSO-d_6) 8.66 and 8.85 (d, H_6 and H_7), 2.39 (s, Me), 3.3 (broad s, NH), $J_{6,7}$ = 2.1 Hz.

4-Amino-2-phenylpteridine-3-oxide (**6b**)

(a) A mixture of **5**[1] (0.4 g) and conc H_2SO_4 (2 ml) was heated at 60–70° for 75 min. The cooled mixture was poured on ice (7 g) and neutralized with conc NH_4OH to pH 6, the separated product was filtered and crystallized from EtOAc (yield 0.16 g, 43%), m.p. 223–226°. ^{1}H NMR δ (DMSO-d_6) 8.86 and 9.02 (d, H_6 and H_7), 8.30–8.55 (m, H_2 and H_6), 7.50 (m, H_3, and H_4, and H_5), $J_{6,7}$ = 2 Hz. MS: 239 (M^+, 100%). (Found: C, 60.42; H, 3.95; N, 28.99. Calc. for $C_{12}H_9N_4O$: C, 60.24; H, 3.79; N, 29.28%).

(b) A mixture of **5** (0.15 g) and polyphosphoric acid (1 g) was heated at 100° for 1 hr and then at 130° for 1 hr. The cooled mixture was diluted with water (3 ml) and upon neutralization with conc NH_4OH to pH 6 the product was separated and crystallized from EtOAc to give 50 mg (36%) of the product, identical in all respect with that as described under (a).

2-(Hydrazonomethylamino)pyrazine-3-carboxamide oxime (**7a**)

A mixture of **4** **6a**[1] (0.158 g), hydrazine hydrate (0.21 g of 98%) and MeOH (3 ml) was stirred at room temp for 4 hr. Upon evaporation to dryness, the residue was suspended in EtOH (2 ml), filtered and crystallized from a mixture of EtOH and DMF (yield 0.161 g, 85%), m.p. 189–191°. ^{1}H NMR δ(DMSO-d_6) 8.33 and 8.42 (d, H_5 and H_6), 7.89 (d, CH), $J_{5,6}$ = 2.6, J_{NHCH} = 8.7 Hz. MS: 195 (M^+, 55%). (Found: C, 37.01; H, 4.73; N, 50.39. Calc. for $C_6H_9N_7O$: C, 36.92; H, 4.65; N, 50.23%).

2-(Hydrazonobenzylamino)pyrazine-3-carboxamide oxime (**7b**)

A soln of **6b** (0.3 g) in MeOH (8 ml) was treated with hydrazine hydrate (0.42 g of 98%) and left at room temp for 2 hr. The mixture was heated under reflux for 30 min and upon evaporation an oily residue was obtained and treated with MeOH (2 ml). The product was filtered and crystallized from EtOH (yield 0.225 g, 66%), m.p. 171–173°. ^{1}H NMR δ (DMSO-d_6) 7.94 (s, H_5 and H_6), 7.10–7.60 (m, Ph). MS: 271 (M^+, 17%). (Found: C, 53.15; H, 4.96; N, 36.12. Calc. for $C_{12}H_{13}N_7O$: C, 53.12; H, 4.83; N, 36.14%).

Transformation of 4-aminopteridine 3-oxide in aqueous solution

If **6a** (0.55 g) in water (15 ml) was heated under reflux for 7 hr, upon cooling crystals of **8a** separated (0.4 g, 73%). The filtrate was evaporated to dryness and the residue was heated under reflux in MeOH (5 ml) for 1 min. The mixture was filtered hot to obtain the unreacted **6a** (15 mg, 3%). The filtrate was evaporated to dryness and the residue was identified as **14a** (80 mg), containing a minute amount of **10a**.

8a had m.p. over 310° from water. ^{1}H NMR δ (DMSO-d_6, 130°) 7.96 and 8.10 (d, H_6 and H_7), 7.33 (s, H_2), $J_{6,7}$ = 2.3 Hz. MS: 163 (M^+, 45%). (Found: C, 44.18; H, 3.22; N, 42.87. Calc. for $C_6H_5N_5O$: C, 44.17; H, 3.09; N, 42.93%). **8a**, if suspended in HCl aq (1 : 1) afforded its hydrochloride, m.p. 292–295° (dec) from a mixture of MeOH and diethyl ether. It could be also obtained, if a suspension of **2a** was stirred in HCl aq (1 : 1) for 17 hr at room temp (yield 25%). ^{1}H NMR δ (DMSO-d_6) 8.18 and 8.25 (H_6 and H_7), 7.94 (s, H_2), $J_{6,7}$ = 2.4 Hz. (Found: C, 35.95; H, 3.17; N, 35.32. Calc. For $C_6H_6ClN_5O$: C, 36.11; H, 3.03; N, 35.09%).

