[Chem. Pharm. Bull. 35(12)4972—4976(1987)]

Purines. VI.[1] Reactions of 2-Chloro- and 2-(Methylsulfonyl)-9-phenyl-9*H*-purines with Nucleophiles

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(Received May 18, 1987)

The reactions of 2-chloro-9-phenyl-9*H*-purine (**1**) with sodium methoxide, ethoxide, and phenoxide as *O*-nucleophiles, with butylamine and piperidine as *N*-nucleophiles, and with sodium methylsulfide as an *S*-nucleophile, afforded 2-methoxy- (**3a**), 2-ethoxy- (**3b**), 2-phenoxy- (**3c**), 2-butylamino- (**4a**), 2-piperidino- (**4b**), and 2-methylthio-9-phenyl-9*H*-purine (**5**), respectively. Compound **1** also reacted with ethyl cyanoacetate and phenylacetonitrile as *C*-nucleophiles in the presence of sodium hydroxide in dimethyl sulfoxide to give ethyl α-cyano-9-phenyl-9*H*-purine-2-acetate (**6a**) and α,9-diphenyl-9*H*-purine-2-acetonitrile (**6b**). However, **1** did not react with other active methylene compounds, ketones or potassium cyanide.

On the other hand, 2-(methylsulfonyl)-9-phenyl-9*H*-purine (**2**), prepared easily from **1**, smoothly reacted not only with active methylene compounds but also with ketones and potassium cyanide. When active methylene compounds, such as ethyl cyanoacetate and phenylacetonitrile, were used, **2** gave **6a** and **6b** in good yields. In the cases of ketones and potassium cyanide, the substitution reactions of **2** proceeded to give the corresponding 2-substituted 9*H*-purines (**7** and **8a—d**), as expected.

Keywords——2-chloro-9*H*-purine; 2-(methylsulfonyl)-9*H*-purine; nucleophilic substitution; nucleophile; synthesis

Recently we have reported that a chlorine atom[2] and a methylsulfonyl group[3] at the 6-position on the 9*H*-purine ring can be substituted with nucleophiles, resulting in the introducing of a carbon chain into the 6-position. On the other hand, little work has been reported on introducing a carbon chain into the 2-position of the 9*H*-purine ring. We examined the nucleophilic substitution of a chlorine atom and a methylsulfonyl group at the 2-position and succeeded for the first time in the introduction of functionalized carbons into the 2-position of the 9*H*-purine ring, giving the expected 2-substituted 9-phenyl-9*H*-purines (**5**, **6**, and **7**). In the present paper, we describe these results in detail.

Compound **1** was prepared by the substitution reaction of 5-amino-2,4-dichloropyrimidine with aniline, followed by cyclization of the resulting 5-amino-4-anilino-2-chloropyrimidine with ethyl orthoformate in acetic anhydride.

When a solution of **1** and sodium ethoxide in ethanol was refluxed for 1 h, 2-ethoxy-9-phenyl-9*H*-purine (**3b**) was obtained in good yield. Similar reactions of **1** with sodium methoxide and phenoxide under the same conditions gave 2-methoxy- (**3a**) and 2-phenoxy-9-phenyl-9*H*-purine (**3c**), respectively. When **1** was treated with butylamine and piperidine as *N*-nucleophiles, 2-butylamino- (**4a**) and 2-piperidino-9-phenyl-9*H*-purine (**4b**) were obtained, respectively. The reaction of **1** with sodium methylsulfide as an *S*-nucleophile in dimethylformamide (DMF) at 100 °C gave 2-methylthio-9-phenyl-9*H*-purine (**5**) in 90% yield.

Next, introduction of functionalized carbon substituents into the 2-position was investigated. Compound **1** reacted with ethyl cyanoacetate in the presence of sodium hydroxide in dimethylsulfoxide (DMSO) under the same conditions as those reported[2] for the

