Synthesis of the New Ring System, Pyrazolo[3,4-*d*][1,3]diazepine. A Novel Route for the Synthesis of Azolo[1,3]diazepines [1]

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A reduction of the nitrile group of 5-amino-4-cyano-1-methylpyrazole (**3**) has provided the very versatile compound 5-amino-1-methylpyrazole-4-carboxaldehyde (**4**). The amino group of **4** was protected using dimethylformamide dimethylacetal and the aldehyde group was then reacted with trimethylsilyl cyanide to afford the moisture sensitive compound 5-[[(dimethylamino)methylene]amino]-4-[cyano(trimethylsiloxy)-methyl]-1-methylpyrazole (**10**). The cyano group of the cyanohydrin **10** was reduced using a cobalt boride catalyst to afford an intermediate aminomethyl group which was involved in an *in situ* annulation. This reaction provided 1-methyl-1,4,5,6-tetrahydropyrazolo[3,4-*d*][1,3]diazepin-4-ol, a derivative of the new ring system, pyrazolo[3,4-*d*][1,3]diazepine.

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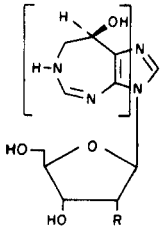
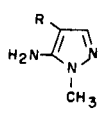
A recent synthesis [2] of the potent adenosine deaminase inhibitor, 8(*R*)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (**1**, pentostatin), has prompted us to report on our efforts in this area which have yielded a new and novel method for the formation of a 4,5-dihydro-3*H*-1,3-diazepin-5-ol ring (Figure 1, in brackets). The nucleosides pentostatin [3a] (**1**), coformycin (**2**) [3b,c], and the methylated aglycone reported herein (**7**) share in common the 4,5-dihydro-2*H*-1,3-diazepin-5-ol moiety fused to a 5-membered heterocyclic

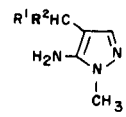


1 R = H
2 R = OH

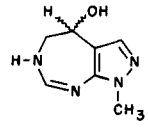
ring. Both coformycin and pentostatin are exceedingly tight-binding inhibitors [4] of human erythrocytic adenosine deaminase, exhibiting a $K_i = 1 \times 10^{-11} M$ and $K_i = 2.5 \times 10^{-12} M$, respectively. In combination with 9-β-D-arabinofuranosyladenine, pentostatin has shown dramatic antitumor effects both *in vitro* [5] and *in vivo* [6]. However, the acute renal toxicity of pentostatin in clinical trials [7] has initiated a search for other [8] strong inhibitors of the enzyme which might lack these unfortunate side effects.



3 R = CN
4 R = CHO



5 R^1 = OH, R^2 = CN
6 R^1 = OH, R^2 = CH_2NH_2



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The primary aim of this study has been to develop a synthetic route for the preparation of certain azolo[1,3]diazepines which are structurally related to coformycin. The route we envisaged for this synthesis was to form the diazepine moiety onto an appropriately substituted azole (*e.g.* compound **3**). A catalytic reduction [8,9] of the cyano group of 5-amino-4-cyano-1-methylpyrazole (**3**) yielded the versatile 5-amino-1-methylpyrazole-4-carboxaldehyde (**4**). We had hoped that an addition [9] of cyanide ion at the aldehyde group of compound **4** would provide us with the cyanohydrin **5**. This cyanohydrin might in turn be catalytically reduced to afford the racemic 5-amino-4-(2-amino-1-hydroxyethyl)-1-methylpyrazole (**6**). Treatment of the diamine **6** with triethyl orthoformate would have provided us with our target compound **7**.

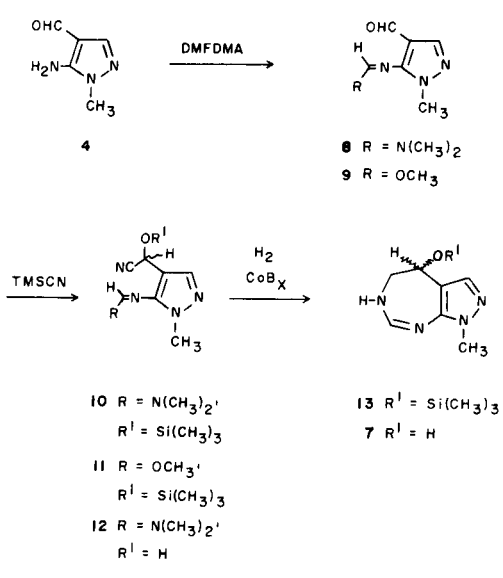
However, our attempts to react a hydrogen cyanide-potassium cyanide mixture (0°, dichloromethane, 4 hours) with **4** yielded only intractable tars from which only dimeric [11] products could be isolated. This led us to explore the possibility of finding an amine blocking group which could serve a dual role, *i.e.*, a group which could function as a protecting group until the annulation reaction, at which time it could provide a ring carbon of the diazepine moiety.

