Versatile Synthesis of 6-Substituted 8-Deazapteridine-2,4-diamines. Formal Total Synthesis of 8,10-Dideazaminopterin

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Dedicated to Professor Dr. H. Achenbach (Erlangen) on the occasion of his 65th birthday

A new synthesis of 4-amino-4-deoxy-8,10-dideazapteroic acid (**11d**) and 6-substituted and 5,6-anellated 8-deazapteridine-2,4-diamines, **10a**, **10d**, **25**, is described. Starting from keteneaminals **1** or **12** and enaminones **4** or β-aminoketone **17** the title compounds can be prepared *via* functional group transformation of 2-amino-3-nitropyridines **5** or nicotinate **13a** yielding 3-amino-α-picolinonitriles **9** which are cyclocondensed with guanidine.

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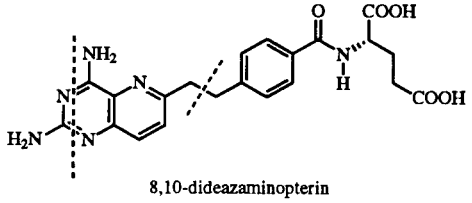
In our recent studies, analogues of trimethoprim and piritrexim as antifolates possessing a 5-deazapteridine-2,4-diamine structure have been synthesized *via* cyanoketeneaminals or 2,4,6-triaminopyrimidine [1].

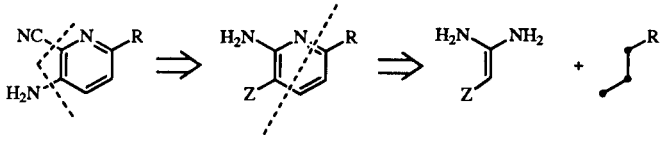
We report now on a versatile synthesis of 6-*alkyl*-substituted 8-deazapteridine-2,4-diamines from keteneaminals as starting material. This new method facilitates the access to 6-alkyl-8-deazapteridines [2]. The powerful antifolate 8,10-dideazaminopterin, a 8-deazapteridine-derivative, has been selected as the target for our strategy. 8,10-Dideazaminopterin is 16 times more potent than the known inhibitor of the dihydrofolate reductase, methotrexate [3].

A short retrosynthetic view, which explains our approach is outlined in Scheme 1. Cleavage of strategic bonds in 8,10-dideazaminopterin leads to 3-amino-α-picolinonitrile which originates from a 2-aminopyridine derivative with a functional group Z (NO_2 or COOR) in position 3. Final retrosynthesis gives rise to a Z-substituted keteneaminal and a 1,3-biselectrophile.

Scheme 1



8,10-dideazaminopterin



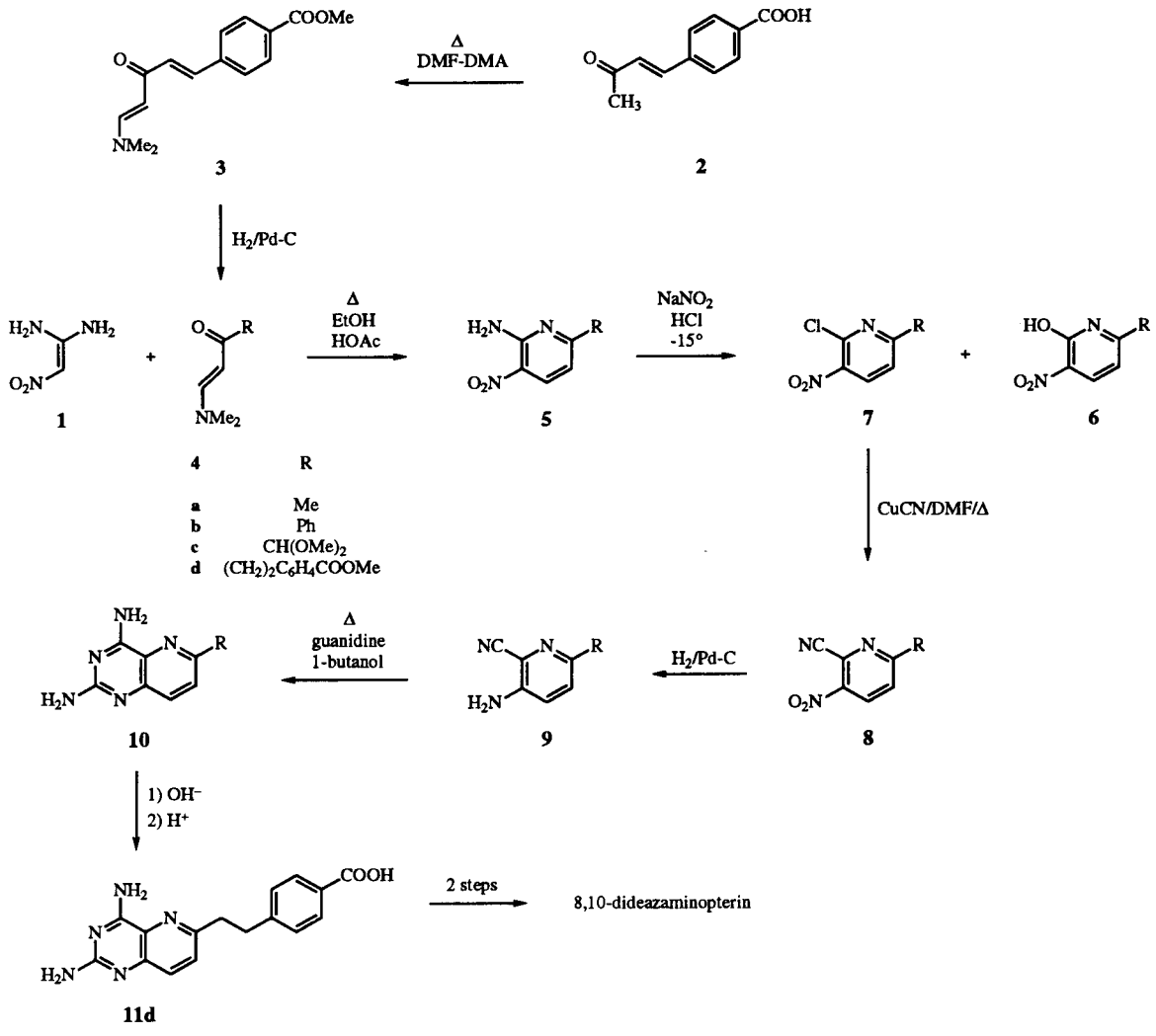
The sequence for the preparation of 8-deazapteridine **10a** starts with a cyclo-condensation of 2-nitroethene-1,1-diamine (**1**) [4] with enaminoketone **4a**. The thus obtained 3-nitropyridin-2-amine **5a** [5] was treated with sodium nitrite in hydrochloric acid (-15°) to yield the chloropyridine **7a** as a major product and the hydroxypyridine **6a** as a minor product. These conditions enabled higher product yields, compared to the previously published procedure [6]. Treatment of **6a** whith phosphoryl chloride/Δ gave some additional **7a**. The subsequent nucleophilic replacement of the chloro substituent in **7a** was achieved by refluxing **7a** with cuprous cyanide in DMF [7]. The reaction product, α-picolinonitrile **8a**, was hydrogenated (Pd/C) to *o*-aminonitrile **9a**. Final cyclocondensation of **9a** with guanidine in *n*-butanol gave the known 6-methylpyrido[3,2-*d*]pyrimidine-2,4-diamine (**10a**) [2]. A similar approach for the synthesis of 6-substituted 8-deazapteridines which possess an alkylamino- or arylthio- group in position 6 was reported by Werbel [8], who started from 2,6-dichloropyridine.

