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]

ALAN D. MCNAUGHT AND GEORGE BOSWORTH BROWN

Division of Biological Chemistry, Sloan-Kettering Institute for Cancer Research, Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University Medical College, New York, New York 10021

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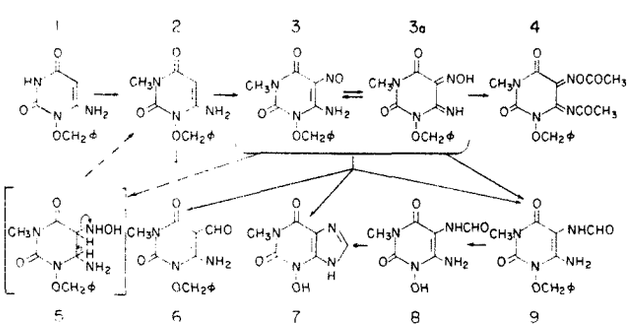
An apparent displacement of a 5-nitroso group by a formyl group was encountered during studies of the synthesis of 1-methylxanthine 3-N-oxide (3-hydroxy-1-methylxanthine) (**7**). The 6-amino-1-benzyloxyuracil (**1**) was synthesized according to Klötzer[2] and then methylated with dimethyl sulfate to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

spectra with a Varian A-60 with tetramethylsilane as the internal standard.

6-Amino-1-benzyloxy-3-methyluracil (2).—To a solution of 2.1 g of 6-amino-1-benzyloxyuracil[2] in 20 ml of 0.5 *N* NaOH was added 1 ml of dimethyl sulfate. After 2.5 hr of stirring at room temperature, the precipitate was collected and recrystallized from ethanol–water to yield 1.0 g of **2**, mp 223°. At pH 6.4 and at 11.0 it shows λ_{max} 267 mμ and λ_{min} 237 mμ.

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.11; H, 5.44; N, 16.88.

6-Amino-1-benzyloxy-3-methyl-5-nitrosouracil (3).—A suspension of 466 mg of **2** in 30 ml of a 1:1 ethanol–water mixture containing 0.84 ml of acetic acid was cooled. To the ice-cold suspension was added an ice-cold solution of 300 mg of sodium nitrite in 3 ml of water. The mixture was stirred for 2 hr at 0° and then filtered, and the violet solid obtained was recrystallized from ethanol to yield 300 mg of **3**, mp 189°. In water it shows λ_{max} 217 and 318 mμ; it decomposes rapidly in alkali.

Anal. Calcd for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.11; H, 4.40; N, 20.35.

The nmr spectrum of **3** in DMSO-d_6 showed τ values of 2.5, 5 H (C_6H_5–); 4.8, 2 H (–CH_2–); 6.7, 3 H (CH_3N=); 0.5, 1 H (exchangeable =NH); −2.3, 1 H (exchangeable =N–OH). This indicates that in this solvent it exists largely in the form of **3a**.

A colorless diacetyl derivative **4** of **3a** was obtained by warming **3** in acetic anhydride for 2 min on a steam bath and removing the acetic anhydride by evaporation with continual addition of dry ethanol.

Anal. Calcd for $C_{16}H_{16}N_4O_6$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.81; H, 4.56; N, 15.80.

Heating 15 hr at 100° in an excess of 97% formic acid, evaporation, and careful recrystallization from ethanol and water also yielded a derivative, a crude, pink sample which was obtained in 60% yield, and a colorless sample which was obtained in 20% yield after four recrystallizations. The clay derivatives are sensitive to moisture, and dilute solutions in water give a spectrum identical with that of the parent nitroso compound.

6-Amino-1-benzyloxy-5-formyl-3-methyluracil (6).—To 600 mg of **3** dissolved in the minimum quantity of 97% formic acid, about 50 mg of Raney nickel was added. The mixture was stirred for 15 min at room temperature and the catalyst was then collected. The filtrate was warmed for 10 min on a steam bath, an equal volume of acetic anhydride was added, and the mixture was allowed to reflux for 1 hr. Some nickel salt was collected and the filtrate was evaporated to dryness with repeated ethanol addition to remove all traces of solvents. The solid obtained was dissolved in the minimum quantity of boiling ethanol, the solution was cooled, and the precipitate was filtered and discarded. Concentration of the filtrate yielded 320 mg of **6** recrystallized from ethanol–water, mp 190°, identical with the compound obtained from heating **2** for 40 min on a steam bath in formic acid–acetic anhydride solution.[3]

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.61; H, 4.80; N, 15.15.

The nmr spectrum of **6** in DMSO-d_6 showed τ values: 2.5, 5 H (C_6H_5–); 4.8, 2 H (–CH_2–); 6.8, 3 H (CH_3—N=); 0.2, 1 H (—CH=O); 1.2, 1 H (exchangeable =NH); 0.3, 1 H (exchangeable =NH), consistent with the assigned structure in which the protons of the amino group are expected to be nonequivalent because of tautomerism with, or hydrogen bonding to, the aldehyde function.

