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A Novel N-Amination Method and Its Application to the Preparation of N-Aminoheterocycles

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A novel N-amination method was investigated under various conditions and optimum reaction condition was established. The method was successfully applied for the synthesis of 1-aminoindoles, 1-aminobenzimidazole, and 9-aminopurines. Some chemical reactivity of 9-aminopurines was investigated.

Keywords——hydroxylamine O-sulfonic acid; N-aminoindoles; N-aminopurines; nuclear Overhauser effect; ^{13}C nuclear magnetic resonance spectra

In our previous papers, we reported a direct method for the synthesis of 1-aminoindoles[2] and also discussed the chemical behavior of their N-amino group toward aldehydes, α,β-unsaturated aldehydes, 1,3-dicarbonyl compounds, and 1,4-diketone.[3,4]

The experimental procedure for the preparation of 1-aminoindoles involved the addition of hydroxylamine O-sulfonic acid[5] (5 mmol) to a stirred suspension of indoles (1 mmol) and crushed potassium hydroxide (25 mmol) in anhydrous dimethylformamide. After violent and exothermic reaction ceased, the product was extracted with benzene and isolated by column chromatography over silica gel. As the reaction gave variable yields of 1-aminoindoles, we repeated the amination reaction under various conditions in order to establish an optimum reaction condition and the result is summarized in Tables I and II.

The reaction was carried out using excess sodium hydride in place of potassium hydroxide, expecting that the formation of the indole sodium salt in adevance might enhance the yield of 1-aminoindole (2), but 2 was not detected in the reaction mixture (run 1). The yield of 2 increased gradually in proportion to the ratio of potassium hydroxide to sodium hydride (runs 2 and 3). However, high reaction temperature resulted in a low yield (run 4). When potassium hydroxide alone was used, the yield increased up to 39.3% (run 5), implying

Table I. N-Amination of Indole (1)

Run No.	Indole (1) (g)	Abs. DMF (ml)	Base (g) NaH	Base (g) KOH	NH_2OSO_3H (g)	Reaction Temp. (°C)	Reaction Time (hr)	Recovery (g)	1-Aminoindole (2) Yield (g)	1-Aminoindole (2) Yield (%)
1	0.355	10	1.185	—	0.703	Room temp	Over night	Quant.	0	0
2	0.350	6	0.270	0.556	0.678	r.t.	o.n.	0.215	0.049	12.5
3	0.357	7	0.159	0.856	0.691	r.t.	o.n.	0.242	0.064	16.3
4	0.363	7	0.164	0.768	0.730	84	o.n.	0.246	0.036	8.8
5	1.552	25	—	15.528	5.540	r.t.	4	0.716	0.678	39.3

1) Location: *Tamagawa 2–28–10, Setagaya-ku, Tokyo 158, Japan.*
2) M. Somei and M. Natsume, *Tetrahedron Lett.*, **1974**, 461.
3) M. Somei and M. Natsume, *Tetrahedron Lett.*, **1974**, 3605.
4) M. Somei, M. Matsubara, and M. Natsume, *Chem. Pharm. Bull.* (Tokyo), **23**, 2891 (1975).
5) R. Gösl and A. Meuwsen, *Chem. Ber.*, **92**, 2521 (1959).

Table II. N-Amination of 3-Methylindole (3)

Run No.	3-Methyl-indole (3) (g)	Abs. DMF (ml)	KOH (g)	NH_2OSO_3H (g)	Reaction Temp.	Reaction Time	Recovery (g)	1-Amino-3-methyl-indole (4) (g)	1-Amino-3-methyl-indole (4) (%)
6	1.456	30	15.156	4.952	r.t.	2 hr	0.619	0.655	40.5
7	0.552	10 + H_2O 3	4.633	2.416	r.t.	1 hr 20 min	0.500	0	0
8	2.700	50	24.500	11.292	r.t.	1 hr	0.711	1.995	66.5

Table III. Reaction of 1-Amino-3-phenylthioindole (5) with Base

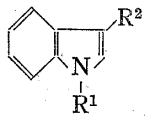
Run No.	Solvent	Base	Reaction Temp. (°C)	Reaction Time (hr)	3-Phenylthio-indole (6) (%)	Recovery of 5 (%)
9	Abs. DMF	KOH	55—60	1	49.5	20.0
10	Abs. DMF + H_2O (20%)	KOH	35—40	1	26.7	61.5
11	Abs. DMF	NaH	r.t.	3.25	52.4	17.0
12	Abs. DMSO	KOH	70—75	1	91.7	0

Table IV. Reaction of 1-Amino-3-methylindole (4) with Base

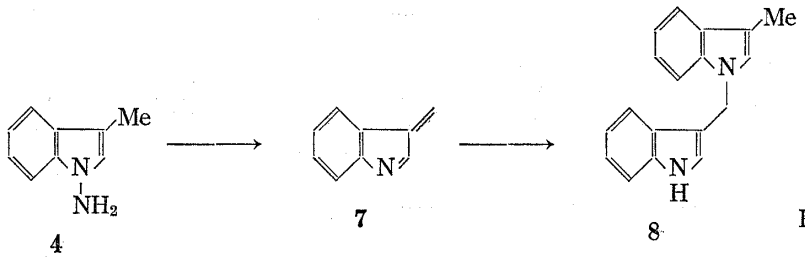
Run No.	Solvent	Base	Reaction Temp. (°C)	Reaction Time (hr)	3-Methyl-indole (3) (%)	Recovery of 4 (%)	Formation of 8 (%)
13	Abs. DMF	KOH	65—75	1	40.4	16.0	15.7
14	Abs. DMF + $CH(COOEt)_2$ $CH(COOEt)(NHAc)$	KOH	120—130	0.5	7.9	80.3	0
15	Abs. DMF + H_2O (33%)	KCN	97—102	1	0	97.0	0

Table V. Solvent Effect in the N-Amination of 3-Methylindole (3)

Solvent	1-Amino-3-methyl-indole (4) (%)
Abs. DMF	66.5
Abs. DMSO	30.2
Abs. benzene	0



1: $R^1=R^2=H$ **3**: $R^1=H$, $R^2=Me$ **5**: $R^1=NH_2$, $R^2=SPh$
2: $R^1=NH_2$, $R^2=H$ **4**: $R^1=NH_2$, $R^2=Me$ **6**: $R^1=H$, $R^2=SPh$



Ph=phenyl

Chart 1

that potassium hydroxide had really been a suitable base for this reaction. No desired product was detected in the reaction medium containing water (run 7). Shortening of the reaction time increased the yield (runs 6 and 8), and this fact together with the knowledge of run 4, seemed to suggest that deamination took place while 1-aminoindoles were present in the reaction mixture. Therefore, 1-aminoindoles (**4**, **5**) were treated with bases without hydroxylamine O-sulfonic acid, and its result is summarized in Tables III and IV. Deamination was actually observed either with potassium hydroxide or sodium hydride and was complete in dimethyl sulfoxide (run 12). The formation of 3-methyl-indol-3′-ylmethylindole (**8**; run 13) might be attributed to cleavage of the N–N bond in 1-amino-3-methylindole, affording 3-methyleneindolenine (**7**) as an intermediate, which was subsequently attacked by 3-methylindole as illustrated in Chart 1. An attempt to trap the intermediate was carried out by the addition of diethyl α-acetaminomalonate in the reaction mixture but only retardation of deamination was observed (run 14). The solvent effect is summarized in Table V, which revealed clearly that anhydrous dimethylformamide was the most suitable solvent.

From these results we can conclude that N-amination should be carried out with following points in mind: (i) Water or moisture should be avoided. (ii) The most suitable solvent and base are anhydrous dimethylformamide and potassium hydroxide. (iii) Rapid work-up is necessary, because N-amination and deamination are competitive in this reaction, although the former reaction is more rapid than the latter.

