GENERAL METHOD FOR DETERMINATION OF CONFIGURATION OF STEROID-17-YL METHYL GLYCOLATES AT C-20

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Kinetic examination for methoxycarbonylations of the isomeric steroid-17-yl methyl glycolates at C-20 and plots of the amount of each isomer produced by a reaction of their corresponding steroids with cupric acetate in absolute methanol provide a general and facile method for determination of the configuration of the steroid-17-yl methyl glycolates at C-20.

KEYWORDS anti-inflammatory steroid; C-20 configuration ; conformational analysis; methoxycarbonylation; dioxolanone

Therapeutic use of anti-inflammatory steroids is limited by their diverse systemic and adverse effects. To overcome this limitation, efforts toward discovery of steroidal compounds demonstrating separation of topical anti-inflammatory activity from potentially harmful side effects have increased. [1-8] Our most recent efforts toward this goal include the syntheses of the various types of steroidal methyl glycolates from common steroids such as prednisolone, dexamethasone and hydrocortisone, and we found some of the compounds possessing extremely strong vasoconstrictor activity without pituitary-adrenal suppression. [9]

It is already known that methanolic cupric acetate catalyzes the transformation of steroid glyoxal (20-keto-21-aldehydes) to the corresponding methyl glycolates (20-hydroxy-21-acid methyl ester) as an epimeric mixture at C-20. The configuration at C-20 of a pair of epimeric 20-acetoxy pregnanes can be established by comparing their molecular optical rotations. A simple rule, formulated by Fieser *et al.*,[10] states that a (20 S)-acetoxy compound of any type is more dextrorotatory than its (20 R)-acetoxy epimer. However this rule is empirical and not applicable to 5β-pregnane 21-oic acid derivatives, but the results are entirely opposite to Fieser's rule. Here we wish to report a facile and widely applicable method for determination of the configuration at C-20 of the epimeric methyl glycolates.

Thus, methyl 20-dihydroprednisolonates (**1** and **2**) known as antedrugs,[2] methyl 20-dihydrodexasonates (**3** and **4**)[13] and 20-dihydrohydrocortisonates (**5** and **6**) were prepared from their corresponding prednisolone, dexamethasone and hydrocortisone according to the method by Lewbart *et al.*[11,12] and characterized based on the spectral data.

