Carbohydrate Research, 189 (1989) 149–160
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SYNTHESIS OF NITROGEN-BRIDGED PURINE-LIKE *C*-NUCLEOSIDES FROM ETHYL 2,5-ANHYDRO-6-*O*-BENZOYL-D-ALLONODITHIOATE

HASSAN S. EL KHADEM*, JOSHUA KAWAI†,
Department of Chemistry, The American University, 4400 Massachusetts Ave., N.W., Washington, D.C. 20016 (U.S.A.)

AND DAVID L. SWARTZ‡
Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931 (U.S.A.)

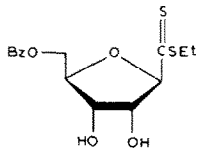
(Received July 28th, 1988; accepted for publication, December 12th, 1988)

ABSTRACT

Ethyl 2,5-anhydro-6-*O*-benzoyl-D-allonodithioate (**1**) was coupled with aminomethyl- and hydrazino-azines to afford the title compounds. Specifically, **1** was coupled with 2-(aminomethyl)pyridine to afford 3-β-D-ribofuranosylimidazolo-[1,5-*a*]pyridine, with 2-hydrazinopyrazine to yield 3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]pyrazine, and with 2-hydrazinopyrimidine to form a 3-substituted 1,2,4-triazolo[4,3-*a*]pyrimidine which underwent a Dimroth rearrangement to yield 2-β-D-ribofuranosyl-1,2,4-triazolo[1,5-*a*]pyrimidine. Finally, compound **1** was coupled with 2-hydrazino-4-hydroxy-6-methylpyrimidine to yield 7-methyl-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]-5(8*H*)-pyrimidone.

INTRODUCTION

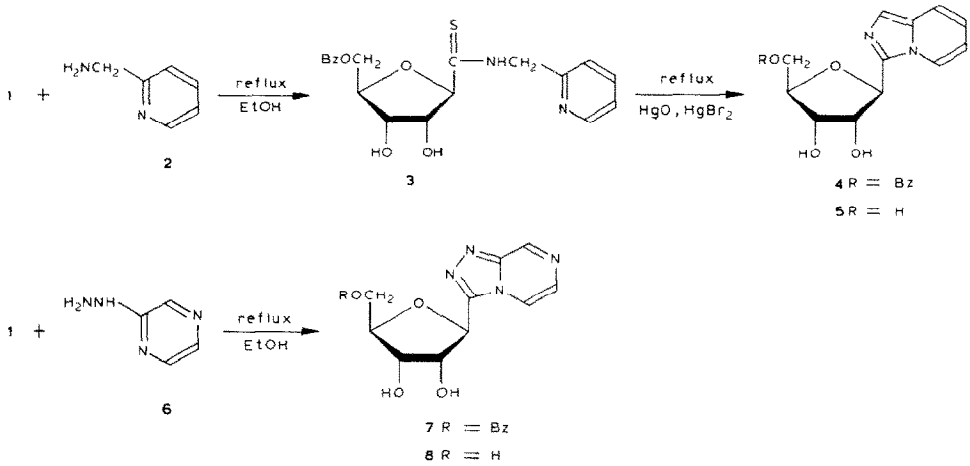
In a previous study[1], it was shown that ethyl 2,5-anhydro-6-*O*-benzoyl-D-allonodithioate (**1**) reacts under mild conditions with such heterocyclic diamines as 5,6-diamino-1,3-dimethyluracil to afford purine-like *C*-nucleosides of the β configu-



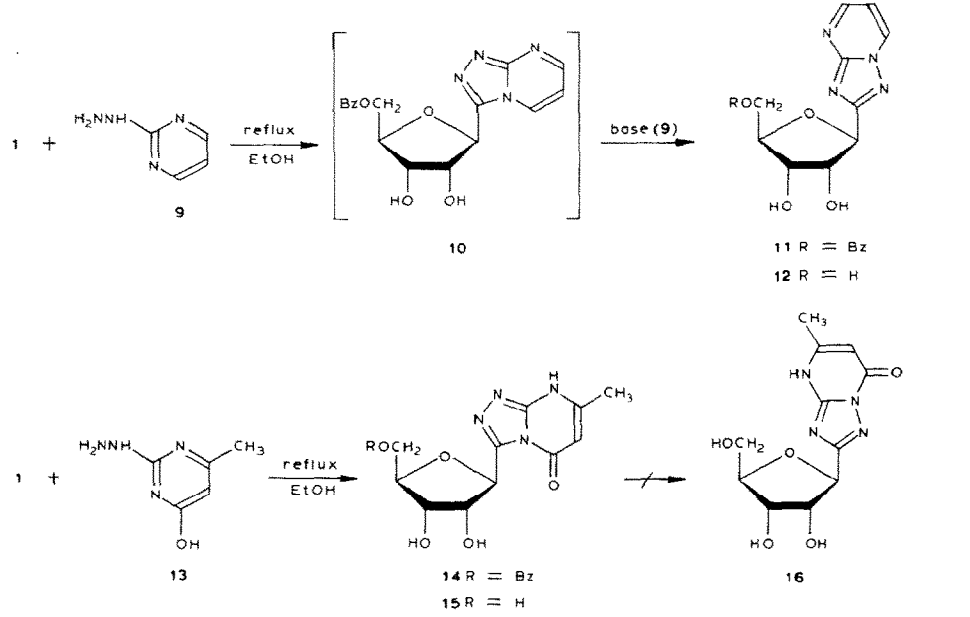
1

*To whom correspondence should be addressed.
†Present address: Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35487-9671, U.S.A.
‡Present address: Pfanstiehl Laboratories, Inc., 1219 Glen Rock Avenue, Waukegan, Illinois 60085-0439, U.S.A.

