1-Aminohypoxanthine and Analogues

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Received February 4, 1985

1-Aminohypoxanthine (**1a**), a new positional isomer of guanine, has been obtained from 5-aminoimidazole-4-carboxylic acid hydrazide and triethyl orthoformate. Pyrazolo **11** and triazolo **21** analogues of **1** result from similar reactions of the corresponding o-aminoazole hydrazides. An indirect synthesis involving excess orthoester and hydrolysis of the resulting intermediate **6** was found most effective for **1**, but **11** may be prepared directly from 3-aminopyrazole-4-carboxylic acid hydazide and orthoesters. Triazoles proved most resistant to fused pyrimidinone formation. The riboside of **1a** (1-aminoinosine) has been synthesized, indicating the versatility of the method.

Hypoxanthine derivatives, analogues and glycosides are active in a wide spectrum of biological and therapeutic areas [1]. Although numerous natural and synthetic modifications have been investigated, certain simple but novel substituent patterns remain unexplored. Among these, 1-aminohypoxanthine (**1**) is particularly interesting in view of its simple isomeric relationship to guanine. Similarly,
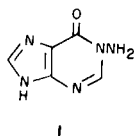

the pyrazolo and triazolo analogues of **1** are closely related to other molecules of biological significance *eg.* allopurinol [2], M and B 22,948 [3], and the 8-azapurines [4]. Apart from brief mention of 1-amino-6-imino-7-methylpurine [5] and, more recently, certain 1-amino-3-deazaguanine derivatives [6], members of the 1-aminohypoxanthine series have not been previously described. It is notable, however, that 1-hydroxyxanthine is carcinogenic [7]. The present article reports the preparation of **1**, its riboside and several analogous compounds.

Anthranilic hydrazide reacts with orthoesters to produce 3-amino-3,4-dihydro-4-quinazolinones **2**, as well as isomeric 2-(2-aminophenyl)-1,3,4-oxadiazoles **3** and 3,4-dihydro-1,3,4-benzotriazepin-5-ones **4**. Recent investigations have delineated the product forming paths and indicated
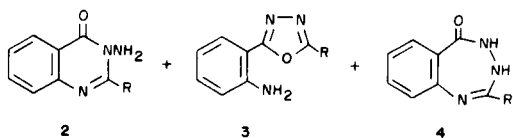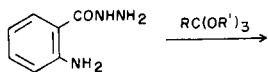
conditions favorable for the formation of each type of product [8-10]. Since **2** is the benzo analogue of **1**, this mode of reaction using o-aminoazole hydrazides appeared to offer a convenient route to 1-aminohypoxanthines. However, mechanistic considerations suggested potential difficulties in applying the reaction to the heterocyclic hydrazides. Formation of **2** depends on the nucleophilicity of the o-amino group [8]. Decreased o-amino nucleophilicity in the azole hydrazides, as compared with anthranilic hydrazide, would thus be expected to favor the competing cyclization to oxadiazole. The benzotriazepinones **4** are formed reversibly and rearrange easily to the more stable isomers **2** and **3** [8]. Additionally, the presence of adjacent nucleophilic nitrogens in the azole nuclei could lead to alternative cyclizations, as have been observed elsewhere [11].

Initial experiments reflected the difficulties discussed above. In marked contrast to anthranilic hydrazide, only low yields of **1a** (<10%) were isolated when equivalent quantities of 5-aminoimidazole-4-carboxylic acid hydrazide and triethyl orthoformate were employed (Scheme 1).

Scheme I

a. R = H
b. R = Me
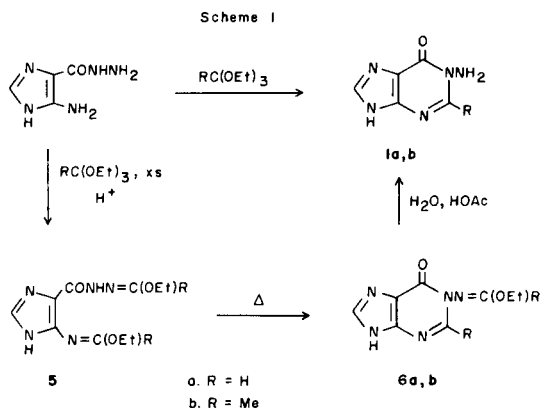
Excess refluxing orthoester and acid catalysis, on the other hand, provided a less direct but more efficient route to **1a**. Under these conditions, condensation of 2 equivalents of orthoester is probable. Intermediate **5** (not isolat-

ed) possesses appropriate functionality (amide adjacent to imidate) for the facile thermal cyclization to **6**, as observed in the related cyclization of anthranilamide to 4-quinazol-inone where the corresponding intermediate was isolated [8]. Mild acid hydrolysis of **6a** gave 1-aminohypoxanthine (**1a**) in overall yield of 85%.

