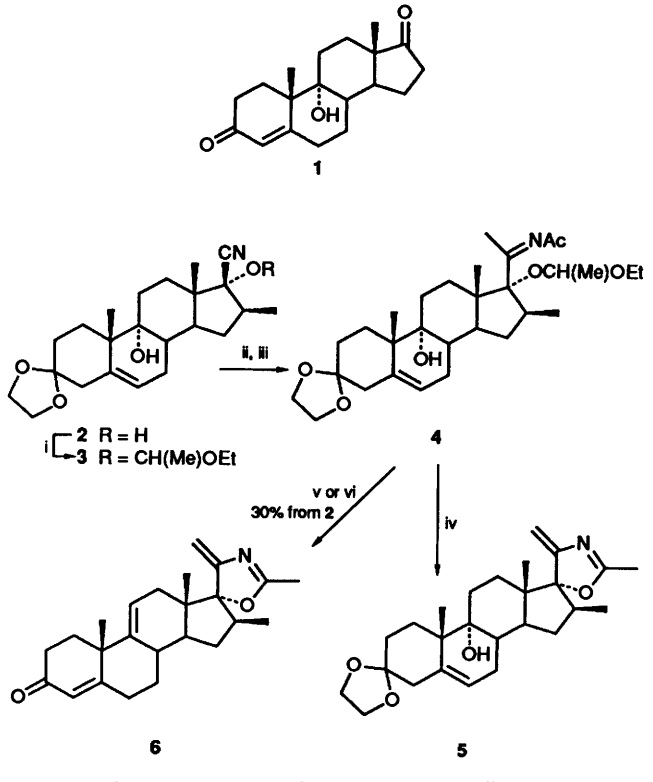
A Corticoid Synthesis from 9α-Hydroxyandrost-4-ene-3,17-dione *via* a Steroidal Oxazoline

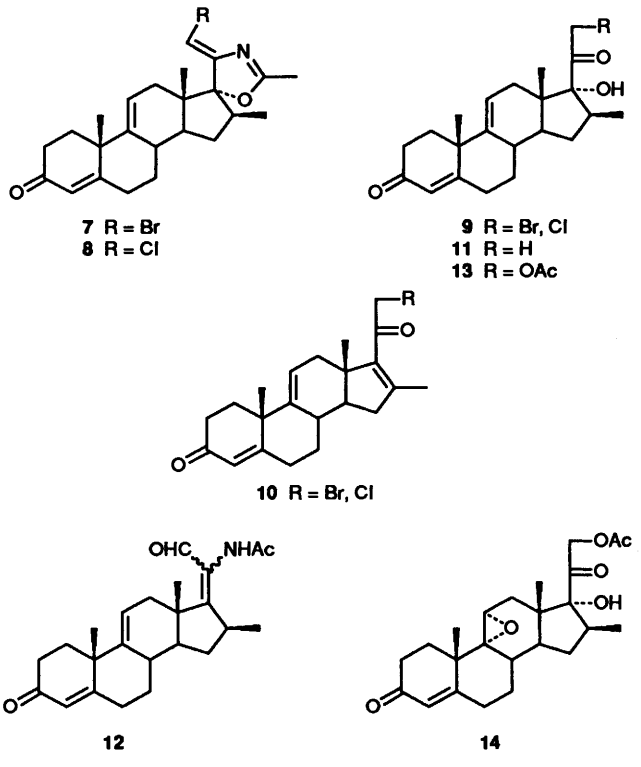
Nicholas I. Carruthers,*† David R. Andrews,* Sohaila Garshasb and Robert A. Giusto
Schering-Plough Research, Chemical Development, Union, NJ 07083, USA

The synthesis of 21-acetoxy-17α-hydroxy-16β-methylpregna-1,4,9(11)-triene from 9α-hydroxyandrost-4-ene-3,17-dione *via* a 17-cyanohydrin and a 17-oxazoline is described.

