Note

(*p*-Bromophenyl)osotriazoles from inositols*†

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On simultaneous oxidation and bromination of sugar phenylosazones with aqueous bromine, El Khadem and co-workers[1,2] obtained a series of crystalline (*p*-bromophenyl)osotriazoles of sugars in good yield.

In continuation of studies on cyclitols[3], the products resulting from treatment of three inosose phenylosazones with aqueous bromine have now been examined. As expected[1], the products were (*p*-bromophenyl)osotriazoles, albeit they were isolated in only 28–42% yield. It has been found in this laboratory that preparation of (*p*-bromophenyl)osotriazoles from inositols is a laborious process as compared to isolation of sugar (*p*-bromophenyl)osotriazoles.

The n.m.r. spectra of the tetraacetates **1b**, **2b**, and (**1b**+**2b**), of the tetrabenzoate (**1c**+**2c**), and of their parent compounds on protonation ("decoupling") of their hydroxyl groups with a trace of a strong acid, show a symmetrical pattern (presence of a simple, two-fold axis of symmetry in an AA′BB′ system) similar to those reported[3] for unsubstituted phenylosotriazoles from inositols, and different from those of sugar phenylosotriazoles[4]. However, the n.m.r. spectra of triacetate **3b**, tribenzoate **3c**, and their parent compound (**3a**) do not show a symmetrical pattern; protons H-6, H-6′, and H-5 apparently belong to ABX systems‡.

In addition to preparation of their acetates or benzoates, the phenylosotriazoles were oxidized with periodate, to afford new dialdehydes.

The preparation and some of the properties of the (*p*-bromophenyl)osotriazoles **1a** and **2a**, respectively, from the enantiomorphs 1D-*chiro*-inositol and 1L-*chiro*-inositol via the corresponding inosose osazones, and of the tetraacetates **1b** and **2b**, are summarized in Table I; this Table also includes data on the preparation of 3D-3,5/4-trihydroxy-1,2-cyclohexanedione (*p*-bromophenyl)osotriazole (**3a**) and its deriv-

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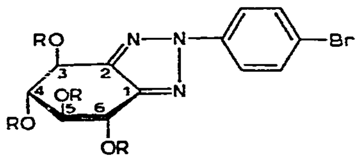
*Dedicated to Dr. Nelson K. Richtmyer in honor of his 70th birthday.

†Part VIII. Methods in Inositol Chemistry. For Part VII, see *Carbohyd. Res.*, 17 (1971) 419. The nomenclature is in accordance with the IUPAC–IUB Tentative Nomenclature for Cyclitols [*Europ. J. Biochem.*, 5 (1968) 1], with the trivial name in parentheses. The trivial name "inosose" for any pentahydroxycyclohexanone is used where convenient.

‡A discussion of the n.m.r. spectra of compounds **1a**, **2a**, (**1a**+**2a**), and **3a** will be included in a forthcoming publication describing the preparation of unsubstituted phenylosotriazoles from inositols.



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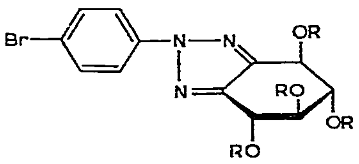

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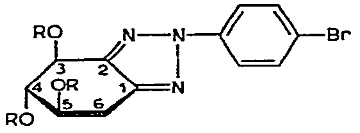

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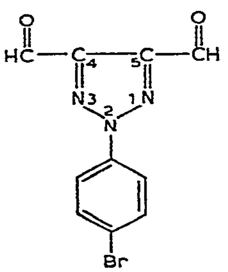
a R = H
b R = Ac
c R = Bz



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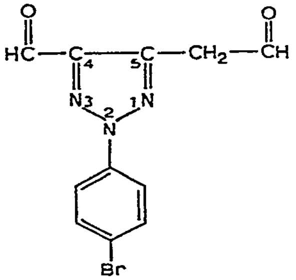

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atives **3b**, **3c**, and **5**. Examination of the i.r. spectra of the D, L, and DL forms [compounds **1a**, **2a**, and (**1a**+**2a**) in Table II] revealed some differences. Whereas the i.r. spectra of the D and L forms (compounds **1a** and **2a**) were the same, the i.r. spectrum of the DL form showed extra bands at 1505, 1440, 1050, 890 and 798 cm^{-1}, the band at 1012 cm^{-1} was absent (a characteristic triplet at 1012, 1000, and 990 cm^{-1} was observed for the D and L forms only), and band intensities in the 1350–1250-cm^{-1} region were different from those for the D and L forms.

