Synthesis and Biological Evaluation of 4-Quinolone Ribosides

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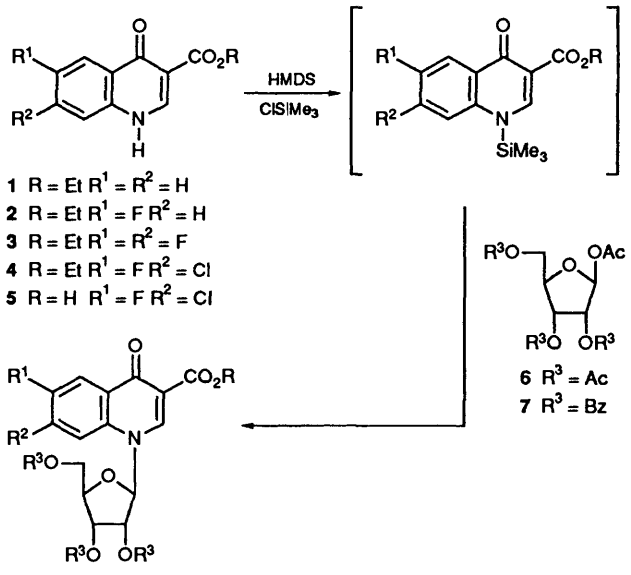
The preparation of ribosides of 4-oxoquinoline-3-carboxylic acid derivatives is described. All the reported compounds were evaluated for antiviral and antibacterial activity.

Nucleoside analogues in which the heterocycle and/or the sugar moiety have been modified are important targets when seeking compounds with biological activity.[1] In this context, and continuing with our studies on the 4-quinolone system[2] we now wish to report the synthesis and biological screening of ribosides of 4-oxoquinoline-3-carboxylic acid derivatives.[3] These compounds were selected because the heterocycle itself has interesting biological properties as either a dehydrogenase inhibitor,[4] or antiviral[5] or, especially, antibacterial agent,[6] and also because its glycosylation had not been previously studied (only few references on 4-quinoline nucleosides have appeared in the literature).[7]

The synthesis of these nucleosides (Scheme 1) was achieved

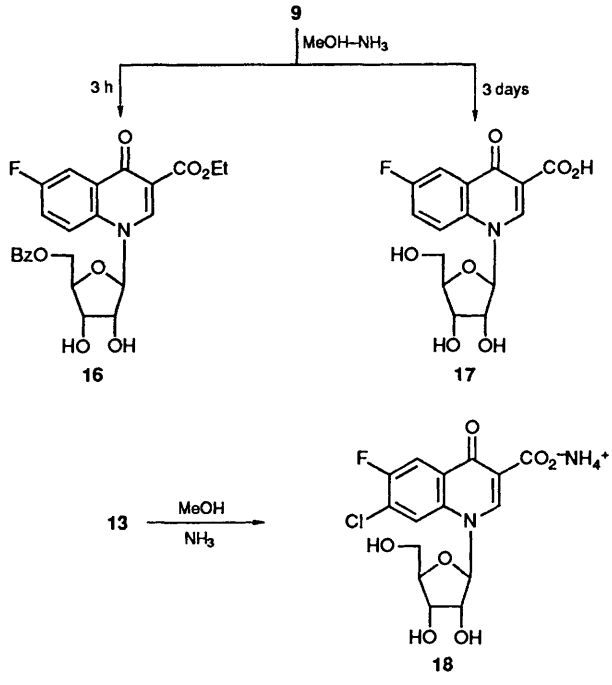


1 R = Et $R^1 = R^2 = H$
2 R = Et $R^1 = F$ $R^2 = H$
3 R = Et $R^1 = R^2 = F$
4 R = Et $R^1 = F$ $R^2 = Cl$
5 R = H $R^1 = F$ $R^2 = Cl$