Other evidence that the formyl group of **6** is attached to the 5 position rather than to the 6-amino group is provided by comparison of the ultraviolet spectrum with those of a number of compounds synthesized by Pfleiderer.[3] Compounds possessing a 5-formyl group have a spectrum exhibiting two maxima. For instance, 6-amino-5-formyl-1,3-dimethyluracil shows λ_{max} 245 and 285 mμ, whereas those with the 6-formyl-amino group show only one maximum, for instance, 6-formylamino-1,3,5-trimethyluracil shows λ_{max} 274 mμ. In water, compound **6** shows λ_{max} at 247 and 282 mμ and minima at 235 and 260 mμ, and it decomposes in alkali. It is also significant that **6** would neither brominate nor nitrosate.

The foregoing preparation was repeated with 2 g of **3** as far as the removal of the acetic anhydride–formic acid mixture. The solid residue was then extracted with 200 ml of boiling ethanol and the remaining solid was dissolved in hot alcoholic ammonia. Neutralization of this solution with acetic acid produced a white precipitate which was collected and reextracted with cold aqueous ammonia. The residue appeared to be largely **9**, from its ultraviolet spectrum. Evaporation of the ammonia from this solution yielded about 50 mg of a compound identical with **7** from its ultraviolet spectrum. A small quantity of **9** was also obtained by partial evaporation of the original ethanolic extract. The initial fractions were deep red in color but about 100 mg of white solid (230° dec) with the same ultraviolet spectrum as **9** could be obtained.

6-Amino-5-formyl-1-hydroxy-3-methyluracil.—A solution of 272 mg of **6** in 100 ml of ethanol was reduced with hydrogen at 1 atm with a 10% palladium-on-charcoal catalyst. There was an uptake of 1 mole after 15 min. After filtration, the solution was evaporated, and 100 mg of the N-hydroxypyrimidine analogous to **6** crystallized, mp 250° dec. Upon addition of ferric chloride it gives a deep red.

Anal. Calcd for $C_6H_7N_3O_4$: C, 38.93; H, 3.81; N, 22.70. Found: C, 39.11; H, 3.34; N, 22.74.

Longer reduction times produced no further detectable uptake of hydrogen, but the nmr spectrum of the product showed a splitting of the $CH_3N <$ peak probably indicating slow deoxygenation to produce a second compound.

6-Amino-1-*N*-benzyloxy-5-formylamino-3-methyluracil 9.—This was more conveniently synthesized by reduction of **3** with zinc dust. A solution of 1 g of **3** in 10 ml of 1 *N* HCl and 30 ml of 97% formic acid was stirred with 100 mg of zinc dust for 30 min, at which time the color had disappeared. The zinc was collected; solvents were removed by evaporation. The residue was recrystallized from ethanol–water to yield 0.8 g of **9** (mp 230° dec). At pH 6.0 it shows λ_{max} 266 mμ (ε 14,000) and λ_{min} 236 mμ (ε 4000). At pH 11 it shows λ_{max} 268 mμ (ε 8400) and λ_{min} 237 mμ (ε 2800), probably reflecting hydrolysis of the formyl group.

Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.69; H, 4.85; N, 19.19.

Ring closure of **9** was attempted with refluxing acetic anhydride, with 1 *N* NaOH at 100°, with formamide at 180°, with refluxing acetic anhydride–formic acid, with dry heat at 210°, and with acetic anhydride at room temperature (3 weeks). No ring closure resulted, but there was often loss of the benzyl group.

1-Methylxanthine 3-*N*-Oxide (7).—A solution of 300 mg of **9** in the minimum quantity of formic acid was reduced with hydrogen and a 10% palladium-on-charcoal catalyst at 1 atm, with consumption of 1 mole of H_2. Upon evaporation of the formic acid, after removal of the catalyst, a white residue was obtained which gave a purple color with ferric chloride and showed a shift of the λ_{max} from the λ_{max} of **9** (267 mμ) to 283 mμ in alkali, indicating the presence of **8**. This residue was mixed with 10 ml each of acetic anhydride and formic acid, and the mixture was refluxed for 30 min. The solvents were evaporated with continual addition of ethanol, and the residue was dissolved in dilute aqueous ammonia. Neutralization of the solution with acetic acid precipitated 140 mg of **7** which was reprecipitated in the same way to purify it. It can be recrystallized from water but its solubility is less than 10^{-3} m at 50°. It gives a pale tan ferric chloride test and has a melting point over 400°. It shows a pK of 5.63 ± 0.04 at 20°, spectrophotometrically in 0.001 *M* buffers,[8] and at pH 2 shows λ_{max} 231, 283 mμ (ε 7800 and 11,400) and λ_{min} 255 mμ (ε 3600); at pH 8 and 10 λ_{max} 207, 237, 291 mμ (ε 22,000, 9200, and 11,900), λ_{min} 261 (3200). It is unstable at pH 11.

Anal. Calcd for $C_6H_6N_4O_3 \cdot 0.5H_2O$: C, 37.70; H, 3.69; N, 29.31. Found: C, 37.87; H, 3.90; N, 29.32.

Registry No.—**2**, 14002-12-1; **3**, 14002-13-2; **4**, 14002-14-3; **6**, 14002-15-4; **7**, 14002-16-5; **9**, 14002-17-6; 6-amino-5-formyl-1-hydroxy-3-methyluracil, 14002-18-7.

Acknowledgment.—We wish to acknowledge the capable assistance of Marvin J. Olsen with the nmr data and of Thomas G. Winn with spectra and pK determinations.

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