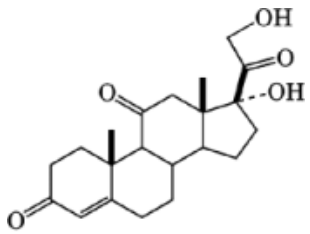
Kirk-Othmer Encyclopedia of Chemical Technology.

HORMONES, ADRENAL-CORTICAL

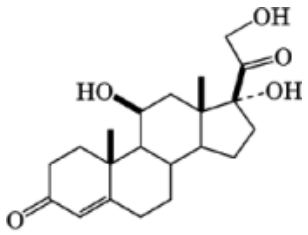
Since the introduction of cortisone (**1**) (1948) and hydrocortisone (**2**) (1951), adrenal-cortical hormones have remained an important and unreplaced drug class. Though not without adverse effects, these compounds have continued to be the drug of choice in the treatment of afflictions ranging from the moderate skin rash to severe acute inflammatory disorders, and are included in many other therapeutic regimes.

The adrenal cortex releases both mineralocorticoids (from the zona glomerulosa) and glucocorticoids (from the zona fasciculata/reticularis). In addition, some androgenic and estrogenic steroids are synthesized by the adrenal gland. Once released by the adrenal cortex, the primary endogenous function of glucocorticosteroids is in influencing carbohydrate and protein metabolism. Mineralocorticoids regulate sodium reabsorption in the collecting tubules of the kidney. As with the mineralocorticoids, the generation of glucocorticosteroids is intricately balanced; where the production and regulatory process malfunctions, the result is either an excess (eg, Cushing's syndrome) or a deficiency (eg, Addison's disease) in glucocorticoid levels.

However, corticosteroids and their metabolites (1) were early recognized as possessing powerful antiinflammatory and immunomodulatory properties. Even prior to 1950, reports of the antiarthritic properties of cortisone (**1**) by Hench and co-workers (2) indicated the potential for these compounds to reduce the suffering of patients with inflammatory diseases. This awareness, combined with the first synthesis of naturally occurring glucocorticoids (11-desoxycorticosterone), led not only to the massive increase in research in the area of steroid synthesis and physiology, but to a Nobel prize in 1950 for early steroid pioneers Hench, Reichstein, and Kendall.



(**1**)



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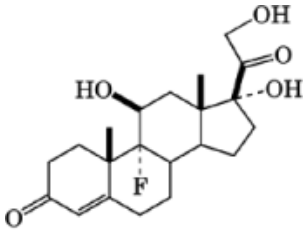
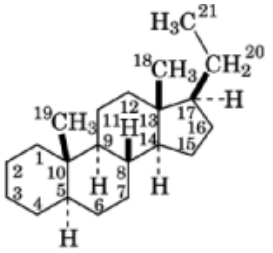


(**3**)

Progress in the field received further impetus with the development of synthetic steroids exhibiting activities far greater than that of the natural hormones. The synthesis of 9 α-fluorocortisol (**3**), described in 1953 by Fried and Sabo (3), opened the way for development of many more highly active antiinflammatory agents, and indeed some of today's most active antiinflammatory agents (ca 1997) bear some resemblance to this 9α-fluorinated steroid.

Comprehensive reviews treating the pharmacological structure–activity relationships of glucocorticosteroids (4–7) and mineralocorticoids (8) have been published, as well as reviews of the mechanism of action (9, 10). All natural adrenocorticoids are derivatives of the planar ring system 5α-pregnane (**4**). Substituents lying above the plane of the rings are assigned a β-configuration, indicated by a dotted line. Angular methyl groups at C-10 and C-13 have the β-configuration and are often shown simply by solid bonds. Tertiary hydrogen atoms at C-8, C-9, C-14, and C-17 are usually omitted unless their stereochemistry differs from that shown in (**4**).



(**4**)

1. Clinical Use of Adrenal-Cortical Steroids

The predominant clinical use of corticosteroids is a result of their associated antiinflammatory properties. These are commonly used as topicals for the suppression of symptoms, including inflammation, occurring in a

particular disease state; these compounds are rarely considered curative in their usage. Many other disease states do, however, respond well symptomatically to treatment with corticosteroid therapy. Some of these (11) are listed below.

Antiinflammatory Activity	
Adrenocortical insufficiency	Allergic conditions and conjunctivitis
Organ transplants	Cerebral edema
Liver disease	GI diseases; ulcerative colitis and anorectal disorders
Adrenogenital syndrome	
Nephrotic syndrome	Bacterial meningitis
Acute spinal cord injury	Rheumatic disorders and collagen diseases
Hypercalemia	Ophthalmic, otic, and nasal disorders
Hematologic disorders	Dermatologic diseases
Myasthenia gravis	Respiratory diseases
Neoplastic disease	

Mineralocorticoid therapy is a less common, though still important aspect of the medicinal use of adrenal-cortical steroids. Very important applications include use in treating adrenocortical insufficiency or in other adrenocoritcoid replacement therapies, and in the management of salt-losing forms of congenital adrenogenital syndrome. Aldosterone, owing to its short half-life, is not used therapeutically; desoxycorticosterone acetate (a natural aldosterone precursor) and fludrocortisone are the only clinically significant mineralocorticoidal agents.

1.1. Topical Corticosteroids Currently Available

Table 1 includes compounds listed in *Drug Facts and Comparisons* (FC) (12) and the *AHFS Drug Index* (DI) (13). The compounds listed by FC as topical antiinflammatories were placed within a range of Low to Very High Potency (see Table 1). The DI list indicates a range from I (most active) to VI (least active), shown next to drug names listed in the table. Some compounds have more than one activity class, depending on the method of administration and concentration; in these cases, the higher class is listed. As has been noted elsewhere in the literature, activity . . .

. . . may vary considerably depending on the vehicle, site of application, disease, the individual patient, and whether or not an occlusive dressing is used. The approximate relative activity is based principally on vasoconstrictor assay and/or clinical effectiveness in psoriasis (11).

Table 1. Topical Corticosteroid Compounds—*Drug Facts and Comparisons*[a] vs *AHFS Drug Information*[b]

				Degree of potency[d]			
Substance	Chemical name	Structure number	Level of activity[c]	Very high	High	Medium	Low
β-methasone dipropionate	9-fluoro-11β-hydroxy-16β-methyl-17α,21-bis(1-oxopropanoxy)-pregna-1,4-diene-3,20-dione		I	X			
clobetasol propionate	21-chloro-9-fluoro-11β-hydroxy-16β-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione	(**102**)	I	X			
diflorasone diacetate	17,21-bis(acetyloxy)-6α,9-difluoro-11β-hydroxy-16β-methylpregna-1,4-diene-3,20-dione	(**100**)	I	X			

Table 1. ***Continued***

Substance	Chemical name	Structure number	Level of activity[c]	Degree of potency[d]			
				Very high	High	Medium	Low
halobetasol propionate	21-chloro-6α,9-difluoro-11β-hydroxy-16β-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione			X			
amcinonide	21-(acetyloxy)-16,17α-[cyclopentylidenebis(oxy)]-9-fluoro-11β-hydroxypregna-1,4-diene-3,20-dione		II		X		
β-methasone valerate	9-fluoro-11β,17α,21-trihydroxy-16β-methyl-17-[(1-oxopentyl)oxyl]-pregna-1,4-diene-3,20-dione	(**99**)	III		X		
desoximetasone	9-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione		II		X		
fluocinonide	21-(acetyloxy)-6α,9-difluoro-11β-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione		II		X		
fluocinolone acetonide	6α,9-difluoro-11β,21-dihydroxy-16α,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione		IV		X		
halcinonide	21-chloro-9-fluoro-11β-hydroxy-16α,17-[(1-methylethylidene)bis(oxy)]-pregn-4-ene-3,20-dione		II		X		
mometasone acetonide			III				
triamcinolone acetonide	9-fluoro-11β,21-dihydroxy-16α,17-[(1-methylethylidene)-bis(oxy)]-pregna-1,4-diene-3,20-dione	(**49**)	III		X		
β-methasone benzoate	17-(benzoyloxy)-9-fluoro-11β,21-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione		III			X	
clocortolone pivalate	9-chloro-21-(2,2-dimethyl-1-oxopropoxy)-6α-fluoro-11β-hydroxy-16α-methylpregna-1,4-diene-3,20-dione					X	
flurandrenolide	6α-fluoro-11β,21-dihydroxy-16α,17-[(1-methylethylidene)-bis(oxy)]-pregn-4-ene-3,20-dione		IV			X	
fluticasone propionate	6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(1-oxopropoxy)-androsta-1,4-diene-17β-carbothioic acid, *S*-fluoromethyl ester					X	
hydrocortisone butyrate	11β,21-dihydroxy-17-(1-oxobutoxy)-pregn-4-ene-3,20-dione		V			X	
hydrocortisone valerate prednicarbate	11β,21-dihydroxy-17-[(1-oxopentyl)oxy]-pregn-4-ene-3,20-dione		V			X	
mometasone fluroate	9α,21-dichloro-17-[(2-furanyl-carbonyl)oxy]-11β-hydroxy-16α-methyl-pregna-1,4-diene-3,20-dione		V			X	
aclometasone dipropionate	7α-chloro-11β-hydroxy-16α-methyl-17α,21-bis(1-oxopropanoxy)-pregna-1,4-diene-3,20-dione		VI				X

Table 1. ***Continued***

Substance	Chemical name	Structure number	Level of activity[c]	Degree of potency[d]			
				Very high	High	Medium	Low
desonide	11β,21-dihydroxy-16α,17-[(1-methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione		VI				X
dexamethasone	9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione	(**74**)					X
dexamethasone sodium phospate	9-fluoro-11β,21-dihydroxy-16α-methyl-21-(phosphonooxy)-pregna-1,4-diene-3,20-dione, disodium salt						X
hydrocortisone	11β,17,21-trihydroxy-pregn-4-ene-3,20-dione						X
hydrocortisone acetate	21-(acetyloxy)-11β,17-dihydroxy-pregn-4-ene-3,20-dione						X

[a] Ref. 12.
[b] Ref. 13.
[c] Ranging from I (most active) to VI (least active), as specified by the DI (13).
[d] Range in which compounds listed by FC were placed (12).

2. Adrenocortical Biosynthesis and Metabolism

Corticosteroids are biosynthesized from cholesterol and released as needed by the adrenal cortex; they are not stored. Cholesterol undergoes a series of irreversible oxidations during which carbons 22 through 27 are cleaved, resulting in pregnenolone. Reversible isomerization of Δ^5 to Δ^4 results in progesterone, the key intermediate in both mineralocoritcoid and glucocorticoid biosynthesis. Cortisol is the product of the 11β-, 17α-, and 21-oxidations (flavoprotein, cytochrom P-450-mediated) of progesterone; aldosterone is the result of oxidations at the 11β-, 18-, and 21-positions. Glucocorticosteroid biosynthesis is outlined in Figure 1, and key steps in the mineralocorticoid biosynthesis are highlighted in Figure 2.

The major metabolic transformations of the adrenal-cortical hormones generally follow the metabolism of cortisol, which undergoes the following conversions *in vitro:*

2.0.0.1. Cortisol-Cortisone Conversion. Under normal conditions, this equilibrium slightly favors the oxidized compound. Similarly, the conversion of corticosterone to 11-deoxycorticosterone is also mediated by the 11β-hydroxysteroid dehydrogenase enzyme system and requires NAD(P)$^+$/NAD(P)H. This conversion is especially important both in the protection of the human fetus from excessive glucocorticoid exposure, and in the protection of distal nephron mineralocorticoid receptors from glucocorticoid exposure (14). The impairment of this conversion is thought to result in hypertension associated with renal insufficiency (15).

