Kinetics of Decomposition and Formulation of Hydrocortisone Butyrate in Semiaqueous and Gel Systems

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Abstract □ The stability of hydrocortisone butyrate in semiaqueous and formulated gel systems has been investigated. It was shown that hydrocortisone butyrate underwent reversible isomerization to the C-21 ester of butyric acid. This ester then hydrolyzed to hydrocortisone, which in turn degraded to a complex mixture of compounds. This step is metal catalyzed and can be inhibited by the addition of EDTA [disodium(ethylenedinitrilo)tetraacetate]. The kinetics of decomposition is modeled using nonlinear regression analysis, and the rate constants for the various decomposition pathways are quantified.

Keyphrases □ Hydrocortisone butyrate—decomposition in semiaqueous and gel systems, kinetics □ Kinetics—decomposition of hydrocortisone butyrate in semiaqueous and gel systems □ Decomposition—hydrocortisone butyrate in semiaqueous and gel systems, kinetics □ Dosage forms, topical—hydrocortisone butyrate, decomposition in semiaqueous and gel systems, kinetics

Hydrocortisone butyrate (I) is available in various formulations for topical application. Studies *in vivo* have shown that the ester is many times more active than the parent alcohol, hydrocortisone (1). The presence of the ester function appears to improve delivery of corticosteroids to the site of action as well as increase steroidal activity by imparting resistance to the cutaneous metabolic enzymes involved in the disposition of the steroids from the site of action (2, 3).

Steroid-17-esters, however, readily rearrange to the thermodynamically more stable but topically less active (1) 21-esters under nonideal conditions (4). It was shown that in some extemporaneously diluted ointments, the half-life of betamethasone valerate may be <1 hr at room temperature (5). Previous studies (6, 7) showed that hydrocortisone butyrate (I) underwent acyl migration to the 21-ester (II) followed by hydrolysis of this ester to hydrocortisone (III). This paper reports the formulation and stability of the steroid in semiaqueous and gel systems.

EXPERIMENTAL

Steroid Analysis—High-performance liquid chromatography (HPLC) analyses were performed on an apparatus constructed from a constant-flow solvent pump[1], an injector[2] fitted with a 20-μl loop, and a variable-wavelength monitor[3] equipped with an 8-μl flow-cell. Aqueous acetonitrile[4] mixtures were used as the mobile phase, and hydrocortisone acetate (0.08 mg/ml) was the internal standard for reverse-phase chromatography on a 10-cm, 5-μm ODS column[5]. Normal-phase chromatography was performed as previously described (7) using caffeine (0.1 mg/ml) as the internal standard.

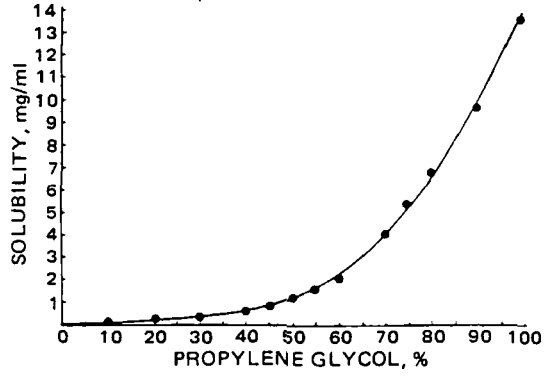

Figure 1—*Solubility profile of hydrocortisone butyrate (I) in aqueous propylene glycol mixtures at 25°.*

HPLC-grade solvents[4], propylene glycol BP[6], hydrocortisone[7], and the buffer salts[8] were purchased from various manufacturers. The hydrocortisone butyrate[9] and the gelling agents[10] were gifts and were used as supplied.

Preparation of Gels—To prepare a carboxypolymethylene polymer gel, 0.8 g of the polymer was dissolved in 30 g of propylene glycol and ~45 g of water. The product was neutralized with 2.5 ml of 2.5 *N* NaOH, and 0.1 g of the steroid was incorporated into the resultant gel using the remaining 20 g of propylene glycol. The gel was adjusted to 100 g with water to produce a 0.1% w/w hydrocortisone butyrate gel for subsequent studies. Entrapped air was removed by vacuum suction in a desiccator.

The other gel systems were prepared as recommended by the manufacturers. Initial experiments with these systems showed that, following topical application, unacceptable films were formed on the skin. All subsequent formulations, therefore, were carried out with the carboxypolymethylene polymers.

Preparation of Aqueous Propylene Glycol–Steroid Solutions—Both nonbuffered and buffered aqueous propylene glycol solutions were used in the kinetic experiments. Aqueous propylene glycol solutions (50% v/v) were adjusted to the required pH by addition of sodium hydroxide. These are referred to as nonbuffered solutions although such solutions should possess some buffer capacity. The buffered aqueous propylene glycol solutions were prepared by mixing equal volumes of propylene glycol and McIlvaine's citrate buffer adjusted to a constant ionic strength of 0.5 *M* with potassium chloride (8). As expected, addition of propylene glycol to an aqueous buffer produced large changes in the pH. Typically, a buffer with an initial pH of 6.91 was altered to pH 7.60 on dilution with an equal volume of propylene glycol. The pH quoted in the stability studies are all final values in the aqueous propylene glycol systems.

Solubility of Hydrocortisone Butyrate—The solubility of hydrocortisone butyrate (I) in aqueous propylene glycol or propylene glycol was determined by adding excess steroid to 10 ml of the appropriate propylene glycol solution preheated to 80°. The suspension was then placed in an ultrasonic bath for 15 min and transferred to a shaking water bath, maintained at 25°. The solution was filtered after overnight storage at this temperature, and an aliquot of the filtrate was assayed by HPLC. Initial estimates were obtained using normal-phase chromatography (6) and confirmed by reverse-phase chromatography. No decomposition was observed during the storage under the conditions described.

