anhydride (distilled from Mg) to give a yellow suspension. After 1 h of stirring, the mixture was poured onto 50 mL of H_2O, neutralized with solid NH_4Cl, and extracted with 3 × 25 mL of ether. The combined organics were washed with brine and dried (Na_2SO_4). Solvent was removed under aspirator pressure to give crude yellow crystals. The solid was recrystallized twice from hexane and sublimed (80–90 °C bath temperature, 0.01 mm) to yield 2.387 g. The mother liquors were concentrated and chilled (−5 °C) to give a second crop of solid that was recrystallized and sublimed as above and combined with the first crop to yield 3.137 g (75%) of **14**. An analytical sample recrystallized from ether melted at 116–119 °C; IR 1785, 1720, 1660, 1450 cm^{-1}; NMR δ 1.77 (br s, 3 H, vinyl $-CH_3$), 2.14 (s, 3 H, $-O_2CCH_3$), 1.80–3.00 (complex, 6 H), 5.48 (br s, 1 H, vinylic H), 6.25 (d, $J \approx 6$ Hz, 1 H, C-3 H), 7.66 (d, $J \approx 6$ Hz, 1 H, C-4 H), 8.10 (s, 1 H, C-11 H). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.06; H, 7.12.

1-Ethylidene-4,8-dimethylspiro[4.5]dec-7-one (16).[2b] In a 100-mL round-bottom flask was placed 5.71 g (30.0 mmol) of anhydrous CuI (Fischer) in 20 mL of ether (distilled from $LiAlH_4$). The mechanically stirred slurry was cooled to −70 °C in a dry ice/2-propanol bath and MeLi (64.5 mL, 59.5 mmol) was added via syringe. After 0.5 h **14** (1.14 g, 5.0 mmol) in 25 mL of ether was added over 5 min giving an orange slurry. The mixture was quenched 1 h later by addition of 5% HCl and poured onto 50 mL of H_2O, and the organic layer separated. The aqueous layer was extracted with 4 × 40 mL of ether. The combined organics were washed with saturated $Na_2S_2O_3$ (100 mL) and brine, dried (Na_2SO_4), and distilled to remove solvent yielding a gold-brown oil, shown by GLC to be two major components (95%) in a ratio of 7:1. Preparative GLC of the major peak provided an analytical sample [NMR δ 0.88 (d, J = 7 Hz, 3 H, C-4 methyl), 1.65 (br s, 3 H, vinyl $-CH_3$), 2.05 (d, J = 7 Hz, 3 H, ethylidene $-CH_3$), 1.96–2.10 (complex, 8 H), 2.66 (dd, J = 8, 18 Hz, 1 H, C-3 H), 5.47 (br s, 1 H, vinylic H), 6.00 (q, J = 7 Hz, 1 H, C-11 H)] interpreted as the Z isomer.[2b] The minor peak was identified as the E isomer having the ethylidene resonances at δ 1.85 (d, J = 7 Hz, 3 H, ethylidene $-CH_3$) and 6.77 (q, J = 7 Hz, 1 H, ethylidene H).

1-Isopropyl-4,8-dimethylspiro[4.5]dec-7-en-2-one (17).[16] As above, 15 mmol of lithium dimethylcuprate was prepared at 0 °C. The crude oil **15** in 5 mL of ether was added dropwise and the reaction mixture stirred for 1 h. After an identical workup 9.25 mg of oil was obtained, 98% pure by GLC (82.5% yield): IR 1740, 1467, 2452 cm^{-1}; NMR δ 0.88 (dd, J = 2, 7 Hz, 6 H, isopropyl CH_3), 1.09 (d, J = 7 Hz, 3 H, C-4 $-CH_3$), 1.63 (br s, 3 H, vinyl $-CH_3$), 1.70–2.70 (complex, 11 H), 5.38 (br s, 1 H, vinylic H); mol wt (calcd for $C_{15}H_{24}O$, 220.183), 220.184.

(±)-Acorone (3). In a flamed 25-mL round-bottom flask was placed 500 mg (2.28 mmol) of **17** in 10 mL of THF (Na/benzophenone). $BH_3{\cdot}SMe_2$ (Aldrich, 150 μL, 1.61 mmol) was added via a septum inlet and the solution stirred for 2 h. One milliliter of 3 N NaOH followed by 1 mL of 30% H_2O_2 were added and the reaction mixture stirred for an additional 1 h. The solution was poured onto 15 mL of H_2O and the organic layer separated. The aqueous layer was extracted with 2 × 5 mL of ether, saturated with NaCl, and reextracted with 2 × 5 mL of ether. The combined organics were washed with brine, dried (Na_2SO_4), and stripped of volatiles under vacuum to yield 519 mg of pale yellow oil. No starting material was present by GLC and NMR.

