for 5 days, cooled (5 °C), and treated cautiously with 65 mL of saturated NaCl. After stirring overnight, the insoluble material was removed by filtration. The filter cake was stirred with a solution of 25 mL of saturated NaCl and 600 mL of glyme. This mixture was heated under reflux for 1 h and filtered hot. The combined filtrates were concentrated to give an oil which was dissolved in CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and removed to afford 37.4 g (76%) of crude **17b** as an oil. The IR and NMR of the crude product showed the absence of starting oxime and supported the proposed structure. TLC showed principally one component.

2-(3-Pyridyl)-3-(4-toluenesulfonamido)propyl 4-Toluenesulfonate (20b). To a stirred, cooled (0 °C) solution of 35.2 g (0.23 mol) of crude **17b** in 335 mL of dry pyridine was added in portions 96.9 g (0.51 mol) of purified 4-toluenesulfonyl chloride.[28] After stirring for 2 h, the solution was allowed to stand in the cold (5 °C) overnight and was then diluted to 3 L with H_2O and ice. After vigorous scratching, the precipitated gum solidified. It was collected, washed with H_2O, and dried over NaOH in vacuo to yield 66.5 g (48%, based on **23**) of **20b** which was of sufficient purity for subsequent reaction: mp 150–153 °C.

Analytically pure **20b** was obtained by column chromatography of the crude solid on SiO_2 (CH_2Cl_2 → 10% acetone/CH_2Cl_2), followed by two recrystallizations from CH_3CN: mp 167.5–168 °C; IR (Nujol) 3080 (NH), 1362, 1172, 1152, 1095, 985, 817, 660 cm^{-1}; NMR (Me_2SO-d_6) δ 2.43 (s, 3, CH_3), 2.48 (s, 3, CH_3), 3.13 (m, 3, $CHCH_2N$), 4.31 (d, 2, J = 5 Hz, CH_2O), 7.53 (m, 10, 4- and 5-Py and Ph H), 8.45 (m, 2, 2- and 6-Py H), NH resonance was not assignable. Anal. $C_{22}H_{24}N_2O_5S_2$: C, H, N, S.

3-(3-Pyridyl)-1-(4-toluenesulfonyl)azetidine (20b) was obtained as a semisolid (77%) from crude **20b** by the method described for the preparation of **13**. The crude product was chromatographed on SiO_2 (30:1, C_6H_6 → 10% acetone/C_6H_6) to yield a solid which was decolorized in boiling *tert*-butyl alcohol with charcoal. The *tert*-butyl alcohol was removed and the resulting solid was triturated with Et_2O to give analytically pure **20b** (38%): mp 95–96.5 °C; IR (Nujol) 1429, 1340, 1155, 1097, 709, 672 cm^{-1}; NMR ($CDCl_3$) δ 2.48 (s, 3, CH_3), 3.93 (m, 5, azetidinyl H), 7.47 (m, 6, 4- and 5-Py and Ph H), 8.21 (m, 2, 2- and 6-Py H); mass spectrum m/e (rel intensity) 288 (0.5, M^+), 105 (100), 91 (29.9). Anal. $C_{15}H_{16}N_2O_2S$: C, H, N, S.

3-(3-Pyridyl)azetidine (5) was prepared from **20b** in 27% yield using the method described for the synthesis of **3**: bp 93–97 °C (0.15 mm); GLC and NMR indicated >95% purity; IR (neat) 3295 (NH), 1577, 1482, 803, 713 cm^{-1}; NMR ($CDCl_3$) δ 2.04 (s, 1, NH), 3.91 (m, 5, azetidinyl H), 7.26 (1, m, 5-Py H), 7.72 (m, 1, 4-Py H), 8.50 (m, 2, 3- and 5-Py H); mass spectrum m/e (rel intensity) 134 (3.7, M^+), 105 (100), 104 (33.3), 78 (18).

Analysis was obtained on the dipicrate salt which was formed in EtOH and recrystallized from H_2O: mp 200–201 °C. Anal. $C_{20}H_{16}N_8O_{14}$: C, H, N.

