$J$ = 6.0 Hz, $C_3$ H), 5.25 (d, 1 H, $J$ = 15.0 Hz, $CH_B$ of benzyl), 6.81 (s, 1 H, $C_7$ H), 7.31 (s, 5 H, aromatic).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.93. Found: C, 72.28; H, 6.43; N, 9.92.

**2-Benzyl-6-hydroxyl-3,5-dimethyl-4-oxo-4,5-dihydro-2*H*-pyrrolo[3,4-*c*]pyridine (23).** To a stirred suspension of 1 g (0.026 mol) of LAH in 40 mL of dry THF under a nitrogen atmosphere was added 2 g (0.007 mol) of **11f** gradually over the period of 20 min. The mixture was refluxed for 12 h. After being allowed to stand overnight, the mixture was cautiously treated with 5 mL of $H_2O$, 5 mL of 15% NaOH, and 10–20 mL of $H_2O$. The insoluble material was removed by filtration, and the filtrate was concentrated in vacuo. This was chromatographed on a silica gel column with chloroform as an eluent. Fractions with similar $R_f$ values were combined and evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol to yield 0.3 g (16%) of **23** as yellow needles: mp 148–152 °C; IR (KBr) 1700, 1660, 1590, 1538 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.52 (s, 3 H, 3-$CH_3$), 3.25 (s, 3 H, 5-$CH_3$), 3.78 (s, 2 H, $C_7$ H's), 5.03 (s, 2 H, $CH_2$ of benzyl), 6.4 (s, 1 H, $C_1$ H), 6.9–7.5 (m, 5 H, aromatic).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.68; H, 6.02; N, 10.46.

**Registry No. 1a**, 541-59-3; **1b**, 930-88-1; **1c**, 1631-26-1; **2a**, 7318-00-5; **2c**, 870-85-9; **2d**, 1020-67-3; **3c**, 78753-77-2; **3d**, 66668-10-8; **3e**, 78753-79-4; **3f**, 78753-78-3; **3g**, 78753-81-8; **3j**, 78753-76-1; **4c**, 80049-15-6; **4d**, 80049-16-7; **4h**, 80049-17-8; **4i**, 80049-18-9; **8a**, 80049-19-0; **8b**, 80049-20-3; **9**, 80049-21-4; **10e**, 80049-22-5; **11c**, 80049-23-6; **11d**, 80049-24-7; **11f**, 80049-25-8; **11g**, 80049-26-9; **11h**, 80049-27-0; **11i**, 80049-28-1; **11j**, 80049-29-2; **12b**, 80049-30-5; **13**, 1072-87-3; **15**, 80049-31-6; **16**, 80049-32-7; **18**, 21396-42-9; **19a**, 66668-08-4; **19b**, 80049-33-8; **21a**, 80049-34-9; **21b**, 80049-35-0; **23**, 80049-36-1; benzylamine, 100-46-9; ethyl acetoacetate,, 141-97-9; urea, 57-13-6; citraconic anhydride, 616-02-4; 2-methyl-*N*-carbamylmaleamic acid, 80049-37-2; 3-methyl-*N*-carbamylmaleamic acid, 80049-38-3; *N*-carbamylcitraconimide, 7564-40-1; 2,4-pentanedione, 123-54-6.

# New Hydantoin Synthesis via a Reactive 5-Oxo-6-methylenepyrimidine Intermediate[1]

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Treatment of the 1-substituted 5-acetoxy-6-(acetoxymethyl)uracils **4a** and **4b** with very dilute sodium hydroxide solution and then with acid affords the 5-methylhydantoins **7a** and **7b**, respectively, in 75% yield. UV, NMR, and chemical evidence shows that this new type of hydantoin synthesis proceeds via the exocyclic methylene intermediates **5a** and **5b**. The N-unsubstituted diacetate **4c** similarly affords 5-methylhydantoin (**7c**, 58% yield), although the intermediate in this case exists as the methyl tautomer **13**. A mechanism that explains the formation of **5a,b** and **13** in terms of the generation and ring contractions of the pyrimidine exocyclic enones **3** is discussed. The 1,3-dimethyl intermediate **5a** is stable at pH 13–14, but the 1-methyl analogue **5b** rearranges under these conditions to give 2,3-dihydro-6-(hydroxymethyl)-2-oxo-1*H*-imidazole-4-carboxylic acid (**16**). This reaction also affords small amounts of the 5,5′-methylenebis[imidazole] compound **18**.

5-Hydroxyuracil and its N-substituted derivatives (**1**, Scheme I) are phenolic substances that undergo a variety of electrophilic substitution reactions at the C-6 position.[2] For example, we showed some years ago[2f] that the sodium salt of 1-methyl-5-hydroxyuracil (**1b**) reacts with formaldehyde to give the 6-hydroxymethyl derivative **2b** in good yield, and we have since extended this observation to include the 1,3-dimethyl- and 1,3-unsubstituted compounds **2a** and **2c**. During our studies of the chemistry of the diols **2** and the corresponding diacetates **4**, we have found that some of their reactions involve the intermediacy of the pyrimidine enone **3**, a highly reactive species that is of interest in view of the alkylating properties and possible antitumor activities expected for such structures.[3] As far as we are aware, reactions involving **3** have not been described before, although an unsuccessful attempt to generate **3c** via a retro-Diels–Alder reaction of a pyrimidine-[4,5-*e*]-1,3-oxazine-6,8-dione was recorded recently.[4] In the present paper, we describe the conversion of the diacetates **4** into a variety of imidazole derivatives by a series of in situ reactions that involve the generation and ring contraction of enones **3a–c**.[5]

As illustrated in Figure 1, treatment of dilute aqueous solutions of **4a** with sodium hydroxide results in the rapid loss of the original absorption at 277 nm and the appearance of a new peak at 242 nm. The process is complete within 15 min, and, judging from the sharp isosbestic points at 223 and 255 nm, it proceeds in an essentially quantitative manner. Several lines of evidence establish that the 242-nm-absorbing intermediate in Figure 1 is the ring-contracted, exocyclic olefin **5a**. The UV spectrum is in accord with this structure,[6] as is the $^1H$ NMR spectrum

(1) This investigation was supported by funds from the National Cancer Institute (Grants CA-24821 and 08748) and from the American Cancer Society (Grant CH-169).

