Rotatory Dispersion of Sugar Heterocycles. II. Benzimidazoles and Quinoxalines

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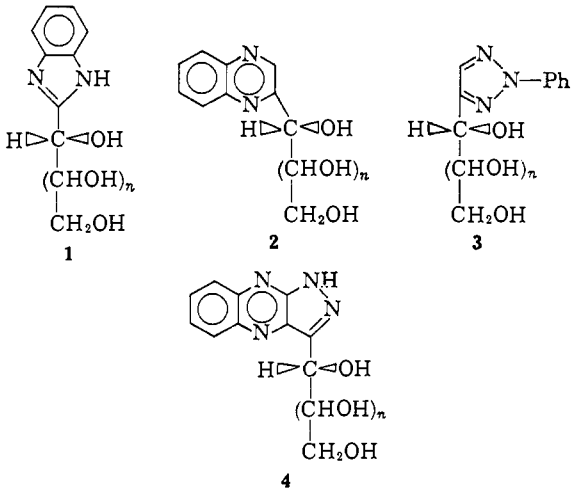
Abstract: The optical rotatory dispersion of polyhydroxyalkylquinoxalines can be correlated with absolute stereochemistry at the two asymmetric centers nearest the chromophore (C-3 and C-4 of the parent sugar). The rotatory dispersion of polyhydroxyalkylbenzimidazoles, -quinoxalines, and -2-phenyl-1,2,3-triazoles derived from sugars can be grouped into families of curves of decreasing rotatory power: *arabino*, *xylo*, and *ribo–lyxo*. This order is not greatly dependent on the hydrogen bond donating or accepting properties of the solvent but is destroyed by acetylation implying that intramolecular hydrogen bonding plays a significant role in conformational stabilization.

Several methods exist for incorporating one or more skeletal carbon atoms of sugars into aromatic heterocycles. Observation of Cotton effects in the rotatory dispersion or ellipticity extrema in circular dichroism spectra of such heterocyclic derivatives of sugars provides a potential method of assigning absolute stereochemistry.[1] We have found that *S* chirality at C-1′ of polyhydroxyalkylbenzimidazoles (**1**) and -quinoxalines (**2**) in methanol is associated with dextrorotation at long wavelength and with a positive Cotton effect centered about the longest wavelength optically active absorption maximum for each of these compounds. Lyle and Piazza have made a similar observation for osotriazoles[2] (**3**). Further effects of structure on conformational populations and rotatory power of the polyhydroxyalkyl chain are evident from comparison of a large number of benzimidazole and quinoxaline derivatives of sugars. Modifying effects of asymmetric centers more remote than C-1′ will be considered in the present communication.



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

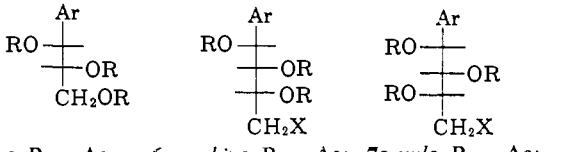
Benzimidazole derivatives have been used widely in characterizing aldonic acids, particularly the longer chain aldonic acids resulting from the addition of hydrogen cyanide to aldoses. The homologation introduces a new center of asymmetry which can be assigned *R* or *S* chirality on the basis of Richtmyer and Hudson's benzimidazole rule for long-wavelength rotatory power.[3]

Quinoxalines resemble phenylosazones as characterizing derivatives for sugars in that C-2 epimeric pairs of sugars give a single phenylosazone or quinoxaline derivative. Phenylosazones exhibit mutarotation[4] while the corresponding quinoxalines do not. Despite the complicating mutarotation, phenylosazones have been the favored sugar-characterizing derivative because of their good crystallizing properties and their extremely low solubility in water. The analogous quinoxaline derivatives are generally much more soluble in water and ethanol making their isolation more difficult in some cases. Quinoxalines are of particular interest as derivatives for characterizing sugars and for rotatory dispersion study because of the possibility of converting them into flavazoles[5] (**4**), derivatives which can in turn be used for characterization and rotatory dispersion work.

Results and Discussion

The quinoxaline isolation problem has been overcome by purifying the refractory quinoxalines as the fully acetylated derivatives and then saponifying in methanolic ammonia. In this way crystalline quinoxalines have been prepared for the first time from L-arabinose and L-sorbose. In addition noncrystalline, analytically pure acetylated quinoxalines have been prepared from L-rhamnose and L-arabinose.

Conformation of the Polyacetoxyalkyl Chain. It has been suggested[6] on the basis of the observed coupling constants that 2-(D-*arabino*-tetraacetoxybutyl)-



5a-*threo*, R = Ac; **b**, R = H

6a-*arabino*, R = Ac; X = OAc; **b**, R = H; X = OH; **c**, R = Ac; X = H

7a-*xylo*, R = Ac; X = OAc; **b**, R = H; X = OH; **c**, R = H; X = NHAc

(1) W. S. Chilton and R. C. Krahn, *J. Amer. Chem. Soc.*, **89**, 4129 (1967).