0008-6215/89/$ 03.50



ration. The yields were usually higher than those obtained when 2,5-anhydro-D-allonic acid[2], 2,5-anhydro-D-allonoimidates[3], or 2,5-anhydro-D-allonothioimidates[4–8] were used for coupling. More recently[9–11], ethyl dithioacetate was coupled with 2-hydrazinopyrimidine, and it was found that the 1,2,4-triazolo[4,3-*a*]pyrimidine formed undergoes Dimroth rearrangement readily. For example, 3-methyl-1,2,4-triazolo[4,3-*a*]pyrimidine rearranges to 2-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine, and 3,7-dimethyl-1,2,4-triazolo[4,3-*a*]-5(8*H*)-pyrimidone yields 2,5-dimethyl-1,2,4-triazolo[1,5-*a*]-7(4*H*)pyrimidone. The aim of the present work was to synthesize nitrogen-bridged *C*-nucleosides (for testing as antiviral agents) by coupling synthon **1** with aminomethylpyridine and some hydrazinodiazines. Thus, compound **1** was



coupled with 2-(aminomethyl)pyridine (**2**) to give 3-β-D-ribofuranosylimidazolo[1,5-*a*]pyridine (**5**), with 2-hydrazinopyrazine (**6**) to afford 3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]pyrazine (**8**), and with 2-hydrazinopyrimidine (**9**) to form 3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]pyrimidine (**10**), which underwent a Dimroth rearrangement to give 2-β-D-ribofuranosyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**12**). Finally, compound **1** was coupled with 2-hydrazino-4-hydroxy-6-methylpyrimidine (**13**) to afford 7-methyl-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]-5(8*H*)-pyrimidone (**15**). From the results of previous investigations[9–11] it was expected that compounds **10** and **15** would undergo Dimroth rearrangement to give **12** and 5-methyl-2-β-D-ribofuranosyl-1,2,4-triazolo[1,5-*a*]-7(4*H*)-pyrimidone (**16**), respectively. Compound **10** did rearrange to give nucleoside **12**, but **15** resisted the basic conditions used for deblocking[12], so that no rearranged nucleoside **16** was isolated.

RESULTS AND DISCUSSION

Compound **1** was refluxed with 2-(aminomethyl)pyridine (**2**) in ethanol to afford a thioamide, 2-[(2,5-anhydro-6-*O*-benzoyl-D-allonothioamido)methyl]-pyridine (**3**) in 31% yield. This compound was cyclized by refluxing with a mixture of mercuric oxide and mercuric bromide in ethanol to give a blocked *C*-nucleoside, 3-(5-*O*-benzoyl-β-D-ribofuranosyl)imidazolo[1,5-*a*]pyridine (**4**). The latter was treated with methanolic ammonia to afford the desired *C*-nucleoside, 3-β-D-ribofuranosylimidazolo[1,5-*a*]pyridine (**5**) in 18% overall yield. The longest-wavelength u.v. absorption maxima of the blocked and unblocked *C*-nucleoside (compounds **4** and **5**) were close to the absorption of the previously studied 3-methylimidazolo-[1,5-*a*]pyridine[13] (A) (λ_{max} 291, 289 *versus* 284 nm) as may be seen from Table I. Likewise, the ^{1}H-n.m.r. resonances of the *N*-heterocyclic protons in the spectra of compounds **5** and A[14] were very similar (see Table II).

When compound **1** was refluxed in ethanol with 2-hydrazinopyrazine (**6**), a blocked nucleoside, 3-(5-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolo[4,3-*a*]pyrazine (**7**), was produced. On treatment with methanolic ammonia at room temperature compound **7** afforded 3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]pyrazine (**8**). The longest-wavelength u.v. absorptions of the blocked and deblocked *C*-nucleosides (**7** and **8**) were quite close to those of the previously prepared 3-methyl-1,2,4-triazolo[4,3-*a*]pyrazine[15] (B) (λ_{max} 300, 296 *versus* 303 nm; see Table I). Likewise, the ^{1}H-n.m.r. resonances for the *N*-heterocyclic protons of both compounds were quite similar (see Table II). The anomeric proton of the blocked nucleoside (**7**) appeared as a doublet (J 2.4 Hz; δ 5.50), like that of the unblocked nucleoside (**8**), which was somewhat obscured by overlapping with hydroxyl signals. Accordingly, **7** and **8** were assigned β configurations.

When compound **1** was refluxed with 2-hydrazinopyrimidine (**9**) in ethanol, it afforded a blocked nucleoside (**11**). Its u.v. spectrum (see Table I) clearly indicated that it had undergone a Dimroth rearrangement, as evidenced by an absorption at λ_{max} 273 nm which was quite close to that of the rearranged 2-methyl-1,2,4-tri-

