Controlled Drug Release from Polymeric Delivery Devices V: Hydroxy Group Effects on Drug Release Kinetics and Thermodynamics

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Abstract □ The effects of progesterone hydroxylation on silicone matrix drug release kinetics and thermodynamics were investigated. Hydroxylation at positions 11, 17, and/or 21 substantially reduced progesterone release. The magnitude of this reduction depended on the number and position of the hydroxy groups and could be attributed to decreased polymer matrix diffusivity (D_m) and polymer solubility (C_p). Thermodynamically, hydroxy group addition to positions 11 and/or 21 reduced the activation energy for matrix diffusion ($E_{d,m}$) but increased the solvation energy for dissolution in silicone polymer ($\Delta H_{T,m}$). Adding an hydroxy group to position 17 increased the $E_{d,m}$ but decreased the $\Delta H_{T,m}$. The overall ($E_{d,m} + \Delta H_{T,m}$) values were relatively constant and independent of hydroxylation.

Keyphrases □ Dosage forms—controlled release, progesterone from silicone matrix, effect of hydroxylation, kinetics, thermodynamics □ Progesterone—controlled-release dosage forms, effect of hydroxylation on release from silicone matrix □ Hydroxylation—progesterone, effect on release from silicone matrix □ Steroids—controlled-release dosage forms, progesterone, effect of hydroxylation on release from silicone matrix

The idea of replacing daily drug administration with a polymeric controlled-release device has recently generated much interest (1). The high silicone polymer steroid permeability has led to development of drug-filled and drug-dispersed silicone devices for long-term intrauterine, intravaginal, subcutaneous, and transdermal drug administration (2–15).

An *in vitro* system for direct, rapid drug release characterization was recently developed (16). Two types of drug release mechanisms, matrix controlled and partition controlled, were observed when the drug release profiles from silicone devices were followed daily using this system (17–19). Controlled drug release kinetics and thermodynamics under these two processes were analyzed (18–20).

Normalized steroid permeability coefficients appear to depend on the steroidal structure (21). For drugs with a high permeability coefficient (across the vaginal membrane) (P_m), like progesterone, intravaginal absorption is mainly controlled by the permeability of the vaginal surface aqueous hydrodynamic diffusion layer. For drugs with a low P_m value, such as hydrocortisone, intravaginal uptake is determined mainly by molecular transport across the vaginal membrane. This difference in absorption may be due to the hydroxy groups in the steroid. The transdermal permeability constants were also reported to be influenced by the presence of hydroxy groups on the progesterone molecules (22).

Effects of hydroxy groups on the controlled-release kinetics and thermodynamics of progesterone and its derivatives were studied in this investigation as a step in the design of controlled-release drug delivery systems.

EXPERIMENTAL

Silicone devices were prepared by thoroughly mixing 0.5–2.0 parts of progesterone derivative crystals, 7.5 parts of dimethyl polysiloxane elastomer[1], and one part of silicone fluid[2] with a rotator[3] at 1000 rpm for 7 min. One drop (0.02 ml) of stannous octoate[1], as catalyst, was then incorporated and thoroughly mixed for another minute. The mixture was deaerated under vacuum for 4 min and delivered by an extrusion pump[4] into Tygon tubing[5] (0.63-cm i.d.). The silicone polymer was allowed to cure at 60° for 1 hr. After proper cross-linking, the resulting medicated silicone device was removed from the tubing mold and cut into the desired lengths for *in vitro* drug elution studies.

The *in vitro* drug elution studies were conducted by immersing one medicated silicone device in each test tube containing 10 ml of 50% (v/v) polyethylene glycol 400–water. The test tubes were sealed with screw caps and shaken at a constant 40 oscillations/min in a water bath thermostated at 37, 45, 50, or 55°. The medicated silicone devices were transferred to new elution solution every 24 hr for 7 days. The drug concentration in each test tube was analyzed spectrophotometrically[6] after appropriate dilution with spectral grade methanol. The drug released every 24 hr from each device and the drug released from a unit surface area of the device (Q) were calculated.

The techniques for determining drug solubility in silicone polymer and in 50% (v/v) polyethylene glycol 400–water were reported previously (16).

