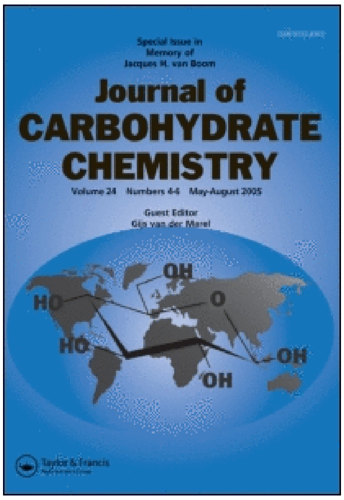

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CIRCULAR DICHROISM OF POLYACETOXYALKYLPYRAZOLO-(3,4-b)QUINOXALINES

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ABSTRACT

The circular dichroism spectra of a series of polyacetoxyalkylpyrozolo(3,4-b)quinoxalines showed multiple Cotton effects with opposite sign to that of the corresponding polyhyroxylalkyl analogs having the same configuration of the side chain. Polyacetoxyalkyl analogs having the S chirality at the C-1' in the Fischer projection formula showed a positive Cotton effect centered at the long-wavelength absorption and those possessing the R chirality showed a negative Cotton effect at the same region. The sign of the Cotton effect at the long-wavelength absorption is in accord with the rotation at the sodium D line.

INTRODUCTION

The correlation between optical rotation at the sodium D line and the configuration at the asymmetric centers in carbohydrates has been formulated in useful rules, especially those

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of Hudson.[1,2] For saccharide heterocyclic derivatives having more than one asymmetric carbon, it was found that the sign of rotation at the sodium D line depends only on the configuration of the asymmetric carbon atom α to the heterocycle ring. This was used for the determination of the configuration of the asymmetric carbon atom; C-2 of benzimidazoles[2] and C-3 of phenylosotriazoles.[3-5] 1-Phenyl-3-(polyhydroxyalkyl)pyrazolo-(3,4-b)quinoxaline analogs[6] did not show identical correlation between optical rotation at the sodium D line and the α asymmetric carbon atom (C-4 of the original sugar). However, their circular dichroism (CD) spectra indicated direct correlation between the sign of the Cotton effect at the long-wavelength absorption and the configuration at the α asymmetric carbon atom (C-1'). This allowed the determination of the configuration of C-4 of the original sugar.

Optical rotatory dispersion (ORD) and circular dichroism spectral studies of polyhydroxyalkyl benzimidazoles, quinoxalines,[7] and phenylosotriazoles[8] indicated identical correlation between the sign of the Cotton effect and the configuration at the α asymmetric carbon atom. This allowed the determination of the configuration of the α asymmetric carbon atom (C-1'), C-2 and C-3 of the original sugar, from the Cotton effect.

Polyacetoxyalkyl derivatives of benzimidazoles[7] and glycosulose phenylosotriazoles,[8] showed a Cotton effect of the same sign as the nonacetylated analogs. In the present work the circular dichroism spectra of a series of 1-phenyl-3-(polyacetoxyalkyl)pyrazolo-(3,4-b)quinoxalines 1-5, were studied and correlated to the configuration of the α asymmetric carbon (C-1') in these compounds.

The CD spectra of compounds 1-5 in 1,4-dioxane (Fig. 1) showed a wide Cotton effect at the long-wavelength absorption (340-490 nm). Compounds 1 and 3 possessing S chirality at the α asymmetric carbon (C-1') because the 1'-OAc group is to the

