(+)-Occidol (22). A solution of 0.452 g (2.26 mmol) of **21** in 3 mL of THF was added to a solution of 0.715 g (2.25 mmol) of mercuric acetate in 2.5 mL of H_2O and 2.5 mL of THF. After the mixture was stirred for 1.5 h, 2.5 mL of 3 N NaOH followed by 2.5 mL of 0.5 N $NaBH_4$ in 3 N NaOH was added. The mixture was extracted twice with 10 mL of ether, and the combined ether extracts were washed with 3 N NaOH, 5% HCl, and H_2O. After the extracts were dried ($MgSO_4$) and evaporated, the product was adsorbed onto a short silica gel column and eluted with pentane (300 mL) followed by acetone (200 mL). On evaporation the acetone fraction yielded 0.327 g (66% yield) of occidol (**22**)[19] as a semicrystalline mass. A portion of the product was purified by preparative TLC (silica gel, 40% ether/pentane) and showed $[\alpha]_D^{25}$ +34° (*c* 1.46, $CHCl_3$) (lit.[19a] $[\alpha]_D$ +164°). Recrystallization of the remainder from hexane afforded occidol displaying mp 99–100 °C, indicating the racemate had selectively crystallized (lit.[19b] mp 101–102 °C); IR (CCl_4) 2.76, 3.39, 6.78, 6.85, 6.94, 6.99, 7.25, 7.33, 8.66, 8.94, 9.71, 10.5, 10.9, 11.1 μ; NMR ($CDCl_3$) 1.28 (s, 6, CH_3) 2.21 (s, 6, $ArCH_3$), 6.90 ppm (s, 2, ArH).

Registry No. 1 isomer 1, 71616-11-0; 1 isomer 2, 71616-12-1; **3**, 1470-91-3; **4**, 71616-13-2; *cis*-**5**, 71616-14-3; *trans*-**5**, 71616-15-4; **6**, 71616-16-5; **7**, 31188-03-1; **8**, 22070-24-2; **9**, 71616-17-6; **10**, 526-85-2; **15**, 71616-18-7; *cis*-**16**, 71616-19-8; *trans*-**16**, 5003-59-8; **17**, 17066-67-0; **18**, 5945-72-2; **19**, 71616-20-1; **20**, 71616-21-2; **21**, 71616-22-3; **22**, 5986-36-7; 2,3-dimethyl-2-butene, 563-79-1; 2-methyl-2-butene, 513-35-9; 1-methylcyclohexene, 591-49-1; 1-*p*-menthen-9-ol, isomer 1, 13835-30-8; 1-*p*-menthen-9-ol, isomer 2, 13835-75-1.

Synthesis of the Sulfonyl Analogue of Hypoxanthine, Imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide[1]

Bao-Shan Huang and James C. Parham*

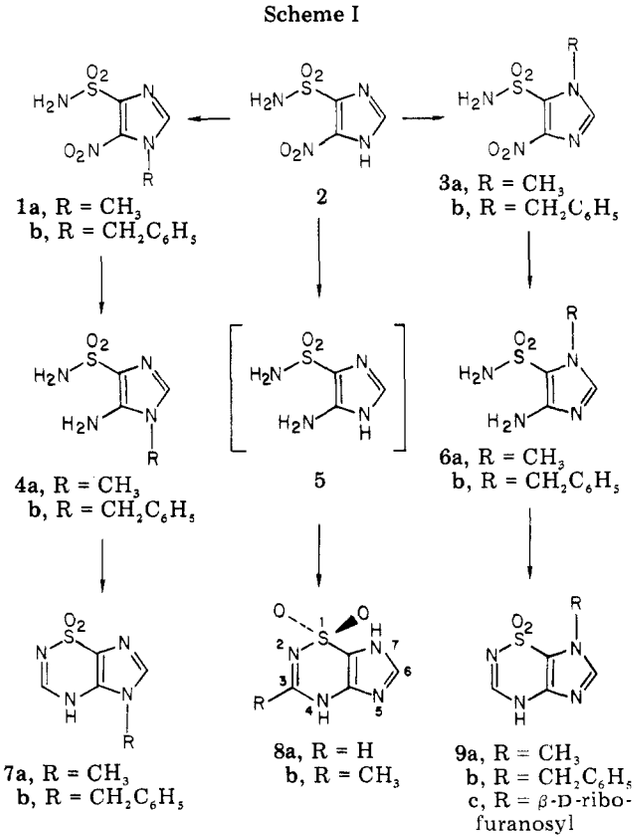
Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received April 12, 1979

The unsubstituted imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide was prepared in good yield by reduction of 4(5)-nitroimidazole-5(4)-sulfonamide and immediate ring closure of the unstable aminoimidazole intermediate. Ribosylation of the product by the modified Hilbert–Johnson method afforded a single nucleoside analogue, which is shown to be the 7-(β-D-ribofuranosyl) derivative by comparison of its properties to those of the 5- and 7-methyl derivatives.