In order to prove our method, further enaminones of type **4**, *i.e.* derivatives **4b-d**, were cyclocondensed with **1** and the resulting products were treated in the above mentioned way.

The replacement of the chlorosubstituent in **7b** (R = Ph) [5] by cyanide proceeded only in low yields (12%). Therefore no further reactions with **8b** were performed. 6-Bromomethylpyrido[3,2-*d*]pyrimidine-2,4-diamine or the 6-hydroxymethyl derivative are important intermediates for the synthesis of 8,10-dideazaminopterin [9]. In a new approach for the synthesis of the latter compound 6-dimethoxymethyl-3-nitropyridin-2-amine (**5c**) was used as starting material. Sodium nitrite/hydrochloric acid treatment of **5c**, which possesses a latent aldehyde group in position 6, unfortunately led to a mixture of compounds which could not be separated.

For the formal total synthesis of 8,10-dideazaminopterin an enaminone with a phenethyl side chain was required. The synthesis which is outlined in Scheme 2 started from benzylidene acetone derivative **2** [10]. Treatment of **2** with *N,N*-dimethylformamide dimethyl acetal under reflux gave the styryl-enaminone **3** as a methylester, which was hydrogenated to the phenethyl enaminone **4d**. Subsequent cyclocondensation with 2-nitroethene-1,1-diamine (**1**) gave rise to the pyridine **5d**.

Scheme 2

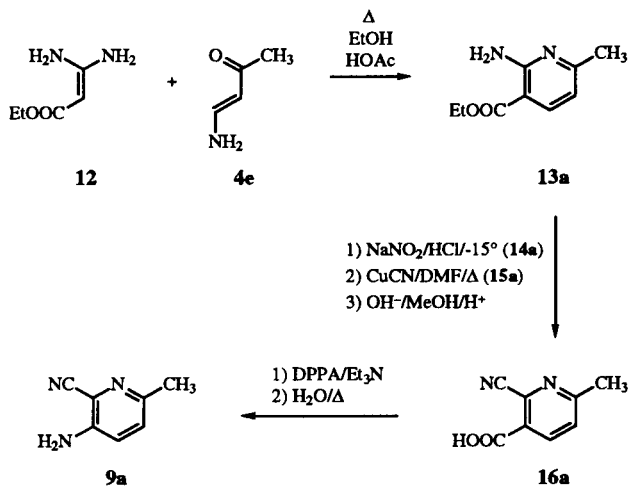


The following functional group transformations provided the chloropyridine **7d**, the α-picoline **8d** and the *o*-aminonitrile **9d**, which was reacted with guanidine in boiling 1-butanol to the butyl ester **10d** (R = $COOC_4H_9$). Final hydrolysis of this ester afforded the known 4-amino-4-deoxy-8,10-dideazapteroic acid **11d**, a key intermediate for the preparation of 8,10-dideazaminopterin [4] or 8,10-dideazatetrahydrofolic acid [11].

It is interesting to note that in the synthesis of 8,10-dideazaminopterin by DeGraw [3] the linkage between a functional 8-deazapteridine and a formylbenzoic acid derivative is performed by a Wittig reaction in a late stage of the synthesis, in contrast to our approach, where the linkage is achieved *via* aldol condensation in the beginning of the sequence.

In order to establish our "keteneaminal way" to 8-deazapteridine-2,4-diamines, we also tested ethyl 3,3-diaminoacrylate (**12**) [12] as a further useful keteneaminal. Cyclocondensation of **12** with **4e** proceeded smoothly and led to ethyl nicotinate **13a** [13] which was treated in the reported way with sodium nitrite/hydrochloric acid (**14a**) followed by an exchange reaction with cuprous cyanide/DMF (**15a**) and hydrolysis of the ester moiety. The carboxylic group in **16a** was converted to an amino function (**9a**) by a modified Curtius rearrangement using diphenylphosphonic azide treatment [14] in *tert*-butyl alcohol followed by hydrolysis of the intermediately formed isocyanate (see Scheme 3). However, the overall yield of **9a** with this keteneaminal was lower than in the case of 2-nitroethene-1,1-diamine (**1**). Finally, as a model compound for a rigid 7,10-ethano-8,10-dideazaminopterin, the pyrimido[5,4-*b*]quinoline-2,4-diamine **25**, was synthesized from 2-nitroethene-1,1-diamine (**1**) and Mannich-base **17**. Refluxing of the starting materials in ethanol gave rise to 1,4-dihydropyridine **18**. By reacting **1** with β-aminoketone **17** in boiling DMF the pyridine **19** was obtained. Sodium nitrite/hydrochloric acid treatment of pyridines **18** or **19**, respectively, yielded the chloro

