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OXIDATION OF ALCOHOLS BY ELECTROCHEMICALLY REGENERATED NICKEL OXIDE HYDROXIDE. SELECTIVE OXIDATION OF HYDROXYSTEROIDS[1]

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Abstract—Primary alcohols, α,ω-diols and secondary alcohols are easily transformed into carboxylic acids, dicarboxylic acids or ketones, respectively, by heterogeneous oxidation with nickel oxide hydroxide electrochemically regenerated at a nickel hydroxyde electrode. The results are discussed in comparison to those of the nickel peroxide and chromic acid oxidation. The oxidation rate decreases with increasing steric hindrance of the alcohol, thus allowing the selective oxidation of the 3-position in hydroxysteroids.

Even with so many available methods for alcohol oxidation there is still a demand for new, versatile and selective oxidation procedures. As electron transfer is involved in any oxidation reaction, electrochemical anodic oxidation of alcohols seems an interesting alternative which may avoid some disadvantages of the existing chemical methods. Above all, by using the electric current as oxidation reagent low-valent transition metal compounds, which could lead to environmental pollution in chromic acid or permanganate oxidation, are excluded. Work-up is easy since the electrochemical oxidation proceeds heterogenously; in addition, the heterogeneous oxidation could lead to new selectivities by requiring adsorption and definite orientation of the substrate at the surface of the electrode.

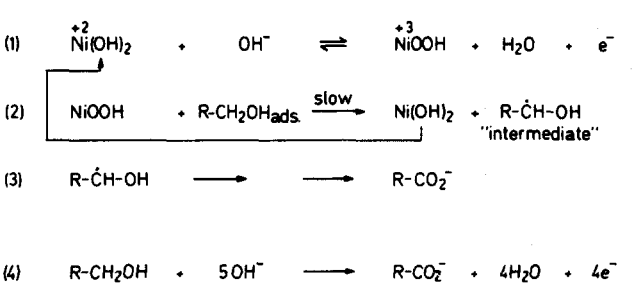
Since direct electro-oxidation of alcohols at platinum or carbon anodes is of only limited preparative value due to the high oxidation potentials required,[2] we thought that indirect electrochemical oxidation at a nickel hydroxide electrode would be a promising approach to the realization of our concept. Following the mechanism first proposed by Fleischmann and Pletcher[3] and recently confirmed by Robertson[4] (Scheme 1), a black surface layer of a nickel(III)oxide hydroxide, similar to the well known oxidant nickel peroxide,[5] is continuously electroregenerated from nickel(II)hydroxide deposited on a nickel net or sheet (eqn 1). Oxidation takes place by heterogeneous chemical reaction between the oxide hydroxide and the adsorbed alcohol (eqn 2). By radical hydrogen abstraction in the rate-determing step,[6] a α-hydroxy-radical is produced as intermediate, which is readily oxidized to a carboxylate in the case of a primary alcohol (eqn 3). The summarized anode reaction (eqn 4) reveals the electrocatalytic nature of the oxidation process, oxidation of a primary alcohol to the carboxylate requiring nothing but electrons and hydroxide ions as reagents.

The nickel hydroxide electrode has previously been used for alcohol oxidation by Vertes[7] and later by Fleischmann and Pletcher.[3,8] These authors were however mainly interested in the electroanalytical and mechanistic aspects of the reaction, whereas the preparative application remained limited to few and most simple aliphatic alcohols, some benzylic alcohols[8] and di-O-isopropylidene-L-sorbose.[7,9] It is the aim of our present investigation to examine the scope and limitations of this interesting anodic oxidation reaction by studying a variety of primary alcohols, secondary alcohols and diols, to investigate the influence of steric hindrance on the oxidation rate under the conditions of preparative electrolysis and to make use of these effects for the selective oxidation of hydroxysteroids.

Primary alcohols

The oxidation of primary alcohols results in high yields of the corresponding carboxylic acids (Table 1), either in electrolyte A (aqueous 1M sodium hydroxide) or at a somewhat slower rate in electrolyte B (50% t-butanol, 50% water, 0.2M potassium hydroxide).[10] In the latter case, t-butanol is used as cosolvent to increase the solubility of poorly water soluble compounds.

Short-chain alcohols are effectively oxidized at room temperature, whereas higher temperatures (70°) are



Scheme 1

required for the oxidation of long-chain or α-branched primary alcohols. These observations indicate that (in agreement with earlier electroanalytical measurements[3,7]) the reactivity of the primary alcohols decreases with increasing chain length and increasing steric hindrance of the alcohol. The high yields obtained even in the oxidation of long-chain alcohols like 1-decanol **1** or 1-octadecanol **2** by our electrochemical method are in contrast to the nickel peroxide oxidation which is applicable only to short-chain alcohols.[5]

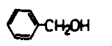
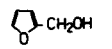
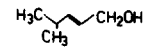
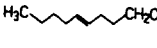
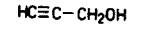
The influence of chain-length and α-branching on the reaction rate can be observed in aqueous sodium hydroxide as well as in the presence of the cosolvent. It therefore cannot be explained by a decrease of water solubility, but must be attributed to the lower tendency of long or bulky alcohols to be adsorbed at the surface of the electrode. Similar observations have been made in nickel peroxide oxidation[5] and in oxidations at platinum catalysts,[11] so these effects seem to be typical for heterogeneous oxidation reactions in polar media. By raising the temperature to 70°, the heterogeneous chemical reaction between the nickel oxide hydroxide and the alcohol will be accelerated.

