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Antiinflammatory Activity of 17-Esters of 6α,9α-Difluoro-21-deoxyprednisolone

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Several 17-monoesters of 6α,9α-difluoro-21-deoxyprednisolone were prepared and tested for their antiinflammatory activity. Propionate **11** and butyrate **12** displayed a high topical activity.

The availability of corticosteroid 17-monoesters, via 17,21-orthoesters,[2] allowed us to develop a general route to their 21-deoxy analogues by reductive elimination of the 21-hydroxyl group.[3] In spite of the lack of a function considered essential for the corticoid activity, some 21-deoxycorticosteroids have been reported to display topical antiinflammatory activity,[4] which is markedly increased by the presence of protective groups at C-16 and C-17 like acetonides[5] and esters at C-17.[6]

In a previous paper we described the high antiinflammatory activity of 17,21-alkyl orthoesters, 17-monoesters, and 17,21-diesters of 6α,9α-difluoroprednisolone.[7] Here we wish to report the synthesis and some biological properties of 17-esters of 6α,9α-difluoro-21-deoxyprednisolone.

The compounds were obtained from 6α,9α-difluoroprednisolone 17-monoesters according to the already published procedure[3] involving the preparation of the 21-tosylates and the subsequent reduction in situ through the corresponding 21-iodo derivatives.

Yields, melting points, specific optical rotations, and analytical data of the compounds are given in Table I.

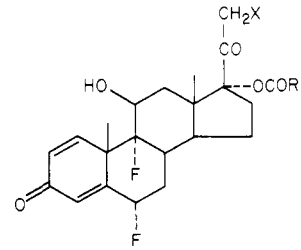
Biology and Evaluation. The 17-esters of 6α,9α-difluoro-21-deoxyprednisolone **10–13** have been assayed for their antiexudative activity by the granuloma pouch test according to Selye.[8] The compound was injected into the pouch of rats on day 5 or injected subcutaneously daily from day 2 to day 10. Autopsy was performed on day 11.

The compounds have been assayed also in the vasoconstriction test on volunteers according to the modification described by Falconi and Rossi.[9] In all cases reference compounds have also been tested. The results are shown in Tables II and III.

With the exception of acetate **10**, the 21-deoxy-17-esters displayed a high local antiexudative activity, greater than that of free deoxydifluoroprednisolone **14**[10] and of the corresponding 21-hydroxy esters investigated, propionate **2** and benzoate **4**. Evaluation of **13** vs. **4** in the same test after daily subcutaneous treatment revealed that the 21-deoxy derivative displayed a lower systemic antiexudative activity.

In the vasoconstriction test, compounds **10–12** proved

Table I



No.	R	X	Yield,[a] %	Mp, °C	$[\alpha]_D$, deg	Formula	Analyses
4	C_6H_5	OH	70	228–231	+14.2	$C_{28}H_{30}F_2O_6$	C, H
7	C_2H_5	OTs	89	205–207	+14	$C_{31}H_{36}F_2O_8S$	C, H, S
8	C_3H_7	OTs	98	125[b]	−12.2	$C_{32}H_{38}F_2O_8S$	C, H, S
9	C_6H_5	OTs	85	204–206	−21	$C_{35}H_{36}F_2O_8S$	C, H, S
10	CH_3	H	45[c]	258–260	+24	$C_{23}H_{28}F_2O_5$	C, H
11	C_2H_5	H	72	235–237	+20.5	$C_{24}H_{30}F_2O_5$	C, H
12	C_3H_7	H	68	219–221	−19.7	$C_{25}H_{32}F_2O_5$	H[d]
13	C_6H_5	H	54	282–284	−6.6	$C_{28}H_{30}F_2O_5$	C, H

[a] Yield is of analytically pure material. [b] With decomposition. [c] Overall yield. Intermediate 21-tosylate **6** was not isolated. [d] C: calcd, 66.65; found, 66.20.

Table II. Antiexudative Activity[a]

Compd	% inhibn of exudate formation	
	0.002 μmol	0.02 μmol
10[b]	18	13
11[b]	47	67
12[b]	60	81
13[b]	71	90
14[b]	<5	35
2[b]	<5	41
4[b]	46	70
13[c]	<5	35
4[c]	20	62

[a] Data obtained from three different assays, each dose group including ten rats. All compounds dissolved in sesame oil. [b] Single treatment into pouch with the doses indicated. [c] Subcutaneous treatment for 9 days with the daily doses indicated.

to be markedly more active than betamethasone 17-valerate. On the basis of already published data, they are more active than the corresponding 21-hydroxy derivatives but less active than many 6,9-difluoroprednisolone 17,21-diesters.[7]

Our results confirm that the 21-hydroxy group is not essential for the antiinflammatory activity, if substituents are present which are able to increase the energy of binding with the receptors and/or the metabolic stability. In particular, compounds **11** and **12** displayed a topical antiinflammatory activity comparable with that of the most active known compounds.

Experimental Section

Melting points were taken in a capillary apparatus and are uncorrected. Optical rotations were determined in dioxane at 24 °C ($c \sim 1$). UV were determined in 95% EtOH and IR in Nujol mull. Absorption bands of these spectra were as expected. TLC were done using 250-μ thin layers (Fluorosil G) and 8:2 C_6H_6–Me_2CO. All analytical samples appeared as single spots on TLC. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

6α,9α-Difluoroprednisolone 17-Monoesters (1–4). Acetate **1**, propionate **2**, and butyrate **3** were known from the previous work of Gardi et al.[7] The benzoate **4** was prepared by a modified procedure[11] utilizing 6α,9α-difluoroprednisolone 17,21-methyl orthobenzoate (**5**) as starting material: mp 204–206 °C; [α] +57°. Anal. ($C_{29}H_{32}F_2O_6$) C, H.

21-Tosylates (6–9). To a solution, cooled at 0 °C, of the proper 17-monoester (10 g) in 1:1 Py–CH_2Cl_2 (100 mL), TsCl (15 g) dissolved in 1:1 Py–CH_2Cl_2 (100 mL) was added. After keeping overnight at 0–5 °C, the mixture was poured into ice–water. Products were isolated as usual and recrystallized from CH_2Cl_2–Et_2O. Acetate **6**, which failed to crystallize, was not fully isolated and characterized.

21-Deoxy-17-esters (10–13). To a solution of the proper 21-tosylate (5 g) in Me_2CO (500 mL), NaI (25 g) was added. The reaction mixture was refluxed for 50 h, then treated with AcOH (30 mL), and further refluxed for 1 h. After addition of a 10% aqueous solution of $NaHSO_3$ (250 mL) and concentration under reduced pressure, the product was recovered by filtration and crystallized from Me_2CO–Et_2O.

Table III. Vasoconstrictive Activity in Man[a]

Compd	Rel potency
Betamethasone 17-valerate	1
10	1.5
11	2.5-3
12	2.5-3
13	≤1

[a] Each compound was tested on 24 subjects at three dose levels (0.02, 0.06, and 0.18 μg).

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