The ready availability of 9α-hydroxyandrost-4-ene-3,17-dione **1** from the fermentation of soy sterols, together with the rise in cost of traditional sapogenin sourced raw materials has made **1** an important starting material for corticosteroids.[1] We have recently shown that **1** can be converted into the 9α-hydroxy-16β-methyl-17β-cyanohydrin **2** and subsequently converted into 16β-methyl corticoids *via* a 17α-hydroxy pregnane.[2] This approach required the development of a novel set of reaction conditions to effect 9,11-dehydration in the presence of the 17α-hydroxypregnane without causing any undesired D-homo rearrangement. Conversion of the 17α-hydroxy pregnane into a corticoid was then accomplished *via* a multi-step procedure requiring temporary protection of the A-ring enone. To overcome this shortcoming, we envisaged converting cyanohydrin **2** into an oxazoline which could behave as a latent corticoid. An oxazoline would be stable to dehydration conditions and then permit ready functionalization at C-21 without the need for A-ring blocking. Thus, **2** was converted into the ethoxyethyl ether **3** which was treated with methyllithium followed by acetic anhydride to give the acetamide **4**. The acetamide was readily cyclized to the oxazoline **5** upon treatment with acetic anhydride–acetic acid. More conveniently, treatment with chlorosulfonic acid or Vilsmeier reagent followed by aqueous work up gave the 9,11-unsaturated oxazoline **6** (Scheme 1). In this manner, introduction of 9,11 unsaturation was concomitant with formation of the desired oxazoline. Treatment of **6** with pyridinium hydrogen bromide perbromide, or household bleach, commercially more attractive, gave the bromide **7** (95%) and the chloride **8** (92%) respectively. Acid hydrolysis of **7** or **8** to our surprise[3] gave none of the desired corticoids **9**, but instead afforded the 16,17-unsaturated products **10**. Hydrolysis of the oxazolines *via* oxazolinium salts also proved unsuccessful. However, the oxazoline **6** was readily hydrolysed under acidic conditions to **11**. These results suggested that direct oxygenation of **6** may produce hydrolytically more labile products. Therefore, the oxidation of **6** with mCPBA (in the presence and absence of sodium hydrogen carbonate) was investigated and found to give a mixture of the aldehydes **12**. More successful was the reaction of **6** with oxone‡

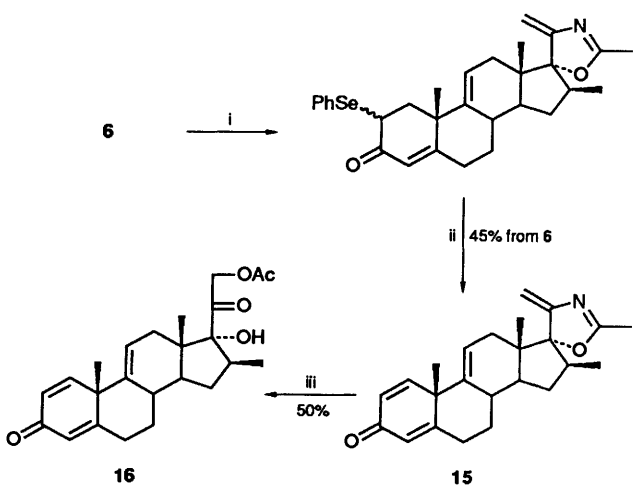


Scheme 1 i, CH_2=CHOEt, pyridine·HCl, CH_2Cl_2; ii, MeLi, cumene, THF, 35 °C; iii, Ac_2O; iv, Ac_2O, AcOH; v, $ClSO_3H$; vi, DMF, $SOCl_2$, CH_2Cl_2



† *Present address:* Schering-Plough Research, Bloomfield, NJ 07003, USA.

‡ Oxone, potassium peroxymonosulfate, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. Oxone is a registered trademark of E. I. du Pont de Nemours and Company.



Scheme 2 i, LHMDS, $(PhSe)_2$; ii, $NaIO_4$, water, MeOH; iii, Oxone, water, sulfolane

in aqueous sulfolane which gave **13** (45%) together with small amounts of **11**, **12** and **14**, together with products of A-ring oxidation. When the reaction was maintained at pH 7, **11** was the major product, whereas at pH 3–4 the yield of **13** was optimal. The less enolizable A-ring dienone **15** was prepared (Scheme 2) and subjected to the same oxygenation conditions to give **16**. Conversion of **16** into the potent antiinflammatory betamethasone can be readily achieved by known procedures.[4]

