Registry No.—**2**, 69291-96-9; **3**, 92-47-7; **4**, 22242-84-8; **4** *tert*-butyldimethylsilyl ether, 69291-97-0; **5**, 69291-98-1; **6**, 69291-99-2; **7**, 69292-00-8; **8**, 69292-01-9; **9** sodium salt, 69292-03-1; **10**, 59488-94-7; **11a**, 69292-02-0; **11b**, 69350-10-3; **12**, 69350-11-4; **13a**, 69292-04-2; **13b**, 69350-12-5; lithium bromoacetate, 64916-53-6; *tert*-butyldimethylchlorosilane, 18162-48-6; ethyl bromoacetate, 105-36-2; ethyl 4-(*tert*-butyldimethylsilyloxy)-7-methyl-1-ketoindan-2-acetate, 69331-26-6; methyl formate, 107-31-3.

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Intramolecular Thermal Reactions of the Derivatives of 5′-Azido-5′-deoxyuridine. New Feasible Route to the Regio- and Stereospecific Synthesis of Reversed Nucleosides Carrying a Substituted Five-Membered Heterocycle

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With a view to probing the reactivity of the "naked" 5,6-double bond of uracil nucleosides as a dipolarophile, 1-(5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**1a**) and its 5-deuterated analogue (**1b**), N^3-methylated analogue (**1c**), and 2′,3′-*O*-ethoxymethylene analogue (**1d**) were synthesized and submitted to an intramolecular thermal reaction, which yielded a high yield of N^1,5′-anhydro-N^{ω}-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-allophanoyl-1,2,3-triazole (**3a**), its N^{β}-methyl analogue (**3b**), and its 2′,3′-*O*-ethoxymethylene analogue (**3c**), respectively. 6,5′-Imino-1-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**4a**) and its N^3-methyl analogue (**4b**) were respectively isolated as byproduct in the case of **1a** and **1c**. Intermediacy of the triazoline, **2**, was confirmed for the formation of **3** and **4**. **3a** with methanol, ammonia, and hydrazine gave 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-ureido-1-β-D-ribofuranose (**8a**), its 4-carboxamido analogue (**8b**) and its 4-carboxyhydrazido analogue (**8c**), respectively. Similarly, their 2,3-ethoxymethylene analogues **6a** and **6b** were obtained from **3c**. **6a,b** were deprotected to 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-1-ureido-1-β-D-ribofuranose (**7a**) and its 4-carboxamido analogue **7b**. Diazotization of **8a** yielded 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-β-D-ribofuranose (**11a**) and its 1-*O*-acetate (**12a**). Analogous treatment of **8b** afforded the corresponding 4-carboxamido analogues, **11b** and **12b**. Deacetonation of **11a,b** and/or **12a,b** gave 5-(4-carboxamido-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-1-β-D-ribofuranose (**13a**) and its 4-carboxamido analogue (**13b**). Some synthetic implications are suggested for the formation of **3**.

Much effort has been devoted to the study of photodimerization[1,2] and photocycloaddition of pyrimidines to electron-rich monoolefins[3] as a model for photochemical transformation of natural nucleic acids and for preparative chemistry aiming at direct carbon–carbon bond formation and functionalization. On the other hand, there are only few examples which use the 5,6-double bond of pyrimidines as a dipolarophile: the hitherto known two cases are 1,3-dipolar cycloaddition reactions of an azide with pyrimidine nuclei activated with 5-nitro or 5-bromo substituent.[4,5] In these cases, addition is usually followed by elimination of the activating group to furnish directly aromatized cycloadducts. The possibility of thermal 1,3-dipolar cycloaddition to the "naked" 5,6-double bond of pyrimidine nucleosides was suggested by the known ground state reactivity of these heterocyclic bases. It is well established[6] that the 6 position of pyrimidine nucleosides can accept nucleophiles in the manner of a Michael reaction, while the 5 position is vulnerable to attack by electrophiles. This behavior is explicable on the basis of a simple HOMO–LUMO consideration[7] and is reflected in the synthesis of 6,5′-*O*-,[8] 6,5′-*S*-,[9] and 6,5′-*N*-cyclopyrimidine nucleosides.[10]

Synthetic exploitation of pyrimidines as dipolarophiles or dienophiles is important in view of the great variability of the expected products and the direct use of natural nucleosides with a given stereochemistry involving, among others, that of the anomeric position. From this point of view, 1-(5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**1a**)[11] is a readily accessible, simple model compound for roughly evaluating the reactivity of the "naked" 5,6-double bond with 1,3-dipoles. A preliminary communication[12] has reported the major results of the intramolecular thermal reactions of **1a** and the 5-deuterated analogue **1b**, which lead to a regiospecific synthesis of some 4-substituted triazole reversed nucleosides. This paper describes the details of this work with additional experiments and accompanying observations.

Synthesis of the Substrates 1a–d for 1,3-Dipolar Cycloaddition. **1a** was synthesized nearly as described[11] except that a one-to-one mixture of sodium azide and ammonium chloride or tetraethylammonium chloride was used rather than lithium azide at the azidation step. **1b** was synthesized starting from 5-deuterated uridine[13] essentially in the same way with **1a**, avoiding recrystallization from protic solvents

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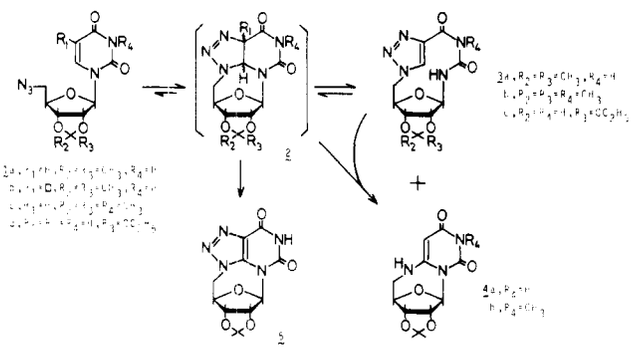
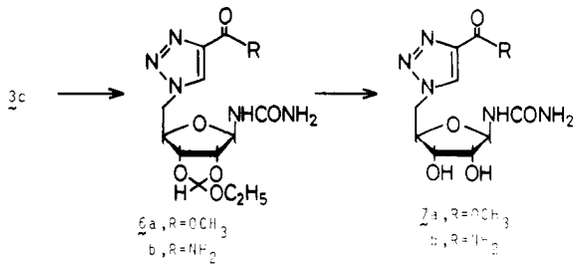
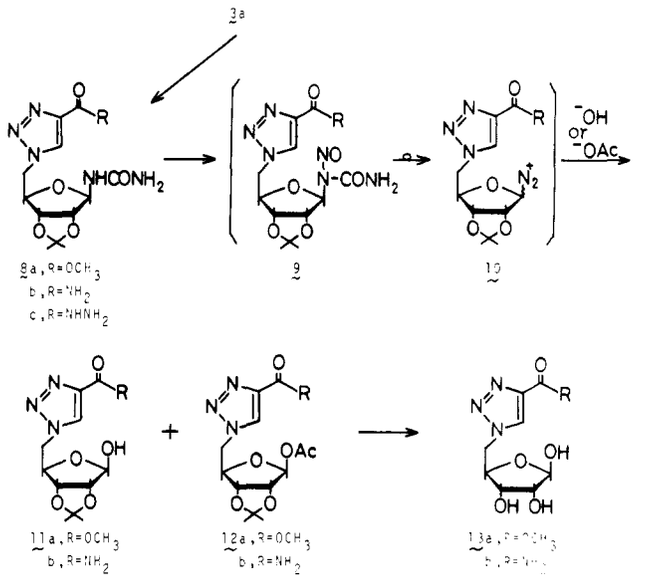
Scheme I