Storage and Assay of Gel—The hydrocortisone butyrate gels were stored at 60° in a water bath. Samples of ~1.2 g were withdrawn at appropriate intervals, and 5 ml of 0.5% w/v hydrochloric acid was added to quench the reaction. The tubes were shaken until homogeneous, and 10 ml of chloroform was added. The chloroform extracts were assayed by HPLC (6). Recovery studies showed a mean value of 99.17 ± 0.52% on six replicate determinations.

Storage and Assay of Aqueous Propylene Glycol–Steroid Solutions—The solutions (1 mg/ml) were stored in water baths maintained

[1] Altex 100A model.
[2] Rheodyne 7120.
[3] Pye LC3.
[4] Fisons Ltd (UK).
[5] Hypersil-ODS.
[6] McCarthys Ltd.
[7] Sigma Chemical Co. (UK).
[8] British Drug Houses.
[9] Brocades Ltd UK.
[10] Carbopol 940 (carboxypolymethylene polymers), Goodrich Chemical Co.; Klucel HF (hydroxypropylcellulose), Natrosal (hydroxyethylcellulose), and sodium carboxymethylcellulose, Hercules Ltd.

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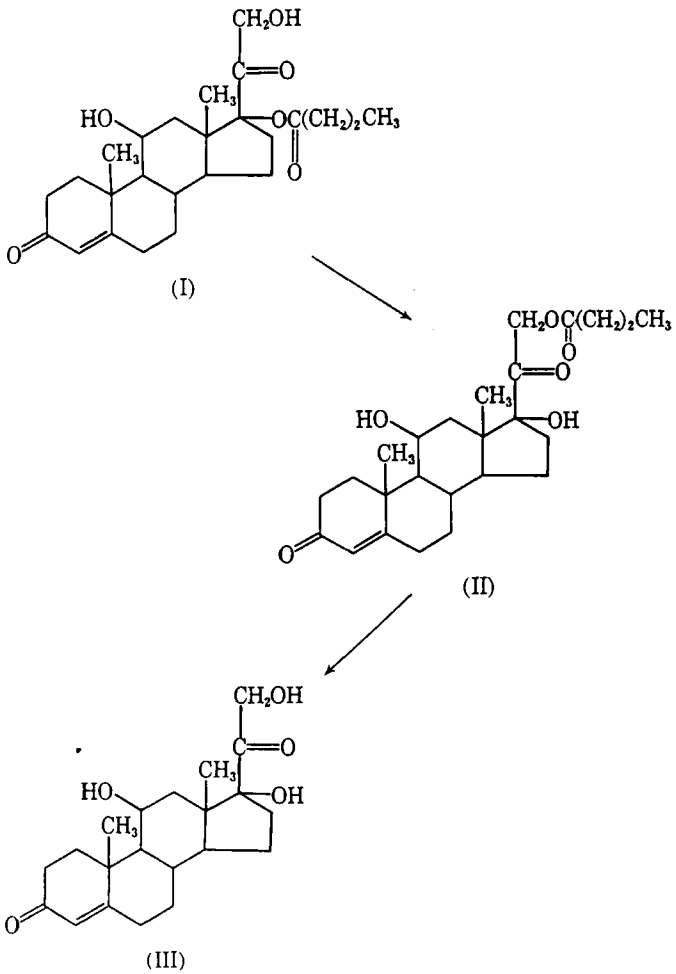

Scheme I: Decomposition pathway of hydrocortisone butyrate.

at 60°, and 1-ml aliquots were withdrawn at appropriate intervals for assay by reverse-phase HPLC. The reaction was halted by the addition of 4 ml of 0.024 *M* hydrochloric acid in 50% aqueous acetonitrile. Such diluted samples could be stored at 4° for at least a week without measurable decomposition. The samples were diluted with an additional 5 ml of the acetonitrile–hydrochloric acid mixture which contained 0.16 mg/ml of hydrocortisone acetate as an internal standard. When hydrocortisone was studied alone, an internal standard concentration of 0.32 mg/ml was used to obtain more precise data. EDTA [disodium(ethylenedinitrilo)tetraacetate] (0.05% w/v) was added when indicated.

RESULTS AND DISCUSSION

Products commercially available indicate that a 0.1% w/w hydrocortisone butyrate concentration would be a useful starting point when formulating a topical preparation of the steroid. To enhance percutaneous absorption of the steroid from the gel system, it was necessary to optimize the thermodynamic activity of the steroid in the formulation. Since a solution system was considered desirable, the continuous phase vehicle ideally should be chosen in such a way that the concentration of steroid is as close as possible to the saturation concentration. To do this quantitatively, a solubility profile of hydrocortisone butyrate in aqueous propylene glycol, the chosen continuous phase, was constructed (Fig. 1). On the basis of the data obtained, a 48% w/w propylene glycol in water solution was chosen for formulating the 0.1% w/w hydrocortisone butyrate gel.

Analysis of the steroids by HPLC and by reference to authentic specimens showed that, like betamethasone valerate, hydrocortisone butyrate (I) isomerizes to the corresponding C-21 ester of butyric acid (II), which then hydrolyzes to hydrocortisone (III) as shown in Scheme I.

