Stereochemistry of the Bucherer-Bergs Reaction and a Modified Strecker Reaction on Tetrahydro-2*H*-pyran-3-ones

Serkos A. Haroutounian, Minas P. Georgiadis* and Moschos G. Polissiou

Agricultural University of Athens, Chemistry Laboratory, Iera odos 75,
Athens 11855, Greece

Received May 25, 1989

Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

The stereochemical aspects of the Bucherer-Bergs reaction and a modified Strecker reaction on tetrahydro-2*H*-pyran-3-one derivatives have been studied in details through the use of several nmr techniques. It was found that, in both reactions, the orientation of the substituents introduced on C-3 of the pyran ring, depends from the number and nature of the substituents on the neighbouring C-2 atom.

J. Heterocyclic Chem., **26**, 1283 (1989).

Introduction.

One of the most convenient routes for the synthesis of α-amino acids involves the reaction of aldehydes or ketones with ammonium carbonate and sodium cyanide to form spirohydantoins (the Bucherer-Bergs reaction [1]), followed by hydrolysis of the latter to α-amino acids.The alternative route from the same starting materials is *via* α-amino nitriles (the Strecker reaction [2]), which generally by hydrolysis gives the geometrical isomers of the same products, but in poorer yields. Recently we have proposed a modification of the classical Strecker method [3], yielding α-benzylamino nitriles and α-amino nitriles (of a broad variety of carbonyl containing compounds) in almost quantitative yields. All the above reactions lead to products with remarkable stereospecificity and their configuration depends on the stereochemical aspects of the starting ketones as well as the reaction conditions [4]. Since various geometrical isomers showed different biological activity, the configuration of spirohydantoins [5], α-benzylamino nitriles [6] and α-amino acids [7,8] have great biological importance. Earlier researchers have studied in detail the stereochemical aspects of these reactions for a variety of starting materials [9,10]. Especially the structural assignments of cyclic amino acids, synthesized *via* Bucherer-Bergs or Strecker routes have been controversial, and contradictory assignments have appeared in the literature for a variety of cyclohexanone derivatives [4,10]. For example the Bucherer-Bergs reaction on 4-*t*-butylcyclohexanone [4] gave predominantly one isomeric hydantoin (amino group with an axial orientation), while the Strecker reaction on the same starting material gave a product with the other possible orientation (amino group at the equatorial position).

In our efforts to synthesize new, biologically active oxygen-containing isosteres of β-dihydroxy phenylalanine (DOPA) [11] and β-dihydroxy phenylethylamine (DOPAMINE) [6], we have performed the classical Bucherer-Bergs reaction, as well as a new high yield modification of Strecker reaction on tetrahydro-2*H*-pyran-3-one derivatives and have studied the stereochemical aspects of the products. Our structural assignments are based on spectroscopical data (^{1}H nmr, ^{13}C nmr and 2D nmr), which lead to unequivocal identification of the various geometrical isomers. The ease of synthesis and isolation of these highly functionalized products, along with their remarkable stereospecificity, make them attractive starting materials for the synthesis of more complex molecules of biological interest.

EXPERIMENTAL

The synthesis and purification of the compounds used in this work was achieved by using methods which have been described in our previous papers [6,12]. The ^{1}H nmr and ^{13}C nmr spectra were recorded on a Nicolet NT 360 (at 360 MHz and 90 MHz respectively) spectrometer at 20° temperature in the indicated solvents. Chemical shifts are reported in parts per million from tetramethylsilane as internal standard (δ scale). The 2D nmr spectra (Homonuclear proton NOESY experiment) were obtained on a General Electric GE-300 spectrometer and carried out with the usual pulse sequence RD-π/2-t_1-π/2-t_m-π/2-t_2, where RD is the relaxation delay (1.5 s) and t_m is the mixing time (500 ms). The t_1 value of 10 μs was used with 256 equidistant increments (Δt_1 = 600 μs), and zero filling was used. The digital resolution along both axes was 16.0 Hz/point and 256 scans were taken.