1-Methyl-3-(3-pyridyl)azetidine (6) was prepared from **5** in 59% yield using the method described for the preparation of **4**: bp 63–65 °C (0.15 mm); IR (neat) 1577, 1483, 1429, 1025, 802, 711 cm^{-1}; NMR ($CDCl_3$) δ 2.37 (s, 3, CH_3), 3.17 (m, 2, azetidinyl H), 3.70 (m, 3, azetidinyl H), 7.22 (m, 1, 5-Py H), 7.66 (m, 1, 4-Py H), 8.48 (m, 2, 2- and 6-Py H); mass spectrum m/e (rel intensity) 148 (13.0, M^+), 106 (73.0), 105 (100), 104 (34.9).

Analysis was obtained on the dipicrate salt, which was formed in EtOH and recrystallized from H_2O, mp 191–192 °C. Anal. $C_{21}H_{18}N_8O_{14}$: C, H, N.

Acknowledgment. We are indebted to Dr. Thomas S. Osdene and Professor Norman H. Cromwell of the University of Nebraska for encouraging us to carry out this research and thank them and Professor Alfred Burger of the University of Virginia for stimulating discussions. We are also grateful to Dr. J. F. Whidby, Dr. T. Phil Pitner, Mr. Ronald Bassfield, Mr. Larry Morgan, and Dr. Manuel C. Bourlas for NMR spectral analyses, Mr. Gunars Vilcins and Dr. Gary Forrest for IR analyses, and Mr. David F. Glenn for mass spectral analyses.

Registry No. **3**, 62247-27-2; **3** dipicrate, 70892-01-2; **4**, 62247-28-3; **5**, 62247-32-9; **5** dipicrate, 70892-02-3; **6**, 62247-33-0; **6** dipicrate, 62247-34-1; **7**, 62247-21-6; **8**, 62247-22-7; **10**, 62247-23-8; **11**, 62247-24-9; **12**, 62247-25-0; **13**, 62247-26-1; **14**, 70892-03-4; **16a**, 29753-99-9; **17b**, 62247-29-4; **18a**, 70892-04-5; **19a**, 70892-05-6; **20a**, 70892-06-7; **20b**, 62247-30-7; **21a**, 70892-07-8; **21b**, 62247-31-8; **22a**, 4363-13-7; **23**, 62287-08-5; 3-pyridinecarboxaldehyde, 500-22-1; malonic acid, 141-82-2; 3-(2,2-dicarboxyvinyl)pyridine diammonium salt, 70892-08-9; 3-(3-pyridyl)acrylic acid, 1126-74-5.

The Chichibabin Reaction of Purines with Potassium Amide in Liquid Ammonia[1]

Nico J. Kos, Henk C. van der Plas,* and Beb van Veldhuizen

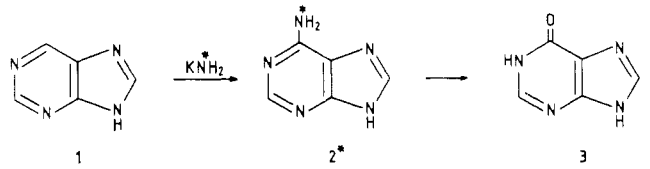
Laboratory of Organic Chemistry, Agricultural University, De Dreijen 5, 6703 BC Wageningen, The Netherlands

Received March 26, 1979

Reaction of purine and 2-methyl- and 8-methylpurine with potassium amide in liquid ammonia leads to the formation of adenine and 2-methyl- and 8-methyladenine, respectively. 6-Methyl- and 6,8-di-*tert*-butylpurine do not react. It was proven by applying ^{15}N-labeled potassium amide that the amination reactions do *not* involve opening of the pyrimidine ring. Low temperature NMR spectroscopy showed that in solutions of purine and 2-methylpurine in potassium amide–liquid ammonia an anionic σ complex at position 6 is formed. 8-Methylpurine on the contrary only showed the presence of a monoanion and a dianion.