2.0.0.2. A-Ring Reduction. This is an irreversible reaction which is a foremost determinant of the secretion rate of cortisol (double bonds and C-3 carbonyl). Catalyzed predominantly by cortisone β-reductase and 3α-hydroxysteroid dehydrogenases, 5β sterols result, although 5α sterols are more prevalent in the case of other glucocorticoids. Urocortisol and urocortisone result from the metabolism of cortisol and cortisone, respectively. Compounds can be complexed to glucuronic acid at this point.

2.0.0.3. C-20 Reduction. Two stereoisomers can result from this transformation, although cortisol is thought to act primarily with (R)20β-hydroxysteroid dehydrogenase. This is a first step in the metabolism of corticosterone.

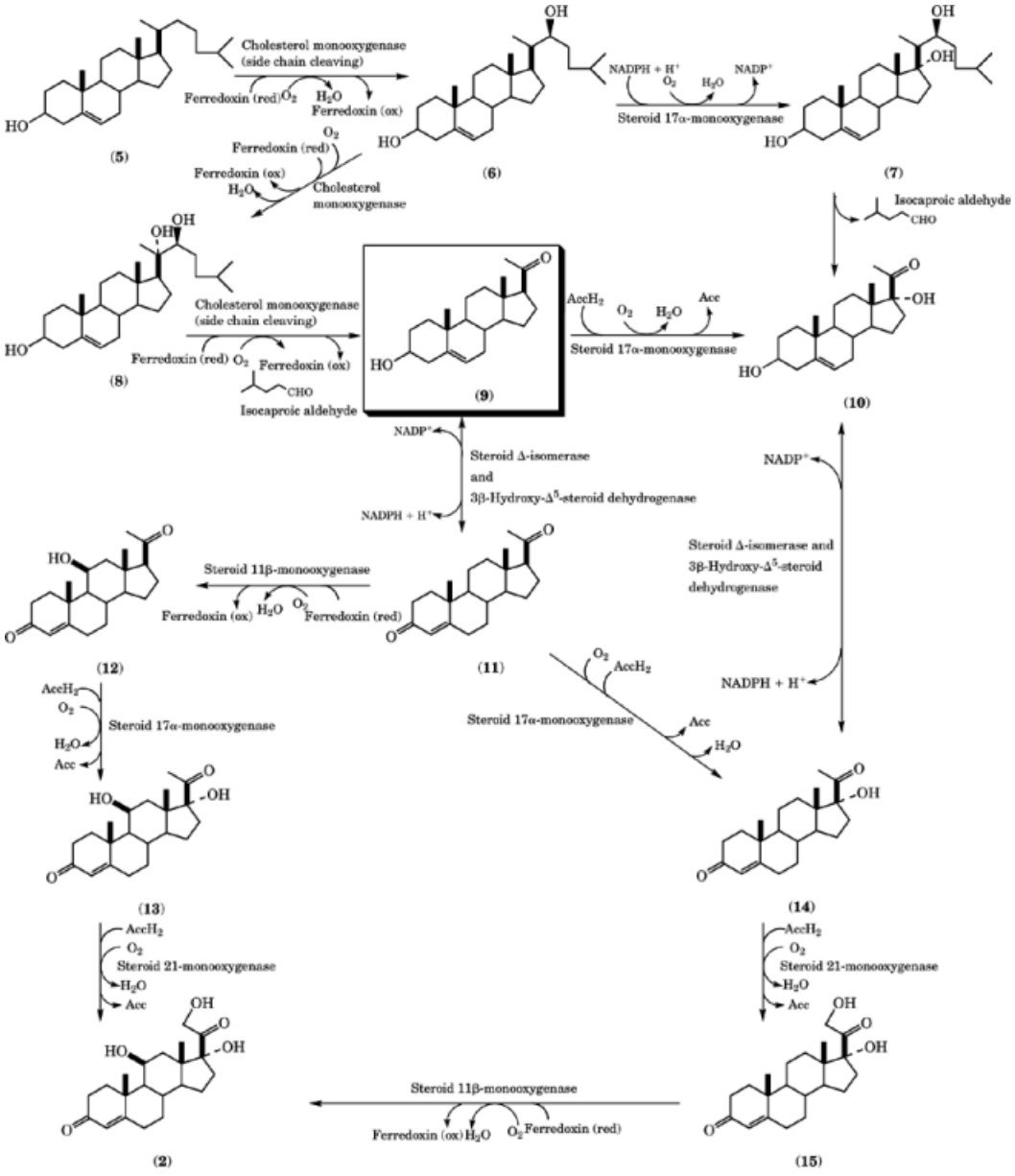


Fig. 1. Biosynthetic pathways for formation of cortisol from cholesterol.

2.0.0.4. Cleavage of C-17 Acyl/Alkyl Substituents. Resulting primarily in cholan-17-ones, this is a relatively minor metabolic pathway. Corticosterone is not known to undergo this transformation before excretion.

2.0.0.5. C-6 Hydroxylation. This biotransformation is more predominant in infants than in adults, and can prevent other metabolic transformations.

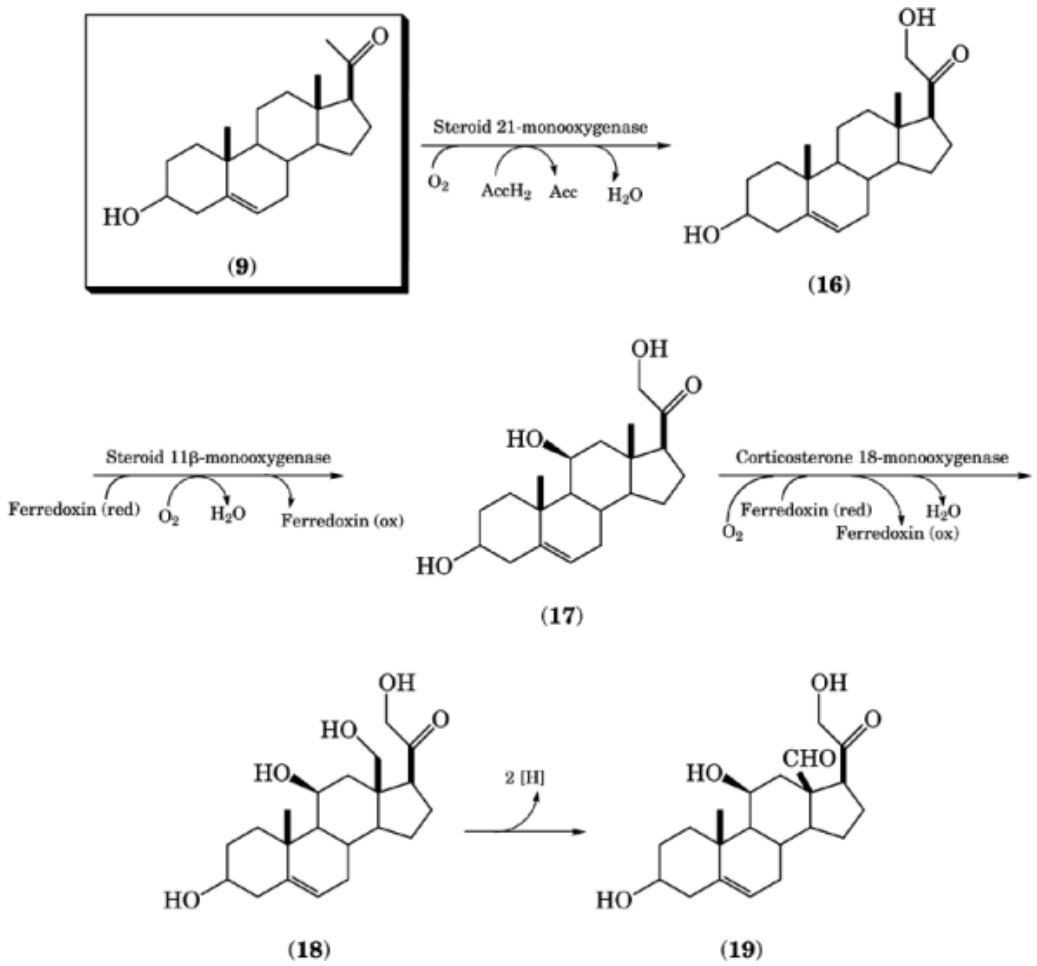


Fig. 2. Key steps in the mineralocorticoid biosynthesis.

2.0.0.6. Glucuronidation. Complexation of the steroid to glucuronic acid, most predominantly via the C-3 hydroxyl, leads to a considerable portion of the excreted metabolites of all glucocorticoids. In infants, sulfurylation (formation of a sulfate ester) is also predominant (16).

2.0.0.7. Other Reactions. Most of the metabolites of cortisol are neutral (alcohol or glucuronide complex) compounds. However, oxidation at C-21 to C-21 carboxylic acids (17) accounts for some of the identifiable metabolites of glucocorticoids (18).

Compounds having the 16,17 ketal, eg, budesonide, amcinonide, fluocinonide, halcinonide, triamcinolone acetonide, and flurandrenolide, also undergo metabolism by routes that parallel that of cortisol metabolism. Unsymmetrical acetals such as budesonide are also metabolized by routes not available to the more metabolically stable symmetrical 16α,17α-isopropylidiene-dioxysubstituted compounds (desonide, flunisolide, and triamcinolone acetonide). Isozymes within the cytochrome P450 3A subfamily are thought to catalyze the metabolism of budesonide, resulting in formation of 16α-hydroxyprednisolone and 6β-hydroxybudesonide (19, 20) (Fig. 3) in addition to the more common metabolic steps (oxidation via Δ^6, reduction of Δ^3, etc).

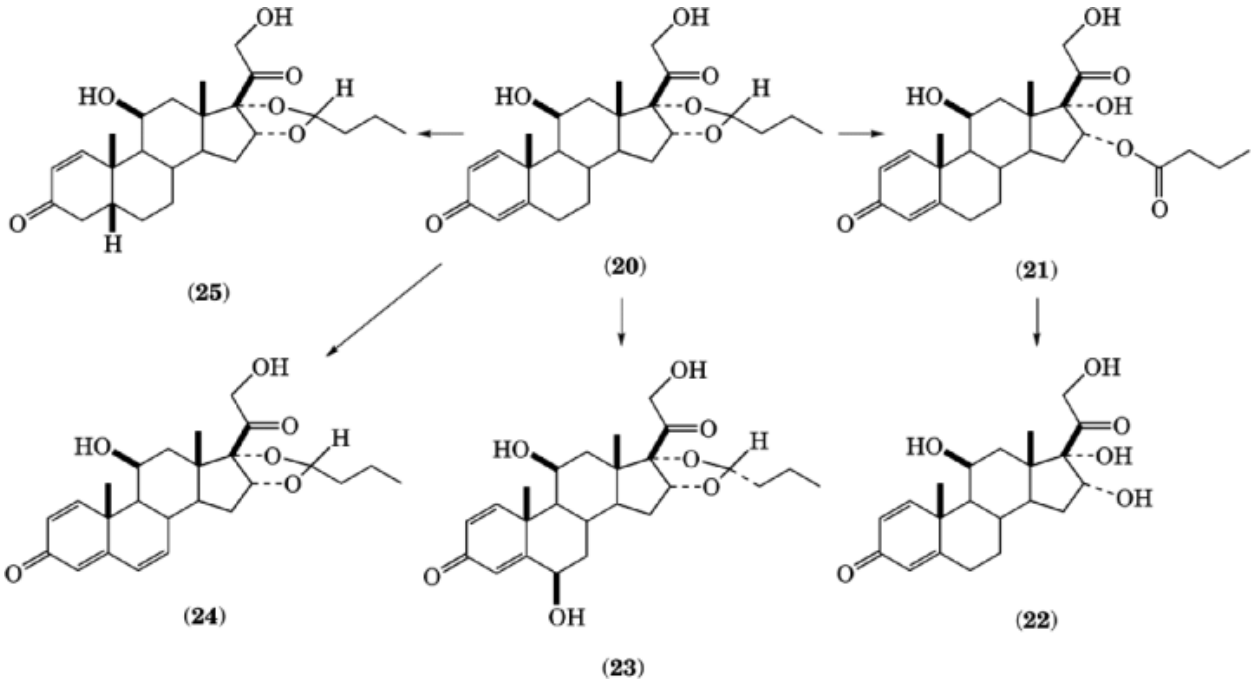


Fig. 3. Metabolism of 22*R*-budesonide in human liver microsomes.