Among unsaturated primary alcohols, benzylic type alcohols are most readily oxidized. From 2-hydroxymethylfuran **3**, furan-2-carboxylic acid is obtained in 79% yield, whereas ring-opened products would be formed under acidic conditions. In the oxidation of olefinic alcohols, the yields depend on the position of the double bond. 2- and 3-alkenols give poor yields due to a partial oxidative cleavage at the double bond, whereas high yields are obtained from 4-alkenols like *E*-4-heptene-1-ol **4** (82%) or *E*-4-nonene-1-ol **5** (68%). In contrast, Jones oxidation of **4** and **5** afforded the corresponding carboxylic acids in only 52 and 62% yield, respectively,[12] due to ester formation as the predominant side reaction.[13] The nickel peroxide oxidation of olefinic alcohols other than 2-alkenols has not yet been reported.[5] In our hands, oxidation of **4** and **5** with nickel peroxide resulted in very poor yields of the carboxylic acids (8%);[12] in addition, strong adsorption of the organic compounds on the voluminous nickel salts formed made the work-up

Table 1. Oxidation of primary alcohols to carboxylic acids $R—CH_2OH \xrightarrow[\text{Anode}]{\text{NiOOH-}} R—CO_2H$

Alcohol	Electrolyte	Yield[a] [%]	Time and Temperature	Current [A]
Short-chain alcohols				
n-C_3H_7—CH_2OH	A	85	2 h, 70°	4
	B	92	15 h, 25°	0.6
n-C_5H_{11}—CH_2OH	A	64	5 h, 25°	4
	B	91	15 h, 25°	0.6
n-C_6H_{13}—CH_2OH	A	84	5 h, 25°	4
n-C_7H_{15}—CH_2OH	A	65	6 h, 25°	4
	A	89	4 h, 70°	4
	B	49	20 h, 25°	0.6
Long-chain and α-branched alcohols				
n-C_8H_{17}-CH_2OH	A	89	7 h, 70°	4
	B	13	22 h, 25°	0.6
n-C_9H_{19}—CH_2OH (1)	B	12	66 h, 25°	0.6
	A	27	4 h, 25°	4
	A	87	7 h, 70°	4
n-$C_{11}H_{23}$-CH_2OH	A	80	8 h, 70°	4
n-$C_{17}H_{35}$—CH_2OH (2)	A	77	8 h, 75°	4
CH_3-CH_2-CH(CH_3)-CH_2OH	A	67	3.5 h, 25°	4
CH_3-CH_2-CH(C_2H_5)-CH_2OH	A	51	3.5 h, 25°	4
	A	73	3.5 h, 70°	4
n-C_4H_9—CH(C_2H_5)—CH_2OH	A	31	5 h, 25°	4
	A	76	7 h, 70°	4

Table 1. (*Contd*)

Unsaturated alcohols				
	A	86	1.5 h, 25°	4
 (3)	A	79	2 h, 25°	4
	A	10[b]	1 h, 5°	4
	B	34	17 h, 25°	0.6
 (4)	A	82[c]	4 h, 25°	4
 (5)	A	68[c]	8 h, 70°	4
 (6)	A	51[d]	2 h, 5°	4

[a] Yield of isolated product

[b] Accompanied by considerable amounts of 2-methylpropanoic acid

[c] In collaboration with I. Langer and W. Seidel, our institute

[d] Carried out in a divided cell

Electrolyte A: 1 M $NaOH/H_2O$

Electrolyte B: 0.18 M KOH/50 % ^tBuOH/50 % H_2O

difficult. The oxidation of 2-propyne-1-ol (**6**) has to be carried out in a divided cell to prevent electrocatalytic hydrogenation of the triple bond at the cathode. Oxidation at the nickel hydroxide electrode, followed by easy work-up, normally yields carboxylic acids of high purity, sometimes accompanied by negligible amounts (< 2%) of lower homologs of the carboxylic acid. In the oxidation of longer-chain alcohols in electrolyte B, minor quantities (< 10%) of aldol adducts may be obtained as non-acidic by-products.

It must be emphasized that the electrolysis conditions are extremely simple, the equipment being limited to things accessible in any modern laboratory: a nickel net anode, a stainless steel cathode, a direct current power supply and a beaker as electrolysis cell. Before each electrolysis, the nickel net should be activated by deposition of a nickel hydroxide surface layer which considerably enhances the reactivity of the anode.

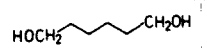
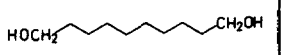
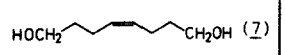
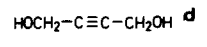
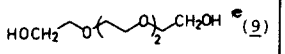
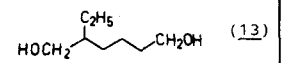
α,ω-Diols

From α,ω-diols, the corresponding dicarboxylic acids are obtained in very good yields (Table 2). As was shown by taking *Z*-4-octene-1,8-diol **7** as an example, it is hardly possible to get comparable yields of dicarboxylic acids with commonly used chemical oxidants. Jones oxidation of **7** by both the normal[14] and the inverse[15] procedure gave *Z*-4-octenedioic acid in 0 and 18% yield, respectively, the main products being tetrahydrofuran derivatives formed by intramolecular attack on the double bond. Compared to our electrochemical method (80% yield), oxidation of **7** by pyridinumdichromate in dimethylformamide[16] proved to be the best alternative (65% yield); however, separation of the product from the polar solvent was difficult in this case. Nickel peroxide oxidation of **7** yielded 45% of the hydroxy-acid **8** under mild reaction conditions (1.3 equivalents of peroxide, 2 h, 25°, 1M NaOH), whereas under more vigorous conditions (3 equiv. peroxide, 2 h, 80°, 1M NaOH) maleic acid was formed by attack on the allylic positions. These observations indicate that despite all structural similarities between nickel peroxide and the nickel oxide hydroxide electrochemically produced,[17] there are differences in reactivity.

Oxidation of tetraethylene glycol **9**, results in 50% yield of the trioxa acid **10**, which is of interest as a potential complexing agent in detergents.[18] **10** is accompanied by 16% of the dioxa acid **11** and 3% of the oxa acid **12**. **11** and **12** are formed by oxidative ether cleavage; the nickel oxide does not attack the C–H bonds α to the hydroxy groups, but those in α-position to the ether linkages.