The crude oil was dissolved in 15 mL of acetone and treated dropwise with Jones reagent until a faint red color persisted.[3b] Water (15 mL) was added and the mixture extracted with 4 × 5 mL of CH_2Cl_2. The combined organics were washed with brine, dried (Na_2SO_4), and stripped of solvent to yield 447 mg of yellow oil (80%). GLC analysis (15 ft × 0.125 in., 20% Carbowax 20M on Chromosorb W AW, 200 °C, FID detector) indicated the oil to be a mixture of acorone (55%) and isoacorone (45%) accounting for 96% of the total (identical with authentic samples[14]) and 4% of an unidentified component. The oil was dissolved in hexane/$CHCl_3$ and placed in a freezer overnight. Crystals were deposited which were recrystallized from hexane/$CHCl_3$ and sublimed (80 °C bath temperature, 0.1 mm) to yield 47 mg, mp 98–102 °C. Crystals (10.2 mg) were dissolved in heptane with a trace of ether and chilled. The crystals which were deposited were recrystallized from heptane to yield 6.7 mg of long needles, mp 101.5–103.5 °C, identical with authentic (+)-acorone (mp 96.0–97.5 °C)[3b] by NMR, IR, and GLC. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.26; H, 9.89. Found: C, 76.14; H, 9.97.

Registry No.—**3**, 61475-94-3; **4**, 61426-14-0; **5**, 61426-17-3; **6**, 6739-07-7; **8**, 61426-15-1; **9**, 38002-45-8; **10**, 61426-16-2; **11**, 61426-18-4; **13**, 61426-19-5; **14**, 61426-20-8; **15** isomer A, 61426-21-9; **15** isomer B, 61426-22-0; (*Z*)-**16**, 61426-23-1; (*E*)-**16**, 61475-95-4; **17** isomer A, 61426-24-2; **17** isomer B, 61475-96-5; **21**, 61475-97-6; acrolein, 107-02-8; isoprene, 78-79-5; *tert*-butylamine, 75-64-9; ethyl formate, 109-94-4; lithium dimethylcuprate, 15681-48-8.

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Purine *N*-Oxides. 66. Synthesis of 9-Hydroxyadenine[1]

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The synthesis of 9-hydroxyadenine, by a variation of the Shaw purine synthesis, involved the condensation of ethyl *N*-(dicyanomethyl)formimidate tosylate (**2**) with benzyloxyamine to a cyanoimidazole derivative **3** which was then ring closed to the purine derivative. This is the third adenine *N*-oxide isomer available for carcinogenicity testing.

The biological studies on the oncogenicity of purine *N*-oxides have demonstrated that adenine 1-*N*-oxide[2] is a mild oncogen with respect to the strong oncogen, 3-hydroxyxanthine,[3] whereas adenine 3-*N*-oxide is not oncogenic.[4] 9-Hy-

droxyadenine was required to shed further light on the relationship between the structure and oncogenicity of adenine *N*-oxides.

Of the routes to purine *N*-oxides, the simplest is the direct oxidation of a purine with peroxy acids and only one isomer is obtained from a given purine. Adenine is oxidized to adenine 1-*N*-oxide[5] while guanine yields guanine 3-*N*-oxide.[6] From these two *N*-oxides, many other purine 1- and 3-*N*-oxides have been derived.[7,6] Adenine 3-oxide has been obtained by two routes. In one, 7-aminothiazolo[5,4-d]pyrimidine was oxidized to its 6-oxide, in analogy to oxidation of adenine at position 1. With base, the 7-aminothiazolopyrimidine 6-oxide is rearranged to 6-mercaptopurine 3-oxide,[8] which can be oxidized to the 6-sulfono- and that aminated to the adenine 3-oxide.[9] Amination of 6-chloropurine 3-oxide also yields adenine 3-oxide.[10]

Recently the synthesis of the 6-oxopurines 9-hydroxyhypoxanthine, xanthine, and guanine has been accomplished[11] from a common starting material, namely 2-amino-2-cyanoacetamide via 5-amino-1-benzyloxyimidazole-4-carboxamide. However, an imidazole carboxamide is not applicable in synthesis of 6-amino derivatives, which require an appropriate imidazole carboxamidine or carbonitrile.