A number of compounds that closely resemble the presumed transition state for certain reactions have proved to be potent, specific inhibitors of enzymes that effect those reactions.[2-5] Several examples of such "transition state analogue" inhibitors have been reported for enzymes that catalyze aminations or deaminations. The sulfone and sulfoximine derivatives of L-methionine inhibit glutamine synthetase,[6] while several alcohol derivatives, including 1,6-dihydro-6-(hydroxymethyl)nebularine,[3,7] coformycin,[8] and tetrahydrouridine,[9] are excellent inhibitors of adenosine or cytidine deaminases. The transition state analogues for these reactions all have an overall geometry close to that of the natural substrate but contain a tetrahedrally substituted atom at the position associated with reaction in the normal substrate. The imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide system, **8a** (Scheme I), is an isosteric analogue of hypoxanthine in which the 6-carbonyl has been replaced by a sulfonyl moiety. The tetrahedral arrangement of atoms in the sulfonamide of **8a** suggested that appropriate nucleoside derivatives of it might prove to be stable transition-state analogues for enzymatic transformations at the 6-position of purines.[10] For example, the 5-ribosyl derivative, **7** (R = β-D-ribofuranosyl), might be a transition-state analogue inhibitor for adenosine deaminase while the 5-(5′-phosphoribosyl) derivative might act as such an inhibitor of adenylosuccinate synthetase. Despite the obvious structural similarity of the imidazo-[4,5-*e*]thiadiazine ring system to the purine system and the

Scheme I



(1) This investigation was supported in part by Grant No. CA 08748 and CA 18965 awarded by the National Cancer Institute, DHEW.
(2) R. Wolfenden, *Annu. Rev. Biophys. Bioeng.*, **5**, 271 (1976).
(3) R. Wolfenden, *Acc. Chem. Res.*, **5**, 10 (1972).
(4) G. E. Lienhard, *Annu. Rep. Med. Chem.*, **7**, 249 (1972).
(5) R. N. Linquist in "Drug Design", Vol. 5, E. J. Ariens, Ed., Academic Press, New York, 1975, pp 24–80.
(6) W. B. Rowe and A. Meister, *Biochemistry*, **12**, 1578 (1973), and references therein.
(7) B. Evans and R. Wolfenden, *J. Am. Chem. Soc.*, **92**, 4752 (1970).
(8) P. W. K. Woo, H. W. Dion, S. M. Lange, L. W. Dahl, and L. J. Durham, *J. Heterocycl. Chem.*, **11**, 641 (1974).
(9) R. M. Cohen and R. Wolfenden, *J. Biol. Chem.*, **246**, 7561 (1971).
(10) An approach to the synthesis of a related transition state analogue possessing a tetrahedrally substituted phosphorus atom at the same position was recently reported (P. A. Bartlett, J. T. Hunt, J. L. Adams, and J. C. E. Gehret, *Bioorg. Chem.*, **7**, 421 (1978)).

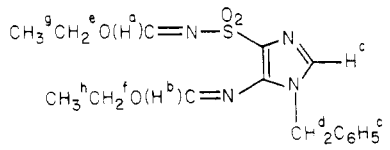
0022-3263/79/1944-4046$01.00/0

wide variety of benzo-1,2,4-thiadiazine 1,1-dioxides that have been prepared as antihypertensive,[11] diuretic,[12] and hyperglycemic agents,[13] few examples of imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxides have been prepared.[14,15] All but one[15] of those contained a methyl substituent at N(7), as in **9a**, which would prevent the introduction of the ribosyl moiety at N(5) that is important for the binding of substrates to adenosine deaminase[16] and essential for binding to adenylosuccinate synthetase.[17] That the unsubstituted ring system, **8a**, was not prepared previously can be attributed to the high instability of the requisite precursor, 4(5)-aminoimidazole-5(4)-sulfonamide (**5**), reported by several groups.[15,18-21] We now report the synthesis and properties of the unsubstituted imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide **8a** and the structure of the nucleoside obtained by ribosylation of the trimethylsilyl derivative of it.

Results and Discussion

4(5)-Aminoimidazole-5(4)-sulfonamide (**5**) was reported to be too unstable to be isolated following catalytic reduction of the nitroimidazole **2**, and our initial effects to isolate **5** as the hydrochloride salt, following earlier procedures,[18,21] confirmed those studies. Since both *N*-methyl derivatives of **5**, **4a**, and **6a** are stable,[14,18] an obvious route to **8a** would be via derivatives of **5** containing an *N*-alkyl substituent that could be removed after cyclization. Both *N*-benzyl derivatives, **1b** and **3b**, were obtained by alkylation of the anion of **2** with benzyl bromide.[22] Catalytic reduction of those afforded the amines **4b** and **6b**, which were stable and could be cyclized with $CH(OEt)_3$ to the 5- and 7-benzyl derivatives, **7b** and **9b**, of **8a**. The structures of the 1-benzyl-4(and 5)-nitroimidazole-5(and 4)-sulfonamides **1b** and **3b** and the amines **4b** and **6b** were confirmed by synthesis of and comparison in properties to the known methylnitroimidazolesulfonamides **1a** and **3a**[18,21,23-25] and the amines **4a**[18] and **6a**.[14,18] Cyclization of the amines **4** and **6** afforded the known 7-methyl derivative **9a**,[14] the previously unreported 5-methyl derivative **7a**, and the 5- and 7-benzyl derivatives **7b** and **9b** of **8a**.

Studies on the conditions for ring closure of the alkylated aminoimidazoles **4** and **6** indicated that the presence of an alkyl group adjacent to the amine, as in **4**, impaired cyclization. While **6** could be cyclized readily to **9** at 80–100 °C in 30–60 min, **4** could be recovered unchanged under those conditions and required a higher temperature (135–155 °C) and longer reaction time to induce cyclization to **7**. In the case of the hindered benzylamine **4b**, a bis(ethoxymethylene) intermediate, **10**, was isolated. Selective hydrolysis of the ethoxymethylene group from the sulfonamide function of **10** in the presence of water afforded an intermediate that did cyclize readily with base to **7b**.