The success of the indirect route is attributable to the formation and subsequent cyclization of **5**. In this manner the more difficult *o*-amino cyclization path, required when equivalent reactants are used, is circumvented, and other possible side reactions are minimized. The 2-methyl derivative **1b** was similarly prepared in overall 76% yield.

Structure **1a** is supported by spectroscopic data and chemical evidence. Carbonyl absorption in the ir (1685 cm^{-1}) excludes the isomeric oxadiazole structure (*cf.* **3**), and the presence of the imidazole H in the nmr (broad exchangeable singlet, *ca.* δ 13) eliminates **7**. In principle, the latter could arise from **5** *via* cyclization involving an imidazole N, followed by hydrolysis. Condensation of **1a** with

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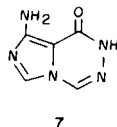
p-nitrobenzaldehyde to give the 5-*p*-nitrobenzalamino derivative is indicative of a primary amino group. This, its color [12], and the dissimilarity of its nmr spectrum with a known imidazo-1,3,4-triazepin-5-one [8] ruled out formation of that isomer (*cf.* **4**).

The applicability of the method to more complex systems was demonstrated by the convenient synthesis of the riboside of **1a**. Hydrazinolysis of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside) gave the required aminohydrazide **8**. Treatment with excess ortho-

8   9
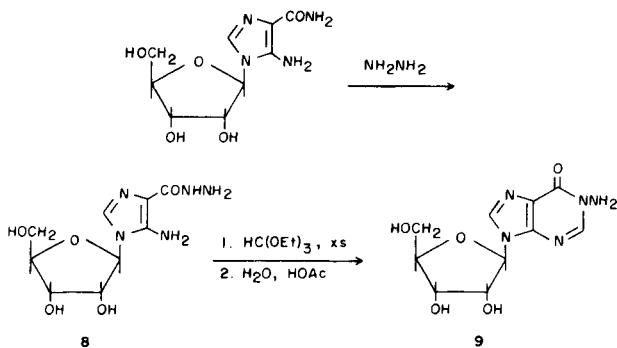
ester followed by hydrolysis of the uncharacterized intermediate (*cf.* **6**, Scheme 1) gave the new riboside, 1-aminoinosine (**9**), in overall 43% yield. Control experiments showed that inosine itself reacts with triethyl orthoformate, presumably to form cyclic orthoesters involving the ribose hydroxyls, but mild hydrolysis (aqueous acetic acid) quantitatively regenerates the inosine. Thus no attempt

was made to isolate the intermediate(s) derived from **8**.

Unlike the 1-aminohypoxanthines **1**, pyrazolo analogues **11a-c** (5-amino-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-ones) were obtained directly from 3-aminopyrazole-4-carboxylic acid hydrazide (**10**), without recourse to excess orthoester and subsequent hydrolysis (Scheme 1). Enhanced nucleophilicity of the 3-amino group of **10** as compared with 5-aminoimidazole-4-carboxylic acid hydrazide may

10   a, R = H   11a-c
                      b, R = Me
                      c, R = Ph
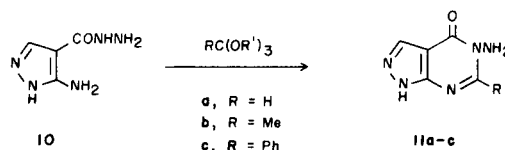
well account for the difference. Although **11a-c** can also be prepared by hydrolysis of the corresponding alkoxymethylene derivatives **12a-c**, the indirect route offers no synthetic advantage in the pyrazolo series. Compounds **11a-c** are of particular interest as 1-amino derivatives of biologically active and therapeutically useful allopurinol [2,13].

12a-c   a, R = H
                  b, R = Me
                  c, R = Ph
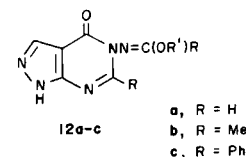
Previous investigation of the reaction of anthranilic hydrazide and various orthoesters (RC(OR')$_3$) showed increased yields of oxadiazole as the bulk of R was increased [8]. The same effect is apparent with **10**. Substantial amounts of 2-(3-amino-4-pyrazolyl)-5-phenyl-1,3,4-oxadiazole (**13**) were formed with trimethyl orthobenzoate (R = Ph). The product distribution, however, is markedly solvent dependent; use of ethanol rather than diglyme solvent allowed isolation of **11c** in satisfactory yield. Consistent with the proposed mechanism [8], cyclization of the terminally acetylated aminohydrazide **14** gave the anticipated 5-acetylamino compound **15**. In agreement with the assigned structure, **15** was also obtained by acetylation of **11a**.

