New Synthesis of 5*H*-Pyrrolo[3,2-*d*]pyrimidines via Pyrimido[5,4-*c*]pyridazines[1]

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A new, practical synthesis of 5*H*-pyrrolo[3,2-*d*]pyrimidines (**5**, **8**, and **15**) from 6-methyl-5-phenylazopyrimidines (**1**, **6**, and **12**, respectively) is described. The method involves conversion of the pyrimidines to the intermediate pyrimido[5,4-*c*]pyridazines (**4**, **7**, and **14**) by treatment with formylating agents such as *tert*-butoxybis(dimethylamino)methane (BBDM). Hydrogenolytic ring contractions to the 5*H*-pyrrolo[3,2-*d*]pyrimidines complete the sequence. Two other methods related to this conversion are also discussed.

The recently demonstrated antitumor activity of some pyrazolo[1,5-*a*]-1,3,5-triazine C-nucleosides[2] which are synthetic isosteres of common naturally occuring purine nucleosides has induced us to undertake the synthesis of the corresponding 5*H*-pyrrolo[3,2-*d*]pyrimidine C-nucleosides which are also isosteres of these natural metabolites. We describe herein some synthetic model studies which were developed specificaily for their applicability to the preparation of potentially active C-nucleoside analogues.

A survey of methods for the preparation of 5*H*-pyrrolo[3,2-*d*]pyrimidines has appeared recently.[3] From these and other reported syntheses[4] we can classify the strategic approaches to this heterobicyclic system into three broad categories: (a) from pyrimidines substituted at C-5 by a nitro group which facilitates the nucleophilic substitution of a C-4 chloro group by a suitable carbon nucleophile,[5,6] or (b) from a 5-acylamino-4-methylpyrimidine by application of the Madelung indole synthesis utilizing strong base at high temperatures,[7] or (c) from a 4-methyl-5-nitropyrimidine by condensation of the methyl group with diethyl oxalate,[8] substituted benzaldehydes,[9] or activated DMF derivatives[4b] followed by reduction of the nitro group and concomitant ring closure.

Of all three general strategies, the last seemed most applicable to the synthesis of C-7 ribosylated 5*H*-pyrrolo[3,2-*d*]-pyrimidines. Of particular relevance to this study was the reported use of DMF–dimethyl acetal or DMF–dimethyl sulfate complex for the conversion of 5-nitro-1,3,6-trimethyluracil to a 6-(2-dimethylaminovinyl) derivative which afforded the 5*H*-pyrrolo[3,2-*d*]pyrimidine by hydrogenation of the nitro group.[4b] Applicability of this procedure to the C-nucleosides however seemed doubtful in view of the unstable nature of the ribofuranosyl entity (which probably would contain an acid labile group) to the generally harsh conditions necessary for the nitration of pyrimidines[10] and also because of the reported ability of DMF–dimethyl acetal to methylate the relatively acidic NH groups of pyrimidines (thus leading to unwanted N-1 and N-3 dimethylated 5*H*-pyrrolo[3,2-*d*]pyrimidines).[11]

The possible utilization of a 5-arylazo group in lieu of a 5-nitro radical was therefore considered since arylazo groups can generally be introduced in pyrimidines under relatively mild conditions either at the diacyl stage of their primary synthesis or at the pyrimidine stage itself.[10,12] Furthermore, the electron-withdrawing effect of this group could be readily modulated by suitable choice of its phenyl substituents. Utilization of *tert*-butoxybis(dimethylamino)methane (BBDM)[13] which has been reported to formylate activated methylene groups[14] was also considered as a possible substitute for DMF–dimethyl acetal.