RESULTS AND DISCUSSION

***In Vitro* Progesterone Derivative Release**—The chemical structures and hydroxy group locations of progesterone derivatives are illustrated in Table I. Their *in vitro* release profiles are shown in Fig. 1. Controlled release of progesterone and its hydroxy derivative from silicone devices at steady state followed the matrix-controlled process previously seen for other progesterone derivatives (6, 19). As expected from Eq. 1, the cumulative amount of progesterone derivative released (Q) is linearly proportional to the square root of time ($t^{1/2}$) (18):

$$Q = [D_m(2A - C_p)C_p t]^{1/2} \quad \text{(Eq. 1)}$$

where D_m is the effective drug diffusivity in the polymer matrix, A is the drug content in a unit volume of silicone device, and C_p is the drug solubility in the silicone polymer. The drug release flux is defined as:

$$Q/t^{1/2} = [D_m(2A - C_p)C_p]^{1/2} \quad \text{(Eq. 2)}$$

and can be estimated from the slope of the Q *versus* $t^{1/2}$ plots (Fig. 1). Hydroxylation of progesterone reduced $Q/t^{1/2}$. This reduction depended on the hydroxy group number and location (Table II). An hydroxy group at either the 11- or 17-position had the most drastic effect on progesterone release from a silicone device, producing a more than fivefold decrease in $Q/t^{1/2}$ compared to a 1.5-fold reduction when the hydroxy group was at the 21-position.

The presence of two hydroxy groups further reduced $Q/t^{1/2}$. Hydroxy groups at the 11- and 21-positions yielded a 13.5-fold reduction in $Q/t^{1/2}$ and hydroxy groups at 17 and 21 resulted in a 28-fold decrease. The addition of a second hydroxy group at the 17-position had a more significant

[1] Silastic 382 medical grade, Dow Corning Corp., Midland, MI 48640.
[2] Silicone medical fluid 360, Dow Corning Corp., Midland, MI 48640.
[3] Cole-Parmer Instrument, Chicago, IL 60680.
[4] Searle Laboratories, Chicago, IL 60680.
[5] R5340-3, Norton, Inc., Akron, OH 44309.
[6] Coleman 124D spectrophotometer (double beam), Perkin-Elmer.

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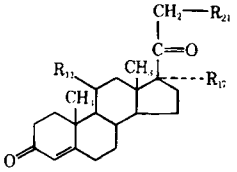

Table I—Melting Points of Progesterone Derivatives

	Compound	R_{21}	R_{11}	R_{17}	Melting Point[a]
I	Progesterone	H	H	H	129.0°
II	Desoxycorticosterone	OH	H	H	141.5°
III	11α-Hydroxyprogesterone	H	OH	H	165.5°
IV	17α-Hydroxyprogesterone	H	H	OH	215.0°
V	Corticosterone	OH	OH	H	181.0°
VI	17α-Hydroxydesoxycorticosterone	OH	H	OH	216.8°
VII	Hydrocortisone	OH	OH	OH	220.0°

[a] Median value of the literature melting-point range.

influence on $Q/t^{1/2}$ than did a second hydroxy group at the 11-position (compare VI with V). With three hydroxy groups (VII), $Q/t^{1/2}$ was reduced by 35 times, from 3.368 mg/cm²/day$^{1/2}$ for progesterone to 0.096 mg/cm²/day$^{1/2}$ for hydrocortisone (Table II).

Mechanistic Analysis of Hydroxy Group Effects—Equation 2 suggests that the reductions in $Q/t^{1/2}$ in response to the addition of hydroxy groups could reflect changes in the progesterone matrix diffusivity (D_m) and/or the polymer solubility (C_p). Theoretically, hydroxy groups should add hydrophilicity and change the progesterone stereochemical configuration.

Equation 2 indicates that $Q/t^{1/2}$ should be linearly dependent on $(2A - C_p)^{1/2}$ (Fig. 2). The slope of $Q/t^{1/2}$ *versus* $(2A - C_p)^{1/2}$ should be defined by $(D_m C_p)^{1/2}$. If the value of C_p, the progesterone derivative solubility in silicone polymer, is known or experimentally determined, the magnitude of D_m, the matrix diffusivity in a silicone device, can be calculated (Table III).

