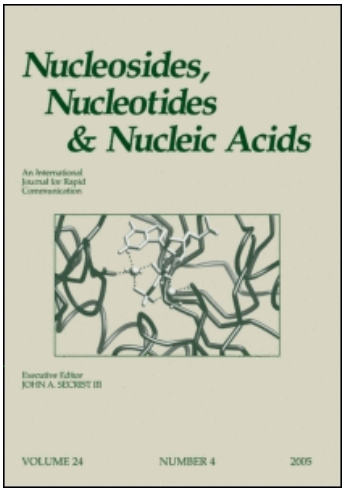

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Kim, Sungjoong , Won, Wooyeon and Kang, Yonghan(1997) 'Ring Opening Reaction of Pyrazolo[3,4-*c*]Maleimide Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 16: 10, 2025 — 2033
To link to this Article: DOI: 10.1080/07328319708002553
URL: http://dx.doi.org/10.1080/07328319708002553

NUCLEOSIDES & NUCLEOTIDES, 16(10&11), 2025-2033 (1997)

RING OPENING REACTION OF PYRAZOLO[3,4-*c*]MALEIMIDE NUCLEOSIDES

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ABSTRACT: Synthesis of pyrazolo[3,4-*c*]maleimide nucleosides was attempted, but ring opening reaction of the maleimide part was observed during ammonolysis of sugar-protected pyrazolo[3,4-*c*]maleimide nucleosides. The isolated pyrazole nucleosides were characterized by NMR spectra and X-ray analysis.

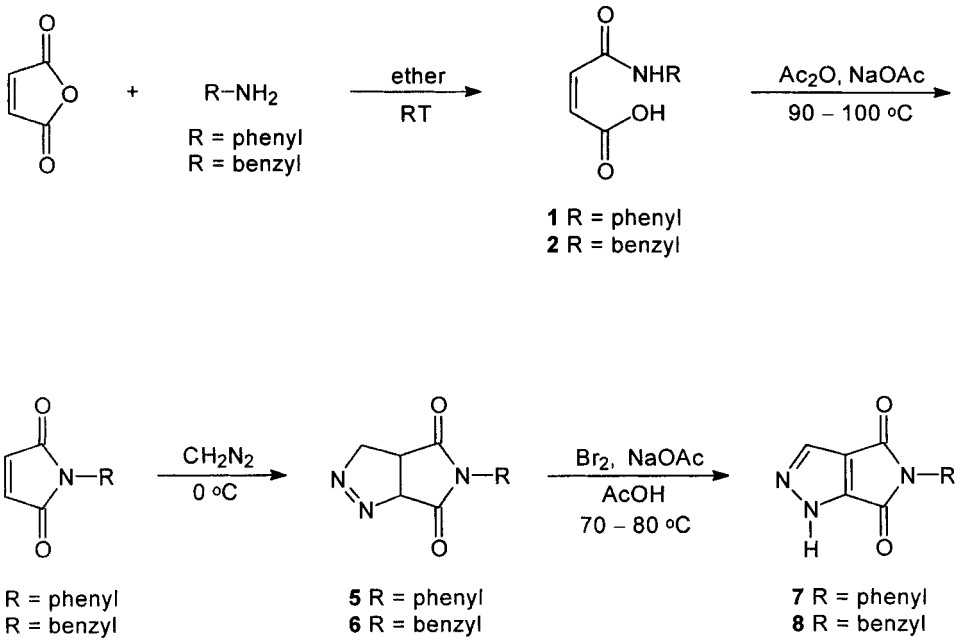
INTRODUCTION

A great variety of nucleoside analogs have been widely used as antiviral and antitumor agents.[1,2] More recently, 3'-azido-3'-deoxythymidine (AZT),[3] 2',3'-dideoxyinosine (ddI),[4] and 2',3'-dideoxy-cytidine (ddC)[5] have been approved as antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection, but synthetic nucleoside modification has been focussed on the transformation of the sugar moiety.[5~9] The present work targets the synthesis of azapentalene nucleosides which are composed of a fused 5,5-membered ring system. There have been only a few attempts to develop the potential antiviral agents with azapentalene nucleosides in the literature.[10] In this paper synthesis of 5-substituted pyrazolo[3,4-*c*]maleimide nucleoside is presented.