Taking these points into consideration, this N-amination method was successfully applied to benzimidazole, and 1-aminobenzimidazole (**9**) was obtained in 12.7% yield. As a number of 1-aminobenzimidazoles was reported to be prepared through a series of reactions,[6] this N-amination method has made it possible to synthesize **9** in one step with ease. The compound (**9**) was treated with acetonylacetone in the presence of acetic acid to afford 1-2′,5′-dimethyl-

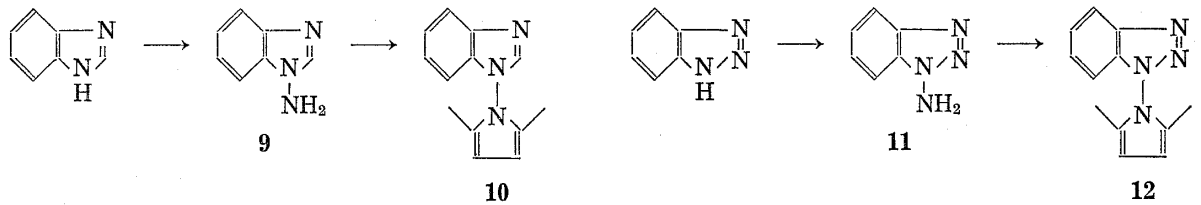


Chart 2

6) C. Hanna and F.W. Schueler, *J. Am. Chem. Soc.*, **74**, 3693 (1952); W. Ried and G. Urlass, *Ber.*, **86**, 1101 (1953); R.A. Abramovitch and K. Schofield, *J. Chem. Soc.*, **1955**, 2326; C.G. Overberger, J.G. Lombardino, and R.G. Hiskey, *J. Am. Chem. Soc.*, **79**, 6430 (1957); M.N. Sheng and A.R. Day, *J. Org. Chem.*, **28**, 736 (1963).

pyrrol-1′-ylbenzimidazole (**10**), which was obtained in 24.6% yield from benzimidazole. When this N-amination method was applied to 1,2,3-benzotriazole, only 1-amino-1,2,3-benzotriazole (**11**) was obtained in a poor yield (6.6%) and the corresponsing 2-amino derivative was not detected. Treatment of **11** with acetonylacetone afforded 1-2′,5′-dimethylpyrrol-1′-yl-1,2,3-benzotriazole (**12**) in 85.3% yield.

In the field of purine derivatives, no general and direct route to 9-aminopurine has so far been reported, and synthetic methods for 9-aminopurines have been described through a number of reaction steps.[7] By the N-amination method, 6-benzylaminopurine (**13**) afforded 9-amino-6-benzylaminopurine (**14**) in 25.5% yield, together with the production of an isomeric N-amino product (**15**) in 5.1%. Acetonylacetone was reacted with **14** in acetic acid to give 6-benzylamino-9-2′,5′-dimethylpyrrol-1′-ylpurine (**16**) in 61.7% yield, and **16** was obtained in 17.9% overall yield when the reaction was carried out without isolation of **14**. Treatment of **16** with acetic anhydride gave 6-acetamidobenzyl-9-2′,5′-dimethylpyrrol-1′-ylpurine (**17**) in 92.8% yield.

The structure of 9-amino-6-benzylaminopurines was estabiliahed as follows: Ultraviolet (UV) spectra of **13**, **14**, **16**, and **17** exhibited absorption maxima at 272, 272.5, 271, and 279.5 nm, respectively, in 95% ethanol, and no shift of the maximum was observed in the case of **16** by the addition of aqueous sodium hydroxide, suggesting that these compounds are 9-substituted purines.[8]

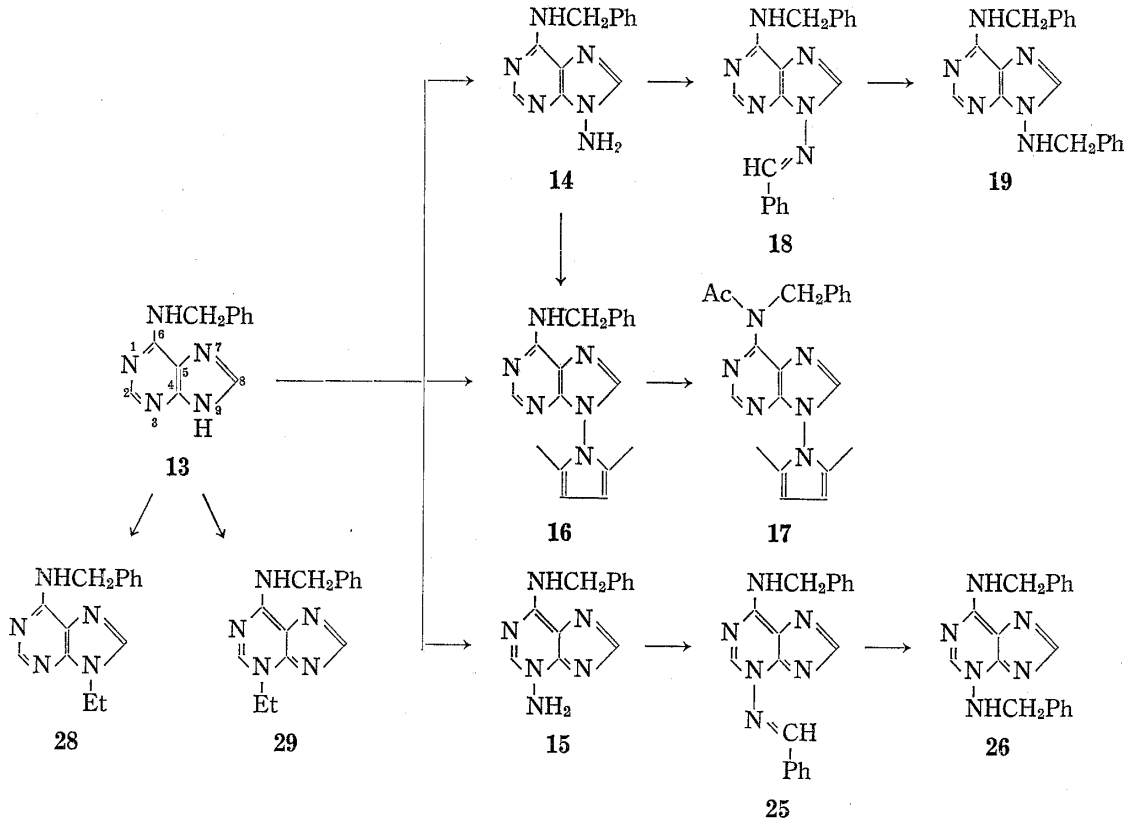


Chart 3

7) J.A. Montgomery and C. Temple, *J. Am. Chem. Soc.*, **82**, 4592 (1960); C.L. Leese and G.M. Timmis, *J. Chem. Soc.*, **1961**, 3818; C. Temple, R.L. McKee, and J.A. Montgomery, *J. Org. Chem.*, **28**, 923, 2257 (1963); M.H. Krackov and B.E. Christensen, *ibid.*, **28**, 2677 (1963); C. Temple, B.H. Smith, and J.A. Montgomery, *ibid.*, **33**, 530 (1968).

8) B.R. Baker, R.E. Sehaub, and J.P. Joseph, *J. Org. Chem.*, **19**, 638 (1954); R.K. Robins and H.H. Lin, *J. Am. Chem. Soc.*, **79**, 490 (1957); T. Kunieda and B. Witkop, *J. Org. Chem.*, **35**, 3981 (1970).

In the proton magnetic resonance (PMR) spectral study of purine derivatives, hydrogen-deuterium exchange is well established to occur at their C-8 position,[9] and therefore, the C-8 proton signals can be asigned in the NMR spectra of **13** and **16**, which showed aromatic protons at δ 7.99 and 8.23, and at δ 7.80 and 8.45, respectively. The compounds (**13** and **16**) were deuterated when refluxed in a mixture of deuterium oxide and tetradeuteromethanol, and the PMR spectra of the deuterated compounds revealed that the proton signals resonating at a higher magnetic field (δ 7.99 or 7.80) was proved to be ascribable to C-8 protons in 6-benzylaminopurine derivatives. Then, nuclear Overhauser effect (NOE) was measured in **16** and **17**, the latter exhibiting purine protons at δ 8.16 and 8.70. When the methyl group in the pyrrole ring was irradiated, NOE was detected at δ 7.80 signal of **16** and at δ 8.16 signal of **17** by 15.3% and 18.8%, respectively, and no effect was observed at benzyl and C-2 protons. Thus, the site of the amination in **14** was unequivocally determined to be the 9-position.

The compound (**14**) was condensed with benzaldehyde to afford 9-benzylideneamino-6-benzylaminopurine (**18**) in 88.2% yield. It is notable that the benzylidene proton appeared