TABLE I

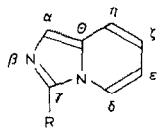
ULTRAVIOLET SPECTRAL DATA

Compound	*Solvents*	λ_{max}, λ_{min} *in nm [log ε]*
3	95% EtOH	λ_{max} 269 [3.84], 231 [3.81]
		λ_{min} 247 [3.80], 214 [3.64]
	0.01M HCl	λ_{max} 269 [3.98], 236 [4.02]
		λ_{min} 250 [3.96], 215 [3.82]
	0.01M NaOH	λ_{max} 263 [3.90], 221 [3.92]
		λ_{min} 243 [3.78]
4	95% EtOH	λ_{max} 291 [3.71], 280 [3.52], 270 [3.77], 220 [4.44]
		λ_{min} 287 [3.69], 273 [3.77], 253 [3.57]
5	95% EtOH	λ_{max} 289 [3.30], 279 [3.36], 269 [3.30], 219 [3.91]
		λ_{min} 285 [3.26], 272 [3.26], 248 [2.80]
	0.01M HCl	λ_{max} 316 [3.44][a], 305 [3.53][a], 284 [3.78], 263 [3.63][a], 242 [3.39][a], 234 [3.54][a]
		λ_{min} 280 [3.75], 249 [3.30]
	0.01M NaOH	λ_{max} 327 [3.74][a], 290 [4.17][a], 280 [4.22], 268 [4.09][a], 220 [4.35]
		λ_{min} 306 [3.68], 286 [4.17], 248 [3.68]
7	MeOH and	λ_{max} 300 [3.36], 284 [3.39], 275 [3.39], 265 [3.35][a], 238 [3.72][a]
	0.01M HCl	λ_{min} 291 [3.35], 279 [3.36], 256 [3.33]
8	H_2O,	λ_{max} 296 [3.45], 271 [3.32], 263 [3.30][a]
	0.01M HCl, and	λ_{min} 274 [3.31], 266 [3.30], 245 [3.24]
	0.01M NaOH	
11	95% EtOH	λ_{max} 273 [3.93], 232 [4.23][a]
		λ_{min} 250 [3.73]
12	H_2O	λ_{max} 278 [4.33]
		λ_{min} 232 [4.03]
14	MeOH,	λ_{max} 296 [4.25], 230 [4.41][a]
	0.01M HCl, and	λ_{min} 260 [3.95]
	0.01M NaOH	
	0.01M HCl	λ_{max} 291 [3.63], 235 [3.85]
		λ_{min} 262 [3.21]
	0.01M NaOH	λ_{max} 306 [3.50], 300 [3.56], 266 [3.50]
		λ_{min} 303 [3.52], 280 [3.35], 244 [3.36]
15	MeOH	λ_{max} 299 [3.99], 250 [3.73]
		λ_{min} 260 [3.72], 274 [3.39], 235 [3.69]
	0.01M HCl	λ_{max} 292 [4.12], 244 [3.88]
		λ_{min} 261 [3.56], 228 [3.78]
	0.01M NaOH	λ_{max} 305 [4.20], 265 [3.98]
		λ_{min} 279 [3.83], 240 [3.65]

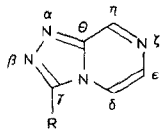
[a]Inflection.

azolo[1,5-*a*]pyrimidine (D)[17] (at 276 nm) and much lower than that of the unrearranged 3-methyl-1,2,4-triazolo[4,3-*a*]pyrimidine (C) (at 305 nm)[16,*]. Upon treatment with methanolic ammonia, the free *C*-nucleoside (**12**) was obtained in 45% yield. It showed an absorption maximum (at 278 nm) similar to that of compound D, indicating that it was also a [1,5-*a*]pyrimidine. The ^1H- and ^{13}C-n.m.r.-

*In ref. 9, it was reported that 3-methyl-1,2,4-triazolo[4,3-*a*]pyrimidine isomerizes when heated with a catalytic amount of 2-hydrazinopyrimidine to give 2-methyl-1,2,4-triazolo-[1,5-*a*]pyrimidine.



A R = Me
5 R = D-ribofuranosyl



B R = Me
7,8 R = D-ribofuranosyl

TABLE II

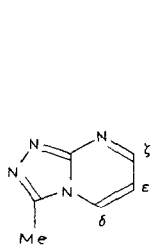
^{1}H-N.M.R.-SPECTRAL DATA FOR 3-SUBSTITUTED IMIDAZOLO[1,5-*a*]PYRIDINES (A[a], **5**) AND 3-SUBSTITUTED 1,2,4-TRIAZOLO[4,3-*a*]PYRAZINES (B[b], **7** AND **8**) (δ, J IN Hz, Me_2SO-d_6)

H atom	*A*[c]	**5**[c]	*B*[d,e]	**7**[d]	**8**[d]
H-α	7.25 s	7.45 m			
H-δ	8.02 m	8.45 m	8.00 d ($J_{\delta\varepsilon}$ 5.0)	7.88 d ($J_{\delta\varepsilon}$ 5.0)	7.93 d ($J_{\delta\varepsilon}$ 4.5)
H-ε	6.60 m	6.70 m	8.52 dd ($J_{\varepsilon\delta}$ 5.0, $J_{\varepsilon\eta}$ 1.4)	8.50 dd ($J_{\varepsilon\delta}$ 5.2, $J_{\varepsilon\eta}$ 2.6)	8.78 m
H-ζ	6.60 m	6.70 m			
H-η	7.45 m	7.45 m	9.42 d ($J_{\eta\varepsilon}$ 1.4)	9.32 ($J_{\eta\varepsilon}$ 3.0)	9.42 s

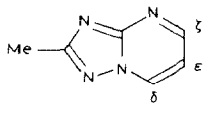
[a]A, 3-methylimidazolo[1,5-*a*]pyridine (see ref. 14 for Me). [b]B, 3-methyl-1,2,4-triazolo[4,3-*a*]pyrazine (see ref. 15). [c]60 MHz. [d]200 MHz. [e]1 drop of D_2O.