RESULTS AND DISCUSSION

According to the literature,[11,12] 5-phenyl-1*H*-pyrazolo[3,4-*c*]maleimide (**7**) was synthesized from *N*-phenylmaleic acid (**1**) which is obtainable from maleic anhydride. *N*-Phenylmaleimide (**3**) was produced by treatment of *N*-phenylmaleic acid (**1**) with sodium acetate in acetic anhydride. 7,8-Dihydro-3-hydro-5-phenyl-3*H*-pyrazolo[3,4-*c*]maleimide (**5**) was obtained by [3+2] cycloaddition of *N*-phenylmaleimide (**3**) and diazomethane. During bromination of compound **5**, the brominated product was converted by *in situ* dehydrobromination to the 5-phenyl-1*H*-pyrazolo[3,4-*c*]maleimide (**7**). In a similar manner, the corresponding 5-benzyl-1*H*-pyrazolo[3,4-*c*]maleimide (**8**) was prepared from maleic anhydride and benzylamine (Scheme 1).

Condensation of **7** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) in the presence of tin(IV) chloride was achieved according to the Vorbrüggen method[13] to give 2-(2,3,5-tri-*O*-benzoyl-β-D-

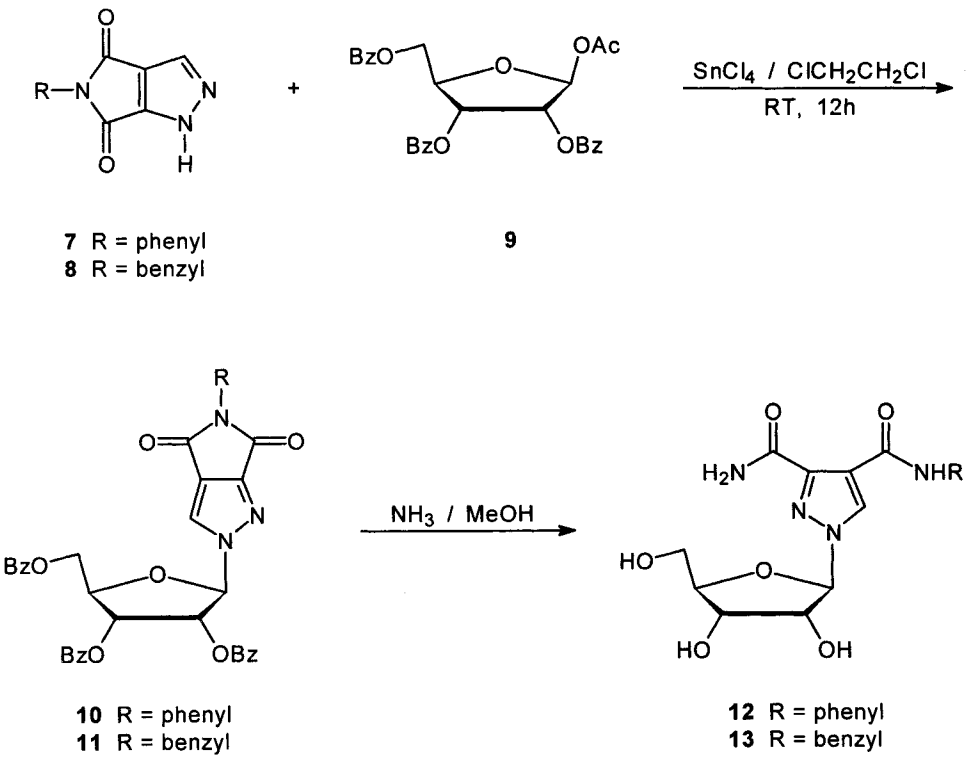


SCHEME 1

ribofuranosyl)-5-phenyl-pyrazolo[3,4-*c*]maleimide (**10**) in 66% yield. 2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-benzyl-pyrazolo[3,4-*c*]maleimide (**11**) was also obtained from **8** in 60% (Scheme 2). ^{1}H NMR Spectra of **10** and **11** showed the presence of H-C(1') were at 6.74 ppm with J = 2.40 Hz and at 6.68 ppm with J = 2.48 Hz.

Compound **10** was treated with methanolic ammonia saturated at 0°C, but the ^{1}H NMR spectrum of the isolated product **12** shwoed the unexpected three D_2O exchangable peaks at 8.18, 8.34, and 13.04 ppm. Compound **12**, therefore, was expected to be 3-carbamoyl-4-(*N*-phenylcarbamoyl)-1-(β-D-ribofuranosyl)-pyrazole. This result indicates that during the deprotecting of compound **10**, the maleimide ring has opened by ammonia. The peaks of 8.18 and 8.34 ppm of compound **12** are explainable by the intramolecular hydrogen bond between the amino proton of 3-carboxamide and N-2. Similar phenomena were observed in the ^{1}H NMR spectra of pyrazole-3-carboxamide and imidazole-4-carboxamide derivatives.