Pyrimidine Derivatives and Related Compounds. 4. A Route for the Synthesis of Pyrazolo[3,4-*e*]-*as*-triazines, Pyrazolo[3,4-*d*]pyrimidines, and Pyrazolo[1,5-*c*]-*as*-triazines

Mohamed Hilmy Elnagdi,* Mohamed Rifaat Hamza El-Moghayar, Daizy Hana Fleita, Ebtisam Abdel Aziz Hafez, and Sherif Mahmoud Fahmy

Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R., Egypt, and the American University in Cairo, A.R., Egypt

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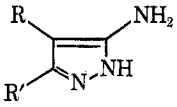
5-Amino-3-phenylpyrazole (**1a**) reacts with benzoyl isothiocyanate (**2**) to yield 5-amino-4-benzoylthiocarbamoyl-3-phenylpyrazole (**1b**). On the other hand, the 5-amino-4-arylazopyrazoles **1c–e** reacted with **2** to yield thiourea derivatives **3b–d** which could be cyclized into the pyrazolo[3,4-*e*]-*as*-triazine derivatives **5a–c**. 5-Amino-4-cyano-3-cyanomethylpyrazole (**1f**) reacted with **2** to yield 4-amino-3-cyanomethyl-6-mercapto-1*H*-pyrazolo[3,4-*d*]pyrimidine (**7**). **1a** was diazotized and the resulting diazonium salt was coupled with a variety of active methylene β functional compounds to afford pyrazolo[1,5-*c*]-*as*-triazine derivatives. The intermediate coupling products could be isolated in some cases. The behavior of the pyrazolo[1,5-*c*]-*as*-triazine derivatives **11a–c** toward the action of hydroxylamine, ethanolic sodium ethoxide, and acetic–hydrochloric acid mixture is reported.

The considerable biological and medicinal activities of pyrazolopyrimidines[1–4] and of pyrazolotriazines,[5–7] as adenine analogues, antagonists, and antitumor agents[8,9] have stimulated recent interest in the synthesis of derivatives of these ring systems. In continuation of our previous work,[10–15] we have investigated a variety of synthetic routes to pyrazolo[3,4-*d*]pyrimidines, pyrazolo[3,4-*e*]-*as*-triazines, and pyrazolo[1,5-*c*]-*as*-triazines. This work has led to some new procedures for the synthesis of several known heterocyclic systems from 5-aminopyrazoles in good yields and under milder conditions than previously reported.

The reaction of 5-aminopyrazoles with acetyl isothiocyanate and with ethoxycarbonyl isothiocyanate is straightforward and affords the expected pyrazol-5-ylthiourea derivatives which cyclize readily to pyrazolo[1,5-*a*]-*as*-triazines in base.[16–18] We have found, however, that 5-amino-3-phenylpyrazole (**1a**) reacts with benzoyl isothiocyanate (**2**), in refluxing acetone, to give 5-amino-4-benzoylthiocarbamoyl-3-phenylpyrazole (**1b**) as the only product. The ^{1}H NMR spectrum of this product revealed the absence of a signal at δ 5–7.3 ppm for C_4 proton[19] indicating substitution at this position. Moreover, the chemical behavior of **1b** is different from that expected for pyrazolylthiourea derivatives (cf. possible alternative structure **3a** or **4**) and resembles that of pyrazole-4-carboxylic acid derivatives. Thus, **1b** was recovered largely unchanged when refluxed in pyridine solution or in aqueous 2 N NaOH solution (cf. the hydrolysis of *N*-(pyrazol-5-yl)-*N'*-acetylthioureas under these conditions in ref 16 and 17). When **1b** was heated with Ac_2O, 5-acetamido-3-phenylpyrazole (**3b**) was formed in 90% yield. Compound **3b** was also obtained by the action of Ac_2O on **1a**. These results parallel the facile decarboxylation of 5-aminopyrazole-4-carboxylic acid derivatives under acidic conditions.[20] Although the position of NH_2 signals depends much on solvent and concentration of solutions, the downfield shift of the NH_2 protons of **1b** (8.18 ppm) as compared with previously reported values for NH_2 protons in 5-aminopyrazoles[19] may be attributed to deshielding of these protons by the adjacent benzoylthiocarbamoyl groups at C_4. A similar effect on the NH_2 protons due to action of the adjacent thiocarbamoyl moiety has been observed.[21]