Scheme II



Scheme III



or high-temperature treatments at the steps of intermediate synthesis as far as possible. The structure of **1b** was confirmed by IR (νN_3 2115 cm^{-1}, KBr) and ^1H NMR spectrum ($CDCl_3$) (H_6 resonantes at 7.3 ppm as a singlet). Methylation of **1a** with *N,N*-dimethylformamide dimethylacetal[14] gave 5′-azido-5′-deoxy-2′,3′-*O*-isopropylidene-N^3-methyluridine (**1c**) quantitatively. 5′-Azido-5′-deoxy-2′,3′-*O*-ethoxymethyleneuridine (**1d**) was also synthesized similarly with **1a** (see Experimental Section) starting from 2′,3′-*O*-ethoxymethyleneuridine (probably a mixture of diastereomers) obtained by the procedure described.[15] The reasons for the use of **1c** and **1d** will be referred to later.

Intramolecular 1,3-Dipolar Cycloaddition Reactions of 1a–d. Heating **1a** in dry toluene at 110 °C gave a precipitate which consisted of N^1,5′-anhydro-N^ω-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)-4-allophanoyl-1,2,3-triazole (**3a**) as major product (80%) and 6,5′-imino-1-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)uracil (**4a**) (5.3%). The former compound did not absorb above 210 nm and exhibited a rather eccentric ^1H NMR spectrum (see Experimental Section), in which the heteroaromatic proton signal at 8.23 ppm and the imino resonance at 5.35 ppm interacting with that of the anomeric proton were particularly suggestive of a structure formed by C_6–N^1 cleavage. The structure of **3a** was reinforced by its subsequent reactions. Compound **4a** was easily characterized by its spectroscopic properties which were also consistent with those of an authentic sample prepared by Ueda and co-workers via an alternative route involving three steps from 5′-amino-5′-deoxy-2′,3′-*O*-isopropylideneuridine.[16]

In search for the most plausible intermediate, **2**, for the formation of **3a** and **4a**, **1a** and equimolar 2,3-dichloro-5,6-dicyano-1,4-benzoquinon (DDQ) were heated in toluene under similar conditions to give the known 8-azaxanthine derivative **5**[5] and **4a**, no trace of **3a** being detected by TLC. On heating **3a** with DDQ in toluene as above, the concurrent formation of **4a**, **5**, and an uncharacterizable product was observed. These experiments clearly indicate that **2** and **3a** are interconvertible at this temperature and the immediate precursor of **4a** is **2**.[17] The previous communication[12] has not referred to occurrence of any cycloreversion of **2** to **1a**. More recently, we observed partial reversion of **3a** to **1a** when **3a** was heated in dioxane at 110 °C using a rather large volume of this solvent to make the reaction homogeneous. Several small-scale experiments have shown that the detectable thermodynamic products are only **3a** and **4a** irrespective of solvent polarity. Thus, the use of DMF, pyridine, dioxane, tetrachloroethane, or acetic acid gave a similar product distribution, except that the use of acetic acid accelerated the reaction in favor of formation of **4a** and an uncharacterizable insoluble product rather than **3a**, and that a homogeneous reaction in DMF seemed to raise the yield of **4a**.[18] Although the close scrutiny of all these events was excluded largely due to the difficulty of separating the tightly running[19] **3a** and **4a** and to the general material shortage, we can now depict the main events leading ultimately to **4a** as in Scheme I. This is the first synthesis of an N-bridged nucleoside by triazoline decomposition that could be economically used by further elaboration when needed. The same experiment using a 5-deuterated azide (**1b**) also gave **3a** and **4a**, indicating a net 1,3-shift of 5-D to N^ω. An analogous thermal reaction using **1c** proceeded in a homogeneous solution, giving **3b** and **4b** in 55 and 7.7% yield, respectively. **3b** was synthesized initially for the purpose of inspecting regioselectivity in subsequent nucleophilic cleavage, but was not further pursued. Repeated attempts to deprotect **3a** in acidic media were not successful since an intractable mixture was obtained. Hence, in view of the need for deprotection of future products, we also conducted the same experiment using **1d**. The product distribution was quite similar to the reaction of **1a**; the major product **3c** was isolated as stereohomogeneous crystals. The structures of **3b,c** and **4b** are now obvious on the basis of spectral comparison with **3a** and **4a** (see Experimental Section). Several trials for the selective deprotection of **3c** also failed presumably owing to the presence of an acid-sensitive *N,O*-acetal partial structure. On the other hand, a separate cyclization experiment using 5′-azido-5′-deoxy-2′,3′-di-*O*-acetyluridine[11] resulted in complete recovery of the starting material, suggesting that the cyclization to **2** is assisted by the rigid 2′,3′-acetal.[20]