[14-16] Reaction of **11** under the same condition gave 4-(*N*-benzylcarbamoyl)-3-carbamoyl-1-(β-D-ribofuranosyl)pyrazole (**13**). A broad doublet at 7.91~8.15 ppm was identified as NH_2 of the 3-carbamoyl group, while the peak at 10.94 ppm as NH of the 4-*N*-benzylcarbamoyl group.

In order to investigate the structure in more detail, X-ray analysis was performed. Fig. 1 shows the molecular structure and the atomic numbering scheme. The crystal data and structure refinements are listed in Table 1. The list of bond distances and angles is given in Table 2. In particlular, the N(2)-C(6)-



SCHEME 2

C(9) angle is 117.4°, which is smaller than 131.2° of the C(7)-C(6)-C(9) angle as expected by proton NMR spectra. It is possible to understand that the C(6)-C(9)-N(3) angle of 116.6° is due to the construction of the five membered ring by intramolecular hydrogen bonding.

EXPERIMENTAL

General Melting points were measured using a Büchi 530 apparatus and the obtained data were uncorrected. ^{1}H NMR spectra were recorded using a Varian unity +300 (300 MHz) spectrometer with TMS as an external standard (δ in ppm, J in Hz). Analytical TLC was carried out with pre-coated silica gel plates (Merck 60 F254, 0.25 mm). Low resolution electron impact mass spectra (MS) at 45 eVwere determined by direct probe sample introduction with a Kratos profile spectrometer. UV spectra were recorded with a Shimadzu UV-160A spectrophotometer. X-ray diffraction analysis data were collected for the θ range 1.5-27.5° with graphite-monochromated Mo Kα radiation (λ = 0.7107 Å) equipped with an Enraf-Nonius CAD4 computer controlled kappa axis diffractometer. The structure was characterized by SHELXL-86 methods and parameters were refined on SHELXL-93 by full-matrix least-

