SYNTHESIS OF 1,7-DIDEAZA-2'-DEOXYADENOSINE AND RELATED PYRROLO[2,3-b] PYRIDINE 2'-DEOXY-β-D-RIBONUCLEOSIDES: STEREOSELECTIVE PHASE-TRANSFER GLYCOSYLATION VIA THE NUCLEOBASE ANION

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Abstract——The synthesis of 1,7-dideaza-2'-deoxyadenosine (1) and related pyrrolo[2,3-b]pyridine 2'-deoxy-β-D-ribofuranosides is described. Glycosylation of the anions of the pyrrolo[2,3-b]pyridines 5a or 5b with 2-deoxy-3,5-di-O-(p-toluoyl)-α-D-erythro-pentofuranosyl chloride (6) has been carried out under phase-transfer conditions (MeCN, solid KOH, TDA-1, 25°C) and was complete within less than 15 min. The reaction was stereoselective and β-nucleosides were formed exclusively. The position of glycosylation as well as the anomeric configuration were assigned by NOE difference spectroscopy. Compound 1 was extremely stable against acid or base and was not deaminated by adenosine deaminase.

INTRODUCTION

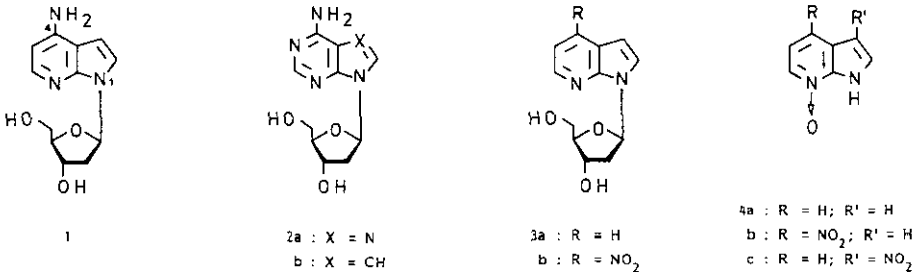
Pyrrolo[2,3-b]pyridine (1,7-dideazapurine) nucleosides are isosteric to purine nucleosides but have a reduced number of proton acceptor sites (nitrogens 1 and 7). According to that one can expect differences in protonation, glycosylic bond stability, formation of Watson-Crick base pairs, and interaction with nucleoside-metabolizing enzymes.

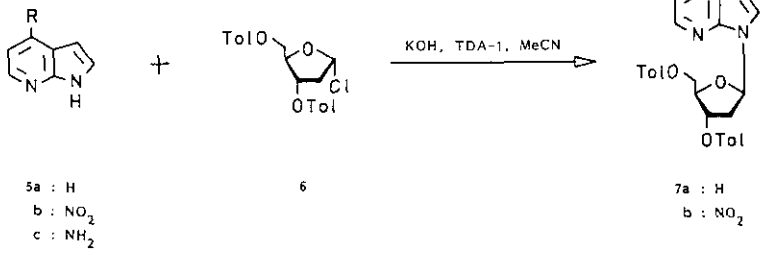
The synthesis of dideazapurine nucleosides was encountered with difficulties resulting from problems of regio- and stereoselectivity during the application of conventional glycosylation techniques [1]. In 1983 our laboratory has developed a regio- and stereoselective method for pyrrolo[2,3-d]pyridine 2'-deoxy-β-D-ribonucleoside synthesis [2]. The protocol uses phase-transfer conditions and depends on the glycosylation of a nucleobase anion [3]. Recently, nucleobase anion glycosylation has been applied to other heterocyclic systems [4,5], including 3,7-dideazapurines [6]. We are now employing this technique for the synthesis of 1,7-

dideaza-2'-deoxyadenosine [7] and related pyrrolo[2,3-b]pyridine 2'-deoxyribofuranosides.