The relative reactivities of different primary alcohols were determined by co-electrolyzing equal amounts of the alcohols in the same cell. Thus, it was shown that 2-ethyl-1-hexanol is less reactive by a factor 8 compared to 1-hexanol and by a factor 3 compared to 1-octanol. However, attempts to oxidize selectively only the less hindered 6-hydroxy group of 2-ethyl-1,6-hexanediol **13** failed. Partial oxidation of **13** under mild conditions (5°, 3 h, 4 Faraday mol^{-1} **13**) yielded 19% of the expected hydroxy acid **14**, 6% of the regioisomeric hydroxy-acid **15** and surprisingly 37% of the dicarboxylic acid **16** besides unchanged starting compound (35%). These results reflect the enhanced reactivity of the diols. Obviously, the more hydrophilic character of the diols leads to stronger adsorption at the electrode, possibly in

Table 2. Oxidation of α,ω-diols to dicarboxylic acids $HOCH_2—R—CH_2OH \xrightarrow[\text{Anode}]{NiOOH-} HO_2C—R—CO_2H$

Alcohol	Electrolyte	Yield[a] [%]	Time[b] and Temperature	Current [A]
	A	84	5 h, 25°	4
	A	85	7 h, 80°	4
	B	63	24 h, 30°	0.6
 (7)	A	80	2 h, 80°[c]	2
 [d]	A	55	3 h, 20°	4
 [e] (9)	A	50	8 h, 5°	0.8
 (13)	A	78	4 h, 80°[c]	2

[a] Yield of isolated product

[b] Time required to 40 mmol α,ω-diol

[c] 10 mmol of α,ω-diol used

[d] Carried out in a divided cell

[e] Controlled potential electrolysis at +0.6 V vs. Hg/HgO/1 M NaOH reference electrode.

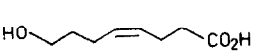
Electrolyte A: 1 M $NaOH/H_2O$

Electrolyte B: 0.3 M KOH/50 % ^tBuOH/50 % H_2O

form of a chelate complex. Adsorption and oxidation of the first hydroxy group of a diol facilitates the oxidation of the second in a cooperative manner, thus favouring the formation of dicarboxylic acids.

ω-Hydroxycarboxylic acids were detected as intermediates in the oxidation of the other diols, too, though in relative small amounts due to the cooperative effect discussed. However, in the oxidation of both alkanols and alkanediols, no aldehyde intermediates could be detected in electrolyte A; negligible quantities of aldehyde were observed in electrolyte B. It is to be assumed that under the alkaline conditions used the aldehydes are activated by formation of gem-diolates **17**[19] which are readily oxidized further to the corresponding carboxylic acids; diolate formation can account for the product distribution observed in the oxidation of benzylic alcohols,[8] which could not be explained up to now.

Oxidation of primary alcohols at silver oxide and copper oxide electrodes was less satisfactory due to a



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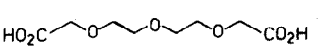

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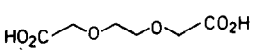

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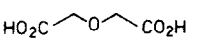

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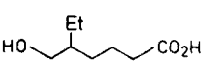

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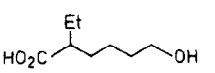

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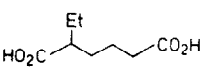

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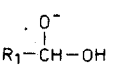

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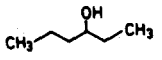
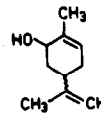
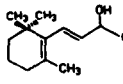
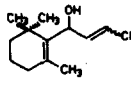
Table 3. Oxidation of secondary alcohols to ketones $R{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}R \xrightarrow[\text{Anode}]{\text{NiOOH}} R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R$

Alcohol	Electrolyte	Yield[a] [%]	Time and Temperature	Current [A]
	B	70[b] (77)	16 h, 25°	0.5
	A	65[c]	1.5 h, 25°	1.5
	B	80[b]	5 h, 25°	0.6
	B	38[c]	25 h, 25°	0.6
	B	72[c] (79)	65 h, 25°	0.4
 (18)	B	72[c] (>90)	24 h, 25°	0.6
 (19)	B	81[c] (>90)	34 h, 25°	0.4
 (20)	B	75[d] (85)	24 h, 25°	0.1
 (21)	B	59[d] (79)	34 h, 25°	0.1
 (26)	B	9[d]	68 h, 25°	0.2

[a] Yield referred to consumed alcohol given in parentheses

[b] Isolated as the 2,4-dinitrophenylhydrazone derivative

[c] Yield determined by gas chromatography

[d] Yield of isolated product

Electrolyte A: 1 M $NaOH/H_2O$

Electrolyte B: 0.1 M KOH/50 % ^tBuOH/ 50 % H_2O

considerable corrosion of these anodes which was only partly reduced by use of a divided cell. Thallium (III) oxide, chemically prepared or deposited on a platinum electrode, did not even react with benzylic alcohol and showed slow reaction with aliphatic aldehydes.

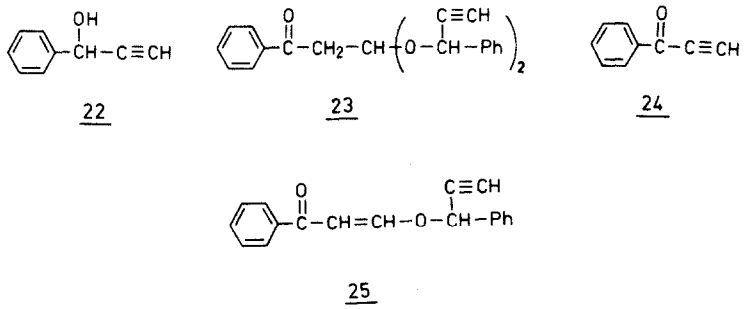
Secondary alcohols

Oxidation of a variety of acyclic, cyclic and bicyclic secondary alcohols, including the allylic alcohols carveol **20** and β-ionol **21**, leads to the corresponding ketones normally in 70–80% yield (Table 3). As in other cases some starting compound could be re-isolated, yields referred to consumed alcohol usually are somewhat higher.

In a side-reaction, 10–15% carboxylic acids are produced by oxidative cleavage of the ketone enolates. However, these by-products do not interfere with the isolation of the ketones since they remain in the alkaline solution during work-up. Higher temperatures favour the oxidative degradation of the ketones. Aldol adducts could not be detected as by-products.

Oxidation of 1-phenyl-2-propyne-1-ol **22** gave the acetal **23** as the main product (28%) accompanied by 4% of ketone **24** and unchanged starting compound (**22**; 56%). The acetal **23** is probably formed by nucleophilic addition of the alcohol **22** to the activated triple bond of the ketone **24**. The enol ether **25** was isolated as an intermediate in this reaction.