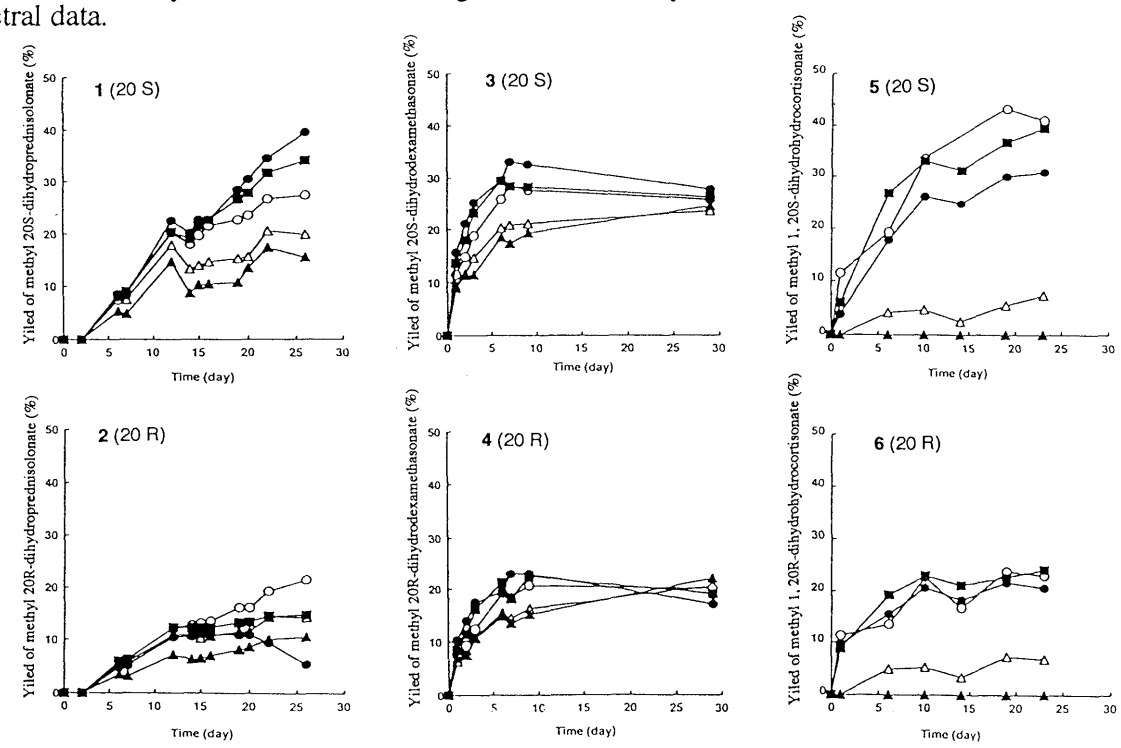


Fig. 1. Time Courses for the Formation of Methyl Glycolates (20S and R) from Steroids
All reactions have been done by stirring a mixture of each steroid and $Cu(OAc)_2$ in dry methanol at room temperature. $Cu(OAc)_2$ /Steroid(molar ratio): 0.1, ▲; 0.2 , △; 0.5 , ○; 1.0 , ■; 2.0 , ●.

On the formation of the methyl prednisolonates under various conditions, we recognized the preferable formation of the less polar compound **1** (20 S) over the more polar compound **2** (20 R) in the presence of sufficient amount of catalyst (more than 0.5 equivalent), in contrast to the results reported by Lewbart *et al.* [11]in which they described the ratio of **1:2** as simply 1:1. This was also recognized in the transformation of dexamethasone and hydrocortisone to their corresponding methyl glycolates (**3** and **4**) and (**5** and **6**), respectively. Thus the less polar compounds **3** and **5** as well as compound **1** are also the preferable compounds. Based on these results, we tentatively assigned the compounds **3** and **5** to possess 20 S configuration, and the compounds **4** and **6** to have 20 R configuration.

Preferable formation of 20 S over 20 R could be explained based on the conformational analysis of the acetal intermediates **7a** and **7b**[11], in which the bond between C-17 and C-20 would be fixed by a chelation of copper with the carbonyl group at C-20 and the hydroxy group at C-17α. Thus the migration of hydride ion at C-21 to C-20 proceeds *via* more stable intermediates **7a** in which the acetal group is located far from the methyl group at C-18 to provide **1**, **3**, and **5** as main products.

