Rearrangement of 3,4-Dihydro-4-methyl-5-(ureidocarboxy)-1*H*-pyrimidin-2-one to Uracils via an Intramolecular Diastereoface Differentiating Reaction[1]

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Received June 1, 1979

From the acid-catalyzed reaction of urea and propiolic acid in azeotroping benzene, we have obtained uracil and 3,4-dihydro-4(*R,S*)-methyl-5-(ureidocarboxy)-1*H*-pyrimidin-2-one. Hydrolysis of the latter in aqueous acid yields the single enantiomeric pair 5,1a,4a (*R*) and 5,1a,4a (*S*) of 5-methyl-*cis*-1a,4a,5,6-tetrahydro-1*H*,3*H*,8*H*-2,4,7-trioxopyrimido[4,5-*d*]pyrimidine, which is formed via an intramolecular diastereoface differentiating reaction. In addition, five other hydrolysis products were isolated in lesser amounts: 5-(1-hydroxyethyl)uracil, uracil, 5-(1-ureidoethyl)uracil, 3,4-dihydro-4(*R,S*)-methyl-5-carboxamido-1*H*-pyrimidin-2-one, and *trans*-1,3-bis(uracil-5-yl)but-1-ene. The proof of structure of these derivatives is presented, along with a mechanistic scheme for their formation.

In an effort to find an efficient synthesis of nitrogen-15 enriched uracil as part of our work in studying the physicochemical properties of nucleic acid derivatives, we investigated the condensation of urea and propiolic acid under two sets of conditions similar to those recently reported in the literature.[2,3] The use of polyphosphoric acid[2] as a dehydrating agent and acid catalyst allowed us to synthesize uracil-*1,3*-$^{15}N_2$ in 77% yield based upon the urea-$^{15}N_2$ starting material.[4,5] The second set of reaction conditions gave lower yields of uracil, along with a second previously unreported condensation product. In this work, we shall discuss the isolation and identification of this second reaction product, along with a rearrangement it undergoes in aqueous acid.

Results and Discussion

The reaction of urea and propiolic acid (1) in azeotroping benzene, in the presence of a catalytic amount of sulfuric acid (Scheme I) provided uracil (**2**) in about 30% yield, along with 15–37% of a new product which we have identified as 3,4-dihydro-4(*R,S*)-methyl-5-(ureidocarboxy)-1*H*-pyrimidin-2-one (**3**). The structure of **3** was assigned on the basis of UV and NMR data and their comparison with literature spectra for analogous 3,4-dihydro-1*H*-pyrimidin-2-ones.[6] The assignment of the five D_2O-exchangeable N–H protons in the NMR spectrum of **3** is particularly instructive. The N–H(1) (δ 9.05) and N–H(3) (δ 7.19) signals were assigned on the basis of signal narrowing in double-irradiation experiments in which these protons or H(6) and H(4), respectively, were irradiated. The two signals at 7.10 and 7.93 ppm were assigned to the side-chain NH_2 protons H(A) and H(B) on the basis of their behavior in a variable-temperature experiment. These signals undergo successive broadening, followed by coalescence and narrowing to a singlet, as expected for such an exchange process.[7] The remaining signal at 9.76 ppm was assigned to the H(C) proton.[8]

Scheme I

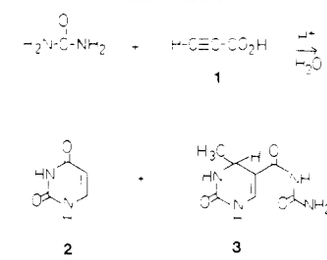

Chart I

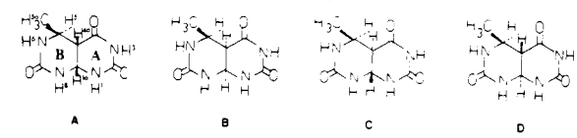

Table I. Proton NMR Data for Compound 5 (Me_2SO-d_6)

chemical shifts			coupling constants	
proton position	ppm	multiplicity[a]	interaction	best value, Hz
1	8.02	br s	$J_{1,1a}$[c]	3.4
1a	4.84	ψ t[b]	$J_{1a,4a}$	4.9
3	10.31	s	$J_{4a,5}$	3.4
4a	2.75	ψ t[b]	$J_{5,5a}$	6.7
5	3.84	m	$J_{5,6}$	3.6[d]
5a (CH_3)	1.12	d	$J_{8,6}$[c]	~0[e]
6	6.55	br s		
8	6.66	s		

[a] Appearance of the spectrum in the absence of decoupling and added D_2O. [b] ψ t = pseudotriplet. [c] $J_{1,1a}$ was distinguished from $J_{1a,4a}$ via decoupling of the H(1) proton. [d] From decoupling the CH_3 we obtained $J_{4a,5} + J_{5,6} = 7.0$ Hz and from a similar experiment after addition of D_2O $J_{4a,5} = 3.7$ Hz. [e] Bandwidth of H(8) comparable to that of H(3).

