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SYNTHESIS OF 8-AZAPURINES GLYCOSIDES STARTING FROM 1-AZIDOGLYCOSIDES†

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Abstract—An improved synthesis of 8-aza hypoxanthyl-α- (and -β-) mannopyranosides and -β-ribofuranosides starting from 1-azidoglycosides is reported. In the manno series, the anomeric configuration of the products is controlable and the mechanism of this control is discussed.

The 8-azapurines and their glycosides are interesting cytotoxic[1-8] compounds. The syntheses of the latter are carried out either by fusion reaction between an ose and a modified heterocycle[9-11] or by the construction of the heterocycle, starting from a 1-azidoglycoside.[11]

Since we have devised a good method for obtaining these azido sugars,[12] we wish to demonstrate their usefulness in purine glycoside synthesis. This paper is devoted to the synthesis of 8 - azahypoxantyl - α - (and - β -) manno-pyranosides and -β-ribofuranosides (8-azapurine) using this technique. These syntheses are characterised by yields which are higher than those of previously published procedures and by the fact that we are able to control the α/β stereochemistry of the azidosugar reaction, at least in the manno series.

RESULTS AND DISCUSSION

The access to 1-azidoglycosides lies in the direct conversion of the free anomeric hydroxyl group into the azido one owing to activation in the phosphonium salt, followed by a substitution by the mesityloxy-tris(dimethylamino)-phosphonium azide (scheme 1).

Formation of the vic-triazolo ring

In order to do this, we began by using Tolman's procedure[13] based on the action of powdered potassium hydroxide on a solution of the azido compound and cyanoacetamide in aqueous dimethylformamide at room temperature for 6 hours. With the starting materials **1**, **2** and **3**, which are of 1-2 *cis* configuration, we systematically obtained good yields of the 5 - amino - 4 - carboxamido - vic - triazologlycosides **4**, **5** and **6**, which are of 1-2 *trans* configuration (Table 1).

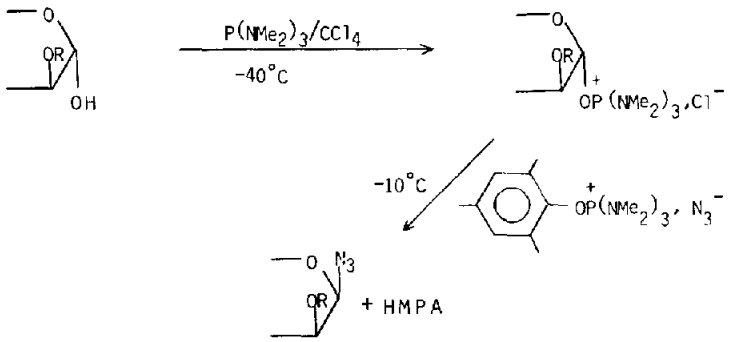
We originally considered decreasing the reaction time by previously preparing the cyanacetamido carbanion, with sodium hydride in anhydrous dimethylformamide, and by allowing it to react, in a second step, still in an anhydrous medium, on the 1-azidoglycoside. While this did not decrease so much the reaction time, we nevertheless observed an interesting fact. With the manno derivative **3**, we obtained **7** as the major product, which is anomeric of **6** and corresponds to a retention of configuration. In order to understand this fact and to be able to prepare the **6** or **7** pure isomers at will (for they are not easily separated), we undertook a short study of the influences of the nature of the solvent and of the base. Our results are summarized in Table 2.

The best conditions for obtaining retention of configuration at the anomeric carbon atom involve sodium hydride in dimethylformamide as a solvent at 0°.

To account for the inversion in the case of the 2,3,5-tribenzylarabinose series, Tolman[13] proposed a two step mechanism, with the opening of the osidic ring. Below, we have adapted this to our case of the 1 - azido - 2,3; 5,6 - di - *O* - isopropylidene β - D-mannopyranoside **3** (scheme 2).

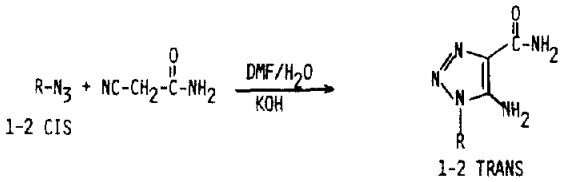
To explain the anomeric inversion, Tolman invoked the opening of the intermediate **A**, arising from the initial attack of the acetamido anion, into the intermediate **B**. This latter undergoes ring closure into **C**, with an opposite anomeric configuration, which leads to **6**.

†This is a part of the "Doctorat d'Etat" of F. Chretien.