Results and Discussion.

In our efforts to synthesize new, more potent oxygen containing isosteres of sympathomimetic amines, we have utilized as a working hypothesis that their parent compound is β-phenylethylamine [13] and the minimal structural requirement valid for dopamine (DA(D_2)) antagonist activity, is that the distance of a vector directed from the center of the phenyl group to a basic N atom should be 5-6.5 Å [14]. Furthermore we have relied on Molecular Mechanics calculation results [6], which indicated that in the case of sympathomimetic amine analogous which contain the pyran ring, the necessary structural requirement was fulfilled only when a diaxial orientation of both phenyl

and amino group was achieved or for the case of γ-phenylpropylamine derivatives (with the phenyl group at equatorial orientation). In order to achieve this synthetic goal, we have performed the Bucherer-Bergs and the modified Strecker reactions selectively on various tetrahydro-2*H*-pyran-3-one derivatives.

Stereochemistry of Tetrahydro-2*H*-pyran-3-ones [15].

In 1971 Allinger and Tribble [16] calculated, using a force field approach, that in 2-methyl-2-phenylcyclohexanone **2a** the conformational energies of methyl (1.7 Kcal/mol) and phenyl (3.0 Kcal/mol) groups should not be additive and the conformation with the larger phenyl group in the axial position was preferred at equilibrium by 0.9 Kcal/mol. This comes about because the most stable conformation of the axial phenyl group (phenyl perpendicular to the bisector plane of the cyclohexane chair) is not perturbed by introduction of a geminal methyl substituent. However in the absence of the geminal methyl group (monosubstitution), the conformation with the phenyl substituent at the equatorial position **1a** of the bisector plane of the cyclohexane chair is thermodynamically the most stable [17]. The above predictions were revealed in 1981 by Eliel and Manoharan [18] with the aid of spectroscopical measurements.

In the case of tetrahydro-2*H*-pyran-3-one derivatives we have used 2D nmr spectroscopy (NOESY experiment) and confirmed the stereochemical assignments shown in Scheme I.

Scheme I

1 2

Compound	-X-	-R_1	-R_2
1a	-CH_2-		-H
1b	-O-		-OCH_3
2a	-CH_2-	$-CH_3$	
2b	-O-	$-CH_3$	CH_3O- 

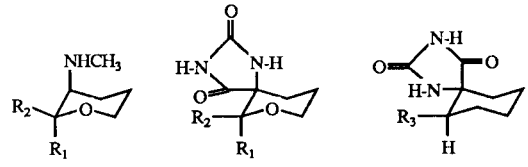
More specifically for 6-methoxy-2-(3,4-methylenedioxyphenyl)tetrahydro-2*H*-pyran-3-one **1b** the axial orientation of the methoxy group may be proved by ^{1}H nmr, considering the couplings $J_{6,5}$ = 2.9 Hz and $J_{6,4}$ = 0 and the anomeric effect [19]. Furthermore in a two dimentional NOESY experiment the fact that the protons of the methoxy group showed strong nOe correlation with H(2) and no correlation with H_{arom} unequivocally confirms the stereochemistry of **1b**. On the other hand in a similar experiment for 2-(*p*-methoxyphenyl)-2-methyltetrahydro-2*H*-pyran-3-one **2b** the strong nOe correlation H(6) ⇝ H_{arom} and lack of any H(6) ⇝ CH_3 proved the assignments for compound **2b**.

Configuration of Spirohydantoins.

Previous works on spirohydantoins have established that the Bucherer-Bergs reaction on a variety of cyclic ketones furnishes exclusively one isomeric spirohydantoin, the one with the 4′-carbonyl group in the less sterically hindered equatorial (exo) position [4,9]. The conformational assignments were based on ir, nmr and X-ray crystallography findings and were in accordance with those expected from a detailed consideration of steric effects on a kinetically determined product (the Bucherer-Bergs product). Even though the above discussed preferred equatorial orientation of the 4′-carbonyl group was studied in details for products derived from anchored cyclohexanones [4], in the case of 2-phenyl cyclohexanone [10] the Bucherer-Bergs reaction gave spirohydantoin **5** with the amino group at equatorial orientation, while the Strecker reaction led to an α-amino nitrile with the amino group at axial position.