Availability of **3a** and **3c** in good to excellent yields and the presence of the multifunctional allophanoyl chain (–CO–NH–CO–NH–) gave an impetus to further transformations, among which nucleophilic scission was examined. Heating **3a** or **3c** in refluxing methanol allowed regiospecific methanolysis to afford 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-ureido-1-β-D-ribofuranose (**8a**) (Scheme III) or its 2′,3′-*O*-ethoxymethylene analogue (**6a**) (Scheme II). This initial finding was encouraging in view of the recent, broad scope of synthesis of nucleosides containing five-membered polyazaheterocycles[21] and also of the multiple

implication endowed to "reversed" nucleosides.[22,23] Since we desired these compounds in deprotected form for biological evaluation, **8a** was submitted to acidic treatment. However, the isopropylidene unit turned out to be too hard to remove without side reactions. Finally, we chose to concentrate on the 2′,3′-*O*-ethoxymethylene analogue, **3c**, for this purpose (Scheme II). Treatment of **3c** with ethanol saturated with ammonia gave 5-(4-carboxamido-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-ethoxymethylene-1-ureido-1-β-D-ribofuranose (**6b**) in 80% yield. Both **6a** and **6b** exhibited UV absorptions at around 210 nm consistent with a 4-carbonyl-1,2,3-triazole structure[24] and similar ^{1}H NMR spectra, in which the anomeric proton signal appeared at 5.25 ppm as the doublet of doublets with $J_{1,2}$ = 2.0 Hz and $J_{1,NH}$ = 6–8.5 Hz for both compounds. The β configuration assigned to these compounds is evident as judged by the small H_1–H_2 coupling constants and, further, there are no mechanistic reasons for epimerization at the anomeric carbon.[25] Brief treatment of **6a,b** with 90% trifluoroacetic acid[27] gave the desired 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-1-ureido-1-β-D-ribofuranose (**7a**) and its 4-carboxamido analogue (**7b**). Although the yields described in this paper are moderate, the hydrolysis reactions are selective and complete as judged by TLC.

The high-yield synthesis of **6a,b** further spurred us to examine chemical modification of the ureido parts. Although the ureido group itself is a quite versatile synthon for constructing heterocyclic bases, chemical degradation at the anomeric position seemed to be of particular interest to us, since this position is of major stereochemical concern in nucleosides. For this purpose, we decided to start with 2′,3′-*O*-isopropylidene analogues (Scheme III). Thus, 5-(4-carboxamido-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-ureido-1-β-D-ribofuranose (**8b**) and its 4-carboxyhydrazido analogue, **8c**, were synthesized in like manners in excellent yields. For the synthesis of **8c**, ethanolic hydrazine of concentration below 0.2 M is recommendable to exclude side reactions. The structures of **8a–c** are evident on the basis of analysis and spectroscopic data described in the Experimental Section. **8a** was submitted to a mild nitrosation reaction using excess sodium nitrite in 80% acetic acid to give two less polar products, which were successfully separated and characterized as 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-β-D-ribofuranose (**11a**) and its 1-*O*-acetyl analogue (**12a**).[28] Similar treatment of **8b** with a large excess of sodium nitrite gave 5-(4-carboxamido-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-2,3-*O*-isopropylidene-1-β-D-ribofuranose (**11b**) and its 1-*O*-acetyl analogue (**12b**).[28] For all these compounds, the assigned β configuration is doubtless as judged by the ^{1}H NMR spectra, in which no H_1–H_2 couplings were discernible. Although we abandoned optimization of the yields of **11** and **12**, the stereohomogeneity of these compounds was assured. This nitrosation reaction must have proceeded **9**, **10**, or further 1-carbocation presumably stabilized by neighboring oxygen with or without ion pair formation.[29] To our best knowledge, this is the first example of transformation through an anomeric diazo species in the area of nucleosides or carbohydrates. At the present stage, we are not prepared to explain the strict retention of configuration. Deprotection of **11a** or the double deprotection of **12a** smoothly proceeded in 90% trifluoroacetic acid to provide 5-(4-methoxycarbonyl-1,2,3-triazol-1(1*H*)-yl)-5-deoxy-1-β-D-ribofuranose (**13a**). Similar treatment of a mixture of **11b** and **12b** gave its 4-carboxamido analogue (**13b**). These hydrolysis reactions generally proceeded without side reactions as judged by TLC and accordingly the rather low yields described herein should be attributed to loss during the workup procedures.

In conclusion, the intramolecular 1,3-dipolar cycloaddition of the 5′-azido group to the "naked" 5,6-double bond of uracil nucleosides has been effectively realized. It is accompanied by an unprecedented N^1–C_6 cleavage which is subject to recyclization. The overall result provides not only a short route to cyclonucleosides such as **5** or **4** but also allows use of the C_4–C_5–C_6 unit in the uracil skeleton as a "masked" synthon for synthesizing reversed nucleosides carrying substituted polyazaheterocycles that are bonded to the sugar moiety at a defined position.[30] Moreover, the concurrently introduced β-ureido function could be transformed in a variety of ways which includes the synthesis of the double-headed nucleosides.

Experimental Section

All the melting points are uncorrected. The ultraviolet spectra were measured on a Jasco Model ORD/UV-5 spectrophotometer. The ^{1}H NMR spectra were determined using a JNM C-60 HL spectrometer and Me_4Si as an internal standard, while some 100-MHz spectra were recorded with a Varian HA-100 spectrometer in the Research Laboratory, Takeda Chemical Industries Co., Ltd. The CD spectrum of compound **4a** was recorded with a Jasco Model J-20 recording spectropolarimeter in the laboratory of the Japan Spectroscopic Co., Ltd. Elemental analyses were conducted by Miss Y. Kawai using a Perkin-Elmer 240 elemental analyzer in this laboratory. For preparative scale TLC, glass plates coated with a 2-mm thickness of Wakogel B-5 silica gel were used after activating at 110 °C for 7–10 h. All evaporations were carried out in vacuo at or below 40 °C.

5′-Azido-5′-deoxy-2′,3′-*O*-isopropylidene-N^3-methyluridine (1c). A mixture of **1a** (200 mg, 0.65 mM) and DMF–acetal (0.26 mL, 2.6 mM) in dry chloroform (6 mL) was heated to reflux for 4 h. The mixture was evaporated and the residual paste was submitted to preparative TLC using silica gel (10 × 20 cm) and chloroform/ethyl acetate (1:1). Elution of the main band with acetone gave 215 mg (99%) of glass (**1c**) which contained 0.25 mol equiv of acetone: IR (KBr) 2110 cm^{-1} (ν_{N_3}); UV (MeOH) 256 nm (ε 11 000); ^{1}H NMR ($CDCl_3$, solvent resonance excluded) δ 1.35 (3 H, s, Me), 1.57 (3 H, s, Me), 3.30 (3 H, s, N^3–Me), 3.60 (2 H, d, $J_{4',5'}$ = 5.5 Hz, 5′-methylene), 4.25 (1 H, m, $H_{4'}$), 4.7–5.1 (2 H, m, $H_{2'}$ and $H_{3'}$), 5.65 (1 H, d, $J_{1',2'}$ = 2.0 Hz, $H_{1'}$), 5.77 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), and 7.30 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_6).