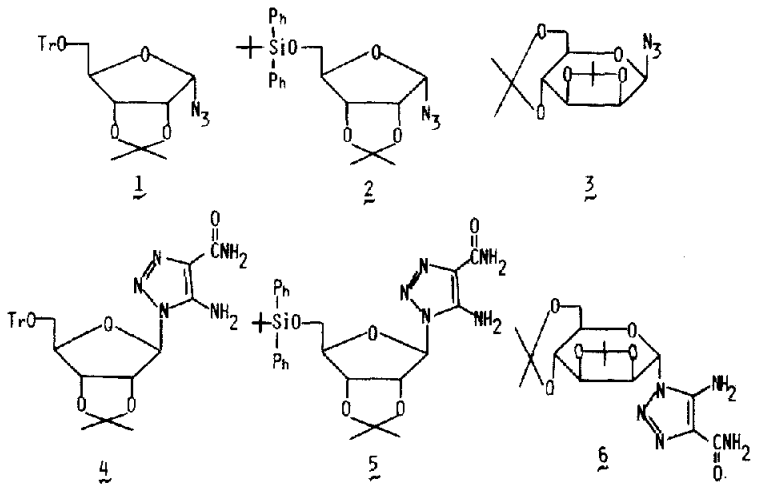
Scheme 1.

Table 1. Synthesis of 5-amino-4-carboxamido vic-triazolo nucleosides



STARTING MATERIAL	PRODUCT	YIELD % (a)
1	4	70
2	5	77
3	6	80

(a) PURE PRODUCT, ISOLATED BY CHROMATOGRAPHY



This mechanism seems fairly suited to explaining our results by making the supplementary assumption that the intermediate **A** can directly close itself into **7** as does **C** into **6**. The intermediate **C** is probably thermodynamically more stable than **A** but depending upon the natures of the solvent and of the cation, **A** and **B** are more or less stabilized relative to each other. Study of Table 2 does not lead to an easy explanation for the nature of the stabilization. The hydrogen bonding between water and the oxygen atom of **B** can be suggested in runs number 1, 2 and 3, but it is then rather difficult to account for run 12 in which the same results are obtained in hexamethylphosphoramide, an aprotic solvent.

Alternatively, it seems attractive to call upon the "hard and soft theory" for the ions involved. On this basis a plausible assumption is the following. In order to avoid the formation of **6**, the equilibrium **A**⇄**B** must be displaced to the left. The **A** form is a harder anion than the **C** one due to the α effect.[14] The harder the cation M^+ the more the **A** form will be stabilized and a soft cation will stabilize rather the **C** form. In run number 3 the ratio **7**/**6** is higher than in run number 2. This result is in agreement with the fact that the cation Na^+ (H_2O) is harder than K^+ (H_2O).

In anhydrous solvents such as dimethylformamide (runs number 12, 13), the ratio **7**/**6** changes as previously, depending upon the nature of the cation.

In run number 15, in which the sodium cation is complexed by a crown ether, and thus softer than the uncomplexed sodium cation, the amount of retention decreases. We do not fully understand the results with the lithium cation (runs number 4, 7, 11) which is known to be highly complexing.

This analysis is all the more difficult as the thermodynamic/kinetic control, we called upon above, plays a role only for the intermediate stages **A**, **B** and **C**. In effect, the paths from **A** to **7** and from **C** to **6**, *via* the hydrolysis of an amidure, must be irreversible; in fact, compound **7** replaced in the reaction medium, overnight and at room temperature, does not lead to **6**.

Finally, it must be pointed out that, under the best conditions, described above, we were not able to secure the products with retention of configuration starting from the ribo derivatives **1** and **2**; this is probably due to the greater strain of the five membered ring which makes opening easier giving the intermediate **B**.

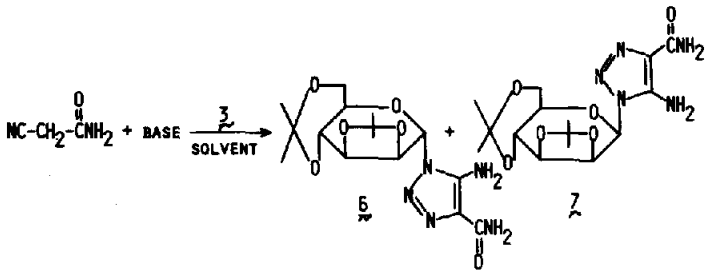
Pyrimidone ring formation

This was performed, using Tolman's method,[13] by the reaction of diethoxymethylacetate followed by treatment with methanolic ammonia. Our results are given in Table 3.

The removal of the protective group

This is performed with aqueous trifluoroacetic acid (50%) at room temperature for the two manno deriva-

Table 2. Cyanoacetamid condensation: Results concerning the influences of the nature of the solvent and of the base



RUN	BASE	SOLVENT	TEMPERATURE	TIME (HOURS)	6 % (a)	7 % (a)	TOTAL YIELD % (b)
1	KOH	DMF/H_2O	R.T.	5	100	-	80
2	"	"	0°	6	100	-	83
3	NaOH	"	0°	2	65-70	30-35	76
4	LiOH	"	0°	1.5	75-70	25-30	70
5	KH	DMF	0°	0.5	40	60	75
6	NaH	"	0°	2	10-15	85-90	92
7	LiH	"	0°	6.5	40	60	75
8	KH	DME	R.T.	6.5	30	70	80
9	NaH	"	0°	20	15-20	85-80	95
10	"	"	R.T.	6.25	20-25	80-75	95
11	LiH	"	"	10	40-45	60-55	70
12	KH	HMPA	0°	0.75	100	-	70
13	NaH	"	0°	0.5	30-35	70-65	80
14	"	DMF+$LiClO_4$	0°	1	10-15	85-80	80
15	"	DMF CROWN ETHER 18-6	0°	0.5	40	60	75

