iridinecarboxylate (**1b**) by comparison of the ir and nmr spectra with the spectra of a known sample.

Reaction of *trans*-1-*tert*-Butyl-3-chloro-4-methyl-2-azetidinone (2c) with Sodium Hydroxide. The azetidinone (**2c**, 0.30 g, 1.7 mmol) was dissolved in dioxane (1 ml), and the resulting solution was added to a solution of sodium hydroxide (0.18 g, 45.0 mmol) in water (2 ml). Water was added until the mixture became clear, and the resulting solution was left at room temperature for 21 days. It was washed with chloroform and evaporated to a white solid. Nmr observation showed that about 30% of the solid consisted of sodium *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate (**1c**). The other components of the mixture were not characterized.

Registry No.—**1a**, 24719-64-0; **1b**, 50562-57-7; **1c**, 50562-58-8; **2a**, 23120-47-0; **2b**, 50562-60-2; **2c**, 50562-61-3; **3b**, 50562-62-4; **3c**, 50562-63-5; **4b**, 50562-64-6; **4c**, 50562-65-7; **11**, 574-45-8; methyl *cis*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate, 34863-28-0; methyl *trans*-1-*tert*-butyl-3-methyl-2-aziridinecarboxylate, 34856-93-4.

Supplementary Material Available. Nmr spectra of representative key compounds described in this paper (*e.g.*, **2a, 2b, 2c, 3b, 3c,** and **4a**) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-902.

References and Notes

(1) (a) A portion of these results was presented as a Communication: J. A. Deyrup and S. C. Clough, *J. Amer. Chem. Soc.*, **91**, 4590 (1969). (b) Support of the National Science Foundation (Grant GP 17642) is gratefully acknowledged.
(2) Cf. J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **35**, 3424 (1970).
(3) (a) J. Brois, *J. Org. Chem.*, **27**, 3532 (1962); (b) J. A. Deyrup and R. B. Greenwald, *J. Amer. Chem. Soc.*, **87**, 4538 (1965).
(4) (a) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968); V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970); A. G. Hortmann and D. A. Robertson, *J. Amer. Chem. Soc.*, **94**, 2758 (1972); R. H. Higgins and N. H. Cromwell, *ibid.*, **95**, 120 (1973).
(5) G. A. Olah and P. J. Szilagyi, *J. Amer. Chem. Soc.*, **91**, 2949 (1969).
(6) G. A. Olah and M. B. Comisarov, *J. Amer. Chem. Soc.*, **88**, 4442 (1966).
(7) J. C. Sheehan and J. W. Frankenfield, *J. Org. Chem.*, **27**, 628 (1962).
(8) G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *J. Amer. Chem. Soc.*, **84**, 2733 (1962).
(9) J. M. Conia, *Angew. Chem.*, **7**, 570 (1968).
(10) R. Graeve and G. H. Wahl, Jr., *J. Chem. Educ.*, **41**, 279 (1964).
(11) J. R. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965, p 914.

The Reaction of 6-Amino- and 6-Hydrazinopyrimidines with Diethyl Azodicarboxylate. A New Method for Carbon-5 Functionalization of Pyrimidines[1]

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6-Amino- and 6-hydrazinopyrimidines are shown to react with diethyl azodicarboxylate to give 5-(1,2-dicarbethoxyhydrazino) derivatives. The synthetic potential of this simple method for the direct introduction of nitrogen into the 5 position of the pyrimidine ring is illustrated by a synthesis of 1,3-dimethyluric acid from 1,3-dimethyl-6-aminouracil by reaction with diethyl azodicarboxylate, reduction to 1,3-dimethyl-5-carbethoxyamino-6-aminouracil, and thermal ring closure.

