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Synthesis of New Purine, Pteridine, and Other Pyrimidine Derivatives*

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Abstract—The reaction of malononitrile dimer with phenyl isothiocyanate gave (6-amino-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene)malononitrile which was then used as starting material in the synthesis of pharmacologically important fused pyrimidine derivatives, such as 4-dicyanomethylidene-1,5-diphenyl-2-thioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine, 6-cyano-4-dicyanomethylidene-7-methylsulfanyl-5-oxo-1-phenyl-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine, 6-dicyanomethylidene-3-phenyl-2-thioxo-1,2,3,6-tetrahydro-9*H*-purine, and 6-substituted 4-dicyanomethylidene-7-oxo-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydropteridines.

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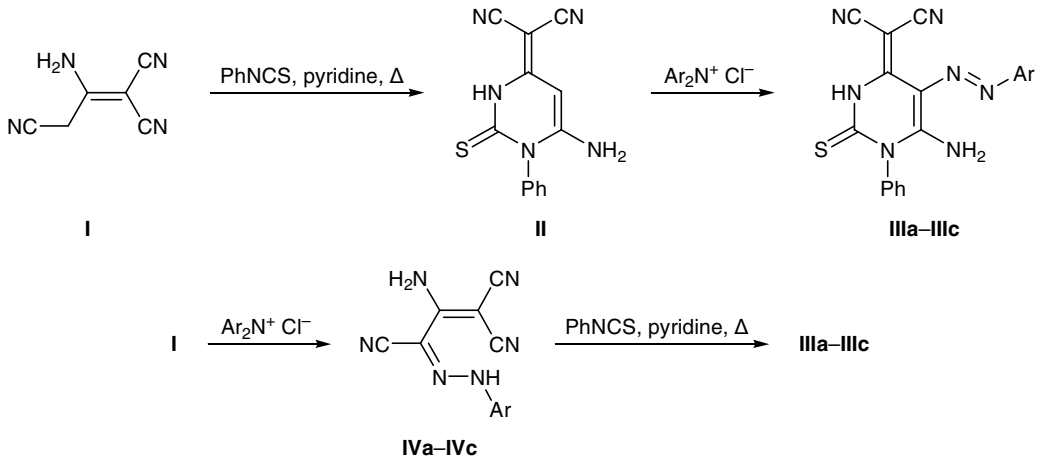
Pyrimidine is the parent heteroring of a very important group of compounds that are extensively studied due to their occurrence in living systems. Compounds containing a pyrimidine ring have been reported as antibacterial and antifungal agents, as well as those exhibiting anti-HIV activity [1–4]. Substituted aminopyrimidine fragments are present in molecules of marketed drugs, such as antiatherosclerotic Aronixil, antihistaminic Thonzylamine, antianxiolytic Buspirone, antipsoriatic Enazadrem, and other medicinally relevant compounds [5–7]. Pyrido[2,3-*d*]pyrimidines (deaza analogs of pteridines) and their oxo derivatives also attract interest as potential biologically active substances [8]. Taking into account the above stated, in the present article we report on the synthesis of new functionally substituted fused pyrimidine derivatives on the basis of 2-(6-amino-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene)malononitrile (**II**).

We recently studied reactions of phenyl isocyanate with compounds having an activated methylene group [9, 10]. 6-Aminopyrimidine **II** was synthesized by reaction of phenyl isothiocyanate with malononitrile

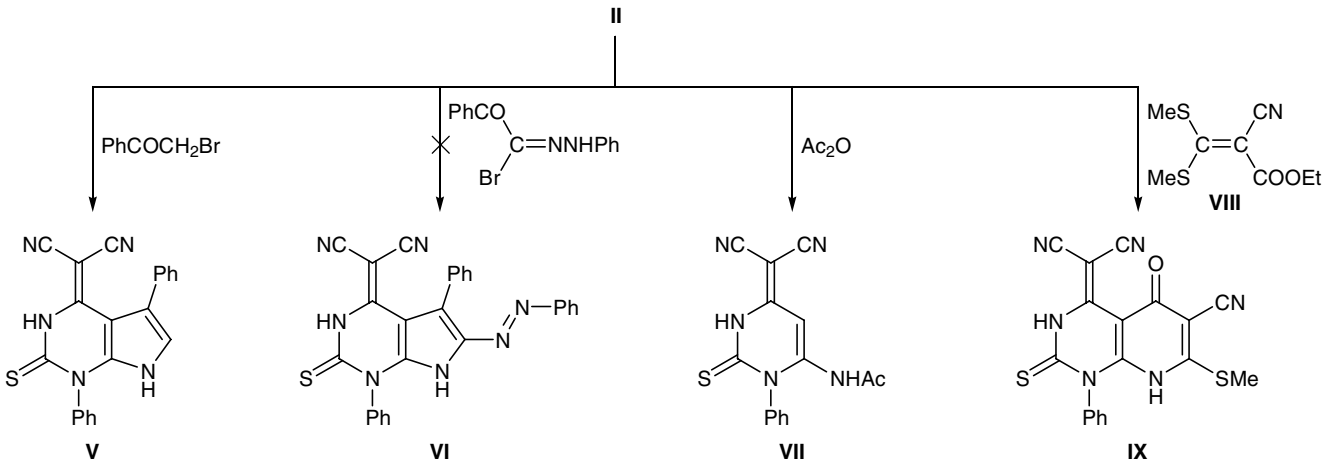
Scheme 1.



