Rotatory Dispersion of Sugar Heterocycles

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Abstract: The rotatory dispersions of ten different heterocycles prepared from sugars have been measured in order to find derivatives suitable for assigning stereochemistry. For a large number of polyhydroxyalkyl quinoxalines and benzimidazoles the sign of the longest wavelength Cotton effect is negative when the nearest center of asymmetry, C-1′, has *R* chirality. Similar correlations are likely to be found with other heterocycles once sufficient examples have been examined. Stereochemistry of all centers of asymmetry of hexoses may be studied by making use of the benzimidazole, quinoxaline, flavazole, and anhydroosazone derivatives.

One of the early applications of optical rotatory dispersion to the solution of a structural problem was the establishment in 1937 of *R* chirality at C-2 of the naturally occurring amino sugars glucosamine and galactosamine.[1] Following this early success relatively little headway has been made in the use of rotatory dispersion and circular dichroism for the elucidation of sugar stereochemistry. One of the deterrents to ready application of rotatory dispersion techniques to sugar stereochemistry problems is the lack of a chromophore in the readily accessible ultraviolet region. The long wavelength tailing of a Cotton effect associated with lactal and hydroxyl oxygen n–σ^* transitions with maxima between 150 and 170 mμ can be observed.[2] Stereochemistry of the anomeric center appears to be derivable from inspection of the near side of this Cotton effect.

A second possibility for application of rotatory dispersion to sugars is to modify the sugar by introduction of a chromophore. A number of chromophores have been introduced: xanthate ester,[3] phenylazo group,[4] and glycol thiocarbonate esters.[5] The corresponding Cotton effects have been measured, but because of brevity of the individual studies or the uncertainty as to the position of substitution, ring size, or conformational populations, no correlation of absolute stereochemistry with sign or magnitude of the Cotton effect has been attempted. A few systematic studies have led to stereochemistry–rotatory dispersion correlations for aldono-γ-lactones,[6] osotriazoles,[7] 1-deoxy-1-nitroalditols,[8] and saccharide nitrate esters.[9]

Structure–optical rotation correlations at a single wavelength, generally 589 mμ, have been proposed in great number in the study of sugar stereochemistry.[10] Many of these correlations have been made for acyclic derivatives of sugars,[11] particularly for polyhydroxyalkyl aromatic heterocycles.[12] In addition, the use of rotation enhancement by cuprammine complexes of sugar glycols has been put on a sound empirical basis[13] and extended to the solution of stereochemistry problems.[14] The structure–rotation correlations made with rigid bicyclic cuprammine complexes provide clear-cut relationships because the single wavelength measurements are made at the mercury blue line, 436 mμ, a wavelength which falls within the broad, low-intensity envelope of the cuprammine–glycol absorption ($\lambda_{\max}$ 600 mμ); the measurements are influenced by a relatively large circular dichroism.

In contrast, rules for prediction of the sign of rotation of benzimidazole, quinoxaline, osotriazole, and other heterocyclic derivatives of sugars were developed for the sodium D line, 589 mμ, a wavelength which lies well beyond any electronic absorptions of these heterocycles. Such structure–rotation correlations must be independent of any effects of circular dichroism. For 2-substituted benzimidazoles the longest wavelength absorption detectable by circular dichroism is at 245 mμ. In addition, extremely weak activity of either the 278- or 281-mμ band can be seen as a shoulder on the 245-mμ Cotton effect in the rotatory dispersion spectrum (Figure 1). The substituted quinoxaline (Figure 2) and substituted phenylosotriazole (Figure 3) show Cotton effects associated with the longest wavelength absorp-

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[1] P. Pfeiffer and W. Christeleit, *Z. Physiol. Chem.*, **245**, 197 (1937); 247, 262 (1937); P. Karrer, *Helv. Chim. Acta*, 20, 407 (1937).

[2] I. Listowsky, G. Avigad, and S. Englard, *J. Am. Chem. Soc.*, **87**, 1766 (1965); S. Englard, G. Avigad, and I. Listowsky, *Carbohydrate Res.*, **2**, 380 (1966).

