Tetrahedron Vol. 37, No. 20, pp. 3467 to 3471, 1981
Printed in Great Britain.

0040-4020/81/203467-05$02.00/0
Pergamon Press Ltd

^{13}C NMR SPECTROSCOPY OF 4,5- AND 5,6-DOUBLE BOND ISOMERS OF SPIRO-3-STEROIDAL KETONE DERIVATIVES

THE DETERMINATION OF THE STRUCTURES OF STEROIDAL THIAZOLIDINES

K. B. SLOAN,* N. BODOR and R. J. LITTLE

Department of Medicinal Chemistry, College of Pharmacy J. Hillis Miller Health Center, University of Florida, Gainesville, FL 32610, U.S.A.

(*Received in USA 9 February* 1981)

Abstract—The thiazolidine isomers obtained upon the reaction of aminoethanethiols with α,β-unsaturated steroidal ketones were found to be double bond positional isomers based on their optical rotations and ^{1}H and ^{13}C NMR spectra. The ^{13}C NMR spectra of analogous ketals, hemithioketals and a thioketal of steroidal ketones were also reported, and ^{13}C NMR spectroscopy was shown to be a convenient method of assigning the position of the double bond in the double bond isomers for all four of these derivatives. Finally, ^{13}C NMR spectroscopy was found to be useful in determining that thiazolidine formation was stereospecific to give only one C-3-isomer.

In a recent report on the synthesis and topical antiinflammatory activity of thiazolidine prodrugs[1] of hydrocortisone and hydrocortisone 21-acetate, [2a,b] we noted that the stereochemical consequences of the condensation of hydrocortisone 21-acetate with L-cysteine ethyl ester hydrochloride were complicated by the possibilities that the amino acid could racemize during the course of the reaction, that two isomers could form at C-3 and that the double bond could stay in the 4,5-position or shift to the 5,6-position.

The position of this double bond has biological as well as chemical significance because the thiazolidines were to be used as prodrugs.[1] Hydrolysis of the 4,5-double bond isomer isomer would immediately regenerate the biologically active α,β-unsaturated ketone. On the other hand, if the double bond were in the 5,6-position, an intermediate isomerization step *in vivo* by Δ^5-3-ketoisomerase[3] would be necessary to regenerate the parent steroid. However, the exact distribution of this enzyme throughout the body is not known. It is certain that the adrenals are a particularly rich source, but other tissues are also known to contain significant quantities of this enzyme. Thus, the distribution and ultimately the delivery of the parent steroid from the thiazolidine would quite possibly depend not only on the rate of hydrolysis of the thiazolidine, but also of the rate of isomerization of the double bond if the steroid thiazolidine was the 5,6-double bond isomer. Since we had shown that the thiazolidine derivatives were two to five times more active than their parent steroids and also exhibited less systemic toxicity in animal studies, [2a,b] it was important to determine the position of the double bond in the structures of the thiazolidines to adequately interpret the results of the biological activity and insure that the steroid species that was being delivered was the active α,β-unsaturated carbonyl parent species.

In this paper, we describe the determination of the structure of the thiazolidines of α,β-unsaturated steroidal ketones and especially those of hydrocortisone 21-acetate using optical rotations, ^{1}H and ^{13}C NMR spectroscopy. In addition, in order to assure that the assignments of the olefinic carbons in the ^{13}C NMR spectra of the thiazolidines were valid, the ^{13}C NMR spectra of the ethylene ketal and hemithioketal double bond isomers were obtained for comparison with those of the thiazolidines. Therefore, we have also reported the salient features of the ^{13}C NMR spectra of 4,5- and 5,6-double bond isomers of the steroidal ethylene ketals, thioketal and hemithioketals. These were useful in determining the structure of the thiazolidines.

