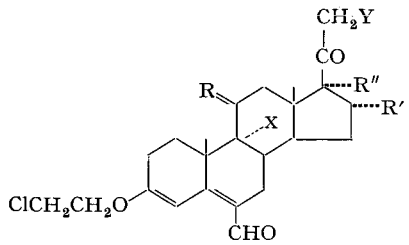
Synthesis of 3-(2'-Chloroethoxy)-6-Formyl-$\Delta^{3,5}$-Pregnadienes. A New Class of Highly Active Anti-Inflammatory Corticosteroids

In the course of an extensive investigation started some years ago in our laboratories on the action of the Vilsmeier-Haack-type reagent on ketosteroids and derivatives[1], we have examined the transformations performed by this reagent on cycloethyleneketals derived from Δ^4-3-ketosteroids. Some of the compounds obtained showed interesting biological activities.

The 3-cycloethyleneketal[2] (II) of 9α-fluoro-cortisone-21-acetate[3] (I) was dissolved in trichloroethylene and treated for 3 h at 70 °C with the reagent prepared from dimethylformamide and phosphorus oxychloride (DMF-$POCl_3$); after decomposition of the resulting complex with aqueous CH_3COONa and usual work-up, we isolated 3-(2'-chloroethoxy)-6-formyl-9α-fluoro-$\Delta^{3,5}$-pregnadien-17α,21-diol-11,20-dione-21-acetate[4] (III, m.p. 250–252°; λ_{max} = 216,320 nm (ε = 10,600, 15,200); $[\alpha]_D$ + 5.5°). By hydrolysis with aqueous H_2SO_4 in acetone at room temperature, III gave 6-hydroxymethylen-9α-fluoro-Δ^4-pregnen-17α,21-diol-3,11,20-trione-21-acetate (m.p. 227–235°; λ_{max} = 246 nm (ε = 11,200; λ_{max}^{NaOH} 254 nm); $[\alpha]_D$ + 69°). The λ_{max} value together with the absence of the $FeCl_3$-reaction excludes[5] the presence of the formyl group at C-2; moreover the presence in the IR-spectrum of a CH=C stretching band at 3050 cm^{-1} and the absence of bands in the 1600 cm^{-1} region due to a chelated β-dicarbonyl group[6] rules out the position 4 for the formyl group which thus must be at C-6.

III was also prepared by treating the 3-(2'-chloroethyl)-enolether derived from I[7] (obtained[8] by the action of 2-chloroethyl-orthoformate[9] on I) with the DMF-$POCl_3$ reagent[10].

By mild alkaline hydrolysis of III, the corresponding 21-OH derivative (IV, m.p. 220–223°; λ_{max} = 216, 320 nm (ε = 9500, 15,800); $[\alpha]_D$ − 35°) was obtained; esterification of IV with pentanoic acid anhydride gave the amorphous 21-pentanoate V (m.p. 85–95°; λ_{max} = 216, 317 nm (ε = 11,000, 10,200); $[\alpha]_D$ + 22°). The 21-desoxo derivative VII (m.p. 223–226°; λ_{max} 216, 320 nm (ε = 10,500, 15,200); $[\alpha]_D$ − 60°) of IV was prepared via the 21-mesylate VI (m.p. 200–205°) and treatment of VI with NaI-CH_3COOH[11].



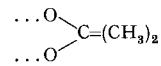
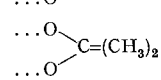
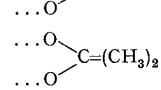
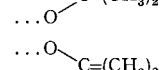
Compound	X	Y	R	R'	R''
III	F	$OCOCH_3$	O	H	OH
IV	F	OH	O	H	OH
V	F	$OCO(CH_2)_3CH_3$	O	H	OH
VI	F	OSO_2CH_3	O	H	OH
VII	F	H	O	H	OH
VIII	Cl	$OCOCH_3$	αH,βOH	H	OH
IX	F	$OCOCH_3$	αH,βOH	H	OH
X	F	OH	αH,βOH	H	OH
XI	F	$OCOCH_3$	αH,βOH	CH_3	OH
XII	Cl	$OCOCH_3$	αH,βOH	CH_3	OH
XIII	F	$OCOCH_3$	αH,βOH		
XIV	F	$OCO(CH_2)_3CH_3$	αH,βOH		
XV	F	H	αH,βOH		
XVI	F	$OCOCH_3$	O		

Table I

Compound	ED_{50} mg granuloma pouch[21]	
	Local	Os
III	0.006	0.08
IV	0.017	0.046
V	~ 0.051	> 0.300
VII	0.073	0.100
VIII	0.01	0.2
IX	0.066	0.04
X	0.20	–
XI	0.005	0.053
XII	0.017	0.300
XIII	0.001	0.105
XIV	0.005	0.30
XV	0.012	> 0.100
XVI	0.052	0.16

[1] R. SCIAKY and U. PALLINI, Tetrahedron Letters *1964*, 1839; R. SCIAKY and F. MANCINI, Tetrahedron Letters *1965*, 137.

