A Kinetic and Mechanistic Study on the Thermal Decomposition Reactions of cis- *and* trans- *fused 1,2,4-Trioxanes*

Lázaro F.R. Cafferata*[1], Rene Jeandupeux, Gustavo P. Romanelli, Carmen M. Mateo and Charles W. Jefford[2]

[1]Laboratorio LADECOR and CINDECA (CONICET), Facultad de Ciencias Exactas, Universidad Nacional de La Plata.

[2]Charles W. Jefford, Department of Organic Chemistry, University of Geneva.

Un estudio cinético y acerca del mecanismo de las reacciones de descomposición térmica de los 1,2,4-trioxanos cis *y* trans *condensados.*

Un estudi cinètic i sobre el mecanisme de les reaccions de descomposició tèrmica dels 1,2,4-trioxans condensats cis *i* trans.

Recibido: 17-IX-2002

RESUMEN

Se compararon la cinética de las reacciones de descomposición térmica de artemisinina (1), un *cis*-1,2,4-trioxano, y de *trans*-3,3-dimetil-1,2,4-trioxano (6), en soluciones de benceno, tolueno y de metanol, en tubos cerrados, entre las temperaturas de 100,1 °C y 171,4 °C. *Se determinaron las constantes de velocidad de pseudo* primer orden de ambos peróxidos cíclicos hasta conversiones de ca. 60%. Los valores de los parámetros de activación y los productos de reacción indican rupturas homolíticas de la unión O-O de sus moléculas como paso *determinante de las velocidades de reacción, seguido* de fragmentaciones en etapas. Las energías libres de activación ($\Delta G^{\ddagger}$) para las reacciones de 1 y 6 en benceno y tolueno, calculadas en el mencionado ámbito de temperaturas, poseen valores de 30,7 y 35,1 kcal/mol, respectivamente, los que son evaluados considerando sus diferentes configuraciones moleculares. Además, las *velocidades de descomposición de los trioxanos examinados* son sensibles a efectos del solvente de reacción.

Palabras clave: cis- y *trans*-1,2,4-Trioxanos - Artemisinina - Termólisis - Cinética de reacción.

SUMMARY

The kinetics of the thermal decomposition reactions of artemisinine (1), a *cis*-fused 1,2,4-trioxane, and *trans*-3,3-dimethyl-1,2,4-trioxane (6) in solutions of benzene, toluene, and methanol in sealed tubes were compared at temperatures *between 100.1° and 171.4 °C. Pseudo first*-order rate constant values were determined for conversions of both cyclic peroxides up to ca. 60%. The activation parameters and the composition of the reaction products were indicative of homolytic cleavage of their O-O bonds as the rate-determining steps followed by stepwise fragmentation. The free energies of activation ($\Delta G^{\ddagger}$) for 1 and 6 reactions in the aromatic solvents were calculated at the middle of each temperature range, giving values of 30.7 and 35.1 kcal/mol, respectively, which are evaluated considering their different molecular configurations. Furthermore, the rates of the thermal decomposition reactions of those trioxanes were sensitive to solvent effects.

Key words: cis- and *trans-* fused 1,2,4-Trioxanes - Artemisinine - Thermolysis -Reaction Kinetics.

RESUM

Es compara la cinètica de les reaccions de descomposició tèrmica de l'artemisinina (1), un *cis*-1,2,4-trioxà, i del *trans*-3,3-dimetil-1,2,4-trioxà (6), en solucions de benzè, toluè i de metanol, en tubs tancats, entre les tem*peratures de 100,1 °C y 171,4 °C. Es determinen les cons*tants de velocitat de pseudo-primer ordre d'ambdós peròxids cíclics fins a conversions de *ca.* 60%. Els valors dels paràmetres d'activació i els productes de reacció indiquen ruptures homolítiques de la unió O-O de les seves molècules com pas determinant de les velocitats de reacció, seguit de fragmentacions en etapes. Les energies lliures d'activació ($\Delta G^{\ddagger}$) per a les reaccions d'1 i 6 en benzè i toluè, calculades en el mencionat àmbit de temperatures, tenen valors de 30,7 i 35,1 kcal/mol, respectivament, havent-se avaluat considerant les seves diferents configuracions moleculars. A més, les velocitats de descomposició dels trioxans examinats són sensibles a efectes del dissolvent de reacció.