spectra confirmed that the blocked and deblocked nucleosides had undergone Dimroth rearrangements. The signals of the three *N*-heterocyclic protons, H-δ, H-ε, and H-ζ, of both nucleosides (**11** and **12**) were quite close to those of 2-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (D) (see Table III), and were different from those of the unrearranged 3-methyl-1,2,4-triazolo[4,3-*a*]pyrimidine (C). Thus, H-δ of the *C*-nucleosides **11** and **12** appeared at δ 9.34 and 9.43, respectively, and that of the rearranged compound D, at δ 9.34, whereas that of the unrearranged compound C appeared at δ 8.85. The coupling constants of the anomeric proton signals of **11** (J 2 Hz) and **12** (J 5 Hz), at 5.00 and 4.89 p.p.m., respectively, indicated that the nucleosides obtained had β configurations. The chemical shifts of the ^{13}C-n.m.r. spectrum of the deblocked nucleoside **12** were also similar to those of 2-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine (D) (see Table IV) and quite different from those of the unrearranged 3-methyl-1,2,4-triazolo[4,3-*a*]pyrimidine (C). Accordingly, the blocked and the deblocked *C*-nucleosides were respectively assigned the structures 2-(5-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolo[1,5-*a*]pyrimidine (**11**) and 2-β-D-ribofuranosyl-1,2,4-triazolo[1,5-*a*]pyridimidine (**12**).

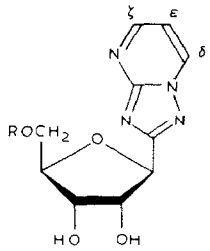
Finally, compound **1** was refluxed with 2-hydrazino-4-hydroxy-6-methylpyrimidine (**13**) in ethanol, to afford, in 24% yield, 3-(5-*O*-benzoyl-β-D-ribofuranosyl)-7-methyl-1,2,4-triazolo[4,3-*a*]-5(8*H*)pyrimidone (**14**)[12]. The other possible isomer, namely, 2-(5-*O*-benzoyl-β-D-ribofuranosyl)-5-methyl-1,2,4-triazolo[1,5-*a*]-7(4*H*)-pyrimidone, was not isolated. Upon treatment with methanolic ammonia at room temperature, compound **14** yielded 7-methyl-3-β-D-ribofuranosyl-



C



D



11 R = Bz

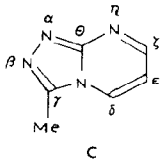
12 R = H

TABLE III

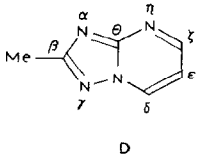
^{1}H-N.M.R.-SPECTRAL DATA FOR 3-METHYL-1,2,4-TRIAZOLO[4,3-*a*]PYRIMIDINE (C) AND 2-SUBSTITUTED 1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES (D, **11**, AND **12**) (200 MHz, δ, J IN Hz, Me_2SO-d_6)

H atom	*C*	*D*	**11**	**12**
H-δ	8.85[a] dd ($J_{\delta\varepsilon}$ 7, $J_{\delta\zeta}$ 2)	9.34[a] dd ($J_{\delta\varepsilon}$ 7, $J_{\delta\zeta}$ 2)	9.34 dd [$J_{\delta\varepsilon}$ 7, $J_{\delta\zeta}$ 2]	9.43 dd ($J_{\delta\varepsilon}$ 7, $J_{\delta\zeta}$ 1)
H-ε	7.13[a] ($J_{\varepsilon\delta}$ 8, $J_{\varepsilon\zeta}$ 4)	7.32[a] q ($J_{\varepsilon\delta}$ 8, $J_{\varepsilon\zeta}$ 5)	[b]	7.42 q ($J_{\varepsilon\delta}$ 7, $J_{\varepsilon\zeta}$ 4)
H-ζ	8.70[a] dd ($J_{\zeta\varepsilon}$ 4, $J_{\zeta\delta}$ 2)	8.85[a] dd ($J_{\zeta\varepsilon}$ 5, $J_{\zeta\delta}$ 2)	8.90 dd [$J_{\zeta\varepsilon}$ 4, $J_{\zeta\delta}$ 2]	8.93 dd ($J_{\zeta\varepsilon}$ 4, $J_{\zeta\delta}$ 1)
Me	2.66[a] s	2.54[a] s		

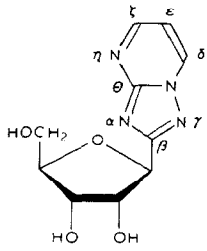
[a]See ref. 9. [b]Hidden by Ar protons.



C



D



12

TABLE IV

^{13}C-N.M.R.-SPECTRAL DATA FOR 3-METHYL-1,2,4-TRIAZOLO[4,3-*a*]PYRIMIDINE (C) AND 2-SUBSTITUTED 1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES (D, **12**) (50 MHz, δ, J IN Hz, Me_2SO-d_6)

Carbon atom	*C*	*D*	**12**
C-β		165.2[a,b]	167.3[a]
C-γ	142.1[a]		
C-δ	131.9[b]	136.6[b]	137.2
C-ε	108.5[b]	110.2[b]	110.9
C-ζ	152.3[b]	154.7[b]	155.5
C-θ	154.0[b]	154.7[a,b]	154.9[a]
Me	9.8[b]	14.6[b]	

[a]Quarternary carbon atoms. [b]See ref. 9.

