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Concept and Development of a Potent Topical Corticosteroid [1][2]

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Abstract. In a rational approach to identify an ultrapotent compound for the treatment of therapy-resistant dermatoses, Weirich's modification [8] of McKenzie's skin vasoconstriction assay (HVK test) has been used as the essential selection criteria. In a primary phase, a quantitative relationship between the HVK activity of 25 derivatives of corticosterone substituted in various positions of the skeleton, and their lipophilicity (log P) was established. The specific lipophilicity-independent interactions were accounted for by the inclusion of 'indicator variables' into the regression analysis. The highly significant results allowed to localize an optimal log P range and to identify the influence of various substituents. In a next phase, the evidence of the first HVK analysis was refined by considering 28 additional compounds. On the basis of the confirmed facts, six 21-chloro-6 α -fluoro compounds were specifically synthesized and submitted to dermatopharmacological testing. Finally, CGP 14458 (= 21-chloro-6 α ,9-difluoro-11 β -hydroxy-16 β -methyl-3,20-dioxopregna-1,4-dien-17 α -yl propionate) which was predicted to be the most potent representative of these series, whose synthesis is described in detail, showed indeed to be the most effective compound. Clinical trials with this compound – halobetasol propionate/Ultravate® (ulobetasol/Miracorten®) – confirmed its unique efficacy, especially in the treatment of severe, chronic plaque psoriasis.

General

The corticosteroid hormones produced by the adrenals, as well as their more potent synthetic analogues, are representing a type of compounds of vital importance to men, showing a very broad spectrum of activity.

During the past decades, beside the classical systemic application of glucocorticosteroids, which, in spite of the great popularity of NSAID's, is still considered to be the essential treatment of many life-threatening diseases, there have been introduced into therapy the so-called dermatocorticoids (DC). Their use for the topical treatment of skin allergies, inflammations, and proliferating dermatoses of the human skin has become indispensable.

Some fifteen years ago, we have decided to try to use a rational [9] approach to the development of a 'superstrong' DC for an effective treatment of obstinate dermatoses which do not respond to the treatment with strong compounds, e.g. betamethasone valerate.

Besides the classical antiinflammatory tests, like e.g. Tonelli's 'rat-ear-dermatitis-inhibition test' [10], a high activity of the test compounds in one of the most relevant dermato-pharmacological assays – the McKenzie's 'human-skin vasoconstriction test' [11] – in a version developed in our laboratories (the HVK test) [8] was chosen for the characterization of DC's as the primary selection criteria.

It has been shown in many reports about percutaneous resorption that the flux, I, of a compound completely dissolved in a vehicle, through the skin is strongly dependent on its lipophilicity. According to Scheuplein [12], this fact can be mathematically expressed by the following equation:

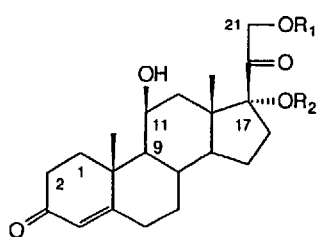
$$I = \frac{dQ}{dt} = \frac{P_m \cdot D_m \cdot \Delta(C_s)}{d}$$

P_m = partition coefficient *stratum corneum*/vehicle

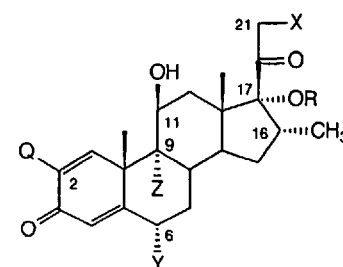
D_m = diffusion coefficient in *stratum corneum*

$\Delta(C_s)$ = difference in concentration through the *stratum corneum*

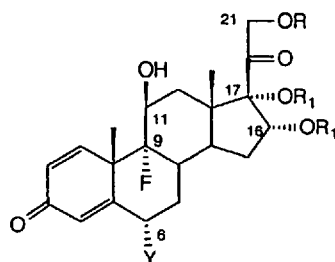
d = diameter of the *stratum corneum*



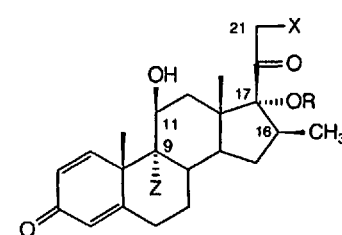
Series: HYDROCORTISONE



Series: DEXA-/FLUMETHASONE



Series: TRIAMCINOLONE / FLUOCINOLONE



Series: BETAMETHASONE

[Q, Y, Z = H, Hal; X = Cl, OAc, OH; R, R₁, R₂ = H, Ac; R₁+R₂ = C(CH₃)₂]

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In a steady state, the amount of the compound transported per time unit through the skin is proportional to the partition coefficient between the vehicle and the *stratum corneum*.

We have, therefore, decided to try to deduce in the first part of our study a quantitative correlation between the HVK activity of the test compounds and their lipophilicity expressed as partition coefficients in the system octanol/H₂O, which is believed to mimic the *in vivo* situation best.

For the first step of our investigation, we have selected a series of 25 steroids belonging to four different groups of DC's, namely, those of hydrocortisone (HC), dexamethasone/flumethasone, triamcinolone/flucinolone and betamethasone. The lipophilicity has been manipulated mainly by variation of the substituents in positions 2, 9, and 21 of the steroid nucleus.

In (Figs. 1–4), the logarithms of the relative potencies, $\log W_{rel}$, are plotted against the $\log P$ values of the compounds. In spite of the relative large deviations of the single points from the parabola calculated by multiple regression, a clear-cut dependence is observed between the vasoconstrictor activity and the $\log P$ value. In addition, a presumably optimal $\log P$ area can be observed in the range of about 3.5–4.5.

The next step consisted in a refinement of the regression by inclusion of *indicator variables* in the so-called mixed *Hansch-Free-Wilson* approach [13]. Indicator variables, X_{ij} , are discrete variables which can assume the value of either 0 or 1, describing thereby the presence or absence of a specific substituent. The corresponding coefficients, A_{ij} , calculated by multiple linear regression express the contributions of the particular substituents to the overall activity. By admixing the $\log P$, a separation can be achieved between the lipophilicity-dependent contributions and specific interactions of the substituents at the molecular level. In our specific analysis, it has been shown that only the 6 α -fluorine, the 16 β -Me group, and the 16,17-acetonide grouping give statistically significant contributions and have, therefore, to be considered.