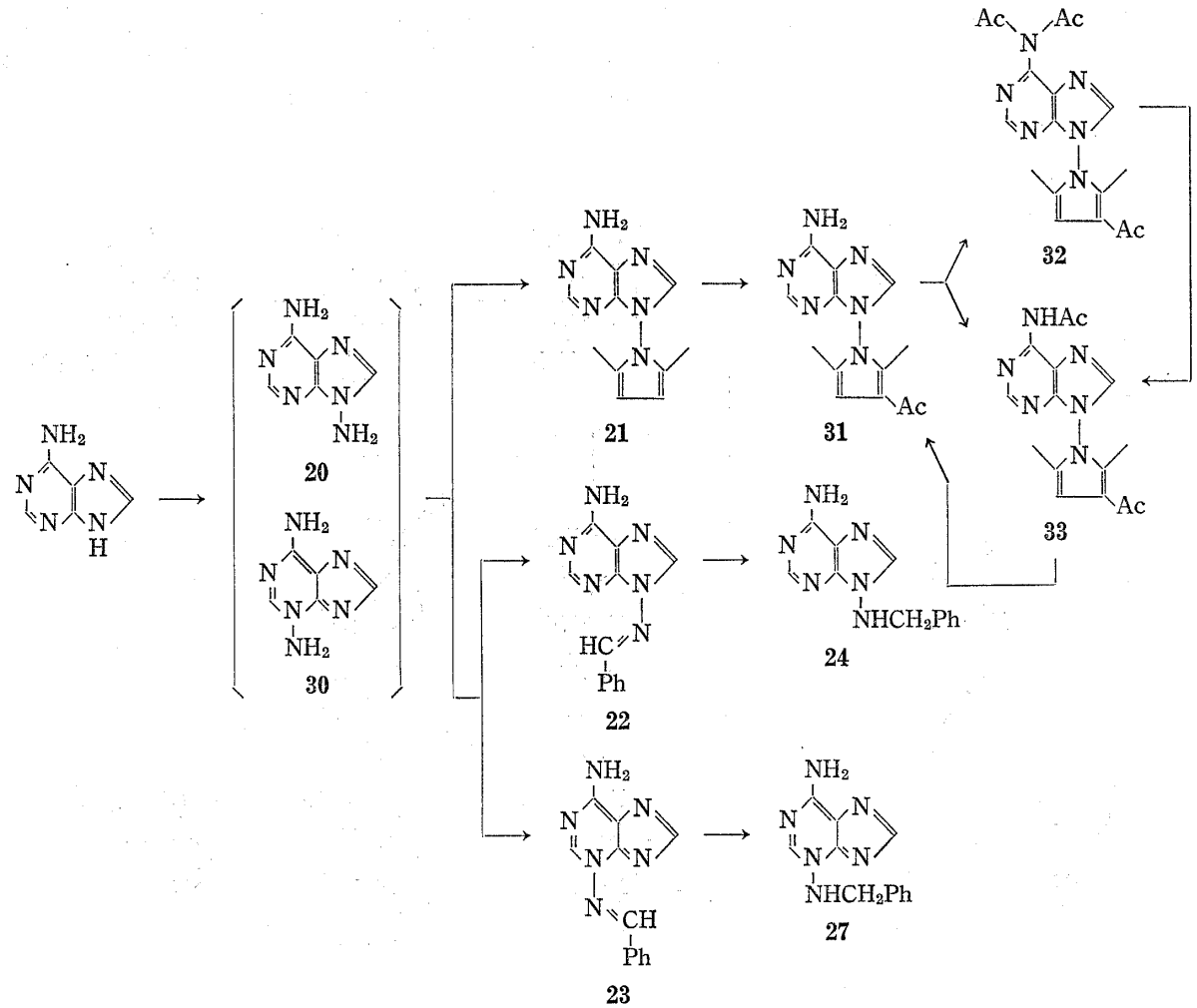


Chart 4

9) M.L. Eidinoff and J.E. Knoll, *J. Am. Chem. Soc.*, **75**, 1992 (1953); M.P. Schweizer, S.I. Chen, G.K. Helmkamp, and P.O.P. Ts'O, *ibid.*, **86**, 696 (1964); F.J. Bullock and O. Jardetzky, *J. Org. Chem.*, **29**, 1988 (1964); J.M. Harris and J.C. Randall, *Chem. and Ind.*, **1965**, 1728; J.M. Rice and G.O. Dudek, *J. Am. Chem. Soc.*, **89**, 2719 (1967); P.O.P. Ts'O, N.S. Kondo, R.K. Robins, and A.D. Broom, *ibid.*, **91**, 5625 (1969); F. Bergman, D. Lichtenberg, and Z. Neimann, *J. Chem. Soc.* (*D*), *Chem. Commun.*, **1969**, 992; W.J. Wechter, *Coll. Czech. Chem. Commun.*, **35**, 2003 (1970); M. Maeda, M. Saneyoshi, and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **19**, 1641 (1971).

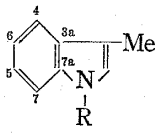
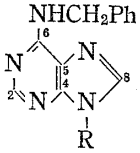
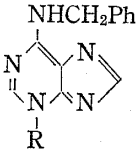
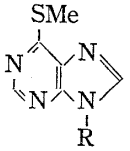
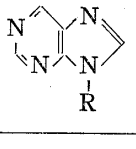
at δ 10.05 in its PMR spectrum, and this fact might be the result of the deshielding effect of N-3. The compound (**18**) was easily reduced with sodium borohydride to give 6,9-bis(benzylamino)purine (**19**) in a quantitative yield.

6-Aminopurine was similarly N-aminated, but the isolation of 6,9-diaminopurine (**20**) itself has so far been unsuccessful. Therefore, after amination, the reaction mixture was reacted with acetonylacetone in acetic acid and 6-amino-9-2′,5′-dimethylpyrrol-1′-ylpurine (**21**) was obtained in 9.6% overall yield. The structural proof was obtained by the same method as stated in the case of **14**. The compound (**21**) exhibited two aromatic protons (δ 7.96 and 8.45) in its PMR spectrum and on irradiation of the methyl group in the pyrrole ring, NOE was observed at δ 7.96 signal by 11.5%. This evidence, together with the UV absorption maximum at 261 nm both in neutral and alkaline ethanol (6-aminopurine, 261 nm), established the product (**21**) to be a 9-substituted purine.

When the N-aminated reaction mixture derived from 6-aminopurine was treated with benzaldehyde, 6-amino-9-benzylideneaminopurine (**22**) and isomeric benzylideneaminopurine (**23**) were obtained in 4.6% and 0.35% yield, respectively. The compound (**22**) exhibited benzylidene proton at δ 10.04 and UV absorption maxima at 266.5 and 286 nm (shoulder), and these data were very similar to those of **18** [276 and 290 nm (shoulder)]. The compound (**22**) was easily reduced to 6-amino-9-benzylaminopurine (**24**; 262.5 nm) in a quantitative yield.

The by-product (**15**) of the N-amination reaction of 6-benzylaminopurine (**13**) was similarly condensed with benzaldehyde and gave the corresponding benzylideneamino derivative (**25**) in 97.4% yield, and its UV absorption spectrum (maxima at 265 and 336 nm) was similar to that of **23** (maxima at 270.5 and 327.5 nm). Both **25** and **23** were reduced with sodium borohydride to dihydro compounds (**26** and **27**) in a poor yield, and this result was in sharp contrast to the 9-substituted derivatives. UV spectra of **15**, **26**, and **27** showed absorption

Table VI. CMR Data of Indole and Purine Derivatives ($CDCl_3$, ppm from TMS)

		C_2	C_3	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}
	R=Me	127.1	110.8	129.6	119.5	122.0	119.5	109.6	137.9
	4: R=NH_2	127.1	108.0	126.7	118.9	121.7	118.9	108.2	137.0
		C_2			C_4	C_5	C_6		C_8
	**28**: R=Et	152.5			149.2	119.2	154.5		140.4
	14: R=NH_2	152.4			149.3	117.5	154.5		141.9
	**29**: R=Et	152.6	149.0	121.1	153.4	143.3			
	15: R=NH_2	152.4	150.0	121.5	152.8	143.8			
	R=ribosyl[a]	151.5	148.0	131.3	160.5	143.1			
	34: R=NH_2	151.5	148.1	129.4	159.9	145.6			
	R=Me[a]	151.9	151.4	133.5	147.4	147.4			
	35: R=NH_2	152.4	151.5	132.6	148.2	148.2			

a) M.-T. Chenon, R.J. Pugmire, D.M. Grant, R.P. Panzica, and L.B. Townsend, *J. Am. Chem. Soc.*, **97**, 4627 (1975).

maxima at 295, 297, and 273 nm, suggesting that these compounds might be 3-substituted purines (3-ethyl-6-benzylaminopurine, 296 nm; 3-methyl-6-aminopurine, 274 nm[10]).

Confirmation of this assumption was achieved by the following procedures. i) ^{13}C-nuclear magnetic resonance (CMR) spectrum of an N-amino derivative was compared with that of a corresponding N-alkyl derivative in order to find out some correlations between two spectra. ii) 3-Ethyl-6-benzylaminopurine (**29**) was synthesized by the standard method and its structure was established by observation of NOE. iii) Bearing the relationship of the procedure i) in mind, correspondence was found in the CMR spectra between N-amino derivative in question (*i.e.*, **15**) and 3-ethyl derivative (**29**).

The CMR spectrum of 1-amino-3-methylindole (**4**) was compared with that of 1,3-dimethylindole (Table VI) and a marked resemblance was detected between chemical shifts of the corresponding carbon atoms. The same similarity was also observed in the CMR spectra of 9-amino-6-benzylaminopurine (**14**) and 6-benzylamino-9-ethylpurine, and these facts strongly suggested that the position of N-substitution of an unknown N-aminoheterocycle could be determined by comparing its CMR spectrum with those of known N-alkyl derivatives.