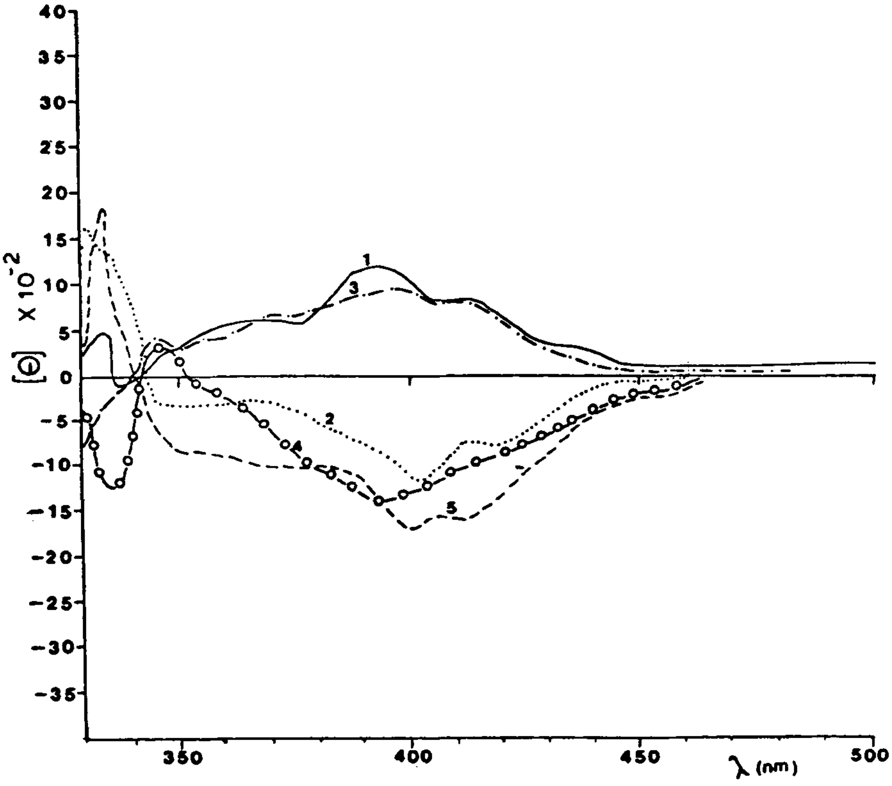
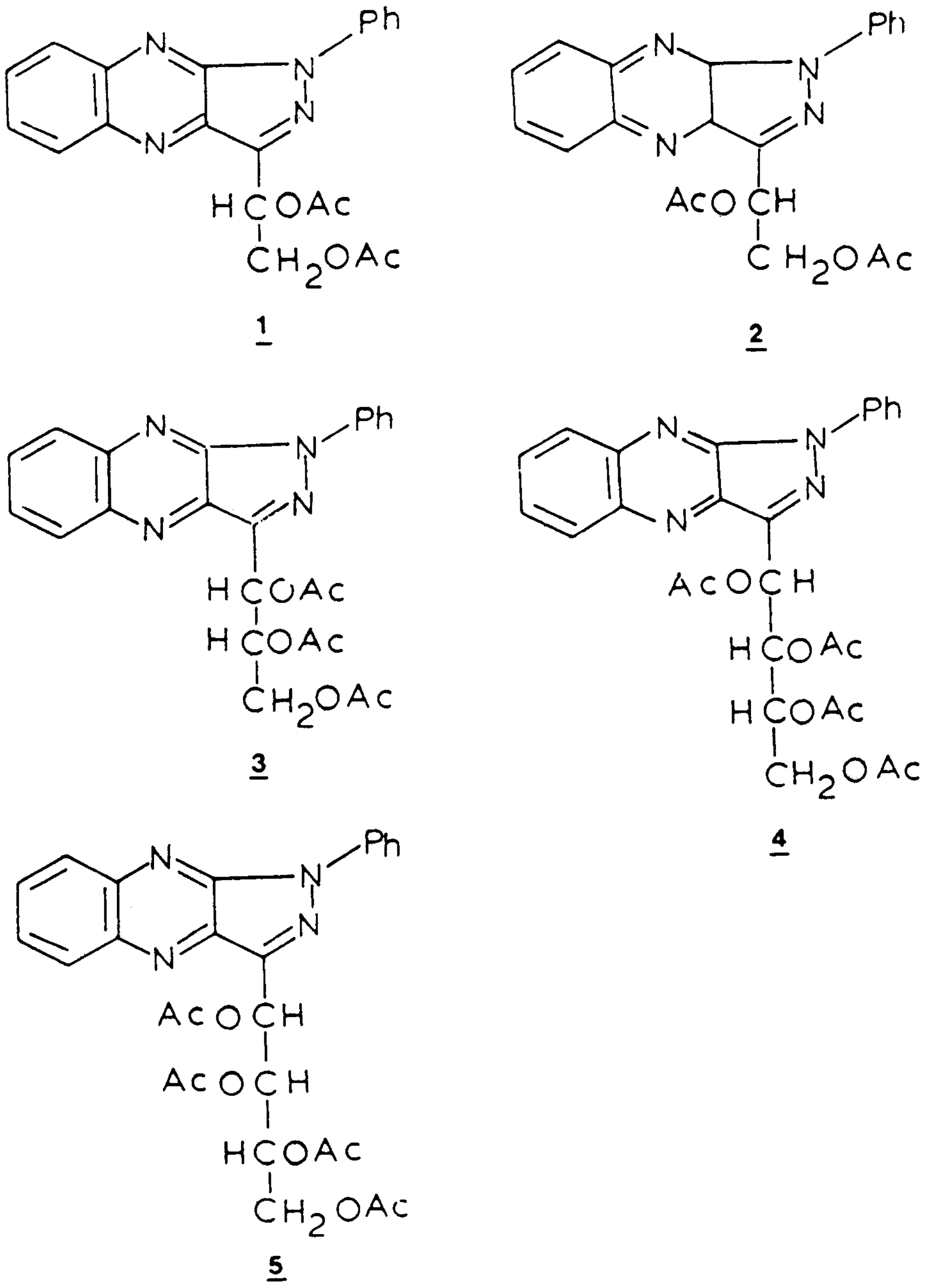