III, **IV**, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**).

* The text was submitted by the authors in English.

Scheme 2.



dimer (**I**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile) [11] in boiling pyridine (Scheme 1). The reaction gave the only product whose elemental composition corresponded to the formula $C_{13}H_8N_5S$. It was identified as 6-amino-4-dicyanomethyliden-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine (**II**) on the basis of the IR, ^{1}H NMR, and mass spectra. The IR spectrum of **II** contained strong absorption bands in the region 3466–3333 cm^{-1} due to stretching vibrations of the NH_2 and NH groups, and the band at 2195 cm^{-1} was assigned to the cyano groups. In the ^{1}H NMR spectrum of **II** we observed a singlet at δ 6.80 ppm, which corresponds to proton on C^5 in the pyrimidine ring; protons of the aromatic ring and NH group gave a multiplet at δ 7.05–7.40 ppm; and protons of the amino group resonated as a broadened singlet at δ 8.60 ppm.

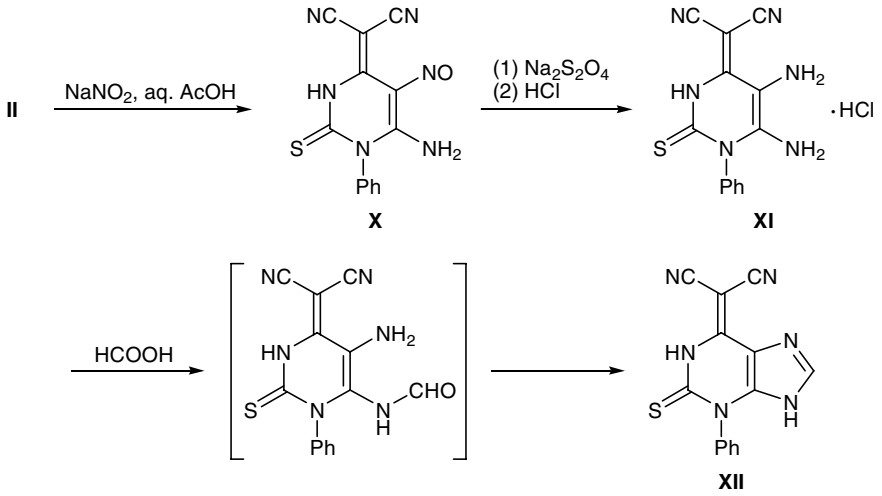
By diazo coupling of 6-aminopyrimidine **II** with aromatic diazonium salts we obtained the corresponding 5-aryldiazenyl derivatives **IIIa**–**IIIc** (Scheme 1) whose structure was confirmed by spectral data and independent syntheses from phenyl isothiocyanate and arylazo derivative **IV** of malononitrile dimer in boiling pyridine. Compound **IIIa** displayed in the IR spectrum absorption bands at 3394–3236 (NH_2, NH) and 2229 cm^{-1} (C≡N). The ^{1}H NMR spectrum of **IIIc** contained a singlet at δ 3.80 ppm (CH_3O), multiplet in the region δ 7.05–7.65 ppm due to aromatic protons, and downfield singlets at δ 9.20 (NH) and 11.45 ppm (NH_2). In the mass spectrum of **IIIb** we observed the molecular ion peak with *m*/*z* 385 ($C_{20}H_{15}N_7S$).