RESULTS AND DISCUSSION

Apart from 1,7-dideazapurine ribonucleosides [8-11] no 2'-deoxynucleoside was known in the beginning of our studies. As pyrrolo[2,3-b]pyridines are only weak nucleophiles at the pyrrole moiety [12], pyrroline derivatives have been used during glycosylation reaction [8-11]. However, from our experience with pyrrole-fused heterocycles it is more advantageous to generate the pyrrolyl anion which is highly nucleophilic and has the ability to react regio- and diastereoselectively with appropriately protected halogenoses [13]. As the reaction is carried out in acetonitrile with excess KOH and the cryptand TDA-1 as catalyst [14] we have searched for a suitable 1H-pyrrolo[2,3-b]pyridine which is readily soluble in the reaction mixture, forms an anion under that conditions and carries an 4-substituent which can be easily converted into that of the final molecule.





4-Nitro-1H-pyrrolo[2,3-b]pyridine (5b) [11,15] shows such favourable properties as the nitro group enhances acidity of the pyrrole system and the molecule is soluble in the reaction mixture. Compound 5b is accessible from 1H-pyrrolo[2,3-b]pyridine (5a) by a three step reaction sequence. Oxidation of 5a with m-chloroperbenzoic acid in dichloromethane furnished the N-oxide 4a [15]. The latter was subjected to

nitration to give the two isomeric nitro compounds 4b and 4c [11,16]. Compound 4b was separated from 4c by column chromatography and was isolated as main product. Deoxygenation of the nitro N-oxide 4b with PCl_3 gave 5b, which was subjected to solid-liquid phase-transfer glycosylation.

Glycosylation of 5b was carried out in acetonitrile with a five-fold excess of powdered KOH and in the presence of the cryptand TDA-1 [14]. The reaction proceeded at room temperature under vigorous stirring. Tlc-monitoring showed that the glycosylation was complete within less than 15 min by formation of only one glycosylation product. Chromatographic work-up gave yellow needles (78%) with an elemental analysis of compound 7b. The small ^1H nmr chemical shift-difference between H-4' and H_2-5' pointed to β-configuration [17]. As it was difficult to carry out structural assignment on the protected molecule Zemplen-deprotection (MeONa/MeOH) was performed, which furnished a crystalline nucleoside being then subjected to rigorous nmr-analysis.

The position of glycosylation as well as the anomeric configuration of this nucleoside was determined by the combination of ^1H nmr and NOE difference spectroscopy. ^1H Nmr data of 1H-pyrrolo[2,3-b]pyridine (7-azaindole) (5a) have been already reported by Cox and Sankar [18]. The chemical shifts of 5b were calculated from increments of substituents [19]. As we have shown that only β-nucleosides give a NOE of H-4' if H-1' is irradiated [20] this technique was employed on the deprotected glycosylation product of 5b. The NOE data of Table 1 immediately confirmed β-configuration. As an NOE was also observed for H-2 the glycosylation position was N-1.

Table 1. NOE Difference Data (%) of Pyrrolo[2,3-b]pyridine and Pyrrolo[2,3-d]-pyrimidine 2'-Deoxyribonucleosides upon Irraditaion of 1'-H [a].

Compd	H-2 (H-4)[c]	H_a-2'	H-4'	Compd	H-2	H_a-2'	H-4'
1[b]	9.8	5.0	2.4	3a	3.0	6.3	2.4
2b [20]	2.5	5.6	2.0	3b	2.5	6.7	2.1

[a] DMSO-d_6; 23°C; [b] 63°C; simultaneous saturation of H-1' and H-3; [c] pyrrolo[2,3-d]pyrimidine numbering in parenthesis.

Thus the glycosylation product of 5b was 7b which yielded 3b upon deprotection. Next, 3b was subjected to catalytic hydrogenation. Chromatographic purification yielded crystalline 1. Compound 1 migrates faster on tlc (CH_2Cl_2-MeOH, 9:1) than the parent 2a, which was expected from its more lipophilic character.

Table 2. ^{13}C Nmr Chemical Shifts of Pyrrolo[2,3-b]pyridines and Related Nucleosides in DMSO-d_6.