The addition of hydroxy groups to progesterone decreased D_m and C_p but increased C_s, the solubility of progesterone derivatives in 50% (v/v) polyethylene glycol 400–water (Table III). The decrease in matrix diffusivity (D_m) could be due to the alterations in the stereochemical configuration of the progesterone molecule. On the other hand, the increase in C_s and the decrease in C_p could be related to increased progesterone hydrophilicity due to the addition of hydrophilic hydroxy groups.

If hydroxy groups change progesterone hydrophilicity, they also should change the progesterone partitioning behavior from the silicone device toward the elution solution. As expected, the K_{obs} calculated from C_s/C_p varied with the number and position of hydroxy groups added (Table III). The partition coefficient, K_{obs}, is theoretically related to the standard Gibbs free energy (ΔF_d) of desorption, *i.e.*, the energy gained by a molecule on desorption from the polymer phase into the elution solution (23):

$$\Delta F_d = -RT \ln K_{obs} \qquad \text{(Eq. 3)}$$

If it is assumed (24) that ΔF_d can be expressed additively in terms of the individual contributions of the nonpolar progesterone skeleton (ΔF_p) and the polar hydroxy group (ΔF_{OH}), then:

$$\Delta F_d = \Delta F_p + n(\Delta F_{OH}) \qquad \text{(Eq. 4)}$$

It is also known that:

$$\Delta F_p = -RT \ln K_p \qquad \text{(Eq. 5)}$$

where K_p is the solution–polymer partition coefficients for progesterone itself. Combining Eqs. 3–5 yields:

$$\ln K_{obs} = \ln K_p - \frac{n(\Delta F_{OH})}{RT} \qquad \text{(Eq. 6a)}$$

or:

$$\log K_{obs} = \log K_p - \frac{n(\Delta F_{OH})}{2.303RT} \qquad \text{(Eq. 6b)}$$

As expected from Eq. 6*b*, the K_{obs} values were first order dependent on the number (n) of hydroxy groups on the progesterone molecule (Fig. 3). From the slope ($-\Delta F_{OH}/2.303RT$) of the linear log K_{obs} *versus* n plots, the ΔF_{OH} values were computed (Table IV). Depending on the system temperature, the addition of hydroxy groups onto the progesterone molecule yielded a contribution of ΔF_{OH} from −1.419 to −1.684 kcal/mole to the Gibbs free energy of desorption (ΔF_d). Without the hydroxy groups, the progesterone molecule partitioning from a silicone device toward an elution solution required a Gibbs free energy of desorption (ΔF_p) of 0.321–0.108 kcal/mole; with the hydroxy groups, the overall ΔF_d was improved to −1.098–−1.550 kcal/mole (Table IV). In other words, the addition of hydroxy groups enhanced the interfacial partitioning of the progesterone molecule from a silicone device to an elution medium.

As reported previously (24), K_{obs} for monosubstituted hydroxy progesterone was also dependent on the substituent hydroxy group position (Table III). From the following relationship:

