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Original Scientific Paper

Transformations of 4-Amino-5-cyanopyrimidines. The Synthesis and Transformations of Pyrimido-/4,5-d/Pyrimidines

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Several new approaches to the synthesis of pyrimido/4,5--d/pyrimidines are described. 5-Cyano-4-(*N*,*N*-dimethylaminomethyleneamino)-2-methylthiopyrimidine (*2*) and 5-cyano-4-ethoxyethyleneamino-2-methylthiopyirimidine (*12*) cyclize with hydrazine into 3-amino-4-imino-2-methylthio-3,4-dihydropyrimido/4,5-d/pyrimidine (*3*) which can be deaminated into 4-amino-2-methylthiopyrimido/4,5-d/pyrimidine (*4*). On the other hand, 5-cyano-4-hydroxyiminomethyleneamino-2-methylthio- (*14*) and -2-methoxopyrimidine (*15*) cyclize thermally into 4-amino-7-methylthio- (*16*) and 4-amino-7-methoxypyrimido/4,5-d/pyrimidine 3-oxide (*17*), respectively.

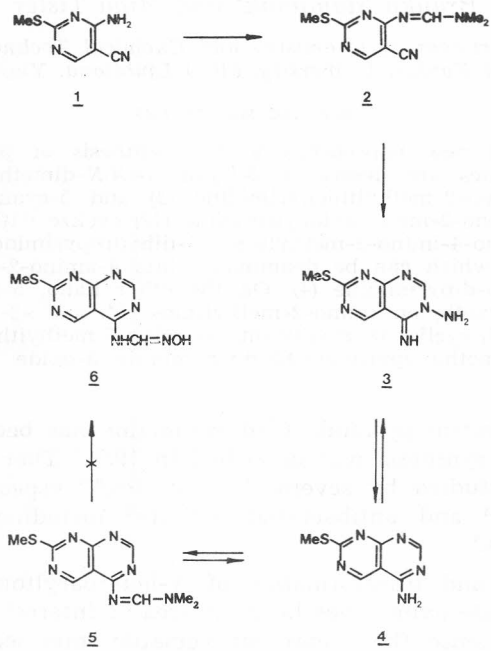
The bicyclic system pyrimido/4,5-d/pyrimidine has been very little investigated. The first synthesis was described in 1958.[1] Thereafter, this bicyclic system has been studied by several laboratories,[2–8] especially in connection with its diuretic[2,3] and antibacterial activity[6] including structure-activity relationship studies.[9]

The synthesis and transformation of *N*-heteroarylformamidines and *N*--heteroarylformamide oximes has been an area of interest in our laboratories for several years, since they represent versatile intermediates for the preparation of many bicyclic and polycyclic systems. Recently, we have described some new simple methods for the preparation of oxazolo/4,5-c/quinoline,[10] oxazolo/4,5-d/pyridine,[11] oxazolo/5,4-d/pyrimidine,[12] oxazolo/4,5-d/pyridazine,[13] and oxazolo/5,4-c/pyridazine[14] derivatives, isothiazolo/4,5-b/pyrazines[15] and isoxazolo/5,4-b/pyridines,[15] imidazo/1,2-x/azines,[16] furo/2,3-c/pyridazines,[17] and several other systems,[18,19] including fused pyrimidines, such as pyridopyrimidines[20] and their 3-oxides[21–23] and pteridines and their 3-oxides.[24–28]

As an extension of this latter type of reactions we report in this communication several new methods for the preparation of pyrimido/4,5-d/pyrimidine derivatives.

According to the first method, 5-cyano-4-(*N*,*N*-dimethylaminomethyleneamino)-2-methylthiopyrimidine (*2*), prepared from 4-amino-5-cyano-2-methylthiopyrimidine (*1*)[2] and N,N-dimethylformamide dimethyl acetal (DMFDMA), was converted with hydrazine hydrate into 3-amino-4-imino-7-methylthio--3,4-dihydropyrimido/4,5-d/pyrimidine (*3*) in 21% yield. The structure of this compound was established by deamination of the amino group at position 3 to afford 4-amino-7-methylthiopyrimido/4,5-d/pyrimidine (*4*) in 27% yield, identical with the compound prepared from 4-amino-5-cyano-2-methylthiopyrimidine (*1*) with formamide[2] or (trisformamino)methane in 90% yield.

