tanes,[4] I is expected to display only very weak (*ca.* 2.5 cps) couplings.

Analysis of the spectrum is facilitated by examination of spectra obtained in benzene and trifluoroacetic acid solutions. Although the mechanism by which aromatic solvent-induced shifts are produced is in doubt,[5] there is no question of the considerable utility of this solvent. Figure 2 shows the spectrum of II in benzene; the nonequivalency of H_A and H_B has been removed, giving a close approximation to a first-order A_2X system, with apparent $J = 6.6$ cps.

Trifluoroacetic acid, which presumably protonates II on nitrogen, enhances the distinction between the methylene protons. As shown in Figure 3, the low-field peak, H_X, is now a quartet, the separation between the outermost lines ($|J_{AX} + J_{BX}|$) being 17.0 cps. The other parameters are $J_{AB} = 13.8$ cps, $J_{AX} = 6.6$ cps, $J_{BX} = 10.4$ cps, and $\delta_{AB} = 21.5$ cps. The changes in coupling constants are assumed to result from changes in bond lengths and angles, caused by the positive charge on nitrogen.

Thus, the spectra in all three solvents are consistent with the ABX interpretation, and therefore with the hexahydro-1,3,5-trithia-6b-azacyclopenta[*c*,*d*]pentalene structure.

It is interesting to speculate on the mechanism of formation of II. In Chart I we have outlined our suggestion,[6] based on the reaction reported by Thiel[2] between ammonia and mercaptoacetaldehyde. The ammonia required for the formation of the Schiff base may come from decomposition of the ammonium dithiocarbamate to CS_2 and NH_3 (a readily established equilibrium), or from ammonium chloride formed in the reaction $NH_2CS_2NH_4 + ClCH_2CHO \rightarrow NH_2CS_2CH_2CHO + NH_4Cl$.

We should like to point out also that II is capable of optical activity; we are presently engaged in attempts to separate it into enantiomers. Other chemical and spectroscopic studies of this interesting molecule are also in progress.

Registry No.—II, 5692-45-5.

(4) R. C. Fort, Jr., and P. von R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).
(5) R. C. Fort, Jr., and T. R. Lindstrom, *Tetrahedron*, **23**, 3227 (1967).
(6) A referee has suggested an alternate mechanism, in which the cyclization is initiated by the attack of mercaptide ion from mercaptoacetaldehyde upon the Schiff's base. We regard the lifetime of this anion as short under the essentially neutral reaction conditions, and therefore prefer the mechanism of Chart I. A conclusive statement, of course, must await the results of our further studies.

Acylation of 5-Aminotetrazoles

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The formylation of aromatic amines by reaction with N,N-dimethylformamide and sodium methoxide was reported[1] to give good yields and to afford a simple, easily performed method. As part of our contin-

(1) G. R. Pettit and E. K. Thomas, *J. Org. Chem.*, **24**, 895 (1959); G. R. Pettit, M. V. Kalnins, T. M. H. Liu, E. G. Thomas, and K. Parent, *ibid.*, **26**, 2563 (1961).