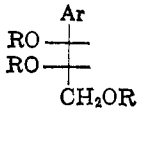
(2) G. G. Lyle and M. J. Piazza, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, Abstracts, paper C-10.

(3) N. K. Richtmyer, *Advan. Carbohydrate Chem.*, **6**, 175 (1951).

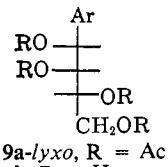
(4) For leading references see H. El Khadem, M. L. Wolfrom, and D. Horton, *J. Org. Chem.*, 30, 838 (1965).

(5) H. Ohle and R. Liebig, *Ber.*, **75**, 1536 (1942).

(6) D. Horton and M. J. Miller, *J. Org. Chem.*, 30, 2457 (1965).

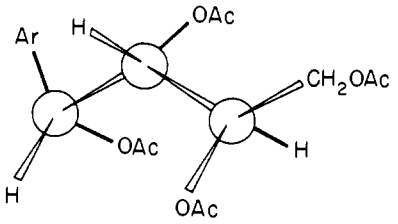


8a-*erythro*, R = Ac
b, R = H



9a-*lyxo*, R = Ac
b, R = H

quinoxaline in carbon tetrachloride solution has a high content of staggered conformation **10.** Conformation



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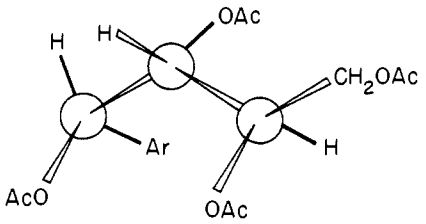

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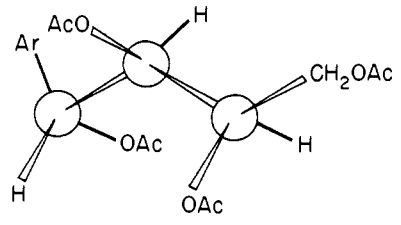
10 minimizes nonbonded interactions between small–medium–large sets of groups at the end of each carbon–carbon bond. A similar consideration of nonbonded interactions about pairs of adjacent carbon atoms for the *lyxo* compound (Table I) predicts a most stable conformation **12** in accord with the observed coupling



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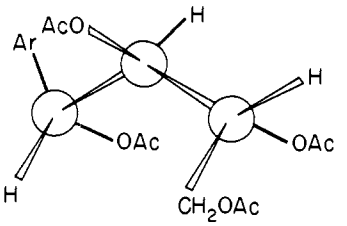
constants,[7] but fails to explain the observed coupling constants in the case of the *xylo*, *threo*, and *erythro* compounds which do not appear to be as conformationally homogeneous.

Table I. Chemical Shifts and Coupling Constants of Quinoxaline Acetates in Carbon Tetrachloride

	5a-*threo*	**6a**-*arabino*	**6c**-*arabino*	**7a**-*xylo*	**8a**-*erythro*	**9a**-*lyxo*
δ_{H_1},	6.22, d	6.28, d	6.24, d	6.15, d	6.28, d	6.13, d
δ_{H_2},	5.70, m	5.72, q	5.56, q	5.73, q	5.77, m	5.82, q
$J_{1,2}$,	5.5	3.0	3.5	6.5	5.5	7.5
$J_{2,3}$,		8.5	7.5	5.0		3.0

(7) Coupling constants cited are observed splittings. In most cases relative chemical shifts are sufficiently great that observed splittings should be close to the true coupling constants. In the least favorable case, **6a**, δ_{H_2,H_3}, is 22 cps and $J_{2,3}$, is 8.5 cps. For discussion of problems involved in attempting to make more than a qualitative interpretation of conformation from coupling constants, see L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, 51 (1964); and M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2871 (1963).

The analysis of nonbonded interactions at the end of each carbon–carbon bond fails to take into account longer range nonbonded interactions such as between substituents at C-1′ and C-3′ and fails to consider any acetoxy–acetoxy dipole interaction. Dipole interactions involving the acetoxy group have been invoked to explain the conformational preferences of *threo*- and *erythro*-2,3-diacetoxybutanes,[8] and anomeric glycosyl acetates.[9] Although it is not known to what extent dipole interactions affect the conformational equilibrium of the polyacetoxyalkyl chain, it should be noted that conformation **11**, in which dihedral angles of 180° between all pairs of acetoxy groups are achieved, is also consistent with the coupling constants observed for the *arabino* compound and must be considered as a possible contributing conformation. Similarly the staggered conformation **13** of the *lyxo* compound, with



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maximum distance between acetoxy groups, is also consistent with the nmr data. Thus for both *lyxo* and *arabino* stereochemistries two of the nine possible staggered conformations can account for the nmr data; one of each pair represents minimized nonbonded interactions at the end of carbon–carbon bonds and the other represents maximum separation of acetoxy groups.