As is shown in Fig. 2, the standard deviation, after introducing the above discussed corrections, is clearly in the region of the reproducibility of the biological data. This very positive result, combined with the relatively strict additivity of the $\log P$ contributions of the individual substituents on the steroid skeleton, and, therefore, with the calculability of the integral $\log P$ value of the compound, allowed us in the second series of our experiments to

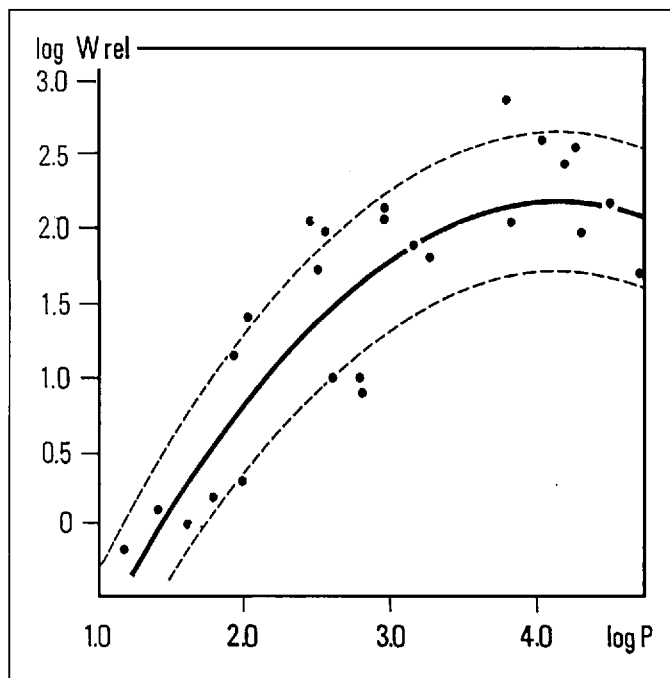


Fig. 1. 1st HVK Test (human skin vasoconstriction assay).
 $\log W_{rel} = \log \frac{DMWD_{HC}}{DMWD} = -2.79 + 2.36 \log P - 0.28 (\log P)^2$; $n = 25$, $r = 0.862$, $s = 0.470$.

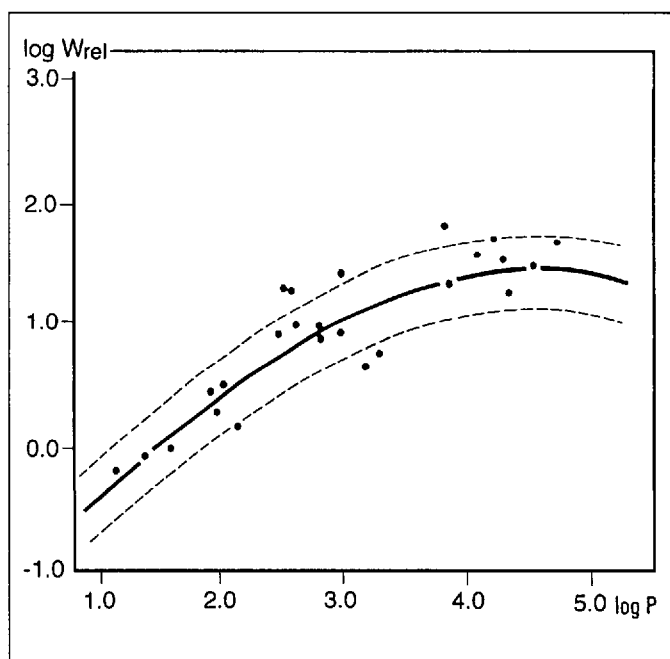


Fig. 2. 1st HVK Test. Computed values corrected by the increments of the substituents deduced from mixed analysis. $\log W_{rel} = -1.59 + 1.29 \log P - 0.13 (\log P)^2 + 0.70 (6-F) + 1.02 (16\beta\text{-CH}_3) + 0.42 (16,17\text{-Acetonid})$; $n = 25$, $r = 0.96$, $s = 0.306$.

synthesize new derivatives, whose vasoconstrictor activity would be expected to be distinctly superior to that of compounds which we have already tested. Of special interest appeared to be the fact that a 6 α -F substituent having a strong positive effect upon the activity, showed *no* measurable contribution to the lipophilicity.

In the second analysis, there have been included 28 additional compounds. As mentioned before, particular attention has been paid to the 6 α -F compounds.

The relative potencies, $\log W_{rel}$, shown in Fig. 3 as a function of $\log P$, are situated in the expected range. The points carrying a CGP number correspond to six intentionally synthesized compounds and to the most active DC known up today – to

clobetasol propionate (CGP 9'555), the active ingredient of *Glaxo's Dermovate*[®]. The inclusion of indicator variables leads to the shown equation (Fig. 4) [14].

The correlation having an r value of 0.98 and a standard deviation of $s = 0.29$ can be considered as highly satisfactory.

Below, there are reproduced the structures of the six already mentioned compounds showing a particularly high activity in the HVK test and differing in respect to their configuration at C(16), the substitution at C(2) and C(9) and in the number of C=C bonds.

They were subjected to an extended secondary screening and compared with each other in respect to activity and side

effects. A synopsis of the results obtained in the 4 most important dermatopharmacological tests [15] is presented in Fig. 5.

The UV-dermatitis inhibition test in guinea pigs as well as the 'croton-oil-dermatitis-inhibition test' in rabbits do not permit a clear differentiation of the compounds. Significant differences in favour of CGP 14'458 – the 6 α -F analogue of clobetasol propionate (CGP 9'555) – are, however, observed in the two most relevant experiments, *i.e.* in the HPLH and in the HVK test. The former allows to measure the degree of inhibition of mitosis and of the psoriasis-like hyperplasia produced by the action of hexadecane in the epithelium of the guinea pig skin. The HVK

activity is represented in this graph as a percentage of the factor $2000 \times \text{HC}$. The second parameter is a measure for the intensity of the blanching reaction.

On the basis of these data and of the results of skin tolerability tests, CGP 14'458 (ulobetasol [16]/*Miracorten*[®]; halobetasol propionate [17]/*Ultravate*[®] [18]) has been selected for clinical testing.

Chemistry

Four different synthetic approaches to CGP 14'458 (11) were evaluated and led finally to a technically acceptable procedure. One of them [19] is presented in the *Scheme*.

Beclomethasone [20] (1) appeared to be an ideal starting material for the planned synthesis. The corresponding orthoester 2 generated 9 β ,11-epoxide 3, which was selectively hydrogenated in position 1(2) under the known conditions of homogeneous catalysis in dioxane solution, to yield the mono-unsaturated ketone 4. Under acidic conditions the orthoester group was selectively hydrolyzed to the 21-hydroxy-17 α -propionyloxy derivative 5. Via the 21-mesylate 6, the desired 21-Cl compound 7 was formed. The introduction of an F-atom into position 6 α was achieved by fluorination of the enol ether 8. Under the influence of FCIO_3 in $\text{THF}/\text{H}_2\text{O}$ besides a small amount of the 4-F isomer, unexpectedly, the 6 α -F compound 9 was formed *directly* [20]. The opening of the epoxide proceeded smoothly under the treatment of 9 with a mixture of HF and urea, forming thus the fluoro hydrine 10 (= CGP 14'457).