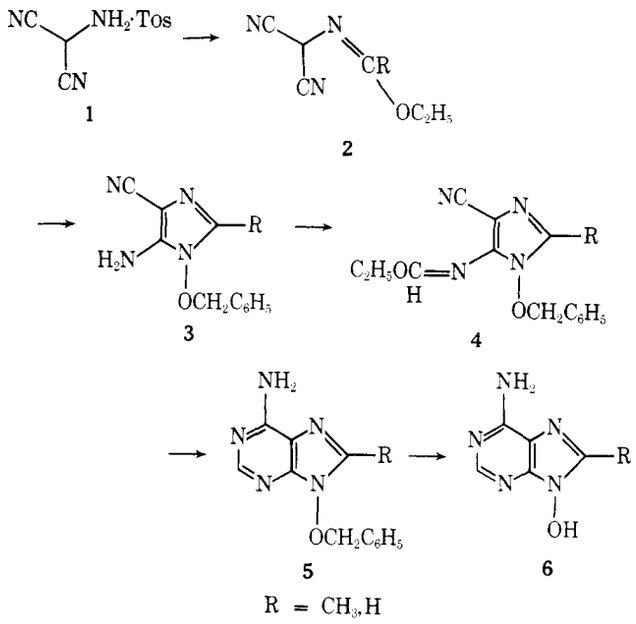
In the course of studies on prebiotic syntheses, Orgel[12] prepared aminomalononitrile and found it to be stable as the *p*-toluenesulfonate. By treating this compound with formamidine acetate, 5-aminoimidazole-4-carbonitrile was obtained and then ring closed to adenine.

Shaw[13] has used the free aminomalononitrile in his synthetic route and has prepared 5-amino-1-cyclohexylimidazole-4-carbonitrile. The synthesis of 9-hydroxyadenine was therefore first attempted from aminomalononitrile. Initially the free amino compound obtained from the tosylate was used to prepare the imino ether but this resulted in complete failure due to the polymerization of the aminomalononitrile on heating in triethyl ortho esters.

Martin[14] has shown that 2-amino-3-methylamino- and 2-methylamino-3-aminopropionic acids can be cyclized to 1-methyl-2-imidazoline-4- and -5-carboxylic acids, respectively, in triethyl orthoformate in the presence of a catalytic trace of hydrochloric acid. These ring closure reactions must have taken place via the imino ether hydrochloride intermediates shown. From previous findings on the catalytic effect of a trace of HCl in the synthesis of 5-amino-1-benzyloxyimidazole-4-carboxamide from an imino ether and benzyloxyamine hydrochloride,[11] coupled with those of Martin,[14] it was decided to first heat the aminomalononitrile tosylate with triethyl orthoacetate on a steam bath. The reaction was monitored by TLC, a new spot of high R_f was observed, and on eluting with ethanol, the UV spectrum showed the characteristic phenyl absorption at 250–260 nm plus a high absorption at 228 nm which is characteristic of imino ethers. This imino ether tosylate, **2** (R = CH_3) (Scheme I), was then refluxed in ethanol with 2 equiv of benzyloxyamine for 4 h to give a good yield of 5-amino-2-methyl-1-benzyloxyimidazole-4-carbonitrile (**3**, R = CH_3). The best yield of 5-amino-1-benzyloxyimidazole-4-carbonitrile (**3**, R = H) was obtained when equimolar quantities of **2** (R = H) and benzyloxyamine were used and reaction time reduced to 1.5 h. The **3** was then treated with triethyl orthoformate on a steam bath for 1 h to give the ethoxymethyleneaminoimidazole derivative (**4**, R = CH_3). 9-Benzyloxy-8-methyladenine (**5**, R = CH_3) was obtained by heating **4** in a steel bomb with ethanolic ammonia at 120 °C for 2 h. Removal of the benzyl group was accomplished with 32% HBr in acetic acid giving a high yield of 9-hydroxy-8-methyladenine (**6**, R = CH_3).

