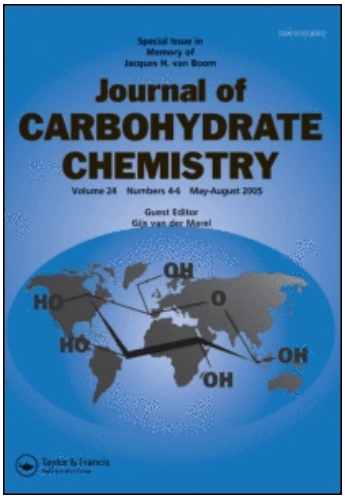

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SOME PHYSICO-CHEMICAL AND BIOLOGICAL PROPERTIES OF TRIAZENO SUGARS

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ABSTRACT

Replacement of the alkyl group of 1-aryl-3-alkyltriazenes with a sugar moiety did not significantly modify their tautomeric behaviour. The same replacement done on 1-aryl-3-alkyl-3-methyltriazenes did not affect to any large extent their rotameric properties. In contrast, the most prominent biological properties, anticancer activity and toxicity, of 1-aryl-3-methyltriazenes disappeared on replacement of the methyl group with a sugar moiety. Unexpectedly, the N-acetyltriazene **15** was highly cytotoxic.

INTRODUCTION

We have shown in a number of instances that the physico-chemical properties of functional groups could be dramatically modified by their attachment to a derivatized sugar molecule. For example, we isolated in a pure form stable sugar gem-bromoazo,[1] dibromoazo[1] and gem-hydroxyazo[2] derivatives although such functional groups are supposed to impart extreme instability to the host molecule. Similarly, we prepared[3] a large number of deoxy(hydro-

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xylamino) sugar derivatives, most of them being significantly more stable than expected from the properties of N-monoalkylhydroxylamines.

Some time ago, we described[4] the first examples of triazeno sugars obtained in a pure form. Triazenes are known, albeit not in full detail, to exhibit interesting tautomeric or rotameric properties. They also constitute a biologically important class of compounds, some of them having useful anticancer properties and being currently used in clinical practice.[5] In carbohydrate chemistry, an attempt towards the synthesis of anticancer triazeno compounds has been made[6] by using 1-triazeno derivatives in the hope that, owing to the stability of a carbocation at the anomeric position of sugars, these compounds would be active. Unfortunately, that was not the case. The physico-chemical properties as well as the biological activities of sugar derivatives bearing a triazeno group at a position other than at the anomeric carbon were unknown. This induced us to expand our previous series of triazeno sugars by synthesizing a few more examples of 3-aryl-1-methyltriazen-1-yl sugars .

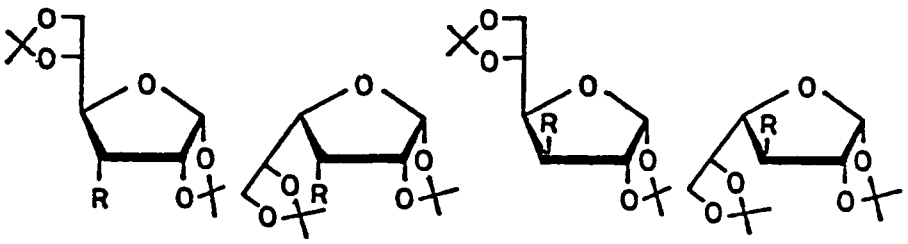
All these compounds were submitted to a dynamic NMR study and some biological testing to determine to what extent the attachment of a sugar moiety onto a triazeno group would affect its physico-chemical or biological properties.

RESULTS AND DISCUSSION

Compounds **1**-**9** have been previously described.[7] Compounds **10** and **11** were obtained by reacting 5-deoxy-1,2-O-isopropylidene-3-O-methyl-5-methylamino-α-D-xylofuranose[8] with the appropriate arenediazonium salt. Treatment of **10** with ammonia gave pure **12**, whereas, under the same conditions, **13** could not be obtained from **11** in pure form but gave NMR spectra in accordance with the proposed structure.

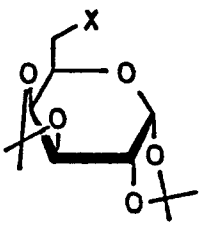
Study of The Tautomeric Equilibrium of The p-Nitrophenyltriazeno Derivatives (1-5 and 8).

