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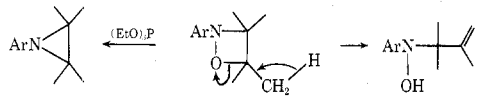

both *p*-trifluoromethylnitrosobenzene and PhNO give "ene"-type products with 2,3-dimethyl-2-butene they do not give any aziridine in the inverse addition in the presence of $(EtO)_3P$. That aziridines are also formed from $C_6F_5N_3$ by photolysis also supports the electrophilic nitrene hypothesis for the addition to olefinic double bonds.
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Purine *N*-Oxides. LXI. 3-Hydroxy-2,3-dihydro-2-oxopurine[1]

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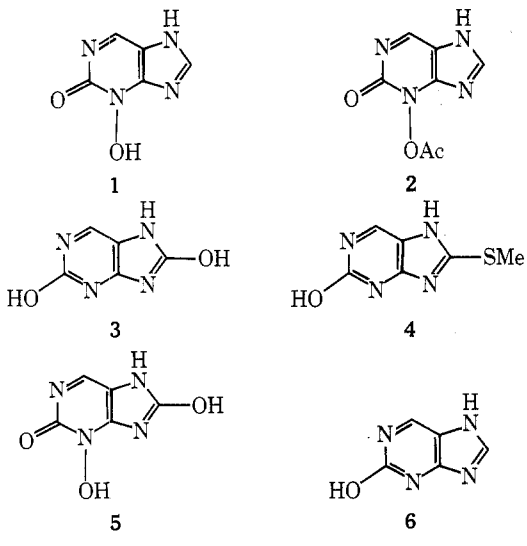
The synthesis and reactivity of 3-hydroxy-2,3-dihydro-2-oxopurine (1) is described. The acetyl and tosyl esters of 1 react with water to give some 2,8-dihydroxypurine and hydrolysis products, while the acetyl ester of 1 prepared in situ reacts with methionine at room temperature to give almost quantitative yield of 2-hydroxy-8-methylmercaptopurine. The xanthine oxidase oxidation of 1 gave good yield of 3,8-dihydroxy-2,3-dihydro-2-oxopurine. The photoirradiation of 1 at pH 3.0 produces 2-hydroxypurine (21%) and a small amount of 2,8-dihydroxypurine (1%), while at pH 9.0 it gives mostly a ring-opened imidazole derivative, a small amount of 2-hydroxypurine, and a trace of 2,8-dihydroxypurine.

It has been reported from this laboratory that esters of 3-hydroxyxanthine[2-6] and some of its methylated derivatives undergo an elimination–substitution reaction to yield 8-substituted xanthines, even at room temperature and in nearly neutral solution. The subsequent studies of some analogs[7-9] of 3-hydroxyxanthines have shown that some π-excessive ring systems can undergo an elimination–substitution reaction similar to that of the esters of 3-hydroxyxanthine.

This paper describes the reactions of 3-hydroxy-2,3-dihydro-2-oxopurine (1). This was prepared by condensation