Anal. Calcd for $C_{13}H_{17}N_5O_5 \cdot \frac{1}{4}CH_3COCH_3$: C, 48.88; H, 5.52; N, 20.73. Found: C, 49.02; H, 5.53; N, 20.70.

5′-Azido-5′-deoxy-2′,3′-*O*-ethoxymethyleneuridine (1d). A mixture of 2′,3′-*O*-ethoxymethyleneuridine (4.24 g, 14.1 mM) and tosyl chloride (2.99 g, 15.5 mM) in pyridine (100 mL) was left at room temperature for 24 h, treated with water (1 mL) at room temperature for 1 h, and then evaporated. The residue was partitioned between ethyl acetate (50 mL) and water (20 mL). The separated organic layer was dried over sodium sulfate and evaporated to give a practically homogeneous foam (5.8 g, 91%) which resisted crystallization. The total was combined with sodium azide (2.5 g, 38.4 mM) and ammonium chloride (2.06 g, 38.4 mM) in DMF (60 mL) and the mixture was stirred at 90 °C for 3.5 h. After cooling the mixture was evaporated and partitioned between ethyl acetate (50 mL) and water (20 mL). The separated organic phase was appropriately worked up and charged on a column (3 × 22 cm) of silica gel (100 mesh). Elution with $CHCl_3$/EtOAc (3:1) afforded 3.04 g (73% based on the tosylate) of homogeneous foam (**1d**): IR (KBr) 2100 cm^{-1} (ν_{N_3}).

Anal. Calcd for $C_{12}H_{15}N_5O_6$: C, 44.31; H, 4.65; N, 21.53. Found: C, 44.52; H, 4.46; N, 21.33.

Thermal Reaction of 1a. 1a (2.0 g, 6.47 mM) in dry toluene (200 mL) was stirred at 110 °C for 30 h. After cooling the solvent was removed, the residue was digested with acetone (40 mL), and the sparingly soluble homogeneous powder (**3a**) was collected by suction. The filtrate was evaporated and the residue again heated in toluene (60 mL) at 110 °C for 25 h. After evaporating the solvent, the residue was digested with acetone (20 mL) and the collected powder again washed in stirring acetone (10 mL) to give another crop of **3a** (total yield 80%). For analysis and spectroscopic measurements, a part was quickly recrystallized from methanol to give crystals of mp 228–231 °C: UV transparent above 210 nm; ^{1}H NMR (Me_2SO-d_6) δ 1.25 (3 H, s, Me), 1.48 (3 H, s, Me), 4.34 (2 H, t, 5′-methylene), 4.47–5.00 (3 H, m, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 5.35 (1 H, d, $J_{1',NH}$ = 7.5 Hz, $H_{1'}$, collapsed to s on D_2O addition), 6.74 (1 H, d, $J_{NH,1'}$ = 7.5 Hz, D_2O exchangeable, ω – NH), 8.23 (1 H, s, triazole 5-H), and 10.16 (1 H, br s, D_2O exchangeable, lactam NH).

Anal. Calcd for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.89; N, 22.65. Found: C, 46.61; H, 5.00; N, 22.73.

The mother liquor separated from the major part of **3a** was sub-

mitted to preparative TLC [20 × 20 cm, $CHCl_3$/MeOH (9:1)] to afford 96 mg (5.3%) of **4a** as crystals of mp 297.5–300 °C dec after recrystallization from acetone: UV (MeOH) 275 nm (ε 20 700); CD (MeOH) [θ] +17.2 × 10^3 (275 nm).

Anal. Calcd for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.12; H, 5.45; N, 14.99.

Thermal Reaction of 1a in the Presence of DDQ. A mixture of **1a** (200 mg, 0.647 mM) and DDQ (180 mg, 0.793 mM) in toluene (20 mL) was stirred at 110 °C for 35 h under an argon stream. The mixture was evaporated and digested with benzene and the solid was collected by suction. This solid mixture was stirred in acetone (8 mL) and filtered to give 25 mg (12.5%) of homogeneous **3a.** The filtrate was evaporated, applied on a silica gel plate (15 × 20 cm), and developed with $CHCl_3$/MeOH (9:1). Elution of the faster moving main band with acetone gave 60 mg (30%) of **5**, while the slower moving band afforded 10 mg (5.5%) of **4a.** These products were identified with authentic samples by IR and UV spectroscopy and TLC.

Thermal Reaction of 1b. 1b (210 mg, 0.68 mM) in toluene (40 mL) was heated at 110 °C for 30 h. Workup of the reaction mixture at this stage as in the case of **1a** permited isolation of 130 mg (62%) of **3a,** identical with the product prepared with **1a.** Another product was neglected.

Thermal Reaction of 3a in the Presence of DDQ. A mixture of **3a** (110 mg) and DDQ (135 mg) in toluene (20 mL) was stirred at 110 °C and TLC control was continued at every 2 or 3 h withdrawing an aliquot from this heterogeneous reaction. After ca. 30 h, the appearance of **4a** as well as **5** as a minor component was indicated. After a total of 90 h, the mixture was evaporated and the residue digested with a large volume of acetone to give 80 mg of solid which was insoluble in all tried solvents including pyridine and DMF. The filtrate contained only **3a, 4a,** and **5** as judged by TLC ($CHCl_3$/MeOH, 9:1) but their separation was abandoned owing to the material paucity.

Thermal Reaction of 1c. Compound **1c** (200 mg, 0.59 mM) in toluene (10 mL) was heated at 110 °C for 28 h and cooled. The reaction solution was evaporated, the residue was stirred in acetone (4 mL), and the practically homogeneous solid of **3b** was collected (60 mg). The filtrate was evaporated, again heated in toluene (6 mL) at 110 °C for 30 h, and evaporated. Trituration of the residue with acetone (3 mL) gave another crop of **3b** (25 mg). Preparative TLC (10 × 20 cm, $CHCl_3$/MeOH, 9:1) with the filtrate gave an additional crop of **3b** (25 mg, total yield 55%) and 14 mg (7.7%) of **4b.** Both products were recrystallized from acetone. **3b:** mp 176–179 °C; UV (MeOH) 215 nm (sh) (ε 10 100); ^{1}H NMR (Me_2SO-d_6) δ 1.22 (3 H, s, Me), 1.46 (3 H, s, Me), 3.07 (3 H, s, N^3–Me), 4.2–4.9 (5 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$, and 5'-methylene), 5.30 (1 H, d, $J_{1',NH}$ = 6.0 Hz, $H_{1'}$, collapsed to s on D_2O addition), 7.15 (1 H, br d, $J_{NH,1'}$ = 6.0 Hz, D_2O exchangeable, ω – NH), and 8.15 (1 H, s, triazole H_5).