10 + PhC(OMe)$_3$ 11c   13

Product Ratio 11c:13 [a]	
Solvent: EtOH	6.5
Diglyme	0.6

[a] See ref [14].
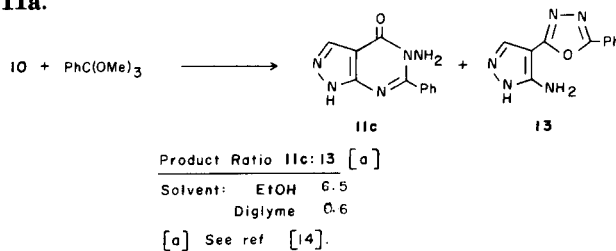
The 5-amino group of 4-acyl-5-amino-1,2,3-triazoles is notably non-nucleophilic [15] and nonbasic [16]. Accordingly, attempts to prepare triazolo analogues of **1** proved difficult. Under various conditions, including excess
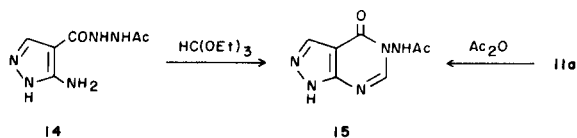
refluxing orthoester and acid catalysis, triazole **16** gave complex mixtures of unidentified materials. Extensive ring decomposition appears probable. Only with trimethyl orthobenzoate in diglyme solvent, conditions favorable for oxadiazole formation, was characterizable product **17** isolated in moderate yield. The absence of carbonyl absorption in the ir, as well as its nmr spectrum, confirmed the oxadiazole structure of **17**.
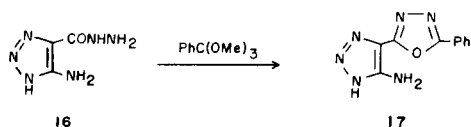
More satisfactory results were obtained with 5-amino-1-benzyl-1,2,3-triazole-4-carboxylic acid hydrazide (**18**, Scheme 2). Mild conditions resulted in the stable initial condensation products **19a-c** [8] which proved resistant to thermal pyrimidinone cyclization.

Cyclized products **20a,b**, however, were obtained by use of excess refluxing orthoester. These, in turn, were hydrolyzed to the 1-aminohypoxanthine analogues **21a,b**. Reaction in diglyme solvent, on the other hand, gave the oxadiazole isomers **22**. As in the pyrazole series, the 5-acetylamino derivative of **21a** was obtained in 70% yield from terminally acetylated **18** (cf. **14**) and triethyl orthoformate.

Attempts to debenzylate **21a** were unsuccesful. Sodium in liquid ammonia [16] led to extensive decomposition, and Pearlman's catalyst (Pd(OH)₂) [17] was ineffective.

The structure of **21a** is supported by its carbonyl absorption in the ir, hydrolysis (10% sulfuric acid) to **18**, and condensation with p-nitrobenzaldehyde. Additionally, the ^{13}C-nmr spectrum of **21a** is essentially identical to that of 1-benzyl-4,5-dihydro-1,2,3-triazolo[4,5-d]pyrimidin-4-one [18].

The results of the investigation indicate the feasibility and limitations of preparing 1-aminohypoxanthines, their pyrazolo analogues, and to a lesser extent the triazolo compounds. Thus, new types of guanine analogues are readily available for biological evaluation.

EXPERIMENTAL

5-Amino-4,5-dihydroimidazo[4,5-d]pyrimidin-4-one (1-Aminohypoxanthine) (**1a**).

A suspension of 5-aminoimidazole-4-carboxylic acid hydrazide [8] (0.621 g, 4.40 mmoles), triethyl orthoformate (7.5 ml) and 1 drop 12M hydrochloric acid was refluxed 26 hours, cooled and diluted with ether (10 ml). Product **6a** (0.847 g, 93%) was collected, washed with ether and dried, mp 202-205°. The nmr of freshly crystallized (ethanol) material was consistent with **6a** but the compound decomposed on standing. A sample of **6a** (0.360 g) was stirred at room temperature with 50% aqueous acetic acid (4 ml) for 19 hours. The initially clear solution deposited **1a** (0.238 g, 91%), mp 308° dec. Two recrystallizations from

Scheme 2
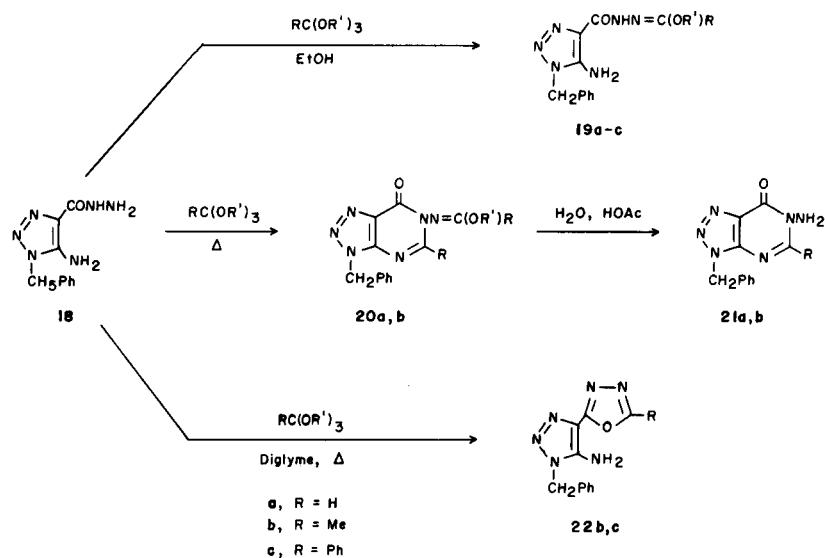
dimethylformamide gave the analytical sample, mp 314°; nmr: δ 12-14 (b, deuterium oxide exchangeable, imidazole H), 8.23, 8.08 (s's, 1H each H$_2$, H$_6$), 5.77 (s, 2H, deuterium oxide exchangeable NH$_2$); ir: 3265, 3160, 3105, 1685 cm^{-1}; uv: λ max = 249 nm (7,800), methanol.