The oxidation of secondary alcohols by nickel peroxide in alkaline solution has not yet been examined.[5] Attempted nickel peroxide oxidation of carveol **20** resul-



22 23 24

25

ted in small conversion even under rigorous conditions, yielding only 15% ketone in electrolyte B (4 equiv. nickel peroxide, 48 h, 25–45°) and 33% ketone in benzene solution (2.5 equiv. nickel peroxide, 48 h, 50°).

The reaction times required for complete oxidation at the nickel hydroxide electrode vary considerably depending on the structure of the secondary alcohol (Table 3). In contrast to the chromic acid oxidation of secondary alcohols,[20] the oxidation rate decreases with increasing steric hindrance. Similar to the oxidation of long-chain or branched primary alcohols, this effect is obviously caused by the lowered adsorption of bulky alcohols at the surface of the electrode. β-Ionol **21** is easily oxidized to β-ionone (59% yield), however, oxidation of the isomeric β-damascol **26** where the hydroxy group is shielded by three adjacent methyl groups remains uncomplete even after 68 h (9% yield). The steric effects were studied in more detail by co-electrolysis experiments. When co-electrolyzed with cyclohexanol, 2-ethylcyclohexanol was 10 times and borneol **18** 5 times less reactive than cyclohexanol. The higher oxidation rate of the sterically more hindered borneol in comparison to 2-ethylcyclohexanol may arise from the higher reactivity of the strained 5-membered ring compared to the six-membered ring. Small differences in reactivity were observed between *cis*- and *trans*- 2-ethylcyclohexanol (1.6:1) and between borneol **18** and isoborneol **19** (1.2:1). These results are best understood by assuming that for a rapid oxidation both the hydroxy group and the C–H bond in α-position to the hydroxy group should be readily accessible.

Hydroxy steroids

In hydroxy steroids, the 3α- and 3β-hydroxy groups are selectively oxidized (Table 4), the nickel hydroxide electrode thus being an electrochemical alternative to chemical methods already existing.[21] The selective oxidation of a 3β- besides a 17β-hydroxy group is difficult by other means since these positions are not too much different in their steric environment. The yield obtained (**28**; 28%) corresponds to that of the Oppenauer oxidation which is the best method reported up to now for the selective oxidation of 3,17-dihydroxy steroids.[21] Additional activation of the 3-position by an allylic double bond increases the selectivity (50% testosterone **30**), however, other oxidants with higher specifity towards allylic alcohols like manganese dioxide should be preferred for this type of oxidation. By extension of the reaction time (25 h) the diols **27** and **29** can be converted into the corresponding diketones in 80% yield. Cholic acid is oxidized exclusively in the 3α-position without any attack on the 7α- and 12α-hydroxy groups. A comparable selectivity has been reported for the oxidation by silver carbonate on Celite[22] and by molecular oxygen on platinum catalysts.[11,23] The yield of 3-ketone **31** is however lowered by concomitant formation of the lactone **32** which becomes the main product when the electrolysis is continued. **32** is formed from **31** by selective oxidative cleavage of the C-3–C-4 bond, followed by lactonization during work-up. The unexpected regioselectivity of this cleavage is explained by the fact that 3-oxo-5β-steroids enolize preferentially towards C-4.[24] The *cis*-A/B-ring junction of **31** seems to facilitate the oxidative cleavage, since no cleavage products were obtained from 5α-hydroxy steroids. The polar carboxylic group in the side-chain is without any influence, oxidation of the 5β-cholanetriol **33** lacking the carboxylic group gave a comparable yield of the 3-ketone **34**, again accompanied by the corresponding cleavage product. The triol **33** was obtained in one step from diolic acid by mixed Kolbe electrolysis with a tenfold excess of acetic acid.

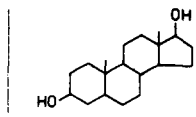
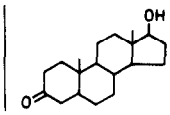
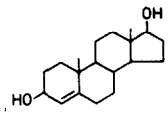
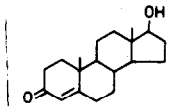
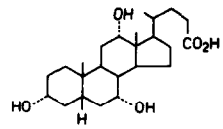
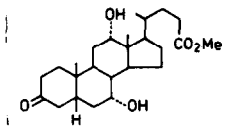
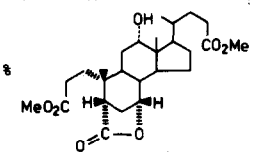
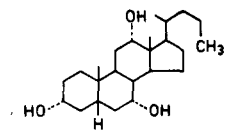
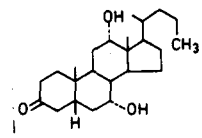
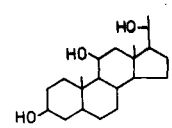
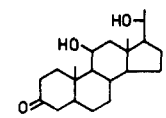
The selective oxidation of a 3β-hydroxy group besides others in 11β- and especially 20β-position, which is successfully realized in the oxidation of the pregnanetriol **35**, is without precedent. The Oppenauer oxidation of similar compounds gives the 3-lactones in only 30% yield;[21] chromic acid, on the other hand, would preferentially attack the 11β-hydroxy group.[21] The remarkable selectivity may be due to the fact that the 20β-hydroxy group is placed on the β-side of the steroid system, remote from the electrode which probably attacks the compound from the less hindered α-side. Accordingly further oxidation of **36** proves to be very difficult; under severe conditions (40°, 4 days), the 20β-position is oxidized in preference to the 11β-hydroxy group. At the nickel hydroxide electrode, the reactivity of the different hydroxy groups examined up to now follows the order: 3β-OH ≈ 3α-OH > 17β-OH ≫ 20β-OH > 11β-OH.

On the basis of the results presented here, a selective oxidation of a 3-hydroxy group should be possible with hydroxy groups present in other positions of the steroid.