The acid-catalyzed reaction that gives rise to **3** may be envisaged to proceed via the mechanisms illustrated in Schemes II and III, in which it is assumed that the initial key intermediate is an allene or a vinyl cation,[9] respec-

(1) This investigation was supported in part by Grant No. CA 08748, awarded by the National Cancer Institute, and Biomedical Research Support Grant No. 5 S07 RR0534-04, awarded by the National Institutes of Health, DHEW, to R.L.L.

(2) Harada, K.; Suzuki, S. *Tetrahedron Lett.* **1976**, 2321.

(3) De Pasquale, R. J. *J. Org. Chem.* **1977**, *42*, 2185.

(4) Lipnick, R. L.; Fissekis, J. D. *J. Labelled Compd. Radiopharm.*, in press.

(5) The *1,3*-$^{15}N_2$ and its deuteriomethyl derivatives were used in an NMR study of uracil monoanion tautomerism: Lipnick, R. L.; Fissekis, J. D. *J. Org. Chem.* **1979**, *44*, 1627.

(6) Sweet, F.; Fissekis, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 8741.

(7) See for example: (a) Summers, B.; Piette, L. H.; Schneider, W. G. *Can. J. Chem.* **1960**, *38*, 681. (b) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.

(8) This chemical shift is similar to that of the N–H(3) proton of dihydrouracil: Chabre, M.; Gagnaire, D.; Nofre, C. *Bull. Soc. Chim. Fr.* **1966**, 108.

(9) Vinyl cation intermediates are well-known,[10] and one such species has been implicated in the acid-catalyzed hydration of phenylpriopiolic acid.[11]

(10) Hanack, M. *Acc. Chem. Res.* **1976**, *9*, 364.

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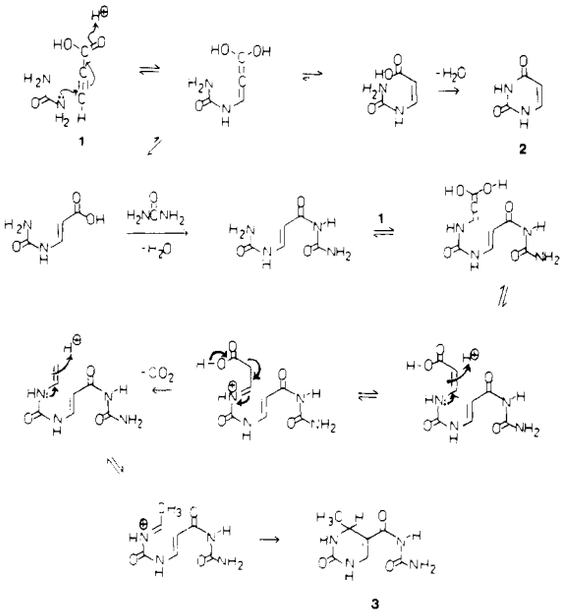
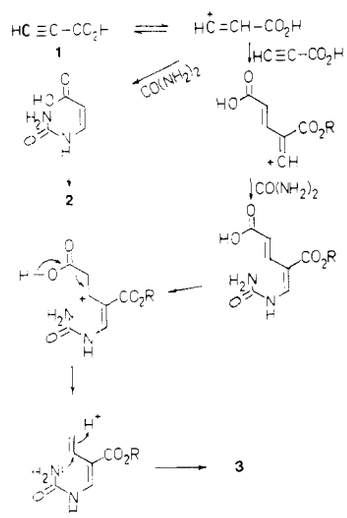
Scheme II



Scheme III



tively. The pathway in Scheme III is consistent with that proposed for the Biginelli reaction[6] which provides a general route to 3,4-dihydropyrimidin-2-ones.

A facile, acid-catalyzed decarboxylation as the one observed here leading to **3** was also encountered by Sweet and Fissekis in their study of the Biginelli reaction.[6] In that instance a decarboxylation product, 5-(carbomethoxy)-4-methyl-3,4-dihydro-2(1*H*)-pyrimidin-2-one, as well as the respective carboxymethyl derivative 5-(carbomethoxy)-4-(carboxymethyl)-3,4-dihydro-2(1*H*)-pyrimidin-2-one, was isolated.