(a) FOUND BY ^1H NMR AT 250 MHZ AFTER ADDITION OF D_2O
(b) AS A MIXTURE OF 6 AND 7 OBTAINED BY CHROMATOGRAPHY

tives **10** and **11** which give rise to **12** and **13**, respectively. In the case of the ribo derivatives, the 8-azainosine **15** is obtained either starting from **8**, by the successive actions of aqueous trifluoro acetic acid (50%) and a Dowex 50 H^+ resin in a tetrahydrofuran/water (1/1, v/v) mixture or starting from **9** by the successive actions of a solution of tetrabutyl-ammonium fluoride in tetrahydrofuran and of a Dowex 50 H^+ resin. In these latter two cases, the 2',3' - di - *O* - isopropylidene - 8 - azainosine **14** is isolated and characterized.

Anomeric structural assignments

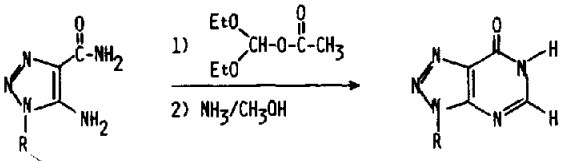
We rely upon optical rotations, ^1H NMR spectra and circular dichroism. For the manno derivatives we have both of the anomers, so that we are able to assign the α/β configuration without ambiguity. On the other hand, in the ribo series, we have only one anomer which is already known.[11] Knowledge of the specific optical rotation and of the $J_{1'-2'}$ coupling constants is not enough to ascertain unequivocally the configurations (Table 4).

Nevertheless, the 8-azainosine exhibits a specific optical rotation of −74.8°, which is little different from that reported by Tolman[11] (−80°). His ^1H NMR spectrum (60 MHz in dimethylsulfoxyde-d_6) includes an anomeric proton signal at $\delta = 6.18$ ppm with a coupling constant $J_{1'-2'} = 4.75$ Hz. These values are identical to those of the work described above. Thus, the compound **15** has the β configuration.

The compounds **4**, **5**, **8**, **9** and **14** are precursors of **15** and the reactions from **4** to **15** do not allow epimerization. So we conclude that **4**, **5**, **8**, **9** and **14** have the β configuration. Moreover, the difference between the two isopropylidene signals (C-2', C-3') is always more than 0.15 ppm; this is characteristic of a β configuration according to the rule proposed by Imbach.[15,16]

Optical measurements, particularly those of circular dichroism, can theoretically offer valuable information

Table 3. Synthesis of 8-aza-hypoxanthyl glycosides



SUBSTRATES	PRODUCTS	YIELD % (a)
4	8	85
5	9	95
6	10	95
7	11	93

(a) PURE PRODUCT, ISOLATED BY CHROMATOGRAPHY

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Tetrahedron

Contents [*continued from front cover*]

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H, s, tBu); 1.37 and 1.57 (6 H, 2 s, isopropylidene); 3.53 (2 H, d, H-5' and H-5''); 4.4 (1 H, d.t, H-4', $J_{4'-5'} = J_{4'-5''} = 5.3$ Hz, $J_{4'-3'} = 2$ Hz); 4.91 (1 H, d.d, H-3', $J_{2'-3'} = 6.6$ Hz); 5.61 (2 H, s, $CONH_2$); 5.72 (1 H, d.d, H-2', $J_{1'-2'} = 1.33$ Hz); 6.01 (1 H, d, H-1', $J_{1'-2'} = 1.33$ Hz); 6–7 (2 H, NH_2); 7.48 (10 H, m, aromatic). UV (ethanol) $\epsilon_{204} = 12430$, $\epsilon_{237} = 14928$, $\epsilon_{221} = 29821$. (Found: C, 58.35; H, 6.81; N, 13.67; Calc. for $C_{25}H_{35}O_5N_5Si$ (513.7) C, 58.46; H, 6.87; N, 13.63%).

5 - Amino 4 - carboxamido - 1 (2',3': 5',6' di - O - *isopropylidène α* - D - *mannopyranosyl*) *vic* - *triazole* **6**. Prepared by method 1 from **3** (285 mg, 1 mM). **6** (295 mg, 80%) was obtained by column chromatography with hexane/AcOEt 1/4 as eluent. $[\alpha]_D^{25} = +55.8°$ (c = 0.22, $CHCl_3$); m.p. (hexane–AcOEt) = 252°; ^1H NMR (δ pyridin D_5 250 MHz) 1.36, 1.40, 1.46 1.56 (12 H, 4 s, isopropylidene); 3.5–5 (5 H, m); 5–12 (1 H, d, H–2', $J_{2'-3'} = 5.5$ Hz); 6.66 (1 H, s, H-1'); 7.52 (2 H, s, $CONH_2$); 8.24 and 8.51 (2 H, 2 s, NH_2). UV (ethanol) $\epsilon_{261} = 6200$, $\epsilon_{236} = 6700$. (Found: C, 48.65; H, 6.31; N, 18.87; Calc. for $C_{15}H_{23}N_5O_6$ (369.4) C, 48.77; H, 6.27; N, 18.96%).