(2) For example, 5-hydroxyuracils undergo the following reactions. (a) Nitrosation: D. Davidson and M. T. Bogert, *Proc. Natl. Acad. Sci. U.S.A.*, 18, 490 (1932). (b) Diazocoupling; M. T. Bogert and D. Davidson, *Ibid.*, 18, 215 (1932). (c) Mannich reactions: D. E. O'Brien, R. H. Springer, and C. C. Cheng, *J. Heterocycl. Chem.*, 3, 115 (1966); D. E. O'Brien, L. T. Weinstock, R. H. Springer, and C. C. Cheng, *ibid.*, 4, 49 (1967). (d) Deuteration: B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, 34, 2636 (1969). (e) Intramolecular hydroxylation: J. Rabi and J. J. Fox, *ibid.*, 37, 3898 (1972); B. A. Otter, E. A. Falco, and J. J. Fox, *ibid.*, 41, 3133 (1976). (f) Hydroxymethylation: B. A. Otter, E. A. Falco, and J. J. Fox, *ibid.*, 36, 1251 (1971).

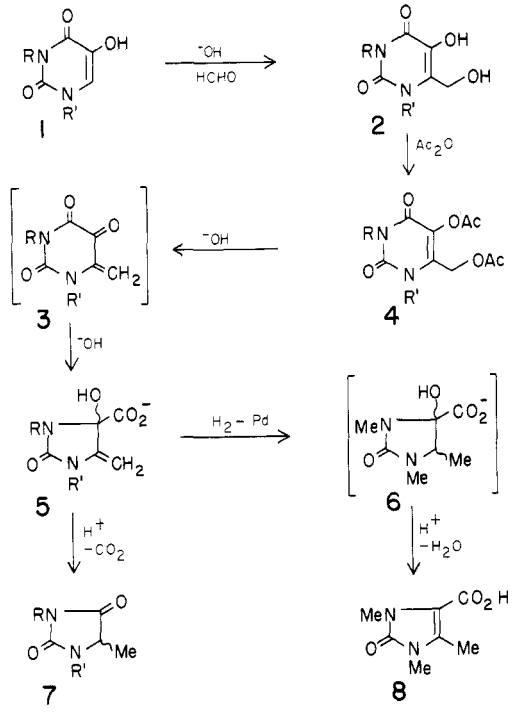
(3) (a) A. J. Lin, B. J. Lillis, and A. C. Sartorelli, *J. Med. Chem.*, 18, 917 (1975), and references therein; (b) H. W. Moore, *Science* 197, 527 (1977).

(4) J. L. Asherson, O. Bilgic, and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 522 (1980).

(5) The enones **3** resemble quinone methides, and, consequently, they share some common properties. For example, enones **3** form spiro dimers in concentrated solutions. This aspect of their chemistry will be described in a later paper.

0022-3263/82/1947-0508$01.25/0 

Scheme I



a series R = R' = Me : b series R=H, R'=Me : c series R=R'=H

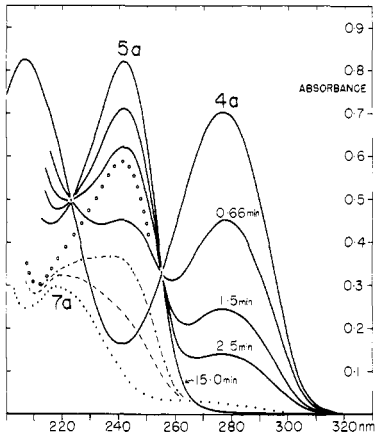
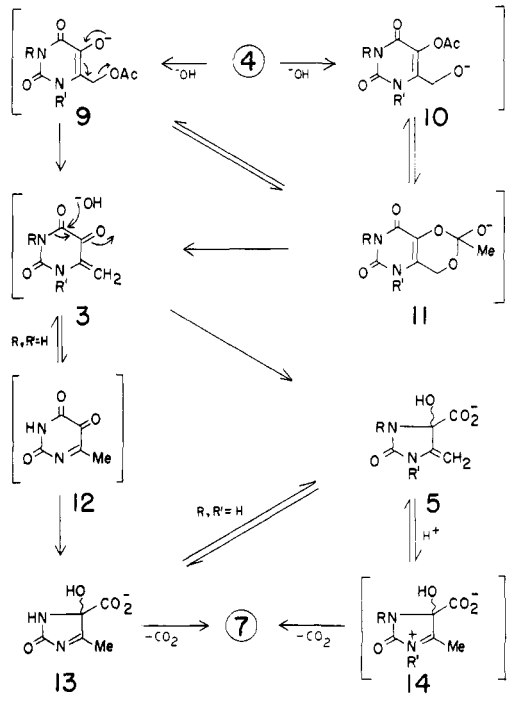



**Figure 1.** UV spectral changes accompanying the reaction of **4a** with sodium hydroxide. The curves were generated by adding 10 μL of 1 N NaOH to an $8 \times 10^{-5}$ M solution of **4a** and were recorded at the indicated time intervals without using a blank. The broken lines illustrate the conversion of **5a** into **7a** that follows the addition of 12 μL of 1 N HCl to the 15-min reaction mixture. These spectra were recorded at 20 s (open circles), 1 min (···), 2 min (- - -), and 5 min (—·—) after the addition of acid.

($D_2O$) of the lyophilized reaction mixture, which shows the pair of doublets (δ 4.42, 4.34: $J_{gem}$ = 2.75 Hz) expected for an enamine-type methylene group.[7a,b] Seven resonances are revealed in the $^{13}C$ NMR spectrum, and only three of these are multiplets (NMe, q, δ 26.2; NMe, q, δ 27.7; $=CH_2$, t, δ 84.0) under proton-coupled conditions. The carboxyl carbon resonates at δ 173.5, while the ring carbons C-2, C-4, and C-5 appear at δ 159.3, 88.6, and 149.1, respectively.[7c] Although the NMR data are consistent with structure **5a**,

Scheme II



an alternative interpretation suggests the possibility that the 242-nm product could be the *gem*-5,5-diol formed by hydration of **3a**. However, the following chemical evidence demonstrates that **5a** is indeed an imidazole rather than a pyrimidine. Hydrogenation of **5a** in the presence of palladium affords a non-UV-absorbing intermediate, presumably **6**, which dehydrates to give the known[8] 2-oxoimidazole-4-carboxylic acid **8** when acidified. Had **5a** been the hydrate of **3a**, the product of these reactions would have been 1,3,6-trimethyl-5-hydroxyuracil, which would be easily distinguished from **8** by its UV spectrum.

Further evidence for the imidazole structure of **5a** is seen in its reactions under weakly acidic conditions (Figure 1), where the 242-nm absorption rapidly decays to give a low-intensity peak at 220 nm. This product was isolated from preparative-scale runs (78% yield from **4a**) and identified as 1,3,5-trimethylhydantoin (**7a**). Surprisingly, this simple hydantoin has not been reported previously, but its structure was clear from the $^1H$ and $^{13}C$ NMR spectra and by comparison with material obtained by N-methylation of the known[9] 1,5-dimethylhydantoin (**7b**).

