References and Notes

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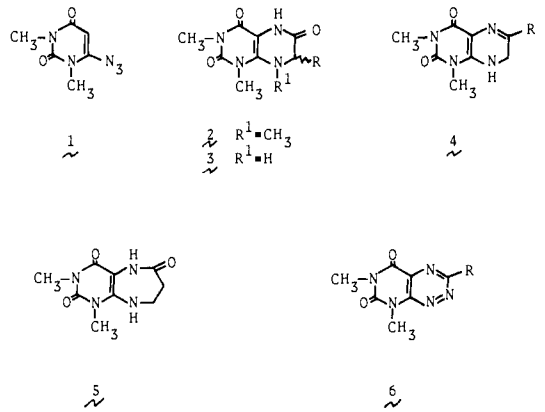
A New Photochemical Synthesis of Lumazines and Fervenulins from 6-Azido-1,3-dimethyluracil

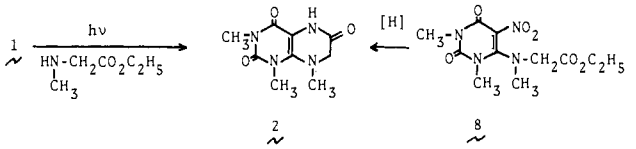
Sir:

We recently described that the photolysis of 6-azido-1,3-dimethyluracil (**1**) in the presence of primary or secondary alkylamines led to the formation of 6-alkylamino-5-amino-1,3-dimethyluracils in high yields via a nitrene intermediate.[1] This photochemical transformation (6-N_3 → 5-NH_2) is a new type of procedure to introduce a nitrogen source into the 5 position of the uracils as compared with conventional methods, i.e., nitration, nitrosation, or the Michael-type addition of diethyl azodicarboxylate.[2]

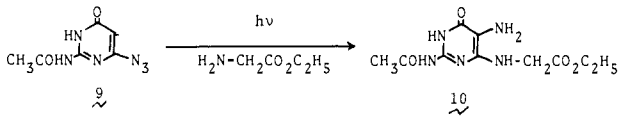


During studies directed toward the development of new synthetic routes to heterocycles employing 6-azidouracils, we have succeeded in obtaining lumazines and fervenulins in a single step and, furthermore, in high yields using amino acid esters, amino ketones, and acylhydrazines in place of alkylamines in the above reaction.

Scheme I



Scheme II



Thus, a mixture of **1** (0.011 M) and *N*-methylglycine ethyl ester (0.033 M) in THF was irradiated[3] for 3 h and the solvent was removed by evaporation. Trituration of the residue with ether gave 7,8-dihydro-1,3,8-trimethyllumazin-6(5*H*)-one (**2**) (Scheme I) in 73% yield: mp 240–241 °C; IR (KBr) 3170 cm^{-1} (NH); UV λ_{max}^{EtOH} 245 nm (log ϵ 6.1), 262 (5.9, sh), 313 (5.9); NMR ($CDCl_3$) δ 2.90, 3.44, and 3.48 (each 3 H, each s, each *N*-CH_3), 3.78 (2 H, s, $COCH_2N$), 8.49 (1 H, br s, NH, deuterium exchangeable). The identification of structure **2** was established by an alternate synthesis[4] of this compound from 6-chloro-1,3-dimethyl-5-nitrouracil (**7**).[5] Thus, treatment of **7** with *N*-methylglycine ethyl ester gave 1,3-dimethyl-6-(*N*-ethoxycarbonylmethyl-*N*-methyl)amino-5-nitrouracil (**8**). Reductive ring closure of **8** by catalytic hydrogenation afforded the lumazine (**2**) which was identical with the product obtained by photolysis of **1**.

Similar irradiation of **1** (0.011 M) and other various amino acid ethyl esters efficiently gave the corresponding 7-substituted lumazin-6-ones (**3a–d**)[6] in good yields. On the irradiation of **1** with β-amino ketones, 6-substituted lumazines (**4a,b**) were obtained (see Table I).