$C_6H_5CON{=}C{=}S$

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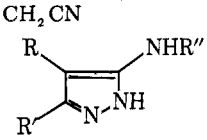
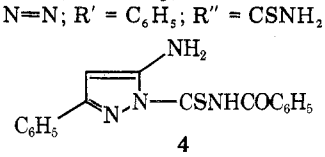
1a, R = H; R' = C_6H_5
b, R = $C_6H_5CONHCS$; R' = C_6H_5
c, R = $C_6H_5N{=}N$; R' = C_6H_5
d, R = *p*-$CH_3C_6H_4N{=}N$; R' = C_6H_5
e, R = $C_6H_5N{=}N$; R' = CH_3
f, R = CN; R' = CH_2CN



3a, R = H; R' = C_6H_5; R'' = $CSNHCOC_6H_5$
b, R = H; R' = C_6H_5; R'' = $COCH_3$
c, R = $C_6H_5N{=}N$; R' = C_6H_5; R'' = $CSNHCOC_6H_5$
d, R = *p*-$CH_3H_6H_4N{=}N$; R' = C_6H_5; R'' = $CSNHCOC_6H_5$
e, R = $C_6H_5N{=}N$; R' = CH_3; R'' = $CSNHCOC_6H_5$
f, R = $C_6H_5N{=}N$; R' = C_6H_5; R'' = $CSNH_2$



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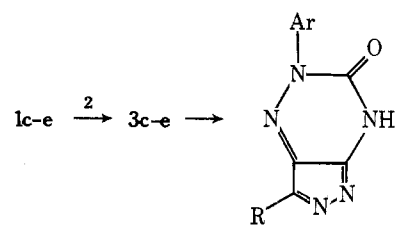
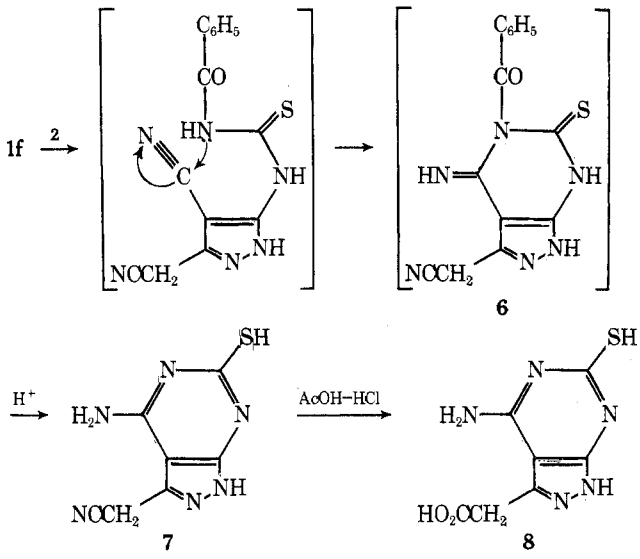
In contrast to the reaction of **1a** with **2** the 5-amino-4-arylazopyrazoles (**1c–e**) reacted with **2** to give the expected pyrazol-5-ylthioureas **3c–e**. When these products were refluxed with acetic acid–hydrochloric acid mixture for a short time, yellow products were obtained in high yields. Structure **5** was suggested for these reaction products on the basis of analytical and spectral data. The reaction of **3c** with hydrazine hydrate in refluxing ethanol give the pyrazolylthiourea derivative **3f**. The cyclization of **3c–e** into **5a–c** constitutes a new, simple, and efficient route for the preparation of pyrazolo[3,4-*e*]-*as*-triazines, only a few of which have been previously reported.[22,23]



1c–e $\xrightarrow{2}$ **3c–e** $\longrightarrow$

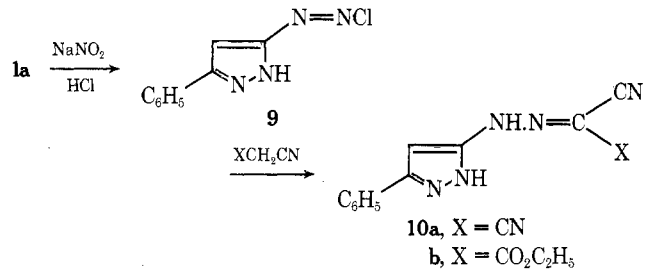
5a, R = Ar = C_6H_5
b, R = C_6H_5; Ar = $C_6H_4CH_3$-*p*
c, R = CH_3; Ar = C_6H_5