Protection of the amine functionality of compound **4** using dimethylformamide dimethylacetal gave the crystalline compound 5-[[(dimethylamino)methylene]amino]-1-methylpyrazole-4-carboxaldehyde (**8**) [12]. We found that this protecting group was stable to all reaction conditions we used except those employing strong base. The treatment of compound **8** with trimethylsilyl cyanide in the pre-

sence of dry, powdered zinc chloride, under an atmosphere of nitrogen, provided an excellent yield of 5-[[(dimethylamino)methylene]amino]-4-(cyano[trimethylsiloxy]-methyl)-1-methylpyrazole (**10**). The trimethylsilyl cyanohydrin **10** is remarkably stable and can be purified by trituration with anhydrous hexane or by silica gel chromatography. The corresponding [(methoxy)methylene]amino protected aldehyde compound **9**, and the similarly protected trimethylsilyl cyanohydrin, compound **11**, were each found [12] to constitute approximately 4-5% of the reaction mixtures and were not routinely isolated, since the mixture (**9** and **11**) could ultimately be converted to the desired product.

Extensive experimentation with different methods of chemical and catalytic reduction of the nitrile group of compound **10** revealed that a catalytic hydrogenation of this group was the superior method. We found that lithium aluminum hydride, [13] a sodium borohydride-trifluoracetic acid complex, [14] or the lithium aluminum hydride-trialkoxide [13] reagents gave in each case no discernible 1,3-diazepine products. In fact, only large amounts of dimeric materials [11] and starting material were isolated. Finally, we found that cobalt boride or nickel boride catalysts [15] under 30-35 atmospheres of hydrogen effected a reduction of the cyano group to the desired aminomethyl group which then participated in a facile *in situ* annulation, with a concomitant loss of dimethylamine. The reduction gave as products the 1-methyl-4-trimethylsiloxy-1,4,5,6-tetrahydropyrazolo[3,4-*d*][1,3]-diazepine (**13**) and 1-methyl-1,4,5,6-tetrahydropyrazolo-[3,4-*d*][1,3]diazepin-4-ol (**7**), as a 3:1 mixture (*vide infra:* tlc analysis and inspection of the ^{1}H-nmr spectrum of the crude mixture). The trimethylsilyl ether **13** was readily converted to compound **7** by a mild acidic hydrolysis of the trimethylsilyl group.

Scheme I



That the 4,5-dihydro-3*H*-1,3-diazepin-5-ol moiety had indeed been formed during this reaction was confirmed by the ^{1}H-nmr spectrum of compound **7** (as an enantiomeric mixture). This spectrum revealed a coupling between the vinylogous H-7 proton and the adjacent N-6 proton as well as resonances for the diastereotopic methylene protons (H-5 and H-5a) and the absence of a resonance peak for the dimethylamine protons (refer to Table 1).

Table 1

^{1}H-NMR (360 MHz) [a] Chemical Shifts for 1-Methyl-1,4,5,6-tetrahydropyrazolo[3,4-*d*][1,3]diazepin-4-ol (**7**)

Proton	Resonance	Multiplicity	J (Hz)
N(6)-H [b]	7.62	bm	
H-7 [c]	6.86	d	$J_{7,6}$ = 4.6
hydroxyl	5.07	d	$J_{OH,4}$ = 5.5
H-4	4.58	sextet	$J_{4,5a}$ = 6.1
			$J_{4,OH}$ = 5.5
			$J_{4,5}$ = 2.1
H-5	3.22	octet [d]	$J_{5,5a}$ = 12.8
			$J_{5,NH}$ = 2.6
			$J_{5,4}$ = 2.1
H-5a	3.02	octet [d]	$J_{5a,5}$ = 12.8
			$J_{5a,4}$ = 6.1
			$J_{5a,NH}$ = 2.6

[a] Spectrum taken in DMSO-d_6 on a WM Bruker instrument with tetramethylsilane as internal standard, s = singlet, d = doublet, b = broad, m = multiplet. [b] Exchanges with deuterium oxide. [c] Simplifies to a singlet upon deuterium exchange of N(6)-H. [d] Simplifies to a quartet upon deuterium exchange of N(6)-H.