It is well known that purines are in general more susceptible to nucleophilic than to electrophilic attack.[2] In basic medium, however, the reactivity toward nucleophiles is often strongly decreased due to deprotonation of the NH of the imidazole ring.[2] Deprotonation has as a further consequence that the pattern of addition of nucleophiles changes. Whereas in neutral purines both positions 6 and 8 are reactive in nucleophilic additions, in the anions of

Scheme I



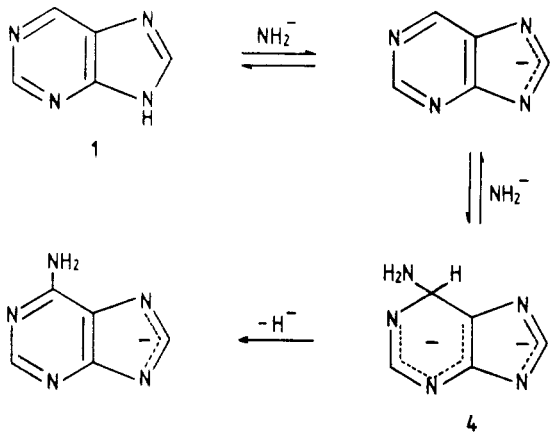
1 2* 3

(1) Part 77 on pyrimidines from this laboratory. For part 76 see: D. A. de Bie, A. Nagel, H. C. van der Plas, G. Geurtsen, and A. Koudijs, *Tetrahedron Lett.*, 649 (1979).

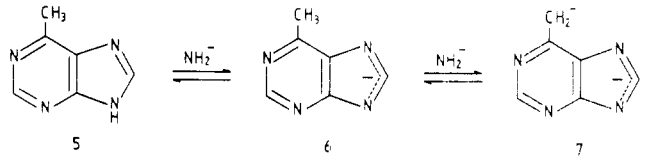
(2) For a review: J. H. Lister in "The Chemistry of Heterocyclic Compounds, Fused Pyrimidines", Part II, D. J. Brown, Ed., Wiley, New York, 1971.

0022-3263/79/1944-3140$01.00/0

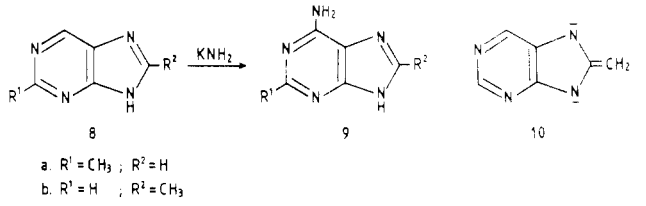
Scheme II



Scheme III



Scheme IV



purines addition to position 8 is found to be prohibited (due to Coulomb repulsion) and addition takes place only at position 6.[2] In both neutral and anionic purines position 2 is the least reactive.[2] The interesting fact, observed for the first time in our laboratory, that pyrimidines[3] and *s*-triazines[4] can undergo Chichibabin amination[5] with potassium amide in liquid ammonia involving partly a ring-opening, ring-closure reaction sequence [S_N(ANRORC) mechanism],[6] induced us to investigate in detail the behavior of purine and of the three isomeric *C*-methylpurines toward the same reagent.

Results and Discussion

Amination of Purine. When purine (1) reacts with 4 equiv of potassium amide in liquid ammonia, adenine (2) is formed as the sole product (Scheme I). The reaction rate of this Chichibabin amination is very low; after 20 h 30% of the purine can still be recovered. However, after 70 h the conversion of 1 into 2 is quantitative. This method of preparation of 2 is new and till now unexplored. The reaction is remarkable since under the conditions of the reaction 1 is certainly present in its anionic form (pK_a purine 8.9),[7] but in spite of that, a nucleophilic attack by the amide ion on this negatively charged species can take place. When the amination was carried out with ^{15}N-labeled potassium amide we found that in the labeled adenine (2)* the label was present exclusively in the nitrogen of the amino group; no trace of ^{15}N label was present in the nitrogen atoms of the ring. This was proven by conversion of 2* into hypoxanthine (3) by diazotization[8] and by determining the ^{15}N content in 2* (% ^{15}N 10.9 (7.6)[9])and 3 (% ^{15}N 0.0 (0.0)[9]) using mass spectrometry. From these results it is evident that in the formation of 2 from 1 no S_N(ANRORC) mechanism[6] is involved but that the amination follows a pathway in which addition of the amide ion takes place at position 6, followed by loss of a hydride ion. This is in agreement with the general observation that in the anion of purine position 6 is the most reactive position for the addition of nucleophiles.[2,10]