10

^1H NMR (ppm): a, 8.46 (s, 1 H); b, 8.22 (s, 1 H); c, 7.50-7.14 (m, 6 H); d, 5.02 (s, 2 H); e, 4.36 (q, 2 H); f, 4.30 (q, 2 H); g, 1.36 (t, 3 H); h, 1.30 (t, 3 H)

Those studies also showed that isolation of the amine was not essential prior to cyclization and suggested that even though the aminoimidazole **5** might be too unstable to be isolated, under appropriately mild conditions it might be possible to cyclize at least some of **5** to **8a** before it decomposed. This indeed proved to be possible. *Rapid* catalytic reduction of 4(5)-nitroimidazole-5(4)-sulfonamide (**2**) with 10% Pd/C and removal of the solvent under reduced pressure while maintaining the solution at *room temperature of slightly below* afforded crude **5** with only minimal decomposition. This was immediately cyclized with $HC(OEt)_3$ in ethanol to afford **8a** in good yield (77%). The structure of **8a** was confirmed by elemental, mass spectral, and NMR analyses and by the similarities of UV spectra and pK_a values of **8a** to those of **7a** and **9a** (Table I). The 3-methyl derivative, **8b**, was obtained similarly by ring closure of **5** with $CH_3C(OEt)_3$. Catalytic reduction of **7b** with Pd/C also afforded some **8a**, but the conversion was not complete even after several days of reaction.

The first pK_a of **8a** (5.59, Table I) is considerably lower than that of most purines[26] and lies between the pK_a's of the two methyl derivatives, **7a** (4.45) and **9a** (6.57), in which only the thiadiazine ring may ionize. This indicates that ionization of **8a** occurs first from N(2, 4) in the thiadiazine ring and then from N(5, 7) in the imidazole ring. The spectral and pK_a data suggest that the neutral species of these compounds exist as an equilibrium of the N(2)H *o*-quinoid and N4)H *p*-quinoid tautomers, rather than in the *o*-quinoid, N(2)H form comparable to the lactam form of hypoxanthine.[27,28] Several studies[29-32] have noted that the pK_a of protons at N(3) or N(9) of purines dissociate at markedly lower pK_a's (ΔpK_a = 1.9–3.4) if a methyl group is present at the adjacent N(9) or N(3) position. For example, the pK_a of the N(3)H of 9-methylxanthine is 2.5 units below that of the corresponding proton in 7-methylxanthine.[29] In contrast, alkyl groups at N(7) or at N(9) of hypoxanthine, which lacks a hydrogen at N(3), cause a slight increase of similar magnitude in the pK_a of the proton at N(1).[33] Thus, an alkyl group at N(5) of **8a** would

(11) W. T. Comer and A. W. Gomoll in "Medicinal Chemistry", A. Burger, Ed., 3rd ed., Wiley-Interscience, New York, 1970, Part II, pp 1056–7.
(12) J. G. Topliss in "Medicinal Chemistry", A. Burger, Ed., 3rd ed., Wiley-Interscience, New York, 1970, pp 992–9.
(13) J. K. Wales, S. V. Krees, A. M. Grant, J. K. Viktora, and F. W. Wolff, *J. Pharmacol, Exp. Ther.*, **164**, 421 (1968).
(14) F. F. Blicke and C. M. Lee, *J. Org. Chem.*, **26**, 1861 (1961).
(15) V. I. Ofitserov, V. S. Mokrushin, Z. V. Pushkareva, and N. V. Nikiforova, *Khim. Geterotsikl. Soedin.*, **8**, 1119 (1976); *Chem. Abstr.*, **86**, 5373 (1977).
(16) R. Wolfenden, D. F. Wentworth, and G. N. Mitchell, *Biochemistry*, **16**, 5071 (1977), and references therein.
(17) M. B. Van Der Weyden and W. N. Kelly, *J. Biol. Chem.*, **249**, 7282 (1974).
(18) M. H. Fisher, W. H. Nickolson, and S. R. Stuart, *Can. J. Chem.*, **39**, 501 (1961).
(19) B. Robinson and M. U. Zubair, *Bull. Chem. Soc. Jpn.*, **50**, 561 (1977).
(20) G. R. Barnes and F. L. Pyman, *J. Chem. Soc.*, 2711 (1927).
(21) L. L. Bennett and H. T. Baker, *J. Am. Chem. Soc.*, **79**, 2188 (1957).
(22) B. S. Huang, M. J. Lauzon, and J. C. Parham, *J. Heterocycl. Chem.*, **16**, 811 (1979).
(23) I. E. Balaban and F. L. Pyman, *J. Chem. Soc.*, **121**, 947 (1922).
(24) K. E. Stensio, K. Wahlberg, and R. Wahren, *Acta Chem. Scand.*, **27**, 2179 (1973).
(25) I. E. Balaban and F. L. Pyman, *J. Chem. Soc.*, **125**, 1564 (1924).
(26) J. H. Lister in "Fused Pyrimidines, Part II, Purines", D. J. Brown, Ed., Wiley-Interscience, New York, 1971, pp 478–96.
(27) A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.*, **2**, 56 (1963).
(28) B. Pullman and A. Pullman, *Adv. Heterocycl. Chem.*, **13**, 130 (1971).
(29) D. Lichtenberg, F. Bergmann, and Z. Neiman, *J. Chem. Soc. C*, 1676 (1971).
(30) D. Lichtenberg, F. Bergmann, and Z. Neiman, *J. Chem. Soc., Perkin Trans. 1*, 1676 (1972).
(31) M. Rahat, R. Bergmann, and I. Tamir, *J. Chem. Soc., Perkin Trans. 1*, 2229 (1974).
(32) M. Rahat, F. Bergmann, and I. Tamir, *Isr. J. Chem.*, **12**, 945 (1974).

not be expected to depress the pK_a of the proton at N(2) if **8a** existed solely in the N(2)H tautomeric form. By analogy to the studies in the xanthine series, the ΔpK_a of 2.12 between **7a** and **9a** is suggestive evidence for the presence of some steric interaction between the N(4)H and N(5)CH_3 in **7a** and, by extension, the presence of some N(4)H tautomer in the neutral species.[34,35] The presence of UV absorption bands in the region of 260–275 nm (Table I), close to the position of but about half the intensity of similar bands observed for purines,[26] would be consistent with the presence of some of the N(2)H tautomer as well.