Table 1 lists the ^{1}H and ^{13}C NMR data, as well as the optical rotations of thiazolidines of hydrocortisone 21-acetate (**1b, 2b**),[2a,2b] progesterone (**3a, 3b, 4a, 4b**)[2c] and testosterone 17β-propionate (**5a, 5b**)[2c] together with the ethylene ketals (**6a, 6b**), thioketal (**8b**) and hemithioketals (**7a, 7b**) of testosterone 17β-propionate. For each series of steroid thiazolidines, except for hydrocortisone 21-acetate, two isomers could be obtained. In the testosterone 17β-propionate series, careful fractional crystallization, and in the progesterone series, a judicious choice of reaction conditions, afforded the two isomers (**a, b**).[2c] Inspection of the NMR spectra of the crude reaction mixtures and comparison of those spectra with those of the isolated products showed that the ratio of isomers or of isomers to starting material in the crude mixture were consistent with the ratio of the isomers actually isolated, i.e. there was no change in the composition during crystallization. In each case, the crystallized isomers contained at worst 85%, but in most cases 95%, of the major isomer based upon integration of the ^{1}H NMR C<u>H</u>=C absorptions. These ^{1}H NMR analyses were based on a comparison of the integrations of the broad multiplet for C<u>H</u>=C which was assigned to one isomer (isomer **a**) to the integrations of the broad singlet for C<u>H</u>=C which was assigned to the other isomer (isomer **b**). Since the thiazolidines were observed to decompose on tlc plates and during column chromatography, analyses of the ^{1}H NMR spectra of the isomers

Table 1. Physical and spectral properties of spiro derivatives

	mp	$[\alpha]D^a$	^1H NMR (δ)^b CH=C	C_4	^{13}C NMR (δ)^b C_5	C_6	C_3
1a	175-178°	+103	5.23	121.4	149.7	---	---
2b	150-156°	+154	5.27	122.4	146.4	---	---
3a	127-134°	-11	5.6-5.2	---	140.45	122.5	---
3b	127-134°	+98	5.30	123.1	148.7	---	---
4a	167-170°	-92	5.6-5.2	---	140.6	122.6	---
4b	162-165°	-24	5.23	122.9	148.9	---	---
5a	144-147°	-55	5.53-5.2	---	140.7	122.4	61.8
5b	100-104°	+10	5.30	122.9	148.7	---	61.8
6a	203-205°	-46	5.43-5.13	---	140.5	121.9	109.6
6b	113-114.5°	+75	5.21	120.2	151.4	---	106.4
7a	172-175°	-35	5.4-5.17	---	139.9	122.5	98.1
					140.5		94.4
7b	108-112°	+116°	5.33	123.2	146.1	---	93.3
				123.1	149.1		90.9
8b	160-162°	+111°	5.43	124.2	145.9	---	---

[a] C = approximately 0.5 in $CHCl_3$ except for 5a and 5b which were done in ethanol.

[b] Run in $CDCl_3$, shifts relative to TMS (±0.05 ppm).

was the only reliable means of determining, at least qualitatively, the purity of the isomers.

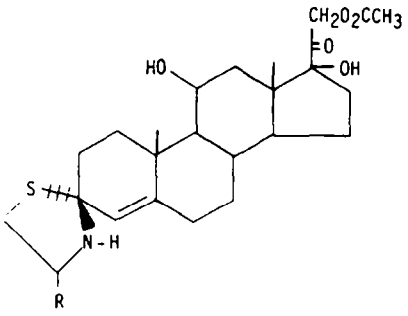
In addition to the differences in their ^1H NMR spectra, the isomeric **a** and **b** thiazolidines showed consistent differences in their ^{13}C NMR spectra and optical rotations. The two olefinic carbon absorptions for the **b** isomers were found at about δ 120 and δ 150, while those for the **a** isomers were found at about δ 120 and δ 140. Similarly, the **a** isomers consistently exhibited a more negative $[\alpha]_D$ value than the **b** iosmers.