Mots clau: cis- i *trans*-1,2,4-Trioxans, Artemisinina, Termolisi, Cinètica de reacció.

*[1] Author to whom correspondence should be addressed. Calle 47, esq. 115, (1900) La Plata, República Argentina.

[2] 30 quai Ernest-Ansermet, 1211 Geneva 4, Switzerland.

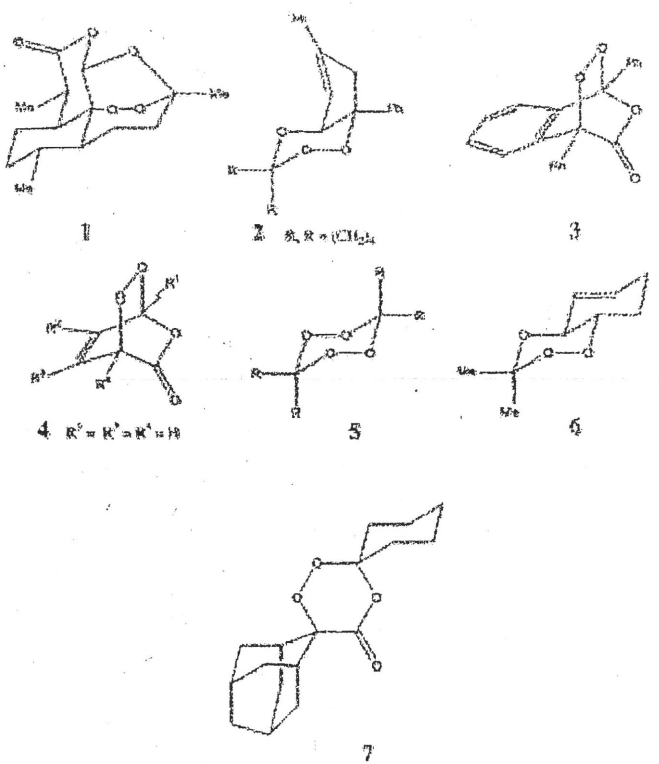
INTRODUCTION

The importance of synthetic 1,2,4-trioxanes has grown considerably in recent years[1] ever since the naturally occurring *cis*-fused trioxane artemisinine (1, Scheme 1) and some of its derivatives achieved prominence as potent antimalarial agents[2]. At first sight, these molecules because they are peroxides, would appear to be thermally unstable. On the contrary, most trioxanes withstand heating to high temperatures. Solid artemisinine (1) can be heated to 190 °C before it decomposes.[3, 4] Simpler bicyclic trioxanes (e.g. 2) are stable up to their melting points[5] and usually only start to decompose in solution at temperatures between 114° and 180 °C. Despite its fragile appearance, the bridged bicyclic 1,2,4-trioxan-5-one (3) needs to be heated in boiling benzene before it expels carbon dioxide.[6] In contrast, the related trioxanone 4 is exceptional and disintegrates spontaneously at room temperature[7], probably due to their less-hindered molecular configuration.

Unlike the structurally comparable 3,3,6,6-tetrasubstituted-1, 2,4,5-tetroxanes (5)[8-12] only a study has been devoted to the thermolyses of 3,6-substituted-1, 2,4-trioxan-5-ones (e.g. 7) followed by their chemiluminescence[13], and a solvent and substituents effect research on the thermolysis of *cis*-6-phenyl-5, 6-(2-phenylpropyliden)-3,3-tetramethylene-1, 2,4-trioxane (2).[14] Now, in order to extend the results so far obtained with this type of cyclic peroxides related to the paludism chemotherapy[15], kinetics and product studies were performed on the thermal decomposition reactions of artemisinine (1), which reveals a proved therapeutic action, and *trans*-3,3-dimethyl-1,2,4-trioxane (6). This one with a different molecular configuration.