5-Amino-4-cyano-3-cyanomethylpyrazole (**1f**) reacted with **2** to yield the pyrazolo[3,4-*d*]pyrimidine derivative **7**. The formation of **7** from **1f** and **2** may be assumed to take place via the benzoylthiourea derivative which then undergoes cyclization to **6**. The latter then decomposes to the final product **7** during purification. Compound **7** was hydrolyzed into the

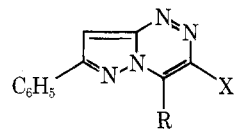


carboxylic acid 8 by the action of acetic acid–hydrochloric acid mixture. The behavior of **1f** toward **2** is similar to that of cyclic enaminonitriles toward the action of isothiocyanates.[24]

Diazotization of 5-aminopyrazoles in strong acids has been reported to afford the corresponding diazonium salts,[25,26] which undergo coupling with phenols to yield pyrazolotriazines by intermolecular condensation.[26] Pyrazole-3-diazonium chloride, when treated with β-keto acids or esters, gave products which spontaneously cyclized to pyrazolo[1,5-*c*]-*as*-triazines.[27] Coupling with compounds such as ethyl cyanoacetate gave azo compounds which also readily cyclized to pyrazolotriazines.[27] In the present work 3-phenylpyrazole-5-diazonium chloride (**9**) was prepared by diazotization



of **1a** and its reactions with a variety of active methylene reagents were investigated. Thus **9** coupled with malononitrile or with ethyl cyanoacetate to yield the corresponding pyrazol-5-ylhydrazones **10a,b** which readily cyclized to the pyrazolo[1,5-*c*]-*as*-triazines **11a,b** in sulfuric acid. Compound **9**



11a, X = CN; R = NH_2
b, X = CN; R = OH
c, X = CN; R = CH_3
d, X = $CO_2C_2H_5$; R = CH_3
e, X = (C:NOH)NH_2; R = NH_2
f, X = (C:NOH)NH_2; R = OH
g, X = (C:NOH)NH_2; R = CH_3
h, X = $CONH_2$; R = NH_2
i, X = $CONH_2$; R = OH
j, X = $CONH_2$; R = CH_3
k, X = CO_2H; R = NH_2
l, X = CO_2H; R = OH
m, X = CO_2H; R = CH_3

reacted with 3-iminobutyronitrile or with ethyl acetoacetate to yield directly the pyrazolo[1,5-*c*]-*as*-triazine derivatives **11c,d**, respectively.

The behavior of **11a–c** toward the action of hydroxylamine, ethanolic sodium ethoxide, and acetic acid–hydrochloric acid mixture was also investigated with the aim of preparing a variety of 6 substituted derivatives of **11**. In this manner, treatment of **11a–c** with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol solution has resulted in the formation of the amidoximes **11e–g.**

Compounds **11a–c** reacted with ethanolic sodium ethoxide to yield the amides **11h–j.**

Treatment of **11a–c** with acetic acid–hydrochloric acid mixture has resulted in the formation of the carboxylic acid derivatives **11k–m.** The ir and ^1H NMR data for all compounds **11a–m** were in good agreement with proposed structures (cf. tables).

Table I. List of the Pyrazolythiourea Derivatives 3c–f

Registry no.	Compd	Crystn solvent	Mp, °C	Yield, %	Formula
60269-77-4	**3c**	EtOH	243	60	$C_{23}H_{18}ON_6S$
60269-78-5	**3d**	AcOH	248	60	$C_{24}H_{20}ON_6S$
59119-57-2	**3e**	EtOH	224	55	$C_{18}H_{16}ON_6S$
60269-79-6	**3f**	AcOH	114	70	$C_{16}H_{14}N_6S$

