methylamine are dehydrated sufficiently that spin coupling of the adjacent N–H and C–H protons is observable in their NMR spectra: K. L. Henold, *Chem. Commun.*, 1340 (1970).
(14) H. Baumgarten, Ed., "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 976.
(15) In a peculiar sense, this result confirms an earlier statement that "One day drying over calcium hydride is found to be as effective as six months refluxing over sodium". See A. S. Brown, *J. Chem. Phys.*, **19**, 1226 (1951).
(16) See, for example, G. Köbrich, W. E. Breckhoff, H. Heinemann, and A. Akhtar, *J. Organomet. Chem.*, **3**, 492 (1965).
(17) W. R. Purdum and G. J. Bartling, *J. Chem. Educ.*, **52**, 120 (1974).
(18) S. C. Watson and J. F. Estham, *J. Organomet. Chem.*, **9**, 165 (1967).
(19) (a) I. Fleming and T. Mah, *J. Chem. Soc., Perkin Trans. 1*, 964 (1975); (b) R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972).
(20) Y. Pocker and W. H. Wong, *J. Am. Chem. Soc.*, **97**, 7097 (1975).
(21) J. F. Coetzee and G. R. Padmanabhan, *J. Phys. Chem.*, **66**, 1708 (1962).
(22) Subsequent distillation from potassium carbonate has been recommended for removal of phosphorus pentoxide residues. See P. Walden and E. J. Birr, *Z. Phys. Chem. (Leipzig)*, **144A**, 269 (1929).
(23) Drying over calcium chloride for "at least a week" has been advocated as a method for obtaining "thoroughly dry" acetonitrile. A. H. Blatt, Ed., "Organic Syntheses", Collect. Vol. I, 2nd ed, Wiley, New York, N.Y., 1946, pp 5–6.
(24) A. Lapidot, J. Reuben, and D. Samuel, *J. Chem. Educ.*, **41**, 570 (1964).
(25) See ref 11, p 759.
(26) These observations appear to support the earlier contention that "pretreatment with potassium hydroxide does more harm than good". See J. F. Coetzee, *Pure Appl. Chem.*, **13**, 429 (1966).
(27) H. J. Dauben Jr., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).
(28) N. Lichtin in "Carbonium Ions", Vol. I, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1968, p 140.
(29) R. L. Meeker, F. Critchfield, and E. T. Bishop, *Anal. Chem.*, **34**, 1510 (1962).
(30) (a) See ref 3e, p 1102. (b) See ref 3e, p 333.

Perhydrogenation of 2,8-Diaminopurine

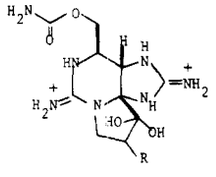
Mark M. Wegner and Henry Rapoport*

Department of Chemistry, University of California, Berkely, California 94720

Received March 7, 1977

2,8-Diaminopurine (**7**) can be hydrogenated over PtO_2 in acidic medium to give 2-imino-4-guanidinomethyl-5-imidazolidinone (**11**) which can itself be further hydrogenated to 2-imino-4-guanidinomethylimidazolidine (**12**). The structures of **11** and **12** were proven by unambiguous synthesis. 2,8-Diamino-6-methylpurine (**37**) also can be hydrogenated in a similar manner to two analogous compounds, as isomeric mixtures, whose structures are inferred by comparison with **11** and **12**. A superior method has been developed for synthesizing the diaminopurines **7** and **37**, involving the condensation of the appropriate triaminopyrimidine with *N*-(methylmercaptochloromethyl)-*p*-toluenesulfonimide (**20**) followed by ring closure via the carbodiimide and detosylation with HF.

Saxitoxin is one of the most potent naturally occurring neurotoxins. It is the sole toxin produced by the marine dinoflagellate *Gonyaulax catenella*[1] and is a minor constituent of the toxins produced by *G. tamarensis*.[2] Ingestion of these dinoflagellates by several species of normally edible shellfish is frequently responsible for their toxicity to man. X-ray crystallographic analysis of two derivatives, the bis-*p*-bromobenzenesulfonate[3] and the ethyl hemiketal dihydrochloride,[4] have established structure **1** for crystalline saxitoxin hydrate, and ^{13}C NMR studies have also established this structure for the molecule in solution.[4] Recently[5] the major toxins of *G. tamarensis*, gonyautoxins II and III, also existing as the hydrates, were postulated to have the closely related structures **2** and **3**, respectively.



1, R=H
2, R=α-OH
3, R=β-OH

Saxitoxin and the gonyautoxins are unique among natural products in that their structures incorporate a tetrahydropurine moiety composed of two guanidine units fused together in an azaketal linkage which remains intact under ordinary conditions. We were therefore interested in preparing a simple model of the tetrahydropurine backbone of saxitoxin, devoid of the fused ketone bearing ring and the peripheral carbamate, for both chemical and biological investigations. We chose to study the catalytic hydrogenation of 2,8-diaminopurine (**7**), which conceivably could lead to 2,8-diiminotetrahydropurine (**10**) or its tautomers, the simplest possible tetrahydropurine model of saxitoxin. We now report the results of our study of the heterogeneous catalytic hydrogenation of 2,8-diaminopurines.

The literature relating to the catalytic reduction of purines is relatively meager. 1,6-Dihydropurine (**5**) has been prepared[6,7] from purine and 6-chloropurine (**4**), and in weak acid **5** was hydrolyzed to 4(5)-aminomethyl-5(4)-aminoimidazole (**6**). Similarly a tetrahydropurine is claimed[8] to result from catalytic reduction of 2,6,8-trichloropurine. More recently,[9] the catalytic reduction of 2,8-diaminopurine (**7**) is reported to yield a compound whose structure was assigned as 2-amino-5-guanidino-1,4,5,6-tetrahydro-6-oxopyrimidine (**8**). These authors also report the preparation of 2,8-diamino-4,5,6,9-tetrahydro-1,7,9-trimethylpurine by sodium borohydride reduction of 2,8-diamino-1,7,9-trimethylpurine, and claim to have electrolytically reduced **7** to **8** plus tetrahydropurine **10**, obtained as an inseparable mixture with another reduction product **9**.

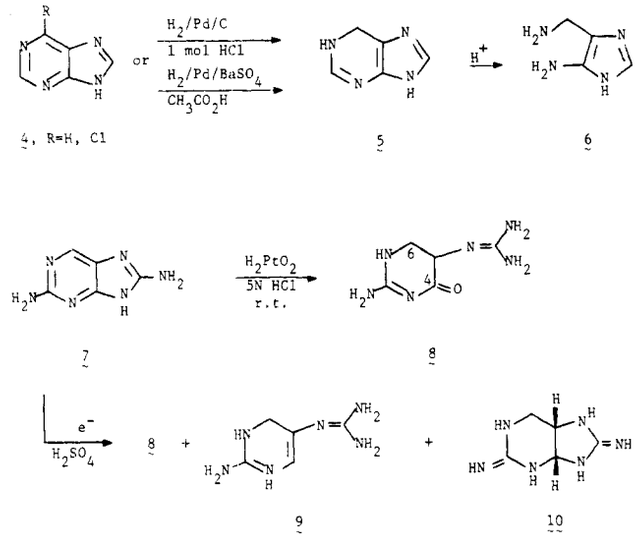
In contrast to that report, we have found that **7** is slowly hydrogenated with a PtO_2 catalyst in hydrochloric acid (pH 1.5) at room temperature and 20 psi pressure to give a single product, A, in quantitative yield. A could be further reduced under more drastic conditions (60 °C, 100 h) to give another product, B, also in quantitative yield. The ^1H NMR spectrum of A·2HCl consisted of a doublet (2 H, J = 5 Hz) and a triplet (1 H, J = 5 Hz); its ^{13}C NMR spectrum is tabulated in Table I.