Therefore, we have developed [16] a short, facile sequence which has yielded the 4,5-dihydro-3*H*-1,3-diazepin-5-ol moiety fused to a pyrazole ring. The mild nature of each of the steps in this sequence should lend applicability of the method to most parent heterocycles. We are currently applying our method to the synthesis of certain azolo[1,3]diazepines as heterocyclic analogs of the nucleoside antibiotic coformycin.

EXPERIMENTAL

General Methods.

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 281 spectrophotometer. Ultraviolet (uv) spectra were recorded on a Hewlett-Packard 8450A UV/Vis spectrophotometer. The ^{1}H nuclear magnetic resonance (^{1}H-nmr) spectra were recorded for *ca.* 10% w/v solutions of the compounds on a Varian EM-360A (60 MHz) spectrometer or 1% w/v solutions of compounds on a WM Bruker (360 MHz) spectrometer operating in an FT mode. Thin layer chromatography was performed using pre-scored SilicAR 7GF Analtech (Newark Delaware) silica gel (0.25 mm layer) plates.

Low pressure chromatography was performed using the silica gel 60 columns: Lobar (E. Merck), size B (25 × 310 mm) or Michell-Miller (Ace Glass), size 22 × 300 mm. A FMI fluid metering pump operating at 1.5-2.5 kg/cm^2 (20-35 lb/in^2) was used to elute components. Flow rates of 5.0-10.0 ml/min were commonly used. An Altex 125 dual wavelength uv

(254 and 280 nm) detector with a preparative flow cell was used to detect uv-absorbing components. All solvents and reagents were "reagent grade" unless otherwise noted. Reaction solvents were dried by distillation (pyridine from BaO; *p*-dioxane from sodium) or by storage over the appropriate activated Linde molecular sieves (dimethylformamide, 4A°; dichloromethane, 3A°). All evaporations were routinely conducted at 30-45° unless otherwise noted. Water aspirator vacuum (10-15 Torr) was used to evaporate low boiling (bp < ethanol) solvents and vacuum pump pressure (0.5-1.0 Torr) was used to evaporate higher boiling solvents.

Hydrogenations at low hydrogen pressure (1-5 atmospheres of hydrogen) were carried out using a Parr hydrogenation apparatus (Model 2911, Parr Instrument Co., Moline, Illinois) and a 500 ml bottle at room temperature. Hydrogenations at high hydrogen pressure (8-25 atmospheres of hydrogen) were carried out using a stainless steel reaction vessel (Model 4051, Parr Instrument Co., Moline, Illinois) and glass sleeve. The contents of the sealed reaction vessel were heated by an oil bath and stirred with a magnetic stir bar and magnetic stirrer (with hot plate) combination.

5-Amino-1-methylpyrazole-4-carboxaldehyde (**4**) [8].

5-Amino-4-cyano-1-methylpyrazole (**3**) (10.0 g, 82 mmoles) [17] was dissolved in 60% aqueous acetic acid (300 ml) with gentle warming. The light yellow solution was purged with a steady stream of nitrogen for 20 minutes and then treated with T-1 Raney nickel [10] (3 g, weighed wet). The mixture was stirred under 1 atmosphere of hydrogen at room temperature for 72 hours. The solution was then filtered through a bed of packed celite (20 g) on a 250 ml sintered glass funnel and the catalyst bed was promptly washed with warm (70°) absolute ethanol (100 ml). The combined filtrates were evaporated to dryness *in vacuo* (water bath, 65°) to afford a yellow syrup. Repeated treatment of this syrup with cold water (6 × 50 ml) and an evaporation of each portion of water *in vacuo* afforded a thick slurry of crystalline material. This material was suspended in 100 ml of cold water and collected by filtration. The filtrate was evaporated by one-half of its volume to afford a second crop of crystals which was collected by filtration and combined with the first crop. The filter cake was washed with cold water (20 ml) and then dried in a vacuum oven (40°, 10-15 Torr) over phosphorus pentoxide for 18 hours to afford 7.5 g (73%) of compound **4** as yellow prisms, mp 158.5-159.5°, lit [9] 148-149°; ^{1}H-nmr (DMSO-d_6): δ 9.60 (s, 1, CHO), 7.55 (s, 1, H-3), 6.70 (br s, 2, NH_2, exch) 3.53 (s, 3, CH_3); ir (potassium bromide): 1650 (CHO), 3320, 3420 (NH_2) cm^{-1}; uv (methanol): λ max, nm (ε) 284 (6,600), 241 (5,900); (*p*H 1): 274 (5,800), 238 (5,600); (*p*H 11): 284 (6,500), 243 (5,100).