Table II. List of the Pyrazolo[1,5-*c*]-*as*-triazine Derivatives 11a–m

Registry no.	Compd	Yield, %	Crystn solvent	Mp, °C	Formula
60269-80-9	**11a**	80	*a*	287	$C_{12}H_8N_6$
60269-81-0	**11b**	75	*b*	246	$C_{12}H_7ON_5$
60269-82-1	**11c**	70	*b*	210	$C_{13}H_9N_5$
60269-83-2	**11d**	65	*b*	149	$C_{15}H_{14}O_2N_4$
60269-84-3	**11e**	45	*c*	300	$C_{12}H_{11}ON_7$
60269-85-4	**11f**	40	*b*	244	$C_{12}H_{10}O_2N_6$
60269-86-5	**11g**	40	*b*	255	$C_{13}H_{12}ON_6$
60269-87-6	**11h**	50	*c*	300	$C_{12}H_{10}ON_6$
60269-88-7	**11i**	53	*d*	222	$C_{12}H_9O_2N_5$
60269-89-8	**11j**	50	*b*	290	$C_{13}H_{11}ON_5$
60269-90-1	**11k**	70	*b*	300	$C_{12}H_9O_2N_5$
60269-91-2	**11l**	75	*c*	300	$C_{12}H_8O_3N_4$
60269-92-3	**11m**	72	*c*	180	$C_{13}H_{10}O_2N_4$

[a] Pyridine. [b] Ethanol. [c] Acetic acid. [d] Methanol.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded (KBr) on a Perkin-Elmer Model 337 spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian A-60 spectrophotometer using Me_4Si as internal standard and chemical shifts are expressed as δ, parts per million. Satisfactory analytical data (±0.3%) were obtained for all compounds listed in Tables I and II.

Reaction of 1a,c–e with Benzoyl Isothiocyanate (2). General Procedure. To a solution of **2** (prepared from 0.12 mol of NH_4SCN and appropriate quantity of BzCl as has been described by Douglass and Dains[28]), 0.1 mol of the compound in acetone (50 ml) was added. The reaction mixture was refluxed for 2 h and then evaporated in vacuo. The remaining product was washed several times with water and then boiled with 100 ml of ethanol. The solid products, **1b, 3c–e,** were collected by filtration and crystallized from ethanol.

1b: colorless crystals; mp 242 °C; yield 22.5 g (0.07 mol, 70%); ir 1670 (benzoyl C=O) and 2550–3450 cm^{-1} (NH bands); ^1H NMR δ 7.4–8.0 (m, 10 H, 2 C_6H_5), 8.18 (d, 2 H, NH_2 lost after D_2O exchange), 11.68 (br, 1 H, amide NH), and 13.28 (br, 1 H, ring NH).

Anal. Calcd for $C_{17}H_{14}ON_4S$: C, 63.35; H, 4.38; N, 17.38; S, 9.96. Found: C, 63.22; H, 4.41; N, 17.35; S, 9.67.

N-(4-Arylazo-3-substituted-pyrazol-5-yl)-*N'*-benzoylthiourea derivatives (**3c–e**), listed in Table I, showed ir bands at 1670 (C=O), 3050–3100, and 3320–3340 cm^{-1} (NH groups). The ^1H NMR spectrum of **3c** showed signals at δ 7.2–8.0 (m, 15 H, 3 C_6H_5), 11.67 (br, 1 H, amide NH), and 13.28 (BR= [H, ring NH).

Action of Ac_2O on 1b. A solution of **1b** (3.0 g) in Ac_2O (25 ml) was refluxed for 3 h and then poured onto water (150 ml). The resulting reaction mixture was boiled till complete decomposition of excess Ac_2O and then left to stand. The solid product, so formed, was collected by filtration and crystallized from water.

3b: colorless crystals; mp 147 °C; yield 1.7 g (0.008 mol, 90%); ir 1690 (acyl CO), 3340 cm^{-1} (NH); ^1H NMR δ 2.0 (s, 3 H, CH_3), 6.18 (s, 1 H,

ring NH), 7.2–8.0 (m, 5 H, C_6H_5), 11.9 (s, H, amide NH, lost after D_2O exchange), and 13.6 (br, ring NH, lost after D_2O exchange).

Anal. Calcd for $C_{11}H_{11}ON_3$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.50; N, 5.59; N, 20.68.

Compound **3b** was also obtained as follows. **1a** (1.0 g) was refluxed in Ac_2O solution (10 ml) for 15 min. The resulting solution was poured onto water and excess Ac_2O was decomposed by boiling in water for a short period. The crystals formed on standing were collected by filtration (0.9 g) and the product was identified (melting point, mixture melting point, and ir) as **3b**.