Transformation of 4-amino-2-phenylpteridine 3-oxide in aqueous solution

The corresponding **6b** (0.22 g) in water (4 ml) was heated under reflux for 28 hr. From the cold mixture **8b** was filtered off (yield 69 mg, 31%) and in the soln **9** was detected by TLC. The above **8b** had m.p. 226–229° from water. ^{1}H NMR δ (DMSO-d_6) 8.73 and 8.95 (d, H_6 and H_7), 7.72 (m, H_3, H_4 and H_5 of Ph), 8.30–8.62 (m, H_2 and H_6 of Ph), $J_{6,7}$ = 2.1 Hz. MS: 239 (M^+, 2%). (Found: C, 60.26; H, 3.95; N, 29.55. Calc. for $C_{12}H_9N_4O$: C, 60.24; H, 3.79; N, 29.28%).

Transformation of 2-benzoylaminopyrazine-3-carboxamide oxime in a solution of sodium hydroxide

A mixture of **5** (50 mg) and NaOH aq (1 ml of 5%) was heated under reflux for 1 min, cooled and neutralized with glacial AcOH to pH 6. The separated product (34 mg, 73%) consisted of a mixture of **9** and **8b**. The mixture was separated by treatment with an NaOH aq (0.5 ml of 5%), filtering the oxadiazolyl derivative (25 mg, 54%) and by neutralization of the filtrate with glacial AcOH, **8b** was obtained (4 mg, 9%).

Reaction between 4-amino-2-phenylpteridine 3-oxide and aqueous sodium hydroxide

(a) Compound **6b** (65 mg) when heated under reflux in NaOH-aq (1 ml of 5%) for 1 min, afforded **9** (13 mg, 20%) upon cooling the mixture. The filtrate was neutralized with glacial AcOH to pH 6 and the separated product was filtered and identified as **8b** (3 mg, 5%). The filtrate was again acidified with conc HCl to pH 2 and upon cooling to 0° **11a** which separated, was filtered and crystallized from glacial AcOH (19 mg, 27%), m.p. about 150° with conversion into **12**. The following spectroscopic and analytical data for **11a** were determined: ^{1}H NMR δ (DMSO-d_6) 8.10 (s, H_5 and H_6), 7.35 (s, Ph), MS: 258 (M^+, 9%). (Found: C, 55.62; H, 4.13; N, 21.76. Calc. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3,90; N, 21.70%).

(b) **6b** (0.4 g) in NaOH aq (6 ml of 5%) was heated under reflux for 10 min until evolution of NH_3 ceased. Upon cooling and neutralization with glacial AcOH to pH 6 the separated **9** containing little **8b** was filtered off (0.1 g). The filtrate was acidified with conc HCl to pH 2 and upon cooling to 0° **11a** was separated and was filtered off (0.2 g, 46%).

Methyl-2-(methoxyiminobenzylamino)pyrazine-3-carboxylate (**11b**).

A suspension of **11a** (0.23 g) in MeOH (6 ml) was treated with excess of diazomethane in diethyl ether. After standing at room temp for 1 day and evaporation, the oily residue was suspended in EtOH (2 ml), cooled, the product was filtered and crystallized from EtOH (yield 50 mg, 20%), m.p. 162–164°. The ferric chloride test, positive in the case of **11a**, was negative. ^{1}H NMR δ (DMSO-d_6) 8.08 (s, H_5 and H_6), 7.32 (s, Ph), 3.91 (s, two Me). MS: 186 (M^+, 48%). (Found: C, 58.85; H, 5.02; N, 19.55. Calc. for $C_{14}H_{14}N_4O_2$: C, 58.73; H, 4.93; N, 19.57.

2-Phenyl-3-hydroxy-4(3H)pteridinone (**12**).