of 5-aminocytosine 1-oxide[7] with triethyl orthoformate in boiling ethanol. Although the reaction was carried out heterogenously, the overall yield of 1 was found to be quite satisfactory. The identity of the compound was confimed by NMR, uv spectra, elemental analysis, and mass spectrum. The uv spectrum of 1 in both acid and neutral media resembles those of 2-hydroxypurine[10] (2,3-dihydro-2-oxopurine).[11,12] The uv of the neutral species of 1 shows a bathochromic shift of 5 nm in long-wavelength major band with respect to that of its parent purine, as do the uv spectra of 3-hydroxyxanthine and its analogs,[7-9] thus confirming that the neutral species of 1 does exist in the *N*-hydroxy form as shown. The basic pK_a (1.79) of 1 was found to be similar to that of 2-hydroxypurine (1.69), which indicates that the addition of the 3-hydroxy function to 2-hydroxypurine has little effect on the protonation. The 3-hydroxy-2,3-dihydro-2-oxopurine is very insoluble in water and purification was achieved only by reprecipitation. Unlike 2-hydroxypurine,[13] which ring opens to 4,5-diaminopurine even in pH 5 solution, 1 undergoes ring opening slowly only in strong acid solution at room temperature (in 3 *N* HCl $t_{1/2}$ = 4 days). Like 3-hydroxyxanthine, 1 reacted with acetic anhydride to form the acetyl ester of 1 but the isolation of ester in pure form was not successful owing to its ready hydrolysis. When the freshly prepared acetyl ester was boiled with ethanol, it did not give any 8-ethoxy-2-hydroxypurine; instead a small amount of 2,8-dihydroxypurine[10] (2,3,7,8-tetrahydro-2,8-dioxopurine, 3) and unreacted 1 were obtained. Similar treatment of the acetoxypurine with pH 7.00 buffer also gave a small amount of 3. Reaction of 1 with tosyl chloride in pyridine at room temperature for a prolonged period of time gave some 3, but upon refluxing in pyridine most of the 1 decomposed to non-uv absorbing material and no 3 was detectable. The acetyl ester of 1 prepared in situ by the addition of acetic anhydride to an aqueous solution of 1 with methionine present gave almost a quantitative amount of 2-hydroxy-

8-methylmercaptopurine (**4**),[10,14] which was identified by comparison of the uv and chromatographic data with those of an authentic sample. In the absence of methionine, the acetyl ester prepared in situ did not react with water at room temperature to give **3**, but upon prolonged stirring in water the ester hydrolyzed to give **1**. The high yield of **4** was clearly due to the stronger nucleophile, methionine, and constant regeneration of the ester by acetic anhydride. The elimination–substitution reactions of the ester of **1** may proceed via an AE mechanism, that is, the addition of the nucleophile to C-8 followed by elimination and aromatization to the final product.

Xanthine oxidase[15] was found to oxidize the position 8 preferentially, to give mainly 3,8-dihydroxy-2,3-dihydro-2-oxopurine (**5**)[16] with only a small amount of 3-hydroxyxanthine. Since **5** is isomeric to 3-hydroxyxanthine, the identity was readily established by comparison of the uv spectrum of **5** to that of 3-hydroxyxanthine, and by elemental analysis.

Similarities in the reactivities of **1** and 3-hydroxyxanthine suggest that **1** is a potential oncogen, and have led us to compare its photochemical reactions with other purine *N*-oxides.[17] The irradiation of the neutral molecule (at pH 3.0) with 3000-Å light resulted in photoreduction to **6** (21%) and a minor 8-substitution product, identified as 2,8-dihydroxypurine (1%). In contrast, no 8-substitution products were observed from the irradiation of 1- and 3-hydroxyxanthines under similar conditions. Irradiation of the anion (at pH 9.0) also gave 7% of **6**, a trace of **3**, and a major product for which a positive Pauly test suggests an imidazole derivative.

The results of this work show that the acetyl ester of **1** has nearly the same reactivity as that of the corresponding ester of 3-hydroxyxanthine, notably the reaction to give an excellent yield of **4**. Should an ester of **1** be formed in vivo it is likely to react with various sulfur-containing amino acids and other nucleophiles. In collaboration with Dr. M. N. Teller a comparison of the oncogenicity of **1** with that of 3-hydroxyxanthine in rats is planned.[18,19]

Experimental Section

The uv spectra were determined with a Cary 15 spectrophotometer. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. NMR spectra were determined with a Varian A-60 spectrometer, in Me_2SO-d_6 with tetramethylsilane as an internal reference. The melting points are uncorrected. Paper chromatography, ascending, on Whatman No. 1 paper was used to check the purity of each of the compounds prepared. For Dowex-50 chromatography BioRad AG-50, ×8, 200–400 mesh (H^+) resin was used. Photolyses were carried out with a Rayonet photochemical reactor equipped with a 300-nm lamp and a Merry-Go-Round apparatus. All solutions were flushed with a stream of N_2 at least for 30 min prior to irradiation.