$$\Delta F_{OH} = -2.303RT(\log K_{obs} - \log K_p) \qquad \text{(Eq. 7)}$$

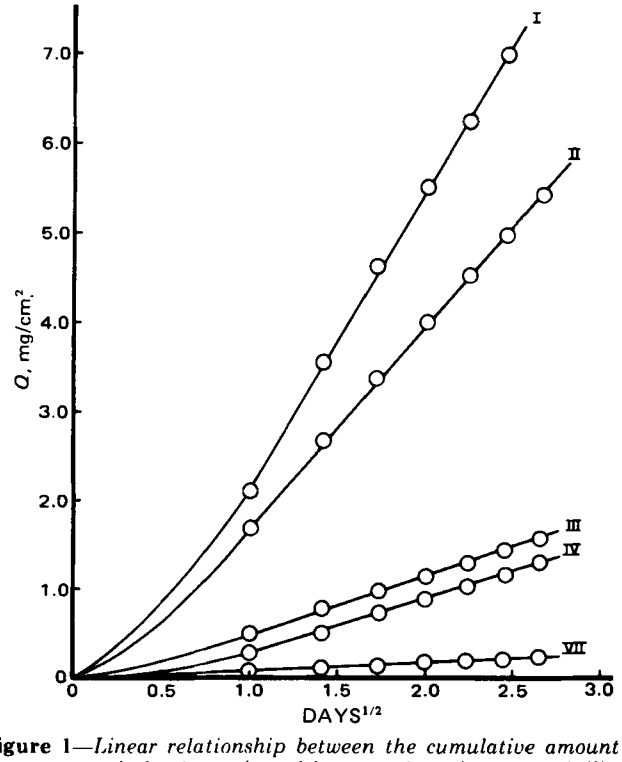

Figure 1—*Linear relationship between the cumulative amount of progesterone derivatives released from a unit surface area of silicone device* (Q) *and time* (t) *in days at 45°.*

Table II—Hydroxy Group Effect on $Q/t^{1/2}$ of Progesterone Derivatives through Silicone Device[a]

Compound	$Q/t^{1/2}$, mg/cm²/day$^{1/2}$
I	3.368
II	2.280
III	0.663
IV	0.623
V	0.249
VI	0.120
VII	0.096

[a] Determined from a silicone device (A = 117.4 mg/cm³) in 50% (v/v) polyethylene glycol 400–water at 45°.

Table III—Hydroxy Group Effect on the Polymer Matrix Diffusivity (D_m)[a], the Solubilities, and the Solution-Polymer Partition Coefficients (K_{obs}) of Progesterone Derivatives

Compound	$D_m \times 10^2$, cm²/day	Solubility, μg/ml ± SD		K_{obs}[d]
		C_s[b]	C_p[c]	
I	6.34	353.3 ± 16.2	594.7 ± 32.3	0.59
II	4.51	1402.1 ± 75.4	205.9 ± 5.4	6.81
III	2.96	575.0 ± 31.8	9.1 ± 0.3	63.2
IV	1.82	442.0 ± 37.4	26.5 ± 1.1	16.7
V	5.82	839.0 ± 9.2	1.23 ± 0.06	682.1
VI	4.16	994.1 ± 57.5	1.48 ± 0.18	671.7
VII	0.76	3987.6 ± 48.2	3.78 ± 0.29	1054.9

[a] Determined at 45°. [b] Aqueous solubility in 50% (v/v) polyethylene glycol 400 solution at 37°. [c] Polymer solubility in silicone medical fluid (20 cv) at 37°. [d] Ratio of C_s over C_p.

the ΔF_{OH} values for 21-OH, 17α-OH, and 11α-OH groups were estimated to be −1.51, −2.06, and −2.88 kcal/mole, respectively, at 37°.

Controlled Drug Release Thermodynamics—The temperature dependency of $Q/t^{1/2}$ is defined by the following relationship (19):

$$\log (Q/t^{1/2}) = \text{constant} - \left(\frac{(E_{d,m} + \Delta H_{T,m})}{4.606R}\right)\left(\frac{1}{T}\right) \quad \text{(Eq. 8)}$$

where $E_{d,m}$ is the activation energy a drug molecule requires to diffuse in a polymer matrix, $\Delta H_{T,m}$ is the energy required for the solvation of drug molecules in the polymer structure, R is the gas constant (1.9872 cal/mole/deg), and T is the absolute temperature. As expected from Eq. 8, the linear log $(Q/t^{1/2})$ *versus* T^{-1} was followed very well (Fig. 4). The values of $(E_{d,m} + \Delta H_{T,m})$ for progesterone and its hydroxy derivatives were similar, ranging from 13.52 (±1.02) to 16.70 (±0.87) kcal/mole (Table V). Compound VI had a slightly higher value (23.62 ± 2.44 kcal/mole). Except for VI, additional hydroxy groups did not significantly affect the total energy requirements for the controlled progesterone derivative release.

Diffusion of drug molecules in the polymer structure is energy dependent (25); the matrix diffusion of progesterone and its hydroxy derivatives requires the activation energy ($E_{d,m}$) defined in the following expression:

$$\log D_m = \log D_m^0 - \left(\frac{E_{d,m}}{2.303R}\right)\left(\frac{1}{T}\right) \quad \text{(Eq. 9)}$$

The linear relationship between log D_m and T^{-1} was followed very well for all compounds tested (Fig. 5). A significant difference in $E_{d,m}$ values was noticed among the progesterone derivatives (Table VI).