In the case of *xylo* stereochemistry the minimum nonbonded interaction conformation and the conformation with maximum distance between acetoxy groups both predict small coupling constants between protons at C-1′ and C-2′ and protons at C-2′ and C-3′. The observed coupling constants, 5.0 and 6.5 cps, have values intermediate between those expected for *gauche* hydrogens and *anti* hydrogens, suggesting that several conformations make significant contributions.

The *arabino* compound **6a** shows considerable conformational homogeneity around the C-1′,C-2′ bond while the *threo* derivative **5a** of the same configuration in the immediate vicinity of the C-1′,C-2′ bond shows little conformational homogeneity. These two compounds differ only in the bulk of one substituent on C-3′, indicating that 1′,3′ substituent interaction must play a significant role in determining relative stability of the different conformations. The stabilizing 3′ substituent can be methyl as well as acetoxymethyl as indicated by the similarities in magnitudes of $J_{1,2}$, and $J_{2,3}$, of acetylated quinoxalines **6a** and **6c**.

Conformation of the Polyhydroxyalkyl Chain. Nmr spectra of the unacetylated quinoxalines in dimethyl sulfoxide are complicated by additional splitting of the signals by coupling with hydroxyl hydrogens. The coupling constants between hydrogens at C-1′ and C-2′ can be obtained from the quartet signal due to hydrogen on C-1′ (Table II). The signal due to hydrogen on C-2′ does not lend itself to first-order analysis

(8) A. A. Bothner-By and C. Naar-Colin, *ibid.*, **84**, 743 (1962).
(9) For leading references see C. B. Anderson and D. T. Sepp, *J. Org. Chem.*, **32**, 607 (1967).

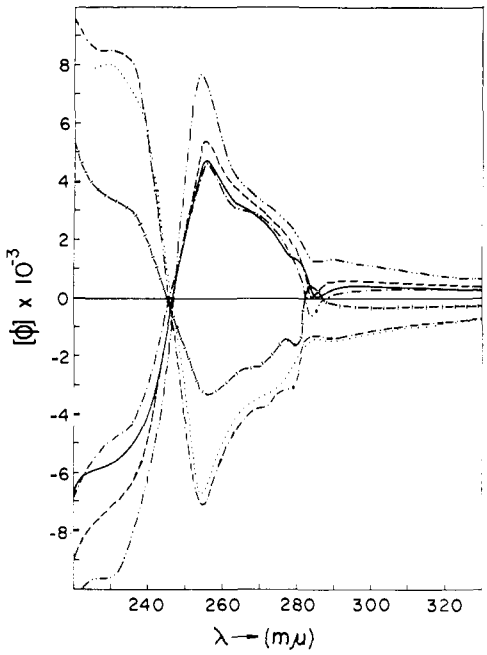


Figure 1. ORD of benzimidazoles in methanol: —·—, 2-(D-*galacto*-pentahydroxypentyl)benzimidazole; – – –, 2-(D-*gluco*-pentahydroxypentyl)benzimidazole; ———, 2-(D-*ribo*-tetrahydroxybutyl)benzimidazole; —·—, 2-(D-*glycero*-D-*gulo*-hexahydroxyhexyl)benzimidazole; —|— 2-(L-*gulo*-pentahydroxypentyl)-benzimidazole; . . . ., 2-(D-*arabino*-tetrahydroxybutyl)benzimidazole; — — ·, 2-(D-*altro*-pentahydroxypentyl)benzimidazole.

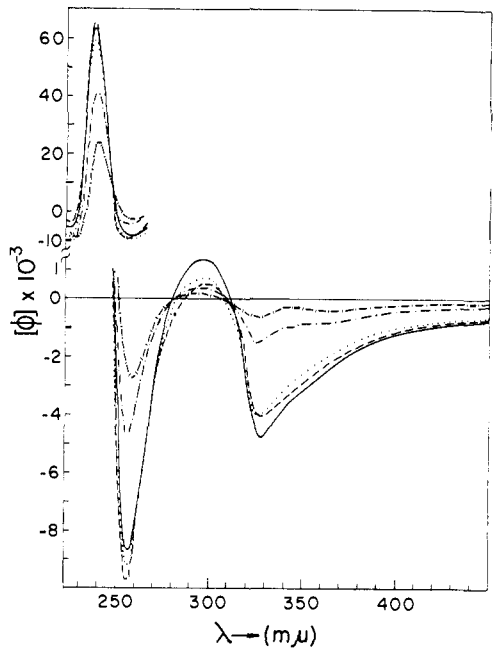


Figure 2. ORD of quinoxalines in methanol: —|—, 2-(D-*lyxo*-tetrahydroxybutyl)quinoxaline (**9b**); —·—, 2-(L-*erythro*-trihydroxybutyl)quinoxaline (**8b**); . . . ., 2-(L-*xylo*-tetrahydroxybutyl)quinoxaline (**7b**); – – –, 2-(D-*threo*-trihydroxypropyl)-quinoxaline (**5b**); ———, 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline (**6b**).