To obtain adequate HPLC resolution of the steroids, three aqueous acetonitrile mixtures were necessary. Quantitation of I and II was carried out using a 50% v/v acetonitrile–water mixture. Under these conditions, hydrocortisone showed significant overlap with other minor decomposition products (Fig. 2*a*). Decreasing the acetonitrile concentration prolonged the retention times of all the steroids. The quantitative assay of hydrocortisone was possible with a mobile phase consisting of 35% v/v acetonitrile–water (Fig. 2*b*). Although I and II were resolved from the other steroids using this weaker solvent, the quantitation was not satisfactory because of peak broadening. In the initial stages of decomposition, a 40% v/v acetonitrile–water mixture was adequate in resolving hydrocortisone for quantitative assay (Fig. 2*c*). Considerable time could be saved using this system instead of the 35% v/v aqueous acetonitrile mixture. Whenever possible, therefore, the 40% mixture was chosen for assaying hydrocortisone in the presence of the other steroids.

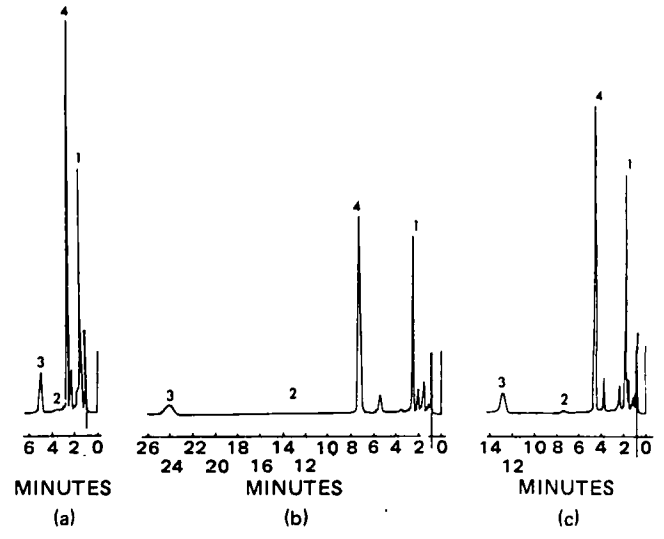

Figure 2—*HPLC separation of I from its decomposition products using an aqueous acetonitrile mobile phase at concentrations of 50% (a), 35% (b), and 40% v/v (c). Key: (1) hydrocortisone; (2) I, (3) II; (4) internal standard.*

Where the assay solutions were diluted prior to injection, care was taken to ensure that the final solvent composition was identical to that used for the standard solution. This was necessary because, as previously reported (9), peak height ratios can show considerable variation, depending on the solvent used.

Kinetic analysis of the gel data (Fig. 3) showed that disappearance of I followed first-order kinetics. Unlike betamethasone valerate (5, 6), however, the overall decomposition did not follow a sequential first-order pattern. Monitoring the decomposition at various pH values showed that the isomerization of I to the C-21 ester (II) was base catalyzed, and pH dependent (Table I). Such base catalysis has been shown in semisolid systems (7, 9, 10). The changes in pH do not appear to be the only factor of importance, since dilution of a betamethasone valerate ointment with a different ointment base significantly altered the decomposition rate even though the pH was near that of the stable undiluted product (7).

To dissociate any effects produced by the gelling agent from other effects, the kinetics of decomposition of I was followed in the absence of the vinyl polymer. The data obtained showed that the decomposition was again pH dependent (Table II); but, unlike the gel system, even the disappearance rate of I in this nonbuffered system did not follow first-order kinetics. The profile for the three steroids in a 50% v/v aqueous propylene glycol system adjusted to pH 7.9 with sodium hydroxide is illustrated in Fig. 4. At this stage it was postulated that base was consumed during at least one of the reactions involved in the overall degradation of I since there was a pH change of ~2 units. To test this, the decomposition was

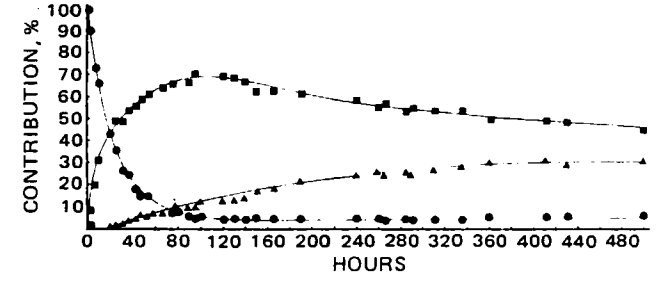

Figure 3—*Profile for I (●), II (■), and hydrocortisone (▲) during the decomposition at 60° of I in a gel system (initial pH 6.78).*

Table I—Effect of pH on the Isomerization of Hydrocortisone Butyrate[a] in a Gel System at 60°

pH	Observed Rate Constant,[b] $hr^{-1} \times 10^4$
6.78	412
5.07	11.5
4.42	6.6

[a] To C-21 ester of butyric acid. [b] Rate constant refers to the overall disappearance of the 17-butyrate.

Table II—Effect of pH on the Decomposition of Hydrocortisone Butyrate[a] in the Aqueous Propylene Glycol Mixture[b] at 60°

pH	Hydrocortisone-butyrate, %	Hydrocortisone-21-butyrate, %	Hydrocortisone, %
7.89	87	8	0
9.95	4	57	37
11.17	0	0	77

[a] Steroid composition at 30 min. [b] 50% v/v.

followed in buffered aqueous propylene glycol systems. Under such conditions one would expect linearization of the data if the reaction sequence was indeed a sequential, irreversible, first-order pathway (Table III, model 1). In fact, the data obtained gave a reasonable fit when subjected to nonlinear regression analysis (11). For most stability prediction studies, such a fit would be adequate, and the confidence limits of the data support this (Table IV). For precise modeling, however, the computerized plot of the experimental data against the predicted data using model 1 shows that discrepancies are present (Fig. 5).

