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Synthesis of Naphtho and 4-Bromonaphthotriazole-Ribonucleosides Using Trimethylsilyl Triflate as a Catalyst

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Treatment of 1-trimethylsilylnaphtho[2,3-d]-1,2,3-triazole (II) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (III) in the presence of trimethylsilyl trifluoromethanesulphonate led to an anomeric mixture of the corresponding 1-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)-naphtho[2,3-d]-1,2,3-triazole (IV) and 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-naphtho [2,3-d]-1,2,3-triazole (V). Separation of the anomers was achieved by chromatographical means. Debenzoylation of (IV) and (V) led to the free nucleosides (VI) and (VII) respectively. Similarly a mixture of 1-(2.3,5-tri-O-benzoyl-α) (XI) and 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-bromonaphtho [2,3-d]-1,2,3-triazole (XII) was prepared and separated by chromatographical means. Structural proofs are based on ^1H, ^{13}C NMR and MS spectra. The ribosylation of naphtho[2,3-d]-1,2,3-triazole (I) by dry fusion method afforded a very low yield of the protected ribonucleosides (IV) and (V).

Key Words: Naphtho [2,3-d]-1,2,3-triazole, 4-Bromonaphtho[2,3-d]-1,2,3-triazole, 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose, Trimethylsilyl triflate.

INTRODUCTION

Various triazole derivatives are used as chemotherapeutic agents[1–5], as they have antibacterial[6, 7], antituberculous, anti-inflammatory and fungicidal activities[8], as well as an inhibitory activity of adenosine and AMP deaminases[9]. They also have many applications[10] and are used for preparation of peptidomimetics[11]. Synthetic nucleosides often exhibit enhanced biochemical activity compared to the corresponding aglycon[12, 13]. It was of interest to ribosylate naphtho[2,3-d]-1,2,3-triazole and its 4(9)-bromo derivative under the Vorbruggen coupling condition[14], as an extension of work using fusion method[15].

EXPERIMENTAL

Melting points were determined on a Tottoli capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were taken on Jeol NMR spectrometer ECP 400 in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. Chemical shifts are given in δ ppm and coupling constants (J) are given in Hz.

TABLE-1

^{1}H NMR SPECTRA OF NAPHTHO [2,3-d]-1,2,3-TRIAZOLES IN DMSO-d_6* OR $CDCl_3$
(δ-values in ppm, *J* in Hz)

	Aromatic protons	Sugar protons								NH
		1′-H	2′-H	3′-H	4′-H	5′-H_A	5′-H_B	2′-OH	3′-OH	5′-OH	
I*	8.41 s (2H, 4-H & 9-H) 8.0 dd (2H; *J* = 7, 3; 5-H & 8-H) 7.50 dd (2H; *J* = 7, 3; 6-H & 7-H)										15.04 bs
IV	8.60 s (1H, 4-H) 8.12–7.90 m (6H, Bz. *ortho* H) 7.84 d (1H, *J* = 8, 5-H) 7.61–7.24 m (12H, 1-H, 6-H, 7-H, Bz. *meta* & *para* H) 6.96 pt (2H, 8-H & 9-H)	**	6.19 pt	6.09–6.08 m	5.43–5.42 m	4.90 dd *J* = 12, 3	4.78 dd *J* = 12, 3				
V	8.60 s (1H, 4-H) 8.02 s (1H, 9-H) 8.00–7.99 m (7H, 5-H & Bz. *ortho* H) 7.63–7.52 m (4H, 8-H & Bz. *para* H) 7.44–7.38 m (8H, 6-H, 7-H & Bz.) *meta* (H)	6.90 d *J* = 3	6.67 pt	6.35 pt	4.97–4.95 m	4.83 dd *J* = 12, 3	4.64 dd *J* = 12, 3				
VII*	8.04 s (1H, 4-H) 7.86 s (1H, 9-H) 7.49 d (1H, *J* = 9, 5-H) 7.45 d (1H, *J* = 9, 8-H) 6.95-6.89 m (2H, 6-H & 7-H)	5.89 d *J* = 5	4.40 pt	4.24 pt	3.64 dd *J* = 8, 4	3.21 dd *J* = 12, 3	3.21 dd *J* = 12, 3	4.84 bs	4.48 bs	3.90 bs	

s = Singlet; bs = broad singlet; d = doublet; dd = doublet of doublet; pt = pseudotriplet; m = multiplet.
**Covered by aromatic protons.