[3] Y. Tsuzuki, K. Tanabe, M. Akagi, and S. Tejima, *Bull. Chem. Soc. Japan*, 37, 162 (1964); D. Horton and M. L. Wolfrom, *J. Org. Chem.*, 27, 1794 (1962); D. Sjöberg, D. J. Cram, L. Wolf, and C. Djerassi, *Acta Chem. Scand.*, **16**, 1079 (1962).

[4] M. L. Wolfrom, A. Thompson, and D. R. Lineback, *J. Org. Chem.*, 27, 2563 (1962); E. O. Bishop, G. J. F. Chittenden, R. D. Guthrie, A. F. Johnson, and J. F. McCarthy, *Chem. Commun.*, 93 (1965).

[5] G. E. McCasland, S. Furuta, A. Furst, L. F. Johnson, and J. N. Schoolery, *J. Am. Chem. Soc.*, **83**, 2335 (1961); C. Djerassi, H. Wolf, D. A. Lightner, E. Bunnenberg, K. Takeda, T. Komeno, and K. Kuriyama, *Tetrahedron*, **19**, 1547 (1963).

[6] T. Okuda, S. Harigaya, and A. Kiyomoto, *Chem. Pharm. Bull.* (Tokyo), 12, 504 (1964); R. J. Abraham, L. D. Hall, L. Hough, K. A. McLauchlan, and H. J. Miller, *J. Chem. Soc.*, 748 (1963).

[7] *Cf.* G. G. Lyle and M. J. Piazza, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, 10C.

[8] C. Satoh, A. Kiyomoto, and T. Okuda, *Chem. Pharm. Bull.* (Tokyo), 12, 518 (1964).

[9] Y. Tsuzuki, K. Tanabe, K. Okamoto, and N. Yamada, *Bull. Chem. Soc. Japan*, **39**, 2269 (1966).

[10] Isorotation rule: C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909); W. Klyne, *Biochem. J.*, **47**, xli (1950). Lactone rule: C. S. Hudson, *J. Am. Chem. Soc.*, 32, 338 (1910); **61**, 1525 (1939).

[11] Phenylhydrazide rule: C. S. Hudson, *J. Am. Chem. Soc.*, **39**, 492 (1917); P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **31**, 623 (1917). Amide rule: C. S. Hudson, *J. Am. Chem. Soc.*, 40, 813 (1918); C. S. Hudson and K. P. Monroe, *ibid.*, **41**, 1140 (1919); C. S. Hudson and S. Komatsu, *ibid.*, **41**, 1141 (1919); K. Freudenberg and W. Kuhn, *Ber.*, **64**, 703 (1931). Aldononitrile rule: V. Deulofeu, *Advan. Carbohydrate Chem.*, **4**, 149 (1949).

[12] Benzimidazoles: N. K. Richtmyer and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 1612 (1942). Furans: F. Garcia-Gonzalez, *Advan. Carbohydrate Chem.*, **11**, 97 (1956). Quinoxalines: W. S. Chilton, Ph.D. Thesis, University of Illinois, 1963. Osotriazoles: H. El Khadem, *J. Org. Chem.*, **28**, 2478 (1963); J. A. Mills, *Australian J. Chem.*, **17**, 277 (1964). Pyrroles: F. Garcia-Gonzalez and A. Gomez, *Advan. Carbohydrate Chem.*, 20, 313 (1965). Generalized rule: H. El Khadem and Z. M. Shafei, *Tetrahedron Letters*, 1887 (1963).

[13] R. E. Reeves, *Advan. Carbohydrate Chem.*, **6**, 107 (1951).

[14] M. Hichens and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **85**, 1547 (1963); J. R. Dyer and A. W. Todd, *ibid.*, **85**, 3896 (1963); S. Umezawa, T. Tsuchiya and K. Tatsuta, *Bull. Chem. Soc. Japan*, **39**, 1235, 1244 (1966).