5 - *Amino* 4 - *carboxamido* - 1 (2',3':5',6' *di* - O - *isopropylidene*

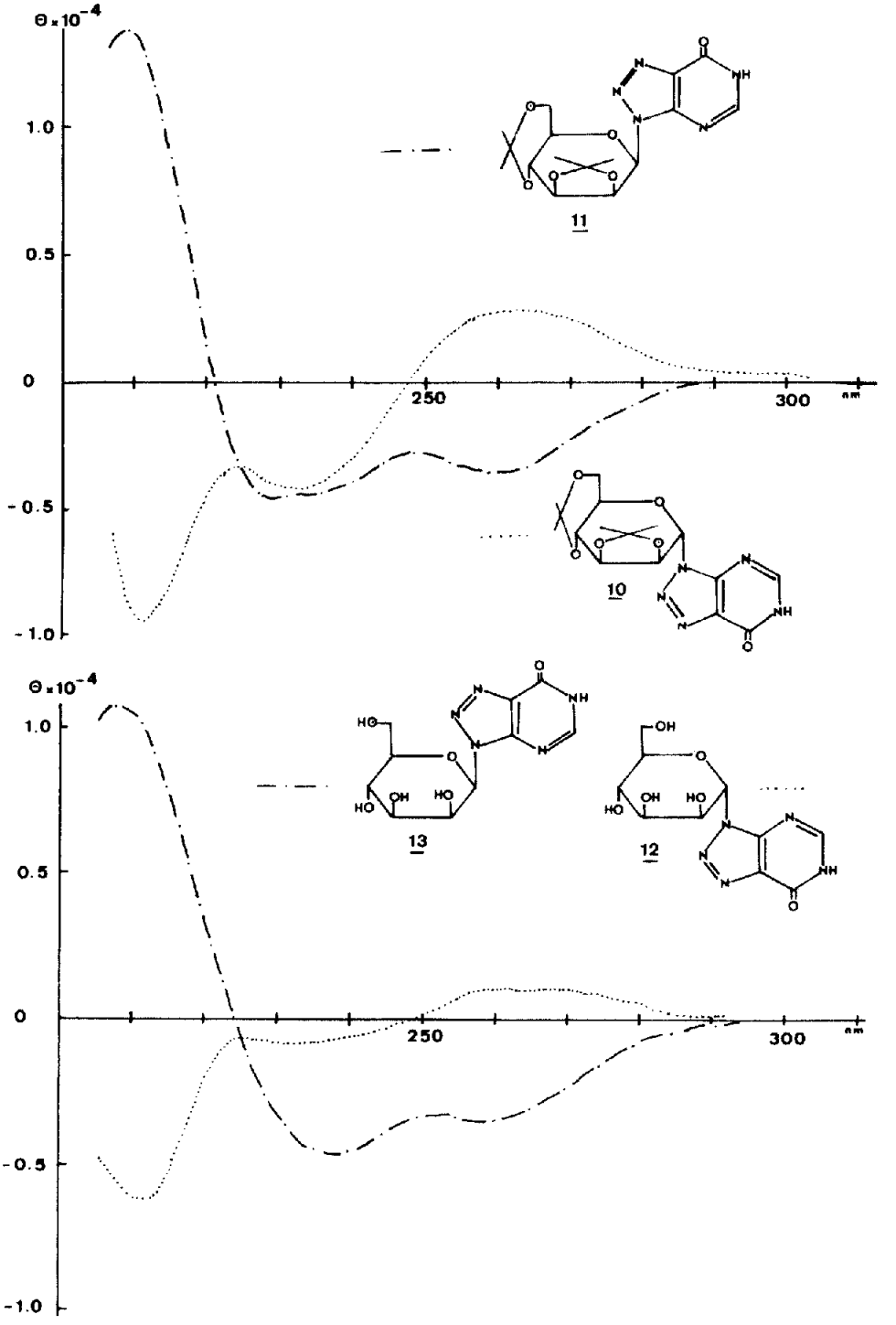

Fig. 1. CD spectra of **10**, **11**, **12** and **13** in EtOH.

β- D - *mannopyranosyl*) *vic triazole* **7**. Prepared by method 2 from **3**. **7** could not be isolated as a pure product. ^{1}H NMR (*δ* pyridin D_5 250 MHz) 1.29, 1.45, 1.67 (12 H, 3 s, isopropylidene); 3.60 to 4.10 (3 H, m); 4.24 (1 H, d.d, H − 4', $J_{3'-4'}$ = 8 Hz); 4.60 (1 H, d.d, H − 3', $J_{2'-3'}$ = 5 Hz); 4.84 (1 H, d.d, H − 2', $J_{1'-2'}$ = 2.5 Hz); 6.78 (1 H, d, H − 1'); 6.82 (2 H, s, $CONH_2$); 8.18 and 8.36 (2 H, 2 s, NH_2).