We attempted to confirm chemically the structure of **3** via a hydrolysis reaction under acidic conditions. The reaction mixture was resolved on an ion-exchange column, and six UV-absorbing products (Scheme IV), comprising about a 61% yield, were isolated and identified.

3,4-Dihydro-4(*R*,*S*)-methyl-5-carboxamido-1*H*-pyrimidin-2-one (**4**) results from the partial hydrolysis of the 5-ureidocarboxy group.

The major reaction product (**5**) is derived from **3** through a nucleophilic attack of the 5-ureidocarboxy group at C(6).

(11) Noyce, D. S., Sr.; Matesich, M. A.; Peterson, P. E. *J. Am. Chem. Soc.* **1967**, *89*, 6225.

Scheme IV

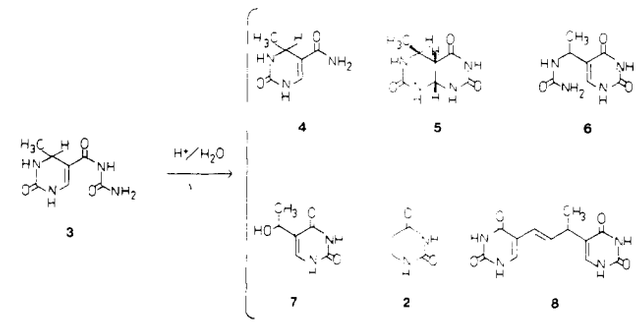


Chart II

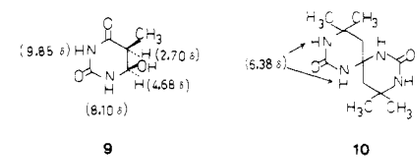
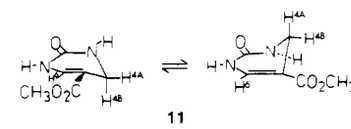


Chart III



While, in principle, this reaction may generate the four stereoisomers, A, B, C, and D (Chart I), only one was detected. The chemical shift assignment for the NMR spectrum of **5** (Table I) was facilitated by reference to *cis*-5-hydroxy-5,6-dihydrothymine[12] (**9**) and to 4,4,10,10-tetramethyl-2,8-dioxo-1,3,7,9-tetraazaspiroundecane[13] (**10**) (Chart II), which serve as models for the dihydrouracil and tetrahydropyrimidinone ring components, respectively. These assignments for **5** (Table I) were confirmed through selective decoupling experiments and/or exchange with D_2O. In each instance, the observed results were consistent with those expected from the proton–proton interactions in **5**.

A consideration of the stereodependence of the vicinal coupling $J_{1a,4a}$ allows us to distinguish between the trans- (C, D) and cis-fused (A, B) stereoisomers of **5** (Chart I). In the structurally rigid trans isomers, H(1a) and H(4a) are restricted exclusively to a trans-aa relationship, and $J_{1a,4a}$ should fall in the range 9.5-10.3 Hz; in the conformationally flexible cis isomers, H(1a) and H(4a) are either cis-ae or cis-ea, and $J_{1a,4a}$ should fall in the range 3.3–6.1 Hz.[14] The $J_{1a,4a}$ coupling for **5** (4.9 Hz) is clearly within the latter range, indicating a cis fusion. Each of the two cis isomers A and B (Chart I) may exist as one of two interconvertible conformers ($A_1 \rightleftharpoons A_2$, $B_1 \rightleftharpoons B_2$) defined respectively by the stereochemical relationship trans-ee, trans-aa, and cis-ae, cis-ea between H_{4a} and H_5. A comparison of the experimental values of $J_{4a,5}$, $J_{1a,8}$, and $J_{5,6}$ for **5** to those estimated[17] for each of these conformers

(12) Rouillier, P.; Delmau, J.; Nofre, C. *Bull. Soc. Chim. Fr.* **1966**, 3515.

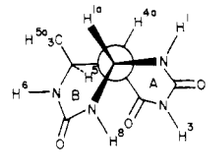
(13) NMR data in Me_2SO-d_6, this work (see Experimental Section); the chemical nonequivalence of the two types of N–H signals is consistent with their observed magnetic nonequivalence on addition of pyridine-d_5.

(14) These ranges are taken from a series of 5,6-dihydrouracil derivatives[15,16] whose H(5) and H(6) protons are in similar electronic environments and are related by similar ranges of H–N–C–H dihedral angles.

(15) Batterham, T. J. "NMR Spectra of Simple Heterocycles"; Wiley-Interscience: New York, 1973; pp 116–7.