By the same sequence of reactions used for the preparation of 9-hydroxy-8-methyladenine, the desired 9-benzyloxyadenine (**5**, R = H) and 9-hydroxyadenine (**6**, R = H) were

Scheme I



synthesized. The UV spectrum of the anion of 9-hydroxyadenine has a strong absorption (ϵ 20.8 × 10^{-3}) at 234 nm which is over twice that of the second maximum at 262 nm. The absorption of the neutral species, ϵ 11.8 × 10^3 at 245 nm, compared to the value at 234 nm for the monoanion indicates that the neutral species has a considerable proportion of the *N*-oxide tautomer, presumably with a proton on N-7. The predominant tautomer in the neutral species is the *N*-hydroxy derivative, whereas in the monoanion the *N*-oxide form predominates, in agreement with the deductions previously made for the strong absorption in the 215–240-nm range for purine *N*-oxides that are considered to be due to >N→O or the enol anion >N–O⁻.[15-17]

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. NMR spectra were determined on a Varian A-60 spectrometer in $(CH_3)_2SO$-d_6 as solvent with Me_4Si as internal standard. Chemical shifts are reported in parts per million (δ), and signals are quoted as s (singlet), d (doubled), t (triplet), and q (quartet). UV spectra were measured using a Unicam Model SP800. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. For TLC Eastman chromatographic silica gel sheets were used with solvent systems indicated and viewed under UV or developed with iodine. The pK_a values were determined spectrophotometrically by methods described.[18,19] The silica gel used is grade 923 (100–200 mesh, Davison).

5-Amino-2-methyl-1-benzyloxyimidazole-4-carbonitrile (3, R = CH_3). Aminomalononitrile *p*-toluenesulfonate (12.67 g, 0.05 mmol) and 75 ml of triethyl orthoacetate were warmed on a steam bath for about 1 h, or when TLC (1:1 petroleum ether–ether) of the reaction mixture indicated that the reaction was complete, that is, until the absence of aminomalononitrile tosylate. The excess triethyl orthoacetate was removed in vacuo and benzyloxyamine (12 g, 0.1 mol) in 250 ml of ethanol was added to the residue. The solution was heated under reflux for ~4 h until the TLC (1:1 petroleum ether–ether) indicated that **2** had completely disappeared and a new UV absorbing spot was present. The ethanol was removed in vacuo and the residue was chromatographed on silica gel. Elution with 1:1 petroleum ether–ether gave two compounds; the first was ethyl *N*-benzyloxyacetimidate and the second the excess benzyloxyamine. Elution with anhydrous ether removed a non-UV-absorbing material of unknown structure which could be detected only when TLC was developed with I_2. On eluting with ether, containing 3.5% EtOH, the required imidazole was obtained. Evaporation of the solvent and recrystallization from ethyl acetate–petroleum ether gave white needles of **3** (R = CH_3): yield 4.5 g (39%); mp 144–145 °C; UV λ_{max} (EtOH) 217 nm (ϵ 7.3 × 10^3), 247 (10.0 × 10^3); NMR δ 7.40 (s, 5, $OCH_2C_6H_5$), 4.24 (bs, 2, NH_2), 5.09 (s, 2, $OCH_2C_6H_5$), 2.02 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.30; H, 5.34; N, 24.47.

9-Benzyloxy-8-methyladenine (5, R = CH_3). A solution of 5-amino-1-benzyloxy-2-methylimidazole-4-carbonitrile (456 g, 0.002 mmol) in triethyl orthoformate was warmed on a steam bath until TLC (1:1 petroleum ether–$CHCl_3$) showed the absence of **3**. The excess triethyl orthoformate was removed in vacuo and the residue was dissolved in saturated ethanolic ammonia and heated in a steel bomb at 120 °C for 3 h. The mixture was evaporated to dryness and the residual gum was chromatographed over silica gel. Elution with 9:1 $CHCl_3$–EtOH gave pure **5** (R = CH_3). Recrystallization from ethyl acetate–petroleum ether afforded white needles of 9-benzyloxy-8-methyladenine (391 mg, 76%): mp 174–175 °C; UV λ_{max} (pH 1) 210 nm (ϵ 23.5 × 10^3), 263 (13.4 × 10^3); NMR δ 8.33 (s, 1, 2-CH), 7.73 (s, 5, $CH_2C_6\mathbf{H}_5$), 6.60 (bs, 2 NH_2), 5.40 (s, 2, $OC\mathbf{H}_2C_6H_5$), 2.10 (s, 3, CCH_3).

Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.04; H, 4.94; N, 27.37.

9-Hydroxy-8-methyladenine (6, R = CH_3). 9-Benzyloxy-8-methyladenine (**5**, R = CH_3) (255 mg, 0.001 mmol) was warmed on a steam bath in 4 ml of 32% HBr in glacial acetic acid for 3.5 h. The reaction mixture was cooled and the HBr salt was collected and washed thoroughly with ether. The product was dissolved in hot water containing a few drops of concentrated ammonia, treated with charcoal, and precipitated by the addition of glacial acetic acid. The 9-hydroxy-8-methyladenine (**6**, R = CH_3) was collected, washed with water, ethanol, and ether, and dried at 78 9 °C over P_2O_5: yield 126 mg (79%); UV λ_{max} (pH 1) (+) 217 nm (ϵ 16.0 × 10^3), 263 (12.2 × 10^3); pH 5.0 (0) 246 nm (ϵ 10.6 × 10^3), 261 (11.5 × 10^3), pH (−), 235 nm (ϵ 20.2 × 10^3), 265 (9.0 × 10^3); pK_a's 3.95 (±0.07), 6.00 (±0.1).

