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Note

Symmetrical phenylosotriazoles from inositols*†

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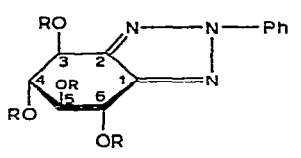
As part of a study of the chemistry of inositol derivatives[1,2], the D (**1a**), L-, and DL- forms of 3,5/4,6-tetrahydroxy-1,2-cyclohexanedione phenylosotriazole (1,2-diketo-*myo*-inositol phenylosotriazole) have been prepared from the corresponding inosose phenylosazones using mercuric acetate; the yields are better (40–50%) than those obtained with the cupric sulfate reagent[3].

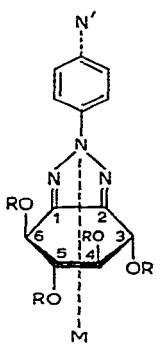
Based on p.m.r. studies, inositol phenylosotriazoles are either (*1*) symmetrical, having a simple, two-fold axis of symmetry (C_2) and, hence, equivalence of the protons interchanged by these symmetry operations (*e.g.*, in the AA'BB' system, for **1a** and its esters, and the analogous *p*-bromophenylosotriazoles[2]), or (*2*) non-symmetrical. The latter group involves alkyl-substituted inositol phenylosotriazoles and those having a methylene group in the cyclohexane ring.

The inositol phenylosotriazoles were prepared from 1D- or 1L-*chiro*-inositol *via* the corresponding inosose osazones[4], and numerous esters (**1b–j**) were prepared. The



1 (D form)
2 refers to the L form)

a R = H
b R = Ac
c R = C_2H_5CO
d R = n-C_3H_7CO
e R = i-C_3H_7CO
f R = i-C_4H_9CO
g R = $C_5H_{11}CO$
h R = Me_3CCO
j R = Bz



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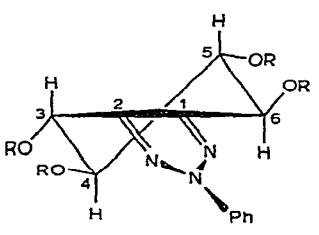

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*Dedicated to Dr. Horace S. Isbell, in honor of his 75th birthday.

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

osotriazole **1a** (and the L and DL forms) was degraded by sodium metaperiodate to the known 2-phenyl-2*H*-1,2,3-triazole-4,5-dicarboxaldehyde[3].

The p.m.r. spectra of inositol phenylosotriazole (after decoupling of the hydroxyl protons with a trace of strong acid) and of a variety of ester derivatives (Table I) revealed the presence of a simple, two-fold axis of symmetry (3), and the ring-proton signals were symmetrical about a midpoint, making them a new example of the AA'BB' system[5–9]. Only the p.m.r. spectrum of the DL-tetraisobutyrate showed the maximum resolved lines (Fig. 1; AA' 8 lines, and BB' 8 lines) of the 24 transitions required for an AA'BB' system.

The molecular parameters (L, M, and N) needed for calculating the coupling constants and chemical shifts ($\nu_0\delta$, see Tables II and III) were calculated by the procedure of Pople and co-workers[5,10], and parameter K was deduced from the equation of Dischler and Englert[11], as applied by Abraham[12] and by Garbisch[7].

From inspection of Dreiding models, it appeared that the favoured conformation for the tetraisobutyrate was the half-chair conformation $^5H_4$ (**4**). The $J_{BB'}$ value of 10.0 Hz for H-4 and H-5 indicates a *trans*-diaxial orientation; the $^5H_4$ conformation would also have H-5 and H-6 axial, and this fits the value ($J_{AB'}$ 8.5 Hz) calculated. The small coupling-constants for H-3/H-6 ($J_{AA'}$ 1.0 Hz) and H-4/H-6 ($J_{AB'}$ 0.5 Hz) indicate the influence of the neighbouring, planar osotriazole ring, and