Application of the classical Bucherer-Bergs reaction on compound **1b** yielded exclusively one isomeric spirohydantoin, the 6-(*p*-methoxyphenyl)-6-methyl-7-oxa-1,3-diazaspiro[4,5]decane-2,4-dione **4** (Scheme II). The structural assignments for this compound were based at the following line of evidences:

Scheme II



3 4 5

R_1: CH_3O  R_2: $-CH_3$ R_3: 

(1) ^{1}H NMR.

A general and simple criterion to discover the isomeric purity of spirohydantoins in rigid systems is the study of the N(1′)-H signal in the ^{1}H nmr spectra [8]. Thus compound **4** showed only one N(1′)-H signal (δ 8.34), while in case of the opposite configuration this signal should be appeared more upfield (at 6 ppm about). Aromatic and angular methyl protons were also affected by the different contribution of the diamagnetic anisotropic effect of the 4′-carbonyl group, by a manner that only an equatorial orientation of this group may affect. Thus the protons of the angular methyl of compound **4** appeared (Table I) at

lower field (δ 1.72) than the corresponding protons of compound **3** [11], due to the deshielding effect of the 4'-carbonyl group. On the other hand the observed upfield shift (7.46 → 7.27) of the ortho aromatic protons may be explained by the shielding effect of the lone pair electrons of the 4'-carbonyl oxygen atom.

Table I

^{1}H NMR Chemical Shifts of Compounds **3** and **4**

	Compound **4** (DMSO-d_6)	Compound **3** (Deuteriochloroform)
CH_3	1.72 m	1.54 m
H(4)	2.33 m	1.91 m
H(5)	1.92 m	1.91 m
H(6)	3.90 m	3.88 m
H_{arom}	7.27 (d, J = 8. 9 Hz)	7.46 (d, J = 8.8 Hz)
H_{arom}	6.83 (d, J = 8. 9 Hz)	6.87 (d, J = 8.8 Hz)

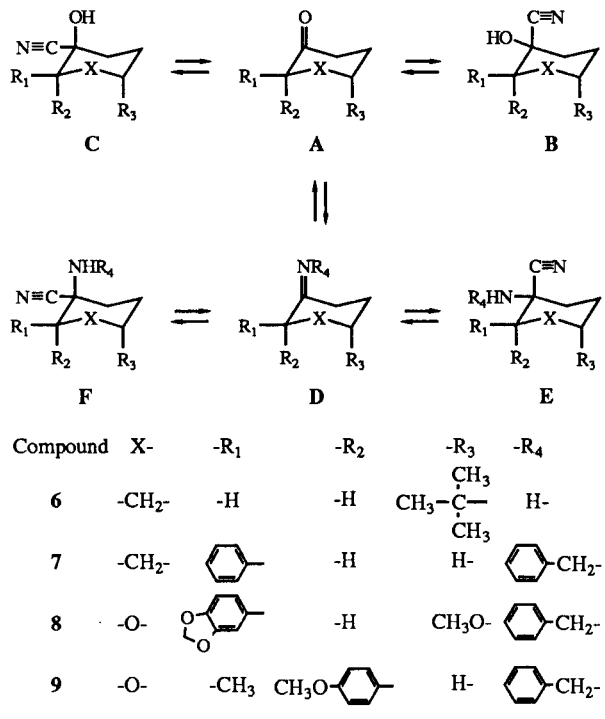
(2) ^{13}C NMR.