Finally, dehydrogenation of 10 by DDQ in dioxane generated our target compound CGP 14'458 (11). The structures of all the intermediates and of the final substance were confirmed by analysis and by spectroscopic data (*cf. Exper. Part*).

Contemporarily with the development of a synthetic procedure, the optimization of the vehicles for adequate cream and ointment for CGP 14'458 was pursued by our galenics department. Using a mechanical arrangement [22] as a crude model for the *in vivo* liberation of the active compound from the formulation, a tailor-made ointment for CGP 14'458 on a hydrocarbon base was obtained, containing more than 5% of propylene glycol.

During the last eight years the two formulations (ointment and cream) of CGP 14'458 have been clinically tested. Special attention was given to applications in cases of severe chronic psoriasis.

In one of the studies [23], in a double-blind, multicentre, dose-finding trial by dermatologists in Germany and Switzerland in 336 patients with chronic, plaque psoriasis, 126 of whom had severe symptoms, the success rates (described as 'healed' or 'marked improvement') were 77% with 0.02% CGP 14'458 ointment, 90% with 0.05% CGP 14'458 and 80% with CGP 9'555 ointment (*Table*). These results clearly show that the optimum therapeutic effect of a topical corticosteroid depends not only on the potency of the compound but also on the concentration of the active ingredient.

In another double-blind, parallel-group trial [24], 0.05% CGP 14'458 ointment was also more effective than 0.05% CGP 9'555 ointment in 134 patients with severe, chronic, plaque psoriasis. The success rates were 96% with CGP 14'458

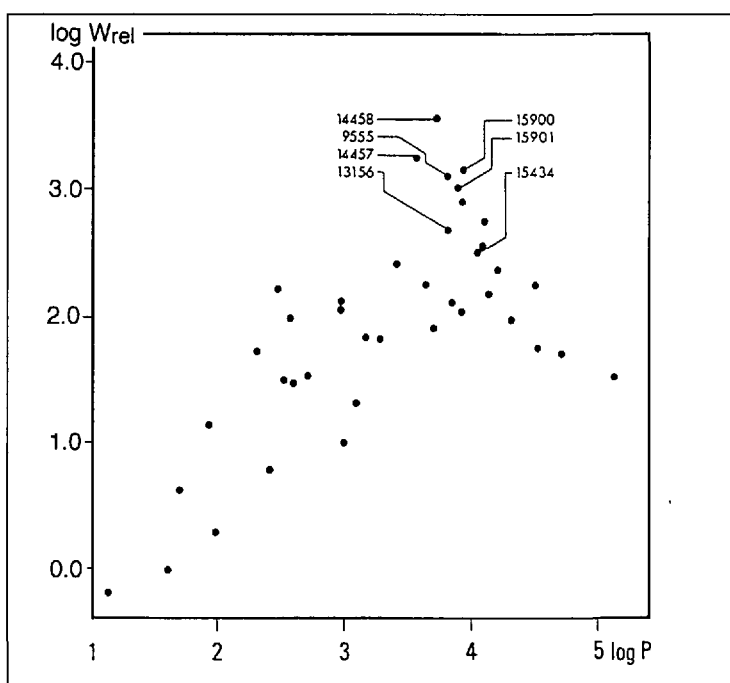


Fig. 3.
2nd HVK Test

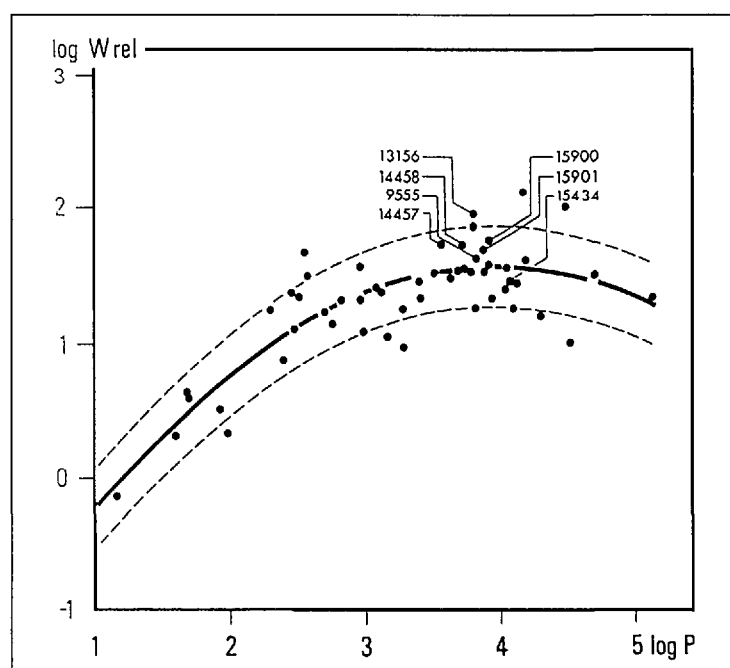


Fig. 4.
2nd HVK Test. Computed values corrected by the increments of the substituents deduced from mixed analysis. $\log W_{\text{rel}} = -1.67 + 1.62 \log P - 0.20 (\log P)^2 + \sum A_{ij} X_{ij}$; $n = 53$, $r = 0.961$, $s = 0.29$. For the values of A_{ij} see [14].