TABLE I

OBSERVED CHEMICAL SHIFTS OF INOSITOL PHENYLOSOTRIAZOLES

Compound	*Solvent*	*Chemical Shift*[a] (*Hz*)	*Approximate chemical shift* (δ, *p.p.m.*)[b]	
			H_A *protons (center)*	H_B *protons (center)*
1a+2a	$(CD_3)_2SO$–D_2O[c]	65.9	3.77	4.85
1a+2a	$(CD_3)_2SO$–CF_3CO_2H	65.2	3.56	4.65
1a+2a	D_2O–NaOMe	64.8	3.78	4.86
1a+2a	C_5D_5N	63.3	4.44	5.39
2b	$CDCl_3$	42.4	5.63	6.33
2b	$CDCl_3$+Eu(fod)$_3$[d]	44.0	6.05[d]	6.76[d]
2b	CF_3CO_2H	40.4	5.80	6.46
1b+2b	$(CD_3)_2SO$	43.0	5.70	6.41
1c+2c	$CDCl_3$	44.0	5.60	6.33
1d+2d	$CDCl_3$	42.9	5.62	6.35
1d+2d	$CDCl_3$+Eu(fod)$_3$ (5%)	43.9	5.95	6.66
1e+2e	$CDCl_3$	43.1	5.68	6.40
1f+2f	$CDCl_3$	43.5	5.65	6.38
1g+2g	$CDCl_3$	44.0	5.66	6.38
1h+2h	$(CD_3)_2SO$	30.6	5.23	5.71
1j+2j	$CDCl_3$	35.0	6.23	6.82

[a]Calculated chemical shifts ($\nu_0\delta$). [b]Measured from tetramethylsilane between transitions AA' (lines 1,2; 9,6; 7,12; 3,4) and BB' (lines 1,2; 9,6; 7,12; 3,4), respectively. [c]Addition of 5% of $Eu(Cl)_3$ in D_2O caused broadening of the quartet lines. [d]Original solution of **2b** (180 mg in 0.85 ml of $CDCl_3$) was mixed with Eu(fod)$_3$ (25 mg); the observed, lanthanide chemical-shift was compared to the chemical shift of **2b** in chloroform only.

TABLE II

PARAMETERS USED FOR CALCULATING COUPLING CONSTANTS (J) AND CHEMICAL SHIFTS ($\nu_0\delta$) OF THE PHENYLOSOTRIAZOLE TETRABENZOATE **1j–2j**

Parameters[a]	*Transition*	*Observed frequency (Hz)*		*Observed value from spectra (Hz)*		*Assignment*	*Coupling constants (J) and chemical shifts ($\nu_0\delta$) (Hz)*					
		H_A *protons*	H_B *protons*	H_A *protons*	H_B *protons*		H_A *protons*		H_B *protons*		H_A+H_B *average*	
N 5.5	1→3; 2→4	405	363.8	21.0	−20.2	$J_{AB}+J_{AB'}$	$J_{AA'}$	0.3	$J_{AA'}$	−0.15	$J_{AA'}$	0.0075
M −6.7	9→10; 11→12	403	366.0	19.0	−18.0	$J_{AA'}+J_{BB'}$	$J_{BB'}$	7.0	$J_{BB'}$	7.35	$J_{BB'}$	7.17
K 7.3	2→4; 7→8	401.8	367.6	17.8	−17.2	$J_{AA'}+J_{BB'}$	J_{AB}	5.11	J_{AB}	5.35	J_{AB}	5.23
$(M^2+L^2)^{1/2}$	9→11; 10→12	399.5	369.6	15.5	−15.0							
L 5.23	(calc.)					$J_{AB}-J_{AB'}$	$J_{AB'}$	0.4	$J_{AB'}$	0.35	$J_{AB'}$	0.375
$(\nu_0\delta^2+N^2)^{1/2}$	1+3; 2+4	394.5	375	10.5	−9.5		$\nu_0\delta$	35.8	$\nu_0\delta$	34.6	$\nu_0\delta$	35.2

[a]Parameters L, M, N, and K were calculated according to Refs. 5–7 and 10–12.