OTHER ELECTROCHEMICAL METHODS

The alcohol oxidation at the nickel hydroxide electrode is superior to other electrochemical methods so far reported. Oxidation at lead dioxide electrodes in acidic solution normally yields considerable amounts of esters[2] and seems to be better only for alkynols.[25] Oxidations by electrochemically regenerated halogens or thioether radical cations have hitherto been restricted to secondary alcohols, whereas the yields are usually poor with primary or unsaturated alcohols.[26]

Table 4. Selective oxidation of hydroxy steroids

Alcohol	Yield[a] and Product	Temperature/ Current/ Time
 27	28 %  b 28	25° C 0.1 A 12 h
 29	50 %  c 30	25° C 0.1 A 8 h
	38 %  d 31 + 22 %  32	25° C 0.1 A 3 h
 33	38 %  34	25° C 0.1 A 5 h
 35	78 %  e 36	25° C 0.1 A 6 h

Electrolyte: 0.0 1 M KOH/50 % ^{t}BuOH/50 % H_2O

[a] Yield of isolated product

[b] Besides 3 % 3β-hydroxy-5α-androstan-17-one, 30 % 5α-androstane-3,17-dione and 17 % unconsumed 27. 5α-Androstane-3α,17β-diol gave similar results.

[c] Besides 38 % 4-androstene-3,17-dione and 7 % unconsumed 29.

[d] 17 % Cholic acid re-isolated. Esterification was done during work-up.

[e] 10 % 35 re-isolated. Oxidation under severe conditions (40° C, 4 days) gave 24 % 36, 11 % 11β-hydroxy-5α-pregnane-3,20-dione and 2 % 20β-hydroxy-5α-pregnane-3,11-dione. No oxidation of 35 took place with nickel peroxide.

CONCLUSIONS

The nickel hydroxide electrode proves to be an effective and versatile alternative to conventional chemical oxidants. The most important advantages of this method are the easy work-up, an aqueous electrolyte, favourable electrolysis conditions and the use of the electric current as reagent. Further application of this electrode to the oxidation of amines[27] and other compounds is currently under investigation in our laboratory.

EXPERIMENTAL

The structures of products already described in the literature were confirmed by comparing their NMR, IR and mass spectra with the data reported. ^{1}H-NMR spectra were obtained with Varian HA 100 or Bruker WM 300 spectrometers, ^{13}C-NMR spectra with a Bruker WH 90 spectrometer, using $CDCl_3$ as solvent and Me_4Si as internal standard. IR spectra were recorded on a Perkin–Elmer 421 instrument; mass spectra were obtained with a Varian SM 1 or CH 7 spectrometer or by GC-MS using a Varian MAT 111. Melting points were determined with a Kofler hot stage apparatus and are uncorrected. The purity of starting compounds and products was checked by glc, normally using a 3 m × 2 mm glass column with 5% FFAP on Chrombosorb W. Gas chromatographic separation of hydroxysteroids was done after silylation with MSTFA on a 25 m × 0.3 mm glass capillary with 0.3% SE 30. Organic extracts were dried over $MgSO_4$ and evaporated at reduced pressure. t-Butanol (Merck) was used as cosolvent without further purification.

Electrolysis cell

Electrolyses were usually carried out in a 300 ml glass cell previously described in detail[10] with a nickel net anode (250 cm^2, supplied by C. M. Pieper & Co., D-5800 Hagen 5) and a cylindrical stainless steel cathode. Additional pumping of the electrolyte was required only when long-chain alcohols were oxidized in the absence of the cosolvent. The reaction temperature was regulated by the help of a thermostat. Electrolyses at room temperature could also be performed in a 600 ml beaker. A divided cell was constructed by placing a ceramic diaphragm between anode and cathode. The oxidation of hydroxysteroids was carried out in a "Swiss roll' cell[28] of 0.3 m^2 electrode area; the electrolyte (400 ml) was circulated by pumping with an Eheim pump 1022.

Conditions of electrolysis

Electrolyte A. 1 molar aqueous sodium hydroxide. *Electrolyte B.* t-Butanol/water (1:1) containing 0.1–0.3 mol l^{-1} potassium hydroxide. Constant current electrolysis (Heinzinger potentiostat TNs 300–1500 or any other direct current power supply) at current densities usually between 2.4 mA/cm^2 (i = 0.6 A) and 16 mA/cm^2 (i = 4 A); cell voltages 1.8–2.3 V in an undivided cell.

Activation of the electrode. Before each electrolysis, a thin nickel oxide hydroxide surface layer was deposited on the nickel net in 0.1 N nickel sulfate 0.1 N sodium acetate/0.005 N sodium hydroxide solution.[29] By manual or mechanical pole-changing, the nickel net was used alternately as anode or cathode for short periods (5–10 sec), until a black surface layer had been formed (0.5 Cb/cm^2; current density 1 mA/cm^2).

I. *General procedure for oxidation of primary alcohols and α,ω-diols (Tables 1 and 2)*

30–40 mmol of the substrate were electrolyzed in 280 ml of electrolyte A or B, respectively, following the electrolysis conditions given in the Tables. The alkaline electrolyte was extracted with ether (3 × 10 ml) to remove unchanged starting compound; in electrolyte B, separation of t-butanol was facilitated by saturating the electrolyte with NaCl before ether extraction. The carboxylic acids were isolated by acidification with 12N hydrochloric acid, followed by ether extraction (3 × 100 ml); the crude acids (purity >95%) were purified further by bulb-to-bulb distillation or recrystallization. In the oxidation of short-chain primary alcohols and α,ω-diols, ether extraction was continuous (24 h).

II. *General procedure for oxidation of secondary alcohols (Table 3)*

40 mmol of the secondary alcohol were electrolyzed in 280 ml electrolyte A or electrolyte B (glc or tlc control). The alkaline electrolyte was then saturated with NaCl and extracted with ether (3 × 100 ml). The organic extract was evaporated at reduced pressure, and the residual ketone was purified by column chromatography or hplc. If isolation of the ketone was not required, only the ether was evaporated at normal pressure; the yield was then determined by gas chromatography or as the 2,4-dinitro-phenylhydrazone derivative. Acid by-products were isolated from the alkaline aqueous phase by acidification and usual work-up.