Many fused heterocyclic systems, especially those including a pyrimidine ring, exhibit analgesic, antihypertensive, and antiinflammatory activity and are used as herbicides and plant growth regulators [12–16]. The reaction of 6-aminopyrimidine **II** with phenacyl bromide in boiling ethanol in the presence of a catalytic amount of triethylamine gave pyrrolopyrimidine derivative **V** (Scheme 2). The formation of pyrrole ring is the result of alkylation of the amino group, followed by intramolecular heterocyclization involving the C^5 atom in the pyrimidine ring and the carbonyl group in the substituent at the amino group [17]. The structure of compound **V** was assigned on the basis of its elemental composition and spectral data. The IR spectrum of **V** contained absorption bands at 3300 and 3180 cm^{-1}, belonging to stretching vibrations of the two NH groups, and cyano group absorption at 2200 cm^{-1}. The pyrrole CH proton signal appeared in the ^{1}H NMR spectrum of **V** at δ 5.6 ppm, aromatic multiplet was located in the region δ 7.1–7.8 ppm, and two broadened singlets from the NH protons (D_2O-exchangeable) were present at δ 8.3 and 9.2 ppm. We failed to synthesize phenyldiazenylpyrrolo[2,3-*d*]pyrimidine **VI** by reaction of **II** with 2-bromo-1-phenyl-2-phenylhydrazonoethan-1-one.

Treatment of 6-aminopyrimidine **II** with acetic anhydride gave acetylaminopyrimidine **VII** which showed in the IR spectrum absorption bands at 3205, 2200, and 1676 cm^{-1} corresponding to stretching vibrations of the NH and CN groups and amide carbonyl, respectively. The molecular ion peak ($[M]^+$, *m*/*z* 309) in the mass spectrum of **VII** had a relative intensity of 35%, while the base peak was that with *m*/*z* 266 $[M - COCH_3]^+$ (100%).

Fused pyridopyrimidine **IX** was synthesized by reaction of compound **II** with ethyl 2-cyano-2,3-bis-(methylsulfanyl)prop-2-enoate (**VIII**) [18] in boiling dimethylformamide containing a catalytic amount of triethylamine (Scheme 2). The structure of **IX** was confirmed by the spectral and analytical data. Stretch-

Scheme 3.

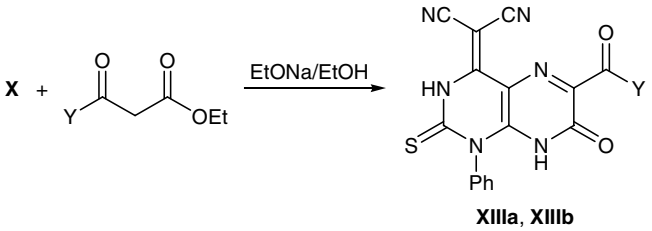


ing vibrations of the NH groups gave rise to an absorption band at 3330 cm^{-1} in the IR spectrum; and bands at 2216 and 1700 cm^{-1} were assigned to vibrations of the C≡N and C=O groups, respectively. Protons of the methylsulfanyl groups resonated in the ^1H NMR spectrum as a singlet at δ 2.60 ppm, the NH signals were located at δ 8.4 and 9.6 ppm (D_2O-exchangeable), and aromatic protons gave a multiplet in the region δ 7.2–8.0 ppm.

Two main synthetic approaches to the fused purine system are known. The first of these includes synthesis of an imidazole derivative, followed by pyrimidine ring closure. The second route (which was used in the present work) implies initial synthesis of a 5,6-diaminopyrimidine derivative [19, 20] which is then brought into condensation with an appropriate one-carbon component to close the second (pyrrole) ring. Our interest in purine derivatives originates from the facts that such purine derivatives as theophylline, caffeine, and theobromine are widely distributed in the nature and that they exhibit versatile biological activity [21]. Compound **II** was converted into purine derivative **XII** in three steps. In the first step, 6-aminopyrimidine **II** was subjected to nitrosation with sodium nitrite in acetic acid; in the IR spectrum of 5-nitroso compound **X** thus formed we observed absorption bands at 3420–3280 (NH_2), 3220 (NH), and 2220 cm^{-1} (CN), while its ^1H NMR spectrum lacked singlet at δ 6.80 ppm corresponding to 5-H in the initial pyrimidine. The second step was reduction of nitroso compound **X** with sodium dithionite to obtain daminopyrimidine **XI**. Heating of the latter in boiling formic acid afforded the target 6-dicyanomethylidene-3-phenyl-2-thioxo-1,2,3,6-tetrahydro-9*H*-purine (**XII**) (Scheme 3). No absorption bands assignable to amino groups were present in the IR spectrum of **XII**, and its ^1H NMR spectrum contained a singlet at δ 8.05 ppm due to CH proton in the imidazole ring.

