J. steroid Biochem. Vol. 27, No. 4–6, pp. 837–843, 1987
Printed in Great Britain.

0022-4731/87 $3.00 + 0.00

Proceedings of the VII International Congress on Hormonal Steroids (Madrid, Spain, 1986)

24. Chemistry of Steroid Antagonists

STRUCTURE–ACTIVITY RELATIONSHIPS OF A SERIES OF NOVEL TOPICAL CORTICOSTEROIDS*

THOMAS L. POPPER, MARGARET J. GENTLES, TED T. KUNG, JOSEPH BERKENKOPF, BARRY N. LUTSKY, ARTHUR S. WATNICK and ELLIOT L. SHAPIRO

Pharmaceutical Research Division, Schering-Plough Corporation, Bloomfield, NJ 07003, U.S.A.

Summary—The effect of various heteroaroyl groups in the 17-position of topical corticosteroids has been studied. The corticosteroids esterified at C_{17} were of 9α,11β-dichloro, 9α-chloro 11β-hydroxy and 9α-fluoro 11β-hydroxy series. Among the 17-acyl groups 2′-furoates were most extensively investigated, although 2′-thenoates, 3′-thenoates and 3′-furoates were also examined. Many of these esters exhibited enhanced topical anti-inflammatory potencies. The most potent compounds investigated were the 21-chloro 17(2′-furoates) either in the 9α,11β-dichloro, or in the 9α-chloro 11β-hydroxy series. These compounds were at least 6 times as potent as betamethasone 17-valerate. Among 16-substituents studied 16α-methyl compounds had the highest potency. Topical anti-inflammatory potencies were determined by using a 5-day modification of the croton oil ear assay in mice. The more potent compounds were also evaluated in the *P. ovale* induced chronic psoriaform lesion in the guinea-pig.

INTRODUCTION

Since the original demonstrations [1, 2] of the efficacy of cortisol and cortisol 21-acetate in the treatment of dermatological disorders, extensive research has been carried out towards more effective topical corticosteroid therapy [3]. The more potent analogs of cortisol, i.e. prednisolone, triamcinolone, dexamethasone and betamethasone, were synthesized for treatment of systemic disease, but were useful topically when formulated in appropriate vehicles. Further chemical modifications, as the 16,17-acetonides, 17- and/or 21-esters of antiinflammatory glucocorticosteroids as triamcinolone and betamethasone led to compounds very widely used in local steroid therapy. Most of the topical corticosteroids in current clinical use belong to these structural categories, although there are important examples of 17-deoxy 21-esters, and 17-oxygenated 21-chloro corticosteroids too.

In this communication we describe a novel series of corticosteroid 17-esters where the 17-acyl functionality is derived from heteroaromatic radicals. We found that esters of furan- and thiophenecarboxylic acids when introduced to the 17-position of a variety of corticosteroids possess very high topical anti-inflammatory potency. The first part of this paper will deal with their synthesis, whereas the structure–activity relationships which have been derived will be discussed in more detail in the second part.

EXPERIMENTAL

Synthesis of corticosteroid 17-heteroarylcarboxylates

In searching for a general process which allows rapid synthesis of a variety of 17-esters we used an esterification procedure recently published [4] for a specific application. Thus, with the use of the appropriate acid chloride and a nitrogen base, such as 4-dimethylaminopyridine (DMAP) for activation of the acylating agent, a large number of 17-heteroaromatic esters were prepared (Fig. 1):

The acylation reaction of the 17-hydroxy group was preferentially carried out (a) in the 9,11-dichloro series, (b) in the 9(11) series, and (c) in the 11-keto series, substrates having no additional hydroxyl function, in order to avoid unwanted esterification (Fig. 2).

Using the methodology described above we prepared a variety of diesters, with the 17-ester being a heteroarylcarbonyl, in the 9α,11β-dichloro (**II**), the 9α-chloro 11β-hydroxy (**V**) and the 9α-fluoro 11β-hydroxy (**VIII**) series.

Removal of the 21-ester with selective hydrolysis using $HClO_4$–MeOH, followed by conversion via the 21-mesylate to the 21-chloro 17-ester in the $\Delta^{9(11)}$-series (d) or in the 9α-fluoro 11β-hydroxy series (e) is shown in Fig. 3.