RESULTS AND DISCUSSION

The rates of decomposition at various fixed temperatures of 1 in benzene, and 6 in toluene and in methanol (Table I) as monitored by the disappearance of the corresponding trioxane, were clearly first order with correlation factors in the range 0.987 - 0.999. Although the rates for 6 reaction were not actually determined at different concentrations, it is assumed that as their concentrations were sufficiently low ($< 5 \times 10^{-3}$ moles · dm^{-3}), the observed rate constants values (k_{obs}) should be independent of the initial concentrations. However, artemisinine (1), which exhibits the lowest solubility of the two trioxanes examined, proved to be an exception. For its thermolysis at the highest experimental temperature (120.1 °C) in benzene solution, the value of



Scheme 1

TABLE I

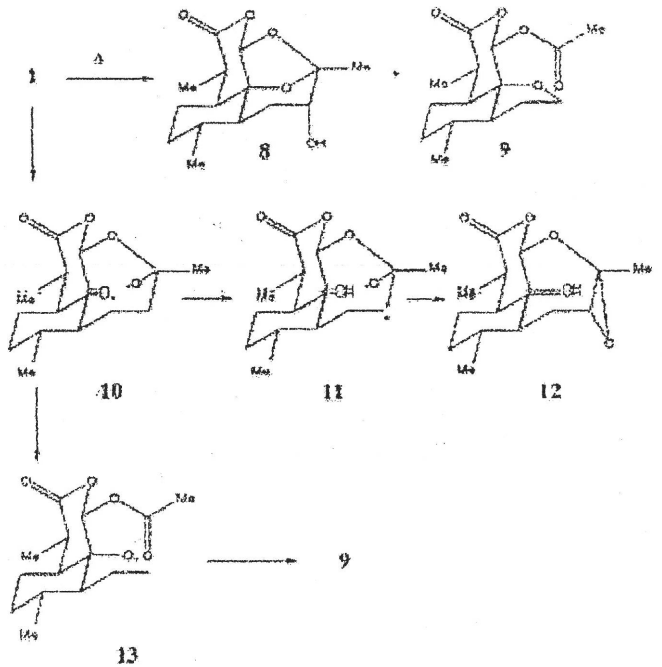
First-Order Rate Constants Values for the Thermolysis of 1 and 6 in Solution at Different Temperatures.

Temperature °C	Solvent	10^3 x [Trioxane][a] moles · dm^{-3}	$10^4 \times k_{obs}$, s^{-1} 1	$10^4 \times k_{obs}$, s^{-1} 6
100.1	Benzene	0.7	9.2	
110.1	"	0.7	27.7	
120.1	"	0.7	69.1	
120.1	"	1.7	88.7	
135.2	Toluene	2.0		1.1
140.2	"	2.0		2.0
147.2	"	2.0		4.0
156.2	"	2.0		10.2
165.6	"	2.0		23.9
171.4	"	2.0		41.5
114.6	Methanol	5.0		15.0
125.4	"	2.0	150	
125.4	"	5.0		45.4
131.8	"	5.0		85.2
140.2	"	5.0		190
145.4	"	5.0		307

[a] *Trioxane Initial concentrations.*

k_{obs} was about 1.3 times greater when the initial concentration was increased 2.4 fold. The cause of this effect may be due to induced or co-operative decomposition of that trioxane. A similar behavior was observed in the thermolysis of the 1,2,4,5-tetroxanes[9] but at relatively higher initial concentrations (> 20 x 10^{-3} moles · dm^{-3}).