because of the small chemical shift between hydrogens on C-3′ and C-4′. The coupling constants $J_{1'2'}$ are generally of the same magnitude as those obtained from the corresponding acetates in carbon tetrachloride solution.

Table II. Chemical Shifts and Coupling Constants of Some Substituted Quinoxalines in DMSO

	5b- *threo*	**6b-** *arabino*	**7b-** *xylo*	**8b-** *erythro*	**9b-** *lyxo*
$H_{1'}$	5.02, q	5.24, q	5.04, q	4.87, q	4.97, q
$H_{2'}$	3.78, m		3.96, m	3.96, m	4.02, m
$J_{1'2'}$	2.5	1.0	3.5	6.0	8.0

The Rotatory Dispersion Correlation. The rotatory dispersions of seven polyhydroxyalkylbenzimidazoles in methanol (Figure 1) show the relationship of negative Cotton effect centered at 245 mμ with *R* chirality at C-1′ and positive Cotton effect with *S* chirality at C-1′ The same relationship applies to benzimidazoles in dimethyl sulfoxide solvent although most of the Cotton effect region is obscured by solvent absorption. Polyhydroxyalkyl quinoxalines in methanol (Figures 2 and 3) or in dimethyl sulfoxide (Figure 4) have negative Cotton effects centered at 315 mμ associated with *R* chirality at C-1′.[10] The same correlation holds for the O-acetyl derivatives of the quinoxalines in methanol and in chloroform solvent.

The correlation of absolute stereochemistry at C-1′ with optical rotatory dispersion can be expected to be

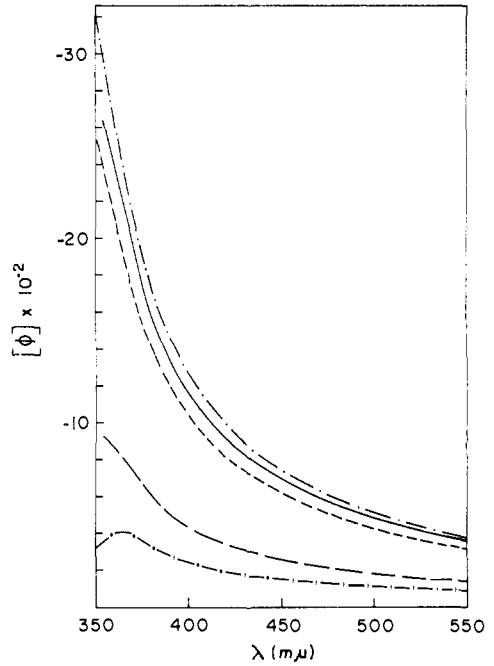


Figure 3. ORD of quinoxalines in methanol: —·—, 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline (**6b**); ———, 2-(D-*threo*-trihydroxypropyl)quinoxaline (**5b**); – – –, 2-(L-*xylo*-tetrahydroxybutyl)quinoxaline (**7b**); ———, 2-(D-*lyxo*-tetrahydroxybutyl)-quinoxaline (**9b**); —|—, 2-(L-*erythro*-trihydroxybutyl)quinoxaline (**8b**).

useful only if all examples possess roughly the same relative populations of conformations about the bond from C-1′ to the chromophore. Pure rotamers **14**, **15**, and **16** would be expected to have optical rotatory dispersions differing in magnitude and even sign.[11]

(10) A second, much larger, apparent negative Cotton effect centered at 246 mμ can be shown by circular dichroism measurement to be a composite of a negative Cotton effect centered at 242 mμ superimposed on a positive Cotton effect centered at 231 mμ.

(11) J. H. Brewster and J. G. Buta, *J. Amer. Chem. Soc.*, **88**, 2233 (1966).