TABLE III

CALCULATED COUPLING-CONSTANTS (J) AND CHEMICAL SHIFTS ($\nu_0\delta$) IN Hz OF INOSITOL PHENYLOSOTRIAZOLES

1a–2a[a]		1a–2a[b]		2b(p-*Br*)[c,d]		1b(p-*Br*)[c,d]		1b[d]		2b[d]	
$J_{AA'}$	1.9	$J_{AA'}$	1.45	$J_{AA'}$	−0.3	$J_{AA'}$	−0.2	$J_{AA'}$	−0.1	$J_{AA'}$	−0.05
$J_{BB'}$	7.6	$J_{BB'}$	6.55	$J_{BB'}$	8.4	$J_{BB'}$	8.9	$J_{BB'}$	8.8	$J_{BB'}$	9.4
J_{AB}	9.6	J_{AB}	8.10	J_{AB}	6.5	J_{AB}	6.6	J_{AB}	6.7	J_{AB}	6.4
$J_{AB'}$	−1.8	J_{AB}	−0.8	$J_{AB'}$	0.5	$J_{AB'}$	0.4	$J_{AB'}$	−0.1	J_{AB}	0.2
$\nu_0\delta$	65.9	$\nu_0\delta$	65.2	$\nu_0\delta$	42.6	$\nu_0\delta$	42.9	$\nu_0\delta$	43.9	$\nu_0\delta$	42.4

[a]In Me_2SO-d_6–D_2O. [b]In Me_2SO-d_6–CF_3CO_2H. [c]Prepared according to Ref. 1. [d]In $CDCl_3$.

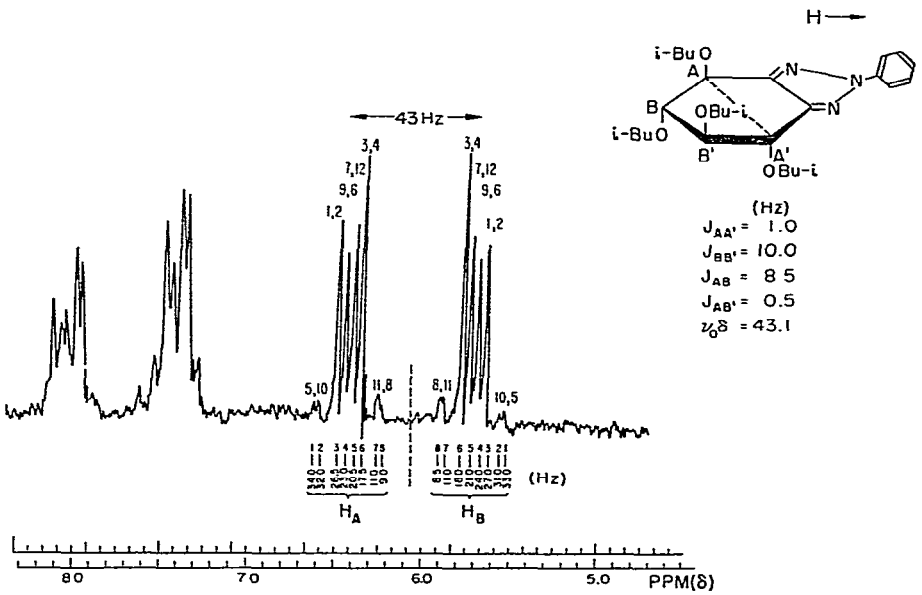

Fig. 1. P.m.r. spectrum (60 MHz, $CDCl_3$) of the ring protons of DL-inositol phenylosotriazole tetraisobutyrate. The transitions 1→3, 9→12, 1→3→7, and 2→4→8 were used to calculate ν_A and ν_B, and the J values (see Tables II and III).

are consistent with the half-chair conformation, which is isoconformational with a half-chair conformation of the cyclohexene ring[13,14]. Using values calculated from an electron-diffraction study of cyclohexene[15], the dihedral angles (ϕ) for vicinal hydrogens in **4** (compared with values, shown in parentheses, deduced by application of the Karplus equation[16]) were $\phi_{5,6}$ 150° (125), $\phi_{4,5}$ 57° (66), and $\phi_{3,4}$ 47° (50). The correlation fits only approximately with one of two possible half-chair conformations of the tetraisobutyrate shown in **4**.