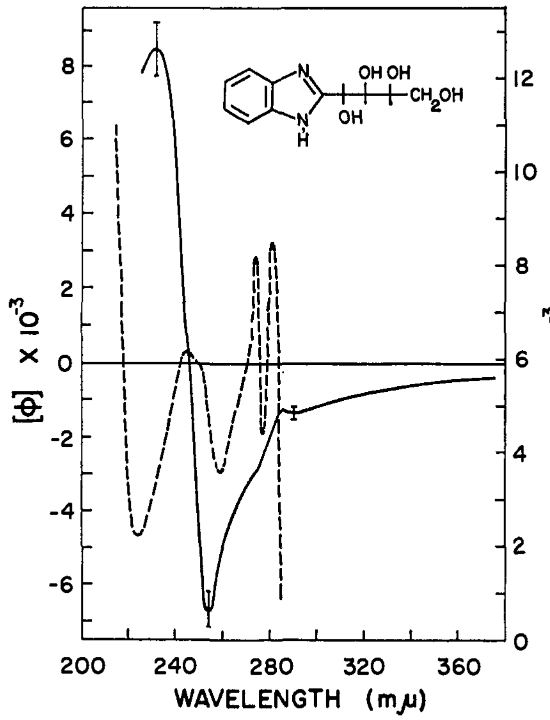

Figure 1. Spectra of 2-(D-*arabino*-tetrahydroxybutyl)benzimidazole in methanol: ultraviolet, - - -; ORD, —.

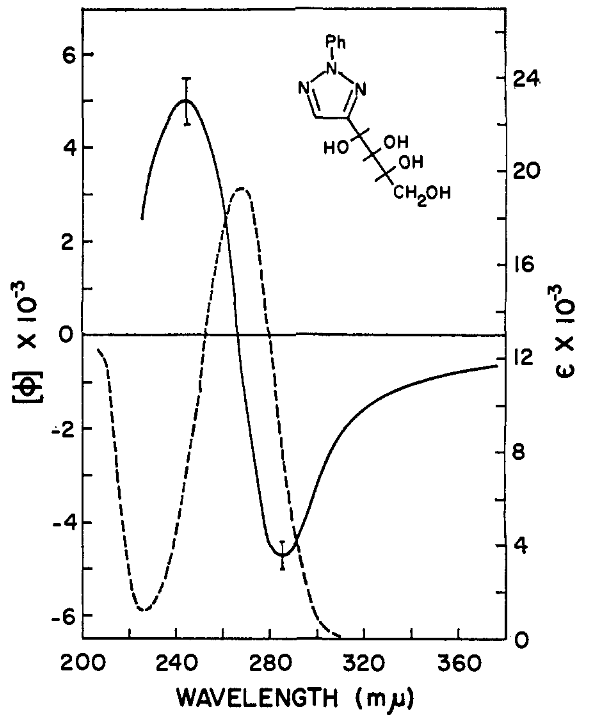

Figure 3. Spectra of 4-(D-*arabino*-tetrahydroxybutyl)-2-phenyl-1,2,3-triazole in methanol: ultraviolet, - - -; ORD, —.

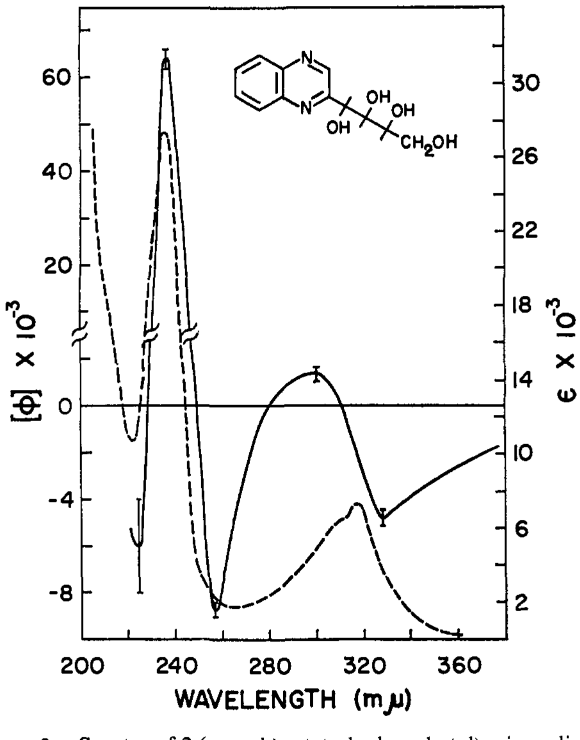

Figure 2. Spectra of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline in methanol: ultraviolet, - - -; ORD, —.