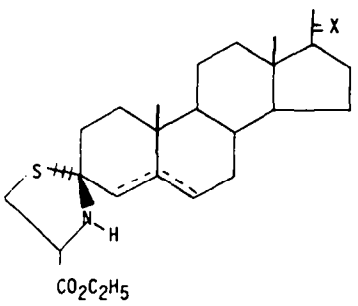
Djerassi,[4] Barton[5] and Dean[6] have shown that the $[\alpha]_D$ values for the 5,6-double bond isomer in any steroid series is more negative ($\Delta[M]D \cong 450°$) than the 4,5-double bond isomer. Thus, the optical rotation data (Table 1) suggested that the **a** isomers were 5,6-double bond thiazolidine isomers while the **b** isomers were the 4,5-double bond thiazolidine isomers. However, only one isomer was available from the hydrocortisone 21-acetate series, and although its optical rotation was strongly positive, it seemed reasonable to conclude that if optical rotation was the only criteria for assigning the structures, the optical rotations of both isomers or other supporting data were needed.

Conveniently, the ^1H and ^{13}C NMR data were also consistent with the assignment of the **b** isomer to the 4,5-double bond structure. The CH=C absorptions in the ^1H NMR spectra of the **a** isomers were broad multiplets. Since the 6-proton in the 5,6-double bond isomer constitutes the X portion of an ABX pattern and also experiences allyic coupling, it should be a multiplet. On the other hand, the CH=C absorptions of the **b** isomers were broad singlets (half-height width of about 4 cps). Since the 4-proton in the 4,5-double bond isomer experiences only allylic and 1,3-coupling, it should be a broad singlet. Thus, the shape of the ^1H NMR CH=C absorptions fit the structure assignment had been based on the optical rotation data.

The carbon absorptions in the region from δ 150 to δ 120 in the ^{13}C NMR spectra were first established as being due to olefinic carbons by comparison of the ^{13}C NMR spectra of the isomers with the ^{13}C NMR spectra of steroids of comparable structures. Thus, the 4,5- and 5,6-double bond isomers of the ethylene ketal of testosterone 17β-propionate (**6a, 6b**) were prepared according to the method of Dean and Christiansen.[6] The ^{13}C NMR spectrum of the 5,6-double bond ethylene ketal isomer (**6a**) showed olefinic carbon absorptions at δ 122 and δ 141 which corresponded to the position of the carbon absorptions in the **a** isomers. In addition, its optical rotation was, as expected from analogy to the ethylene ketal double bond isomers of testosterone 17β-acetate,[6] more negative than the 4,5-double bond isomer (**6b**), and its ^1H NMR absorption due to CH=C was a broad multiplet. On the other hand, the ^{13}C NMR spectrum of the 4,5-double bond ethylene ketal (**6b**) showed olefinic carbon absorptions at δ 120 and δ 151 corresponding to the position of the carbon absorptions in the **b** isomers. Its ^1H NMR absorption due to CH=C was a broad singlet. Coupling between the 6-carbon and hydrogen in the **a** isomer series and the 4-carbon and hydrogen in the **b** isomers series obtained from off-resonance band ^{13}C decoupling experiments clearly established the identity of the 6- and 4-olefinic carbon absorptions in the thiazolidine and the ketal **a** and **b** isomers, respectively.

The ^{13}C NMR spectra of the 5,6-double bond isomers of the hemithioketal (**7a, 7b**) and the 4,5-double bond isomer of the thioketal (**8b**) of testosterone 17β-propionate are also reported in Table 1. The thioketal was previously synthesized and assigned the 4,5-double bond structure.[7] On the other hand, the pair of hemithioketal