Steroids having the greatest number of substituents generally have the slowest rate of metabolism. Groups that appear to activate by effects on metabolism include 2β-methyl, which stabilizes the resulting molecule to the action of the 4,5-reductase (21) and to the action of 20-keto reductase (22). Similarly, 6α-methyl protects the A ring against metabolic destruction (22). Again, the introduction of 16α-hydroxyl, as in triamcinolone (**48**), prolongs the half-life (23). The 16α-methyl and 16β-methyl groups have similar action. Triamcinolone is unusual in that it is metabolized principally to the 6β-hydroxy derivative (23).

3. Mechanism of Action of Antiinflammatory Steroids

3.1. Receptor Structures for Glucocorticoids and Mineralocorticoids

The effects of adrenal-cortical steroids are thought to result from their interaction with intracellular receptors, and a great deal of attention has been given to the task of determining the structure and function of the glucocorticoid receptor (GR) as well as the mineralocorticoid receptor (MR). Though studied in less detail, the primary function of the MR seems to be nearly identical to that of the GR, with the primary differences being the restricted expression of the MR (limited mostly to tissues in the kidney, colon, salivary and sweat glands, and hippocampus), and the different proteins encoded by the activated DNA-receptor complex. The highly homologous GR and MR proteins are also very similar in action, and the description of the more thoroughly examined GR is adequate for the understanding of the MR structure and function.

The primary structure of the GR has been identified as a 795 residue protein. Though there does not yet exist an x-ray structure, a significant amount of 3-D structure elucidation of the GR has been made. The GR is a member of the nuclear receptor superfamily, which includes receptors for other steroids, vitamin D, and thyroid hormones, and some other various proteins (24). A high degree of homology is found between receptors

in this class, and each contains a similar domain make-up. These domains (sections of primary structure) each have a functional duty, and generally describe regions of hormone binding, nuclear translocation, dimerization, DNA binding, and transactivation (25).

Within the carboxyl terminus portion of the protein (residues 518–795) is the ligand (hormone) binding domain (HBD) (25). It is here that much of the interaction of the receptor with hsp90 occurs (26) (thought to be residues 595 to 614 of the rat GR (27)). Three of five cystein residues in this area are spaced close together in the binding pocket (28), and two of these are critical to the receptor's ability to bind specifically glucocorticoids (29). Binding of the hormone to the HBD allows the activation of the receptor to the DNA-binding state, and during this process, the conformation of the protein changes, in part the result of the dissociation of hsp90. Antiglucocorticoids and certain other modulators as well as sodium molybdate will interact with this domain and inhibit activation.

The DNA binding domain is highly conserved among species, and changes to the amino acid sequence in this region result in changes in receptor function (30). A structural feature which characterizes the GR-DNA binding domain are the two so-called zinc fingers, in each of which two zinc $(+2)$ ions are held in place by tetrahedral coordination to neighboring cystein residues (31). These zinc fingers, common to the nuclear receptor superfamily, are not exactly the same as those found in *Xenopus TFIIIA,* in which histidine residues are also associated with the metal (32, 33). The zinc in the GR is thought to stabilize the α-helices at the carboxy ends of the fingers as well as aid in carboxy-terminal module folding, needed in the dimerization of the proteins (34). Though the entire glucocorticoid receptor (GR) tertiary structure has yet to be elucidated, some of the components of the structure, including the DNA-binding domain, have been depicted through molecular modeling studies (35), nmr investigations (36), and the crystal structure data from GR protein fragments (34). Solution-state analysis of the DNA-binding domain complexed to a nucleotide sequence (double helix) reveals areas where an α-helixal substructure interacts with the nucleotide. This DNA-receptor complex structure is supported by the crystal structure of a similar DNA-receptor fragment (DBD) complex. Clear dimeric interaction can be seen, along with the general shape of the zinc finger region.

Two domains, $\tau 1$ and $\tau 2$, exist which affect the GR post-DNA binding transcription activity (37). The major ($\tau 1$) transactivation domain is 185 amino acid residues in length with a 58-residue α-helical functional core (38). The $\tau 1$ domain is located at the *N* terminus of the protein; the minor ($\tau 2$) transactivation domain residues on the carboxy-terminal side of the DNA binding domain.

3.2. Mechanism of Action

The process by which adrenocortial steroids impart their action is based on the action of the steroid on a receptor (MR or GR). One result of this process is the lag between optimum pharmacologic activity and peak blood concentrations. The stages of GR goes through in becoming active can be divided into five general steps (39), and each step is mediated by the glucocorticoid receptor (GR).

(*1*) *Subcellular Localization.* Some debate still exists (ca 1997) as to whether GRs are cytoplasmic or nuclear in nature (40, 41), though it is believed that the interaction of hormone and receptor occurs in the cytoplasm. Compounds with high binding affinities (glucocorticoid agonists or antagonists) result in complete translocation of these receptors into the nucleus (42). Phosphorylation sites on the GR do not seem to play a role in hormone-inducible nuclear translocation. Sequences controlling nuclear localization have been identified within steroid receptors in the hinge region. The glucocorticoid receptor has a second nuclear localization signal in the hormone binding domain (43).

(*2*) *Association with Heat Shock Proteins (hsp).* Unactivated GRs are complexed with a number of protein factors which play various roles in the binding of ligand to the receptor, as well as the localization, DNA binding, and transactivation of the GR. The proteins, including hsp90, hsp70, hsp56, CyP40 and p23 (an acidic protein), have been implicated as part of an assembled complex that is able to activate GR to the ligand binding state; this complex is termed a foldsome (44, 45). Hsp90 has been shown to be associated with the ligand-binding

portion (C terminus) of the receptor (26), perhaps even blocking this site, though it is needed for the GR ligand-binding domain to be in the proper conformation for ligand binding (46). Hsp70 assists the binding of hsp90 to the receptor. Upon ligand binding, the heat shock proteins dissociate and the receptors become active in dimerization, DNA binding, and transcriptional enhancement (47). Though these hsp proteins do block certain DNA binding sites on the receptor, protein-free receptor studies have indicated that the free receptor still needs to be bound to hormone in order to bind to DNA.

(*3*) *Hormone binding.* The ligand-binding domain of the steroid hormone receptors encompasses almost the entire C terminus of these proteins. This domain is also credited with having the functions of hormone-dependent dimerization and transactivation. The ligand-binding domain of the glucocorticoid receptor appears to repress transcription in the absence of hormone, and this transrepression is reversed by hormone. Active glucocorticoid receptor agonists bind tightly to the hormone receptor to elicit their action. Binding of glucocorticoids to the GR hormone-binding domain transforms the receptor into an activated complex able to interact with DNA sequences called the glucocorticoid response elements (GREs) of target genes. One difference between the MR and GR is in the affinities each has for cortisol and aldosterone. Both of these steroids bind to the MR (type I corticosteroid receptor), and cortisone also binds to the GR (type II corticosteroid receptor). The enzyme 11β-hydroxysteroid dehydrogenase plays an important role in converting cortisol to a less active cortisone, thus allowing aldosterone to bind freely to the MR.

(*4*) *Dimerization and DNA binding.* The active regulatory form of the GR is thought to be dimeric. The GR binds to a palindromic DNA sequence (GRE), either as a GR dimer (48), or perhaps as a GR monomer followed by binding of a second GR. Crystallographic studies with GR fragments containing the DNA-binding domain have indicated that this dimerization occurs upon binding to the half-site of the GRE (34). Members of the steroid hormone receptor superfamily contain a highly conserved DNA-binding domain of about 70 residues, which are complexed around two tetrahedrally coordinated zinc atoms.

(*5*) *Transactivation.* Protein synthesis is initiated or inhibited by the action of the activated GR on DNA. The use of glucocorticoids leads to antiinflammatory effects by first controlling gene expression, which subsequently leads to the synthesis and/or suppression of inflammation regulatory proteins.

One such regulatory protein, inducible by a number of glucocorticoids, is the 37kDa protein Lipocortin 1 (LC-1) (49, 50). Dexamethasone directly effects *de novo* LC-1 synthesis, leading to direct increases in intra- and extracellular LC-1 concentrations, occurring most notably at the cell surface (51). Prednisolone increases extracellular and decreases intracellular concentrations (52) of LC-1. Studies with LC-1 and with an active LC-1 segment show direct involvement of this protein in inhibiting neutrophil activation via inhibition of the release of elastase, PAF, leukotriene B4, and arachidonic acid (53), as well as an inhibition of neutrophil adhesion to endothelial monolayers (54, 55). LC-1 inhibits various types of prostanoid (inflammation mediator) production; it also suppresses thromboxane A_2 release from perfused lungs (56) and has thus been shown to inhibit inflammation in the rat paw (carragenen-induced edema) inflammation model (57). This is a result of LC-1 inhibition of phospholipase A_2, which converts membrane phospholipids to arachidonic acid, along with its effect on other cellular components of certain inflammatory responses (10, 58). Antibodies raised against LC-1 are able to reverse the antiinflammatory action of LC-1 (59–61). Corticosteroids reduce phospholipase A_2 activity, which results in the diminished release of arachidonic acid, and this subsequently leads to limiting the formation of prostaglandins, thromboxane, and the leukotrienes (9, 62).

Glucocorticoids have been shown to inhibit gene transcription of other proteins involved in the inflammatory process, including the key inflammation mediators called cytokines (IL-1, IL3–6, IL8, GM-CSF, TNFα) (10, 58, 63–65). Steroids have been also shown to suppress the formation of cytokine receptors (10); dexamethasone, in particular, downregulates gene transcription of angiotensin II type 2 receptors (66).

Mineralocorticoids follow a mechanistic route similar to that of glucocorticoids, though differing in the proteins expressed. The activated MR-DNA complex promotes the expression of aldosterone-induced proteins (AIPs), which then act to increase Na^+ conductance of the luminal membrane and concurrently increase Na^+ pump activity of the basolateral membrane. These actions result from a number of AIP-influenced cellular

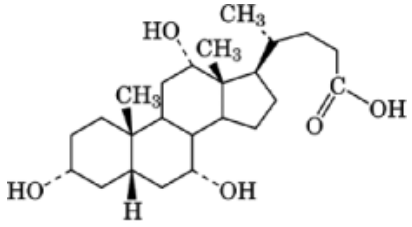
characteristics, including a modification of tight junction permeability, an increase in membranous Na^+ channels and pumps, activation of silent Na^+ channels and pumps, and an increase in mitochondrial ATP-production-related enzymes.