Treatment of 6-methyl-4-oxo-5-phenylazo-2-thioxo-1*H*,3*H*-pyrimidine (**1**) with BBDM in hot, dry DMF overnight afforded unexpectedly 6-dimethylamino-8-oxo-2-phenylpyrimido[5,4-*c*]pyridazine (**4**) as a major product (52% yield) together with a small amount of 2-dimethylamino-6-methyl-4-oxo-3*H*-pyrimidine[12] (**2**, <10%). By careful TLC monitoring of the reaction it was found that **2** was readily formed as a primary product which was slowly converted to the final product **4** (as shown in Scheme I) presumably via the short-lived intermediate **3**. Further evidence for this proposed sequence was obtained from the conversion of **2** to **4** in 76% yield by treatment with BBDM under the conditions described above. This cyclization of **2** to **4** is reminiscent of the recently reported conversion of 3-amino-4-phenylazophenol to a 6-oxo-2-phenyl-1,2,4-benzotriazine by treatment with ethyl orthoformate[15] which, like BBDM, is also a formylating agent. The identities of **2** and **4** were established by ^{1}H NMR data and by elemental analyses. The unexpected formation of **2** could be best explained by initial alkylation of the thioxo group with BBDM followed by displacement of the S-alkyl radical by dimethylamine (possibly produced during the alkylation step or from partial degradation of BBDM in hot DMF[13]).

Hydrogenation of the pyrimidopyridazine **4** over Pd/C in glacial acetic acid afforded 2-dimethylamino-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**5**) in 78% yield. Reduction of **4** with Raney nickel in ethanol gave the same product in lower yields. Identity of **5** was confirmed on the basis of ^{1}H NMR data, elemental analysis, and the close resemblance of its ultraviolet data with that of the known 2-amino derivative **15**.[16] This reductive ring contraction necessarily involves three steps: (a) hydrogenolytic cleavage of the N_1–N_2 bond, (b) an additional hydrogenating step, and (c) ring closure to **5** with simultaneous liberation of aniline. The exact order of these events (each of which could involve a large number of postulable intermediates) is uncertain.

Similarly, treatment of 6-methyl-5-phenylazouracil **6** with BBDM in DMF afforded the now-expected pyrimido[5,4-*c*]pyridazine **7** which was converted by hydrogenolysis to the known 2,4-dioxo-1*H*,3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**8**).[16,17] Application of this procedure to 6-methyl-5-phenylazoisocytosine (**12**) afforded pyrimido[5,4-*c*]pyridazine **13** as an N^6-dimethylaminomethylene derivative, which was readily unblocked by treatment with ammonium hydroxide[11] to afford **14**. Hydrogenolysis of **14** over Pd/C in acetic acid afforded the desired 2-amino-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**15**).[16]

Various modifications of this general procedure have been investigated to further extend the flexibility of this approach to the synthesis of 5*H*-pyrrolo-[3,2-*d*]pyrimidines. Because the use of BBDM for cyclization to the pyridazines involves strongly basic conditions it was of interest to explore the use of other formylating reagents under different conditions. Thus, treatment of **12** with triethyl orthoformate at room