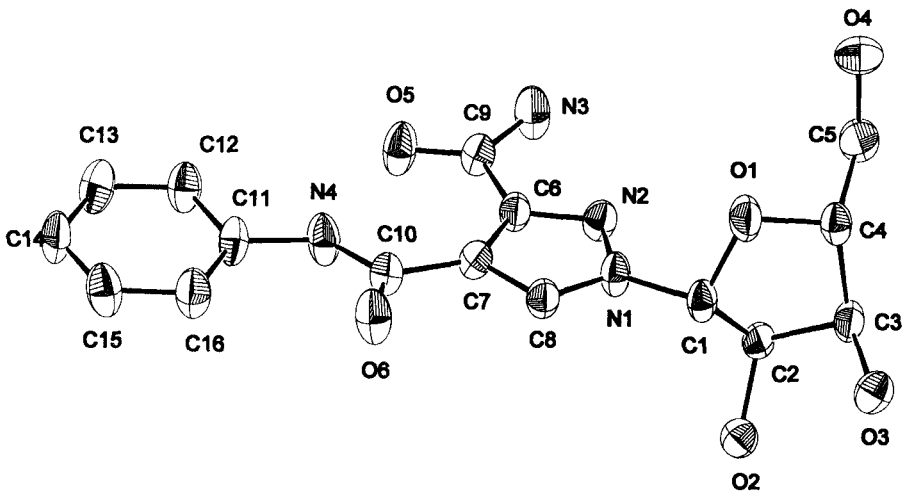


Figure 1. ORTEP view of
3-Carbamoyl-4-(*N*-phenylcarbamoyl)-1-(*β*-D-ribofuranosyl)pyrazole (**12**).

squares. Elemental analyses were performed by National Institute of Technology & Quality (NITQ), Kwacheon, Korea.

N-Benzylmaleamic acid (2)

Benzylamine (42.9 g, 0.4 mol) dissolved in anhydrous diethyl ether (70 ml) was added slowly to a solution of maleic anhydride (20 g, 0.2 mol) in anhydrous diethyl ether (400 ml) at 15 ~ 20 ℃. After stirring at room temperature for 1 h, the precipitate was filtered and then washed with ether. 38.2 g of *N*-benzylmaleamic acid was obtained (93% yield): mp 126 ℃; R_f = 0.5 (ethyl acetate : ethanol = 4 : 1, v/v);

N-Phenylmaleimide (3)

This product was prepared in 95% yield from *N*-phenylmaleamic acid (**1**) and acetic anhydride according to the method of Cava, *et al.*[11]: mp 88.7 ℃ (Lit.[11] 89 ℃); R_f = 0.83 (methylene chloride : MeOH = 9 : 1, v/v); MS *m/z* (rel. intensity, %) 173(M^+, base), 77(21); UV (MeOH) λmax 281nm (sh, ε 4300), 225 (sh, ε 7400), 203(ε 14100).

N-Benzylmaleimide (4)

A mixture of *N*-benzylmaleamic acid (**2**) (10.3 g, 50 mmol) and acetic anhydride (50 ml) was heated at 80 ℃ for 40 min, then cooled to room temperature. The solution was added to a ice-cooled saturated $NaHCO_3$ solution. The precipitate was collected by filtering and 5.8 g of *N*-benzylmaleimide (**4**) was

TABLE 1. Crystal data and structure refinement for 3-carbamoyl-4-(*N*-phenylcarbamoyl)-1-(β-D-ribofuranosyl)pyrazole (**12**).

Emperical formular	$C_{16}H_{18}N_4O_6$
Formular weight	362.34
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unite cell dimensions	a = 6.872(5) Å, α = 90.000(10) deg.
	b = 11.696(1) Å, β = 90.000(10) deg.
	c = 20.092(2) Å, γ = 90.000(10) deg.
Volume	1615.0(2) $Å^3$
Z	4
Density (calculated)	1.490 Mg/m^3
Absorption coefficient	0.116 min^{-1}
F(000)	760
Crystal size	0.4 x 0.3 x 0.25 mm
Theta range for data collection	2.01 to 27.46 deg.
Index ranges	0<=h<=8, 0<=k<=15, 0<=l<=26
Reflections collected	1962
Independent reflections	1960 [R(int) = 0.0116]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1960 / 0 / 238
Goodness-of-fit on F^2	1.173
Final R indices [I>2δ(I)]	R1 = 0.0568, wR2 = 0.1231
R indices (all data)	R1 = 0.0758, wR2 = 0.1313
Absolute structure parameter	2(3)
Largest diff. peak and hole	0.201 and -0.315 e. $Å^3$