Anal. Calcd. for C$_5$H$_5$N$_5$O: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.75; H, 3.35; N, 46.28.

The *p*-nitrobenzaldehyde derivative (4,5-dihydro-5-(*p*-nitrobenzal)am-inoimidazo[4,5-*d*]pyrimidin-4-one) was prepared (88%) by refluxing **1a** (0.217 g, 1.44 mmoles) and *p*-nitrobenzaldehyde (0.218 g, 1.44 mmoles) in ethanol (20 ml) for 17 hours, pale yellow solid, mp 311-312° dec.

Anal. Calcd. for C$_{12}$H$_8$N$_6$O$_3$: C, 50.71; H, 2.84; N, 29.57. Found: C, 50.64; H, 2.87; N, 29.52.

4,5-Dihydro-5-(1-ethoxyethylidene)amino-6-methylimidazo[4,5-*d*]pyrimid-in-4-one (6b).

Prepared as for **6a** was using triethyl orthoacetate, 90%, mp 233-234° (ethanol); nmr: δ 12.8-13.6 (b, deuterium oxide exchangeable, imidazole H), 8.02 (s, 1H, H$_2$), 4.35 (q, 2H, CH$_3$C*H*$_2$), 2.37 (s, 3H, C$_6$-CH$_3$), 1.78 (s, 3H, CH$_3$C=N), 1.37 (t, 3H, C*H*$_3$CH$_2$).

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.11; H, 5.63; N, 29.73.

5-Amino-4,5-dihydro-6-methylimidazo[4,5-*d*]pyrimidin-4-one (1b).

Prepared from **6b** as for **1a**, 84%, mp 265-266° (ethanol); nmr: δ *ca.* 13 (b, deuterium oxide exchangeable, imidazole H), 8.07 (s, 1H, H$_2$), 5.78 (s, 2H, NH$_2$), 2.58 (s, 3H, CH$_3$); ir: sh 1700, 1685 cm^{-1}.

Anal. Calcd. for C$_6$H$_7$N$_5$O: C, 43.64; H, 4.27; N, 42.40. Found: C, 43.57; H, 4.31; N, 42.35.

5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylic Acid Hydrazide (8).

A solution of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (5.00 g, Sigma) in hydrazine hydrate (50 ml) was refluxed 23 hours then evaporated under reduced pressure to a red gum. After 3 coevaporations with ethanol the residue was refluxed for 0.5 hour with ethanol (40 ml) and the light yellow solid collected: 4.76 g, 90% crude, mp 158-165°; tlc (chloroform-methanol v/v 7:3) showed a slightly contaminated product. Two recrystallizations from methanol gave analytically pure product, mp 188-189°, reported 186-187° [19].

5-Amino-4,5-dihydro-1-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyrimidin-4-one (1-Aminoinosine) (9).

A suspension of **8** (1.011 g, 3.70 mmoles), triethyl orthoformate (22 ml) was refluxed 89 hours (starting material not present by tlc), then evaporated to an amorphous solid. This material was directly hydrolyzed at room temperature by stirring with 50% aqueous acetic acid for 24 hours. Removal of the solvent (50°) gave yellow-brown crystals which were recrystallized from methanol (80 ml): 0.50 g (48%), mp 220-222° dec. Additional recrystallizations (methanol) gave pure product, mp 222-223° dec; nmr: δ 8.90, 8.85 (s's, 1H each, H$_2$, H$_6$), 6.18 (s, 2H, deuterium oxide exchangeable, NH$_2$), 6.20 (d, 1H, H$_{1'}$), 5.83-5.43 (m, 3H, H$_{2',3',4'}$), 4.80-4.35 (m, 3H, deuterium oxide exchangeable, OH), 3.88 (m, 2H, H$_{5'}$); ir: 3350, 3238, 3139, 1660 cm^{-1}.

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_5$: C, 42.41; H, 4.63; N, 24.73. Found: C, 42.28; H, 4.68; N, 24.65.

5-Amino-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one (11a).