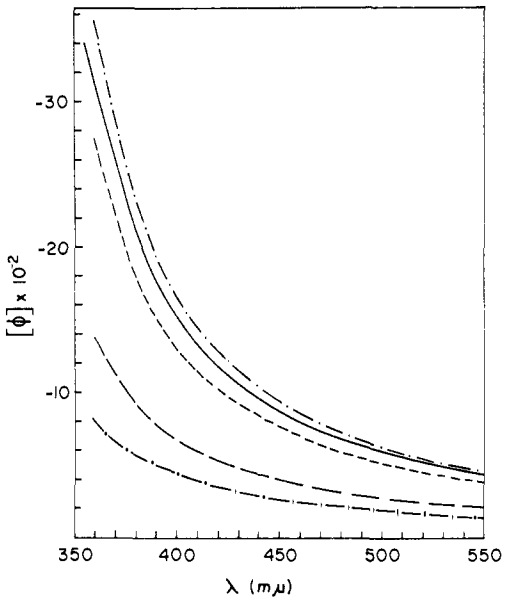


Figure 4. ORD of quinoxalines in dimethyl sulfoxide: — · —, 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline (**6b**); ———, 2-(D-*threo*-trihydroxypropyl)quinoxaline (**5b**); - - - -, 2-(D-*xylo*-tetrahydroxybutyl)quinoxaline (**7b**); — — —, 2-(L-*erythro*-trihydroxypropyl)quinoxaline (**8b**); —|—, 2-(D-*lyxo*-tetrahydroxybutyl)-quinoxaline (**9b**).

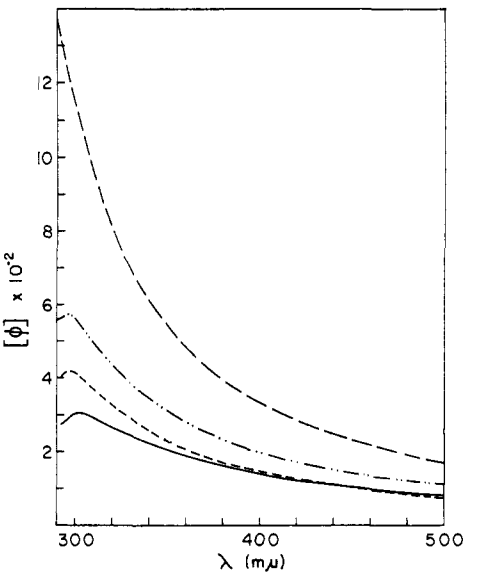
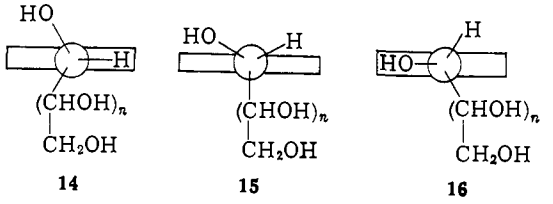


Figure 5. ORD of benzimidazoles in methanol: — — —, superimposed spectra of 2-(L-*arabino*-tetrahydroxybutyl)-, 2-(D-*galacto*-pentahydroxypentyl)-, and the enantiomer of 2-(D-*altro*-pentahydroxypentyl)benzimidazoles; —· ·—, 2-(D-*gluco*-pentahydroxypentyl)benzimidazole; - - - -, 2-(D-*ribo*-tetrahydroxybutyl)benzimidazole; ———, the enantiomer of 2-(L-*gulo*-pentahydroxypentyl)benzimidazole.

The observed ORD will be a weighted average of the ORD of these and all other rotamers about the C-1′ to chromophore bond.



In the polyhydroxyalkyl heterocycles the major factors affecting rotamer distribution are likely to be nonbonded interactions, dipole–dipole interactions, and hydrogen bonding to hydroxyls, to the heteroatom unshared electron pair, and to the π system of the aromatic heterocycle. Hydrogen bonding definitely affects the shape of the molecule about C-2′ and C-3′ (*vide infra*). It may have a role in determining the rotamer distribution about the C-1′ heterocycle bond; however, the C-1′ correlation is valid for quinoxalines in which the carbon chain length is altered, the terminal hydroxyl is replaced, as in **6c** and **7c**, or all hydroxyls are acetylated (Table III).

Two-Center Correlation. While the absolute stereochemistry at C-1′ of polyhydroxyalkylquinoxalines determines the *sign* of the Cotton effect in methanol, stereochemistry at more remote centers has an influence on the *amplitude* of the effect. Compounds with *threo* relationship at C-1′ and C-2′ have higher amplitude Cotton effects than *erythro* compounds. Quinoxalines with *threo* relationship at C-1′ and C-2′ also have higher rotatory power at long wavelength. It is apparent from Table III that acetylation of the hydroxyls destroys this difference between *threo* compounds (**5**, **6**, and **7**) and *erythro* compounds (**8** and **9**). This change in relative amplitude of the Cotton effect may be caused by conformational population shifts accompanying removal of all possibility of conformational stabilization by hydrogen bonding.