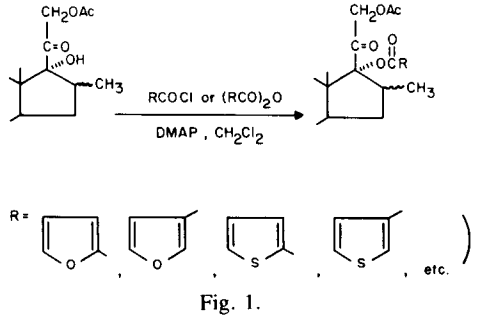
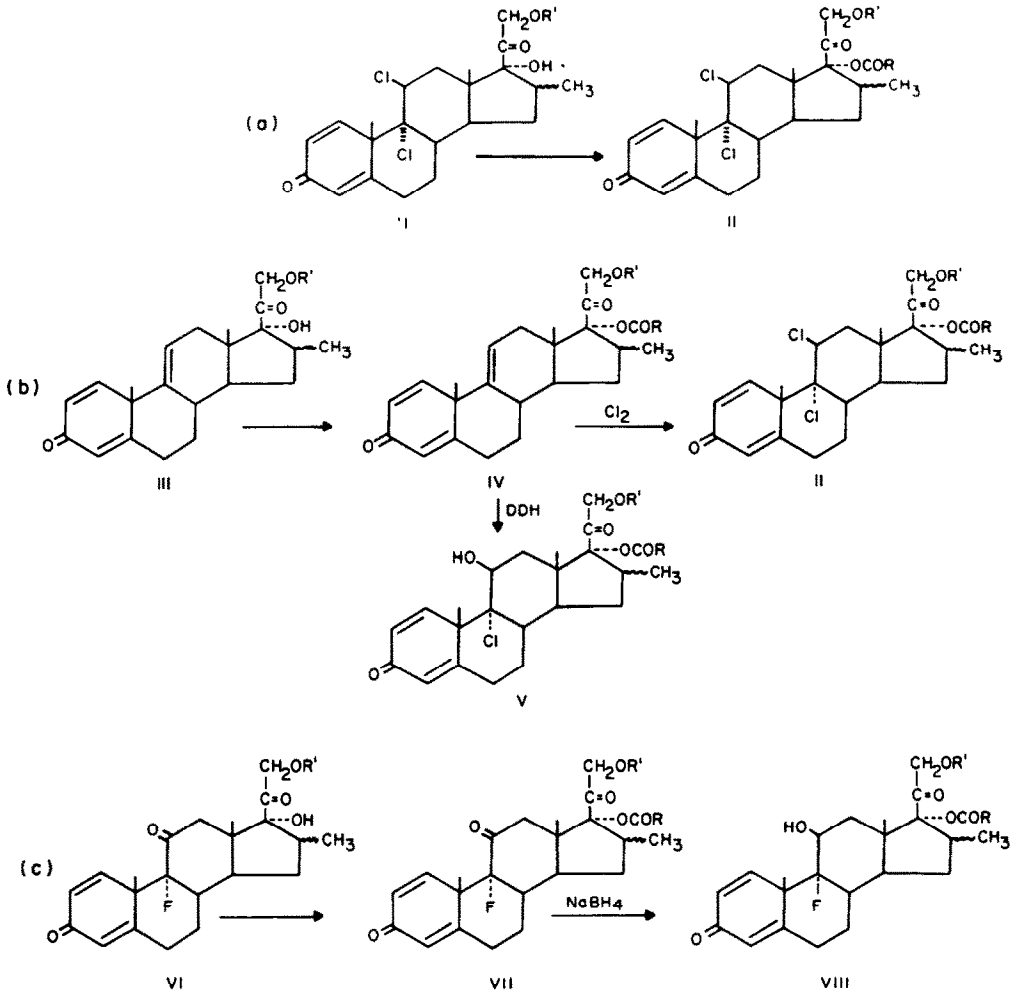


Fig. 1.

*This paper is dedicated to Professor George Büchi for the occasion of his 65th birthday.