A suspension of 3-aminopyrazole-4-carboxylic acid hydrazide [20] (2.82 g, 20.0 mmoles), triethyl orthoformate (3.26 g, 22.0 mmoles) and diglyme (40 ml) was refluxed 92 hours, then evaporated under reduced pressure to give essentially pure **11a** (2.60 g, 86%), mp 293-296°; recrystallization from water, mp 296-297°; nmr: δ *ca.* 13.5 (b, deuterium oxide exchangeable, pyrazole H), 8.20, 8.08 (s's, 1H each H$_3$, H$_6$), 5.47 (s, 2H, deuterium oxide exchangeable NH$_2$); ir: 1698 cm^{-1}; uv: λ max = 250 nm (5,980), methanol.

Anal. Calcd. for C$_5$H$_5$N$_5$O: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.67; H, 3.39; N, 46.34.

5-Amino-4,5-dihydro-6-methylpyrazolo[3,4-*d*]pyrimidin-4-one (11b).

Prepared with triethyl orthoacetate as for **11a**, 58% (water), mp 252-253°; nmr: δ *ca.* 13 (v broad, pyrazole H), 7.88 (s, 1H, H$_3$), 5.35 (s, 2H, deuterium oxide exchangeable, NH$_2$), 2.62 (s, 3H, CH$_3$). Compound **11b** was also obtained by hydrolysis of **12b** (H$_2$O-HOAc) (68%).

Anal. Calcd. for C$_6$H$_7$N$_5$O: C, 43.64; H, 4.27; N, 42.40. Found: C, 43.58; H, 4.30; N, 42.38.

5-Amino-4,5-dihydro-6-phenylpyrazolo[4,5-*d*]pyrimidin-4-one (11c).

A solution of 3-aminopyrazole-4-carboxylic acid hydrazide (2.821 g, 20.0 mmoles), triethyl orthobenzoate (4.00 g, 22.0 mmoles) and ethanol (40 ml) was refluxed 99 hours and the crystallized product was collected, 3.08 g (68% crude), mp 234-240°. Three crystallizations (ethanol) gave 1.80 g (40%), mp 271-272°; nmr: δ *ca.* 13.5 (b, pyrazole H), 8.25 (s, 1H, H$_3$), 7.3-8.0 (m, 5H, Ar), 5.58 (s, 2H, deuterium oxide exchangeable, NH$_2$).

Anal. Calcd. for C$_{11}$H$_9$N$_5$O: C, 58.14; H, 3.99; N, 30.82. Found: C, 58.24; H, 4.04; N, 30.81.

Alkoxymethyleneamino Derivatives 12a-c.

Solutions of 3-aminopyrazole-4-carboxylic acid hydrazide (1.41 g, 10.0 mmoles), orthoester (25 ml) and 1 drop of 12*M* hydrochloric acid were refluxed (20-25 hours), then evaporated and the residue recrystallized. The nmr spectra were in agreement with the assigned structures.

4,5-Dihydro-5-ethoxymethylenaminopyrazolo[4,5-*d*]pyrimidin-4-one (12a).

This compound was obtained in a yield of 79%, mp 202-204° (ethanol), unstable on standing.

4,5-Dihydro-5-(1-ethoxyethylidine)amino-6-methylpyrazolo[3,4-*d*]pyrimid-in-4-one (12b).

This compound was obtained in a yield of 61%, mp 223-224° (ethyl acetate).

Anal. Calcd. for C$_{10}$H$_{13}$N$_5$O$_2$: C, 51.05; H, 5.57; N, 29.77. Found: C, 51.14; H, 5.58; N, 29.72.

4,5-Dihydro-5-(1-methoxybenzylidene)amino-6-phenylpyrazole[4,5-*d*]pyr-imidin-4-one (12c).

This compound was obtained in a yield of 61%, mp 286-287° (ethanol).

Anal. Calcd. for C$_{19}$H$_{15}$N$_5$O$_2$: C, 66.08; H, 4.48; N, 20.28. Found: C, 65.95; H, 4.67; N, 20.29.

A second minor isomer was isolated from the filtrate, mp 212-213° (ethanol). The ir spectra were essentially identical but the nmr differed for the CH$_3$ (δ 3.93 and 3.82, respectively), suggesting *syn/anti* isomers.

Anal. Calcd. for C$_{19}$H$_{15}$N$_5$O$_2$: C, 66.08; H, 4.48; N, 20.28. Found: C, 66.33; H, 4.72; N, 20.24.

2-(3-Amino-4-pyrazolyl)-5-phenyl-1,3,4-oxadiazole (13).

A suspension of 3-aminopyrazole-4-carboxylic acid hydrazide (2.82 g, 20.0 mmoles), triethyl orthobenzoate (4.00 g, 22.0 mmoles) and diglyme (40 ml) was refluxed 92 hours, then evaporated under reduced pressure. The residue recrystallized (ethanol) to give 2.04 g (45%), mp 224-227°. Three additional recrystallizations gave the analytical sample, mp 233-234°; nmr: δ 12.5 (b, pyrazole H), 8.17 (s, 1H, pyrazole H$_3$), 7.6-8.1 (m, 5H, Ar), 5.93 (b, 2H, deuterium oxide exchangeable NH$_2$); ir: 1620 cm^{-1}.