The formation of adenine from the anion of 1 raises the interesting question of which step in the amination is rate determining.[11] Two possibilities can be considered. The first one is that the addition of the negatively charged amide ion to position 6 of the anion of 1 is rate determining. It leads to dianion 4 as intermediate σ adduct (Scheme II). The second possibility, also reasonable, is that the aromatization step yielding the monoanion of adenine is rate determining.

Our first attempt to tackle this problem was to measure the influence of deuterium at position 6 on the rate of amination. A competition experiment between purine and 6-deuteriopurine, however, met with little success, since 6-deuteriopurine was found to undergo a slow D/H exchange under the reaction conditions. An attempt to detect the intermediate 4 by ^1H and ^{13}C NMR spectroscopy was more successful. When 1 was dissolved in liquid ammonia containing potassium amide (0.07–0.5 mmol of 1 in 1 mL of liquid ammonia containing 4–10 equiv of potassium amide) the ^1H and ^{13}C NMR spectra showed first the formation of the anion of 1. Then the anion is slowly converted into a σ adduct as indicated by a strong upfield shift of 3.04 ppm for one of the hydrogens and 76.1 ppm for one of the carbon atoms (change of hybridization of $sp^2 \rightarrow sp^3$) (see Table I and II). The appearance of signals of the adduct leads at the same time to a disappearance of the signals of the anion of 1. The upfield shift values are in good agreement with those reported in the literature.[10,13,14] No splitting of the proton signal at δ 5.75 into a triplet was observed due to a fast hydrogen exchange[13] caused by the large excess of potassium amide. That the formation of the adduct takes place at position 6 was unequivocally proven by comparing the ^1H and ^{13}C NMR spectra of 6- and 8-deuteriopurine in liquid ammonia containing potassium amide (Tables I and II). These results strongly indicate that the second step in the am-

(3) C. A. H. Rasmussen and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **97**, 288 (1978).
(4) Gy. Simig and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **95**, 113, 125 (1976).
(5) The term "Chichibabin amination" refers to a reaction in which the hydrogen in an aromatic heterocycle is replaced by an amino group.
(6) The term S_N(ANRORC) mechanism (Addition of the Nucleophile, Ring Opening and Ring Closure) refers to a reaction in which an opening of the heterocyclic ring occurs. For a review: H. C. van der Plas, *Acc. Chem. Res.*, 11, 462 (1978).
(7) S. Lewin and M. A. Barnes, *J. Chem. Soc. B*, 478 (1966).
(8) M. Krüger, *Z. Physiol. Chem.*, 18, 444 (1886).
(9) The number in brackets refers to a duplicate experiment; the accuracy of the mass spectrometric determinations is ±0.2%.
(10) A σ adduct on position 6 has been found for purine and some derivatives with barbituric acid and 2-thiobarbituric acid and potassium hydrosulfite [W. Pendergast, *J. Chem. Soc., Perkin Trans. 1*, 2759 (1973); 2240 (1975)] but covalent hydration has never been found [A. Albert, *J. Chem. Soc. B*, 438 (1966)].
(11) Studies on the Chichibabin amination in pyridines have shown that the second step, i.e. the aromatization step, is considered rate determining [S. V. Kessar, U. K. Nadir, and Manmohan Singh, *Indian J. Chem.*, 11, 826 (1973)]. This is also shown by the observation of an intermediary σ adduct with triazine and pyrimidine derivatives (see ref 3 and 4).
(12) (a) E. Breitmaier and W. Voelter, *Tetrahedron*, **30**, 3941 (1974); (b) R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.*, **93**, 1880 (1971).
(13) J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas*, **93**, 231 (1974).
(14) J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *Org. Magn. Reson.*, 7, 86 (1975).