(R'=CH_3CO, C_2H_5CO, C_3H_7CO, CH_3OCH_2CO; DDH = 1,3-dichloro-5,5-dimethylhydantoin).

Fig. 2.

RESULTS

Structure–activity relationships of the 17-heteroaryloxy corticosteroids

Croton-oil-induced ear inflammation in mice. Topical anti-inflammatory activity was determined in mice by a modification of the method of Tonelli *et al.*[5]. Compounds ranging in concentration from 10^{-4} to 10^{-6}% (w/v), were dissolved in a mixture of 0.6–0.7% croton oil in a vehicle containing 20% pyridine, 5% water and 74% diethyl ether (v/v). Ten-μl aliquots of each test solution were applied to the inner aspect of both pinnae of the test animals, daily, for 5 days. Five hours following the last treatment the animals were sacrificed and 6-mm punch biopsies of both ears were removed and weighed. Using the mean of left plus right ear punch weights, potencies were determined relative to betamethasone 17-valerate (compound 38). These values are shown in Table 1 for comparison purposes, relative potencies of betamethasone 17,21-dipropionate (compound 39) and hydrocortisone (compound 40) are also listed.

P. ovale*-induced chronic psoriaform lesions in guinea-pigs.* The histopathology of psoriasis is characterized by acanthosis, parakeratosis, abnormalities of cellular differentiations, and infiltration of leukocytes. Effects of corticosteroids on these parameters have been extensively studied in man. Recently, Rosenberg *et al.*[6] reported that topical application of killed *Pityrosporum ovale* (*Malassezia ovalis*) on rabbit skin produced a lesion resembling psoriasis. This supports the suggestion that *P. ovale*, a lipophilic yeast, is associated with several skin disorders in man, including psoriasis [7–10]. We selected the guinea-pig to study a *P. ovale*-induced psoriaform because of the analogous anatomical character and percutaneous absorption patterns between guinea-pig skin and human skin [11–13]. On repeated application of killed *P. ovale* suspensions we are able to induce classic psoriaform lesions in