FIG. 1. CD spectra, in 1,4-dioxane of:
1, (———) 3-(di-O-acetyl-D-*glycero*-dihydroxyethyl)-1-phenyl-pyrazolo(3,4-b)quinoxaline;
2, (•••••) 3-(di-O-acetyl-L-*glycero*-dihydroxyethyl)-1-phenyl-pyrazolo(3,4-b)quinoxaline;
3, (—•—•—) 1-phenyl-3-(tri-O-acetyl-D-*erythro*-glycerol-1-yl)-pyrazolo(3,4-b)quinoxaline;
4, (—o—o—) 1-phenyl-3-(tetra-O-acetyl-D-*arabino*-1-yl)pyrazolo-(3,4-b)quinoxaline;
5, (– – –) 1-phenyl-3-(tetra-O-acetyl-D-*lyxo*-tetritol-1-yl)-pyrazolo(3,4-b)quinoxaline.


Ph
N
N
N
N
HCOAc
CH2OAc
1
AcOCH
CH2OAc
2
HCOAc
HCOAc
CH2OAc
3
AcOCH
HCOAc
HCOAc
CH2OAc
4
AcOCH
AcOCH
HCOAc
CH2OAc
5

SCHEME 1

right in the Fischer projection formula, showed a positive Cotton effect. Compounds 2, 4 and 5 possessing R chirality, showed a negative Cotton effect at the same region. This observation is opposite to the Cotton effect sign of the non-acetylated analogs having the same configuration of the polyhydroxyalkyl chain. Other asymmetric centers remote from the base moiety affect only the amplitude at this region. Compounds 4 and 5 having the arabino and lyxo configuration, respectively, showed higher amplitude than compound 2 having the L-glycero configuration.

The ultraviolet absorption spectra of 1-phenyl-3-(polyhydroxyalkyl)pyrazolo(3,4-b)quinoxaline analogs[9] have three characteristic absorption bands at λ 276, 335, and 410 nm. The ultraviolet absorption spectra of compounds 1-5 (Table 1) showed the same absorption bands and a shoulder at λ 230-233 nm. The absorption in the ultraviolet is much more intense than in the visible region. The λ 410 nm absorption is proportional to the concentration and is associated with n-II* transition.[9-12]

The CD absorption at the long-wavelength region is manifested by the configuration at the α asymmetric carbon for 1-phenyl-3-(polyhydroxyalkyl)pyrazolo(3,4-b-)quinoxaline analogs and their polyacetoxyalkyl derivatives 1-5. The observed sign inversion of the Cotton effect at the long-wavelength absorption for compounds 1-5, compared to the CD spectra of their unsubstituted analogs,[6] cannot be ascribed to an acetyl group absorption, since the chromophoric ester group absorbs at low-wavelength region (200-300 nm).[10,13] However, it may be explained by the distortion of the intramolecular hydrogen bonding between the C-1' hydroxyl group and the aromatic heterocycle, and that between the hydroxyl groups.[14] This distorsion of the hydrogen bonding affects the shape of the molecule and its conformational population.

No correlation between the optical rotation at the sodium D line and the configuration of C-1' for the unsubstituted 1-phenyl-3-(polyhydroxyalkyl)pyrazolo(3,4-b)quinoxaline analogs could be obtained. However, the polyacetoxyalkyl derivatives 1-5 presented specific rotation $[\alpha]_D$ in accord with Hudson isorotation rules[1,2] and the generalized rotation rule for heterocyclic and aromatic compounds by El Khadem.[4] Compounds 1 and 3 having the S configuration at C-1' showed positive rotation at the sodium D line, and those having the R configuration (compounds 2, 4, and 5) showed negative rotation. In addition, the sign of rotation at the sodium D line was in accord with the sign of the Cotton effect at the long-wavelength region (see Table 1).