Reaction of the trimethylsilyl derivative of **8a** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of $SnCl_4$[36,37] gave one major tribenzoylribosyl derivative of **8a**. Removal of the benzoyl groups provided the free nucleoside. This product can be assigned the 7-(β-D-ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide structure **9c** by several criteria. NOE[38] experiments with **9a**, **9b**, and **9c**, irradiating the CH_3, CH_2, and the C(1)'H resonances, respectively, consistently enhanced the downfield ring methine signal. This not only identified that signal as the C(6) hydrogen in the imidazole ring but also demonstrated that the ribosyl substituent of **9c** was present on the same ring as that of the substituent of the imidazole-substituted derivatives **9a** and **9b**. In confirmation of this assignment, deuterium exchange of the NH of **9c** collapsed the upfield methine signal (thiadiazine ring) to a sharp singlet. This relative order of NMR absorbances, i.e., imidazole hydrogen further downfield than the hydrogen on the 6-membered ring, is comparable to that observed in hypoxanthine[39] and in inosine.[40] The pK_a of **9c** (6.36) is much lower than would be expected for ionization of an imidazole proton in a 2- or 4-substituted derivative of **8a** but is comparable to that for ionization of the thiadiazine proton in **7a** and **9a**. The close correspondence of the UV spectral values and the pK_a value of **9c** to those of the 7-methyl derivative, **9a**, and the distinct difference from those properties of the isomeric 5-methyl derivative, **7a** (Table I), provided clear evidence that the nucleoside **9c** is the 7-ribosyl derivative. The structures of the two methyl derivatives, **7a** and **9a**, are unequivocally established by the choice of the known methylnitroimidazolesulfonamide starting materials, **1a** and **3a**, respectively. An indication that the sugar was present in the β configuration was provided by the large $\Delta\delta$ (22 ppm) between the chemical shifts of the two methyl groups in the NMR spectrum of the isopropylidene derivative of **9c**. A difference ≥0.18 ppm has been reported as being indicative of the β configuration in ribofuranosyl nucleosides.[41] Thus the nucleoside formed by direct introduction of the sugar onto the preformed heterocycle **8a** is not the requisite 5-ribosyl derivative corresponding in structure to inosine.

In summary, the unsubstituted imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide ring system (**8a**) can be prepared in good yield from the unstable 4(5)-aminoimidazole-5(4)-sulfonamide (**5**). Unlike the structurally analogous

Table I. Spectral Data and pK_a's

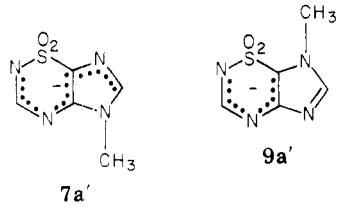
pH	charge	λ_{max},[a] nm ($10^{-3}\epsilon$)	apparent pK_a[b-f]
		Imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (**8a**)	
1	0	225 (3.0), 262 (2.7)	5.59 (0.03)[b]
8	−1	228 (2.7), 271 (4.5)	11.0[c]
13	−2	[230] (2.8), 272 (3.8)	
		5-Methylimidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (**7a**)	
1	0	[218] (2.5), 266 (3.4)	4.45 (0.04)[d]
8	−1	[225] (2.9), 273 (4.6)	
		7-Methylimidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (**9a**)	
1	0	232 (3.6), 263 (2.5)	6.57 (0.03)[d]
8	−1	244 (3.6), 265 (3.1)	
		7(β-D-Ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (**9c**)	
3		232 (3.8), 259 (2.6)	6.36 (0.04)[b]
9		245 (3.9), 267 (3.7)	
		3-Methylimidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (**8b**)	
1		225 (3.5), 257 (3.1)	
8		225 (3.3), 267 (5.2)	
13		[230] (3.2), 269 (4.6)	
		5-Benzylimidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (**7b**)	
f		271 (5.3)	
13		273 (6.7)	
		7-Benzylimidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (**9b**)	
1		232 (3.6), 260 (2.7)	
13		250 (4.3), 267 (4.0)	

[a] Brackets indicate a shoulder. [b] Determined potentiometrically at 21 °C in 0.001 M solutions by procedures described.[43] [c] Estimated from isobestic spectra. [d] Determined spectrophotometrically[43] in 0.01 M buffers[44] at 21 °C. [e] Values in parentheses are deviations (±). [f] Determined in CH_3OH.

(33) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).

(34) The *p*-quinoid 4-H tautomer was also reported to be the predominant contributor in benzo[*e*]-1,2,4-thiadiazine 1,1-dioxide (F. C. Novello, S. C. Bell, E. L. A Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960)).