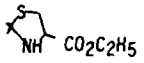


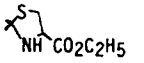
1b R = $CO_2C_2H_5$

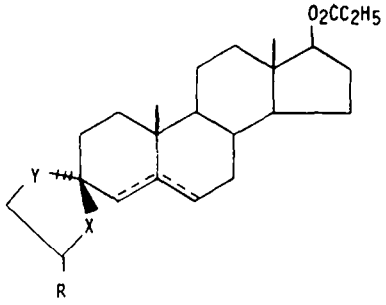
2b R = H

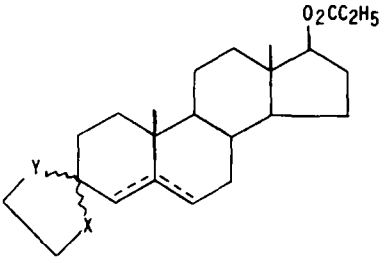
3a $\Delta^{5,6}$, X = O

3b $\Delta^{4,5}$, X = O

4a $\Delta^{5,6}$, X = 

4b $\Delta^{4,5}$, X = 





5a $\Delta^{5,6}$, R = $CO_2C_2H_5$, Y = S, X = NH

5b $\Delta^{4,5}$, R = $CO_2C_2H_5$, Y = S, X = NH

6a $\Delta^{5,6}$, R = H, X = Y = O

6b $\Delta^{4,5}$, R = H, X = Y = O

7a $\Delta^{5,6}$, X = O, Y = S

7b $\Delta^{4,5}$, X = O, Y = S

8b $\Delta^{4,5}$, X = Y = S

double bond isomers have not been reported previously. They were prepared and isolated using the same methods that were used for the ketal isomers.[6] In each case the structue assignments based on the optical rotations and ^1H NMR spectra were consistent with the structure assignment based on considerations of the ^{13}C NMR spectra, and each fit cleanly into either the **a** or **b** isomer series. Thus, in each series the ^{13}C and ^1H NMR and optical rotation data were consistent with the **a** isomer series being the 5,6-double bond isomer and the **b** series being the 4,5-double bond isomer. In addition, the consistency of the data from the three sources of information made it possible to confidently assign isomer **b** structures to thiazolidines **1** and **2** where only one isomer was isolated, to confirm the 4,5-double bond structure of the thioketal **8b** and to assign the structures to the hemithioketal double bond isomer as shown.

Since 4,5- and 5,6-double bond isomers of the ketals, hemithioketals and thiazolidines had been isolated in the testosterone 17β-propionate series, we attempted to find conditions that would give us the 5,6-double bond thioketal isomer (**8a**). Prolonged (6 hr) treatment of the thioketal (**8b**) with *p*-toluene-sulfonic acid* (*p*-ts) in refluxing benzene failed to cause the 4,5-double bond isomer to isomerize significantly to the 5,6-double bond isomer; apparently decomposition of the thioketal took place to a greater extent than did any isomerization.

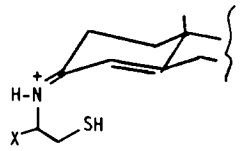
On the other hand, the 4,5-double bond isomer is probably obtained first in the formation of the other derivatives. The conditions used to obtain mixtures of the 4,5- and 5,6-double bond ketal and hemithioketal isomers (about 0.03 equivalents of *p*-ts) required longer reaction times to completely convert the steroids to the spiro derivatives than if larger quantities of *p*-ts were used. If the reactions were analyzed before the reactions were complete, the reaction mixtures were composed predominantly of the 4,5-double bond isomer. In addition, it was found that by using the free bases of the aminoalkylthiols instead of their hydrochlorides in the condensation reactions the 4,5-double bond isomers of the 3-steroidal thiazolidines could be obtained instead of the mixture of 4,5- and 5,6-double bond isomers that were usually obtained from progesterone and testosterone. These observations suggest that the 4,5-double bond isomer is obtained initially in the formation of the spiro derivatives of α,β-unsaturated ketones and that

acid catalysis (an amine hydrochloride in the case of the thiazolidines) is required to isomerize the 4,5- to the 5,6-double bond isomer.