In order to synthesize a specimen for the comparison of CMR spectrum of **15**, 6-benzylaminopurine (**13**) was treated with triethyl phosphate in dimethylformamide,[11] and two products, 9- and 3-ethyl derivatives (**28** and **29**) were obtained. The structure of **29** (PMR, δ 7.95, 8.00) was again deduced from the NOE study of its PMR spectrum and 15% of NOE was observed between methylene proton of the N-ethyl group and an aromatic proton at δ 8.00, the same phenomenon being characteristic in the case of 6-amino-3-ethylpurine[12] (PMR, δ 8.03, 8.27), where the NOE between the N-ethyl methylene proton and the δ 8.27 proton was 23%. As shown in Table VI, ^{13}C chemical shifts of 3-ethyl derivative was found to be very close to those of **15**, and therefore, the structure of **15** was confirmed as 3-amino-6-benzylaminopurine. Since the UV absorption spectra of two benzylideneamino derivatives (**25** and **23**) were similar to each other, **23** was also considered to be derived from the 3-aminated product and 3,6-diaminopurine (**30**) was concluded to be produced as a by-product by the N-amination reaction of 6-aminopurine.

Next, some reaction of the pyrrole derivative (**21**) was studied. When **21** was refluxed with acetic anhydride and treated subsequently with aqueous 2 N sodium hydroxide, 6-amino-9-2′,5′-dimethyl-3′-acethylpyrrol-1′-ylpurine (**31**) was produced in 34.1% yield, accompanied with the recovery of **21** in 40% yield, and the evidence that the acetyl moiety was introduced into the pyrrole ring was provided by the PMR spectrum of **31**. 6-Amino proton appeared as a broad singlet at δ 6.31—6.66 (2H, disappeared by the addition of deuterium oxide) and 2′- and 5′-methyl protons showed a different chemical shift. Furthermore, C-4′ proton on the pyrrole ring appeared as a quartet (1H, J=1 Hz).

The compound (**31**) was further refluxed with acetic anhydride and afforded 6-diacetylamino-9-2′,5′-dimethyl-3′-acetylpyrrol-1′-ylpurine (**32**) and 6-acetylamino-9-2′,5′-dimethyl-3′-acetylpyrrol-1′-ylpurine (**33**) in 30.5 and 37.0% yield, respectively. The compound (**32**) was found to be extremely unstable and easily changed to **33** during purification over silica gel, and this change was accomplished more readily by the action of alkali. The compound (**32**) showed an infrared (IR) absorption band at 1720 cm^{-1}, a molecular ion peak at *m/e* 354 in its mass spectrum, and equivalent 6H singlet at δ 2.42 in its PMR spectrum. On the other hand, **33** showed IR band at 1705 cm^{-1}, molecular ion peak at *m/e* 312, and 1H broad singlet at δ 9.35—9.55 (amide-NH, disappeared by the addition of deuterium oxide). These data were in good agreement with the structure of **32** and **33**. **33** was easily converted to **31** by

10) R.N. Prasad and R.K. Robins, *J. Am. Chem. Soc.*, **79**, 6401 (1957); E.D. Bergmann, H.W. Feilchenfeld, and Z. Neiman, *J. Chem. Soc.* (*B*), **1970** 1335.
11) K. Yamauchi, M. Hayashi, and M. Kinoshita, *J. Org. Chem.*, **40**, 385 (1975).
12) T. Fujii and T. Saito, *Chem. Pharm. Bull.* (Tokyo), **21**, 1954 (1973).

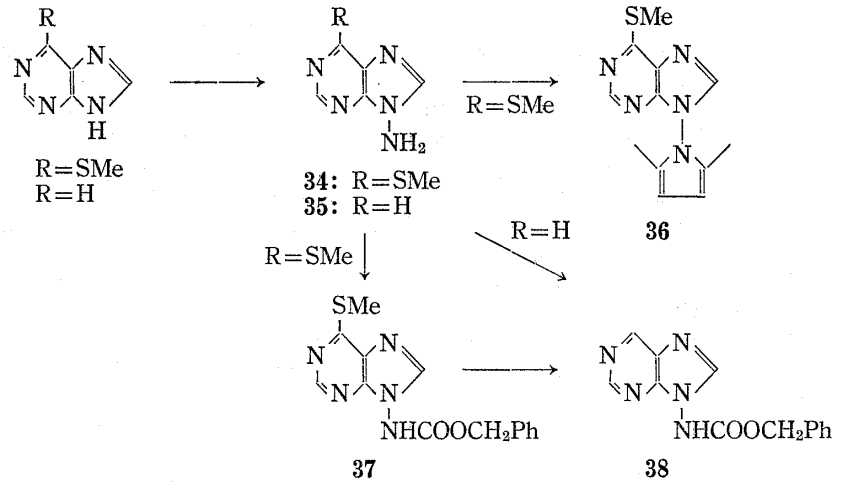


Chart 5

the action of aqueous 2 N sodium hydroxide, and such ready hydrolysis has been reported in the chemistry of 6-aminopurines.[13]

6-Methylthiopurine and purine itself were subjected to this amination reaction and single products, **34** and **35** were obtained in 11% and 6% yield, together with 83% and 63% recovery of the starting material, respectively. CMR data of **34** and **35** were compared with the corresponding N-alkyl derivatives (Table VI) and both were proved to be 9-amino derivatives. The compound (**34**) was reacted with acetonylacetone in a usual manner and afforded 9-2′, 5′-dimethylpyrrol-1′-yl-6-methylthiopurine (**36**) in 69.9% yield, whereas **34** was benzyloxycarbonylated to **37** in 77% yield, and desulfurization of the latter was achieved with Raney-nickel in refluxing ethanol to give **38** in 62% yield. 9-Aminopurine (**35**) was also benzyloxycarbonylated to **38**, and identification of both samples supported the structure of **35**.

The present method may be applicable to a variety of heterocyclic compounds, but is not effective for compounds containing an acidic NH group. Thus, 3-acetylindoles, phenothiazine, 6-mercaptopurine, and 6-hydroxypurine were not N-aminated, and these were recovered intact.

Experimental

Melting points were obtained on Yanagimoto micro-melting point apparatus and are not corrected. Ultraviolet absorption spectra were recorded on Hitachi EPS-3 UV spectrophotometer. Infrared absorption spectra were determined on Hitachi 215 IR spectrophotometer. Proton magnetic resonance spectra were measured at 60 MHz on Varian A-60 A spectrometer. Mass spectra were taken on Hitachi RMS-4 spectrometer. Merck silica gel PF_{254} and Merck alumina GF_{254} (Type E) were used for the preparative thin-layer chromatography (prep TLC).

Preparation of 1-Aminoindole (2) and 1-Amino-3-methylindole (4) (Table I and II)——Run 1: Hydroxylamine O-sulfonic acid (703 mg) was added to a stirred solution of indole sodium salt, prepared from indole (355 mg) and 50% NaH (1.185 g, washed with benzene three times), in anhyd. dimethylformamide (DMF) (10 ml). After violent exothermic reaction ceased, the reaction mixture was allowed to stand overnight at room temperature with stirring and extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was chromatographed over silica gel using CH_2Cl_2–hexane (1: 1) and indole was recovered in quantitative yield.

Run 2—4: To a stirred DMF solution of indole sodium salt, prepared from indole and 50% NaH (washed with benzene), crushed KOH was added and then hydroxylamine O-sulfonic acid was added to the resulting suspension. The mixture was stirred overnight at room temperature or at 84° (Run 4) and worked up in the usual way as stated in Run 1. The product was chromatographed over silica gel using CH_2Cl_2–hexane (1: 1). The earlier eluate gave the recovered indole. Further elution of the column with the same solvent system afforded 1-aminoindole[2] (**2**).

13) A.H. Schein, *J. Med. Pharm. Chem.*, **5**, 302 (1962).

Runs 5, 6, and 8: Hydroxylamine O-sulfonic acid was added to a stirred suspension of indole or 3-methylindole and crushed KOH in anhyd. DMF. After violet exothermic reaction ceased, stirring was continued for the appropriate time at room temperature. After usual work-up, **2** or **4** was obtained, accompanied by the recovery of the starting material. 1-Amino-3-methylindole (**4**), mp 59.5—60.5°. *Anal.* Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 73.90; H, 7.09; N, 19.00. IR ν_{max}^{KBr} cm^{-1}: 3600—3000, 1450, 735. NMR (CCl_4) δ: 7.77 (3H, d, J=1 Hz), 5.72 (2H, br. s, disappeared by the addition of D_2O), 3.30 (1H, q, J=1 Hz), 3.17—2.50 (4H, m). MS *m/e*: 146 (M^+), 130.

Run 7: In this case, the mixture of anhyd. DMF (10 ml) and H_2O (3 ml) was used as a solvent. Only the recovery of the starting material was observed.

Behavior of 1-Aminoindoles with Bases——Run 9: To a solution of 1-amino-3-phenylthioindole (**5**, 25 mg) in anhyd. DMF (2 ml), crushed KOH (712 mg) was added. The mixture was allowed to stand at 55—60° for 1 hr with stirring. The solution gradually turned to clear green. After addition of H_2O, the reaction mixture was extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was subjected to prep TLC (silica gel) using CH_2Cl_2–hexane (7:3). The upper band gave 3-phenylthioindole (**6**, 11.5 mg, 49.5%). The lower band gave the recovery of the starting material (5 mg, 20%).