3 - 2,3' - O - *isopropylidene* - 5' - O - *trityl β* - D - *ribofuranosyl*) *vic triazole* (4,5-*d*) *pyrimid* - 7 - *one* **8**. **4** (637 mg, 1 mM) was heated to 100° with diethoxymethyl acetate (2 ml) for 3 hr. The orange solution was concentrated in vacuo, and the resulting amber syrup was dissolved in methanolic NH_3 (40 ml saturated at 0°) and allowed to stand in a sealed vessel at room temperature for 15 hr. The solution was evaporated to dryness and the residue was purified by column chromatography with AcOEt as eluent to give white crystals of **8** (440 mg, 85%). m.p. (hexane–AcOEt) = 128–130°; $[\alpha]_D^{25} = -25.5°$ (c = 1.83, $CHCl_3$); ^{1}H NMR (*δ* $CDCl_3$ 60 MHz) 1.38 and 1.62 (6 H, 2 s, isopropylidene); 3.22 (2 H, m, H − 5' and H − 5''); 4.66 (1 H, m, H − 4'); 5.0 (1 H, d.d, H − 3', $J_{3'-4'}$ = 2.3 Hz, $J_{2'-3'}$ = 6 Hz); 5.6 (1 H, d, H − 2'); 6.66 (1 H, s, H − 1'); 7.35 (15 H, m, aromatic); 7.51 (1 H, s, H − 5). UV (ethanol) ϵ_{257} = 12000. (Found: C, 67.15; H, 5.10; N, 13.01; Calc. for $C_{31}H_{29}O_5N_5$ (551.6) C, 67.51; H, 5.26; N, 12.70%).

3 - (2',3' - O - *isopropylidene* - 5' - O - *terbutyldiphenylsilyl β* - D - *ribofuranosyl*) *vic triazolo* (4,5 − *d*) *pyrimid* - 7 - *one* **9**. **5** (513 mg, 1 mM) was treated as described above to give **9** (497 mg, 95%) after column chromatography with AcOEt as eluent. m.p. (hexane–AcOEt) = 80°; $[\alpha]_D^{25} = -27.9°$ (c = 1.18, $CHCl_3$); ^{1}H NMR (*δ* $CDCl_3$ 250 MHz) 1.0 (9 H, s, tBu); 1.4 and 1.64 (6 H, 2 s, isopropylidene); 3.72 (2 H, m, H − 5' and H − 5''); 4.51 (1 H, t.d, H − 4', $J_{4'-5'} = J_{4'-5''}$ = 7.3 Hz, $J_{4'-3'}$ = 2.7 Hz); 5.10 (1 H, d.d, H − 3', $J_{2'-3'}$ = 7.3 Hz); 5.58 (1 H, d.d, H − 2', $J_{1'-2'}$ = 2 Hz); 6.55 (1 H, d, H − 1'); 7.45 (10 H, m, aromatic); 8.38 (1 H, s, H − 5); 10.10 (1 H, large s, N − H). UV (ethanol) ϵ_{256} = 81112, ϵ_{208} = 11022. (Found: C, 59.91; H, 6.50; N, 13.15; Calc. for $C_{26}H_{33}O_5N_5Si$ (523.7) C, 59.63; H, 6.35; N, 13.37%).

3 - (2',3':4',6' - *di* - O - *isopropylidene α* - D - *mannopyranosyl*) *vic triazolo* (4,5 − *d*) *pyrimid* - 7 - *one* **10**. **6** (369 mg, 1 mM) was treated as described for **8** to afford **10** (360 mg, 95%) after column chromatography with AcOEt as eluent. m.p. (hexane–AcOEt) = 252° (with decomposition); $[\alpha]_D^{25} = +44.2°$ (c = 0.57, $CHCl_3$); ^{1}H NMR (*δ* DMSO D_6 60 MHz) 1.42, 1.54 and 1.62 (12 H, 3 s, isopropylidene); 3.44 to 5.07 (7 H, m); 6.62 (1 H, s, H − 1'); 8.51 (1 H, s, H − 5). UV (ethanol) ϵ_{255} = 10940. (Found: C, 50.25; H, 5.87; N, 18.15; Calc. for $C_{16}H_{21}N_5O_6$ (379.4) C, 50.65; H, 5.58; N, 18.46%).

3 - (2',3':4',6' - di - O - *isopropylidene β* - D - *mannopyrannosyl*) *vic triazolo* (4,5-*d*) *pyrimid* - 7 - *one* **11**. **7** was treated as described for **8** to afford **11** (95%) after column chromatography with AcOEt as eluent. m.p. (hexane-AcOEt) > 250° (with decomposition); $[\alpha]_D^{25} = -20.5°$ (c = 0.81, $CHCl_3$); ^{1}H NMR (*δ* DMSO D_6 60 MHz) 1.22, 1.35 and 1.54 (12 H, 3 s, isopropylidene); 3.29–4.78 (7 H, m); 6.64 (1 H, d, H − 1', $J_{1'-2'}$ = 3.35 Hz); 8.26 (1 H, d, H − 5, become s with D_2O); 12.77 (1 H, large s, NH). UV (ethanol) ϵ_{255} = 10276. (Found: C, 49.39; H, 5.70; N, 18.35; Calc. for $C_{16}H_{21}N_5O_6$ (379.4); C, 50.65; H, 5.58; N, 18.46%).

