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A Highly Efficient, Indirect Electrooxidation of 6β-Methyl-3β,5α-dihydroxy-16α,17α-cyclohexanopregnan-20-one to the Corresponding 5α-Hydroxy-3,20-dione Using a Mediatory Couple of Sodium Bromide and Substituted 2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO)

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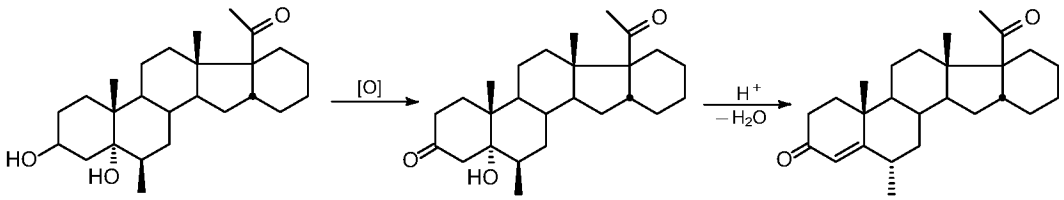
6β-Methyl-3β,5α-dihydroxy-16α,17α-cyclohexanopregnan-20-one **1**, when electrolysed in the presence of 4-substituted TEMPO in a two-phase system of CH_2Cl_2–aqueous NaBr, is oxidised chemoselectively and in high yield into 6β-methyl-5α-hydroxy-16α,17α-cyclohexanopregnan-3,20-dione **2**.

6β-Methyl-3β,5α-dihydroxy-16α,17α-cyclohexanopregnan-20-one **1** and 6β-methyl-5α-hydroxy-16α,17α-cyclohexanopregnan-3,20-dione **2** are intermediates in the preparation of 6α-methyl-16α,17α-cyclohexanopregesterone **3** (Scheme 1) *i.e.* progestin, used for the treatment of hormonal diseases and known to be about 10 times more active than native hormone progesterone.[1–3]

Oxidation of the 3,5-diol **1** to the 3,5-ketol **2** (Scheme 1) was carried out by the Jones procedure with chromic acid in acetone.[3] Owing to the poor solubility of the diol **1** in acetone (*ca.* 6 g dm^{-3}) it required large volumes of organic solvents and, in addition, gave a large amount of dangerous sewage containing chromium salts. The disadvantages of progestin **3** preparation in Scheme 1, using the chemical oxidation method, make it impractical for large scale synthesis of the valuable compound **3**.



1 **2** **3**

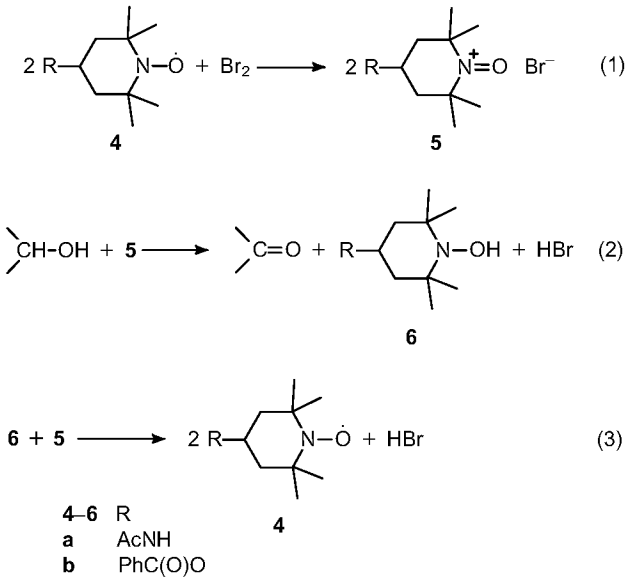
Scheme 1

In the search for an alternative oxidative method we have utilized electrooxidative dehydrogenation of alcohols using a mediatory couple of 4-substituted 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO)–sodium bromide.[4,5] The electrochemical process is operative with a catalytic amount of TEMPO and is carried out in a two-phase system of CH_2Cl_2–aqueous NaBr buffered with aqueous $NaHCO_3$ (or sodium acetate) in an undivided cell. The method was successfully used for the preparation of a wide variety of aldehydes and ketones from the corresponding alcohols (steroid alcohols not being among them).