Anal. Calcd for $C_{13}H_{17}N_5O_5$: C, 48.30; H, 5.30; N, 21.66. Found: C, 48.56; H, 5.22; N, 21.66.

4b: mp 194–197 °C; UV (MeOH) 275 nm (ε 19 300); ^{1}H NMR (Me_2SO-d_6) δ 1.27 (3 H, s, Me), 1.42 (3 H, s, Me), 2.8–3.4 (2 H, m, 5'-methylene), 3.09 (3 H, s, N^3–Me), 4.46 (1 H, m, $H_{4'}$), 4.72 (2 H, s, $H_{2'}$ and $H_{3'}$), 5.03 (1 H, s, H_5), 6.40 (1 H, s, $H_{1'}$), and 6.85 (1 H, br d, $J_{NH,H_{5a}}$ = 6.0 Hz, D_2O exchangeable, NH).

Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.87; H, 5.80; N, 14.23. Found: C, 53.16; H, 5.81; N, 14.18.

Thermal Reaction of 1d. Compound **1d** (1.87 g, 5.75 mM) in toluene (180 mL) was stirred at 110 °C for 25 h. The product distribution indicated by TLC was similar with the reactions of **1a–c.** The mixture was concentrated to ca. half volume to give a gelatine containing a solid precipitate. Hence, the total was again heated at 90 °C until the gel disappeared and quickly filtered by suction while hot. The collected solid was stirred in chloroform (20 mL) at room temperature and filtered to give TLC-homogeneous **3c** (680 mg). The combined filtrates were evaporated, the residue again heated in toluene (100 mL) at the same temperature for 21 h, and the mixture filtered while hot. The obtained solid material was thoroughly stirred in chloroform (20 mL) to give additional **3c** (273 mg). The filtrate was submitted to preparative TLC [20 × 20 cm, $CHCl_3$/MeOH (85:15)] to give a further 20 mg of **3c.** The total solid was recrystallized from acetone to afford 950 mg (51%) of **3c** as crystals: mp above 290 °C; UV (MeOH) transparent above 210 nm; ^{1}H NMR (Me_2SO-d_6 + $CDCl_3$, 2:1) δ 1.15 (3 H, t, Me), 3.52 (2 H, q, methylene of OC_2H_5), 4.35 (2 H, m, 5'-methylene), 4.6–4.9 (3 H, m, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 5.40 (1 H, d, $J_{1',NH}$ = 7.5 Hz, collapsed to s on D_2O addition, $H_{1'}$), 6.00 (1 H, s, methine of the ethoxymethylene group), 6.84 (1 H, d, $J_{NH,1'}$ = 7.5 Hz, D_2O exchangeable, ω – NH), 8.20 (1 H, s, triazole H_5), and 10.10 (1 H, s, D_2O exchangeable, lactam NH).

Anal. Calcd for $C_{12}H_{15}N_5O_6$: C, 44.31; H, 4.65; N, 21.53. Found: C, 44.30; H, 4.76; N, 21.68.

Another product was neglected.

Synthesis of 6a. 3c (100 mg, 0.31 mM) in methanol (40 mL) was heated to reflux for 30 h and cooled. After evaporation the residue was purified by preparative TLC (10 × 20 cm, $CHCl_3$/MeOH, 9:1) and recrystallized from methanol to give 86 mg (78%) of **6a** as crystals of mp 191–193 °C: UV (MeOH) 213 nm (δ 14 000); ^{1}H NMR (Me_2SO-d_6) δ 1.20 (3 H, t, Me), 3.52 (2 H, q, methylene of OC_2H_5), 3.85 (3 H, s, OMe), 4.16–4.36 (1 H, m, H_4), 4.60–4.90 (4 H, m, H_2, H_3, 5-methylene), 5.25 (1 H, dd, $J_{1,NH}$ = 8.5 Hz, $J_{1,2}$ = 2.0 Hz, collapsed to d on D_2O addition, H_1), 5.78 (2 H, br s, D_2O exchangeable, NH_2), 6.05 (1 H, s, methine of the ethoxymethylene group), 7.05 (1 H, d, $J_{NH,1}$ = 8.5 Hz, D_2O exchangeable, NH), and 8.64 (1 H, s, triazole H_5).

Anal. Calcd for $C_{13}H_{19}N_5O_7$: C, 43.70; H, 5.36; N, 19.60. Found: C, 43.49; H, 5.29; N, 19.75.

Synthesis of 6b. Compound **3c** (300 mg, 0.92 mM) and saturated ethanolic ammonia (36 mL) were combined in a pressure tube and sealed. The mixture was vigorously stirred at 40 °C for 1.5 h and evaporated and the remainder was digested with a small amount of ethanol. The solid collected by suction proved to be TLC homogeneous. The filtrate was evaporated and the residue triturated with a small volume of acetone to give another crop of solid. Recrystallization of the combined solid from methanol gave 220 mg (71%) of **6b:** mp 218–220 °C; UV (MeOH) 211 nm (ε 13 400); ^{1}H NMR (Me_2SO-d_6) δ 1.10 (3 H, t, Me), 3.50 (2 H, q, methylene of OC_2H_5), 4.3 (1 H, m, H_4), 4.5–4.8 (4 H, m, H_2, H_3, and 5-methylene), 5.25 (1 H, dd, $J_{1,NH}$ = 6.0 Hz, $J_{1,2}$ = 2.0 Hz, collapsed to d on D_2O addition, H_1), 5.82 (2 H, s, D_2O exchangeable, ureido NH_2), 6.03 (1 H, s, methine of the ethoxymethylene group), 7.00 (1 H, d, $J_{NH,1}$ = 6.0 Hz, D_2O exchangeable, NH), 7.48, 7.82 (each 1 H, br s, D_2O exchangeable, carboxamide), and 8.43 (1 H, s, triazole H_5).

Anal. Calcd for $C_{12}H_{18}N_6O_6$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.98; H, 5.17; N, 24.62.