Since the stereochemistry of the spirohydantoin **5** has already been established by spectroscopical and X-ray data [10], the configuration of spirohydantoin **4** may be established by comparing the deshielding-shielding effects of the spirohydantoin moiety at ^{13}C nmr for each molecule. More specifically we have recorded the ^{13}C nmr spectra of spirohydantoins **4, 5** and their starting materials **1a, 2b** on the same instrument, temperature, concentration and solvents. The chemical shifts are listed in Table II and the measured deshielding-shielding effects may be pictured by the difference of the chemical shifts between the starting ketones and the spirohydantoins for the different class of compounds. Since there is a distinct deshielding-shielding effect of the spirohydantoin moiety for these two different classes of compounds (evaluated by differences up to 3 ppm), one can assume that the spirohydantoins **4** and **5** have different stereochemistry.

Configuration of α-Benzylaminonitriles.

The mechanism and the configuration of the reaction products for the synthesis of α-aminonitriles *via* the Strecker route for cyclohexanone derivatives **6** (Scheme III), have already been discussed by Edward and Jitrangsri [4]. They have found that the α-aminonitrile **6E** is the

Scheme III



Compound	X-	-R_1	-R_2	-R_3	-R_4
6	-CH_2-	-H	-H	$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-$	H-
7	-CH_2-		-H	H-	
8	-O-		-H	CH_3O-	
9	-O-	-CH_3		H-	

predominant product (95 to 5 over compound **6F**), along with an amount of cyanohydrin byproducts (**6B** and some **6C**). The detailed investigation of the reaction mechanism and various equilibria as well as the isolation of compound **6F** is difficult since α-aminonitriles and its hydrochlorides are quite unstable.

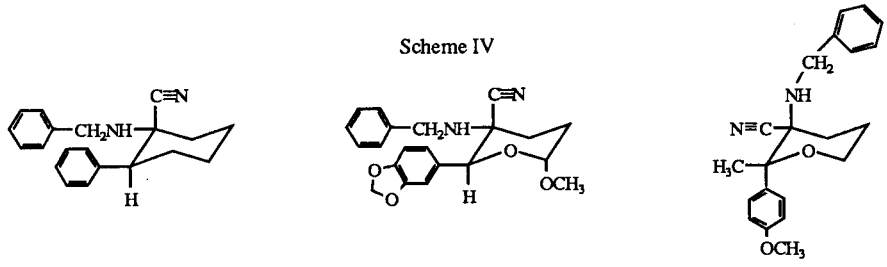
Recently we have described a convenient, high yield modification of the classical Strecker reaction which leads to the formation of α-benzylamino nitriles [3]. This thermodynamically controlled synthesis proceeds at 60° in absolute methanol *via* the formation of the imine of benzylamine, **7D, 8D, 9D**, and *in situ* addition of hydrogen cyanide (from potassium cyanide and acetic acid). We have performed this reaction on both carbocyclic **7** and heterocyclic **8, 9** compounds and received only one stereoisomeric α-benzylaminonitrile as the product, while no trace of cyanohydrin byproducts were observed. This may reflect

Table II

^{13}C NMR Chemical Shifts of Spirohydantoins **4, 5** and their Starting Materials **2b, 1a**

Compound No.	Solvent	Ring Carbons C-1	C-2	C-3	C-4	C-5	C-6	Aromatic Carbons C'-1	C'-2 C'-6	C'-3 C'-5	C'-4	Other Carbons C=O	C=O	-CH_3	CH_3O-
1a	Deuteriochloroform	34.4	56.9	209.7	41.7	24.9	27.4	138.5	128.1	127.8	126.4	---	---	---	---
5	DMSO-d_6	27.7	48.0	66.8	35.0	21.2	25.8	140.5	129.1	128.0	127.0	156.9	177.5	---	---
Difference		6.7	8.9	142.9	6.7	3.7	1.6	-2.0	-1.0	-0.2	-0.6	---	---	---	---
2b	Deuteriochloroform	---	85.0	209.1	36.7	27.3	61.4	132.2	126.2	114.1	158.9	---	---	27.4	55.1
4	DMSO-d_6	---	79.1	68.6	28.7	21.1	61.2	136.3	128.0	113.7	159.3	157.1	177.8	21.2	55.8
Difference		---	5.9	140.5	8.0	6.2	0.2	-4.1	-1.8	-0.4	-0.4	---	---	6.2	-0.7