3 - (*α* - D - *mannopyranosyl*) *vic triazolo* (4,5-*d*) *pyrimid-7-one* **12**. **10** (379 mg, 1 mM) was dissolved in an aqueous trifluoroacetic acid solution (50%) (3 ml). The mixture was kept for 1 hr at room temperature and evaporated to dryness *in vacuo*. The crude crystals were stored over KOH overnight in vacuo in order to remove the trifluoroacetic acid. **12** was recrystallized in a mixture of H_2O/MeOH (293 mg, 98%). m.p. = 189–190°; $[\alpha]_D^{25} = +37°$ (c = 0.81, DMF); ^{1}H NMR (*δ* DMSO D_6 60 MHz) 6.09 (1 H, s, H − 1'); 8.33 (1 H, s, H − 5); 12.87 (1 H, s, NH). UV (ethanol) ϵ_{255} = 6353. (Found C, 40.22; H, 4.40; N, 23.25; Calc. for $C_{10}H_{13}O_6N_5$ (299.2) C, 40.13; H, 4.34; N, 23.41%).

3-(*β-D-mannopyranosyl*) *vic triazolo* (4,5-*d*) *pyrimid-7-one* **13**. **13** (290 mg, 97%) was obtained as described above from **11** (379 mg, 1 mM). m.p. = 172–173° (H_2O/MeOH); $[\alpha]_D^{25} = +6.5°$ (c = 0.69, DMF); ^{1}H NMR (*δ* DMSO D_6 250 MHz) 6.0 (1 H, s, H-1'); 8.23 (1 H, s, H-5). UV (ethanol) ϵ_{255} = 8400. (Found C, 39.80; H, 4.52; N, 23.31; Calc. for $C_{10}H_{13}O_6N_5$ (299.2) C, 40.13; H, 4.34; N, 23.41%).

3-(2',3'-O-*isopropylidene β-D-ribofuranosyl*) *vic triazolo* (4,5-*d*) *pyrimid-7-one* **14**. (a) From **8** (552 mg, 1 mM) was dissolved in an aqueous trifluoroacetic acid solution 50% (3 ml). The mixture was kept at room temperature and the reaction was monitored by tlc (AcOEt as eluent). The mixture was evaporated to dryness and purified by column chromatography to afford **14** (267 mg, 90%).

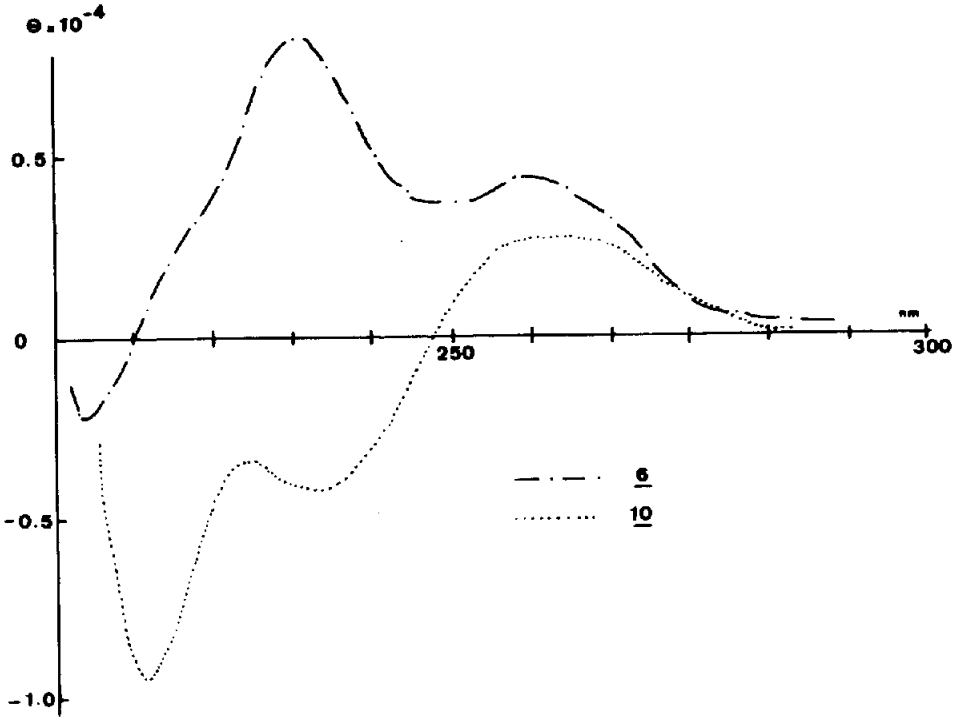

Fig. 2. CD spectra of **6** and **10** in EtOH.