Table I. ^{1}H NMR Data (δ Values) of Purines, Methylpurines, and Its Several Deuterio Derivatives in Liquid Ammonia Containing Potassium Amide

		H-2	H-6	H-8	$CH_3(CH_2^-)$
purine	anion	8.58	8.79	8.12	
	adduct	6.95	5.75	6.83	
6-deuteriopurine	anion	8.62		8.15	
	adduct	6.96		6.85	
8-deuteriopurine	anion	8.61	8.82		
	adduct	6.99	5.76		
6-methylpurine	anion	8.48		8.06	2.68
	dianion	7.24		7.09	3.02[a]
6-methyl-8-deuteriopurine	anion	8.48			2.68
	dianion	7.21			3.01[a]
2-methylpurine	anion		8.68	8.05	2.60
	adduct		5.69	6.83	1.77
2-methyl-8-deuteriopurine	anion		8.71		2.63
	adduct		5.71		1.80
8-methylpurine	anion	8.42	8.54		2.48
	dianion	7.35	6.77		2.48
6-deuterio-8-methylpurine	anion	8.40			2.44
	dianion	7.29			2.44
6,8-di-*tert*-butylpurine	neutral ($CDCl_3$)	9.00			1.61 and 1.65

[a] AB quartet (J = 3 Hz).

Table II. ^{13}C NMR Data of Purines and Reaction Intermediates in Me_2SO-d_6 and Liquid Ammonia Containing Potassium Amide

		C-2	C-4	C-5	C-6	C-8	$CH_3(CH_2^-)$
purine	neutral[12a]	152.2	154.7	130.5	145.6	146.1	
	anion[12b]	149.5	160.7	134.5	143.7	156.9	
	adduct	153.6	147.5	118.3	67.6	138.9	
2-methylpurine	neutral	161.0	155.0	128.8	145.3	145.3	25.5
	anion	156.7	164.5	134.5	143.3	158.4	25.7
	adduct	158.4	149.3	116.7	67.7	138.8	27.0
8-methylpurine	neutral	151.5	155.9	131.2	143.3	156.2	15.1
	anion	148.4	165.2	138.5	140.7	168.2	18.6
	dianion	143.8	*a*	*a*	115.8	*a*	47.5
6-amino-8-methylpurine	neutral	151.6	*c*	*c*	*c*	*c*	14.6
6,8-di-*tert*-butylpurine[b]	neutral ($CDCl_3$)	149.7	153.8	132.5	163.0	168.5	

[a] These data could not be obtained due to slow decomposition with the large excess of potassium amide. It was therefore also very difficult to obtain ^{13}C NMR spectra of 6-methylpurine in liquid ammonia with potassium amide. [b] The signals of 6- and 8-*tert*-butyl groups appear at 38.6 and 29.4 ppm and 34.1 and 29.3 ppm, respectively. This shows that one of the *tert*-butyl groups must be at position 8 (H. C. van der Plas and A. Koudijs, unpublished results). The coupling constant for C-2 (J_{C-H} = 202 Hz) further shows that the other *tert*-butyl group must be at position 6 (see ref 17). [c] These data could not be obtained due to the very low solubility of this compound; however the position of the two signals and the coupling constant for C-2 (J_{C-H} = 197 Hz) show that this structure must be correct.

ination, the aromatization step, is thus the rate-determining step. The data further prove that addition of the amide ion to the anion of purine is *easily* possible.[15]

6-Methylpurine. In order to investigate whether the presence of a substituent at position 6 would lead to amination at another position, we investigated 6-methyl- (**5**) and 6,8-di-*tert*-butylpurine. It can be expected that the amination of methylpurines by potassium amide will be strongly retarded due to formation of a dianion through proton abstraction of both the NH and the methyl group. We found that the reaction of **5** with potassium amide in liquid ammonia for 140 h did not give a product. An ^{1}H NMR spectrum of this solution first showed the formation of anion **6**, which, with a larger excess of potassium amide, was completely converted into the dianion **7** as illustrated by the appearance of the CH_2^- signal as an AB quartet[16] (Scheme III, Table I). The ^{1}H NMR signals were assigned by comparison with those of 6-methyl-8-deuteriopurine. 6,8-Di-*tert*-butylpurine, from which only a monoanion and *no* dianion can be formed, was found to be completely inactive. These experiments show that blocking of position 6 in the purine ring does not lead to another position for nucleophilic attack!