The integrated form of the rate equations were used in the computation. These (Eqs. A1–A4) and equations relevant to the other kinetic models used in this study are listed in *Appendix I*. The kinetic parameters are listed in Tables IV–VIII.

Both previous (12) and the present data show that other products besides II and the free alcohol are produced during the decomposition at 60°. HPLC of a decomposed sample (Fig. 2) clearly demonstrates the complexity of the pathways. Hansen and Bundgaard (12) have reported that at least seven products are formed during the decomposition of hydrocortisone. If the decomposition of hydrocortisone to other products were all first-order parallel processes, the sequential first-order model would hold because the rate constant for the decomposition (K_3) would then equal the sum of the individual rate constants.

The possibility that experimental error accounted for the results was discounted by repeating the experiment: similar deviations were noted in both sets of data. There was good agreement between the estimates for the rate constants (Table IV). Two alternative models to account for the discrepancies are possible. The first is that the isomerization of I to II is reversible, and that the reverse rate constant is not negligible (Table III, model 2). An analogous situation has been previously reported in studies on tricyclic antidepressants (13, 14). In a recent study, Anderson and Taphouse showed that acyl migration from the C-21 to the C-17 position was also possible with methylprednisolone hemisuccinate (15). The second alternative is that I hydrolyzes to hydrocortisone directly and not solely *via* the formation of II (Table III, model 3). To test these possibilities, the hydrolysis of II was followed in samples initially free of I (Table VI, $|B|_0 = 100\%$). Formation of I would show any reversibility. This was the case, and the kinetic parameters for this system under identical conditions are shown in Table V. The improved fit to the model can be seen in Fig. 6. Since K_1 is ~14 times greater than K_4, these rate

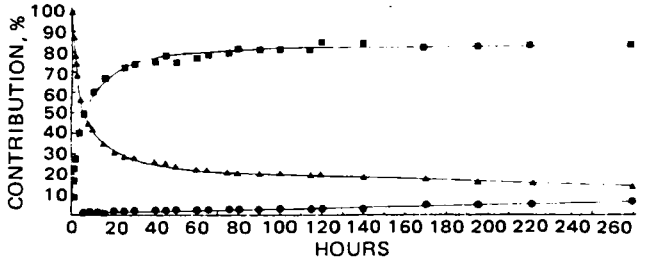

Figure 4—*Profile of I (▲), II (■), and hydrocortisone (●) during the decomposition at 60° of the steroid-17-ester in an aqueous propylene glycol solution (initial pH 7.9).*

Table III—Kinetic Models for the Decomposition of Hydrocortisone Butyrate

Model	Decomposition Scheme
1	$I \xrightarrow{K_1} II \xrightarrow{K_2} III \xrightarrow{K_3} IV$
2	$I \underset{K_4}{\overset{K_1}{\rightleftharpoons}} II \xrightarrow{K_2} III \xrightarrow{K_3} IV$
3	$I \underset{K_4}{\overset{K_1}{\rightleftharpoons}} II \xrightarrow{K_2} III \xrightarrow{K_3} IV$, $II \xrightarrow{K_5} III$

constants are expected to be imprecise when derived from experiments where the initial concentration of I is zero. This is reflected in the wide confidence limits (Table VI).

It is interesting to note that the reverse rate constant for betamethasone valerate isomerization to the C-21 ester was negligible (6), while the ratio of the forward and reverse rate constants for methylprednisolone hemisuccinate was 3–5 (15). The diacidic nature of succinic acid and the C-16 methyl group in betamethasone may explain the observed differences. The free acid function of prednisolone is able to interact freely with the C-17 hydroxyl group without ester function cleavage. In betamethasone, the C-17 hydroxyl group is sterically hindered to a greater extent than in the other two steroids. Its interaction with the C-21 ester function, therefore, is associated with a higher energy barrier and hence a lower reverse rate constant. The experiment does not exclude reversibility in the hydrolysis of I. Therefore, the decomposition of hydrocortisone was studied in the presence of an equimolar amount of sodium butyrate and in the absence of the esters. A control was carried out without the sodium butyrate: no hydrocortisone ester was detected throughout the run, and the rate constants in the control and test systems (0.0096 and 0.0102 hr^{-1}, respectively) were equal within experimental error. Having confirmed that the isomerization, but not the hydrolysis, of I was reversible, the fit to models 2 and 3 were compared to exclude

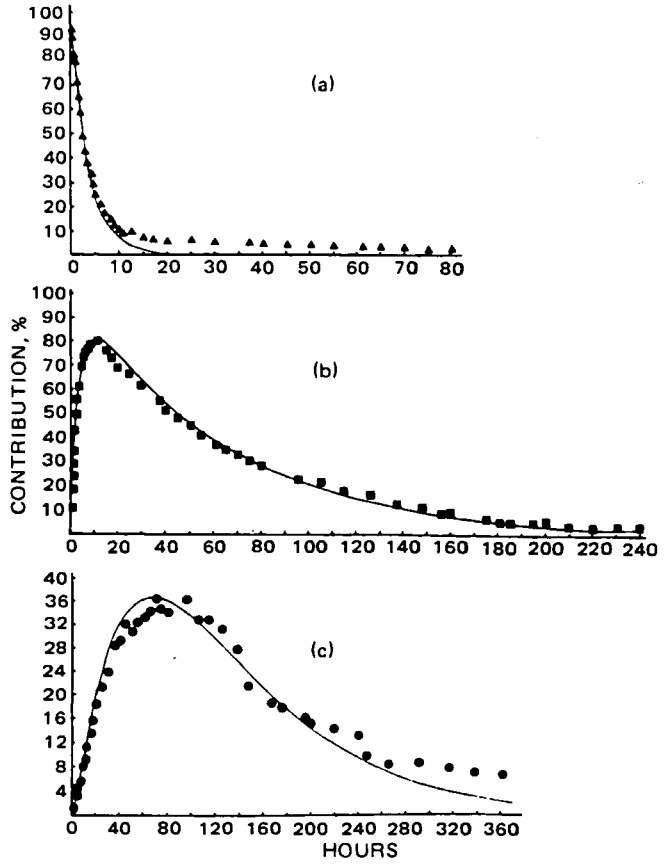

Figure 5—*Profiles for I (a), II (b), and hydrocortisone (c) during the decomposition at 60° of the steroid-17-ester in a buffered aqueous propylene glycol solution (50% v/v, pH 7.6). The lines represent the theoretical predictions according to model 1.*