Synthesis of 7a. A solution of **6a** (70 mg, 0.2 mM) in 90% trifluoroacetic acid (2 mL) was left at room temperature for 10 min and quickly evaporated. The residue was repeatedly coevaporated with methanol to remove the residual trifluoroacetic acid. Recrystallization of the residue from methanol gave 40 mg (68%) of **7a** as needles of mp 169–171 °C: UV (MeOH) 214 nm (ε 10 900); mass spectrum *m/e* 128 (4-methoxycarbonyl-1,2,3-triazole + H), 127 (4-methoxycarbonyl-1,2,3-triazole cation), 97 (4-carbonyl-1,2,3-triazole + H, relative intensity 68.3), 96 (4-carbonyl-1,2,3-triazole cation, 100), 68 (96-CO, 10.3), 69 (68 + H); ^{1}H NMR (Me_2SO-d_6) δ 3.54–3.64 (1 H, m, H_4), 3.72–4.07 (2 H, m, 5-methylene), 3.85 (3 H, s, OMe), 4.52–4.65 (2 H, m, H_2 and H_3), 5.0–5.18 (3 H, m, reduced to one proton d with $J_{1,2}$ = 4.0 Hz on D_2O addition, H_1, C_2–OH, and C_3–OH), 5.58 (2 H, s, D_2O exchangeable, NH_2), 6.62 (1 H, d, $J_{NH,1}$ = 10.0 Hz, NH), and 8.58 (1 H, s, triazole H_5).

Anal. Calcd for $C_{10}H_{15}N_5O_6$: C, 39.87; H, 5.07; N, 23.25. Found: C, 39.94; H, 5.17; N, 23.08.

Synthesis of 7b. A solution of **6b** (60 mg) in 90% trifluoroacetic acid (2.4 mL) was left at room temperature for 15 min and quickly evaporated. The residue was repeatedly coevaporated with methanol and again dissolved in methanol (30 mL). The solution was neutralized with anion exchange resin, IRA-93 (OH form), and filtered. The resin was thoroughly washed with methanol (300 mL) and the combined methanolic solution was evaporated to give a crystalline residue, which was recrystallized from methanol to give ca. 30 mg (58%) of **7b** as fine needles: mp 209–211 °C; UV (MeOH) 210 nm (ε 14 200); mass spectrum *m/e* 113 (4-carboxamido-1,2,3-triazole + H, rel intensity 12.3), 112 (4-carboxamido-1,2,3-triazole cation, 100), 97 (4-carbonyl-1,2,3-triazole + H, 6.6), 96 (97-H, 93.7), 69 (1,2,3-triazole + H); ^{1}H NMR (Me_2SO-d_6) δ 3.73–4.18 (3 H, m, H_4 and 5-methylene), 4.48–4.60 (2 H, m, H_2 and H_3), 5.18 (1 H, d, J = 5.0 Hz, D_2O exchangeable, C_2–OH or C_3–OH), 5.35 (1 H, d, J = 4.0 Hz, D_2O exchangeable, C_3–OH or C_2–OH), 5.46 (1 H, dd, $J_{1,NH}$ = 10.0 Hz, $J_{1,2}$ = 3.0 Hz, collapsed to d on D_2O addition, H_1), 5.83 (2 H, s, D_2O exchangeable, ureido NH_2), 6.42 (1 H, d, $J_{NH,1}$ = 10.0 Hz, D_2O exchangeable, NH), 7.38, 7.73 (each 1 H, br s, D_2O exchangeable, carboxamide), and 8.35 (1 H, s, triazole H_5).

Anal. Calcd for $C_9H_{14}N_6O_5 \cdot {}^1/_4CH_3OH$: C, 37.76; H, 5.14; N, 28.56. Found: C, 37.90; H, 4.88; N, 28.68.

Synthesis of 8a. Compound **3a** (500 mg, 1.62 mM) in methanol (200 mL) was heated to reflux for 30 h and the mixture was evaporated. The residue was recrystallized from water to give 480 mg (87%) of **8a:** mp 136–138 °C; UV (MeOH) 214 nm (ε 10 100); ^{1}H NMR (Me_2SO-d_6 + $CDCl_3$, 2:1) δ 1.30 (3 H, s, Me), 1.47 (3 H, s, Me), 3.88 (3 H, s, OMe), 4.15–4.85 (5 H, m, H_2, H_3, H_4, and 5-methylene), 5.33 (1 H, d, $J_{1,NH}$ = 8.0 Hz, collapsed to s on D_2O addition, H_1), 5.64 (2 H, s, D_2O exchangeable, NH_2), 7.14 (1 H, d, $J_{NH,1}$ = 8.0 Hz, D_2O exchangeable, NH), and 8.43 (1 H, s, triazole H).

Anal. Calcd for $C_{13}H_{19}N_5O_6$: C, 45.74; H, 5.61; N, 20.52. Found: C, 45.98; H, 5.33; N, 20.38.

Synthesis of 8b. Finely powdered **3a** (800 mg, 2.59 mM) and a saturated ethanolic solution of ammonia (100 mL) were combined in a pressure tube and the total was vigorously stirred at room temperature for 4 h. The mixture was evaporated and the residue recrystallized from methanol to give 725 mg (85.9%) of **8b:** mp 212–215 °C; UV (MeOH) 210 nm (ϵ 13 800); ^{1}H NMR (Me_2SO-d_6) δ 1.28 (3 H, s, Me), 1.44 (3 H, s, Me), 4.16–4.40 (1 H, m, H_4), 4.5–4.85 (4 H, m, H_2, H_3, and 5-methylene), 5.28 (1 H, dd, $J_{1,NH}$ = 8.6 Hz, $J_{1,2}$ = 2.6 Hz, collapsed to d on D_2O addition, H_1), 5.76 (2 H, s, D_2O exchangeable, ureido NH_2), 7.04 (1 H, d, $J_{NH,1}$ = 8.6 Hz, D_2O exchangeable, NH), 7.41–7.75 (each 1 H, br s, D_2O exchangeable, carboxamide), and 8.41 (1 H, s, triazole H_5).

Anal. Calcd for $C_{12}H_{18}N_6O_5 \cdot \frac{1}{2}H_2O$: C, 42.98; H, 5.71; N, 25.07. Found: C, 43.01; H, 5.61; N, 25.21.