5-[[(Dimethylamino)methylene]amino]-1-methylpyrazole-4-carboxaldehyde (**8**) and 5-Methoxymethyleneamino-1-methylpyrazole-4-carboxaldehyde (**9**).

The aldehyde **4** (5.0 g, 40 mmoles) was suspended in anhydrous methylene chloride (50 ml) and treated with dimethylformamide dimethylacetal (DMFDMA, 5.9 ml, 44 mmoles) under anhydrous conditions. The reaction mixture was stirred for 3 hours at room temperature and then evaporated to dryness *in vacuo* to afford a light yellow oil. This oil was kept under vacuum pump pressure and room temperature for 18 hours. Thin layer chromatograms of this material revealed compound **8** (R_f = 0.35, ethyl acetate) as the predominant product and the presence of compound **9** as a very minor product (R_f = 0.45, ethyl acetate). An aliquot of this mixture (0.5 g) was chromatographed on a Michell-Miller column (300 mm length) using a low pressure chromatography apparatus. The mixture was separated using ethyl acetate-methylene chloride (1:1/v:v) as eluent and a flow rate of 6 ml/minute monitoring fractions by tlc (ethyl acetate). Fractions containing compound **9** were pooled and evaporated to dryness *in vacuo* to afford 20 mg of a white solid which was unstable to moisture, mp 55-57°; ^{1}H-nmr (deuteriochloroform): δ 9.75 (s, 1, CHO), 8.53 (s, 1, CH=N), 7.70 (s, 1, H-3), 3.53 (s, 3, N(1)-CH_3), 3.00, 2.92 (s, s; 3,3, *N,N*-dimethyl); uv (methanol): λ max, nm (ε), 318 (7,700), 234 (26,300).

Anal. Calcd. for $C_8H_{12}N_4O$: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.56; H, 6.78; N, 30.97.

Elemental analyses (C, H, N) of the crude reaction mixtures were found to be well within experimental limits as calculated for the predominant product, compound **8**. Therefore, these mixtures were routinely used for the next step without prior separation of the two compounds **8** and **9**. The yield of crude product was 7.2 g (100%).

5-[[(Dimethylamino)methylene]amino]-4-(cyano[trimethylsiloxy]methyl)-1-methylpyrazole (**10**) and 5-[[(Methoxy)methylene]amino]-4-(cyano[trimethylsiloxy]methyl)-1-methylpyrazole (**11**).

The mixture composed of compounds **8** and **9** (7.2 g, 40 mmoles as calculated for compound **8** was dissolved in trimethylsilyl cyanide [18] (TMSCN, 6.0 ml, 56 mmoles) with gentle warming in a scrupulously dried 50 ml round bottom flask. While maintaining a dry nitrogen atmosphere, dry, powdered zinc chloride (30 mg) was introduced and the flask sealed with a rubber septum.

The reaction mixture was stirred for 30 minutes at room temperature and then additional TMSCN (2 ml) was added using a syringe. After a few minutes of stirring, the mixture solidified. The yellow cake was broken up, triturated with anhydrous hexane (3 × 25 ml) and then filtered to give 10.0 g (90%) of a mixture of **10** and **11** as a brilliant yellow solid. Further purification of this cyanohydrin mixture was effected using a Merck Lobar silica gel "B" column which had been previously eluted with a solution of 2,2-dimethoxypropane in ethyl acetate (170 ml, 3% v/v). Ethyl acetate-methylene chloride (1:1/v:v) was used as the eluent and a flow rate of 5.0 ml/min was maintained throughout the separation. The eluates were monitored using an Altex uv detector (254 nm, 280 nm) and tlc (ethyl acetate-methylene chloride, 1:1/v:v) analysis of each fraction. The mixture of trimethylsilyl cyanohydrins (**10** and **11**) was first to elute and fractions 10-18 (7 ml/fraction) were pooled and evaporated *in vacuo* to give nearly colorless rosettes, 7.5 g (70%), mp 128-130°. This material was susceptible to moisture and was kept in a vacuum dessicator over phosphorus pentoxide during storage; ^{1}H-nmr (deuteriochloroform): δ 8.00 (s, 1, CH=N), 7.43 (s, 1, H-3), 5.55 (s, 1, methine), 3.70 (s, 3, CH_3), 3.10 (s, 6, *N,N*-dimethyl), 0.2 (s, 9, trimethylsilyl). The methoxy protons of compound **11** were just discernible at δ 4.00 in the spectrum of this mixture; uv (methanol) λ max, nm (ε) 265 (10,700), 234 (11,500). A sample (500 mg) of the mixture of trimethylsilyl cyanohydrins was recrystallized from 50% aqueous ethanol (10 ml) to yield a sample of the cyanohydrins **12** for analysis; ^{1}H-nmr (deuteriochloroform): δ 8.00 (s, 1, CH=N), 7.55 (s, 1, H-3), 6.53 (d, 1, -OH, exch), 5.33 (d, 1, H-4), 3.70 (s, 3, N-CH_3), 3.23 (s, 6, *N,N*-dimethyl).