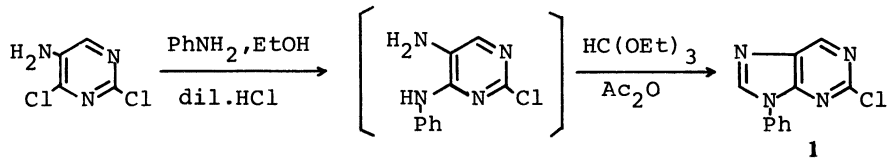

Chart 1

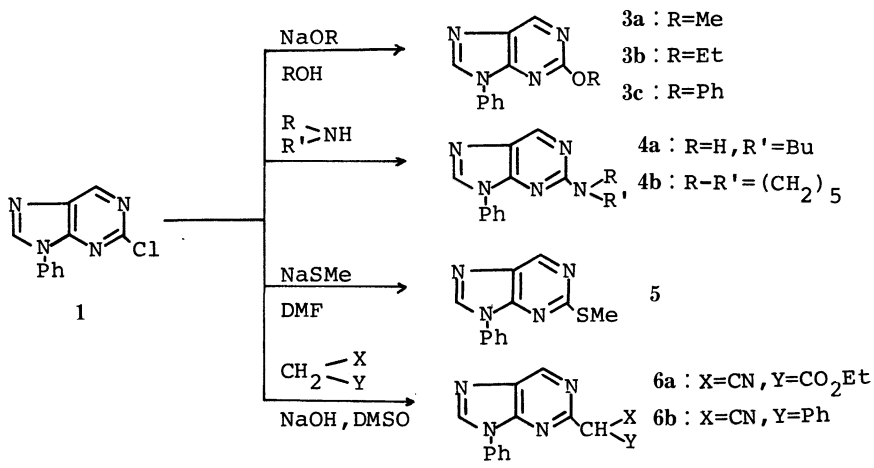

Chart 2

reaction of 6-chloro-9-phenyl-9*H*-purine, that is, heating at 100 °C for 1 h, to give ethyl α-cyano-9-phenyl-9*H*-purine-2-acetate (**6a**) in 29% yield. Similarly, **1** and phenylacetonitrile gave α,9-diphenyl-9*H*-purine-2-acetonitrile (**6b**) in 23% yield. However, when other active methylene compounds, ketones, and potassium cyanide were used, the desired products were not obtained. It appeared from the above results that the chlorine atom at the 2-position of the 9*H*-purine ring was less reactive to carbanions than that at the 6-position.

We have reported the nucleophilic substitution reactions of 2-(methylsulfonyl)-quinoxaline,[4] 1-(methylsulfonyl)phthalazine,[5] 4-(methylsulfonyl)cinnoline,[6] and 6-(methyl-sulfonyl)-9-phenyl-9*H*-purine[3] with carbanions and concluded that the methylsulfonyl group was replaced by carbanions more easily than the chlorine atom. In connection with such reactivity of the methylsulfonyl group, we examined the reaction of 2-(methylsufonyl)-9-phenyl-9*H*-purine (**2**) with carbanions.

2-Methylthio-9-phenyl-9*H*-purine (**5**) was oxidized with potassium permanganate in acetic acid to give **2** in 76% yield. Compound **2** smoothly reacted not only with active methylene compounds but also with potassium cyanide and ketones. Treatment of **2** with potassium cyanide in DMSO at 100 °C for 1 h afforded 9-phenyl-9*H*-purine-2-carbonitrile (**7**) in 74% yield, though the same reaction did not take place in the case of **1**.

Nucleophilic substitution reactions of **2** with active methylene compounds and ketones in the presence of potassium hydroxide in DMSO did not take place, but the reaction in tetrahydrofuran (THF) in the presence of sodium hydride instead of potassium hydroxide resulted in the formation of the desired products. Thus, when a solution of **2** and ethyl cyanoacetate in THF in the presence of sodium hydride was refluxed for 3 h, **6a** was obtained in 58% yield. Compound **2** and phenylacetonitrile also gave **7b** in 58% yield. Although the yields were low, the reaction of **2** with acetone and 2-butanone resulted in the formation of 1-(9-phenyl-9*H*-purin-2-yl)-2-propanone (**8b**) and 3-(9-phenyl-9*H*-purin-2-yl)-2-butanone