Compd	C-2(C-6)[b]	C-3(C-5)	C-3a(C-4a)	C-4	C-5	C-6(C-2)	C-7a
1	122.0	98.6	108.4	148.6	100.2	143.4	148.1
2b [21]	121.4	99.4	102.8	157.3	-	151.3	149.5
3a	126.4	100.8	120.8	128.9	116.4	142.4	147.2
3b	132.0	100.4	113.0	145.0	110.4	142.9	150.5
4a	126.7	102.4	124.2	120.1	116.3	131.3	138.5
4b	131.5	102.5	116.8	135.7	113.6	131.3	140.7
4c[c]	120.3	117.4	128.4	118.7	131.6	133.4	138.3
5a	126.1	99.7	119.7	128.1	115.5	142.5	148.5
5b	132.5	99.7	112.0	144.8	109.5	142.7	152.2
5c [16]	121.1	98.3	107.6	148.7	99.5	142.9	148.6
7a	126.1	101.5	120.9	129.0	116.8	142.7	147.5
7b	132.0	100.9	113.3	145.2	110.8	143.3	150.6

	C-1'	C-2'	C-3'	C-4'	C-5'	C=O	CH_3
1	84.4	a	71.5	87.4	62.5		
2b	83.2	39.6	70.9	81.7	62.0		
3a	83.0	a	71.2	87.2	62.2		
3b	83.3	a	71.0	87.6	61.7		
7a	81.0	36.0	75.3	83.2	64.4	21.2/3	165.4/6
7b	81.4	36.2	75.1	83.7	64.2	21.2/3	165.4/6

a) Superimposed by DMSO; b) () pyrrolo[2,3-d]pyrimidine numbering; c) tentative.

As no unequivocal proof of ^{13}C nmr chemical shifts of the pyrrolo[2,3-b]pyridines 4a-c and 5a-c was available and data of corresponding nucleosides were unknown we have assigned those spectra (Table 2) by the [^{1}H, ^{13}C] nmr correlation spectroscopy in combination with the COLOC-spectra. Cross-peak correlation of the spectra of compounds 1, 3b, and 4a allowed the assignment of carbons 2, 3, 4, 5 and 6. As the signal of carbon-4 of compound 1 was more intensive than those of the bridge-head carbons it was assigned on that basis. The bridge-head carbons of compound 1 showed almost the same chemical shifts as those of 2'-deoxytubercidin (2b). Therefore, C-3a and C-7a assignment followed that of 2b. The same method was employed in case of the bridge-head carbons of compound 3b. For the assignment of carbon-4 the COLOC-spectrum was measured, which showed long-range couplings of C-4 with H-5 and H-6. As the chemical shifts of the aglycons were similar to those of base moieties of the nucleosides aglycon-assignment was deduced from the glycosylation products.

Apart from the nucleosides 1 and 3b the nebularine derivative 3a has been prepared under the same conditions as desribed for 3b. The glycosylation yield of 7a was somewhat lower than in case of 7b but nevertheless the reaction proceeded without α-nucleoside formation. The glycosylation position as well as the anomeric configuration were assigned by NOE difference spectroscopy (Table 1). ^{13}C Nmr signal assignment of 5a was possible using the coupling pattern of table 3.

Table 3. $J_{C,H}$ Values [Hz][a] of Compounds 1 and 5a.

$J_{C,H}$	1	5a	$J_{C,H}$	1	5a
C(2), H-C(2)	186.1	184.2	C(4), H-C(4)	-	161.5
H-C(3)	8.0	7.6	H-C(5)	8.1	6.8
H-C(1)	-	3.5	C(5), H-C(5)	158.9	161.6
H-C(1')	4.3	-	H-C(4/6)	8.5	8.9
C(3), H-C(3)	174.6	173.7	C(6), H-C(6)	173.3	176.7
H-C(2)	6.9	9.9	H-C(5)	3.1	7.0
H-C(4)	-	3.0	H-C(4)	-	4.2

a) Data taken from ^{13}C nmr spectra measured in DMSO-d_6.

Zemplen-deprotection of 7a yielded 3a, which was obtained crystalline after chromatographic purification. Compound 3a as 2'-deoxynebularine itself shows strong fluorescence (MeOH) at 376 nm if exitated at 317 nm.