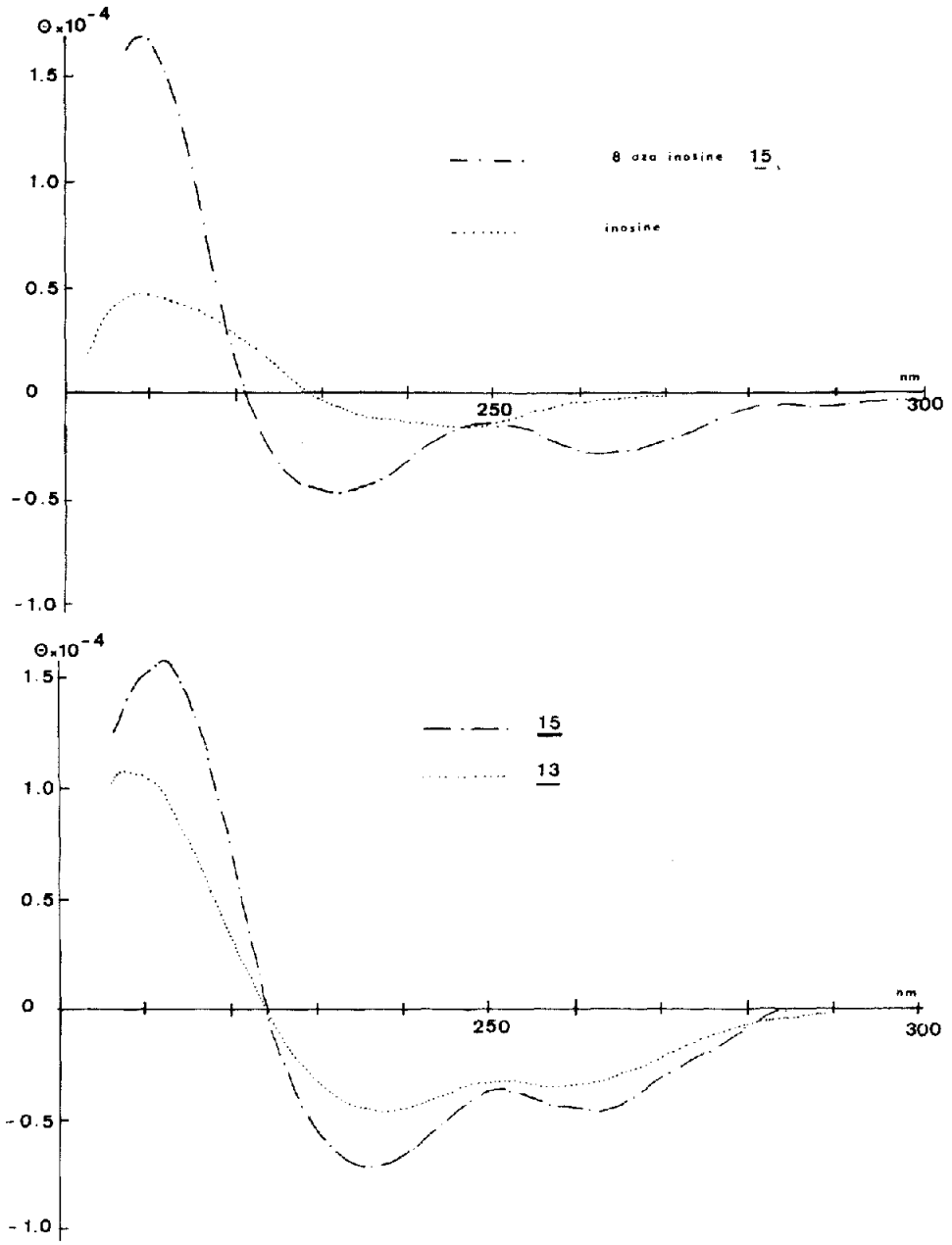

Fig. 3. CD spectra of inosine, 8-azainosine **15** and **13** in EtOH

(b) *From* **9**. **9** (524 mg, 1 mM) was added to a solution of tetrabutylammonium fluoride (300 mg) in tetrahydrofurane (4 ml) and kept at room temperature. Work up and purification as above give **14** (282 mg, 95%). M.p. 184–185° (H_2O/MeOH); $[\alpha]_D^{25} = -52.8°$ (c = 1.06, H_2O–MeOH); ^1H NMR (δ DMSO D_6 250 MHz) 1.35 and 1.53 (6 H, 2s, isopropylidene); 3.38 (2 H, m, H-5′ and H-5″); 4.2 (2 H, m, H-4′ and OH); 5.0 (1 H, d.d, H-3′, $J_{3'-4'} = 2$ Hz); 5.53 (1 H, d.d, H-2′, $J_{2'-3'} = 6$ Hz); 6.37 (1 H, d, H-1′, $J_{1'-2'} = 1.3$ Hz); 7.69 (1 H, s, NH); 8.31 (1 H, s, H-5). UV (ethanol) $\epsilon_{255} = 9700$. (Found: C, 44.60; H, 4.89; N, 23.12; Calc. for $C_{11}H_{15}N_5O_5$ (297.3) C, 44.44; H, 5.09; N, 23.56%).

