Reaction of 4,5-Diaminopyrimidine and Ethyl Acetoacetate: Synthesis and Chemistry of Isomeric Dihydropyrimido[4,5-*b*][1,4]diazepinones (1,2)

Mervyn Israel, S. Karin Tinter, Dorothy H. Trites, and Edward J. Modest

The Children's Cancer Research Foundation and the Departments of Biological Chemistry and Pathology, Harvard Medical School

Depending upon reaction conditions, 4,5-diaminopyrimidine and acetoacetic ester gave a variety of condensation products, including the two isomeric dihydropyrimido[4,5-*b*][1,4]-diazepinones. Under conditions leading to bicyclic products, the formation of 1,5-dihydro-4-methyl-2*H*-pyrimido[4,5-*b*][1,4]diazepin-2-one (**2**) was strongly favored. The isomeric 3,5-dihydro-2-methyl-4*H*-4-one compound (**4**) was best obtained by cyclization of ethyl 3-(4-amino-5-pyrimidylamino)crotonate (**3**) under base catalysis. Thermal rearrangement of **2** and **4** proceeded, in each instance, with loss of the isopropenyl moiety and gave 8-purinone. Compound **4** underwent ring contraction under the influence of alkoxide to yield a product which was shown to be the 7-isopropenyl-8-purinone (**6**).

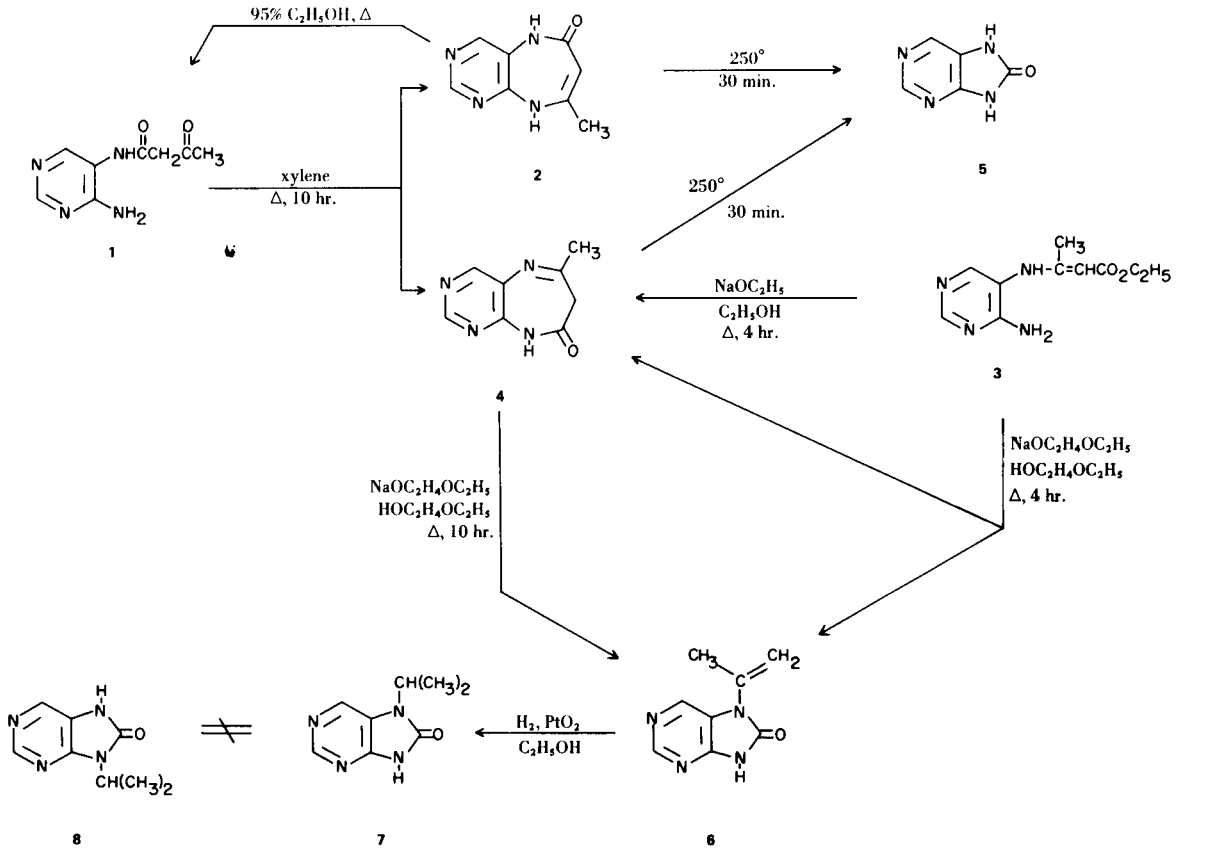
Initial attempts in these laboratories to prepare derivatives of the then unknown pyrimido[4,5-*b*][1,4]diazepine ring system involved condensation of 4,5-diaminopyrimidines with β-diketones and were based upon methods reported by, for example, Thiele and Steimmig (3), and Barltrop and coworkers (4) for the synthesis of the analogous 1,5-benzodiazepines. However, reaction of 4,5-diaminopyrimidine with 2,4-pentanedione in boiling methanol failed to yield the desired bicyclic product, but instead afforded an uncyclized enolic Schiff base *via* condensation at the 5-amino group (5). X-ray analysis (6) confirmed the structural assignment and showed, further, that in the solid state the 4-amino group of the pyrimidine moiety resided in a separate plane and was far removed from the oxygen function. The rigidity of the double bond system in the Schiff base product appeared to act as a barrier to cyclization. A similar imino-enol was obtained from the reaction of 2,4,5-triamino-6-methylthiopyrimidine with 2,4-pentanedione (7).

