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(13) National Institutes of Health Predoctoral Fellow, 1965–present.
(14) Leeds and Northrup Fellow (National Science Foundation administered), 1965–1966; National Science Foundation Fellow, 1966–present.
(15) NATO Postdoctoral Fellow, 1965–1966.

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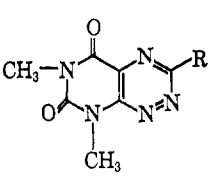
A New Method for C-5 Functionalization of Pyrimidines. New Routes to Azapteridines and Purines. Synthesis of Fervenulin[1]

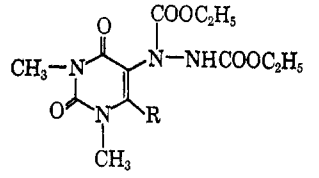
Sir:

A convenient new method for the introduction of nitrogen into the 5 position of pyrimidines has been found in the reaction of 6-amino- and -hydrazinopyrimidines, unsubstituted in position 5, with diethyl azodicarboxylate[2] in dimethylformamide or chlorobenzene suspension to give 5-(1,2-dicarbethoxyhydrazino) derivatives. Representative pyrimidines which undergo this reaction include 6-aminouracil (61%, mp 260.1° dec),[3] 2,6-diamino-4(3H)-pyrimidinone (55%, mp 251–252° dec), 2,4,6-triaminopyrimidine (37%, mp 240–241° dec), 2,6-diamino-4-(p-toluidino)pyrimidine (55%, mp 220.4° dec), 2,6-diamino-4-chloropyrimidine (40%, mp 204.7° dec), 2-dimethylamino-4,6-diaminopyrimidine (89%, mp 233.7° dec), 2-methylthio-4,6-diaminopyrimidine (67%, mp 244.2° dec), and 4-amino-6(1H)-pyrimidinone (59%, mp 228.3° dec). These adducts are versatile intermediates for the synthesis of pyrimido[5,4-*e*]-*as*-triazines (7-azapteridines), pyrimido[4,5-*e*]-*as*-triazines (6-azapteridines), and purines, as demonstrated below.

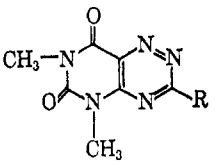
Fervenulin (Planomycin; 1,3-dimethyl-7-azalumazine, **1**), isolated from *Streptomyces fervens* n.sp.[4] and from *Streptomyces rubrireticuli*,[5] has been synthesized[6] and shown to be a representative of the pyrimido[5,4-*e*]-*as*-triazine group of antibiotics[7] which are known to possess an interesting spectrum of biological activities.[8] We report two new syntheses of this antibiotic by application of our new procedure for C-5 functionalization of pyrimidines. Thus, treatment of a dimethylformamide suspension of 1,3-dimethyl-6-hydrazinouracil[9] with a slight excess of diethyl azodicarboxylate, warming to 80°, and cooling gave 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-hydrazinouracil (**2**), mp 201.0° dec (63%). Reaction of **2** with phosphorus oxychloride in dimethylformamide (Vilsmeier–Haack formylation conditions) *resulted in its conversion in a single step* to Fervenulin (**1**),[4–7] mp 175.7° (40%), identical in all respects (melting point, mixture melting point, and uv, ir, and nmr spectra) with the natural antibiotic.



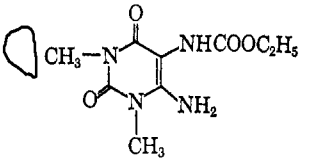
1, R = H
3, R = OH
4, R = Cl
5, R = $NHNH_2$



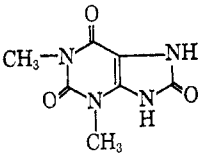
2, R = $NHNH_2$
7, R = NH_2



6, R = H
8, R = OH
9, R = Cl
10, R = $NHNH_2$



11



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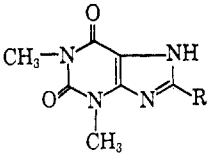

13, R = $N(CH_3)_2$
14, R = $N(CH_3)C_6H_5$

A second synthesis of **1** was achieved as follows. Stirring **2** with either sodium ethoxide or ethanolic potassium hydroxide at 0° effected cyclization directly to 1,3-dimethyl-6-hydroxy-7-azalumazine (**3**), mp 251.4° (63%). Refluxing phosphorus oxychloride converted **3** into the corresponding chloro derivative **4**, mp 147.0° (30%), which with anhydrous hydrazine in ethanol gave 1,3-dimethyl-6-hydrazino-7-azalumazine (**5**), mp 221.2° (48%). Oxidation of this derivative by stirring an aqueous suspension with mercuric oxide[10] for 3 hr gave Fervenulin (**1**) (41%).