We also used 2-acetylamino-6-azidopyrimidin-4(3*H*)-one (**9**) instead of **1** for this reaction. Irradiation of **9**[7] with glycine ethyl ester in THF for 5 h and the resulting precipitate being collected by filtration gave 2-acetylamino-5-amino-6-(*N*-ethoxycarbonylmethyl)aminopyrimidin-4(3*H*)-one (**10**) (Scheme II), mp 213–214 °C, in quantitative yield. Although the predicted cyclization to a pterin did not occurr, the pyrimidone **10** is a potential intermediate for 6-hydroxypterin.[8]

Furthermore, when a solution of **1** and β-alanine ethyl ester in THF was irradiated, 7,8-dihydro-1,3-dimethyl-9*H*-pyrimido[4,5-*b*]-5,9-diazepine-2,4,6(1*H*,3*H*,5*H*)-trione (**5**) was obtained in 59% yield: mp 200–201 °C; UV λ_{max}^{EtOH} 267 nm (log ϵ 4.9), 297 (5.0); NMR (DMSO-d_6) δ 2.60 (2 H, m,

Table I. Photochemical Formation of Lumazines

Amino acid ethyl ester or amino ketone	Product	R	Mp, °C	Yield, %
Glycine ethyl ester	**3a**	H	285	69
Alanine ethyl ester	**3b**	CH_3	270	76
Phenylalanine ethyl ester	**3c**	$C_6H_5CH_2$	223–225	55
Methionine ethyl ester	**3d**	$CH_3S(CH_2)_2$	197–200	61
Phenacylamine	**4a**	C_6H_5	255–257	75
p-Bromophenacylamine	**4b**	*p*-BrC_6H_4	260–262	70

Table II. Photochemical Formation of 3-Substituted Fervenulins

Acylhydrazine	Product	R	Mp, °C	Yield, %
Formylhydrazine	**6a**	H	174–175	55
Acetylhydrazine	**6b**	CH_3	124–126	68
Benzoylhydrazine	**6c**	C_6H_5	278–279	81
Phenylacetylhydrazine	**6d**	$C_6H_5CH_2$	190–192	72
Isonicotinoylhydrazine	**6e**	4-Pyridyl	260–262	60

$COCH_2$), 3.15 and 3.31 (each 3 H, each s, each N-CH_3), 5.30 (2 H, m, $NHCH_2$), 6.90 (1 H, br s, 5-NH, deuterium exchangeable), 9.40 (1 H, br s, 9-NH, deuterium exchangeable).

This method is not only useful as a new method for synthesizing the lumazines as described above but also it is widely applicable as a general method for the synthesis of 7-azalumazines (fervenulins).

Thus, after irradiation of **1** (0.011 M) and formylhydrazine (0.033 M) in THF for 3 h with aeration, the solvent was evaporated therefrom, and the residue was subjected to column chromatography (silica gel–chloroform) to obtain fervenulin (**6a**, R = H), mp 174–175 °C (lit.[9] mp 178 °C), in 55% yield. The structure was identical with an authentic sample prepared according to the procedure reported by Yoneda et al.[10]

Similarly, a mixture of **1** and various acylhydrazines in THF was irradiated to give the corresponding 3-substituted fervenulins (**6b–e**) in high yields (see Table II).

We have also studied a reaction of **1** with amino acid esters, amino ketones, or acylhydrazines with heating but we could not isolate the desired products. This suggests that the formation of these lumazines and fervenulins requires photochemical activation.

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(3) Irradiation was carried out in a flask equipped with a Pyrex-jacketed immersion lamp until disappearance of 1 (monitored by TLC) was complete. The light source was a Riko-UVL 100W high-pressure mercury arc lamp.
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(6) All new compounds gave satisfactory elemental analyses and spectral properties consistent with the assigned structure.
(7) (a) Irradiation of **9** in the presence of primary or secondary amines gave 6-alkylamino-2,5-diaminopyrimidin-4(3*H*)-ones, which are significant intermediates for pterins,[7b] in one step and good yields.[7c] (b) W. Pfleiderer, *Angew. Chem. Int. Ed. Engl.*, **3**, 194 (1964). (c) S. Senda, unpublished results.
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(9) E. C. Taylor and F. Sowinski, *J. Org. Chem.*, **40**, 2321 (1975).
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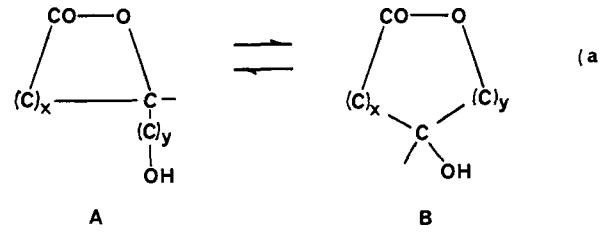
A Translactonization Route to Macrocyclic Lactones