The ^{13}C NMR spectra of the thiazolidines was also useful in determining the stereochimistry of the reaction at the steroidal 3-carbon (C-3). The mechanism for the formation of thiazolidines[8] implicates the carbinolamine **9** and subsequently the imine **10** as the productive intermediates in the condensation. Nucleophilic attack by the thiol on the less hindered α-side of the steroid to form the thiazolidine should then result in β-nitrogen and α-sulfur in the thiazolidine.[9] On the other hand, if the condensation were not stereospecific, the ^{13}C NMR spectrum would show two absorptions for the C-3 absorption.[10] Besides the carbonyl carbons, the C-5 and the carbon of interest (the C-3), the only other carbons in the steroids **5a** and **5b** without any hydrogens attached to them were the 10- and 13-carbons. Inspection of the single frequency off-resonance band decoupled spectra of the ethylene ketal isomers **6a** and **6b**, where the C-3 absorptions (singlets at δ 109.61 and δ 106.35, respectively) were clearly separated from the region where the 10- and 13-carbon absorptions should appear, established that the 10- and 13-carbons absorptions appeared at about δ 37 and δ 42, respectively. The off-resonance band decoupled spectra of the thiazolidines **5a** and **5b** showed, in addition to the assigned carbonyl carbon, the 5-, 10- and 13-carbons absorptions, only one other carbon without any protons attached. That single absorption appeared at δ 61.79, which was about where the C-3 absorption in the steroid thiazolidines was expected.[10] Thus, analysis of the ^{13}C NMR spectra and the mechanism of thiazolidine formation supports the contention that only one of two possible C-3 isomers was obtained during thiazolidine formation and suggests that the β-nitrogen α-sulfur isomer was formed, as shown in the structures of the thiazolidines in Fig. 1.

In contrast to the ^{13}C NMR spectra of the thiazolidine isomers which were clearly one isomer from the number of olefinic carbon and C-3 absorptions, the ^{13}C NMR spectra of the hemithioketals (**7a, 7b**) showed multiple olefinic and C-3 absorptions. The intensities of the more intense absorptions due to the olefinic and C-3 absorptions were about three times that of the less intense absorptions which are recorded in Table 1 as the second set of absorptions for isomers **7a** and **7b**. The effect that the change in the stereochemistry at C-3 has on the spiroconjugation of the hemithioketal with the olefin can be seen in the relatively large differences observed in the chemical shifts of the olefinic carbons in **7b**. On the other hand, little effect on the olefin carbon absorptions, with the limits of the accuracy of spectrophotometer, were observed on the non-spiroconjugated hemithioketal isomer **7a**.

Although racemization was possible at the 4'-position of the thiazolidine, no change in the optical rotation of samples of **1** was observed after **1** had been recovered from a sequential treatment of **1** with aqueous acid to give the iminium ion **11** (UV max in 10% ethanol phosphate buffer pH 2.0 of 280 nm)[11] and bicarbonate neutralization. Attempts to hydrolyze the thiazolidines completely and to determine the optical rotation of the released cysteine ethyl ester in the instance of **1** resulted in inconsistent results apparently due to oxidation reactions of the cysteine ethyl ester.



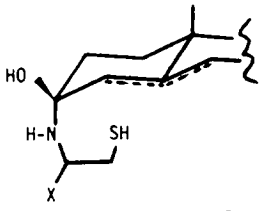
11

EXPERIMENTAL

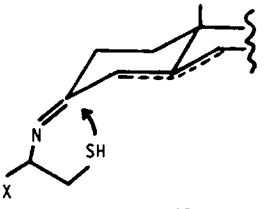
TLC were run on Brinkman Polygram Sil G/UV 254; ether. M.p. (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on a Varian T-60 (^1H), a Bruker WP-80 (^{13}C) at University of Kansas or on a Joel JNM-FX 100 (^{13}C) at the University of Florida. IR spectra were obtained on a Beckman AccuLab 4 infrared spectrophotometer. Optical rotations were obtained using a Perkin Elmer 141 polarimeter. Microanalyses were performed by Midwest Microlab, Ltd., Indianopolis, Indiana. The testosterone 17β-propionate, cysteine ethyl ester and aminoethanethiol hydrochlorides were purchased from Sigma. The mercaptoethanol, glycol and ethanedithiol were obtained from Aldrich. The thiazolidines were prepared as previously described[2b,2c] from the reaction of steroid with the aminoalkylthiol or their hydrochlorides in pyridine.