Experimental

2′,16β-Dimethyl-4′-methylenespiro[androsta-4,9(11)-diene-17,5′-(4′H)-oxazol]-3-one **6**.—3,3-Ethylenedioxy-17α-(1-ethoxyethoxy)-9α-hydroxy-16β-methylandrost-5-ene-17β-carbonitrile **3**[2] (1.77 g, 3.85 mmol) in Et_2O (3 cm^3) was cooled to 0 °C and treated with MeLi in cumene (1.3 mol dm^{-3}; 16 cm^3, 21 mmol). The reaction mixture was heated at 40 °C for 5 h, cooled to room temperature then added to a solution of Ac_2O (2.9 cm^3, 30.8 mmol) in Et_2O (5 cm^3) at 0 °C. The solution was warmed to room temperature, stirred for 3 h and then washed with phosphate buffer (2 × 25 cm^3), 5% aqueous $NaHCO_3$ (2 × 25 cm^3), dried ($MgSO_4$), filtered and evaporated to give an oil. Chromatography (silica gel: 8% acetone in toluene) afforded N-[3,3-ethylenedioxy)-17α-(1-ethoxyethoxy)-9α-hydroxy-16β-methylpregn-5-en-20-ylidene]acetamide **4** (0.8 g, 40%). Acetamide **4** (0.52 g, 1.0 mmol) was dissolved in CH_2Cl_2 (8 cm^3) and treated with $ClSO_3H$ (0.2 cm^3, 3.01 mmol) in CH_2Cl_2 (2 cm^3) whilst the reaction mixture was maintained at −20 to −10 °C. It was then diluted with CH_2Cl_2 (50 cm^3) and washed with 5% aqueous $NaHCO_3$ (25 cm^3) and water (25 cm^3), dried (Na_2SO_4), filtered and evaporated to give an oil. Chromatography (silica gel: 33% EtOAc in hexane) of the latter gave **6** (0.3 g, 82%), m.p. 166–167 °C (Found: M^+, 365.2355. $C_{24}H_{31}NO_2$ requires *M*, 365.2355); δ_H(300 MHz, $CDCl_3$) 0.76 (3 H, s, 18-Me), 1.08 (3 H, d, *J* 6, 16β-Me), 1.31 (3 H, s, 19-Me), 2.02 (3 H, s, Me), 4.31 (1 H, s, 21-H), 5.24 (1 H, s, 21-H), 5.48 (1 H, d, *J* 6, 11-H) and 5.71 (1 H, s, 4-H).

21-Acetoxy-17α-hydroxy-16β-methylpregna-4,9(11)-diene **13**.—A fresh solution of oxone (0.2 g, 0.325 mmol) in water (2 cm^3)/sulfolane (4 cm^3) was prepared and the pH adjusted to pH 3–4 by addition of 0.1 mol dm^{-3} aqueous Na_2CO_3. To the solution was then added the oxazoline **6** (0.1 g, 0.274 mmol) and the mixture stirred at room temperature for 6 h with the pH maintained at pH 3–4 by addition of 0.1 mol dm^{-3} aqueous Na_2CO_3. The mixture was extracted with EtOAc (50 cm^3), and the extract dried ($MgSO_4$), filtered and evaporated to afford an oil. Solution yield 43%. (In a typical procedure the progress of the reaction was monitored by HPLC using a Zorbax ODS column eluting with 30% water in MeCN, 1 cm^3 min^{-1} (λ = 254 nm). In this manner, solution yields could be quantitatively determined for process optimization). Chromatography (silica gel: 50% EtOAc in hexane) gave a homogeneous sample of **13** (0.030 g), m.p. 216–217 °C (Found: C, 71.9; H, 7.8. $C_{24}H_{32}O_5$ requires C, 71.97; H, 8.05); δ_H(300 MHz, $CDCl_3$) 0.74 (3 H, s, 18-Me), 1.13 (3 H, d, *J* 7, 16β-Me), 1.29 (3 H, s, 19-Me), 2.14 (3 H, s, OAc), 4.91 (2 H, ABq, *J* 18, 21-CH_2), 5.52 (1 H, d, *J* 7, 11-H) and 5.71 (1 H, s, 4-H).

Acknowledgements

We thank Carmen Alvarez and Vincent Sarna for skilled technical assistance. Spectroscopic and analytical results for compounds **6**, **13** and **16** are available as a Supplementary publication [Sup. No. 56883 (8 pp.)].*

References

1 (*a*) I. Nitta and H. Ueno, *New Synthesis of Corticoids*, in *Yuki Gosei Kagaku Kyokaishi*, 1987, **45**, 445; (*b*) D. H. R. Barton, W. B. Motherwell and S. Z. Zard, *Actual. Chim. Ther.*, 1984, II series, 39; (*c*) J. Redpath and F. J. Zeelen, *Chem. Soc. Rev.*, 1983, **12**, 75.
2 N. I. Carruthers, S. Garshasb and A. T. McPhail, *J. Org. Chem.*, 1992, **57**, 961.
3 Compare with the results of Barton and co-workers; (*a*) D. H. R. Barton, W. B. Motherwell and S. Z. Zard, *Nouv. J. Chim.*, 1982, **6**, 6, 295; (*b*) D. H. R. Barton, W. B. Motherwell and S. Z. Zard, Fr. Demande FR 2 493 324/1982 to Roussel-UCLAF.
4 USP 3 164 618/1965 to Schering Corporation.

Paper 2/01264B
Received 9*th March* 1992
Accepted 31*st March* 1992

* For details of the Supplementary publications scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans 1*, 1992, Issue 1.