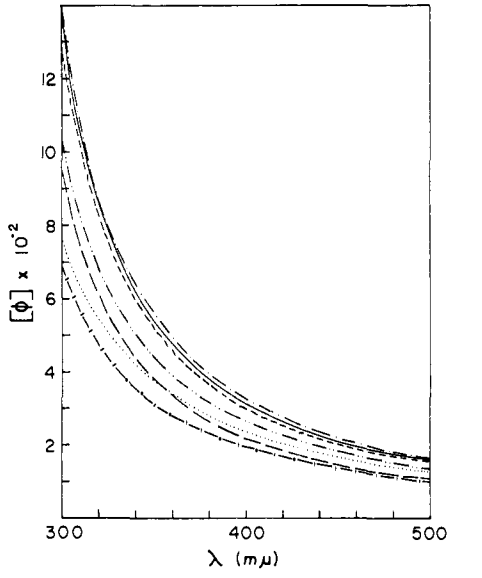


Figure 6. ORD of benzimidazoles in dimethyl sulfoxide: — · — 2-(L-*arabino*-tetrahydroxybutyl)benzimidazole; ———, 2-(D-*galacto*-pentahydroxypentyl)benzimidazole; - - - -, the enantiomer of 2-(D-*altro*-pentahydroxypentyl)benzimidazole; —· ·—, 2-(D-*gluco*-pentahydroxypentyl)benzimidazole; . . . ., 2-(D-*glycero*-D-*gulo*-hexahydroxyhexyl)benzimidazole; — — —, 2-(D-*ribo*-tetrahydroxybutyl)benzimidazole; —|—, the enantiomer of 2-(L-*gulo*-pentahydroxypentyl)benzimidazole.

With benzimidazole derivatives *threo* stereochemistry at C-1′,C-2′ is distinguished from *erythro* at long wavelength (Figures 5 and 6) by greater rotatory power. The tendency of the *threo*-benzimidazoles to have greater rotatory power than *erythro* was noted at the sodium D-line by Richtmyer and Hudson.[12] Mills

(12) N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, **64**, 1612 (1942).

Table III. Amplitude of Second Cotton Effect (about 250 mμ) of 2-Substituted Quinoxalines in Methanol

Stereochemistry	Compd	Δφ	Acetyl derivative	Δφ
5-*threo*	5b	−75,000	5a	−34,000
6-*arabino*	6b	−73,000	6a	−40,000
			6c	−39,000[a]
7-*xylo*	7b	−68,000	8a	−41,000
8-*erythro*	8b	−46,000		
9-*lyxo*	9b	−27,000	9a	−58,000

[a] Value calculated from enantiomer.

noted a similar relationship in the long wavelength rotatory power of 2-phenyl-1,2,3-triazoles (osotriazoles) prepared from sugars.[13] Although the single wavelength correlations do not seem to be sufficiently reliable for assigning two centers of asymmetry from one derivative, it does appear possible to assign two centers for quinoxalines by using the amplitude of the Cotton effect.

Three-Center Correlation. By comparison of the long wavelength rotatory dispersion of benzimidazoles (Figures 5 and 6) and quinoxalines (Figures 3 and 4), it is evident that the curves are further subdividable into families related to the stereochemistry at the *three* closest centers of asymmetry. Compounds having *arabino* stereochemistry at the three centers adjacent to the aromatic heterocycle form a family of curves with the greatest absolute magnitude of rotation in the long wavelength region for both quinoxalines and benzimidazoles. *xylo* stereochemistry gives the next largest absolute rotation and the families with *ribo* or *lyxo* stereochemistry have the lowest magnitude. A fourth center has almost no observable effect. Curves for *altro*- and *galacto*-pentahydroxypentylbenzimidazoles,[14] both of which have *arabino* stereochemistry at C-1′ through C-3′, fall almost on top of the curve for 2-(D-*arabino*-tetrahydroxybutyl)benzimidazole. It has been noted earlier that for osotriazoles in pyridine at 589 mμ, compounds with *arabino* stereochemistry consistently have the highest absolute rotation.[13] It is also apparent from previously published data that osotriazoles with *xylo* stereochemistry fall into a group with slightly lower rotatory power and that *ribo* and *lyxo* stereochemistries form an indistinguishable low rotatory power group.

For purposes of sugar structural determination and identification by optical rotatory dispersion it has been thought desirable to extend structure–rotation correlation to several centers of asymmetry. In applying these correlations to derivatives of sugars of unknown stereochemistry it is necessary to recognize that methoxyl, amino, acetamido, deoxy, and other groups, frequently found to replace hydroxyls in naturally occurring sugars, may greatly perturb the conformational populations and invalidate some of these multicenter correlations.

