^{1}H NMR CONFORMATIONAL ANALYSIS OF ACYLATED GLYCEROLYL FLAVAZOLES

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الخلاصـــة :

لقد وضُع : [١ - أريل - ٣ - (D - أرثيرو - ١ و ٢ و ٣ - ثلاثي أسيتوكسي بروبيل) - ٦ و ٧ - " ثنائي ميثيل فلافازولات " ومتشابهاتها أل (L - ثريو)] - تحت الاختبار باستخدام طيف الطنين النووي المغناطيسي . وأمكن استنتاج الهيئة المميزة من بيانات الأزدواج الغَـزَلي . وتبيّن أنَّ الهيئة المفضلة لمتشابهات أل (D - أريثرو) غالباً ما تكون متعرجة zigzag . بينما تكون متشابهات أل (L - ثريو) في الغالب على هيئة منجل . بينما تكون متشابهات أل (بنزويلوكسي) على هيئة ملتوية في حالة متشكلات (D - أريثرو) .

ABSTRACT

The conformation of 1-aryl-3-(D-*erythro*-1,2,3-triacetoxypropyl)-6,7-dimethyl-flavazoles and their L-*threo* analogs have been examined by ^{1}H NMR spectroscopy. The favored conformation can be deduced from the spin-spin coupling data. The most popular conformation of the D-*erythro* analogs is the extended zigzag conformations, whereas the sickle conformation of the L-*threo* analogs is the most popular one. However, a bent conformation is the most popular for the benzoyloxy analogs of the D-*erythro* isomers.

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^{1}H NMR CONFORMATIONAL ANALYSIS OF ACYLATED GLYCEROLYL FLAVAZOLES [1]

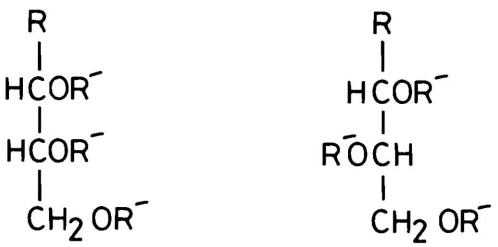
INTRODUCTION

The conformational analysis of organic molecules has attracted much attention, as a consequence of the advanced development of spectroscopic methods; in particular ^{1}H NMR spectroscopy has been used extensively in this respect [2, 3]. The analysis is accomplished by estimating the dihedral angle between two C–H bonds in a saturated fragment from the values of the vicinal proton–proton coupling, based on the theoretical work of Karplus [4]. The effect of the conformation of a polyol on the mode of its reactions [5] attracted our attention [6]. The present report enumerates the favored conformations in solution, as determined by ^{1}H NMR spectroscopy, of 1-aryl-3-(D-*erythro*-1,2,3-triacyloxypropyl)-6,7-dimethylflavazoles and their L-*threo* analogs. These compounds could be of potential value as antibacterial, antiinflammatory, and analgesic agents [7].

RESULTS AND DISCUSSION

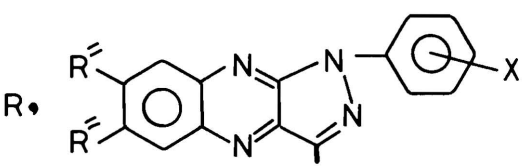
The compounds **2** and **3** required for the present study were prepared, respectively, by the acetylation and benzoylation of **1**. The ^{1}H NMR spectra (Table 1) of the compounds were measured in chloroform-*d*. The acetoxymethyl groups resonated as a series of sharp singlets between δ 2.00–2.20. The two methyl groups on the flavazole ring appeared as a singlet near δ 2.5 and the aromatic protons as a complex multiplet near δ 8.0. The C-1 proton of the polyacetoxy and benzoyloxyalkyl side chains gave rise to a doublet near δ 6.7 and singlet near δ 7.2, respectively, whose spacing gave $J_{1,2}$. The signal next upfield of H-1 was assigned to H-2; it appeared as a multiplet near δ 6.0 or 6.6 for the acetate and benzoate, respectively. The methylene protons of the terminal acyloxymethyl group resonated at highest field of the protons on the chain, near δ 4.4 and 4.6 for the acetates and for those of the benzoates near δ 4.8 and 5.1, as the A and B portions of an ABX system, from which the remaining coupling constants were measured. The difference in chemical shift between the protons in the acetates and benzoates is due to the different shielding effects. The spectra of the other examples were analyzed in previous reports [9] and the coupling constants were used in the present work to estimate their favored conformations. The ratio of chemical shift difference to coupling constant for coupled protons was of sufficient magnitude to ensure that the spacing measured approximate closely to the true coupling constants.