Compound **11a** (0.1 g) was heated at 200°/1.3 kPa for 10 min and the product was crystallized from glacial AcOH (yield 60 mg, 65%), m.p. 260–263°. ^{1}H NMR δ (DMSO-d_6) 8.85 and 9.03 (d, H_6 and H_7), 7.77–7.98 (m, H_2, and H_6), 7.55 (m, H_3, and H_4, and H_5), $J_{6,7}$ = 2.1 Hz. MS: 240 (M^+, 100%). (Found: C, 60.20; H, 3.56; N, 23.19. Calc. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.33%).

If the above product (38 mg) was heated with dilute NaOH aq (1 ml of 5%) under reflux for 5 min, upon cooling and acidification with conc HCl **11a** was obtained in 61% yield (25 mg).

Reaction of 2-phenyl-4-hydroxyaminopteridine in the presence of alkali

(a) If a mixture of **8b** (14 mg) and NaOH aq (1 ml of 5%) was heated under reflux for 30 min, upon acidification with glacial AcOH a mixture of the starting compound and **9** (12 mg) was obtained. The mixture was separated by treatment with NaOH aq (0.5 ml of 5%) and filtering off the undissolved oxadiazolyl derivative (yield 7 mg, 50%). From the filtrate upon acidification the starting compound (1 mg, 7%) was isolated.

(b) If a mixture of **8b** and NaOH aq was heated under reflux for 1 min upon acidification only the starting compound was isolated.

4-(N,N-Dimethylaminomethyleneamino)pteridine 3-oxide (**13a**)

A mixture of **6a** (0.46 g) and N,N-dimethylformamide dimethyl acetal (2g) was heated at 105° for 3.5 hr, evaporated and the residue was crystallized from a mixture of $CHCl_3$ and petroleum ether, (yield 0.42 g, 68%), m.p. 210–213° (dec). ^{1}H NMR δ ($CDCl_3$) 9.52 (s, CH), 8.64 (s, H_2), 8.45 and 8.50 (d, H_6 and H_7), 3.14 (s, Me), 3.17 (s, Me), $J_{6,7}$ = 1.8 Hz. MS: 218 (M^+, 25%). (Found: C, 49.86; H, 4.84; N, 38.49. Calc. For $C_9H_{10}N_6O$: C, 49.53; H, 4.62; N, 38.52%).

If a methanolic soln of the compound obtained was left at room temp for 4 hr, the starting **6a** was obtained in 9% yield. In aqueous soln of NaOH (5%) the product was converted after 75 min at room temp into **10b** and a small amount of **10a**. With a methanolic soln of free hydroxylamine, the product was transformed after 75 min at room temp into **14b** (yield 60%) and in the filtrate **14a** was detected by TLC.

4-(N,N-Dimethylaminomethyleneamino)-2-methylpteridine 3-oxide (**13b**)

This compound was prepared in a similar manner to **6c** in 58% yield, m.p. 187–189° (dec) from EtOAc. ^{1}H NMR δ ($CDCl_3$) 8.12 and 8.20 (d, H_6 and H_7), 9.10 (s, CH), 3.02 (s, NMe_2), 2.67 (s, Me), $J_{6,7}$ = 1.8 Hz. MS: 232 (M^+, 96%). (Found: C, 47.94; H, 6.23; N, 32.58. Calc. for $C_{10}H_{12}N_6 0.1.5H_2O$: C, 47.31; H, 5.72; N, 33.11%).

4-(N,N-Dimethylaminomethyleneamino)-2-phenylpteridine 3-oxide (**13c**)

This was prepared from **6b** as described above for the 2-unsubstituted compound in 84% yield, m.p. 197–200° from benzene. ^{1}H NMR δ(DMSO-d_6) 8.86 and 8.92 (d, H_6 and H_7), 9.43 (s, CH), 8.10–8.32 (m, H_2, and H_6), 7.36–7.57 (m, H_3, and H_4, and H_5), 3.17 (s, two Me), $J_{6,7}$ = 1.8 Hz. MS: 294 (M^+, 14%). (Found: C, 61.00; H, 4.80; N, 28.45; Calc. for $C_{15}H_{14}N_6O$: C, 61.20; H, 4.79; N, 28.56%).