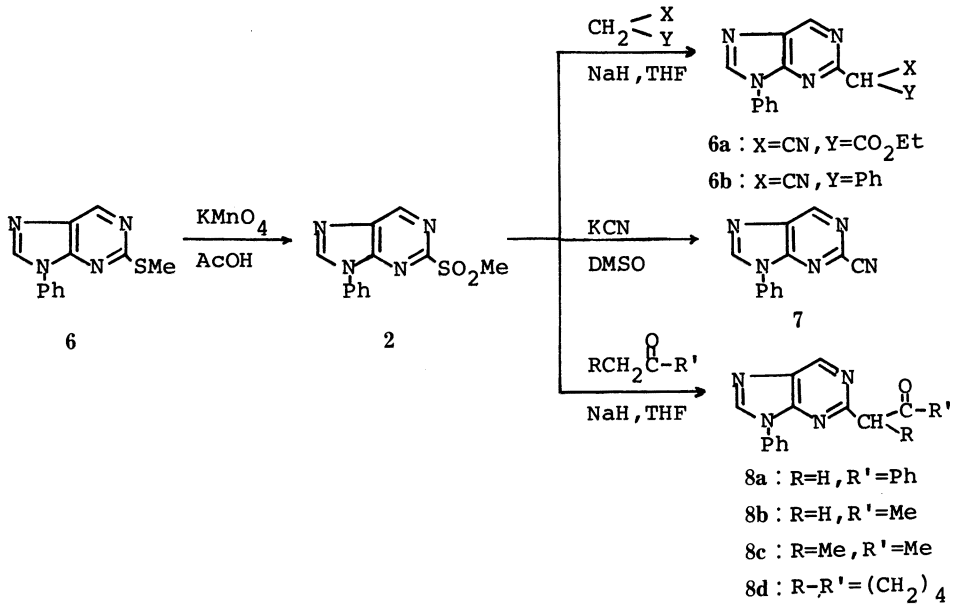

Chart 3

(**8c**). On the other hand, **2** smoothly reacted with acetophenone and cyclohexanone to give 2-(9-phenyl-9*H*-purin-2-yl)acetophenone (**8a**) and 2-(9-phenyl-9*H*-purin-2-yl)cyclohexanone (**8d**) in 62% and 63% yields, respectively.

We concluded that the chlorine atom and methylsulfonyl group at the 2-position were less reactive to carbanions than those at the 6-position in the 9*H*-purine ring, and the methylsulfonyl group was more reactive to carbanions than the chlorine atom at the 2-position in the 9*H*-purine ring. The substitution reaction of the methylsulfonyl group in **2** with nucleophiles is a useful method for the introduction of functionalized carbons into the 2-position of the 9*H*-purine ring.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a Jasco IRA-1 grating IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz and 23 °C with a Hitachi R-24 high-resolution ^{1}H-NMR spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.

2-Chloro-9-phenyl-9*H*-purine (1)——A mixture of 5-amino-2,4-dichloropyrimidine (18 g, 0.11 mol), aniline (10.2 g, 0.11 mol), concentrated HCl (4.5 ml), EtOH (45 ml), and H_2O (290 ml) was refluxed for 1 h. The precipitate, 5-amino-4-anilino-2-chloropyrimidine, was filtered off. Yield, 14.5 g. A mixture of the crude 5-amino-4-anilino-2-chloropyrimidine (14.5 g, 0.066 mol), ethyl orthoformate (90 ml), and acetic anhydride (90 ml) was refluxed for 3 h. The EtOH was removed under reduced pressure. The residue was diluted with H_2O and the mixture was made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give **1** as colorless needles, mp 169—170 °C. Yield, 10 g (64%). *Anal.* Calcd for $C_{11}H_7ClN_4$: C, 57.27; H, 3.04; N, 24.30. Found: C, 57.34; H, 3.10; N, 24.48. ^{1}H-NMR ($CDCl_3$) δ: 7.28—7.73 (5H, m, Ph), 8.23 (1H, s, C^8-H), 8.89 (1H, s, C^6-H).

2-Methoxy-9-phenyl-9*H*-purine (3a)——1) A mixture of **1** (0.5 g, 2.2 mmol), NaOMe (0.6 g, 11.1 mmol), and MeOH (20 ml) was refluxed for 1 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with benzene and recrystallized from benzene to give **3a** as colorless needles, mp 110—112 °C. Yield, 0.42 g (86%). *Anal.* Calcd for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.49; H, 4.25; N, 24.64. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s, OCH_3), 7.27—7.74 (5H, m, Ph), 8.47 (1H, s, C^8-H), 9.17 (1H, s, C^6-H).