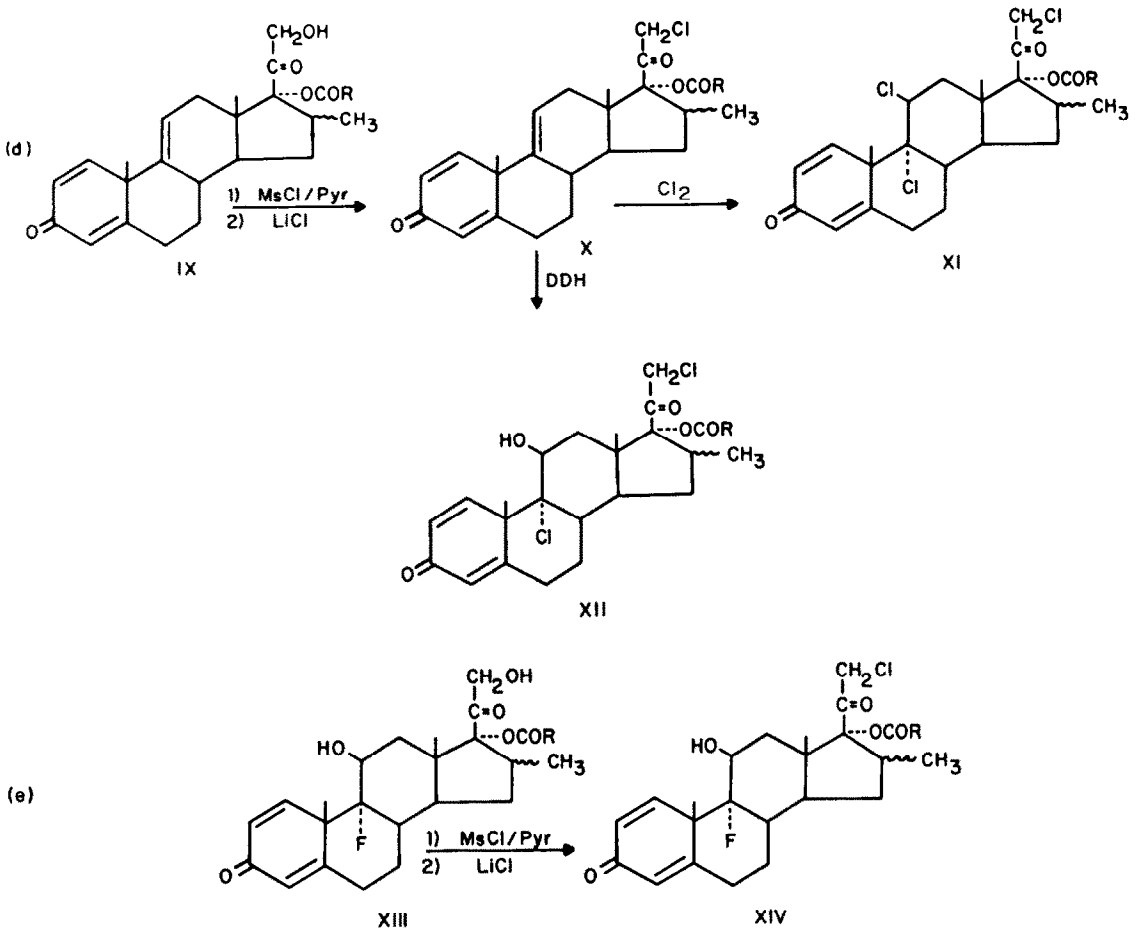


Fig. 3.

guinea-pigs, and these lesions responded to topical corticosteroid therapy.

Psoriaform lesions are induced by 10 repeated daily applications of heat-killed *P. ovale* suspension to the outer surface of the right ear of young male Hartley guinea-pigs. Starting on the eleventh day, a 0.12-ml aliquot of the test steroid in pyridine–water–ether (20:5:75) is applied on the lesioned ear daily for 14 days. Twenty-four hours after the last application of the drug the animals are sacrified, equal portions of the drug-treated and control ears are excised, fixed, and evaluated histologically for the severity of acanthosis. Potency of the test drugs is determined by comparing the reduction of mean acanthosis to that obtained by betamethasone 17-valerate (Table 2).

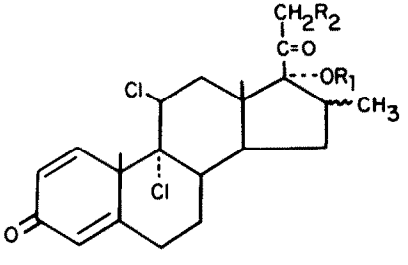
DISCUSSION

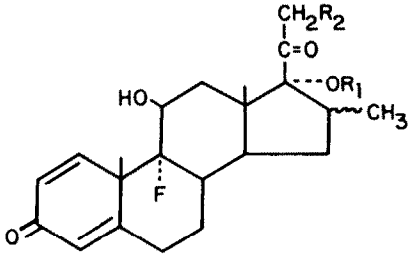
It is apparent from inspection of Table 1 that introduction of 17-heteroaryl carboxylates affects the topical anti-inflammatory potencies of various series differently.

In the 9,11-dichloro series, the potency of the 17,21-diesters with the exception of the 17(2'-thenoate) 21-acetate (compound 4) and 17(2'-furoate) 21-methoxyacetate (compound 7) did not significantly differ from the standard betamethasone valerate. Replacement of the 21-acyl function with chlorine, and in one case with fluorine, led to significant enhancement in topical anti-inflammatory potency. Thus, the 21-chloro 17(2'-furoate) (compound 8) was 8 times as potent as betamethasone valerate in the croton oil ear assay, and 6 times as potent in the guinea-pig *P. ovale* assay (Table 2). Other 21-halogeno 9,11-dichloro 17-heteroaroyl esters with significantly enhanced topical potency were the 21-chloro 17(2'-thenoate) (compound 10), the 21-fluoro 17(2'-furoate) (compound 11) and the 6α-fluoro compound (compound 14), all at least 3 times as potent as standard.

