

Facile Synthesis of 9-Alkylpurines: Preparation of Some 9-Ethylpurine Derivatives (1,2)

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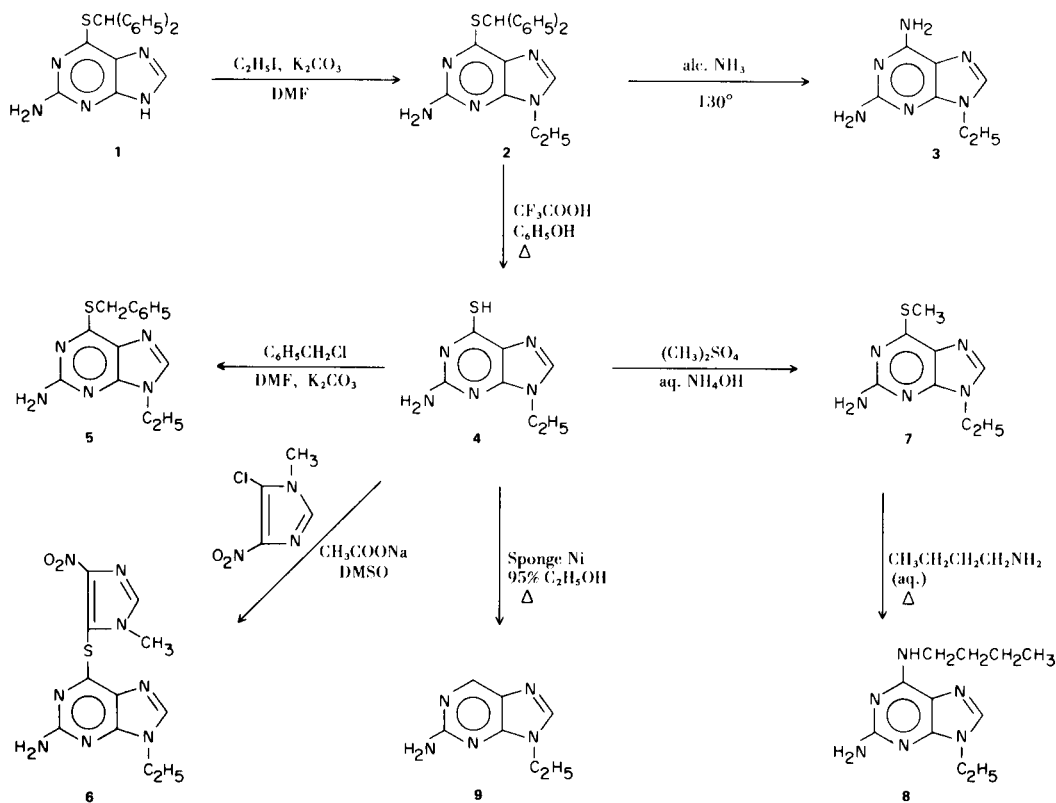
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Recently, in connection with the preparation of some 9-steroidal-6-mercaptapurine products (3), Carroll and Phillip (4) reported that conversion of 6-mercaptapurine to its diphenylmethylthioether derivative served not only to protect the mercapto function during subsequent alkylation of the purine ring but also, due to the steric bulk of the substituent at the purine 6-position, to hinder attack by the alkylating agent at the 7-position. We should like now to describe the synthesis of some required 2,6-disubstituted-9-ethylpurine compounds by means of a sequence which utilized the regioselective alkylation tech-