2) A mixture of **2** (0.3 g, 1.1 mmol), NaOMe (0.3 g, 5.5 mmol), and MeOH (5 ml) was refluxed for 1 h. The solvent was removed under reduced pressure. The crude product was purified by SiO_2 column chromatography with benzene and recrystallized from benzene to give **3a**. Yield, 0.2 g (84%).

2-Ethoxy-9-phenyl-9*H*-purine (3b)——A mixture of **1** (0.2 g, 0.87 mmol), NaOEt (0.29 g, 4.3 mmol), and EtOH (15 ml) was refluxed for 1 h. The same work-up of the reaction mixture as described for **3a** gave **3b**, colorless needles from petroleum benzin–benzene, mp 117—121 °C. Yield, 0.17 g (82%). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 65.50; H, 5.06; N, 22.93. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.48 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.27—7.81 (5H, m, Ph), 8.08 (1H, s, C^8-H), 8.85 (1H, s, C^6-H).

2-Phenoxy-9-phenyl-9*H*-purine (3c)——A mixture of **1** (0.2 g, 0.87 mmol), NaOPh (0.49 g, 4.3 mmol), and PhOH (5 ml) was heated at 100 °C for 3 h. The same work-up of the reaction mixture as described for **3a** gave **3c**, colorless needles from petroleum benzin–benzene, mp 130—131 °C. Yield, 0.23 g (92%). *Anal.* Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.44. Found: C, 70.73; H, 4.14; N, 19.38. ^{1}H-NMR ($CDCl_3$) δ: 7.15—7.70 (10H, m, N–Ph, O–Ph), 8.11 (1H, s, C^8-H), 8.78 (1H, s, C^6-H).

2-Butylamino-9-phenyl-9*H*-purine (4a)——A mixture of **1** (0.2 g, 0.87 mmol) and $BuNH_2$ (3 ml) was refluxed for 3 h. The excess $BuNH_2$ was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from petroleum benzin–benzene to give **4a** as yellow needles, mp 113—115 °C. Yield, 0.14 g (62%). *Anal.* Calcd for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.36; H, 6.33; N, 26.20. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH). ^{1}H-NMR ($CDCl_3$) δ: 0.74—1.16 (3H, m, $NCH_2CH_2CH_2C\underline{H}_3$), 1.32—1.84 (4H, m, $NCH_2C\underline{H}_2C\underline{H}_2CH_3$), 3.27—3.64 (2H, m, $NC\underline{H}_2CH_2CH_2CH_3$), 7.24—7.79 (5H, m, Ph), 7.89 (1H, s, C^8-H), 8.63 (1H, s, C^6-H).

9-Phenyl-2-piperidino-9*H*-purine (4b)——1) A mixture of **1** (0.2 g, 0.87 mmol) and piperidine (3 ml) was heated at 100 °C for 3 h. The same work-up of the reaction mixture as described for **4a** gave **4b**, yellow needles from petroleum benzin, mp 78—79 °C. Yield, 0.14 g (59%). *Anal.* Calcd for $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07. Found: C, 68.48; H, 6.14; N, 24.97. ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.85 (6H, m, $N<\underline{CH}_2\atop CH_2>(\underline{CH}_2)_3$), 3.62—4.05 (4H, m, $N<\underline{CH}_2\atop CH_2>(\underline{CH}_2)_3$), 7.33—7.78 (5H, m, Ph), 7.89 (1H, s, C^8-H), 8.70 (1H, s, C^6-H).

2-Methylthio-9-phenyl-9*H*-purine (5)——A mixture of **1** (10 g, 0.043 mol), 15% aqueous NaSMe (40.5 g, 0.086 mol), and DMF (50 ml) was heated at 100 °C for 3 h. The mixture was diluted with H_2O and extracted with benzene. The crude product was purified by SiO_2 column chromatography with benzene and recrystallized from benzene to give **5** as colorless needles, mp 136—138 °C. Yield, 9.5 g (90%). *Anal.* Calcd for $C_{12}H_{10}N_4S$: C, 59.48; H, 4.16; N, 23.13. Found: C, 59.70; H, 4.16; N, 23.45. ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, s, SCH_3), 7.26—7.77 (5H, m, Ph), 8.08 (1H, s, C^8-H), 8.80 (1H, s, C^6-H).