4. Synthesis of Glucocorticoids

4.1. Hydrocortisone and Prednisolone

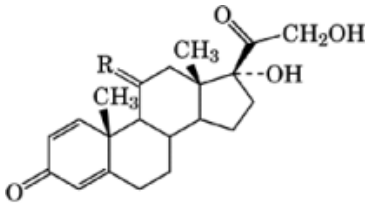
Following the discovery of the antiinflammatory actions of cortisone (**1**) and cortisol (**2**), there was a need not only to develop highly efficient routes to the corticoids, but to discover novel structures with fewer side effects than those of the corticoids, eg, sodium and water retention, reduced carbohydrate tolerance (steroid diabetes), osteoporosis, and depressed host defense.

A major difficulty in the manufacture of corticosteroids was the lack of an abundant raw material containing an 11-oxygenated function. This problem initially was solved by using 12α-hydroxylated cholic acid (**26**) (obtained from ox bile); later it was converted into cortisone acetate by a 32-stage process (66). A more recent development in procuring readily available starting material was the discovery that perfusion of cortexone (**16**) through the adrenal gland gives corticosterone (**17**), albeit in low yield, thereby demonstrating the existence of enzymes capable of hydroxylating progesterone derivatives at position C-11. Microorganisms capable of introducing an 11β-hydroxyl group into a steroid were discovered. *Rhizopus arrhizus* transformed progesterone (**11**)—which was readily available from diosgenin or from the soybean sterol, stigmasterol (**27**)—into 11α-hydroxyprogesterone (**28**) in excellent yield; even better results were obtained using *Rhizopus nigricans* (67). Other organisms include *Corynebacterium simplex* which converts cortisone (**1**) and cortisol (**2**) into their 1-dehydro derivatives, prednisone (**29**) and prednisolone (**30**) (68), respectively. These steroids surpassed their parent hormones in antirheumatic and antiallergic activity and produced lower mineralocorticoid activity and other side effects. Nearly all corticoids on the market other than cortisone are 1-dehydro steroids.



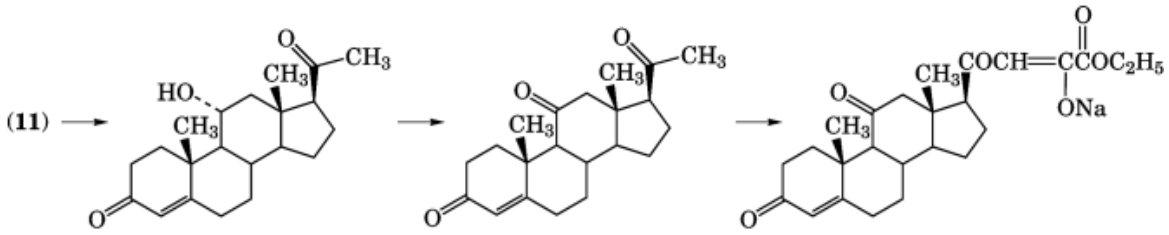
(**26**)

The classic process of corticosteroid manufacture employs stigmasterol (**27**), obtained from soybean oil, as the raw material. The sterol is first oxidized to stigmastadien-3-one (**31**) by the Oppenauer method. Ozonolysis of the latter in methylene chloride/1% pyridine yields 3-oxobisnorchol-4-enyl aldehyde (**32**) (69). Azeotropic distillation of the aldehyde with piperidine containing a trace of *p*-toluenesulfonic acid (pTS) leads to formation of the enamine (**33**) (70) which, when oxidized with sodium dichromate in anhydrous acetic acid, gives progesterone (**11**) in high yield. Microbiological oxidation of the (resulting) progesterone (**11**) with *Rhizopus nigricans* yields 11α-hydroxyprogesterone (**28**) in yields exceeding 90% (67). The latter is oxidized to 11-oxoprogesterone (**34**), which is condensed with diethyl oxalate in the presence of sodium methoxide to yield the 21-ethoxyoxalyl derivative (**35**). The last compound is treated with bromine giving the 21,21-dibromo-21-carbethoxylate, which is treated without isolation

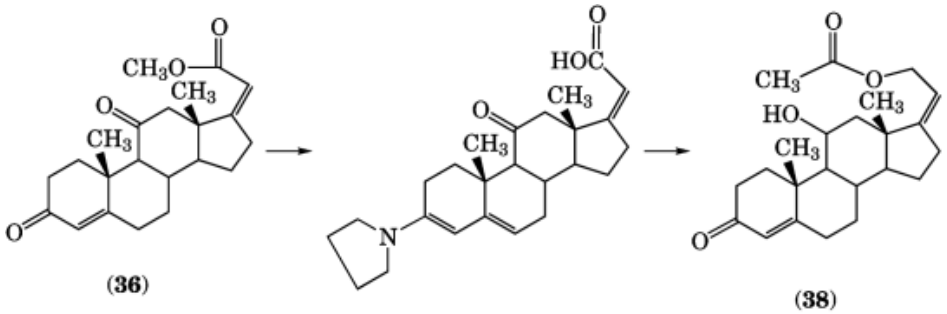


(30) R = H, OH

(29) R = O



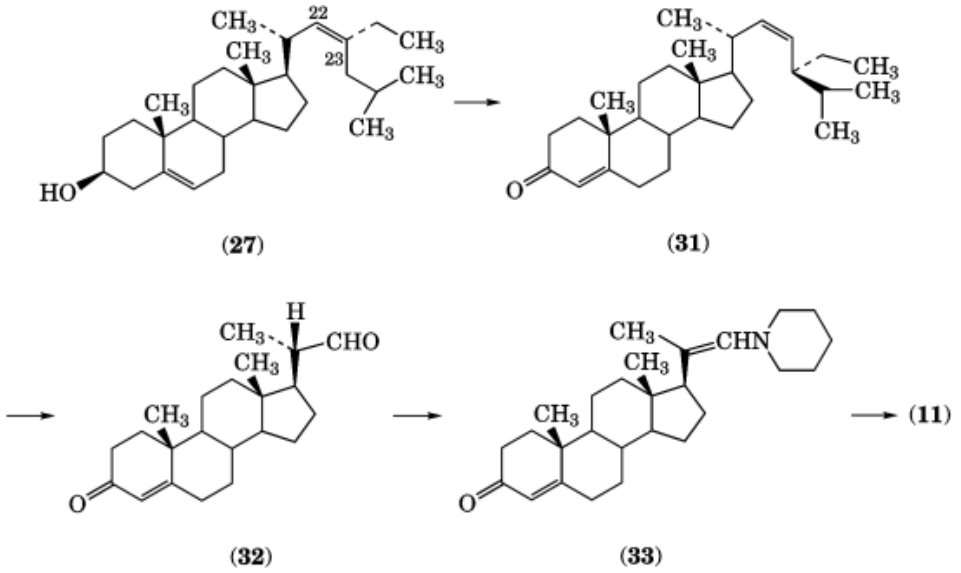
(11) → (28) → (34) → (35)



(36) → (37) → (38)

with sodium methoxide whereby it undergoes Favorski rearrangement to give the methyl-*cis*-pregn-17-enoate derivative (**36**). Protection of the 3-oxo-Δ^4-system in (**36**) (as the enamine (**37**) permits reduction of the 11-oxo- and carbomethoxy groups with diisobutyl aluminum hydride or $LiAlH_4$ in dibutyl ether. Regeneration of the 3-oxo function and acetylation gives (**38**). Oxidation of the latter with phenyliodosoacetate in *t*-butanol in the presence of a catalytic amount of OsO_4 gives hydrocortisone acetate (**2**, acetate) (71).

The manufacture of prednisolone (**30**) follows a similar route. 11-Oxo-progesterone (**34**) is treated with two molar equivalents of diethyl oxalate and sodium methoxide in *t*-butanol. The product (**39**) is acidified and treated with



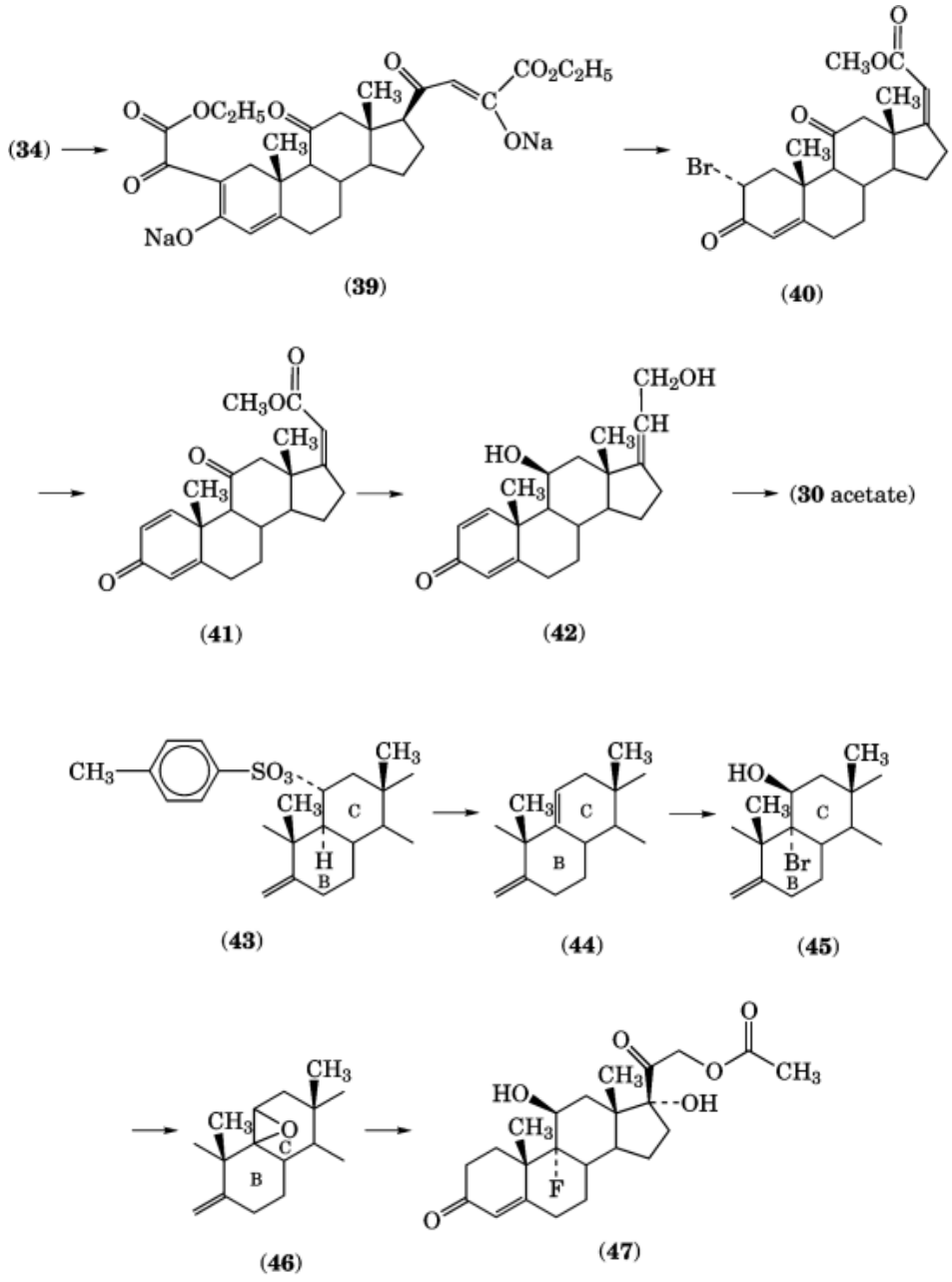
three moles of bromine/$NaOCOCH_3$/CH_3CO_2H to yield a tribromo derivative which undergoes Favorski rearrangement on treatment with $NaOCH_3$/CH_3OH to give the 2-bromopregnenoic acid derivative (**40**). Dehydrobromination with Li_2CO_3 in refluxing dimethylformamide yields the 1,4-diene (**41**), which is treated with dimethylamine in the presence of titanium chloride (72) to yield the 3-enamine. The 3-enamine is treated to form the 3,11-dienamine which can be converted into prednisone (**29**). Reduction with diisobutylaluminum hydride and regeneration of the 3-oxo moiety furnishes (**42**), which is converted after acetylation by hydrogen peroxide (with OsO_4 as catalyst) into prednisolone 21-acetate (**30**-acetate).