Experimental Section

Optical rotatory dispersion measurements were made at ambient temperature on a Cary Model 60 spectropolarimeter. Nmr spectra were measured on a Varian A-60 spectrometer. Reagent-grade solvents were used for all spectral determinations. Rotatory dispersions were determined at concentration ranges of 0.2–1.0 g/l. above 300 mμ and 0.01–0.1 g/l. below 400 mμ.

Materials. D-*altro*-, D-*galacto*-, D-*gluco*-, and D-*gulo*-pentahydroxypentylbenzimidazoles, D-*arabino*- and D-*ribo*-tetrahydroxybutylbenzimidazoles, and D-*glycero*-D-*gulo*-hexahydroxyhexylbenzimidazole were prepared by previously described methods.[3,14] D-*threo*-Trihydroxypropylquinoxaline and D-*arabino*- and D-*lyxo*-tetrahydroxybutylquinoxalines and their O-acetyl derivatives were prepared by the procedures of Ohle and Kruyff.[15]

2-(L-*erythro*-Triacetoxypropylquinoxaline (8a). A suspension of 15.0 g (0.1 mol) of L-arabinose, 11.0 g (0.1 mol) of *o*-phenylenediamine, 10.0 ml (0.2 mol) of hydrazine hydrate, and 6.0 ml (0.1 mol) of acetic acid in 200 ml of pyridine was stirred and heated at 100° for 5 hr. The solution was decanted from a small amount of oily substance and concentrated *in vacuo*. The oily residue was extracted with 200 ml of hot propanol. The oil which precipitated on cooling was discarded and the solvent removed to give an oil containing crystals. This product was acetylated by dissolving it in 60 ml of pyridine and 60 ml of acetic anhydride. After 20 hr 7.33 g of N,N′-diacetyl-*o*-phenylenediamine, mp 184°, was removed by filtration. Evaporation of the solvent and trituration of the residue with benzene gave an additional 3.12 g (55% total recovery) of N,N′-diacetyl-*o*-phenylenediamine. The benzene solution was extracted three times with 25-ml portions of 6 *N* sulfuric acid, extracted with water, and decolorized with charcoal. Removal of benzene gave 17.96 g of a clear light brown oil.

The oil (2.45 g) was further purified by elution from a 23 × 1.7 cm column of alumina with 2:3 chloroform–carbon tetrachloride. Evaporation of solvent *in vacuo* gave 1.27 g of a pale yellow oil with the ultraviolet spectrum of a quinoxaline; λ_{max}^{MeOH} 237 mμ (ε 35,100), 310 mμ (shoulder, ε 6100), 318 mμ (ε 7100).

Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.91; H, 5.15; N, 8.25.

2-(L-*erythro*-Trihydroxypropyl)quinoxaline (8b). A solution of 5.79 g (0.017 mol) of chromatographed triacetate **8a** in 300 ml of absolute methanol was saturated with liquid ammonia at 0° and kept at 2° for 20 hr. Evaporation of the solvent left an oily residue from which most of the acetamide was removed by sublimation at 60° *in vacuo*. The remaining oil was adsorbed onto a silica gel column from chloroform solution. The column was washed successively with chloroform, benzene, ether, and ethyl acetate. Finally, elution with acetone removed the adsorbed quinoxaline. Removal of acetone left a yellow-brown oil which slowly crystallized. Recrystallization from acetone–chloroform gave 1.93 g (52.4%) of product, mp 121.5–122°. The ultraviolet spectrum in methanol showed λ_{max} 236 mμ (ε 28,300), 309 mμ (shoulder, ε 6120), and 317 mμ (ε 7020).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.88; H, 5.55; N, 12.52.

2-(L-*xylo*-Tetraacetoxybutyl)quinoxaline (7a). A solution of 9.0 g (0.050 mol) of L-sorbose, 5.5 g (0.051 mol) of *o*-phenylenediamine, 6 ml (0.105 mol) of acetic acid, and 10.0 ml (0.206 mol) of hydrazine hydrate in 100 ml of pyridine was heated 4 hr on a steam bath. Solvent was removed and the oily residue was extracted with 200 ml of boiling propanol. Evaporation of the propanol left a partly crystalline mass, 12.05 g. This material was acetylated with pyridine and acetic anhydride. After removal of solvent the residue was extracted with benzene, and the benzene solution was decanted from 3.14 g of crystals of N,N′-diacetyl-*o*-phenylenediamine. After extraction with 6 *N* sulfuric acid and treatment with charcoal the benzene solvent was removed leaving 13.20 g of light brown, oily acetylated quinoxaline.

A portion of the oil (1.88 g) was further purified by elution from a 150-g column of alumina. One liter of carbon tetrachloride–chloroform eluted 0.96 g of liquid 2-(L-*xylo*-tetraacetoxybutyl)-quinoxaline.