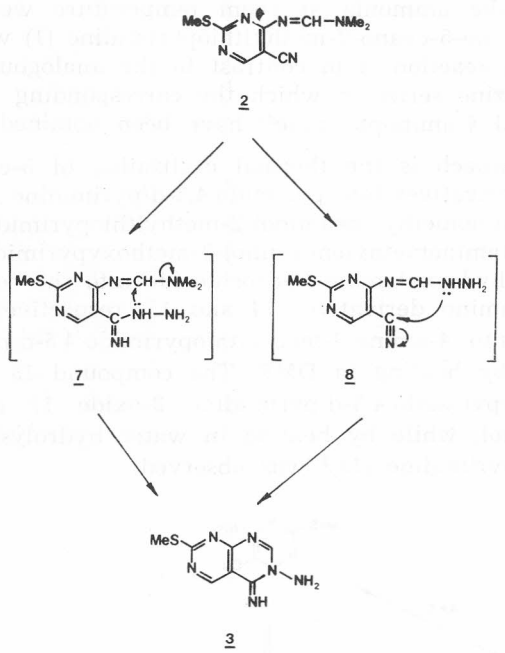
The compound *4* gave with DMFDMA the corresponding 4-(*N*,*N*-dimethylaminomethyleneamino)-7-methylthiopyrimido/4,5-d/pyrimidine (*5*) in 32% yield. The attempted conversion of this compound with hydroxylamine into the corresponding 4-hydroxyiminomethylamino-7-methylthiopyrimido/4,5-d/pyrimidine (*6*), as an intermediate in the synthesis of tricyclic systems, failed. The starting amino compound *4* was isolated instead.



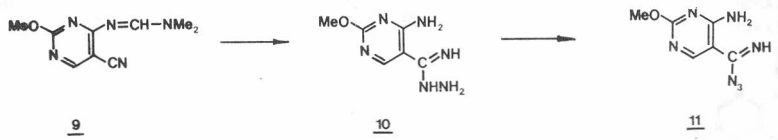
1 2 6 3 5 4

The formation of pyrimido/4,5-d/pyrimidine derivative *3* can be explained by the formation of two different intermediates. 4-(*N*,*N*-Dimethylaminomethyleneamino)-2-methylthiopyrimidine-5-carboxamidrazone (*7*) could be formed in the reaction of the cyano group of the compound *2* with hydrazine, while 5-cyano-4-(*N*,*N*-dimethylaminomethylenehydrazino)-2-methylthiopyrimidine (*8*) in the reaction of the amidine group with hydrazine. Both intermediates could cyclize into the bicyclic compound *3*. However, since they

cyclize very easily, we have not been able to isolate any of these intermediates.



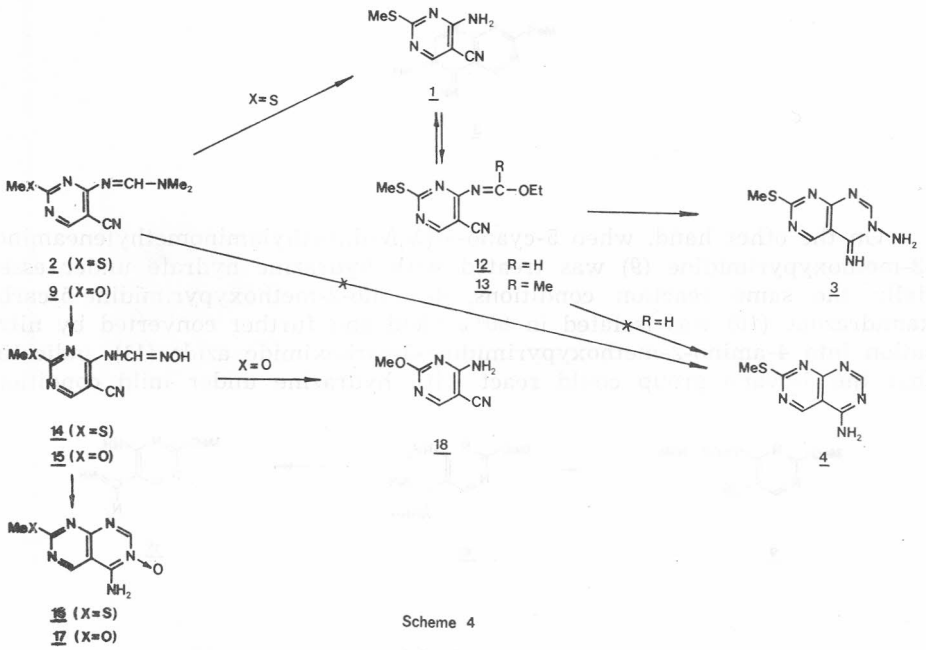
On the other hand, when 5-cyano-4-(*N*,*N*-dimethylaminomethyleneamino)-2-methoxypyrimidine (*9*) was treated with hydrazine hydrate under essentially the same reaction conditions, 4-amino-2-methoxypyrimidine-5-carboxamidrazone (*10*) was isolated in 80% yield and further converted by nitrosation into 4-amino-2-methoxypyrimidine-5-carboxamide azide (*11*), indicating that the 5-cyano group could react with hydrazine under mild conditions.