2-Aryl-2,3-dihydro-7-substituted-3-oxo-4*H*-pyrazolo[3,4-*e*]-*as*-triazine (5a–c). To a suspension of each of **3c–e** (3.0 g) in acetic acid (20 ml), 2 ml of concentrated hydrochloric acid was added. The reaction mixture was refluxed for 30 min and then poured onto water. The solid products **5a–c** were collected by filtration and crystallized from acetic acid. Compounds **5a–c** are all buff in color.

5a: mp 230 °C; yield 1.62 g (0.006 mol, 80%).

Anal. Calcd for $C_{16}H_{11}ON_5$: C, 66.42; H, 3.83; N, 24.21. Found: C, 66.44; H, 3.79; N, 24.05.

5b: mp 220 °C; yield 1.73 g (0.006 mol, 82%).

Anal. Calcd for $C_{17}H_{13}ON_5$: C, 67.31; H, 4.32; N, 23.09. Found: C, 67.33; H, 4.39; N, 23.08.

5c: mp 120 °C; yield 7.33 g (0.006 mol, 65%).

Anal. Calcd for $C_{11}H_9ON_5$: C, 58.14; H, 3.99; N, 30.82. Found: C, 58.07; H, 4.10; N, 31.00.

Compounds **5a–c** showed ir bands at 1700 (ring C=O) and 3320 cm^{-1} (NH).

1-(4-Phenylazo-3-phenylpyrazol-5-yl)-2-thiourea (3f). A suspension of **3c** (2.0 g) in ethanol (80 ml) was treated with hydrazine hydrate (2 ml, 80%). The reaction mixture was refluxed for 4 h and then evaporated in vacuo. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallized from acetic acid. Compound **3f** is listed in Table I.

4-Amino-3-cyanomethyl-6-mercapto-1*H*-pyrazolo[3,4-*d*]pyrimidine (7). A solution of 0.1 mol of **1f** in pyridine (100 ml) was treated with a solution of 0.1 mol of **2** (prepared as described above) in 50 ml of acetone. The reaction mixture was refluxed for 2 h and then evaporated in vacuo. The product, so formed, dissolved in water and the resulting solution was acidified with hydrochloric acid. The resulting solid product was collected by filtration and crystallized from acetic acid to yield 8.0 g (0.04 mol, 40%) of **7**. Recrystallization of this product from acetic acid afforded analytically pure sample.

7: mp 220 °C; ir 1650 (δ NH_2), 2255 (unconjugated CN), 3250 and 3480 cm^{-1} (ν NH_2).

Anal. Calcd for $C_7H_6N_6S$: C, 40.78; H, 2.94; N, 40.77; S, 15.52. Found: C, 40.58; H, 3.21; N, 40.67; S, 15.59.

4-Amino-3-carboxymethyl-6-mercapto-1*H*-pyrazolo[3,4-*d*]pyrimidine (8). To a mixture of acetic acid (30 ml) and hydrochloric acid (8.0 ml), 3.0 g of **7** was added and the mixture was refluxed for 2 h. The solvent was removed in vacuo and the residue was treated with a little water. The solid product, which separated on standing, was collected by filtration and crystallized from acetic acid to yield 1.5 g (0.008 mol, 44%) of **8:** mp 260 °C; ir 1700 (CO) and broad band from 2500 to 3300 cm^{-1} (OH dimer and NH groups).

Anal. Calcd for $C_7H_7O_2N_5S$: C, 37.34; H, 3.13; N, 31.11; S, 14.21. Found: C, 37.51; H, 3.3; N, 31.00; S, 14.27.

3-Phenylpyrazole-5-diazonium Chloride (9). A suspension of **1a** (0.1 mol) in acetic acid (80 ml) was treated with hydrochloric acid (30 ml, 37.5%). The mixture was heated to produce a clear solution and then cooled to 5 °C. A solution of $NaNO_2$ (7.0 g) in 30 ml of water was then gradually added with stirring. The reaction mixture was left in a refrigerator for 2 h, then poured onto cold water. The solid product separated was collected by filtration and washed several times with hot ethanol to afford an analytically pure sample of **9**, mp 168 °C, yield 11.4 g (0.055 mol, 55%).

Anal. Calcd for $C_9H_7N_4Cl$: C, 52.35; H, 3.38; N, 27.10; Cl, 17.19. Found: C, 52.01; H, 3.65; N, 26.89; Cl, 16.97.