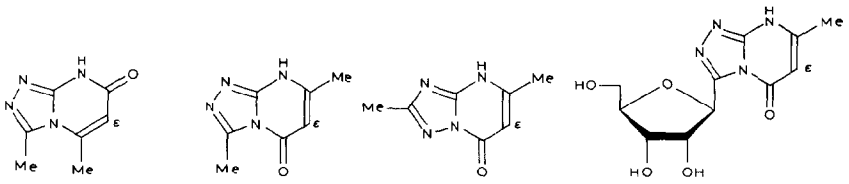


TABLE V

^{1}H-N.M.R.-SPECTRAL DATA FOR 3,5-DIMETHYL-1,2,4-TRIAZOLO[4,3-*a*]-7(8*H*)-PYRIMIDONE (E), 3,7-DIMETHYL-1,2,4-TRIAZOLO[4,3-*a*]-5(8*H*)-PYRIMIDONE (F), 2,5-DIMETHYL-1,2,4-TRIAZOLO[1,5-*a*]-7(4*H*)-PYRIMIDONE (G), AND 3-SUBSTITUTED 1,2,4-TRIAZOLO[4,3-*a*]-5(8*H*)-PYRIMIDONE (**14** AND **15**) (200 MHz, δ, J IN Hz, Me_2SO-d_6)

H atom	*E*	*F*	*G*	**14**	**15**
ε	5.91[a] s	5.56[a] s	5.78[a] s	5.6[b] s	5.63 s
Me (triazole)	2.63[a] s	2.69[a] s	2.34[a] s		
Me (pyrimidine)	2.56[a] s	2.23[a] s	2.30[a] s	2.3[b] s	2.28 s

[a]See ref. 9. [b]60 MHz.

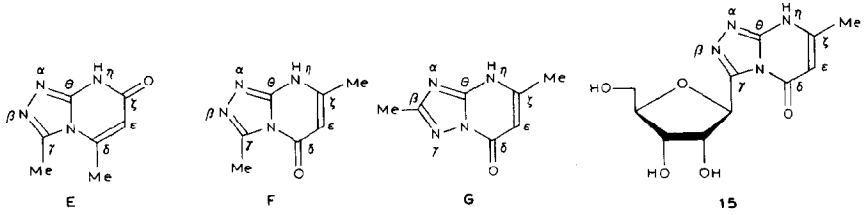


TABLE VI

^{13}C-N.M.R.-SPECTRAL DATA FOR 3,5-DIMETHYL-1,2,4-TRIAZOLO[4,3-*a*]-7(8*H*)-PYRIMIDONE (E), 3,7-DIMETHYL-1,2,4-TRIAZOLO[4,3-*a*]-5(8*H*)-PYRIMIDONE (F), 2,5-DIMETHYL-1,2,4-TRIAZOLO[1,5-*a*]-7(4*H*)-PYRIMIDONE (G), AND 3-SUBSTITUTED 1,2,4-TRIAZOLO[4,3-*a*]-5(8*H*)-PYRIMIDONE (**15**) (50 MHz, δ, J IN Hz, Me_2SO-d_6)

Carbon atom	*E*	*F*	*G*	**15**
C-β			155.5[a]	
C-γ	145.4[a]	150.2[a]		150.3
C-δ	143.9[a]	160.2[a]	150.8[a]	159.6
C-ε	107.6[a]	96.2[a]	98.1[a]	94.4
C-ζ	160.8[a]	143.3[a]	160.6[a]	145.6
C-θ	149.2[a]	157.5[a]	151.0[a]	157.5
Me (triazole)	13.8[a]	13.3[a]	14.2[a]	
Me (pyrimidine)	18.1[a]	21.3[a]	18.6[a]	21.5

[a]See ref. 9.

1,2,4-triazolo[4,3-*a*]-5(8*H*)-pyrimidone (**15**) in 38% yield. Although the corresponding model compound, 3,7-dimethyl-1,2,4-triazolo[4,3-*a*]-5(8*H*)-pyrimidone (F) rearranges to 2,5-dimethyl-1,2,4-triazolo[1,5-*a*]-7(4*H*)-pyrimidone (G) under acidic conditions[14], no such rearrangement product as compound **16** was isolated. The u.v. absorption maxima of nucleoside **15** at 299 and 250 nm were quite close to those of 3,7-dimethyl-1,2,4-triazolo[4,3-*a*]-5(8*H*)-pyrimidone (F)[17] at 298 and 248 nm, and quite different from those of the isomeric 3,5-dimethyl-1,2,4-triazolo[4,3-*a*]-7(8*H*)-pyrimidone (E)[17] (at 248 nm) and of the rearranged 2,5-dimethyl-1,2,4-triazolo[1,5-*a*]-7(4*H*)-pyrimidone (G) (at 272 and 238 nm)[17]. The chemical shifts of the ^{1}H- and ^{13}C-n.m.r.-spectral signals (see Tables V and VI) of nucleosides **14** and **15** were also quite similar to those of the unrearranged 3,7-dimethyl-1,2,4-triazolo[4,3-*a*]-7(8*H*)-pyrimidone (F), and different from both its isomer 3,5-dimethyl-1,2,4-triazolo[4,3-*a*]-7(8*H*)-pyrimidone (E) and the rearranged 2,5-dimethyl-1,2,4-triazolo[1,5-*a*]-7(4*H*)-pyrimidone (G). The anomeric proton of nucleoside **15**, measured at 200 MHz, appeared clearly as a doublet (*J* 4 Hz) at 5.51 p.p.m., indicating that it had the β configuration. Accordingly, the blocked and unblocked nucleosides **14** and **15** were respectively assigned the structures 3-(5-*O*-benzoyl-β-D-ribofuranosyl)-7-methyl-1,2,4-triazolo[4,3-*a*]-5(8*H*)-pyrimidone and 7-methyl-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*a*]-5(8*H*)-pyrimidone.