(16) See also: Kondo, Y.; Witkop, B. *J. Am. Chem. Soc.* **1968**, *90*, 764. This is an example of the use of the Karplus equation for cis,trans assignment in 5,6-dihydrothymine derivatives.

Table II. Vicinal Interproton Couplings for 5 Compared to Those Estimated for Structures A_1, A_2, B_1, and B_2[a]



A_1

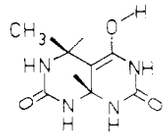
parameter	exptl value	conformer A_1	A_2	B_1	B_2
H(1a)-C-N-H(8), deg		80-110	40-50	40-50	80-110
$J_{1a,8}$, Hz[b]	~0	1-1.5	3.7-4.5 (4.2)[c]	3.7-4.5 (4.2)[c]	1-1.5
H(5)-C-N-H(6), deg		20-40	80-110	20-40	80-110
$J_{5,6}$, Hz[b]	3.3	3.7-4.5	1-1.5	3.7-4.5	1-1.5
H(4a)-C-C-H(5), deg		60	170	60	60
$J_{4a,5}$, Hz[d]	3.4	3.7 (trans-ee)	11.3 (trans-aa)	3.7 (cis-ae)	3.7 (cis-ea)

[a] Dihedral angles for A_1, A_2, B_1, and B_2 were measured directly from Dreiding models. Each of the H-C-N-H torsional angles is comparable to the corresponding one observed in dihydrouracil derivatives in the solid state.[18,19] [b] Estimated values for $J_{1a,8}$ and $J_{5,6}$ are based upon the $J_{1,6}$ couplings observed in a series of 5,6-dihydrouracil derivatives.[20] [c] $J_{1,6e}$ for 6-hydroxy-5-methyl-5,6-dihydrouracil.[21] [d] From estimated vicinal couplings across the $N-CH_2-CH_2-C$ fragment in N-methylpiperidine[22] for which $J_{cis}^{exp} = 3.7$ Hz and $J_{trans}^{exp} = 7.5$ Hz. Since this molecule exhibits nearly trigonal projection symmetry[22] with the two CH_2 groups almost perfectly staggered, it can be assumed that $J_{cis} \simeq J_{trans\text{-}ee}$. From this equation and the relationship $J_{trans}^{exp} = (J_{trans\text{-}ee} + J_{trans\text{-}aa})/2$ we derive $J_{trans\text{-}aa} = 2J_{trans}^{exp} - J_{cis}^{exp} = 11.3$ Hz.

(Table II) reveals that only conformer A_1 is consistent with all three of them.

A puckered conformation of **3** in which the methyl substituent achieves a pseudoaxial orientation finds ample experimental support[23] (see Chart III). It is also supported by theoretical considerations. A Dreiding model of **3** suggests that the sp^3 hybridized C(4) carbon is slightly puckered out of the approximately coplanar arrangement created by the remaining atoms of the dihydropyrimidinone ring.[28] This puckering may flip above and below the plane of the ring. The conformer in which the 4-methyl group is pseudoaxial appears to be energetically favored over the alternative conformer in which the pseudoequatorial methyl group is involved in a gauche interaction with the 5-ureidocarboxy substituent.

On the basis of this conformational arrangement, we can envision the stereochemistry at C(1a) in **5** to be determined by an initial diastereoface-differentiating attack of the amido nitrogen trans to the bulky methyl group, thus eliminating isomers B and D (Chart I) from further consideration. The endocyclic 5,6 double bond thus serves as an sp^2 prochiral center.[29] The obtained overall anti addition must result from the formation of the thermodynamically more stable isomer **5** (or A) from the enol species **12** since kinetic control of the reaction is expected



12

to lead to a trans ring fusion (i.e., C) via protonation at the less hindered face.[30] The origin of the apparent energetic preference for a cis ring fusion is attributed primarily to the avoidance of a gauche interaction between the methyl substituent at C(5a) and the C(4) carbonyl rather than to ring strain.[31]

We consider the remaining compounds **2** and **6**–**8**, isolated from the acid hydrolysis of **3** (Scheme IV), to derive from **5** via tautomerization of the C(4) carbonyl, followed by a reverse 1,3-addition and ring opening of enol **12** to give initially **6**, which was actually isolated albeit in small quantity. This pathway for cleavage of **5** may be energetically more favorable than reopening to **3**, since this

(17) Since Karplus parameters (Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11; *J. Chem. Soc.* **1963**, 85, 2870) for such an H-N-C-H fragment are unknown, estimates of the expected couplings for each such conformation were based upon a series of electronically similar and conformationally defined models.

