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APPLICATIONS OF CHROMOUS CHLORIDE—II[1]

THE REDUCTION OF SOME STEROIDAL NITRO-COMPOUNDS

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Abstract—The reduction by chromous chloride of 6-nitrocholesteryl acetate and some 5α-chloro-6β-nitro-steroids to 5α-hydroxy-6-oximino steroids is described.

IN RECENT years chromous salts have been shown to be versatile reducing agents possessing a selectivity which complements that of other reducing agents. Thus the reduction of alkyl halides can lead to replacement by hydrogen, to elimination or to dimerization dependent upon the environment of the halogen, the anion associated with the chromous ion and the solvent.[2] The addition of hydrogen donors to the reduction of steroidal bromohydrins has been shown[3] to favour the formation of the corresponding alcohol. Reduction of halogen can occur selectively in the presence of carbonyl and olefinic functions. αβ-Epoxy-ketones are reduced to the corresponding β-hydroxy-ketone or αβ-unsaturated-ketone by these reagents.[4] Mechanistic studies of the reduction of alkyl halides have demonstrated[2, 3, 5] the intervention of a free-radical followed by the formation of an alkyl-chromium derivative which subsequently undergoes protonolysis, elimination, or reacts with a further molecule of alkyl halide to give dimeric products. In their initial studies on the reducing ability of chromous salts, Traube and Passarge[6] noted that alkaline solutions of chromous chloride reduced inorganic nitrates to ammonia. However, the reduction of organic nitro compounds by chromous chloride has not been explored in detail. It is the purpose of this paper to describe the reduction of some steroidal nitro compounds. By embodying the nitro group in a relatively rigid aliphatic environment, it was hoped to clarify the stereochemical consequences of the reaction. We have shown that the reaction follows a different course in an aromatic environment. These results will be described later.

The nitro compounds required for this study were prepared by literature methods[7, 8]

1 J. R. Hanson and E. Premuzic, *Tetrahedron Letters* 5441 (1966).

2 W. C. Kray and C. E. Castro, *J. Am. Chem. Soc.* **86**, 4603 (1964); and subsequent papers. L. H. Slaugh and J. H. Riley, *Tetrahedron* **20**, 1005 (1964); J. K. Kochi and P. E. Mocado, *J. Org. Chem.* **30**, 1134 (1965).

3 D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse and M. M. Pechet, *J. Am. Chem. Soc.* **88**, 3016 (1966); C. H. Robinson, O. Gnoj, E. P. Oliveto and D. H. R. Barton, *J. Org. Chem.* **31**, 2749 (1966).

4 W. Cole and P. L. Julian, *J. Org. Chem.* **19**, 131 (1954).

5 J. K. Kochi and D. D. Davis, *J. Am. Chem. Soc.* **86**, 5264 (1964); J. K. Kochi and D. Buchanan, *J. Am. Chem. Soc.* **87**, 853 (1965).

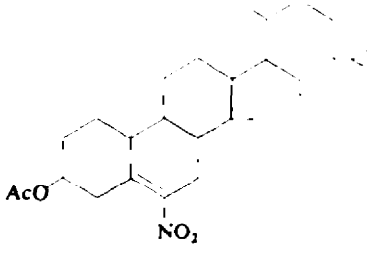
6 W. Traube and W. Passarge, *Ber. Dtsch. Chem. Ges.* **49**, 1692 (1916).

7 C. A. Anagnostopoulos and L. F. Fieser, *J. Am. Chem. Soc.* **76**, 532 (1954).

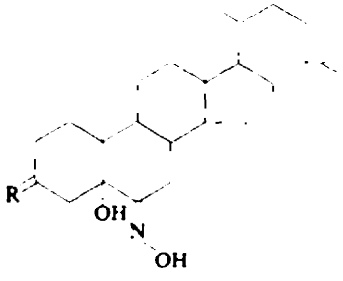
8 W. A. Harrison, Sir E. R. H. Jones, G. D. Meakins and P. A. Wilkinson, *J. Chem. Soc.* 3210 (1964).

or minor variations. Thus 3β,5α-dichloro-6β-nitrocholestane was prepared by the addition of nitrosyl chloride to cholesteryl chloride in ether containing potassium acetate.