These NMR data suggested that A was not a reduced purine with an intact bicyclic ring system but rather the five-membered monocyclic imidazolidinone **11**. The ^{13}C NMR absorption at δ 173 is clearly assigned to the amide carbonyl, and the simple doublet–triplet pattern of the ^1H NMR spectrum implies the freely rotating methylene group of **11**. The alternative six-membered ring structure **8** previously proposed[9] for the 2,8-diaminopurine reduction product should display

Table I. ^{13}C NMR Data[a] for 2,8-Diaminopurine (7) Reduction Products

C atom	A (11) δ	A (11) Mult[b]	A′[c] δ	C atom	B (12) δ	B (12) Mult[b]	B′[c] δ
2 or 8	158.3	(s)	158.6	2 or 8	159.4	(s)	159.4
			158.2				159.1
2 or 8	157.2	(s)	156.2	2 or 8	157.2	(s)	156.2
							152.3
4	58.8	(d)	63.0	4	54.0	(d)	58.7
			62.0				58.1
5	173.5	(s)	173.2	5 or 6	45.5	(t)	50.3
							50.1
6	40.8	(t)	48.4	5 or 6	43.9	(t)	45.3
			47.9				44.2
9			16.7	9			16.2
			14.8				15.6

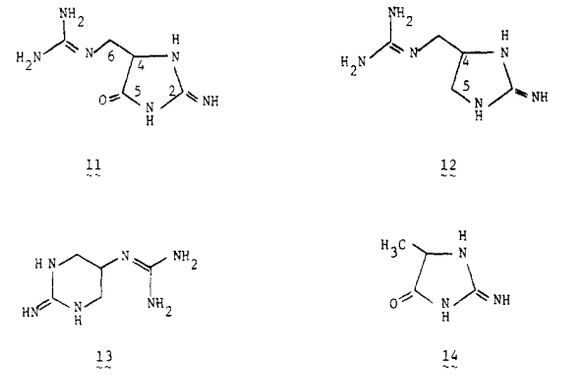
[a] Parts per million relative to dioxane (δ 66.5). [b] Assignments for 11 and 12 are based on proton off-resonance decoupled spectra and predicted chemical shifts. [c] Assignments for A′ and B′ are based on correlations with similar absorptions for 11 and 12.



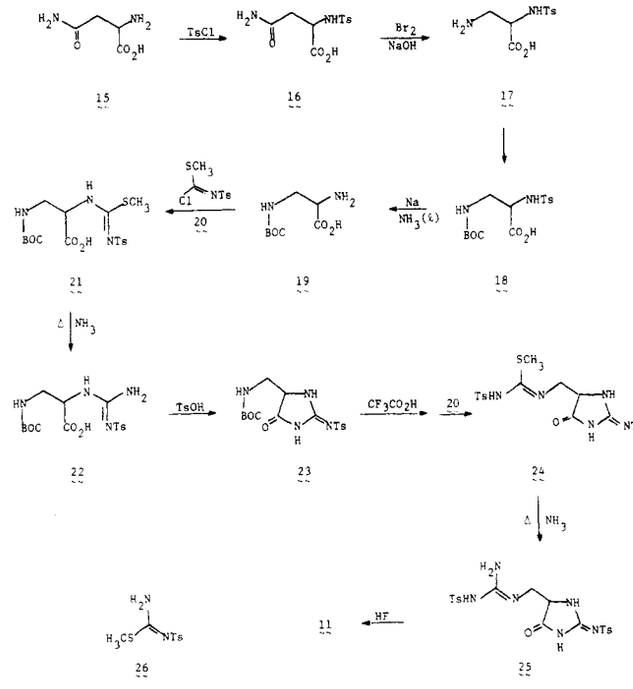
a much more complex ^1H NMR spectrum. One would expect the two C-6 protons in 8 to be nonequivalent and therefore to couple with each other and in a nonequivalent manner with the C-5 proton. A·2HCl has an ultraviolet absorption maximum in water at 223 nm (ε 7800), in a good agreement with the value of 223 nm (ε 9200) that we find under the same conditions for alacreatinine (14).[10] Elemental analysis of the sulfate salt of A is also consistent with structure 11.

The ^1H NMR of B·2HCl is considerably more complex than that of A, and its ^{13}C NMR absorptions are also tabulated in Table I. Replacement of the δ 173 absorption in A with a higher field absorption in B, all the other absorptions staying relatively constant, suggests that the carbonyl of 11 has merely been reduced to a methylene, and therefore the imidazolidine 12 was proposed as the structure for B. ^{13}C NMR off-resonance decoupling experiments (see Table I) show that there are two different kinds of methylene carbons in B, and thus rule out the alternative symmetrical six-membered ring structure 13. B·2HCl has no specific ultraviolet absorption above 210 nm, in agreement with the loss of the acylguanidine chromophore, and elemental analysis of the sulfate salt of B is also consistent with structure 12.

In order to conclusively establish the structures of A and B, unambiguous syntheses of 11 and 12 were undertaken. Asparagine (15) is ideally suited as a starting material for a two-stage guanylation synthesis of 11 since it contains two kinds of inherently different nitrogen functionality. N^{α}-*p*-Toluenesulfonylamino-N^{β}-*tert*-butyoxycarbonyl-L-α,β-diaminopropionic acid (L-18) has been prepared[11,12] from *p*-toluenesulfonyl-L-asparagine (L-16). The tosyl group of 18 was then removed with sodium in liquid ammonia and without isolation the intermediate N^{β}-*tert*-butyloxycarbonyl-L-α,β-diaminopropionic acid (L-19) was reacylated with benzyloxycarbonyl chloride.



Following the above literature procedures we were easily able to prepare DL-18 from DL-asparagine. For our purpose, the sodium and liquid ammonia removal of the tosyl group from DL-18 was immediately followed by acylation with *N*-(methylmercaptochloromethyl)-*p*-toluenesulfonimide (20)[13] to give the isothiourea 21 in 90% yield. This was then con-



verted to the guanidino acid **22** by treatment with liquid ammonia. We have found this two-step procedure superior to direct guanylation with *S*-methyl-*N*-*p*-toluenesulfonylisothiourea (**26**) which is usually a poor reaction and frequently fails completely; **20**, however, condenses readily at room temperature even with very hindered amines to give good yields of the corresponding isothioureas. Conversion to the guanidine with liquid ammonia is also usually quite efficient, and combined yields of 60% can be routinely realized.