(18) Rohrer, D. C.; Sundaralingam, M. *Acta Crystallogr., Sect. B* **1970**, *26*, 546.

(19) Furberg, S.; Jensen, L. H. *J. Am. Chem. Soc.* **1968**, *90*, 470.

(20) Katritzky, A. R.; Nesbit, M. R.; Kurtev, B. J., Lyapova, M.; Pojarlieff, I. G. *Tetrahedron* **1969**, *25*, 3807.

(21) Rouillier, P.; Delmau, J.; Duplan, J.; Nofre, C. *Tetrahedron Lett.* **1966**, 4189.

(22) Lambert, J. B. *Acc. Chem. Res.* **1971**, *4*, 87. Lambert, J. B.; Sun, H.-N. *Org. Magn. Reson.* **1977**, *9*, 621.

(23) The $J_{3,4}$ coupling in **3** may be related to $J_{1,6}$ in 5-substituted 5,6-dihydrouracil derivatives, in which $J_{1,6e} = 3.7$–4.5 Hz and $J_{1,6a} = 1.0$–1.5 Hz.[20,21] The observed value ($J_{3,4} = 3.1$ Hz) suggests a predominance of the pseudoaxial conformer in which H(4) is pseudoequatorial. This conclusion is also consistent with the absence of a detectable allylic coupling, $^4J_{4,6}$, which should be either close to 0 or about 2.6 Hz for interaction involving an equatorial and axial type hydrogen at H(4), respectively.[24,25]

(24) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5561.

(25) In the case of a similar compound, 5-(carbomethoxy)-3,4-dihydro-2(1*H*)-pyrimidin-2-one[26] (**11**), the NMR spectrum (in Me_2SO-d_6 following D_2O addition) shows the H(4) protons to be magnetically equivalent (via rapid flipping on the NMR time scale between axial and equatorial environments) such that one signal is observed at 3.94 ppm. This signal is split into a doublet with $J_{4,6} = 0.9$ Hz.[27] Similarly, the H(6) signal at 7.12 ppm is split into a triplet with the same coupling. This value falls midway between the two extremes for coupling to an axial or equatorial proton[24] as expected for a 1:1 equilibrium involving fast exchange between the two environments.

(26) This compound was synthesized according to Sweet and Fissekis.[6] The NMR data was obtained in Me_2SO-d_6.

(27) NMR measurement with 16K data points in this instance.

(28) The value $J_{1,6} = 6.1$ Hz is similar to that observed in uracil (5.5 Hz) and supports the concept of coplanarity in this portion of the ring.

(29) Izumi, Y.; Tai, A. "Stereo-differentiating Reactions"; Academic Press: New York, 1977; pp 128, 135 ff.

(30) An alternative concerted 1,2 trans addition is considered unlikely on steric grounds as, irrespective of the isomer produced (A or B), it would require the approach of either the amido group or the proton to occur from the more hindered face.

(31) If the 5,6-dihydrouracil ring is taken as a model of ring A in **7**, the dihedral angle C(4)–C(5)–C(6)–N(1) observed in 5,6-dihydrouracil[18] (45°) and 5,6-dihydrothymine[19] (58°) by X-ray crystallography suggests that an adjustment to the approximately 60° dihedral angle required for its trans fusion to a second ring may not be difficult to achieve.

alternate route avoids the strain inherent in **3** and leads to a net increase in resonance stabilization with the formation of the aromatic uracil ring. This explanation is consistent with our findings from a second experiment in which a pure sample of **5** was reacted under similar conditions. Two of the products isolated from this reaction (**2** and **7**) were obtained earlier in the reaction of **3** (Scheme IV); a third product, 5-vinyluracil, is also the proposed intermediate in the formation of **8**[32] isolated from the hydrolysis of **3** (Scheme IV).

From the relative yields obtained, most of **6** is converted to 5-(1-hydroxyethyl)uracil (**7**) via S_N1 hydrolysis at C(1') with loss of urea. A second rearrangement product is uracil (**2**), formed from **7** via a retro-aldol condensation with loss of acetaldehyde, as has been observed similarly in the case of 5-(hydroxymethyl)uracil.[33] Additional evidence for this retro-aldol condensation was provided by a separate reaction of **7** under similar acid-catalyzed conditions which gave a mixture of **2** and **8**.

The small amount of *trans*-1,3-bis(uracil-5-yl)but-1-ene (**8**) obtained from this reaction is the product of dimerization of the carbonium ion derived from **7** and 5-vinyluracil as noted by Walker and co-workers.[32]

Compounds **3**, **5**, and **10** were tested for antineoplastic activity in P815 and L1210 cell lines and all were found to have ID_{50}'s > 100 in these systems.