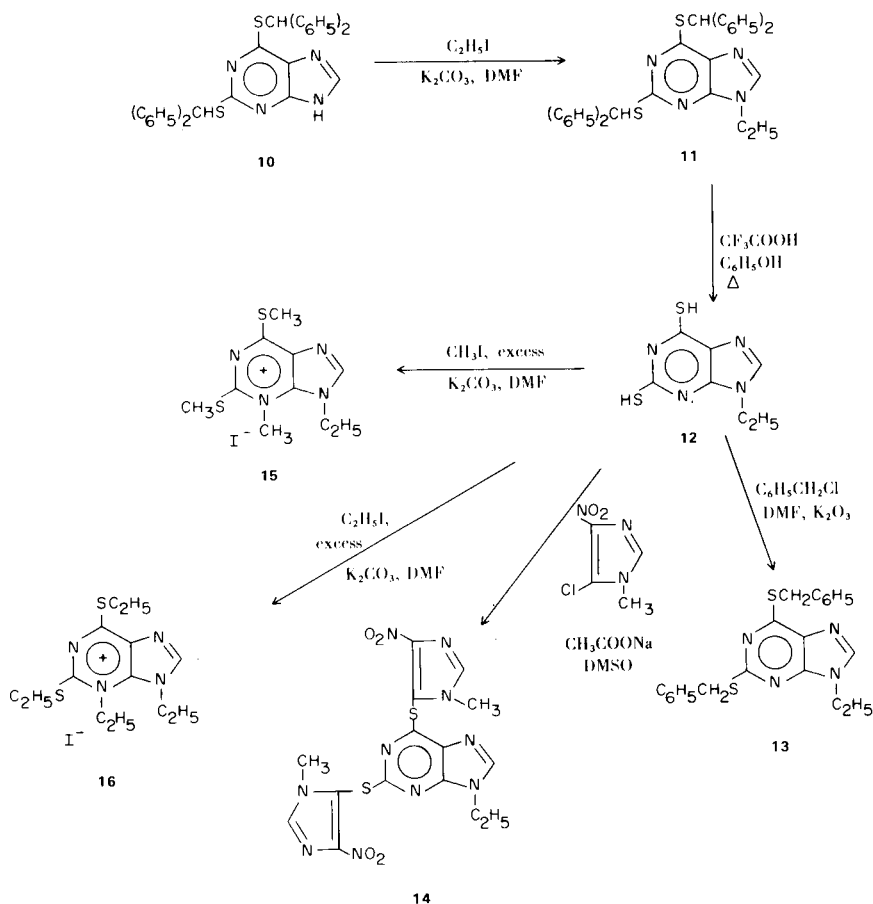
nique of Carroll and Phillip, together with standard purine functional group conversion reactions.

2-Amino-6-purinethiol (6-thioguanine) and 2,6-purinedithiol were used as starting materials in this investigation; the various products derived from them are shown in Schemes I and II, respectively. In Scheme I, ethylation of 2-amino-6-diphenylmethylthiopurine (1) gave the 9-ethyl product, 2, uncontaminated by any 7-isomer (tlc evidence). Nucleophilic displacement of the entire diphenylmethylthio function of 2 by ammonia in alcohol under pressure afforded 2,6-diamino-9-ethylpurine (3)

SCHEME I



SCHEME II



(5). Cleavage of the thioether function in **2** gave the known (6) 2-amino-9-ethyl-6-purinethiol (9-ethyl-6-thioguanine, **4**). Treatment of **4** with α -chlorotoluene and 1-methyl-4-nitro-5-chloroimidazole yielded **5** and the azathiopurine analog **6**, respectively. Treatment of the *S*-methyl compound **7**, obtained from **4** by the method of Noell and Robins (6), with an aqueous solution of *n*-butylamine gave 2-amino-6-*n*-butylamino-9-ethylpurine (**8**). Dethiation of **4** gave 2-amino-9-ethylpurine (**9**).

In a similar fashion (Scheme II), ethylation of 2,6-bis(diphenylmethylthio)purine (**10**) occurred exclusively at the 9-position to give **11**. Cleavage of the thioether functions in **11** afforded 9-ethyl-2,6-purinedithiol (**12**). Treatment of **12** with α -chlorotoluene and 1-methyl-4-nitro-5-chloroimidazole afforded **13** and **14**, respectively. The purinium iodides **15** and **16** were obtained by reaction of **12** with excess methyl iodide and ethyl iodide, respectively. The formation in these reactions of trialkylated derivatives of **12** was indicated first by nuclear magnetic resonance spectrometry and then by microchemical analysis, which also confirmed the presence of iodine in the

products. Assignment of the extra alkyl group in **15** and **16** at the 3-position is based upon reports that 6-methylthiopurine and 9-methyl-6-methylthiopurine both methylate further at position 3 (7-9).

In addition, but not shown in Scheme II, two known 9-ethylpurine products, 9-ethylpurine (**10**) and 9-ethylxanthine (**11**), were obtained from **12** by dethiation and by dilute acid hydrolysis, respectively. The structures of all products have been rigorously established by microchemical analysis, and by infrared, ultraviolet, and nuclear magnetic resonance spectral data.