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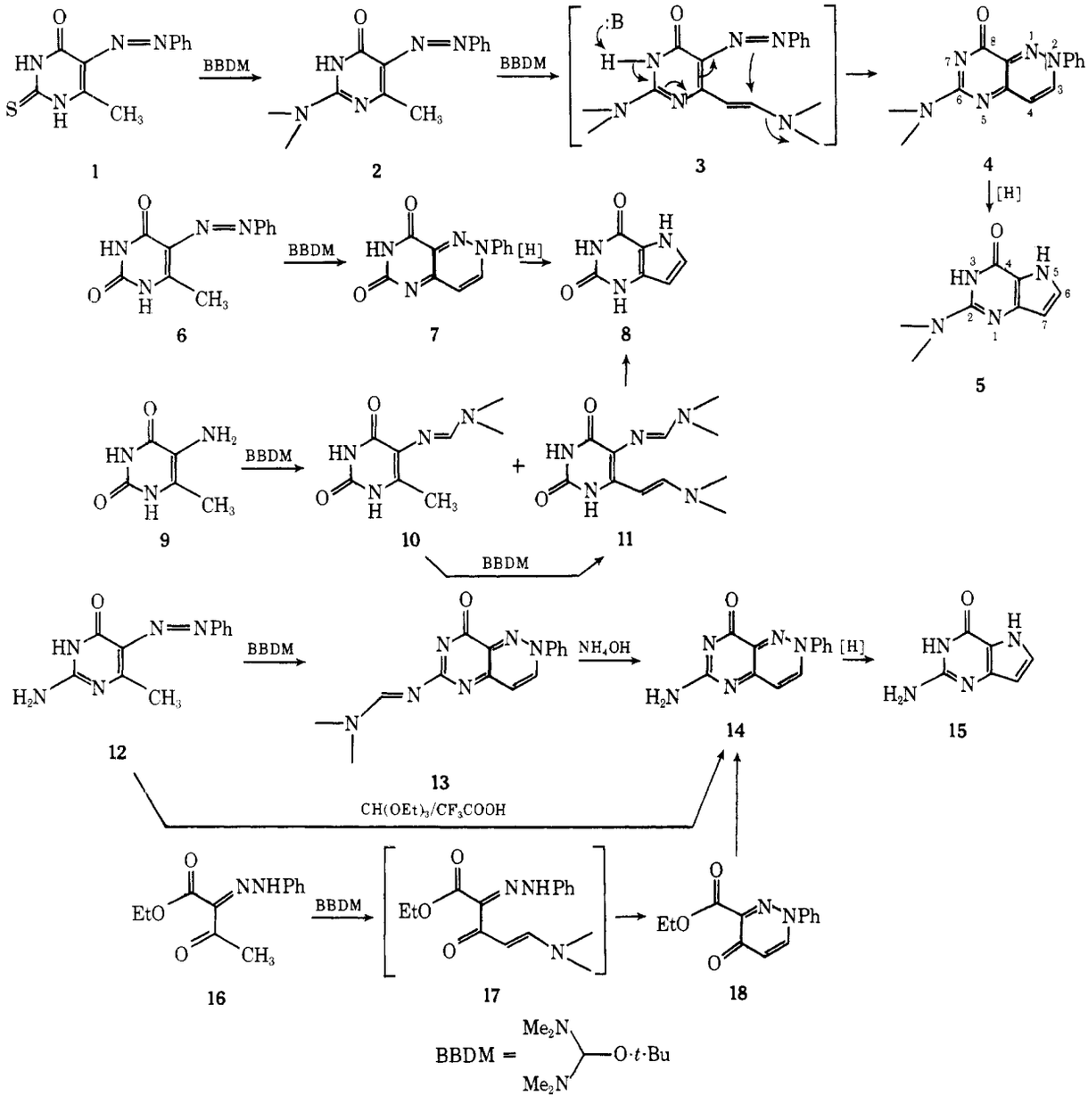
Scheme I



temperature in the presence of trifluoroacetic acid afforded directly pyrimido[5,4-*c*]pyridazine **14**, which was isolated as its trifluoroacetate salt in 87% yield.

While all methods described so far involve the initial elaboration of a pyrimidine ring followed by cyclization of the pyridazine ring to give the pyrimido[5,4-*c*]pyridazine system, it is possible to invert this sequence. Thus, pyrimido[5,4-*c*]-pyridazine **14** was also obtained from 2-phenylazoacetoacetate **16** (a possible synthetic precursor of all phenylazopyrimidines **1**, **6**, and **12**[10]) by reaction with BBDM to afford oxopyridazine **18** (presumably via intermediate **17**) in 87% yield. Subsequent treatment of **18** with guanidine carbonate in refluxing ethanol afforded **14** in 85% yield. Several attempts to obtain satisfactory yields of a 6-thioxo- or 6-methylthiopyrimidopyridazine by cyclization of **18** with thiourea or *S*-methylisothiourea have been so far unsuccessful.