Experimental Section

Methods. Proton NMR spectra were obtained on a JEOL-PFT-100 spectrometer operating in the Fourier transform mode. Spectra were usually recorded at a 1.25-kHz sweep width and with 8K data points, yielding a nominal resolution of 0.3 Hz. The symbols E and ES in the description of these spectra indicate protons which exchange rapidly and slowly, respectively, on adding D_2O. The UV spectra were obtained with a Varian Superscan 3 spectrophotometer. The mass spectra were obtained on a Du Pont Model 21-492 spectrometer operating in the chemical ionization mode with isobutane as the reagent gas. In all chromatographic separations, water, which was first deionized and glass distilled, was used as an eluant and delivered at a constant rate by means of a Cole Parmer Masterflex peristaltic pump.

The UV-absorbing, chromatographically homogeneous fractions were combined and evaporated to dryness in tared flasks under vacuum with a Buchler-flask evaporator. Microanalyses were obtained from Spang Microanalytical Laboratory, Eagle Harbor, MI. For compounds **4** and **6**, which were obtained in small quantity, the elemental composition was determined by high-resolution mass spectrometry on a CEC 110B high-resolution mass spectrometer. The chemical ionization mass spectra, which we obtained as well for these derivatives, are consistent with the assigned structures.

3,4-Dihydro-4(*R,S*)-methyl-5-(ureidocarboxy)-2(1*H*)-pyrimidin-2-one (3). Urea and propiolic acid (**1**) were reacted with a catalytic quantity of concentrated sulfuric acid in a procedure similar to that of De Pasquale.[3] In a typical experiment, a 1.10-mL (1.25 g, 0.0179 mol) sample of propiolic acid (Aldrich, 98%), 1.07 g (0.0179 mol) of dry urea (Fisher, certified reagent), 30 mL of anhydrous benzene (reagent, dried over molecular sieves), and 1 or 2 drops of concentrated sulfuric acid were mixed together in a round-bottom flask. The flask was fitted with a Dean–Stark trap, and the mixture was allowed to reflux overnight with magnetic stirring. The following morning a small amount of water had collected in the trap, and the previously homogeneous mixture now exhibited a second gummy phase at the bottom of the flask. The solvent was taken to dryness, and the gummy product was dissolved in a small quantity of warm water, applied to a 2.5 × 90 cm column packed with Dowex AG-50W-X8 resin, 200–400 mesh, H^+ form (Bio-Rad Laboratories), and eluted with water. In typical experiments we obtained 0.60–0.63 g of uracil (30–31%) and 0.26–0.66 g of **3** (15–37%) in addition to much smaller amounts of other unidentified products. The highest yield of **3** resulted from an experiment in which the rapid removal of water product was optimized. In this case, the solution was refluxed the most vigorously, the head of the Dean–Stark trap was heated with electrical tape, and the Dean–Stark trap itself was filled with molecular sieves. The uracil fractions were identified by comparison of their UV and NMR spectra with those obtained from an authentic sample.

Compound **3** was recrystallized from hot water: mp 242–254 °C; NMR (Me_2SO-d_6) δ 1.14 (d, 3, CH_3, J = 6.3 Hz), 4.22 (dq, 1, **H**CCH_3, $J_{3,4}$ = 3.1 Hz), 7.10 (br s, 1, N(H)**H**(A)), 7.19 (br s, 1, N-**H**(3)), 7.44 (d, 1, H(6), $J_{1,6}$ = 6.1 Hz), 7.93 (br s, 1, N(H)**H**(B)), 9.05 (br s, 1, NH(1)), 9.76 (br s, 1, N**H**$CONH_2$); UV λ_{max} (pH 7) 293 nm; λ_{max} (pH 10) 289, 345 nm. Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.37; H, 5.04; N, 28.25.

Rearrangement of 3. A 516-mg (2.60 mmol) sample of **3** was allowed to reflux overnight in 100 mL of 0.2 N sulfuric acid. The solution was cooled and concentrated at room temperature on a rotary evaporator to a few milliliters, the concentrate was applied to a 2.5 × 90 cm column packed with Dowex AG-50W-X8 resin, 200–400 mesh, H^+ form (Bio-Rad Laboratories), and eluted with water. Six separate components were resolved, and each component was subjected to repeated chromatography until each compound was chromatographically pure.

Peak I: 300–400 mL, 5-(1-hydroxyethyl)uracil (**7**), 73 mg (18%), recrystallized from EtOH. NMR and UV data are in agreement with those previously reported for this compound.[32]

Peak II: 400–500 mL, uracil (**2**), 18 mg (6%). Spectral data (UV, NMR) are in agreement with literature values[34] and our measurements using an authentic sample (Sigma).