An overall mechanistic picture of the conversion of the pyrimidine diacetate **4a** into the hydantoin **7a** is given in Scheme II. The parent diol **2a** is not an intermediate in these reactions, as indicated by the absence of new absorption in the 300–320-nm region of Figure 1 and by the observed stability of **2a** (anion $\lambda_{max}$ 318 nm) under the reaction conditions. The initial step must therefore involve partial hydrolysis of **4a** to give either of the monoacetates **9a** or **10a**. Elimination of the remaining acetoxy group, either directly from **9a** or from **10a** via the cyclic ion **11a**, then generates the enone **3a**. A base-catalyzed ring contraction of **3a**, involving N-3,C-4 migration similar to that observed for 6-unsubstituted 5-hydroxyuracils[2d] and alloxan[10] (2,4,5,6-pyrimidinetetrone), leads to **5a**. This

(6) See A. G. Cook, Ed., "Enamines: Synthesis, Structure and Reactions", Marcel Dekker, New York and London, 1969.

(7) (a) W. H. Paudler and J. Lee, *J. Org. Chem.*, **36**, 3921 (1971). (b) L. E. Overman, S. Tsuboi, and S. Angle, *ibid.*, **44**, 2323 (1979). (c) The chemical shifts of the olefinic carbons are within the ranges expected for enanines; see M. G. Ahmed and P. J. Hickmott, *J. Chem. Soc., Perkin Trans 2*, 838 (1977).

(8) H. Biltz and H. Bülow, *Justus Liebigs Ann. Chem.*, **457**, 103 (1927).

(9) S. Gabriel, *Justus Liebigs Ann. Chem.*, **348**, 75 (1906).

(10) For reviews of the alloxan-to-alloxanic acid rearrangement, see: (a) G. M. Badger and J. W. Clarke-Lewis, "Molecular Rearrangements", P. de Mayo, Ed., Wiley-Interscience, New York 1963, Part 1, Chapter 10; (b) H. C. van der Plas, "Ring Transformations of Heterocycles", Academic Press, London and New York, 1973.

multistep process requires 3 equiv of sodium hydroxide, and this amount was found by experiment to be necessary for converting **4a** into **5a**.

The formation and ring contraction of **3a** are clearly very fast reactions. No spectral evidence for the intermediates (**9a**, **10a**, **3a**) is apparent under the conditions of Figure 1, although a transient yellow coloration (possibly **3a**) is seen during the addition of sodium hydroxide to more concentrated solutions of **4a**. It is also noteworthy that **3a** undergoes exclusive ring contraction, at least in dilute solution, without any observable nucleophilic attack of hydroxide ion on the methylene group,[11] which would afford the diol **2a**.

The decarboxylation of **5a** in acid to give hydantoin **7a** probably proceeds via the iminium ion **14a**. In agreement with this formulation, treatment of **5a** with acetic acid-$d_4$ affords partially deuterated **7a** (5 D, $CD_2H$ and/or $CH_2D$), together with smaller amounts (~25%) of fully deuterated (5 D, $CD_3$) material. Preformed **7a** does not itself incorporate deuterium under these conditions.

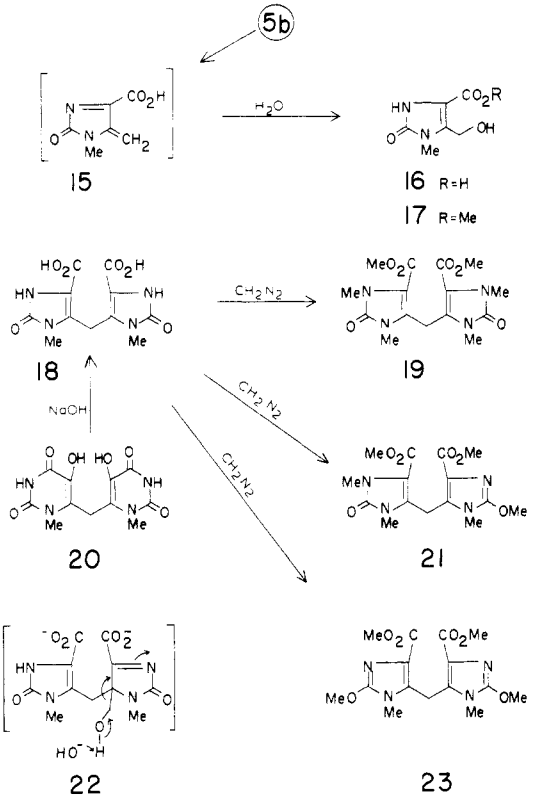
The foregoing transformations (Schemes I and II) are not restricted to the 1,3-disubstituted case but are also successful for the diacetates **4b** and **4c**. For example, the 1-methyl diacetate **4b** affords 1,5-dimethylhydantoin (**7b**, 75%) via an intermediate (**5b**) that absorbs at 235 nm. Similarly, sequential base–acid treatment of the N-unsubstituted diacetate **4c** leads to 5-methylhydantoin in 58% yield.[12] In this case, however, the UV absorption of the intermediate appears as a small shoulder at 225 nm rather than as a discrete peak as observed for **5a** and **5b**. This UV difference is probably related to the fact that the intermediate **5c** can exist as its methyl tautomer **13**. In fact, $D_2O$ solutions containing the intermediate generated from **4c** do not show any $^1H$ resonances at all, which is consistent with rapid deuterium incorporation via a **5c** ⇌ **13** equilibrium. In addition, the $^{13}C$ NMR spectrum, although less clear-cut than the 1,3-disubstituted case (**5a**), shows a methyl signal ($\delta$ 23.1) consistent with the presence of **13**. Intermediate **13** could also be formed directly from the methyl tautomer (**12**) of **3c**.

The two-step conversion of compounds **4** into **7** represents a new type of pyrimidine-to-hydantoin transformation.[13] The method is attractive in its simplicity since it requires only the manipulation of pH, and it may prove to be useful for preparing 5-methylhydantoins containing more complicated N-1 substituents. Such compounds cannot normally be obtained by direct N-alkylation of the parent hydantoin.[14] It may also be possible to expand the scope of the reaction by using 5-hydroxyuracils substituted at C-6 with $\alpha$-acetoxyalkyl groups. This possibility, together with studies of pyrimidines containing other C-2 substituents, is currently being examined.