We have found that electrolysis of diol **1** in the presence of 3 mol% of 4-AcNH-TEMPO **4a** or 4-BzO-TEMPO **4b** in an undivided cell equipped with a graphite anode and a stainless steel cathode at 5–10 °C and with passage of 2.7 F mol^{-1} of electricity based on **1** gave the target ketol **2** in 88–90% yield, practically without waste.† In addition, the electrolysis and the subsequent isolation of **2** required substantially less volume of organic solvent as compared with Jones oxidation. This allowed us to readily prepare ketol **2** on a large scale and with high quality.

† An undivided cell (10 cm diameter, 17.5 cm height and *ca.* 1 dm^3 volume) equipped with a graphite plate anode (6 × 10 cm) and a stainless steel wire net as cathode (6 × 10 cm) placed 50 mm apart, was used. It was also fitted with a mechanical stirrer placed between the electrodes, a cooling jacket, a condenser and a thermometer. Diol **1** (12 g, 30 mmol) and 4-AcNH-TEMPO (**4a**, 192 mg, 0.9 mmol) in CH_2Cl_2 (300 ml) were combined with aqueous 25% NaBr and 5% $NaHCO_3$ (pH 8.6, 500 ml) in the cell. The electrodes were immersed in the upper layer of the resulting two-phase solution and the mixture was electrolysed at 5–10 °C under a constant current of 800 mA (cur-

The mechanism of the electrochemical process catalysed by 4-substituted TEMPO is identical to that of alcohol dehydrogenation under the action of such oxidants as chlorine and bromine,[6,7] sodium and calcium hypochlorites,[8,9] sodium bromite[9] and others.[10] The following three reactions form its basis: (*a*) *in situ* oxidation of TEMPO **4** to *N*-oxoammonium salt **5**, (*b*) oxidative dehydrogenation of alcohols with salt **5**, as a result of which it converts into hydroxylamine **6** and (*c*) fast regeneration of TEMPO **4** from **6** under the action of salt **5** [11] (Scheme 2 with bromine as oxidant).



Scheme 2

Electrochemical reactions in the overall process play an important role in the formation of active bromine species ($Br^{\cdot}$, Br^{+}, Br_2), hydrogen and sodium hydroxide (Scheme 3), from aqueous NaBr.

$$2NaBr \rightarrow 2Na^{+} + 2Br^{-}$$
$$2Br^{-} - 2e^{-} \rightarrow 2Br^{\cdot} \rightarrow Br_2$$
$$\text{or } Br^{-} - 2e^{-} \rightarrow Br^{+}$$
$$2H_2O + 2e^{-} \rightarrow H_2 + 2OH^{-}$$
$$2Na^{+} + 2OH^{-} \rightarrow 2NaOH$$

Scheme 3

The sodium hydroxide formed neutralizes HBr resulting from reactions (2) and (3), and thus provides regeneration of NaBr. The process efficiency is determined by reaction (2).[11] Some aspects dealing with the effect of alcohol structure on the selectivity of their oxidation under the action of salts **5** are considered in ref. 11. However, we have not succeeded in converting ethylcholeate 3,7-diacetate and 2-phenoxyethanol to ethyldehydrocholeate 3,7-diacetate and 2-phenoxyacetaldehyde, respectively. The reasons for such behaviour of the alcohols and relations between the alcohol structure and reactivity in reaction **2** are under study.

The advantages of electrooxidative dehydrogenation for the preparation of ketol **2** from diol **1**, as well as the simplicity of the process and the easy control and turnover of the mediators, offer potential possibilities for large scale synthesis of progestin **3**.

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rent density: 20 mA cm^{-2}) with efficient stirring (applied voltage: 3–4 V). Upon passage of 2.7 F mol^{-1} of electricity based on diol **1** (reaction time: 3 h), the latter was completely oxidized (TLC control). Further evidence for complete oxidation of diol **1** was a colour change of the organic phase from slightly yellow to brown. Brown is a typical colour for oxoammonium salt solutions. The mixture was then treated with MeOH (1 ml) to destroy the excess of salt **5a**, the organic phase was separated from the aqueous phase and the latter was extracted with CH_2Cl_2 (100 ml). The combined extracts were then washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was then stirred for 15 min with hexane (100 ml) and filtered to give 10.6 g (88%) of ketol **2**, that did not require additional purification for its further use. Using 4-BzO-TEMPO as a mediator ketol of the same quality was obtained in 90% yield.

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