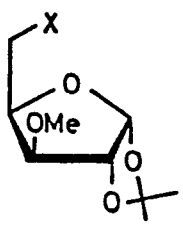
SCHEME



1 **2** **3** **4**

R = N=N-NH-$C_6H_4NO_2$-p

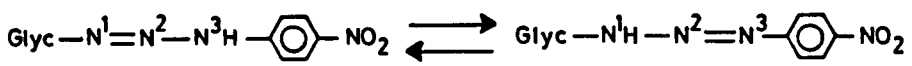




5 X = N=N-NH-$C_6H_4NO_2$-p
6 X = NMe-N=N-$C_6H_4NO_2$-p
7 X = N=N-NH-C_6H_4COOMe-o
15 X = NAc-N=N$C_6H_4NO_2$-p

8 X = N=N-NH-$C_6H_4NO_2$-p
9 X = NMe-N=N-$C_6H_4NO_2$-p
10 X = NMe-N=N-C_6H_4COOMe-o
11 X = NMe-N=N-C_6H_4COOEt-p
12 X = NMe-N=N-$C_6H_4CONH_2$-o
13 X = NMe-N=N-$C_6H_4CONH_2$-p
14 X = NHMe

The equilibrium between the two tautomeric forms A and B has been studied by variable temperature ^1H NMR spectroscopy for



A **B**

compounds **1**, **2**, **5** and **8**. The data from compounds **3** and **4** were not usable due to very low relative concentration (ca. 5%) of the

tautomer **B**. At 35°C, the NMR spectra (90 MHz) was very badly resolved, the well resolved time-averaged spectra appearing above +50°C and the spectra of the two separate isomers being clearly distinguishable below -50°C. The aromatic proton region of the spectra was the most sensitive to temperature . Aromatic signals of **B** (azo type) and **A** (anilino type) have been identified by comparison with those of p-nitrophenylazo sugars and sugar hydrazones resp. from previous work in this Laboratory.[9] This was confirmed, in the case of **2**, by a $^{3}J_{HN,3}$ coupling. By using their integral values, the NH signals of **A** were easily assigned, the more deshielded ($9.6 < \delta < 10.4$) corresponding to the tautomer **A** ($8.84 < \delta < 9.00$ for the tautomer **B**). Spectra of compounds **1**, **2** and **5** were measured in chloroform-d whereas tetrachloroethylene was used for **8** which decomposed in chloroform. To render comparison possible the dynamic NMR study of **1** was done in both solvents.

The free energy of activation was deduced from the measured coalescence temperature t_c. The equilibrium constant K was directly extracted from the spectra for temperatures lower than t_c and, in the other cases, estimated by assuming that the observed shift was the result of the time averaging of the shifts of the two separate tautomers (neglecting any possible temperature induced change of these individual values). The thermodynamic and kinetic data concerning the equilibrium **A** $\overset{<---}{--->}$ **B** are presented in Table 1.

It is noted that only in chloroform solutions does the equilibrium constant depend on the temperature. The triazene **7** exists only in the form **A** owing to a hydrogen bond between the ortho NH and the ester carbonyl group as shown for similar compounds.[10]

To obtain information on the mechanism of the site exchange, a larger number of solvents have been used in the case of compound **1**. At low temperature, the tautomer **A** is most generally preponderent. The $\Delta G^{\ddagger}$ values at t_c are close to 15 Kcal Mol $^{-1}$ in chloroform, values similar to those noted[11] for simpler tria-

TABLE 1

Kinetic and Thermodynamic Data of the Tautomeric Equilibrium of Disubstituted Triazenes

Compound	Solvent	t_c	$\Delta\nu$(Hz)	$\Delta G^{\ddagger}$ at t_c	ΔH_o^a	ΔS_o (e.u.)	K^b
1	$CDCl_3$	20	32.4	14.6	1.40±0.07	3.60±0.20	0.3<K<0.7
1	$CDCl_3$ +5% CH_3OH	20	27.0	14.9	0.23±0.35	-0.6±1	0.5
1	$CDCl_3$ +5% CD_3OD	20	27.0	14.9	0.27±0.37	-0.3±1	0.5
1	$CDCl_3$ +5% DMSO/d_6	30	22.5	15.5	0.31±0.15	-0.48±0.4	0.5
1	$CDCl_3$ +30% DMSO/d_6	50	24.3	16.5	0.35±0.16	-0.68±0.5	0.37
1	C_2Cl_4	30	19.8	15.4	0.17±0.25	1.08±0.7	1.25
1	C_2Cl_4 +5% DMSO/d_6	40	17.0	16.2	0.05±0.53	-1.89±1.4	0.38
2	$CDCl_3$	25	25.2	15.0	1.48±0.4	4.9±1.5	0.5<K<0.9
8	C_2Cl_4	40	26.0	15.8	-0.12±0.4	-1.19±1.2	0.7
8	C_2Cl_4 +5% DMSO/d_6	55	23.4	16.8	0.33±0.16	-0.76±0.5	0.4
5	$CDCl_3$	30	25.2	15.3	1.75±0.08	6.45±0.2	0.45<K<2

a. In kcal Mol^{-1}.
b. K depends significantly on the temperature only when the solvent is $CDCl_3$.