Electron impact (EI) MS spectra were carried on Shimadzu GCMSQP5050A spectrometer, DB-1 glass column 30 m, 0.25 mm, ionization energy 70 eV, at Chemistry Department, College of Science, King Saud University. Thin layer chromatography was performed on silica gel sheets F 1550 LS 254 of Schleicher & Schull, preparative thick layer chromatography on glass plates 20 × 20 cm coated with a 0.2 cm layer of silica gel PF_{254} of Merck/Darmstadt and column chromatography on Merck silica gel 60 (particle size 0.063–0.2 mm).

Synthesis of Naphtho[2,3-d]-1,2,3-triazole (I)

It was prepared by reported method[16] and characterized by its m.p., ^1H NMR (Table-1), ^{13}C NMR (Table-2) and MS: m/z (%) 169 (43) $[M]^{+\bullet}$ ($C_{10}H_7N_3$), 141 (100), 140 (52), 114 (93), 88 (24).

TABLE-2

^{13}C NMR SPECTRA OF NAPHTHO[2,3-d]-1,2,3-TRIAZOLES IN DMSO-d_6^* OR $CDCl_3$ (δ-Values IN ppm)

	Aromatic Carbons	Sugar carbons					
		1′-C	2′-C	3′-C	4′-C	5′-C	C=O
I*	132.16, 130.90, 128.76, 127.00, 125.91						
IV	145.00–106.40 (20 lines)	87.36	82.21	72.14	71.14	64.20	166.20, 165.80, 165.00
V	145.57–105.83 (18 lines)	89.11	80.97	74.02	71.80	63.85	166.20, 165.40, 165.20
VII*	144.95, 132.55, 130,76, 130,17, 128.82, 127.94, 126.26, 124.53, 117.01, 106.76	91.13	85.71	73.13	70.54	61.82	

Synthesis of 1-Trimethylsilyl-naphtho[2,3-d]-1,2,3-triazole (II)

It was prepared by reported method[15]

Synthesis of 1-(2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl)-naphtho-[2,3-d]-1,2,3-triazole (IV) and 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-naphtho[2,3-d]-1,2,3-triazole (V)

A suspension of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose **(III)** (2.97 g, 5.90 mmol) in trimethylsilyl triflate (10 mL) was added to a solution of the silylated base **(II)** in absolute dichloroethane (50 mL). The mixture was stirred at room temperature for 24 h, then extracted with saturated solution of $NaHCO_3$.

The organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure (20 mm Hg) to yield an amorphous foam (2.47 g, 68.7%) of the anomeric mixture **(IV + V)**. The mixture was separated on silica gel column (50 × 4 cm) by chromatography using 1,2-dichloroethane/ethyl acetate (30/1) as an eluant to yield as the faster running fraction β-anomer **(V)**, further purification has been done on preparative TLC using 1,2-dichloroethane/ethyl acetate (20/1) to yield (0.77 g, 76%) of **(V)** as an amorphous solid, m.p. 127–128°C. Collection of the slower running fraction and evaporation yielded the α-anomer **(IV)**, which was also purified on preparative TLC using 1,2-dichloroethane/ethyl acetate (20/1) to yield (0.047 g, 4%) of **(IV)** as solid foam, m.p. 128–129°C MS of **(IV)** m/z (%) 613 (6) $[M]^{+\bullet}$ ($C_{36}H_{27}N_3O_7$), 445 (8), 201 (11), 105 (100), 77 (25), 51 (3). MS spectrum of **(V)** was identical to that of **(IV)**.

Synthesis of 1-α-D-Ribofuranosyl-naphtho[2,3-d]-1,2,3-triazole (VI)

Compound **(IV)** (0.06 g, 0.1 mmol) was added into a methanolic sodium methoxide solution (30 mg in 100 mL of absolute methanol) and then stirred for 4 h at room temperature. After addition of water (10 mL) the solution was neutralized with acetic acid and evaporated three times with water (10 mL), twice with methanol (20 mL) and left for 1 day, then filtered, dried and crystallized from water to yield colourless crystals (0.01 g, 34.5%), m.p. 190–192°C (decomp.). Lit.[15] 186–190°C (decomp.). MS: m/z (%) 301 (24) $[M]^{+\bullet}$ ($C_{15}H_{15}N_3O_4$), 169 (100), 143 (61), 141 (31), 127 (38), 126 (81), 114 (28), 88 (7).