The different polarimetric results for compounds 1-5 and their unsubstituted analogs,[6] calls the attention to the fact

TABLE 1

Specific Rotation $[\alpha]_D$ (degrees) and UV Absorption data for Compounds 1-5.

Compound	$[\alpha]_D^{20}$,	$CHCl_3$	λ_{max}^{MeOH}	(log ε)
1	+83.0,	c 2.30	233sh (4.4), 267 (4.7), 334 (4.1), and 408 (3.6).	
2	-78.5,	c 2.24	233sh (4.3), 267 (4.6), 334 (4.0), and 408 (3.5).	
3	+60.7,	c 1.95	230sh (4.3), 264 (4.6), 333 (4.0), and 408 (3.5).	
4	- 9.34,	c 2.13	233sh (4.3), 267 (4.7), 335 (4.1), and 408 (3.6).	
5	-20.94,	c 2.13	233sh (4.4), 265 (4.7), 333 (4.1), and 408 (3.6).	

that caution should be taken in drawing conclusions from rotation at the sodium D line and from the Cotton effect in the CD spectra, as well.

EXPERIMENTAL

General. Melting points are uncorrected. UV absorption spectra were recorded with a Cary 17 Instrument. Circular dichroism measurements were recorded with a Cary 60 spectropolarimeter, at dynode voltage not > 0.75 kV at concentrations (33-39 μg/mL) at 22 °C. Mass spectra were obtained with AEI Ms 902 spectrometer. Combustion analyses were performed in the Chemistry Department, Purdue University, W. Lafayette, IN.

Preparation of 1-phenyl-3-(polyacetoxyalkyl)-pyrazolo-(3,4-b)quinoxalines. Each of the compounds; 3-(di-O-acetyl-D-glycero-dihydroxyethyl)-1-phenyl-(pyrazolo(3,4-b)quinoxaline[15] (1), 3-(di-O-acetyl-L-glycero-dihydroxyethyl)-1-phenylpyrazolo-(3,4-b)quinoxaline[15] (2), and 1-phenyl-3-(tri-O-acetyl-D-erythro-glycerol-1-yl)pyrazolo(3,4-b)quinoxaline[16] (3), were prepared by acetylation of the corresponding 1-phenyl-3-(polyhydroxyalkyl)-pyrazolo(3,4-b)quinoxaline analogs with a mixture of acetic anhydride and pyridine by the normal procedure. Each product was recrystallized several times from methanol and all had melting points in good agreement with the literature values.

1-Phenyl-3-(tetra-O-acetyl-D-arabino-1-yl)pyrazolo(3,4-b)-quinoxaline (4). This compound was prepared from 1-phenyl-3-(D-arabino-tetritol-1-yl)pyrazolo(3,4-b) quinoxaline[17] by the same procedure, recrystallized from methanol as yellow needles, mp 146-147 °C, mass spectral data: m/z 535 (4, M + 1), 534 (14, M), 372 (28, M - AcOH), 276 (26, BHCHOH, where B = 1-phenylpyrazolo(3,4-b)quinoxaline moiety), 245 (14, B), 77 (14, ph), and 43

(100, CH_3CO); accurate measurement of the molecular ion peak: Found: 534.1747 (Calc. 534.1751).

Anal. Calcd for $C_{27}H_{26}N_4O_8$: C, 60.65; H, 4.91; N, 10.49. Found: C, 60.43; H, 5.10; N, 10.50.

1-Phenyl-3-(tetra-O-acetyl-D-lyxo-tetritol-1-yl)pyrazolo-(3,4-b)quinoxaline (5). This compound was obtained as yellow needles from methanol, mp 164-166 °C, mass spectral data: m/z: 535 (4, M + 1), 534 (14, M), 372 (31, M - AcOH), 276 (20, BHCHOH), 275 (62, BCHOH), 245 (13, B), 77 (10, ph), and 43 (100, CH_3CO); accurate measurement of the molecular ion peak: Found: 534.1747 (Calc. 534.1751).

Anal. Calcd for $C_{27}H_{26}N_4O_8$: C, 60.65; H, 4.91; N, 10.49. Found: C, 60.80; H, 4.89; N, 10.44.

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