TABLE I
ACYLATION OF 5-AMINOTETRAZOLES

Acylated tetrazole	Registry no.	Acylation method	Time of heating, hr	Product yield, %	Recrystallization solvent	Mp, °C[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
5-Formamido	13958-60-6	$NaOCH_3$, DMF[b]	1.0	87.1	DMSO[b]	241 dec[c]	21.24	2.67	61.94	21.21	2.72	61.20
5-Formamido		HCOOH	4.0	89.7								
1-Methyl-5-formamido	14002-03-0	$NaOCH_3$, DMF	1.5	90.5	Absolute alcohol	140–142	28.35	3.97	55.10	28.11	4.24	55.01
1-Methyl-5-formamido		HCOOH	2.0	0.0								
2-Methyl-5-formamido	14002-04-1	$NaOCH_3$, DMF	1.5	50.8	Benzene	128–129	28.35	3.97	55.10	28.50	4.19	54.90
2-Methyl-5-formamido		HCOOH	2.0	80.0								
5-Acetamido	6158-77-6	$NaOCH_3$, DMAC[b]	3.0	47.6	Alcohol	277–278 dec[d]	28.35	3.97	55.10	28.52	3.99	54.92
5-Acetamido		Ac_2O	1.5[e]	51.2								
1-Methyl-5-acetamido	6154-02-5	$NaOCH_3$, DMAC	1.0	62.4	Methyl alcohol	166.5–167.5[f]	34.04	5.00	49.62	33.94	4.90	49.34
1-Methyl-5-acetamido		Ac_2O	2.0	37.1								
2-Methyl-5-acetamido	6154-06-9	$NaOCH_3$, DMAC	0.5	31.9	Water	152–153[g]	34.04	5.00	49.62	34.31	5.27	49.73
2-Methyl-5-acetamido		Ac_2O	2.0	27.1								
5-Benzamido	6158-74-3	$NaOCH_3$, DMBA[b]	0.75	94.7	DMF	281–282 dec[h]	50.79	3.73		50.75	3.88	
5-Benzamido		BzCl, NaOH, H_2O	1.0	10.6								
5-Benzamido		2BzCl, 2.1NaOH, H_2O[i]	2.0	20.1								
5-Benzamido		2BzCl, $2Na_2CO_3$, H_2O[i]	4.0	41.8								

[a] Melting points were measured with a Thomas-Hoover capillary melting point apparatus and were uncorrected. [b] DMF = N,N-dimethylformamide; DMAC = N,N-dimethylacetamide; DMBA = N,N-dimethylbenzamide; DMSO = dimethyl sulfoxide; BzCl = benzoyl chloride. [c] Evolved gas and turned plastic without discoloration at 241°, then resolidified and darkened above 300° without melting. [d] Lit.[4] 269° dec. [e] After 4.5 hr, 2-acetamido-5-methyloxadiazole was obtained in 51.8% yield, but no 5-acetamidotetrazole was obtained. [f] Lit. 164°, R. Stolle, K. Ehrmann, D. Rieder, H. Wille, H. Winter, and F. Henke-Stark, *J. Prakt. Chem.* **134**, 282 (1932). [g] Lit.[7] 153–154°. [h] Lit. 280° dec, L. E. Brady and R. M. Herbst, *J. Org. Chem.*, **24**, 922 (1959). [i] Numbers indicate number of moles.

uing interest in tetrazoles,[2] this method was used for the formylation of 5-aminotetrazole and its 1- and 2-methyl-substituted derivatives (Table I). The formylation of 5-aminotetrazoles and the formyl derivatives have not been reported previously. An extention of this method to acetylation and benzoylation by reaction with N,N-dimethylacetamide and N,N-dimethylbenzamide gave the 5-acetamido- and 5-benzamidotetrazoles (Table I). These reactions apparently have not been reported previously for any type of amine.

5-Aminotetrazole and 2-methyl-5-aminotetrazole also were formylated by refluxing with formic acid (Table I). 1-Methyl-5-aminotetrazole, however, could not be formylated with either 88 or 99.5% formic acid.

The formamidotetrazoles hydrolyze rapidly in hot, dilute hydrochloric acid and in boiling water. The hydrolysis is slow enough in cold dilute hydrochloric acid however, that the compounds can be isolated readily by precipitation from the reaction mixtures merely on acidification. The 1-methyl-5-formamidotetrazole slowly decomposed at room temperature, its melting point being depressed several degrees after standing several months. Insufficiently purified material decomposed quite rapidly in a closed container giving a strong odor of formic acid after standing several days at 5°. 5-Formamidotetrazole and its 2-methyl derivative are stable on standing.

Prior work[3,4] has shown that 5-substituted tetrazoles, including 5-aminotetrazole, are converted to oxadiazoles in acylation reactions employing acid chlorides or anhydrides. We have verified that on terminating the reactions early, acylated 5-aminotetrazoles can be isolated. The yields, however, are greatly reduced or eliminated by formation of oxadiazoles. Acylation with dimethylamides and sodium methoxide, on the other hand, produces the amidotetrazoles in good-to-excellent yields without oxadiazole formation.