3-Hydroxy-2,3-dihydro-2-oxopurine (1). 5-Aminocytosine 1-oxide hydrochloride[7] (4,5-diamino-2-hydroxypyrimidine 3-*N*-oxide, 1.0 g) was added to a solution of triethyl orthoformate (5 ml) in ethanol (99%, 25 ml). The reaction was carried out heterogeneously, with the solid heated in suspension under reflux for 5 hr. The mixed precipitate (780 mg) was collected by filtration. The precipitate was suspended in water (5 ml) and the acidity was adjusted to pH 6 with 1 *N* NaOH, from which the free base of **1** (670 mg, 79%) was isolated directly. An analytical sample was prepared by reprecipitation from dilute alkali by acid: mp 204° dec; NMR (TFA) δ 9.00, 9.23; uv (pH −0.2), 325 nm ($\epsilon \times 10^{-3}$ 5.99), 262 (6.88); (pH 3.6) 355 (2.67), 318 (5.24), 283 (3.08), 274 (3.12), 213 (14.1); (pH 7.3) 334 (5.56), 277 (4.64), 271 (4.54); (pH 11) 325 (5.99), 283 (6.86); pK_a's 1.78 ± 0.11, 5.38 ± 0.05, 9.28 ± 0.03; chemical ionization mass spectrum *m/e* 153 (M + 1), 151 (M − 1), 137 (M + 1 − 16), 136 (M + 1 − 17), 110 (M + 1 − 44).

Anal. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.83. Found: C, 39.35; H, 2.70; N, 36.90.

Reaction of 3-Hydroxy-2,3-dihydro-2-oxopurine with Tosyl Chloride. Tosyl chloride (380 mg) was added to a solution of **1** (152 mg) in pyridine (5 ml), and the mixture was stirred at room temperature for 1 week. The dark brown solid (89 mg) was precipitated by the addition of ether. The NMR spectrum of the product showed multiplet signals for pyridine protons (10.0–5.8 ppm). The solid was dissolved in a small amount of 1 *N* NaOH, and the solution was absorbed in a Dowex-50 (H^+) column. Elution with 1 *N* HCl gave 2,8-dihydroxypurine[12] (11 mg), and with 2 *N* HCl gave 5-aminocytosine 1-oxide[7] (18.1 mg) and 5-aminocytosine (29 mg).

3-Acetoxy-2,3-dihydro-2-oxopurine (2). Acetic anhydride (1 ml) was added to a solution of **1** (132 mg) in acetic acid (2 ml) and stirred at room temperature for 2 weeks. Ether (50 ml) was added to the reaction mixture, and the precipitate formed was collected and dried in vacuo. NMR in TFA showed the signals at 2.30 (CH_3CO–), 8.98, and 9.22 ppm (6- and 8-H). The compound was too unstable to permit purification, and it was used without further purification.

3,8-Dihydroxy-2,3-dihydro-2-oxopurine. A. Freshly prepared **2** (118 mg, 0.608 mmol) was boiled with methanol (25 ml) for 4 hr. The solution was evaporated to dryness in vacuo. Chromatography of the residue over a Dowex-50 (H^+) column with 0.1–2 *N* HCl gave 2,8-dihydroxypurine[13] (5.97×10^{-2} mmol, 10%), **1** (2.38×10^{-1} mmol, 39%), and 4,5-diaminopyrimidine (1.22×10^{-1} mmol, 20%).

B. Freshly prepared **2** (150 mg, 0.72 mmol) in pH 7.0 phosphoric acid buffer (0.05 M, 45 ml) was stirred at room temperature for 24 hr. The mixture was absorbed on a Dowex-50 (H^+) column. Eluting with 1 *N* HCl gave a small amount of 3,8-dihydroxy-2,3-dihydro-2-oxopurine (<1%).