In a preliminary communication we reported[1] the reduction of 6-nitrocholesteryl acetate (I) with 0·1N chromous chloride in refluxing tetrahydrofuran to give the oxime II of 3β-acetoxy-5α-hydroxycholestan-6-one in 80% yield. The identity of the product was confirmed by preparation of the oxime from 3β-acetoxy-5α-hydroxycholestan-6-one. During this correlation a discrepancy was noted in the physical constants recorded in the literature.[9] It was found that use of the standard pyridine-hydroxylamine hydrochloride procedure brought about some hydrolysis of the 3β-acetate to give a mixture of the 3β-hydroxy and 3β-acetoxy derivatives.



I

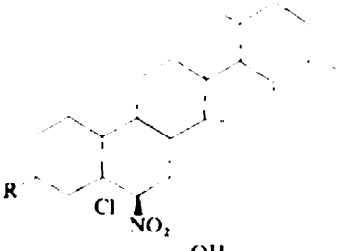


II R = OAc, H

VI R = OH, H

VII R = O

VIII R = Cl, H



III R = OH, H

IV R = O

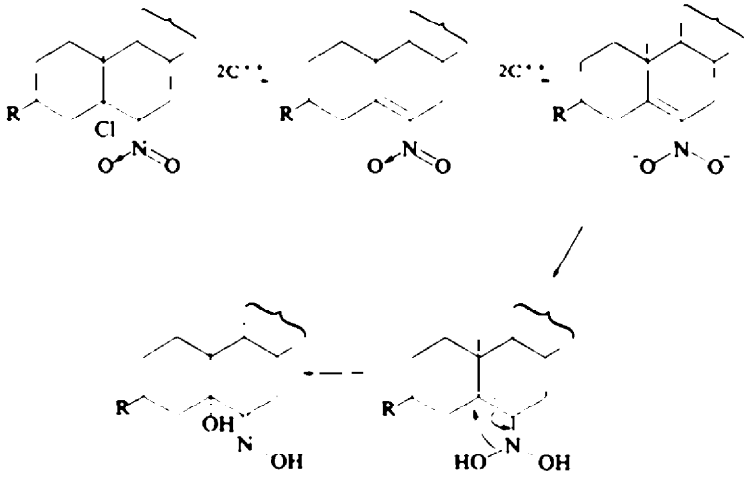
V R = Cl, H

[9] R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.* **62**, 516 (1940)

When 5α-chloro-6β-nitrocholestan-3β-ol (III), 5α-chloro-6β-nitrocholestan-3-one (IV) and 3β,5α-dichloro-6β-nitrocholestane (V) as representative examples of polyfunctional steroidal nitro-compounds, were treated with acidic 0·1N chromous chloride in refluxing tetrahydrofuran, the corresponding 5α-hydroxy-6-oximes were obtained in good yield. In the absence of chromous chloride the compounds did not undergo elimination of hydrogen chloride. Furthermore the hydroxy-oximes which were obtained possess a 5α-OH group. Their identities in the cases of the 3β-hydroxy and 3β-chloro compounds were confirmed by an unambiguous preparation of the oximes. Thus hydroxylation[10] of cholesteryl chloride with hydrogen peroxide:formic acid gave the 5α:6β-diol. Oxidation with chromium trioxide gave the 6-ketone from which the oxime was prepared by the standard procedure without displacing the 3β-chlorine atom. In the reduction of the dichloro-compound only the 5α-chlorine was displaced. 3β-Chlorocholest-5-ene was stable to reduction under these conditions.