The i.r. spectra of the tetraacetates of the D and L forms (compounds **1b** and **2b**) were identical, and were somewhat different from that of the tetraacetate of the DL form (**1b**+**2b**), particularly in the 800–650-cm^{-1} region. The DL form did not show clear bands at 800, 760, and 700 cm^{-1} that were observed for the D or L form; also, the spectra showed a marked difference in intensity of the bands in the 1000–900-cm^{-1} region from those for the D or L form.

In all instances, the i.r. spectra of the D, L, and DL forms of a compound in solution were identical.

EXPERIMENTAL

General. — N.m.r. spectra were recorded with a Varian A-60 spectrometer*, with tetramethylsilane ($\tau = 10.00$) as the internal standard. Optical rotations were

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*Mention in this article of certain commercial instruments does not constitute endorsement by the National Bureau of Standards.

determined, for the solution in a 1-dm cell, with a Perkin–Elmer Model 141 automatic polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 257 grating spectrophotometer, and u.v. spectra were recorded with a Beckman DK-2 or Cary 14 spectrophotometer. Analyses were made by William Schmidt of the Microchemical Analysis Section of this Division.

DL-*3,5/4,6-Tetrahydroxy-1,2-cyclohexanedione* (p-*bromophenyl*)*osotriazole* [DL-*1,2-diketo*-myo-*inositol* (p-*bromophenyl*)*osotriazole*] (**1a**+**2a**). — Into an ice-cold (0°) suspension of bromine (25 g; 8 ml; 156 mmoles) in water (250 ml) in a glass-stoppered Erlenmeyer flask surrounded by ice was introduced portionwise, with vigorous stirring during 45 min, dry, finely ground, crude DL-3,5/4,6-tetrahydroxy-1,2-cyclohexanedione bis(phenylhydrazone) (DL-*myo*-inosose-1 phenylosazone)[5] (5 g). Stirring was continued for an additional 2 h, and then the mixture was kept in a refrigerator for 18 to 24 h. White to pinkish white crystals of crude (**1a**+**2a**) (350–400 mg, m.p. 252–254°) separated and were removed by filtration or decantation, leaving a dark, semisolid residue. The latter was stirred with an ice-cold, saturated, aqueous solution of sodium hydrogen sulfite ($NaHSO_3$, 50 ml) for 30 min in an ice-bath, to give a purple, crystalline solid (7.2 g, air-dried). Digestion of this solid with ether (50 ml) for 15 min, followed by filtration and washing with ether until the filtrate was free from a purple pigment [λ_{max}^{MeOH} 245 (sh), 308, and 482 nm], gave brownish white crystals of crude (**1a**+**2a**); yield 3.8–4.1 g. The product was further purified by recrystallization from 1:1 (v/v) acetone–pentane or from hot water. Extraction of the crude product (1 g) with hot water (50 ml) in the presence of carbon, followed by filtration and cooling of the filtrate, gave lustrous, white crystals (500 mg, 42% yield)* of (**1a**+**2a**); twice-recrystallized sample, dried for 1 h at 110°/0.1 torr had m.p. 258–260°; λ_{max}^{MeOH} 278 nm (ε_{mM} 35.3); R_F 0.55 [plate of unactivated silica gel with 3:1:1 (v/v) water–*tert*-butyl alcohol–acetic acid, followed by a spray of 3M sulfuric acid in methanol (spray A), and heating of the plate for 2 min at 110°, dark spot].

Anal. Calc. for $C_{12}H_{12}BrN_3O_4$: C, 42.12; H, 3.53; N, 12.27. Found:** C 42.20; H 3.60; N 12.20.

When introduction of the phenylosazone was limited to 1 to 3 min, the yield of of the (*p*-bromophenyl)osotriazole (**1a**+**2a**) was 20–21%; when the reaction was conducted at room temperature, the yield of (**1a**+**2a**) decreased to 10–15%. However when the bromine oxidation was conducted in the presence of sodium acetate buffer at 0°, the yield of the osotriazole (**1a**+**2a**) was approximately the same as described for aqueous bromine.

Tetraacetate (**1b**+**2b**). — A mixture of osotriazole (**1a**+**2a**) (0.15 g), acetic anhydride (10 ml), and pyridine (1.5 ml) was stirred at 95° until dissolution was complete (3 min), and the solution was kept for 2 h at room temperature. Decomposition with ice–water, followed by recrystallization from 80% aqueous ethanol (carbon),

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*The corresponding overall yields, based on water-extracted material were: for **1a**, 28; for **2a**, 32; and for **3a**, 40%.