Run 10: To a solution of **5** (26 mg) in anhyd. DMF (2 ml) and H_2O (0.5 ml), crushed KOH was added. After the usual work-up and prep-TLC were obtained **5** (16 mg, 61.5%) and **6** (6.5 mg, 26.7%).

Run 11: 50% NaH (23 mg, washed with benzene) was added to a solution of **5** (53 mg) in anhyd. DMF (2 ml). After stirring for 3.25 hr at room temperature, usual work-up afforded **5** (9 mg, 17.0%) and **6** (26 mg, 52.4%).

Run 12: Anhyd. dimethylsulfoxide was used as a solvent in place of DMF. **5** (23 mg) was changed exclusively to **6** (19 mg, 91.7%).

Run 13: To a solution of 1-amino-3-methylindole (50 mg) in anhyd. DMF (3 ml), crushed KOH (1.027 g) was added. The mixture was allowed to stand at 65—75° for 1 hr with stirring. After addition of H_2O, the reaction mixture was extracted with benzene. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was subjected to prep TLC (silica gel) using CH_2Cl_2–hexane (3:7). The upper band gave **3** (18 mg, 40.4%). The middle band gave 3-methyl-indol-3′-ylmethylindole (**8**, 7 mg, 15.7%). Recrystallization from MeOH afforded colorless prisms, mp 144—145°. *Anal.* Calcd. for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 82.82; H, 6.20; N, 10.72. IR ν_{max}^{KBr} cm^{-1}: 3410, 1607. PMR (CCl_4) δ: 2.25 (3H, d, J=1 Hz), 5.28 (2H, s, CH_2), 6.58 (1H, br. s), 6.75 (1H, br. s), 6.83—7.66 (9H, m, 1H disappeared by the addition of D_2O). MS *m/e*: 260 (M^+), 131, 130. The lower band gave **4** (8 mg, 16%).

Run 14: In this case, ethyl α-acetaminomalonate was added. After usual work-up, the residue was subjected to prep TLC to afford **3** (7.9%) and **4** (80.3%).

Run 15: To a solution of **4** (60 mg) in anhyd. DMF (2 ml) and H_2O (1 ml), KCN (1.700 g) was added. The mixture was stirred at 97—102° for 1 hr. After usual work-up, only **4** (58 mg, 97.0%) was obtained.

1-Aminobenzimidazole (**9**)——Hydroxylamine O-sulfonic acid (4.912 g) was added to a stirred suspension of benzimidazole (2.059 g) and crushed KOH (13.20 g) in anhyd. DMF (40 ml). After stirring for 15 min, H_2O was added to the reaction mixture and the resulting solution was shaken with benzene. The benzene solution was washed with H_2O, dried over Na_2SO_4 and evaporated. Since the separation of the products was difficult, a part of the residue (1.113 g) was subjected repeatedly to prep TLC (silica gel) and 1-aminobenzimidazole (**9**) was obtained, accompanied with benzimidazole. 1-Aminobenzimidazole (**9**), colorless leaflets from MeOH, mp 154.5—155.5°. *Anal.* Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 62.94; H, 5.30; N, 31.28. IR ν_{max}^{KBr} cm^{-1}: 3600—3000, 1640, 738. PMR ($CDCl_3$) δ: 4.84 (2H, br. s, disappeared by the addition of D_2O), 7.16—8.03 (4H, m), 7.91 (1H, s). MS *m/e*: 133 (M^+). The rest of the residue was reacted with acetonylacetone to give **10**. From the yield of **10**, the yield of **9** was calculated to be 12.7%.

1-2′,5′-Dimethylpyrrol-1′-ylbenzimidazole (**10**)——Hydroxylamine O-sulfonic acid (1.820 g) was added to a stirred suspension of benzimidazole (1.029 g) and crushed KOH (5.787 g) in anhyd. DMF (20 ml). After stirring for 20 min, H_2O was added and the mixture was extracted with CH_2Cl_2–MeOH (9:1). The CH_2Cl_2 layer was washed with H_2O, dried over Na_2SO_4, evaporated *in vacuo* to leave an oil, which was dissolved in AcOH (4 ml). To this solution, a solution of acetonylacetone (775 mg) in MeOH (1 ml) was added. After stirring for 90 hr at room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2–MeOH (95:5), and washed subsequently with H_2O, aqueous sodium bicarbonate, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed over silica gel using CH_2Cl_2. The earlier eluate gave a 1:1 mixture of **10** and acetonylacetone (849 mg), which was dissolved in MeOH (14 ml), and 2,4-dinitrophenylhydrazine (91 mg) and acetic acid (1 ml) were added to this solution. After stirring for 17 hr, precipitate was filtered. The filtrate was evaporated *in vacuo* to leave an oil, which was worked up as usual and resulting syrup was purified by chromatography over silica gel using CH_2Cl_2 to afford colorless prisms (474 mg, 24.6%), mp 90—91° from CCl_4. *Anal.* Calcd. for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 74.12; H, 6.38; N, 19.78. IR ν_{max}^{KBr} cm^{-1}: 1423, 1220, 730. PMR (CCl_4) δ: 1.90 (6H, s), 5.83 (2H, s), 6.87—7.43 (3H, m), 7.87 (1H, s), 7.63—7.91 (1H, m). MS *m/e*: 211 (M^+), 118.

1-Amino-1,2,3-benzotriazole (11)——Hydroxylamine O-sulfonic acid (2.669 g) was added to a stirred suspension of 1,2,3-benzotriazole (1.002 g) and crushed KOH (7.320 g) in anhyd. DMF (16.8 ml). After stirring for 10 min, H_2O was added to the reaction mixture and the solution was extracted with benzene, and then with CH_2Cl_2–MeOH (97:3). Both extracts were combined, washed with H_2O, dried over Na_2SO_4 and the solvent was evaporated to give crystals, which were purified by prep TLC (silica gel) using CH_2Cl_2–MeOH (98:2) to give **11** (75 mg, 6.6%). Recrystallization from benzene gave colorless prisms, mp 83—84° (lit.[14] mp 84°). *Anal.* Calcd. for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.66; H, 4.54; N, 41.45. PMR ($CDCl_3$) δ: 3.53 (2H, s, disappeared by the addition of D_2O), 7.15—7.78 (3H, m), 7.78—8.13 (1H, m). MS *m/e*: 134 (M^+). To the water layer, benzoyl chloride (1.550 g) was added and the mixture was allowed to stand for 6 days. The reaction mixture was extracted with CH_2Cl_2–MeOH (95:5). The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed over silica gel using CH_2Cl_2–hexane (1:1). The earlier eluate gave 1-benzoyl-1,2,3-benzotriazole (1.031 g, 55.2%), mp 113—114°. IR ν_{max}^{KBr} cm^{-1}: 1708. Further elution of the column with CH_2Cl_2 afforded only benzoic acid. Thus, 2-amino-1,2,3-benzotriazole was not detected.

1-2′,5′-Dimethylpyrrol-1′-yl-1,2,3-benzotriazole (12)——To a solution of **11** (26 mg) and acetonylacetone (32 mg) in MeOH (2 ml), acetic acid (1 ml) was added, and the mixture was allowed to stand for 142 hr with stirring at room temperature. Evaporation of the mixture left an oil, which was dissolved in CH_2Cl_2, washed subsequently with aqueous sodium bicarbonate, H_2O, and the solvent was evaporated. The residue was subjected to the prep TLC (silica gel) using CH_2Cl_2 to afford **12** (35 mg, 85.3%). Recrystallization from hexane gave colorless leaflets, mp 90—91°. *Anal.* Calcd. for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.93; H, 5.80; N, 26.45. MS *m/e*: 212 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1418, 772, 741. PMR (CCl_4) δ: 1.89 (6H, s), 5.90 (2H, s), 7.15—7.75 (3H, m), 8.00—8.31 (1H, m).