Another possible alternate route to the 5*H*-pyrrolo[3,2-*d*]pyrimidine system was explored by reaction of 5-amino-6-methyluracil (**9**) (which is readily available from reduction of **6**) with an excess of BBDM in DMF. Initial conversion of **9** to the 5-*N*-dimethylaminomethylene derivative **10** occurred at room temperature.[11] Higher temperatures and longer reaction times however were necessary to convert **10** to the desired dimethylaminovinyl derivative **11**. Even under such forcing conditions the reaction yielded only equal amounts of **10** and **11**. After separation, product **11** could be readily converted to **8** in 88% yield by treatment with ammonium hydroxide at room temperature. The intermediate formed in conversion **11** → **8** presumably would be the corresponding 5-amino-6-(2-dimethylaminovinyl) derivative which would spontaneously ring close to **11** by attack of the free 5-NH_2 group on the vinylic function with liberation of dimethylamine.

One interesting physical property common to all pyrimido[5,4-*c*]pyridazines (**4**, **7**, **13**, and **14**) described in this investigation is the characteristic fluorescence they emit when spotted on silica gel plates illuminated by near ultraviolet light. This property facilitated considerably the visual detection and identification of these intermediates. Another common feature to these pyrimidopyridazines is the appearance of a pair of doublets ($\delta_{H\text{-}3}$ ~9.2, $\delta_{H\text{-}4}$ ~7.4, and $J_{3,4}$ = 7.1–7.6 Hz) in their ^1H NMR spectra. The ^1H NMR of the corresponding pyrrolopyrimidines **5**, **8**, and **15** on the other hand exhibit two apparent triplets caused by additional

coupling with the pyrrolo-NH group (δ_{H-6} ~7.2, δ_{H-7} ~6.0 and $J_{6,7} \sim J_{6,NH} \sim J_{7,NH} \sim 2.7$ Hz).

It is apparent from these model studies that the utilization of 6-alkyl-5-arylazopyrimidines (or of their synthetic precursors) in conjunction with various formylating agents can serve as a simple and versatile synthetic route to 5*H*-pyrrolo[3,2-*d*]pyrimidine systems.

Further investigations of the scope of the transformations described above and of their direct application to the synthesis of 7-ribosylpyrrolo[3,2-*d*]pyrimidine C-nucleosides are now underway in our laboratory and will be the subject of a separate report.

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were obtained with a Jeol PS-100 spectrometer with Me_4Si as internal standard; ultraviolet and visible absorption data were determined with a Varian Super-Scan 3 ultraviolet–visible spectrophotometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (TLC) was performed on microscope slides coated with Merck silica gel GF-254 and the components were visualized either by UV and visible absorption or in an iodine vapor tank. Column chromatography was performed on Woelm silica gel (70–230 mesh).

6-*N*-Dimethylamino-8-oxo-2-phenylpyrimido[5,4-*c*]pyridazine (4) and 2-*N*-dimethylamino-6-methyl-4-oxo-3*H*-5-phenylazopyrimidine (2). To a solution of **1**[12] (1.23 g, 10 mmol) in DMF (10 mL, dried over molecular sieve 4 Å) was added BBDM (5 mL). The reaction mixture was stirred for 16 h at 60–65 °C and then cooled in an ice bath. The resulting precipitate was collected by filtration and washed with DMF to afford crude product **4** (0.8 g, 52%) as a chromatographically homogeneous yellow solid. One recrystallization from DMF afforded the analytical sample: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.18 (s, 3 H, NCH_3), 3.28 (s, 3 H, NCH_3), 7.44 (d, 1 H, H-4, $J_{3,4}$ = 7.6 Hz), 7.48–7.92 (m, 5 H, C_6H_5), 9.16 (d, 1 H, H-3); UV (pH 1) λ_{max} 202 (ϵ 20 810), 272 (9 460), 344 (sh) (17 840), 379 nm (21 890), λ_{min} 244 (ϵ 5 140), 298 nm (6 490); (pH 7) λ_{max} 204 (ϵ 24 600), 309 (12 970), 390 nm (19 730), λ_{min} 246 (ϵ 4 860), 337 nm (9 460); (pH 13) λ_{max} 219 (ϵ 17 300), 309 (12 430), 390 nm (19 180), λ_{min} 246 (ϵ 4 860), 337 nm (ϵ 9 730). Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.81; H, 4.81; N, 26.03.