6-Aminopyrimidines unsubstituted at position 5 react with a wide variety of electrophiles (NO^+, NO_2^+, X^+, $RC{=}O^+$, etc.) to give 5-substituted derivatives which number among the most versatile and useful of pyrimidine intermediates.[2] We have now examined the reaction of a number of 6-amino- and 6-hydrazinopyrimidines with diethyl azodicarboxylate and have found that the products are 5-(1,2-dicarbethoxyhydrazino)pyrimidines.[3] These Michael adducts, which possess a reduced nitrogen substituent at position 5, have proved to be versatile synthetic intermediates. The present paper describes this new procedure for C-5 functionalization of pyrimidines;[4] subsequent papers will report the conversion of these adducts to 6- and 7-azapteridines, including the antibiotics fervenulin[4] and 2-methylfervenulone (MSD-92).[5]

Our results are summarized in Tables I and II. The reaction proceeds with remarkable ease when run in suspension in hot dichlorobenzene. Under these conditions the reactants slowly dissolve, and the product then generally crystallizes directly from the hot reaction solution. Electron-withdrawing substituents which reduce the nucleophilicity of the pyrimidine ring towards electrophilic reagents (*e.g.*, **5**), not surprisingly, retard the reaction. Furthermore, the reaction is either retarded or inhibited with 6-hydrazinopyrimidines if the proton adjacent to the ring is substituted by an alkyl group (*e.g.*, **13** and **15**). This observation suggests that the diethyl azodicarboxylate–6-amino- (or 6-hydrazino-) pyrimidine reaction may involve a cyclic transition state similar to that proposed for the reaction of diethyl azodicarboxylate with olefins,[6] where a concerted mechanism with little or no charge development is involved. Proton abstraction from the allylic position of the olefin would thus have its counterpart in the present case in N–H abstraction from the 6 substituent. When such a cyclic transition state is not feasible

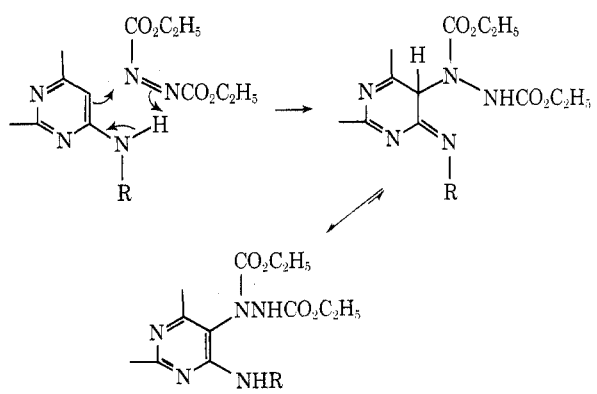
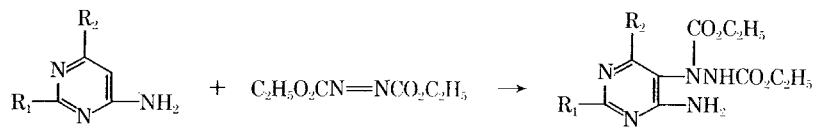


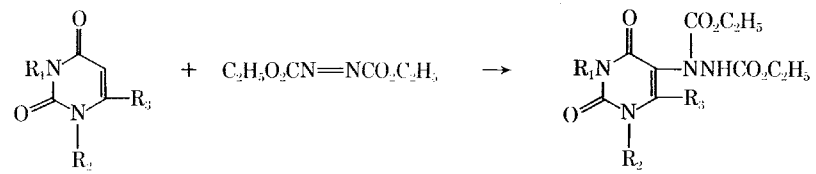
Table I
Formation of 5-(1,2-Dicarbethoxyhydrazino)pyrimidines from 6-Aminopyrimidines and Diethyl Azodicarboxylate