2-Methylpurine. When 2-methylpurine (**8a**) is reacted with potassium amide in liquid ammonia for 70 h a tarry mass is obtained from which 2-methyladenine (**9a**, 20%) can be isolated; 5% of **8a** can be recovered (Scheme IV). The structure of **9a** was proven by mass spectroscopy and comparison of the ^{13}C NMR spectrum[17] and the UV spectrum[18] with those reported in the literature. The ^{1}H and ^{13}C NMR spectra of solutions of **8a** in liquid ammonia containing potassium amide showed the presence of an adduct at position 6 as shown by the upfield shift of 2.94 ppm for H-6 and 77.6 ppm for C-6. This adduct was slowly formed from the anion of 2-methylpurine (Table I and II). The assignment of the ^{1}H signals was unequivocally established by comparison with the signals of 2-methyl-

(15) This has also been found in 4-(methylamino)-5-bromopyrimidines. In these compounds a proton is abstracted from the substituent to form an anion, but in that case the formation of a σ adduct could not be shown [C. A. H. Rasmussen, H. C. van der Plas, P. Grotenhuis, and A. Koudijs, *J. Heterocycl. Chem.*, **15**, 1121 (1978)].

(16) 4-Methyl- and 4-methyl-5-bromopyrimidine (see ref 13) and 2-methylpyridine [J. A. Zoltewicz and L. S. Helmick, *J. Org. Chem.*, **38**, 658 (1973)] show a splitting of the methylene group into an AB pair of doublets (J = 2.3 Hz) when dissolved in liquid ammonia containing potassium amide. This is due to the rescinding of free rotation and the resulting difference in chemical environment of the methylene protons.

(17) M. C. Thorpe and W. C. Coburn, *J. Magn. Reson.*, **15**, 98 (1974).

(18) E. C. Taylor, O. Vogel, and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959); J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 318 (1944).

8-deuteriopurine. We found no spectroscopic evidence for the presence of a dianion, although this does not exclude the presence of this species in a very low concentration.

8-Methylpurine. After reacting 8-methylpurine (**8b**) with potassium amide for 70 h a tarry mass was obtained; we recovered 25% of **8b** and isolated 8-methyladenine (**9b**) in 25% yield. The structure of this product was confirmed by mass spectroscopy, ^{13}C-NMR spectroscopy, and comparison of the UV spectrum with that reported in the literature.[19] Reaction with ^{15}N-labeled potassium amide gave ^{15}N-labeled 8-methyladenine (% ^{15}N 7.4 (7.1)[9]). Diazotization[8] yielded unlabeled 8-methylhypoxanthine (% ^{15}N 0.0 (0.0)[9]) showing that the formation of **9b** from **8b** does not proceed via a ring-opening reaction. Compound **8b** thus reacts identically as purine toward potassium amide. Attempts to obtain spectroscopic evidence for the intermediacy of a σ adduct failed. The ^1H and ^{13}C NMR spectrum of a solution of **8b** in liquid ammonia containing potassium amide showed besides the monoanion only the presence of a dianion. This is clearly indicated by the small upfield shift observed: 1.07 ppm for H-2, 1.77 ppm for H-6, and 24.9 ppm for C-6 (Tables I and II). The ^{13}C signal of the side chain carbon was split into a triplet indicating the presence of a CH_2^- group. However in the ^1H NMR spectrum the signal of the hydrogens of the side chain at δ 2.48 appeared as a singlet instead of an AB quartet as observed for the signal of the CH_2^- group in 6-methyladenine. This is certainly due to the fact that both hydrogens are in a symmetrical chemical environment toward the imidazole ring (see formula **10**). It is unlikely that this *di*anion could be an intermediate in the amination (in case addition of an amide ion would take place it gives a *tri*anion); it seems therefore more likely that an adduct between a monoanion and the amide ion must be present in the solution, although in a concentration too low to be detected by NMR spectroscopy. We observed that 6-deuterio-8-methylpurine undergoes a rapid D/H exchange during the NMR measurements. This behavior is in remarkable contrast to the very slow D/H exchange observed with 6-deuteriopurine.