Although the decarboxylative rearrangements **5** → **7** are the major reactions occurring under acidic conditions, a second type of reaction does compete to a small extent. This is reflected in the UV changes shown in Figure 1, where acidification of **5a** causes a small increase in absorption in the 270–275-nm region that is not accounted for by the formation of **7a** (220 nm). The same phenomenon occurs more extensively on acidification of **5b**, and in this case we have identified the minor product as the 5-(hydroxymethyl)imidazole **16** (Scheme III, 9% yield) and further characterized it as the methyl ester **17**. By analogy, the minor product formed from **5a** is probably the 3-methyl derivative of **16**. The formation of these products may simply involve protonation of the 4-hydroxyl groups followed by $S_N2'$ allylic rearrangement. Alternatively, acid-catalyzed elimination of the 4-hydroxyl groups to give **15** (from **5b**) or the 3-methyl iminium ion analogous to **15** (from **5a**) followed by addition of water to the terminal methylene groups could also afford the observed 5-hydroxymethyl products.

An elimination–addition mechanism involving **15** apparently operates when **5b** is treated with ~0.6 N sodium

Scheme III



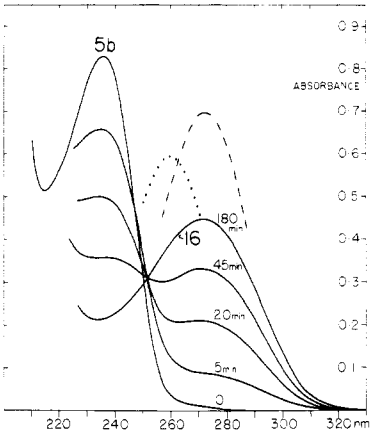




**Figure 2.** UV spectral changes accompanying the formation of **16** from **5b**. Compound **5b** was generated from **4b** as described in Figure 1 for **5a**, and the solution was adjusted to ~0.6 M in sodium hydroxide by the addition of 0.1 mL of 50% NaOH. The broken lines indicate the spectrum of **16** in its monoanion (···) and neutral (- - -) forms and were obtained by adjusting the pH of the 180-min reaction mixture to ~7 and ~1, respectively.

(11) Minor amounts of **2a** are formed when the reaction **4a** → **5a** is performed in more concentrated solutions, but it is not clear if this is formed by hydrolysis of **4a** or via nucleophilic attack of hydroxide ion on **3a**.

(12) Both **4b** and **4c** exist as anions under the reaction conditions of Figure 1 and therefore are converted into their respective intermediates at a slower rate ($t_{1/2} \approx 4$ min) than that observed for the nondissociable **4a**.

(13) The conversion of pyrimidines to hydantoins appears to be uncommon but has been recorded for 5-amino- and 5-bromobarbituric acids. Examples are given in ref 10.

(14) E. Ware, *Chem. Rev.*, **46**, 403 (1950).

hydroxide (Figure 2), a reaction which leads efficiently to the 5-hydroxymethyl compound **16** at room temperature. The 1,3-dimethyl derivative **5a**, which cannot undergo a similar elimination of water, is fairly stable in ~1 N sodium hydroxide solution, as shown by less than a 5% decrease in its UV absorption over a 2-h period.

When the base-catalyzed conversion of **5b** into **16** was conducted in more concentrated solutions, a small amount of a second carboxylic acid product (**18**, 9% yield) was isolated in addition to **16** (70% yield). The structure of **18** was evident from integration of its $^1$H NMR spectrum ($CH_2/CH_3$ ratio of 1:3) and by the type of products obtained by methylation with diazomethane. Three such methylated products were obtained: two of them, **19** (51%) and **23** (2%), are symmetrical compounds, judging from their NMR spectra, but the third compound (**21**, 24%) proved to be the product of mixed O- and N-methylation. The lack of symmetry of **21** gives rise to six separate methyl signals in the $^1$H NMR spectrum, clearly indicative of the 5,5′-methylenebis structure of these compounds.

The structure of **18** was also confirmed by the finding that 6,6′-methylenebis[5-hydroxyuracil][2f] (**20**) undergoes ring contraction in hot sodium hydroxide to give material identical with that obtained from **4b** via **5b**. The relatively severe conditions required for the **20** → **18** ring contraction (14 h at 100 °C, excess 0.1 N NaOH) serve to emphasize the extraordinary ease with which the enones **3a–c** undergo ring contraction to give **5a–c** (very fast at room temperature, 1 equiv of sodium hydroxide).

Apart from the finding that **16** itself is not converted into **18** when treated with 1 N sodium hydroxide, we have no experimental data that bears on the mechanism of formation of **18** from **5b**. One possibility is that **16** condenses with **15** to give an intermediate (**22**) which could loose formaldehyde to generate **18**. In this regard it should be noted that 5-unsubstituted 2-oxoimidazole-4-carboxylic acids are known to undergo electrophilic attack at the C-5 position,[15] but it remains to be shown that 5-substituted compounds such as **16** are also susceptible to reactions of this type.

## Experimental Section

**General Procedures.** Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were measured on Cary Model 15 and Unicam SP-800 spectrometers. Thin-layer chromatography (TLC) was performed on 250-μm silica gel $GF_{254}$ plates (2.8 × 8 cm; Analtech, Inc.), and separated materials were detected with ultraviolet light and/or by spraying with sulfuric acid in ethanol (10% v/v) followed by charring. Preparative separations were effected on 500-μm (20 × 20 cm) plates. Nuclear magnetic resonance spectra were obtained with a JEOL PFT-100 instrument operating at 100 MHz for $^1$H and 25.15 MHz for $^{13}$C spectra. Methyl-$d_6$ sulfoxide was used as the solvent for $^1$H spectra, unless otherwise stated, with tetramethylsilane as an internal standard. $^{13}$C shifts were measured relative to $Me_2SO$-$d_6$ and corrected to the $Me_4Si$ scale after determination of the $Me_2SO$-$d_6$ chemical shift in the particular solvent combination being used. Microanalyses were performed by Spang Microanalytical Laboratory. All evaporations were carried out in vacuo; lyophilizations were carried out on a Virtis automatic freeze–drying apparatus, Model 10-010.

**1,3-Dimethyl-6-(hydroxymethyl)-5-hydroxyuracil (2a).** 1,3-Dimethyl-5-hydroxyuracil[16] (**1a**; 1.56 g, 10 mmol) was hydroxymethylated as described previously[2f] for the preparation of the 1-methyl analogue **2b**. The yield of **2a** was 1.30 g, (70% in two crops): mp 187–188 °C; UV ($H_2O$) $\lambda_{max}$ 287.5 nm, $\lambda_{min}$ 249; UV (pH 10) $\lambda_{max}$ 318, 244 nm; $\lambda_{min}$ 276, 230 nm; NMR δ 8.59 (1 H, s, 5-OH), 5.43 (1 H, t, $CH_2OH$), 4.49 (2 H, d, $CH_2$, $J_{H,OH}$ = 5.5 Hz), 3.39 (3 H, s, $N_3$ $CH_3$), 3.22 (3 H, s, $N_1$ $CH_3$).