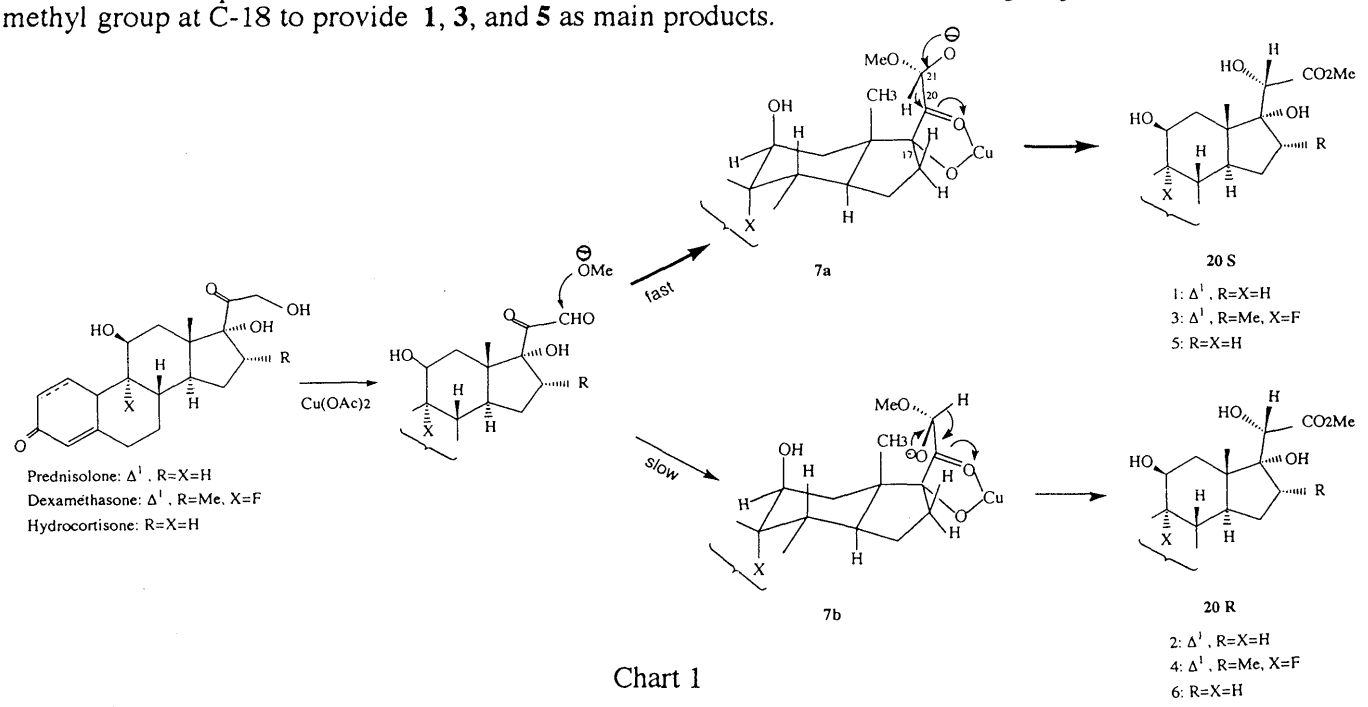


Chart 1

More reliable determination of the configuration at C-20 has ben achieved by the conformational analysis on the transformation of the dimethyl ester **8** and its epimer **10** to the corresponding dioxolanones **9** and **11**. In the intermediate **10**, more intense interaction exists between C-18 methyl group and C-20 methoxycarbonyl group than the interaction between C-18 methyl and C-20 proton in **8**. Hence the reaction rate in cyclization of **8** (20 S) would be faster than that of **10** (20 R).

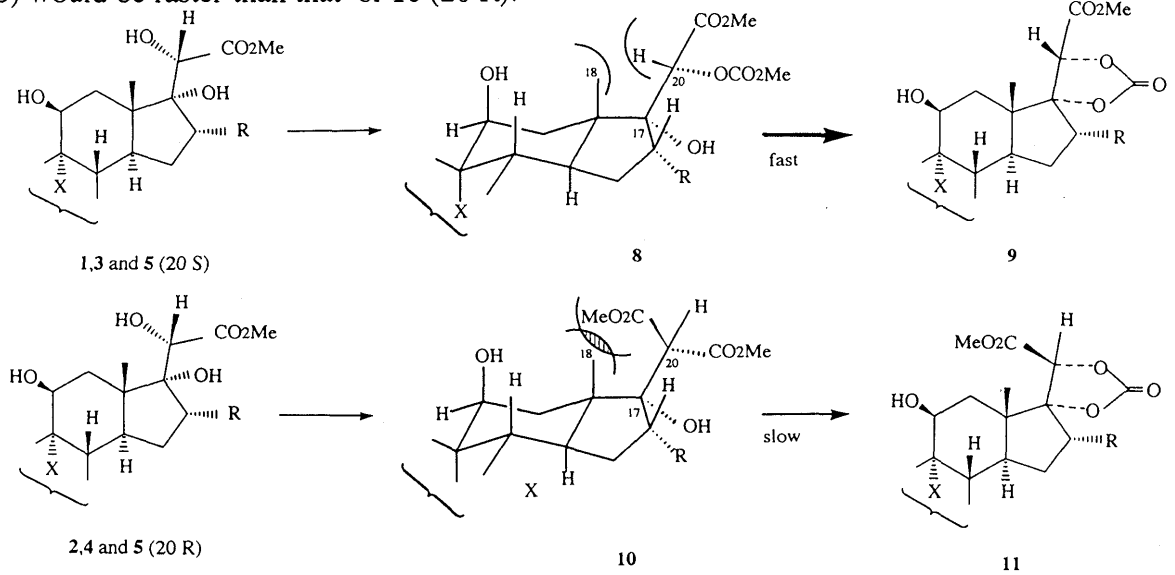
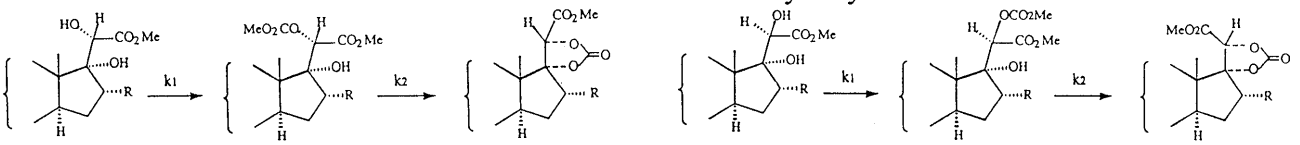