Similarly, 4-amino-5-cyano-2-methylthiopyrimidine (*1*) was converted with triethyl orthoformate or triethyl orthoacetate into the corresponding 5-cyano-4-ethoxymethyleneamino-2-methylthiopyrimidine (*12*) and 5-cyano-4-ethoxyethylideneamino-2-methylthiopyrimidine (*13*), respectively. When the compound *12* was treated with hydrazine hydrate, 3-amino-4-imino-3,4-dihydropyrimido/4,5-d/pyrimidine (*3*) was formed in 16% yield. On the other hand, attempts to prepare 4-amino-7-methylthiopyrimido/4,5-d/pyrimidine (*4*) by

treatment of either 5-cyano-4-(*N*,*N*-dimethylaminomethyleneamino)-2-methylthiopyrimidine (*2*) or 5-cyano-4-ethoxymethyleneamino-2-methylthiopyrimidine (*12*) with methanolic ammonia at room temperature were not successful. In both cases 4-amino-5-cyano-2-methylthiopyrimidine (*1*) was isolated as the only product. This reaction is in contrast to the analogous reactions in the pyridine and pyrazine series in which the corresponding 4-aminopyrido/2,3-d/pyrimidine[22] and 4-aminopteridine[24] have been obtained, respectively.

The third approach is the thermal cyclization of 5-cyano-4-hydroximimethyleneamino derivatives into pyrimido/4,5-d/pyrimidine 3-oxides. 5-Cyano-4-(*N*,*N*-dimethylaminomethyleneamino)-2-methylthiopyrimidine (*2*) and 5-cyano-4-(*N*,*N*-dimethylaminomethyleneamino)-2-methoxypyrimidine (*9*) were transformed with hydroxylamine hydrochloride into the corresponding 4-hydroxyiminomethylamino derivatives *14* and *15*, respectively. The compound *14* was cyclized into 4-amino-7-methylthiopyrimido/4,5-d/pyrimidine 3-oxide *16* in 51% yield by heating in DMF. The compound *15* was cyclized into 4-amino-7-methoxypyrimido/4,5-d/pyrimidine 3-oxide *17* in 31% yield by heating in methanol, while by heating in water hydrolysis into 4-amino-5-cyano-2-methoxypyrimidine (*18*)[2] was observed.



Scheme 4

EXPERIMENTAL

Melting points were taken on a Kofler hot stage. ^{1}H NMR spectra were obtained on a JEOL JNM C60-HL spectrometer with TMS as internal standard, mass spectra on a Hitachi-Perkin Elmer mass spectrometer RMU-6L, IR spectra on Perkin-Elmer 727B spectrometer, and elemental analyses for C, H, and N on a Perkin-Elmer CHN Analyser 240 C.

5-Cyano-4-(N,N-dimethylaminomethyleneamino)-2-methylthiopyrimidine (2)

A mixture of 4-amino-5-cyano-2-methylthiopyrimidine (*1*) and DMFDMA (80 mg) in toluene (2 ml) was heated under reflux for 3 hours. The volatile components were evaporated in vacuo and the dry residue recrystallized from a mixture of chloroform and petroleum ether to give 5-cyano-4-(*N,N*-dimethylaminomethyleneamino)-2-methylthiopyrimidine (*2*). Yield 85 mg (77%), m. p. 104—105 °C.