zenes. Replacing chloroform with tetrachloroethylene increased the energy barrier by ca. 1 Kcal Mol^{-1}. Addition of CH_3OH (5%) to chloroform had no noticeable effect whereas addition of DMSO either to chloroform (5 and 30%) or to tetrachloroethylene (5%) solutions increased the $\Delta G^{\ddagger}$ value to 16-17 Kcal Mol^{-1}. No kinetic nor thermodynamic isotopic effect was noted either when using CD_3OD instead of CH_3OH or when using a triazene whose NH had been previously exchanged to ND. These data show that there is little or no overall N-H bond breaking in the transition state, that the transition state is only slightly charged and more sensitive to anion than to cation destabilization. This cannot rule out the proposal[11] of a radical mechanism but could also correspond to a concerted ionic mechanism.

Restricted Rotation of Trisubstituted Triazenes.

At 35°C, the spectra of compounds **9-13** were poorly resolved. Decreasing the temperature permitted the observation of the spectra of two rotamers (s-cis and s-trans). Amongst the signals, the N-methyl absorptions were particularly well separated, the more deshielded being assigned to the s-cis isomer.

The major kinetic and thermodynamic data of this transformation are collected in Table 2 and show that the ΔG values are close to those of 1,1-dimethyl-3-p-nitrophenyltriazene[12] and intermediate between those of trialkyltriazenes[13] (10-13 Kcal Mol^{-1}) and alkoxycarbonyltriazenes[14] (18-19 Kcal Mol^{-1}).

In all cases, the s-trans rotamer is more stable than the s-cis and as the ΔH_0 values are almost zero, the equilibrium constant does not depend on the temperature. So, the differences in the ΔG_0 values from one compound to the other are due to differences in ΔS_0. On the other hand, the position of the equilibrium depends more on the nature of the phenyl substituent than on its position (ortho or para).

Biological Properties

1-Aryl-3,3-dimethyltriazenes are known to possess anticancer activity, one of them, the 5-(3,3-dimethyl-1-triazeno)imidazole

TABLE 2

Kinetic and Thermodynamic Data of the ~ Rotameric Equilibrium of Triazenes **6** and **9**-**13**

Compound	Solvent	t_C(NMe)	$\Delta\nu$ (Hz)	$\Delta G^{\ddagger a}$ at t_C	K	ΔH_o^a	ΔS_o(e.u.)	ΔG_o at 0°C
9[b]	C_2Cl_4	65	27.9	17.2±0.2	~0.3	0.07±0.13	-2.0±0.3	0.7
9[b]	$CDCl_3$	45	28.8	16.2±0.2			-2.4	
6[b]	C_2Cl_4	65	31.5	17.1±0.2	~0.45	~0	-1.6	0.5
11[c]	$CDCl_3$	40	64.0	15.4±0.2	0.38	~0	-1.9	0.57
13[c]	$CDCl_3$	40	65.0	15.4±0.2	0.23	~0	-3	0.68
10[c]	$CDCl_3$	35	64.0	15.4±0.2	0.36	~0	-2	0.6
12[c]	$CDCl_3$	55	68.0	16.1±0.2	0.2	~0	-3.2	0.95

a. In kcal Mol^{-1}.
b. 90 MHz spectra.
c. 200 MHz spectra.

(DTIC) being clinically used in the treatment of melanoma.[5] These compounds are highly toxic and all attempts to disjoin their useful from their toxic properties have failed.[14] An interesting qualitative structure-activity relationship has been proposed:[15,16] 1-aryltriazenes bearing on N-3 a methyl group and another, readily metabolizable, alkyl group have anticancer activity and are more stable than DTIC at physiological pH.[17]

Under these conditions, compounds **10**-**12** were good candidates for anticancer testing which was done at the NIH on mice bearing a P388 lymphokytic leukemia. They showed to be inactive (%TC ranging from 91 to 102 for doses of 100-400 mg/kg).