tion maxima at 315 and 260 mμ. For all of these compounds the rotatory dispersion spectra exhibit a plane curve over a broad region from 400 mμ to the sodium D line.

The success of structure–rotation correlations at 589 mμ for these heterocycle-containing compounds is therefore related to the differential index of refraction of right and left circularly polarized light rather than differential absorption. Each of the asymmetric centers of the polyhydroxyalkyl side chain contributes to the resultant differential refraction, but the contribution is largest at C-1′, which is, by virtue of its proximity to the aromatic heterocycle, the only asymmetric center with four groups of distinctly different polarizabilities. Contributions of C-2′ and C-3′ to long wavelength optical activity are small because these centers have two substituents of almost equal polarizabilities (aliphatic carbon).

Cotton effects of these same compounds should also be correlatable with absolute stereochemistry. We have conducted a preliminary survey of the rotatory dispersion behavior of quinoxalines, benzimidazoles, osotriazoles, and a number of other sugar derivatives to find compounds which may be suitable for determination of structure of new sugars by optical rotatory dispersion methods. A number of derivatives readily prepared from sugars look promising. As an example, for methanol solutions of benzimidazole derivatives of simple monosaccharides[15] the following correlation has been found. *Those 2-(n-polyhydroxyalkyl)benzimidazoles possessing S chirality at C-1′ have a positive Cotton effect centered at 245 mμ.* A negative Cotton effect indicates *R* chirality at C-1′. Rotatory dispersion can thus be used to determine the absolute stereochemistry at C-2 of sugars. A similar correlation for quinoxalines[16] permits assignment of absolute stereochemistry at C-3 of the parent sugar: *2-(n-polyhydroxyalkyl)-quinoxalines with S chirality at C-1′ have a positive Cotton effect centered at 315 mμ.*[17]

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(15) Benzimidazoles prepared from D-arabinose, D-ribose, D-glucose, D-galactose, D-altrose, L-gulose, and D-glycero-D-guloheptose were examined.

(16) Model compounds examined include D-*arabino*-, D-*lyxo*-, and L-*xylo*-tetrahydroxybutylquinoxalines and L-*erythro*- and D-*threo*-trihydroxypropylquinoxalines.

(17) A similar correlation applies to the complex Cotton effect centered about the 237-mμ absorption.

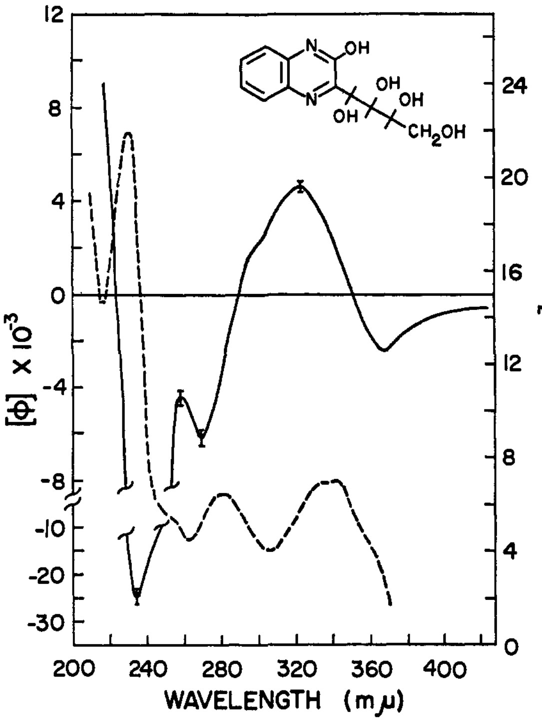


Figure 4. Spectra of 2-hydroxy-3-(D-*arabino*-tetrahydroxybutyl)-quinoxaline in methanol: ultraviolet, ---; ORD, —.