Anal. Calcd for $C_{20}H_{22}N_2O_8$: mol wt, 418.1376. Found: mol wt, 418.137 (mass spectral).

2-(L-*xylo*-Tetrahydroxybutyl)quinoxaline (7b). A solution of 11.3 g of acetylated quinoxaline **7a** in 350 ml of methanol was saturated with ammonia at 0° and allowed to stand for 36 hr at 2°. The solvent was evaporated under a nitrogen atmosphere and the partly crystalline residue was recrystallized twice from methanol to give 1.79 g of 2-(L-*xylo*-tetrahydroxybutyl)quinoxaline, mp 149–150°, 17% yield from L-sorbose.

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Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.76; H, 5.80; N, 11.47.

2-(L-*arabino*-1′,2′,3′-Triacetoxybutyl)quinoxaline (Enantiomer of 6c). A suspension of 18.0 g (0.1 mol) of rhamnose hydrate, 11.0 g (0.1 mol) of *o*-phenylenediamine, 10 ml (0.21 mol) of anhydrous hydrazine, and 6.0 ml (0.1 mol) of acetic acid in 200 ml of pyridine was stirred at 100° for 4 hr. The clear red solution was concentrated *in vacuo*. The residue was extracted with 200 ml of propanol. The alcoholic extract was decolorized with charcoal and concentrated. Treatment of the oily, amber residue with 120 ml of pyridine–acetic acid, 1:1, gave 5.37 g of crystalline N,N′-diacetyl-*o*-phenylenediamine, which was removed by filtration. Concentration of the filtrate and trituration of the residue with 150 ml of benzene gave an additional 4.63 g (61% total recovery) of N,N′-diacetyl-*o*-phenylenediamine. The benzene filtrate was extracted three times with 25-ml portions of 6 *N* sulfuric acid, extracted with water, and decolorized with charcoal. Removal of the benzene gave 24.3 g of red-brown oil.

A portion of the oil (8.03 g) was further purified by elution from a 250-g column of alumina with carbon tetrachloride–chloroform solvent. One liter of solvent eluted 2.48 g of liquid 2-(L-*arabino*-1′,2′,3′-triacetoxybutyl)quinoxaline which was freed of solvent by heating in a rotary evaporator under vacuum until constant pressure readings were obtained; uv spectrum λ_{max}^{MeOH} 236 mμ (ε 31,500), 309.5 mμ (shoulder, ε 5600), and 317.5 mμ (ε 6500).

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.91; H, 5.74; N, 7.65.

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The Synthesis of Deamino-oxytocin by the Solid Phase Method[1]

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Abstract: Deamino-oxytocin, a highly potent analog of oxytocin, has been synthesized by the solid phase method. The fully protected polypeptide-nitrated resin compound, S-benzyl-β-mercaptopropionyl-O-benzyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycyl nitrated resin, was prepared and cleavage of the peptide chain from the resin was effected by ammonolysis. Debenzylation of the protected polypeptide followed by oxidative cyclization of the resulting deamino-oxytoceine yielded deamino-oxytocin. The purified deamino-oxytocin crystallized readily from water. This crystalline analog possessed full biological activity.

The solid phase method[3–5] has facilitated the synthesis of peptides since it offers speed and simplicity as well as good yields. We therefore desired to apply this solid phase technique to the synthesis of analogs of the posterior pituitary hormones oxytocin and vasopressin. To this end the synthesis of deamino-oxytocin,[6–9] a highly potent crystalline analog of oxytocin, was undertaken.

The synthesis of deamino-oxytocin by the resin method essentially followed the procedure outlined previously for the synthesis of angiotensins by this technique,[5] except for the fact that the polymer support was used in the nitrated form[3] in order to facilitate the subsequent cleavage of the peptide by ammonolysis.[10] *t*-Butyloxycarbonyl (Boc) amino acids were used and N,N′-dicyclohexylcarbodiimide[11] was the coupling reagent except for the coupling of the asparagine and glutamine residues. The latter were incorporated into the growing peptide chain by means of their nitrophenyl esters[12] since nitrile formation has been observed in coupling reactions involving these amino acids when N,N′-dicyclohexylcarbodiimide was used as the coupling reagent.[13] However, once the glutamine and asparagine residues have been incorporated into the peptide chain, carbodiimide may be used for subsequent couplings without danger of nitrile formation.[14,15]

Boc-glycine was esterified to nitrated chloromethylcopolystyrene–2% divinylbenzene, and the stepwise synthesis was carried through eight cycles[5] to give the fully protected polypeptide-nitrated resin compound, S-benzyl-β-mercaptopropionyl-O-benzyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycyl nitrated resin.

In preliminary runs incomplete coupling was encountered in extending the chain beyond the glutamine

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