Synthesis of 1-β-D-Ribofuranosyl-naphtho[2,3-d]-1,2,3-triazole (VII)

Compound **(V)** (0.69 g, 1.22 mmol) was debenzoylated by the same procedure as **(IV)**, recrystallized from water to give a pale yellow powder (0.29 g, 86.7%), m.p. 190–191°C (decomp.). Lit.[15] m.p. 187°C (decomp.). MS spectrum was as that of **(VI)**.

Synthesis of (IV) and (V) by dry fusion method[17]

A mixture of **(I)** (1.69 g, 0.01 mol) and **(III)** (0.6 g, 1.2 mmol) was triturated in a mortar, then heated on a sand bath at 170–190°C under reduced pressure (20 mm Hg) for 2 h. The reaction was followed by TLC, which indicated a very low yield of the products.

Synthesis of 4(9)-Bromonaphtho[2,3-d]-1,2,3-triazole (IX)

It was prepared according to Lit.[18] m.p. 240°C, Lit. 244°C. MS m/z (%): 219 (58) $[M\text{-}N_2]^{+\bullet}$ ($C_{10}H_6NBr^{79}$); 221 (56) $[M\text{-}N_2]^{+\bullet}$ ($C_{10}H_6NBr^{81}$); 140 (71); 139 (100); 113 (59).

Synthesis of 1-Trimethylsilyl-4-bromonaphtho[2,3-d]-1,2,3-triazole (X)

A suspension of **(IX)** (1.0 g, 4.0 mmol) and a few crystals of ammonium sulfate

in hexamethyldisilazane (HMDS) (20 mL) was refluxed under dry condition with stirring for 3 days to form a clear solution. The excess of HMDS was distilled off in vacuum to yield **(X)** quantitatively. The material was pure enough for further reaction.

Synthesis of 1-[2,3,5]-tri-O-benzoyl-α-D-ribofuranosyl-4-bromonaphtho-[2,3-d]-1,2,3-triazole (XI) and 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-4-bromonaphtho[2,3-d]-1,2,3-triazole (XII)

A suspension of **(III)** (2.51 g, 4.0 mmol) in trimethylsilyl triflate (10 mL) was added to a solution of the silylated base **(X)** in absolute dichloroethane (50 mL). The mixture was stirred at room temperature for 24 h, then extracted with saturated solution of $NaHCO_3$, the organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure (20 mm Hg) to yield an amorphous foam (1.5 g, 54%) of the anomeric mixture **(XI + XII).** The mixture was separated on silica gel column (50 × 4 cm) by chromatography using the eluant system 1,2-dichloroethane/ethyl acetate (25/1) to yield as the faster running fraction the β-anomer **(XII)** (0.20 g, 2%) as an amorphous solid, m.p. 79–80°C. Collection of the slower running fraction and evaporation yielded the α-anomer **(XI)** (0.17 g, 1%) as an amorphous solid, m.p. 69–70°C.