8 R = Et $R^1 = R^2 = H$ $R^3 = Bz$
9 R = Et $R^1 = F$ $R^2 = H$ $R^3 = Bz$
10 R = Et $R^1 = F$ $R^2 = H$ $R^3 = Ac$
11 R = Et $R^1 = R^2 = F$ $R^3 = Bz$
12 R = Et $R^1 = R^2 = F$ $R^3 = Ac$
13 R = Et $R^1 = F$ $R^2 = Cl$ $R^3 = Bz$
14 R = Et $R^1 = F$ $R^2 = Cl$ $R^3 = Ac$
15 R = H $R^1 = F$ $R^2 = Cl$ $R^3 = Bz$

Scheme 1

using the silylation procedure.[8] With this aim, quinolones **1**–**5** were first refluxed in hexamethyldisilazane and trimethylchlorosilane and then treated with 1,2,3,5-tetra-*O*-acetyl-or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoses **6** and **7**, respectively. From the different reaction conditions used the best involved 1,2-dichloroethane as solvent and $SnCl_4$ as catalyst. The crude reaction products were carefully purified by column chromatography affording ribosides **8**–**15** in acceptable yields.



Scheme 2

Deprotection of some of these ribosides was carried out by standard procedures (Scheme 2). Benzoyl derivatives **9** and **13** were treated with methanol–ammonia at room temperature to give partially or fully deblocked nucleosides depending on the reaction conditions used. Thus, compound **9** afforded the 5'-benzoyl compound **16** after 3 h, whilst after 3 days complete debenzoylation and hydrolysis of the ester occurred to give the 3-carboxy derivative **17**. In the case of **13**, the ammonium salt **18** and not the free carboxylic acid was obtained after 5 days. This can be explained by taking into account the fact that the acidity of the 4-quinolone system increases when successive halogen atoms are introduced in positions 6,7 and 8 of the quinolone nucleus as has been recently described for the ethoxycarbonyl derivatives.[9]

The structures of the newly synthesized compounds have been established according to their UV and NMR spectroscopic data, presented in Tables 1, 2 and 3. The site of glycosylation was assigned to N-1 on the basis of UV data by comparison with suitable alkyl models previously reported[10] (Table 1) and was confirmed by NOE experiments.

In all the NMR spectra, the singlet appearing at lowest field was attributed to the 2-H of the heterocyclic system. The anomeric protons appear as doublets around 6.5 ppm when the ribose is benzoylated, and somewhat more shielded (6.0–6.2 ppm) for the acetyl derivatives (Table 2). In all cases, only one anomer was detected but with the value of the coupling

Table 1 UV Spectroscopic data (MeOH) for ribosides **8**–**18**

Compound	λ_{max}/nm (log ε)									
8		321	309	[298]	[280]		[251]		224	[212]
		(4.04)	(4.10)	(4.01)	(3.87)		(4.12)		(4.68)	(4.60)
9	330	317		[295]	[280]		[254]		228	[212]
	(3.98)	(4.04)		(3.95)	(3.83)		(4.11)		(4.68)	(4.54)
10		323	312	[293]			251	243	[235]	212
		(3.79)	(3.80)	(3.66)			(3.94)	(3.96)	(3.92)	(4.09)
11		323	311		[281]		252		227	[212]
		(4.02)	(4.02)		(3.84)		(4.20)		(4.72)	(4.53)
12	327		315	290			251	424	[233]	210
	(3.73)		(3.77)	(3.73)			(3.84)	(3.92)	(3.87)	(4.15)
13	333	320		[297]	[281]	259	[250]		227	
	(4.08)	(4.11)		(4.00)	(3.93)	(4.42)	(4.43)		(4.80)	
14	331	319		[296]		259	250	[242]	[222]	213
	(3.98)	(4.00)		(3.91)		(4.29)	(4.30)	(4.24)	(4.29)	(4.31)
15	332	320			[282]	257	250		226	
	(4.04)	(4.01)			(3.84)	(4.42)	(4.42)		(4.70)	
16	331	318		295		[254]		[245]		212
	(4.02)	(4.09)		(4.03)		(4.15)		(4.25)		(4.45)
17	333	320		297		[254]		246	[237]	212
	(3.97)	(4.03)		(3.95)		(4.17)		(4.24)	(4.20)	(4.48)
18		322	[308]	[299]		260	252			213
		(3.67)	(3.61)	(3.59)		(4.02)	(4.02)			(4.06)
A[a]	328		315				256	249	226	
	(4.02)		(4.12)				(4.26)	(4.28)	(4.36)	
B[b]				286					236	
				(3.78)					(4.68)	

[a] **A** = 1-Ethyl-3-ethoxycarbonyl-4-quinolone (ref. 10). [b] **B** = 3-Ethoxycarbonyl-4-ethoxyqinoline (ref. 10).