Anal. $C_9H_{11}N_5S$ (221.28) calc'd: C 48.85; H 5.01; N 31.65%
found: C 48.79; H 5.37; N 31.45%

^{1}H NMR spectrum ($CDCl_3$/TMS) δ: 2.50 (s, SMe), 3.20 (s, NMe_2), 8.37 (s, H_6), 8.75 (s, N=CH).

3-Amino-4-imino-7-methylthio-3,4-dihydropyrimido/4,5-d/pyrimidine (3)

a) A mixture of 5-cyano-4-(*N,N*-dimethylaminomethyleneamino)pyrimidine (*2*) (200 mg) and hydrazine hydrate (99%, 3 ml) was stirred for 15 minutes at room temperature. The precipitate was collected by suction and washed with methanol to give 3-amino-4-imino-7-methylthio-3,4-dihydropyrimido/4,5-d/pyrimidine (*3*). Yield 40 mg (21%), m. p. >300 °C. Mass spectrum: $m/e = 208$ (M^+). ^{1}H NMR spectrum (DMSO-d_6/TMS) δ: 2.44 (s, SMe), 4.57 (br. s, $NHNH_2$), 8.46 (s, H_2 and H_5).

b) A mixture of 5-cyano-4-ethoxymethyleneamino-2-methylthiopyrimidine (*12*) (100 mg) and hydrazine hydrate (99%, 25 mg) in anhydrous ethanol (3 ml) was stirred for 15 minutes at room temperature. The precipitate was collected by suction and washed with hot ethanol to give the comopund *3*. Yield 15 mg (16%). The IR spectrum of this compound was identical with that of the compound described under a).

The compound *3* was used without further purification for the preparation of

4-Amino-7-methylthiopyrimido/4,5-d/pyrimidine (4)

a) A mixutre of 4-amino-5-cyano-2-methylthiopyrimidine (*1*) (92 mg) and (trisformamino)methane (150 mg) was heated for 45 minutes at 185 °C. After cooling, methanol (1 ml) was added and the precipitate collected by suction. Sublimation (250 °C, 5 torr) gave 4-amino-7-methylthiopyrimido/4,5-d/pyrimidine (*4*). Yield 97 mg (91%), m. p. >300 °C, lit.[2] m. p. >300 °C.

Anal. $C_7H_7N_5S$ (193.23) calc'd: C 43.51; H 3.65; N 36.24%
found: C 43.84; H 3.60 N 35.89%

^{1}H NMR spectrum (DMSO-d_6/TMS, 120 °C) δ: 2.55 (s, SMe), 8.00 (br. s, NH_2), 8.45 (s, H_5), 9.4 (s, H_2).

b) To a mixture of 3-amino-4-imino-7-methylthio-3,4-dihydropyrimido/4,5-d/pyrimidine (*3*) (150 mg) in hydrochloric acid (conc., 4 ml) a solution of sodium nitrite (140 mg) in water (3 ml) was added dropwise at 0 °C. The mixture was neutralized with solid sodium hydrogen carbonate and the precipitate was collected by suction to give the compound *4*. Yield 38 mg (27%), m. p. >300 °C, lit.[2] m. p. >300 °C. The IR spectrum of this compound was identical with that of the compound described under a) and with the compound prepared according to lit.[2]

c) To a solution of 4-(*N,N*-dimethylaminomethyleneamino)-7-methylthiopyrimido/4,5-d/pyrimidine (*5*) (100 mg) in methanol (2 ml), hydroxylamine hydrochloride (80 mg) was added and the mixture was stirred for 2 days at room temperature. The precipitate was collected by suction and washed with methanol to give the compound *4*. Yield 13 mg (17%). The IR spectrum of this compound was identical with that of the compound described under a).