Scheme IV



7E 8E 9F

the fact that the reaction conditions (acidic environment, absence of water) do not favor the establishment of various equilibria of Scheme III. Furthermore the exact configuration of the reaction product is resumed from both thermodynamical and stereochemical limitations. In the case that there is substitution and stereochemical hinderence at the next carbon atom, the bulky nature of benzylamine group limits the possible orientations of benzylamine and cyanide moieties. The α-benzylaminonitriles reported in the paper were stable and their stereochemistry at C-3 (Scheme IV) was established by the aid of a 2D-nmr NOESY experiment.

More specifically for compound **8E** a representative NOESY spectrum is shown in Figure I. In this spectrum there is a strong nOe correlation between the aromatic protons of the two phenyl groups and a weak correlation

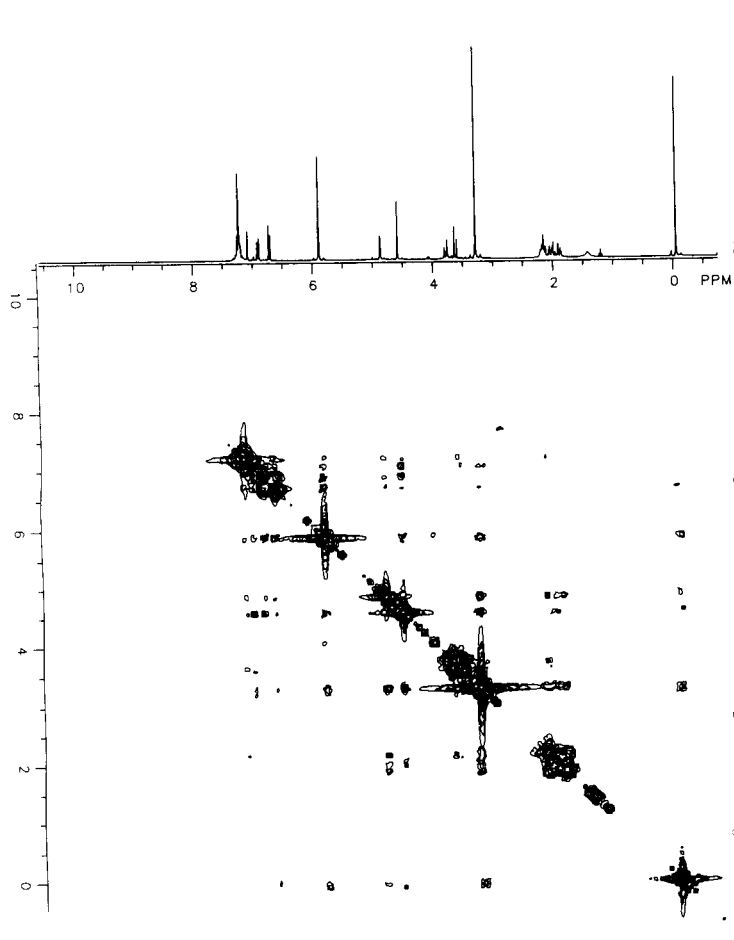


Figure I. Proton NOESY (300 MHz) spectrum of **8E**; ^{1}H nmr (deuteriochloroform, TMS): δ 7.23 [s, 5H, H-Ar], 7.13 [s, 1H, H(2)-Ar], 6.95 [dd, J = 9, 2.7, 1H, H(6)-Ar], 6.76 [d, J = 9, 1H, H(5)-Ar], 5.95 [s, 2H, CH_2O], 4.93 [m, 1H, H-C(6)], 4.63 [s, 1H, H-C(2)], 3.82 [d, J = 12.5, 1H, CH_2N], 3.62 [d, J = 12.5, 1H, CH_2N], 3.34 [s, 3H, CH_3], 2.20 [m, 2H, H-C(4)], 2.06 [m, 1H, H-C(5)], 1.96 [m, 1H, H-C(5)], 1.53 [br, NH].