III. *General procedure for oxidation of hydroxy steroids (Table 4)*

1 mmol of the hydroxy steroid was dissolved in 200 ml t-butanol, a solution of potassium hydroxide (0.23 g; 4 mmol) in 200 ml water is added with stirring, and the resulting solution was electrolyzed in a "Swiss roll" electrolysis cell (tlc or capillary GC control). If necessary, some potassium hydroxide was added during electrolysis. Work-up is done by saturating the electrolyte with NaCl, followed by ether extraction (3 × 100 ml), evaporation of the organic extracts at reduced pressure and purification of the residual products by column chromatography or HPLC.

Competition experiments were carried out by co-electrolyzing identical amounts of different alcohols in the same cell until half of the electricity required for complete oxidation had been passed. The ratio of reactivity was given by the relative yields of the different products formed (determined gas chromatographically or by isolation of the products). Oxidations with *chemical oxidants* followed general procedures described in the literature. *Hydroxy steroids* were obtained from the corresponding ketones by reduction with $LiAlH_4$ in dry tetrahydrofuran.

Preparation of Z-4-octene-1,8-diol

Z-4-Octene-1,8-diol (**7**) was obtained by reduction of *Z*-4-octenedioic acid dimethylester[30] (9.20 g, 46 mmol) with $LiAlH_4$ (3.50 g, 92 mmol) in 100 ml ether and purified by bulb-to-bulb distillation (90–95°/0.02 torr); yield 3.64 g (55%). IR: ν_{max} = 3600–3040; 3005; 2930; 2860; 1050 cm^{-1}; ^{1}H-NMR: δ = 1.43–1.90 (m, 4H, –C$\underline{H}_2$–); 1.90–2.43 (m, 4H, –C$\underline{H}_2$–CH=); 2.77–3.33 (s, 2H, –O$\underline{H}$, exchangeable with D_2O); 3.33–3.83 (t, 4H, –C$\underline{H}_2$OH); 5.06–5.63 (m, 2H, –C$\underline{H}$=C$\underline{H}$–); MS: *m/e* 144 (0.5%, M$^+$); 126 (2%); 114 (3%); 108 (4%); 67 (100%); Found: C, 66.53; H, 11.16. Calc. for $C_8H_{16}O_2$: C, 66.63; H, 11.18%.

Oxidation of tetraethylene glycol

Oxidation of tetraethylene glycol (**9**) (30 mmol) following procedure I yielded a mixture of 3,6,9-trioxaundecanedioic acid (**10**) (50%), 3,6-dioxaoctanedioic acid (**11**) (16%) and 3-oxapentanedioic acid (**12**) (3%), separated by preparative GC after esterification with diazomethane. 3,6,9-Trioxaundecanedioic acid dimethylester showed IR: ν_{max} = 2960; 2880; 1740; 1140–1110 cm^{-1}; ^{1}H-NMR: δ = 3.75 (m, 14H, CH_3O_2C– and O–C$\underline{H}_2$C$\underline{H}_2$–O–); 4.20 (s, 4H, –O–C$\underline{H}_2$–CO_2CH_3); MS (DCI): *m/e* 251 (100%, M$^+$ + H); MS (EI): *m/e* = 250 (0%, M$^+$); 161 (1%); 147 (2%); 133 (1%); 117 (100%); Found: C, 48.12; H, 7.36; Calc. for $C_{10}H_{18}O_7$: C, 48.00; H, 7.25%. 3,6-Dioxaoctanedioic acid dimethylester showed IR: ν_{max} = 2960; 2920; 1745; 1150–1110 cm^{-1}; ^{1}H-NMR: δ = 3.80 (m, 10H, CH_3O_2C– and –O–C$\underline{H}_2$C$\underline{H}_2$–O–); 4.22 (s, 4H, –O–C$\underline{H}_2$–CO_2CH_3); MS (EI): *m/e* = 206 (0%, M$^+$); 174 (7%, M$^+$ –CH_3OH); 147 (4%); 117 (100%); Found: C, 46.56; H, 6.83; Calc. for $C_8H_{14}O_6$: C, 46.60; H, 6.84%. 3-Oxapentanedioic acid dimethylester: MS (EI): *m/e* 162 (0%, M$^+$); 130 (5%, M$^+$ – CH_3OH); 103 (29%); 74 (65%); 45 (100%); Found: C, 44.34; H, 6.37; Calc. for $C_6H_{10}O_5$: C, 44.45; H, 6.21%.

Preparation of 2-ethyl-1,6-hexanediol

2-Ethyl-1,6-hexanediol **13** was obtained by reduction of 2-ethyladipic acid dimethylester[31] (16.46 g; 72 mmol) with $LiAlH_4$ (5.42 g; 143 mmol) in 150 ml ether and purified by bulb-to-bulb distillation (92–95°/0.01 torr); yield 10.08 g (96%). IR: ν_{max} =

3500–3020; 2930; 2870; 1030 cm^{-1}; ^{1}H-NMR: δ = 0.70–1.00 (m, 3H, CH_3–); 1.07–1.72 (m, 9H, $-CH_2-$ and $-CH-$); 3.00 (s, 2H, –OH, exchangeable with D_2O); 3.37–3.73 (m, 4H, $-CH_2OH$); MS: *m/e* 146 (0.5%, M^+); 116 (2%); 110 (2.5%); 98 (36%); 97 (24%); 69 (36%); 55 (100%); Found: C, 65.64; H, 12.69; Calc. for $C_8H_{18}O_2$: C, 65.71, H, 12.41%.