EXPERIMENTAL

Corrected melting-points were determined on a Kofler-block apparatus preheated to 10° below the actual melting-point and then heated at the rate of 1°/min. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. Merck silica gel 60 (0.063–0.200 mm) was used for column chromatography. 2-(Aminomethyl)pyridine (**2**) was purchased from Fluka Chemical Co., and 2-hydrazino-4-hydroxy-6-methylpyridine (**13**), from Aldrich Chemical Co., Inc. U.v. spectra were recorded with a Perkin–Elmer 323 spectrophotometer, and are described as λ_{max} [log ε] followed by λ_{min} [log ε]. I.r. spectra were recorded with a Perkin–Elmer 735 spectrophotometer calibrated with polystyrene. ^{1}H-N.m.r. spectra were recorded at 60 MHz with a Varian EM-360 spectrometer; and at 200 MHz, in the F.t. mode, with a Varian XL 200 instrument. Tetramethylsilane (Me_4Si) or sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) was used as an internal standard. ^{1}H-N.m.r. data are described as b, broad; d, doublet; dd, doublet of doublets; m, multiplet; q, quartet; s, singlet; and t, triplet; followed by coupling constant (*J*, in Hz), the number of protons determined by integration, and the positions of the protons. F.t. ^{13}C-n.m.r. spectra were recorded with a Varian XL 200 instrument at 50 MHz.

*2-[2,5-Anhydro-6-O-benzoyl-*D*-allono(thioamido)methyl]pyridine* (**3**). — A solution of ethyl 2,5-anhydro-6-*O*-benzoyl-D-allonodithioate (**1**; 1.92 g, 5.6 mmol) and 2-(aminomethyl)pyridine (**2**; 0.62 g, 5.7 mmol) in abs. ethanol (10 mL) was

refluxed for 2 d, and then evaporated to dryness *in vacuo*. The syrup obtained was dissolved in 2:1 ethyl acetate–benzene, and the solution applied to a column (3 × 19 cm) of silica gel which was eluted with the same solvent system. The desired product (1.37 g, 37%) crystallized from acetone–petroleum ether (b.p. 40–60°) in colorless needles; m.p. 130–133°, $[\alpha]_D$ +19.0° (*c* 0.13, 95% ethanol); ν_{max}^{KBr} 1705 (C=O) and 1170 cm^{-1} (C=S).

Anal. Calc. for $C_{19}H_{20}N_2O_5S$: C, 58.75; H, 5.19; N, 7.21; S, 8.25. Found: C, 58.81; H, 5.01; N, 7.27; S, 8.17.

3-(5-O-Benzoyl-β-D-ribofuranosyl)imidazolo[1,5-a]pyridine (**4**). — A suspension of compound **3** (469 mg, 1.2 mmol), mercuric bromide (22 mg, 0.06 mmol), and mercuric oxide (400 mg, 1.85 mmol) in ethanol (15 mL) was refluxed for 1 day. The syrup obtained after filtration, and evaporation of the filtrate, was dissolved in 4:1 ethyl acetate–benzene, and chromatographed on a column (2 × 30 cm) of silica gel that was eluted first with the same solvent system, and then with 4:1 ethyl acetate–pyridine. The fraction eluted with 4:1 ethyl acetate–benzene afforded 85 mg (20%) of a syrup having R_F 0.15 in t.l.c.; $[\alpha]_D$ −10.6° (*c* 0.24, 95% ethanol); ν_{max}^{Nujol} 3340 (OH), 2960–2880 (CH), and 1716 (C=O).

Anal. Calc. for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 63.77; H, 5.11; N, 7.78.

3-β-D-Ribofuranosylimidazolo[1,5-a]pyridine (**5**). — A solution of compound **4** (170 mg, 0.48 mmol) in dry methanol (20 mL) saturated with ammonia was kept for 2 d at room temperature, and then evaporated to dryness *in vacuo*. The residue was washed with ethyl ether (3 × 20 mL), dissolved in 8:2:1 ethyl acetate–pyridine–water, and chromatographed on a column (2 × 17 cm) of silica gel eluted with the same solvent system. The first 20 mL was discarded, and the next fraction (30 mL) afforded the desired product in crystalline form (22 mg, 18%). After recrystallization from ethanol, the product had m.p. 190.5–191°, $[\alpha]_D$ −75.6° (*c* 0.09, 95% ethanol); ν_{max}^{KBr} 3455 (OH), 3098 (Ar), 2900, and 2860 cm^{-1} (CH); ^{1}H-n.m.r. data (Me_2SO-d_6; 60 MHz): δ 5.10 (m, 2 H, O*H*-2′,3′), 4.55 (m, 1 H, H-1′), 4.00 (m, 2 H, H-2′,3′), and 3.5 (m, 3 H, H-4′,5′a,5′b) (see Table II for data on *N*-heterocyclic protons).

Anal. Calc. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.35; H, 5.61; N, 11.15.