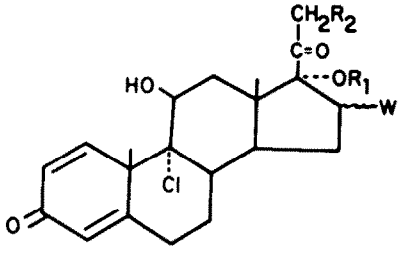
In the 9α-fluoro 11β-hydroxy series, the 17,21-diesters showed consistently higher potencies than the standard betamethasone valerate. This is unusual as dexamethasone 17,21-diesters, to which the above compounds belong, have been rarely reported to possess significant topical potencies, and no such compound has been clinically introduced [3]. The most potent compound in the series was the 17(2'-furoate) 21-propionate (compound 19) which was 6 times as potent as standard. Other compounds in the series with high potency were the 17(2'-furoate)

Table 1. Topical anti-inflammatory potencies of corticosteroid 17-heteroaroyl esters in the croton oil assay

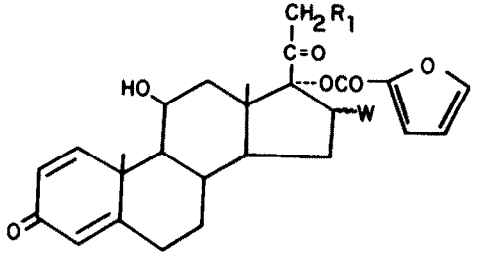




Compound no.	R_1	R_2	C_{16}-CH_3/W	Additional feature	Topical potency*
1	2′-Furoyl	$OCOCH_3$	α	—	1.2 (0.74–2.10)
2	3′-Furoyl	$OCOCH_3$	α	—	1.4 (1.25–1.61)
3	2′-Thenoyl	$OCOCH_3$	α	—	0.8 (0.23–1.34)
4	3′-Thenoyl	$OCOCH_3$	α	—	3.2 (2.10–4.27)
5	2′-Furoyl	$OCOCH_3$	β	—	1.7 (0.81–2.85)
6	2′-Furoyl	OH	α	—	0.9†
7	2′-Furoyl	$OCOCH_2OCH_3$	α	—	3.0 (0.34–4.81)
8	2′-Furoyl	Cl	α	—	8.2 (4.41–13.1)
9	3′-Furoyl	Cl	α	—	1.7 (1.8–2.68)
10	2′-Thenoyl	Cl	α	—	3.3 (2.55–4.35)
11	2′-Furoyl	F	α	—	4.0 (2.55–5.35)
12	2′-Furoyl	Cl	β	—	0.8†
13	2′-Furoyl	$OCOCH_3$	α	6α-F	1.8 (1.46–2.04)
14	2′-Furoyl	Cl	α	6α-F	3.0 (1.23–4.87)
15	2′-Furoyl	$OCOCH_3$	α	—	2.2 (1.53–2.90)
16	3′-Furoyl	$OCOCH_3$	α	—	3.2 (1.45–4.64)
17	2′-Thenoyl	$OCOCH_3$	α	—	2.9 (2.23–3.84)
18	2′-Furoyl	$OCOCH_3$	β	—	0.2 (0.19–0.28)
19	2′-Furoyl	$OCOC_2H_5$	α	—	6.8 (4.24–9.19)
20	2′-Furoyl	$OCOCH_2OCH_3$	α	—	3.2 (2.53–3.55)
21	2′-Furoyl	Cl	α	—	2.3 (1.26–3.77)
22	3′-Furoyl	Cl	α	—	1.2 (0.83–1.54)
23	2′-Thenoyl	Cl	α	—	2.6 (1.46–3.82)
24	2′-Furoyl	Cl	β	—	0.9†
25	3′-Furoyl	Cl	α	11-one	1.7†
26	2′-Furoyl	$OCOCH_3$	$=CH_2$	—	1.1 (0.41–1.92)



27	2′-Furoyl	$OCOCH_3$	α	—	4.4 (1.28–7.82)
28	2′-Furoyl	$OCOCH_2OCH_3$	α	—	4.3 (0.88–7.90)
29	2′-Furoyl	Cl	α	—	6.1 (2.50–11.55)
30	2′-Thenoyl	Cl	α	—	4.5 (3.40–5.52)
31	2′-Furoyl	F	α	—	4.4 (2.36–7.67)
32	2′-Furoyl	Cl	α	6α-F	5.1 (4.50–5.70)
33	2′-Furoyl	$OCOCH_3$	$=CH_2$	—	2.2 (2.01–2.48)