It should be noted that Carroll and Phillip reported finding traces of other alkylated products, in addition to the 9-alkyl derivative, on alkylation of 6-diphenylmethylthiopurine (**4**), whereas, as described above, ethylation of **1** and **10** gave, in each instance, a single product. Alkylation of **1** with the more reactive α -chlorotoluene in dimethylsulfoxide in the presence of potassium carbonate did, however, afford a mixture of products, 75% of the 9-benzyl compound and 6% of the 7-isomer, after separation by column chromatography on silica gel. The

resulting 9-isomer/7-isomer ratio of 12.5 is some 2.5 times the isomer ratio value reported by Carroll and Phillip for the benzylation of the desamino analog of **1** under identical conditions (4). The electron-releasing substituent at the 2-position of **1** thus additionally favored alkylation of the 9-position, presumably by enhancing the nucleophilicity of the imidazole nucleus. We suggest that the positive electronic effect provided by an electron-releasing substituent at the 2-position and the steric hindrance at the 7-position provided by the bulky 6-diphenylmethylthioether function offer the most favorable substitution pattern for regioselective 9-alkylation of the purine ring.

Although our work was essentially limited to 9-ethylpurine derivatives, we believe that the approach used here is convenient and versatile and has broad applicability to the synthesis of an almost limitless variety of 9-alkylpurine compounds.

EXPERIMENTAL (12)

Melting points were taken by the capillary method on a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Massachusetts) and are uncorrected. Nmr spectra were obtained by means of a Varian A-60 spectrometer with tetramethylsilane as the internal standard; the solvent was anhydrous deuteriodimethylsulfoxide stored over Linde 4A molecular sieves, unless otherwise specified; s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Ultraviolet absorption spectra were measured with Cary Model 11 and Model 15 spectrophotometers and are expressed as λ max (solvent) nm (ϵ); spectra at pH 1 were run in 0.01 *N* hydrochloric acid and at pH 10 in 0.05 *M* sodium carbonate-sodium borate buffer. Thin layer chromatography was carried out on Eastman Chromagram plates, with 1-butanol:acetic acid:water (4:1:1 by volume) as the solvent system; the plates were visualized by ultraviolet light.

2-Amino-6-diphenylmethylthiopurine (**1**).

Compound **1** was prepared from 2-amino-6-purinethiol according to the procedure used by Carroll and Phillip (4) to prepare 6-diphenylmethylthiopurine from 6-purinethiol. The product (78% yield) was crystallized from methanol; m.p. 227-228°; nmr: δ 6.31 (2H, s, NH₂), 6.76 (1H, s, SCH₂), 7.33 [10H, m, (C₆H₅)₂], and 7.91 (1H, s, purine-8-H) ppm; uv: (ethanol) 243 (14,800) and 313 (13,500).

Anal. Calcd. for C₁₈H₁₅N₅S: C, 64.83; H, 4.54; N, 21.00; S, 9.61. Found: C, 64.60; H, 4.57; N, 21.34; S, 9.45.

2-Amino-9-ethyl-6-diphenylmethylthiopurine (**2**).

To a well stirred mixture of 6.0 g. (0.016 mole) of **1**, 2.49 g. (0.016 mole) of anhydrous potassium carbonate, and 35 ml. of *N,N*-dimethylformamide was added 2.20 g. (0.016 mole) of ethyl iodide. The mixture was stirred at room temperature for 2.5 hours, then poured into 2 liters of cold water, and the solid product was collected after 30 minutes. Crystallization of the crude material from ethanol-ether gave 4.5 g. (69%) of **2**, m.p. 206-207°; nmr: δ 1.33 (3H, t, $J = 15$ Hz, >NCH₂CH₃), 4.00 (2H, q, $J = 22$ Hz, >NCH₂CH₃), 6.48 (2H, s, NH₂), 6.78 (1H, s, SCH₂), 7.33 [10H, m, (C₆H₅)₂], and 7.95 (1H, s, purine-8-H) ppm; uv: (ethanol) 247 (14,100) and 313 (14,300).

Anal. Calcd. for C₂₀H₁₉N₅S: C, 66.44; H, 5.30; N, 19.37; S, 8.87. Found: C, 66.63; H, 5.21; N, 19.57; S, 8.83.