Scheme 3

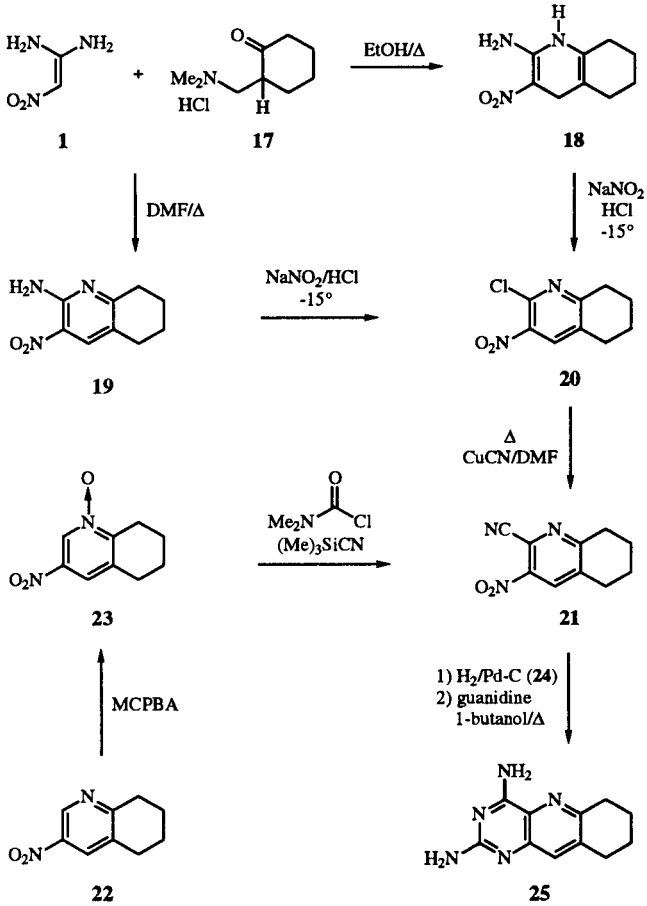


12 4e 13a 9a 16a

compound **20** which was converted to the quinolinenitrile **21**. Since this exchange reaction proceeded only with minor yields, an alternative approach to **21** was tested.

Stirring of the 3-nitroquinoline **22** [15] with 3-chloroperoxybenzoic acid in dichloromethane yielded the *N*-oxide **23**. The latter was reacted with cyanotrimethylsilane/dimethylcarbamoyl chloride [16] to give the quinolinenitrile **21** in good yields. Final hydrogenation (**24**) and cyclocondensation with guanidine gave rise to the anellated pyrido[3,2-*d*]-pyrimidine-2,4-diamine **25** (see Scheme 4).

Scheme 4



1 17 18 19 20 23 21 22 25

EXPERIMENTAL

All melting points were determined using a Büchi-530 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer-1740 spectrometer. The uv-spectra were recorded on a Perkin-Elmer-Lamda 5 instrument. The ^1H and ^{13}C nmr spectra were obtained with a Bruker-BZH-360/52 instrument with tetramethylsilane as the internal standard. The mass spectra were recorded on a Finnigan-4500 instrument at 70eV.

Methyl (*E,E*)-4-(5-Dimethylamino-3-oxo-1,4-pentadien-1-yl)benzoate (**3**).

A mixture of **2** [9] (500 mg, 2.63 mmoles), *N,N*-dimethylformamide dimethyl acetal (627 mg, 5.26 mmoles) and *p*-toluenesulphonic acid (15 mg) was heated at reflux for 7 hours. The yellow solid was collected and purified by mplc on silica gel (chloroform:methanol 99:1, v/v) to give 423 mg (62%), mp 178-180°; ir (potassium bromide): 3025 and 3003 (CH), 1714 (ester CO), 1651 cm^{-1} (ketone CO); ^1H nmr (DMSO-d_6): δ 2.87 and 3.14 (br 2s, each, 3H, NMe_2), 3.86 (s, 3H, OMe), 5.30 (d, 1H, 4'-H, J = 12.5 Hz), 7.15 (d, 1H, 2'-H, J = 16 Hz), 7.42 (d, 1H, 1'-H, J = 16 Hz), 7.77 (d, 1H, 5'-H, J = 12.5 Hz), 7.76-7.82 (m, 2H, 3-H and 5-H), 7.93-7.99 ppm (m, 2H, 2-H and 6-H); ms: m/z 259 (M^+).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.56; H, 6.61; N, 5.41. Found: C, 69.38; H, 6.77; N, 5.39.

Methyl (*E*)-4-(5-Dimethylamino-3-oxo-4-penten-1-yl)benzoate (**4d**).

To a solution of **3** (500 mg, 1.93 mmoles) in ethyl acetate (150 ml) was added 150 mg of palladium (10% on carbon). The mixture was hydrogenated for 3 hours at room temperature (2 bar), filtered through Celite and the solvent was evaporated *in vacuo*. The residual oil was purified by distillation *in vacuo* to yield 267 mg (53%), mp 53-55°; ir (potassium bromide): 3005 (CH), 1715 (ester CO), 1651 (ketone CO); ^1H nmr (deuteriochloroform): δ 2.62-2.71 (m, 2H, 1'-H), 2.95-3.06 (m, 2H, 2'-H), 2.72-3.10 (br s, 6H, NMe_2), 5.01 (d, 1H, 4'-H, J = 12.5 Hz), 7.25-7.32 (m, 2H, 3-H and 5-H), 7.53 (d, 1H, 5'-H, J = 12.5 Hz), 7.91-7.97 ppm (m, 2H, 2-H and 6-H); ms: m/z 261 (M^+).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.32; H, 7.36; N, 5.34.

6-Dimethoxymethyl-3-nitropyridin-2-amine (**5c**).

A solution of **4c** [17] (4.33 g, 0.025 mole) and 2.58 g (0.025 mole) of 2-nitroethene-1,1-diamine (**1**) in ethanol/acetic acid (8:2, v/v) (250 ml) was heated at reflux for 6 hours. After being cooled to room temperature a black precipitate was collected by filtration. The solid was heated at reflux with ethanol/water (8:2, v/v) and filtered. After cooling below 10° the yellow needles were collected to yield 1.60 g (33%), mp 102-104°; ir (potassium bromide): 3481, 3279 and 3164 (NH_2), 2975 and 2835 (CH), 1504 cm^{-1} (NO_2); ^1H nmr (DMSO-d_6): δ 3.34 (s, 6H, $HC(OMe)_2$), 5.13 (s, 1H, $HC(OMe)_2$), 6.83 (d, 1H, 5-H, J = 8

Hz), 7.95 (br s, 2H, NH_2, deuterium oxide-exchangeable), 8.42 (d, 1H, 4-H, J = 8 Hz); ms: m/z 213 (M^+).

Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 44.89; H, 5.18; N, 19.44.

Methyl 4-[2-(2-Amino-3-nitro-6-pyridyl)ethyl]benzoate (**5d**).

A solution of **4d** (706 mg, 2.70 mmoles) and 278 mg (2.70 mmoles) of 2-nitroethene-1,1-diamine (**1**) in ethanol/acetic acid (8:2, v/v) (90 ml) was heated 5 hours at reflux. The mixture was cooled below 8°. The precipitate was collected by filtration and crystallized from ethanol, yield 586 mg (72%), mp 129-131°; ir (potassium bromide): 3460, 3272 and 3146 (NH_2), 1704 (CO), 1573 cm^{-1} (NO_2); uv (methanol): λ max 384 nm (ε 9,036); ^1H nmr (DMSO-d_6): δ 2.95-3.12 (m, 2H, 1-H, ethyl), 3.40-3.55 (m, 2H, 2-H, ethyl), 3.83 (s, 3H, OMe), 6.64 (d, 1H, 5-H, pyridine, J = 8.5 Hz), 7.35-7.42 (m, 2H, 3-H and 5-H), 7.84-7.91 (m, 4H, 2-H, 6-H and NH_2), 8.28 ppm (d, J = 8.5 Hz, 1H, 4-H, pyridine); ^{13}C nmr (DMSO-d_6): δ 34.1 (C-1, ethyl), 39.5 (C-2, ethyl), 52.5 (OMe), 113.0 (C-5, pyridine), 125.5 (C-3, pyridine), 127.8 (C-1), 129.3 and 129.7 (C-2, C-6 and C-3, C-5), 139.6 (C-4, pyridine), 147.3 (C-4), 153.6 (C-2, pyridine), 166.6 (CO), 168.9 (C-6, pyridine); ms: m/z 301 (M^+).

Anal. Calcd. for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 60.49; H, 5.06; N, 13,91.

2-Chloro-3-nitro-6-phenylpyridine (**7b**).

To a cooled (-15°) suspension of **5b** (430 mg, 2.00 mmoles) in hydrochloric acid (15 ml) was added slowly sodium nitrite (2.76 g, 0.04 mole). The reaction mixture was stirred overnight at room temperature and a yellow solid was filtered, washed with water and dried *in vacuo*. The solid was purified by mplc on silica gel (chloroform:methanol 98:2, v/v) and crystallized from methanol to give 211 mg (45%), mp 112-113°; ir (potassium bromide): 3081 (CH), 1577, 1567, 1526 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): δ 7.51-7.55 (m, 3H, 3'-H, 4'-H and 5'-H), 7.82 (d, 1H, 5-H, J = 8.5 Hz), 8.01-8.05 (m, 2H, 2'-H and 6'-H), 8.32 ppm (d, 1H, 4-H, J = 8.5 Hz); ms: m/z 236/234 (M^+).

Anal. Calcd. for $C_{11}H_7ClN_2O_2$: C, 56.31; H, 3.01; N, 11.94. Found: C, 56.79; H, 3.02; N, 12.01.

Methyl 4-[2-(2-Chloro-3-nitro-6-pyridyl)ethyl]benzoate (**7d**).

A solution of **5d** (603 mg, 2.00 mmoles) in hydrochloric acid (40 ml) was treated with sodium nitrite (5.52 g, 0.08 mole) and stirred overnight at room temperature. The solid was filtered, washed with water and separated by column chromatography on silica gel (cyclohexane:ethyl acetate 8:2, v/v), yield 391 mg (61%), mp 107-109°; ir (potassium bromide): 3080 and 3007 (CH), 1713 (CO), 1525 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): δ 3.13-3.23 (m, 4H, CH_2CH_2), 3.90 (s, 3H, OMe), 7.12 (d, 1H, 5-H, pyridine, J = 8 Hz), 7.22-7.27 (m, 2H, 3-H and 5-H), 7.94-7.98 (m, 2H, 2-H and 6-H), 8.11 (d, 1H, 4-H, pyridine, J = 8 Hz); ms: m/z 320 (M^+).

Anal. Calcd. for $C_{15}H_{13}ClN_2O_4$: C, 56.17; H, 4.09; N, 8.73. Found: C, 56.70; H, 4.13; N, 8.72.

6-Methyl-3-nitropyridine-2-carbonitrile (**8a**).

A suspension of **7a** (535 mg, 3.10 mmoles) and cuprous cyanide (555 mg, 6.20 mmoles) in *N,N*-dimethylformamide (25 ml) was heated under reflux for 6 hours. After being cooled to room temperature the mixture was treated with water (25 ml) and a brown precipitate was filtered and extracted with methylene chloride. The filtrate also was extracted with methylene chloride. The combined extracts were dried and evaporated *in vacuo*. The residual oil was separated by mplc on silica gel (cyclohexane:ethyl acetate 7:3, v/v) yielding 248 mg (49%), mp 47-48.5°; ir (potassium bromide): 2250 (CN), 1516 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): δ 2.76 (s, 3H, CH_3), 7.61 (d, 1H, 5-H, J = 8.8 Hz), 8.49 ppm (d, 1H, 4-H, J = 8.8 Hz); ^{13}C nmr (deuteriochloroform): δ 24.6 (Me), 114.0 (CN), 127.2 and 127.6 (C-2 and C-5), 133.1 (C-4), 144.7 (C-3), 165.9 ppm (C-6); ms: m/z 163 (M^+), 117 (M^+-NO_2).

Anal. Calcd. for $C_7H_5N_3O_2$ (163.14): C, 51.38; H, 3.09; N, 25.76. Found: C, 51.42; H, 3.58; N, 25.69.

3-Nitro-6-phenylpyridine-2-carbonitrile (**8b**).