The favored conformation of acyclic sugar derivatives like that of other molecules having unbranched chains, has been assumed to be a planar arrangement of the carbon chain, in which the largest groups along each carbon–carbon bond are in antiparallel disposition, unless this results in a 1,3-interaction of oxygen atoms on the chain. A qualitative corrections for the effects of substituent electronegativity were made by assuming that proton-coupling constants



1, R′ = H
2, R′ = Ac
3, R′ = Bz

4, R′ = H
5, R′ = Ac



a: R″ = H, X = 3-Cl
b: R″ = Me, X = H
c: R″ = Me, X = 4-Br
d: R″ = Me, X = 3-Cl
e: R″ = Me, X = 4-Cl

Scheme 1.

Table 1. ^{1}H NMR and IR Spectral Data.

	2b	2c	2e	3b	3c	3e
^{1}H NMR						
H-1	6.68 (d)	6.74 (d)	6.67 (d)	7.18 (s)	7.18 (s)	7.15 (s)
$J_{1,2}$	6.0 Hz	6.0 Hz	6.0 Hz			
H-2	5.98 (m)	6.04 (m)	6.00 (m)	6.56 (m)	6.59 (m)	6.57 (m)
H-3′	4.43 (q)	4.44 (q)	4.40 (q)	4.80 (q)	4.85 (q)	4.83 (q)
$J_{2,3'}$	6.0 Hz	6.0 Hz	6.0 Hz	6.0 Hz	6.0 Hz	6.0 Hz
$J_{3,3'}$	12.0 Hz	12.0 Hz	12.0 Hz	12.0 Hz	12.0 Hz	12.0 Hz
H-3	4.63 (q)	4.67 (q)	4.63 (q)	5.10 (q)	5.13 (q)	5.10 (q)
$J_{2,3}$	4.5 Hz	4.5 Hz	4.5 Hz	4.5 Hz	4.5 Hz	4.5 Hz
MeCO	2.00 (s)	2.00 (s)	1.97 (s)			
MeCO	2.03 (s)	2.03 (s)	2.00 (s)			
MeCO	2.20 (s)	2.20 (s)	2.20 (s)			
2Me	2.53 (s)	2.50 (s)	2.50 (s)	2.52 (s)	2.53 (s)	2.56 (s)
				2.48 (s)	2.50 (s)	2.53 (s)
Aromatic	8.04 (m)	8.02 (m)	8.00 (m)	7.80 (m)	7.90 (m)	7.80 (m)
IR						
C=N	1600	1595	1600	1600	1600	1600
OCO	1750	1745	1745	1730	1730	1730

<4 Hz represent vicinal protons having a *gauche* orientation, and that coupling constants >7 Hz indicate principally an antiparallel orientation of vicinal protons.

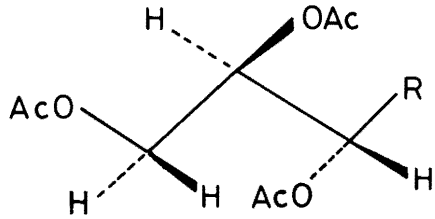
The coupling constants, based on the first order analysis of the spectra, between vicinal protons in the acetates **2b–e** having D-*erythro* configurations, were found to be identical, indicating that their glycerolyl side chains adopt similar conformations in solution in deuterated chloroform, irrespective of the substituents.

The examination of the extended zigzag conformation **6** of **2** indicated that the H-1–H-2 are in a *trans* arrangement (**10**). The measured value of $J_{1,2}$ is 6.0 Hz, which indicates that **6** represents the only extensive population of **2**, because **10** requires a value >7.0 Hz. The intermediate values of $J_{2,3}$ (4.5 Hz) and $J_{2,3'}$ (6.0 Hz) suggest a substantial population of more than one rotational state along the terminal C–C bond; particularly **12** and **13** which have H-2 antiparallel to one H-3 proton. However, the rotamer **13** from the conformation **6** would suffer a 1,3-interaction. These data led to the conclusion that the sickle conformation **7**, that can be achieved by a rotation around C-1–C-2 bond, may contribute to a minor extent.