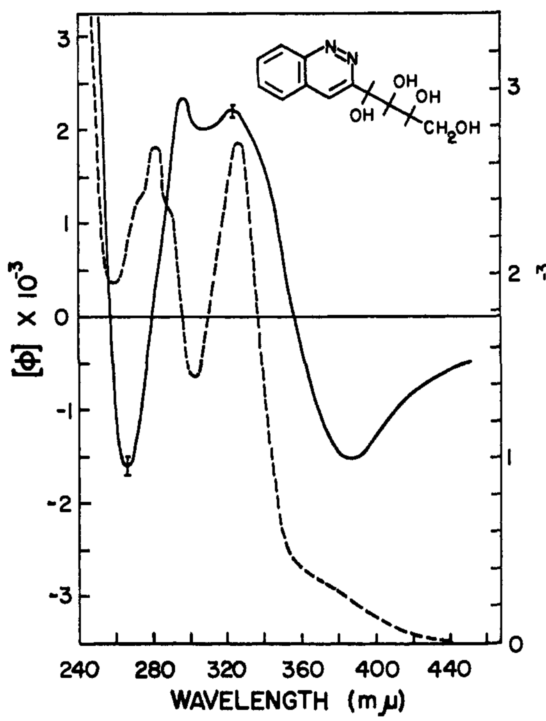
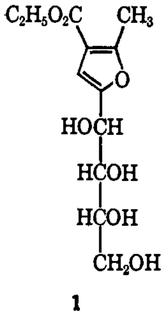


Figure 5. Spectra of 3-(D-*arabino*-tetrahydroxybutyl)cinnoline: ultraviolet, ---; ORD, —.

It is probable that absolute configuration at the nearest center of asymmetry will have the major influence on the sign of the Cotton effect for other optically active polyhydroxyalkyl aromatic heterocycles. Derivatives are available which permit structure–rotatory dispersion investigation at all four centers of asymmetry of hexoses. In addition to the use of benzimidazoles and quinoxalines for assignment of stereochemistry at C-2 and C-3 of hexoses, C-3 stereochemistry may be studied using the osotriazole derivative, the 2-hydroxyquinoxaline prepared from the 2-ketoaldonic acid (Figure 4), the cinnoline produced as a side product in the osazone reaction (Figure 5), or the pyrazine derivatives of 2-amino sugars (Figure 6). The furan derivative **1** is poorly suited to rotatory dispersion work compared to quinoxalines, osotriazoles, and cinnolines because it exhibits only a weak Cotton effect associated with the 251-mμ maximum. Configuration at C-4 may be studied using the flavazole **2a** or 1-phenylflavazole derivative **2b** which exhibit Cotton effects centered at about 390 and 410 mμ, respectively. Although flavazole Cotton effects are weak, the long wavelength side of a negative Cotton effect is readily distinguishable for both **2a** and **2b**. Stereochemistry at C-5 follows from inspection of the rotatory dispersion of the anhydroosazone (Figure 7).



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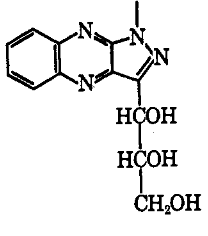