Only a few examples of the isomeric pyrimido[4,5-*e*]-*as*-triazine (6-azapteridine) system are known,[11–14] but some derivatives are reported to have antiviral activity.[15] We also report the synthesis of 1,3-dimethyl-6-azalumazine (**6**), a structural isomer of Fervenulin, by a further

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(2) (a) E. Fahr and H. Lind, *Angew. Chem. Intern. Ed. Engl.*, **5**, 372 (1966); (b) M. D. Sidell, Massachusetts Institute of Technology Seminar in Organic Chemistry, Dec 13, 1966.
(3) Yields and melting points refer to the 5-(1,2-dicarbethoxyhydrazino) adducts. Most melting points below 300° were determined on a Mettler FP-1 apparatus; rate of heating 2°/min, initial insertion temperature 5° below the melting point. Satisfactory microanalytical and spectral data were obtained for all compounds reported.
(4) T. E. Eble, E. C. Olson, C. M. Large, and J. W. Shell, *Antibiot. Ann.*, 227 (1959–1960).
(5) K. Tanabe, Y. Asahi, M. Nishikawa, T. Shima, Y. Kuwada, T. Kanzawa, and K. Ogata, *Takeda Kenkyusho Nempo*, **22**, 133 (1963); *Chem. Abstr.*, **60**, 13242 (1964).
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(9) W. Pfleiderer and K.-H. Schündehütte, *Ann.*, **612**, 158 (1958).
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(11) L. Heinisch, W. Ozegowski, and M. Mühlstädt, *Chem. Ber.*, **97**, 5 (1964).
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(13) L. Heinisch, *ibid.*, **100**, 893 (1967).
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application of this reaction. A mixture of 1,3-dimethyl-6-aminouracil and a slight excess of diethyl azodicarboxylate in a chlorobenzene suspension gave 1,3-dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**7**), mp 147.3° (77%). Portionwise addition of lead tetraacetate to **7** in glacial acetic acid solution at 50–55° over a period of 1 hr gave upon cooling 1,3-dimethyl-7-hydroxy-6-azalumazine (**8**), mp 281.7° dec (66%) (lit.[11] mp 284–285° dec). Chlorination with phosphorus oxychloride to the 7-chloro derivative **9**,[16] mp 250.5° (98%), conversion with hydrazine hydrate in ethanol at room temperature to **10**, mp 247.2° (95%), and finally stirring overnight at room temperature with mercuric oxide[10] in water gave 1,3-dimethyl-6-azalumazine (**6**), mp 212.4° (49%).

1,3-Dimethyl-5-(1,2-dicarbethoxyhydrazino)-6-aminouracil (**7**) also proved to be a convenient intermediate for purine synthesis. Thus, refluxing **7** for 1 hr in anhydrous formic acid or for 3 hr in ethanol with excess Raney nickel resulted in cleavage of the N–N bond to give 1,3-dimethyl-5-carbethoxyamino-6-aminouracil (**11**), mp 213.2° (74%),[17] which was converted to 1,3-dimethyluric acid (**12**), mp 412–415° dec (87%),[18] on heating. The latter compound could be prepared directly from **7** in 52% yield by heating with formamide and anhydrous formic acid. Phosphorus oxychloride in dimethylformamide converted **7** to 8-dimethylaminotheophylline (**13**), mp 337–338° (72%), while phosphorus oxychloride and N-methylformanilide in toluene gave 8-(N-methylanilino)theophylline (**14**), mp 273° (67%). This appears to be a general method for the synthesis of 8-aminopurines.

(16) This compound is reported to melt at 251–253°.[11] Previous attempts to convert this compound to 1,3-dimethyl-6-azalumazine were reported to be unsuccessful.

(17) W. Traube, *Ber.*, **33**, 3035 (1900), reported mp 206–207°.

(18) H. Biltz and M. Heyn, *Ann.*, **423**, 185 (1921), reported mp 408–410° dec.