Compd no.	R_1	R_2	Reaction solvent	Temp, °C	Time	Yield, %	Mp, °C, dec	Product formula[f]	Analyses: Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	H	OH	DMF	125	2 hr	67[a]	230–231	$C_{10}H_{15}N_5O_5$	42.10	5.31	24.55	41.91	5.31	24.36
2	NH_2	NH_2	DMA	120	0.5 hr	37[b]	240–241	$C_{10}H_{17}N_7O_4$	40.13	5.72	32.76	40.02	5.84	32.58
3	NH_2	$NHC_6H_4CH_3(p)$	ClC_6H_5	40[c]	10 min	90[a]	221–222	$C_{17}H_{23}N_7O_4$	52.43	5.95	25.18	52.34	6.11	25.03
4	$(CH_3)_2N$	NH_2	ClC_6H_5	110	1 min	90[a]	237–238	$C_{12}H_{21}N_7O_4$	44.02	6.46	29.96	44.01	6.41	30.01
5	NH_2	Cl	ClC_6H_5	Reflux	3.5 hr	22[d]	202–203	$C_{10}H_{15}ClN_6O_4$	37.69	4.74	26.37	38.05	4.88	26.21
6	NH_2	OH	ClC_6H_5	135	5 min	74[a]	250–252	$C_{10}H_{16}N_6O_5$	39.99	5.37	27.99	40.08	5.30	28.03
7	SCH_3	NH_2	ClC_6H_5	123	5 min	67[e]	245–246	$C_{11}H_{18}N_6O_4S$	39.98	5.49	25.40	39.94	5.73	25.15

[a] Recrystallized from ethanol. [b] Purified by extraction with hot ethanol, evaporation of the solvent, dissolution of the residue in hot acetonitrile, and cooling. [c] The reaction is exothermic at this temperature and heating is therefore stopped at this point. [d] Recrystallized from 1-propanol. [e] Recrystallized from acetonitrile. [f] Registry no. are, respectively, 49810-27-7, 49810-28-8, 49809-99-6, 49810-00-6, 49810-01-7, 49810-02-8, 49810-03-9.

Table II
Formation of 5-(1,2-Dicarbethoxyhydrazino)uracils from 6-Amino- (or Hydrazino-) uracils and Diethyl Azodicarboxylate