Table 2 300 MHz NMR spectroscopic data (δ_H) for ribosides **8**–**18**

	δ_H												
Compound	1'-H	2'-H	3'-H	4'-H	5'a-H	5'b-H	CH_2		CH_3	2-H	5-H	6-H	7-H	8-H
8	6.54	5.99	5.90	4.93	4.86	4.83	4.19	4.07	1.24	9.00	8.52	7.89–7.95		8.08
	(d)	(t)	(t)	(m)	(dd)	(dd)	(dc)	(dc)	(t)	(s)	(dd)	(m)		(dd)
9	6.45	6.00	5.89	4.92	4.86	4.81	4.20	4.09	1.24	8.96	8.16	—	—	7.67
	(d)	(t)	(t)	(m)	(dd)	(dd)	(dc)	(dc)	(t)	(s)	(dd)			(dd)
10	6.24	5.51	5.41			4.33–4.55			1.39	8.90	8.15	—	7.42	7.53
	(d)	(t)	(dd)			(m)			(t)	(s)	(dd)		(m)	(dd)
11	6.49	5.96	5.91	4.98	4.85		4.11	3.99	1.17	8.93	8.17	—	—	7.64
	(d)	(t)	(dd)	(m)	(m)		(dc)	(dc)	(t)	(s)	(dd)			(dd)
12	6.07	5.48	5.41			4.31–4.54			1.37	8.84	8.27	—	—	7.44
	(d)	(t)	(dd)			(m)			(t)	(s)	(dd)			(dd)
13	6.47[a]	5.91[a]	5.90[a]	4.94[a]	4.87[a]	4.84[a]	4.19	4.09	1.23	8.97	8.20	—	—	7.84
	(m)	(m)	(m)	(m)	(m)	(m)	(dc)	(dc)	(t)	(s)	(t)			(d)
14	6.15	5.47	5.40	4.54	4.44		4.33–4.40		1.37	8.86	8.23	—	—	7.67
	(d)	(t)	(dd)	(m)	(m)		(m)		(t)	(s)	(d)			(d)
15	6.45	5.80–5.88		4.92	4.83		—	—	—	9.17	8.17	—	—	7.95
	(d)	(m)		(m)	(m)					(s)	(d)			(d)
16	6.15	4.28	4.20	4.48	4.69	4.55	3.91	3.70	1.06	8.87		7.45–7.96		
	(d)	(dd)	(t)	(m)	(dd)	(dd)	(dq)	(dq)	(t)	(s)		(m)		
17	6.13	4.21	3.98	4.11	3.76	3.67	—	—	—	9.21	8.00	—	7.78	8.05
	(d)	(t)	(t)	(m)	(dd)	(dd)				(s)	(dd)		(m)	(dd)
18	6.00				4.21–3.62		—	—	—	9.07	7.95	—	—	8.08
	(d)				(m)					(s)	(d)			(d)

[a] Calculated parameters.

constant $J_{1',2'}$ in the range 4.5–5.9 Hz it was not possible to determine the anomeric configuration. However, the β-anomer was tentatively assigned on the basis of mechanistic criteria.[11]

The remainder of the glycosidic protons were attributed by means of double resonance experiments. In the case of nucleoside **13** a strong second order effect appeared, and thus COSY and NOE experiments and a spin system simulation with the PANIC program, were necessary to assign all the chemical shifts and coupling constants. Irradiation on the anomeric proton (δ 6.47) produced an 18% NOE effect on the signal at δ 7.84 corresponding to the 8-H of the heterocycle. This means that the sugar moiety is at the N-1 position and that the nucleoside lies probably in the *syn* conformation.