This shows that whereas the replacement of an alkyl group of a triazene by a sugar moiety does not modify significantly the tautomeric or rotameric properties of the molecule, the same kind of operation can dramatically change its biological properties. Most 1-aryl-3,3-dimethyltriazenes are active anticancer agents and although their activity decreases when the electronegativity of the substituent of the phenyl nucleus increases, even 1-*p*-nitrophenyl-3,3-dimethyltriazene was calculated[18] to have significant anticancer activity. The replacement of a methyl group by a sugar moiety decreases both the toxicity and the anticancer activity of these compounds. This is somewhat similar to the observation[19] that increasing the length of the carbon chain of the alkyl substituent of 3-alkyl-1-(4-carboxyphenyl)-3-methyltriazenes decreased their activity, the heptyl derivative being inactive but still highly toxic at a 400 mg/kg daily dose.

EXPERIMENTAL

General procedures. see ref. 20.

5- Deoxy-5-(3-o-carbomethoxyphenyl-1-methyltriaz-2-en-1-yl)-1,2,-O-isopropylidene-3-O-methyl-α-D-xylofuranose (**10**). To a - solution of **14** (434 mg, 2 mmol) in water (10 mL) was added dropwise at 0°C 13.5 mL of a solution of o-carbomethoxybenzene-

diazonium chloride prepared by reacting methyl o-aminobenzoate (951 mg, 6.3 mmol in 30 mL HCl 1 N) and $NaNO_2$ (450 mg, 6.5 mmol in 10 mL H_2O). The reaction medium was maintained alkaline by addition of 10% NaOH. After decantation the precipitate was washed (2x20 mL H_2O),and dissolved in Et_2O (20 mL). The organic phase was dried (Na_2SO_4) concentrated, yielding a solid whose recrystallisation (i-Pr_2O / hexane) gave 595 mg (78.5%) of **10** : mp 47.8 - 48.6° C; Rf 0.4 (Et_2O / hexane 1:1); $[\alpha]_D^{23}$ + 11.8° (c 1.0, $CHCl_3$); UV(EtOH) : 300 (8860), 232 (4050); IR (KBr) : 1730 (CO), 1600, 1580, 1550, 1505 (Ph), 1480 (Ar-N), 1450 (N=N), 1380 and 1360 (CMe_2); ^1H NMR (200 MHz, 20°C, $CDCl_3$) : 1.32 and 1.50 (2s, 2x3, CMe_2), 3.30 (broad s, 3, NMe), 3.43 (s, 3, C-OMe), 3.72 (d, 1, $J_{3,4}$ 3.5, H-3), 3.88 (s, 3, COOMe), 3.94 (broad m, 1, H_a-5), 4.20 (broad m, 1, H_b-5), 4.45 (broad m, 1, H-4), 4.62 (d, 1, $J_{1,2}$ 3.7, H-2), 5.92 (d, 1, H-1), 7.20 (m, 1, H-4'- Ph), 7.40 (m, 2, H-5',H-6'-Ph), 7.63 (d, 1, H-3'-Ph); SM : 379 (15 $M^{+\cdot}$), 364 (16 $M^{+\cdot}$ -Me·), 348 (5), 336 (8), 278 (3), 193 (7, $MeN_3Ar^{+\cdot}$), 163 (18), 151 (34), 135 (100), 105 (4).

Anal. Calcd for $C_{18}H_{25}N_3O_6$ (379.42) : C, 56.98; H, 6.64; N, 11.07. Found : C, 56.88; H, 6.58; N,11.12.

5-Deoxy-5-(3-p-carboethoxyphenyl-1-methyltriaz-2-en-1-yl)-1,2-O-isopropylidene-3-O-methyl-α-D-xylofuranose (**11**). Treatment of a solution of **14** (868 mg, 4 mmol) in water (20 mL) with 27 mL of a solution of p-carboethoxybenzenediazonium chloride prepared from ethyl p-aminobenzoate (951 mg in 30 mL of HCl N) and $NaNO_2$ (414 mg in 10 mL H_2O) gave after preparative silica gel thick layer chromatography (Et_2O / hexane 1:1) 834 mg (53%) of **11** : Syrup, Rf 0.55 (Et_2O / hexane 1:1); $[\alpha]_D^{23}$ + 5.5° (c 1.0, $CHCl_3$) ; UV (EtOH) : 325 (21050), 227 (5900) ; IR (film) : 1720 (CO), 1600, 1580, 1550, 1510 (Ph), 1480 (Ar-N), 1450 (N=N), 1380 and 1360 (CMe_2) ; ^1H NMR (200 MHz, 24°C, $CDCl_3$) : 1.32, 1.56 (2s, 2x3, CMe_2), 1.40 (t, 3, J 7.5 CH_2CH_3), 3.30 (s, 3, NMe), 3.45 (s, 3, OMe), 3.72 (d, 1, $J_{3,4}$ 3.0, H-3), 3.97 and 4.20 (2 broad m, 1, H-5), 4.38 (q,2, CH_2CH_3), 4.60 (d, 1, $J_{1,2}$ 4.0, H-2),