^{1}H NMR(DMSO-d_6) δ 4.4 (d, 2H, C$\underline{H_2}$-Ph), 6.3 (d, 1H, C_2H), 6.5 (d, 1H,C_3H), 7.4 (m, 5H, phenyl), 9.4 (s, 1H, NH), 14.6 (s, 1H, CO_2H); UV (MeOH) λmax 258nm (sh, ε 5100), 207 (ε 23400); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.64; H, 5.48; N, 7.02.

obtained after recrystallization from *n*-hexane (61% yield) : mp 69.2 ℃; R_f = 0.82 (methylene chloride : methanol = 9 : 1, v/v); ^{1}H NMR(DMSO-d_6) δ 4.6 (s, 2H, C$\underline{H_2}$-Ph), 7.1(s, 2H, C_3H,C_4H), 7.3 (m, 5H, phenyl); MS *m/z* (rel. intensity, %) 187(M^+, base), 91(78); UV (MeOH) λmax 303nm (ε 400), 225 (sh, ε 8900), 209(ε 14100); Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.28; H, 4.98; N, 7.72.

7,8-Dihydro-3-hydro-5-phenyl-3*H*-pyrazolo[3,4-*c*]maleimide (5)

Diazomethane in diethyl ether was added slowly to a ice-cooled solution of *N*-phenylmaleimide (**3**) (8.66 g, 0.05 mol) in dry diethyl ether until the yellow color of the reaction mixture did not disappear.

TABLE 2. Bond length [Å] and angles [deg] for 3-Carbamoyl-4-(N-phenylcarbamoyl)-1-(β-D-ribofuranosyl)pyrazole (**12**).

O(1)-C(1)	1.418(6)	O(1)-C(4)	1.452(5)	O(2)-C(2)	1.409(6)
O(3)-C(3)	1.428(5)	O(4)-C(5)	1.413(6)	O(5)-C(9)	1.234(5)
O(6)-C(10)	1.418(6)	N(1)-C(8)	1.338(5)	N(1)-N(2)	1.346(4)
N(1)-C(1)	1.454(5)	N(2)-C(6)	1.331(5)	N(3)-C(9)	1.316(5)
N(4)-C(10)	1.335(5)	N(4)-C(11)	1.419(5)	C(1)-C(2)	1.516(6)
C(2)-C(3)	1.526(6)	C(3)-C(4)	1.535(7)	C(4)-C(5)	1.514(6)
C(6)-C(7)	1.421(5)	C(6)-C(9)	1.490(5)	C(7)-C(8)	1.362(5)
C(7)-C(10)	1.489(6)	C(11)-C(16)	1.379(6)	C(11)-C(12)	1.393(6)
C(12)-C(13)	1.364(6)	C(13)-C(14)	1.372(7)	C(14)-C(15)	1.376(7)
C(15)-C(16)	1.388(6)				