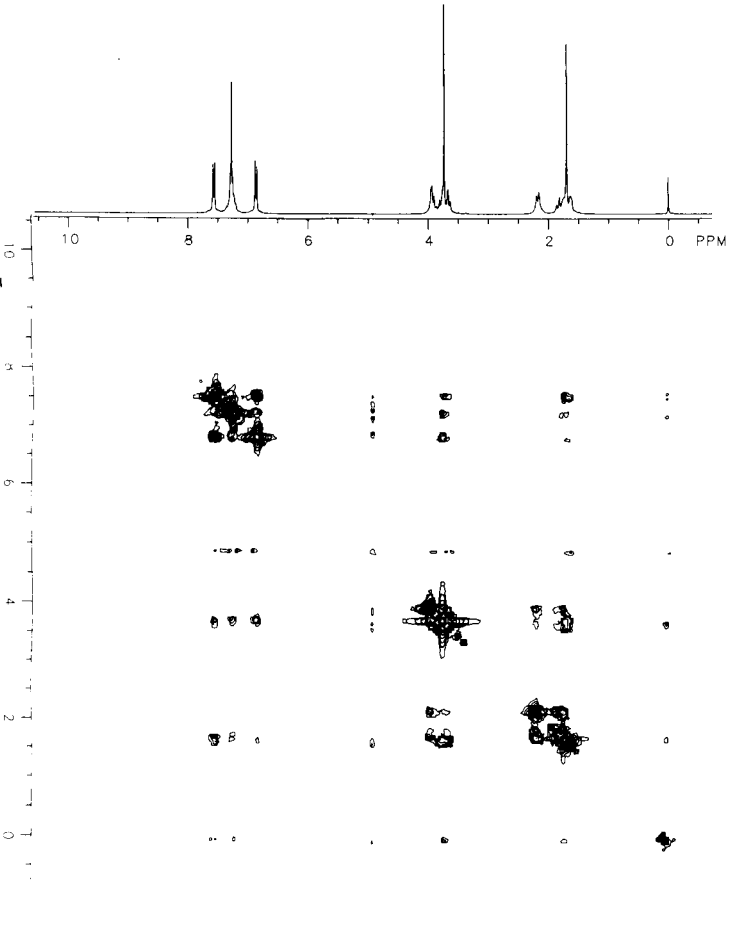


Figure II. Proton NOESY (300 MHz) spectrum of **9F**; ^{1}H nmr (deuteriochloroform, TMS): δ 7.57 [d, J = 9, 2H, H(2,6)-Ar], 7.25 [m, 5H, H-Ar], 6.87 [d, J = 9, 2H, H(3,5)-Ar], 3.91 [m, 2H, CH_2N], 3.77 [s, 3H, CH_3O], 3.74 [m, 2H, H-C(6)], 2.19 [m, 2H, H-C(4)], 1.83 [m, 2H, H-C(5)], 1.72 [s, 3H, angular CH_3], 1.60 [br, NH].

between the protons of the methylenedioxy group and the aromatic protons of benzylamine. These interactions along with a very weak nOe correlation between H(4) and one proton of CH_2 of benzylamine (they are distinct due to restricted rotation) and the lack of any cross peaks between H(5) and CH_2 of benzylamine, clearly demonstrate the equatorial orientation of benzylamine group. Thus the cyanide group has an axial position (Scheme IV).

In the case that there is stereochemical hinderence at the next carbon atom (compounds **9**), the stereochemistry may be determined by a similar 2D-nmr (NOESY) experiment (Figure II). More specifically the presence of cross peaks between the CH_2 of benzylamine and H(4), H(5), as well as the lack of any nOe correlation between the angular methyl group and the protons of benzylamine moiety, unequivocally confirms the stereochemistry of compound **9F** (Scheme IV). Thus in this case the bulky benzylamine group has the less sterically hindered axial orientation, while the cyanide group is at an equatorial position.