(35) A referee has suggested that the difference in pK_a's between **7a** and **9a** (and presumably between 7- and 9-methylxanthine) could instead be due to a greater stabilization of the anion of **7a** because of the extension of conjugation of the negative charge into the imidazole ring, as in



7a' **9a'**

7a'. A comparable C(6) carbanionic resonance contributor in **9a** is precluded by the N(7) methyl group. The fact that there is little difference between the pK_a's of 7- and 9-methylhypoxanthine,[33] for which a similar argument might also be advanced, argues against this interpretation. Furthermore, if this interpretation were correct, then the presence of significant negative charge density at C(8) of the monoanion of 9-methylxanthine, relative to that at C(8) of the monoanion of 7-methylxanthine, should be reflected in the $\Delta\delta$ of the C(8) proton between the neutral and monoanionic forms of those compounds. However, the $\Delta\delta$ for the C(8) hydrogens of 7- and 9-methylxanthine upon ionization is very close (+0.14 ppm vs. +0.17 ppm; 9:1 $(CD_3)_2SO$–D_2O, 70 °C)[29] and is of comparable magnitude to those for the C(8) hydrogens of 7- and 9-methylhypoxanthine (+0.17 and +0.19 ppm, respectively; D_2O, 70 °C) (F. Bergmann, D. Lichtenberg, and Z. Neiman, *Jerusalum Symp. Quantum Chem. Biochem.*, **2**, 320 (1970). Values reported there in cps have been converted to ppm.)

(36) T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull.*, **12**, 1471 (1964).

(37) U. Niedballa and H. Vorbrüggan, *J. Org. Chem.*, **39**, 3654 (1974), et seq.

(38) A. L. Thakkar, L. G. Tensmeyer, R. B. Hermann, and W. L. Wilham, *Chem. Commun.*, 524 (1970).

(39) D. Lichtenberg, F. Bergmann, and I. Rengel, *J. Magn. Reson.*, **6**, 600 (1972).

(40) A. D. Broom and G. H. Milne, *J. Heterocycl. Chem.*, **12**, 171 (1975).

(41) (a) J. L. Imbach, J. L. Barascut, B. L. Kam, and C. Tapiero, *Tetrahedron Lett.*, 129 (1974); (b) C. Tapiero and J. L. Imbach in "Nucleic Acid Chemistry", L. B. Townsend and R. S. Tipson, Eds., Wiley-Interscience, New York, 1978, Part II, pp 1055–9, and references therein.

purine, hypoxanthine, **8a** appears to have a significant contribution of the *p*-quinoid 4*H* tautomer in the neutral species. Perhaps because of the presence of that tautomer, ribosylation of **8a** occurs almost exclusively at the 7-position to afford the β-anomer of the nucleoside **9c**.

Experimental Section

^1H NMR spectra were determined in Me_2SO-d_6 by using Me_4Si as an internal standard with a JEOL PFT-100 NMR spectrometer; UV spectra were determined with a Cary 15 recording spectrophotometer or a Varian SuperScan 3 ultraviolet–visible spectrophotometer. Optical rotations were measured with a P&I Model A photoelectric polarimeter using a 1-mL microcell. Infrared spectra were determined in KBr pellets with a Perkin-Elmer Infracord spectrophotometer. Melting points were determined with a Mel-Temp apparatus and were uncorrected. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Catalytic reductions were performed at 1 atm.

5-Methylimidazo[4,5-e]-1,2,4-thiadiazine 1,1-Dioxide (7a). 1-Methyl-5-nitroimidazole-4-sulfonamide (**1a**; 0.50 g, 2.4 mmol) in 120 mL of EtOH was reduced with H_2 and 5% Pd/C (1.0 g; 30 min). The mixture was filtered, and the filtrate was evaporated to dryness under vacuum to give 0.415 g (97%) of 1-methyl-5-aminoimidazole-4-sulfonamide (**4a**): NMR δ 7.19 (s, 1 C(2)H), 6.84 (br s, 2, exch SO_2NH_2), 5.35 (br s, 2, exch NH_2), 3.39 (s, 3, CH_3).

A solution of 0.14 g (0.80 mmol) of **4a** in 0.4 mL of $HC(OEt)_3$ and 8 mL of DMAC was heated at 150–155 °C for 3 h; the cooled solution was treated with Norite (ca. 50 mg) and filtered. The filtrate was added dropwise with stirring into 200 mL of Et_2O to precipitate the product, **7a**, which was collected and washed with Et_2O; yield 0.12 g (81%). This was recrystallized from water to afford colorless platelets: mp >320 °C; mass spectrum, *m/e* (rel intensity) 186 (2, M^+), 161 (2), 81 (2), 69 (3); NMR δ 13.03 (s, 1, exch NH), 7.90 (s, 1, CH), 7.80 (s, 1, CH), 3.68 (s, 3, CH_3); IR 1170, 1370 cm^{-1} (SO_2NH).[42] The analytical sample was dried under vacuum (P_2O_5) at 20 °C for 2 days.

Anal. Calcd for $C_5H_6N_4O_2S$: C, 32.25; H, 3.25; N, 30.09; S, 17.22. Found: C, 32.18; H, 3.22; N, 30.11; S, 17.28.

7-Methylimidazo[4,5-e]-1,2,4-thiadiazine 1,1-Dioxide (9a). 1-Methyl-4-nitroimidazole-5-sulfonamide (**3a**; 1.01 g, 4.9 mmol) in 240 mL of EtOH was reduced with 5% Pd/C (1.0 g). The solution was filtered, and then the solvent was removed under vacuum from the filtrate to give 0.81 g (94%) of 1-methyl-4-aminoimidazole-5-sulfonamide (**6a**): NMR δ 7.39 (s, 1, CH), 7.25 (s, 2, exch SO_2NH_2), 5.05 (s, 2, exch NH_2), 3.62 (s, 3, CH_3).