2,6-Diamino-9-ethylpurine (**3**) (13).

A solution containing 3.0 g. (8 mmoles) of **2** in 500 ml. of absolute ethanol saturated with ammonia at -40° was heated in a stainless steel bomb at 130° for 20 hours. The solvent was evaporated to dryness and the residue was triturated under ether until solid. Crystallization of the crude material from ethanol afforded 1.2 g. (85%) of **3**, m.p. 225-226°; nmr: δ 1.33 (3H, t, $J = 15$ Hz, >NCH₂CH₃), 4.00 (2H, q, $J = 22$ Hz, >NCH₂CH₃), 5.83 (2H, s, 6-NH₂), 6.71 (2H, s, 2-NH₂), and 7.70 (1H, s, purine-8-H) ppm; uv: (ethanol) 266 (8200) and 283 (10,200), (pH 1) 253 (9900) and 293 (9700), (pH 10) 254 (8500) and 280 (10,600).

Anal. Calcd. for C₇H₁₀N₆: C, 47.16; H, 5.66; N, 47.16. Found: C, 47.09; H, 5.38; N, 47.46.

2-Amino-9-ethyl-6-purinethiol (**4**).

A mixture of 3.0 g. (8 mmoles) of **2**, 3.0 g. of phenol, and 10 ml. of trifluoroacetic acid was refluxed for 35 minutes. The trifluoroacetic acid was removed under reduced pressure and to the residue was added 500 ml. of ether. The resulting suspension was stirred, then filtered to collect the solid material. The crude product was crystallized from water and dried at 100° over phosphorus pentoxide; 1.3 g. (81%); m.p. 301-303° [lit. (6) m.p. 299-302°]; nmr: δ 1.35 (3H, t, $J = 15$ Hz, >NCH₂CH₃), 4.00 (2H, q, $J = 24$ Hz, >NCH₂CH₃), 6.73 (2H, s, 2-NH₂), and 7.88 (1H, s, purine-8-H) ppm.

2-Amino-6-benzylthio-9-ethylpurine (**5**) Hydrochloride.

To a well stirred mixture of 0.5 g. (2.5 mmoles) of **4**, 0.353 g. (2.5 mmoles) of anhydrous potassium carbonate, and 4 ml. of *N,N*-dimethylformamide under a nitrogen atmosphere was added 0.324 g. (2.5 mmoles) of α -chlorotoluene. The mixture was stirred at 55-60° for 1 hour, allowed to cool, and poured into 20 ml. of cold water. The resulting suspension was stirred vigorously for 15 minutes, then allowed to stand overnight at 5°. The water was decanted and the residue, which was not entirely solidified, was dissolved in a small volume of methanol. The methanolic solution was saturated with anhydrous hydrogen chloride to precipitate the hydrochloride salt of **5**, which was crystallized from methanol-ether; 0.52 g. (63%), m.p. 110-111°; nmr: δ 1.41 (3H, t, $J = 15$ Hz, >NCH₂CH₃), 4.15 (2H, q, $J = 22$ Hz, >NCH₂CH₃), 4.68 (2H, s, SCH₂), 7.31 (5H, m, C₆H₅), and 8.46 (1H, s, purine-8-H) ppm; uv: (ethanol) 241 (14,300) and 312 (13,100), (pH 1) 248.5 (8900), 264 (8000), and 324 (11,100), (pH 10) 222 (11,400), 247 (5700), and 313 (6600).

Anal. Calcd. for C₁₄H₁₅N₅S·HCl: C, 52.23; H, 5.02; N, 21.76. Found: C, 52.08; H, 5.07; N, 21.55.

2-Amino-9-ethyl-6-(1-methyl-4-nitroimidazolyl-5)thiopurine (**6**).