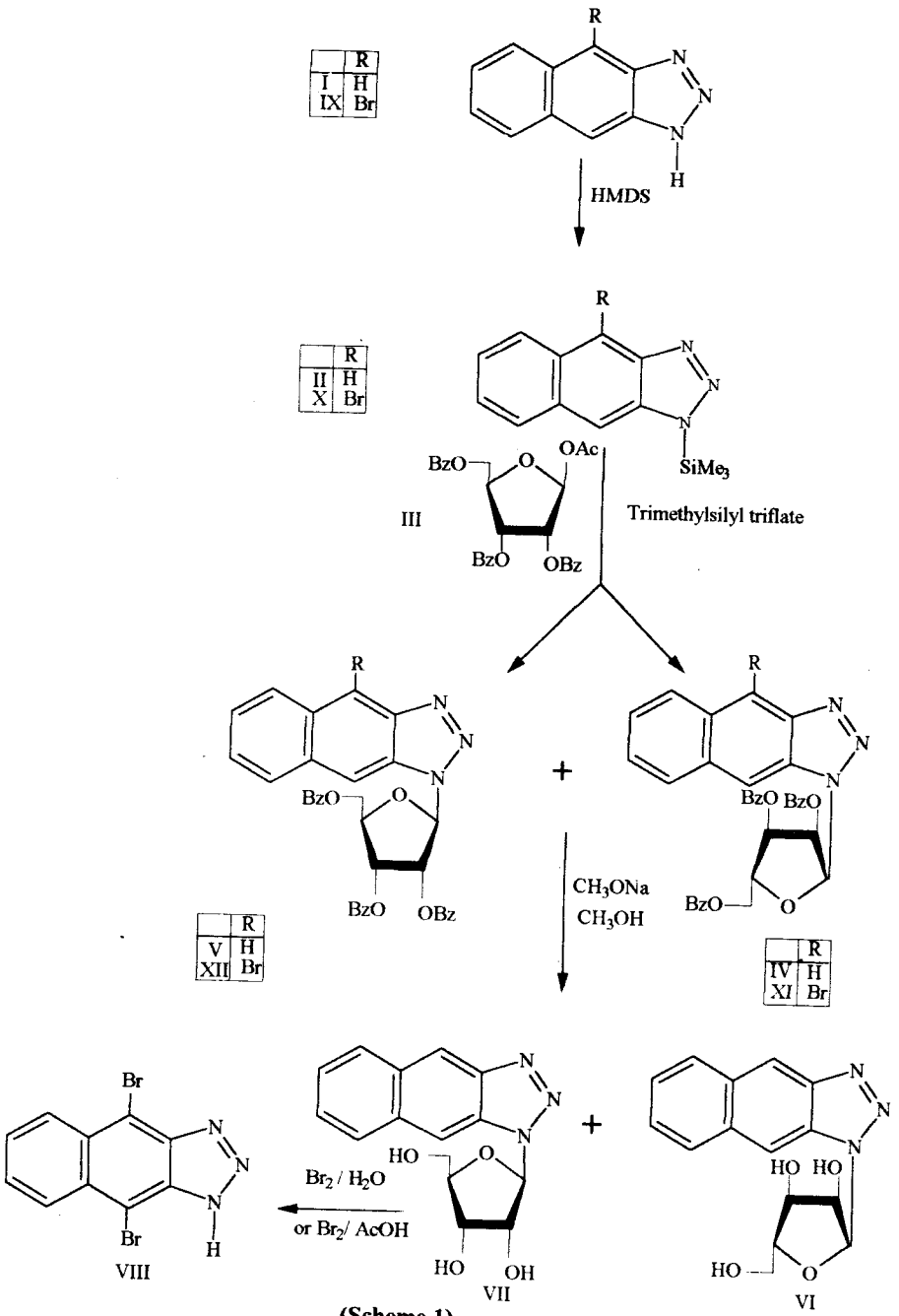
MS of compound **(XI)** m/z (%): 691(2) $[M^{+\bullet}]$ ($C_{36}H_{26}Br^{79}N_3O_7$), 693 (2) [M + 2] ($C_{36}H_{26}Br^{81}N_3O_7$); 445 (8); 201 (17); 105 (100); 77 (25).

MS of compound **(XII)** m/z (%): 445 (16) [M-$C_{10}H_5BrN_3$]; 201 (17); 105 (100); 77 (25).

RESULTS AND DISCUSSION

The starting material naphtho[2,3-d]-1,2,3-triazole **(I)** has been obtained by a known procedure from 2,3-diaminonaphthalene and nitrous acid. The ribosylation of the silylated heterocycles was successfully achieved in the presence of the Lewis acid catalyst, trimethylsilyl trifluoromethanesulphonate (trimethylsilyl triflate). Thus treatment of 1-trimethylsilyl naphtho-[2,3-d]-1,2,3-triazole **(II)** with 1-O-acetyl-2,3,5-tri-O-benzoyl-(β-D-ribofuranose in the presence of trimethylsilyl triflate led to the formation of a mixture of mainly two compounds in 76% yield, which turned out to be the N-1 α **(IV)** and β-anomer **(V).** Their separation into the pure compounds was achieved by silica gel chromatography using the eluant 1,2-dichloroethane/ethyl acetate (30/1). Debenzoylation to the free ribosides **(VI)** and **(VII)** was performed by Zemplen's method[19] applied to the purified anomers **(Scheme 1).**

Constitution and assignment of the configuration of the glycosidic linkage can be depicted from the ^1H (Table-1) and ^{13}C NMR (Table-2) spectra. There is good agreement with earlier findings[20–24] on other ribofuranosides that in an anomer pair, the chemical shift of the anomeric 1′-H of the α-D-riboside appears at a


R
I H
IX Br
HMDS
SiMe3
II H
X Br
III
Trimethylsilyl triflate
CH3ONa
CH3OH
V H
XII Br
IV H
XI Br
Br2 / H2O
or Br2/ AcOH
VIII
VII
VI