3-(5-O-Benzoyl-β-D-ribofuranosyl)-1,2,4-triazolo[4,3-a]pyrazine (**7**). — A solution of 2-hydrazinopyrazine (**6**)[18,19] (334 mg, 3 mmol) and dithioate **1** (1.25 g, 3.7 mmol) in dry methanol (25 mL) was refluxed for 48 h, cooled, and evaporated to dryness *in vacuo*. The residue was dissolved in 4:1 ethyl acetate–benzene and chromatographed on a column (3 × 30 cm) of silica gel by eluting first with the same solvent system (120 mL) and then successively with 4:1 ethyl acetate–pyridine (120 mL) and 3:1 ethyl acetate–pyridine (150 mL). Upon evaporation, the first 300-mL fraction afforded crystals (54 mg, 5%), which, after two recrystallizations from ethanol, had m.p. 202–205°, $[\alpha]_D$ −195.3° (*c* 0.17, 95% ethanol); ν_{max}^{KBr} 3200 (OH), 2972 and 2880 (CH), and 1718 cm^{-1} (C=O); ^{1}H-n.m.r. data (Me_2SO-d_6, 1

drop of D_2O; 60 MHz): δ 7.57 (m, 5 H, Ar), 5.50 (d, $J_{1',2'}$ 2.4 Hz, 1 H, H-1'), 4.95 (m, 1 H, H-2'), and 4.35 (m, 4 H, H-3',4',5'a,5'b) (see Table II for data on *N*-heterocyclic protons).

Anal. Calc. for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72. Found: C, 57.36; H, 4.63; N, 15.66.

*3-β-*D*-Ribofuranosyl-1,2,4-triazolo[4,3-*a*]pyrazine* (**8**). — A solution of compound **7** (287 mg, 0.8 mmol) in dry methanol (80 mL) presaturated with dry ammonia gas was kept overnight at room temperature, and evaporated to dryness at 40° *in vacuo*, and the residue washed successively with ether (2 × 30 mL) and hot benzene (3 × 30 mL). The residue crystallized from a small volume of ethanol (yield 167 mg, 83%), and was recrystallized from ethanol–acetone in yellowish-white needles; m.p. 144–146°, $[\alpha]_D$ −83.1° (*c* 0.13, water); ^{1}H-n.m.r. data (Me_2SO-d_6, 60 MHz): δ 5.25 (m, 3 H, H-1', O*H*-2',3'), 4.52 (m, 1 H, H-2'), 4.05 (m, 1 H, H-3'), and 3.56 (m, 3 H, H-4',5'a,5'b) (see Table II for data on *N*-heterocyclic protons).

Anal. Calc. for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.78; H, 4.87; N, 22.09.

*2-(5-*O*-Benzoyl-β-*D*-ribofuranosyl)-1,2,4-triazolo[1,5-*a*]pyrimidine* (**11**). — A solution of compound **1** (3.23 g, 9.4 mmol) and 2-hydrazinopyrimidine[20] **9** (1.04 g, 9.4 mmol) in dry 1-propanol (25 mL) was refluxed for 2 d, cooled, and evaporated to dryness *in vacuo*, and a solution of the residue in 8:2:1 ethyl acetate–pyridine–water applied to a column (3 × 21 cm) of silica gel and eluted with the same solvent system. The title compound (255 mg, 8%), after recrystallization from ethanol, had m.p. 143–144°, $[\alpha]_D$ −23.8° (*c* 0.17, 95% ethanol); ν_{max}^{Nujol} 3220 (OH), 3060 (Ar), 1714 (C=O), and 1270 cm^{-1} (OH); ^{1}H-n.m.r. data (Me_2SO-d_6, 200 MHz): δ 8.00 and 7.50 (m, 6 H, Ar and H-6), 5.30 (m, 2 H, O*H*), 5.00 (d, $J_{1',2'}$ 2, Hz, 1 H, H-1'), and 4.40 (m, 5 H, H-2',3',4',5'a,5'b) (see Table III for data on *N*-heterocyclic protons).

Anal. Calc. for $C_{17}H_{16}N_4O_5$: C, 57.30; H, 4.53; N, 15.72. Found: C, 57.24; H, 4.42; N, 15.72.

*2-β-*D*-Ribofuranosyl-1,2,4-triazolo[1,5-*a*]pyrimidine* (**12**). — A solution of compound **11** (160 mg, 0.5 mmol) in dry methanol (20 mL) saturated with ammonia was kept for 2 d at room temperature and then evaporated to dryness *in vacuo* at room temperature. The residue was washed successively with ethyl ether (3 × 10 mL) and warm benzene (3 × 10 mL), and then crystallized from ethanol; yield 51 mg (54%); m.p. 181–181.5°, $[\alpha]_D$ −40.0° (*c* 0.16, water); ν_{max}^{KBr} 3450 (OH), 3070 (Ar), 2940 and 2920 cm^{-1} (CH); ^{1}H-n.m.r. data (Me_2SO-d_6, 200 MHz): δ 5.28 (d, *J* 5 Hz, 1 H, O*H*-2'), 5.06 (d, *J* 5 Hz, 1 H, O*H*-3'), 4.89 (d, $J_{1',2'}$ 5 Hz, 1 H, H-1'), 4.79 (t, *J* 6 Hz, 1 H, O*H*-5'), 4.34 (m, 1 H, H-2'), 4.09 (m, 1 H, H-3'), 3.93 (dd, *J* 4 and 9 Hz, 1 H, H-4'), and 3.55 (m, 2 H, H-5') (see Table III for *N*-heterocyclic protons); ^{13}C-n.m.r. data (Me_2SO-d_6): δ 79.1 (C-1'), 75.4 (C-2'), 71.4 (C-3'), 85.0 (C-4'), and 62.2 (C-5') (see Table IV for data on *N*-heterocyclic carbon atoms).

Anal. Calc. for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.46; H, 4.73; N, 22.13.