A solution of **7b** (315 mg, 1.34 mmoles) and 240 mg (2.68 mmoles) of cuprous cyanide in *N,N*-dimethylformamide (10 ml) was heated at reflux. After 4 hours, the mixture was cooled to room temperature, diluted with water (30 ml) and a brown precipitate was filtered. The filtrate was treated with methylene chloride, the organic layer was separated, dried (sodium sulfate) and evaporated. The residual oil was purified by mplc on silica gel (cyclohexane:ethyl acetate 8:2, v/v), yield 37 mg (12%), mp 169-171°; ir (potassium bromide): 3098 (CH), 2240 (CN), 1525 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): δ 7.54-7.60 (m, 3H, 3'-H, 4'-H and 5'-H), 8.15 (d, 1H, 5-H, J = 9 Hz), 8.12-8.16 ppm (m, 2H, 2'-H and 6'-H), 8.64 (d, 1H, 4-H, J = 9 Hz); ms: m/z 225 (M^+), 179 (M^+-NO_2).

Anal. Calcd. for $C_{12}H_7N_3O_2$: C, 63.99; H, 3.13; N, 18.66. Found: C, 64.04; H, 3.15; N, 17.85.

Methyl 4-[2-(2-Cyano-3-nitro-6-pyridyl)ethyl]benzoate (**8d**).

A mixture of **7d** (160 mg, 0.50 mmole) and 90 mg (1.00 mmole) of cuprous cyanide in *N,N*-dimethylformamide (8 ml) was heated at reflux for 3 hours. After being cooled to room temperature, water (10 ml) was added and a brown precipitate was filtered. The filtrate was extracted with methylene chloride. The organic solvent was dried (sodium sulfate) and evaporated *in vacuo*. The residue was separated by mplc on silica gel (cycloxane:ethyl acetate 7:3, v/v), yield 81 mg (52%), mp 118-119°; ir (potassium bromide): 3081 and 3035 (CH), 1713 (CO), 1531 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 3.15-3.25 (m, 2H, 1-H, ethyl), 3.27-3.35 (m, 2H, 2-H, ethyl), 3.91 (s, 3H, OMe), 7.20-7.29 (m, 2H, 3-H and 5-H), 7.42 (d, 1H, 5-H, pyridine, J = 8.5 Hz), 7.93-7.99 (m, 2H, 2-H and 6-H), 8.43 (d, 1H, 4-H, pyridine, J = 8.5 Hz); ms: m/z 311 (M^+).

Anal. Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.92; H, 4.24; N, 13.03.

3-Amino-6-methylpyridine-2-carbonitrile (**9a**).

Method A.

To a solution of **8a** (41 mg, 0.25 mmole) in ethyl acetate (20 ml) was added 164 mg of palladium (10% on carbon) and the mixture was hydrogenated (3.6 bar) for 7.5 hours at room temperature. After filtration through Celite the solvent was removed under reduced pressure and the residue was purified by mplc on silica gel (cyclohexane:ethyl acetate 6:4, v/v) to yield 32 mg (96%), mp 138-140°; ir (potassium bromide): 3452 and 3404 (NH_2), 3008 (CH), 2223 cm^{-1} (CN); ^1H nmr (deuteriochloroform): δ 2.44 (s, 3H, Me), 4.27 (br s, 2H, NH_2, deuterium oxide-exchangeable), 7.03 and 7.13 (2d, each, 1H, 4-H and 5-H, J = 8 Hz); ms: m/z 133 (M^+).

Anal. Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.12; H, 5.33; N, 31.09.

Method B.

A solution of **16a** (176 mg, 1.08 mmoles), diphenylphosphoric azide (298 mg, 1.08 mmoles) and triethylamine (109 mg, 1.08 mmoles) in *tert*-butyl alcohol (50 ml) was heated at reflux for 3 hours. Water (10 ml) was added and the reaction mixture was refluxed for 1 hour. After being cooled to room temperature methylene chloride was added and the organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. The residue was purified by mplc on silica gel (chloroform:methanol 98:2, v/v) to give 53 mg (37%).

Methyl 4-[2-(3-Amino-2-cyano-6-pyridyl)ethyl]benzoate (**9d**).

To a solution of **8d** (59 mg, 0.19 mmole) in ethyl acetate (70 ml) was added 59 mg of Palladium (10% on carbon) and the mixture was hydrogenated at room temperature (3.6 bar) for 5 hours. The mixture was filtered through Celite and the solvent was evaporated *in vacuo* to give 34 mg (64%), mp 143-144°; ir (potassium bromide): 3435, 3358 and 3245 (NH_2), 2223 (CN), 1702 (CO), 1651, 1609, 1490 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.95-3.10 (m, 4H, CH_2CH_2), 3.90 (s, 3H, OMe), 4.30 (br s, 2H, NH_2, deuterium oxide-exchangeable), 6.97 (s, 2H, 4-H and 5-H, pyridine), 7.19-7.25 (m, 2H, 3-H and 5-H), 7.90-7.96 ppm (m, 2H, 2-H and 6-H); ms: m/z 281 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.60; H, 5.07; N, 14.97.

6-Methylpyrido[3,2-*d*]pyrimidine-2,4-diamine (**10a**).

To a stirred solution of guanidine hydrochloride (54 mg, 0.56 mmole) and sodium (13 mg, 0.56 mmole) in 1-butanol (10 ml) was added **9a** (37 mg, 0.28 mmole). The reaction mixture was heated under reflux for 7 hours. A white solid was filtered and the filtrate was evaporated *in vacuo*. The residue was separated by mplc on silica gel (chloroform:methanol 8:2, v/v) to yield 33 mg (67%), mp 239-240° (lit 241° [2]); ir (potassium bromide): 3410, 3312 and 3171 (NH_2), 1684, 1651, 1573, 1514, 1451 cm^{-1}; uv (methanol): λ max 341 nm (ε 1,734); ^1H nmr (deuteriochloroform): δ 2.59 (s, 3H, Me), 4.97 (br s, 2H, NH_2, deuterium oxide-exchangeable), 6.01 (br s, 2H, NH_2, deuterium oxide-exchangeable), 7.54 and 7.64 ppm (2d, each, 1H, 7-H and 8-H, J = 8.5 Hz); ms: m/z 175 (M^+).

Butyl 4-Amino-4-deoxy-8,10-dideazapteroate (**10d**).