C(1)-O(1)-C(4)	109.3(4)	C(8)-N(1)-N(2)	112.2(3)
C(8)-N(1)-C(1)	125.9(3)	N(2)-N(1)-C(1)	121.9(3)
C(6)-N(2)-N(1)	104.6(3)	C(10)-N(4)-C(11)	129.1(4)
O(1)-C(1)-N(1)	109.7(4)	O(1)-C(1)-C(2)	106.0(3)
N(1)-C(1)-C(2)	114.7(4)	O(2)-C(2)-C(1)	110.0(4)
O(2)-C(2)-C(3)	115.0(4)	C(1)-C(2)-C(3)	101.8(4)
O(3)-C(3)-C(2)	111.0(4)	O(3)-C(3)-C(4)	108.7(4)
C(2)-C(3)-C(4)	101.8(4)	O(1)-C(4)-C(5)	109.1(4)
O(1)-C(4)-C(3)	106.5(4)	C(5)-C(4)-C(3)	112.0(4)
O(4)-C(5)-C(4)	109.2(4)	N(2)-C(6)-C(7)	111.4(3)
N(2)-C(6)-C(9)	117.4(3)	C(7)-C(6)-C(9)	131.2(4)
C(8)-C(7)-C(6)	103.6(3)	C(8)-C(7)-C(10)	120.3(4)
C(6)-C(7)-C(10)	136.1(4)	N(1)-C(8)-C(7)	108.3(3)
O(5)-C(9)-N(3)	121.7(4)	O(5)-C(9)-C(6)	121.7(4)
N(3)-C(9)-C(6)	116.6(4)	O(6)-C(10)-N(4)	123.9(4)
O(6)-C(10)-C(7)	119.8(3)	N(4)-C(10)-C(7)	116.3(4)
C(16)-C(11)-C(12)	119.7(4)	C(16)-C(11)-N(4)	124.5(4)
C(12)-C(11)-N(4)	115.8(4)	C(13)-C(12)-C(11)	119.9(4)
C(12)-C(13)-C(14)	121.2(4)	C(13)-C(14)-C(15)	118.8(4)
C(14)-C(15)-C(16)	121.3(4)	C(11)-C(16)-C(15)	119.0(4)

After stirring in an ice-bath for 1 h, the reaction mixture was kept at 0 ℃ overnight. The precipitate was collected on filter and washed with ether to give 9.1 g (85% yield) of solid : mp 180.9 ℃ (Lit.[12] 178.5~179.5 ℃); R_f = 0.64 (methylene chloride : methanol = 15 : 1, v/v) ; ^{1}H NMR(DMSO-d_6) δ 3.48(m, 1H, C_8H), 4.94 (m, 2H, C_3H), 5.97 (d, 1H, C_7H), 7.45 (m, 5H, phenyl); MS *m/z* (rel. intensity, %) 215(M^+, 29), 187(M-N_2, 57), 77 (16), 68(base); UV (Methylene chloride) λmax 322nm (sh, ε 1600), 281 (sh, ε 10700), 257(sh, ε 15100), 231(ε 20900) ; Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.53. Found: C, 61.65; H, 4.23; N, 19.47.

5-Benzyl-7,8-dihydro-3-hydro-3*H*-pyrazolo[3,4-*c*]maleimide (6)

In a similar manner as mentioned above *N*-benzylmaleimide (**4**) (5 g, 0.03 mol) was treated with diazomethane to give 5.7 g (93% yield) of **6** as a solid : mp 132 ℃; R_f = 0.71 (methylene chloride :

methanol = 20 : 1, v/v); ^{1}H NMR(DMSO-d_6) δ 3.4 (m, 1H, C_8H), 4.5 (s, 2H, C$\underline{H_2}$-Ph), 4.9 (m, 2H, C_3H), 5.9 (d, 1H, C_7H), 7.3 (m, 5H, phenyl); MS *m/z* (rel. intensity, %) 229(M^+, 27), 201(M-N_2, 26), 91(86), 68(base); UV (Methylene chloride) λmax 337nm (sh, ε 2100), 278 (ε 11700), 271(ε 12000), 236 (ε 38000); Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.17; H, 4.82; N, 18.10.