Sir:

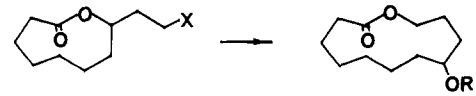
The invention of new synthetic methodology is one of the more crucial métiers for the development of effective syntheses for complex biologically active macrocyclic lactones and lactams.[1] In this communication we demonstrate that internal translactonization (i.e., internal transesterification) represents a useful new approach to the generation of macrocyclic lactones. The reversibility of the translactonization reaction, under either acid or base catalysis, implies that this process normally will lead to thermodynamically controlled products. Thus, it can also be expected to provide quite precise information concerning the relative stabilities of isomeric lactones of different ring size. The general type of translactonization which is described herein can be summarized by eq a.



A B (a)

There are a number of aspects of this reversible change which can be anticipated on general structural and mechanistic grounds. For example, if $x = 2$ the γ-lactone A can be expected to be considerably more stable than the larger cycle B; thus the observed transformation in this series will be ring contraction (B → A) and not ring expansion. Also the rate of the interconversion can be expected to drop as y increases from 1 to 2 to 3 to 4 (≡ transition state bridge ring sizes 5, 6, 7, 8, respectively).

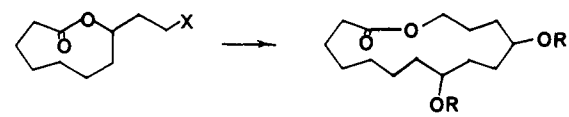
The lactone acid **1**,[2] mp 66–67 °C, IR max 1711 and 1726 cm^{-1} (film),[3] was reduced to the corresponding primary alcohol (**2**, oil) by reaction with 1.1 equiv each of triethylamine and ethyl chloroformate in THF to form the mixed anhydride and treatment with 4 equiv of sodium borohydride at 0 °C for 15 min (83% overall yield). Exposure of the 9-membered lactone **2** to 1 mol % p-toluenesulfonic acid in methylene chloride at 23–25 °C for 2 h effected internal translactonization to form the 12-membered hydroxy lactone **3** in 97% yield (IR max in $CHCl_3$ at 1723 cm^{-1}), also characterized as its acetate (**4**, 2 equiv of acetyl chloride–pyridine in methylene chloride at 25 °C for 2 h, 97% yield). The transformation of **2** into **3** could



1, X = COOH
2, X = CH_2OH
3, R = H
4, R = CH_3CO

also be effected (more slowly and somewhat less efficiently) by heating with 2 equiv of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dimethylformamide (DMF) at 120 °C for 25 h.[4] The ring expansion of **2** by three members to form **3** is obviously driven mainly by the relative instability of the 9-membered cyclic system.[5]

The acid **1** also served as a starting point for the generation of a 15-membered lactone by a *six*-carbon ring expansion. Conversion of **1** to the 2-pyridinethiol ester[6] followed by reaction in THF with the Grignard reagent from 3-*tert*-butyldimethylsilyloxy-1-bromopropane[7] (excess magnesium turnings in THF at 23 °C under argon) afforded[6c] the keto lactone **5** in 84% yield. Reduction of **5** with sodium borohydride in ethanol at 0 °C followed by desilylation with 3 equiv of tetra-n-butylammonium fluoride in THF at 23 °C gave the dihydroxy lactone **6** (90%). Ring expansion of **6** was effected by treatment with a catalytic amount of p-toluenesulfonic acid



5, X = $CO(CH_2)_3OSiMe_2tBu$
6, X = $CH(OH)(CH_2)_3OH$
7, R = H
8, R = CH_3CO

in methylene chloride at 23 °C for 36 h to give the 15-membered lactone **7**[8] in 90% yield as a mixture of cis and trans isomers (ratio ~1:1). The cis and trans diol lactones **7** were separated by chromatography on silica gel (2:1 methylene chloride–acetone). Each of the pure isomers was converted to the corresponding diacetate **8** in >95% yield using acetyl chloride in pyridine at 23 °C. The same lactone diols **7** were