Pteridine derivatives are used in a variety of fields, e.g., as drugs in pharmaceutics [22] and base components of several nucleosides in biology [23]; other biological activities of pteridine derivatives were also reported [24]. We synthesized pteridines **XIIIa** and **XIIIb** by heating 5-nitrosopyrimidine **X** with ethyl acetoacetate and diethyl malonate, respectively, in the presence of sodium ethoxide (Scheme 4). The structure of **XIIIa** and **XIIIb** was determined on the basis of their analytical and spectral data.

Scheme 4.



XIII, Y = Me (**a**), EtO (**b**).

EXPERIMENTAL

The melting points were determined on an Electrothermal Gallenkamp melting point apparatus and were not corrected. The IR spectra were recorded in KBr on a Mattson 5000 FTIR spectrometer. The ^1H NMR spectra were measured from solutions in $CDCl_3$ or DMSO-d_6 on a Bruker WP 300 instrument using tetra-

methylsilane as internal reference. The mass spectra (electron impact, 70 eV) were run on a Finnigan MAT 212 mass spectrometer. The elemental analyses were obtained at the microanalytical unit, Faculty of Science, University of Mansoura, Egypt.

(6-Amino-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene)malononitrile (II). Phenyl isothiocyanate, 0.01 mol, was added to a solution of 0.01 mol of malononitrile dimer **I** in 30 ml of anhydrous pyridine. The mixture was heated for 2 h under reflux, allowed to cool down to room temperature, poured into ice water, and neutralized with dilute hydrochloric acid for complete precipitation. The precipitate was filtered off, washed with water, and recrystallized from ethanol. Yield 72%, green crystals, mp 225°C. IR spectrum, ν, cm^{-1}: 3466, 3381, 3333 (NH_2, NH); 2195 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.80 s (1H, 5-H), 7.05–7.40 m (6H, H_{arom}, NH), 8.60 br.s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 267 $[M]^+$ (100). Found, %: C 58.37; H 3.44; N 26.26. $C_{13}H_9N_5S$. Calculated, %: C 58.41; H 3.39; N.20. *M* 267.31.

[5-(Aryldiazenyl)-6-amino-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene]malononitriles IIIa–IIIc (*general procedure*). *a*. A solution of 0.01 mol of compound **II** in 50 ml of ethanol containing 4.0 g of sodium acetate was cooled to 0°C, and a cold solution of 0.01 mol of the corresponding arenediazonium chloride (prepared by addition of a cold solution of 0.7 g of sodium nitrite in 10 ml of water to a cold suspension of 0.01 mol of the corresponding aromatic amine in 3 ml of concentrated hydrochloric acid under stirring) was added under continuous stirring. The mixture was stirred for 2 h at 0–5°C and diluted with water, and the precipitate was filtered off, dried, and recrystallized from ethanol–DMF (3:1).

b. A mixture of 0.005 mol of compound **IV** and 0.005 mol of phenyl isothiocyanate in 30 ml of anhydrous pyridine was heated for 2 h under reflux. The mixture was allowed to cool down to room temperature, poured into cold water, and neutralized with dilute hydrochloric acid for complete precipitation. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol–DMF (3:1). Compounds **IIIa**–**IIIc** obtained in such a way were fully identical to samples isolated as described in *a*.

[6-Amino-1-phenyl-5-(phenyldiazenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene]malononitrile (IIIa). Yield 65%, red crystals, mp >300°C. IR spectrum, ν, cm^{-1}: 3394, 3301, 3236 (NH_2, NH); 2229 (CN); 1627 (C=C); 1549 (N=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.10–7.60 m (10H, H_{arom}), 9.35 s (1H, NH), 10.80 s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 371 $[M]^+$ (35). Found, %: C 61.62; H 3.67; N 26.28. $C_{19}H_{13}N_7S$. Calculated, %: C 61.44; H 3.53; N 26.40. *M* 371.42.