4-(N,N-Dimethylaminomethyleneamino)-7-methylthiopyrimido /4,5-d/pyrimidine (5)

To a suspension of 4-amino-7-methylthiopyrimido/4,5-d/pyrimidine (*4*) (85 mg) in toluene (2 ml), DMFDMA (80 mg) was added and the mixture was heated under

reflux for 3 hours. The precipitate was, after cooling, collected by suction and recrystallized from methanol to give 4-(*N*,*N*-dimethylaminomethyleneamino)--7-methylthiopyrimido/4,5-d/pyrimidine (*5*). Yield 35 mg (32%), m. p. 180—181 °.

Anal. $C_{10}H_{12}N_6S$ (248.31) calc'd: C 48.37 H 4.87 N 33.84%
found: C 48.37; H 4.82; N 33.57%

^{1}H NMR spectrum (DMSO-d_6/TMS) δ: 2.57 (s, SMe), 3.20 (s) and 3.25 (s) (NMe_2), 8.75 (s, H_5), 9.0 (s, N=C*H*), 9.4 (s, H_2).

5-Cyano-4-(N,N-dimethylaminomethyleneamino)-2-methoxypyrimidine (9)

A mixture of 4-amino-5-cyano-2-methoxypyrimidine (*18*)[2] (100 mg) and DMFDMA (80 mg) in toluene (2 ml) was heated under reflux for 3 hours. The volatile components were evaporated in vacuo and the dry residue washed with methanol to give 5-cyano-4-(*N*,*N*-dimethylaminomethyleneamino)-2-methoxypyrimidine (*9*). Yield 109 mg (80%), m. p. 135—137 °C.

Anal. $C_9H_{11}N_5O$ (205.22) calc'd: C 52.68; H 5.40; N 34.13%
found: C 52.51; H 5.46; N 34.41%

^{1}H NMR spectrum (DMSO-d_6/TMS) δ: 3.09 (s) and 5.19 (s) (NMe_2), 3.95 (s, OMe), 8.55 (s, H_6), 8.75 (s, N=CH).

4-Amino-2-methoxypyrimidine-5-carboxamidrazone (10)

A mixture of 5-cyano-4-(*N*,*N*-dimethylaminomethyleneamino)-2-methoxypyrimidine (*9*) (200 mg) and hydrazine hydrate (99%, 2 ml) was stirred for 18 hours at room temperature. The precipitate was collected by suction and recrystallized from a mixture of chloroform and methanol to give 4-amino-2-methoxypyrimidine-5--carboxamidrazone (*10*). Yield 70 mg (40%), m. p. 192—195 °C.

Anal. $C_6H_{10}N_6O$ (182.19) calc'd: C 39.56; H 5.53; N 46.13%
found: C 39.45; H 5.67; N 46.32%

^{1}H NMR spectrum (DMSO-d_6/TMS) δ: 3.77 (s, OMe), 5.0 (br. s, NH_2), 5.67 (br. s, NH_2) 8.35 (s, H_6).

4-Amino-2-methoxypyrimidine-5-carboxamide azide (11)

To a solution of 4-amino-2-methoxypyrimidine-5-carboxamidrazone (*9*) (65 mg) in hydrochloric acid (conc., 4 ml) a solution of sodium nitrite (50 mg) in water (3 ml) was added dropwise at 0°C. The resulting solution was neutralized with solid hydrogen carbonate and the mixture was left for 3 hours at 0 °C. The precipitate was collected by suction and washed with methanol to give 4-amino-2-methoxypyrimidine-5-carboxamide azide (*11*). Yield 15 mg (22%), m. p. 140 °C (decomp.).

Anal. $C_6H_7N_7O$ (193.17) calc'd: C 3731; H 3.65; N 50.76%
found: C 37.15; H 3.75; N 50.48%

IR spectrum (KBr) $\nu_{N_3} = 2140$ cm^{-1}.

5-Cyano-4-ethoxymethyleneamino-2-methylthiopyrimidine (12)

A suspension of 4-amino-5-cyano-2-methylthiopyrimidine (*1*) (100 mg) in triethyl orthoformate (4 ml) was heated under reflux for 7 hours. Chloroform (2 ml) was added to the oily residue obtained after evaporation of volatile components in vacuo. The dry residue, obtained after evaporation of chloroform in vacuo, was washed with methanol to give 5-cyano-4-ethoxymethyleneamino-2--methylthiopyrimidine (*12*). Yield 46 mg (35%), m. p. 93—95 °C.