To a solution of guanidine hydrochloride (96 mg, 1.00 mmole) and sodium (23 mg, 1.00 mmole) in 1-butanol (10 ml) was added **9d** (51 mg, 0.18 mmole). The reaction mixture was heated at reflux for 8 hours and the pale yellow solid was collected by filtration, yield 40 mg (61%), mp 218-220°; ir (potassium bromide): 3445, 3328 and 3117 (NH_2), 2960 and 2873 (CH), 1698 (CO), 1662, 1636, 1611, 1567 cm^{-1}; uv (methanol): λ max 342 nm (ε 4,315); ^1H nmr (DMSO-d_6): δ 0.93 (t, 3H, $OCH_2CH_2CH_2CH_3$, J = 7 Hz), 1.41 (sext, 2H, $OCH_2CH_2CH_2CH_3$, J = 7 Hz), 1.63-1.72 (m, 2H, $OCH_2CH_2CH_2CH_3$), 3.06-3.21 (m, 4H, 9-H and 10-H), 4.25 (t, 2H, $OCH_2CH_2CH_2CH_3$, J = 6.5 Hz), 6.07 (br s, 2H, NH_2, deuterium oxide-exchangeable), 7.24 (br s, 2H, NH_2, deuterium oxide-exchangeable), 7.39 (d, 1H, 7-H, J = 8.5 Hz), 7.46 (d, 1H, 8-H, J = 8.5 Hz), 7.39-7.43 ppm (m, 2H, aromatic protons), 7.84-7.88 (m, 2H, aromatic protons); ms: m/z 365 (M^+), 174 (M^+-$CH_2C_6H_4COOC_4H_9$).

Anal. Calcd. for $C_{20}H_{23}N_5O_2$: C, 65.85; H, 6.34; N, 19.28. Found: C, 65.97; H, 6.29; N, 19.51.

4-Amino-4-deoxy-8,10-dideazapteroic Acid (**11d**).

Butyl 4-amino-4-deoxy-8,10-dideazapteroate (**10d**) (30 mg, 0.08 mmole) was dissolved in 5 ml of a mixture of an aqueous solution of sodium hydroxide (35% w/w) and methanol (70 ml) and the mixture was stirred at room temperature. After 3 days the solution was neutralized with 2*N* hydrochloric acid and the solid was collected to give 23 mg (93%), mp 347-350°; ir (potassium bromide): 3344 (NH_2), 3117 (OH), 1667 (CO), 1608, 1584, 1536 cm^{-1}; uv (methanol): λ max 335 nm (ε 526); (*p*H 11): λ max 344 (ε 711); ^1H nmr (DMSO-d_6): δ 3.08-3.20 (m, 4H, 9-H and 10-H), 6.20 (br s, 2H, NH_2, deuteriomethanol-exchangeable), 7.33 (br s, 2H, NH_2, deuteriomethanol-exchangeable), 7.35-7.40 (m, 2H, 3-H and 5-H), 7.41 (d, 1H, 7-H, J = 8 Hz), 7.48 (d, 1H, 8-H, J = 8 Hz), 7.82-7.87 ppm (m, 2H, 2-H and 6-H); ms: m/z 309 (M^+), 174 (M^+-$CH_2C_6H_4COOH$).

Anal. Calcd. for $C_{16}H_{15}N_5O_2 \cdot 1.75H_2O$ (340.86): C, 56.38; H, 4.43; N, 20.55. Found: C, 56.30; H, 4.40; N, 19.98.

Ethyl 2-Chloro-6-methylnicotinate (**14a**).

Ethyl 2-amino-6-methylnicotinate (**13a**) (901 mg, 5.00 mmoles) was dissolved in hydrochloric acid (20 ml) and cooled to -15°. The solution was treated slowly with sodium nitrite (6.90 g, 0.02 mole) and stirred at room temperature for 3 hours. After diluting with water (30 ml), the mixture was extracted with ether. The ether extract was washed with water, dried (sodium sulfate) and the solvent was removed *in vacuo*. The residual oil crystallized at 2-8° to yield 309 mg (31%), mp 33-34° (lit 34° [18]); ir (potassium bromide): 3030 and 3015 (CH), 1733 (CO), 1062 cm^{-1} (Aryl-Cl); ^1H nmr (DMSO-d_6): 1.32 (t, 3H, OCH_2CH_3, J = 7 Hz), 2.52 (s, 3H, Me), 4.33 (q, 2H, OCH_2CH_3, J = 7 Hz), 7.42 (d, 1H, 5-H, J = 7.5 Hz), 8.14 ppm (d, 1H, 4-H, J = 7.5 Hz); ms: m/z 201/199 (M^+).

Ethyl 2-Cyano-6-methylnicotinate (**15a**).

Ethyl 2-chloro-6-methylnicotinate (**14a**) (399 mg, 2.00 mmoles) and 358 mg (4.00 mmoles) of cuprous cyanide were heated at reflux in *N,N*-dimethylformamide (15 ml) for 8 hours. The mixture was treated with water, a brown precipitate was filtered and extracted with boiling toluene. The filtrate was extracted with methylene chloride. The extracts were combined, dried (sodium sulfate) and evaporated *in vacuo*. The residual oil was separated by mplc on silica gel (cyclohexane:ethyl acetate 8:2, v/v) to give 198 mg (52%), mp 79-81°; ir (potassium bromide): 3029, 2991 and 2941 (CH), 2242 (CN), 1729 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 1.46 (t, 3H, OCH_2CH_3, J = 7 Hz), 2.68 (d, 3H, Me, J = 0.5 Hz), 4.49 (q, 2H, OCH_2CH_3, J = 7 Hz), 7.46 (dd, 1H, 5-H, J_1 = 8.5 Hz, J_2 = 0.5 Hz), 8.30 ppm (d, 1H, 4-H, J = 8.5 Hz); ^{13}C nmr DMSO-d_6): δ 13.8 (OCH_2CH_3), 23.8 (Me), 62.0 (OCH_2CH_3), 116.2 (CN), 126.9, 127.1 (C-3 and C-5), 131.7 (C-2), 139.8 (C-4), 162.6 (C-6), 163.7 ppm (CO); ms: m/z 190 (M^+), 145 (M^+-C_2H_5O).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.05; H, 5.10; N, 14.72.

2-Cyano-6-methylnicotinic Acid (**16a**).