34	$OCOCH_3$	—	α	6α-F	2.1 (1.0–3.07)
35	$OCOCH_3$	—	$=CH_2$	—	1.2 (0.58–2.20)
36	$OCOC_2H_5$	—	α	—	1.5 (0.94–2.06)
37	$OCOCH_3$	—	H	—	0.9 (0.64–1.11)

Betamethasone 17-valerate	38	1.0 (standard)
Betamethasone 17,21-dipropionate	39	1.4 (0.68–2.20)
Hydrocortisone	40	0.01 (0.01–0.011)

*Statistically derived estimated cumulative potencies relative to betamethasone 17-valerate (1.0). Numbers in parentheses are estimated 95% level confidence intervals of pooled estimates.

†Single assay.

Table 2. Topical potencies of corticosteroid 17-heteroaroyl esters in the P. ovale guinea-pig ear assay

Compound No.	Topical potency*
1	5.24 (3.20–9.57)
8	6.06 (5.59–6.53)
10	0.68 (0.36–1.23)
15	2.28 (1.67–2.89)
21	3.00 (0.47–8.40)
27	3.92 (2.38–7.08)
29	3.82 (1.99–10.36)
37	—†
38 (betamethasone 17-valerate)	1.00 (standard)
39 (bethamethasone 17,21-dipropionate)	1.87 (1.09–3.85)
40 (hydrocortisone)	0.036 (0.01–0.08)

*Statistically derived potency relative to betamethasone 17-valerate (1.0). Numbers in parentheses are estimated 95% level confidence intervals of pooled estimate.
†Inhibition (62%) at 0.05% (100 μl/day).

21-methoxyacetate (compound 20), 17(3'-furoate) 21-acetate (compound 16) and 17(2'-thenoate) 21-acetate (compound 17), all 3 times as potent as betamethasone valerate. Two compounds in this series (compounds 15 and 21) were tested in the guinea pig *P. ovale* model (Table 2) showing comparable potency to that measured in the croton oil ear assay. The 21-chloro 17-esters (compounds 21 and 23) were twice as potent as standard. Thus in the 9α-fluoro 11β-hydroxy series introduction of a 21-halogen has not shown the strong potency-enhancing effect observed in the 9α,11β-dichloro series and in the 9α-chloro 11β-hydroxy series.

In the 9α-chloro 11β-hydroxy series both the 21-halogeno 17-esters and a few representative 17,21-diesters showed high topical anti-inflammatory potencies. Thus, the 21-chloro 17(2'-furoate) (compound 29) was 6 times as potent as betamethasone valerate. In the guinea-pig *P. ovale* assay (Table 2), (compound 29) was approximately 4 times as potent as standard. The 21-chloro 17(2'-thenoate) (compound 30), the 21-fluoro 17(2'-furoate) (compound 31) and the 6α-fluoro analog (compound 32) were all at least 4 times as potent as standard. Two diesters in this series (compounds 27 and 28) also showed the same high topical potency noted for the 21-halogeno 17-esters. The high potency of compound 27 was also confirmed in the guinea-pig *P. ovale* model (Table 2). Overall, the 9α-chloro 11β-hydroxy series provided the most consistently potent topical anti-inflammatory agents.

Among the 17-acyl functions the 2'-furoates were examined most extensively. Representative 3'-furoates, 2'-thenoates, and 3'-thenoates were prepared in most active series, and did not show significant differences from the 2'-furoates. In the course of this work a few nitrogen-containing heteroaromatic esters as well as substituted furoates and thenoates were also prepared, but showed lower potencies. It is worthwhile to note that the 17(2'-furoate) 21-methoxyacetates (compounds 7, 20 and 28) consistently showed high topical anti-inflammatory potencies compared with other 17,21-diesters.