Experimental Section

^{13}C and ^1H NMR spectra were obtained with a Varian XL-100-15 spectrometer, equipped with a Varian 620/L16K computer. ^1H spectra were recorded also on a Jeol C-60H spectrometer, equipped with a JES-VT-3 variable temperature controller. When measuring in Me_2SO-d_6 internal Me_4Si was used as standard. When measuring in liquid ammonia the sample temperature was ca. −50 °C. For ^{13}C NMR spectra trimethylamine was used as internal standard. These spectra were converted to the Me_4Si scale by adding 47.5 ppm. Typical ^{13}C spectral parameters were as follows: spectral width 5120 Hz, acquisition time 0.8 s, pulse delay 1.2 s, pulse width 10 μs. For ^1H spectra NH_3 was used as standard. The spectra were converted to the Me_4Si scale by adding 0.95 ppm. Mass spectra and ^{15}N contents were determined on an AEI MS-902 mass spectrometer. IR spectra were obtained with a Perkin-Elmer 237 and an Hitachi EPI-G3 and UV spectra with a Beckman Acta CIII.

Preparation of Starting Materials. Purine[20] **and 2-methyl-**[21] **and 8-methylpurine**[22] were prepared as described in the literature. 6-Methylpurine was purchased from Sigma and adenine from Merck. ^{15}N-labeled ammonia was prepared by reacting ^{15}N-labeled ammonium nitrate (from VEB Berlin-Chemie) with potassium hydroxide.

6,8-Di-*tert*-butylpurine. Purine (1.3 g), 0.15 g of silver nitrate, and 6.5 g of pivalic acid were dissolved in a solution of 1 g of sulfuric acid in 10 mL of water.[23] With stirring 10 g of ammonium peroxydisulfate dissolved in 30 mL of water was added in 45 min, followed by an additional 45 min of stirring. The solution was made alkaline with aqueous sodium hydroxide and extracted with chloroform. The extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by column chromatography on silica gel using chloroform/ethyl acetate 1:1 as eluent, followed by sublimation in vacuo [160–180 °C (15 mm)] and recrystallization from hexane: yield 1.7 g (67%); mp 194–195 °C. Anal. Calcd for $C_{13}H_{20}N_4$: C, 67.20; H, 8.68. Found: C, 67.50; H, 8.81. The structure was proven by ^1H and ^{13}C NMR spectroscopy (see Table I and II).

8-Deuterio- and 2-methyl-8-deuteriopurine were obtained by refluxing purine and 2-methylpurine, respectively, in deuterium oxide.[24]

6-Deuterio-8-methylpurine was prepared by the same method.[24] The position of deuteration was proven by NMR spectroscopy.[25]

6-Deuteriopurine was prepared by introducing oxygen in a solution of 6-hydrazinopurine (prepared from 6-chloropurine)[26] in deuterium oxide containing sodium hydroxide.[27] For NMR measurements the deuterium labeled compounds were diluted to about 50% deuterium content.

Reactions with Potassium Amide. Purine (1 mmol) was reacted with 4 mmol of potassium amide dissolved in 15 mL of dry liquid ammonia. After 20 or 70 h the reaction was quenched with ammonium sulfate, the ammonia was evaporated, and the residue was extracted with methanol. Separation of the products was achieved by column chromatography or preparative TLC with mixtures of methanol and chloroform as eluent.