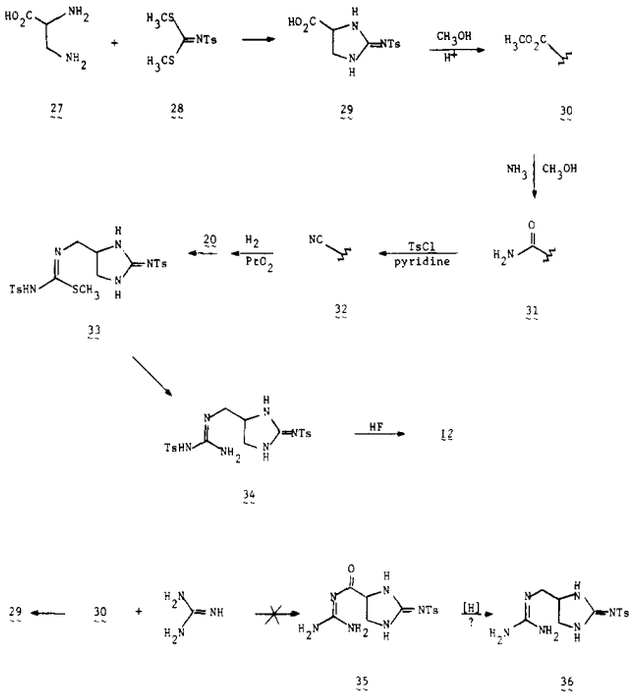
The guanidino acid **22** was not characterized or purified but was immediately cyclized with *p*-toluenesulfonic acid in refluxing THF to the imidazolidinone **23.** As might be expected from the presence of the acid-labile *t*-Boc group, the yield in this ring-closure step was only moderate (40–60%). The *t*-Boc group was removed with cold anhydrous trifluoroacetic acid and the intermediate reacylated with **20** to give the isothiourea **24** in 83% yield. Amination with liquid ammonia then gave the bistosylguanidine **25** in 61% yield. Treatment of **25** with anhydrous HF[14] followed by ion exchange chromatography gave the detosylated 2-imino-5-imidazolidinone **11** which was identical in all respects with compound A, obtained from the reduction of **7.**

The preparation of **12** was more straightforward since there is no potentially ambiguous cyclization involved. The imidazolidine ring was prepared in the first step by condensation of DL-diaminopropionic acid (**27**) with *S,S*-dimethyl *N*-*p*-toluenesulfonyliminodithiocarbonimidate (**28**)[14] to give **29** in 73% yield. The carboxy group of **29** was then converted into the tosylguanidino side chain of **34** by esterification to **30,** treatment of **30** with alcoholic ammonia to give amide **31,** and dehydration of **31** to nitrile **32** with *p*-toluenesulfonyl chloride in pyridine. Hydrogenation to the amine followed by immediate acylation with **20** gave the isothiourea **33,** and treatment with ammonia then gave the bistosylguanidine **34** which was detosylated with anhydrous HF to give the 2-iminoimidazolidine **12.** Individual product yields from **30** to **34** were from 73 to 92%. Imidazolidine **12,** so prepared, was found to be identical in all respects with compound B, obtained from the reduction of **7.**

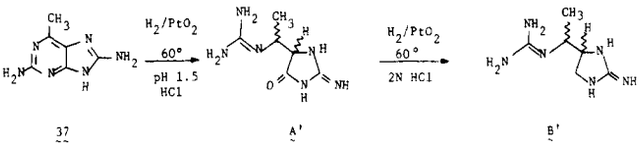
We had originally tried to save some steps in the reaction sequence leading to **12** by attempting to prepare acylguanidine **35** directly from ester **30** and guanidine (as the free base, prepared by passage of methanolic guanidine hydrochloride through an ion exchange column); hopefully **35** could then be reduced to **36.** However, only the acid **29** was recovered from the reaction, presumably resulting from hydrolysis by water contamination in the methanolic guanidine.

We have thus shown that the two products A and B, obtained from the catalytic hydrogenation of 2,8-diaminopurine (**7**), are respectively the 2-imino-5-imidazolidinone **11** and the 2-iminoimidazolidine **12.** We can now confidently make the ^{13}C NMR absorption assignments for both compounds as shown in Table I, and the doublet and triplet ^1H NMR pattern of **11** can be explained in terms of simple methylene–methine coupling. The appearance of a more complex ^1H NMR spectrum for **12** is due to the presence of the newly introduced ring methylene protons. The ^1H NMR spectrum of our A (**11**) appears to be identical with that reported[9] for product **8** resulting from the catalytic and electrolytic reduction of **7.** The dipicrate of our **11** had the same melting point and showed the same infrared absorption values as those reported for "8" dipicrate. Therefore we conclude that the previous structural assignment, based solely on an unlikely ^1H NMR interpretation, is incorrect, and should be revised to structure **11.**

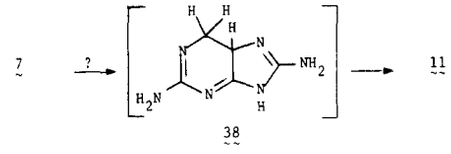
We also hydrogenated 2,8-diamino-6-methylpurine (**37**) under similar conditions and found that two reduction products, A′ and B′, were formed, analogous to A and B on the basis of spectral and chromatographic properties. A′ and B′ appear to be the epimeric mixture shown. The ^{13}C NMR



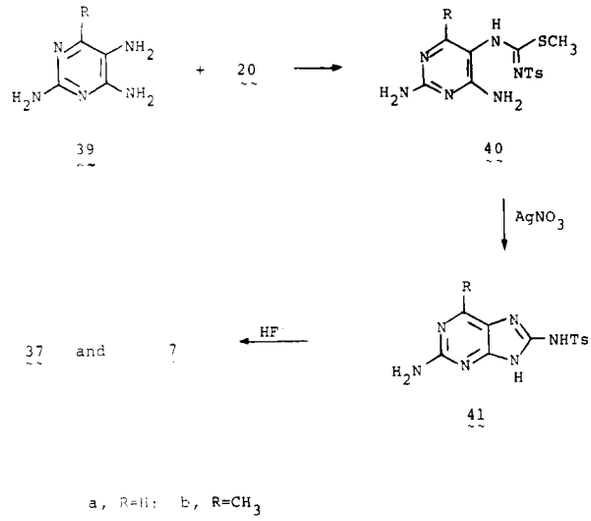
spectra (Table I) of A′ and B′ are very similar to those of A and B with the exception that most of the signals of the former group are doubled. The ^1H NMR spectra of A′ and B′ display distinct methyl doublets, but in a manner that suggested the presence of two different compounds, and the methyl signals are shifted in a manner consistent with the presence of two separate species on going from 60 to 100 to 220 Mz spectrometers.