**Sample dried at room temperature was the monohydrate. Found: C, 39.95; H, 3.80; N, 11.60.

TABLE I

PHYSICAL PROPERTIES OF (p-BROMOPHENYL)OSOTRIAZOLES FROM INOSITOLS AND A CYCLOHEXANEPENTOL

p-(*Bromophenyl*)-*osotriazole*	*Recrystallization solvent*	*M.p. (degrees)*	$[\alpha]_D^{25}$ *(degrees)*	λ_{max}^{MeOH} *(nm)*	ε_{mM}	*Elemental analysis*[a]							
						Formula	*Calculated*			*Found*			
							C	*H*	*N*	*C*	*H*	*N*
[b]1a	Water	250–252	+141[c]	277	34.8	$C_{12}H_{12}BrN_3O_4$[d]	42.12	3.53	12.27	42.15	3.50	12.22
1b	80% EtOH	133–135	−16.2[e] → −15.4	274	30.9	$C_{20}H_{20}BrN_3O_8$	47.07	3.95	8.23	47.10	3.92	8.18
[f]2a	Water	254–256	−143[g] → −103	277	35.1	$C_{12}H_{12}BrN_3O_4$[h]	42.12	3.53	12.27	42.20	3.60	12.3
2b	95% EtOH	132–134	+15.6[i] → +14.6	274	31.2	$C_{20}H_{20}BrN_3O_8$	47.07	3.95	8.23	47.12	3.98	8.16
[j]3a	MeOH	223–224	−65.6[k] → −65.2	273	26	$C_{12}H_{14}BrN_3O_7$[l]	41.87	4.10	12.20	41.75	4.04	12.12
3b	95% EtOH	166–118	−28.2[m] → −26.3	272	28.5	$C_{18}H_{20}BrN_3O_7$[n]	45.97	4.28	8.93	46.08	4.28	8.75
3c	Aq. EtOH–acetone	126–128°	−4.61[p] → −4.28	232 276	55.3 31.8	$C_{33}H_{24}BrN_3O_7$[q]	62.08	3.79	6.58	62.04	3.80	6.69
[r]5	Aq. AcOH–acetone	112–114		273	27	$C_{11}H_{10}BrN_3O_3$[s]	42.33	3.46	13.46	42.15	3.21	13.73

[a]Sample dried for 2 h at 110°/0.1 torr, unless otherwise specified. [b]3D-3,5/4,6-Tetrahydroxy-1,2-cyclohexanedione (p-bromophenyl)osotriazole, prepared from 1D-*chiro*-inositol *via myo*-inosose-1 phenylosazone[5]. [c]At c 0.053 in water; rotation measured at 2 min after dissolution, unless otherwise indicated. [d]Sample dried at room temperature was the trihydrate. *Anal.* Found: C, 36.50; H, 4.20; N, 10.80. [e]At c 0.255 in chloroform, after 24 h. [f]3L-3,5/4,6-Tetrahydroxy-1,2-cyclohexanedione (p-bromophenyl)osotriazole, prepared from 1L-*chiro*-inositol *via* D-*myo*-inosose-1 phenylosazone[5]. [g]At c 0.045 in water, after 24 h. [h]Sample dried at room temperature was the trihydrate. *Anal.* Found: C, 36.60; H, 4.15; N, 10.52. [i]At c 0.214 in chloroform, after 24 h. [j]3D-3,5/4-Trihydroxy-1,2-cyclohexanedione (p-bromophenyl)osotriazole, prepared *via* the phenylosazone, from (+)-*proto*-quercitol[5]. [k]At c 0.194 in pyridine, after 24 h. [l]Sample recrystallized from methanol, and dried at room temperature, had an analysis corresponding to that calculated for the monohydrate; however, recrystallization from water gave the sesquihydrate. *Anal.* Found: C, 40.81; H, 4.25; N, 11.72. [m]At c 0.190 in chloroform, after 24 h. [n]Sample recrystallized from 95% EtOH and dried for 1 h at 78°/0.1 torr had an analysis corresponding to that calculated for the monohydrate. [o]The compound shrinks at 116°. [p]At c 0.825 in chloroform, after 24 h. [q]The product was recovered by extraction into chloroform; it was dried for 2 h at 78°/0.1 torr, but final removal of traces of moisture was difficult. [r][2-(p-Bromophenyl)-4-C-formyl-2H-1,2,3-triazol-5-yl]acetaldehyde; the n.m.r. spectrum of **5** (Me_2SO-d_6) showed two, non-equivalent, aldehyde protons, at τ −0.1 and 1.40. Treatment of **5** with phenylhydrazine gave pale-yellow crystals, m.p. 184–189° (from aq. AcOH), presumably having a bis(phenylhydrazone) structure; λ_{max}^{MeOH} 232 (ε_{mM} 21); 270 (~19) and 347 nm (~44); n.m.r. data: (Me_2SO-d_6) τ −0.64 (non-chelated N–H) and 1.58 ($-\overset{|}{\underset{|}{C}}-H$); ν_{max}^{KBr} 3300m, 3290w (OH, NH), 1646w, 1575w (C=N), 1600s, 1490s (phenyl ring), 1530 (N–H bending), 1160s (Ph–N); fingerprint region; 1442m, 1420m, 1402m, 1355s, 1340m, 1310w, 1260s, 1160s, 1100m, 1080s, 1070s, 1040m, 1030m, 1012m, 968s, 915, 890m, 860m, 830s, 810w, 800w. 780w. 755s, 700s, and 665w cm^{-1}. [s]The compound was difficult to dry; it was dried for 2 h at 78°/0.1 torr, and then had an analysis corresponding