The failure of β-diketones to yield diazepines with 4,5-diaminopyrimidines led us to try β-ketoesters as possible cyclizing agents, especially in view of the successful syntheses of dihydro-1,5-benzodiazepinones *via* condensation of *o*-phenylenediamine with ethyl trifluoroacetoacetate (8) and with ethyl acetoacetate (9). Extension of the reaction of ethyl acetoacetate to 4,5-diaminopyrimidine, an unsymmetrical heteroaromatic diamine, necessarily introduced the added problem of two possible isomeric diazepinone products (**2** and **4**), the formation of which presumably depended upon whether initial reaction at the more basic 5-amino function (10) occurred with the keto carbonyl or the carbethoxy carbonyl of the β-ketoester. We have recently described the condensation of ethyl acetoacetate with a related unsymmetrical diamine, 2,3-diaminopyridine, from which reaction, either of the two possible diazepinone isomers could be obtained depending upon the reaction conditions (11). We now wish to report on the reaction of 4,5-diaminopyrimidine and ethyl acetoacetate under a variety of reaction conditions and the synthesis and chemistry of the two isomeric pyrimidodiazepinones, **2** and **4**, the structures of which have been unequivocally established by preparation from unambiguous precursors.

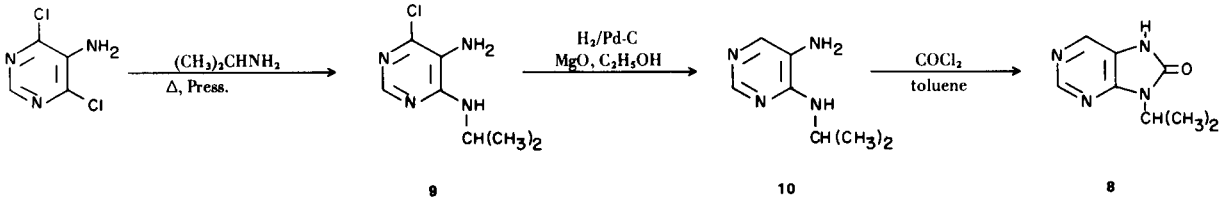
The reaction of 4,5-diaminopyrimidine and ethyl acetoacetate in boiling xylene was reported in a preliminary communication by Nyberg, Noell, and Cheng (12) to yield the diazepinone **2**. While the work we will describe confirms this structural assignment, we have found the reaction of the pyrimidinediamine with acetoacetic ester to be quite complicated and capable of yielding a variety of products. Thus, depending upon reaction conditions, the reactants can give the amide **1**, the diazepinone **2**, the pyrimidinylcrotonate **3**, or the isomeric diazepinone **4**, or mixtures of two or more of these compounds, and at least one other product as well (13). In Table I are shown some representative yield figures for this reaction under various conditions. In general, it appears that high reaction temperatures (140-180°) favor formation of the amide (**1**), which cyclizes fairly rapidly to diazepinone **2** under these conditions. Low reaction temperatures (80-105°) and the presence of acid favor the formation of the crotonate ester (**3**), which does not cyclize to diazepinone **4** except under strongly basic conditions.

As indicated in Table I, when 4,5-diaminopyrimidine

SCHEME I



SCHEME II

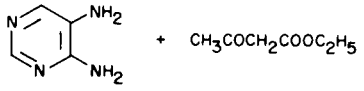


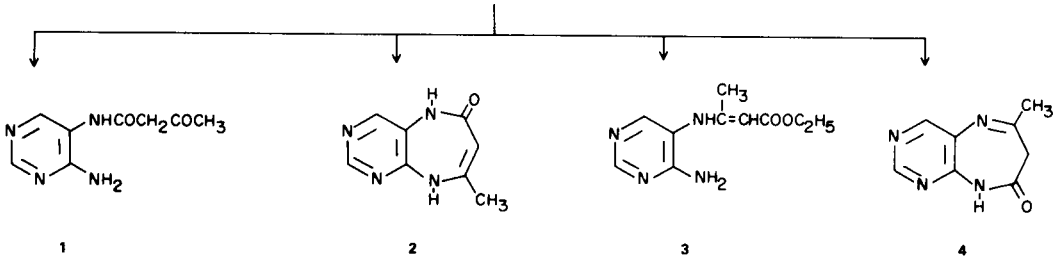
was heated at 180° for 5 minutes with excess ethyl acetoacetate, the amide **1** was formed exclusively and in high yield. The structure of **1** was ascertained by its nuclear magnetic resonance spectrum and by microchemical analysis, both of which indicated loss of the ethoxy moiety from the starting β-ketoester. When an identical reaction mixture was allowed to warm at 180° for 15 minutes, there was obtained a diminished yield of **1**, together with a 40% yield of a product, $C_8H_8N_4O$, m.p. 250-252°, the ultraviolet and nuclear magnetic resonance spectral features of which were essentially in agreement with the values reported for **2** (12). Under these conditions, it certainly appears that **2** is formed by way of the amide **1**. However, the formation of **2** under different reaction conditions may not proceed in the same manner (*vide infra*).