Anal. Calcd for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.41. Found: C, 43.68; H, 4.37; N, 42.32.

5-Amino-1-benzyloxyimidazole-4-carbonitrile (3, R = H). The reaction was performed in the same manner as above, employing aminomalononitrile *p*-toluenesulfonate (6.34 g, 0.025 mmol) and 30 ml of triethyl orthoformate and warming on a steam bath until TLC indicated the absence of the first starting material. After the excess triethyl orthoformate was removed in vacuo, benzyloxyamine (3 g, 0.025 mmol) in 100 ml of ethanol was added and the mixture was refluxed for approximately 1.5 h. Ethanol was then removed in vacuo and the residue was chromatographed as before for the 2-methyl derivative (**3**, R = CH_3). Recrystallization from ethyl acetate–petroleum ether afforded white crystals of **3** (R = H): 985 mg (19%); mp 140–141 °C; UV λ_{max} (EtOH) 216 nm (ϵ 10.5 × 10^3), 245 (12.0 × 10^3); NMR 6.84 (s, 1, 2C-H), 7.37 (s, 5, $C_6\mathbf{H}_5CH_2$), 5.08 (s, 2, $OC\mathbf{H}_2C_6H_5$), 5.00 (bs, 2, NH_2).

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.74; H, 4.67; N, 26.16.

9-Benzyloxyadenine (5, R = H). **3** (R = H) (4.28 mg, 0.002 mmol) and triethyl orthoformate 10 ml) were warmed on a steam bath until TLC (1:1 petroleum ether–$CHCl_3$) showed absence of the imidazole (45 min). The excess of ortho ester was removed in vacuo. The residual oil was reacted immediately in a sealed bomb with saturated ethanolic ammonia at 120 °C for 3 h. Subsequently the reaction mixture was taken to dryness and chromatographed as for the 8-methyl compound. Recrystallization from ethyl acetate–petroleum ether yielded white crystals of **5** (R = H), 363 mg (75%): mp 165–166 °; UV λ_{max} (pH 1) 210 nm (ϵ 25.4 × 10^3), 258 (15.1 × 10^3); λ_{max} (pH 7) 205 nm (ϵ 23.8 × 10^3), 260 (14.0 × 10^3); NMR δ 8.40 (s, 1, 2-CH), 7.40 (s, 1, 8-CH), 7.33 (s, 5, $C_6\mathbf{H}_5CH_2$), 5.37 (s, 2, $OC\mathbf{H}_2C_6H_5$), 6.63 (s, 2, NH_2).

Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.75; H, 4.53; N, 29.02.

9-Hydroxyadenine (6, R = H). The debenzylation of **5** (R = H) (241 mg, 0.001 mmol) was carried out as above. The free base was obtained from the hydrobromide salt by dissolving in hot dilute ammonia, treatment with charcoal, and precipitating by the addition of glacial acetic acid. The white crystals were collected, washed with water, ethanol, and ether, and dried in vacuo over P_2O_5 at 78 °C: yield 115 mg (78%); UV λ_{max} (pH 1) 215 nm (ϵ 17.4 × 10^3), 261 (13.0 × 10^3); λ_{max} (pH 4.6) 245 nm (ϵ 11.8 × 10^3), 259 (12.1 × 10^3); λ_{max} (pH 10) 234 nm (ϵ 20.8 × 10^3), 262 (9.0 × 10^3); pK_a's 3.59 (±0.05), 5.7 (±0.1).

Anal. Calcd for $C_5H_5N_5O$: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.52; H, 3.42; N, 46.18.

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Registry No.—**1**, 5098-14-6; **3** (R = CH_3), 61193-34-8; **3** (R = H), 61193-35-9; **5** (R = CH_3), 61193-36-0; **5** (R = H), 61193-37-1; **6** (R = CH_3), 61193-38-2; **6** (R = H), 61193-39-3; triethyl orthoacetate, 78-39-7; benzyloxyamine, 622-33-3; triethyl orthoformate, 122-51-0.

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