4.2. 9-Fluoro Derivatives of Corticoids

The 11-tosylate (**43**) of 11-epicortisol 21-acetate has been treated with sodium acetate/acetic acid in the hope of enforcing epimerization of the 11α-hydroxyl group. Surprisingly, the 9,11-ene (**44**) was formed by cis-elimination of the tosyl group. Addition of hypobromous acid gave the bromohydrin (**45**), which was converted by sodium acetate into the 9β,11β-epoxide (**46**). The latter was treated with hydrofluoric acid to give 9α-fluorohydrocortisone acetate (fludrocortisone acetate) (**47**). When tested in patients with rheumatoid arthritis, fludrocortisone acetate (**47**) proved to be 10 times more potent than hydrocortisone acetate. In contrast to hydrocortisone, which has only moderate mineralocorticoid activity, fluorocortisone acetate produces edema through salt and water retention. However, it has found clinical use in the treatment of patients with Addison's disease. Virtually every corticoid analogue prepared subsequent to (**47**) was routinely converted into the 9α-fluoro derivative, and nearly all of the corticoids in use contain this moiety.

4.3. 16α-Hydroxy Derivatives of Corticoids and their Acetonides

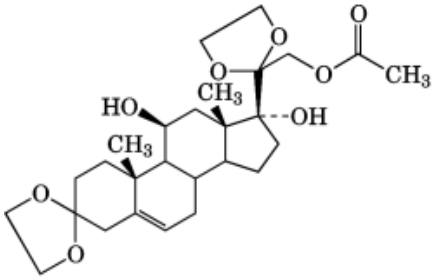
The preparation of 16α-hydroxy-9α-fluoroprednisolone (**48**) from the 3,20-bisethylene ketal of hydrocortisone acetate (**49**) has been reported (73). The latter was dehydrated with thionyl chloride in pyridine to yield the 4,9(11),16-triene (**50**). The 16,17-unsaturated linkage was selectively hydroxylated with OsO_4/pyridine to yield the 16α,17α-diol (**51**), which was converted into the 9α-fluoro-11β-hydroxy steroid (**52**) by the procedure outlined in (**44**) $\longrightarrow$ (**47**). Microbiological oxidation with *Corynebacterium simplex* gave the 1-dehydro derivative, triamcinolone (**48**). Triamcinolone possesses high glucocorticoid and antiinflammatory



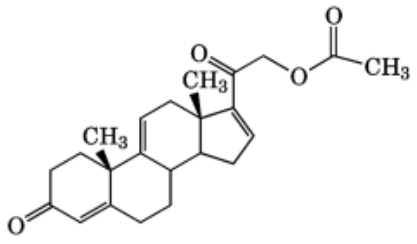
activity and, because of the presence of the 16α-hydroxyl group, is almost entirely devoid of salt-retaining activity. It had been shown that steroidal 16α,17α-dihydroxy-pregnan-20-ones readily forms acetonides, and application of this reaction to triamcinolone (**48**) yields triamcinolone acetonide (**53**) (74) which significantly exceeds the parent steroid in topical antiinflammatory activity. 16α-Hydroxyprednisolone 16α,17α-acetonide (desonide) (**54**) has been introduced into clinical practice (75).

4.4. Methylated Glucocorticoids

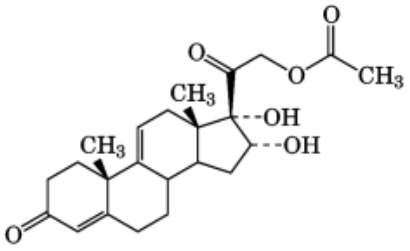
The preparation of 2α-methyl-9α-fluorocortisol has been reported (76). This compound shows enhanced glucocorticoid activity and greatly enhanced mineralocorticoid activity, so much that it surpasses aldosterone (**19**) in sodium-retaining and potassium-excreting potency. Attention was then turned to the preparation of 6-methylated corticoids



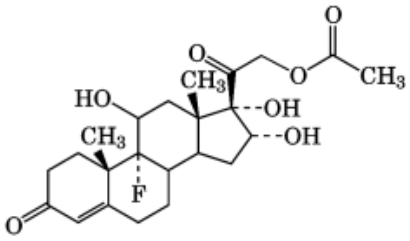
(**49**)



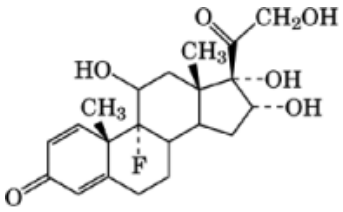
(**50**)



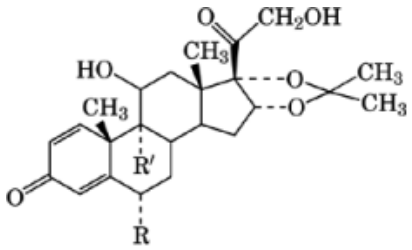
(**51**)



(**52**)

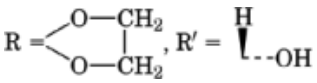


(**48**)



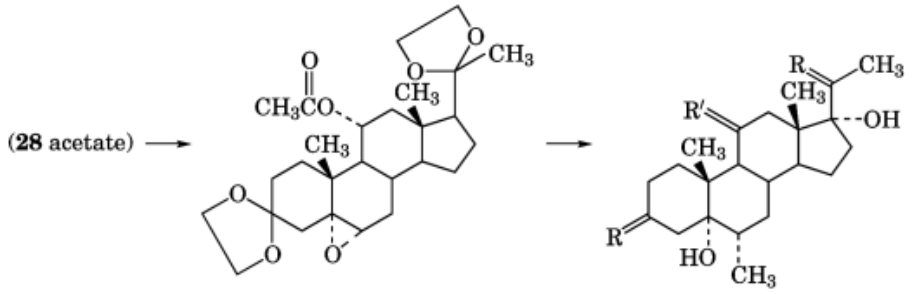
(**53**) R = H; R′ = F
(**54**) R = R′ = F
(**92**) R = F; R′ = H

when potentiation of glucocorticoid activity linked to negligible mineralocorticoid activity resulted: 6α-methylprednisolone (**55**) proved to be the compound of choice. It was prepared from 11α-hydroxyprogesterone acetate (**28**-acetate), which was converted into the bis-ethylene ketal and then by reaction with peracetic acid into the 5α,6α-epoxide (**56**). The latter compound was treated with methyl magnesium bromide (when fission of the epoxide ring occurred) to give the 5α-hydroxy-6β-methyl-bis-ketal (**57**)

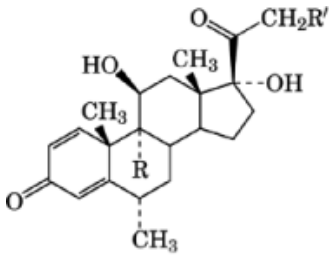


Removal of the ketal protecting groups, followed by oxidation with sodium dichromate in acetic acid gave 5α-hydroxy-6β-methyl-5α-pregnane-3,11,20-trione (**57**) (R = R′ = O). The latter was submitted to oxalylation, dibromination, Favorski rearrangement, and zinc dust reduction (see (**39**) $\longrightarrow$ (**40**)) to yield 3,11-diketo-6α-methylpregna-4,17(20)-dien-21-oic acid (**58**) (see also (**36**)). The last compound was converted into the pyrrolidyl enamine (cf (**37**)) which, on reduction with $LiAlH_4$ and regeneration of the 3-keto group by treatment with buffered methanol followed by acetylation, gave 11β,21-dihydroxyl-6α-methylpregna-4,17(20)-dien-3-one acetate (**59**). Oxidation with phenyliodosoacetate in *t*-butanol/pyridine in the presence of catalytic OsO_4 furnished 6α-methylhydrocortisone, which subsequently was converted into 6α-methylprednisolone by microbiological oxidation with *Septomyxa affinis* (77). The potentiating effect of the 6α-methyl group upon glucocorticoid activity is well illustrated by the observation that 16α,17α-isopropylidene-6-methylpregna-1,4-diene-3,20-dione (**60**) (77) is an excellent topical antiinflammatory agent even though it lacks the 11β-hydroxyl group characteristic of the natural glucocorticoids (78) and originally believed to be essential for glucocorticoid activity. The 21-desoxycorticoid 11β,17α-dihydroxy-9α-fluoro-6α-methylpregna-1,4-diene-3,20-dione (fluoromethalone) (**61**) also is an excellent topical antiinflammatory steroid (79).

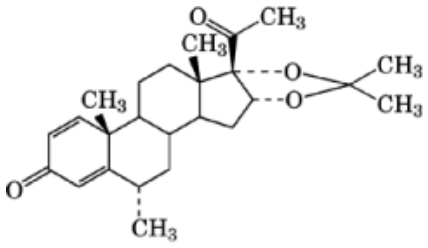
Methylation of hydrocortisone/prednisolone in positions C-4, C-7, C-12, and C-21 failed to give useful products. Methylation at C-16, in contrast, led to 16α- and 16β-methyl-9α-fluoroprednisolones which were exceptionally useful. Both series were prepared using 3α-acetoxy-5α-pregn-16-ene-11,20-dione derived from desoxycholic acid (80). A much shorter route was subsequently developed from 16-dehydropregnenolone (**62**) which was readily available from diosgenin.



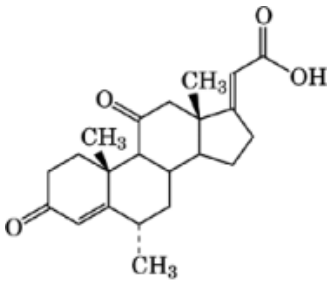
(**56**) (**57**)



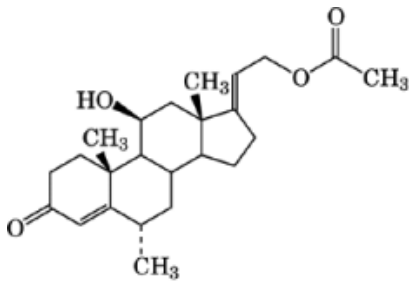
(**55**) R = H, R′ = OH
(**91**) R = F, R′ = H



(**60**)



(**58**)



(**59**)

Pregnadienolone (**62**) was converted into 16α-methylpregnenolone (**63**) by reaction with CH_3MgI/Cu_2Cl_2 (81). Catalytic hydrogenation of the last compound gave the 5α-pregnane derivative (**64**) which passed smoothly on enforced acetylation into the enol acetate (**65**). The latter, on treatment with peracetic acid, yielded the epoxide (**66**), which was converted into 17α-hydroxy-16α-methyl-5α-pregnan-20-one (**67**). Bromination of the last compound at C-21 gave (**68**) from which, by metathesis with acetate ion, 21-acetoxy-3β,17α-methyl-5α-pregnan-20-one (**69**) was obtained. Chromic acid oxidation of the last compound yielded the 3-one (**70**), which was converted using the 2,4-dibromo derivatives (**71**) into the 1,4-dien-3-one (**72**). Microbiological hydroxylation furnished the 11-epi 16α-methyl prednisolone (**73**) converted by standard procedures into 9α-fluoro-16α-methyl-11β,17α-trihydroxypregna-1,4-diene-3,20-dione (9α-fluoro-16α-methylprednisolone; dexamethasone) (**74**) (82). The last compound is used in the diagnosis of Cushing's syndrome.