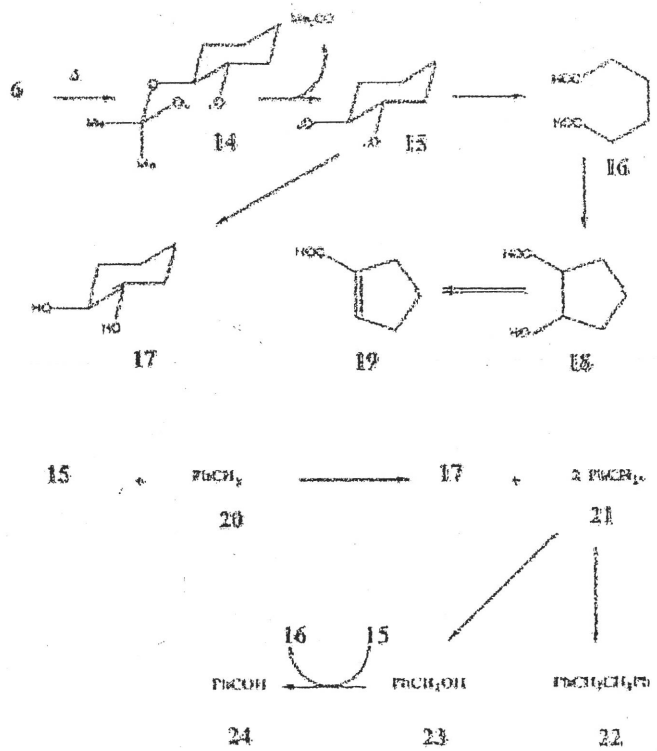
On the whole, the low values of the observed rate constants confirm the previously qualitative reports already mentioned of the thermal stability of the 1,2,4-trioxanes[4]. However, it appears that at roughly the same temperature (120°-135 °C) in aromatic solvents the trioxanes here studied display rate constants values in the order 1 > 6, which would reflects structural and configuration differences. This behavior is not expected because the rate determining steps for the unimolecular thermolysis of both molecules should be the rupture of their O-O peroxydic bonds. Actually it has been suggested that heating 1 cause the O-O bond to break homolytically.[3, 4] For the thermolysis of 6 it was already demonstrated that the rate-determining step is also the cleavage of their peroxydic bond. Artemisinine (1) is a *cis*-fused tetracyclic cage-type molecule in which the trioxane ring is locked in a boat conformation, whereas the *trans*-fused trioxane 6 like *trans*-decalin[10] cannot undergo conformational inversion. In this case the first-formed oxygen biradicals, in the toluene solvent, would be held close together thereby favouring a faster recombination within the solvent cage to the initial *trans*-trioxane molecules.



Scheme 2

Concerning the kinetic solvent effects on the thermolyses here considered, the rate constants for 1 and 6 reactions were significantly faster in methanol than in the hydrocarbons (Table 1). The differential solvent effect may be ascribed to the steric environments situated around the cyclic peroxide molecules. This may be due to the configurations of their corresponding reaction transition states. In the *trans*-fused bicyclic trioxane 6 both the α and β faces of the molecule are equally accessible to the solvent molecules leading to a relatively more stable transition state. On the other hand, it is known that the peroxydic bond in 1 molecule is shielded so that a potential complexing agent or solvent can only approach on one side.[17] Thus, compared to 6 reaction, solvating the 1 transition state should be less effective, rendering less thermal stability. Similar solvent effects have been shown to operate for those 1,2,4,5-tetroxanes that are substituted by non-bulky substituents.[11] However, it is significant that the trioxanes investigated in this work, despite their remarkable structural differences, display commensurate values of thermal stability. Furthermore, the free energies of activation ($\Delta G^{\ddagger}$) for 1 and 6 reactions in the aromatic solvents, calculated at the middle of each temperature range of the thermolysis, give values of 30.7 ± 1.2 and 35.1 ± 0.2 kcal/mol, respectively. Those values for the thermolysis of the trioxanes are typical of highly stable peroxides. Related examples are trioxane 7 (Scheme 1) and adamantylideneadamantane-1,2-dioxetane. The former exhibits an activation energy of 35.6 kcal/mol[18]; the latter resembles 1 in having a rigid policyclic structure and like 1 gives a similar value for the free energy of activation.[19] The values of $\Delta G^{\ddagger}$ for 6 in toluene and methanol, taken in the middle temperature range of 153.3° and 130.0 °C, respectively, are close to that previously found[19] (39.9 ± 1.4 kcal/mol) in *n*-octane at 175 °C. Therefore, on kinetics grounds it is reasonable to assume that the trioxanes examined decompose in much the same way by initial homolytic breakage of the O-O bond. Furthermore, the product compositions arising from 1 and 6 thermolysis are consistent with a first-formed dioxy-biradical which then has the chance to decompose or react further with external molecules such as solvent to give secondary products. Thus, the products of 1 reaction[9] provide an instructive precedent (Scheme 2).

Here, 8 and 9 are only explicable in terms of stepwise radical processes. According to ferrous ion-catalysed studies[20, 21] on artemisinine reaction it is now thought that the path leading to 8 starts from the dioxy-biradical 10 which rearranges to the C-centred biradical 11 by 1,5-hydrogen atom shift. Closure of this to the epoxide 12 followed by internal attack of the hydroxyl group gives 8. In the case of biradical 10 arising from 1 reaction, it has two courses of reaction that are dictated by the architecture of the molecule: the first has already been discussed; the second course is driven by the thermodynamic stability that is acquired by



Scheme 3

the simultaneous formation of the acetate group and the C-centred radical 13. As the latter lies close to the residual oxy-radical they immediately couple so creating the tetrahydrofuran 9.