In their communication, Nyberg and coworkers (12) claimed that condensation of 4,5-diaminopyrimidine and ethyl acetoacetate in boiling xylene afforded a 38% yield of a diazepinone product, together with an unspecified quantity of amide **1**, obtained by washing the crude reaction product with hot ethanol. This isolation of amide

TABLE I

Reaction of 4,5-Diaminopyrimidine with Ethyl Acetoacetate (a)





1 2 3 4

Molar Ratio (b)	Solvent	Temperature (°C.)	Time	Percent Yield 1	2	3	4
8.26	(c)	180 (d)	5 minutes	84	----	----	--
8.26	(c)	180 (d)	15 minutes	34	40	----	--
1.50	xylene	140	5.5 hours	----	48	----	1
5.00 (e)	(f)	105	1.25 hours	32	----	54	--
1.16	None	105	24 hours	----	61	----	--
1.50	95% ethanol (g)	80	8 days	----	----	56	--

(a) Yield figures are given only for purified products formed in isolable quantity. All reaction mixtures were carefully scrutinized and oftentimes traces of other products were detected by tlc. (b) Ratio of β-ketoester to diamine. (c) Solvent was excess ethyl acetoacetate. (d) Bath temperature. (e) This reaction also gave a small quantity of a bis-pyrimidinylaminocrotonamide (see reference 13). (f) Excess ethyl acetoacetate plus 0.01 ml. of concentrated hydrochloric acid/gram of diamine. (g) With 5% zinc chloride.

served as presumptive evidence for the characterization of the diazepine derivative as **2**.

Repeating this reaction according to the published conditions, we found a 48% purified yield of **2**. The crude reaction product and all mother liquors and washings were carefully examined. However, in contrast to Nyberg, Noell, and Cheng (12), the use of ethanol was completely avoided in the work-up. No isolable quantity of amide (**1**) was ever found, although there was present a small yield (1%) of the isomeric diazepinone **4**, m.p. 237-239°.

We believe the isolation of **1** by the previous investigators to have been an artifact resulting from hydrolysis of **2** during hot ethanol washings. It is now recognized that **2** is easily hydrolyzed to **1** under these conditions. Attempted crystallization of **2** (previously purified by high vacuum sublimation) from 95% ethanol resulted in the formation of **1**. This hydrolysis was promoted by base, the presence of which reduced the time of reaction but afforded essentially the same final yield of **1**.

Reaction of essentially equimolar quantities of 4,5-diaminopyrimidine and ethyl acetoacetate at 105° for 24 hours afforded **2** as the exclusive product in 61% yield. However, when 4,5-diaminopyrimidine was treated with a 4-fold excess of ethyl acetoacetate at 105° for 1.25 hours in the presence of a trace of hydrochloric acid, no diazepinone product was formed. These conditions led to a product mixture composed of 32% of **1** and 54% of the crotonate ester **3**, the yield figures relating to the starting diamine. Compound **3** was also prepared by reaction of 4,5-diaminopyrimidine and acetoacetic ester in boiling 95% ethanol in the presence of 5% zinc chloride for 8 days. Although considerably longer in time, this latter method afforded the crotonate product exclusively in 56% yield.

The structure of **3** was clearly established by microchemical analysis and by infrared, ultraviolet, and nuclear magnetic resonance spectral features. The nmr spectrum in deuteriochloroform showed the continued presence of an ethoxy function and showed, further, a 1 proton vinyl peak and a 1 proton broad –NH– signal at δ 4.87 and 9.60 p.p.m., respectively.

The synthesis of **2** and **4** by other than direct condensation of 4,5-diaminopyrimidine and ethyl acetoacetate and some of the reactions of the isomeric diazepinones are shown in Scheme I. Already mentioned is the facile hydrolysis of **2** to **1**.