Anal. Calcd. for C$_{11}$H$_9$N$_5$O: C, 58.14; H, 3.99; N, 30.82. Found: C, 57.91; H, 4.04; N, 30.76.

3-Aminopyrazole-4-carboxylic Acid (*N*-2-Acetyl)hydrazide (14).

A suspension of 3-aminopyrazole-4-carboxylic acid hydrazide (2.00 g, 14.1 mmoles) and acetic anhydride (25 ml) was stirred at room temperature for 50 minutes, the product filtered and washed with ether and cold water. Recrystallization from water (25 ml) gave 1.72 g (67%), mp 261-263°.

Anal. Calcd. for C$_6$H$_9$N$_5$O$_2$: C, 39.35; H, 4.95; N, 38.23. Found: C, 39.36; H, 4.97; N, 38.21.

5-Acetylamino-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one (15).

A solution of **14** (1.28 g, 7.00 mmoles), triethyl orthoformate (1.14 g, 7.70 mmoles) and dimethylformamide (30 ml) was refluxed 70 hours, then

evaporated to dryness under reduced pressure. Crystallization of the residue from ethanol (60 ml) gave **15** (0.66 g, 49%), mp 297-298°. The same product (ir, nmr, mp) was obtained (84%) by refluxing **11a** (0.68 g), acetic anhydride (0.51 g) and *p*-dioxane (7 ml) for 4 hours; nmr: δ 11.0-12.8 (b, 2H, deuterium oxide exchangeable, pyrazole and amide NH), 8.27, 8.13 (s's, 1H each H$_2$, H$_6$), 2.10 (s, 2H, CH$_3$).

Anal. Calcd. for C$_7$H$_7$N$_5$O$_2$: C, 43.53; H, 3.65; N, 36.26. Found: C, 43.63; H, 3.70; N, 36.17.

2-(5-Amino-1,2,3-triazol-4-yl)-5-phenyl-1,3,4-oxadiazole (17).

A suspension of **16** (1.42 g, 10.0 mmoles), trimethyl orthobenzoate (2.00 g, 11.0 mmoles) and diglyme (20 ml) was refluxed 75 hours, then evaporated to a tan solid. After stirring with ethyl acetate (20 ml) the crude product (1.00 g, 44%) was collected, mp 230-235°. Two recrystallizations from ethanol-water (2:1) gave **17**, mp 245-246° dec; nmr δ *ca.* 14.5 (b, triazole H), 8.05-7.60 (m, 5H, Ar), 6.15 (s, 2H, deuterium oxide exchangeable, NH$_2$); ir: 1638, 1610 cm^{-1}.

Anal. Calcd. for C$_{10}$H$_8$N$_6$O: C, 52.63; H, 5.53; N, 36.83. Found: C, 52.59; H, 5.56; N, 36.81.

Alkoxymethylenamino Derivatives 20a,b.

Solutions of **18** [21] (2.32 g, 10.0 mmoles) and orthoester (25 ml) were refluxed (**20a**, 22 hours, **20b**, 92 hours). Product **20a** crystallized on cooling; **20b** was obtained by removal of the solvent and recrystallization. The nmr spectra were in agreement with the assigned structures.

1-Benzyl-4,5-dihydro-5-ethoxymethylenamino-1,2,3-triazolo[4,5-*d*]pyrimidin-4-one (20a).

This compound was obtained in a yield of 62%, mp 156-157° (ethanol).

Anal. Calcd. for C$_{14}$H$_{14}$N$_6$O$_2$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.31; H, 4.74; N, 28.16.

2-Benzyl-4,5-dihydro-5-(1-ethoxyethylidene)amino-6-methyl-1,2,3-triazolo[4,5-*d*]pyrimidin-4-one (20b).

This compound was obtained in a yield of 61%, mp 122-123° (ethanol).

Anal. Calcd. for C$_{16}$H$_{18}$N$_6$O$_2$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.91; H, 5.59; N, 25.77.

5-Amino-1-benzyl-4,5-dihydro-1,2,3-triazolo[4,5-*d*]pyrimidin-4-one (20a).

Prepared by hydrolysis of **20a** (84%) as with **1a**. Alternatively, a suspension of **18** (5.84 g, 23.0 mmoles), triethyl orthoformate (3.79 g, 25.6 mmoles), absolute ethanol (40 ml) and 5 drops of 12*M* hydrochloric acid were refluxed 26 hours. After overnight refrigeration the product (3.58 g, 69%) was collected and washed with cold ether, mp 140-145°. Two recrystallizations from ethanol gave pure **21a**, mp 145-147°; nmr (deuteriochloroform): δ 8.50 (s, 1H, H$_6$), 7.45 (m, 5H, Ar), 5.73 (s, 2H, CH$_2$), 5.03 (s, 2H, deuterium oxide exchangeable, NH$_2$); ^{13}C-nmr (DMSO): δ 154.9 (C$_4$), 152.7 (C$_6$), 137.5, 135.2 (C$_{3a}$, C$_{1a}$), 128.7, 128.1, 127.8 (Ar), 49.8 (CH$_2$); ir: 1715 cm^{-1}.

