Reactions of Hydrazoic Acid with Ketenimines

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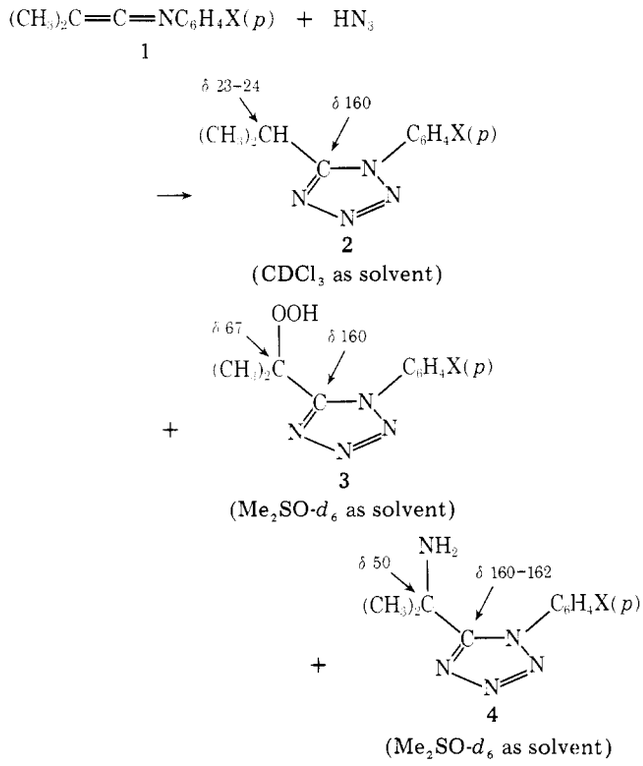
The reactions of hydrazoic acid with *N*-aryldimethylketenimines in the presence of atmospheric oxygen result in the formation of three types of tetrazoles, **2a,b, 3a,b,** and **4a,b.** Derivatives of **4a** are also prepared. The ^{13}C NMR data are discussed and X-ray structures are shown for **3b** and **4b.**

The reactions of hydrazoic acid with several classes of heterocumulenes are well known; isocyanates and ketenes produce carbamoyl azides,[1] isothiocyanates[2] and thioketenes[3] furnish 1,2,3,4-thiatriazoles, and carbodiimides yield 5-(monosubstituted)aminotetrazoles[4] or guanyl azides.[5] With ketenimines, several pathways can be considered a priori, including the formation of α-azidoenamines,[6] isotriazoles,[7] and tetrazoles.[8] In view of our interest in the chemistry of vinyl azides and their possible decomposition via isotriazoles into azirines,[9] we have investigated the title reactions.

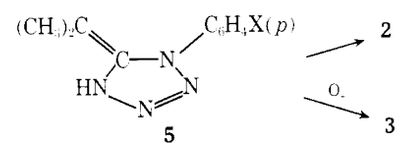
Reaction Products. We have found that *N*-aryldimethylketenimines **1a,b** react with hydrazoic acid in ether and



a, X = H, yields 26:13:24%; b, X = CH_3, yields 57:26:16%

without the exclusion of atmospheric oxygen to give the expected tetrazoles **2a,b** as well as two unexpected derivatives, **3a,b** and **4a,b.** When the reaction was carried out under a continuous flow of nitrogen gas, the hydroperoxide **3** was not observed in the ^1H NMR spectrum of the crude reaction mixture. Since **2** is stable toward oxygen at room temperature, the formation of **3** is assumed to result from air oxidation of **5**,[10] which is the normal precursor of **2a,b.**

The tetrazoles **4a,b** precipitated from the reaction mixture as salts of HN_3 (IR 2000 cm^{-1}), which were converted into the



free bases upon melting or heating in carbon tetrachloride as solvent. Their formation can be rationalized by addition of hydrazoic acid on both the C=C and C=N double bonds of **1a,b** to give the spiro adduct **6,** followed by acid-catalyzed decomposition of the triazoline moiety as shown in Scheme I. Neither **2a,b** nor **3a,b** could be converted into **4a,b** upon treatment with hydrazoic acid.

