A Further Synthesis of the Corticosteroid Side Chain starting with a Suitable 17-Ketone

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The readily available olefin (**8**) is easily converted into the synthetically useful enamide (**15**) *via* the nitrosyl chloride adduct (**9**).

The recent availability of 17-oxosteroids by microbiological degradation of abundant sterols[1] has prompted us[2] and others[3] to develop efficient methods for the partial synthesis of corticosteroids from such ketones. Enones such as (**1**) have also been synthetic targets since they are immediate precursors of the clinically important 16-substituted glucocorticoids (**2**)[4]. A suitable substituent in this position reduces the normally undesirable mineralocorticoid activity and increases the lifetime of the drug by retarding the metabolic degradation of the fragile dihydroxy acetone side chain.

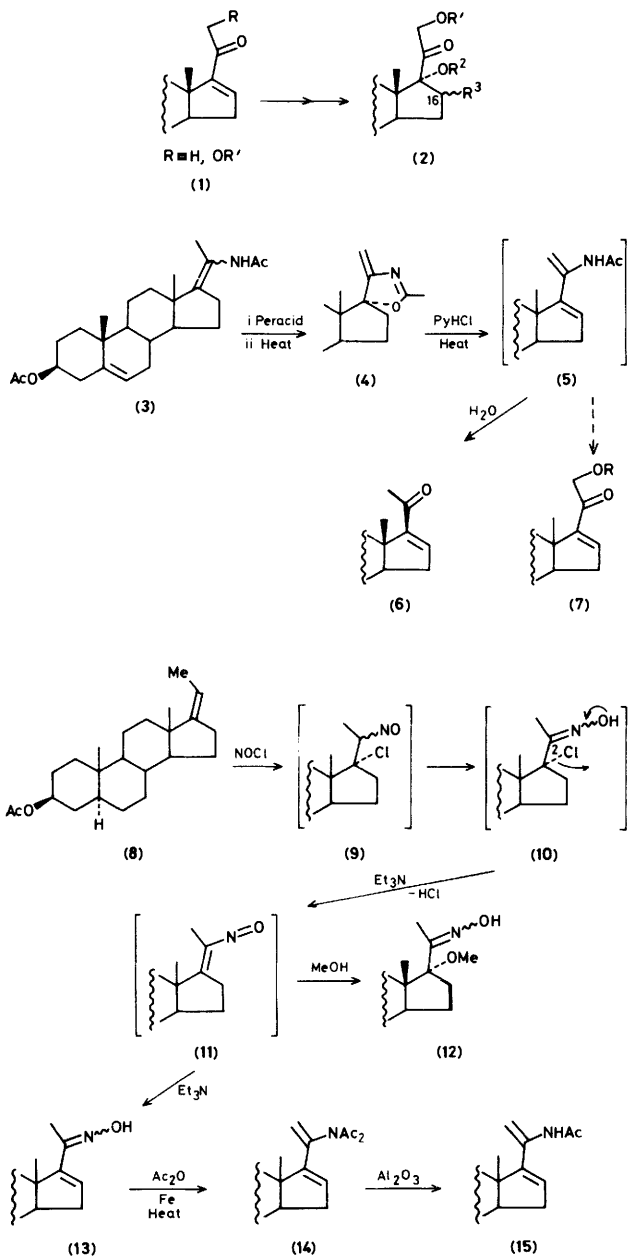
Some time ago, we showed[2b] that the oxazoline (**4**), easily obtained from the enamide (**3**), underwent a ring-opening reaction when heated in molten pyridinium hydrochloride to give, after hydrolysis of the intermediate (**5**), the enone (**6**) in 60% yield. We have been able to increase the yield to 90% by using *N*,*N*-dimethylacetamide as co-solvent. Operation under rigourously anhydrous conditions resulted in complex mixtures of, presumably, double bond isomers of compound (**5**), but we were unable to isolate the latter pure. Given the importance of this intermediate as a potential precursor to the more substituted enone (**7**), we considered an alternative route to such enamides from 17-oxosteroids.

Olefins of type (**8**) are readily available from 17-oxosteroids by a suitable Wittig reaction.[5] Electrophilic nitration of (**8**) under various conditions however resulted in intractable mixtures. This was almost certainly due to a Kägi–Miescher[6] type rearrangement followed by further reaction with the nitrating agent. In order to functionalise the double bond without concomitant skeletal rearrangement, we examined the use of nitrosyl chloride. This reagent has been successfully used with terpenes and is known to induce very little Wagner–Meerwein type rearrangement even with norbornene.[7]

Reaction of the pregnene (**8**) with nitrosyl chloride in dichloromethane at 0 °C was almost instantaneous. Evaporation of the solvent and treatment of the residue with methanolic triethylamine gave the oxime (**12**) in *ca.* 50% unoptimised yield. This compound is surely formed by addition of methanol to the vinyl nitroso derivative[8] (**11**). This latter is produced by rearrangement of the nitroso chloride (**9**) (or its dimer) to the chloro oxime (**10**), followed by base induced elimination of HCl.

When triethylamine in THF–H_2O was used, the nitroso chloride (**9**) reacted to give the α,β-unsaturated oxime (**13**) as a mixture of isomers. Without purification, this was reduced with iron powder in acetic anhydride to the *N*,*N*-diacetyl eneimide (**14**) in 85% overall yield from the pregnene (**8**). This sequence of reactions may be easily carried out in one pot and no chromatography is required.