Synthesis of 8c. A suspension of **3a** (200 mg, 0.65 mM) in a 0.1 M ethanolic solution of hydrazine monohydrate (25 mL) was stirred at room temperature for 2 h. The mixture was evaporated and coevaporated with ethanol a couple of times and the residue was recrystallized from methanol to give 204 mg (88%) of **8c** as an amorphous solid: mp 171–173 °C; UV (MeOH) 210 nm (ϵ 10 600); ^{1}H NMR (Me_2SO-d_6 + $CDCl_3$, 2:1) δ 1.28 (3 H, s, Me), 1.44 (3 H, s, Me), 3.2–3.8 (2 H, br s, D_2O exchangeable, hydrazino NH_2), 4.1–4.9 (5 H, m, H_2, H_3, H_4, and 5-methylene), 5.28 (1 H, dd, $J_{1,NH}$ = 9.0 Hz, $J_{1,2}$ = 1.2 Hz, collapsed to d on D_2O addition, H_1), 5.78 (2 H, s, D_2O exchangeable, ureido NH_2), 7.12 (1 H, d, $J_{NH,1}$ = 9.0 Hz, D_2O exchangeable, ureido NH), 8.40 (1 H, s, triazole H_5), and 9.3–9.7 (1 H, br s, D_2O exchangeable, hydrazino NH).

Anal. Calcd for $C_{12}H_{19}N_7O_5 \cdot \frac{1}{2}CH_3OH$: C, 42.01; H, 5.92; N, 27.44. Found: C, 42.07; H, 5.79; N, 27.51.

Synthesis of 11a and 12a. To an ice-cooled stirred solution of **8a** (1.0 g, 2.93 mM) in 80% acetic acid (20 mL) was added sodium nitrite (1.0 g, 14.5 mM) in several portions. After the mixture became homogeneous, the solution was left at 0 °C for 2 days and evaporated. The residue was repeatedly co-evaporated with ethanol to remove the residual acetic acid and then extracted with hot acetone (50 mL). Evaporation of the acetone solution gave a foam, which crystallized from a small volume of methanol to afford 180 mg of practically homogeneous **12a.** The filtrate was submitted to preparative TLC [20 × 20 cm, $CHCl_3$/MeOH (9:1)], giving from the farthermost reaching band 70 mg of **12a** (total yield 25.0%), from the second band 260 mg (29.7%) of **11a,** and from the slowest moving band 320 mg (32%) of the starting material (**8a**).

11a: mp 153–155 °C (MeOH); UV (MeOH) 214 nm (ϵ 8800); ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6, 3:1) δ 1.34 (3 H, s, Me), 1.45 (3 H, s, Me), 3.95 (3 H, s, OMe), 4.4–4.9 (5 H, m, H_2, H_3, H_4, and 5-methylene), 5.50 (1 H, d, $J_{1,OH}$ = 4.0 Hz, collapsed to s on D_2O addition, H_1), 6.5 (1 H, d, $J_{OH,1}$ = 4.0 Hz, D_2O exchangeable, OH), and 8.6 (1 H, s, triazole H_5).

Anal. Calcd for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.73; N, 14.04. Found: C, 48.36; H, 5.67; N, 14.07.

12a: mp 183–186 °C (MeOH); UV (MeOH) 214 nm (ϵ 8600); ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, s, Me), 1.47 (3 H, s, Me), 2.08 (3 H, s, acetyl), 3.95 (3 H, s, OMe), 4.55–4.95 (5 H, m, H_2, H_3, H_4, and 5-methylene), 6.20 (1 H, s, H_1), and 8.15 (1 H, s, triazole H_5).

Anal. Calcd for $C_{14}H_{19}N_3O_7$: C, 49.26; H, 5.61; N, 12.31. Found: C, 49.01; H, 5.56; N, 12.52.

Synthesis of 11b and 12b. Sodium nitrite (690 mg, 10 mM) was added to a stirred ice-cooled solution of **8b** (335 mg, 1 mM) in 80% acetic acid (7 mL). After the solid nitrite went into solution, the total was left at 0 °C for 42 h. Sodium nitrite (345 mg, 1 mM) was added and the mixture was left at 0 °C for an additional 2 days. TLC at this stage revealed a small amount of the starting material with two major products. After evaporation, the residue was extracted with hot acetone and the obtained acetone extract was digested with a small volume of water to give a solid mixture, which was charged on three sheets of silica gel plates (20 × 20 cm) and developed twice with $CHCl_3$/MeOH (9:1). The combined faster running bands were eluted with acetone/MeOH (1:1) to give 93 mg (27.2%) of **12b** as a homogeneous glass that showed mp 160–163 °C after drying under high vacuum at 50 °C and powdering: UV (MeOH) 210 nm (ϵ 15 100); ^{1}H NMR ($CDCl_3$/Me_2SO-d_6, 1:1, solvent signal excluded) δ 1.30 (3 H, s, Me), 1.42 (3 H, s, Me), 2.10 (3 H, s, acetyl), 4.5–5.0 (5 H, m, H_2, H_3, H_4, and 5-methylene), 6.03 (1 H, s, H_1), 7.44–7.75 (each 1 H, br s, D_2O exchangeable, carboxamide), and 8.55 (1 H, s, triazole H_5).

Anal. Calcd for $C_{13}H_{18}N_4O_6 \cdot \frac{1}{2}MeOH$: C, 47.37; H, 5.89; N, 16.37. Found: C, 47.60; H, 5.60; N, 16.38.

Elution of the combined slower moving bands with the same solvent mixture gave a crystalline solid, which was recrystallized from ethyl acetate at a mild temperature below 75 °C to give 67 mg (20.4%) of **11b** as crystals of mp 205–207 °C: UV (MeOH) 211 nm (ϵ 14 100); ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6, 1:1, solvent resonance excluded) δ 1.29 (3 H, s, Me), 1.40 (3 H, s, Me), 4.35–4.95 (5 H, m, H_2, H_3, H_4, and 5-methylene), 5.34 (1 H, d, $J_{1,OH}$ = 3.5 Hz, collapsed to s on D_2O addition, H_1), 6.90 (1 H, d, $J_{OH,1}$ = 3.5 Hz, D_2O exchangeable, OH), 7.40–7.70 (each 1 H, br s, D_2O exchangeable, carboxamide), and 8.55 (1 H, s, triazole H_5).

Anal. Calcd for $C_{11}H_{16}N_4O_5 \cdot \frac{1}{2}CH_3CO_2C_2H_5$: C, 47.55; H, 6.14; N, 17.06. Found: C, 47.27; H, 5.92; N, 17.21.

Synthesis of 13a. Method A. A solution of **12a** (210 mg, 0.62 mM) in 90% trifluoroacetic acid (3.5 mL) was left at room temperature for 2 h and evaporated. The residue was repeatedly co-evaporated with ethanol and finally dissolved in methanol (10 mL). The solution was neutralized with IRA-93 resin (OH form) and filtered and the resin was washed with methanol (200 mL). The methanolic solution was concentrated to a small bulk and submitted to preparative TLC [10 × 20 cm, $CHCl_3$/MeOH (9:1)]. Elution of the relevant portion with methanol gave a glass, which was recrystallized from a small volume of water to afford 70 mg (37.2%) of **13a:** mp 96–98 °C; UV (MeOH) 214 nm (ϵ 9500); ^{1}H NMR ($CDCl_3$) δ 3.5–4.8 (8 H, m, reduced to 5 H, m, on D_2O addition, OH × 3, H_2, H_3, H_4, and 5-methylene), 3.91 (3 H, s, OMe), 4.92 (1 H, s, H_1) and 8.28 (1 H, s, triazole H_5) (solvent signal excluded).