(Scheme 1)

lower field compared to the corresponding β-form. It was noted that in almost all cases there was a distinct separation and coupling of the sugar protons, which conclusively proves the assigned constitution. Each of 1-(2,3,5-tri-O-benzoyl-α-D-ribofuranosyl)-naphtho[2,3-d]-1,2,3-triazole **(IV)** and 1-(2,3, 5-tri-O-benzoyl-α-D-ribofuranosyl)-4-bromonaphtho-[2,3-d]-1,2,3-triazole **(XI)**, however, shows some anomaly by the separation of 2 aromatic protons form the broad multiplet and their shift to higher field at δ 6.97 ppm for **(IV)** and at δ 6.99 ppm for **(XI)**. These two protons form pseudo-triplet (singlet + doublet). It is very likely that the singlet is derived from 9-H and doublet (with an *ortho* coupling constant of 8.0 Hz) from 8-H. These protons are shifted to higher field by the influence of the 2′- and 3′-O-benzoyl groups at the sugar moiety. The anomeric protons in **(IV)** and **(XI)** are hidden under the aromatic multiplet at δ 7.61–7.24 ppm for **(IV)** and the aromatic multiplet at δ 7.54–7.21 ppm for **(XI)**.

Trials have been made to prepare the 4-bromo derivative of the nucleoside **(VII)** *via* its direct bromination using bromine dissolved in water or bromine dissolved in acetic acid, but these trials led to the cleavage of the C—N bond and formation of 4,9-dibromonaphtho-[2,3-d]-1,2,3-trizole **(VIII)** instead of the expected brominated nucleoside. This cleavage of the C—N glycosidic linkage may be due to the evolution of HBr during the bromination process. The structure of **(VIII)** was confirmed by ^{1}H NMR spectral data, which showed a multiplet (2H) at δ 8.09 ppm for 5-H and 8-H and another multiplet (2H) at δ 7.35 ppm for 6-H and 7-H and the disappearance of 4-H and 9-H singlets, which confirmed the substitution at the 4 and 9 position of the naphthotriazole nucleus by two bromine atoms. The mass spectrum of compound **(VIII)** showed a molecular ion peak $[M]^{+\bullet}$, at m/z = 325 ($C_{10}H_5Br_2{}^{79}N_3$), [M + 2] at m/z = 327 ($C_{10}H_5Br^{79}\ Br^{81}N_3$) and [M + 4] at m/z = 329 ($C_{10}H_5Br_2{}^{81}N_3$) in the ratio 1 : 2 : 1 indicating the presence of two bromine atoms and fragments due to loss of N_2 at m/z = 297 ($C_{10}H_5Br_2{}^{79}N$), 299 ($C_{10}H_5Br^{79}Br^{81}N$) and 301 ($C_{10}H_5NBr_2^{81}$) of relative abundance ratio 1 : 2 : 1.

Bromination of naphthotriazole **(I)** using bromine in acetic acid afforded **(IX)** which was characterized by its melting point and MS spectral data that showed two fragments due to $[M\text{-}N_2]^{+\bullet}$, at m/z = 219 ($C_{10}H_6NBr^{79}$)and at m/z = 221 ($C_{10}H_6NBr^{81}$) of relative abundance ratio 1 : 1.

4(9)-Bromonaphtho[2,3-d]-1,2,3-triazole **(IX)** was silylated with hexamethyldisilazane (HMDS), then treated with the protected sugar **(III)** in the presence of trimethylsilyl triflate to yield a mixture of mainly two compounds in 54% yield, which turned out to be the N-α **(XI)** and β-anomers **(XII)** **(Scheme 1)**. Their separation into pure compounds was achieved by silica gel chromatography using 1,2-dichloroethane/ethyl acetate (25/1) as an eluant. Their structures were confirmed by ^{1}H-NMR (Table-3) and MS spectral data (see Experimental). The MS spectrum of **(XI)** is characterized by two peaks, one at m/z = 691 for $[M]^{+\bullet}$ ($C_{36}H_{26}Br^{79}N_3O_7$) and the second at m/z = 693 for $[M + 2]^{+\bullet}$ ($C_{36}H_{26}Br^{81}N_3O_7$) of relative abundance ratio 1 : 1.