3-Phenylpyrazol-5-ylhydrazonomesoxalonitrile (10a). A solution of malononitrile (0.1 mol) in ethanol (100 ml) was treated with a suspension of sodium acetate (10 g) in 50 ml of water. A solution of **9** (0.1 mol) in 50 ml of acetic acid was then added with stirring. The solid product, obtained on standing, was collected by filtration and washed several times with hot water. An analytically pure sample of **10a** was prepared by extracting the solid product (13.0 g, 0.005 mol, 55%) so obtained by hot ethanol and filtration while the solution was hot. **10a:** mp >300 °C; ir 1630 (C=N), 2235 (CN), and 3220, 3330 cm^{-1} (NH groups); ^1H NMR δ 6.2 (1 H, ring CN), 7.4–8.0 (5 H, C_6H_5), 12.7 (1 H, hydrazone NH), and 13.3 (1 H, ring NH).

Anal. Calcd for $C_{12}H_8N_6$: C, 61.00; H, 3.41; N, 35.58. Found: C, 61.22; H, 4.15; N, 35.30.

Ethyl 3-Phenylpyrazol-5-ylhydrazonocyanoglyoxalate (10b). This compound was prepared from ethyl cyanoacetate and **9** in the same manner as **10a** and was obtained as a cream-colored solid in a 60% yield: mp 196 °C; ir 1725 (ester CO), 2190 (conjugated CN), and 3310–3325 cm^{-1} (NH groups); ^1H NMR δ 1.43 (t, 3 H, ester CH_3), 4.45 (q, 2 H, ester CH_2), 6.2 (s, 1 H, ring CH), 7.4–8.0 (m, 5 H, C_6H_5), 12.3 (br, NH), 13.3 (br, NH), and 13.3 (br, 1 H, ring NH).

Anal. Calcd for $C_{14}H_{13}O_2N_5$: C, 59.35; H, 4.63; N, 24.72. Found: C, 59.54; H, 4.61; N, 25.00.

Cyclization of 10a,b. A mixture of each of **10a,b** (3.0 g) and concentrated H_2SO_4 (2.0 ml) was kept at room temperature for 30 min. The mixture was then diluted with water and neutralized by addition of ammonia, and the resulting products were collected by filtration. The reaction products, **11a,b,** are listed in Table II.

6-Cyano-7-methyl-2-phenylpyrazolo[1,5-*c*]-*as*-triazine (11c). This compound was obtained from reaction of 3-iminobutyronitrile and **9** using the same experimental conditions described for coupling of **9** with malononitrile. The reaction product is listed in Table II.

6-Ethoxycarbonyl-7-methyl-2-phenylpyrazolo[1,5-*c*]-*as*-triazine (11d). This compound was prepared by coupling of **9** and ethyl acetoacetate as described for synthesis of **11c** and is listed in Table II.

Reaction of 11a–c with Hydroxylamine. To a suspension of the nitrile (0.1 mol) in ethanol (100 ml) a solution of NH_2OH·HCl (0.1 mol) in 30 ml of water and 10 g of anhydrous sodium acetate were added. The reaction mixture was refluxed for 3 h and then poured onto water. The solid product formed was collected by filtration and crystallized from the proper solvent. The amidoxime derivatives **11e–g** are listed in Table II.

2-Phenyl-7-substituted-pyrazolo[1,5-*c*]-*as*-triazine-3-carboxyamide (11h–j). To a sodium ethoxide solution (prepared from 1 g of sodium metal and 80 ml of ethanol), 0.02 mol of each of **11a–c** was added. The reaction mixture was then refluxed for 3 h, left to cool, poured over water, and acidified with concentrated hydrochloric acid. The solid product, so formed, was collected by filtrated and crystallized. The reaction products, **11h–j,** are listed in Table II.

2-Phenyl-7-substituted-pyrazolo[1,5-*c*]-*as*-triazine-3-carboxylic Acid (11k–m). To a mixture of acetic acid (30 ml), water (5 ml), and hydrochloric acid (5.0 ml, 35.5%) 3.0 g of each of **11a–c** was added and the mixture was refluxed for 6 h. The solvent was then removed in vacuo and the remaining solid product was purified by dissolution in sodium carbonate, filtration of insoluble impurities, and reprecipitation by acidification. The carboxylic acid derivatives **11k–m,** listed in Table II, were purified by crystallization from the proper solvent.