2'-Deoxyadenosine (2a) exhibits a pK_a value of 3.8 and is protonated at N-1 [22] (for this chapter purine numbering is used). We have determined the pK_a value of 1 in Teorell-Stenhagen buffer and have found a pK_a of 3.6 (Table 4). As compound 1 lacks two nitrogens compared to dA and increasing pK_a values were found from dA over c^7A_d (2b) to $c^3c^7A_d$ (Table 4) one would expect a higher pK_a value. In order to show that N-3 and not N-9 is the first protonation site of pyrrolo[2,3-b]pyridines we have measured the ^{15}N nmr INEPT spectra of the neutral and protonated species of 5a in DMSO-d_6. The pyrrole nitrogen of the neutral form of 5a is located at -241.9 ppm exhibiting two coupling constants: $^1J(N(9), H\text{-}N(9))$ = 105.2 Hz and $^2J(N(9), H\text{-}C(8))$ = 8.7 Hz. The pyridine nitrogen-3 showed a $^2J(N(3), H\text{-}C(2))$ = 11.8 and was located at -110.73 ppm. By addition of an equivalent of CF_3COOH N-3 showed an upfield shift of 61.3 ppm, now located at -172.05 ppm whereas the pyrrole nitrogen was almost unaffected (0.5 ppm upfield shift; located at -241.9 ppm). This demonstrates that in case of 5a N-3 is the first protonation site, a result which is expected to be the same in case of compounds 1 and 3a.

Table 4. pK_a-Values of Base-Modified 2'-Deoxyribofuranosides [a].

Compd	pK_a	Compd	pK_a
2-Deoxyadenosine (2a) [23]	3.8	2'-Deoxynebularine	2.1
7-Deaza-2'-deoxyadenosine (2b)	5.3	7-Deaza-2'-deoxynebularine	4.3
3,7-Dideaza-2'-deoxyadenosine [6]	8.6	3,7-Dideaza-2'-deoxynebularine [6]	8.1
1,7-Dideaza-2'-deoxyadenosine (1)	3.6	1,7-Dideaza-2'-deoxynebularine	3.6
		1H-Pyrrolo[2,3-b]pyridine (5a)	4.1

[a] Measured in Teorell-Stenhagen buffer [24].

Compound 1 is extremely stable against acid or base. This is shown by an experiment in which 1 is treated with 1 N HCl for 1 h not leading to N-glycosylic bond hydrolysis a process which rapidly occurs on 2'-deoxyadenosine [24]. Moreover,

compound 1 is stable during heating in 1 N NaOH a process which would lead to imidazole ring opening of 2.

Apart from the hydrolytic stability compound 1 as its ribonucleoside [25] is resistant against adenosine deaminase which rapidly deaminates 2. Further work which investigates the synthetic and biosynthetic incorporation of 1 into DNA-fragments is in progress.

EXPERIMENTAL

Melting points were determined on a Linström apparatus (Wagner & Munz, W. Germany) and are not corrected. Elemental analysis were performed by Mikroanalytisches Laboratorium Beller, Göttingen, West Germany). ^{1}H Nmr and ^{13}C nmr spectra were recorded on a Bruker AC-250 spectrometer; δ values are in ppm relative to Me_4Si or HNO_3 as the internal standard. Uv spectra were measured on a 150-20-spectrophotometer (Hitachi, Japan); Thin-layer chromatography (tlc) was carried out on silica gel plates Sil G-25 UV_{254} (Macherey-Nagel & Co, West Germany); visualization was made by 254 nm-irradiation. Solvent systems : (A), CH_2Cl_2; (B), CH_2Cl_2-MeOH 9:1; (C) CH_2Cl_2-EtOAc 95:5; (D) CH_2Cl_2-EtOAc 3:2. Powdered KOH was bought from Fluka (Buchs, Switzerland) and TDA-1 from Aldrich (Steinheim, West Germany). Column chromatography was performed on silica gel 60 H (Merck, Darmstadt, West Germany). The columns were connected with a Uvicord S detector and an UltroRac II fraction collector (LKB Instruments, Sweden).

1-(2-Deoxy-3,5-di-O-(p-toluoyl)-β-D-erythro-pentofuranosyl)-4-nitro-1H-pyrrolo[2,3-b]pyridine (7b).