Anal. $C_9H_{10}N_4OS$ (222.27) calc'd: C 48.63; H 4.54; N 25.21%
found: C 48.26; H 4.48; N 25.24%

^{1}H NMR spectrum ($CDCl_3$/TMS) δ: 1.25 (t, CH_2Me), 2.55 (s, SMe), 4.5 (q, CH_2Me), 8.55 (s, H_6). $J_{CH_2Me} = 6.2$ Hz.

Transformation of 5-Cyano-4-ethoxymethyleneamino-2-methylthiopyrimidine (12) and 5-Cyano-4-(N,N-dimethylaminomethyleneamino)-2-methylthiopyrimidine (2) with Methanolic Ammonia into 2-Amino-5-cyano-2-methylthiopyrimidine (1)

A solution of 5-cyano-4-ethoxymethylenamino-2-methylthiopyrimidine (*12*) (150 mg) in methanol saturated with gaseous ammonia (5 ml) was left for 24 hours at room temperature. The dry residue, obtained after evaporation of volatile components in vacuo, was recrystallized from aqueous acetic acid (1 : 1) to give 2-amino-5-cyano-2-methylthiopyrimidine (*1*). Yield 34 mg (30%). Its IR spectrum was identical with that of an authentic sample prepared according to lit.[2]

5-Cyano-4-(*N,N*-dimethylaminomethyleneamino)-2-methylthiopyrimidine (*2*), under essentially the same reaction conditions, was transformed into 2-amino-5-cyano-2-methylthiopyrimidine (*1*).

5-Cyano-4-ethoxyethylideneamino-2-methylthiopyrimidine (13)

A mixture of 4-amino-5-cyano-2-methylthiopyrimidine (*1*) (100 mg) and triethyl orthoacetate (3 ml) was heated under reflux for 7 hours. Chloroform (2 ml) was added to the oily residue obtained after evaporation of volatile components in vacuo. The crystals were collected by suction and washed with methanol to give 5-cyano-4-ethoxyethylideneamino-2-methylthiopyrimidine (*13*). Yield 60 mg (50%), m. p. 67—71 °C.

Anal. $C_{10}H_{12}N_4OS$ (236.29) calc'd: C 50.83; H 5.12; N 23.71%
found: C 50.66; H 5.22; N 23.45%

^{1}H NMR spectrum ($CDCl_3$/TMS) δ: 1.35 (Ot, CH_2Me), 2.07 (s, C—Me), 2.53 (s, SMe), 4.3 (q, CH_2Me), 8.50 (s, H_6), $J_{CH_2Me} = 6.5$ Hz.

5-Cyano-4-hydroxyiminomethyleneamino-2-methylthiopyrimidine (14)

To a solution of 5-cyano-4-(*N,N*-dimethylaminomethyleneamino)-2-methoxypypyrimidine (*2*) (90 mg) in methanol (3 ml), hydroxylamine hydrochloride (80 mg) was added and the mixture was stirred for 3 hours at room temperature. The precipitate was collected by suction, washed with water and recrystallized from a mixture of DMF and water to give 5-cyano-4-hydroxyiminomethyleneamino-2-methylthiopyrimidine (*14*). Yield 15 mg (18%). The compound *14* cyclized in heating at 90 °C into 4-amino-7-methylthiopyrimido/4,5-d/pyrimidine 3-oxide (*16*).

Anal. $C_7H_7N_5OS$ (209.23) calc'd: C 40.18; H 3.37; N 33.47%
found: C 40.13; H 3.57; N 33.08%

^{1}H NMR spectrum (DMSO-d_6/TMS) δ: 2.50 (s, SMe), 7.95 (s, NHC*H*), 8.70 (s, H_6), 11.05 (br. s, OH).

5-Cyano-4-hydroxyiminomethyleneamino-2-methoxypyrimidine (15)

To a solution of 5-cyano-4-(*N,N*-dimethylaminomethyleneamino)-2-methoxypyrimidine (*9*) (100 mg) in methanol (5 ml), hydroxylamine hydrochloride (50 mg) was added and the mixture was stirred for 1 hour at room temperature. The precipitate was collected by suction and washed with methanol to give 5-cyano-4-hydroxyiminomethyleneamino-2-methoxypyrimidine (*15*). Yield 17 mg (18%). Compound *15* cyclized above 60 °C into 4-amino-7-methoxypyrimido/4,5-d/pyrimidine 3-oxide (*17*).