A solution of **6a** (0.54 g, 3.1 mmol) in 15 mL of EtOH and 0.7 g of $HC(OEt)_3$ was refluxed for 1 h. To the cool solution was added CH_2Cl_2 (~150 mL) to precipitate **9a**, 0.48 g (84%), which was recrystallized from H_2O (C) to afford 0.25 g of colorless platelets: mp >330 °C (lit.[14] mp >340 °C); mass spectrum, *m/e* (rel intensity) 186 (30, M^+), 95 (8); NMR δ 11.32 (s, 1, exch NH), 7.98 (s, 1, CH), 7.90 (s, 1, CH), 3.78 (s, 3, CH_3); irradiation of the methyl protons at δ 3.78 produced a 9% increase in the integration of the signal at δ 7.98, as expected for NOE enhancement;[38,39] IR 1160, 1370 cm^{-1}.

5-Benzylimidazo[4,5-e]-1,2,4-thiadiazine 1,1-Dioxide (7b). 1-Benzyl-5-nitroimidazole-4-sulfonamide[22] (**1b**; 0.66 g, 2.3 mmol) in 200 mL of EtOH was reduced with H_2 and 5% Pt/C (0.50 g) and then filtered. The filtrate was evaporated to dryness under vacuum to afford 1-benzyl-5-aminoimidazole-4-sulfonamide (**4b**): 0.53 g (90%); NMR δ 7.38–7.28 (m, 6, C_6H_5 and C(2)H), 6.88 (s, 2, exch SO_2NH_2), 5.43 (s, 2, exch NH_2), 5.08 (s, 2, CH_2).

The crude amine, **4b**, was dissolved in 30 mL of $HC(OEt)_3$, and the solution was heated at 110–140 °C for 90 min. The solvent was removed under vacuum. An NMR spectrum of the solid residue indicated the presence of a bis(ethoxymethylene) intermediate, **10**, rather than **7b**. The intermediate was induced to cyclize by dissolving the product in CH_3OH and adjusting the apparent pH of this solution to ca. 8 by the addition of 1 N NaOH. Reaction progress of **10** to **7b** was monitored by TLC (silica gel, CH_3OH/EtOAC, 1/9); the R_f values were as follows: 0.04, **7b**; 0.55, **4b**; 0.80, **10**. The product was isolated by acidifying the solution with HOAc, reducing the volume to ca. 5 mL, and adding that dropwise to CH_2Cl_2 to precipitate **7b**, yield 0.44 g (71% from **1b**). This was recrystallized from CH_3OH/H_2O (C) to give 0.18 g of **7b** as tan needles: mp 227–278 °C dec; mass spectrum, *m/e* (rel intensity) 262 (15, M^+), 106 (19); NMR δ 12.91 (s, 1, NH), 7.99 (s, 1, C(6)H), 7.90 (s, 1, C(3)H), 7.50–7.18 (m, 5, C_6H_5), 5.35 (s, 2, CH_2). The analytical sample was dried under vacuum (80 °C, $CaCl_2$) for 2 days.

Anal. Calcd for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36; S, 12.22. Found: C, 50.25; H, 3.86; N, 21.41; S, 12.13.

7-Benzylimidazo[4,5-e]-1,2,4-thiadiazine 1,1-Dioxide (9b). 1-Benzyl-4-nitroimidazole-5-sulfonamide[22] (**3b**; 1.20 g, 4.3 mmol) in 150 mL of EtOH was reduced catalytically (1.20 g, 10% Pd/C). The solution was filtered, the filtrate was concentrated to ca. 40 mL under vacuum, 12 mL of $HC(OEt)_3$ was added, and then the solution was heated at reflux for 30 min. When the mixture was cooled, the product precipitated and was collected, washed with EtOH, and air dried; yield 0.68 g (61%). This was recrystallized from EtOH (C) to yield colorless crystals: mp 275–276 °C dec; mass spectrum, *m/e* (rel intensity) 262 (23, $M^{+\cdot}$), 92 (8); NMR δ 12.92 (s, 1, exch NH), 8.17 (s, 1, C(6)H), 7.90 (s, 1, C(3)H), 7.36 (s, 5, C_6H_5), 5.33 (s, 2, CH_2).

Irradiation of the CH_2 protons at 5.33 ppm caused a 20% increase in the integration of the signal at 8.17 ppm. The analytical sample was dried under vacuum ($CaCl_2$, 80 °C) for 2 days.

Anal. Calcd for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36; S, 12.22. Found: C, 50.46; H, 3.88; N, 21.44; S, 12.23.

1-Benzyl-4-aminoimidazole-5-sulfonamide (6b). From a reduction of **3b**, comparable to that described above, the amine **6b** was isolated as colorless needles: NMR δ 7.43 (s, 1, CH), 7.32–7.24 (m, 7, C_6H_5 and SO_2NH_2), 5.24 (s, 2, CH_2), 5.15 (s, 2, NH_2).

Imidazo[4,5-e]-1,2,4-thiadiazine 1,1-Dioxide (8a). Method A. 4(5)-Nitroimidazole-5(4)-sulfonamide (**2**; 4.00 g, 20.8 mmol) in 600 mL of EtOH and 45 mL of $HC(OEt)_3$ was reduced with H_2 and 10% Pd/C (4.0 g; 1.5 h), and then the mixture was filtered and the filtrate evaporated to dryness under vacuum, *maintaining the solution temperature below 20 °C*. The residue containing crude **5** was dissolved in 30 mL of $HC(OEt)_3$ and 100 mL of EtOH, and the solution was heated to boiling for 1.5 h, gradually removing the EtOH, and then cooled and filtered. The filtrate was concentrated under vacuum to ca. 8 mL, and the precipitate was collected to yield 2.75 g (77%) of **8a** as a tan solid. The crude product was recrystallized from $EtOH/H_2O$ (C) to afford **8a** as colorless needles: yield 1.54 g (43%); mp >300 °C; mass spectrum, *m/e* 172 (M^+), 145 (M – HCN)$^+$, 81 (M – HCN – SO_2)$^+$, 64.1 (SO_2)$^+$; NMR δ 13.44 (s, 1, NH), 13.22 (s, 1, NH), 8.00 (s, 1, C(6)H), 7.87 (s, 1, C(3)H); IR 1180, 1380 cm^{-1} (SO_2NH).[42] The analytical sample was dried under vacuum (70 °C, overnight).