A mixture of 0.5 g. (2.5 mmoles) of **4**, 0.41 g. (2.5 mmoles) of 1-methyl-4-nitro-5-chloroimidazole, and 0.21 g. (2.5 mmoles) of anhydrous sodium acetate in 10 ml. of dry dimethylsulfoxide was heated at 110° for 5 hours. The mixture was cooled and poured into 30 ml. of cold water. The yellow precipitate was crystallized from 50% aqueous acetone to give 0.66 g. (80%) of **6**, m.p. 231-232°; nmr: δ 1.38 (3H, t, $J = 15$ Hz, >NCH₂CH₃), 3.75 (3H, s, NCH₃), 4.10 (2H, q, $J = 22$ Hz, >NCH₂CH₃), 6.53 (2H, s, 2-NH₂), 8.05 (1H, s, imidazole-2-H), and 8.23 (1H, s, purine-8-H) ppm; uv: (ethanol) 224 (32,400) and 312 (13,500), (pH 1) 240 (13,300) and 318 (12,900), (pH 10) 217 (30,000), 245 (10,800), and 312 (13,900).

Anal. Calcd. for $C_{11}H_{12}N_8O_2S$: C, 41.23; H, 3.78; N, 34.98; S, 10.00. Found: C, 41.07; H, 3.68; N, 35.18; S, 10.28.

2-Amino-6-*n*-butylamino-9-ethylpurine (**8**) Dihydrochloride.

A solution of 0.20 g. (1 mmole) of **7** [prepared from **4** by the procedure of Noell and Robins (6)] in 5 ml. of 40% aqueous *n*-butylamine was heated in a sealed glass tube at 130° for 48 hours. The reaction mixture was evaporated to dryness and the residue was taken up in a small volume of methanol. The methanolic solution was saturated with dry hydrogen chloride; ether was added to precipitate the product. Crystallization of the crude material from ethanol-ether gave 0.21 g. (68%) of **8** as the dihydrochloride salt, m.p. 224-225°; nmr: δ 0.93 [3H, t, $(CH_2)_2CH_3$], 1.35 (3H, t, $>NCH_2CH_3$), 1.50 [4H, m, $(CH_2)_2$], 3.71 (2H, broad, 6- NCH_2CH_2), 4.16 (2H, q, $J = 22$ Hz, $>NCH_2CH_3$), 8.56 (1H, s, purine-8-H), and 9.66 (5H, broad, 2- NH_3^+ and 6- NH_2^+) ppm; uv: (ethanol) 223 (20,900), 254 (10,000), and 284 (12,000), (pH 1) 253 (10,900) and 290 (11,500), (pH 10) 260 (9100) and 283 (14,300).

Anal. Calcd. for $C_{11}H_{18}N_6 \cdot 2HCl$: C, 42.99; H, 6.57; N, 27.35. Found: C, 43.21; H, 6.65; N, 27.25.

2-Amino-9-ethylpurine (**9**).

To a solution of 0.70 g. (3.5 mmoles) of **4** in 150 ml. of 95% ethanol was added 10 ml. of Davison sponge nickel catalyst suspended in water (apparent bulk density 0.9) (14). The solution was maintained at reflux with vigorous mechanical stirring for 1 hour. The reaction solution was decanted while hot and the nickel slurry left in the flask was washed four times with 50 ml. portions of hot 95% ethanol. The washings were added to the original decantate and the entire alcoholic solution was evaporated to dryness. The residue was sublimed at 110° (0.005 mm.) to give 0.26 g. (45%) of **9**, m.p. 124-125°; nmr (d_6 -acetone): δ 1.45 (3H, t, $J = 15$ Hz, $>NCH_2CH_3$), 2.91 (2H, broad, 2- NH_2), 4.20 (2H, q, $J = 22$ Hz, $>NCH_2CH_3$), 7.98 (1H, s, purine-6-H), and 8.55 (1H, s, purine-8-H) ppm; uv: (ethanol) 222 (22,600), 243 (4100), and 308 (5900), (pH 1) 246 (2800), 265 (1400), and 314 (3400), (pH 10) 242 (3600) and 304 (5900).

Anal. Calcd. for $C_7H_9N_5$: C, 51.51; H, 5.56; N, 42.92. Found: C, 51.64; H, 5.56; N, 42.69.

2,6-Bis(diphenylmethylthio)purine (**10**).