Anal. Calcd. for $C_9H_{13}N_5O \cdot \frac{1}{4}H_2O$: C, 51.06; H, 6.38; N, 33.10. Found: C, 51.23; H, 6.46; N, 33.01.

The individual aldehydes, compounds **8** and **9**, were each treated with TMSCN/zinc chloride and each aldehyde gave a different and distinct trimethylsilyl cyanohydrin product. These products were each purified using low pressure chromatography techniques described earlier for the crude mixture. The trimethylsilyl cyanohydrins obtained from these reactions were characterized using ^{1}H-nmr spectra and by comparison of these spectra with the spectrum taken of the mixture obtained after low pressure chromatographic purification. The ^{1}H-nmr (deuteriochloroform) spectrum of compound **11** exhibited: δ 8.30 (s, 1, CH=N), 7.50 (s, 1, H-3), 5.40 (s, 1, methine), 4.00 (s, 3, CH_3O), 3.75 (s, 3, N-CH_3), 0.20 (s, 9, trimethylsilyl). The ^{1}H-nmr spectrum of compound **10** was identical to the spectrum obtained from the mixture of compounds **10** and **11**, but without the background peaks observed for the minor component.

1-Methyl-1,4,5,6-tetrahydropyrazolo[3,4-*d*][1,3]diazepin-4(*R,S*)-ol (**7**).

A 500 ml Parr stainless steel reaction vessel which had been fitted with a scrupulously dried glass sleeve was charged with a solution of the trimethylsilyl cyanohydrins (compounds **10** and **11**; 0.25 g, 0.89 mmole as calculated for compound **10**) in dry *p*-dioxane (40 ml). This solution was purged with dry nitrogen for 20 minutes. Nickel boride (NiB_x) catalyst [15] (0.30 g, weighed wet) was repeatedly washed with dry *p*-dioxane (4 × 10 ml) by decantation and the final suspension was added to the purged solution of trimethylsilyl cyanohydrins. The stainless steel vessel was sealed, flushed with hydrogen (3 × 40 psi), filled with 125 psi of

hydrogen, and then heated to 110° over a magnetic stirrer. An equilibrium pressure of 140 psi of hydrogen was maintained for 19 hours. After this time, the reaction mixture was filtered through a bed of packed Celite (6 g) on a 60 ml sintered glass funnel and the catalyst bed was promptly washed with methanol (3 × 15 ml). The *p*H of the filtrates was adjusted to 5 with 7.5 ml of 0.1 *N* aqueous acetic acid and the amber solution was warmed (55°) on a steam bath for two hours. The mixture was then evaporated to dryness *in vacuo* to afford a dark oil. The oil was repeatedly dissolved in absolute ethanol (3 × 15 ml) and each portion was evaporated to dryness *in vacuo* to afford a yellowish residue. Trituration of this yellowish residue with methylene chloride (5 ml) gave a white amorphous solid which was collected by filtration. the solid was dissolved in water (5 ml) and then lyophilized to afford 95 mg (66%) of **7** as a white hygroscopic solid, mp 230° dec. For ^{1}H-nmr data, refer to Table 1 in the text; uv (methanol): λ max, nm (ε) 275 (10,200); (*p*H 1): 241 (6,900); (*p*H 11): 274 (11,500).

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.58; H, 6.07; N, 32.73. Found: C, 50.82; H, 6.15; N, 33.00.

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[1] This investigation was supported by grant number CA-28381 awarded by the National Cancer Institute D.H.E.W., and the U.N.D.P./-World Bank/W.H.O. Special Program for Research and Training in Tropical Diseases and the Scientific Working Group on Filariasis (800134).

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[12] Reaction of the *ortho*-amino aldehyde **4** with dimethylformamide dimethylacetal gave excellent yields of the corresponding [(dimethylamino)methylene]amino product, compound **8**. However, the product contained a small amount of the [(methoxy)methylene]amino product, compound **9**. When these compounds were separated on silica gel, compounds **8** and **9** were shown to give different and distinct trimethylsilyl cyanohydrins **10** and **11**, respectively. Compounds **10** and **11** were in turn hydrogenated to afford an identical mixture of compounds **13** and **7**, in each case.

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