A solution of compound 5b (400 mg, 2.5 mmol) [11] in anhydrous MeCN (50 ml) containing KOH (0.67 g, 12 mmol) and TDA-1 (0.04 ml, 0.1 mmol) was stirred for 1h at room temperature under argon atmosphere. 2-Deoxy-3,5-di-O-(p-toluoyl)-α-D-erythro-pentofuranosyl chloride (6) (1.16 g, 3.0 mmol) [26] was added while stirring was continued for another 20 min. Insoluble material was removed by filtration and the filtrate was evaporated under reduced pressure to give a dark oil. This was chromatographed on silica gel (column: 20 x 4 cm, A). The content of the main zone was isolated and crystallized from i-PrOH yielding yellow needles (990 mg, 78%), mp 120°C; tlc (A) R_f 0.5. Uv λ_{max} (MeOH) 355, 338, 239 nm (ε = 3400, 3200, 4500). Anal. calcd for $C_{28}H_{25}N_3O_7$: C, 65.24; H, 4.89; N, 8.15. Found C, 65.39; H, 4.95; N, 8.01.

^{1}H Nmr (DMSO-d_6): δ = 2.37 and 2.40 (2s, 6H, 2 CH_3), 2.78 (m, 1H, H-2'$_b$), 3.19 (m, 1H, H-2'$_a$), 4.59 (m, 3H, H-4' and H-5'), 5.77 (m, 1H, H-3'), 6.92 (pt, 1H, J = 6.5 Hz, H-3'), 7.09 (d, 1H, J = 3.5 Hz, H-3), 7.97 (d, 1H, J = 5.4 Hz, H-5), 8.21 (d, 2H, J = 3.5 Hz, H-2), 8.55 (d, 1H, J = 5.4 Hz, H-6) and other aromatic protons.

1-(2-Deoxy-β-D-erythro-pentofuranosyl)-4-nitro-1H-pyrrolo[2,3-b]pyridine (3b).

Compound 7b (400 mg, 0.85 mmol) was dissolved in MeOH saturated with ammonia (100 ml) and stirred at 50°C for 24 h. The solution was evaporated to dryness, the residue adsorbed on silica gel 60 (3 g) and applied to the top of a silica gel column (12 x 4 cm). Eluation with solvent (D) gave a main zone from which compound 3b was isolated and crystallized (i-PrOH) yielding yellow crystals (160 mg, 67.4%); mp 155°C; tlc (D) R_f 0.1. Uv λ_{max} (MeOH) 357, 339, 283 nm (ε = 4600, 4200, 1300). Anal. calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.65; H, 4.85; N, 14.99.

^{1}H Nmr (DMSO-d_6): δ = 2.30 (m, 1H, H_b-2'), 2.57 (m, 1H, H_a-2'), 3.57 (m, 2H, H-5'), 3.87 (m, 1H, H-4'), 4.41 (m, 1H, H-3'), 4.98 (t, 1H, J = 5.4 Hz, OH-5'), 5.34 (d, 1H, J = 4.1 Hz, OH-3'), 6.79 (pt, 1H, J = 6.7 Hz, H-1'), 7.07 (d, 1H, J = 3.6 Hz, H-3), 7.96 (d, 1H, J = 5.3 Hz, H-5), 8.22 (d, 2H, J = 3.6 Hz, H-2), 8.54 (d, 1H, J = 5.3 Hz, H-6).

4-Amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1H-pyrrolo[2,3-b]pyridine (1).

A solution of compound 3b (200 mg, 0.72 mmol) in MeOH (200 ml) containing MeOH/NH_3 (saturated at 0°C, 1 ml) was hydrogenated in the presence of Pd-charcoal (55 mg, 10% Pd) at room temperature for 3h. The reaction mixture was warmed up and filtered. The filter residue was washed twice with hot MeOH (200 ml) and the filtrate was evaporated to dryness. The colorless residue crystallized from water yielding colorless needles (140 mg, 78%); mp > 265°C; tlc (B) R_f 0.6. Uv λ_{max} (MeOH) 298, 292, 271 nm (ε = 9800, 11000, 9100). Anal. calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.99; H, 6.18; N, 16.68.