The acquisition of thermodynamic stability governs the mechanism of thermolysis of 6. The loss of a molecule of acetone from the dioxy-biradical 14 (Scheme 3), generates the *trans*-dioxy biradical 15.

The scission of this moiety creates adipaldehyde (16). Surprisingly, even in benzene solution, 15 manage to react with a hydrogen-atom donor to afford traces of *trans*-1,2-cyclohexanediol (17). In methanol as solvent, 16 undergoes aldol condensation to give first 18 and then cyclopentenal (19) on dehydration. As before, 15 is reduced to the diol 17. In toluene solution, much less 16 as product is observed (Table II). Clearly, the dioxy-biradical 15 is promptly intercepted by molecules of toluene (20), abstracting hydrogen atoms to form the diol 17 and the benzyl radical (21). Dimerization of the latter accounts for the provenance of bibenzyl (22), while benzyl alcohol (23) and benzaldehyde (24) presumably arise from 20. Subsequently, 23 could also donate hydrogen atoms to 15 thereby accounting for the production of benzaldehyde (24) and the diol 17. This mechanistic picture is supported by the fact that the amounts of the toluene-derived products increase with temperature, reaction time, and initial concentration of 6 in the solutions.

TABLE II

Products Arising from the Thermolyses of 6 in *Different Solvents*[a].

Trioxane[b]	Solvent	Reaction Products[c]
6 (0.024)	Benzene	adipaldehyde (16, 97%), acetone (3%), *trans*-1,2-cyclohexanediol (17, traces)
6 (0.023)	Methanol	cyclopentenal (19, 92%), adipaldehyde (16, 4%), *trans*-1,2-cyclohexanediol (17, 4%), acetone (traces)
6 (0.013)	Toluene	benzaldehyde (24, 90%), benzyl alcohol (23, 5%), cyclopentenal (19, 3%), dibenzyl (22, 2%), adipaldehyde (16, traces), *trans*-1,2-cyclohexanediol (17, traces) acetone (traces).

[a] For reaction conditions see EXPERIMENTAL; [b] Initial molar concentrations of trioxane; [c] Indicated in order of relative abundance; Ratios expressed as % of otal GC-MS peak areas (TIC mode) of all the reaction products observed.

CONCLUSIONS

The chief findings of the present study are the high thermal stability of the 1,2,4-trioxane ring and the stepwise manner by which 1 and 6 decompose after initial homolysis of the O-O bond. Both trioxanes reactions are characterised by free energies of activation of similar magnitude. Nevertheless, conformational and configurational differences are seen. The *trans*-fused bicyclic skeleton of 6 exposes both sides of the peroxide bond thereby favouring a stabilising solvent effect. For 1 reaction the attack of the solvent molecules would be less marked owing to greater shielding of the peroxydic bond. Moreover, the decomposition products for both trioxanes reactions, especially the formed in toluene solution, are typical of those originating from stepwise radical processes.

The present results parallel those obtained for the thermolysis of substituted 1,2,4,5-tetroxanes in the gas[8] and solution phase[9] and for other *cis*-fused 1,2,4-trioxanes.[14,28] They too decompose by unimolecular homolysis of the O-O bond in a stepwise mechanism characterised by the activation parameters, the values of which fall within a narrow range influenced by steric[10] and solvent effects.[11,12,14]

EXPERIMENTAL

Materials

Natural artemisinine (1) was extracted in this laboratory from Artemisia annua L., and conveniently purified according to a literature method.[21] Some experiments were performed with a commercial sample (Sigma-Aldrich Co., USA) kindly given by Professor Luis Bruno Blanch. *trans*-3,3-dimethyl-1,2,4-trioxane (6) was prepared as already reported.[22] The purity of 1 and 6 were checked by RP-HPLC and *GC analysis. Commercial solvents of analytical grade were* used for the kinetic experiments. They were purified prior to use by *appropriate techniques*[23] and distilled from a saturated solution of the sodium salt of ethylenediaminetetracetic acid (Na_2EDTA). The foregoing treatment removed traces of metallic ions that would otherwise catalytically accelerate the thermal decompositions.