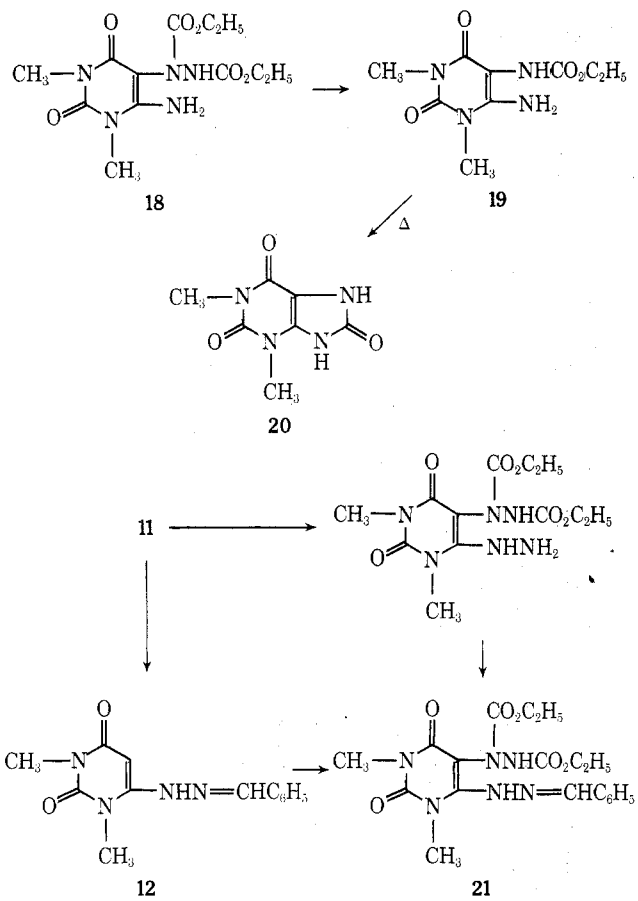


Compd no.	R_1	R_2	R_3	Reaction solvent	Temp, °C	Time	Yield, %	Mp, °C	Product formula[g]	Analyses: Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
8	H	H	NH_2	DMA	140	50 min[a]	61[b]	259–260 dec	$C_{10}H_{15}N_5O_6$	39.86	5.02	23.25	39.58	5.16	23.41
9	CH_3	CH_3	NH_2	[c]			77[b]	146–148	$C_{12}H_{19}N_5O_6$	43.77	5.81	21.26	43.54	5.87	21.35
10	CH_3	CH_3	$NHCH_3$	ClC_6H_5	Reflux	15 min	90[b]	129–131	$C_{13}H_{21}N_5O_6$	45.48	6.16	20.40	45.61	6.33	20.18
11	CH_3	CH_3	$NHNH_2$	DMF	[d]		60[b]	204–205 dec	$C_{12}H_{20}N_6O_6$	41.86	5.86	24.41	42.03	5.83	24.32
12	CH_3	CH_3	$NHN{=}CHC_6H_5$	DMF	Reflux	5 min	73[b]	193–195	$C_{19}H_{24}N_6O_6$	52.77	5.60	19.44	53.07	5.75	19.42
13	CH_3	CH_3	$N(CH_3)NH_2$	ClC_6H_5	Reflux	5 min	6[b]	175–176	$C_{13}H_{22}N_6O_6$	43.57	6.19	23 45	43.70	6.32	23.60
14	CH_3	CH_3	$N(CH_3)NHCHO$	DMF	125	2 hr	57[b]	159–160 dec	$C_{14}H_{22}N_6O_7$	43.52	5.74	21.75	43.34	5.65	21.51
15	CH_3	H	$N(CH_3)NH_2$												
16	CH_3	H	$N(CH_3)N{=}CH$-$C_6H_4OCH_3(p)$	DMF	120	2 hr	67[b]	221–222 dec	$C_{20}H_{26}N_6O_7$	51.94	5.66	18.17	51.93	5.73	17.92
17	CH_3	H	$N(CH_3)NHCH_3$	ClC_6H_5	120	5 min	71[e]	111–112[f]	$C_{13}H_{21}N_6O_6 \cdot 0.5C_6H_6$	48.48	6.10	21.20	48.81	6.09	21.30

[a] After the initial exothermic reaction (at 140°) had subsided, three successive additional portions (0.1 equiv each) of diethyl azodicarboxylate were added at 10-min intervals. [b] Recrystallized from ethanol. [c] See Experimental Section. [d] 1 equiv of diethyl azodicarboxylate was added dropwise to a suspension of the pyrimidine in DMF at such a rate that the temperature of the reaction mixture did not rise above 50° (1.5 hr). Stirring was then continued for 2 hr at room temperature. [e] Recrystallized from benzene. [f] Solvate with 0.5 mol of benzene. [g] Registry no. are, respectively, 49810-12-0, 18969-87-4, 49810-14-2, 18969-82-9, 49810-16-4, 49810-17-5, 49810-18-6, 49810-19-7, 49810-20-0.

(*e.g.*, **13**, **15**), competing tetrazene formation[7] may intervene, although no attempt was made to isolate and identify these sensitive materials. It is interesting to note that elimination of this potentially competitive pathway by conversion of the $-N(CH_3)NH_2$ substituent to a benzylidene (**12**, **16**), formyl (**14**), or N_1,N_2-disubstituted derivative (**17**) leads again to successful Michael addition at position 5 of the pyrimidine ring, although yields are decreased and more drastic conditions appear to be necessary.

The structures of the 5-(1,2-dicarbethoxyhydrazino)pyrimidine Michael adducts were confirmed in every case by nmr spectroscopy (disappearance of the characteristic pyrimidine C-5 aromatic proton resonance), and, in the case of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**18**), by chemical evidence as well. Thus, Raney nickel or Leuckart (formic acid) reduction of **18** resulted in cleavage of the N-N bond to give 1,3-dimethyl-5-carbethoxyamino-6-aminouracil (**19**), identical with an authentic sample prepared by the reaction of 1,3-dimethyl-5,6-diaminouracil with ethyl chloroformate.[8] Furthermore, heating of **19** resulted in ring closure to 1,3-dimethyluric acid (**20**), identical with an authentic sample. This latter reaction comprises a new synthetic approach to purines involving the direct introduction into position 5 of the pyrimidine ring of a reduced nitrogen substituent capable of eventual incorporation into the imidazole ring of the final purine.