Table IV—Rate Constants for the Decomposition of Hydrocortisone Butyrate According to Model 1 [a]

Data Set	Calculated Rate Constants[b], hr^{-1}	95% Confidence Limits	Correlation Coefficient[c]
1	$K_1 = 0.290 \pm 0.005$	0.281–0.300	0.999 (A)
	$K_2 = 0.016 \pm 0.0003$	0.016–0.017	0.995 (B)
	$K_3 = 0.0173 \pm 0.001$	0.016–0.019	0.979 (C)
2	$K_1 = 0.288 \pm 0.004$	0.260–0.277	0.998 (A)
	$K_2 = 0.016 \pm 0.0003$	0.015–0.016	0.995 (B)
	$K_3 = 0.015 \pm 0.0004$	0.014–0.016	0.987 (C)

[a] As defined in Table III with initial conditions: $|A|_0 = 100\%$ and $|B|_0 = |C|_0 = 0$. [b] Reactions in buffered (pH 7.6) aqueous propylene glycol (50% v/v) at 60°. [c] Function designation in parentheses.

Table V—Rate Constants for the Isomerization and Decomposition of Hydrocortisone Butyrate According to Model 2 [a]

Data Set	Calculated Rate Constants[b], hr^{-1}	95% Confidence Limits	Correlation Coefficient[c]
1	$K_1 = 0.308 \pm 0.00485$	0.299–0.318	1.000 (A)
	$K_2 = 0.016 \pm 0.00026$	0.016–0.017	0.997 (B)
	$K_3 = 0.017 \pm 0.00057$	0.016–0.018	0.983 (C)
	$K_4 = 0.020 \pm 0.00253$	0.015–0.025	
2	$K_1 = 0.292 \pm 0.00321$	0.285–0.298	0.999 (A)
	$K_2 = 0.016 \pm 0.00015$	0.0157–0.0164	0.999 (B)
	$K_3 = 0.015 \pm 0.00024$	0.015–0.016	0.989 (C)
	$K_4 = 0.025 \pm 0.00163$	0.021–0.028	

[a] As defined in Table III with initial conditions: $|A|_0 = 100\%$ and $|B|_0 = |C|_0 = 0$. [b] Reactions in buffered (pH 7.6) aqueous propylene glycol (50% v/v) at 60°. [c] Function designation in parentheses.

Table VI—Rate Constants for the Isomerization and Decomposition of Hydrocortisone Butyrate According to Model 2 [a]

Calculated Rate Constants[b], hr^{-1}	95% Confidence Limits	Correlation Coefficients[c]
$K_1 = 0.348 \pm 0.195$	(−) 0.041–0.737	0.983 (A)
$K_2 = 0.015 \pm 0.00019$	(−) 0.258–0.051	0.999 (B)
$K_3 = 0.019 \pm 0.00038$	0.150–0.016	0.983 (C)
$K_4 = 0.024 \pm 0.0135$	0.018–0.020	

[a] As defined in Table III with initial conditions: $|A|_0 = 0$, $|B|_0 = 100\%$, and $|C|_0 = 0$. [b] Reactions in buffered (pH 7.6) aqueous propylene glycol (50% v/v) at 60°. [c] Function designation in parentheses.

the possibility that I is converted directly to hydrocortisone. The statistical data and the plots (Figs. 6 and 7) show that direct conversion was likely. Because of the small magnitude of the rate constant for the direct conversion of the I to hydrocortisone (K_5) relative to the other routes, the estimate for its value is imprecise, as is evident in the wide span of 95% confidence limits (Table VII).

Preliminary work on the effect of buffers on the decomposition indicated that the decomposition rates of I to II and of the latter to III were not significantly affected by doubling the buffer concentration. However, the rate of hydrocortisone disappearance was increased (Tables VII and VIII). Recent work has shown that the decomposition of III was metal catalyzed and that EDTA significantly decreased the rate of decomposition (12). Indeed, buffer effects were rationalized on the basis of trace metal contaminants both for hydrocortisone (12) and prednisolone (16). In the present system, the isomerization and hydrolysis steps were unaffected; these steps were not expected to be metal catalyzed. Using different batches of the same grade[11] of buffer salts, the same rate constants for the decomposition of III were obtained (Table IX). However, this does not exclude metal catalysis.

The effect of EDTA on the decomposition therefore was investigated. In addition to explaining in part the mechanism of decomposition, the data was expected to aid in selecting suitable methods for stabilizing the hydrocortisone formulations. Additionally, it had been suggested that some of the decomposition products were potentially immunogenic (17). When compared with control systems (free from the chelating agent),

[11] Analar.