5-Acetamidotetrazole and its 1- and 2-methyl-derivatives[5] also were prepared with acetic anhydride to compare the yields with those obtained using dimethylacetamide and sodium methoxide. 5-Benzamidotetrazole was prepared with benzoyl chloride in aqueous sodium hydroxide and sodium carbonate to compare yields, and to establish that 2-benzamido-5-phenyloxadiazole was not formed in aqueous alkali. The results are summarized in Table I. The yields of the acetamidotetrazoles are comparable, but the yields of 5-benzamidotetrazole are much greater for the procedure using dimethylbenzamide and sodium methoxide. 2-Benzamido-5-phenyloxadiazole could not be isolated from the reaction with benzoyl chloride in aqueous alkali. Probably the oxadiazole is not formed since the anionic tetrazolate ring produced in aqueous alkali could not be acylated. Lower yields of 5-benzamidotetrazole in this reaction are due to slow benzoylation and hydrolysis of the benzoyl chloride. However, the tetrazolate anion is stabilized by resonance[2,6] so that thermal splitting of the ring and further reaction does not occur. In nonaqueous medium where oxadiazoles are formed, substitution of the acyl group on the tetrazole ring, rather than splitting of the ring, probably is the initial step in the formation of oxadiazoles.[3] It would appear that acylonium attack on the ring destabilizes the ring, causing it to split even more readily than thermal splitting of the unsubstituted ring.

(2) F. Einberg, *ibid.*, **29**, 2021 (1964).

(3) R. Huisgen, J. Sauer, H. J. Sturm, and J. H. Markgraf, *Chem. Ber.*, **93**, 2106 (1960); R. Huisgen, H. J. Sturm, and M. Seidel, *ibid.*, **94**, 1555 (1961).

(4) R. Stolle, E. Schick, F. Henke-Stark, and L. Krauss, *ibid.*, **62B**, 1118 (1929).

(5) This was done since little attention had been given to yields of amidotetrazoles in previously reported[3,4] acylations.

Experimental Section

Reagent-grade reagents were used without further purification except that dimethylformamide and dimethylacetamide were dried over activated Linde Molecular Sieve, Type 4A. Anhydrous 5-aminotetrazole was obtained from its monohydrate by heating at 110° overnight and cooling in a desiccator over "Drierite." The 1- and 2-methyl-5-aminotetrazoles were prepared according to the method described by Henry and Finnegan[7] using dimethyl sulfate as methylating agent.

Acylation with N,N-Dimethylamides and Sodium Methylate.—The general acylation procedure was the following. A mixture of anhydrous 5-aminotetrazole (0.1 mole), the appropriate dimethylamide (100 ml), and sodium methoxide[1,8] (0.2 mole) was stirred and the temperature was raised to 120–130° during 20 to 40 min. Heating at 120–130° was continued for another 15 min to 3 hr (Table I). Evolution of dimethylamine and slight refluxing began at about 80°. After heating, the reaction mixture was cooled and filtered. The filtrate then was evaporated to near dryness on the steam bath under reduced pressure and the remaining solids were combined with the filtered solids, slurried in methylene dichloride, filtered, washed with methylene chloride, and dried. The solids were dissolved or partially dissolved in a minimum quantity of ice water and the solutions were made acidic with concentrated hydrochloric acid. For the 1- and 2-methyl-5-aminotetrazoles the mixtures were neutralized to a pH of about 6, while for the unsubstituted 5-aminotetrazole the mixture was made acidic to a pH of about 3. The crystalline precipitates were collected on a filter, washed with cold water, and recrystallized from a suitable solvent (Table I). Yields, melting points, and analytical data are given in Table I.

Formylation with Formic Acid.—Formic acid, 88%, 50 ml, was refluxed with anhydrous 5-aminotetrazole and its 2-methyl derivative, 0.2 mole. After refluxing (time given in Table I), the excess formic acid was removed under reduced pressure with warming. The products then were crystallized from a suitable solvent (Table I). Yields are given in Table I. The compounds were shown by infrared spectra and melting points to be identical with those obtained by the above method. 1-Methyl-5-formamidotetrazole could not be isolated from the reaction of 1-methyl-5-aminotetrazole with 88 or 99.5% formic acid.