Anal. $C_7H_7N_5O_2$ (193.17) calc'd: C 43.53; H 3.65%
found: C 43.71; H 3.45%

^{1}H NMR spectrum (DMSO-d_6/TMS δ: 3.90 (s, OMe), 7.88 (d, NHC*H*), 8.75 (d, N*H*CH), 8.70 (s, H_6), 10.95 (s, OH).

Hydrolysis of 5-Cyano-4-hydroxyiminomethyleneamino-2-methoxypyrimidine (15) into 4-Amino-5-cyano-2-methoxypyrimidine (18)

A mixture of 5-cyano-4-hydroxyminomethyleneamino-2-methoxypyrimidine (*15*) (100 mg) in water (3 ml) was heated under reflux for 3 hours. The precipitate was,

after cooling, collected by suction and recrystallized from ethanol to give 4-amino--5-cyano-2-methoxypyrimidine (*18*). Yield 28 mg (36%). Its IR spectrum was identical with that of an authentic sample prepared according to lit.[2].

4-Amino-7-methylthiopyrimido/4,5-d/pyrimidine 3-Oxide (16)

A solution of 5-cyano-4-hydroxyiminomethyleneamino-2-methylthiopyrimidine (*14*) (100 mg) in DMF (1 ml) was heated under reflux for 1 minute. After cooling the precipitate was collected by suction and washed with methanol to give 4-amino--7-methylthiopyrimido/4,5-d/pyrimidine 3-oxide (*16*). Yield 51 mg (51%), m. p. 279—281 °C.

Anal. $C_7H_7N_5OS$ (209.23) calc'd: C 40.18; H 3.37; N 33.47%
found: C 40.56; H 3.45; N 33.16%

^{1}H NMR spectrum (DMSO-d_6/TMS, 152 °C) δ: 2.60 (s, SMe), 8.90 (s, H_5), 9.60 (s, H_2).

4-Amino-7-methoxypyrimido/4,5-d/pyrimidine 3-Oxide (17)

A solution of 5-cyano-4-hydroxyiminomethyleneamino-2-methoxypyrimidine (*15*) (55 mg) in methanol (4 ml) was heated under reflux for 1 hour. After cooling, the precipitate was collected by suction and washed with methanol to give 4-amino--7-methoxypyrimido/4,5-d/pyrimidine 3-oxide (*17*). Yield 31 mg (31%), m. p. 260—266 °C.

Anal. $C_7H_7N_5O_2$ (193.17) calc'd: C 43.53; H 3.65; N 36.26%
found: C 43.77; H 3.87; N 35.98%

Mass spectrum: $m/e = 193$ (M^+). ^{1}H NMR spectrum (DMS-d_6/TMS, 150 °C) δ: 3.98 (s, OMe), 8.75 (s, H_5), 9.54 (s, H_2).

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POVZETEK

Transformacije 4-amino-5-cianopirimidinov. Sinteze in pretvorbe pirimido/4,5-d/pirimidinov

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V tem delu so opisane nekatere nove sinteze pirimido/4,5-d/pirimidinov. 5-Ciano-4-(*N*,*N*-dimetilaminometilenamino)-2-metiltiopirimidin (*2*) in 5-ciano-4-etoksietilidenamino-2-metiltiopirimidin (*12*) ciklizirajo s hidrazinom v 3-amino-4-imino-2-metiltio-3,4-dihidropirimido/4,5-d/pirimidin (*3*), ki ga lahko deaminiramo do 4-amino-2-metiltiopirimido/4,5-d/pirimidina (*4*). Na drugi strani pa 5-ciano-4-hidroksiimino-methilenamino-2-methiltio- (*14*) in -2-metoksipirimidin (*15*) ciklizirata termično v 4-amino-7-metiltio- (*16*) in 4-amino-7-metoksipirimido/4,5-d/pirimidin 3-oksid (*17*).