Most of the 6-aminopyrimidines examined were well-known, commercially available intermediates. 1,3-Dimethyl-6-hydrazino- (**11**) and 1,3-dimethyl-6-(1-methylhydrazino)uracil (**13**) were prepared by treatment of 1,3-dimethyl-6-chlorouracil[9] with hydrazine and methylhydrazine, respectively, using chloroform as solvent rather than excess hydrazine solution as previously described.[9] The requisite 1,3-dimethyl-6-chlorouracil was prepared by chlorination of 1,3-dimethylbarbituric acid, which we found to be more conveniently prepared by acid hydrolysis of 1,3-dimethyl-6-aminouracil than by condensation of malonic acid with 1,3-dimethylurea.[10]

The structures of the 6-(1-methylhydrazino)uracils **13** and **15** and of 1,3-dimethyl-6-hydrazinouracil (**11**) followed from the observation that they formed benzylidene derivatives with aromatic aldehydes. The product (**12**) of the reaction of **11** with benzaldehyde reacted with diethyl azodicarboxylate to give an adduct (**21**) identical with that formed by reaction of benzaldehyde with the initial adduct formed from diethyl azodicarboxylate with **11**.

3-Methyl-6-(1-methylhydrazino)uracil (**15**)[11] and 3-methyl-6-(1,2-dimethylhydrazino)uracil (**17**) were similarly prepared from 3-methyl-6-chlorouracil and methylhydrazine or 1,2-dimethylhydrazine, respectively.

Experimental Section

Formation of 5-(1,2-Dicarbethoxyhydrazino)-6-amino- (or hydrazino-) pyrimidines. General Procedure. To a suspension of the 6-amino- (or hydrazino-) pyrimidine in the appropriate solvent was added 1 equiv of diethyl azodicarboxylate, and the mixture was heated as specified in Tables I and II. Depending on the solubility of the product in the solvent employed, the 5-(1,2-dicarbethoxyhydrazino) derivative was either isolated by filtration, or the solvent was evaporated under reduced pressure and the residue recrystallized (see Tables I and II).

1,3-Dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (18). A stirred suspension of 108.5 g (0.7 mol) of 1,3-dimethyl-6-aminouracil (**9**) in a mixture of 122.0 g (0.7 mol) of diethyl azodicarboxylate and 300 ml of chlorobenzene was heated to reflux in an oil bath maintained at 150–160°. A vigorous reaction accompanied by considerable foaming occurred, and it became necessary to remove the heat source. The reaction continued spontaneously for several minutes and, after it had subsided, heating was resumed for an additional 20 min. The reaction mixture was then filtered, the filtrate cooled, and the copious crop of ivory-colored crystals collected by filtration, washed with benzene followed by ether, and dried; yield (product solvated with chlorobenzene) 290 g, mp 66–70°. Repeated recrystallization of a small sample from benzene resulted in exchange of benzene for chlorobenzene of solvation: mp 88–90°; nmr ($CDCl_3$) 1.26 (t, 6, CH_3CH_2O), 3.30 (s, 3, CH_3N), 3.39 (s, 3, CH_3N), 4.21 (m, 4, CH_3CH_2O), 6.37 (s, 2, NH_2), 7.35 (s, 6, C_6H_6), and 7.98 ppm (s, 1, NH). The remainder of the product (solvated with chlorobenzene) was dissolved in 1500 ml of boiling water and the solution heated briefly until steam distillation of the chlorobenzene was complete. The solution was then decolorized with charcoal, filtered, and cooled, and the colorless crystals which separated were collected by filtration: yield 165 g (70%) of the hemihydrate, mp 142–144° dec.

Anal. Calcd for $C_{12}H_{19}N_5O_6 \cdot 0.5H_2O$: C, 42.60; H, 5.96; N, 20.70. Found: C, 42.33; H, 5.85; N, 20.75.

The anhydrous material, mp 146–148° dec, was prepared by recrystallization from absolute ethanol followed by drying *in vacuo* at 65° for 24 hr.

Anal. Calcd for $C_{12}H_{19}N_5O_6$: C, 43.77; H, 5.81; N, 21.26. Found: C, 43.54; H, 5.87; N, 21.35.