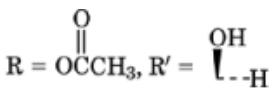
Introduction of a 16β-methyl group into the corticosteroid molecule was effected by a reaction (83) whereby a 16-dehydropregnenolone (**62**) was treated with diazomethane to form the pyrazoline (**75**) which was decomposed with perchloric acid in acetone to give the 16-methylpregn-16-en-20-one derivative (**76**). Catalytic hydrogenation yielded the 16β-methyl intermediate (**77**), which was converted into 9α-fluoro-16β-methyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione (9α-fluoro-16β-methylprednisolone, betamethasone) (**78**) by standard procedures (80).

Hecogenin has been used as starting material for the preparation of betamethasone (**78**); this genin is found in the sisal plant, *Agave sisalana.* The 12-oxo group present in hecogenin (**79**) is transferred to C-11 (84). Bromination of hecogenin in benzene yields the 11α,23a-dibromo derivative (**80**). The latter is treated with sodium hydroxide in aqueous *t*-butanol to yield the crystalline 23-bromo-ketal (**81**) which is acetylated and then debrominated with zinc dust. Reduction with calcium/liquid ammonia yields 11-oxotigogenin (**82**), which is converted into betamethasone (**78**) by standard procedures.

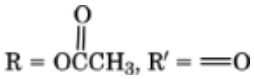
A variant of the 16-methyl group is 9α-fluoro-16-methylene-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione (fluprednylene) (**83**) (85).

4.5. 6-Fluorocorticoids

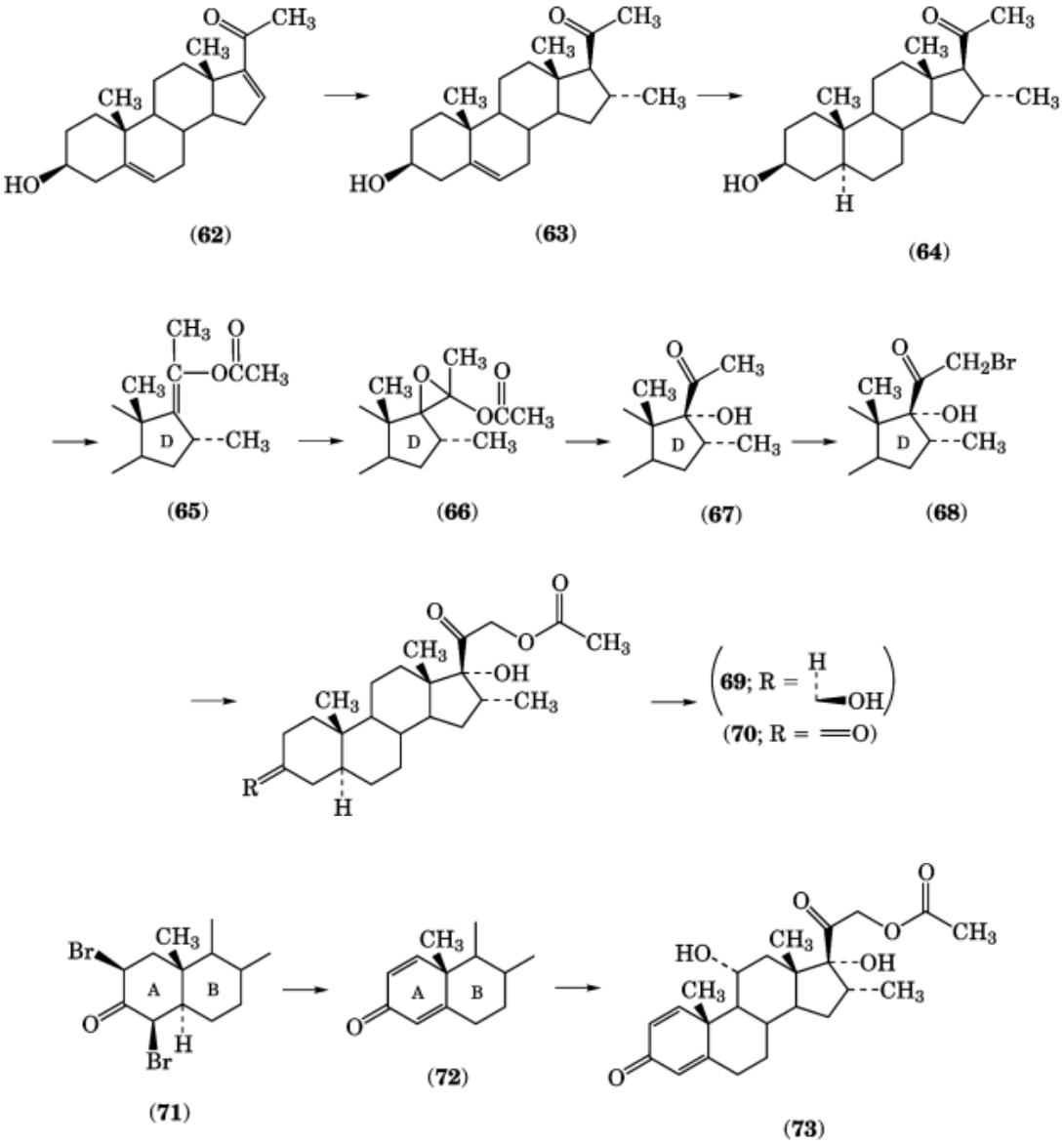
The 6α-fluoro substituent resembles the 6α-methyl group in strongly potentiating glucocorticoid activity. 6α-Fluoro-16α-methyl-prednisolone (paramethasone) (**84**) was prepared from 16α-methylpregnenolone (acetate) (**63**). The 5α,6α-epoxide (**85**) of the last compound was treated with boron trifluoride to yield the 6β-fluoro-5α-hydrin (**86**) which gave the enol triacetate (**87**) with acetic anhydride/acetyl chloride. Reaction with perphthalic acid gave the 17α-hydroxy-20-one (**88**) which was converted into the 21-acetoxy-derivative (**89**) by the standard bromination/acetoxylation procedure. Oxidation

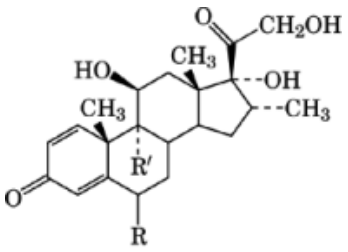


to the 3-one (**89**), followed by treatment with hydrogen chloride and cautious

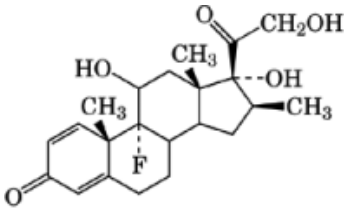


alkaline hydrolysis gave 17α,21-dihydroxy-6α-fluoro-16α-methylpregn-4-ene-3,20-dione (**90**), converted into 6α-fluoro-16α-methyl-11β,17α,21-trihydroxy-

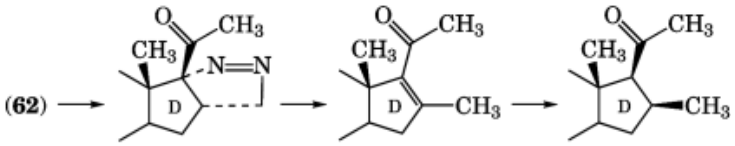




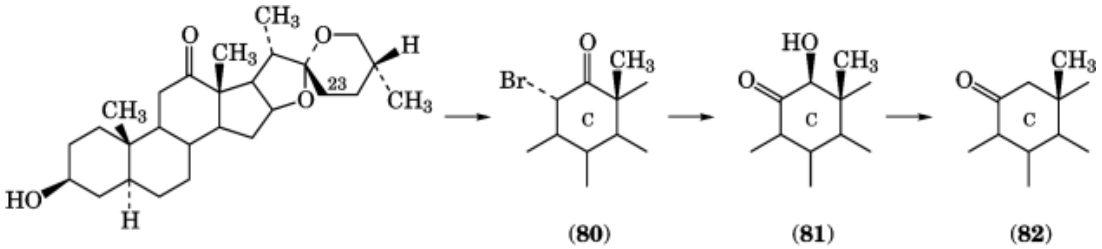
(**74**) R = H, R′ = F
(**84**) R = F, R′ = H
(**61**) R = R′ = F



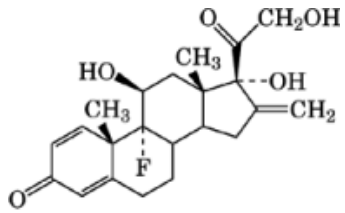
(**78**)



(**62**) (**75**) (**76**) (**77**)



(**79**) (**80**) (**81**) (**82**)



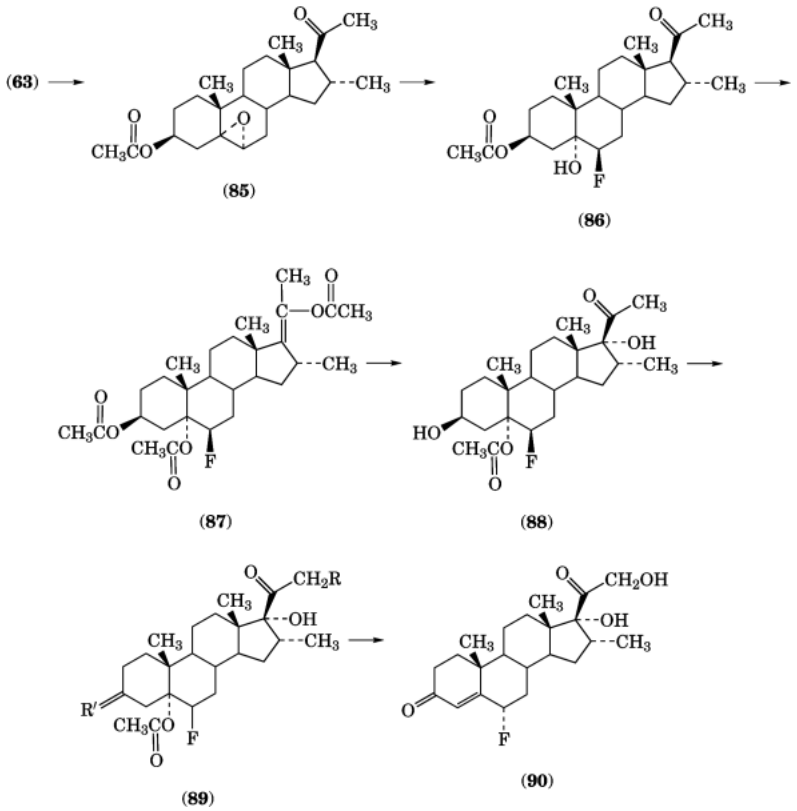
(**83**)

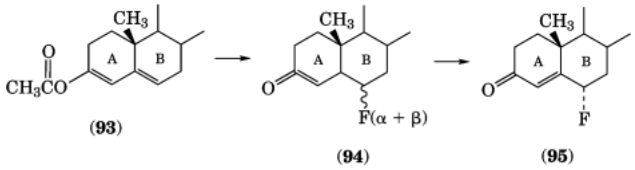
pregna-1,4-diene-3,20-dione (*para*-methasone) (**84**) and into 6α,9α-difluoro-16α-methyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione (flumethasone) (**91**) by standard procedures (86). The same general procedure was used to prepare 6α,9α-difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-dien-3,20-dione-16,17-acetonide (fluocinolone acetonide) (**54**) (87), which proved to be extremely effective by the topical route and is widely used as a standard for determining the potency of new corticoids. 6α-Fluoro-11β,16α,17α,21-tetrahydroxypregna-1:4-diene-3,20-dione-16α,17α-acetonide (flurandrenolone acetonide) (**92**) also was prepared (88).