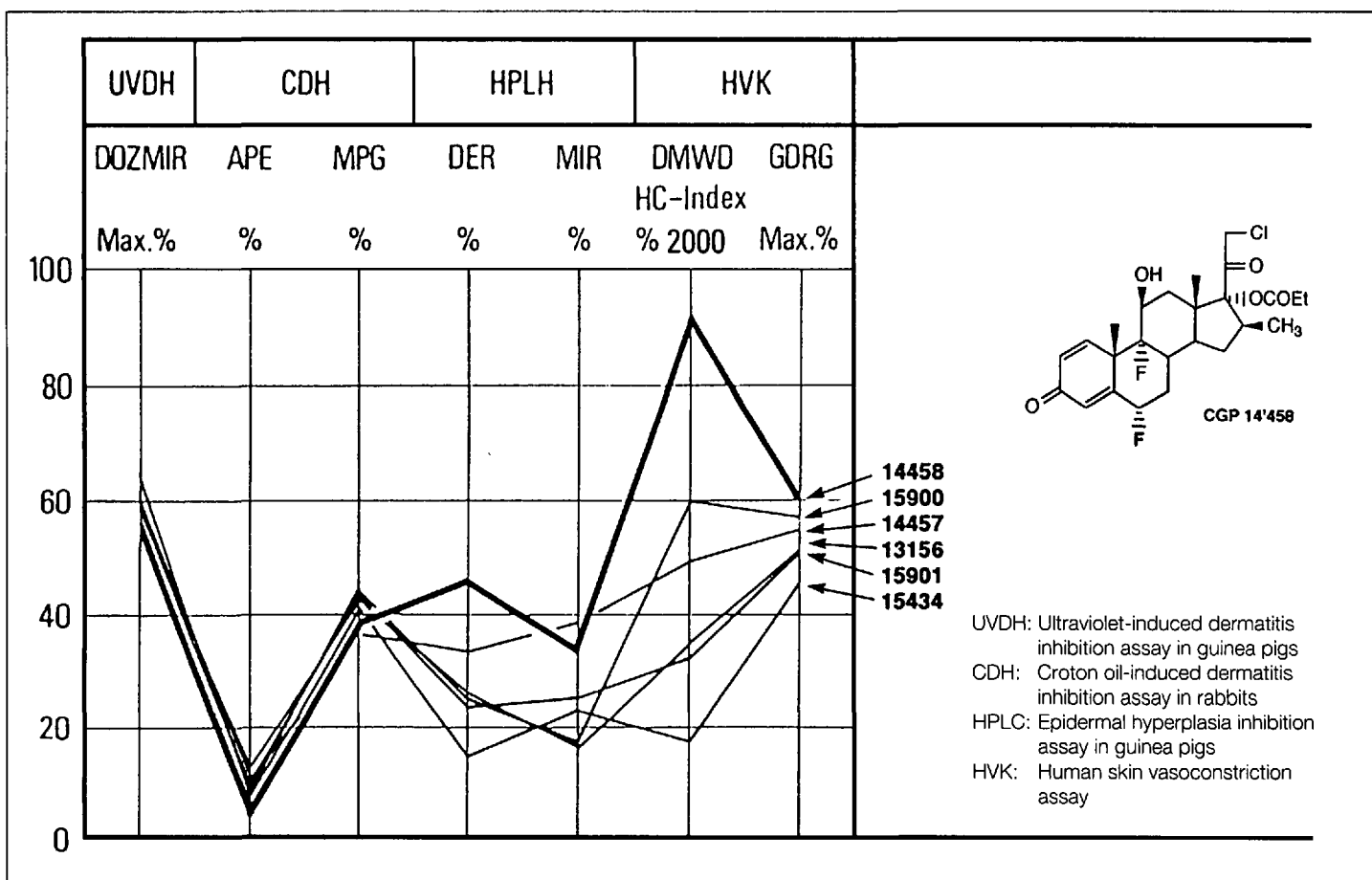
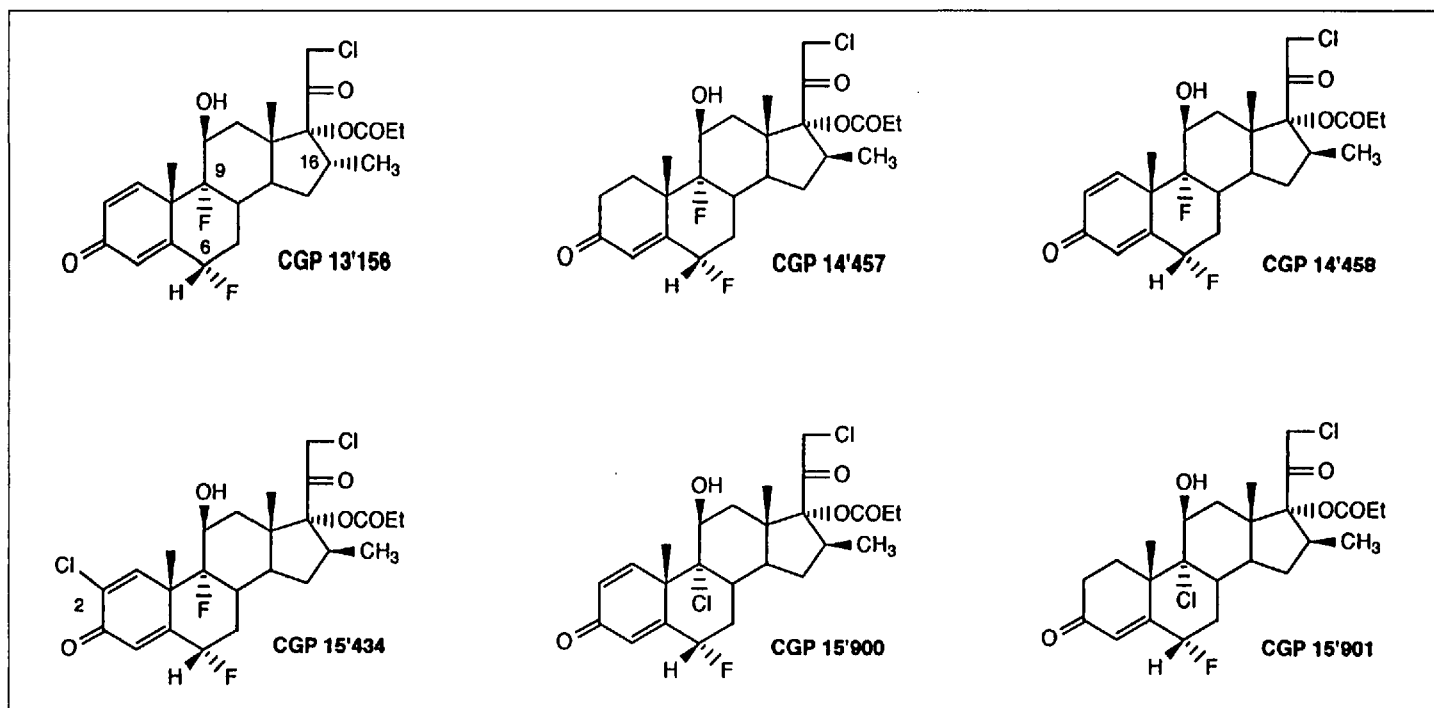


Fig. 5. Dermatopharmacologic activity

ointment and 91% with CGP 9'555 ointment. Adverse effects were reported in a smaller percentage of patients treated with 0.05% CGP 14'458 ointment than in those treated with 0.05% CGP 9'555 ointment (7.5% vs. 12%).

Thus, 0.05% CGP 14'458 (*Miracorten*[®]) ointment proved more effective than 0.05% CGP 9'555 (*Dermovate*[®]), the

most potent topical corticosteroid used worldwide in clinical practice since 1974.

The registration of CGP 14'458 is meanwhile pursued in various countries. It has been already introduced into the market in the United States in January 1991 by *Westwood-Squibb Pharmaceuticals (Bristol-Myers Squibb)* under the proprietary name of *Ultravate*[®] [25].