Transformation of (**14**) into the desired enamide (**15**) was effected quantitatively by simple adsorption on alumina.[9] The efficient construction of the enamide side chain from 17-ketones is thus completed.



Experimental

Melting points are uncorrected. Unless otherwise stated, n.m.r. data are for deuteriochloroform solutions with $SiMe_4$ as

internal standard. I.r. spectra are of Nujol mulls. Sodium sulphate was used as the drying agent for organic layers. $[\alpha]_D$ Values were determined in $CHCl_3$.

3β-*Acetoxypregna*-5,16-*dien*-20-*one* (**6**).—A mixture of the oxazoline[2b] (**4**) (190 mg) and pyridinium hydrochloride (2 g) in *N*,*N*-dimethylacetamide (6 ml) was heated at 110 °C for 3 h. Water (2 ml) was added and the mixture heated to reflux for 5 h, poured into water, and extracted with dichloromethane. Evaporation of the solvents gave a residue which was acetylated with acetic anhydride (2 ml) and *N*,*N*-dimethylaminopyridine (DMAP, a few crystals) in dichloromethane (5 ml). The excess of anhydride was destroyed with aqueous sodium carbonate. The organic layer was dried, filtered through a plug of silica, and evaporated to give the enone (**6**) as a crystalline solid (150 mg, 90%), m.p. and mixed m.p. 170—173 °C (from methanol).

3β-*Acetoxy*-17α-*methoxypregnan*-20-*one Oxime*. (**12**).—Nitrosyl chloride was passed into ice cold dichloromethane (5 ml) until a deep burgundy colour developed. The olefin[5a] (**8**) (200 mg) was added and after 2—3 min, the solvents were evaporated and replaced with methanol (10 ml) and triethylamine (1 ml) (a little warming was necessary to effect dissolution). After 4—5 h at room temperature, the solvents were evaporated and the residue chromatographed on silica ($CH_2Cl_2 \rightarrow CH_2Cl_2$–$Et_2O$, 1:1) to give the *oxime* (**12**) as white crystals (116 mg, *ca.* 50%), m.p. 178—193 °C (methanol), $[\alpha]_D$ − 13° (*c* 0.8); $\nu_{max.}$ 3 220 and 1 710 cm^{-1}; δ_H 9.05 (1 H, br NOH), 4.70 (1 H, br, 3α-H), 3.20 (3 H, s, MeO), 2.10 (3 H, s, Oac), 1.90 (3 H, s, 21-Me), and 0.85 and 0.65 (6 H, s, 18- and 19-Me); *m*/*z* 405 (M^+) and 388 ($M^+ - 17$) (Found: C, 71.3; H, 9.8; N, 3.45. $C_{24}H_{39}NO_4$ requires C, 71.07; H, 9.69; N, 3.45%).

3β-*Acetoxy*-20-(N,N-*diacetylamino*)*pregna*-16,20-*diene* (**14**).—The olefin (**8**) (150 mg) was treated with nitrosyl chloride as above. After evaporation of the dichloromethane, the residue was taken up in THF (6 ml) and water (1 ml). Triethylamine (1 ml) was added and the mixture heated to 60 °C for 2 h, poured into 5% K_2CO_3, extracted with dichloromethane and the organic layer dried and evaporated. The residue was then heated in acetic anhydride (5 ml) in the presence of iron powder (1 g) for 4 h at 100 °C. The mixture was then filtered, extracted with dichloromethane and the organic layer washed with water and aqueous K_2CO_3, dried, and evaporated. Crystallisation of the residue from methanol gave the *diacetyl enamide* (**14**) (164 mg, *ca.* 85%), m.p. 194—198 °C (methanol), $[\alpha]_D = -10°$ (*c* 0.3), $\nu_{max.}$ 1 720, 1 705, and 1 625 cm^{-1}; δ_H 5.70 (1 H, br, 16-H), 5.60 (1 H, br s, 21-H), 5.15 (1 H, br s, 21-H), 4.70 (1 H, br, 3α-H), 2.40 (6 H, s, -NAc_2), 2.05 (3 H, s, OAc) and 1.00 and 0.85 (6 H, s, 18 and 19-Me) (Found: C, 73.25; H, 8.75; N, 3.1. $C_{27}H_{39}NO_4$ requires C, 73.44; H, 8.90; N, 3.17%).

3β-*Acetoxy*-20-*acetamidopregna*-16,20-*diene* (**15**).—The imide (**14**) (31 mg) was adsorbed on alumina (*ca.* 5 g, activity II—III) using a little dichloromethane. After *ca.* 2 h, the column was washed with MeOH–CH_2Cl_2 (1:5) to give after evaporation of the solvents a crystalline *enamide* (**15**) (28 mg, 100%), m.p. 168—173 °C (methanol), $[\alpha]_D = +22°$ (*c* 0.4), $\nu_{max.}$ 1 720, 1 695, and 1 620 cm^{-1}; δ_H 6.60 (1 H, br, NH), 5.85 (2 H, br, 16-H and 21-H), 5.00 (1 H, large, 21-H), 4.75 (1 H, br, 3α-H), 2.15 (3 H, s, NAc), 2.05 (3 H, s, OAc), and 1.00 and 0.85 (6 H, s, 18 and 19-Me) (Found: C, 74.85; H, 9.15; N, 3.6. $C_{25}H_{37}NO_3$ requires C, 75.15; H, 9.33; N, 3.51%).

Acknowledgements

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