The $\Delta H_{T,m}$ values, which were computed from the difference between $(E_{d,m} + \Delta H_{T,m})$ (Table V) and $E_{d,m}$ (Table VI), are also given in Table VI. Again, a significant variation in $\Delta H_{T,m}$ values was observed from one progesterone derivative to another. The results in Table VI suggested that hydroxy group addition to position 11 or 21 reduced the matrix

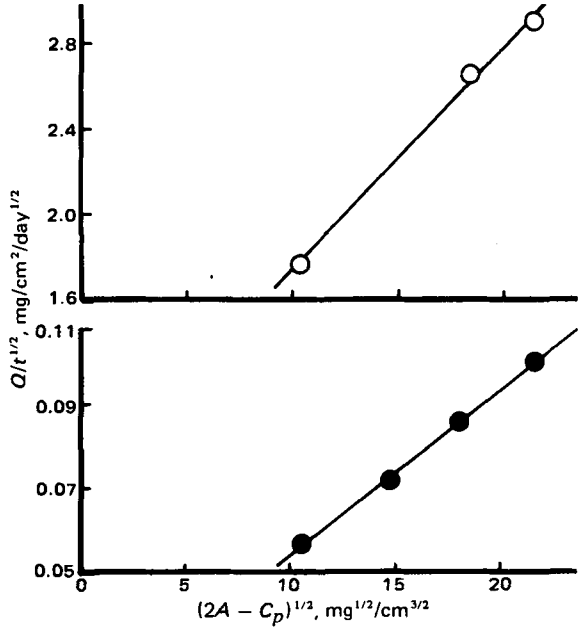

Figure 2—*Dependency of* $Q/t^{1/2}$ *values on* $(2A - C_p)^{1/2}$. *The slope is defined by* $(D_m C_p)^{1/2}$. *Key:* ○, *progesterone; and* ●, *hydrocortisone.*

Table IV—Gibbs Free Energies of Desorption of Hydroxyprogesterones at Various Tmperatures

Temperature	ΔF_{OH}, kcal/mole	ΔF_p, kcal/mole	ΔF_d, kcal/mole
37°	−1.419	0.321	−1.098
45°	−1.515	0.256	−1.259
50°	−1.638	0.108	−1.530
55°	−1.684	0.134	−1.550

Table V—Energy Required for the Controlled Release of Progesterone and Its Hydroxy-Substituted Derivatives from Silicone Devices

Compound	$(E_{d,m} + \Delta H_{T,m})$[a], kcal/mole ± SD
I	15.25 ± 2.26
II	13.52 ± 1.02
III	14.95 ± 0.75
IV	14.30 ± 1.42
V	16.30 ± 0.32
VI	23.62 ± 2.44
VII	16.70 ± 0.87

[a] Mean ±SD of the measurements from four drug concentrations (54.25–228.81 mg/cm³) at four temperatures (37–55°).