Experimental Part

Chemistry [26]

9 α -Chloro-11 β -hydroxy-16 β -methyl-3,20-dioxopregna-1,4-diene-17 α ,21-diyl Ethyl Ortho-propionate (2). TsOH · H₂O (250 mg, 1.3 mmol) was added to a stirred suspension of beclomethasone [20] (5.00 g, 12.2 mmol) in a mixture of THF (50 ml) and ethyl ortho-formate (6.25 ml,

Scheme

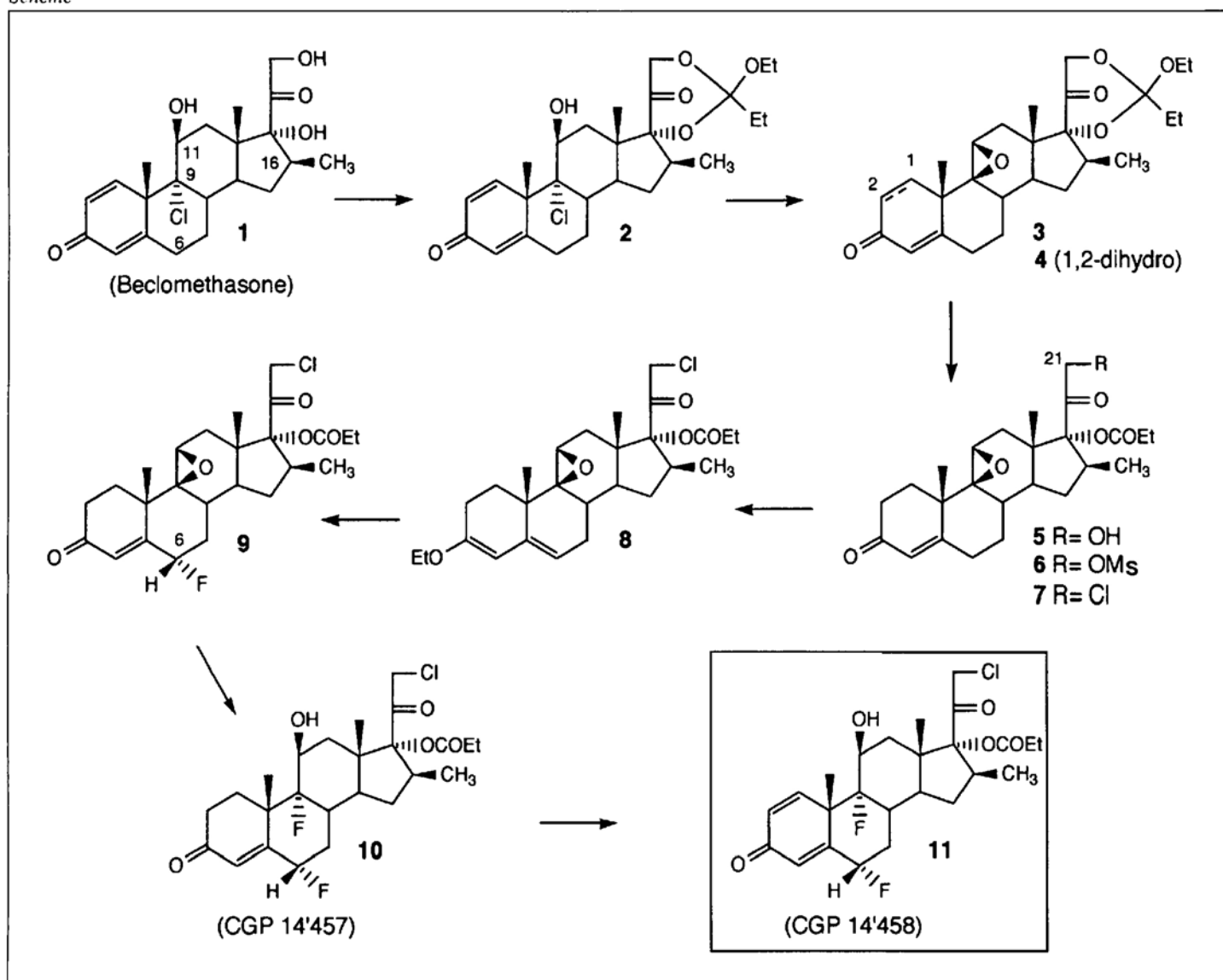
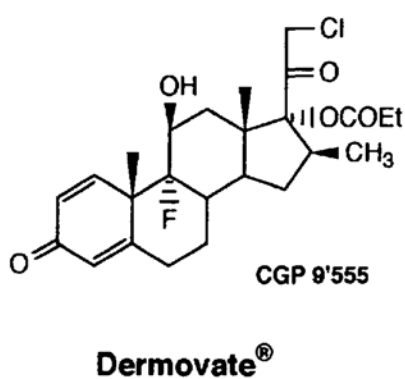
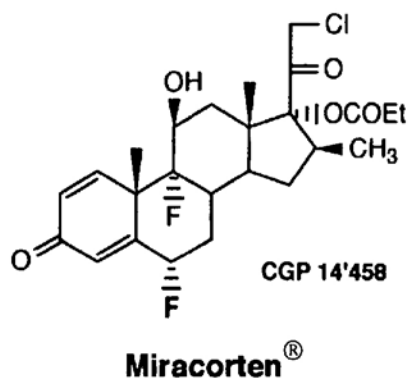


Table. Double-Blind Multicentre Clinical Trial [23]. 336 patients with severe chronic psoriasis.



31.5 mmol). The soln. was stirred at ambient temp. for 75 min. Then, pyridine (2.5 ml, 31 mmol) and AcOEt (500 ml) were added, and the soln. was washed thrice with saline, the aq. phases were extracted with AcOEt, the combined org. phases dried (Na₂SO₄) and evaporated: 6.30 g (theory: 6.00 g) of essentially pure 2, which was used in the next step without further purification. 300 mg of the above crude product were twice recrystallized (CH₂Cl₂/Et₂O/EtOH): 200 mg of pure 2. M.p. 162–164° (dec.). [α]_D = +104.3 (c = 0.372, CHCl₃). UV (EtOH): 239 (15'200). IR (CH₂Cl₂): 3615, 1725, 1670, 1630. ¹H-NMR (CDCl₃): 0.96 (s, 3 H); 1.00 (s, 3 H); 1.18 (3m, 7 H); 1.66 (s, 3 H); 2.05 (d, J = 3.17, 1 H); 3.50 (m, 2 H); 3.85, 4.04 (AB, J_{AB} = 16.7, 2 H); 4.56 (q, J = 3.7, 1 H); 6.09 (t, J = 1.9, 1 H). Anal. calc. for C₂₇H₃₇ClO₆ (493.04): C 65.78, H 7.57, Cl 7.19; found: C 65.52, H 7.48, Cl 7.18.