2-Amino-3-(1',2',4'-oxadiazolyl-3')pyrazine (**15a**)

(a) A soln of **13a** (0.11 g) in HCl (3 ml of 1 : 1) was stirred 3 hr at room temp, neutralized and the separated product filtered (yield 65 mg, 79%). Upon extraction of the filtrate with $CHCl_3$ (3 × 3 ml) some more of the product was obtained (10 mg, 12%), m.p. 169–171° (dec) from EtOH. ^{1}H NMR δ(DMSO-d_6) 7.60 and 7.80 (d, H_5 and H_6), 9.29 (s, H_3), $J_{5,6}$ = 2.3 Hz. MS: 163 (M^+, 70%). (Found: C, 44.14; H, 3.02; N, 42.94. Calc. for $C_6H_5N_5O$: C, 44.17; H, 3.09; N, 42.93%).

(b) A soln of **13b** (45 mg) in HCl aq (1 ml of 1 : 1) was stirred for 90 min at room temp, water (1 ml) was added and upon neutralization with $NaHCO_3$ the mixture was extracted with $CHCl_3$ (3 × 4 ml) to obtain **15** (47%) of the product, identical in all respects with that as described under (a).

(c) A similar treatment with HCl aq of **17a** afforded upon neutralization the same product in 71% yield.

(d) Similarly, **15c** was transformed in the presence of HCl aq at room temp in the above product in 80% yield.

Transformations of 2-amino-3-(1',2',4'-oxadiazolyl-3')pyrazine.

(a) Compound **15a** (35 mg) in water (3 ml) was heated under reflux for 1 hr. The residue, obtained after evaporation to dryness, consisted of **10a** with some **10b**.

(b) With a 5% NaOH aq the **15a** was transformed at room temp after 35 min into **10b** in admixture with a small quantity of **10a**.

2-Benzoylamino-3-(1',2',4'-oxadiazolyl-3')pyrazine (**15b**)

A soln of **13c** (0.12 g) in HCl (1 ml of 1 : 1) was left at room temp for 35 min and the formed suspension was diluted with water (2 ml) and neutralized with solid $NaHCO_3$ to pH 6. The product was filtered off and crystallized from EtOH (yield 87 mg, 80%), m.p. 160–162°. ^{1}H NMR δ(DMSO-d_6) 8.83 and 8.90 (d, H_5 and H_6), 9.80 (s, H_3), 7.90–8.12 (m, H_2 and H_6 of Ph), 7.62 (m, H_3, H_4, H_5 of Ph), $J_{5,6}$ = 2.3 Hz. MS: 267 (M^+, 100%). (Found: C, 58.52; H, 3.44; N, 25.92. Calc. for $C_{13}H_9N_5O_2$: C, 58.42; H, 3.39; N, 26.21%).

2-(N,N-Dimethylaminomethyleneamino)-3-(1',2',4'-oxadiazolyl-3') pyrazine (**16a**)

(a) A soln of **13a** (0.218 g) and dimethylamine hydrochloride (0.15 g) in MeOH (4 ml) was stirred at room temp for 5 hr. Upon evaporation the residue was treated with water (3 ml) and the soln extracted with $CHCl_3$ (2 × 3 ml). The oily product was dissolved in a small amount of $CHCl_3$, petroleum ether was added until cloudiness appeared and after cooling to −15° the separated crystals were filtered off (yield 90 mg, 41%), m.p. 107–110°. ^{1}H NMR δ(DMSO-d_6) 8.17 and 8.12 (d, H_5 and H_6), 8.47 (s, CH), 9.60 (s, H_3) 2.90 and 3.07 (s, NMe_2), $J_{5,6}$ = 2.4 Hz. MS: 218 (M^+, 100%). (Found: C, 49.55; H, 4.74; N, 38.71. Calc. for $C_6H_{10}N_6O$: C, 49.53; H, 4.62; N, 38.52%).

(b) A mixture of **15a** (50 mg) and N,N-dimethylformamide dimethyl acetal (0.1 g) in $CHCl_3$ (2 ml) or toluene was heated under reflux for 15 min. The oily residue, obtained after evaporation of the solvent, was crystallized from a mixture of $CHCl_3$ and petroleum ether. The product (yield 55 mg, 82%) was identical in all respects with the compound obtained as described under (a).