For the inositol phenylosotriazoles in methyl sulphoxide-d_6 (Table III), the coupling constants (J_{AB}) of 9.6 and 8.1 Hz for H-5 and H-6 indicate a *trans*-diaxial orientation and an almost exclusive existence in the half-chair conformation, in

contrast to most of the esters (Table I), which have J_{AB} values of 5–7 Hz; the isobutyrate is exceptional in having J_{AB} 8.5 Hz. Literature[17,18] J values for *trans*-diaxial protons are in the range 5–9.6 Hz.

In addition to the expected solvent and lanthanide shifts, the chemical shifts for H_A and H_B of the inositol phenylosotriazoles (Table I) reflect stereoelectronic factors. With increase in length of the carbon chain in the ester group, the chemical shift is generally lower, and electronic deshielding of the protons by the ester group (particularly by the benzoate) is apparent (Table I). For example, the observed chemical shifts of H_A and H_B of the unsubstituted osotriazole **1a** are δ 3.77 and 4.85 ($\nu_0\Delta_{AB}$ ~65 Hz; Me_2SO-d_6–D_2O), δ 5.70 and 6.41 ($\nu_0\Delta_{AB}$ ~43 Hz; Me_2SO-d_6) for the DL-tetraacetate, and δ 6.23 and 6.82 ($\nu_0\Delta_{AB}$ ~35 Hz) for the DL-tetrabenzoate.

Proton shielding can arise from molecular charge-distribution, the electric field, magnetic anisotropy, dispersion forces, ring currents, and hybridization[19], and, as found for acyclic alkanes, on C–H bond electrons[20].

Deshielding would be expected[20] with progressive replacement of a C–H bond by a C–C bond, as in the sequence $-CH_3$, $C-CH_2-$, and $(C-)_2-CH-$. For the esters in Table I, the increased deshielding of H_A and H_B by the adjacent ester group in the series acetate–hexanoate is only slight and contrasts with the appreciable deshielding observed for the DL-tetrakis(trimethylacetate) (see Table I). It was also expected that H-3 and H-6 in **1a** and its esters would be deshielded most by the osotriazole ring, whereas H-4 and H-5 would be less shielded in the half-chair conformation **4**. Additional deshielding in the unsubstituted inositol phenylosotriazoles (*e.g.*, **1a** in