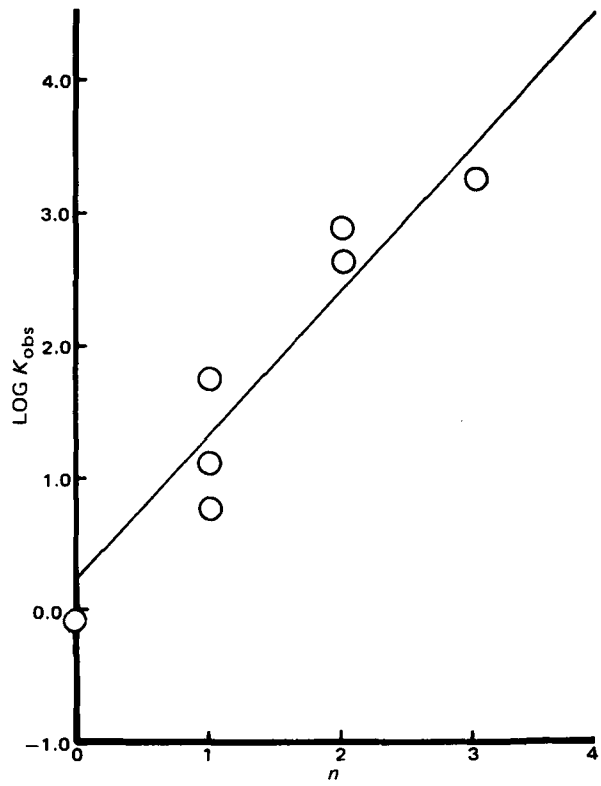

Figure 3—*Dependence of log* K_{obs}, *solution-polymer partition coefficient, on the number of hydroxy groups* (n) *on the progesterone molecule (Eq. 6). From the slope, a* ΔF_{OH} *value of 1.515 kcal/mole was computed (45°).*

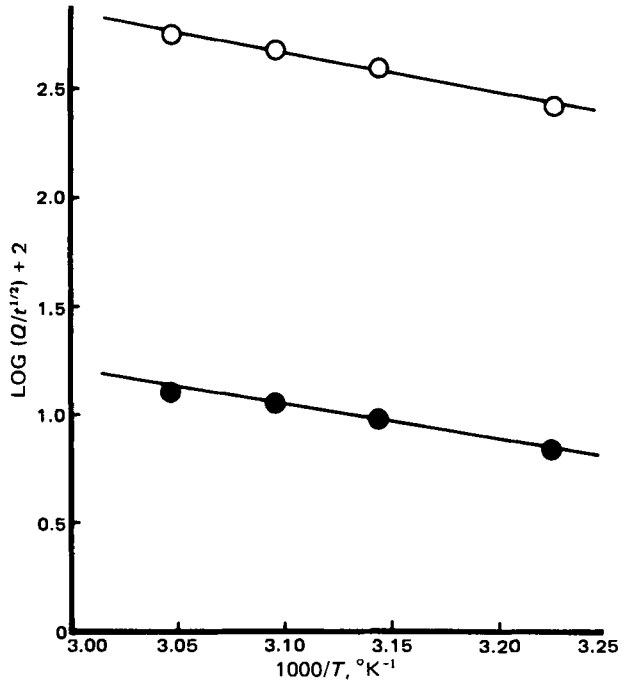

Figure 4—*Temperature dependence of* $Q/t^{1/2}$ *of progesterone* (○) *and hydrocortisone* (●). *The values of* $(E_{d,m} + \Delta H_{T,m})$ *were calculated from the slopes as 16.61 and 17.07 kcal/mole for progesterone and hydrocortisone, respectively.*

diffusion activation energy ($E_{d,m}$) but increased the solvation energy ($\Delta H_{T,m}$). Hydroxy group addition to position 17 increased $E_{d,m}$ but decreased $\Delta H_{T,m}$ (Table VI). The addition of more than one hydroxy group to the progesterone molecule gave a composite effect.

The $\Delta H_{T,m}$ values can also be determined from the temperature dependency of drug solubility (C_p) in a liquid silicone polymer (19), as expected from:

$$\log C_p = \text{constant} - \left(\frac{\Delta H_{T,m}}{2.303R}\right)\left(\frac{1}{T}\right) \qquad \text{(Eq. 10)}$$

A good $\log C_p$ *versus* T^{-1} linearity was achieved experimentally (Fig. 6). The $\Delta H_{T,m}$ values determined in the liquid silicone polymer (Table VII) agreed with the data generated in the polymerized, solid silicone matrix (Table VI), except for progesterone derivatives with one hydroxy group