9β,11-Epoxy-16β-methyl-3,20-dioxopregna-1,4-diene-17α,21-diyl Ethyl Orthopropionate (3). To a stirred soln. of crude 2 (6.0 g; cf. Example 1) in CHCl₃ (6.0 ml) and MeOH (420 ml), 1.0N NaOH (180 ml) was added, and stirring continued at ambient temp. for 50 min. The mixture was diluted with CHCl₃ (600 ml) and H₂O (400 ml). The aq. phase was re-extracted twice with CHCl₃ (200 ml), and the combined org. solns. were dried (Na₂SO₄) and evaporated. The crude oily product

	CGP 14'458 0.02% ointment	CGP 14'458 0.05% ointment	CGP 9'555 0.05% ointment
Complete clearance or marked improvement	77%	90%	80%
Adverse local effects	2%	4%	6%

No clinically detectable systemic adverse effects observed.

was chromatographed (150 g alumina II/N, CH_2Cl_2). The first homogeneous fractions (4.7 g) yielded, after crystallization, 3.35 g of pure **3**. M.p. 166–168°. $[\alpha]_D^{25} = +35.6$ ($c = 0.590$, CHCl_3). UV (EtOH): 249 (15'750). IR (CH_2Cl_2): 1725, 1666, 1630 1610, 1061, 1035. $^1\text{H-NMR}$ (CDCl_3): 0.89 (s, 3 H); 0.93 (t, $J = 7.4$, 3 H); 1.16–1.17 (3m, $J = 7$, $J = 9.7$, 7 H); 1.45 (s, 3 H); 1.82 (q, $J = 7.4$, 2 H); 3.22 (m, 1 H); 3.45 (m, 2 H); 3.86, 4.0 (AB, $J_{AB} = 16.65$, 2 H); 6.17 (m, 1 H); 6.22 (A of AB, $d, d, J_{AB} = 10.2$, $J = 1.8$, 1 H); 6.61 (B of AB, $J_{AB} = 10.2$, 1 H). Anal. calc. for $\text{C}_{27}\text{H}_{36}\text{O}_6$ (456.58): C 71.03, H 7.95; found: C 70.96, H 7.95.

9 β ,11-Epoxy-16 β -methyl-3,20-dioxopregna-4-ene-17 α ,21-diyl Ethyl Orthopropionate (4). A soln. of **3** (3.20 g, 7.01 mmol) in dioxane (250 ml) was hydrogenated in the presence of $\text{RhCl}[(\text{Ph})_3\text{P}]_3$ (0.32 g, 0.21 mmol), until no more H_2 was absorbed (15 h). The soln. was evaporated *in vacuo*, the brownish crystalline residue dissolved in CH_2Cl_2 and filtered through alumina II/N (70 g). Crystallization of the crude fractions (3.5 g) from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{hexane}$ yielded pure **4** (2.26 g; additional amount of the substance was recovered by crystallization of the mother liquor). M.p. 181–184°. $[\alpha]_D^{25} = -10.0$ ($c = 0.810$, CHCl_3). UV (EtOH): 242 (14'440). IR (CH_2Cl_2): 1725, 1665, 1620, 1060, 1032. $^1\text{H-NMR}$ (CDCl_3): 0.88 (s, 3 H); 0.96 (t, $J = 7.4$, 3 H); 1.15 (m, 7 H); 1.43 (s, 3 H); 3.44 (m, 1 H); 3.48 (m, 2 H); 3.89, 4.02 (AB, $J_{AB} = 16.65$, 2 H); 5.8 (s, 1 H). Anal. calc. for $\text{C}_{27}\text{H}_{38}\text{O}_6$ (458.60): C 70.71, H 8.35; found: C 70.41, H 8.41.

9 β ,11-Epoxy-21-hydroxy-16 β -methyl-3,20-dioxopregna-4-ene-17 α -yl Propionate (5). A suspension of **4** (3.0 g, 6.55 mmol) in EtOH (150 ml) and 8.8 ml of a soln. of oxalic acid (2.0 g, 6.9 mmol) in H_2O (20 ml) were stirred at 40° for 40 min. The mixture was poured on ice-cold sat. NaHCO_3 (85 mmol) and stirred for additional 5 min. Workup (CHCl_3) yielded crude **5** which was used without purification in the next step. An anal. sample was recrystallized from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$. M.p. 159–161°. $[\alpha]_D^{25} = -4.2$ ($c = 0.311$, CHCl_3). UV (EtOH): 243 (14'180). IR (CH_2Cl_2): 3700, 1735, 1720, 1668, 1620, 1225, 1190, 1175. $^1\text{H-NMR}$ (CDCl_3): 0.85 (s, 3 H); 1.18 (t, $J = 7.9$, 3 H); 1.39 (d, $J = 6.9$, 3 H); 1.44 (s, 3 H); 3.13 (t, $J = 4.4$, 1 H); 3.48 (m, 1 H); 4.01, 4.09 (dAB, $J_{AB} = 17.7$, $J_{A,OH} = J_{B,OH} = 4.4$, 2 H); 5.81 (s, 1 H). Anal. calc. for $\text{C}_{25}\text{H}_{34}\text{O}_6 \cdot 0.25 \text{H}_2\text{O}$ (434.5): C 69.04, H 7.94; found: C 68.92, H 8.04.

9 β ,11-Epoxy-21-mesyloxy-16 β -methyl-3,20-dioxopregna-4-ene-17 α -yl Propionate (6). To a soln. of crude **5** (170 mg, 0.40 mmol) in pyridine (1.7 ml) and CH_2Cl_2 (0.85 ml) was added at 4° MsCl (0.054 ml, 0.70 mmol). The mixture was kept for 16 h at 4°, then diluted with CH_2Cl_2 and subsequently washed with ice-cold 2N HCl , sat. NaHCO_3 and H_2O . The amorphous crude product was crystallized, ($\text{CH}_2\text{Cl}_2/\text{acetone}/\text{Et}_2\text{O}$) to give pure **6** (90 mg). M.p. 118–121°. $[\alpha]_D^{25} = +9.3$ ($c = 0.431$, CHCl_3). UV (EtOH): 143 (14'320). IR (CH_2Cl_2): 1735 (ester + ketone), 1665, 1620, 1355, 1176, 1040. $^1\text{H-NMR}$ (CDCl_3): 0.90 (s, 3 H); 1.19 (t, $J = 7.4$, 3 H); 1.36 (d, $J = 6.9$, 3 H); 1.44 (s, 3 H); 3.20 (s, 3 H); 3.48 (br. s, 1 H); 4.66, 4.75 (AB, $J_{AB} = 16.5$, 2 H); 5.81 (s, 1 H). MS: 508 (M^+), 434 ([$M-\text{HOCOEt}$] $^+$), 419 ([434- CH_3] $^+$), 315 ([$M-\text{COC}_2\text{H}_4/\text{COCH}_2\text{OSO}_2\text{CH}_3$] $^+$), 297 ([315- H_2O] $^+$). Anal. calc. for $\text{C}_{26}\text{H}_{36}\text{O}_8\text{S}$ (508.63): C 61.40, H 7.13, S 6.30; found: C 61.72, H 7.21, S 6.28.