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Ion Injection. Excited t-$C_4H_9^+$ Reactions in Liquid Isobutylene

Sir:

Vibrationally excited ions exhibit less selectivity in their reactions than thermal ions. Ions produced in the liquid phase are expected to be thermalized rapidly at the time of formation. However, vibrationally excited ions are commonly produced in the gas phase both by electron or photon impact and by ion–molecule reactions. In the ion-injection method,[1-3] ions are produced by photolysis in the gas phase and injected into the liquid with an electric field. Thus the possibility arises for injecting excited ions into the liquid and for examining whether these excited ions will show reactive selectivity in the liquid phase. The formation and reaction of t-$C_4H_9^+$ in isobutylene by the ion-injection method illustrate these possibilities.

Isobutylene was photolyzed by krypton resonance lines (10 eV) to produce only the $C_4H_8^+$ ion which then reacted by eq 1. The t-$C_4H_9^+$ ion was injected into

$$C_4H_8^+ + i\text{-}C_4H_8 \longrightarrow t\text{-}C_4H_9^+ + C_4H_7 \quad (1)$$

liquid isobutylene at −128° by an electric field of 60 V/cm. Only C_8 and C_{12} products are observed under our experimental conditions.[3] The distribution of C_8 products was measured by gas chromatography.[3] The dependence of the C_8 products on added argon and neon and on temperature is shown in Tables I and II, respectively.

Table I. Effect of Added Argon and Neon on C_8 Products from t-$C_4H_9^+$ Reaction with Liquid Isobutylene[a]

Added gas		C_8 product distribution, %[b]			
Type	Pressure, torr	224-TMP[c]	224-TMP-2[d]	223-TMP[e]	344-TMP-2[f]
None		4	49	19	28
Ar	0.05	4	55	16	25
Ar	0.10	4	59	14	23
Ar	0.20	3	62	13	22
Ar	0.50	3	67	12	18
Ar	1.0	4	65	11	18
Ar	2.0	4	71	10	15
Ar	3.0	4	76	7	13
Ar	5.0	5	76	8	11
Ar	10.0	4	78	8	10
Ar	12.0	4	77	7	12
Ar	15.0	5	76	8	11
Ne	1.0	5	52	17	26
Ne	2.0	5	55	15	25
Ne	5.0	4	51	17	28
Ne	10.0	4	49	18	29

[a] Conditions: −400 V, 120-min photolysis, −128° (0.04 torr of isobutylene). [b] Relative C_8 yield and C_8/C_{12} ratio are constant for all experiments. [c] 2,2,4-Trimethylpentane, ±1%. [d] 2,4,4-Trimethylpentene-2, ±4%. [e] 2,2,3-Trimethylpentane, ±2%. [f] 3,4,4-Trimethylpentene-2, ±2%.

Table II. Phase and Temperature (Vapor Pressure) Effects on C_8 Products from t-$C_4H_9^+$ Reaction with Isobutylene

Vapor pressure, μ	Temp, °C	Per cent C_8 in products[a]	224-TMP[b] (% of C_8)	244-TMP-2[c] (% of C_8)	223-TMP[d] (% of C_8)	344-TMP-2[e] (% of C_8)
540	−110	75	4	49	20	27
280	−115	70	4	52	16	28
140	−120	74	5	49	17	29
80	−124	73	5	50	18	27
40	−128	76	4	49	19	28
6	−138	76	5	60	14	21
4	−140[f]	80	6	84	4	6
1	−145[g]	91	7	84	3	6

[a] 120-min photolysis time. [b] 2,2,4-Trimethylpentane, ±1%. [c] 2,4,4-Trimethylpentene-2, ±4%. [d] 2,2,3-Trimethylpentane, ±2%. [e] 3,4,4-Trimethylpentene-2, ±3%. [f] Freezing point. [g] Solid.

The reaction selectivity of t-$C_4H_9^+$ can be measured quantitatively from the C_8 products. The per cent of 2,2,4-trimethylpentane plus 2,4,4-trimethylpentene-2 represents the percentage of attack of t-$C_4H_9^+$ at the primary double-bond carbon in isobutylene, and the per cent of 2,3,3-trimethylpentane plus 3,4,4-trimethylpentene-2 represents the percentage of attack of t-$C_4H_9^+$ at the tertiary double-bond carbon in isobutylene. Thermal ions preferentially attack at the primary double-bond carbon.

The C_8 reaction product yields illustrate that t-$C_4H_9^+$ reacts nonselectively at both the primary and tertiary carbons in isobutylene. t-$C_4H_9^+$ is formed by reaction 1 which is estimated to be 10–20 kcal/mole exothermic in the gas phase. It is postulated that vibrationally

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(2) J. J. Sparapany, *ibid.*, **88**, 1375 (1966).

(3) N. S. Viswanathan and L. Kevan, *ibid.*, **89**, 2482 (1967).