An alternative route to 6α-fluorosteroids was developed by treating the enol acetate (**93**) of a Δ^4-3-one with perchloryl fluoride in aqueous dioxane to obtain a mixture of the 6-fluoro-epimers (**94**) which were converted into the 6α-fluoro-Δ^4-3-ones (**95**) on treatment with H^+.

4.6. 17-Acylated Corticoids

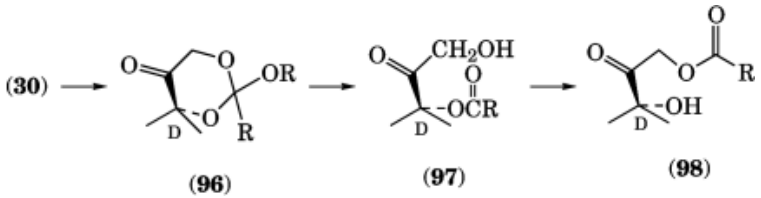
The corticoid side-chain of (**30**) was converted into the cyclic ortho ester (**96**) by reaction with a lower alkyl ortho ester $RC(OR')_3$ in benzene solution in the presence of *para*-toluenesulfonic acid (88). Acid hydrolysis of the product at room temperature led to the formation of the 17-monoesters (**97**) in nearly quantitative yield. The 17-monoesters (**97**) underwent acyl migration to the 21-monoesters (**98**) on careful heating with H^+. In this way, prednisolone 17α,21-methylorthovalerate was converted quantitatively into prednisolone 17-valerate, which is a very active antiinflammatory agent (89). The intermediate ortho esters also are active. Thus, 17α,21-(1′-methoxy)-pentylidenedioxy-1,4-pregnadiene-11β-ol-3,20-dione [(**96**), $R' = CH_3$, $R = C_4H_9$] is at least 70 times more potent than prednisolone (89). The above conversions





(93) (94) (95)

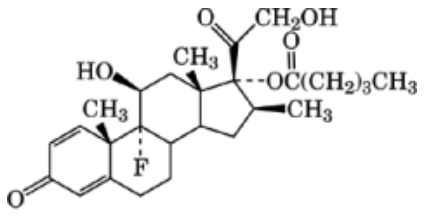
were applied to the betamethasone series, and the resultant β-methasone 17-valerate (**99**) had high topical activity in the McKenzie-Stoughton vasoconstrictor assay (90). The related β-methasone benzoate was developed independently (91). A number of ortho esters and 17,21-diesters derived from 6α,9α-difluoroprednisolone were prepared (92) and were at least 1000 times more active than cortisol in the granuloma pouch assay. In addition, di-esters, eg, the 17-propionate 21-butyrate and 17-butyrate-21-acetate, were 3.5 times more potent than betamethasone valerate in vasoconstriction tests in humans. The 17-propionate and 17-butyrate of 6α,9α-difluoro-21-desoxyprednisolone were



(96) (97) (98)

2.5–3.0 times more potent than betamethasone valerate in the vasoconstriction assay in humans (93). In addition to the ortho ester route to 17-acylated corticoids, the facile and nearly quantitative diacylation of the corticoid side chain using a lower acid/acid anhydride admixed with ortho phosphoric acid also was reported (94).

Recently developed 17-acylated corticoids include 6α,9α-difluoro-16β-methyl-11β17α,21-trihydroxypregna-1,4-diene-3,20-dione diacetate (diflorasone diacetate) (**100**) (95); 9α-chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate (beclomethasone dipropionate) (**101**) (96); and 21-chloro-11β,17α-dihydroxy-9α-fluoro-16β-methylpregna-1,4-diene-3,20-dione 17-propionate (clobetasol propionate) (**102**) (97). In addition to the preceding corticoids which contain the dihydroxy acetone side chain, a number of products have been developed that lack an 17α-hydroxyl moiety. 6α-Fluoro-16α-methyl-1,4-pregnadiene-11β,21-diol-3,20-dione (fluocortolone) (**103**) was the first product of this type to be introduced into therapy as an antiinflammatory agent (98). 11β-Hydroxy-16α,17α,21-trimethylpregna-1,4-diene-3,20-dione (**104**) was compared to betamethasone valerate (**99**) in a number of antiinflammatory assays and they were approximately equipotent. In contrast to betamethasone valerate (99), however, it did not suppress adrenal function on systemic administration or reduce skin weight on topical administration.



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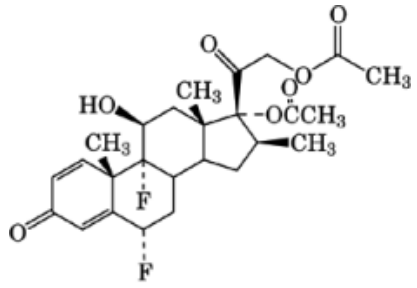
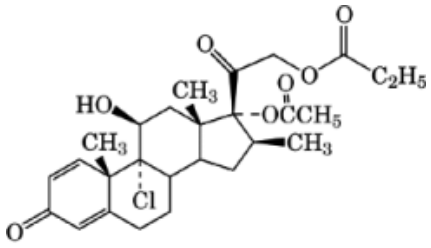


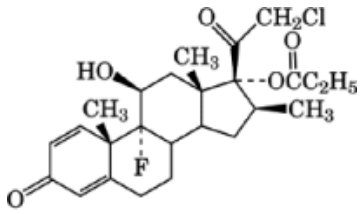
(**100**)

4.7. 20-Ketopregnan-21-oic Acids, the 17β-Carboxy Androstanes, and the D-Homocorticoids

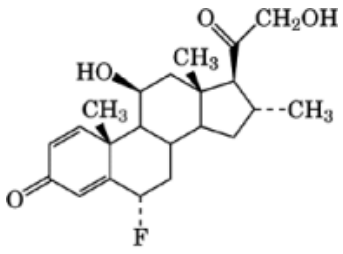
In the course of studies on the metabolism of fluocortolone (**103**) the formation of the water-soluble carboxylic acid (**105**, R = H) was reported. As a free 21-hydroxyl is not necessary for antiinflammatory activity, it was concluded that the esters (**105**, R = alkyl) of the preceding metabolite would possess antiinflammatory activity on topical administration but would be devoid of systemic activity when hydrolysis to the free acid occurs followed by



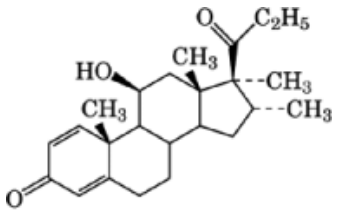
(**101**)



(**102**)



(**103**)



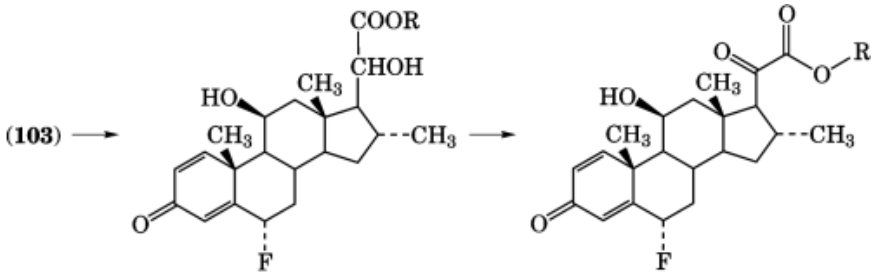
(**104**)

rapid elimination (100). The required esters (**105**, R = alkyl) were readily prepared by oxidation of fluocortolone (**103**) with alcoholic cupric acetate (101) whereby a mixture of the 20α- and 20β-hydroxypregnanoic esters (**106**) was obtained followed by oxidation with manganese dioxide to give the esters (**105**). Biological studies reveal that the esters (**105**) are highly active in the (topical) vasoconstriction assay but are devoid of systemic antiinflammatory activity as shown by the liver glycogen, paw edema, thymus involution, and other assays, and they were without mineralocorticoid activity. The butyl ester (fluocortin butyl ester) (**105**, R = C_4H_9) was selected for clinical study as a topical corticosteroid devoid of systemic activity (102). Urinary metabolites of prednisolone likewise contain products with β-glycolic and β-glyoxalic side chains. The methyl ester (**106**) of the latter in the paw edema assay is least effective if administered orally or intraperitoneally and most effective if administered topically or subcutaneously (103).

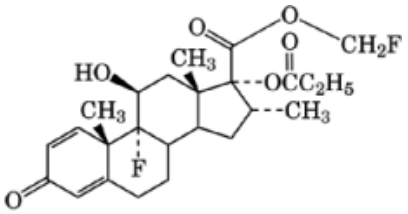
Another series of antiinflammatory carboxylic acids that are derived from cortienic acid (**107**), a minor adrenal metabolite, has been described (104, 105). Esterification of both the 17α-hydroxyl group and the carboxylic acid of (**107**) were required to develop a compound of high topical potency with low systemic activity. Peak activity was generally associated with a 17α-propionoxy group and a 17β-fluoromethoxy carbonyl (eg, (**108**)), or 17β-methoxycarbonyl residue.

The D-homo-corticoids represent the last group of antiinflammatory steroids worthy of mention (106).

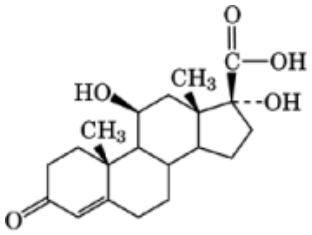
In 1973 D-homo corticosteroids (**109–112**), eg, D-homo-9α-fluoroprednisolone acetate (**111**) were reported to have antiinflammatory activity (107). Compounds such as 21-acetoxy-11β-fluoro-9α-chloro-17aα-hydroxy-D-homo-pregn-4-en-3,20-dione (**110**) had especially strong topical activity with weak systemic activity (108). Other preparations of D-homocorticoids included



(**106**) (**105**)

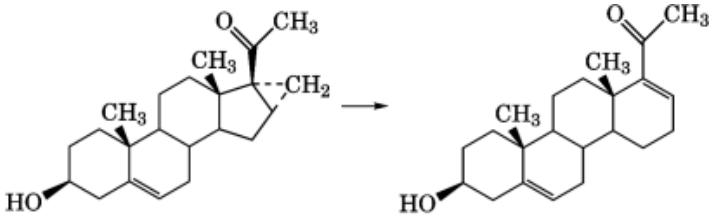


(**108**)

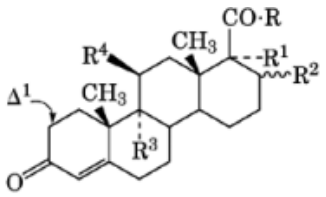


(**107**)

11β-hydroxy-3,20-dioxo-17α-methyl-D-homo-1,4-pregnadien-21-oic acid methyl ester (**111**), which was thought to have high topical antiinflammatory activity with insignificant systemic activity (109). An important result of the D-homocorticoid work was the development of a convenient synthesis of Δ^{17}-D-homopregnenolone (**113**) from the readily available 16α,17α-cyclomethylene pregnenolone (**114**) by acid-catalyzed rearrangement (110). Conversion of (**113**) into D-homocorticoids followed conventional routes. A number of patents covering D-homocorticoids had been issued and covers compounds such as 11β-hydroxy-17aα-propionyloxy-3-oxo-D-homoandrost-4-ene-17aβ-carboxylic acid chloromethyl ester (**112**) (111).