It seemed that the first stage in the reduction might involve the reductive elimination of hydrogen chloride. Hence by analogy with the reduction of bromohydrins,[3] addition of a hydrogen donor such as butan-1-thiol might alter the course of the reaction. However, addition of excess butan-1-thiol to the reaction of 5α-chloro-6β-nitrocholestan-3β-ol completely inhibited reduction. The same result was obtained with 3β,5α-dichloro-6β-nitrocholestane and 6-nitrocholesteryl acetate. In the presence of a small amount of butan-1-thiol and a large excess of chromous chloride the 5α-hydroxy-6-oxime formed the sole product.

The following mechanism can account for the formation of the α-hydroxy-oximes.



In support of this, the reaction was shown to require four equivalents of chromous chloride. A mechanism of this kind would predict an *anti* rather than a *syn* stereochemical arrangement of the hydroxyl and oxime-OH. Although it is rather a weak correlation anti-benzaldoxime shows a C=N stretching frequency at 1650 cm^{-1} whilst syn-benzaldoxime shows a signal at 1640 cm^{-1}. The compounds prepared in this investigation show a C=N stretching at 1650 cm^{-1}. No useful correlation in this context could be found in the 3500 cm^{-1} region of the spectrum.

[10] L. F. Fieser and S. Rajagopolan, *J. Am. Chem. Soc.* 71, 3938 (1949).

Two related reactions are pertinent to these observations. Firstly zinc and acetic acid reduction of 4-methyl-2-nitropent-2-ene gave rise to, *inter alia*, the oxime of 3-hydroxy-4-methylpentan-2-one.[11] Secondly reduction of 6-nitrocholesteryl chloride with zinc and acetic acid gave a 20% yield of the oxime of 3β-chloro-5α-cholestan-6-one possibly through the intervention of an alkenyl-hydroxylamine.[12] The formation of α-hydroxy-oximes contrasts with the formation of a 4:6-isoxazole on irradiation[13] of 6-nitrocholesteryl acetate.

We have found that the oxime chromophore shows a Cotton effect in its ORD curve and a corresponding CD absorption. The first extremum lies near 236 mμ just within the measurable range. Although these results will be described elsewhere, the measurement was used in these experiments as it forms a clear distinction from the parent nitro-compounds which show a band corresponding to the n-π* absorption of the nitro group at 280 mμ.[14]

EXPERIMENTAL

UV spectra were determined on a Unicam SP.800 spectrometer IR spectra were determined as nujol mulls on a Unicam SP.200 spectrometer. Rotations were determined, unless otherwise stated, in $CHCl_3$ soln on a Perkin-Elmer 141 polarimeter. ORD and CD was measured on a JASCO ORD/UV 5 spectrometer. Mass spectra were determined on a AEI MS. 9 mass spectrometer. M.ps were determined on a Kofler hot-stage and are uncorrected. Microanalyses were carried out by Dr. A. Bernhardt, Mulheim, Germany.

Chromous chloride (0·1N) was prepared[15] by the reduction of chromic chloride (14·7 g/l.) with Zn and standardized potentiometrically against $CuSO_4$ to give solns which were 0·1N + 0·02 with respect to Cr^{2+}. All operations with this reagent were carried out in a N_2 atmosphere.

Preparation of nitro steroids. 6-Nitrocholesteryl acetate had m.p. 103–104°, $[\alpha]_D$ −78° (*c*, 1·1; lit.,[7] 104°, $[\alpha]_D$ −80°). 5α-Chloro-6β-nitrocholestan-3β-ol had m.p. 94·5–97°, $[\alpha]_D$ −84° (*c*, 5·3; lit.,[8] 96–100°, $[\alpha]_D$ −83°). 5α-Chloro-6β-nitrocholestan-3-one had m.p. 138–139°, $[\alpha]_D$ −87° (*c*, 1·9; cf. lit.,[8] 153–155°, $[\alpha]_D$ −86°).