2-Formylamino-3(1',2',4'-oxadiazolyl-3')pyrazine (**15c**)

A soln of **13a** (0.1 g) in formic acid (0.6 ml of 98%) was left at room temp for 35 min and poured onto ice (4 g). Upon netralization with solid $NaHCO_3$ the product was filtered off and crystallized from MeOH (yield 70 mg, 80%), m.p. 160–162°. ^{1}H NMR δ (DMSO-d_6) 8.57 (s, H_5 and H_6), 9.93 (s, H_3), 9.33 (s, CHO). MS: 191 (M^+, 43%). (Found: C, 44.03; H, 2.75; N, 36.85. Calc. for $C_5H_5N_5O_2$: C, 43.98; H, 2.64; N, 36.64%).

2-Hydroxyiminomethylamino-3-(1',2',4'-oxadiazolyl-3')pyrazine (**17a**)

(a) A mixture of **13a** (0.11 g) and hydroxylamine hydrochloride (50 mg) in water (2 ml) was left at room temp for 2 hr. The product was filtered off and crystallized from a mixture of MeOH and DMF (yield 80 mg, 77%), m.p. about 190° (dec). ^{1}H NMR δ(DMSO-d_6) 7.96 and 8.07 (d, H_5 and H_6), 7.65 (d, CH), 9.47 (s, H_3), $J_{5,6}$ = 2.3, J_{NHCH} = 9 Hz. MS: 206 (M^+, 20%). (Found: C, 41.00; H, 2.86; N, 40.59. Calc. for $C_5H_6N_6O_2$: C, 40.78; H, 2.93; M, 40.77%).

(b) A mixture of **15a** (35 mg), N,N-dimethylformamide

dimethyl acetal (90 mg) and $CHCl_3$ (1 ml) was heated under reflux for 15 min. Evaporation left an oily residue and the crude **16a** was dissolved in MeOH (1 ml) and treated with hydroxylamine hydrochloride (40 mg). After 30 min at room temp the solvent was evaporated and the residue was suspended in water (1 ml) to give the product (yield 36 mg, 81%), identical with the compound as obtained under (a).

2-(N,N-Dimethylaminomethyleneamino)-3-(5'-methyl-1',2',4'-oxadiazolyl-3')pyrazine (**16b**)

A mixture of **15d** (0.16 g)[2] and N,N-dimethylformamide dimethyl acetal (0.26 g) was heated at 105° until complete dissolution occurred (about 8 min). Upon evaporation to dryness, the product was crystallized from a mixture of $CHCl_3$ and petroleum ether (yield 0.15 g, 72%), m.p. 108–110°. ^{1}H NMR δ(DMSO-d_6) 8.12 and 8.27 (d, H_5 and H_6), 8.45 (s, CH), 2.90 and 3.07 (s, NMe_2), 2.61 (s, Me), $J_{5,6}$ = 2.4 Hz, MS: 232 (M^+, 100%). (Found: C, 52.61; H, 5.66; N, 35.86. Calc. for $C_{10}H_{12}N_6O$: C, 51.71; H 5.21; N, 36.19%).

2-Hydroxyiminomethylamino-3-(5'-methyl-1',2',4'-oxadiazolyl-3')-pyrazine (**17b**)

A mixture of the **16b** (0.2 g), hydroxylamine hydrochloride (80 mg) and MeOH (3 ml) was stirred at room temp for 1 hr. Upon evaporation the residue was suspended in water (2 ml) and the product was filtered off and crystallized from MeOH (yield 0.17 g, 95%), m.p. 212–214° (dec) ^{1}H NMR δ(DMSO-d_6) 7.88 and 7.98 (d, H_5 and H_6), 7.58 (d, CH), 2.57 (s, Me) 9.77 (d, NH), $J_{5,6}$ = 2.3, J_{NHCH} = 9.0 Hz. MS: 220 (M^+, 48%). (Found: C, 43.37; H, 38.01. Calc. for $C_8H_8N_6O_2$: C, 43.64; H, 3.66; N, 38.17%).

2-Acetoxyiminomethylamino-3-(5'-methyl-1',2',4'-oxadiazolyl-3')-pyrazine (**17c**).