gave tetraacetate (**1b**+**2b**) as colorless prisms; 0.12 g (60%); m.p. 199–200°; $\lambda_{\max}^{\text{MeOH}}$ 274 nm (ε_{mM} 31.3); R_F 0.38 in 3:1:1 (v/v) benzene–ethyl acetate–acetic acid (solvent B) with spray A and heating, dark spot.

Anal. Calc. for $C_{20}H_{20}BrN_3O_8$: C, 47.07; H, 3.96; N, 8.24. Found: C, 46.90; H, 3.90; N, 8.20.

Tetrabenzoate (**1c**+**2c**). — A solution of osotriazole (**1a**+**2a**) (300 mg) in pyridine (5 ml) at 50° was cooled to 30° and treated, with stirring, with benzoyl chloride (1.5 ml); the mixture was stirred for a further 30 min, and poured into 5% aqueous potassium carbonate solution (50 ml). The resultant syrup or semi-solid was separated by decantation, washed with water, and stirred with 1:1 (v/v) methanol–acetone (30 ml) at room temperature. The product solidified within 10 min; after short cooling in an ice-bath, it was filtered off, and washed with cold methanol; yield of crude (**1c**+**2c**) ~475 mg. A sample (450 mg) was dissolved in 1:1 (v/v) methanol–chloroform, filtered through a layer of carbon, and the filtrate concentrated to incipient crystallization, giving white crystals (yield 420 mg). A sample dried for 2 h at 110°/0.1 torr had m.p. 226–228°; $\lambda_{\max}^{\text{MeOH}}$ 231 (ε_{mM} 56.3) and 276 nm (32.3).

Anal. Calc. for $C_{40}H_{28}BrN_3O_8$: C, 63.33; H, 3.72; N, 5.53. Found: C, 63.23: H, 3.60; N, 5.60.

*2-(*p*-Bromophenyl)-2H-1,2,3-triazole-4,5-dicarboxaldehyde* (**4**). — *p*-(Bromophenyl)osotriazole (**1a**+**2a**) (0.31 g, 1.1 mmoles) in water (15 ml) was stirred with aqueous sodium metaperiodate solution[6] (15 ml, 0.71 g, 3.6 mmoles) for 4 h at room temperature, and kept for 20 h at room temperature. Crude dialdehyde (0.2 g, m.p. 152–154°) separated, and was filtered off and successively recrystallized from aqueous acetone (carbon) and acetone (with concentration and cooling), to give lustrous prisms of **4**, m.p. 158–160°. A twice-recrystallized sample was dried for 2 h at 110°/0.1 torr and analyzed.

Anal. Calc. for $C_{10}H_6BrN_3O_2$: C, 42.87; H, 2.16; N, 14.99. Found: C, 42.69; H, 2.08; N, 14.86.

T.l.c. in solvent B, followed by alkaline silver nitrate spray and heating, showed a dark spot at R_F 0.77; $\lambda_{\max}^{\text{MeOH}}$ 274 nm (ε_{mM} 27); p.m.r. data (Me_2SO-d_6): τ 0.8 (two, equivalent, aldehyde protons).

Treatment of **4** with phenylhydrazine gave pale-yellow crystals, m.p. 145–147° (from aq. ethanol), presumably having a bis(phenylhydrazone) structure; $\lambda_{\max}^{\text{MeOH}}$ 245 (ε_{mM} 22.3), 295 (18.6), and 363 nm (44.9); n.m.r. data (Me_2SO-d_6): τ −1.12 (non-chelated N–H) and 1.60 $(-\overset{|}{\underset{|}{C}}-H)$; $\nu_{\max}^{\text{KBr}}$ 3440s, 3320w (OH, NH), 1595s, 1490s (phenyl ring), 1530m (N–H bending[7]), 1140s (Ph–N)[7]; fingerprint region: 1440m, 1410w, 1380w, 1340m, 1300w, 1285w, 1260s, 1225w, 1140s, 1070s, 1010w, 995w, 970s, 902s, 888m, 845m, 755s, 700m, and 670w cm^{-1}. The u.v. and visible spectra of this bis(phenylhydrazone) resembled those of bis(phenylhydrazones) from glyoxal or pyruvaldehyde[8].

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