The isolation of the 2-imino-5-imidazolidinone **11** was unexpected in view of the previous reports[6,7] of dihydropurine (**5**) formation from reduction of **4.** In a parallel fashion, one would expect that an initial dihydropurine resulting from **7,** because of the intact imidazole, would not easily cleave to **11.** To explain the behavior we observed, an initial "abnormal" 5,6-dihydropurine intermediate **38** might be involved, lacking the stable imidazole structure, which would then hydrolyze to give **11.** At this point, however, there is no experimental evidence to support an intermediate such as **38** since only **11** and **7** can be seen, by ^1H NMR, in partially completed reductions of **7.**



For the hydrogenation studies we required an efficient synthesis of purines **7** and **37,** which was found in a simple three-step process involving first the condensation of the corresponding triaminopyrimidines **39** with **20** to give good yield of the isothioureidopyrimidines **40,** with the position of acylation at N-5 assumed. These compounds were cyclized via a carbodiimide intermediate, generated by $AgSCH_3$ elimination,[15] to the 8-*p*-toluenesulfonylaminopurines **41.** Treatment with anhydrous HF as before gave the desired purines **7** and **37** in overall yields of 50 and 91%, respectively.



a, R=H; b, R=CH_3

Experimental Section

Melting points were taken in open capillaries, unless otherwise specified, and are uncorrected. ^1H NMR spectra were determined at 60 MHz using Me_4Si as an internal standard (δ 0) unless otherwise noted and ^{13}C NMR spectra were determined at 25.14 MHz. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley. All evaporations were done in vacuo using a Berkeley rotary evaporator.

Hydrogenation of 2,8-Diaminopurine (7) to 2-Imino-4-guanidinomethyl-5-imidazolidinone (11). 2,8-Diaminopurine hydrochloride (7, 665 mg, 3.58 mmol) and 100 mg of PtO_2 in dilute HCl (55 mL, pH 1.5) were hydrogenated at 20 psi on a Parr shaker at room temperature for 46 h. The reaction mixture was filtered and the filtrate evaporated at 40 °C to give 840 mg of a residue that solidified into a crystalline mass on standing: ^1H NMR (220 MHz, D_2O, external Me_4Si) δ 4.8 (t, 1 H, J = 5 Hz), 3.9 (d, 2 H, J = 5 Hz); ^{13}C NMR (see Table I). A portion of the crude dihydrochloride was dissolved in water and passed through a Bio-Rad AG 21K anion exchange column (SO_4^{2-} form) to give the sulfate as fine needles (from water), mp 222–224 °C dec; UV (H_2O) λ_{max} 223 nm (ϵ 7800).

Anal. Calcd for $C_5H_{12}N_6O_5S\cdot\frac{1}{4}H_2O$: C, 22.0; H, 4.6; N, 30.8. Found (hygroscopic): C, 22.1; H, 5.0; N, 30.6.

The dipicrate, prepared from the dihydrochloride, had mp 220–221 °C dec (capillary), 227–228 °C dec (hot stage) after recrystallization from water: IR (KBr) ν_{max} 1778, 1704, 1672, 1636 cm^{-1} (lit.[9] values for a compound to which structure 8 was assigned: mp 227.5 °C; IR ν_{max} 1780, 1711, 1680, 1635 cm^{-1}).

2-Imino-4-guanidinomethylimidazolidine (12). 11 (200 mg, 0.82 mmol) as the dihydrochloride and 110 mg of PtO_2 were taken up in dilute HCl (55 mL, pH 1.5) and hydrogenated at 20 psi on a Parr shaker for 100 h at 60 °C. The reaction mixture was filtered and the filtrate evaporated to give 197 mg (97%) of a glassy residue: ^1H NMR (220 MHz, D_2O, external Me_4Si) δ 4.3 (m, 1 H), 3.8 (t, 1 H), 3.5 (d, 1 H), 3.4 (br s, 2 H); ^{13}C NMR (see Table I). A portion of the crude dihydrochloride was treated by the above ion exchange procedure to give the sulfate salt, mp 307–310 °C dec (from water).

Anal. Calcd for $C_5H_{14}N_6O_4S$: C, 23.6; H, 5.6; N, 33.1. Found: C, 23.6; H, 5.4; N, 33.3.

Hydrogenation of 2,8-Diamino-6-methylpurine (37) to Product A′. 2,8-Diamino-6-methylpurine (37, 636 mg, 3.17 mmol) and 100 mg of PtO_2 were hydrogenated in HCl (30 mL, pH 1.5) for 48 h at 60 °C and 35 psi on a Parr shaker. After filtration and evaporation of the solvent the glassy residue (720 mg) was applied to an ion exchange column (Bio-Rad AG-50 X8, 400 mesh; H^+ form; 50 mL bed volume) and eluted with 2 N HCl. Fractions of 15 mL were collected and analyzed by TLC (silica gel, phenol saturated with H_2O, visualized with Weber spray[16]). Fractions 80–110 gave 275 mg of product A′ (red Weber streak, R_f 0.1–0.3) and fractions 130–200 gave 212 mg (33%) of 37 (green Weber spot, R_f 0.5). A′ had ^1H NMR (D_2O, external Me_4Si) δ 4.8 (q at 60 MHz, t at 220 MHz, 1 H), 4.2 (m at 60 and 220 MHz, 1 H), 1.5 (d of d at 60 MHz, t at 220 MHz, 3 H); ^{13}C NMR (see Table I). A portion of the dihydrochloride was treated by the AG-21K ion exchange procedure to give the sulfate salt as fine needles (from water), mp 200–225 °C dec, UV (H_2O) λ_{max} 224 nm (ϵ 7400).

Anal. Calcd for $C_6H_{14}N_6O_5S\cdot H_2O$: C, 23.8; H, 6.0; N, 27.8. Found: C, 24.1; H, 6.0; N, 27.7.

Hydrogenation of 2,8-Diamino-6-methylpurine (37) to Product B′. 37 (654 mg, 3.46 mmol) and 110 mg of PtO_2 were hydrogenated in HCl (55 mL, pH 1.5) for 118 h at 60 °C and 20 psi on a Parr shaker. An additional 100 mg of catalyst was added after 46 h. After filtration and evaporation of the filtrate the glassy residue (540 mg) was chromatographed on the Bio-Rad AG-50 system used for product A′ above. On the basis of TLC and ^1H NMR, fractions containing 50 mg of A′ and fractions containing 228 mg of B′, as a glassy solid (purple Weber streak, R_f 0.1–0.3), were collected. B′ had ^1H NMR (60 MHz, D_2O, external Me_4Si) δ 4.7–3.6 (m, 4 H), 1.5 (t, 3 H); ^1H NMR (220 MHz, D_2O, external Me_4Si) δ 4.5 (m, 1 H), 4.2 (m, 2 H), 3.9 (m, 1 H), 1.5 (d of d, 3 H); ^{13}C NMR (see Table I). An unsuccessful attempt was made to secure a crystalline sulfate derivative by the above AG-21K ion exchange procedure.