TABLE II

Ultraviolet and Infrared Spectral Data

Compound	Ultraviolet λ max (ethanol),	nm (ε)	λ max (*p*H 1),	nm (ε)	λ max (*p*H 10),	nm (ε)	Infrared (a) λ max (KCl), μ
1	235 279	(9,200) (5,400)	252	(9,800)	234 279	(10,300) (12,700)	2.96, 3.02, 3.10, 5.81, 6.03, 6.28, 6.51, 6.72, 7.01
2	232 257 310	(20,100) (13,100) (4,100)	289	(10,300)	230 253 307	(14,200) (11,600) (4,500)	3.03, 3.22, 3.30, 5.90, 6.11, 6.21, 6.52, 6.85, 6.93, 7.10
3	230 278	(11,400) (16,000)	284	(8,900)	230 280	(10,500) (14,800)	2.86, 3.00, 3.18, 3.31, 6.09, 6.22, 6.35, 6.75, 7.00, 7.09
4(b)	235 320				233 290		2.99, 3.11, 3.20, 3.31, 3.38, 6.02, 6.39, 6.62, 6.94, 6.97, 7.13
6	240 (c) 282	(5,600) (9,000)	283	(7,800)	287	(12,200)	2.88, 3.25, 3.39, 3.62, 3.74, 5.70, 6.05, 6.22, 6.72, 7.08, 7.21, 7.30
7	241 281	(4,000) (15,700)	265 (c) 285	(9,300)	254 (c) 288		2.87, 3.12, 3.22, 3.32, 5.80, 6.17, 6.24, 6.75, 6.97, 7.29, 7.47
8	240 279	(3,300) (11,300)	282	(11,600)	262 (c) 288		2.90, 3.14, 3.24, 3.29, 5.82, 6.18, 6.29, 6.80, 6.91, 7.20, 7.32
9	267 296		280 (c) 304		263 290		2.89, 2.99, 3.06, 3.35, 6.11, 6.35, 6.69, 6.81, 6.99, 7.08, 7.45
10	261 297						2.89, 2.98, 3.07, 3.35, 6.09, 6.30, 6.78, 7.09, 7.42

(a) Significant peaks appearing between 2.5 and 7.5 μ. (b) U.v. spectrum of yellow 3,5-dihydro tautomer. Freshly sublimed material was colorless and gave λ max (ethanol) 226 (inflection) and 281 nm. (c) Inflection.

It was earlier noted that, at 180°, compound **2** is almost surely formed *via* the intermediacy of amide **1**. However, when preformed amide was suspended and heated in xylene, there was formed not only diazepinone **2** (75% yield) but also a 6-12% yield of the isomeric diazepinone **4**. This unexpected formation of **4** might be explained by the possible intermediacy of a bis-pyrimidinylaminocrotonamide (13), which might then undergo cyclization to afford either **2** or **4**.

Treatment of **3** with sodium ethoxide in refluxing ethanol afforded the alternate diazepinone, **4**, in high yield. In contrast to **2**, compound **4** was not hydrolyzed in 95% ethanol; in fact, the analytical sample of **4** was prepared by crystallization from this solvent. Compound **4** was also purified by high vacuum sublimation. Freshly sublimed material was colorless [uv: λ max (ethanol) 226 (inflection) and 281 nm]. The white material turned yellow upon exposure to light and air and exhibited an ultraviolet absorption spectrum identical with that of material crystallized from ethanol [λ max (ethanol) 235 and 320 nm]. We believe this to be another example of the existence of distinct tautomeric forms of diazepinones, similar to an example we recently described in detail (11).

Thermal rearrangement (14) of compounds **2** and **4** at 250° without solvent did not give the expected isopropenylpurinones, but afforded, in each instance, the unsubstituted 8-purinone (**5**). The formation of **5** presumably involved the intermediacy of the 7- and 9-isopropenyl-8-purinones. Although a temperature of 250° smoothly converted 3,5-dihydro-2-phenyl-4*H*-pyrido[2,3-*b*][1,4]-diazepin-4-one into 1,3-dihydro-1-α-styryl-2*H*-imidazo-[4,5-*b*]pyridin-2-one (15), apparently the 7- and 9-isopropenyl-8-purinones were easily prone to dealkylation at this temperature. Compounds **2** and **4** are the only condensed dihydrodiazepinones so far encountered in these laboratories which fail to give the expected *N*-

alkenylimidazolone rearrangement product (14, 16).

Davoll (9) reported that the diazepinone resulting from the reaction of *o*-phenylenediamine and ethyl acetoacetate underwent base catalyzed ring contraction to an isopropenylbenzimidazolone. Treatment of **2** with sodium 2-ethoxyethoxide in hot 2-ethoxyethanol, according to Davoll's conditions (9), gave intractable tars from which no useful product could be obtained. Treatment of **4** under similar conditions did give rise to an isopropenylpurinone. A 31% yield of the same purinone, together with a 6% yield of **4**, was formed when **3** was heated in 2-ethoxyethoxide for 4 hours; presumably, longer reflux would have resulted in higher yields of the substituted purinone.