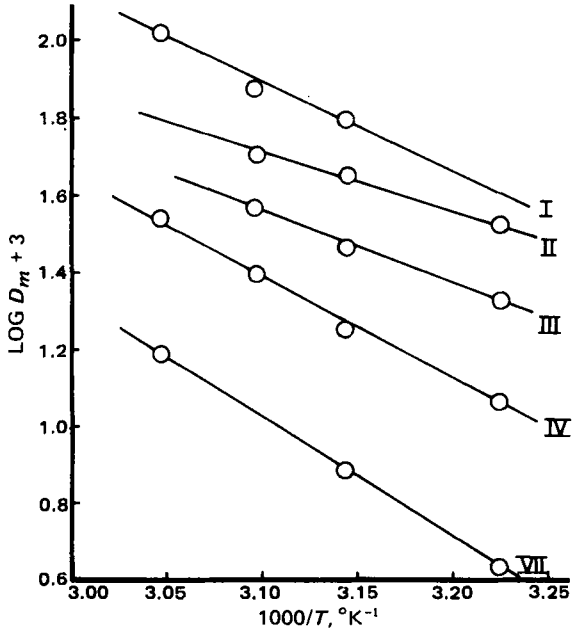

Figure 5—*Temperature dependency of* D_m *(effective diffusivity in silicone matrix) of progesterone derivatives.*

Table VI—Hydroxy Group Effect on the Activation Energy for Matrix Diffusion ($E_{d,m}$) and the Solvation Energy ($\Delta H_{T,m}$) of Progesterone Derivatives in Silicone Polymer

Compound	$E_{d,m}$, kcal/mole	$\Delta H_{T,m}$, kcal/mole ± *SD*
I	10.39	4.86 ± 2.26
II	6.34	7.18 ± 1.02
III	6.88	8.07 ± 0.75
IV	12.19	2.11 ± 1.42
V	3.12	13.18 ± 0.32
VI	11.04	12.58 ± 2.44
VII	14.43	3.01 ± 0.50

Table VII—$\Delta H_{T,s}$ and $\Delta H_{T,m}$ Values for Progesterone and Its Hydroxyl Derivatives

Compound	Solvation Energies, kcal/mole[a]	
	$\Delta H_{T,s}$[b]	$\Delta H_{T,m}$[c]
I	10.22	5.49
II	7.17	8.80
III	6.55	7.88
IV	6.11	8.27
V	7.42	12.99
VI	6.74	8.72
VII	6.48	12.71

[a] Determined at four temperatures (37–55°). [b] Solvation energy in 50% (v/v) polyethylene glycol 400 solution. [c] Solvation energy in silicone medical fluid (20 cv).

at position 17. Apparently, the addition of an hydroxy group at position 17 produces stereochemical configuration and/or physicochemical changes, which become apparent only in a solid polymer matrix and not in a polymer fluid.

The aqueous solubility (C_s) of progesterone and its hydroxy derivatives was also temperature dependent (19), as defined by:

$$\log C_s = \text{constant} - \left(\frac{\Delta H_{T,S}}{2.303R}\right)\left(\frac{1}{T}\right) \qquad \text{(Eq. 11)}$$

As expected from Eq. 11, $\log C_s$ is linearly dependent on T^{-1} (Fig. 6). The hydroxy group addition reduced $H_{T,s}$, the solvation energy (by 3.48 ± 0.48 kcal/mole) (Table VII), leading to an improvement of aqueous solubility (C_s in Table III). However, the number of hydroxy groups did not

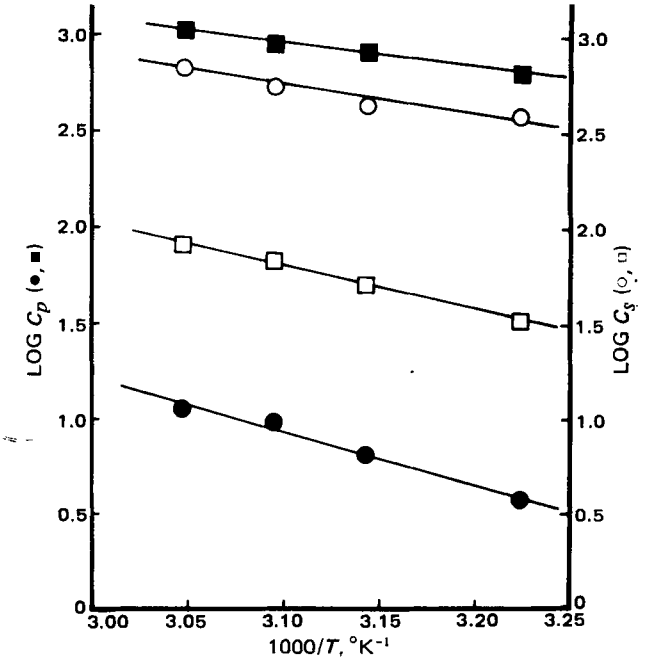

Figure 6—*Temperature dependency of polymer solubility* (C_p) *and aqueous solubility* (C_s) *of progesterone* (■ *or* □) *and hydrocortisone* (● *or* ○). *The* $\Delta H_{T,m}$ *and* $\Delta H_{T,s}$ *values were 5.49 and 10.22 kcal/mole for progesterone and 12.71 and 6.48 kcal/mole for hydrocortisone, respectively.*