3β,5α-Dichloro-6β-nitrocholestane. (V). Nitrosyl chloride (2·75 g) in ether (15 ml) was added in the cold to a soln of 3β-chlorocholest-5-ene (5 g) and anhyd AcOK (1·5 g) in ether (50 ml) and the mixture allowed to stand at −10° for 8 days. The soln was poured into ice water and extracted with ether. The extract was washed with $NaHCO_3$ aq, dried and evaporated. *3β,5α-Dichloro-6β-nitrocholestane* (4·6 g) crystallized from acetone–MeOH as prisms, m.p. 107–109°; $[\alpha]_D$ −83·5° (*c*, 0·5). (Found: C, 66·8; H, 9·2; N, 2·8; Cl, 14·8. $C_{27}H_{44}NO_2Cl_2$ requires: C, 66·4; H, 9·6; N, 2·9; Cl, 14·6%.) ν_{max} 1552 (NO_2) and 760 (Cl) cm^{-1} *m/e* 487. ORD (380–310 mμ *c*, 0·2; 310–250 mμ *c*, 0·04 in CH_2Cl_2): $[\phi]_{380}$ −1705; $[\phi]_{340}$ −3789; $[\phi]_{308}$ −8653; $[\phi]_{283}$ 0; $[\phi]_{270}$ +5926; $[\phi]_{250}$ +7704. CD (410–336 mμ *c*, 1·02; 336–314 *c*, 0·2; 314–264 *c*, 0·04 in CH_2Cl_2): $[\theta]_{410}$ +25; $[\theta]_{380}$ +69; $[\theta]_{340}$ 0; $[\theta]_{310}$ −4703; $[\theta]_{286}$ −14738; $[\theta]_{264}$ −7839.

Chromous chloride reductions

(i) *6-Nitrocholesteryl acetate* (I). 6-Nitrocholesteryl acetate (3 g) in THF (200 ml) was treated under N_2 with 0·1N chromous chloride (485 ml) for 3 hr under reflux. The soln was cooled, concentrated and extracted with $CHCl_3$. The extract was washed with $NaHCO_3$ aq, dried and evaporated to give the *oxime* of II which crystallized from MeOH–H_2O–EtAc (7:2:1) as needles (2·5 g), m.p. 128–131° $[\alpha]_D$ −40·6, *c*, 0·343 in MeOH. (Found: C, 70·7; H, 10·3; N, 3·3; O, 15·5. $C_{29}H_{50}NO_4 \cdot H_2O$ requires: C, 70·5; H,

[11] J. Wiemann and O. Convert, *C.R. Acad. Sci., Paris* **258**, 4285 (1964).
[12] I. A. Kaye, U. Weiss and R. J. Highet, *Steroids* **1**, No. 8, 1 (1966).
[13] J. T. Pinhey and E. Rizzardo, *Chem. Comm.* **1**, 362 (1965).
[14] J. R. Bull, J. P. Jennings, W. Klyne, G. D. Meakins, P. M. Scopes and G. Snatzke, *J. Chem. Soc.* 3152 (1965); G. Snatzke, *Ibid.* 5002 (1965).
[15] A. I. Vogel, *Textbook of Inorganic Analysis* p. 340. Longmans, London (1964).

10·3; N, 2·8; 16·2%) ν_{max} 3400 (OH), 1710 (acetate), 1650 (C=N), 1275 (acetate), 1160 (C–O) cm^{-1} *m e* 475. ORD (570–270 mμ *c*, 0·34; 270–230 mμ *c*, 0·034 in MeOH) $[\phi]_{570}$ −221; $[\phi]_{500}$ −305; $[\phi]_{400}$ −582; $[\phi]_{300}$ −1663; $[\phi]_{250}$ −2979; $[\phi]_{236}$ −4157; $[\phi]_{230}$ −4019. CD (300–260 *c*, 0·034; 280–236 *c*, 0·017; path length 0·2 dm 272–236 in MeOH) $[\theta]_{300}$ −3204; $[\theta]_{270}$ −10,157; $[\theta]_{260}$ −8817; $[\theta]_{256}$ −6407; $[\theta]_{246}$ −13,729; $[\theta]_{240}$ −21,967.