Anal. Calcd. for C$_{11}$H$_{10}$N$_6$O: C, 54.54; H, 4.16; N, 34.69. Found: C, 54.61; H, 4.18; N, 34.63.

Hydrolysis of **21a** (10% sulfuric acid, 1 hour) followed by neutralization with ammonium hydroxide and cooling gave **18** (67%).

The *p*-nitrobenzaldehyde derivative (1-benzyl-4,5-dihydro-5-*p*-nitrobenzalamino-1,2,3-triazolo[4,5-*d*]pyrimidin-4-one) was prepared (72%) by refluxing **21a** (0.25 g, 1.1 mmoles), *p*-nitrobenzaldehyde (0.16 g, 1.1 mmoles), ethanol (16 ml), dimethylsulfoxide (4 ml) and 1 drop of 12*M* hydrochloric acid for 2 hours, mp 260-262° (ethanol).

Anal. Calcd. for C$_{18}$H$_{13}$N$_7$O$_3$: C, 57.60; H, 3.49; N, 26.12. Found: C, 57.47; H, 3.60; N, 26.17.

5-Amino-1-benzyl-4,5-dihydro-6-methyl-1,2,3-triazolo[4,5-*d*]pyrimidin-4-one (21b).

A sample of **20b** (0.20 g, 0.61 mmole) and 50% aqueous acetic acid was heated on the steam bath 2 hours, then evaporated to dryness. The tlc (chloroform-methanol, 9:1) showed the absence of **20b** and 2 products in approximately equal quantities. Recrystallization from ethanol-water (4:1) (5 ml) gave **21b** (0.06 g, 38%), mp 110-112°; nmr (deuteriochloro-

form): δ 7.80 (m, 5H, Ar), 5.98 (s, 2H, CH$_2$), 5.37 (s, 2H, deuterium oxide exchangeable, NH$_2$), 2.93 (s, 3H, CH$_3$). Structure assigned on the basis of the nmr spectrum.

5-Amino-1-benzyl-1,2,3-triazole-4-carboxylic Acid (*N*-2-Acetyl)hydrazide.

A suspension of **18** (1.00 g, 4.31 mmoles) and acetic anhydride (12 ml) was stirred at room temperature for 20 minutes then filtered and the product washed with ether (1.11 g, 94%). Recrystallization from water (280 ml) gave product, mp 279-280° dec.

Anal. Calcd. for C$_{12}$H$_{14}$N$_6$O$_2$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.56; H, 5.18; N, 30.61.

5-Acetylamino-1-benzyl-4,5-dihydro-1,2,3-triazolo[4,5-*d*]pyrimidin-4-one.

A solution of 5-amino-1-benzyl-1,2,3-triazole-4-carboxylic acid (*N*-2-acetyl)hydrazide (1.00 g, 3.65 mmoles), triethyl orthoformate (0.60 g, 4.0 mmoles) and dimethylformamide (15 ml) was refluxed 73 hours. The dark solution was evaporated to dryness under reduced pressure and the residue was crystallized from ethanol (0.73 g, 70%), mp 207-215°. Two recrystallizations gave product, mp 217-218°; nmr: δ 8.55 (s, 1H, H$_6$), 7.27 (m, 6H, Ar and NH), 5.77 (s, 2H, CH$_2$), 2.13 (s, 3H, CH$_3$); ir: 1717, 1682 cm^{-1}.

Anal. Calcd. for C$_{13}$H$_{12}$N$_6$O$_2$: C, 54.93; H, 4.26; N, 29.56. Found: C, 54.93; H, 4.26; N, 29.54.

The same compound (ir, nmr, mp) was obtained by refluxing **21a** (0.40 g, 1.7 mmoles) and acetic anhydride (0.18 g, 1.8 mmoles) in pyridine (2 ml) for 1 hour (93%).

2-(5-Amino-1-benzyl-1,2,3-triazol-4-yl)-5-methyl-1,3,4-oxadiazole (22b).

A suspension of **8** (2.09 g, 8.61 mmoles), triethyl orthobenzoate (1.40 g, 8.61 mmoles) and diglyme (15 ml) was refluxed 66 hours then refrigerated overnight. The collected product (1.45 g, 66%) was recrystallized from ethanol-chloroform (1:1), mp 245-246°; nmr: δ 7.25 (m, 5H, Ar), 6.57 (s, 2H, deuterium oxide exchangeable, NH$_2$), 5.45 (s, 2H, CH$_2$), 2.53 (s, 3H, CH$_3$); ir: 1638, 1620 cm^{-1}.