change $\Delta H_{T,s}$ [mean value ($\pm SD$) of 6.75 ($\pm$0.48) kcal/mole], although the more hydroxy groups added, the higher the aqueous solubility. The C_s value increased 1.25–11.29-fold.

The data in Table III indicated that the addition of an hydroxy group at position 21 remarkably affected the solution solubility (C_s). With the addition of a 21-OH group, the C_s increased almost fourfold, from 353.3 ($\pm$16.2) (I) to 1402.1 ($\pm$75.4) (II) μg/ml. The significance of the 21-OH group in progesterone derivative solubility enhancement can be demonstrated by removing the 21-OH group by acetylation. Desoxycorticosterone acetate formation reduced C_s substantially to 249.9 ($\pm$2.1) μg/ml. The reduction of C_s was accompanied by an increase in $\Delta H_{T,s}$, the solvation energy, from 7.17 to 10.99 kcal/mole. For desoxycorticosterone acetate, C_s and $\Delta H_{T,s}$ were very close to the value for progesterone (353.3 ± 16.2 μg/ml and 10.22 kcal/mole, respectively). A similar result was achieved when the 21-OH group of hydrocortisone (VII) was acetylated to form hydrocortisone acetate.

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Cobaltous Chloride-Induced Hypothermia II: Pretreatment with Sympathoplegics, Antihistamines, and Narcotic Antagonists

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Abstract □ Body temperature depression was noted in rats, mice, and hamsters following intraperitoneal cobaltous chloride administration (25 mg/kg). Intracerebral cobalt injection elicited hypothermia in rats and mice but not in hamsters. Body temperature depression appeared to be centrally mediated in rats and mice and peripherally mediated in hamsters. The effect of intraperitoneal and intracerebral pretreatment with phentolamine, diphenhydramine, propranolol, cimetidine, and naloxone on the mouse rectal temperature response to cobalt (25 mg/kg ip) was noted. Systemic phentolamine injection (intraperitoneal) did not alter the cobalt response, whereas intracerebral administration partially antagonized cobalt-induced hypothermia, indicating that antagonism was mediated centrally. Pretreatment with propranolol and cimetidine failed to modify the temperature response. Intracerebral diphenhydramine did not influence cobalt hypothermia. However, this agent reduced the cobalt response when given intraperitoneally, presumably through a peripheral inhibitory mechanism. The intracerebral injection of naloxone 30 min prior to cobalt slightly enhanced hypothermia, apparently through a central action. Intracerebral 6-hydroxydopamine injection depleted brain norepinephrine and dopamine but exhibited no apparent influence on cobalt-induced hypothermia.

Keyphrases □ Hypothermia—cobaltous chloride induced, effect of phentolamine, diphenhydramine, propranolol, cimetidine, naloxone, rats, mice, hamsters, species specificity, central *versus* peripheral effects □ Cobaltous chloride—hypothermia, rats, mice, hamsters, effect of phentolamine, diphenhydramine, propranolol, cimetidine, naloxone, species specificity □ Sympathoplegics—effect on cobaltous chloride-induced hypothermia □ Antihistamines—effect on cobaltous chloride-induced hypothermia □ Narcotic antagonists—effect on cobaltous chloride-induced hypothermia

Many agents interfere with thermoregulatory control as a result of their influence on the central nervous system (CNS). Intracerebral dopamine and norepinephrine injections into conscious mice caused hypothermia (1). Similarly, histamine and oxotremorine injection into the lateral ventricles produced a dose-related fall in body temperature (2–4). Hypothermia, due solely to a decrease in heat production, was reported following a single central morphine injection in rats (5, 6).

Recent studies in this laboratory showed that cobaltous

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