9-Amino-6-benzylaminopurine (14)——Hydroxylamine O-sulfonic acid (2.235 g) was added to a stirred suspension of 6-benzylaminopurine (682 mg) and crushed KOH (5.150 g) in anhyd. DMF (30 ml). After stirring for 10 min, the reaction mixture was cooled with ice, neutralized with acetic acid, and evaporated *in vacuo* to dryness. The resulting residue was dissolved in CH_2Cl_2–MeOH (95:5), washed with H_2O and evaporated. The residue was chromatographed over aluminum oxide using CH_2Cl_2–MeOH (97:3). The earlier eluate (187 mg) gave crystals, which were recrystallized from MeOH to afford colorless needles **14** (143 mg). The mother liquir was purified by prep TLC (silica gel) using CH_2Cl_2–MeOH (95:5), to give further crop of **14** (32 mg). Total yield of **14** was 175 mg (25.5%). The second eluate (173 mg) was subjected repeatedly to the prep TLC (silica gel) and isomeric amino compound (**15**, 35 mg) was obtained. 9-Amino-6-benzylaminopurine (**14**), colorless needles, mp 176—177°. *Anal.* Calcd. for $C_{12}H_{12}N_6$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.87; H, 4.99; N, 34.75. MS *m/e*: 240 (M^+), 224. UV $\lambda_{max}^{95\%EtOH}$ nm: 272.5. PMR ($CDCl_3$) δ: 4.91 (2H, d, J=6 Hz, changed to a singlet by the addition of D_2O), 5.04 (2H, br. s, disappeared by the addition of D_2O), 6.29—6.68 (1H, m, disappeared with D_2O), 7.26—7.43 (5H, m), 7.78 (1H, s, C_8–H), 8.39 (1H, s, C_2–H). IR ν_{max}^{KBr} cm^{-1}: 3600—3000, 1620. 3-Amino-6-benzylaminopurine (**15**), colorless leaflets from MeOH, mp 248—249°. *Anal.* Calcd. for $C_{12}H_{12}N_6$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.85; H, 5.39; N, 35.04. MS *m/e*: 240 (M^+), 224. UV $\lambda_{max}^{95\%EtOH}$ nm: 295. PMR (75% CD_3OD–$CDCl_3$) δ: 4.95 (2H, br. s), 7.20—7.56 (5H, m), 7.93 (1H, s), 8.36 (1H, s). IR ν_{max}^{KBr} cm^{-1}: 3675—2800, 1618. The last eluate was the recovery of 6-benzylaminopurine (**13**). Repeated prep TLC of the second eluate gave further crop of **13**, and total yield of **13** was 385 mg.

6-Benzylamino-9-2′,5′-dimethylpyrrol-1′-ylpurine (16)——i) Acetonylacetone (30 mg) and **14** (43 mg) were dissolved in AcOH (3 ml). The mixture was stirred for 44 hr at room temperature, and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2, washed subsequently with aqueous sodium bicarbonate, H_2O, and dried over Na_2SO_4. Evaporation of the solvent gave crude product, which was purified by the prep TLC (silica gel) using CH_2Cl_2–MeOH (99:1) to afford crystals (**16**, 35 mg, 61.7%).

ii) 6-Benzylaminopurine (**13**, 760 mg) was N-aminated by the same procedure described above, using hydroxylamine O-sulfonic acid (2.389 g), KOH (5.462 g), and anhyd. DMF (30 ml). The residue was dissolved in AcOH (25 ml), acetonylacetone (430 mg) was added, and the mixture was stirred for 44 hr at room temperature and evaporated *in vacuo* to leave an oil, which was worked up as described in i). The residue (1.453 g) was chromatographed over silica gel using CH_2Cl_2–MeOH (97:3). The earlier eluate gave the mixture of **16** and acetonylacetone (353 mg), which was treated with 2,4-dinitrophenylhydrazine (397 mg) as described in the preparation of **10**. After the usual work-up, the product was subjected to prep TLC (silica gel) to afford **16** (192 mg, 17.9%). Recrystallization gave colorless prisms, mp 132—133°. *Anal.* Calcd. for $C_{18}H_{18}N_6$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.73; H, 5.75; N, 26.63. IR ν_{max}^{KBr} cm^{-1}: 1620. UV $\lambda_{max}^{95\%EtOH}$ nm: 271. MS *m/e*: 318 (M^+), 225. PMR ($CDCl_3$) δ: 1.96 (6H, s), 4.96 (2H, d, J=6 Hz, changed to a singlet by the addition of D_2O), 5.96 (2H, s), 6.33—6.71 (1H, br. s, disappeared by the addition of D_2O), 7.25—7.60 (5H, m), 7.80 (1H, s, C_8–H), 8.45 (1H, s, C_2–H). Further elution of the column gave the recovery of **13** (358 mg).

6-Acetylbenzylamino-9-2′,5′-dimethylpyrrol-1′-ylpurine (17)——A solution of **16** (20 mg) in acetic anhydride (3 ml) was refluxed for 23.5 hr. Evaporation of the reagent gave the crude **17**, which was repeated-

14) C.D. Campbell and C.W. Rees, *J. Chem. Soc.* (*D*), *Chem. Commun.*, **1965**, 192.

ly purified by prep TLC (silica gel) using CH_2Cl_2–MeOH (99: 1) and **17** was obtained as a colorless oil. *Anal.* Calcd. for $C_{20}H_{20}N_6O$: C, 66.65; H, 5.59; N, 23.32. Found: C, 66.27; H, 5.60; N, 23.61. UV $\lambda_{max}^{95\%EtOH}$ nm: 279.5. MS *m/e*: 360 (M^+), 317. IR ν_{max}^{film} cm^{-1}: 1685, 1573. PMR ($CDCl_3$) δ: 1.91 (6H, s), 2.43 (3H, s), 5.61 (2H, s), 5.97 (2H, s), 7.10—7.45 (5H, m), 8.16 (1H, s, C_8–H), 8.78 (1H, s, C_2–H).

9-Benzylideneamino-6-benzylaminopurine (18)——To a solution of 9-amino-6-benzylaminopurine (**14**, 30 mg) in acetic acid (2 ml), benzaldehyde (76 mg) was added. After stirring for 4 hr at room temperature, the mixture was evaporated *in vacuo* to leave an oil, which was dissolved in CH_2Cl_2–MeOH (95: 5) and washed subsequently with aqueous sodium bicarbonate, H_2O, and dried over Na_2SO_4. The solvent was removed *in vacuo* to leave needles (39 mg), which were recrystallized from MeOH to give the pure **18** (36 mg, 88.2%) as colorless prisms, mp 235—236°. *Anal.* Calcd. for $C_{19}H_{16}N_6$: C, 69.49; H, 4.91; N, 25.60. Found: C, 69.57; H, 5.17; N, 25.70. IR ν_{max}^{KBr} cm^{-1}: 1618. PMR (50% CD_3OD–$CDCl_3$) δ: 4.90 (2H, s, CH_2), 8.23 (1H, s, C_8–H), 8.46 (1H, s, C_2–H), 10.05 (1H, s, N=CH). UV $\lambda_{max}^{95\%EtOH}$ nm: 276, 296 (sh). MS *m/e*: 328 (M^+), 225, 224.

6,9-Bis(benzylamino)purine (19)——To a stirred suspension of **18** (19 mg) in MeOH (10 ml) and CH_2Cl_2 (5 ml), $NaBH_4$ (124 mg) was added. After stirring for 1 hr at room temperature, the solvent was removed to leave crystals, which were dissolved in CH_2Cl_2–MeOH (95: 5), washed with H_2O, and dried over Na_2SO_4. The solvent was removed to afford colorless leaflets (19 mg, quantitative), which were recrystallized from MeOH to give the pure **19**, mp 177—178°. *Anal.* Calcd. for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 69.37; H, 5.71; N, 25.08. IR ν_{max}^{KBr} cm^{-1}: 1616, 1590. MS *m/e*: 330 (M^+), 225, 224. UV $\lambda_{max}^{95\%EtOH}$ nm: 271.5. PMR (25% CD_3OD–$CDCl_3$) δ: 4.39 (1H, s), 4.86 (1H, s), 7.20—7.50 (10H, benzene protons), 7.51 (1H, s), 8.42 (1H, br. s).

6-Amino-9-2′,5′-dimethylpyrrol-1′-ylpurine (21)——Hydroxylamine O-sulfonic acid (3.651 g) was added to a stirred suspension of 6-aminopurine (963 mg) and crushed KOH (7.001 g) in anhyd. DMF (30 ml). After stirring for 15 min, the reaction mixture was cooled with ice, neutralized with acetic acid, and evaporated *in vacuo* to dryness. The resulting residue and acetonylacetone (769 mg) were dissolved in acetic acid (50 ml) and stirred for 62 hr at room temperature. The mixture was evaporated to give a solid, which was dissolved in 2 N NaOH solution and the solution was shaken with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried over Na_2SO_4, and evaporated to leave crystals, which were purified by the prep TLC (silica gel) using CH_2Cl_2–MeOH (95: 5) to give pure **21** (155 mg, 9.6%). Recrystallization from MeOH gave colorless prisms, mp 230—231° (dec.). *Anal.* Calcd. for $C_{11}H_{12}N_6$: C, 57.88; H, 5.30; N, 36.82. Found: C, 57.86; H, 5.26; N, 36.59. IR ν_{max}^{KBr} cm^{-1}: 1662, 1646, 1604, 1587. PMR ($CDCl_3$) δ: 1.98 (6H, s, pyrrole CH_3), 5.99 (2H, s, pyrrole H), 6.18—6.50 (2H, br. s, NH_2, disappeared by the addition of D_2O), 7.96 (1H, s, C_8–H), 8.45 (1H, s, C_2–H). MS *m/e*: 228 (M^+), 135. UV $\lambda_{max}^{95\%EtOH}$ nm: 261.