To a mixture of an aqueous solution of sodium hydroxide and 70 ml methanol was added 190 mg (1.00 mmole) of **15a**. The mixture was stirred for 1 hour at room temperature. Ether (25 ml) was added and the colorless solid was collected by filtration, washed with ether and dissolved in 2*N* hydrochloric acid. The solution was extracted with ethyl acetate, dried (sodium sulfate) and the organic solvent was evaporated *in vacuo* to yield 110 mg (68%), mp 165°; ir (potassium bromide): 2916 (OH), 2243

(CN), 1724 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ 2.60 (s, 3H, Me), 7.71 (d, 1H, 5-H, J = 8 Hz), 8.33 (d, 1H, 4-H, J = 8 Hz), 8.35 ppm (br s, 1H, COOH, deuterium oxide-exchangeable); ms: m/z 162 (M^+).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.30; H, 4.33; N, 17.31.

1,4,5,6,7,8-Hexahydro-3-nitroquinolin-2-amine (**18**).

A solution of **1** (258 mg, 2.50 mmoles) and **17** (479 mg, 2.50 mmoles) in ethanol (35 ml) was heated at reflux for 13 hours. The yellow solid was filtered and crystallized from ethanol, yield 298 mg (61%), mp 175-178°; ir (potassium bromide): 3474, 3449, 3273, 3142 and 3083 (NH and NH_2), 2938 and 2860 (CH), 1641, 1570, 1503 cm^{-1}; uv (methanol): λ max 340 nm (ε 6,166); ^1H nmr (DMSO-d_6): δ 1.51-1.68 (m, 4H, 6-H and 7-H), 1.64-1.93 and 1.93-2.02 (2m, each, 2H, 5-H and 8-H), 3.07 (s, 2H, 4-H), 8.49 (br s, 1H, NH, deuterium oxide-exchangeable); ms: m/z 195 (M^+), 100.

Anal. Calcd. for $C_9H_{12}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.42; H, 6.57; N, 21.59.

5,6,7,8-Tetrahydro-3-nitroquinolin-2-amine (**19**).

A solution of **17** (1.34 g, 7.00 mmoles) and **1** (722 mg, 7.00 mmoles) in *N,N*-dimethylformamide (15 ml) was heated for 5 hours at reflux. After being cooled to room temperature the mixture was diluted with water (30 ml) and a brown precipitate was collected. The solid was added to ether (50 ml) and the mixture was heated at reflux and filtered. The filtrate was dried (sodium sulfate) and evaporated to dryness *in vacuo*. The residue was crystallized from ethanol to yield 649 mg (48%), mp 160-161°; ir (potassium bromide): 3474, 3449, 3277 and 3142 (NH_2), 2943, 2924 and 2851 (CH), 1645, 1625, 1570, 1501 cm^{-1} (NO_2); uv (methanol): λ max 397 nm (ε 5,140); ^1H nmr (DMSO-d_6): δ 1.67-1.86 (m, 4H, 6-H and 7-H), 2.60-2.75 (m, 4H, 5-H and 8-H), 7.63 (br s, 2H, NH_2, deuterium oxide-exchangeable), 8.07 ppm (s, 1H, 4-H); 193 (M^+).

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.82; H, 5.77; N, 21.75.

2-Chloro-5,6,7,8-tetrahydro-3-nitroquinolin-2-amine (**20**).

A solution of **19** (696 mg, 3.60 mmoles) or **18** (703 mg, 3.60 mmoles) in hydrochloric acid (10 ml) was cooled to -15°. Sodium nitrite (5.17 g, 0.075 mole) was added slowly in 1 hour to the reaction mixture. After diluting with water (20 ml) the mixture was stirred at room temperature for 1 hour. The solid was collected, washed with water and crystallized from methanol to yield 436 mg (57%), mp 61-62°; ir (potassium bromide): 3074, 2943 and 2860 (CH), 1586, 1565, 1525 (NO_2), 1022 cm^{-1} (Aryl-Cl); ^1H nmr (deuteriochloroform): δ 1.77-2.01 (m, 4H, 6-H and 7-H), 2.82 (t, 2H, 5-H, J = 6.5 Hz), 2.96 (t, 2H, 8-H, J = 6.5 Hz), 7.97 ppm (s, 1H, 4-H); ms: m/z 214/212 (M^+), 168/166 (M^+-NO_2).

Anal. Calcd. for $C_9H_9ClN_2O_2$: C, 50.79; H, 4.27; N, 13.28. Found: C, 50.76; H, 4.30; N, 12.61.

5,6,7,8-Tetrahydro-3-nitroquinoline-2-carbonitrile (**21**).

Method A.

A mixture of **20** (255 mg, 1.20 mmoles) and 161 mg (1.80 mmoles) of cuprous cyanide in *N,N*-dimethylformamide (8 ml) was heated for 10 hours at reflux. The mixture was diluted with water (15 ml) and filtered. Methylene chloride was added to the filtrate and the organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. The residue was purified by mplc on silica gel (cyclohexane: ethyl acetate 7:3, v/v) to yield 63 mg (26%), mp 112-113°; ir (potassium bromide): 3074 (CH), 2239 (CN), 1591, 1568, 1521 cm^{-1} (NO_2); ^1H nmr (DMSO-d_6): δ 1.74-1.83 (m, 2H, 6-H), 1.84-1.93 (m, 2H, 7-H), 2.98 (t, 2H, 5-H, J = 6.5 Hz), 3.06 (t, 2H, 8-H, J = 6.5 Hz), 8.25 ppm (s, 1H, 4-H); ms: m/z 203 (M^+), 157 (M^+-NO_2).

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.50; H, 4.50; N, 20.88.

Method B.

To a solution of **23** (485 mg, 2.50 mmoles) and 2.98 g (0.03 mole) of trimethylsilyl cyanide in methylene chloride (20 ml) was added drop by drop 1.07 g (0.01 mole) of *N,N*-dimethylcarbamoyl chloride and the mixture was stirred at room temperature for 14 days. The mixture was treated with a saturated solution of sodium carbonate and the organic layer was separated, dried (calcium chloride) and evaporated *in vacuo*. The residue was purified by mplc on silica gel (cyclohexane:ethyl acetate 7:3, v/v) to give 249 mg (49%).

5,6,7,8-Tetrahydro-3-nitroquinoline *N*-Oxide (**23**).