It is worth mentioning that the methylene protons of the 3-ethoxycarbonyl residue of all the prepared ribosides are anisochronous and appear as multiplets (16 signals). This might be explained assuming the *syn* conformation for the ribosides, as can be experimentally observed for compound **16**. In this case intramolecular interactions might occur between the methylene protons and the carbonyl oxygen of the 5'-acyl remainder of the sugar moiety. As is well known, the more frequent conformation found in natural nucleosides is the

Table 3 Coupling constants (Hz) for ribosides **8–18**

Compound	J^a/Hz															
	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$	$J_{5,7}$	$J_{5,F6}$	$J_{5,F7}$	$J_{6,8}$	$J_{7,8}$	$J_{8,F6}$	$J_{8,F7}$	J_{CH2gem}	J_{CH2CH3}
8	5.1	5.1	5.1	2.7	3.7	−13.0	8.0	1.4	—	—	1.4	8.5	—	—	−10.8	7.1
9	5.2	5.2	5.2	2.6	3.7	−12.5	—	3.0	8.8	—	—	9.4	4.1	—	−10.8	7.1
10	5.3	5.3	4.4	—	—	—	—	3.1	8.7	—	—	9.5	4.2	—	—	7.1
11	5.4	5.4	4.1	—	—	—	—	—	10.3	8.9	—	—	6.2	11.7	−10.8	7.1
12	5.9	5.9	3.8	—	—	—	—	—	10.4	8.9	—	—	6.1	11.7	—	7.1
13	4.5[b]	3.8[b]	3.1[b]	2.9[b]	2.7[b]	−11.8[b]	—	—	8.9	—	—	—	5.6	—	−10.7	7.1
14	5.8	5.8	3.7	—	—	—	—	—	9.0	—	—	—	5.6	—	—	7.1
15	4.9	—	—	—	—	—	—	—	8.3	—	—	—	5.6	—	—	—
16	3.0	5.1	5.1	2.4	4.4	−12.7	—	—	—	—	—	—	—	—	−10.8	7.1
17	4.0	4.0	4.0	3.1	4.1	−12.1	—	3.1	9.0	—	—	9.5	4.4	—	—	—
18	4.3	—	—	—	—	—	—	—	9.3	—	—	—	6.0	—	—	—

[a] 300 MHz. [b] Calculated parameters.

anti one[12] unless the pyrimidine or purine ring have been substituted at the 6- or 8-position, respectively.

Biological Activity.—The new 4-quinolone ribosides synthesized **8–18** were evaluated for their antibacterial and antiviral activity in a wide variety of assay systems. None of them showed antibacterial activity at concentrations < 32 μg cm^{-3}. The antiviral assays were carried out in E_6SM, Vero and HeLa cell cultures. No marked antiviral activity was observed with any of the compounds. Nucleosides **16** and **17** inhibited some viruses [vaccinia virus and reovirus (compound **16**) and herpes simplex-2 and reovirus (compound **17**), respectively] at a concentration of 70 μg cm^{-3}, which was 3- to 6-fold below their cytotoxicity threshold. This cytotoxicity:activity ratio is not sufficient to consider **16** and **17** specific antiviral agents.

Experimental

M.p.s were determined with a Reichert-Jung Thermovar and are uncorrected. ^{1}H NMR spectra were recorded with a Varian XL-300 (300 MHz), using $(CH_3)_4Si$ as internal standard. *J*-Values are given in Hz. Typical spectral parameters were: spectral width 10 ppm, pulse width 9 ms (57°), data size 32 K. NOE difference spectra were measured under the same conditions, using a presaturation time of 3 s.