Chart 2

Table I. Reaction Rates on the Transformation of Methyl Glycolates in to Dioxolanones



1, 3 and 5 (20 S) 12, 14 and 16 (20 S) 2, 4 and 6 (20 R) 13, 15 and 17 (20 R)

Reaction rate constants	Starting materials					
	Methyl prednisolonates		Methyl dexasonates		Methyl hydrocortisonates	
	1 (20S)	**2** (20R)	**3** (20S)	**4** (20R)	**5** (20S)	**6** (20R)
k_1 (min)$^{-1}$	1.26×10^{-2}	3.10×10^{-2}	1.0	0.62	—a)	—a)
k_2 (min)$^{-1}$	5.57×10^{-4}	2.20×10^{-4}	3.67×10^{-3}	1.96×10^{-3}	4.15×10^{-4}	1.86×10^{-4}
(20S k_2 / 20R k_2)	(2.53)		(1.87)		(2.23)	

a) Rate of this reaction was so fast that k_1 is not able to calculate.
All reactions have been done by treatment of each methyl glycolate with methyl chloroformate (3 eq.) and 4-(dimethylamino)pyridine (4 eq.) in dry dichloromethane at room temperature.

Based on this speculation, methoxycarbonylations of each epimer (**1** and **2**), (**3** and **4**) and (**5** and **6**) were examined, and the results are shown in Table I.

As found in Table I, formation rates, k_2, of each of the dioxolanones **12, 14** and **16** derived from the preferable compounds (less polar) which are supposed to possess 20 S configuration are 2.53, 1.87 and 2.23 times faster than those of the dioxolanones **13**, **15** and **17** derived from the corresponding isomeric compounds (more polar), as we predicted.

These results suggest that our speculation and discussion on the C-20 configurations are reliable and provide a general method to determine the configuration at C-20 of the steroid derivatives possessing the same type of functional groups at C-17.

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12) A solution for each steroid, prednisolone, dexamethasone and hydrocortisone (20 mg each), in absolute methanol was added dropwise to a solution of cupric acetate (0.11 M) in absolute methanol under conditions in the molar ratio of cupric acetate of each steroid being 0.1, 0.2, 0.5, 1.0, and 2.0, and the mixture was stirred at room temperature for 26 days. Time courses for the formation of each pair of the products (**1** and **2**), (**3** and **4**) and (**5** and **6**) were followed by high performance liquid chromatography.
13) S. U. Hong, K. H. Park, J. S. Chae, J. W. Lee, C. S. Kim, J. K. Kim, *Drugs Exptl. Clin. Res.*, **XV**, 511 (1989): Although compounds **3** and **4** have been known, the authors did not give any spectral data and proof for determination of the configuration at C-20.

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