Deuteration of 21 and 16——The compound (**21**, 20 mg) was dissolved in a mixture of CD_3OD (Merck 99.7%, 1.5 ml) and D_2O (Merck 99.75%, 1 ml) and refluxed for 20 hr. The solvent was removed and the residue was dissolved in MeOH. After a few min, MeOH was removed to afford deuterated product as colorless prisms. PMR ($CDCl_3$) δ: 1.98 (6H, s), 5.99 (2H, s), 6.18—6.50 (2H, br. s), 7.96 (0.55H, s), 8.45 (1H, s).

In the case of **16** (32 mg), the same grade of D_2O (1.5 ml) and CD_3OD (3.5 ml) was used. After the same work-up, the corresponding deuterated product was obtained. PMR ($CDCl_3$) δ: 1.96 (6H, s), 4.96 (2H, d, J=6 Hz), 5.96 (2H, s), 6.33—6.71 (1H, br. s), 7.25—7.60 (5H, m), 7.80 (0.49H, s), 8.45 (1H, s).

6-Amino-9-benzylideneaminopurine (22) and 6-Amino-3-benzylideneaminopurine (23)——Hydroxylamine O-sulfonic acid (2.913 g) was added to a stirred suspension of 6-aminopurine (973 mg) and crushed KOH (9.885 g) in anhyd. DMF (30 ml). After stirring for 10 min, the reaction mixture was cooled with ice, neutralized with acetic acid, and evaporated *in vacuo* to dryness. The resulting residue and benzaldehyde (825 mg) was dissolved in acetic acid (50 ml) and stirred for 20 hr at room temperature. The reaction mixture was evaporated to give a solid, which was dissolved in 2 N NaOH solution and the solution was extracted with CH_2Cl_2–MeOH (95: 5). The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to leave a solid, which was recrystallized from MeOH to afford colorless needles (**22**, 68.5 mg). The mother liquor was subjected to prep TLC (silica gel) using CH_2Cl_2–MeOH (95: 5). The upper band gave further crop of **22** (10.5 mg). Total yield of **22** was 79.0 mg (4.6%). The lower band gave isomeric compound (**23**, 6 mg, 0.35%). The compound (**22**), colorless leaflets, mp 240—241°. *Anal.* Calcd. for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.42; H, 4.30; N, 35.27. IR ν_{max}^{KBr} cm^{-1}: 3680—2600, 1665, 1601. MS *m/e*: 238 (M^+), 135. UV $\lambda_{max}^{95\%EtOH}$ nm: 266.5, 286 (sh). PMR (30% CD_3OD–$CDCl_3$) δ: 7.41—7.68 (3H, m), 7.80—8.08 (2H, m), 8.26 (1H, s), 8.37 (1H, s), 10.04 (1H, s). The compound (**23**), colorless fine needles from MeOH, mp 273—274°. *Anal.* Calcd. for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.31; H, 4.31; N, 35.06. IR ν_{max}^{KBr} cm^{-1}: 3680—2800, 1640. MS *m/e*: 238 (M^+), 135. UV $\lambda_{max}^{95\%EtOH}$ nm: 270.5, 327.5. PMR (20% CD_3OD–$CDCl_3$) δ: 7.46—7.75 (3H, m), 7.81—8.06 (2H, m), 8.43 (1H, s), 8.82 (1H, s), 9.00 (1H, s).

6-Amino-9-benzylaminopurine (24)——To a stirred suspension of **22** (35 mg) in MeOH (12 ml), $NaBH_4$ (131 mg) was added. After stirring for 10 min at room temperature, the solvent was removed in a reduced pressure to leave crystals, which were dissolved in CH_2Cl_2–MeOH (95: 5), washed with H_2O, and dried over Na_2SO_4. The solvent was removed to afford colorless prisms (**24**, 34 mg, quantitative). Recrystallization from MeOH gave colorless prisms, mp 194—195°. *Anal.* Calcd. for $C_{12}H_{12}N_6$: C, 59.98; H, 5.03; N, 34.98.

Found: C, 59.75; H, 5.19; N, 35.00. MS *m/e*: 240 (M^+), 135. UV $\lambda_{max}^{95\%EtOH}$ nm: 262.5. IR ν_{max}^{KBr} cm^{-1}: 3635—2600, 1657, 1597. PMR (15% CD_3OD–$CDCl_3$) δ: 4.42 (2H, br. s, NCH_2), 7.59 (1H, s), 7.15—7.50 (5H, m), 8.38 (1H, s).

6-Benzylamino-3-benzylideneaminopurine (**25**)——To a solution of **15** (28 mg) in acetic acid (2 ml), benzaldehyde (63 mg) was added. After stirring for 24 hr at room temperature, the mixture was evaporated *in vacuo* to leave an oil, which was dissolved in CH_2Cl_2–MeOH (95: 5) and washed subsequently with aqueous sodium bicarbonate, H_2O, and dried over Na_2SO_4. The solvent was removed in a reduced pressure to afford leaflets. Recrystallization from MeOH gave colorless leaflets (**25**, 34.5 mg). The mother liquor was subjected to prep TLC (silica gel) using CH_2Cl_2–MeOH (95: 5) and further crop of **25** (2.5 mg) was obtained. Total yield of **25** was 37 mg (97.4%). mp 253—254°. *Anal.* Calcd. for $C_{19}H_{16}N_6$: C, 69.49; H, 4.91; N, 25.60. Found: C, 69.70; H, 5.21; N, 25.09. IR ν_{max}^{KBr} cm^{-1}: 3640—3000, 1650. MS *m/e*: 328 (M^+), 225, 224. UV $\lambda_{max}^{95\%EtOH}$ nm: 265, 336. PMR (20% CD_3OD–$CDCl_3$) δ: 4.97 (2H, br. s, NCH_2), 7.30—7.75 (8H, m), 7.86—8.16 (2H, m), 8.03 (1H, s), 8.63 (1H, s), 10.46 (1H, s, N=CH).

6-Amino-3-benzylaminopurine (**27**)——To a solution of **23** (6 mg) in MeOH (3 ml), $NaBH_4$ (10 mg) was added. After stirring for 10 min at room temperature, the solvent was removed in a reduced pressure. The resulting residue was dissolved in CH_2Cl_2–MeOH (95: 5) and washed with H_2O, dried over Na_2SO_4, and evaporated to afford colorless needles (**27**, 1 mg). MS *m/e*: 240 (M^+), 135. UV $\lambda_{max}^{95\%EtOH}$ nm: 273.5. PMR (10% CD_3OD–$CDCl_3$) δ: 4.31 (2H, br. s, NCH_2), 7.25—7.45 (5H, m), 7.91 (1H, s), 8.35 (1H, s).

3,6-Bis(benzylamino)purine (**26**)——To a solution of **25** (26 mg) in MeOH (4 ml) and CH_2Cl_2 (2 ml), $NaBH_4$ (23 mg) was added. After stirring for 20 min at room temperature, the solvent was removed *in vacuo*. The resulting residue was dissolved in CH_2Cl_2–MeOH (95: 5) and washed with H_2O, dried over Na_2SO_4, and evaporated to afford an oil, which was subjected to prep TLC (silica gel) using CH_2Cl_2–MeOH (97: 3). The upper band gave colorless prisms (**26**, 4 mg). Recrystallization from CH_2Cl_2 gave prisms, mp 228—229°. IR ν_{max}^{KBr} cm^{-1}: 3680—2700, 1642. UV $\lambda_{max}^{95\%EtOH}$ nm: 297. MS *m/e*: 330 (M^+), 301, 225. PMR (10% CD_3OD–$CDCl_3$) δ: 4.46 (2H, s, NCH_2), 4.83 (2H, s, NCH_2), 7.30—7.45 (10H, benzene protons), 7.86 (1H, s), 7.99 (1H, s).

6-Amino-9-2′,5′-dimethyl-3′-acetylpyrrol-1′-ylpurine (**31**)——A solution of 6-amino-9-2′,5′-dimethylpyrrol-1′-ylpurine (**21**, 102 mg) in acetic anhydride (15 ml) was refluxed for 19 hr with stirring. The mixture was evaporated to give black residue, which was dissolved in MeOH (5 ml). To the solution, 2 N NaOH (1 ml) was added and refluxed for 1 min. The solvent was removed in a reduced pressure to leave an oil, which was dissolved in CH_2Cl_2–MeOH (9: 1), washed with H_2O, dried over Na_2SO_4 and evaporated. The resulting residue was subjected repeatedly to prep TLC (aluminum oxide) using CH_2Cl_2–MeOH (97: 3). The upper band gave the recovery of **21** (41 mg, 40.2%). The lower band gave colorless crystals (**31**, 41 mg, 34.1%). Recrystallization from benzene gave colorless prisms, mp 194—195° (dec.). *Anal.* Calcd. for $C_{13}H_{14}N_6O$: C, 57.76; H, 5.22; N, 31.10. Found: C, 57.59; H, 5.36; N, 31.04. IR ν_{max}^{KBr} cm^{-1}: 3700—2800, 1660—1640, 1600, 1585. MS *m/e*: 270 (M^+), 227, 135. PMR ($CDCl_3$) δ: 2.00, 2.28, 2.45 (each 3H, s), 6.31—6.66 (2H, br. s, disappeared by the addition of D_2O), 6.43 (1H, q, J=1 Hz), 7.96 (1H, s), 8.43 (1H, s).