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.23; H, 5.30; N, 15.11.

**6-(Hydroxymethyl)-5-hydroxyuracil (2c).** 5-Hydroxyuracil[17] (1.28 g, 10 mmol) was hydroxymethylated as described[2f] for the preparation of **2b** except that a smaller excess of aqueous formaldehyde (1.2 mL, 37% solution, ~15 mmol) was used.[18] Pure **2c** (1.15 g, 73%), which crystallized from the deionized and concentrated (40 mL) reaction mixture at room temperature, shows the following: mp >300 °C (darkens above 210 °C); UV ($H_2O$) $\lambda_{max}$ 280 nm, $\lambda_{min}$ 244.5; UV (pH 10) $\lambda_{max}$ 310 nm, 241, $\lambda_{min}$ 273, 230 nm; NMR δ 11.17 (1 H, br s, $N_3$ H), 10.00 (1 H, br s, $N_1$ H), 8.32 (1 H, s, 5-OH), 5.17 (1 H, t, $CH_2OH$), 4.25 (2 H, d, $CH_2$, $J_{H,OH}$ = 5.5 Hz).

Anal. Calcd for $C_5H_6N_2O_4$: C, 37.98; H, 3.83; N, 17.72. Found: C, 37.92; H, 3.88; N, 17.63.

**5-Acetoxy-6-(acetoxymethyl)-1,3-dimethyluracil (4a), 5-Acetoxy-6-(acetoxymethyl)-1-methyluracil (4b), and 5-Acetoxy-6-(acetoxymethyl)uracil (4c).** Acetic anhydride (5 mL) was added to solutions of the diols **2a–c** (3 mmol) in pyridine (15 mL), and the mixtures were stored at room temperature for 1 h. The solutions were then cooled in ice; methanol was added to hydrolyze the excess anhydride, and the mixtures were evaporated essentially to dryness.

Pure **4a** was obtained via a conventional EtOAc–$H_2O$ workup of the residue. Material was recrystallized from EtOAc–*n*-hexane: 620 mg (76%); mp 114–115 °C; UV ($H_2O$) $\lambda_{max}$ 207 nm (ε 10400), 277 (8900), $\lambda_{min}$ 241 (2000); NMR δ 5.07 (2 H, s, $CH_2$), 3.39 (3 H, s, $N_3$ Me), 3.20 (3 H, s, $N_1$ Me), 2.26 (3 H, s, 5-OAc), 2.07 (3 H, s, $CH_2OAc$).

Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.85; H, 5.30; N, 10.49.

Compound **4b** (483 mg, 63%) crystallized on addition of ethanol to the evaporated reaction mixture: mp 204–205 °C (shrinks at 190 °C); UV ($H_2O$) $\lambda_{max}$ 206 nm (ε 9900), 277 (9250); $\lambda_{min}$ 239 (1500); UV (pH ~11) $\lambda_{max}$ 275 nm (ε ~6600),[19] $\lambda_{min}$ 250 (~4100);[19] NMR δ 11.87 (1 H, br s, $N_3$ H), 5.03 (2 H, s, $CH_2$), 3.31 (3 H, s, $N_1$ $CH_3$), 2.24 (3 H, s, 5-OAc), 2.07 (3 H, s, $CH_2OAc$).

Anal. Calcd for $C_{10}H_{12}N_2O_6$: C, 46.88; H, 4.72; N, 10.93. Found: C, 46.97; H, 4.79; N, 10.87.

Compound **4c** (600 mg, 83%) crystallized on addition of water to the evaporated reaction mixture: mp 255–258 °C dec (shrinks at 240 °C); UV ($H_2O$) $\lambda_{max}$ 205 nm (ε 10500), 268 (8625), $\lambda_{min}$ 234 (2000); UV (pH ~11) $\lambda_{max}$ 293 nm (ε ~8700),[19] $\lambda_{min}$ 248 (~1500);[19] NMR δ 11.53 (1 H, br s, $N_3$ H), 11.13 (1 H, br s, $N_1$ H), 4.77 (2 H, s, $CH_2$), 2.22 (3 H, s, 5-OAc), 2.04 (3 H, s, $CH_2OAc$).

Anal. Calcd for $C_9H_{10}N_2O_6$: C, 44.63; H, 4.16; N, 11.57. Found: C, 44.72; H, 4.22; N, 11.62.

**DL-5-Methylhydantoin (7c)** was prepared essentially as outlined by Finkbeiner.[20] Pure material obtained by vacuum sublimation showed the following properties: $R_f$ 0.35 ($CHCl_3$–MeOH, 9:1 v/v);[21] UV ($H_2O$) $\lambda_{max}$ 205 nm (sh, ε ~3500); UV (0.1 N NaOH) $\lambda_{max}$ 222 nm (ε 6200); $^1$H NMR δ 10.57 (1 H, br s, $N_3$ H), 7.98 (1 H, br s, $N_1$ H), 4.03 (1 H, 8 lines, H-5, $J_{1,5}$ = 1.2 Hz, $J_{5,Me}$ = 7.0 Hz), 1.22 (3 H, d, Me); $^{13}$C NMR ($H_2O$–$Me_2SO$-$d_6$, 2:1 v/v) δ 180.6 (C-4), 159.9 (C-2), 55.7 (C-5), 17.7 (Me).

**DL-1,5-Dimethylhydantoin (7b)** was prepared from *N*-methyl-DL-alanine[22] according to the method of Gabriel.[9] Material was recrystallized from ethyl acetate–*n*-hexane: mp 120–121 °C

(15) H. Tanaka and T. Ueda, *J. Heterocycl. Chem.*, **16**, 411 (1979).
(16) Compound **1a** was prepared according to the method described for the corresponding 1-methyl-3-benzyl compound.[2d]
(17) D. Davidson and O. Baudisch, *Chem. Ber.*, **58**, 1685 (1925).
(18) If a larger amount of aqueous formaldehyde is used, for example ~25 mmol (2 mL of a 37% aqueous solution), the crystalline material obtained contains roughly equal amounts of **2c** and a second product which appears to be (NMR) either the 1,6- or 3,6-bis(hydroxymethyl) compound.
(19) Approximate values because of rapid decrease in UV absorption at this pH.
(20) H. Finkbeiner, *J. Org. Chem.*, **30**, 3414 (1965).
(21) The 5-methylhydantoins (**7**) give distinctive colors when the $H_2SO_4$/EtOH-sprayed TLC plate is heated briefly. **7a** gives a yellow spot, **7b** a reddish brown spot, and **7c** a purple spot; all of them change to dark brown on prolonged heating.
(22) P. J. Fodor, V. E. Price, and J. P. Greenstein, *J. Biol. Chem.*, **180**, 193 (1949).