The reaction of testosterone 17β-propionate with mercaptoethanol. A benzene soln (40 ml) of testosterone 17β-propionate (2.0 g, 0.0059 mol) and 2.0 g (0.025 mol) of mercaptoethanol were refluxed for 7 hr in the presence of *p*-toulenesulfonic acid (33 mg), using a Dean-Stark trap to collect water. The mixture was extracted with 50 ml of 5% NaOH. The benzene layer was dried over $MgSO_4$, treated with one drop of pyridine and concentrated to give a colorless gum. The gum was triturated with 10 ml MeOH and filtered to give 0.7 g (m.p. 110–165°) of white solid which contained mostly the 5,6-double bond isomer based on its ^1H NMR spectrum. The 0.7 g was crystalized from methanol (7 ml) to give 0.40 g (m.p. 172–175°, 16% yield) of the 5-androstene-17β-propionyloxy-3-spiro-2'-(1',3'-oxathiolane); tlc (silica gel, ether) Rf 0.63; IR (KBr) 1730 cm^{-1} (s) (C=O); ^1H NMR ($CDCl_3$) δ 5.4–5.17 (m, 1, C$\underline{H}$=C), 4.56 (t, 1, C$\underline{H}$–O_2C), 4.13 (t, 2, $C\underline{H}_2$–O), 3.07 (t, 2, $C\underline{H}_2$–S), 1.13 (t, 3, $C\underline{H}_3CH_2CO_2$), 1.01 (s, 3, $C\underline{H}_3$–C), 0.8 (CH_3–C) and 2.8–0.4 (m, 19, $C\underline{H}_2$ and C$\underline{H}$); $[\alpha]_D^{25} - 35°$ (C=0.48, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 139.9, 140.5 (C_5), 122.5 (C_6) and 98.1, 94.4 (C_3). (Found: C, 71.18; H, 9.01. Calc. for $C_{24}H_{36}O_3S$: C, 71.24; H, 8.97%).

The filtrate from the first filtration above was cooled in the refrigerator overnight to give 0.55 g (m.p. 100–108°) of white



9



10

Fig. 1.

solid which was predominantly the 4,5-double bond isomer. It was recrystallized from 3 ml MeOH to give 0.30 g (m.p. 111–116°, 12% yield) of 4-androstene-17β-propionyloxy-3-spiro-2'-(1',3'-oxathiolane): tlc, IR and ^{1}H NMR were essentially identical with the 5-androstene oxathiolane except the CH=C absorption in the ^{1}H NMR was a broad singlet centered at δ 5.33 instead of a multiplet; ^{13}C NMR ($CDCl_3$) δ 123.2, 123.1 (C_4), 146.1, 149.1 (C_5) and 93.3, 90.9 (C_3); $[\alpha]_D^{25}$ + 116° (C = 0.57, $CHCl_3$). (Found: C, 71.39; H, 9.08. Calc. for $C_{24}H_{36}O_3S$: C, 71.24; H, 8.97%).

The reaction of testosterone 17β-propionate with ethylene glycol. A benzene (200 ml) suspension of testosterone 17β-propionate (3.0 g, 0.0087 mol) containing 14 ml ethylene glycol and 45 mg of *p*-toluenesolfonic acid was heated at reflux for 5 hr using a Dean-Stark trap to collect the water that formed. The biphasic system that resulted upon cooling the mixture was extracted with $NaHCO_3$ (3 × 200 ml, 2N) and water (200 ml). The benzene soln was separated and dried over Na_2SO_4, treated with 0.25 ml pyridine and concentrated *in vacuo*. The NMR spectrum of the residue showed that about equal amounts of the $\Delta^{4,5}$ and $\Delta^{5,6}$-ethylene ketals were present as well as unreacted starting material. The residue was immediately triturated with 20 ml hot acetone containing one drop pyridine. The suspension that resulted was immediately filtered and dried to give 0.72 g (m.p. 198–204°, 21% yield) 5-androsterene-17β-propionyloxy-3-spiro-2'-(1',3'-dioxolane). The acetone filtrate was diluted with 30 ml MeOH and allowed to crystallize further to give an additional 0.25 g (m.p. 195–203°, 7% yield) $\Delta^{5,6}$-ethylene ketal. An analytical sample was obtained by crystallization from acetone with a drop of pyridine: m.p. 203–205°, lit.,[12] m.p. 201–202°; IR (KBr) 1730 cm^{-1} (s) (C=O); ^{1}H NMR ($CDCl_3$) δ 5.47–5.2 (m, 1, CH=C), 4.63 (t, 1, CH–O_2C), 3.93 (s, 4, CH_2–O), 1.05 (s, 3, CH_3–C), 0.81 (s, 3, CH_3–C) and 2.8–0.8 (m, 24, CH_3, CH_2 and CH); ^{13}C NMR ($CDCl_3$) δ 174.7 (CO_2), 140.5 (C_5), 121.9 (C_6) and 109.6 (C_3); $[\alpha]_D^{25}$ –46°(C = 0.59, $CHCl_3$). (Found: C, 73.95; H, 9.29. Calc. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34%).