(**114**) (**113**)



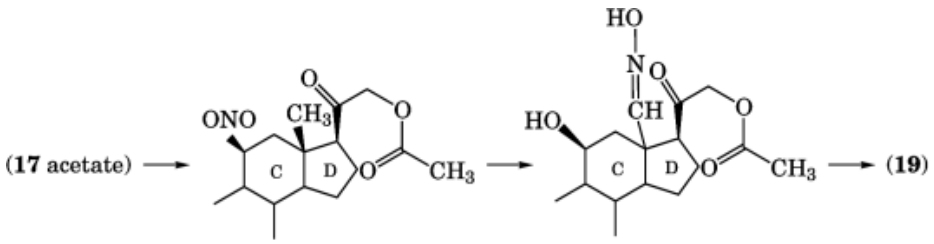
		R	R^1	R^2	R^3	R^4
(109)	Δ^1	CH_2OCCH_3 (O)	OH	H	F	OH
(110)		CH_2OCCH_3 (O)	OH	H	Cl	F
(111)	Δ^1	$COCH_3$ (O)	H	α-CH_3	F	OH
(112)		OCH_2Cl	OCC_2H_5 (O)	H	H	OH

5. The Mineralocorticoids

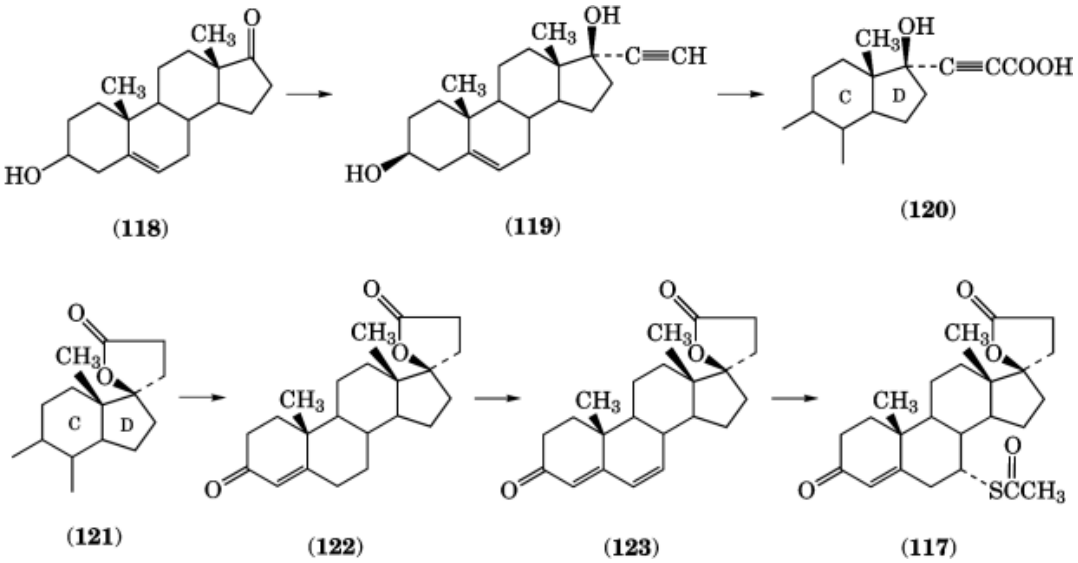
Studies have shown that aldosterone (**19**) (112, 113) from adrenal extracts was intensely active in the survival and sodium retention assays in the adrenalectomized rat.

A photochemical partial synthesis of aldosterone (**19**) made the hormone available on an industrial scale for the first time (114). Corticosterone acetate (**51**; acetate) is treated with nitrosyl chloride in pyridine at 20°C to yield the 11-nitrite (**115**). Irradiation of (**115**) leads to rearrangement with formation of the C_{18}-oxime (**116**). Removal of the oxime residue with nitrous acid furnishes aldosterone (**19**) in excellent yield.

Hyperaldosteronism is accompanied by elevation of blood pressure (115), and can be treated with an aldosterone antagonist, eg, spironolactone (**117**) which



(115) **(116)**



(118) (119) (120) (121) (122) (123) (117)

is synthesized from dehydroepiandrosterone (DHA) (**118**) (116). Ethynylation of DHA gives the 17β-hydroxy-17α-ethinyl derivative (**119**), which is converted using its ethynyl Grignard derivative and treatment with CO_2 into the 21-carboxylate (**120**). Hydrogenation leads to formation of the lactone (**121**), which is converted by the Oppenauer method into the 3-oxo-Δ^4-lactone (**122**). The last compound is treated with chloranil in *t*-butanol to give the 4,6-diene (**123**) which adds thioacetic acid to give spironolactone (**117**). The market for mineralocorticoids is extremely modest as their main value lies in the treatment of Addison's disease.

6. Adrenal-Cortical Steroid Antagonists

Antagonists of glucocorticoid and mineralocorticoid activity have found increased use clinically in the treatment of hypertension, Cushing's disease, and heightened intraocular pressure.

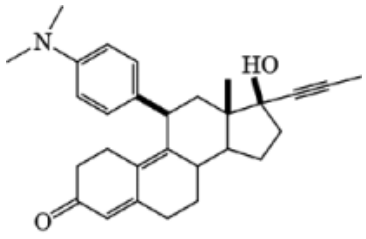
Some general structural features that lead to both observed differences in steroidal conformation (via x-ray structures) and to noticable effects in bioactivity (RBAs, agonism vs antagonism, magnitude of activity, etc) are the following: (*1*) Unsaturation of the A-ring: Alteration of the A ring conformation. Except for the A-ring diazoles, all the GR antagonist known have the 4-ene-3-one structure. As this is shared with the most potent glucocorticoids, it is thought that this structural feature increases binding affinity to the steroid receptor (117). (*2*) The hydroxy groups at C-11, C-17, and C-21, although not necessary for a compound to bind to the GR, seem to be individually or collectively responsible for agonistic activity (though some compounds with hydroxyls at one or more of these positions (eg, RU-486 (**124**) and dexamethasone oxetanone (**125**), still act as GR antagonist). The absence of any of these hydroxyls may be one factor related to antagonistic activity (117), though not necessarily a determining factor. The lack of a hydroxyl at C-11 is a noticeable factor in the case of some GR antagonists. Where as all antiinflammatory glucocorticoid agonists have a hydroxyl at C-11 (or are readily solvolyzed to a C-11 OH), many antagonists though not all have no hydroxy moiety at C-11. For example, compounds that have shown antagonistic, eg, ZK 98299 (**126**), or mixed agonist activities, eg, RU-486 (**124**), each have substantially bulky groups at C-11.

An interesting comparison between agonist and antagonist to the GR is that of dexamethasone (**74**) (agonist) with dexamethasone oxetanone (**125**) (antagonist). The x-ray structures of these compounds indicate that all four rings overlap very well and thus should fit into the ligand binding site in a similar manner. As

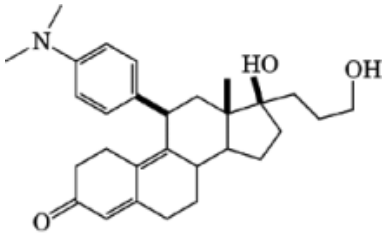
with differences in the magnitude of agonist activity, the agonist/antagonist distinction may be the result of chemical factors, including the hydrogen bond-donating or accepting ability of the ligand. In this example, both compounds can accept a hydrogen bond at C-20, though only the agonist is able to donate hydrogen bonds (117).

The most useful GR antagonist clinically is RU-486 (118, 119), which also shows significant PR antagonism. This compound has been characterized more completely as a partial antagonist in certain cell lines (120, 121), and has thus sometimes been called a type II antagonist. Although type II antagonist-occupied receptor can bind to DNA, it cannot interact productively with the DNA in a manner equivalent to interaction of an agonist-occupied receptor (122). RU-486 blocks the transactivation of the GR and inhibits the production of associated proteins, notably dexamethasone-induced extracellular LC-1 (55).

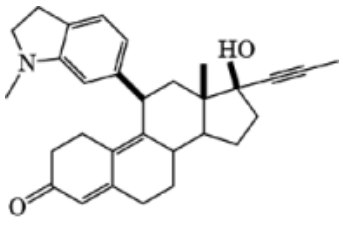
The defining feature of RU-486 is the 11β-aryl moiety. Most steroidal GR antagonists include 11β-aryl or other 11β substituents. The tight binding affinity of RU-486 to the GR is presumed to be in part the result of a tight fit of this 11β-aryl component in a lipophillic pocket within the GR hormone binding region. ZK 98299 is an 11β-aryl GR antagonist very similar in structure to RU-486, though it is a pure (type I) antagonist. Like RU-486, it also has antiprogestational activity. The 11β-*N*-methyldihydroindol-5-yl analogue of RU-486 (**127**), another compound with GR antagonistic properties and a strong GR binding affinity, has a rotomer which fits well in the space (11β-pocket) occupied by the 11β-substituent of RU-486.



(**124**)



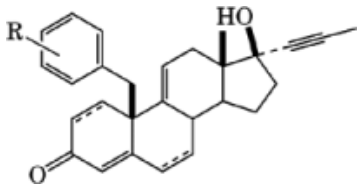
(**126**)



(**127**)

Another class of glucocorticoid antagonists, the 10β-androstanes, eg, RU-39305 (**128**) and RU-43044 (**129**), also bind tightly to the GR (Table 2). Relative binding affinitys (RBA) to the GR (vs dexamethasone) do not lead to clear SARs in regard to unsaturation at Δ1 or Δ6. However, space-filling models indicate a similarity between the 3-D space occupied by the 10β- and 11β-compounds (123), although the aromatic moiety of RU-39305 (**128**) is not in the same orientation as that of RU-486. These compounds have very little affinity for the progesterone receptor (PR).

Table 2. Relative Binding Affinities of 10β-Androstanes[a]

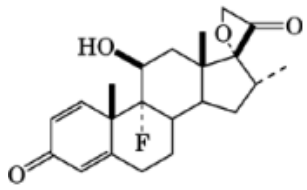


RU Code(Structure number)	Unsaturation	R	ThymusGR RBA[b]	PR RBA	ThymocytesIC$_{50}$ nM
39305		H	57	<0.1	100
43044		*p*-CH_3	130	<0.2	200
43065		*p*-CH_3	17	<0.1	500
46759	Δ1, Δ6	*p*-CH_3	33	<0.1	500
44068	Δ1	*p*-CH_3	15	<0.1	>1000
44427	Δ6	*p*-CH_3	3	<0.1	1000

[a] Adapted from Ref. 123.

[b] Dexamethasone = 100.

Research conducted by Simons using antiglucocorticoids, including compounds which covalently bind to the GR (124), eg, dexamethasone 21-mesylate, has better defined the structure and function of the GR. Spiro C-17 oxetanes have shown potent antiglucocorticoid activity in whole cell systems (125, 126).



(125)

Although both the 10β- and the 11β-group have been found to be important in connection with many GR antagonists, neither is a requirement for antiglucocorticoid activity. Cortexolone (**15**) acts as a GR antagonist in the true sense of the term, blocking GR transactivation (127–129) although it does not include an 11β-substituent.

Spironolactone is the most clinically useful steroidal aldosterone antagonist, and unlike GR antagonists, this compound is utilized much more frequently than aldosterone agonists. Interfering with Na^+ reabsorption and K^+ secretion in the late distal segment, this compound is predominantly used with other diuretics. Canrenone, an olefinic metabolite of spironolactone, and potassium canrenoate, in which the C-17 lactone has been hydrolyzed open, are also potent mineralocorticoid antagonists.

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