C. Heating **2** in Ac_2O–HOAc for 2 hr yielded 2,8-dihydroxypurine (13%).

2-Hydroxy-8-methylmercaptopurine (4). Acetic anhydride (100 μl) was added to a mixture of **1** (80.9 mg, 0.54 mmol) and *dl*-methionine (164 mg, 1.1 mmol) in water (20 ml) at room temperature. After 24 hr of stirring at room temperature, the insoluble, unchanged starting material (39 mg, 49%) was separated by filtration, and the filtrate was adsorbed in Dowex-50 (H^+) column. Elution of the column with 1 *N* HCl gave the 2-hydroxy-8-mercaptopurine[14] (1.32 mmol, 25%) followed by 8-methionium-2-hydroxypurine (2.23×10^{-2} mmol, 4.2%). The latter was converted to **4** by heating with 0.01 *N* NaOH on a steam bath for 2 hr. The filtered, unchanged starting material (39 mg) was treated the same way as above in water (25 ml) and gave a quantitative yield of **4**.

3,8-Dihydroxy-2,3-dihydro-2-oxopurine (5). Xanthine oxidase (0.4 ml, with activity to oxidize xanthine to uric acid at 45 μmol min^{-1} ml^{-1}) was added to 3-hydroxy-2,3-dihydro-2-oxopurine (100 mg, 2000 ml of water) solution and stirred at room temperature for 7 days. The solution was concentrated to a small volume (10 ml) and the insoluble starting material (46 mg, 46%) was collected. Chromatography of the filtrate over a Dowex-50 (H^+) column with 0.5 *N* HCl gave a trace of 3-hydroxyxanthine (0.32 mg, 0.3%, followed by a small amount of unknown material, and 3,8-dihydroxy-2,3-dihydro-2-oxopurine (40.2 mg, 36%), $FeCl_3$ blue color: uv (pH 0) 272 nm (ϵ 8.25×10^3); mp 270° dec.

Anal. Calcd for $C_5H_4N_4O_3$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.52; H, 2.62; N, 33.15.

Registry No.—**1**, 54643-52-6; **2**, 54643-53-7; **4**, 10179-94-9; **5**, 54643-54-8; 5-aminocytosine 1-oxide hydrochloride, 54643-55-9.

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Reactions of α-Azidovinyl Ketones with β-Keto Esters

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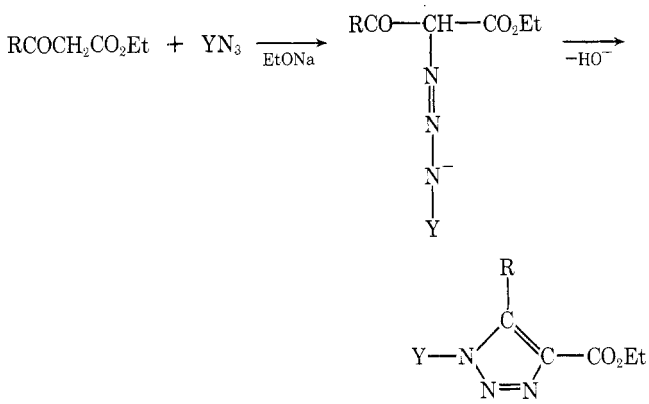
The base-catalyzed reactions of ethyl acetoacetate with α-azidochalcone, α-azido-(*m*-nitrobenzylidene)acetophenone, and α-azidobenzylideneacetone, as well as the reaction of ethyl benzoylacetate with α-azidobenzylideneacetone, were found to give substituted triazolycyclohexanones (**5a,b** and **8a,b**). Ethyl benzoylacetate also reacted with α-azidochalcone or its nitro-substituted derivative, but yielded the N-1-substituted triazoles **10a,b.** Structure assignment of all the products was essentially based upon ^1H and ^{13}C NMR analysis and further confirmed by analytical and other spectral data.