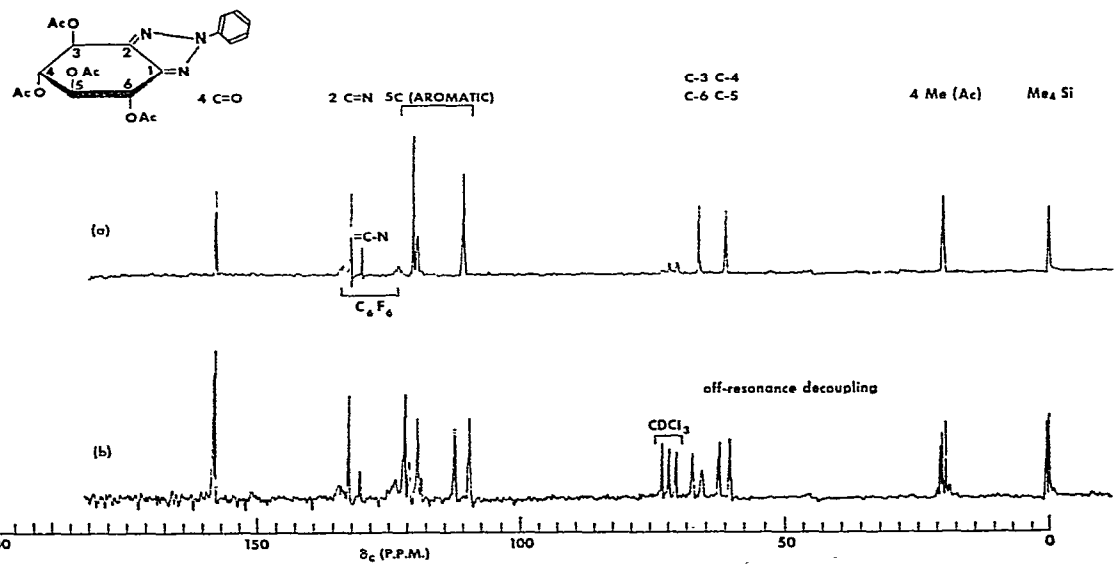

Fig. 2. Fourier-transform, ^{13}C-n.m.r. spectra ($CDCl_3$, 22.6 MHz) of D-inositol phenylosotriazole tetra-acetate (a) with proton decoupling, and (b) with off-resonance, continuous-wave, proton decoupling.

Table I) might also arise by the formation of intramolecular hydrogen bonds between HO-3 or HO-6 and N-1 or N-2 of the triazole ring; a similar effect has been observed in the phenylosotriazoles of sugars[21].

The symmetrical structure (AA'BB' pattern) of L-inositol phenylosotriazole tetra-acetate is indicated by the simplicity of its proton-decoupled ^{13}C-n.m.r. spectrum (chloroform-*d*, Fig. 2a). To facilitate chemical-shift assignments, a partially decoupled (off-resonance decoupling) spectrum (Fig. 2b) was also recorded. The two singlets (Fig. 2a) at δ_C 71.4 and 66.2 p.p.m. must have derived from two equivalent pairs (C-3,C-6 and C-4,C-5, respectively) of ^{13}C; on partial decoupling (Fig. 2b), these singlets became doublets, thus indicating their association with methine carbon nuclei. The tentative chemical-shift assignment of a pair C-3,C-6 (Fig. 2a) to lower field (δ_C 71.4 p.p.m.) reflects the influence of the neighbouring phenylosotriazole group.

Whereas the i.r. spectra of the D (**1a**) and L forms of inositol phenylosazone were identical, that of the DL form showed extra bands at 1290, 1280, and 1250 cm^{-1}; bands at 1220, 1200, and 1110 cm^{-1} were absent (characteristic doublets at 980 and 890 cm^{-1}, and characteristic triplets at 980, 770, and 660 cm^{-1} were observed for the D and L forms only), and band intensities in the region 1350–1250 cm^{-1} were different from those of the D and L forms.

Essentially similar results were obtained for the tetra-acetates of the D and L forms, particularly in the regions 1400–1300 and 850–600 cm^{-1}. The DL form did not show clear bands at 1030, 1010, 950, and 850 cm^{-1}, or the doublet at 1530 cm^{-1} observed for the D and the L forms.

EXPERIMENTAL

Materials. — DL-3,5/4,6-Tetrahydroxy-1,2-cyclohexanedione bis(phenylhydrazone) (DL-*myo*-inosose 1-phenylosazone), and the D and L enantiomorphs were prepared and purified as already reported[4].

N.m.r. spectra were recorded* with Varian A-6 60-MHz and Bruker 90-MHz spectrometers. Fourier transform, ^{13}C-n.m.r. spectra were recorded using a Bruker HFX-11 instrument, equipped with a pulse amplifier (model B-SV-2P) operating at 22.6 MHz (f_1), a phase-modulated, broad-band decoupling amplifier (model B-SV-2) at 90 MHz (f_2), and internal, heteronuclear field-frequency stabilization on the ^{19}F signal of hexafluorobenzene at 84.7 MHz (f_0).

A solution of D-inositol phenylosotriazole tetra-acetate (180 mg) in $CDCl_3$–C_6F_6–Me_4Si (1 ml, 9:1:1) was excited either in the single-coil, or crossed-coil modes with pulse-widths (f_1) of 40 μsec. For confirmation of spectra assignments by off-resonance, proton decoupling (ORPD technique)[22] was used. ^{13}C chemical shifts (p.p.m. +0.1 p.p.m. from tetramethylsilane) were measured by means of a programme written in symbolic coding for the 1074-PDP8E computer combination, and were

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

4Me (Ac, 20.7, 20.9), C-4,C-5 (66.2), C-3,C-6 (71.4), 5C (aromatic, 119.5, 128.7, 129.5), =C–N (139.9), 2C=N (142.2), 4C=O (169.7, 170.0).