2-(Methylsulfonyl)-9-phenyl-9*H*-purine (2)——A solution of $KMnO_4$ (4.7 g, 0.03 mol) in H_2O (50 ml) was added to a stirred solution of **5** (3.6 g, 0.015 mol) in AcOH (30 ml). The mixture was stirred for 1 h at room temperature, then sodium hydrogen sulfite was added, and the whole was extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give **2** as colorless needles, mp 197—199 °C. Yield, 3.1 g (76%). *Anal.* Calcd for $C_{12}H_{10}N_4O_2S$: C, 52.55; H, 3.67; N, 20.43. Found: C, 52.15; H, 3.60; N, 20.34. IR ν_{max}^{KBr} cm^{-1}: 1142, 1306 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 3.31 (3H, s, SO_2CH_3), 7.27—7.74 (5H, m, Ph), 8.47 (1H, s, C^8-H), 9.17 (1H, s, C^6-H).

Ethyl α-Cyano-9-phenyl-9*H*-purine-2-acetate (6a)——1) A mixture of **1** (0.2 g, 0.87 mmol), NaOH (0.07 g, 1.74 mmol), ethyl cyanoacetate (0.2 g, 1.74 mmol), and DMSO (3 ml) was heated at 100 °C for 1 h. The mixture was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give **6a** as colorless needles, mp 240 °C (dec.). Yield, 78 mg (29%). *Anal.* Calcd for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.75; H, 4.17; N, 22.79. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O), 2200 (CN). ^{1}H-NMR (CF_3COOH) δ: 1.40 (3H, t, J=6 Hz, $OCH_2C\underline{H}_3$), 4.32 (2H, q, J=6 Hz, $OC\underline{H}_2CH_3$), 7.50 (5H, m, Ph), 9.08 (1H, s, C^8-H), 9.14 (1H, s, C^6-H).

2) A mixture of **2** (0.3 g, 1.1 mmol), 50% NaH (in oil) (0.06 g, 1.2 mmol), ethyl cyanoacetate (0.14 g, 1.2 mmol), and THF (5 ml) was refluxed for 3 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give **6a**. Yield, 0.19 g (58%).

α,9-Diphenyl-9*H*-purine-2-acetonitrile (6b)——1) A mixture of **1** (0.5 g, 2.2 mmol), NaOH (0.25 g, 4.4 mmol), phenylacetonitrile (0.52 g, 4.4 mmol), and DMSO (8 ml) was heated at 100 °C for 1 h. The reaction mixture was worked up essentially in the same way as described for **6a** under item 1). The eluate with benzene–$CHCl_3$ (1 : 1) was recrystallized from petroleum benzin–benzene to give **6b** as colorless needles, mp 128—131 °C. Yield, 0.15 g (23%). *Anal.* Calcd for $C_{19}H_{13}N_5$: C, 73.29; H, 4.21; N, 22.50. Found: C, 73.40; H, 4.18; N, 22.41. IR ν_{max}^{KBr} cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 5.44 (1H, s, $C\underline{H}<\underline{Ph}\atop CN$), 7.01—7.82 (10H, m, N–Ph, $CH<\underline{Ph}\atop CN$), 8.25 (1H, s, C^8-H), 9.02 (1H, s, C^6-H).

2) A mixture of **2** (0.2 g, 0.73 mmol), phenylacetonitrile (0.1 g, 0.88 mmol), 50% NaH (in oil) (0.04 g,

0.88 mmol), and THF (5 ml) was refluxed for 3 h. The same work-up of the reaction mixture as described for **6a** under item 1) gave **6b** (0.13 g) in 58% yield.

9-Phenyl-9*H*-purine-2-carbonitrile (7)——A mixture of **2** (0.2 g, 0.7 mmol), KCN (0.2 g, 3 mmol), and DMSO (3 ml) was heated at 80 °C for 1 h. The mixture was diluted with H_2O and extracted with $CHCl_3$. The product was recrystallized from benzene to give **7** as colorless needles, mp 164—165 °C. Yield, 0.12 g (74%). *Anal.* Calcd for $C_{12}H_7N_5$: C, 65.15; H, 3.19; N, 31.66. Found: C, 65.16; H, 3.11; N, 31.54. IR ν_{max}^{KBr} cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 7.37—7.80 (5H, m, Ph), 8.48 (1H, s, C^8-H), 9.11 (1H, s, C^6-H).