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Registry No.—**1a,** 1572-10-7; **1b,** 60269-93-4; **1c,** 57695-75-7; **1d,** 60269-94-5; **1e,** 57695-74-6; **1f,** 54711-21-6; **2,** 532-55-8; **3b,** 50671-40-4; **5a,** 60269-95-6; **5b,** 60269-96-7; **5c,** 60269-97-8; **7,** 60269-98-9; **8,** 60269-99-0; **9,** 60270-00-0; **10a,** 60270-01-1; **10b,** 60270-02-2; malononitrile, 109-77-3; ethyl cyanoacetate, 105-56-6; 3-iminobutyronitrile, 1118-60-1.

Supplementary Material Available. Ir and ^1H NMR spectral data (2 pages). Ordering information is given on any current masthead page.

References and Notes

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Synthesis of Imidazo[4,5-*b*]pyridines and *v*-Triazolo[4,5-*b*]pyridines. Preparation of 1-Deaza-6-thioguanine Analogues[1]

Carroll Temple, Jr.,* Buford H. Smith, Conrad L. Kussner, and John A. Montgomery

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

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Improved methods for the preparation of 1-deazaguanine (8) and its 8-aza analogue are reported. The preparation of 1-deaza-6-thioguanine (13) either by the thiation of 8 or by the rearrangement of the isomeric 4,6-diaminothiazolo[4,5-*c*]pyridine was unsuccessful. The successful preparation of 13 was accomplished by the removal of the diphenylmethyl group of 2-amino-6-[(diphenylmethyl)thio]-1-deazapurine with refluxing trifluoroacetic acid. 8-Aza-1-deaza-6-thioguanine (26) was prepared by the reaction of the corresponding 6-chloro compound with sodium hydrosulfide. The reversible rearrangement between 26 and 4,6-diamino[1,2,3]thiadiazolo[4,5-*c*]pyridine was demonstrated. In addition, 2-amino-6-(methylthio)-1-deazapurine and its 8-aza analogue were prepared from 2,3,6-triamino-4-(methylthio)pyridine.

Previously we reported the development of synthetic methods for the preparation of the 5,7-diamino derivatives of imidazo[4,5-*b*]pyridine and *v*-triazolo[4,5-*b*]pyridine, the 1-deaza and 8-aza-1-deaza analogues of 2,6-diaminopurine.[2,3] Further work in this area has resulted in the development of procedures for the preparation of the 5-amino-7-thione derivatives of these ring systems, which are the 1-deaza and 8-aza-1-deaza analogues of 6-thioguanine.

The synthesis of the thione **13** from the corresponding chloro compound **24** was unsuccessful because of the unreactive nature of the chloro group toward nucleophilic displacement with sodium hydrosulfide.[2,4] In addition the direct preparation of **13** by the cyclization of a 2,3-diaminopyridine-4-thione precursor (**11**) was unlikely since analogous reactions in the pyrimidine series provided thiazolopyrimidines rather than purines.[5,6] However, the thiation of guanine with P_4S_{10} in pyridine has been reported to give 6-thioguanine[7] and it was anticipated that thiation of the known 1-deaza analogues of guanine, **8** and **9**, might give the desired target compounds **13** and **26**, respectively. Also this route was attractive because both **8** and **9** can be prepared from the common intermediate **7**. In the original synthesis, **8** was obtained in 30% yield by hydrolysis of 2-amino-6-ethoxy-1-deazapurine with 48% HBr.[8] In addition, the triaminopyridine **7** was converted with formic acid to **8** in unspecified yield and with aqueous nitrous acid to **9** in 9% yield.[9,10] Modifications of these reactions gave higher yields of **8** and **9**. The chloropyridine **1**[11] was treated with refluxing 98% HCO_2H to hydrolyze the chloro group. Reaction of the resulting crude pyridin-4-one **4** with ethanolic KOH hydrolyzed the urethane groups to give the intermediate 3-nitropyridine **6** in an overall yield of 75%. Also, the monourethane **2**[12] was converted to **5** with refluxing formic acid. When the crude product from this reaction was treated with ethanolic KOH, **6** was obtained in an overall yield of 82%. Catalytic hydrogenation of **6** to give **7** at atmospheric pressure and room temperature in the presence of Raney nickel was slow and required about 20 h for completion.[13] The resulting triaminopyridine **7** was isolated