Partial oxidation of 2-ethyl-1,6-hexanediol **13**

10 mmol (1.46 g) **13** were electrolyzed following procedure I (5°; 0.3 A) until half the electricity required for complete oxidation had passed (3860 Asec, 4 faraday mol^{-1} **13**). The mixture of 5-ethyl-6-hydroxy-hexanoic acid (**14**; 19%), 2-ethyl-6-hydroxy-hexanoic acid (**15**; 6%) and 2-ethyl-adipic acid (**16**; 37%) was methylated with diazomethane and then separated by hplc. Complete oxidation of **13** at 80° occured without difficulty (Table 2). 5-Ethyl-6-hydroxyhexanoic acid methylester: yield 0.33 g (1.9 mmol, 19%); IR: ν_{max} = 3600–3100, 2960, 2880, 1745, 1050 cm^{-1}, ^{1}H-NMR: δ = 0.70–1.10 (t, 3H, CH_3–); 1.20–2.00 (m, 7H, $-CH_2-$ and $-CH-$); 2.20–2.50 (t, 3H, $-CH_2-CO_2CH_3$); 2.72 (s, 1H, –OH), 3.50–3.66 (m, 5H, $-CH_2OH$ and $-CO_2CH_3$); MS: *m/e* = 175 (1%, $M^+ + H$); 156 (1%); 144 (34%); 125 (18%); 124 (17%); 101 (69%); 87 (97%); 74 (75%); 55 (100%); Found: C, 61.88; H, 10.46, Calc. for $C_9H_{18}O_3$: C, 62.04; H, 10.41%. 2-Ethyl-6-hydroxyhexanoic acid methylester: yield 0.10 g (0.6 mmol, 6%); IR: ν_{max} = 3600–3100; 2960; 2880; 1740; 1050 cm^{-1}; ^{1}H-NMR: δ = 0.70–1.10 (t, 3H, CH_3–); 1.25–2.00 (m, 8H, $-CH_2-$); 2.10–2.50 (m, 2H, $-CH-$ and OH); 3.50–3.80 (m, 5H, $-CH_2OH$ and $-CO_2CH_3$); MS: *m/e* = 175 (1%, $M^+ + H$); 156 (1%); 146 (3%); 144 (4%); 143 (6%); 115 (25%); 102 (70%); 87 (100%); Found: C, 62.20; H, 10.30; Calc. for $C_9H_{18}O_3$: C, 62.04; H, 10.41%. 2-Ethyl-adipic acid dimethyl ester, yield 0.75 g (3.7 mmol, 37%); spectroscopic data in accordance with the structure.

Oxidation of 1-phenyl-2-propyne-1-ol **22**

40 mmol (5.29 g) **22** in 300 ml electrolyte B were electrolyzed in a divided cell following procedure II (5°; 0.6 A; 8100 Asec). Besides 2.94 g (56%) unchanged **22**, 1.46 g (3.7 mmol, 28%) **23** and 0.20 g (1.5 mmol, 4%) **24** were isolated by hplc. Oxidation of 20 mmol (2.64 g) **22** in 400 ml ^{t}BuOH/water (1:1), buffered with Na_2CO_3/$NaHCO_3$ (1:1), gives 0.25 g (0.95 mmol, 10%) **25** as the main product (8 h; 0.6 A; divided cell). 3-Phenyl-3-keto-propanol-di(1-phenyl-2-propyn-1-yl) acetal (**23**); yellow oil. IR: ν_{max}: 3280, 3050, 3020, 2120, 1680 cm^{-1}, ^{1}H-NMR: δ = 2.53–2.69 (m, 2H, ≡CH); 3.33–3.59 (m, 2H, $-CO-CH_2-CH-$); 5.46–5.66 (m, 2H, Ph–CH(OR)–); 5.76–6.10 (m, 1H, $-CH_2-CH(OR)_2$); 7.13–7.69 (m, 13H, aromatic H); 7.76–8.10 (m, 2H, aromatic H); ^{13}C-NMR: δ = 44.4, 44.0 ($-CO-CH_2-CH-$); 68.4, 68.0 ($-C\equiv CH$); 76.2, 75.6 ($-C\equiv CH$); 81.2, 81.4 (Ph–CH(OR)–); 98.0, 98.4 ($-CH(OR)_2$); 126.7, 127.2, 128.2, 128.5, 129.5, 132.8, 133.1, 136.9, 138.0, 138.1 (C aromatic); 196.2, 196.4 (C=O), doubling of the signals due to the mixture of diastereomers formed; MS: *m/e* 394 (0%, M^+); 287 (41%); 262 (58%), 132 (74%), 131 (73%), 115 (88%), 114 (100%). 1-Phenyl-2-propyn-1-one **24**: yellow crystals, m.p. 47–48° (lit[32] 50–51°); IR: 3240, 2100, 1640 cm^{-1}; ^{1}H-NMR: δ = 3.46 (s, 1H, C≡CH); 7.26–7.73, 8.03–8.30 (m, 3H, 2H, aromatic H); MS: *m/e* 130 (100%, M^+). 1-phenyl-3-(1-phenyl-2-propyn-1-oxy)-2-propene-1-one **25**; yellow oil, IR: 3280, 3050, 3020, 2120, 2100, 1670, 1605 cm^{-1}, ^{1}H-NMR: δ = 2.76–2.85 (d, J = 2 Hz, 1H, (C≡CH); 5.70–5.82 (d, J = 2 Hz, 1H, –CH–C≡C); 6.50–6.69 (d, J = 12 Hz, O=C–CH=CH–); 7.17–7.66 (m, 8H, aromatic H); 7.69–8.03 (m, 3H, O=C–CH=CH–O– and 2 aromatic H); MS: *m/e* 262 (100%, M^+); 234 (74%); 233 (88%); 184 (29%); 157 (58%); 116 (93%); high resolution mass measurement, obs. 262.0997; Calc. for $C_{18}H_{14}O_2$: 262.0994.