[2] W. S. ALLEN, H. M. KISSMAN, S. MAURER, I. RINGLER, and M. J. WEISS, J. mednl pharm. Chem. *5*, 133 (1962); the ethyleneketals here described were prepared by the method B reported by A. MARQUET, M. DVOLAITZKY, H. B. KAGAN, L. MAMLOK, C. OUANNES, and J. JACQUES, Bull. Soc. chim. Fr. *1961*, 1822.

[3] J. FRIED and E. F. SABO, J. Am. chem. Soc. *79*, 1130 (1957).

[4] Satisfactory analytical values have been obtained for all the compounds described; m.p. are taken on a Fisher-Johns block and are uncorrected; rotations are determined at 20–22° in $CHCl_3$ unless otherwise noted and at the sodium D line; UV-spectra are in 95% ethanol.

[5] R. O. CLINTON, A. J. MANSON, F. W. STONNER, H. C. NEUMANN, R. G. CHRISTIANSEN, R. L. CLARKE, J. H. ACKERMAN, D. F. PAGE, J. W. DEAN, W. B. DICKINSON, and C. CARABATEAS, J. Am. chem. Soc. *83*, 1478 (1961).

[6] L. J. BELLAMY, *The Infrared Spectra of Complex Molecules* (J. Wiley and Sons Inc., New York 1958), p. 142.

[7] We have found it to be convenient to use the crude enol ethers for the reaction with the DMF-$POCl_3$ reagent.

[8] P. L. JULIAN, E. W. MEYER, W. J. KARPEL, and W. COLE, J. Am. chem. Soc. *73*, 1982 (1951).

[9] J. HEBKY, Colln Czech. chem. Commun. *13*, 442 (1948).

[10] D. BURN, B. ELLIS, P. FEATHER, D. N. KIRK, and V. PETROW, Chem. Ind. *1962*, 1907; Tetrahedron *20*, 797 (1964).

[11] H. REIMANN, R. S. SMITH, and E. P. OLIVETO, J. org. Chem. *26*, 866 (1961).

Table II

	Relative Potency					
	Granuloma pouch			Cotton pellets	Hepatic glycogen[24]	Inhibition[25,26] of total plasmatic corticosterone (FOH = 1)
	local	os	s.c.[21]	local[23]		
F-acetate	1	1	1	1	1	[a]
Fluocinolone acetonide	14	3750	786	2.3	4000	220
Fluorometholone	34	1250	250	9.6	500	83
XIII	680	36	23	6.5	130	29

[a] Not determinable because the compound is fluorescent by itself.

In the same manner starting from the corresponding Δ^4-3-keto-compounds, the following 3-(2′-chloroethoxy)-$\Delta^{3,5}$-6-formyl-steroids[12] were prepared by either of the 2 methods described above: 3-(2′-chloroethoxy)-6-formyl-9α-chloro-$\Delta^{3,5}$-pregnadien-11β,17α,21-triol-20-one-21-acetate[13] (VIII, m.p. 220–221°; λ_{max} = 216, 318 nm [ε = 13,500, 15,000]; $[\alpha]_D$ + 38°); its 9α-fluoro-analogue[13] (IX, m.p. 238–240°; λ_{max} = 216, 324 nm (ε = 10,500, 13,900); $[\alpha]_D$ + 21°) which by alkaline hydrolysis gave the corresponding 21-OH derivate (X, m.p. 225–227°; λ_{max} = 216, 324 nm [ε = 12,840, 18,200]; $[\alpha]_D$ + 10° in dioxane); 3-(2′-chloroethoxy)-6-formyl-9α-fluoro-16α-methyl-$\Delta^{3,5}$-pregnadien-11β,17α,21-triol-20-one-21-acetate[14] (XI, m.p. 228–230°; λ_{max} = 216, 324 nm [ε = 12,200, 15,900]; $[\alpha]_D$ + 2.5°); its 9α-chloroanalogue[14] (XII, m.p. 198–203°; λ_{max} = 217, 325 nm [ε = 12,600, 15,500]; $[\alpha]_D$ + 29°); 3-(2′-chloroethoxy)-6-formyl-9α-fluoro-$\Delta^{3,5}$-pregnadien-11β,16α,17α,21-tetrol-20-one-16α,17α-acetonide-21-acetate[15] (XIII, m.p. 180–182°; λ_{max} = 216, 324 nm [ε = 12,100, 17,100]; $[\alpha]_D$ + 26°) and the corresponding 21-pentanoate[16] (XIV, m.p. 103–105°; λ_{max} = 216, 323 nm [ε = 10,200, 11,700]; $[\alpha]_D$ + 32°); 3-(2′-chloroethoxy)-6-formyl-9α-fluoro-$\Delta^{3,5}$-pregnadien-11β,16α,17α-triol-20-one-16α,17α-acetonide[18] (XV, m.p. 233–235°; λ_{max} = 216, 323 nm [ε = 10,500, 16,100]; $[\alpha]_D$ + 10°); 3-(2′-chloroethoxy)-6-formyl-9α-fluoro-$\Delta^{3,5}$-pregnadien-16α,17α,21-triol-11,20-dione-16α,17α-acetonide-21-acetate[19] (XVI, m.p. 113–115°; λ_{max} = 215, 323 nm [ε = 11,400, 14,800]; $[\alpha]_D$ + 19°).