21-Chloro-9 β ,11-epoxy-16 β -methyl-3,20-dioxopregna-4-ene-17 α -yl Propionate (7). LiCl (41.7 g) and anh. DMF (280 ml) were added to a soln. of **6** (13.9 g) in acetone (200 ml) and heated in an autoclave for 16 h to 80°. The cooled mixture was poured on ice/ H_2O (1 l) and extracted twice with AcOEt . The org. phases were washed with saline, dried (Na_2SO_4), and evaporated *in vacuo*. The crude amorphous product (11.2 g) was chromatographed in toluene/ AcOEt (90:10) on a silica column (550 g) and crystallized from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$: essentially pure **7** (9.9 g). For anal. purpose a sample was recrystallized. M.p. 199–200°. $[\alpha]_D^{25} = +280$ ($c = 0.471$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3): 0.89 (s, 3 H); 1.19 (t, $J = 7.4$, 3 H); 1.37 (d, $J = 6.9$, 3 H); 1.44 (s, 3 H); 3.28 (m, 1 H); 3.94, 4.03 (AB, $J_{AB} = 15.3$, 2 H); 5.81 (s, 1 H). MS: 448/450 (M^+), 392 ([$M-\text{CH}_3\text{CH}=\text{C}=\text{O}$] $^+$), 374 ([$M-\text{EtCOOH}$] $^+$), 359 ([374- CH_3] $^+$), 315 ([392- ClCH_2CO] $^+$), 297 ([315- H_2O] $^+$). Anal. calc. for $\text{C}_{25}\text{H}_{33}\text{O}_5\text{Cl}$ (448.99): C 66.88, H 7.41, Cl 7.90; found: C 66.64 H, 7.34, Cl 8.08.

21-Chloro-9 β ,11-epoxy-3-ethoxy-16 β -methyl-20-oxopregna-3,5-dien-17 α -yl Propionate (8). A soln. (1.35 ml) of $\text{TsOH} \cdot \text{H}_2\text{O}$ (488 mg) in dioxane (5.4 ml) and EtOH (1.1 ml) was added to a soln. of **7** (1.5 g) anh. dioxane (8.0 ml) and methyl orthoformate (2.0 ml). The mixture was stirred for 100 min at ambient temp., poured to ice-cooled 0.5N NaOH (30 ml), and extracted with AcOEt .

The org. phase was washed with saline, dried (Na_2SO_4), and evaporated *in vacuo*. The essentially pure, but rather instable **8** was used in the fluorination step without further purification.

Fluorination of 8. The fluorination was performed in three batches as follows: through a soln. of crude **8** (corresponding to 4.81 g, 7.18 g, and 7.82 g of pure compound) in THF (225 ml, 338 ml, and 378 ml) and H_2O (45 ml, 68 ml, and 74 ml) was bubbled a stream of FCIO_3 (2–3 bubbles per s) for 20 min. The mixture was diluted with AcOEt , successively washed with a soln. of KI and $\text{Na}_2\text{S}_2\text{O}_3$, with saline, ice-cold 1N NaOH , saline, dried (Na_2SO_4), and evaporated *in vacuo* to give a crude amorphous mixture (4.69 g, 7.30 g, and 8.10 g, resp.). All three batches (total amount: 20.09 g) were chromatographed on silica (1 kg) (eluant: toluene/ AcOEt 95:5, 90:10, and 80:20). From the first series of fractions (145–165) and from twice rechromatographed mixed fractions (166–240), 15.6% (corresponding to 3.12 g) of pure **21-chloro-9 β ,11-epoxy-4-fluoro-16 β -methyl-3,20-dioxopregna-4-ene-17 α -yl propionate** were obtained by crystallization. M.p. 197–199°. $[\alpha]_D^{25} = +33$ ($c = 0.465$, CHCl_3). UV (EtOH): 250 (13'740). IR (CH_2Cl_2): 1737 (ester + ketone), 1692, 1646, 1190, 1175. $^1\text{H-NMR}$ (CDCl_3): 0.88 (s, 3 H); 1.19 (t, $J = 7.4$, 3 H); 1.37 (d, $J = 6.4$, 3 H); 1.50 (s, 3 H); 3.49 (br. s, 1 H); 3.95, 4.09 (AB, $J_{AB} = 14.8$, 2 H). MS: 466 (M^+), 410 ([$M-\text{COC}_2\text{H}_4$] $^+$), 392 ([410- H_2O] $^+$), 377 ([392- CH_3] $^+$). Anal. calc. for $\text{C}_{25}\text{H}_{32}\text{ClFO}_5$ (466.98): C 64.30, H 6.91, Cl 7.59; found: C 64.40, H 6.85, Cl 7.91.

Recrystallization of the pure middle fractions (241–380) and of the rechromatographed mother liquors gave 36% (corresponding to 7.2 g) of pure **21-chloro-9 β ,11-epoxy-6 α -fluoro-16 β -methyl-3,20-dioxopregna-4-ene-17 α -yl propionate (9)**. M.p. 178–181°. $[\alpha]_D^{25} = +62.4$ ($c = 0.367$, CHCl_3). UV (EtOH): 237 (13'400). IR (CH_2Cl_2): 1735 (ester + ketone), 1680, 1635, 1192, 1175, 1000. $^1\text{H-NMR}$ (CDCl_3): 0.88 (s, 3 H); 1.18 (t, $J = 7.4$,

3 H); 1.36 (d, $J = 6.5$, 3 H); 1.37 (s, 3 H); 2.42 (q, $J = 7.4$, 2 H); 3.54 (m, 1 H); 3.94, 4.02 (AB, $J_{AB} = 15.3$, 2 H); 5.34 (m, $J_{HH} = 9.25$, 4.62, 1.3, $J_{HF} = 49.5$, 1 H); 6.1 (m, 1 H). MS: 466 (M^+), 448 ([$M-\text{H}_2\text{O}$] $^+$), 466 ([$M-\text{HF}$] $^+$), 431 ([$M-\text{Cl}$] $^+$), 417 ([$M-\text{CH}_2\text{Cl}$] $^+$), 410 ([$M-\text{CH}_3\text{CH}=\text{C}=\text{O}$] $^+$), 392 ([$M-\text{C}_2\text{H}_5\text{COOH}$] $^+$), 389 ([$M-\text{COCH}_2\text{Cl}$] $^+$), 333 ([389- $\text{CH}_3\text{CH}=\text{C}=\text{O}$] $^+$). Anal. calc. for $\text{C}_{25}\text{H}_{32}\text{ClFO}_5$ (466.98): C 64.30, H 6.91, Cl 7.59; found: C 64.25, H 6.83, Cl 7.71.