The thermal rearrangement reaction would have predicted conversion of **4** into **6**. However, it was not known whether ring contraction under conditions of base catalysis would lead to the same product, and it was therefore necessary to determine the structure of the isopropenylpurinone which had been thus obtained. Catalytic reduction of the olefinic double bond in the isopropenyl function gave an isopropylpurinone, m.p. 214-214.5°. The position of attachment of the isopropyl group, at either the 7- or 9-nitrogen, was established by comparison of the sample with 9-isopropyl-8-purinone (**8**) prepared by unambiguous synthesis. The authentic sample of **8** was obtained *via* the route outlined in Scheme II.

Although the two compounds exhibited similar spectral features, comparison of the isopropylpurinone, m.p. 214-214.5°, with the authentic sample of **8**, m.p. 160-161°, failed to establish identity. The isomeric purinone must then be the 7-isopropyl derivative, **7**. Thus, base catalyzed ring contraction of **4** afforded the same isopropenylpurinone, **6**, as would have been formed by thermal rearrangement.

EXPERIMENTAL (17)

Ultraviolet absorption spectra were measured with Cary Model 11 and Model 15 spectrophotometers in 95% ethanol solution, at *p*H 1 (0.01 *N* hydrochloric acid) and at *p*H 10 (0.05 *M* sodium carbonate–sodium borate buffer). Infrared spectra were determined with a Perkin-Elmer Model 137B spectrophotometer. Infrared and ultraviolet spectral data are presented in Table II. Nmr spectra were obtained by means of a Varian Associates A-60 spectrometer, with tetramethylsilane as the internal standard. Melting points were taken by the capillary method in a modified Wagner-Meyer melting point apparatus (18) at a rate of heating of 2°/minute and are corrected for stem exposure. Thin layer chromatography was carried out on Eastman Chromagram plates, with 1-butanol saturated with water as the solvent system; the plates were visualized by ultraviolet light and/or in an iodine chamber. Analytical samples were dried at 60-70° for 20-24 hours *in vacuo* over phosphorus pentoxide.

5-Acetoacetamido-4-aminopyrimidine (**1**).

A. By Direct Synthesis.

A mixture of 200 mg. (1.82 mmoles) of 4,5-diaminopyrimidine and 2.36 g. of ethyl acetoacetate (10 times excess) in a 10 ml. round bottom flask fitted with a short air condenser was heated for 5 minutes in an oil bath at 180°. A clear yellow solution was obtained within 2 minutes. After the reaction mixture had been refrigerated for a few hours, the precipitated solid was collected, washed with ether, and dried (298 mg., 84%). Crystallization of the crude material from absolute ethanol (Darco) returned off-white solid. Two additional crystallizations from acetonitrile gave off-white crystals in analytical purity. Compound **1** did not melt as such, but was converted into **2** upon heating; melting point behavior of **1**: turned yellow at 170-175°, sintered at 180°, and melted to a brown melt at 245-248° [lit. (12) m.p.: 221-225°].

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.51; H, 5.25; N, 28.71.

B. By Hydrolysis of **2**.

Compound **2** (100 mg., 0.57 mmole) was added to 5 ml. of absolute ethanol in which 13 mg. (1 atom. equiv.) of sodium had been dissolved. The solution was refluxed for 6.5 hours and then evaporated to dryness, and the residue was dissolved in water. The *p*H of the resulting solution was adjusted to 6 with glacial acetic acid. After refrigeration, there was collected a solid (60 mg., 55%), which was identical with **1** prepared according to method A.

1,5-Dihydro-4-methyl-2*H*-pyrimido[4,5-*b*][1,4]diazepin-2-one (**2**).

A. From 4,5-Diaminopyrimidine and Ethyl Acetoacetate in Boiling Xylene.

The reaction was run according to the procedure of Nyberg, Noell, and Cheng (12), except that the crude product was washed with xylene; hot ethanol washing was avoided. From the xylene reaction mixture, after overnight refrigeration, there was obtained 6.70 g. (76% crude yield) of **2**. Purification was achieved by trituration with absolute ethanol at room temperature (48% purified yield) or by high vacuum sublimation at 200-220° on a small scale (58% purified yield). Purified samples melted at 250-252° with decomposition [lit. (12) m.p. 250-252° dec.], but showed slightly different u.v. absorption values than those reported (see Table II). Evaporation of the xylene mother liquor left a brown oily residue. Trituration with ether afforded a yellow solid (105 mg., 1%, m.p.: 235-237°), which was identified as **4** by i.r. and u.v. spectral features and by melting point. Careful examination of all washings failed to reveal an isolable quantity of amide **1**.

B. From 4,5-Diaminopyrimidine and Ethyl Acetoacetate at 180° for 15 Minutes.

A mixture of 200 mg. (1.82 mmoles) of diamine and 2.36 g. of ethyl acetoacetate (10 times excess) in a small round bottom flask fitted with an air condenser was heated at 180° (bath temperature) for 15 minutes. Within 2 minutes, a clear yellow solution was achieved; after 9 minutes, fine yellow needles began to deposit. After cooling to room temperature, the yellow solid was collected; 129 mg., 40%, m.p. 250-252°. This material was identical with a sample of **2** previously obtained from the reactants in boiling xylene (method A and reference 12). Addition of ether to the mother liquor, followed by refrigeration, led to a second precipitate. This material, 119 mg., was found to be **1** (34% yield), as evidenced by u.v. spectra and thin layer chromatography.