Table VII—Rate Constants for the Isomerization and Decomposition of Hydrocortisone Butyrate According to Model 3 [a]

Data Set	Calculated Rate Constants[b], hr^{-1}	95% Confidence Limits	Correlation Coefficient[c]
1	$K_1 = 0.310 \pm 0.0077$	0.295–0.325	1.000 (A)
	$K_2 = 0.018 \pm 0.00079$	0.0163–0.019	0.998 (B)
	$K_3 = 0.015 \pm 0.00076$	0.0138–0.017	0.975 (C)
	$K_4 = 0.022 \pm 0.0042$	0.0134–0.030	
	$K_5 = 0.0001 \pm 0.0045$	(−) 0.009–0.009	
2	$K_1 = 0.292 \pm 0.0033$	0.286–0.299	0.999 (A)
	$K_2 = 0.016 \pm 0.00031$	0.215–0.280	0.999 (B)
	$K_3 = 0.015 \pm 0.00024$	0.0155–0.017	0.989 (C)
	$K_4 = 0.025 \pm 0.0017$	0.0146–0.0155	
	$K_5 = 0.0001 \pm 0.0018$	(−) 0.003–0.004	

[a] As defined in Table III with initial conditions: $|A|_0 = 100\%$ and $|B|_0 = |C|_0 = 0$. [b] Reactions in buffered (pH 7.6) aqueous propylene glycol (50% v/v) at 60°. [c] Function designation in parentheses.

a stabilizing effect on hydrocortisone was observed when EDTA was added. As expected, the isomerization and hydrolysis rate constants were not significantly altered (Table X). Comparison of the chromatograms (Fig. 8) for the decomposed solutions shows that the profiles for hydrocortisone and the minor decomposition products were markedly different when the system with added EDTA was compared with a control. At 105 hr, the residual steroid concentrations in the control system were 1.2% for I, 21% for II, and 32.6% for III; the respective concentrations for the system with added EDTA were 1.8, 24, and 52%. No attempt was made to identify the minor decomposition products, but published work suggests that oxidation of the side chain of hydrocortisone (leading to the formation of steroid glyoxals, 17-oxo-steroids, and glycolic acids) was likely (12).

The rate constants for the loss of hydrocortisone were lower for solutions initially containing only hydrocortisone compared with solutions

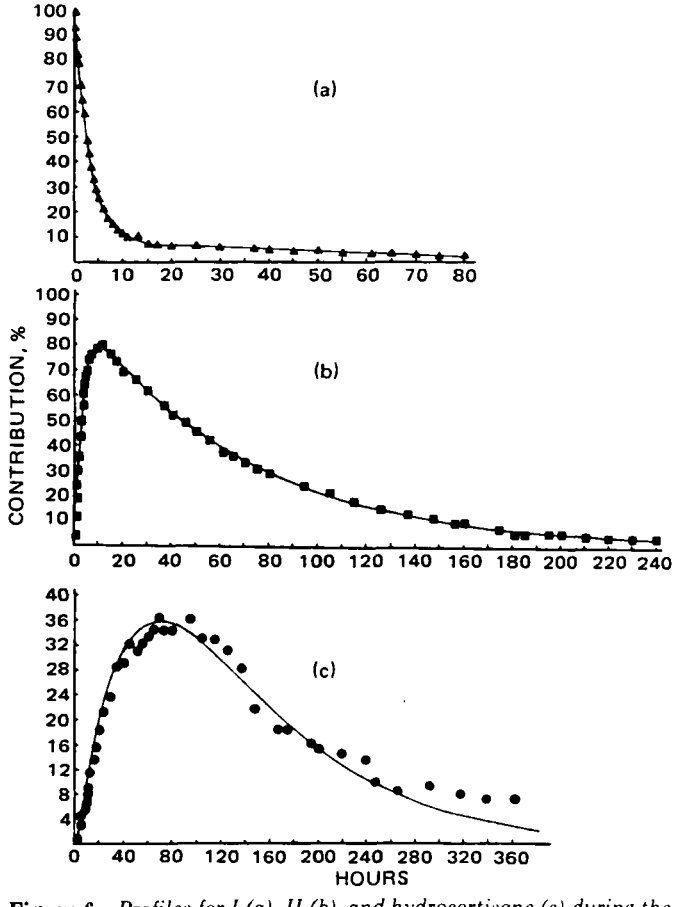

Figure 6—*Profiles for I (a), II (b), and hydrocortisone (c) during the decomposition at 60° of the steroid-17-ester in a buffered aqueous propylene glycol solution (50% v/v, pH 7.6). The lines represent the theoretical predictions according to model 2.*

Table VIII—Rate Constants for the Isomerization and Decomposition of Hydrocortisone Butyrate According to Model 3[a]

Calculated Rate Constants[b], hr^{-1}	95% Confidence Limits	Correlation Coefficient[c]
$K_1 = 0.289 \pm 0.0052$	0.278–0.299	0.999 (A)
$K_2 = 0.016 \pm 0.00034$	0.016–0.017	0.998 (B)
$K_3 = 0.032 \pm 0.0014$	0.029–0.035	0.947 (C)
$K_4 = 0.025 \pm 0.0027$	0.020–0.031	

[a] As defined in Table III with initial conditions: $|A|_0 = 100\%$ and $|B|_0 = |C|_0 = 0$. [b] Reactions in aqueous propylene glycol (50% v/v) at 60°, with twice the added buffer than in the system for Table V. [c] Function designation in parentheses.

initially composed of only I (Tables IV and IX). The rate constant in the latter system had to be obtained by curve-fitting, and, as expected, the value of the rate constant for the loss of hydrocortisone was less accurate than that for the simpler system with hydrocortisone alone. This discrepancy in the rate constants for hydrocortisone disappearance also accounts for the deviation between the predicted and actual hydrocortisone profiles at longer time intervals (Figs. 5–7).