TABLE-3

^{1}H-NMR SPECTRA OF 4-BROMONAPHTHO[2,3-d]-1,2,3-TRIAZOLES IN $CDCl_3$

(δ-values in ppm, *J* in Hz)

	Aromatic protons	Protected sugar protons					
		1′-H	2′-H	3′-H	4′-H	5′-H_A	5′-H_B
XI	8.40 d (1H, *J* = 8.5, 5-H) 8.11–7.82 m (6H, Bz. *ortho* H) 7.54–7.21 m (12H, 1H, 6-H, 7-H, Bz. *meta* & *para* H) 6.99 pt (2H, 8-H & 9-H)	*	6.18 pt	6.08–6.06 m	5.41–5.38 m	4.89 dd (*J* = 12, 4)	4.74 dd (*J* = 12, 4)
XII	8.40d (1H, *J* = 8.5, 5-H) 8.09s (1H, 9-H) 8.02–7.91 m (6H, Bz. *ortho* H) 7.60–7.53 m (4H, 8-H & Bz. *para* H) 7.48–7.35 m (8H, 6-H, 7-H & Bz. *meta* H)	6.88 d (*J* = 4)	6.68 pt	6.32 pt	4.98–4.87 m	4.90 dd (*J* = 12, 4)	4.61 dd (*J* = 12, 4)

*Covered by aromatic protons.

REFERENCES

1. L.B. Townsed and G. Revankar, *Chem. Rev.*, **70**, 399 (1970).
2. K. Elbs, O. Hirschel, F. Wagner, K. Himmler, W. Turk, A. Henrich and W. Lehmann, *J. Parkt. Chem.*, **108**, 209 (1924).
3. R.W. Cunningham, E.J. Fellows and A.E. Livingston, *J. Pharmacol.*, **73**, 312 (1941).
4. V. Rahm and H.N. Pandey, *Chem. Pharm. Bull. (Japan)*, **22**, 2778 (1974).
5. S.S. Parmar, M. Chaudhary, S.K. Chaudhary, S. Kumar and H.R. Spiro, *J. Pharm. Sci.*, **66**, 971 (1977).
6. F.M. Abd-El-Motti, *Bull. Fac. Pharm. (Cairo Univ.)*, **32**, 283 (1994).
7. A.A. Hassan, N.K. Mohamed, A.A. Aly and A.F.E. Mourad, *Pharmazie*, **52**, 23 (1997).
8. J. Lang and H. Tondys, *Pol. J. Pharmacol. Pharm.*, **27**, 211 (1975); *Chem. Abstr.*, **84**, 17236p (1976).
9. P.J. Dudfield, L. Van-Duc, S.D. Lindell and C.W. Rees, *J. Chem. Soc., Perkin Trans.*, **1**, 2937 (1999).
10. J.B. Polya, A.R. Katritzky and C.W. Rees (Eds.), Comprehensive Heterocyclic Chemistry, Vol. 5, Pergamon Press, p. 733 (1984).
11. J. Cesar and M. Sollner, *Synth. Commun.*, **30**, 4147 (2000).
12. M.V. Pickering, P. Dea, D.G. Streeter and J.T. Witkowski, *J. Med. Chem.*, **20**, 818 (1977).
13. J. Skoda, *Prog. Nucleic Acids Res.*, **2**, 214 (1963).
14. H. Vorbruggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.*, **114**, 1234 (1981).
15. A. Hijazi and W. Pfleiderer, *Nucleosides and Nucleotides*, **5**, 243 (1986).
16. P. Friedländer and S.V. Zakrzewski, *Ber. Deut. Chem. Ges.*, **27**, 765 (1894); K. Fries, R. Walter and K. Schilling, *Liebigs Ann. Chem.*, **516**, 264 (1935).
17. T. Sato, T. Shimadate, Y. Ishido, and N.K. Zasshi, *J. Chem. Soc. (Japan)*, **81**, 1440 (1960).
18. K. Fries, R. Walter and K. Schilling, *Liebigs Ann. Chem.*, **216**, 284 (1935).
19. G. Zemplen, A. Gerecs and I. Hadacsy, *Ber. Dtsch. Chem. Ges.*, **69**, 1827 (1936).
20. R.U. Lemieux, R.X. Kullnig, H.J. Bernstein and W.G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).
21. R.U. Lemieux and M. Hoffer, *Can. J Chem.*, **39**, 110 (1961).
22. M.J. Robins and R.K. Robins, *J. Am. Chem. Soc.*, **87**, 4934 (1965).
23. T. Nishimura and B. Shimizu, *Chem. Pharm. Bull.*, **13**, 803 (1965).
24. I.W. Southon and W. Pfleiderer, *Chem. Ber.*, **111**, 996 (1978).

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