Anal. Calcd for $C_4H_4N_4O_2S$: C, 27.91; H, 2.34; N, 32.54; S, 18.62. Found: C, 28.05; H, 2.43; N, 32.45; S, 18.58.

Method B. A 135-mg (0.07-mmol) sample of **7b** in 150 mL of EtOH was reduced with H_2 and Pd/C (20 mg); the progress of the reaction was monitored by TLC (silica gel, CH_3OH/EtOAc, 1/4). After 5 days of reaction the reduction was still incomplete. The formation of **8a** was indicated by the presence of a component migrating with an R_f similar to that of **8a** and was verified by elution of the band corresponding to that of **8a** (R_f 0.54) and comparison of its UV spectra at three pH's to those of a sample of **8a** prepared by method A.

3-Methylimidazo[4,5-e]-1,2,4-thiadiazine 1,1-Dioxide (8b). A solution of crude **5** (0.54 g), obtained from **2** as described above, in 0.6 g of $CH_3C(OEt)_3$ and 40 mL of EtOH was heated under reflux for 40 min and then cooled and evaporated almost to dryness under vacuum. That solution was added dropwise with stirring to CH_2Cl_2 (120 mL) to precipitate **8b**. The product, 0.42 g (68%), was collected and recrystallized from H_2O to yield colorless crystals: mp >320 °C; mass spectrum, *m/e* (rel intensity) 186 (24, M^+), 122 (12), 121 (11); NMR δ 11.43 (s, 1, NH), 7.97 (s, 1, C(6)H), 2.26 (s, 3, CH_3); IR 1210, 1390 cm^{-1}.

Anal. Calcd for $C_5H_6N_4O_2S$: C, 32.25; H, 3.25; N, 30.09; S, 17.22. Found: C, 32.02; H, 3.34; N, 29.84; S, 17.19.

(42) D. J. Pasto and C. R. Johnson in "Organic Structure Determination", Prentice-Hall, Englewood Cliffs, NJ, 1969, pp 132.
(43) A. Albert and E. P. Sergeant in "Ionization Constants of Acids and Bases", Wiley, New York, 1962.
(44) D. D. Perrin, *Aust. J. Chem.*, 16, 572 (1962).

7-(β-D-Ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (9c). A mixture of 1.06 g (6.2 mmol) of imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide (**8a**), 58 g of hexamethyldisilazane, and $(CH_3)_3SiCl$ (1.2 mL) was heated under reflux for 20 h with the exclusion of moisture and then evaporated to dryness under vacuum. To the residue was added 160 mL of dry CH_3CN, 3.42 g (6.8 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, and $SnCl_4$ (1.0 mL). The mixture was stirred at room temperature for 3 h, neutralized to ca. pH 8 with $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried (Na_2SO_4), evaporated to dryness, and chromatographed on silica gel (1:1 petroleum ether/ethyl acetate) to yield the tribenzoyl derivative of **9c**, 3.21 g (84%), as colorless crystals: mp 124–126 °C; NMR δ 11.32 (s, 1, exch NH), 8.11–7.89 (m, 8, C(3)H, C(6)H, and C_6H_5), 7.60–7.32 (m, 9, C_6H_5's), 6.34 (d, 1, J = 4.3 Hz, C(1)'H), 6.09–5.99 (m, 2, C(2)'H and C(3)'H), 4.98–4.86 (m, 3, C(4)'H, C(5)'H_2).

Anal. Calcd for $C_{30}H_{24}N_4O_9S$: C, 58.44; H, 3.92; N, 9.09; S, 5.20. Found: C, 58.46; H, 3.98; N, 8.85; S, 5.21.

A solution of 1.36 g (2.2 mmol) of 7-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide in 150 mL of methanolic ammonia was allowed to react at 20 °C for 2 days, was evaporated to about 15 mL, and was added to 150 mL of CH_2Cl_2 to precipitate the ammonium salt of **9c**; 0.50 g (75%). The salt was converted to **9c** by percolating a CH_3OH solution of the product over a column containing Bio-Rad AG-50 (H^+) and eluting with MeOH. Removal of the solvent under vacuum afforded **9c**, 0.45 g (69%), as colorless crystals: mp 166–169 °C; $[\alpha]^{20}_D$ −48° (*c* 4, H_2O); NMR (Me_2SO-d_6) δ 13.16 (br d, 1, exch NH), 8.39 (s, 1, C(6)H), 7.94 (d, 1, C(3)H), 5.69 (d, 1, J = 4.9 Hz, C(1)'H), 5.57 (d, 1, exch OH), 5.11 (b, 1, exch OH), 4.93 (b, 1, exch OH), 4.39 (b, 1, C(2)'H), 4.08–3.95 (m, 2, C(3)'H and C(4)'H), 3.63 (s, 2, C(5)'H). Addition of D_2O gave 8.37 (s, 1, C(6)H), 7.92 (s, 1, C(3)H), 5.70 (d, 1, J = 4.9 Hz, C(1)'H), 4.42 (t, 1, J = 4.9 Hz, C(2)'H), 4.09 (t, 1, J = 4.9 Hz, C(3)'H), 3.98 (m, 1, C(4)'H), and 3.67 (m, 2, C(5)'H). Irradiation at 5.70 ppm gave a 20% increase in the integration at 8.37 ppm. Irradiation at 4.42 ppm caused the doublet at 5.70 ppm to collapse to a singlet. The analytical sample was dried under vacuum (P_2O_5, 20 °C) overnight.