Compound **4a** has been converted into derivatives **7–12** (see Table I). Thus, **7** and **8** were obtained, respectively, by tosylation and benzoylation of **4a** in ether containing triethylamine or pyridine, and the urea **9** precipitated from the solution when equimolar amounts of **4a** and phenyl isocyanate were reacted in ether at room temperature. When **4a** was treated with a double excess of methyl vinyl ketone at 50 °C, the Michael adduct **10** was obtained. The reaction of **4a** with dimethyl acetylenedicarboxylate at room temperature furnished adduct **11.** The ^1H NMR spectra, taken at several time intervals, indicated that (*E*)-**11** was formed first but underwent slow isomerization into the more stable chelated (*Z*)-**11.** After 30 h at room temperature, a 75:25 mixture of the *E* and *Z* isomers was obtained. This *E*/*Z* adduct was added to a second molecule of dimethyl acetylenedicarboxylate and heated at 60° for 2 days, giving **12.** Its formation is rationalized by a combination of [2 + 2] cycloaddition and valence isomerization.[11]

^{13}C NMR Analysis. The important ^{13}C NMR data of **2, 3,** and **4** are summarized in Table II (see supplementary material). The ring carbon absorption of **2a,b** (δ 160 ppm) is shifted downfield compared with that of *N*-phenyltetrazole (δ 140 ppm).[12] The difference ($\Delta\delta$ = 20 ppm), however, is in complete agreement with what would be expected by substitution of a hydrogen for an isopropyl group.[13] Furthermore, when the hydrogen atom of the isopropyl group in **2** is substituted for an amino group, an increment of about 29 ppm is to be expected.[14] This indeed is found for the sp^3 carbon resonance of **4a,b** (the δ values are indicated in the structures). The derivatives **7–12** exhibit similar CH_3, sp^3 carbon, and ring carbon absorptions as the parent compound **4a** (see Experimental Section in the supplementary material).

We have also noticed that the methyl and sp^3 carbon absorptions of **3b** are shifted when a Me_2SO-d_6 solution of the product was allowed to stand at room temperature for 4 days (respectively, from δ 24.2 to 29.4 ppm and from δ 78 to 67.2 ppm). This phenomenon is ascribed to a change of the intramolecularly chelated form, present initially, into an intermolecularly solvated form. The observed proton shift of the

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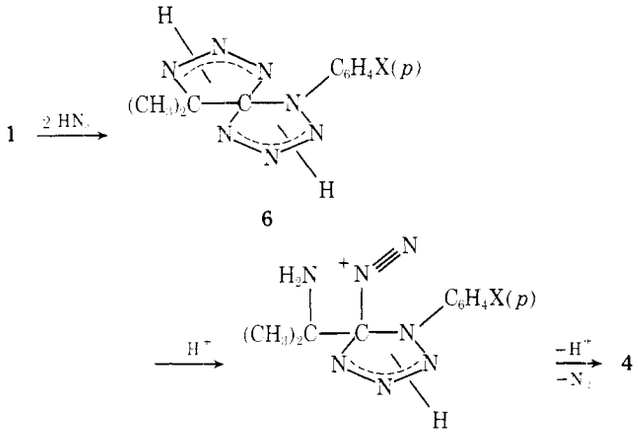
Scheme I



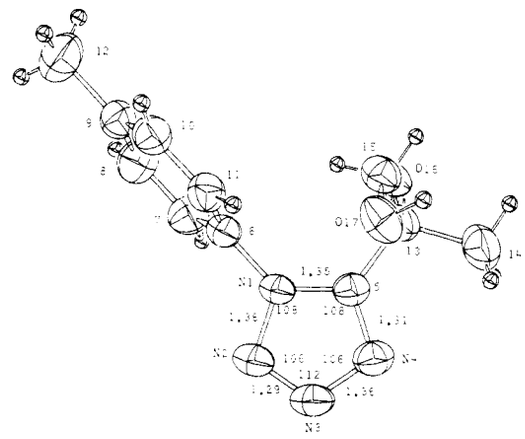


Figure 1. Stereodrawing of compound **3b**.

hydroperoxide substituent from δ 12 to 6 ppm confirms this explanation.

X-Ray Analyses of 3b and 4b. In view of the unexpected formation of **3** and **4**, and the fact that our spectral data are also interpretable in terms of other isomeric structures (which will not be discussed here), we have subjected **3b** and **4b** to an X-ray structure analysis. The structures, as well as the bond lengths (in Å) and internal angles (in degrees) of the tetrazole ring, are given in Figures 1 and 2.