(lit.[9] mp 120–121 °C); $R_f$ 0.52 ($CHCl_3$–MeOH, 9:1 v/v);[21] UV ($H_2O$) $\lambda_{max}$ 217 nm (ε 2900); UV (0.1 N NaOH) $\lambda_{max}$ 233 nm (ε 4500); NMR δ 10.72 (1 H, br s, $N_3$ H), 3.97 (1 H, q, H-5), 2.77 (3 H, s, $N_1$ Me), 1.26 (3 H, d, Me, $J_{5,Me}$ = 7.0 Hz).

DL-**1,3,5-Trimethylhydantoin (7a).** A mixture of **7b** (2.56 g, 20 mmol), methyl iodide (1.5 mL, 24 mmol), and sodium hydroxide (2 mL of a 10 N solution) in methanol (40 mL) was heated under reflux for 4 h. The cooled reaction mixture was acidified (HOAc) and evaporated to dryness. The residue was partitioned between chloroform and water, and the chloroform layer was dried ($Na_2SO_4$) and evaporated to afford **7a** as a slightly discolored, mobile syrup in essentially quantitative yield. Colorless material was obtained by distillation: bp 80 °C (0.8 mm); $R_f$ 0.83 ($CHCl_3$–MeOH, 9:1 v/v);[21] UV ($H_2O$) $\lambda_{max}$ 220 nm (ε 3150), $\lambda_{min}$ 205 (1860); $^1H$ NMR δ 4.01 (1 H, q, H-5), 2.84 and 2.83 (6 H, 2 resolved s, *N*-methyls), 1.29 (3 H, d, Me, $J_{5,Me}$ = 7.0 Hz); $^{13}C$ NMR ($Me_2SO$-$d_6$) δ 178.6 (C-4), 155.9 (C-2), 56.5 (C-5) 27.1 ($N_3$ Me), 24.3 ($N_1$ Me), 14.4 ($C_5$ $CH_3$).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.55; H, 7.12; N, 19.83.

**Reactions Involving Base-Catalyzed Rearrangement of 4a. (i) Sodium 1,3-Dimethyl-4-hydroxy-5-methylene-2-oxoimidazolidine-4-carboxylate (5a).** Sodium hydroxide (1 N, 1 mL, 3 equiv) was added dropwise to a solution of **4a** (90.1 mg, 0.33 mmol) in water (50 mL) at such a rate (~1 h) that the pH was maintained between 10 and 10.5. The UV spectrum of samples (0.15 mL diluted to 5 mL) taken at suitable time intervals showed that the overall process closely approximated the curves shown in Figure 1. The reaction mixture was lyophilized, and the amorphous residue was used to obtain the following data: $^1H$ NMR ($D_2O$) δ 4.42 and 4.34 (2 H, 2 d, =$CH_2$, $J_{gem}$ = 2.75 Hz), 2.94 (3 H, s, $N_1$ Me), 2.74 (3 H, s, $N_3$ Me), 1.90 (s, sodium acetate). In addition, the spectrum contained minor unidentified resonances centered at δ ~3.3. Variable amounts of 1,3,5-trimethylhydantoin (up to 25%) were present in some preparations of **5a**, as indicated by a quartet at δ 4.15 (H-5) and a doublet at δ 1.41 (Me, $J_{5,Me}$ = 7.0 Hz): $^{13}C$ NMR ($H_2O$–$Me_2SO$-$d_6$, 2:1 v/v) δ 181.0 (NaOCOMe), 173.5 ($C_4$ $CO_2Na$), 159.3 (C-2), 149.1 (C-5), 88.6 (C-4), 84.0 (=$CH_2$, t, $J_{C,H}$ = 162 Hz), 27.7 (NMe, q, $J_{C,H}$ = 137 Hz), 26.2 (NMe, q, $J_{C,H}$ = 140 Hz), 25.1 (NaOCO**Me**, q, $J_{C,H}$ = 128 Hz).

**(ii) Deuterated** DL-**1,3,5-Trimethylhydantoin.** A portion of the freeze–dried residue containing **5a** (and ~20% of 1,3,5-trimethylhydantoin) was dissolved in $D_2O$ (5 mL), and the pH was adjusted to ~4 with acetic acid-$d_4$. The solution was evaporated to dryness after 1 h, and the residue was partitioned between water and chloroform. The chloroform layer was dried ($Na_2SO_4$) and concentrated, and the 1,3,5-trimethylhydantoin was isolated by preparative TLC (MeOH–$CHCl_3$, 1:9, v/v). Careful integration of the $^1H$ NMR spectrum ($CDCl_3$) showed that the product was composed of 20% nondeuterated **7a** (present throughout), 20% of fully deuterated **7a** (5 D, $CD_3$), and 60% of partially deuterated **7a** (5 D, $CD_2H$, and/or 5 D, $CDH_2$).[23] These figures indicated that *all* of the **5a** present in the freeze–dried residue is converted to either partially deuterated (75%) or fully deuterated (25%) **7a**.

**(iii) 2,3-Dihydro-1,3,5-trimethyl-2-oxo-1*H*-imidazole-4-carboxylic Acid (15).** 5-Acetoxy-6-(acetoxymethyl)-1,3-dimethyluracil (**4a**, 90.1 mg) was converted into **5a** as described above. When the addition of sodium hydroxide was complete, 10% palladium on carbon catalyst (50 mg) was added, and the mixture was hydrogenated at atmospheric pressure for 1 h, at which time hydrogen uptake had ceased. The catalyst was removed, and the filtrate (pH ~9, containing **6** with no specific UV absorption) was acidified (pH 3.5) with acetic acid. The appearance of the product UV was complete at 2.5 h at room temperature. The solution was deionized with Dowex 50 ($H^+$), and the column effluent was lyophilized to afford a white, crystalline residue. Recrystallization from hot ethanol afforded pure **15**: 38 mg (66%); mp 180–182 °C (lit. mp 179 °C); UV (0.01 N HCl, neutral form) $\lambda_{max}$ 272 nm, $\lambda_{min}$ 231; UV (0.01 N NaOH, anion) $\lambda_{max}$ 258 nm, $\lambda_{min}$ 228; NMR δ 12.65 (1 H, br s, $CO_2H$), 3.30 (3 H, s, $N_3$ Me), 3.14 (3 H, s, $N_1$ Me), 2.35 (3 H, s, 5-Me).

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.37; H, 5.90; N, 16.36.