5.93 (d, 1, H-1), 7.35 - 7.50 and 7.90 - 8.05 (2m, 2x2, Ph) ; SM : 393 (41, $M^{+\cdot}$), 378 (35, $M^{+\cdot}$-Me$^{\cdot}$), 350 (27), 348 (34), 177 (25), 165 (33), 134 (8), 121 (12), 103 (33), 65 (12).

Anal. Calcd for $C_{19}H_{27}N_3O_6$ (393.44) : C, 58.00 ; H, 6.92 ; N, 10.68. Found : C, 58.20 ; H, 6.98 ; N, 10.79

5-Deoxy-5-(3-o-carboxamidophenyl-1-methyltriaz-2-en-1-yl)-1,2-O- isopropylidene-3-O-methyl-α-D-xylofuranose (**12**). To a solution of **10** (456 mg, 1.2 mmol) in dioxane (20 mL) concd NH_4OH (40 mL) was added and the mixture stirred 48 h at room temp. Ammonia and the solvents were removed under vacuum and the residue, washed with ether, afforded 364 mg (83%) of **12** : mp 94.4 - 95.6° C ; Rf 0.5 (Et_2O / hexane 1:1); $[\alpha]_D^{23}$ -5.3° (c 1, $CHCl_3$) ; UV (EtOH) : 315 (3610), 245 (1020) ; IR (KBr) : 3400, 3250 (NH_2), 1650 (CO), 1590 (amide II); ^{1}H NMR (200 MHz, 20°C, $CDCl_3$) : 1.33, 1.48 (2s, 2x3, CMe_2), 3.30 and 3.62 (2 broad s, 3, NMe), 3.46 (s, 3, OMe), 3.77 (broad m, 1, H-3), 4.03 (dd, 1, $J_{4,5a}$ 8.0, $J_{5a,5b}$ 11.0, H_a-5), 4.28 (dd, 1, $J_{4,5b}$ 4.0, H_b-5), 4.42 (broad m, 1, H-4), 4.64 (d, 1, $J_{1,2}$ 4.0, H-2), 5.96 (d, 1, H-1), 5.96 (broad s, 2, NH_2), 7.20 - 7.32, 7.35 - 7.66, 8.20 - 8.38,(3m , 1, 2, 1, Ph); SM : 364 (7, $M^{+\cdot}$), 349 (10, $M^{+\cdot}$ - Me$^{\cdot}$), 216 (16), 148 (50), 136 (40), 120 (100), 105 (10), 102 (8), 92 (23), 77 (7), 71 (6), 65 (14).

Anal. Calcd for $C_{17}H_{24}N_4O_5$ (364.40) : C, 56.03; H, 6.64; N, 15.37. Found : C, 55.95; H, 6.84; N, 15.24.

^{1}H NMR data of 5-deoxy-5-(3-p-carboxamidophenyl-1-methyl-triaz-2-en-1-yl)-1,2-O-isopropylidene-3-O-methyl-α-D-xylo-furanose (**13**). Prepared from **11** as described for **12** , **13** was obtained as a syrup unamenable to analytical purification : ^{1}H NMR (200 MHz, 20°C, $CDCl_3$) : 1.23, 1.39 (2s, 2x3, CMe_2), 3.22 (broad s, 3, NMe), 3.38 (s, 3, OMe), 3.64 (d, 1, $J_{3,4}$ 3.0, H-3), 3.90 (broad dd, 1, H-5a), 4.11 (m, 1, H-5b), 4.36 (broad m, 1, H-4), 4.53 (d, 1, $J_{1,2}$ 4.0, H-2), 5.87 (d, 1, H-1), 6.20 (broad s, 2, NH_2), 7.39, 7.70 (2m, 2x2, Ph).

ACKNOWLEDGEMENTS

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17. It is interesting to note that 15[7] bearing an acetyl group on N-3 was highly cytotoxic (0.7 µg/mL against human fibroblasts MRC5) but devoid of antiviral activity against herpes virus and influenza virus A_2-Victoria.

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