The $J_{1,2}$ of the benzoate **3** is about zero, indicating a dihedral angle near 90°, and this could be gained by rotation around C-1–C-2 to give an intermediate rotameric form between rotamers similar to **10** and **11**. This means that a bent conformation is the most popular for **3**. This may be due to the steric interaction between the C-2-benzoyloxy group and the flavazole ring.

Considerations made for **2** are also applicable to **5**. Thus, the examination of the extended zigzag conformation **8** of **5** indicated that the H-1–H-2 are in a *gauche* arrangement, as represented by the Newman projection **14**, and requires a value <4 Hz for $J_{1,2}$. The measured value was 6.0 Hz indicating the presence of a conformational equilibrium that contained a significant proportion of the rotamer having the H-1 and H-2 in a *trans* arrangement. This could be achieved by rotation around a C–C bond of the glycerolyl residue to afford a sickle conformation such as **9**, where **15** shows the projection of C-1–C-2. It is interesting to note that the same $J_{1,2}$ values in both the *erythro* and *threo* isomers are caused from a similar population of **10** and **11**, and **14** and **15** rotamers, respectively.

The $J_{2,3}$ 4.5 and $J_{2,3'}$ 6.0 Hz were intermediate magnitude indicating that more than one rotameric



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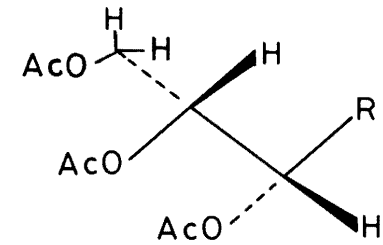

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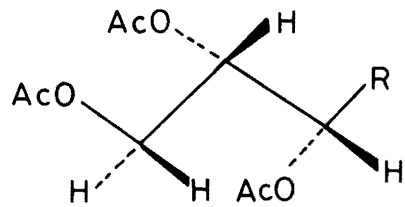

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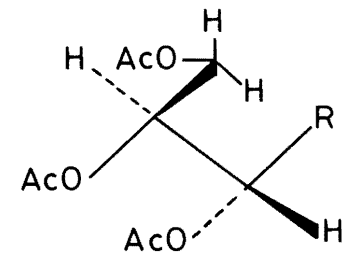

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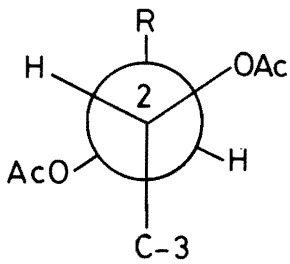

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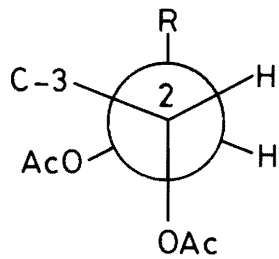

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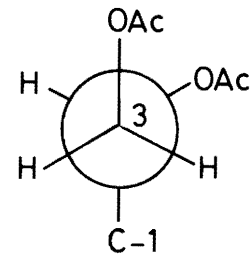

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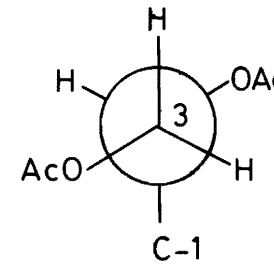

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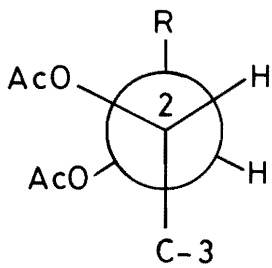

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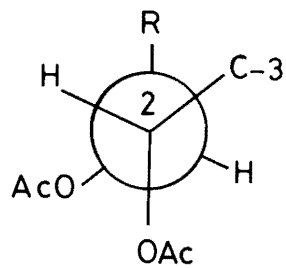