5-Phenyl-1*H*-pyrazolo[3,4-*c*]maleimide (7)

Compound **5** (12 g, 56 mmol) and anhydrous sodium acetate (9.15 g, 112 mmol) were dissolved in 400 ml of glacial acetic acid, and bromine (2.9 ml, 56 mmol) was slowly added to the solution. The reaction mixture was heated at 80 ℃ for 4 h, cooled to room temperature, then evaporated *in vacuo*. Water (100 ml) was added to the residue and the precipitate was collected by filtration, then washed with water to give 8.34 g (70% yield) : mp 237 ℃ (Lit.[12] 232~233 ℃); R_f = 0.3 (methylene chloride : methanol = 20 : 1, v/v); ^{1}H NMR(DMSO-d_6) δ 7.4 (m, 5H, phenyl), 8.5 (s, 1H, C_3H), 14.4 (s, 1H, N_1H); MS *m/z* (rel. intensity, %) 213(M^+, base), 185(M-N_2, 8), 77(29), 67(95); UV (Methylene chloride) λmax 232nm (ε 21900); Anal. Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.00; H, 3.27; N, 19.40.

5-Benzyl-1*H*-pyrazolo[3,4-*c*]maleimide (8)

Analogous to the synthesis of compound **7**, 5-benzyl-1*H*-pyrazolo[3,4-*c*]maleimide (**8**) was prepared from compound **6** (2.3 g, 0.01 mol) in 92% yield as white powder : mp 220 ℃, R_f = 0.26 (methylene chloride : methanol = 20 : 1, v/v); ^{1}H NMR (DMSO-d_6) δ 4.7 (s, 2H, C$\underline{H_2}$-Ph), 7.3 (m, 5H, phenyl), 8.4 (s, 1H, C_3H), 14.3 (s, 1H, N_1H); MS *m/z* (rel. intensity, %) 227(M^+, base), 91(49); UV (Methylene chloride) λmax 284nm (sh, ε 2800), 250 (sh, ε 5600), 229(ε 9500); Anal. Calcd for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.66; H, 3.82; N, 18.23.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-phenylpyrazolo[3,4-c]maleimide(10)

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**9**) (5.0 g, 0.01 mol) and 5-phenyl-1*H*-pyrazolo-[3,4-*c*]maleimide (**7**) (2.3 g, 0.01 mol) were dissolved in 120 ml of dichloroethane. Tin(IV) chloride (5 ml, 0.04 mol) was added slowly to the solution and the mixture was stirred at room temperature for 12 h, then water (150 ml) was added. After stirring 1 h, the organic layer was washed with 10% $NaHCO_3$ solution and with water twice, dried over sodium sulfate and evaporated. The residue was purified by recrystallization from ethanol (4.34 g, 66% yield) : mp 198 ℃; R_f = 0.43 (toluene : ethyl acetate = 9 : 1, v/v); ^{1}H NMR (DMSO-d_6) δ 4.70 (m, 2H, C_5'H), 5.00 (d, 1H, C_4'H), 6.15 (m, 1H, C_3'H), 6.23 (m, 1H, C_2'H), 6.74 (d, 1H, C_1'H, J =2.40), 7.38 ~ 8.07 (m, 20H, phenyl), 8.76 (s, 1H, C_3H); MS *m/z* (rel. intensity, %) 213(M-Sugar, 48), 105(base), 77(51); UV (Methylene chloride) λmax 275nm (ε 3600), 233 (ε 57500); Anal. Calcd for $C_{37}H_{27}N_3O_9$: C, 67.58; H, 4.14; N, 6.39. Found: C, 67.78; H, 4.13; N, 6.46.

2-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-benzyl-pyrazolo[3,4-*c*]maleimide(11)

The synthesis of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-benzyl-pyrazolo[3,4-*c*]-maleimide (**11**) was carried out by the similar procedure of compound **10**. The product was recrystallized from ethanol to give a solid (60% yield) : mp 177 ℃; R_f = 0.54 (toluene : ethyl acetate = 9 : 1, v/v); ^{1}H NMR (DMSO-d_6) δ 4.61 (m, 2H, C_5'H), 4.67 (m, 2H, C$\underline{H}_2$-Ph), 4.98 (d, 1H, C_4'H), 6.13 (m, 1H, C_3'H), 6.20 (m, 1H, C_2'H), 6.68 (d, 1H, C_1'H, J = 2.48), 7.28 ~ 8.0 (m, 20H, CH_2-$\underline{Ph}$, phenyl), 8.68 (s, 1H, C_3H); MS *m/z* (rel. intensity, %) 227(M-Sugar, 1), 105(base) ; UV (Methylene chloride) λmax 275nm (ε 5500), 231 (ε 74100); Anal. Calcd for $C_{38}H_{29}N_3O_9$: C, 67.95; H, 4.35; N, 6.26. Found: C, 67.91; H, 4.10; N, 6.40.