Acknowledgment. This investigation was carried out under the auspices of the Netherlands Foundations for Chemical Research (SON) and with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO). We are indebted to Drs. C. A. Landheer and Mr. W. P. Combé for the mass spectroscopy data, Mr. A. Koudijs for the synthesis of 6,8-di-*tert*-butylpurine, and Mr. H. Jongejan for carrying out the microanalysis.

Registry No. **1**, 120-73-0; **2**, 73-24-5; **5**, 2004-03-7; **6**, 50339-91-8; **7**, 70879-15-1; **8a**, 934-23-6; **8b**, 934-33-8; **9a**, 1445-08-5; **9b**, 22387-37-7; **10**, 70879-16-2; 6-deuteriopurine, 1194-61-2; 8-deuteriopurine, 1660-91-9; 6-methyl-8-deuteriopurine, 13479-71-5; 2-methyl-8-deuteriopurine, 13479-81-7; 6-deuterio-8-methylpurine, 13479-74-8; 6,8-di-*tert*-butylpurine, 70879-17-3; 6-amino-8-deuteriopurine, 70879-18-4; 2-methyl-6-amino-8-deuteriopurine, 70879-19-5; 6-hydrazinopurine, 70879-20-8; 6-chloropurine, 87-42-3; purine anion, 32074-46-7; 6-deuteriopurine anion, 70879-21-9; 8-deuteriopurine anion, 70879-22-0; 6-methyl-8-deuteriopurine anion, 70879-23-1; 6-methyl-8-deuteriopurine dianion, 70879-24-2; 2-methyl-8-deuteriopurine anion, 70879-25-3; 8-methylpurine anion, 70879-26-4; 8-methylpurine dianion, 70879-16-2; 6-deuterio-8-methylpurine anion, 70879-27-5; 6-deuterio-8-methylpurine dianion, 70891-77-9; ammonia-^{14}N, 13767-16-3; ammonium-^{15}N nitrate, 31432-48-1; pivalic acid, 75-98-9.

(19) We suggest that the values reported in the literature (λ_{max} 269 nm at pH 1 and 266 nm at pH 10) were interchanged. We found the same values of λ_{max} but interchanged at the different pHs, thus λ_{max} 266 nm at pH 1 and 269 nm at pH 10. All related compounds (purine λ_{max} 260 nm at pH 0.3 and λ_{max} 271 nm at pH 11, 2-methylpurine λ_{max} 266 at pH 1 and λ_{max} 275 nm at pH 11, 8-methylpurine λ_{max} 264 nm at pH 0 and λ_{max} 274 nm at pH 12, adenine λ_{max} 263 nm at pH 2 and λ_{max} 269 nm at pH 12, 2-methyladenine λ_{max} 266 nm at pH 1 and λ_{max} 271 nm at pH 13, and 2,8-dimethyladenine λ_{max} 269 nm at pH 1 and λ_{max} 271 nm at pH 11) show that the λ_{max} at pH 1 is always lower than at pH 10 [H. C. Koppel and R. K. Robins, *J. Org. Chem.*, **23**, 1457 (1958); see also ref 2].

(20) J. A. Montgomery and C. Temple, *J. Org. Chem.*, **25**, 395 (1960).

(21) R. N. Prasad, C. W. Noell, and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 193 (1959); R. K. Robins, J. W. Jones, and H. H. Lin, *J. Org. Chem.*, **21**, 695 (1956).

(22) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

(23) We applied the same procedure as described before; see H. C. van der Plas and A. Koudijs, *Recl. Trav. Chim. Pays-Bas*, **97**, 159 (1978).

(24) R. J. Pugmire, D. M. Grant, R. K. Robins, and G. W. Rhodes, *J. Am. Chem. Soc.*, **87**, 2225 (1965).

(25) S. Matsuura and T. Goto, *J. Chem. Soc.*, 623 (1965).

(26) This reaction was carried out with hydrazine hydrate instead of anhydrous hydrazine [J. A. Montgomery and L. B. Holum, *J. Am. Chem. Soc.*, **79**, 2185 (1957)].

(27) C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **30**, 3601 (1965).