3-(*β*-O-*ribofuranosyl*) *vic triazolo* (4,5-*d*) *pyrimid-7-one*: 8-*azainosine* **15**. **14** (297 mg, 1 mM) was added to a suspension of resin (Dowex 50 H^+) (400 mg) in a mixture of THF (2 ml) and H_2O (2 ml). The solution was kept at room temperature for 96 h. The resin was filtered and the filtrate was evaporated to dryness *in vacuo*. The crude product was recrystallized from MeOH–H_2O to give **15** (242 mg, 90%) as white crystals. M.p. = 220°; $[\alpha]_D^{25} = -74.8°$ (c = 1.21, DMF); litt.[11] $[\alpha]_D^{25} = -80.9°$ (c = 1, DMF); ^1H NMR (δ DMSO D_6 60 MHz) 6.18 (1 H, d, H-1′, $J_{1'-2'} = 4.75$ Hz); 8.31 (1 H, s, H-5). UV (ethanol) $\epsilon_{254} = 10000$; (H_2O pH 7.5) $\epsilon_{256} = 10313$.

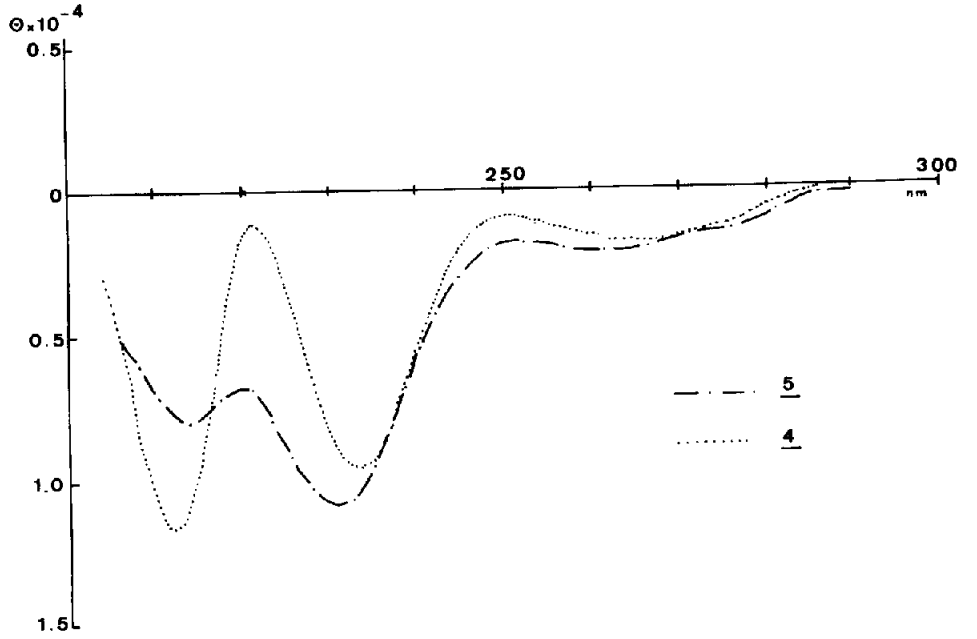

Fig. 4. CD spectra of **4** and **5** in EtOH.

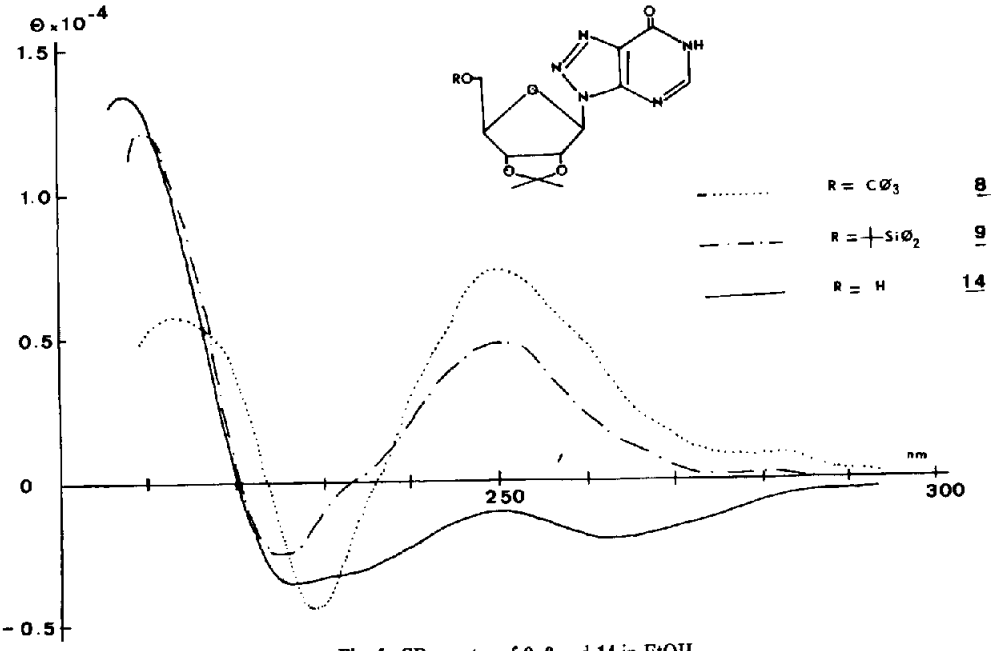

Fig. 5. CD spectra of **8**, **9** and **14** in EtOH.

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