C. From 4,5-Diaminopyrimidine and Ethyl Acetoacetate at 105° for 24 Hours.

A mixture of 0.5 g. (4.5 mmoles) of diamine and 0.69 ml. of ethyl acetoacetate were mixed in a 5 ml. pear-shaped flask equipped with an air condenser and thermometer and heated at 105° (internal temperature) in an oil bath for 24 hours. The yellow-brown reaction mixture was triturated with 20 ml. of acetone. After all the material had hardened, the solid was separated from the acetone by filtration. Crystallization of the crude product, 484 mg. (61%), twice from 1-butanol gave **2**, m.p. 247-249°, but identical in all spectral characteristics with previous samples of **2** prepared by other methods.

D. By Cyclization of **1**.

A mixture of 200 mg. (1.03 mmoles) of amide **1** and 40 ml. of xylene was stirred and heated at reflux for 10 hours. Solid began to deposit from the reaction solution during the reflux period. After cooling to room temperature, the reaction mixture was placed in the refrigerator for 3 days. The solid (**2**, 132 mg., 75%), which had separated, was collected. The mother liquor was taken to dryness and the residue was triturated under a small volume of ether. A second product (**4**, 22 mg., 12%) was recovered. The identity of **2** and **4** was established by i.r. and u.v. spectra and by thin layer chromatography with pure samples.

Ethyl 3-(4-Amino-5-pyrimidylamino)crotonate (**3**).

A. In Ethanol.

A mixture of 5.5 g. (0.05 mole) of 4,5-diaminopyrimidine, 9.76 g. (0.075 mole) of ethyl acetoacetate, and 275 mg. of zinc chloride in 400 ml. of absolute ethanol was heated at reflux for 8 days. Evaporation of the reaction solution to dryness on the rotary evaporator gave a pale yellow residue (9.9 g.), which was extracted with 750 ml. of boiling carbon tetrachloride. Upon cooling, the carbon tetrachloride deposited 6.18 g. (56%) of **3**, m.p. 150-151.5°; nmr (deuteriochloroform): δ 1.27 (3H triplet, J = 14 Hz, $-CH_2CH_3$), 1.82 (3H singlet, $C-CH_3$), 4.17 (2H quartet, J = 22 Hz, $-OCH_2CH_3$), 4.81 (1H, =CH–), 5.67 (2H broad, $-NH_2$), 8.05 and 8.40 (two 1H singlets, pyrimidine ring), and 9.60 (1H broad, –NH–) p.p.m.

Anal. Calcd. for $C_{10}H_{14}N_4O_2$: C, 54.03; H, 6.35; N, 25.21. Found: C, 53.94; H, 6.44; N, 25.39.

B. By Fusion at 105°.

A mixture of 2 g. (18.2 mmoles) of 4,5-diaminopyrimidine, 10 ml. of ethyl acetoacetate, and 0.02 ml. of concentrated hydrochloric acid, in a 25 ml. round bottom flask fitted with an air condenser and thermometer, was heated at 105° (internal temperature) for 1.25 hours in an oil bath. After cooling, the reaction mixture was transferred to a beaker with 100 ml. of ether. The suspension was stirred for a short time and then filtered to separate 1.12 grams of yellow solid (amide **1**, 32% yield). The ether filtrate, upon refrigeration for 3 days, deposited 1.76 g. of **3**. Evaporation of the mother liquor to near dryness, followed by refrigeration, gave an additional quantity of **3**. The combined material, 2.2 g. (54%), after crystallization from carbon tetrachloride, afforded product identical with that obtained by method A.

3,5-Dihydro-2-methyl-4*H*-pyrimido[4,5-*b*][1,4]diazepin-4-one (**4**).

A solution of sodium ethoxide in ethanol was prepared by dissolving 115 mg. (5 mg.-atoms) of sodium in 6.5 ml. of absolute ethanol. To this solution was added 1.1 g. (5 mmoles) of **3**, and the clear orange reaction mixture was refluxed for 4 hours. The solvent was evaporated and the pink colored residue was dissolved in 10 ml. of water. Neutralization of the aqueous solution with glacial acetic acid precipitated a bright yellow solid (784 mg., 89%). Three crystallizations of this material from 95% ethanol, the first time with Darco, gave the analytical sample, yellow needles, m.p. 240-241°. Freshly sublimed material (*via* high vacuum sublimation at 125°) was colorless but turned yellow upon exposure to light and air. The white and yellow forms of **4** each exhibited a characteristic ultraviolet spectrum (see Table II).

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.60; H, 4.68; N, 32.01.

7,8-Dihydro-7-isopropenyl-9*H*-purin-8-one (**6**).