The influence of the 16-substituent is quite consistent throughout the 3 series, with 16α-methyl substitution being the most favorable. Although only a few 16β-methyl 17-heteroaryl carboxylates were prepared, their topical anti-inflammatory potency was usually lower than the corresponding 16α-methyl epimers, i.e. compound 12 vs 8, compound 24 vs 21, compound 18 vs 15, the only exception being compound 5, somewhat more potent than the 16α-methyl (compound 1). However, compound 1 has shown unusually high potency in the guinea-pig *P. ovale* model (Table 2), an assay where compound 5 was not tested. A few representative 16-methylene 17-heteroaryl carboxylates were synthesized, and, at least in two cases, compound 26 vs 15 and compound 33 vs 27, their topical potencies were significantly lower than those of the corresponding 16α-methyl analogs.

The effect of the 6α-fluoro group, normally a potency-enhancing substituent, was somewhat inconsistent. In the 9,11-dichloro series, compound 14, the 6α-fluoro derivative of compound 8, reduced the very high potency by a factor of two, while compound 13 was more potent than the 6-unfluorinated compound, 1. In the 9,21-dichloro series both compound 29 and its 6-fluorinated derivative, compound 32 showed very high topical anti-inflammatory potencies.

In summary, introduction of heteroaroyl esters, partiuclarly the 2'-furoate function into the 17-position of 9α,11β-dichloro-, 9α-chloro 11β-hydroxy, and 9α-fluoro 11β-hydroxy corticosteroids, resulted in significant enhancement of topical anti-inflammatory potency. The 9,21-dichloro 17(2'-furoate) (compound 29) has been evaluated in the clinic and was found to be a highly efficaceous, long-acting topical anti-inflammatory agent.

Acknowledgements—We thank Dr Edwin Peets for helpful discussions and Mrs Trudi Pier for the expert typing of the manuscript.

REFERENCES

1. Sulzberger M. B. and Witten H.: The effect of topically applied compound F in selected dermatoses. *J. invest. Dermat.* **19** (1952) 101–102.
2. Sulzberger M. B., Witten V. H. and Smith C. C.: Hydrocortisone (compound F) acetate ointment in dermatological therapy. *J. Am. med. Ass.* **151** (1953) 468–472.
3. Popper T. L. and Watnick A. S.: In *Anti-Inflammatory Agents* (Edited by R. A. Scherrer and M. W. Whitehouse). Academic Press, New York, Vol. 1 (1974) pp. 245–294.
4. Kerb U., Stahnke M. and Wiechert R.: 17α-(3-Iodobenzyloxy)-9α-chloro-4-pregnen-3,20-diones. Ger-

man Patent 2,748,442, May 3, 1979. *C. A.* **93** (1980) 168494h.
5. Tonelli G., Thibault L. and Ringler I.: A bio-assay for the concomitant assessment of the antiphlogistic and thymolytic activities of topically applied corticoids. *Endocrinology* **77** (1965) 625–634.
6. Rosenberg E. W., Belew P. W. and Bale G.: Effect of topical applications of heavy suspensions of killed *Malassezia ovalis* on rabbit skin. *Mycopathologia* **72** (1980) 147–154.
7. Kikuchi I., Ogata K. and Inone S.: Pityrosporum infections in an infant with lesion resembling erythema annulare centrifugum. *Archs Dermat.* **120** (1984) 380–382.
8. Lober C. W., Belew P. W., Rosenberg E. W. and Bale G.: Patch tests with killed sonicated microflora in patients with psoriasis. *Archs Dermat.* **118** (1982) 322–325.
9. Wilborn W. H. and Montes L. F.: Scanning electron microscopy of yeasts in seborrheic keratoses. *J. cutan. Path.* **7** (1980) 1–7.
10. Rosenberg E. W. and Belew P. W.: Improvement of psoriasis of the scalp with ketoconazole. *Archs. Dermat.* **118** (1982) 370–371.
11. Altmeyer P. and Spregart C.: Animal experiments: investigation on the action of topical corticoids on the guinea pig skin. *Archs dermat. Res.* **266** (1979) 219–225.
12. Anderson K. E., Maibach H. I. and Ango M. D.: The guinea pig: an animal model for human skin absorption of hydrocortisone, testosterone and benzoic acid? *Br. J. Dermat.* **102** (1980) 447–453.
13. Wester R. C. and Noonan P. K.: Relevance of animal models for percutaneous absorption. *Int. J. Pharmaceut.* **7** (1980) 99–110.