To the filtrate and DMF washing was added some crushed ice. Product **2** (25 mg) precipitated as orange needles which were recrystallized from DMF–H_2O to afford the analytical sample: mp 168 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.56 (s, 3 H, CH_3), 3.18 (s, 3 H, NCH_3), 3.29 (s, 3 H, NCH_3), 7.26–7.74 (m, 5 H, C_6H_5), 11.48 (broad s, 1 H, NH exchange with D_2O). Anal. Calcd for $C_{13}H_{15}N_5O$: C, 60.69; H, 5.88; N, 27.22. Found: C, 60.75; H, 5.71; N, 27.26.

Compound **2** was converted to **4** in 76% yield according to the procedure described above for the preparation of **4** from **1**.

2-*N*-Dimethylamino-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (5). A solution of **4** (534 mg, 2 mmol) in 10 mL of glacial acetic acid was hydrogenated in the presence of 10% Pd/C at room temperature and atmospheric pressure for 5 h and then filtered through Celite. The filtrate was evaporated in vacuo, methanol (2 mL) was added to the residue, and the insoluble material was collected and washed with a small amount of ethyl ether to afford **5** (274 mg, 78%) as a white, chromatographically homogenous solid. Recrystallization from hot methanol afforded an analytical sample of **5** as colorless prisms: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.98 (s, 6 H, $N(CH_3)_2$), 6.03 (t, 1 H, H-7, $J_{7,6}$ = 2.8, $J_{7,NH} \sim 2.7$ Hz), 7.16 (t, 1 H, H-6, $J_{6,NH} \sim 2.7$ Hz), 10.58 (broad s, 1 H, NH exchange with D_2O), 11.45 (broad s, 1 H, NH exchange with D_2O); UV (pH 1) λ_{max} 238 (ϵ 23 390), 272 nm (13 930), λ_{min} 256 nm (ϵ 11 430); (pH 7) λ_{max} 230 (ϵ 28 040), 263 (8 750) 282 nm (9 290), λ_{min} 254 nm (ϵ 8 570); (pH 13) λ_{max} 232 (ϵ 27 320) 295 nm (5 180), λ_{min} 275 nm (4 110). Anal. Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.84; H, 5.60; N, 31.43.

6,8-Dioxo-7*H*-2-phenylpyrimido[5,4-*c*]pyridazine (7). A mixture of **6**[12] (1.7 g 7.4 mmol) and BBDM (7 mL) in dry DMF (20 mL) was heated at 60–65 °C for 16 h and evaporated in vacuo. The residue was triturated with ethanol and the suspension was chilled in an ice bath. The yellow precipitate was collected and washed with ethyl ether to give **7** (1.38 g, 78%). An analytical sample was obtained after recrystallization from DMF: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.38 (d, 1 H, H-4, $J_{3,4}$ = 7.3 Hz), 7.59–7.90 (m, 5 H, C_6H_5), 9.12 (d, 1 H, H-3), 11.32 (s, 1 H, NH exchange with D_2O); UV (pH 1) λ_{max} 203 (ϵ 19 510), 306 (shoulder) (9 150), 330 nm (10 490), λ_{min} 286 nm (ϵ 5 370); (pH 7) λ_{max} 205 (ϵ 20 240), 263 (8 290), 324 (12 680), 363 nm (14 880), λ_{min} 240 (ϵ 6 340), 286 (6 590), 336 nm (12 200); (pH 13) λ_{max} 218 (ϵ 10 000), 291 (17 810), 366 nm (12 440), λ_{min} 249 (ϵ 4 150), 320 nm (8 780). Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 59.82; H, 3.46; N, 23.39.