***N*-*p*-Toluenesulfonyl-DL-asparagine (16).** The procedure[17] for the L isomer was used with 0.2 mol of DL-asparagine to give the white, crystalline product in 36% yield, mp 170–173 °C (lit.[17] mp 175 °C for L isomer).

***N*$^{\alpha}$-*p*-Toluenesulfonyl-DL-α,β-diaminopropionic Acid (17).** The procedure[18] for the L isomer was used on 0.07 mol of DL material to give the white, crystalline product in 49% yield, mp 230 °C dec (lit.[18] mp 225–226 °C for L isomer).

Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.5; H, 5.5; N, 10.9. Found: C, 46.4; H, 5.4; N, 10.9.

***N*$^{\alpha}$-*p*-Toluenesulfonyl-*N*$^{\beta}$-*tert*-butyloxycarbonyl-DL-α,β-diaminopropionic Acid (18).** The method[11] for the L isomer was used on 7.75 mmol of DL material to give a white, crystalline product in 96% crude yield. Recrystallization from ethyl acetate gave a product in 84% yield, mp 124–128 °C (lit.[11] mp 127–128 °C for L isomer).

Anal. Calcd for $C_{15}H_{22}N_2O_6S$: C, 50.3; H, 6.2; N, 7.8. Found: C, 50.2; H, 6.2; N, 7.8.

***S*-Methyl-*N*-*p*-toluenesulfonyl-*N*′-(1-carboxyl-2-*tert*-butyloxycarbonylaminoethyl)isothiourea (21).** 16 (1.61 g, 4.5 mmol) was dissolved in liquid NH_3 (cooled in a dry ice–acetone bath) and treated with small pieces of sodium, while the reaction mixture was stirred vigorously, until the blue color persisted for 10 min. The blue color was discharged by addition of NH_4Cl and the white, powdery residue, obtained after removal of the NH_3, was dissolved in a solution of CH_3CN (22 mL) and water (40 mL). Triethylamine (1.35 mL, 9 mmol) and then 20[13] (1.43 g, 5.4 mmol) were added. After stirring for 2.5 h at room temperature, most of the CH_3CN was evaporated and the remaining liquid was extracted twice with ether. The aqueous phase was cooled, acidified to pH 3.5 with cold, saturated citric acid, and extracted with two portions of ether. The combined ether extracts were dried over $MgSO_4$ and evaporated leaving 1.74 g (90%) of a clear, colorless residue: ^1H NMR ($CDCl_3$) δ 9.1 (br s, 2 H, NH), 7.5 (q, 5 H, ArH, NH), 4.5 (br s, 1 H, >CH), 3.6 (br s, 2 H, $>CH_2$), 2.4 (s, 6 H, SCH_3, $ArCH_3$), 1.4 [s, 9 H, $C(CH_3)_3$].

2-*p*-Toluenesulfonylimino-4-*tert*-butyloxycarbonylaminomethyl-5-imidazolidinone (23). 21 (1.74 g, 4.04 mmol) was heated in liquid NH_3 in a sealed tube at 40 °C for 3 h. The crude ammonium salt, obtained after evaporation, was dissolved in cold water, acidified to pH 1.3 with cold saturated citric acid, and extracted into CH_2Cl_2 which was dried over $MgSO_4$. Evaporation of the CH_2Cl_2 gave 1.53 g (95%) of crude guanidino acid 22 to which were added *p*-toluenesulfonic acid monohydrate (72 mg, 0.38 mmol) and 230 mL of THF. The reaction mixture was refluxed for 15 h through a small Soxhlet extractor filled with anhydrous $MgSO_4$. The THF was evaporated and the residue was chromatographed in a column packed with silica gel (160 g) eluting with 7% $CH_3OH/CHCl_3$. Pure 23 (565 mg, 39%) was thus obtained as a white solid: ^1H NMR ($CDCl_3$) δ 9.25 (br s, 1 H), 7.5 (t, 4 H, ArH), 5.1 (br m, 1 H), 4.2 (t, 1 H, >CH), 3.6 (d, 2 H, $>CH_2$), 2.4 (s, 3 H, $ArCH_3$), 1.4 [s, 9 H, $(CH_3)_3C$]; mp 196 °C dec from $CHCl_3$–petroleum ether (bp 30–60 °C).

Anal. Calcd for $C_{16}H_{22}N_4O_5S$: C, 50.2; H, 5.8; N, 14.6. Found: C, 49.8; H, 5.8; N, 14.4.

4-[(Methylmercapto-*N*-*p*-toluenesulfonylimino)methyl]-aminomethyl-2-*p*-toluenesulfonylimino-5-imidazolidinone (24). Cold trifluoroacetic acid (23 mL, freshly distilled) was added to 23 (407 mg, 10.6 mmol) and stirred at 0 °C for 1 h. The TFA was evaporated and the residue was dried briefly under high vacuum and then dissolved in a solution of water (10 mL) and CH_3CN (5 mL) and cooled in an ice bath. Triethylamine (1.0 mL, 10 mmol) and then, dropwise, a chilled solution of 20[13] (282 mg, 1.06 mmol) in CH_3CN (5 mL) were added. The resulting solution was stirred overnight at 0 °C, most of the CH_3CN was evaporated at reduced pressure, an equal volume of water was added to the remaining solution, and the resulting oily product was extracted into CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated to give 618 mg of a solid which, after chromatography on silica gel (90 g, eluting with 4% MeOH/

$CHCl_3$), gave 449 mg (83%) of pure **24** as a white powder: ^1H NMR ($CDCl_3$) δ 7.4 (q, 8 H, ArH), 4.4 (br s, 1 H, >CH), 3.8 (br s, 2 H, $>CH_2$), 2.4 (d, 9 H, SCH_3, $ArCH_3$); mp 196–198 °C from $CHCl_3$.

Anal. Calcd for $C_{20}H_{23}N_5O_5S_3$: C, 47.1; H, 4.6; N, 1.37. Found: C, 46.8; H, 4.6; N, 13.6.

4-[(Amino-*N*-*p*-toluenesulfonylimino)methyl]aminomethyl-2-*p*-toluenesulfonylimino-5-imidazolidinone (25). 24 (449 mg, 0.88 mmol) was heated in a sealed tube with liquid NH_3 at 40 °C for 3 h. The crude product left after evaporation of the NH_3 was chromatographed on silica gel (104 g, eluting with 7% EtOH/$CHCl_3$) to give 250 mg (61%) of pure **25** as a white powder: ^1H NMR (acetone-d_6) δ 7.4 (q, 8 H, ArH), 4.4 (br s, 2 H, $>CH_2$), 2.4 (d, 9 H, SCH_3); mp 211–214 °C from aqueous ethanol.

Anal. Calcd for $C_{19}H_{22}N_6O_5S_2$: C, 47.7; H, 4.6; N, 17.6. Found: C, 47.5; H, 4.6; N, 17.4.