2a, R = H
b, R = C_6H_5

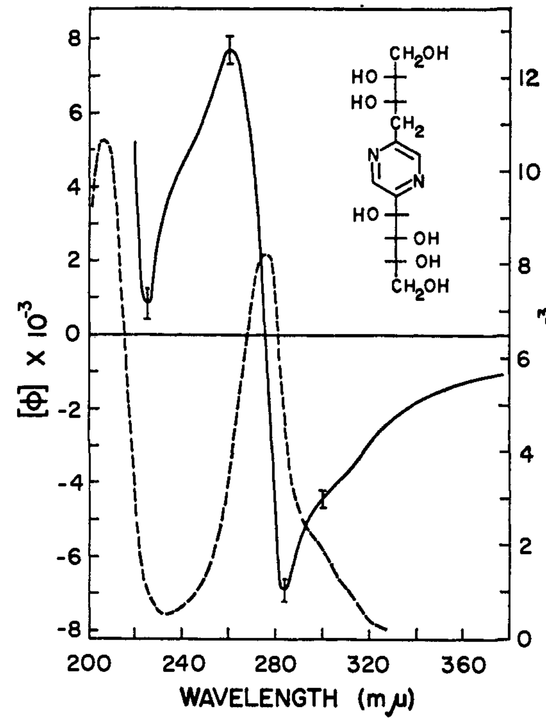

Figure 6. Spectra of 2-(D-*arabino*-tetrahydroxybutyl)-5-(D-*erythro*-2′,3′,4′-trihydroxybutyl)pyrazine: ultraviolet, ---; ORD, —.

These derivatives, possessing a large amplitude Cotton effect, permit assignment of stereochemistry with microgram quantities. Many of the compounds also have very high molar extinction coefficients in the region of observation. Since a considerable proportion of the incident light must be passed through the sample in order to obtain stable rotation measurements, an upper

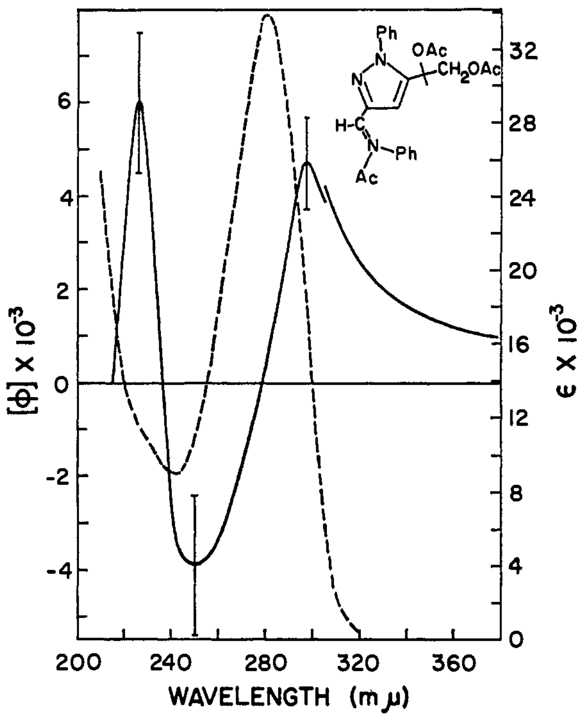

Figure 7. Spectra of 1-phenyl-5-(D-diacetoxyethyl)pyrazole-3-carboxaldehyde-N-acetylphenylhydrazone: ultraviolet, ---; ORD, —.

limit on solution concentration exists which limits the absolute magnitude of the rotation to be measured. Therefore it is not the amplitude of the Cotton effect alone which determines the suitability of a derivative for rotation study, but rather the ratio of Cotton effect amplitude to the maximum extinction coefficient encountered in the spectral region under study. The value of this ratio for the carbonyl group, successfully used in the octant rule,[18] lies in the range of 100–200 while for the compounds presently under study the ratio is an order of magnitude less favorable. Cinnolines, quinoxalines, and benzimidazoles possess the most favorable ratio for further study. Structure–rotatory dispersion correlations for benzimidazoles and quinoxalines will be reported in the following paper.

Experimental Section

Rotatory dispersion measurements were made at 25° with a Cary Model 60 spectropolarimeter in Baker and Adamson methanol. Concentrations from 0.01 to 1 g/l. and cell lengths from 1 to 100 mm were employed. Ultraviolet spectra were measured with a Cary Model 14 spectrophotometer.