2,4-Dioxo-1*H*,3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (8). A solution of **7** (394 mg, 1.6 mmol) in glacial acetic acid (10 mL) was hydrogenated over 10% Pd/C at room temperature at atmospheric pressure for 5 h. After filtration through Celite, the clear solution was evaporated in vacuo and the residue was triturated with a small amount of ethanol. Product **8** (163 mg, 62%) collected by filtration was obtained as a white solid. Recrystallization from methanol afforded an analytically pure sample as colorless needles: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.83 (t, 1 H, H-7, $J_{7,6}$ = 2.8 $J_{7,NH} \sim 2.4$ Hz), 7.13 (t, 1 H, H-6, $J_{6,NH} \sim 2.8$ Hz), 10.55, 10.73, and 11.81 (3 s, 1 H each, NH all exchange with D_2O). Anal. Calcd for $C_6H_5N_3O_2$: C, 47.69; H, 3.33; N, 27.80. Found: C, 47.54; H, 3.37; N, 27.77.

5-(*N*-dimethylaminomethylene)amino-6-methyluracil (10) and 5-(*N*-dimethylaminomethylene)amino-6-(2-dimethylaminovinyl)uracil (11). To a suspension of **9** (1.51 g, 10 mmol) in dry DMF (20 mL) was added BBDM (5 mL). The reaction mixture was heated, with stirring, at 60 °C for 16 h, cooled, and evaporated to dryness in vacuo. The residue was triturated with ethanol to give after filtration crude product **11** as a yellow solid. Recrystallization from ethanol afforded an analytical sample of **11** (550 mg, 21.8%) as yellow needles: mp 242 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.84 (m, 12 H, 2-$N(CH_3)_2$), 5.19 (d, 1 H, $(CH_3)_2NCH_\alpha$=CH_β, J_{CH_α,CH_β} = 13.7 Hz), 7.59 (d, 1 H, CH_α), 8.30 (s, 1 H, $(CH_3)_2NCH$=N), 9.86 and 10.42 (2 broad s, 1 H each, NH exchange with D_2O). Anal. Calcd for $C_{11}H_{17}N_5O_2$: C, 52.58; H, 6.82; N, 27.87. Found: C, 52 62; H, 6.71; N, 27.82.

The filtrate was evaporated to dryness and methanol was added to the residue. Collection of the white precipitated solid and recrystallization from methanol afforded **10** (653 mg, 33%) as prisms: mp 285 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.03 (s, 3 H, CCH_3), 2.85 (s, 6 H, $N(CH_3)_2$), 8.19 (s, 1 H, $(CH_3)_2NCH$=N), 10.48 and 10.85 (2 broad s, 1 H each, NH exchange with D_2O). Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.16; N, 28.55. Found: C, 49.11; H, 5.84; N, 28.66.

Preparation of 8 from 11. To a solution of **11** (100 mg, 0.4 mmol) in methanol (1 mL) was added 57% NH_4OH (5 mL). The reaction mixture was warmed until it cleared and left at room temperature for 2 h. Evaporation to dryness afforded a residue which was suspended in 10 mL of methanol and briefly heated to reflux. Cooling and filtration of the solid gave **8** (28 mg) identical in all respects with authentic material. A second crop of 25 mg (88% total yield) could be obtained from the mother liquor.

6-(*N*-Dimethylaminomethylene)amino-8-oxo-2-phenylpyrimido[5,4-*c*]pyridazine (13) and 6-Amino-8-oxo-2-phenylpyrimido[5,4-*c*]pyridazine (14). To a solution of **12**[12] (4.58 g, 20 mmol) in dry DMF (50 mL) was added BBDM (15 mL) and the mixture was heated for 16 h at 60–65 °C. It was then chilled in an ice bath. The formed precipitate was collected and washed with DMF to afford **13** (4.6 g, 78.4%) as a yellowish-brown solid chromatographically homogeneous: ^{1}H NMR (Me_2SO-d_6) δ 3.10 (s, 3 H, NCH_3), 3.21 (s, 3 H, NCH_3), 7.61–7.95 (m, 6 H, C_6H_5 and H-4), 8.88 (s, 1 H, $(CH_3)_2$-NCH=N), 9.25 (d, 1 H, H-3, $J_{3,4} \simeq 7.1$ Hz).