Finally, the ultimate fractions (486–570) gave, after recrystallization, 1.15 g (5.75%) of non-fluorinated **7**, identical with the compound described in *Example 8*.

21-Chloro-6 α ,9 α -difluoro-1 β -hydroxy-16 β -methyl-3,20-dioxopregna-4-ene-17 α -yl Propionate (10). To a stirred (1.325:1 by weight) mixture of HF/urea (40 ml) at 4°, **9** (2.0 g) was added. The closed PET vessel was kept for 3 h at 4°. The soln. was poured under vigorous stirring into ice-cooled conc. NH_4OH (150 ml), the excess of base neutralized by careful addition of AcOH , and the mixture extracted twice with CHCl_3 . The org. phase was washed with ice-cooled 1N NaOH and H_2O , dried (Na_2SO_4), and evaporated *in vacuo*. The yellowish amorphous residue (2.0 g) was chromatographed on silica (100 g). With toluene/ AcOEt 90:10, 1.9 g of essentially pure **10** (= CGP 14'457) was obtained. M.p. of the recrystallized ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$) 193–194°. $[\alpha]_D^{25} = +115.7$ ($c = 0.172$, CHCl_3). UV (EtOH): 233 (15'820). IR (CH_2Cl_2): 3580, 1736, 1636, 1190, 1073, 1000. $^1\text{H-NMR}$ (CDCl_3): 0.97 (s, 3 H); 1.16 (t, $J = 7.4$, 3 H); 1.39 (d, $J = 6.5$, 3 H); 1.53 (s, 3 H); 2.45 (q, $J = 7.4$, 2 H); 3.95, 4.06 (AB, $J_{AB} = 15.3$, 2 H); 4.41 (m, 1 H); 5.34 (m, $J_{HH} = 9.25$, 4.62, 1.3, $J_{HF} = 49.5$, 1 H); 6.15 (m, 1 H). MS: 487 ([$M+\text{H}$] $^+$), 451 ([487- HCl] $^+$), 437 ([$M-\text{CH}_2\text{Cl}$] $^+$), 430 ([$M-\text{COC}_2\text{H}_5$] $^+$). Anal. calc. for $\text{C}_{25}\text{H}_{33}\text{ClF}_2\text{O}_5$ (486.98): C 61.66, H 6.83, Cl 7.28; found: C 61.55, H 7.01, Cl 7.09.

Dehydrogenation of 10. To a soln. of crude **10** (2.50 g) in dioxane (125 ml), DDQ was added. In a sealed vessel, the mixture was stirred for 24 h at 140° (bath temp.). The soln. was evaporated *in vacuo*, the residue dissolved in CH_2Cl_2 (30 ml, containing a few drops of EtOH), and filtered through a column of 75 g alumina (II/N). The combined fractions (1.8 g) were purified on 10 thick-layer plates (1 m) ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97:3) to yield **21-chloro-6 α ,9 α -difluoro-1 β -hydroxy-16 β -methyl-3,20-dioxopregna-1,4-dien-17 α -yl propionate (11)**. M.p. of the recrystallized sample melts at 220–221°. $[\alpha]_D^{25} = +103.9$ ($c = 0.874$, CHCl_3). UV (EtOH): 237 (16'720). IR (CH_2Cl_2): 3600, 1738, 1675, 1640, 1615, 1190, 1070, 1030, 1000. $^1\text{H-NMR}$ (CDCl_3): 1.00 (s, 3 H); 1.15 (t, $J = 7.4$, 3 H); 1.39 (d, $J = 7.4$, 3 H); 1.55 (s, 3 H); 2.4 (q, $J = 7.4$, 2 H); 3.95, 4.05 (AB, $J_{AB} = 14.8$, 2 H); 4.44 (m, 1 H); 5.41 (m, $J_{HH} = 11.7$, 6.94, 1.3, $J_{HF} = 49.5$, 1 H); 6.38 (dd, $J = 10.17$, 1.85, 1 H); 6.44 (m, 1 H); 7.16 (dd, $J = 10.17$, 1.4, 1 H). MS: 464 ([$M-\text{HF}$] $^+$), 435 ([$M-\text{CH}_2\text{Cl}$] $^+$), 428 ([$M-\text{CH}_3\text{CH}=\text{C}=\text{O}$] $^+$), 410 ([$M-\text{C}_2\text{H}_5\text{COOH}$] $^+$), 407 ([$M-\text{COCH}_2\text{Cl}$] $^+$), 390 ([410- HF] $^+$). Anal. calc. for $\text{C}_{25}\text{H}_{31}\text{ClF}_2\text{O}_5$ (484.97): C 61.92, H 6.44, Cl 7.31; found: C 61.91, H 6.49, Cl 7.59.

Pharmacology [27]

Dermatopharmacological Tests Used for Evaluation:

UVDH (= UV-induced dermatitis inhibition assay in guinea pigs) [28]: Experimental model of inflammation produced by unfiltered UV irradiation of the depilated flanks of guinea pigs. The overall degree of inflammation inhibition elicited by 3 concentrations of a substance at various inspection times allows to rank the tested compounds in order of their acute antiinflammatory effect.

DOZMIR = mean of all the individual values (dose/time) of the intensity of the inhibitory effect in % of maximum possible score.

CDH (= Croton oil - induced ear edema inhibitory assay in rabbits) [29]: Experimental model of dermatitis induced in the ear of the rabbit by the application of a soln. of croton oil. It reveals clearly differentiable inhibitory effects on the rise in skin temperature, the oedema and the increase in the tissue mass due to the inflammatory process.

APE = antiphlogothermal effect,

MPG = mean tissue phlogostatic activity.

HPLH (= Epidermal hyperplasia inhibition assay in guinea pigs) [30]: Allows the evaluation of the inhibitory effect of test compounds on hexadecane-induced hyperplasia of the guinea pig skin, which mimics the therapeutically useful suppressant effect on exaggerated proliferative processes in the epidermis.

DER = reduction of the superficial epitelium tissue,

MIR = reduction of the mitosis in the basal layer of the epithelium.

HVK (= Human skin vasoconstriction assay) [8][31]: Cutaneous vasoconstriction assay performed on healthy volunteers by application of 5 serial dilutions (10^{-3} to 10^{-7} w/w) of the test compounds dissolved in EtOH under occlusion to the volunteers' forearms under double-blind conditions. Visual skoring of the skin blanching is statistically evaluated after removal of the occlusive dressing.

DMWD = Average of the mean active dose - hydrocortisone (HC) - index value in % of the activity of 2000 x HC,

GDRG = overall average of the reactivity degrees in % of the theoretical maximum (measure for the intensity of the activity).

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- [16] The international nonproprietary name.
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- [18] Introduced on the U.S. market by *Westwood-Squibb Pharmaceuticals* (*Bristol-Meyers Squibb Co.*).
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