7-Chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid **5**.—A suspension of quinolone **4**[13] (3.0 g, 0.01 mol) in 2 mol dm^{-3} sodium hydroxide (50 cm^3) and methanol (20 cm^3) was refluxed for 3 h. The methanol was eliminated under reduced pressure and the aqueous solution was neutralized with hydrochloric acid. The solid was filtered off and recrystallized from *N,N*-dimethylformamide (DMF) to yield the *carboxylic acid* **5** (2.2 g, 82%) as a white solid which sublimes over 260 °C (Found: C, 49.4; H, 2.3; N, 6.1. $C_{10}H_5ClFNO_3$ requires C, 49.7; H, 2.1; N, 5.8%); λ_{max}(MeOH)/nm 237, 250, 258, 288sh, 302, 314 and 328 (log ε 4.38, 4.53, 4.54, 3.78, 3.94 and 3.81); δ_H(90 MHz; CF_3CO_2H) 8.40 (1 H, dd, $J_{H8,F}$ 3, 8-H), 8.43 (1 H, dd, $J_{H5,F}$ 6, 5-H) and 9.43 (1 H, s, 2-H)

General Procedure for Glycosylation.—To a solution in 1,2-dichloroethane (30 cm^3) of the silyl derivative of the 4-quinolones **1–5**, prepared by refluxing the base in hexamethyldisilizane (40 cm^3) and trimethylchlorosilane (catalytic amounts) under nitrogen, the corresponding 1-*O*-acetyl ribose derivative dissolved in 1,2-dichloroethane (20 cm^3) and $SnCl_4$ (3 cm^3) was added with vigorous stirring and exclusion of moisture. The resulting mixture was stirred at room temperature for 3 h and was then shaken with saturated hydrogen carbonate solution (50 cm^3). The organic phase was separated, dried over sodium sulfate and evaporated under reduced pressure and purified as indicated for each particular case.

Ethyl 1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylate **8**. According to the general method, quinolone **1**[14] (1.0 g, 4.6 mmol) was allowed to react with the ribose derivative **7** (2.6 g, 5.1 mmol). The residue was purified by silica gel column chromatography using chloroform–methanol (25:1) as eluent to give the *title compound* **8** (2.5 g, 82%) (Found: C, 68.8; H, 4.6; N, 2.0. $C_{38}H_{31}NO_{10}$ requires C, 69.0; H, 4.7; N, 2.1%).

Ethyl 6-fluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylate **9**. Following the general procedure, quinolone **2**[15] (1.0 g, 4.2 mmol) was treated with the ribose derivative **7** (2.4 g, 4.7 mmol). After work-up, the residue was chromatographed on a silica gel column chromatography using chloroform–methanol (25:1) as eluent to give the *title compound* **9** (2.4 g, 83%) (Found: C, 66.8; H, 4.7; N, 2.4. $C_{38}H_{30}FNO_{10}$ requires C, 67.15; H, 4.45; N, 2.1%).

Ethyl 6-fluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)quinoline-3-carboxylate **10**. According to the general procedure, quinolone **2**[15] (1.0 g, 4.2 mmol) was allowed to react with the ribose derivative **6** (1.5 g, 4.7 mmol). After work-up, the residue was chromatographed on a silica gel column using chloroform–methanol (20:1) as eluent to give the *title compound* **10** (0.4 g, 19%) (Found: C, 55.5; H, 5.2; N, 2.5. $C_{23}H_{24}FNO_{10}$ requires C, 56.0; H, 4.9; N, 2.8%).

Ethyl 6,7-difluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylate **11**. Following the general procedure, quinolone **3**[16] (1.0 g, 3.9 mmol) was treated with the ribose derivative **7** (2.2 g 4.3 mmol). After work-up, the residue was chromatographed on a silica gel column using chloroform–methanol (25:1) as eluent to give the *title compound* **11** (2.6 g, 94%) (Found: C, 65.7; H, 4.0; N, 2.0. $C_{38}H_{29}F_2NO_{10}$ requires C, 65.4; H, 4.2; N, 2.2%).

Ethyl 6,7-difluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)quinoline-3-carboxylate **12**. According to the general procedure, quinolone **3**[16] (1.0 g, 3.9 mmol) was allowed to react with the ribose derivative **6** (1.4 g, 4.4 mmol). After work-up, the residue was chromatographed on a silica gel column using chloroform–methanol (25:1) as eluent to give the title compound **12** (0.5 g, 25%) (Found: C, 53.9; H, 4.5; N, 2.4. $C_{23}H_{23}F_2NO_{10}$ requires C, 54.0; H, 4.5; N, 2.7%).

Ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylate **13**. According to the general method, quinolone **4**[13] (1.0 g, 3.7 mmol) was allowed to react with the ribose derivative **7** (2.1 g, 4.1 mmol). The residue was purified by silica gel column chromatography using chloroform–methanol (25:1) as eluent to give the title compound **13** (1.6 g, 60%) (Found: C, 63.7; H, 4.1; N, 1.8. $C_{38}H_{29}ClFNO_{10}$ requires C, 63.9; H, 4.1; N, 2.0%).

Ethyl 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)quinoline-3-carboxylate **14**. Following the general procedure, quinolone **4**[13] (1.0 g, 3.7 mmol) was treated with the ribose derivative **6** (1.3 g, 4.1 mmol). After work-up, the residue was chromatographed on a silica gel column using chloroform–methanol (20:1) as eluent to give the *title compound* **14** (0.3 g, 15%) (Found: C, 52.2; H, 4.7; N, 3.0. $C_{23}H_{23}ClFNO_{10}$ requires C, 52.3; H, 4.4; N, 2.65%).

7-Chloro-6-fluoro-1,4-dihydro-4-oxo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylic acid **15**. According to the general method, quinolone **5** (0.25 g, 1.03 mmol) was allowed to react with the ribose derivative **7** (0.57 g, 1.13 mmol). The residue was purified by silica gel column chromatography using chloroform–methanol (40:1) as eluent to give the title compound **15** (0.13 g, 18%) (Found: C, 63.4; H, 3.75; N, 2.4. $C_{36}H_{25}ClFNO_{10}$ requires C, 63.0; H, 3.7; N, 2.0%).

Ethyl 6-fluoro-1,4-dihydro-4-oxo-1-(5-O-benzoyl-β-D-ribofuranosyl)quinoline-3-carboxylate **16**. Compound **9** (0.5 g, 7.7 mmol) was suspended in methanol saturated with ammonia (30 cm^3) and stirred at room temperature for 3 h. The precipitate was filtered, yielding the *title compound* **16** (0.2 g, 80%) as a white solid, m.p. 188–190 °C (Found: C, 61.3; H, 4.6; N, 2.8. $C_{24}H_{22}FNO_8$ requires C, 61.1; H, 4.7; N, 3.0%).

6-Fluoro-1,4-dihydro-4-oxo-1-(β-D-ribofuranosyl)quinoline-3-carboxylic Acid **17**.—Compound **9** (0.4 g, 0.58 mmol) was suspended in methanol saturated with ammonia (30 cm^3) and stirred at room temperature for 3 days. After removal of the solvent under reduced pressure, the resulting solid was washed with chloroform to give the *title compound* **17** (0.17 g, 85%) as a white solid, m.p. 247–249 °C (Found: C, 53.0; H, 4.1; N, 4.1. $C_{15}H_{14}FNO_7$ requires C, 53.1; H, 4.2; N, 4.1%).

Ammonium 7-Chloro-6-fluoro-1,4-dihydro-4-oxo-1-(β-D-ribofuranosyl)quinoline-3-carboxylate **18**.—Riboside **13** (0.25 g, 0.3

mmol) was suspended in methanol saturated with ammonia (20 cm^3) and stirred at room temperature for 5 days. The solvent was eliminated under reduced pressure and the resulting solid was washed with chloroform, yielding the *title compound* **18** (0.11 g, 80%) as a yellow solid, m.p. 228–230 °C (Found: C, 46.4; H, 3.75; N, 6.9. $C_{15}H_{16}ClFN_2O_{10}$ requires C, 46.1; H, 4.1; N, 7.2%).

Acknowledgements

Financial support from CICYT (project no. FAR 90-746) is gratefully acknowledged.

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Paper 2/05675E
Received 23*rd October* 1992
Accepted 15*th January* 1993