CONCLUSIONS

It has been shown that, in the systems studied, hydrocortisone butyrate (I) underwent reversible isomerization to hydrocortisone butyrate (II). Compound II was then hydrolyzed to hydrocortisone (III) which in turn degraded to a complex mixture of oxidation products. Although the decomposition pathways are complex, they can satisfactorily be modeled by a series of first-order equations. Nonlinear regression analysis of the data indicated that both models 2 and 3 (Table III) satisfactorily described the decomposition, and that model 3 appeared to be a marginally better fit. Direct hydrolysis of I to III and the reverse rate constant for its isomerization to II were so small relative to the hydrolysis rate of II

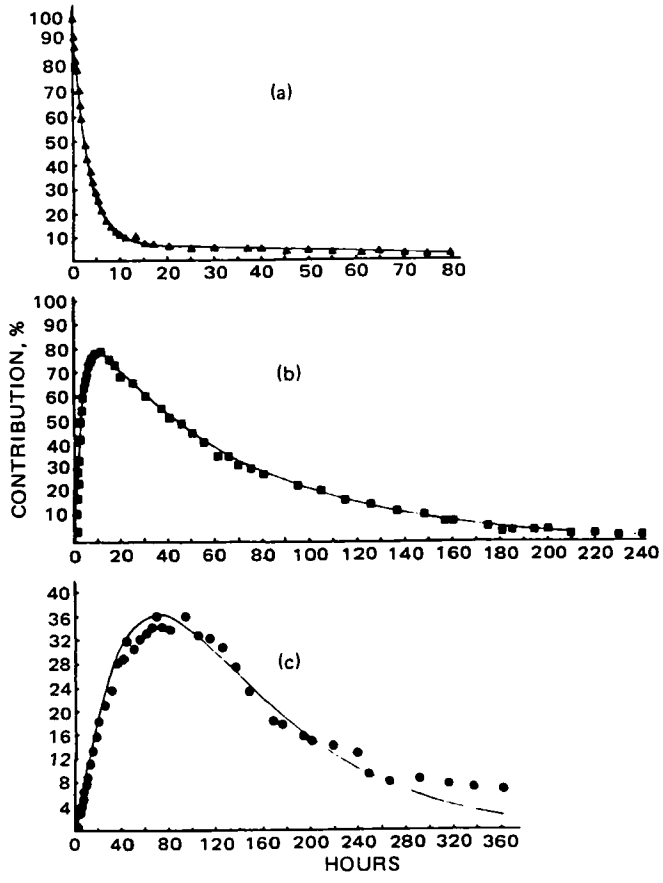

Figure 7—*Profiles for I (a), II (b), and hydrocortisone (c) during the decomposition at 60° of the steroid-17-ester in a buffered aqueous propylene glycol solution (50% v/v, pH 7.6). The lines represent the theoretical predictions according to model 3.*

Table IX—Rate Constants for the Decomposition of Hydrocortisone in Buffered Solutions Using Different Batches of Buffer Salts

Batch	Rate Constant, hr^{-1}
2	0.00964
2	0.01114
1	0.00926
3	0.0107

and the forward rate constant of isomerization that, for most shelf-life predictions, estimates using model 1 (Table III) should be adequate. While the decomposition of III is slow when compared with that of the esters, the suggestion (16) that some of the products may be immunogenic indicates that these slow rates may need to be taken into consideration for the expiration dating of hydrocortisone esters. This requires confirmation; but if such is the case, the more complex models described in this paper should be adequate for this purpose.

APPENDIX

Integrated Rate Equations for Table IV—

$$|A|_t = |A|_0 e^{-K_1 t} \quad \text{(Eq. A1)}$$

$$|B|_t = \frac{|A|_0 K_1}{K_2 - K_1}(e^{-K_1 t} - e^{-K_2 t}) \quad \text{(Eq. A2)}$$

$$|C|_t = |A|_0 \left[\left[\frac{K_1K_2}{(K_2 - K_1)(K_3 - K_1)}\right] e^{-K_1 t} + \left[\frac{K_1K_2}{(K_1 - K_2)(K_3 - K_2)}\right] e^{-K_2 t} + \left[\frac{K_1K_2}{(K_1 - K_3)(K_2 - K_3)}\right] e^{-K_3 t}\right] \quad \text{(Eq. A3)}$$

$$|D|_t = |A|_0 \left[1 - \left[\frac{K_2K_3}{(K_2 - K_1)(K_3 - K_1)}\right] e^{-K_1 t} - \left[\frac{K_1K_3}{(K_1 - K_2)(K_3 - K_2)}\right] e^{-K_2 t} - \left[\frac{K_1K_2}{(K_1 - K_3)(K_2 - K_3)}\right] e^{-K_3 t}\right] \quad \text{(Eq. A4)}$$

Integrated Rate Equations for Table V—

$$|A|_t = |A|_0 \left(\frac{K_2 + K_4 - \gamma_1}{\gamma_2 - \gamma_1} e^{-\gamma_2 t} + \frac{K_4 + K_2 - \gamma_2}{\gamma_1 - \gamma_2} e^{-\gamma_2 t}\right) \quad \text{(Eq. A5)}$$