Peak III: 600–700 mL; 5,1a,4a (*R*) and 5,1a,4a (*S*) mixture of 5-methyl-*cis*-1a,4a,5,6-tetrahydro-1*H*,3*H*,8*H*-2,4,7-trioxopyrimido[4,5-*d*]pyrimidine (**5**); 132 mg (25%); recrystallized from H_2O, mp 292–293 °C; NMR, see Tables I and II; UV λ_{max} (pH 7) 210 nm (sh), 266, 290 (infl); λ_{max} (pH 10) 229 nm, 288.5, 310 (infl); λ_{max} (pH ~14), 328. Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.50; H, 4.90, N, 28.30.

Peak IV: 1300–1600 mL; 3,4-dihydro-4(*R,S*)-methyl-5-carboxamido-1*H*-pyrimidin-2-one (**4**); 24 mg (6%); dec >150 °C; mass spectrum (chemical ionization), *m/e* (rel intensity) 156.1 (100, MH), 140.0 (12.5, MH - CH_4), 139.0 (8.8, MH - NH_3), 138.0 (15.1, MH - H_2O), 113.0 (17.3, MH - O=C=NH), 61.0 (96.6, $CO^+H(NH)_2$); high resolution EI mass spectrum, calcd for $C_6H_9N_3O_2$ *m/e* 155.069 47, found *m/e* 155.071 13; NMR (Me_2SO-d_6) δ 1.09 (d, 3, CH_3, J = 6.4 Hz), 4.16 (dq, 1, **H**CCH_3, $J_{3,4}$ = 2.7 Hz), 6.9 (br s, 2, NH_2), 6.97 (d, 1, H(6), $J_{1,6}$ = 5.5 Hz), 8.66 (br d, 1, NH(1)); UV λ_{max} (pH 7) 207 nm, 278; λ_{max} (pH 10) 280 nm, 330 (sh).

Peak V: 1600–1900 mL, *trans*-1,3-bis(uracil-5-yl)but-1-ene (**8**), 11 mg (3%), recrystallized from H_2O. The UV and NMR spectral data are in agreement with literature values.[32a]

Peak VI: 1600–2200 mL, 5-(1-ureidoethyl)uracil (**6**); 16 mg (3%); sinters and decomposes at 265 °C; NMR (Me_2SO-d_6) δ 1.20 (d, 3, CH_3, J = 7.0 Hz), 4.46 (pseudoquintet, 1, CH_3C**H**), 5.49 (s, 2, C(O)NH_2, ES), 6.19 (d, 1, C(H, CH_3)-N(**H**), J = 8.5 Hz, ES), 7.16 (s, 1, H(6)), 10.74 (br s, 1, NH(1), E), 11.08 (br s, 1, NH(3) E); UV λ_{max} (pH 7) 210 nm, 261.5; λ_{max} (pH 10) 288 nm; mass spectrum (CI), *m/e* (rel intensity) 199.0 (36, MH), 182.0 (9.5, MH - NH_3), 156.0 (26.5, MH - O=C=NH), 139.0 (100.0, MH - $H_2NC(NH_2)$=O); high-resolution EI mass spectrum, calcd for $C_7H_{10}N_4O_3$ *m/e* 198.075 29, found 198.077 86.

Hydrolysis of 5. A 10-mg (0.050 mmol) sample of **5** was dissolved in 50 mL of 0.2 N sulfuric acid and allowed to reflux overnight. The solution was cooled and concentrated under vacuum and applied to a 2.5 × 90 cm column packed with Dowex AG-50W-X8 resin, H^+ form, 200–400 mesh. The two major peaks were identified as 5-(1-hydroxyethyl)uracil (**7**) and uracil (**2**) by comparison of their chromatographic retention times and UV and NMR spectra with those of authentic samples. In addition, a third minor peak was identified similarly as 5-vinyluracil.[35]

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Hydrolysis of 7. A 34-mg (0.218 mmol) sample of **7** was dissolved in 10 mL of 0.2 N sulfuric acid and heated to reflux. At successive time intervals, 1-mL aliquots were applied to a 2.5 × 90 cm column packed with Dowex AG-50W-X8 resin, H^+ form, 200–400 mesh. After 15 h, a small quantity of precipitate was removed by filtration and identified by NMR as **8**. A 1-mL aliquot applied to the column indicated from retention times and UV spectra mostly unreacted **7** and a small amount of uracil (**2**). After 48 h, more precipitated **8** was removed, and the quantity of **7** was found to have decreased significantly, with an increase in the amount of uracil (**2**) formed.