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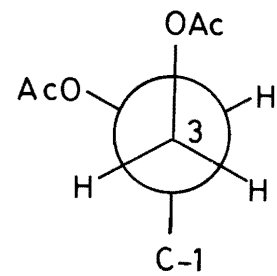

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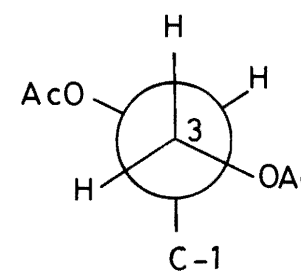

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Scheme 2.

state (such as **16** and **17**) about C-2–C-3 bond must also be significantly populated as in the case of the *erythro* isomer. Consequently, the coupling data do not support the planar zigzag form **8** as the major conformer. It appears that the vicinal *gauche* interactions are sufficient to dictate rotational alterations, since the four substituents as shown in **14** are in *gauche* arrangement with each other. This is accommodated by a major representation of the form **9**.

A similar conformation for that of **4** is also adopted for 1-(3-chlorophenyl)-3-(L-*threo*-1,2,3-triacetoxypropyl) flavazole [8] as its spin–spin coupling of its protons are similar to that of **4**.

EXPERIMENTAL

General Methods

Melting points were determined on a "Meltemp" apparatus and are uncorrected. Infrared spectra were recorded with a Unicam SP 1025 spectrophotometer. ^{1}H NMR spectra were determined with a 90 MHz Varian EM-390 spectrometer for solutions in chloroform-*d* with tetramethylsilane (Me_4Si) as internal reference. The spectra are reported as chemical shifts downfield from Me_4Si. Microanalyses were made in the Unit of Microanalysis, Faculty of Science, Cairo University, Cairo, Egypt.

1-Aryl-3-(D-*erythro*-1, 2, 3-triacetoxypropyl)-6, 7-dimethylflavazole [10] (2).

A solution of **1b–e** (1 mmol) in dry pyridine (10 ml) was cooled and treated with acetic anhydride (5 ml) and the reaction mixture was left overnight at room temperature. It was then poured onto crushed ice, and the product was collected by filtration, and washed with water. It was recrystallized from ethanol in yellow needles (see Table 2).

1-Aryl-3-(D-*erythro*-1, 2, 3-tribenzoyloxypropyl)-6, 7-dimethylflavazole (3).*

A solution of **1b–e** (1 mmol) in dry pyridine (5 ml) was treated with benzoyl chloride (0.2 ml) and the reaction mixture was left overnight at room temperature. It was then poured onto crushed ice, and the product was collected by filtration and washed with water. It was recrystallized from ethanol in yellow needles (see Table 3).

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*Prepared by N. El Shimy

Table 2. Elemental Analysis for 1-Aryl-3-(D-*erythro*-1,2,3-triacetoxypropyl)-6,7-dimethyl-flavazoles.

Compound No.	R	m.p. (°C)	Yield (%)	Molecular formula	Calculated (%)			Found (%)		
					C	H	N	C	H	N
2b	H	206°	72	$C_{26}H_{26}N_4O_6$	63.7	5.3	11.4	63.7	5.0	11.3
2c	Br	164°	75	$C_{26}H_{25}BrN_4O_6$	54.8	4.4	9.8	54.9	3.8	9.6
2e	Cl	166°	77	$C_{26}H_{25}ClN_4O_6$	59.5	4.8	10.7	59.5	4.3	10.6

Table 3. Elemental Analysis for 1-Aryl-3-(D-*erythro*-1,2,3-tribenzoyloxypropyl)-6,7-dimethyl-flavazoles.

Compound No.	R	m.p. (°C)	Yield (%)	Molecular formula	Calculated (%)			Found (%)		
					C	H	N	C	H	N
3b	H	177°	78	$C_{41}H_{32}N_4O_6$	72.8	4.8	8.3	72.9	5.4	8.5
3c	Br	126°	80	$C_{41}H_{31}BrN_4O_6$	65.2	4.1	7.4	65.5	4.4	7.8
3e	Cl	163°	83	$C_{41}H_{31}ClN_4O_6$	69.2	4.4	7.9	68.9	4.5	8.0

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