Optical rotations were determined (1-dm path length) 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 with a Beckman DK-2 or Cary 14 spectrophotometer. Analyses were made by Craig Olson of the Spectrochemical Analysis Section of this Division.

DL-*3,5/4,6-Tetrahydroxy-1,2-cyclohexanedione phenylosotriazole.* — To a warm solution (85–90°) of mercury(II) acetate (25.5 g, 80 mmoles) in 5M acetic acid (200 ml), finely ground, crude DL-3,5/4,6-tetrahydroxy-1,2-cyclohexanedione bis(phenylhydrazone)[4] (7.2 g, 20 mmoles) was introduced portionwise, with stirring, during 5 min. Stirring was continued for an additional 10 min, 10 g of decolourizing carbon was then added, the suspension was stirred at 85° for 5 min and filtered while hot, and the insoluble material washed with warm, 5M acetic acid (50 ml). After the combined filtrate and washings had cooled, the precipitated mercury(I) acetate was collected, and the dark filtrate was treated with additional decolourizing carbon (5 g). The almost clear filtrate was passed through a column of Amberlite IR-120(H^+) resin (150 ml), which was then washed with water (600 ml); the eluate should not produce turbidity with methanolic phenylhydrazine solution [a very sensitive test for mercury(I) and (II) ions]. The eluate was mixed with glacial acetic acid (50 ml), concentrated at 60° to 120–150 ml, and cooled to give the title compound (700 mg), m.p. 276–277°. Concentration of the mother liquors and cooling gave more product (total 2.1–2.5 g, 40–47%). Recrystallisation from methanol gave material having m.p. 277–278°, λ_{max}^{MeOH} 273 nm (ε 34.2); lit.[3] m.p. 278–282° (dec.).

When prepared in a similar manner, the D form had m.p. 234–235°, $[\alpha]_D^{25}$ +108° (*c* 0.2, pyridine), and the L form had m.p. 233–234°, $[\alpha]_D^{25}$ −105° (*c* 0.18, pyridine).

Ester derivatives. — A mixture of the foregoing DL-osotriazole (0.1 g), acetic anhydride (5 ml), and pyridine (1 ml) was stirred at 95° until dissolution was complete (2 min), and then kept for 2 h at room temperature. Decomposition with ice–water, followed by recrystallisation of the precipitate from 80% aqueous ethanol (carbon), gave the tetra-acetate as colourless needles (0.15 g, 70%), m.p. 193–195°, λ_{max}^{MeOH} 274 nm (ε 31.5); lit.[3] m.p. 194–195°.

In a similar manner, the following esters were prepared*: D-tetra-acetate, m.p. 146–147° (from 80% methanol), λ_{max}^{MeOH} 272 nm (ε 31.1), $[\alpha]_D^{25}$ −23° (*c* 0.02, chloroform); L-tetra-acetate, m.p. 145-146°, $[\alpha]_D^{25}$ +21°; DL-tetrapropionate, m.p. 97–98° (from 80% ethanol), λ_{max}^{MeOH} 272 nm (ε 31.2); DL-tetrabutyrate, m.p. 103–104° (from 90% ethanol), λ_{max}^{MeOH} 273 nm (ε 29.6); DL-tetraisobutyrate, m.p. 145-146° (from methanol), λ_{max}^{MeOH} 273 nm (ε 29.4); DL-tetraisopentanoate, m.p. 120–122° (from methanol), λ_{max}^{MeOH} 273 nm (ε 29.2); DL-tetrahexanoate, m.p. 80–81° (from methanol), λ_{max}^{MeOH} 273 nm (ε 29.1); DL-tetrakis(trimethylacetate), m.p. 273–275° (from methanol), λ_{max}^{MeOH} 273 nm (ε 29.5).

*All new compounds gave satisfactory elemental analysis.

The tetrabenzoate, prepared conventionally with pyridine and benzoyl chloride, had m.p. 260–262° (from aqueous ethanol), λ_{max}^{MeOH} 232 (ε 55.7) and 277 nm (ε 32.6).

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