1,3-Dimethyl-5-carbethoxyamino-6-aminouracil (19). Method A. To a suspension of 390 g of Raney nickel (Grace no. 28, freed of excess water by draining with slight suction on a Büchner funnel followed by repeated washing with absolute ethanol) in 750 ml of absolute ethanol was added 25.0 g of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**18**) hemihydrate. The mixture was stirred and heated under reflux for 30 min, the nickel allowed to settle, and the solution decanted. The residual nickel was stirred four times with 500-ml portions of hot absolute ethanol, and the combined decantations were evaporated to 250 ml, filtered, and cooled to give 13.4 g (75%) of **19**, mp 212–213° (lit.[8] mp 206–207°; mixture melting point with authentic material prepared by the literature procedure[8] was 212–213°).

Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.62; H, 5.83; N, 23.13. Found: C, 44.32; H, 5.90; N, 22.93.

Method B. A solution of 5.4 g of 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil in 17 ml of 97–100% formic acid was heated under reflux for 1 hr and concentrated to dryness under reduced pressure. The residue was dissolved in 25 ml of water and again concentrated to dryness. This process was repeated, and the residue was triturated with 1:1 ethanol–ether to give 1.62 g (47%) of crude **19**. Drying and recrystallization from ethanol gave material identical with that prepared by method A.

1,3-Dimethyluric Acid (20). 1,3-Dimethyl-5-carbethoxyamino-6-aminouracil (**19**) (500 mg) was placed in a test tube, in which a slight positive pressure of nitrogen was maintained, which was immersed in an oil bath preheated to 175°. The temperature of the heating bath was then raised to 235° over a period of 45 min. The contents of the reaction vessel were cooled, powdered, recrystallized from water, and dried: yield 0.38 g (93%) of colorless crystals, mp 412–415° (lit.[12] mp 408–410° dec; mixture melting point with authentic material 412–415°).

Anal. Calcd for $C_7H_8N_4O_3$: C, 42.63; H, 4.11; N, 28.56. Found: C, 42.70; H, 4.35; N, 28.60.

1,3-Dimethyl-6-methylaminouracil (10). 1,3-Dimethyl-6-chlorouracil was prepared by the procedure of Pfleiderer and Schündehütte[9] except that it was found more convenient to take up the crude product in chloroform, and to use the resulting solution (dried and filtered) directly. Thus, to 500 ml of a stirred chloroform solution containing 50.9 g (0.30 mol) of 1,3-dimethyl-6-chlorouracil was added over a 20-min period a mixture of 250 ml of ethanol and 93.0 g of a 40% aqueous solution (37.4 g, 1.2 mol) of methylamine. After 24 hr the reaction mixture was concentrated *in vacuo* and the residue washed with cold ethanol, acetone, and then ether to give 67.0 g (quantitative) of the hydrochloride monohydrate, mp 204–205° dec. A 37.4-g (0.182 mol) portion of this material was dissolved in 200 ml of boiling water, cooled slightly, and treated in small portions with 15.1 g (0.182 mol) of solid sodium bicarbonate. Cooling and filtering then gave 28.8 g (quantitative) of the free base of **10**, mp 240–241° dec.

Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.69; H, 6.36; N, 24.75.

1,3-Dimethyl-6-hydrazinouracil (11). To a stirred solution of 131.0 g (0.75 mol) of 1,3-dimethyl-6-chlorouracil in 1 l. of chloroform was added dropwise over a period of 2 hr a solution of 120.0 g (2.03 mol) of 85% aqueous hydrazine hydrate in 200 ml of ethanol. The reaction mixture was maintained at room temperature overnight and concentrated under reduced pressure, and the residue was triturated with 250 ml of ethanol. Filtration then gave 108.1 g (84%) of **11**, mp 239–240° dec. The analytical sample, recrystallized from ethanol, melted at 240–241° dec (lit.[9] mp 216–218°).

Anal. Calcd for $C_6H_{10}N_4O_2$: C, 42.34; H, 5.92; N, 32.92. Found: C, 42.60; H, 6.08; N, 33.13.