3-Carbamoyl-4-(*N*-phenylcarbamoyl)-1-(β-D-ribofuranosyl)pyrazole (12)

Compound **10** (5.1 g, 8 mmol) and methanolic ammonia (150 ml, saturated at 0 ℃) was added to a pressure bottle. The solution was stirred at room temperatrue for 7 h and evaporated under reduced pressure. The residue was evaporated azotropically with methanol under reduced pressure 3~4 times. The residue was washed with 20 ml of hot toluene four times to remove benzamide and recrystallized from ethanol to give 1.7 g of colorless crystals (59% yield) : mp 228 ℃; R_f = 0.5 (ethyl acetate : ethanol= 9 : 1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.60 (m, 2H,C_5'H), 3.99 (m, 1H, C_4'H), 4.20 (m, 1H, C_3'H), 4.43 (m, 1H, C_2'H), 5.05(t, 1H, C_5'OH), 5.23 (d, 1H, C_3'OH), 5.60 (d, 1H,C_2'OH), 5.81 (d, 1H C_1'H, J = 4.3), 7.10 ~ 7.70 (m, 5H, Ph), 8.18 ~ 8.34 (d, NH_2), 8.80 (s, 1H, C_5H) 13.04 (s, 1H, NH); MS *m/z* (rel. intensity, %) 230(M-Sugar, 45), 93(78), 44(base); UV (MeOH) λmax 272nm (ε 10700), 237 (ε 12000), 205 (ε 28200); Anal. Calcd for $C_{16}H_{18}N_4O_6$: C, 53.04; H, 5.01; N, 15.46. Found: C, 53.27; H, 5.12; N, 15.62.

4-(*N*-Benzylcarbamoyl)-3-carbamoyl-1-(β-D-ribofuranosyl)pyrazole (13)

Compound **11** (2.3 g, 3 mmol) was treated with methanolic ammonia (120 ml, saturated at 0 ℃) in a similar manner as described above. The residue was purified by silica gel column chromatography with ethyl acetate as an eluent to give 0.8 g of white powder (59% yield) : mp 149.3 ℃; R_f = 0.34 (ethyl acetate : ethanol= 9 : 1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.60 (m, 2H, C_5'H), 3.95 (t, 1H, C_4'H), 4.16 (m, 1H, C_3'H), 4.38 (m, 1H, C_2'H), 4.48 (d, 2H, C$\underline{H}_2$-Ph), 4.97 (t, 1H, C_5'OH), 5.15 (d, 1H, C_3'OH), 5.53 (d, 1H, C_2'OH), 5.74 (d, 1H, C_1'H, J = 4.12), 7.31 (m, 5H, Ph), 7.91 ~ 8.15 (d, NH_2), 8.63 (s, 1H, C_5H), 10.94 (t, 1H, N$\underline{H}$-CH_2-); MS *m/z* (rel. intensity, %) 227(M-Sugar, 0.6), 106(60), 91(23), 44(base); UV (MeOH) λmax 260nm (sh, ε 8510), 205 (ε 23400); Anal. Calcd for $C_{17}H_{20}N_4O_6$: C, 54.25; H, 5.36; N, 14.89. Found: C, 54.50; H, 5.48; N, 14.84.

ACKNOWLEDGEMENT

This study was supported by Korean Ministry of Education through Research Fund (BSRI-96-3443).

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