The methanol-acetone filtrate was concentrated *in vacuo* to give a waxy solid which was crystallized from 40 ml hot hexane and a drop of pyridine to give 0.50 g (m.p. 113–114.5°, 15% yield) 4-androstene-17β-propionyloxy-3-spiro-2'-(1',3'-dioxolane): IR (KBr) 1730 cm^{-1} (s) (C=O); 1670 cm^{-1} (w) (C=C), ^{1}H NMR ($CDCl_3$) δ 5.23 (s, 1, CH=C); ^{13}C NMR ($CDCl_3$) δ 174.7 (CO_2), 151.4 (C_5), 120.2 (C_4) and 106.4 (C_3); $[\alpha]_D^{25}$ + 75.3° (C = 0.49, $CHCl_3$). (Found: C, 74.39; H, 9.30. Calc. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34%).

Acknowledgements—A substantial part of the experimental work was performed at INTERx Research Corporation, Lawrence, Kansas. The authors wish to thank Bob Drake and Professor Grover Everett of the University of Kansas and Dr. Roy King of the University of Florida for the ^{13}C NMR spectra. The authors also wish to thank Professor Robert Carlson of the University of Kansas for many helpful discussions. This work was partially supported by NIH Contract No. NO1-HD-7-2833.

REFERENCES

[1]V. Stella, *Prodrugs as Novel Drug Delivery Systems* (Edited by T. Higuchi and V. Stella) ACS Symposium No. 14, ACS, Washington, D.C., 1975. A prodrug is a derivative of a drug that is not active itself, but overcomes a specific delivery problem of the drug and then hydrolyzes to release the drug in a controlled manner.

[2a] N. Bodor, K. B. Sloan, R. Little, S. Selk and L. Caldwell, presented in part at the 179th National Meeting of the American Chemical Society, Houston, Texas, 1980; Abstract No. Medi 12; [b]N. Bodor and K. B. Sloan, U.S. Patents 4,069,322, January 17, 1978; 4,239,757, December 16, 1980; [c]N. Bodor and K. B. Sloan, U.S. Patent 4,213,978, July 22, 1980; U.S. Patent application S.N. 886, 589, March 14 1979, allowed.

[3]P. Talalay, *Ann. Rev. Biochem.*, **34**, 347 (1965).

[4]C. Djerassi and M. Gorman, *J. Am. Chem. Soc.* **75**, 3704 (1953).

[5]D. H. R. Barton and W. Klyne, *Chem. Ind.* **755** (1948).

[6]J. W. Dean and R. G. Christiansen, *J. Org. Chem.* **28**, 2110 (1963).

[7]K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, *Helv. Chim. Acta* **45**, 2575 (1962).

[8]R. G. Kallen, *J. Am. Chem. Soc.* **93**, 6236 (1971).

[9]C. Djerassi, M. Shamma and R. Y. Kan, *ibid.* **80**, 4723 (1958).

[10]L. Szilagyi and Z. Gyorgydeak, *ibid.* **101**, 427 (1979).

[11]J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, *ibid.* **78**, 430 (1956).

[12]J. Danken, H. Ringold and B. Loken, U.S. Patent 2,802,825, August 13, 1957.