Anal. Calcd for $C_9H_{13}N_3O_6 \cdot C_2H_5OH$: C, 43.42; H, 5.96; H, 13.81. Found: C, 43.65; H, 5.87; N, 13.66.

Method B. A solution of **11a** (100 mg, 0.33 mM) in 90% trifluoroacetic acid (2 mL) was left at room temperature for 2 h and the mixture was worked up as in method A to give 45 mg (44.1%) of **13a,** identical with the product obtained above in all respects.

Synthesis of 13b. A mixture (160 mg) of **11b** and **12b** obtained from **8b** (335 mg, 1 mM) as described above was dissolved in 90% trifluoroacetic acid (5 mL). The solution was left at room temperature for 4 h, evaporated, and repeatedly coevaporated with methanol. The residue was dissolved in methanol (15 mL), neutralized with IRA-93 resin (OH form), and filtered. The resin was eluted with methanol (200 mL) and the methanolic solution evaporated to give a semisolid residue, which was recrystallized from acetone to give 58 mg (24% based upon **8b**) of amorphous solid (**13b**), which gradually melted between 146 and 157 °C: UV (MeOH) 211 nm (ϵ 13 100); ^{1}H NMR (Me_2SO-d_6) δ 3.5–5.3 (8 H, m, reduced to a 5-proton multiplet merging with a singlet at 5.0 ppm on D_2O addition, H_1, H_2, H_3, C_2–OH, C_3–OH, H_4, and 5-methylene), 6.45 (1 H, d, $J_{OH,1}$ = 4.0 Hz, D_2O exchangeable, C_1–OH), 7.48, 7.88 (each 1 H, br s, D_2O exchangeable, carboxamide), and 8.45 (1 H, s, triazole H_5).

Anal. Calcd for $C_8H_{12}N_4O_5$: C, 39.34; H, 4.95; N, 22.94. Found: C, 39.45; H, 5.07; N, 22.91.

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Registry No.—**1a,** 15083-05-3; **1b,** 69291-51-6; **1c,** 69291-52-7; **1d,** 69291-53-8; **3a,** 66584-19-8; **3b,** 69291-54-9; **3c,** 69291-55-0; **4a,** 66584-20-1; **4b,** 69291-56-1; **5,** 57901-63-0; **6a,** 69291-57-2; **6b,** 69291-58-3; **7a,** 69291-59-4; **7b,** 69291-60-7; **8a,** 66584-21-2; **8b,** 66584-22-3; **8c,** 69291-61-8; **11a,** 66584-23-4; **11b,** 66584-25-6; **12a,** 66584-24-5; **12b,** 66584-26-7; **13a,** 66584-27-8; **13b,** 66584-28-9; 2′,3′-*O*-ethoxymethyleneuridine, 19140-04-6; 2′,3′-*O*-ethoxymethyleneuridine tosylate, 69291-62-9.

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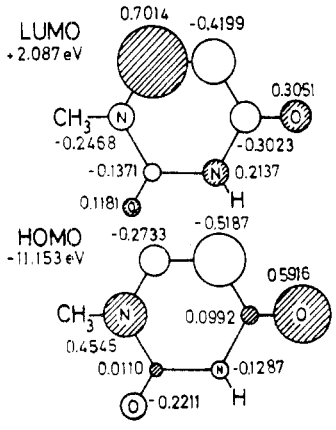

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Structures, Syntheses, and Chemotaxonomic Significance of Some New Acetophenone Derivatives from *Encelia farinosa* Gray

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The resinous exudate of brittle bush (*Encelia farinosa* Gray) contains a number of substituted benzofurans and chromenes. All appear to arise from the biogenic prenylation of resacetophenone. The chromene compounds constitute a remarkable sequence of reduction states of encecalin (**3**) and represent important chemotaxonomic indicators. All the compounds have been characterized on the basis of spectral and chemical methods. A new general synthesis of dimethylchromene derivatives from resorcinol is described.

Brittle bush (*Encelia farinosa* Gray) is an abundant perennial which is indiginous to southern Arizona, growing on rocky slopes at elevations of 1500–3000 ft. It is characterized by a sticky fragrant exudate. This exudate is used by Arizona Indians as an analgesic chewing gum and as an incense. Preliminary investigations of the exudate[1] revealed a number of chromenes and benzofurans derived by prenylated resacetophenone. These two classes of compounds occur almost exlusively in the Compositate family[2] and are valuable in assessing phylogenic relations of genera and species within this family. In light of the possible therapeutic and chemotaxonomic significance of these compounds, we undertook a systematic investigation of *E. farinosa* extracts.

Isolation and Structure Determination

The major constituent of the plant was isolated as optically inactive encecalol ethyl ether (**1**). Although the compound never gave a satisfactory elemental analysis, the molecular ion appeared in the mass spectrum at *m/e* 262, suggesting the composition $C_{16}H_{22}O_3$. This formula was substantiated by the ^{13}C NMR spectrum. That the compound was aromatic was evidenced by the IR spectrum, and an absorption at 1630 cm^{-1} suggested the presence of additonal unsaturation. The 100-MHz ^1H-NMR spectrum of this compound was remarkably simple and displayed the signals characteristic of a dimethylchromene derivative. Singlets at δ 1.33 (6 H) and 3.91 (3 H) corresponded to the *gem*-dimethyl substituents on the chromene ring and to the methoxyl group. The olefinic protons at C-3 and C-4 were displayed as an AB pattern of doublets at δ 5.33 and 6.21 (1 H each, J = 10 Hz). The aromatic protons appeared as singlets at δ 6.28 and 7.00, corresponding to the protons at C-8 and C-5. The two aromatic protons and their observed multiplicity indicated a para relationship. These conclusions, in addition to the remaining signals in the NMR spectrum, led to the formulation of encecalol ethyl ether as **1**, a conclusion that was later substantiated by synthesis.

In addition to **1** there was also obtained in a lesser amount a substance structurally very similar (encecalol methyl ether, **2**). The obvious similarity of the racemic **1** and the optically active **2**, coupled

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