^{1}H Nmr (DMSO-d_6): δ = 2.01 (m, 1H, H_b-2'), 2.60 (m, 1H, H_a-2'), 3.55 (m, 2H, H-5'), 3.83 (m, 1H, H-4') 4.34 (m, 1H, H-3'), 5.21 (m, 1H, OH-5'), 5.62 (m, 1H, OH-3'), 6.19 (d, 1H, J = 5.4 Hz, H-5), 6.27 (s, 2H, NH_2), 6.49 (dd, 1H, J = 5.9 Hz and 8.5Hz, H-1'), 6.55 (d, 1H, J = 3.5 Hz, H-3), 7.29 (d, 1H, J = 3.5 Hz, H-2), 7.70 (d, 1H, J = 5.4 Hz, H-6).

1-(2-Deoxy-3,5-di-O-(p-toluoyl)-β-D-erythro-pentofuranosyl)-1H-pyrrolo-[2,3-b]pyridine (7a).

To a stirred suspension of powdered KOH (0.7 g, 13 mmol) in dry MeCN (100 ml) and TDA-1 (30 mg, 0.1 mmol) compound 5a (500 mg, 4.2 mmol) was added under stirring. After 30 min the halogenose 6 (1.7 g, 4.4 mmol) was added and stirring was continued for another 20 min. Insoluble material was removed by filtration and washed with MeCN. The filtrate was evaporated to dryness yielding an oil which was chromatographed on silica gel (column: 10 x 4 cm). Eluation with solvent (C) gave a colorless foam (1.1 g, 55%); tlc (C) R_f 0.6. Uv λ_{max} (MeOH) 222, 240, 282 nm (ε = 36300, 36300, 9100). Anal. calcd for $C_{28}H_{26}N_2O_5$: C, 71.48; H, 5.57; N, 5.95. Found: C, 71.62; H, 5.60; N, 5.95.

^{1}H Nmr (DMSO-d_6): δ = 2.37 and 2.40, (2s, 6H, 2 CH_3), 2.67 (m, 1H, H_b-2'), 3.15 (m, 1H, H_a-2'), 4.58 (m, 3H, H-4' and H-5'), 5.75 (m, 1H, H-3'), 6.57 (d, 1H, J = 3.7 Hz, H-3), 6.88 (m, 1H, H-1'), 7.15 (m, 1H, H-5), 7.73 (d, 1H, J = 3.7 Hz, H-2), 8.01 (d, 1H, J=1.4 Hz, H4), 8.27 (m, 1H, H-6), and other aromatic protons.

1-(2-Deoxy-β-D-erythro-pentofuranosyl)-1H-pyrrolo[2,3-b]pyridine (3a).

A solution of 7a (1.0 g, 2.1 mmol) in MeOH (saturated with NH_3 at 0°C) was stirred at room temperature for 24 h. The solution was evaporated to dryness, the solid adsorbed on silica gel 60 (4 g), and applied to the top of a silica gel column (15 x 4 cm; B). From the main zone compound 3a was isolated as a colorless solid, which crystallized from i-PrOH in colorless needles. Yield: 340 mg, (68%); mp 203-205°C; tlc (B) R_f 0.3. Uv λ_{max} (MeOH) 287 nm (ε = 8700). Anal. calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.65; H, 6.18; N, 11.80.

^{1}H Nmr (DMSO-d_6): δ = 2.20 (m, 1H, H_b-2'), 2.58 (m, 1H, H_a-2'), 3.55 (m, 2H, H-5'), 3.85 (m, 1H, H-4'), 4.37 (m, 1H, H-3'), 5.07 (t, 1H, J = 5.6 Hz, OH-5'), 5.28 (d, 1H, J = 4.1 Hz, OH-3'), 6.54 (d, 1H, J = 3.6 Hz, H-3), 6.71 (dd, 1H, J = 5.9 Hz and 8.5 Hz, H-1') 7.12 (dd, 1H, J = 7.8 Hz and 4.7 Hz, H-5), 7.75 (d, 1H, J = 3.6 Hz H-2), 7.97 (dd, 1H, J = 7.8 Hz, J = 1.5 Hz, H-4), 8.24 (dd, 1H, J = 4.7 Hz, J = 1.5 Hz, H-6).

ACKNOWLEDGEMENTS

We thank Dr. H. Rosemeyer for valuable discussion of the NMR spectra. Financial support by the Deutsche Forschungsgemeinschaft and the Bundesministerium für Forschung und Technologie is gratefully acknowledged.

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Received, 26th December, 1988