Kinetic and analytical methods

Pyrex glass tubes (6 cm long. x 6 mm external diameter, wall thickness ca. 1 mm), half-filled (ca. 0.4 mL) with a solution of the 1,2,4-trioxane, were thoroughly degassed *in vacuum* at –190 °C and then sealed with a flame-torch. The *ampoules so prepared were immersed in a thermostati*cally controlled silicone oil bath (± 0.1 °C) and withdrawn one-by-one at selected intervals. Cooling the ampoule at 0° C quenched the reaction. The concentration of the trioxane remaining in the solution and the products composition were monitored by GC analysis in a Hewlett-Packard, (Palo Alto, CA, USA) 5890 model, series II Plus instrument, *with N_2 as carrier gas and FID detection at 300 °C.*

Analysis of the products of decomposition of 6 was carried out in a capillary silica-fused 5% phenylmethylsilicone column (Heliflex, RSL-150, bonded FSOT, 30 m length, 0.25 mm internal diameter, 0.25 μm film thickness), programmed from 80 °C (3 min) to 90 °C at a rate of 50 °C/min with the injector port temperature kept at 120 °C. For the kinetics of 1 decomposition, *a silica-fused megabore column* (AT1, Alltech Assoc., Inc., USA) impregnated with polydimethylsiloxane (10 m length x 0.53 mm internal diameter, 1.2 μm film thickness) was used, and programmed from 130 °C (2 min) to 200 °C at a rate of 20 °C/min with the injector port at 180 °C. Solutions (4 μL) were injected using a 7:1 split ratio with N_2 as carrier gas. In this case the analytical results were obtained by the absolute GC quantitative method by using the peak area normalization with a value of 2000 in the area rejection setting of the Hewlett-Packard (Palo Alto, CA, USA) model 3395, recording integrator.

In some runs the GC results for the kinetics of 1 decomposition were corroborated by RP-HPLC analysis. In this instance, a Pharmacia LKB chromatograph equipped with a Spherisorb SuperPack RP-C18 column (100 mm length x 4.0 mm internal diameter, ODS, 2.5 μm), at 25 °C was employed. The mobile phase was MeOH-H2O (7:3, v/v), 0.8 mL/min flow-rate at 12.6 mPa pressure). Samples or standards were dissolved in the same mixture of solvents; 20

µL of solutions were injected with UV detection at 220 nm or in some case, using a Pharmacia LKB differential refractive index detector.

The values of the first-order rate constants for the thermolysis of 1 were calculated by a least mean squares treatment of the data by plotting ln [% artemisinine peak area] against time; in the case of 6 thermolysis, logarithm of the trioxane concentration against reaction time plots were employed. In order to ensure accuracy in the GC analysis the range of experimental temperature had to be narrowly restricted (20° - 36 °C). The free energies of activation parameters reported were obtained from the Eyring equation: $k = k_e T/h \exp(-\Delta G^{\ddagger}/RT)$ where $k_e/h = 2.084 \times 10^{10}$ degree^{-1} s^{-1} and R = 1.986 cal/mol K. Error limits were determined in the usual way[24].

Product analysis

Solutions of 6 in methanol, benzene and toluene in sealed ampoules were decomposed at 150°-180 °C for 4-16 h. The reaction products were identified by comparing the retention times (RT) of the GC peaks with those of authentic samples or by examining the mass spectra obtained by coupling the GC to a Mass Selective Detector (Hewlett-Packard 5972 A model). Under the above GC analytical conditions, the approximate RT values (in min) were the following: 1.8 (acetone), 8.7 (benzaldehyde), 9.6 (cyclopentenal), 10.1 (benzyl alcohol), 10.9 (adipaldehyde), 11.3 (trans-1,2-cyclohexanediol and 15.1(6).

ACKNOWLEDGEMENTS

The authors thank Professor Luis Bruno Blanch (UNLP), who generously supplied a sample of commercial artemisinine and Mr. Mariano Firpo for help with the GC-MS experiments.

BIBLIOGRAPHY

[1]. a) C. W. Jefford. In: «Comprehensive Heterocyclic Chemistry», 2nd. Edtn., A. R.; b) Katritzky, C. W. Rees, E.F.V. Scriven, Eds. Pergamon Press, Oxford, Vol. 6, *Chapter 20*, 861-899 (1996); c) C.W. Jefford. In Advances in Drug Research.