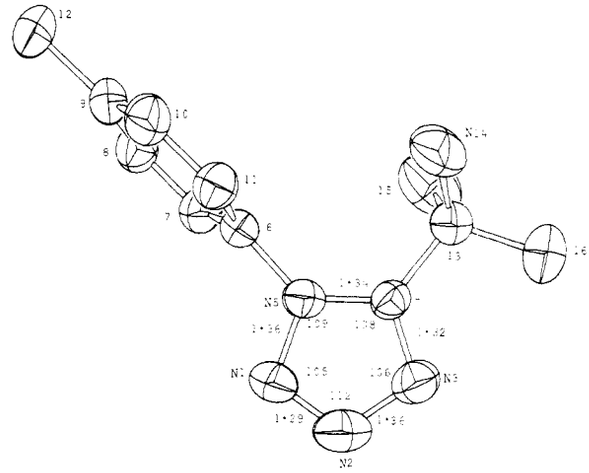


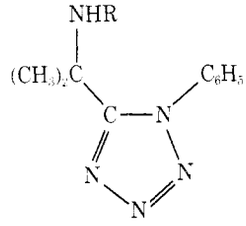
Figure 2. Stereodrawing of compound **4b**.

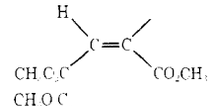
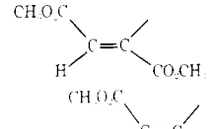
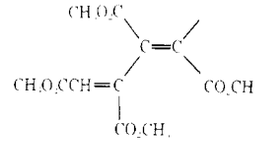
Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 157G spectrometer, mass spectra with an AEI MS-12 instrument, and ^{1}H NMR spectra with a Jeol MH-100 or Varian XL-100 spectrometer. For ^{13}C NMR spectra, the XL-100 apparatus was equipped with a device for pulsed Fourier transform operation. The chemical shifts given are in δ values in parts per million relative to Me_4Si unless otherwise stated. Hydrazoic acid[15] and the ketenimines **1a,b**[16] were prepared as reported.

Reactions of Hydrazoic Acid with Ketenimines. An 8% solution of hydrazoic acid in 80 mL of anhydrous ether was added dropwise to an ice-cooled solution of **1a** (2.2 g) in 15 mL of dry ether. After a reaction time of 2 days at room temperature, the precipitate was filtered off and the filtrate was subjected to column chromatography on silica gel with ethyl acetate–cyclohexane (25:75) as the eluent, giving **2a** and **3a**. The precipitate, which consisted of **4a** and its HN_3 salt (15:85) in 24% overall yield, was suspended in 150 mL of carbon tetrachloride and then heated until the azide-stretching absorption

Table I. Derivatives of 4a



Compd	Registry no.	R	Yield, %	Mp, °C
7	66418-00-6	p-$CH_3C_6H_4SO_2$	19	194–196
8	66418-01-7	C_6H_5CO	14	167.5–168
9	66418-02-8	C_6H_5NHCO	85	203–205
10	66418-03-9	$CH_3COCH_2CH_2$	60	61–62.5
(*E*)-**11**	66418-04-0		47	171–173
(*Z*)-**11**	66418-05-1		16	138–140
12	66418-06-2		45	143–145

at 2135 cm^{-1} disappeared (after ca. 6 h). Upon cooling and partial evaporation of the solvent, **4a** crystallized out in almost quantitative yield.

Compound **2a** was obtained as a colorless oil in 26% yield: IR (neat) 2960, 1240, 1100–1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (d, 6 H, J = 7 Hz), 3.20 (sept, 1 H), 7.3–7.6 (m, 5 H). Anal. Calcd for $M^{+\cdot}$: 188.1061. Found: 188.1072. This compound was identical in all respects with the product obtained from the corresponding imidoyl chloride and sodium azide.[17]

Compound **2b** was similarly obtained in 57% yield: mp 78–79 °C (*n*-hexane–chloroform); IR (KBr) 2960, 2920, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (d, 6 H, J = 7 Hz), 2.48 (s, 3 H), 3.2 (sept, 1 H), 7.3–7.4 (2d, 4 H). Anal. Calcd for $M^{+\cdot}$: 202.1217. Found: 202.1205. This compound was identical in all respects with the product obtained from the corresponding imidoyl chloride and sodium azide.[17]

Compound **3a** was obtained in 13% yield: mp 165 °C dec ($CHCl_3$); IR (KBr) 3200 cm^{-1} (OH); ^1H NMR (Me_2SO-d_6; HMDS as reference) δ 1.44 (s, 6 H, $2CH_3$), 7.52 (s, 5 H), 11.64 (s, 1 H, OH). Anal. Calcd for $C_{10}H_{12}N_4O_2$ (220): C, 54.51; H, 5.49. Found: C, 54.45; H, 5.44.

Compound **3b** was similarly obtained in 26% yield: mp 128–129 °C dec (ether); IR (KBr) 3180 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.60 (s, 6 H), 2.45 (s, 3 H), 9.30 (s, OH), 7.27–7.45 (m, 4 H). Anal. Calcd for $C_{11}H_{14}N_4O_2$ (234): C, 56.37; H, 6.03; N, 23.93. Found: C, 56.24; H, 5.95; N, 23.91.