2-(9-Phenyl-9*H*-purin-2-yl)acetophenone (8a)——A mixture of **2** (0.2 g, 0.73 mmol), 50% NaH (in oil) (0.04 g, 0.88 mmol), acetophenone (0.11 g, 0.88 mmol), and THF (5 ml) was refluxed for 1 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give **8a** as yellow needles, mp 164—165 °C. Yield, 0.14 g (62%). *Anal.* Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.83. Found: C, 72.68; H, 4.44; N, 17.67. IR ν_{max}^{KBr} cm^{-1}: 1635 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 4.72 (1.14H, s, $CH_2C{=}O$), 6.31 (0.43H, s, $C\underline{H}{=}C{-}OH$), 7.25—8.05 (10H, m, N–Ph, $PhC{=}O$), 8.14 (0.43H, s, C^8-H), 8.21 (0.57H, s, C^8-H), 8.90 (0.43H, s, C^6-H), 9.04 (0.57H, s, C^6-H), 14.08—14.42 (0.43H, br, $CH{=}C{-}O\underline{H}$).

1-(9-Phenyl-9*H*-purin-2-yl)-2-propanone (8b)——A mixture of **2** (0.2 g, 0.73 mmol), 50% NaH (in oil) (0.04 g, 0.88 mmol), acetone (0.05 g, 0.88 mmol), and THF (15 ml) was refluxed for 1 h. The same work-up of the reaction mixture as described for **8a** gave **8b**, pale yellow needles from benzene, mp 100—103 °C. Yield, 24 mg (13%). *Anal.* Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.72; H, 4.82; N, 22.23. IR ν_{max}^{KBr} cm^{-1}: 1709 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s, $CH_3C{=}O$), 4.15 (2H, s, $CH_2C{=}O$), 7.26—7.75 (5H, m, Ph), 8.20 (1H, s, C^8-H), 9.00 (1H, s, C^6-H).

3-(9-Phenyl-9*H*-purin-2-yl)-2-butanone (8c)——A mixture of **2** (0.5 g, 1.8 mmol), 50% NaH (in oil) (0.1 g, 2 mmol), 2-butanone (0.15 g, 2 mmol), and THF (10 ml) was refluxed for 1 h. The same work-up of the reaction mixture as described for **8a** gave **8c**, pale yellow needles from benzene, mp 101—104 °C. Yield, 35 mg (7%). *Anal.* Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.22; H, 5.30; N, 20.73. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.60 (3H, d, J=7 Hz, $C\underline{H}_3CH$), 2.15 (3H, s, $C\underline{H}_3C{=}O$), 4.20 (1H, q, J=7 Hz, $CH_3C\underline{H}$), 7.25—7.80 (5H, m, Ph), 8.25 (1H, s, C^8-H), 9.03 (1H, s, C^6-H).

2-(9-Phenyl-9*H*-purin-2-yl)cyclohexanone (8d)——A mixture of **2** (0.2 g, 0.73 mmol), 50% NaH (in oil) (0.04 g, 0.88 mmol), cyclohexanone (0.86 g, 0.73 mmol), and THF (5 ml) was refluxed for 1 h. The same work-up of the reaction mixture as described for **8a** gave **8d**, colorless needles from benzene, mp 138—139 °C. Yield, 0.14 g (63%). *Anal.* Calcd for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.16. Found: C, 69.50; H, 5.49; N, 19.05. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.36—2.08 (4H, m, $C\underline{H}_2\!<\!\begin{matrix}CH_2{-}C\\ C\underline{H}_2CH_2\end{matrix}\!>\!C{-}OH$), 2.08—2.80 (4H, m, $CH_2\!<\!\begin{matrix}C\underline{H}_2{-}C\\ CH_2C\underline{H}_2\end{matrix}\!>\!C{-}OH$), 7.28—7.85 (5H, m, Ph), 8.19 (1H, s, C^8-H), 8.89 (1H, s, C^6-H), 14.03—14.35 (1H, br, $CH_2\!<\!\begin{matrix}CH_2{-}C\\ CH_2CH_2\end{matrix}\!>\!C{-}O\underline{H}$).

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