2-Imino-4-guanidinomethyl-5-imidazolidinone (11). 25 (200 mg, 0.418 mmol) was treated at room temperature with 12 mL of anhydrous HF[14] for 59 h. The HF was evaporated, the residue was removed from the reaction vessel with alternating portions of water and benzene, and the combined aqueous layers were further washed with two more portions of benzene and then filtered directly onto a column of Bio-Rad AG 50X8 50–100 mesh resin (25 mL bed volume, H^+ form). The column was washed with water until neutral and then with 230 mL of 3 N HCl. Since NMR analysis of the residue from the acidic eluate indicated that some tosyl-containing compound was still present, the crude product was further chromatographed on AG 50X8 resin (200–400 mesh, 30 mL bed volume, 2 N HCl eluate), monitoring elution by ultraviolet absorption. Evaporation of the appropriate column fractions gave 97 mg (95%) of **11**·2HCl whose NMR spectra (^1H and ^{13}C), TLC (silica gel, phenol saturated with H_2O, Weber spray) behavior, and sulfate salt were identical with those of the reduction product, A, of 2,8-diaminopurine (**7**).

4-Carboxy-2-*p*-toluenesulfonyliminoimidazolidine (29). DL-Diaminopropionic acid monohydrochloride (**27**, 2.80 g, 20 mmol) was dissolved in 40 mL of 1.0 N NaOH and 180 mL of ethanol and then *S,S*-dimethyl *N*-toluenesulfonyliminodithiocarbonimidate[19] (**28**, 5.50 g, 20 mmol) was added. The solution was held at reflux for 18 h and filtered, and most of the ethanol was evaporated. The resulting neutral aqueous solution was made alkaline with $NaHCO_3$ solution, extracted with 2 × 30 mL of $CHCl_3$, and adjusted to pH 1.3 with 4 N HCl. An oil that separated during acidification was just redissolved by addition of methanol. The resulting solution was extracted with 3 × 20 mL of $CHCl_3$, and the combined $CHCl_3$ extracts were then evaporated to give 3.33 g (59%) of a solid residue: ^1H NMR (Me_2SO-d_6) δ 7.9–7.1 (m, 6 H), 4.3 (q, 1 H), 3.9–3.5 (m, 2 H), 2.4 (s, 3 H). Cooling of the aqueous phase from the above extraction gave an additional 771 mg (14%) of product, mp 205–206 °C from water.

Anal. Calcd for $C_{11}H_{13}N_3O_4S$: C, 46.6; H, 4.6; N, 14.8. Found: C, 46.6; H, 4.7; N, 14.8.

4-Methoxycarbonyl-2-*p*-toluenesulfonyliminoimidazolidine (30). 29 (500 mg, 1.77 mmol) and concentrated H_2SO_4 (1 drop) were refluxed for 19 h in a mixture of methanol (4 mL) and 1,2-dichloroethane (4 mL). The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$ and evaporated to give 530 mg (100%) of a solid that appeared pure by TLC (silica gel, 10% $CH_3OH/CHCl_3$). Recrystallization was effected by dissolving the solid in 10% $CH_3OH/CHCl_3$ and allowing the product to precipitate as a white powder: yield 368 mg (73%); mp 144–146 °C; ^1H NMR (Me_2SO-d_6) δ 7.9–7.1 (m, 6 H), 4.4 (q, 1 H), 3.9–3.5 (m) and 3.6 (s, 5 H), 2.5 (s, 3 H).

Anal. Calcd for $C_{12}H_{15}N_3O_4S$: C, 48.5; H, 5.1; N, 14.1. Found: C, 48.4; H, 5.1; N, 14.2.

4-Carbamoyl-2-*p*-toluenesulfonyliminoimidazolidine (31). 30 (1.0 g, 3.37 mmol) was added to a cold saturated solution of NH_3 in methanol. After reaching room temperature, the solution was stirred for 1 h and then evaporated to give 915 mg (97%) of a glassy solid: ^1H NMR (Me_2SO-d_6) δ 7.4 (m, 8 H, NH, ArH), 4.2 (t, 2 H, >CH), 3.5 (m, 2 H, $>CH_2$), 2.3 (s, 3 H, $ArCH_3$).

4-Cyano-2-*p*-toluenesulfonyliminoimidazolidine (32). 31 (1.79 g, 6.31 mmol) was dissolved in 9.5 mL of pyridine, *p*-toluenesulfonyl chloride was added, and the solution was heated at 50 °C for 23 h. The pyridine was evaporated, $CHCl_3$ was added and evaporated twice, and $CHCl_3$ and then water were added which gave rise to a white precipitate suspended in the $CHCl_3$ layer. This precipitate was collected and washed with cold $CHCl_3$ and water to give 1.19 g (71%) of **32**. An additional 119 mg (7%) was recovered from the $CHCl_3$ mother liquid after standing overnight, mp 210 °C from methanol.

Anal. Calcd for $C_{11}H_{12}N_4O_2S$: C, 49.79; H, 4.95; N, 21.12. Found: C, 49.97; H, 4.63; N, 21.08.

4-[(Methylmercapto-*N*-*p*-toluenesulfonylimino)methyl]aminomethyl-2-*p*-toluenesulfonyliminoimidazolidine (33). 32 (1.02 g, 3.85 mmol) and PtO_2 (400 mg) were suspended in glacial acetic acid (35 mL), and the mixture was hydrogenated on a Parr apparatus at 30 psi for 14 h. The catalyst was removed by filtration, and the filtrate was concentrated to a very small volume. Dilute HCl was added and evaporated twice, dilute HCl was again added, and the resulting cloudy solution was extracted three times with $CHCl_3$. The aqueous phase was evaporated to give 1.16 g (99%) of the amine as a solid: NMR (D_2O, external Me_4Si) δ 7.5 (q, 4 H, ArH), 4.6–3.2 (m, 5 H, >CH and $>CH_2$), 2.4 (s, 3 H, $ArCH_3$).

This solid and triethylamine (1.60 mL, 11.4 mmol) were dissolved in a solution of water (30 mL) and CH_3CN (30 mL). **20** (1.01 g, 3.81 mmol) was added, and the solution was stirred at room temperature for 7 h and then left overnight at 0 °C. The resulting white, powdery precipitate was washed with cold 50% CH_3CN–H_2O: yield 134 g (72%); pure by TLC (silica gel, 15% $CH_3OH/CHCl_3$); mp 183–185 °C from ethyl acetate.

Anal. Calcd for $C_{20}H_{25}N_5O_4S_3$: C, 48.5; H, 5.1; N, 14.1. Found: C, 48.3; H, 5.1; N, 14.2.

4-[(Amino-*N*-*p*-toluenesulfonylimino)methyl]aminomethyl-2-*p*-toluenesulfonyliminoimidazolidine (34). 33 (1.00 g, 2.02 mmol) was heated in liquid NH_3 at 40 °C in a sealed tube for 6 h. The residue, after evaporation of the NH_3, was chromatographed on 105 g of silica gel (7% $C_2H_5OH/CHCl_3$ eluate) to give 782 mg (83%) of pure **34**: mp 211–214 °C; ^1H NMR ($CDCl_3$) δ 7.7–6.5 (m, 13 H, NH, ArH), 4.1–3.0 (br m, 5 H, >CH and $>CH_2$), 2.4 (s, 6 H, $ArCH_3$).