Anal. Calcd for $C_9H_{12}N_4O_6S$: C, 35.53; H, 3.98; N, 18.41; S, 10.54. Found: C, 35.48; H, 4.03; N, 18.22; S, 10.51.

The isopropylidine derivative of **9c** was prepared by reacting a solution of **9c** (0.25 g, 0.8 mmol) in 30 mL of dry acetone with 2 drops of concentrated H_2SO_4 overnight and then neutralizing with NaOEt. The solution was filtered, and the filtrate was evaporated to dryness to afford an oil. This was purified by preparative TLC (silica gel developed in 7.5% CH_3OH in EtOAc), eluted with CH_3OH, and recrystallized from CH_3OH/EtOAc to afford 195 mg (65%) of the isopropylidine derivative of **9c** as the sodium salt: mp 272 °C dec; NMR δ 7.94 (s, 1, CH), 7.14 (s, 1, CH), 5.85 (d, 1, J = 3.3 Hz, C(1)'H), 5.27–5.06 (m, 1, C(2)'H), 4.86–4.77 (m, 2, C(3)'H and 5'-OH), 4.04 (m, 1, C(4)'H), 3.54 (m, 2, C(5)'H), 1.51 (s, 3, CH_3), 1.29 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{15}N_4O_6SNa$: C, 39.36; H, 4.10; N, 15.30; S, 8.76. Found: C, 39.18; H, 4.03; N, 15.24; S, 8.78.

Acknowledgment. We express our appreciation to Dr. George Bosworth Brown for his encouragement and support and thank Mary Jane Lauzon and Michael T. Ricciardi for skilled technical assistance and Marvin J. Olsen, who was supported in part by Grant No. CA 17085, for determining the NMR spectra. Mass spectra were performed at the Mass Spectrometric Biotechnology Resource at the Rockefeller University, New York, NY, which is supported in part by Grant No. RR-862-01 from the Division of Research Facilities and Resources, NIH.

Registry No. 1a, 71518-15-5; **1b**, 71518-16-6; **2**, 6963-63-9; **3a**, 6339-55-5; **3b**, 71518-17-7; **4a**, 71518-18-8; **4b**, 71537-27-4; **5**, 61006-94-8; **6a**, 71518-19-9; **6b**, 71518-20-2; **7a**, 71518-21-3; **7b**, 71518-22-4; **8a**, 71518-23-5; **8b**, 71518-24-6; **9a**, 71518-25-7; **9b**, 71518-26-8; **9c**, 71518-27-9; **9c** tribenzoyl derivative, 71518-28-0; **9c** ammonium salt, 71518-29-1; **9c** isopropylidine derivative sodium salt, 71518-30-4; **10**, 71518-31-5; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 6974-32-9.

Structures and Mechanisms of Formation of the Major Side Products from the Preparation of 4,4-Dimethylcyclohex-2-enone by the Potassium Hydroxide Promoted Annelation of Methyl Vinyl Ketone and Isobutyraldehyde†

Herman O. Krabbenhoft

Chemical Synthesis and Engineering Branch, General Electric Corporate Research and Development Center, Schenectady, New York 12301

Received March 5, 1979

Reaction of equimolar quantities of methyl vinyl ketone and isobutyraldehyde in aqueous methanol in the presence of potassium hydroxide produced 4,4-dimethylcyclohex-2-enone (**1**, 38%), 3-methoxy-4,4-dimethylcyclohexanone (**2**, 2%), (*E*)-4,4-dimethyl-6-(2-methylpropylidene)cyclohex-2-enone (**3**, 25%), 4,4-dimethyl-2-(1-hydroxy-2-methylpropyl)cyclohex-2-enone (**4**, 14%), and 6,6-dimethyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (**5**, 3%). The structures of compounds **2–5** were elucidated from spectral data. Increasing the molar ratio of methyl vinyl ketone to isobutyraldehyde from 2:2 to 2:1.5 to 2:1 resulted in modest improvements in the yield of **1** (42 and 47%, respectively). The mechanisms for formation of the major side products **2–5** are discussed. It was found that 3,4,4-trimethylcyclohex-2-enone and 4,4,5-trimethylcyclohex-2-enone do not interconvert when treated with potassium carbonate in aqueous methanol; similarly, no crossover was observed between 2,4,4-trimethylcyclohex-2-enone and 4,4,6-trimethylcyclohex-2-enone. These results suggested that hydroxy ketone **4** was not formed via a pathway involving a [1,5] sigmatropic shift of hydrogen but rather by an aldol reaction between 3-hydroxy-4,4-dimethylcyclohex-2-enone (or **2**) and isobutyraldehyde followed by the loss of water (or methanol).

In connection with another study, 4,4-dimethylcyclohex-2-enone (**1**) was required. The method usually chosen for the preparation of **1** has been the base-promoted annelation reaction involving methyl vinyl ketone and isobutyraldehyde (eq 1),[1-8] although the enamine approach[9]

† Dedicated to Professor William G. Dauben on the occasion of his 60th birthday.

(1) Franke, W.; Bueren, J. German Patent 833645, 1952.
(2) Eliel, E. L.; Lukach, C. A. *J. Am. Chem. Soc.* **1957**, *79*, 5986.
(3) Bergmann, E. D.; Corret, R. *J. Org. Chem.* **1958**, *23*, 1507.

0022-3263/79/1944-4050$01.00/0