1,3-Dimethyl-6-(benzylidinehydrazino)uracil (12). To a solution of 1.70 g (0.01 mol) of 1,3-dimethyl-6-hydrazinouracil (**11**) in 75 ml of hot aqueous ethanol (2:1) was added a solution of 1.1 g (0.01 mol) of benzaldehyde. The voluminous solid which formed immediately was collected by filtration and recrystallized from ethanol to give 2.35 g (91%) of colorless crystals, mp 270–271° (lit.[9] mp 253°).

Anal. Calcd for $C_{13}H_{13}N_4O_2$: C, 60.68; H, 5.09; N, 21.78. Found: C, 60.50; H, 5.24; N, 21.54.

1,3-Dimethyl-6-(1-methylhydrazino)uracil (13). To a solution of 83.5 g (0.475 mol) of 1,3-dimethyl-6-chlorouracil in 1.5 l. of chloroform was added slowly, over a period of 30 min, a solution of 65.8 g (1.425 mol) of methylhydrazine in 500 ml of chloroform. After stirring for 48 hr at room temperature, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. Trituration of the residue with 100 ml of cold ethanol followed by filtration gave 71.0 g (81%) of colorless crystals of **13**, mp 133–134°. The melting point was not changed upon recrystallization from ethanol.

Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.56; N, 30.42. Found: C, 45.54; H, 6.08; N, 30.21.

1,3-Dimethyl-6-(3,4,5-trimethoxybenzylidene-1-methylhydrazino)uracil was prepared in 92% yield as described above for the preparation of **12**, mp 177–178°.

Anal. Calcd for $C_{17}H_{22}N_4O_5$: C, 56.34; H, 6.12; N, 15.47. Found: C, 56.62; H, 5.96; N, 15.25.

1,3-Dimethyl-6-(2-formyl-1-methylhydrazino)uracil (14). To a mixture of 22.5 g (0.22 mol) of acetic anhydride and 150 ml of formic acid, maintained at 0°, was added gradually 32.0 g (0.20 mol) of 1,3-dimethyl-6-(1-methylhydrazino)uracil (**13**). The mixture was stirred at 0° until solution was complete and then heated at 50–55° for 1 hr. Concentration of the resulting solution under reduced pressure, trituration of the residual oil with cold ethanol, and filtration then gave 23.6 g (55%) of colorless crystals of **14**, mp 169–170°.

Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.71; N, 26.41. Found: C, 45.10; H, 5.71; N, 26.25.

3-Methyl-6-(1-methylhydrazino)uracil (15). To a stirred solution of 23.0 g (0.5 mol) of methylhydrazine in 100 ml of ethanol was gradually added a hot solution of 16.1 g (0.1 mol) of 3-methyl-6-chlorouracil[13] in 300 ml of dioxane. After 16 hr at room temperature, 5.4 g (0.1 mol) of sodium methoxide in 100 ml of methanol was added, the mixture filtered from precipitated sodium chloride, and the filtrate concentrated to give 14.0 g (76%) of colorless crystals of **15**, mp 205–207° (lit.[11] mp 207–209°).

3-Methyl-6-(*p*-anisylidene-1-methylhydrazino)uracil (16) was prepared in the usual manner from 3-methyl-6-(1-methylhydrazino)uracil and *p*-anisaldehyde in hot ethanol: yield 92%, mp 227–228° dec.

Anal. Calcd for $C_{14}H_{15}N_4O_3$: C, 58.52; H, 5.26; N, 19.50. Found: C, 58.32; H, 5.47; N, 19.27.

3-Methyl-6-(1,2-dimethylhydrazino)uracil (17). A stirred, ice-cooled solution of 13.3 g (0.10 mol) of 1,2-dimethylhydrazine dihydrochloride in 25 ml of water was treated with 8.0 g (0.20 mol) of solid sodium hydroxide, the mixture was filtered, and the filtrate was added to a solution of 4.0 g (0.025 mol) of 3-methyl-6-chlorouracil[13] in 300 ml of hot ethanol. The reaction mixture was heated under reflux for 4.5 hr and filtered, and the filtrate was concentrated under reduced pressure. The residual solid was extracted with 100 ml of hot ethanol, and the extract was filtered and again concentrated under reduced pressure. This time the residual solid was extracted with 10 ml of hot acetonitrile and the extract (after filtration) concentrated and cooled to give 3.5 g (76%) of colorless crystals of **17**, mp 179–181°.