To a well stirred mixture of 11.5 g. (0.062 mole) of 2,6-purinedithiol, 17.25 g. (0.124 mole) of anhydrous potassium carbonate, and 200 ml. of *N,N*-dimethylformamide was added 30.62 g. (0.124 mole) of bromodiphenylmethane under a nitrogen atmosphere. The mixture was stirred for 60 hours at room temperature, then poured into 4 liters of water. The resulting suspension, after acidification with acetic acid, was stirred vigorously for 30 minutes and filtered. The crude product was crystallized from methanol to give 19.0 g. (60%) of **10**, m.p. 229-230°; nmr: δ 6.13 (1H, s, 2-SCH<), 6.40 (1H, s, 6-SCH<), 7.33 [20H, broad s, $(C_6H_5)_4$], and 8.36 (1H, s, purine-8-H) ppm; uv: (ethanol) 262 (23,400), 267 (shoulder) (22,500), and 313 (12,600).

Anal. Calcd. for $C_{31}H_{24}N_4S_2$: C, 72.05; H, 4.69; N, 10.84; S, 12.41. Found: C, 71.79; H, 4.57; N, 10.94; S, 12.37.

9-Ethyl-2,6-bis(diphenylmethylthio)purine (**11**).

Compound **11** was prepared from **10** by the same procedure as that used to obtain **2**. The product melted at 84-85° after crystallization from ethanol (83% yield); nmr (d_6 -acetone): δ 1.28 (3H, t, $J = 15$ Hz, NCH_2CH_3), 4.10 (2H, q, $J = 22$ Hz, NCH_2CH_3), 6.21 (1H, s, 2-SCH), 6.55 (1H, s, 6-CH), 7.33 [20H,

m, $(C_6H_5)_4$], and 7.98 (1H, s, purine-8-H) ppm; uv: (ethanol) 237 (19,900), 263 (21,400), 267 (22,500), and 313 (12,600).

Anal. Calcd. for $C_{33}H_{28}N_4S_2$: C, 72.74; H, 5.19; N, 10.28; S, 11.76. Found: C, 72.83; H, 5.07; N, 10.51; S, 11.42.

9-Ethyl-2,6-purinedithiol (**12**).

A mixture of 4.0 g. (7.2 mmoles) of **11**, 8.0 g. of phenol, and 30 ml. of trifluoroacetic acid was refluxed for 1 hour. The trifluoroacetic acid was removed under reduced pressure and the residue was triturated under 500 ml. of ether until solid. For purification, the crude material was dissolved in 50 ml. of 1 *N* sodium hydroxide and precipitated by the addition of acetic acid. The precipitate was washed with water and ethanol and dried at 80° under vacuum (1.42 g., 90%), m.p. 270-271°; nmr: δ 1.33 (3H, t, $J = 15$ Hz, $>NCH_2CH_3$), 4.13 (2H, q, $J = 22$ Hz, $>NCH_2CH_3$), 8.06 (1H, s, purine-8-H), and 12.41 [2H, broad, 2,6-(SH)₂] ppm; uv: (pH 10) 250 (16,600), 283 (16,000), and 347 (12,300).

Anal. Calcd. for $C_7H_8N_4S_2$: C, 39.59; H, 3.80; N, 26.39. Found: C, 39.39; H, 3.78; N, 26.51.

2,6-Bis(benzylthio)-9-ethylpurine (**13**).

Compound **12** was benzylated in the usual manner by means of α -chlorotoluene in *N,N*-dimethylformamide in the presence of potassium carbonate. The product (51% yield) melted at 127-128° after crystallization from methanol; nmr (d_6 -acetone): δ 1.50 (3H, t, $J = 15$ Hz, $>NCH_2CH_3$), 4.33 (2H, q, $J = 22$ Hz, $>NCH_2CH_3$), 4.55 (2H, s, SCH₂-), 4.65 (2H, s, SCH₂-), 7.38 [10H, m, $(C_6H_5)_2$], and 8.16 (1H, s, purine-8-H) ppm; uv: (ethanol) 233 (18,600), 262 (26,900), and 310 (14,600).

Anal. Calcd. for $C_{23}H_{20}N_4S_2$: C, 66.30; H, 4.84; N, 13.45. Found: C, 66.12; H, 4.68; N, 13.23.

9-Ethyl-2,6-bis[(1-methyl-4-nitroimidazolyl-5)-thio]purine (**14**).