Benzoylation with Benzoyl Chloride in Water.—Benzoyl chloride was added during a few minutes to a stirred solution of 5-aminotetrazole monohydrate and sodium hydroxide in the mole ratios 1:1:1, respectively, and 2:1:2, respectively, in water at slow reflux (times given in Table I). After reaction, the mixtures were strongly acidic. Benzoyl chloride, 5-aminotetrazole monohydrate, and sodium carbonate in the mole ratio 2:1:2, respectively, also were reacted in water at reflux. After reaction, the pH of the latter mixture was approximately 7. Concentrated hydrochloric acid was added to the reaction mixtures to give a pH of about 2. The precipitated solids were collected, extracted with boiling water, dried, and extracted with ether. The undissolved solids were dissolved in a minimum quantity of dimethylformamide, and water was added until no further significant precipitation occurred. The solid 5-benzamidotetrazole was collected on a filter. Yields are given in Table I. The compound was shown *via* infrared

(6) J. H. Markgraf, S. H. Brown, M. W. Kaplinsky, and R. G. Peterson, *J. Org. Chem.*, **29**, 2629 (1964).

(7) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, **76**, 923 (1954).

(8) Commercial sodium methylate was used. The container was opened in a glove box, and the sodium methylate was weighed and transferred in a dry, nitrogen atmosphere to avoid exposure to moisture.

spectra and melting points to be identical with that obtained by the above method.

Infrared Spectra of the Acylated Tetrazoles.—All spectra showed two bands in the region, 3030–3300 cm^{-1} (NH stretching), and single bands in the region, 1675–1730 cm^{-1} (C=O). The spectra of all compounds showed two bands in the region, 1515–1630 cm^{-1} (C–N, or C=N), except for 2-methyl-5-formamidotetrazole which showed one band. Three bands appeared in the region of 995–1085 cm^{-1} (tetrazole ring) for all compounds except 5-formamidotetrazole, which showed two bands, and 1-methyl-5-formamidotetrazole, which showed one band. The infrared spectra for the acetamido- and benzamidotetrazoles have recently been reported elsewhere.[9]

(9) V. P. Shchipanov, S. L. Portnova, V. A. Krasnova, Yu. N. Sheinker, and I. Ya. Postovskii, *Zh. Org. Khim.*, **1** (12), 2236 (1965); *Chem. Abstr.*, **64**, 11056*d*.

Purine N-Oxides. XXI. Elimination of a 5 Substituent from a Substituted Uracil. A Synthesis of 3-Hydroxy-1-methylxanthine[1]

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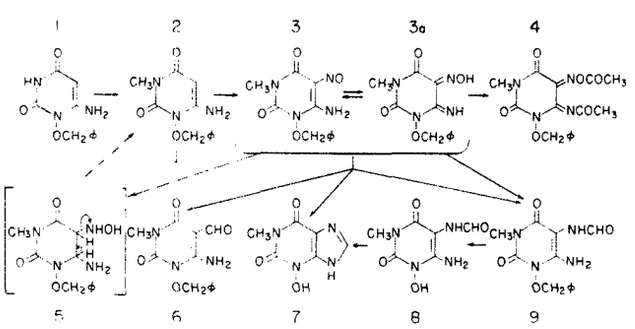
An apparent displacement of a 5-nitroso group by a formyl group was encountered during studies of the synthesis of 1-methylxanthine 3-N-oxide (3-hydroxy-1-methylxanthine) (**7**). The 6-amino-1-benzyloxyuracil (**1**) was synthesized according to Klötzer[2] and then methylated with dimethyl sulfate to yield 6-amino-1-benzyloxy-3-methyluracil (**2**). The 5-nitroso derivative (**3**) of **2** was prepared by reaction with nitrous acid (Scheme I).