Anal. Calcd for $C_7H_{12}N_4O_4$: C, 45.64; H, 6.56; N, 30.42. Found: C, 45.67; H, 6.72; N, 30.40.

Registry No.—**1**, 1193-22-2; **2**, 1004-38-2; **3**, 49753-53-9; **4**, 49810-25-5; **5**, 156-83-2; **6**, 56-06-4; **7**, 1005-39-6; **8**, 873-83-6; **9**, 6642-31-5; **10**, 5770-42-3; **11**, 40012-14-4; **12**, 25774-97-4; **13**, 4318-53-0; **14**, 49810-09-5; **16**, 42748-18-5; **17**, 49810-11-9; **19**, 49810-21-1; **20**, 944-73-0; diethyl azodicarboxylate, 1972-28-7; 1,3-dimethyl-6-chlorouracil, 6972-27-6; 1,3-dimethyl-6-(3,4,5-trimethoxybenzylidene-1-methylhydrazino)uracil, 49810-23-3.

References and Notes

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(2) For a detailed discussion of pyrimidine chemistry, see (a) D. J. Brown, "The Pyrimidines," Vol. XVI in the series "The Chemistry of Heterocyclic Compounds," A. Weissberger and E. C. Taylor, Ed., Wiley–Interscience, New York, N. Y., 1962; (b) D. J. Brown, "The Pyrimidines. Supplement I," 1970, in the same series.

(3) 5-Hydrazinopyrimidines have previously been available (in uniformly poor yield) only by the reaction of 5-bromopyrimidines with hydrazine: (a) ref 2a, p 210; (b) T. Sasaki and M. Ando, *Yuki Gosei Kagaku Kyokai Shi*, **27**, 169 (1969); (c) D. Shiho, N. Takahayashi, and M. Kanaoka, *J. Pharm. Soc. Jap.*, **75**, 808 (1955). For a failure of this reaction, see H. Bredereck, G. Kupsch, and H. Wieland, *Chem. Ber.*, **92**, 583 (1959).

(4) Preliminary report: E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **90**, 1374 (1968).

(5) Preliminary report: E. C. Taylor and F. Sowinski, *ibid.*, **91**, 2143 (1969).

(6) (a) R. Huisgen and H. Pohl, *Chem. Ber.*, **93**, 527 (1960); (b) W. H. Thaler and B. Franzus, *J. Org. Chem.*, **29**, 2226 (1964); (c) B. Franzus and J. H. Surridge, *ibid.*, **27**, 1951 (1962); (d) B. Franzus, *ibid.*, **28**, 2954 (1963); (e) B. T. Gillis and P. E. Beck, *ibid.*, **27**, 1947 (1962); (f) B. T. Gillis and P. E. Beck, *ibid.*, **28**, 3177 (1963); (g) O. Achmatowicz and O. Achmatowicz, *Rocz. Chem.*, **37**, 317 (1963).

(7) Tetrazenes are the formal reaction products of diethyl azodicarboxylate with hydrazines: E. Fahr and H. Lind, *Angew. Chem. Int. Ed. Engl.*, **5**, 372 (1966).

(8) W. Traube, *Ber.*, **33**, 3035 (1900).

(9) W. Pfleiderer and K.-H. Schündehütte, *Justus Liebigs Ann. Chem.*, **612**, 158 (1958).

(10) H. Biltz and H. Wittek, *Ber.*, **54**, 1035 (1921).

(11) G. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Amer. Chem. Soc.*, **84**, 1274 (1962).

(12) H. Biltz and M. Heyn, *Justus Liebigs Ann. Chem.*, **423**, 185 (1921).

(13) G. Nubel and W. Pfleiderer, *Chem. Ber.*, **95**, 1605 (1962).