4,4,10,10-Tetramethyl-2,8-dioxo-1,3,7,9-tetraazaspiroundecane (10). This compound was synthesized according to the procedure of Weinschenk[36] by the condensation of urea and HCl-saturated anhydrous acetone. NMR (Me_2SO-d_6) δ 1.20 (s, 6, 2 CH_3(A)), 1.23 (s, 6, 2 CH_3(B)), 1.87 (A part of AB q, 2, 2 HC**H**), 2.04 (B part of AB q, 2, 2 **H**CH, J = 13.1 Hz), 6.38 (br s, 4, 2 NHC(O)NH); NMR (1:1 Me_2SO-d_6–pyridine-d_5) δ 1.28 (s, 6, 2 CH_3(A)), 1.33 (s, 6, 2 CH_3(B)), 1.91 (A of AB q, 2, 2 HC**H**), 2.17 (B part of AB q, 2, 2 HCH, J = 13.1 Hz), 6.71 (br s, 2, 2 NHC(O)N**H**), 6.83 (br s, 2, 2 **N**HC(O)NH). Our structural assignment for this compound is based on the work of Hatt and Triffett[37] and Hatt, Lichtenwalter, and Riesser.[38,39]

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Acknowledgment. We thank Dr. Joseph H. Burchenal and Ms. Linda Likys for performing the tissue culture testing. We would also like to thank Professor James B. Hendrickson of Brandeis University for helpful discussions. We are grateful to Dr. Catherine E. Costello, Mass Spectrometry Laboratory, Massachusetts Institute of Technology, for providing the high-resolution EI mass spectra.

Registry No. 1, 471-25-0; 2, 66-22-8; 3, 71749-93-4; 4, 71749-94-5; 5, 71749-95-6; 6, 71749-96-7; 7, 71749-97-8; 8, 71749-98-9; 10, 4115-66-6; urea, 57-13-6; 5-vinyluracil, 37107-81-6.

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Chemistry of Diaminomaleonitrile. 5.[1] Dihydropyrazine Synthesis

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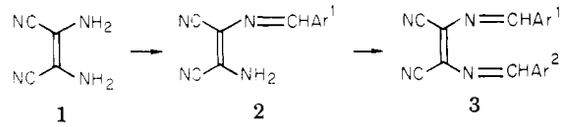
Received June 15, 1979

Condensation of aldehydes with diaminomaleonitrile (DAMN) Schiff bases in the presence of triethylamine at temperatures below 20 °C is accompanied by regiospecific hydration of the nitrile groups to give 3-cyanoacrylamide derivatives, which cyclize readily into 1,2-dihydropyrazines (**6** and/or **7**). The substituent effect on the product ratio (**6**/**7**) is examined, and the reaction mechanism is discussed in terms of a new general reaction pattern of DAMN derivatives. Reactions of **6** and **7** by oxidation, reduction, hydantoin formation with isocyanates, and cyanoethylation are also investigated.

Although many Schiff bases **2** have been prepared by the reactions of aldehydes with diaminomaleonitrile (DAMN, **1**) under relatively mild conditions (20–80 °C/ with or without acid catalyst),[1-4] preparation of bis condensation products **3** has been unsuccessful until recently.



An early attempt to condense a second mole of different aldehyde with **2** resulted in displacement of the aldehyde residue of the original derivative to give a new compound **2** (80 °C/8 h/with acid catalyst).[4] Begland[5,6] found that certain aromatic compounds with structure **3** (and its trans isomer), especially when Ar^1 and/or Ar^2 are (dialkylamino)phenyl, possess brilliant colors and are useful as disperse dyes for dying and printing polyesters. Symmetrical compounds **3** (Ar^1 = Ar^2) have been prepared from aldehydes and either **1** or **2** by direct condensation under somewhat more severe conditions (115–120 °C/with acid or base catalyst) than those of the mono condensations.[5] Unsymmetrical compounds **3** ($Ar^1 \neq Ar^2$), on the other hand, have been prepared by oxidation of *N*-benzyl-*N'*-benzylidene derivatives of **1**,[6] since the direct condensation of different aldehydes with **2** gave a product mixture by concomitant displacement of the aldehyde residues to give the symmetrical compounds **3**. In our experience, the reaction of a Schiff base (**2d**, Ar^1 = $Et_2NC_6H_4$) and aldehydes or ketones with piperidine catalyst resulted in exclusive formation of the symmetrical compound (**3**, Ar^1 = Ar^2 = $Et_2NC_6H_4$).

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