**(iv)** DL-**1,3,5-Trimethylhydantoin (7a).** The diacetate **4a** (90.1 mg, 0.33 mmol) was dissolved in 50 mL of 0.022 N sodium hydroxide. After 10 min at room temperature, when UV assays showed the formation of **5a** to be complete, the solution was acidified to pH 4 with acetic acid. The solution was stored for 30 min and then evaporated to dryness. The residue was triturated with chloroform, the insoluble salts were removed, and the product was isolated by preparative TLC in $CHCl_3$–MeOH (9:1 v/v). The yield of colorless **4a** was 37 mg (78%): TLC, NMR, and UV data were identical with those of **7a** obtained by methylation of **7b** as described above.

**Reactions Involving Base-Catalyzed Rearrangement of 4b. (i)** DL-**1,5-Dimethylhydantoin (7b).** The diacetate **4b** (84.5 mg, 0.33 mmol) was dissolved with stirring in 50 mL of 0.022 N sodium hydroxide, and the solution was kept at room temperature for 40 min. At this time the UV spectra of diluted aliquots (0.15 mL diluted to 5 mL) showed that the formation of **5b** ($\lambda_{max}$ 235 nm) was complete. The solution was acidified with acetic acid to pH 4 and evaporated to dryness after 10 min. The residue was triturated with ethyl acetate (3 × 10 mL) by using sonication, and the combined extracts were filtered. The product (**7b**; 32 mg, 75%) crystallized spontaneously on removal of the solvent and was indistinguishable (melting point, TLC, UV, NMR) from authentic material prepared as described above.

An aqueous solution of the solid material remaining after trituration with ethyl acetate was deionized with Dowex 50 ($H^+$) and then concentrated to dryness. TLC examination ($CHCl_3$–MeOH, 8:1 v/v) showed the absence of **7b** but revealed small amounts of 6-(hydroxymethyl)-5-hydroxy-1-methyluracil (**2b**) together with nonmigrating material. A preparative separation afforded 1 mg of **2b** (further identified by UV) and 5 mg (9%) of the nonmigrating material, which proved to be identical (UV, NMR) with the carboxylic acid **16** described below.

**(ii) 2,3-Dihydro-5-(hydroxymethyl)-1-methyl-2-oxo-1*H*-imidazole-4-carboxylic Acid (16) and 5,5′-Methylenebis-[2,3-dihydro-1-methyl-2-oxo-1*H*-imidazole-4-carboxylic Acid] (18).** The diacetate **4b** (85.4 mg) was converted into **5b** as described above, and the pH of the reaction mixture was adjusted to ~14 by the addition of 2 mL of 10 N sodium hydroxide solution. The solution was stored for 2.5 h at room temperature and then deionized by passage through an excess of Dowex 50 ($H^+$). The effluent and washings were concentrated to ~10 mL, and the crystalline **18** (6 mg, 9%) was removed: mp 270 °C dec (darkens above 240 °C); UV ($H_2O$, monoanion) $\lambda_{max}$ 263 nm, $\lambda_{min}$ 228; UV (0.01 N HCl, neutral form) $\lambda_{max}$ nm, 275, $\lambda_{min}$ 231; UV (0.01 N NaOH, dianion) $\lambda_{max}$ nm, 278, $\lambda_{min}$ 237; NMR δ 12.94 (1 H, vbr, $CO_2H$), 10.59 (1 H, br s, NH), 4.60 (1 H, s, $CH_2$), 3.00 (3 H, s, $N_1$ Me). Since **18** is only sparingly soluble in water, the analytical sample was obtained by dissolution in dilute sodium hydroxide solution followed by reprecipitation with hydrochloric acid.

Anal. Calcd for $C_{11}H_{12}N_4O_6$: C, 44.60; H, 4.08; H, 18.91. Found: C, 44.48; H, 4.22; N, 18.79.

The filtrate obtained after the removal of **18** was evaporated to dryness, and the residue was crystallized from ethanol to afford pure **16**: 40 mg (70%); mp 240–245 °C dec (darkens above 200 °C); UV (pH 7 buffer, monoanion) $\lambda_{max}$ 259 nm (ε 9160), $\lambda_{min}$ 226 (2870); UV (pH 1, neutral form) $\lambda_{max}$ 272 nm (ε 10670), $\lambda_{min}$ 229 (ε 1000); UV (pH 14, dianion) $\lambda_{max}$ 274 nm (ε 7700), $\lambda_{min}$ 235 (2600); NMR δ 10.48 (1 H, s, $N_3$ H), 4.63 (2 H, s, $CH_2$), 3.17 (3 H, s, $N_1$ Me); $CO_2H$ and $CH_2OH$ were not observed, but see the NMR spectrum of methyl ester **17**.

Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 42.01; H, 4.76; N, 16.07.

DL-**5-Methylhydantoin 7c via Rearrangement of 4c.** The diacetate **4c** (80.7 mg, 0.33 mmol) was dissolved in 100 mL of 0.015 M sodium hydroxide solution, and the mixture was stored at room temperature for 2 h. During this time, the UV spectra of diluted aliquots showed the loss of absorption at 294 nm (**4c** anion) and the formation of a shoulder at ~225 nm (tentatively **13**). The reaction mixture was acidified to pH 4 with acetic acid, and the solution was concentrated to dryness. The residue was triturated

(23) The NMR signal from the partially deuterated methyl groups appears as a poorly resolved multiplet within the methyl doublet that arises from nondeuterated **7a**. Since the observed resolution was not improved by using more data points and decreasing the spectral width (digital resolution 0.09 Hz), it is not possible to assign either the $CD_2H$ or $CH_2D$ structure definitively. Both varieties are probably present.

with methanol, and 7c was isolated from the filtrate by preparative TLC ($CHCl_3$–MeOH, 5:1 v/v). The zone immediately above the origin and extending to $R_f$ ~0.45 was removed (the low-intensity absorption of 4c precludes detection by UV illumination) and extracted with methanol. Removal of the solvent afforded crystalline 4c (22 mg, 58%) with TLC, melting point, UV, and NMR properties identical with those of authentic 4c.

The $^{13}C$ NMR spectrum ($H_2O$–$Me_2SO$-$d_6$, 1:2 v/v) of the lyophilized reaction mixture containing the 225-nm-absorbing intermediate shows, in addition to sodium acetate, a methyl signal at δ 23.1 consistent with structure 13. Low-field peaks from nonenhanced carbon atoms were not sufficiently clear to assign with any confidence.