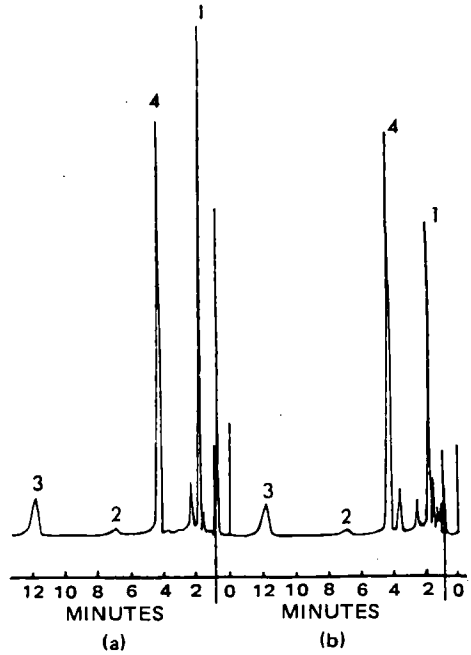

Figure 8—*Chromatograms of decomposed solutions of I in the presence (a) and absence (b) of EDTA. Key: (1) hydrocortisone; (2) I; (3) II (4) internal standard.*

Table X—Decomposition of Hydrocortisone Butyrate in the Presence and Absence of EDTA [a]

Starting Compound	Decomposition Rate Constant, $\times 10^3$ hr^{-1} With EDTA	Without EDTA	
Hydrocortisone	K_3 3.90	11.14	←
Hydrocortisone butyrate	K_1 274	292	
	K_2 14.4	16.1	
	K_3 5.2	15.3	←
	K_4 24.4	24.6	

[a] 0.05% w/v.

$$|B|_t = |A|_0 K_1 \left(\frac{1}{\gamma_2 - \gamma_1} e^{-\gamma_1 t} + \frac{1}{\gamma_1 - \gamma_2} e^{-\gamma_2 t}\right) \quad \text{(Eq. A6)}$$

$$|C|_t = |A|_0 K_1 K_2 \left[\frac{1}{(\gamma_2 - \gamma_1)(K_3 - \gamma_1)} e^{-\gamma_1 t} + \frac{1}{(\gamma_1 - \gamma_2)(K_3 - \gamma_2)} e^{-\gamma_2 t} + \frac{1}{(\gamma_1 - K_3)(\gamma_2 - K_3)} e^{-K_3 t}\right] \quad \text{(Eq. A7)}$$

where $\gamma_1 = \frac{1}{2}\{(K_1 + K_2 + K_4) - [(K_1 + K_2 + K_4)^2 - 4K_1K_2]^{1/2}\}$ (Eq. A8)

and

$$\gamma_2 = \frac{1}{2}\{(K_1 + K_2 + K_4) + [(K_1 + K_2 + K_4)^2 - 4K_1K_2]^{1/2}\} \quad \text{(Eq. A9)}$$

Integrated Rate Equations for Table VI—

$$|A|_t = |B|_0 K_4 \left(\frac{1}{\gamma_2 - \gamma_1} e^{-\gamma_1 t} + \frac{1}{\gamma_1 - \gamma_2} e^{-\gamma_2 t}\right) \quad \text{(Eq. A10)}$$

$$|B|_t = |B|_0 \left(\frac{K_1 - \gamma_1}{\gamma_2 - \gamma_1} e^{-\gamma_1 t} + \frac{K_1 - \gamma_2}{\gamma_1 - \gamma_2} e^{-\gamma_2 t}\right) \quad \text{(Eq. A11)}$$

$$|C|_t = |B|_0 K_2 \left[\frac{K_1 - \gamma_1}{(\gamma_2 - \gamma_1)(K_3 - \gamma_1)} e^{-\gamma_1 t} + \frac{K_1 - \gamma_2}{(\gamma_1 - \gamma_2)(K_3 - \gamma_2)} e^{-\gamma_2 t} + \frac{K_1 - K_3}{(\gamma_1 - K_3)(\gamma_2 - K_3)} e^{-K_3 t}\right] \quad \text{(Eq. A12)}$$

where γ_1 and γ_2 are as defined in Eqs. A8 and A9, respectively.

Integrated Rate Equations for Table VII—

$$|A|_t = |A|_0 \left(\frac{K_4 + K_2 - \gamma_1}{\gamma_2 - \gamma_1} e^{-\gamma_1 t} + \frac{K_4 + K_2 - \gamma_2}{\gamma_1 - \gamma_2} e^{-\gamma_2 t}\right) \quad \text{(Eq. A13)}$$

$$|B|_t = |A|_0 K_1 \left(\frac{1}{\gamma_2 - \gamma_1} e^{-\gamma_1 t} + \frac{1}{\gamma_1 - \gamma_2} e^{-\gamma_2 t}\right) \quad \text{(Eq. A14)}$$

$$|C|_t = |A|_0 \left[\frac{K_1K_2 + K_4K_5 + K_2K_5 - K_5\gamma_1}{(\gamma_2 - \gamma_1)(K_3 - \gamma_1)} e^{-\gamma_1 t} + \frac{K_1K_2 + K_4K_5 + K_2K_5 - K_5\gamma_2}{(\gamma_1 - \gamma_2)(K_3 - \gamma_2)} e^{-\gamma_2 t} + \frac{K_1K_2 + K_4K_5 + K_2K_5 - K_3K_5}{(\gamma_1 - K_3)(\gamma_2 - K_3)} e^{-K_3 t}\right] \quad \text{(Eq. A15)}$$

where

$$\gamma_1 = \frac{1}{2}\{(K_1 + K_2 + K_4 + K_5) - [(K_1 + K_2 + K_4 + K_5)^2 - 4(K_4K_5 + K_1K_2 + K_2K_5)]^{1/2}\} \quad \text{(Eq. A16)}$$

and

$$\gamma_2 = \frac{1}{2}\{(K_1 + K_2 + K_4 + K_5) + [(K_1 + K_2 + K_4 + K_5)^2 - 4(K_4K_5 + K_1K_5 + K_2K_5)]^{1/2}\} \quad \text{(Eq. A17)}$$

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