B. Testa, A. U. Meyer, Eds. Academic Press, New York, Vol. 29, *Chapter. 7*, 271-325 (1997).

[2]. D. L. Klayman. Science, 228, 1049 (1985). H. Ziffer, R.J. Highet, D.L. Klayman. In «Progress in the Chemistry of Organic Natural Products». W. Her, G. W. Kirby, R. E. Moore, W. Steglich, C. Tamm, Eds. Springer, Wien-New York, Vol. 72, 121-214 (1997).

[3]. A. J. Lin, D. L. Klayman, J. M. Hoch, J. V. Silverton, C. F. George: *J. Org. Chem.*, 50, 4504 (1985).

[4]. X. Luo, H. J. C. Yeh, A. Brossi: *Heterocycles*, 23, 881 (1985).

[5]. C. W. Jefford, A. Jaber, J. Boukouvalas, P. Tissot: *Thermochim. Acta, 166, 337 (1991).*

[6]. J. P. Smith, G. B. Schuster: *J. Am. Chem. Soc.*, 100, 2564 *(1978).*

[7]. W. Adam, I. Erden: *J. Am. Chem. Soc.*, 101, 5692 (1979).

[8]. L. F. R. Cafferata, J. D. Lombardo: *Int. J. Chem. Kin.*, 26, 503 (1994).

[9]. L. F. R. Cafferata, J. J. P. Furlong: In «Advances in Oxygenated Processes». A. L. Baumstark, Ed. *JAI Press Inc. Greenwich, CT, Vol. 4, 81-105 (1995).*

[10]. L.F. R. Cafferata, G. N. Eyler, A. I. Cañizo, E. J. Borkowski: *J. Org. Chem.*, 55, 1058 (1990).

[11]. L. F. R. Cafferata, G. N. Eyler, A. I. Cañizo, E. L. Svartman, E. Alvarez: *J. Org. Chem.*, 56, 411 (1991).

[12]. L. F. R. Cafferata, G. N. Eyler, M. V. Mirifico: *J. Org. Chem.*, 49, 2107 (1984).

[13]. a) C. W. Jefford, M. G. H. Vicente: *Heterocycles*, 35, 725 (1993); b) C. W. Jefford, M. C. Josso, M. G. H. Vicente, H. R. Hagemann, D. Lovy, H. Bill: *Helv. Chim Acta*, 77, 1851 *(1994).*

[14]. L. F. R. Cafferata, C. W. Jefford: Molecules 2001, 6, 699.

[15]. *R. Jeandupeux, L. F. R. Cafferata: Acta Farmacéutica* Bonaerense, 14, 91 (1995).

[16]. *D. K. Dalling, D. M. Grant, L. F. Johnson: J. Am. Chem.* Soc., 93, 3678 (1971).

[17]. *K. L. Shukla, T. M. Gund, S. R. Meshnick J. Mol. Graph.*, 13, 215 (1995).

[18]. G. B. Schuster, N. J. Turro, H. C. Steinmetzer, A. Schaap, G. Faler, W. Adam, J. C. Liu: *J. Am. Chem. Soc.*, 97, 7110 (1975).

[19]. G. B. Schuster, L. A. Bryant: *J. Org. Chem.*, 43, 521 (1978).

[20]. L. F. R. Cafferata, C. W. Jefford, R. S. Rimada: *Int. J. Chem. Kin.*, 32, 523 (2000).

[21]. D. L. Klayman, A. J. Lin, N. Acton, J. P. Scovill, J. M. Hoch, W. K. Milhous, A. D. Theohanides, A. S. Dobek: *J. Nat. Prod.*, 47, 715 (1984).

[22]. *G. B. Payne, C. W. Smith: J. Org. Chem., 22, 1682 (1957).*

[23]. J. A. Riddick, W. B. Bunger: «Organic Solvents». 3rd Edtn. *Techniques of Chemistry. A. Weissberger, Ed. Wiley-*Interscience: New York, Vol. II, Chapter V, 572-877 (1970).

24. S. Huyberechts, A. Halleux, P. Kruys: Bull. Soc. Chim. Belg., 64, 203 (1955)