The above **17b** (0.165 g) was treated with Ac_2O (1.5 ml) and warmed until a clear soln was obtained. Upon evaporation to dryness, the residue was crystallized from EtOH (yield, 0.15 g, 76%), m.p. 155–157°. ^{1}H NMR δ(DMSO-d_6) 7.95 and 8.02 (d, H_5 and H_6) 7.96 (d, CH), 10.05 (d, NH), 2.60 (s, Me), 2.12 (s, COMe), $J_{5,6}$ = 2.3, J_{NHCH} = 9.3 Hz. MS: 262 (M^+, 40%). (Found: C, 45.45; H, 3.95; N, 31.88. Calc. for $C_{10}H_{10}N_6O_3$: C, 45.80; H, 3.84; N, 32.05%).

8-(1',2',4'-Oxadiazolyl-3')-s-triazolo(1,5-a)pyrazine (**18a**)

A mixture of **17a** (95 mg) and polyphosphoric acid (0.8 g) was heated at 70° for 3 hr, cooled and dissolved in water (3 ml). Upon neutralization with solid $NaHCO_3$ the soln was extracted with $CHCl_3$ (4 × 4 ml) and the product obtained after evaporation of the solvent was crystallized from EtOH (yield 30 mg, 35%), m.p. about 190° (dec). ^{1}H NMR δ (DMSO-d_6) 8.52 (s, H_2), 8.99 (d, H_5), 8.14 (d, H_6), 9.55 (s, H_5), $J_{5,6}$ = 4.4 Hz. MS: 188 (M^+, 100%). (Found: C, 44.85; H, 2.39; N, 44.67. Calc. for $C_7H_4N_6O$: C, 44.68; H, 2.14; N, 44.67%).

8-(5'-Methyl-1',2',4'-oxadiazolyl-3')-s-triazolo(1,5-a)pyrazine (**18b**).

(a) A mixture of **17b** (0.5 g) and polyphosphoric acid (5 g) was heated at 75° for 1 hr and thereafter for 1.5 hr at 100–110°. The cooled mixture was suspended in water (12 ml), the separated product filtered off (yield 0.27 g, 59%) and the filtrate was extracted with $CHCl_3$ (4 times with 40 ml) to give further amount (70 mg, 16%) of the same product which was crystallized from EtOH, m.p. 248–250°. ^{1}H NMR δ (DMSO-d_6) 8.27 (s, H_2), 8.70 (d, H_5), 7.93 (d, H_6), 2.57 (s, Me), $J_{5,6}$ = 4.4 Hz. MS: 202 (M^+, 71%). (Found: C, 47.45; H, 3.10; N, 41.45. Calc. for $C_8H_6N_6O$: C, 47.52; H, 2.99; N, 41.57%).

(b) A mixture of **17c** (60 mg), water (2.5 ml, or the same amount of glacial AcOH) was heated under reflux for 2 hr and evaporated to dryness. The residue was crystallized from EtOH (yield 14 mg, 30%, if glacial AcOH was used the yield was 39%). The compound was found identical with the product, obtained as described under (a).

8-Cyano-s-triazolo(1,5-a)pyrazine (**19**)

A mixture of **18a** (70 mg) and water (3 ml) was heated under reflux for 1 hr. Upon evaporation the product was crystallized from water (yield 20 mg, 37%), m.p. 147–149°. ^{1}H NMR δ (DMSO-d_6) 8.26 (s, H_2), 8.43 (d, H_5), 7.98 (d, H_6), $J_{5,6}$ = 4.5 Hz. MS: 145 (M^+, 100%). (Found: C, 49.44; H, 2.31; N, 47.99. Calc. for $C_6H_3N_5$: C, 49.65; H, 2.08; N, 48.26%).

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REFERENCES

[1]A. Tomažič, M. Tišler and B. Stanovnik, *Tetrahedron* 37, 1787 (1981).
[2]M. Kočevar, B. Verček, B. Stanovnik and M. Tišler, *Monatsh. Chem.* 113, 731 (1982).
[3]M. Kočevar, B. Stanovnik and M. Tišler, *J. Heterocyclic Chem.* in press.
[4]A. R. Katritzky and J. M. Lagowski, *Chemistry of Heterocyclic N-Oxides*. Academic Press, New York (1971).
[5]M. Gates, *Chem. Revs* 41, 63 (1947).
[6]R. C. Elderfield and A. C. Mehta, *Heterocycl. Compds.* Vol. 9, p. 1. Wiley, New York (1967).
[7]A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.* 474 (1951).
[8]A. Albert, *Ibid.* Perkin I, 1574 (1979).