Anal. Calcd for $C_{19}H_{24}N_6O_4S_2$: C, 49.1; H, 5.2; N, 18.1. Found: C, 48.8; H, 5.2; N, 17.7.

2-Imino-4-guanidinomethylimidazolidine (12). 34 (300 mg, 0.604 mmol) was treated as before with anhydrous HF. Ion exchange chromatography as before gave 140 mg (100%) of a glass whose ^1H and ^{13}C NMR spectra and TLC behavior were identical with those of the hydrochloride of compound B, obtained by hydrogenation. A crystalline sulfate salt was obtained, identical with the sulfate salt of compound B.

2,4-Diamino-5-[(methylmercapto-*N*-*p*-toluenesulfonylimino)methyl]aminopyrimidine (40a). 2,4,5-Triaminopyrimidine[20] (**39a**, 1.25 g, 10 mmol) was dissolved in a solution of water (15 mL) and CH_3CN (5 mL), triethylamine (2.8 mL, 20 mmol), and then, dropwise, a solution of **20** (2.64 g, 10 mmol) in CH_3CN (10 mL) were added. After stirring for 8 h at room temperature, the solvent was evaporated and the residue was washed with hot water and hot $CHCl_3$ to give 2.1 g (60%) of **40a** as a light brown powder: does not melt <300 °C; ^1H NMR (Me_2SO-d_6) δ 7.9–7.3 (m, 6 H, ArH, HetH, NH), 6.3 (br s, 4 H, NH), 2.4 (s, 3 H, $ArCH_3$), 2.3 (s, 3 H, SCH_3).

Anal. Calcd for $C_{13}H_{16}N_6O_2S_2$: C, 44.3; H, 4.6; N, 23.8. Found: C, 44.4; H, 4.6; N, 23.8.

2,4-Diamino-6-methyl-5-[(methylmercapto-*N*-*p*-toluenesulfonylimino)methyl]aminopyrimidine (40b). 20 (46.8 g, 0.178 mol) was dissolved in dry DMF (200 mL) and cooled in an ice bath. To this solution were then added dropwise triethylamine (24.8 mL, 0.178 mol) and a suspension of 0.18 mol of 6-methyl-2,4,5-triaminopyrimidine (**39b**)[21] in warm DMF (760 mL). The reaction mixture was warmed to room temperature and stirred for 3 days. The DMF was evaporated, and the residue was washed with water and then CH_2Cl_2 to give 62.8 g (96%) of **40b** as a pale brown powder: does not melt <300 °C; ^1H NMR (CF_3CO_2D) δ 7.5 (q, 4 H, ArH), 2.42 (m, 9 H, $ArCH_3$, SCH_3, $HetCH_3$).

Anal. Calcd for $C_{14}H_{18}N_6O_2S$: C, 45.9; H, 4.9; N, 22.9. Found: C, 46.2; H, 4.9; N, 22.7.

2-Amino-8-*p*-toluenesulfonylaminopurine (41a). To **40a** (8.26 g, 23.5 mmol) and triethylamine (4.90 mL, 35.3 mmol) dissolved in dry DMF (200 mL) was added dropwise a solution of $AgNO_3$ (4.00 g, 23.5 mmol) in DMF (15 mL). A yellow $AgSCH_3$ precipitate formed immediately, and stirring was continued at room temperature for 2 h and then at 75 °C for 5 h, after which time TLC (silica gel, 20% $C_2H_5OH/CHCl_3$) indicated the absence of starting material. The product appeared as a UV fluorescent spot at R_f 0.3. The mixture was filtered, the filtrate was evaporated, and the residue was dissolved in 10% NaOH. The $AgSCH_3$ precipitate was washed with 10% NaOH and the combined wash and residue solutions were carefully acidified to pH 2 with 4 N HCl, giving rise to **41a**: yield 6.0 g (84%); does not melt <300 °C; ^1H NMR (Me_2SO-d_6) δ 8.0–7.1 (m, 6 H, ArH, HetH, NH), 6.41 (br s, 2 H, NH), 2.3 (s, 3 H, $ArCH_3$).

2-Amino-6-methyl-8-*p*-toluenesulfonylaminopurine (41b). **40b** (46.0, 0.126 mol) and triethylamine (17.5 mL, 0.126 mol) in DMF (950 mL) were treated with $AgNO_3$ (21.4 g, 0.126 mol) in DMF (120 mL) as described above for 1 h at room temperature and 41 h at 75 °C. The isolation procedure followed that for **41a** above and gave 37.9 g

(95%) of **41b** as a white powder: ^{1}H NMR (Me_2SO-d_6) δ 7.5 (q, 4 H, ArH), 6.0 (br s, 2 H, NH), 2.3 (s, 6 H, $ArCH_3$, HetH); crystallized from DMF–95% ethanol, does not melt <300 °C.

Anal. Calcd for $C_{13}H_{14}N_6O_2S$: C, 49.0; H, 4.4; N, 26.4. Found: C, 48.9; H, 4.2; N, 26.0.

2,8-Diaminopurine Hydrochloride (7·HCl). 41a (3.04 g, 10 mmol) was treated with HF as before for 3 h. Ion exchange salt conversion on Bio-Rad AG-50 resin of the crude HF salt gave 1.9 g (100%) of 7·HCl as a yellowish powder: ^{1}H NMR (D_2O, external Me_4Si) δ 8.3 (s); crystallized from aqueous ethanol, does not melt <360 °C.

Anal. Calcd for $C_5H_7N_6Cl$: C, 32.2; H, 3.8; N, 45.0. Found: C, 32.5; H, 3.8; N, 44.8.

2,8-Diamino-6-methylpurine Hydrochloride (37·HCl). 41b (15.0 g, 47.2 mmol) was treated with HF as before for 3 h. Ion exchange on Bio-Rad AG-50 resin gave 9.5 g (100%) of 37·HCl: ^{1}H NMR (D_2O, external Me_4Si) δ 2.65 (s); crystallized from 95% ethanol–ether, does not melt <300 °C.

Anal. Calcd for $C_6H_9N_6Cl$: C, 35.9; H, 4.5; N, 41.9. Found (hygroscopic): C, 35.6; H, 5.0; N, 41.5.