A. From **3**.

A solution of 1.1 g. (5 mmoles) of **3** in 6.5 ml. of 2-ethoxyethanol, in which 115 mg. (5 mg.-atoms) of sodium had been previously dissolved, was boiled for 4 hours. The initial red-brown clear solution became turbid during the reflux. The solvent was evaporated under reduced pressure. The muddy brown residue was taken up in 10 ml. of water and the aqueous solution was neutralized with glacial acetic acid and kept overnight in the freezer. The pink-gray solid which had separated (294 mg., 34%) was crystallized twice from methanol, the first time with Darco. The product, glistening off-white crystals, melted at 196-197°. Nmr (d_6-DMSO): δ 2.20 (3H peak, poorly resolved splitting, $C-CH_3$), 5.25 and 5.32 (1H each, poorly resolved quartets, $=CH_2$), and 8.32 and 8.55 (1H each, pyrimidine ring protons) p.p.m.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.36; H, 4.74; N, 32.11.

B. From **4**.

Compound **4** (440 mg., 2.5 mmoles) was added to a solution of sodium 2-ethoxyethoxide in 2-ethoxyethanol [prepared from 575 mg. (1 atom.-equiv.) of sodium and 10 ml. of 2-ethoxyethanol]. The reaction mixture was stirred and heated at reflux for 9.5 hours. Evaporation of the solvent to near dryness (at vacuum pump pressure) left a syrupy residue, which was taken up in 10 ml. of water. The aqueous solution was neutralized to *p*H 6-7 with glacial acetic acid, then extracted with 3 portions of chloroform (total volume 100 ml.). After decolorization with Darco, the yellow chloroform solution was evaporated and the yellow oily residue was placed for 1 day in the freezer, and then for 2 days in a vacuum desiccator over granulated phosphorus pentoxide. The oil finally hardened into a beige colored solid (215 mg., 49%), which, after crystallization from methanol, was identical with material obtained by method A.

7,8-Dihydro-7-isopropyl-9*H*-purin-8-one (**7**).

A mixture of 200 mg. (1.14 mmoles) of **6** and 100 mg. of platinic oxide in 70 ml. of absolute ethanol was shaken under hydrogen on a Parr apparatus at an initial pressure of 50 p.s.i. Reduction required 48 hours for completion. The catalyst was separated by filtration and the combined ethanol filtrate and washes were evaporated to dryness. The crude product (200 mg., 99%) was crystallized once from water (Darco); white needles, m.p. 214-214.5°.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.91; H, 5.61; N, 31.45. Found: C, 53.99; H, 5.58; N, 31.68.

5-Amino-4-chloro-6-isopropylaminopyrimidine (**9**).

This compound was prepared essentially according to the procedure reported by Montgomery and Temple for the preparation of various other 5-amino-4-chloro-6-alkylaminopyrimidines (19). 5-Amino-4,6-dichloropyrimidine (1.0 g., 6.1 mmoles), isopropylamine (1.5 g., 2.5 mmoles), and absolute ethanol (50 ml.) were charged into a small stainless steel bomb, which was then heated for 6 hours at 125°. The reaction solution was reduced

in volume to 5-10 ml. Addition of 250 ml. of ether afforded off-white solid which had no u.v. absorption (isopropylamine hydrochloride). The ether-ethanol filtrate was taken to dryness. The solid residue (1.02 g., 90%) was crystallized from 750 ml. of heptane (Darco). A sample of the long pale pink needles recovered from heptane (m.p. 182-183°) was purified further for analysis by high vacuum sublimation at 105-110°; white solid, m.p. 182-183°.

Anal. Calcd. for $C_7H_{11}ClN_4$: C, 45.04; H, 5.94; N, 30.02. Found: C, 45.37; H, 6.44; N, 30.15.

5-Amino-4-isopropylaminopyrimidine (**10**).

Dechlorination was accomplished according to the procedure of Montgomery and Temple (19). A mixture of 0.81 g. (4.34 mmoles) of **9**, 0.5 g. of magnesium oxide, 0.25 g. of 5% palladium on charcoal, 25 ml. of water, and 25 ml. of ethanol was shaken under hydrogen for 6 hours on a Parr apparatus at an initial pressure of 31 p.s.i. The catalyst was separated by filtration and washed with ethanol and with water. The combined aqueous ethanol filtrate and washes were evaporated to dryness. The solid which remained (940 mg.), a salt or complex of the product with magnesium chloride, was dissolved in 1 *N* sodium hydroxide. After separation of inorganic matter, the clear filtrate was extracted several times with chloroform. The chloroform extract, when taken to dryness, gave 642 mg. (97%) of crude diamine. Recrystallization of the crude product from heptane several times gave white needles, m.p. 188-189°.

Anal. Calcd. for $C_7H_{12}N_4$: C, 55.24; H, 7.95; N, 36.81. Found: C, 54.57, 54.80; H, 7.96, 8.02; N, 37.31, 37.39.

7,8-Dihydro-9-isopropyl-9*H*-8-purinone (**8**).