The biological data of some of the compounds described are shown in Table I.

From the compounds listed above, XIII has been chosen for a more extensive study; the biological data are summarized in Table II and contrasted with some other corticosteroids.

The inhibitory influence of XIII upon the total plasmatic corticosterone is of a low order when its extremely high local activity is considered; XIII has no sodium-retaining effect and its influence on the glyconeogenesis is negligible. The unique potency of XIII is represented by the extraordinary dissociation of its local and systemic anti-inflammatory activity.

Riassunto. È stata studiata l'azione del reattivo di Vilsmeier-Haack su 3-cicloetilendiossi-Δ^5-steroidi appartenenti ai corticoidi; è stata così ottenuta una serie di 3-(2′-cloroetossi)-6-formil-$\Delta^{3,5}$-pregnadieni, alcuni dei quali hanno mostrato notevoli proprietà antiinfiammatorie con una netta dissociazione dell'attività per somministrazione locale e somministrazione sistemica.

G. Baldratti, B. Camerino, A. Consonni, F. Facciano, F. Mancini, U. Pallini, B. Patelli, R. Sciaky, G. K. Suchowsky, and F. Tani

Istituto Ricerche, S.A. Farmaceutici Italia, Milano (Italy), April 14, 1966.

[12] All the 3-(2′-chloroethoxy)-6-formyl-$\Delta^{3,5}$-steroids showed in the IR, bands at 1640–1652 cm^{-1} (medium) and at 1600–1610 cm^{-1} (strong); these bands have also been noted by Burn et al.[10].

[13] For the starting Δ^4-3-ketones see ref. [3]; the Δ^5-3-ethylene-ketal corresponding to IX had m.p. 220–222°; $[\alpha]_D$ + 126° (dioxane).

[14] For the starting Δ^4-3-ketones see G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, J. Am. chem. Soc. *80*, 3161 (1958).

[15] For the starting Δ^4-3-ketone see C. E. Holmund, L. I. Feldman, N. E. Rigler, B. E. Nielsen, and R. H. Evans, J. Am. chem. Soc. *83*, 2586 (1961); the corresponding Δ^5-3-ethyleneketal was obtained as hemihydrate and had m.p. 145–147°; $[\alpha]_D$ + 102°.

[16] The starting Δ^4-3-ketone was prepared by esterification with pentanoic acid anhydride of 9α-fluoro-Δ^4-pregnen-11β,16α,17α,21-tetrol-3,20-dione-16α,17α-acetonide[17] and had m.p. 138–140°.

[17] J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, J. Am. chem. Soc. *80*, 2338 (1958).

[18] For the starting Δ^4-3-ketone see S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, J. Am. chem. Soc. *81*, 4956 (1959).

[19] The starting Δ^4-3-ketone was prepared by oxidation with the Sarett reagent[20] of 9α-fluoro-Δ^4-pregnen-11β,16α,17α,21-tetrol-3,20 dione-16α,17α-acetonide-21-acetate[15] and had m.p. 218–220°.

[20] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, J. Am. chem. Soc. *75*, 422 (1953).

[21] The method of Robert and Nezamis[22] has been slightly modified in our laboratories. The steroids are administered in a single intradermal injection suspended in 0.2 ml (0.5 carboxymethyl cellulose, 0.4 Tween 80, 0.9 benzyl alcohol, 0.9 NaCl) or once daily by gavage orally throughout 5 consecutive days. The animals are sacrified 1 day after the last administration.

[22] A. E. Robert and J. E. Nezamis, Acta endocr. *25*, 105 (1957).

[23] L. G. Hershberger and D. W. Calhoun, Endocrinology *60*, 153 (1957).

[24] R. O. Stafford, L. E. Barnes, B. J. Bowman, and M. M. Meinzinger, Proc. Soc. exp. Biol. *89*, 371 (1955).

[25] F. Moncloa, F. G. Peron, and R. I. Dorfman, Endocrinology *65*, 717 (1959).

[26] H. Braunsberg and V. H. T. James, Analyt. Biochem. *1*, 452 (1960).