Compound **4a** was obtained in 24–35% yield: mp 84–84.5 °C; IR (KBr) 3360–3380, 1590, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 6 H), 1.96 (s, 2 H), 7.4–7.6 (m, 5 H). Anal. Calcd for $C_{10}H_{13}N_5$ (203): C, 59.09; H, 6.45; N, 34.45. Found: C, 58.93; H, 6.37; N, 34.39.

Compound **4b** was similarly obtained as the HN_3 salt in 16% yield. The free base **4b** exhibited the following characteristics: mp 102–103 °C ($CHCl_3$); IR (KBr) 3380, 3320, 2980, 1580, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 6 H), 1.80 (s, 2 H, NH_2), 2.48 (s, 3 H), 7.36 (s, 4 H). Anal. Calcd for $C_{11}H_{15}N_5$ (217): C, 60.81; H, 6.96; N, 32.23. Found: C, 60.83; H, 6.99; N, 32.08.

Crystal Structure Determination of 3b and 4b. Compound 3b. Crystal data: $C_{11}H_{14}N_4O_2$ (234); monoclinic; a = 7.421 Å, b = 12.588 Å, c = 13.635 Å, β = 100.70°; space group $P2_1/c$, Z = 4. Intensity data were collected on a Syntex tape-controlled diffractometer using Mo Kα radiation, 2θ max = 45°. A total of 1630 independent reflections were measured, of which 1181 were considered as observed. The structure has been solved with the MULTAN 77 program[18] and refined with the X-RAY 72 system[19] to an R factor of 3.9%.

Compound 4b. Crystal data: $C_{11}H_5N_5$ (217); monoclinic; a = 13.565 Å, b = 10.937 Å, c = 8.223 Å, β = 102.48°; space group $P2_1/n$, Z = 4. Intensity data were collected on a Picker card-controlled diffractometer using filtered Mo Kα radiation, 2θ max = 45°. A total of 1550 independent reflections were measured, of which 1103 were considered as observed. The structure has been solved with the MULTAN 77 program[18] and refined with the X-RAY 72 system[19] to an R factor of 9.2%.

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Registry No.—**1a,** 14016-34-3; **1b,** 18779-86-7; **2a,** 66418-07-3; **2b,** 66418-08-4; **3a,** 66418-09-5; **3b,** 66418-10-8; **4a,** 66418-11-9; **4a** NH_3 salt, 66418-12-0; **4b,** 66418-13-1; **4b** NH_3 salt, 66523-90-8; hydrazoic acid, 7782-79-8; dimethyl acetylenedicarboxylate, 762-42-5.

Supplementary Material Available: Tables with ^{13}C NMR data and atomic coordinates of **3b** and **4b,** as well as the Experimental Section for the preparation of compounds **7–12** (4 pages). Ordering information is given on any current masthead page.

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Synthesis of 3′-Azido-2′,3′-dideoxyribofuranosylpurines

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The transglycosylation reaction of 3′-azido-3′-deoxy-5′-*O*-acetylthymidine (**4b**), which is readily available from thymidine, with silylated N^6-octanoyladenine using trimethylsilyl trifluoromethanesulfonate as a catalyst affords a mixture of α and β anomers of 3′-azido-2′,3′-dideoxyadenosine (**5a** and **5b**), which is separable on a silica gel column. Replacement of silylated N^6-octanoyladenine by silylated N^2-palmitoylguanine affords a mixture of product from which α and β anomers of 9-(3-azido-2,3-dideoxy-D-ribofuranosyl)guanine (**7a** and **7b**) can be isolated. The N^7 isomers (**8a** and **8b**) are also obtained, but could not be separated from each other. Treatment of **5b** and **7b** with triphenylphosphine and subsequent hydrolysis afford the corresponding 3′-amino-2′,3′-dideoxy nucleosides **6** and **9** in good yield. A further simplification of this transglycosylation reaction and its applicability to syntheses of ribonucleoside derivatives are demonstrated.

It has recently been observed that the 5′-diphosphates of 2′-azido-2′-deoxyribofuranosylpurines and -pyrimidines inhibit the ribonucleotide reductases of various organisms by interaction with the active sites of these enzymes.[1] This has led to the discovery that 2′-azido-2′-deoxycytidine in particular is an inhibitor of DNA replication in mammalian cells, presumably interfering with DNA initiation.[2] The details of the mechanism of action of this compound are as yet not un-

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