Without further purification, **13** (1 g) was dissolved in 50 mL of 57% NH_4OH and the solution was left at room temperature for 3 h. The yellow precipitate which had formed was filtered and washed with cold water to give **14** (0.70 g, 86%): ^{1}H NMR (Me_2SO-d_6) δ 7.34–8.00 (m, 8 H, C_6H_5, H-4 and NH_2), 9.12 (d, 1 H, H-3, $J_{3,4}$ = 7.4 Hz). Further characterization was possible by converting crude **14** to its analytically pure hydrochloride salt: mp 245 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 7.67–8.00 (m, 6 H, C_6H_5 and H-4), 8.34, 9.28, and 12.65 (3 broad s, 1 H each, NH exchange with D_2O), 9.60 (d, 1 H, H-3, $J_{3,4}$ = 7.3 Hz). Anal Calcd for $C_{12}H_9N_5O$·HCl·H_2O: C, 49.02; H, 4.08; N, 23.83; Cl, 12.08. Found: C, 49.10; H, 4.05; N, 23.83; Cl, 12.05.

2-Amino-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (15). A solution of **14** (1 g, 6.6 mmol) in glacial acetic acid (20 mL) was hydrogenated over 10% Pd/C at room temperature and atmospheric pressure for 5 h. After filtration through Celite, the solution was evaporated to dryness in vacuo. The residue was triturated with ethyl ether to afford the crude product **15** as a white solid. This was further purified by dissolving in 2 N HCl, filtering the insoluble impurities, and carefully neutralizing the clear solution with 1 N NaOH to precipitate **15** (412 mg, 68%) which was collected by filtration: ^{1}H NMR (Me_2SO-d_6) δ 6.05 (t, 1 H, H-7, $J_{7,6}$ = 2.7 Hz, $J_{7,NH} \sim 2.3$ Hz), 6.92 and 11.91 (2 broad s, 3 H, NH_2 and NH, exchange with D_2O), 7.24 (t, 1 H, H-6, $J_{6,7}$ = 2.7 Hz, $J_{6,NH} \sim 2.9$ Hz). An analytical sample was obtained by conversion to its hydrochloride salt. Anal. Calcd for $C_6H_6N_4O$·HCl: C, 38.58; H, 3.75; N, 30.01; Cl, 19.02. Found: C, 38.51; H, 3.83; N, 29.96;

Cl, 19.00.

2-Ethoxycarbonyl-4-oxo-1-phenylpyridazine (18). To a solution of ethyl 2-phenylazoacetoacetate (4.69 g, 20 mmol) in DMF (15 mL) was added BBDM (10 mL) and the mixture was heated at 70 °C overnight. The mixture was then evaporated in vacuo and the residue was chromatographed on 85 g of silica gel with petroleum ether (30–60 °C)–ethyl acetate (1:2) to give, from evaporation of the proper fractions, pyridazinone **18** as a colorless oil (4.24 g, 87%) which spontaneously crystallized on standing. Recrystallization from ethanol afforded an analytically pure sample: mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, CH_3), 4.43 (q, 2 H, CH_2), 6.74 (d, 1 H, H-5, $J_{5,6}$ = 7.9 Hz), 7.45–7.56 (m, 5 H, C_6H_5), 8.33 (d, 1 H, H-6). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.88; H, 5.01; N, 11.39.

Preparation of 14 from 18. A mixture of **18** (3 g, 12.3 mmol), guanidine carbonate (3.3 g, 18.3 mmol), and ethanol (40 mL) was heated to reflux with stirring for 4 h and then cooled in a ice bath. The precipitate was collected and washed thoroughly with cold water to afford **14** (2.5 g, 85%) identical in all respects with an authentic sample prepared from **12** (vide supra).