The reaction of aryl azides and alkyl azides with active methylene compounds under basic conditions to give *v*-triazoles (Scheme I) is called the Dimroth reaction after its discoverer.[1] The mechanism of this synthetically important reaction has been shown to involve a two-step cycloaddition process via a triazene intermediate.[2]

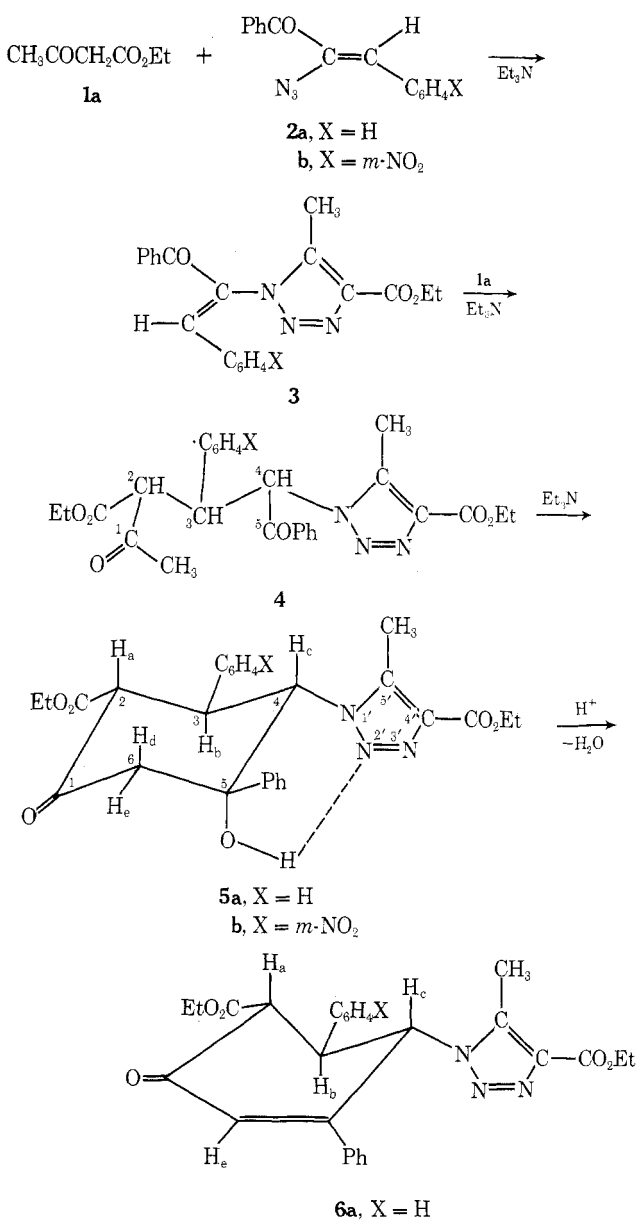
Scheme I
The Dimroth Reaction



Recently, the Dimroth reaction has been extended to simple vinyl azides[3] and β-azidovinyl ketones.[4] In both cases vinyl-substituted *v*-triazoles were obtained. In this paper, we describe our results of the reactions of α-azidovinyl ketones with β-keto esters where the initially formed vinyltriazoles underwent further reaction with the active methylene compounds.

Chemical Results. Treatment of ethyl acetoacetate (**1a**) with α-azidochalcone (**2a**) or its nitrosubstituted derivative **2b** in the presence of triethylamine furnished white, crystalline products to which structures **5a** and **5b** are assigned on the basis of analytical and spectral properties (see discussion NMR). From Scheme II it is apparent that the initially formed Dimroth product **3** has undergone a Michael-type addition with the active methylene compound **1a** in the presence of triethylamine to give **4.** This reaction is expected to occur readily, since the electron density of the olefinic double bond is decreased by the presence of two strong electron-withdrawing substituents. Under the basic reaction conditions, **4** then underwent an intramolecular aldolization, resulting in the formation of **5a,b.** Under acid-

Scheme II



6a, X = H
b, X = *m*-NO_2