Registry No.—7 HCl, 62743-10-6; **8**, 60914-37-6; **11** 2HCl, 62743-11-7; **11** sulfate, 62743-13-9; **11** dipicrate, 62743-14-0; **12** 2HCl, 62743-15-1; **12** sulfate, 62743-17-3; **16**, 62743-18-4; **17**, 24571-53-7; **18**, 62778-08-9; **20**, 2973-83-3; **21**, 62743-19-5; **22**, 62743-20-8; **23**, 62743-21-9; **24**, 62743-22-0; **25**, 62743-23-1; **27** HCl, 54897-59-5; **28**, 2651-15-2; **29**, 62743-24-2; **30**, 62743-25-3; **31**, 62743-26-4; **32**, 62743-27-5; **32** 4-aminomethyl derivative, 62743-28-6; **33**, 62743-29-7; **34**, 62743-30-0; **37**, 60914-60-5; **37** HCl, 33704-87-9; **39a**, 3546-50-7; **39b**, 60914-71-8; **40a**, 62743-31-1; **40b**, 62743-32-2; **41a**, 62743-33-3; **41b**, 62778-09-0; A′ 2HCl epimer 1, 62743-34-4; A′ 2HCl epimer 2, 62743-35-5; A′ sulfate epimer 1, 62743-37-7; A′ sulfate epimer 2, 62743-39-9; B′ 2HCl epimer 1, 62743-40-2; B′ 2HCl epimer 2, 62743-41-3.

References and Notes

(1) E. J. Schantz, J. M. Lynch, G. Vayvaada, K. Matsumoto, and H. Rapoport, *Biochemistry*, **5**, 1191 (1966).
(2) Y. Shimizu, M. Alam, Y. Oshima, and W. E. Fallon, *Biochem. Biophys. Res. Commun.*, **66**, 731 (1975); L. J. Buckley, M. Ikawa, and J. J. Sasner, Jr., *J. Agric. Food Chem.*, **24**, 107 (1976).
(3) E. J. Schantz, V. E. Ghazarossian, H. K. Schnoes, F. M. Strong, J. P. Springer, J. O. Pezzanite, and J. Clardy, *J. Am. Chem. Soc.*, **97**, 1238 (1975).
(4) J. Bordner, W. E. Thiessen, H. A. Bates, and H. Rapoport, *J. Am. Chem. Soc.*, **97**, 6008 (1975).
(5) Y. Shimizu, L. J. Buckley, M. Alam, Y. Oshima, W. E. Fallon, H. Kasai, I. Muira, V. P. Gullo, and K. Nakanishi, *J. Am. Chem. Soc.*, **98**, 5414 (1976).
(6) A. Bendich, P. J. Russell, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954); A. Bendich, *CIBA Found. Symp. Chem. Biol. Purines*, 308–311 (1957).
(7) I. Butula, *Justus Liebigs Ann. Chem.*, **729**, 73 (1969).
(8) S. R. Breshears, S. S. Wang, S. G. Brechtalt, and B. E. Christiansen, *J. Am. Chem. Soc.*, **81**, 3789 (1959).
(9) W. L. F. Armarego and P. A. Reece, *J. Chem. Soc., Perkin Trans. 1*, 1414 (1976).
(10) H. King, *J. Chem. Soc.*, 2374 (1930).
(11) S. Moore, R. P. Patel, E. Atherton, M. Kondo, J. Meienhofer, L. Blau, R. Bittman, and R. K. Johnson, *J. Med. Chem.*, **19**, 766 (1976).
(12) W. Broadbent, J. S. Moreley, and B. E. Stone, *J. Chem. Soc. C*, 2632 (1967).
(13) (a) R. Neidlein and W. Haussmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 521 (1965); (b) T. R. Bosin, R. N. Hanson, J. V. Rodricks, R. A. Simpson, and H. Rapoport, *J. Org. Chem.*, **38**, 1591 (1973).
(14) J. V. Rodricks and H. Rapoport, *J. Org. Chem.*, **36**, 46 (1971).
(15) A. F. Ferris and B. A. Schultz, *J. Org. Chem.*, **28**, 71 (1963).
(16) C. J. Weber, *J. Biol. Chem.*, **78**, 465 (1948).
(17) M. Zaoral and J. Rudinger, *Collect. Czech. Chem. Commun.*, **24**, 1993 (1959).
(18) J. Rudinger, K. Poduska, and M. Zaoral, *Collect. Czech. Chem. Commun.*, **25**, 2022 (1960).
(19) R. Gompper and W. Hagele, *Chem. Ber.*, **99**, 2885 (1966).
(20) D. Brown, *J. Appl. Chem.*, **7**, 109 (1957).
(21) P. D. Landor and H. N. Rydon, *J. Chem. Soc.*, 1113 (1955).

Photochemistry of Phospholenes. 6. Photochemical Polar Addition of Alcohols Involving Participation by Trivalent Phosphorus[1]

Hideo Tomioka, Kazuo Sugiura, Shyoji Takata, Yoshimasa Hirano, and Yasuji Izawa*

Department of Industrial Chemistry, Faculty of Engineering, Mie University, Tsu, Mie, Japan

Received January 31, 1977

Irradiation of 1-phenyl-3-methyl-2-phospholene (**1**) in methanol–xylene solution afforded a mixture of the photoethers **2** and **3** (20%) and the exocyclic isomer **4** (50%). The addition was found to proceed completely regiospecifically. Thus, phenylphospholene **12** afforded 3-methoxyphospholane as a mixture of geometrical isomers upon similar irradiation. However, 2-methyl derivatives **19** were almost completely inert to photoaddition under similar conditions. Labeling studies with methanol-*O*-*d* showed that each of the products was formed in an ionic process involving photoprotonation at C-2. Deuterium was also found to be incorporated at the exo position of **4**, probably via a photochemical 1,3-phosphoryl shift. Investigation of the photoreactions of other phospholenes in alcohol revealed that the presence of trivalent phosphorus adjacent to the double bond is a necessity for the photoprotonation. The photoprotonation of **1** and **12** is therefore interpreted in terms of a reactive excited state displaying charge-transfer character resulting from the interaction of the double bond with the lone pair of electrons.

Simple cyclic isolated olefins, which have difficulty adopting a twisted configuration, undergo a variety of reactions from their excited state, including dimerization and various addition reactions. An example of the latter which has recently received considerable attention is the photosensitized polar addition of alcohols to six- and seven-membered olefins.[2,3] These reactions are believed to proceed through initial protonation of highly strained trans cycloalkenes or orthogonal triplet. In striking contrast, cyclopentene and other highly constrained cyclic olefins exhibit radical behavior on irradiation under similar conditions,[2,4] apparently due to the inability of these olefins to undergo cis → trans isomerization; the radical-type behavior exhibited in those cases probably originates from intermolecular reaction by the 3 (π, π^*) excited state itself. More recently, it has been shown[5] that the direct irradiation of the tri- and, particularly, tetrasubstituted cyclopentenes in hydroxylic media yielded unsaturated as well as saturated ethers. This photochemical behavior appears to involve the nucleophilic trapping of the π, R (3s) Rydberg excited state.

In the course of our studies[1,6] on the photochemistry of phospholenes, we have found[1b] that even five-membered cyclic olefins, in which double bonds are conjugated with trivalent phosphorus, gave the ethers and exocyclic isomer upon direct and/or sensitized irradiation in alcohols. While a large number of simple cyclic olefin systems have been examined as mentioned above, there is little known[7] concerning the role that α-heteroatoms may have on the photochemical polar