[6-Amino-1-phenyl-2-thioxo-5-(*p*-tolyldiazenyl)-1,2,3,4-tetrahydropyrimidin-4-ylidene]malononitrile (IIIb). Yield 73%, red crystals, mp 268°C. IR spectrum, ν, cm^{-1}: 3398, 3305, 3276 (NH_2, NH); 2228 (CN); 1624 (C=C); 1558 (N=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.40 s (3H, CH_3), 7.00–7.50 m (9H, H_{arom}), 9.10 s (1H, NH), 11.20 s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 385 $[M]^+$ (20). Found, %: C 62.47; H 3.73; N 25.58. $C_{20}H_{15}N_7S$. Calculated, %: C 62.32; H 3.92; N 25.44. *M* 385.44.

[6-Amino-5-(*p*-methoxyphenyldiazenyl)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene]-malononitrile (IIIc). Yield 78%, red crystals, mp 280°C. IR spectrum, ν, cm^{-1}: 3438, 3324, 3244 (NH_2, NH); 2237 (CN); 1625 (C=C); 1549 (N=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.80 s (3H, OCH_3), 7.05–7.65 m (9H, H_{arom}), 9.20 s (1H, NH), 11.45 s (2H, NH_2). Found, %: C 59.91; H 3.82; N 24.49. $C_{20}H_{15}N_7OS$. Calculated, %: C 59.84; H 3.77; N 24.42. *M* 401.44.

(1,5-Diphenyl-2-thioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidin-4-ylidene)malononitrile (V). A mixture of 0.005 mol of compound **II**, 0.005 mol of phenacyl bromide, and 4 drops of triethylamine in 30 ml of ethanol was heated for 2 h under reflux. The mixture was allowed to cool down to room temperature and was left overnight. The precipitate was filtered off and recrystallized from dioxane. Yield 58%, yellow crystals, mp >300°C. IR spectrum, ν, cm^{-1}: 3300, 3180 (NH); 2200 (CN); 1600 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.60 s (1H, 6-H), 7.10–7.80 m (10H, H_{arom}), 8.30 s (1H, NH, exchanges with D_2O), 9.20 s (1H, NH, exchanges with D_2O). Mass spectrum, *m*/*z* (I_{rel}, %): 367 $[M]^+$ (88). Found, %: C 68.44; H 3.64; N 19.18. $C_{21}H_{13}N_5S$. Calculated, %: C.65; H 3.57; N 19.06. *M* 367.43.

***N*-[4-(Dicyanomethylidene)-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-6-yl]acetamide (VII).** A mixture of 0.005 mol of 6-aminopyrimidine **II** and 10 ml of acetic anhydride was heated for 4 h at 80–85°C on an oil bath. After cooling to room temperature, the precipitate was filtered off and recrystallized from ethanol. Yield 73%, yellow crystals, mp 260–262°C. IR spectrum, ν, cm^{-1}: 3205 (NH), 2200 (CN),

1676 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.10 s (3H, CH_3), 6.90 s (1H, 5-H), 7.00–7.40 m (5H, H_{arom}), 8.75 s (1H, NH), 10.60 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 309 $[M]^+$ (24). Found, %: C 58.33; H 3.50; N 22.56. $C_{15}H_{11}N_5OS$. Calculated, %: C 58.24; H 3.58; N 22.64. *M* 309.35.

(6-Cyano-7-methylsulfanyl-5-oxo-1-phenyl-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidin-4-ylidene)malononitrile (IX). A mixture of 0.01 mol of compound **II**, 0.01 mol of ethyl 3,3-bis(methylsulfanyl)-2-cyanoprop-2-enoate (**VIII**), and 4 drops of triethylamine in 20 ml of DMF was heated for 4 h under reflux. After cooling to room temperature, the precipitate was filtered off and recrystallized from dioxane. Yield 52%, brown crystals, mp >300°C. IR spectrum, ν, cm^{-1}: 3330 (NH), 2216 (CN), 1700 (C=O), 1550–1590 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.60 s (3H, SCH_3), 7.20–8.00 m (5H, H_{arom}), 8.40 s (1H, NH, exchanges with D_2O), 9.60 s (1H, NH, exchanges with D_2O). Mass spectrum, *m*/*z* (I_{rel}, %): 390 $[M]^+$ (74). Found, %: C 55.59; H 2.63; N 21.41. $C_{18}H_{10}N_6OS_2$. Calculated, %: C55.37; H 2.58; N 21.52. *M* 390.44.