To a solution of **22** (286 mg, 1.60 mmoles) in methylene chloride (5 ml) was added 522 mg (3.20 mmoles) of *m*-chloroperoxybenzoic acid. The mixture was stirred at room temperature for 24 hours. A solution of saturated sodium carbonate was added and the organic layer was separated, dried (sodium sulfate) and the solvent was evaporated *in vacuo*. The residue was crystallized from ethanol to yield 289 mg (93%), mp 159-160°; ir (potassium bromide): 3096, 3056 and 3038 (CH), 1571, 1526, 1483, 1361 (NO_2), 1286 cm^{-1} (*N*-oxide); ^1H nmr (DMSO-d_6): δ 1.65-1.78 (m, 2H, 6-H), 1.79-1.88 (m, 2H, 7-H), 2.77 (t, 2H, 5-H, J = 6.5 Hz), 2.86 (t, 2H, 8-H, J = 6.5 Hz), 7.96 (d, 1H, 4-H, J = 2.5 Hz), 8.89 ppm (d, 1H, 2-H, J = 2.5 Hz); ms: m/z 194 (M^+).

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.42. Found: C, 55.61; H, 5.22; N, 14.48.

3-Amino-5,6,7,8-tetrahydroquinoline-2-carbonitrile (**24**).

To a solution of **21** (200 mg, 0.94 mmole) in ethyl acetate (50 ml) was added 800 mg of Palladium (10% on carbon). The mixture was hydrogenated at room temperature (3.6 bar). After filtration through Celite the solvent was evaporated *in vacuo* to give 150 mg (92%), mp 159-160°; ir (potassium bromide): 3423, 3401 and 3216 (NH_2), 2215 (CN), 1655, 1607 cm^{-1}; ^1H nmr (deuteriochloroform): 1.74-1.81 (m, 2H, 6-H), 1.82-1.90 (m, 2H, 7-H), 2.74 (t, 2H, 5-H, J = 6 Hz), 2.80 (t, 2H, 8-H, J = 6 Hz), 4.21 (br s, 2H, NH_2, deuterium oxide-exchangeable), 6.80 (s, 1H, 4-H); ms: m/z 173 (M^+).

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.37; H, 6.44; N, 23.45.

6,7,8,9-Tetrahydropyrimido[4,5-*b*]quinoline-2,4-diamine (**25**).

Compound **24** (87 mg, 0.50 mmole) was added to a solution of guanidine hydrochloride 478 mg (5.00 mmoles) and sodium (230 mg, 5.00 mmoles) in 1-butanol (20 ml). The mixture was heated at reflux for 12 hours. The solvent was evaporated under reduced pressure and the residue was separated by mplc on silica gel (chloroform:methanol 9:1, v/v) to give 61 mg (57%), mp 305-307°; ir (potassium bromide): 3381, 3321 and 3191 (NH_2), 2942 (CH), 1680, 1658, 1581, 1518 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.70-1.91 (m, 4H, 7-H and 8-H), 2.80-2.90 (m, 4H, 6-H and

5-H), 6.09 (br s, 2H, NH_2, deuterium oxide-exchangeable), 7.15 (br s, 2H, NH_2, deuterium oxide-exchangeable), 7.24 ppm (s, 1H, 10-H); ms: m/z 215 (M^+).

Anal. Calcd. for $C_{11}H_{13}N_5 \cdot 0.75H_2O$: C, 57.75; H, 5.73; N, 30.60. Found: C, 57.67; H, 6.08; N, 30.56.

REFERENCES AND NOTES

[1a] R. Troschütz, *Arch Pharm. (Weinheim),* **322**, 285 (1989); [b] R. Troschütz, M. Zink and T. Dennstedt, *Arch. Pharm. (Weinheim),* **328**, 535 (1995).

[2a] V. Oakes and H. N. Rydon, *J. Chem. Soc.*, 4433 (1956); [b] W. I. Irwin and D. G. Wibberly, *J. Chem. Soc. (C),* 1745 (1967).

[3a] J. I. DeGraw, L. F. Kelly, R. L. Kisliuk, Y. Gaumont and F. M. Sirotnak, *J. Heterocyclic Chem.*, **19**, 1587 (1982); [b] J. I. DeGraw, L. F. Kelly and F. M. Sirotnak, US Patent 4,460,591 (1984); *Chem. Abstr.*, **101**, 211170x (1984).

[4] R. Troschütz and A. Lückel, *Arch. Pharm. (Weinheim),* **324**, 73 (1991).

[5] H. Mertens, R. Troschütz and H. J. Roth, *Liebigs Ann. Chem.*, 380 (1986).

[6] E. D. Parker and W. Shive, *J. Am. Chem. Soc.*, **69**, 63 (1947).

[7] L. Friedmann and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).

[8a] N. L. Colbry, E. F. Elslager and L. M. Werbel, *J. Heterocyclic Chem.*, **21**, 1521 (1984); [b] N. L. Colbry, E. F. Elslager and L. M. Werbel, *J. Med. Chem.*, **28**, 248 (1985).

[9] A. Srinivasan and A. D. Broom, *J. Org. Chem.*, **46**, 1777 (1981).

[10] Y. Masuyama, T. Sakai and Y. Kurusu, *Tetrahedron Letters,* **34**, 653 (1993).

[11] J. I. DeGraw, W. T. Colwell, R. L. Kisliuk, Y. Gaumont and F. M. Sirotnak, *Heterocycles,* **35**, 755 (1993).

[12] H. Meyer, F. Bossert and H. Horstmann, *Liebigs Ann. Chem.*, 1895 (1977).

[13] A. Dornow and P. Karlson, *Ber.*, **73**, 542 (1940).

[14] T. Shiovi, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972).

[15] Y. Tohda, M. Eiraku, T. Nakagawa, Y. Usami, M. Ariga, T. Kawashima, K. Tani, H. Watanabe and Y. Mori, *Bull. Chem. Soc. Japan,* **63**, 2820 (1990).

[16] W. K. Fife, *J. Org. Chem.*, **48**, 1375 (1983).

[17] H. Bredereck, F. Effenberger and H. Botsch, *Chem. Ber.*, **97**, 3397 (1964).

[18] I. G. Morris and A. R. Pinder, *J. Chem. Soc.*, 1841 (1963).