A solution of **10** (0.336 g., 2.2 mmoles) was added to a solution of 2 g. of phosgene dissolved in 23 g. (29 ml.) of toluene. The reaction mixture was stirred and heated to boiling. Reflux was maintained for 5 hours, but, after 1 hour, the original suspension turned to a clear solution. After cooling, the toluene solution was extracted with 10% sodium hydroxide (5 x 15 ml.). The alkaline extract was acidified to *p*H 2-3 with concentrated hydrochloric acid and the aqueous solution was taken to dryness. Extraction of the solid residue first with chloroform, then with absolute ethanol, until the residue no longer showed u.v. absorption, gave, after evaporation, 537 mg. of solid, which was a mixture of product free base and hydrochloride salt. The crude material was dissolved in 20 ml. of water; *p*H of the aqueous solution was 2. The aqueous solution was treated twice with 3 g. of Amberlite IR45 resin. After each resin treatment, the resin was separated and washed with water and with warm ethanol. The washings were added to the original filtrate, and the combined volume was evaporated to dryness. The solid material recovered after the second batch resin treatment (415 mg.) was dissolved in 150 ml. of hot absolute ethanol. A small quantity of insoluble inorganic material was separated. An additional quantity of non-u.v. absorbing material deposited when the ethanol solution was reduced to a volume of 25 ml. and cooled. Evaporation of the mother liquor to dryness gave 282 mg. (72%) of product, which, after several crystallizations from heptane, afforded the analytical sample, m.p. 160-161°.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.88; H, 5.65; N, 31.44. Found: C, 53.84, 53.74; H, 5.67, 5.95; N, 31.87, 31.70.

Acknowledgment.

We are grateful to Mr. Roger J. Cavallo and to Mr. Chester H. Rosansky for the infrared and quantitative ultraviolet spectra.

REFERENCES

(1) This investigation was supported in part by research grant C6516 and research career development award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, Maryland.

(2) Presented in part before the First International Congress of Heterocyclic Chemistry, Albuquerque, New Mexico, July 1967 (M. Israel, S. K. Tinter, D. H. Trites, and E. J. Modest, Abstracts of Papers, Abstract No. 35).

(3) J. Thiele and G. Steimmig, *Ber.*, 40, 955 (1907).

(4a) J. A. Barltrop, C. G. Richards, D. M. Russell, and G. Ryback, *J. Chem. Soc.*, 1132 (1959); (b) J. A. Barltrop, C. G. Richards, and D. M. Russell, *ibid.*, 1423 (1959).

(5) S. Chatterjee, D. H. Trites, and E. J. Modest, *Nature*, 203, 970 (1964).

(6) N. F. Yannoni and J. Silvermann, *ibid.*, 202, 484 (1964).

(7) M. Israel, H. K. Protopapa, S. Chatterjee, and E. J. Modest, *J. Pharm. Sci.*, 54, 1626 (1965).

(8) F. B. Wigton and M. M. Joullié, *J. Am. Chem. Soc.*, 81, 5212 (1959).

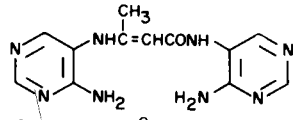
(9) J. Davoll, *J. Chem. Soc.*, 308 (1960).

(10) D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, p. 324.

(11) M. Israel, L. C. Jones, and E. J. Modest, *J. Heterocyclic Chem.*, 4, 659 (1967).

(12) W. H. Nyberg, C. W. Noell, and C. C. Cheng, *ibid.*, 2, 110 (1965).

(13) Another product, recently isolated in low yield from several reactions of 4,5-diaminopyrimidine and ethyl acetoacetate at 105° in the presence or absence of hydrochloric acid, is a bis-pyrimidinylaminocrotonamide:



The product melted at 203-204° after crystallization from methanol. The structure is supported by mass spectral and microchemical analyses (*Anal.* Calcd. for $C_{12}H_{14}N_8O$: C, 50.33; H, 4.94; N, 39.14; C/N, 1.29. Found: C, 50.80; H, 5.13; N, 39.72; C/N, 1.28). The mass spectrum shows a peak of about 5% at m/e 286 for the parent mass ion, relative to two peaks of essentially equal abundance at m/e 110 and 176 corresponding to fragmentation with rearrangement of hydrogen to give the mass ions of 4,5-diaminopyrimidine and a dihydrodiazepinone, respectively. The possible role of this bis-compound in the formation of isomeric diazepinone products is under investigation. We thank Mr. James K. Whitesell, Department of Chemistry, Harvard University, for obtaining the mass spectrum.

(14) M. Israel, L. C. Jones, and E. J. Modest, *Tetrahedron Letters*, 4811 (1968).

(15) M. Israel and L. C. Jones, *J. Heterocyclic Chem.*, 6, 735 (1969).

(16) Unpublished results from these laboratories.

(17) Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee, Werby Laboratories, Boston, Massachusetts, and Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(18) E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, 10, 584 (1938).

(19) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, 79, 5238 (1957); *ibid.*, 80, 409 (1958).

Received May 25, 1970 Boston, Mass. 02115