Materials. 2-(D-*arabino*-Tetrahydroxybutyl)benzimidazole,[19] 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline,[20] 4-(D-*arabino*-tetrahydroxybutyl)-2-phenyl-1,2,3-triazole,[21] 2-hydroxy-3-(D-*arabino*-tetrahydroxybutyl)quinoxaline,[22] 3-(D-*arabino*-tetrahydroxybutyl)cinnoline,[23] 2-(D-*arabino*-tetrahydroxybutyl)-5-(D-*erythro*-2′,3′,4′-trihydroxybutyl)pyrazine[24] and 1-phenyl-5-(D-diacetoxyethyl)pyrazole-3-carboxyaldehyde N-acetylphenylhydrazone[25] were prepared by previously described methods.

Ethyl 2-(D-*arabino*-tetrahydroxybutyl)-5-methyl-4-furoate (1) was prepared by the method of Garcia-Gonzalez,[26] mp 148–149°. The ultraviolet spectrum in methanol showed λ_{max} 251 mμ (ε 4290). ORD in methanol at 25° (*c* 0.09–0.02), $[\phi]_{600}$ −52°, $[\phi]_{589}$ −55°, $[\phi]_{500}$ −85°, $[\phi]_{400}$ −158°, $[\phi]_{300}$ −532°, and $[\phi]_{269}$ −1020 ± 80° (trough).

3-(D-*erythro*-Trihydroxypropyl)flavazole (2a) was prepared by a modification of the method of Ohle and Iltgen.[27] 2-(D-*arabino*-Tetrahydroxybutyl)quinoxaline (3 g) was dissolved in 100 ml of hot 50% acetic acid. Hydrazine hydrate (10 ml, 85%), previously mixed with 20 ml of 50% acetic acid, was added, and the resultant solution was heated at reflux 5 hr. After slight concentration crystals formed in the cooling solution. The product was recrystallized twice from water giving 1.35 g, 43%, of yellow needles, mp 230–231° dec. The ultraviolet spectrum in methanol showed shoulder 390 mμ (ε 4800), λ_{max} 378 (5540), 332 (11,200), and 237 (32,000); ORD in methanol at 25° (*c* 0.08–0.008), $[\phi]_{600}$ −0.3 ± 0.6°, $[\phi]_{589}$ −1.5 ± 0.6°, $[\phi]_{500}$ −17 ± 1°, $[\phi]_{410-413}$ −320 ± 40° (trough), $[\phi]_{355}$ +590 ± 90°, $[\phi]_{350-305}$ (could not be measured), $[\phi]_{300}$ +180 ± 90°, and $[\phi]_{268-270}$ −430 ± 70° (trough).

1-Phenyl-3-(D-*erythro*-trihydroxypropyl)flavazole (2b) was prepared by the method of Ohle and Kruyff.[28] The ultraviolet spectrum in methanol showed λ_{max} 412 mμ (ε 3840), 337 mμ (ε 10,200), and 270 mμ (ε 43,900); ORD in methanol at 25° (*c* 0.04), $[\phi]_{600}$ −32°, $[\phi]_{589}$ −34°, $[\phi]_{500}$ −84°, $[\phi]_{475}$ −128° (trough could not be measured).

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[18] W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(19) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940).

(20) H. Ohle and M. Hielscher, *Ber.*, **71**, 13 (1941).

(21) R. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 735 (1944).

(22) H. Ohle, *Ber.*, **67**, 155 (1934).

(23) H. J. Haas and A. Seeliger, *ibid.*, **96**, 2427 (1963).

(24) R. Kuhn, G. Kruger, H. J. Haas, and A. Seeliger, *Ann. Chem.*, **644**, 122 (1961).

(25) H. El Khadem and M. M. Mohammed-Aly, *J. Chem. Soc.*, 4929 (1963).

(26) F. Garcia-Gonzalez, *Advan. Carbohydrate Chem.*, **11**, 129 (1956).

(27) H. Ohle and A. Iltgen, *Ber.*, **76**, 1 (1943).

(28) H. Ohle and J. J. Kruyff, *ibid.*, **77**, 507 (1944).