6-Diacetylamino-9-2′,5′-dimethyl-3′-acetylpyrrol-1′-ylpurine (**32**) **and 6-Acetylamino-9-2′, 5′-dimethyl-3′-acetylpyrrol-1′-ylpurine** (**33**)——A solution of **31** (20 mg) in acetic anhydride (4 ml) was refluxed for 24 hr. The reagent was removed in a reduced pressure and the resulting residue was subjected to prep. TLC (silica gel) using CH_2Cl_2–MeOH (95: 5). The upper band gave an oil (**32**, 13 mg) containing a small quantity of **33**. Prep TLC was repeated quickly and finally **32** (8 mg, 30.5%) was obtained. MS *m/e*: 354 (M^+), 312, 259. IR ν_{max}^{film} cm^{-1}: 1720 (br). PMR ($CDCl_3$) δ: 2.00 (3H, br. s), 2.27 (3H, s), 2.42 (6H, s), 2.44 (3H, s), 6.47 (1H, q, J=1 Hz), 8.30 (1H, s), 9.04 (1H, s). The lower band gave an oil, which was repeatedly subjected to prep TLC to give the pure **33** (8.5 mg, 37.0%). MS *m/e*: 312 (M^+), 259, 177, 136. IR ν_{max}^{KBr} cm^{-1}: 3700—2800, 1705, 1659. *Anal.* Calcd. for $C_{15}H_{16}N_6O_2 \cdot H_2O$: C, 54.54; H, 5.49; N, 25.53. Found: C, 54.67; H, 5.39; N, 25.44. PMR ($CDCl_3$) δ: 2.00 (3H, s), 2.25, 2.43, 2.71 (each 3H, s), 6.45 (1H, br. s), 8.30 (1H, s), 8.77 (1H, s), 9.35—9.55 (1H, br. s, disappeared by the addition of D_2O). To a solution of **33** (7 mg) in MeOH (0.9 ml), 2 N NaOH (1 ml) was added and stirring was continued for 15 min at room temperature. After usual work-up, **31** (5 mg) was obtained.

9-Amino-6-methylthiopurine (**34**)——Hydroxylamine O-sulfonic acid (5.10 g) was added under cooling to a stirred suspension of 6-methylthiopurine (1.158 g) and crushed KOH (10.7 g) in anhyd. DMF (40 ml). After stirring at room temperature for 45 min, the reaction mixture was neutralized with acetic acid. Evaporation of the mixture *in vacuo* left a syrup, which was chromatographed over silica gel (30 g) using CH_2Cl_2–MeOH (98: 2). Crystals (150 mg) thus obtained were recrystallized from MeOH to give colorless prisms of **34** (134 mg), mp 223—223.5° (dec.). The mother liquor was purified by prep TLC (silica gel) to afford further 6 mg of **34**. Total yield was 140 mg (11%). *Anal.* Calcd. for $C_6H_7N_5S$: C, 39.76; H, 3.89; N, 38.65. Found: C, 39.74; H, 4.11; N, 38.66. IR ν_{max}^{KBr} cm^{-1}: 1643. PMR (50% CD_3OD–$CDCl_3$) δ: 2.73 (3H, s, SCH_3), 8.15 (1H, s), 8.77 (1H, s). MS *m/e*: 181 (M^+), 165. UV $\lambda_{max}^{95\%EtOH}$ nm: 288. CH_2Cl_2–MeOH (95: 5) eluted a solid (*ca.* 1 g), which was recrystallized from H_2O to give the recovery of 6-methylthiopurine (955 mg, 83%).

6-Methylthio-9-2′,5′-dimethylpyrrol-1′-ylpurine (**36**)——To a solution of **34** (13.5 mg) in AcOH (2 ml), a solution of acetonylacetone (51 mg) in AcOH (3 ml) was added. After stirring for 40 hr at room tempera-

ture, the solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed subsequently with aqueous $NaHCO_3$, H_2O, and dried over Na_2SO_4. Evaporation of the solvent gave crystals (17.5 mg), which were purified by prep TLC (silica gel) using CH_2Cl_2–hexane (1: 1) to afford colorless crystals (14.5 mg). Recrystallization from MeOH gave **36** (13.5 mg, 69.9%) as colorless prisms, **mp** 207.5—208.5°. *Anal.* Calcd. for $C_{12}H_{13}NS$: C, 55.57; H, 5.05; N, 27.01. Found: C, 55.47; H, 5.28; N, **26.**89. IR ν_{max}^{KBr} cm^{-1}: 1580, 1568. PMR ($CDCl_3$) δ: 1.95 (6H, s, pyrrole CH_3), 2.80 (3H, s, SCH_3), 5.88 (2H, s, pyrrole H), 8.08 (1H, s, C_8–H), 8.78 (1H, s, C_2–H). MS *m/e*: 259 (M^+), 166, 165. UV $\lambda_{max}^{95\%EtOH}$ nm: 289.

9-Aminopurine (35)——Hydroxylamine O-sulfonic acid (3.16 g) was added under ice-cooling to a stirred suspension of purine (480 mg) and crushed KOH (6.72) in anhyd. DMF (24 ml). Stirring was continued for 1.5 hr and the reaction mixture was neutralized with acetic acid and then evaporated *in vacuo*. The residue was chromatographed over silica gel (30 g) and CH_2Cl_2–MeOH (98: 2) eluted crystalline compound (30 mg), which was recrystallized from MeOH to obtain colorless prisms (**35**, 19 mg), mp 222—223°. Crystals from the mother liquor was purified by prep TLC and total yield of **35** was 31 mg (6%). *Anal.* Calcd. for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.44; H, 3.75; N, 51.99. IR ν_{max}^{KBr} cm^{-1}: 3280, 3170, 1630. MS *m/e*: 135 (M^+). PMR (d_6-DMSO) δ: 6.25 (2H, s, disappeared by the addition of D_2O), 8.50 (1H, s), 8.98 (1H, s), 9.15 (1H, s).

9-Benzyloxycarbonylamino-6-methylthiopurine (37)——To a solution of 9-amino-6-methylthiopurine (**34**, 101 mg) in pyridine (7 ml), *ca.* 30% toluene solution (5 ml) of carbobenzoxy chloride was added, and the mixture was stirred at 55—60° for 10 hr. The solvent was evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2, washed with H_2O, and dried over Na_2SO_4. Removal of the solvent and separation of the residue by prep TLC gave crystalline compound (153 mg) and the recovery of **34** (9 mg, 1%) and the former was recrystallized from ether to afford colorless needles (**37**, 108 mg), mp 142.5—143.5°. Crystals from the mother liquor was purified by prep TLC and total yield of **37** was 135 mg (77%). *Anal.* Calcd. for $C_{14}H_{13}N_5O_2S$: C, 53.32; H, 4.16; N, 22.21. Found: C, 53.36; H, 4.15; N, 22.20. IR ν_{max}^{KBr} cm^{-1}: 1739. MS *m/e*: 315 (M^+), 180. PMR ($CDCl_3$) δ: 2.64 (3H, s), 5.18 (2H, s), 7.34 (5H, s), 7.97 (1H, s), 8.67 (1H, s), 9.91—10.13 (1H, disappeared by the addition of D_2O).

9-Benzyloxycarbonylaminopurine (38)——i) EtOH (9 ml) solution of **37** (132 mg) was refluxed with Raney-Ni (W-2, *ca.* 0.8 g) for 23 hr. The catalyst was removed by filtration over celite and evaporation of the solvent, separation by prep TLC, and recrystallization from $CHCl_3$ gave **38** (69 mg, 62%), mp 203.5—204.5° (dec.). The recovery of **37** (7 mg, 5%) was observed. *Anal.* Calcd. for $C_{13}H_{11}N_5O_2$: C, 57.98; H, 4.12; N, 26.01. Found: C, 57.92; H, 4.20; N, 25.97. IR ν_{max}^{KBr} cm^{-1}: 1738. MS *m/e*: 269 (M^+), 134. PMR (d_6-DMSO) δ: 3.37—3.77 (1H, disappeared by the addition of D_2O), 5.26 (2H, s), 7.43 (5H, s), 8.78 (1H, s), 9.02 (1H, s), 9.25 (1H, s).

ii) A solution of 9-aminopurine (**35**, 23 mg) and *ca.* 30% carbobenzoxy chloride in toluene (1 ml) in pyridine (0.5 ml) was stirred at room temperature for 14 hr. The same work-up as in the case of **37** afforded **38** (5 mg, 11%). Colorless prisms from CH_2Cl_2, mp 203—204° (dec.).

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