The reaction was run as described for the preparation of **6** except that a temperature of 100° was maintained for 8 hours. Compound **12** (0.50 g., 2.4 mmoles), 1-methyl-4-nitro-5-chloroimidazole (0.76 g., 4.6 mmoles), sodium acetate (0.38 g., 4.6 mmoles), and 10 ml. of dimethylsulfoxide afforded, after crystallization from 50% aqueous acetone, 0.8 g. (73%) of **14**, m.p. 257-258° dec.; nmr: δ 1.41 (3H, t, $J = 15$ Hz, $>NCH_2CH_3$), 3.55 [6H, s, $(NCH_3)_2$], 4.21 (2H, q, $>NCH_2CH_3$), 8.06 and 8.11 (1H each, s, imidazole-2-H), and 8.50 (1H, s, purine-8-H) ppm; uv: (ethanol) 231 (31,400) and 297 (19,600).

Anal. Calcd. for $C_{15}H_{14}N_{10}O_4S_2$: C, 38.94; H, 3.05; N, 30.28; S, 13.86. Found: C, 38.70; H, 2.91; N, 30.28; S, 13.79.

9-Ethyl-3-methyl-2,6-bis(methylthio)purinium iodide (**15**).

To a well stirred mixture of 1.0 g. (4.6 mmoles) of **12**, 1.30 g. (9.2 mmoles) of potassium carbonate, and 20 ml. of *N,N*-dimethylformamide was added a 10-fold excess of methyl iodide (6.6 g., 46 mmoles). The mixture was stirred at room temperature for 40 hours, then poured into 1 liter of cold water. The resulting suspension was stirred vigorously for 30 minutes. The crude material was crystallized from methanol-ether to give 1.3 g. (72%) of **15**, m.p. 234-235°; nmr: δ 1.51 (3H, t, $J = 15$ Hz, NCH_2CH_3), 2.66 (3H, s, 6-SCH₃), 2.80 (3H, s, 2-SCH₃), 4.20 (3H, s, NCH₃), 4.38 (2H, q, $J = 22$ Hz, $>NCH_2CH_3$), and 9.85 (1H, s, purine-8-H) ppm; uv: (ethanol) 220.5 (26,000), 265 (21,600), 282 (13,700), and 319 (9600), (pH 1) 222 (19,100), 265 (12,500), 285 (6600), and 320 (6200), (pH 10) 233 (15,400) and 296 (3400).

Anal. Calcd. for $C_{10}H_{15}IN_4S_2$: C, 31.41; H, 3.96; I, 33.19; N, 14.65. Found: C, 31.38; H, 3.89; I, 33.27; N, 14.71.

3,9-Diethyl-2,6-bis(ethylthio)purinium Iodide (**16**).

The procedure used to prepare this compound was the same as that for **15**. From 0.65 g. (4.6 mmoles) of **12** and a 10-fold excess of ethyl iodide there was obtained, after purification from ethanol-ether, 0.63 g. (70%) of product, m.p. 193-194°; mass spectrum (70 e.v.): *m/e* (relative intensity) 268 (100) (**16**-ethyl iodide), 253 (18), 240 (23), 235 (34), 208 (14), 207 (14), 179 (66), 156 (36), 151 (16), 128 (11), 127 (11), 74 (23), and 59 (34); nmr: δ 1.28-1.75 (12H, multiple peaks, 3-NCH₂CH₃, 9-NCH₂CH₃, 2-NCH₂CH₃, and 6-SCH₂CH₃), 3.30 (2H, q, 6-SCH₂CH₃), 3.48 (2H, q, 2-SCH₂CH₃), 4.41 (2H, q, 9-NCH₂CH₃), 4.56 (2H, q, 3-NCH₂CH₃), and 9.96 (1H, s, purine-8-H) ppm; uv: (ethanol) 220.5 (25,600), 260 (19,700), 283 (13,600), and 320 (9300), (pH 1) 226 (25,000), 267 (16,400), 285 (11,600), and 320 (9600), (pH 10) 231 (25,400) and 300 (5900).

Anal. Calcd. for C₁₃H₂₁N₄S₂: C, 36.78; H, 4.99; I, 29.89; N, 13.20. Found: C, 37.07; H, 4.87; I, 29.67; N, 13.22.

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- (12) Analyses were performed by Werby Laboratories, Boston, Massachusetts, and Galbraith Microanalytical Laboratories, Knoxville, Tennessee. The mass spectrum of **16** was provided by Mr. James K. Whitesell, Department of Chemistry, Harvard University, Cambridge, Massachusetts.
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