SCHEME I



Reduction of **3** in ethanolic solution with hydrogen and a Raney nickel catalyst resulted in the uptake of 2 moles of hydrogen, but the product proved insufficiently stable to be isolated, even as the hydrochloride salt. Reduction was therefore performed with Raney nickel and formic acid, and the formic acid solution of the presumed 5-formylamino product (**9**) was refluxed with acetic anhydride. Instead of the expected 1-methyl-3-benzyloxyxanthine, the principal product of this reaction proved to be 6-amino-1-benzyloxy-5-formyl-3-methyluracil (**6**). This compound was identical with a product prepared by direct formylation of **2**, in analogy to Pfleiderer and Strauss' formylation of 6-amino-1,3-dimethyluracil.[3] Treatment of **6** with hydrogen in the presence of palladium–charcoal resulted in rapid loss of the benzyl group, followed by very slow deoxygenation, and 6-amino-5-formyl-1-hydroxy-3-methyluracil was isolated.

The production of **6** does not appear to be the result of a direct displacement of the 5-nitroso group by a formyl group, since heating in formic acid and acetic anhydride results in a colorless derivative which, in water, gives a spectrum identical with that of the nitroso derivative **3**, and corresponds analytically to the diacetyl derivative **4** of the **3a** tautomer. Heating in formic acid alone also resulted in a colorless derivative which reverted to the nitroso derivative in water. Pfleiderer and Kempter[4] have recently obtained similar colorless disubstituted isonitroso derivatives. Compound **3** does exist predominantly in the form **3a** in DMSO, as indicated by nmr studies.

The production of **6** may be explained if it is assumed that the reduction of **3a** with Raney nickel in formic acid occurs 1:2 and 3:4, rather than 1:4, which would lead to **5**, rather than to **9**, and that elimination of hydroxylamine from **5** then leads to **2** (broken arrows in Scheme I). This would then be formylated to give **6**.

A second product isolated from the reaction in which **6** is formed proved to be the desired 3-hydroxy-1-methylxanthine (**7**), but no trace of the 3-benzyloxy derivative was observed. It was found possible to prepare the proper intermediate **9**, which was also a by-product in the above reaction, by reduction of **3** with zinc and dilute hydrochloric acid in the presence of formic acid. All attempts at ring closure to the purine failed. It was, however, possible to prepare the 3-hydroxy-1-methylxanthine (**7**) from **9** after removal of the benzyl group with hydrogen and a palladium–charcoal catalyst to yield **8**, followed by refluxing that N-hydroxypyrimidine with acetic anhydride and formic acid.

It is to be noted that ring closure of **9** is prevented by the presence of the benzyl group on the oxygen. This parallels the observation of Sele[5] that it was not possible to close the ring of the corresponding 1-benzyloxy-3H-pyrimidine to 3-benzyloxyxanthine, but that it was possible to close the N-hydroxy derivative as we have previously shown.[6] However, with a methyl in the place of the benzyloxy group, the closure of the imidazole ring does occur with ease, as in the synthesis of theophylline.[7]

Experimental Section

Melting points are corrected. Ultraviolet spectra were determined with Beckman DK-2 and DU instruments, and nmr

(1) This investigation was supported in part by funds from the Atomic Energy Commission (Contract No. AT[30-1],910) and from the National Cancer Institute (Grant No. CA 08748). A. McN. thanks the Wellcome Foundation for a travel grant.

(2) W. Klötzer, *Monatsh. Chem.*, **95**, 265 (1964).

(3) W. Pfleiderer and G. Strauss, *Ann.*, **612**, 173 (1958).

(4) W. Pfleiderer and F. E. Kempter, *Angew. Chem.*, **79**, 234 (1967).

(5) A. Sele, unpublished.

(6) R. M. Cresswell, H. K. Maurer, T. Strauss, and G. B. Brown, *J. Org. Chem.*, **30**, 408 (1965).

(7) B. Gepner and L. Kreps, *J. Gen. Chem. USSR*, **16**, 179 (1946); Y. Ozaki, *Yakugaku Zasshi*, **80**, 1798 (1960).