3-(5-O-Benzoyl-β-D-ribofuranosyl)-7-methyl-1,2,4-triazolo[4,3-a]-5(8H)-pyrimidone (**14**). — A solution of compound **1** (1.71 g, 5 mmol) and 2-hydrazino-4-hydroxy-6-methylpyrimidine (**13**; 0.70 g, 5 mmol) in dry methanol (300 mL) was refluxed for 19 h, cooled, and evaporated, and the residue applied to a column (2.5 × 29 cm) of silica gel which was eluted with 2:2:1 ethyl acetate–pyridine–water, to yield colorless crystals (454 mg, 24%); m.p. 209–211.5°, after recrystallization from ethanol; $[\alpha]_D$ −89.7° (*c* 0.06, methanol); ^{1}H-n.m.r. data (Me_2SO-d_6, 60 MHz): δ 7.98 (dd, 2 H, *o*-Ar), 7.60 (b, 3 H, *m,p*-Ar), 5.30 (b, 2 H, O*H*-2′,3′), and 5.8, 5.6, and 5.2 (m, 6 H, H-1′,2′,3′,4′,5′a,5′b) (see Table V for data on Me and *N*-heterocyclic protons).

Anal. Calc. for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.70; N, 14.50. Found: C, 55.85; H, 4.72; N, 14.35.

7-Methyl-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-a]-5(8H)-pyrimidone hydrate (**15**). — A solution of compound **14** (236 mg, 0.61 mmol) in methanol (10 mL) presaturated with ammonia was kept for 2 d at room temperature, evaporated *in vacuo* at room temperature, and the amorphous solid (66 mg, 32%) washed successively with ethyl ether (3 × 20 mL) and hot benzene (3 × 20 mL). After recrystallization from water, the product had m.p. 180–185°, $[\alpha]_D$ −4.3° (*c* 0.19, 95% ethanol); ν_{max}^{KBr} 3360 (OH), 2930, 2850 (CH), 1728 (C=O), and 1060 cm^{-1} (CO); ^{1}H-n.m.r. data (Me_2SO-d_6, 200 MHz): δ 5.51 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1′), 5.18, 4.98, and 4.72 (b, 3 H, O*H*), 4.48 (m, 1 H, H-2′), 4.07 (m, 1 H, H-3′), 3.86 (dd, 1 H, *J* 6 and 4 Hz, H-4′) (see Table V for data on Me and *N*-heterocyclic protons); ^{13}C-n.m.r. data (Me_2SO-d_6): δ 76.8 (C-1′), 73.8 (C-2′), 70.7 (C-3′), 84.5 (C-4′), and 61.9 (C-5′) (see Table VI for data on *N*-heterocyclic carbon atoms).

Anal. Calc. for $C_{11}H_{16}N_4O_6 \cdot 2\ H_2O$: C, 41.51; H, 5.70; N, 17.60. Found: C, 41.55; H, 5.26; N, 17.56.

REFERENCES

1 H. S. El Khadem and J. Kawai, *Carbohydr. Res.*, 153 (1986) 271–283.
2 M. Bobek and J. Farkaš, *Collect. Czech. Chem. Commun.*, 34 (1969) 247–252.
3 M. S. Poonian and E. F. Nowoswiat, *J. Org. Chem.*, 45 (1980) 203–208.
4 T. Huynh-Dinh and J. Igolen, *J. Org. Chem.*, 41 (1976) 3124–3128.
5 S. Y.-K. Tam, J.-S. Hwang, F. G. De Las Heras, R. S. Klein, and J. J. Fox, *J. Heterocycl. Chem.*, 13 (1976) 1305–1308.
6 T. Huynh-Dinh, R. S. Safarti, C. Gouyette, and J. Igolen, *J. Org. Chem.*, 44 (1979) 1028–1035.
7 G. Doukhan, T. Huynh-Dinh, E. Bisagni, J.-C. Chernann, and J. Igolen, *Eur. J. Med. Chem.*, 14 (1979) 375–380.
8 P. Allard, T. Huynh-Dinh, C. Gouyette, J. Igolen, J.-C. Chernann, and F. Barre-Sinoussi, *J. Med. Chem.*, 24 (1981) 1291–1297.
9 H. S. El Khadem, J. Kawai, and D. L. Swartz, *Heterocycles*, 28 (1989) 239–248.
10 H. S. El Khadem and J. Kawai, *Abstr. Pap. 194th National Meeting American Chemical Society*, New Orleans, Louisiana, August 30–September 4, 1987, CARB 8.
11 Ph.D. Dissertation of Joshua Kawai, The American University, Washington, D.C., 1988.
12 H. S. El Khadem and J. Kawai, *Abstr. Pap. 196th National Meeting American Chemical Society*, Los Angeles, California, 1988 CARB 1.
13 J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, (1955) 2834–2837.
14 W. W. Paudler and J. E. Kuder, *J. Heterocycl. Chem.*, 3 (1966) 33–37.

15 G. M. BADGER, P. J. NELSON, AND K. T. POTTS, *J. Org. Chem.*, 29 (1964) 2542–2545.
16 D. J. BROWN AND T. NAGAMATSU, *Aust. J. Chem.*, 30 (1977) 2515–2525.
17 C. F. H. ALLEN, H. R. BEILFUSS, D. M. BURNESS, G. A. REYNOLDS, J. F. TINKER, AND J. A. VANALLAN, *J. Org. Chem.*, 24 (1959) 779–7878.
18 P. J. NELSON AND K. T. POTTS, *J. Org. Chem.*, 27 (1962) 3243–3248.
19 S. E. MALLETT AND F. L. ROSE, *J. Chem. Soc., C*, (1966) 2038–2043.
20 K. SIRAKAWA, S. BAN, AND M. YONEDA, *Yakugaku Zasshi*, 73 (1953) 598–601; *Chem. Abstr.*, 48 (1954) 9,362*c*.