Anal. Calcd. for C$_{12}$H$_{12}$N$_6$O: C, 56.24; H, 4.72; N, 32.79. Found: C, 56.15; H, 4.81; N, 32.73.

2-(5-Amino-1-benzyl-1,2,3-triazol-4-yl)-5-phenyl-1,3,4-oxadiazole (22c).

Prepared with trimethyl orthobenzoate as for **22b** (34%), mp 225-226° (ethanol); nmr: δ 7.2-8.1 (m, 10H, Ar), 6.73 (s, 2H, deuterium oxide exchangeable, NH$_2$), 5.55 (s, 2H, CH$_2$); ir: 1628, 1600 cm^{-1}.

Anal. Calcd. for C$_{17}$H$_{14}$N$_6$O: C, 64.14; H, 4.43; N, 26.40. Found: C, 64.07; H, 4.47; N, 26.36.

Acknowledgement.

REFERENCES AND NOTES

[1] For leading references see A. D. Lednicer and L. A. Mitscher, "The Organic Chemistry of Drug Synthesis", Vol 2, John Wiley and Sons, New York, 1980, p 463 *et seq.*; [b] F. Seela, W. Bussman, A. Gotze and H. Rosemeyer, *J. Med. Chem.*, **27**, 981 (1984); [c] L. B. Townsend, R. A. Long, J. P. McGraw, D. W. Miles, R. K. Robins, and H. Eyring, *J. Org. Chem.*, **39**, 2023 (1974); [d] J. C. Martin, C. A. Dvorak, D. F. Smee, T. R. Matthews and J. P. H. Verheyden, *J. Med. Chem.*, **26**, 759 (1983).

[2] R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

[3a] K. R. H. Wooldridge in "Drugs Affecting the Respiratory Systems", D. L. Temple, Jr., ed, ACS Symposium Series 118, American Chemical Society, 1980, Ch 6; [b] G. H. Hitchings, G. B. Elison and L. E. Mackay, U. S. Patent 3,019,224 (1962); *Chem. Abstr.*, **58**, 3443a (1963); [c] W. Mohler and A. Sodar, *Arzneim.-Forsch.*, **21**, 1159 (1971); [d] B. G. Ugarkar, H. B. Cotam, P. A. McKernan, R. K. Robins and G. R. Revankar, *J. Med. Chem.*, **27**, 1026 (1984) and

refs therein.

[4] G. W. Kidder, V. C. Dewey, R. E. Parks and G. L. Woodside, *Science*, **109**, 511 (1949).

[5] E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

[6] G. R. Ravankar, P. K. Gupta, A. D. Adams, N. K. Dalley, P. A. McKernan, P. D. Cook, P. G. Canonico and R. K. Robins, *J. Med. Chem.*, **27**, 1389 (1984).

[7] J. C. Parham, J. Fissekis and G. B. Brown, *J. Org. Chem.*, **32**, 1151 (1967).

[8] P. Scheiner, L. Frank, I. Giusti, S. Arwin, S. A. Pearson, F. Excellent and A. P. Harper, *J. Heterocyclic Chem.*, **21**, 1817 (1984).

[9] N. P. Peet and S. Sunder, *J. Heterocyclic Chem.*, **21**, 1807 (1984).

[10] R. W. Leiby, *J. Heterocyclic Chem.*, **21**, 1825 (1984).

[11] C. Ainsworth, *J. Am. Chem. Soc.*, **77**, 1148 (1955).

[12] All reported benzo- and azolo-1,3,4-triazepin-5-ones are yellow compounds; **1a,b** are colorless.

[13a] D. J. Nelson, C. J. L. Bugge, G. B. Elion, R. L. Berens and J. J. Marr, *J. Biol. Chem.*, **254**, 3959 (1979); [b] J. J. Marr and R. L. Berens, *Mol. Biochem. Parasitol.*, **7**, 339 (1983); [c] J. J. Marr, R. L. Berens and D. J. Nelson, *Science*, **201**, 1018 (1978).

[14] Product distributions determined on unpurified product mixtures by the nmr method previously described; see ref [8].

[15] A. Albert and H. Taguchi, *J. Chem. Soc. C*, 2037 (1973).

[16] J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **78**, 5832 (1956).

[17] P. N. Rylander, "Catalytic Hydrogenation over Palladium Metals", Academic Press, New York, 1976, p 464.

[18] A. Albert, *J. Chem. Soc. C*, 152 (1969).

[19] E. Shaw, *J. Am. Chem. Soc.*, **81**, 6021 (1959).

[20] British Patent 937,878, (1963), CIBA Ltd; *Chem. Abstr.*, **60**, 2955g (1965).

[21] C. T. Lovelette and L. Long, Jr., *J. Org. Chem.*, **37**, 4124 (1972).