(6-Amino-5-nitroso-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene)malononitrile (X). A solution of 0.01 mol of sodium nitrite in 10 ml of water was added dropwise under vigorous stirring to a suspension of 0.01 mol of compound **II** in 30 ml of glacial acetic acid. A red solid separated. The mixture was stirred for 4 h at room temperature, and the precipitate was filtered off, washed with water, and recrystallized from ethanol. Yield 84%, orange crystals, mp 252–253°C. IR spectrum, ν, cm^{-1}: 3420–3280 (NH_2), 3220 (NH), 2220 (CN). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.10–7.40 m (5H, H_{arom}), 8.15 s (1H, NH), 11.10 s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 296 $[M]^+$ (20). Found, %: C 52.84; H.63; N 28.44. $C_{13}H_8N_6OS$. Calculated, %: C 52.70; H 2.72; N 28.36. *M* 296.31.

(5,6-Diamino-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-ylidene)malononitrile hydrochloride (XI). A suspension of 0.02 mol of 6-amino-5-nitrosopyrimidine **X** in 50 ml of hot distilled water was heated on a boiling water bath, and 1.25 g of sodium dithionite was added in portions over a period of 15 min. The mixture lost its color and was stirred for 15 min on heating using a mechanical stirrer and allowed to cool down. The precipitate of 5,6-diaminopyrimidine bisulfite was filtered off, dried, and transferred into a three-necked flask. A solution of 50 ml of concentrated hydrochloric acid in 20 ml of water was added, and the mixture was heated for 1 h on a boiling water bath and cooled. The precipitate was filtered off, washed with acetone, and dried. Yield 56%, yellow powder. IR spectrum, ν, cm^{-1}: 3374–3176 (NH_2, NH), 2216 (CN). Found, %: C 48.76; H 3.52; N 26.26. $C_{13}H_{11}ClN_6S$. Calculated, %: C 48.98; H 3.48; N 26.36. *M* 318.78.

(3-Phenyl-2-thioxo-1,2,3,6-tetrahydro-9*H*-purin-6-ylidene)malononitrile (XII). A suspension of 0.01 mol of 5,6-daminopyrimidine hydrochloride **XI** in 20 ml of formic acid was heated for 2 h under reflux. The mixture was cooled, and the precipitate was filtered off, thoroughly washed with water and cold ethanol, and recrystallized from ethanol. Yield 69%, colorless crystals, mp >300°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 2210 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.00–7.50 m (5H, H_{arom}), 8.05 s (1H, 8-H), 8.55 s (1H, NH), 12.20 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 292 $[M]^+$ (38). Found, %: C 57.73; H 2.84; N 28.65. $C_{14}H_8N_6S$. Calculated, %: C 57.52; H 2.76; N 28.75. *M* 292.32.

4-Dicyanomethylidene-7-oxo-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydropteridines XIIIa and XIIIb (*general procedure*). Ethyl acetoacetate or diethyl malonate, 0.01 mol, was added to a solution of sodium ethoxide prepared from 0.01 mol of metallic sodium and 30 ml of anhydrous ethanol. The mixture was stirred for 30 min at room temperature, 0.01 mol of nitroso compound **X** was added, and the mixture was heated for 6 h under reflux, cooled to room temperature, and poured into ice water. The precipitate was filtered off and recrystallized from ethanol.

(6-Acetyl-7-oxo-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydropteridin-4-ylidene)malononitrile (XIIIa). Yield 70%, yellow crystals, mp 248°C. IR spectrum, ν, cm^{-1}: 3295 (NH); 2210 (CN); 1715, 1680 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.10 s (3H, CH_3), 7.10–7.40 m (5H, H_{arom}), 8.15 s (1H, NH), 12.55 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 362 $[M]^+$ (62). Found, %: C 56.24; H 2.71; N 23.27. $C_{17}H_{10}N_6O_2S$. Calculated, %: C 56.35; H 2.78; N 23.19. *M* 362.37.

Ethyl 4-dicyanomethylidene-7-oxo-1-phenyl-2-thioxo-1,2,3,4,7,8-hexahydropteridine-6-carboxylate (XIIIb). Yield 66%, yellow crystals, mp >300°C. IR spectrum, ν, cm^{-1}: 3310 (NH); 2208 (CN); 1705, 1680 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.25 t (3H, CH_3), 4.10 q (2H, CH_2), 7.10–7.50 m (5H, H_{arom}), 8.10 s (1H, NH), 12.60 s (1H, NH). Mass spec-

trum, *m*/*z* (I_{rel}, %): 392 $[M]^+$ (84). Found, %: C 55.22; H 3.13; N 21.57. $C_{18}H_{12}N_6O_3S$. Calculated, %: C 55.10; H 3.08; N 21.42. *M* 392.39.

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