Oxidation of cholic acid

Oxidation of 1 mmol (0.41 g) cholic acid following procedure III yielded after acidification, esterification with 2,2-dimethoxypropane trace of HCl and subsequent hplc separation 0.16 g (38%) **31** and 0.10 g (22%) **32** besides 0.07 g (17%) recovered starting compound. 7α,12α-Dihydroxy-3-oxo-5β-cholan-24-oic acid methylester **31**, m.p. 175–178° (MeOH)lit[23] 173–175°; IR: ν_{max} = 3560–3300; 1730; 1695 cm^{-1}; ^{1}H-NMR: δ = 0.74 (s, 3H, CH_3–, C-18); 1.00 (m, 6H, CH_3–, C-19 and C-21); 1.00–2.55 (m, 29H); 3.42 (t, 1H); 3.66 (s, 3H, $-CO_2CH_3$); 3.92 (s, 1H, C-7-βH); 4.04 (s, 1H, C-12-βH); MS in accordance with the literature.[33] Additionally 0.01 g of the dimethylketal of **31** were formed during esterification. 7α,12α-dihydroxy-3,4-seco-cholan-3,4,24-trioic acid -3,24-dimethylester-4,7α-lactone **32**; m.p. 130–131°; IR: ν_{max} = 3600–3200; 1760; 1730 cm^{-1}; ^{1}H-NMR: δ = 0.71 (s, 3H, CH_3–, C-18); 0.94 (s, 3H, CH_3–, C-19); 0.98 (d, 3H, CH_3–, C-21); 1.00–2.60 (m, 23H); 3.66 (2 partly resolved s, 6H, $-CO_2CH_3$); 3.98 (s, 1H, C-12-βH); 4.42 (d, 1H, C-7-βH); ^{13}C-NMR, characteristic signals (CD_3OD): δ = 73.0 (–CHOH, C-12); 80.7 (–CHOR, C-7); 176.1, 176.4 ($-C_2O_2CH_3$, C-3 and C-24); 180.2 (O=C–OR, γ-lactone, C-4); MS: *m/e* = 464 (100%, M+); 446 (80%); 433 (34%); 415 (20%); 391 (31%); 331 (90%); 299 (58%), Found: C, 67.22, H, 8.68; Calc. for $C_{26}H_{40}O_7$: C 67.22; H 8.68%.

Preparation of 3α,7α,12α-trihydroxy-5β-cholane **33**

A solution of cholic acid (4.09 g, 10 mmol), acetic acid (6.00 g, 100 mmol) and potassium hydroxide (0.28 g, 5 mmol) in 70 ml abs MeOH has electrolyzed at platinum electrodes (6 cm^2) until the electrolyte became alkaline (pH 7.5). Electrolysis conditions: 1.2 A; 40 V, 200 mA/cm^2; 5°. Work-up by ether extraction and repeated hplc separation yielded 0.53 g (1.4 mmol, 14%) **34** after recrystallization from ethanol/water (1:1); m.p. 189–192°, lit[34] 186–188°; IR: ν_{max} = 3600–3100; 2920; 2860 cm^{-1}; ^{1}H-NMR: δ = 0.69 (s, 3H, CH_3–, C-18); 0.85–0.92 (m, 6H, CH_3–, C-19, C-24); 0.99 (d, 3H, CH_3–, C-21); 1.00–2.34 (m, 27H); 3.35–3.49 (m, 1H, C-3-βH); 3.84 (s, 1H, C-7-βH); 3.99 (s, 1H, C-12-βH); MS: *m/e* = 378 (11%, M^+); 363 (20%); 360 (9%); 342 (100%); 324 (35%); 271 (66%); 253 (56%).

Oxidation of 3α,7α,12α-trihydroxy-5β-cholane **33**

Electrolysis of 0.5 mmol (0.19 g) **33** following procedure III yielded 7α,12α-dihydroxy-3-oxo-5β-cholane (**34**) (0.19 mmol; 0.07 g; 38%); m.p. 206–209° (from ethanol/water 1:1); IR: ν_{max} = 3600–3100; 2920; 2840; 1695 cm^{-1}; ^{1}H-NMR: δ = 0.75 (s, 3H, CH_3–, C-18); 0.88 (t, 3H, CH_3–, C-24); 0.96–1.02 (m, 6H, CH_3–, C-19, C-21); 1.04–2.53 (m, 25H); 3.43 (t, 1H); 3.93 (s, 1H, C-7-βH); 4.08 (s, 1H, C-12-βH); MS: *m/e* = 376 (27%, M^+); 361 (6%); 358 (46%); 340 (15%); 325 (14%); 287 (16%); 269 (100%); Found: C, 76.35; H, 10.71; Calc. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71%.

Preparation of 5α-pregnane-3β,11β,20β-triol **35**

35 was obtained from 5α-pregnane-3,11,20-trione (1.90 g; 5.7 mmol) by reduction with $LiAlH_4$ (2.28 g, 60 mmol) in 300 ml dry THF[35] and purified by repeated recrystallization from 70 ml hexane/acetone (2:1); yield 0.91 g (2.7 mmol, 47%, lit[35] 75%); m.p. 205–208° (lit[35] 203–205°); ^{1}H-NMR: δ = 0.97 (s, 3H, CH_3–, C-18); 1.05 (s, 3H, CH_3–, C-19); 1.13 (d, 1H, CH_3–, C-21); 0.90–2.25 (m, 24H); 3.50–3.65 (m, 1H, C-3-α-H); 3.65–3.77 (m, 1H, C-20); 4.24–4.2° (m, 1H, C-11-αH); MS: *m/e* 336 (7%, M^+).

Oxidation of 5α-pregnane-3β,11β,20β-triol **35**

Electrolysis of **35** (0.34 g, 1 mmol) following procedure III yields 0.26 g (0.78 mmol, 78%) **36** besides 0.04 g (0.1 mmol, 10%) recovered **35** and 0.015 g (0.05 mmol, 5%) 11β-hydroxy-5α-pregnane-3,20-dione. 11β-20β-*Dihydroxy-5α-pregnane-3-one* **36**, m.p. 187–189° (MeOH); IR: ν_{max} = 3600–3300; 2940; 2920; 2860; 1695 cm^{-1}; ^{1}H-NMR: δ = 1.00 (s, 3H, CH_3–, C-18); 1.15 (d, 3H, CH_3–, C-21); 1.28 (s, 3H, CH_3–, C-19); 1.00–2.52 (m, 23H); 3.64–3.76 (m, 1H, C-20); 4.26–4.32 (m, 1H, C-11-αH); MS: *m/e* = 334 (11%, M^+); 316 (100%); 301 (41%); 298 (74%); 283 (47%); 230 (77%); 229 (72%); Found: C, 75.26; H, 10.36, Calc. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.24%. Under severe conditions (4 days, 40°) 24% **36**, 11% 11β-hydroxy-5α-pregnane-3,20-dione and 2% 20β-hydroxy-5α-pregnene-3,11-dione were formed.

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