**Methyl 2,3-Dihydro-5-(hydroxymethyl)-1-methyl-2-oxo-1*H*-imidazole-4-carboxylate (17).** A solution of diazomethane in ether (0.5 mmol, assayed with benzoic acid) was added portionwise to a solution of 16 (86 mg, 0.5 mmol) in methanol (10 mL). After 15 min, the reaction mixture was concentrated to a small volume, and the methyl ester 17 was isolated by preparative TLC ($CHCl_3$–MeOH, 9:1 v/v): 50 mg (54%, from ethyl acetate–hexane); mp 195–197 °C; UV ($H_2O$) $\lambda_{max}$ 273 nm, $\lambda_{min}$ 234; UV (pH 13) $\lambda_{max}$ 292 nm, $\lambda_{min}$ 247; NMR δ 10.67 (1 H, s, $N_3$ H), 5.26 (1 H, t, OH), 4.63 (2 H, d, $CH_2$, $J_{H,OH}$ = 4.6 Hz), 3.73 (3 H, s, $CO_2Me$), 3.19 (3 H, s, $N_1$ Me).

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.18; H, 5.40; N, 14.93.

**5,5′-Methylenebis[2,3-dihydro-1-methyl-2-oxo-1*H*-imidazole-4-carboxylic Acid] (18).** A solution of 6,6′-methylenebis[1-methyl-5-hydroxyuracil] hemihydrate (20; 245 mg, 0.8 mmol) in 50 mL of 0.1 N sodium hydroxide was heated under reflux for 14 h, at which time the shift of the UV spectrum from $\lambda_{max}$ 325 to $\lambda_{max}$ 262 nm (0.125-mL sample diluted to 25 mL) was essentially complete. Acidification of the cooled, yellowish reaction mixture afforded 166 mg (70%) of colorless 18, identical (melting point, UV, NMR) with the material prepared from 4b as described above.

**Methylation of 18.** A stirred suspension of 18 (50 mg) in 75% (v/v) aqueous methanol (20 mL) was treated at room temperature with a large excess of ethereal diazomethane. When all the starting material had dissolved (~1 h), the solvents were removed, and a solution of the residue in chloroform was applied to a preparative TLC plate. The plate was developed in $CHCl_3$–MeOH (18:1, v/v), the appropriate zones were removed and extracted with ethyl acetate. The filtrates were evaporated to give the following materials.

(a) 5,5′-Methylenebis[methyl 2,3-dihydro-1,3-dimethyl-2-oxo-1*H*-imidazole-4-carboxylate] (19): $R_f$ 0.55; 30 mg (50.5%). Material was crystallized from ethyl acetate: mp 226–228 °C; UV (MeOH) $\lambda_{max}$ 282.5 nm, $\lambda_{min}$ 238; NMR ($CDCl_3$) δ 4.83 (1 H, s, $CH_2$), 3.89 (3 H, s, $CO_2Me$), 3.49 (3 H, s, NMe), 3.17 (3 H, s, NMe).

Anal. Calcd for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.72; N, 15.90. Found: C, 51.22; H, 5.78; N, 15.93.

(b) The product of mixed O- and N-methylation (21): $R_f$ 0.67; 14 mg (23.5%). Material was recrystallized from ethyl acetate–*n*-hexane: mp 187–188 °C; UV (MeOH) 276 nm, 265 (sh), $\lambda_{min}$ 232; NMR ($CDCl_3$) δ 4.93 (2 H, s, $CH_2$), 4.08 (3 H, s, OMe), 3.91 (3 H, s, $CO_2Me$), 3.89 (3 H, s, $CO_2Me$), 3.49 (3 H, s, NMe), 3.26 (3 H, s, NMe), 3.15 (3 H, s, NMe).

Anal. Calcd for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.72; N, 15.90. Found: C, 51.16; H, 5.78; N, 15.81.

(c) 5,5′-Methylenebis[methyl 1-methyl-2-methoxyimidazole-4-carboxylate] (23): $R_f$ 0.80; 1 mg (1.7%); mp, indistinct at 200–205 °C (dec with shrinkage above 180 °C); UV (MeOH) $\lambda_{max}$ 264 nm $\lambda_{min}$ 225–240 (flat); NMR ($CDCl_3$) δ 4.99 (1 H, s, $CH_2$), 4.06 (3 H, s, OMe), 3.91 (3 H, s, $CO_2Me$), 3.25 (3 H, s, NMe).

**Registry No.** 1a, 20406-86-4; 2a, 80029-05-6; 2b, 28199-47-5; 2c, 80029-06-7; 4a, 80029-07-8; 4b, 80029-08-9; 4c, 80029-09-0; 5a, 80029-10-3; 5b, 80029-11-4; 7a, 80029-12-5; 7b, 17374-27-5; 7c, 616-03-5; 8, 80029-14-7; 13, 80029-13-6; 16, 80029-15-8; 17, 80029-16-9; 18, 80029-17-0; 19, 80029-18-1; 20, 28199-48-6; 21, 80029-19-2; 23, 80029-20-5; 5-hydroxyuracil, 20636-41-3.

# Synthesis of Oxoaporphines. An Unusual Photocyclization–Photoreduction of 2,3-Diaryl-Δ²-pyrroline-4,5-diones[1]

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The photocyclization of substituted 2,3-diaryl-Δ²-pyrroline-4,5-diones, with a forced *cis*-stilbene geometry, afforded the corresponding phenanthrene derivatives. Concomitant photoreduction of the C-4 carbonyl group to methylene has been observed when triethylamine was used as acid scavenger. The role of the amine in the photocyclization and photoreduction steps is discussed in terms of the results obtained with different amines (triethylamine, pyridine, and *tert*-butylamine). The naturally occurring oxoglaucine, lysicamine, and dicentrinone have been synthesized in good to acceptable yields by Fremy's salt oxidation of the photocyclized products.

Oxoaporphines constitute a small group of isoquinoline alkaloids biogenetically derived from aporphines.[2a] Recently it has been shown that they possess interesting antibacterial as well as antifungal activity against several microorganisms,[2b] thus making them clinically attractive (particularly liriodenine 4c) as antibiotics.

As a continuation of our work on the synthesis of isoquinoline alkaloids we became interested in devising a short and effective route to oxoaporphines and to noraporphines. Classically oxoaporphines are obtained from aporphines or noraporphines by treatment with several oxidizing agents,[3] including a possible biomimetic-like

(1) Presented in part at the 10th International Conference on Photochemistry, Creta, Sept 1981.

(2) (a) M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research 1972–1977", Plenum Press, New York, 1978. See also M. Shamma "The Isoquinoline Alkaloids", Academic Press, New York, 1972. (b) C. D. Hufford, A. S. Sharma, and B. O. Oguntimein, *J. Pharm. Sci.*, **69**, 1180 (1980), and references therein.

(3) These include $CrO_3$ in Py, $MnO_2$, $I_2$, singlet oxygen, etc. See ref 2a for leading references.

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