REFERENCES AND NOTES

[1a] H. T. Bucherer and V. A. Libe, *J. Prakt. Chem.*, **141**, 5 (1934); [b] J. H. Burckhalter and G. Schmied, *J. Pharm. Sci.*, **55**, 443 (1966).

[2a] S. Strecker, *Ann. Chem.*, **155**, 177 (1870); [b] F. Tieman and L. Friedlander, *Ber.*, **13**, 381 (1880).

[3] M. P. Georgiadis and S. A. Haroutounian, *Synthesis*, in press.

[4] J. T. Edward and C. Jitrangsri, *Can. J. Chem.*, **53**, 3339 (1975).

[5a] S. Cortes, Z. K. Liao, D. Watson and H. Kohn, *J. Med. Chem.*, **28**, 601 (1985); [b] R. Sarges, J. Bordner, B. W. Dominy, M. J. Peterson and E. B. Whipple, *J. Med. Chem.*, **28**, 1716 (1985); [c] R. Sarges, R. C. Schnur, J. L. Belletire and M. J. Peterson, *J. Med. Chem.*, **31**, 230 (1988).

[6] M. P. Georgiadis, S. A. Haroutounian and J. C. Bailar Jr., *J. Heterocyclic Chem.*, **25**, 995 (1988).

[7a] D. M. Stout, L. A. Black and W. L. Matier, *J. Org. Chem.*, **48**, 5369 (1983); [b] J. D. Elliot, V. M. Choi and W. S. Johnson, *J. Org. Chem.*, **48**, 2294 (1983).

[8] H. N. Christensen, M. E. Handlogten, J. V. Vadgama, E. Cuesta, P. Ballesteros, G. G. Trigo and C. Averdano, *J. Med. Chem.*, **26**, 1374 (1984).

[9a] J. Bellanato, C. Averdano, P. Ballesteros, E. Cuesta, E. Santos and G. G. Trigo, *Spectrochim. Acta*, **37A**, 965 (1981); [b] P. Smith-Verdier, F. Florencio and S. Garcia-Blanco, *Acta Cryst.*, **835**, 216 (1979); [c] L. Munday, *J. Chem. Soc.*, 4372 (1961).

[10a] J. Ansell, P. Morgan and H. C. Price, *Tetrahedron Letters*, 4615 (1978). and references within; [b] A. Terzis, S. E. Filipakis and D. Metzafos, *Cryst. Struct. Commun.*, **10**, 803 (1981).

[11] S. A. Haroutounian, Ph.D. Thesis, Agricultural University of Athens, Greece, 1987.

[12] M. P. Georgiadis, *J. Heterocyclic Chem.*, **23**, 605 (1986).

[13] S. A. Haroutounian, M. P. Georgiadis, A. K. Delitheos and J. C. Bailar Jr., *Eur. J. Med. Chem.*, **22**, 325 (1987) and references within.

[14a] E. Kyburz, Third SCI-RSC Medicinal Chemistry Symposium, 1985, Cambridge, England, R. W. Lambert, ed, The Royal Society of Chemistry, 1986, pp 109-132; [b] R. Imhof, E. Kyburz and J. Daly *J. Med. Chem.*, **27**, 165 (1984).

[15] For related paper see: M. P. Georgiadis, E. A. Couladouros, M. G. Polissiou, S. E. Filippakis, D. Metzafos and A. Terzis, *J. Org. Chem.*, **47**, 3054 (1982) and references within.

[16] N. L. Allinger and M. T. Tribble, *Tetrahedron Letters*, 3259 (1971).

[17] V. Malatestra and K. U. Ingold, *J. Am. Chem. Soc.*, **103**, 609 (1981).

[18] E. L. Eliel and M. Manoharan, *J. Org. Chem.*, **46**, 1959 (1981).

[19] A. J. Kirby, "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen", Springer-Verlag, New York, 1983.