Preparation of 14 from 12 with Triethyl Orthoformate. A mixture of **12** (229 mg, 1 mmol), triethyl orthoformate (5 mL), and trifluoroacetic acid (2 mL) was stirred overnight at room temperature. To the yellow suspension was added 15 mL of ethyl ether. After stirring for 20 min, the solid was collected by filtration to afford **14** (309 mg, 87.4%) as its analytically pure trifluoroacetate salt: mp >300 °C; UV (pH 1) λ_{max} 203 (ϵ 23 210), 260 (10 000), 328 (shoulder) (16 430), 362 nm (22 500), λ_{min} 241 (ϵ 8 210), 288 nm (7 500); (pH 7) λ_{max} 203 (ϵ 21 100), 292 (18 210), 376 nm (15 000), λ_{min} 247 (ϵ 3 930) 325 nm (6 790); (pH 13) 218 (ϵ 15 000), 292 (22 500), 376 nm (18 210), λ_{min} 247 (ϵ 5 000), 325 nm (8 930). Anal. Calcd for $C_{12}H_9N_5O$:CF_3COOH: C, 47.57; H, 2.83; N, 19.82; F, 16.14. Found: C, 47.60; H, 2.92; N, 19.90; F, 16.17.

Registry No.—**1**, 14985-77-4; **2**, 23947-86-6; **4**, 65996-47-6; **5**, 65996-48-7; **6**, 15020-66-3; **7**, 65996-49-8; **8**, 65996-50-1; **9**, 6270-46-8; **10**, 65996-51-2; **11**, 65996-52-3; **12**, 65996-53-4; **13**, 65996-54-5; **14**, 65996-55-6; **14** HCl, 65996-56-7; **14** CF_3COOH salt, 65996-57-8; **15**, 65996-58-9; **15** HCl, 65996-59-0; **16**, 5462-33-9; **18**, 65996-60-3; BBDM, 5815-08-7.

References and Notes

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Notes

Synthesis of γ-Amino Alcohols

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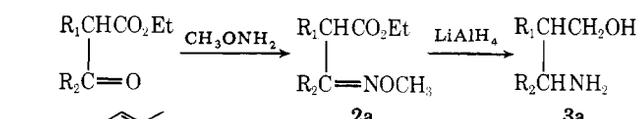
Substituted γ-amino alcohols have been of considerable interest for some time in that they frequently possess interesting pharmacological properties.[1] Their synthesis has been accomplished by a variety of procedures: addition of ammonia or amines to acrylic esters or α,β-unsaturated ketones, followed by reduction;[1b,2] reduction of α-cyano esters;[3] the reduction of isoxazoles or isoxazolines;[4] reduction of Mannich products;[5] and reaction of bromo alcohols with sodium azide followed by reduction.[6] All of these methods suffer from certain restrictions. Addition of amines to acrylates frequently leads to the formation of amides as side products. The reduction of cyano esters precludes preparation of compounds bearing a substituent α to the nitrogen. The synthesis of isoxazoles or isoxazolines is often a difficult undertaking. The Mannich reaction is restricted to the preparation of tertiary amines. Lastly the use of the azide procedure assumes the availability of the precursor bromo alcohol.

In this note we describe a new method for the synthesis of γ-amino alcohols, utilizing 1,3-dicarbonyl compounds as starting materials, which circumvents many of the problems that detract from established procedures.

The ease of preparation of α-formyl and β-keto esters makes them attractive intermediates for the synthesis of γ-amino alcohols. Unfortunately, nitrogen functionality cannot be introduced via oxime formation since the intermediate oximino ester cyclizes spontaneously to an isoxazolone which cannot be reductively cleaved.[7] Use of an alkoxime, however, avoids cyclization since a blocked oximino ester is formed which can then be reduced to give the desired amino alcohol (Scheme I).

The methoxylimine **2a** of ethyl 2-formyl-2-(3-pyridyl)-acetate (**1a**) was reduced with $LiAlH_4$ to the γ-amino alcohol

Scheme I



1a, R_1 =  ; R_2 = H	**2a**	**3a**
b, R_1 = $C_6H_5CH_2$; R_2 = H	**b**	**b**
c, R_1 = C_6H_5; R_2 = H	**c**	**c**
d, R_1 = H; R_2 = C_6H_5	**d**	**d**
e, R_1 = H; R_2 = 	**e**	**e**

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