(ii) 5α-*Chloro*-6β-*nitrocholestan*-3β-*ol* (III). The alcohol (500 mg) in THF (100 ml) was treated with 0·1N chromous chloride (126 ml) under reflux for 3 hr. The soln was cooled, concentrated and extracted with $CHCl_3$. The extract was washed with $NaHCO_3$aq, dried and evaporated to give the *oxime* VI 400 mg which crystallized from moist MeOH as fine needles, m.p. 227–229° (dec) $[\alpha]_D$ −34·7°, *c*, 0·17, MeOH. (Found: C, 74·6; H, 10·8; N, 3·06. $C_{27}H_{48}NO_3$ requires: C, 74·6; H, 10·8; N, 3·2%.) Repetition of this experiment with exactly 4 equivs of chromous chloride gave an 86% yield of the oxime.

(iii) 5α-*Chloro*-6β-*nitrocholestan*-3-*one* (IV). The ketone (1 g) in THF (150 ml) was treated with 0·1N chromous chloride (231 ml) under reflux for 3 hr. The soln was cooled, concentrated and extracted with $CHCl_3$. The extract was washed with $NaHCO_3$aq, dried and evaporated to give the 6-*oxime* of VII which crystallized from MeOH as needles (0·8 g), m.p. 246–248°, $[\alpha]_D$ −22·5° (*c*, 0·18, in CH_3OH:CH_2Cl_2 (1:1). (Found: C, 74·5; H, 10·4; N, 3·4. $C_{27}H_{46}NO_3$ requires: C, 75·1; H, 10·7; N, 3·2%.) ν_{max} 3350 (OH), 1700 (C=O), 1650 (C=N), 1160 (C–O) cm^{-1}, *m e* 431. ORD (388–294 mμ *c*, 0·18; 294–230 mμ *c*, 0·028 in MeOH) $[\phi]_{388}$ −582; $[\phi]_{340}$ −873; $[\phi]_{326}$ −946; $[\phi]_{310}$ −727; $[\phi]_{306}$ −679; $[\phi]_{280}$ −1520; $[\phi]_{260}$ −3040; $[\phi]_{240}$ −4408; $[\phi]_{236}$ −4560; $[\phi]_{230}$ −4256. CD (370–248 mμ *c*, 0·18; 248–232 mμ *c*, 0·028 in MeOH) $[\theta]_{370}$ +416; $[\theta]_{340}$ +384; $[\theta]_{310}$ +640; $[\theta]_{286}$ +2401; $[\theta]_{250}$ 0; $[\theta]_{240}$ −8910; $[\theta]_{236}$ −14,355; $[\theta]_{234}$ −12,375.

(iv) 3β-5α-*Dichloro*-6β-*nitrocholestane* (V). The dichloride (1·5 g) in THF (100 ml) was heated with 0·1N chromous chloride (358 ml) under reflux for 3 hr. The soln was cooled, concentrated and extracted with $CHCl_3$. The extract was washed with $NaHCO_3$aq dried and evaporated, to give the *oxime* VIII of 3β-chloro-5α-hydroxycholestan-6-one (1 g) which crystallized from MeOH as needles, m.p. 185–187° (dec) $[\alpha]_D$ −32·2 *c*, 0·19 in MeOH. (Found: C, 71·9; H, 10·1; N, 3·1; Cl, 8·1. $C_{27}H_{48}NO_2Cl$ requires: C, 71·5; H, 10·6; N, 3·1; Cl, 7·8%.) ν_{max} 3400 (OH), 1650 (C=N), 1160 (C–O) cm^{-1} *m e* 453. ORD (600–284 mμ *c*, 0·185; 284–232 mμ *c*, 0·037 in MeOH) $[\phi]_{600}$ −147; $[\phi]_{400}$ −490; $[\phi]_{340}$ −906; $[\phi]_{294}$ −1714; $[\phi]_{260}$ −2327; $[\phi]_{236}$ −3307; $[\phi]_{232}$ −3185. CD (300–250 mμ *c*, 0·185 in MeOH) $[\theta]_{300}$ −202; $[\theta]_{270}$ −808; $[\theta]_{250}$ −1415.

(v) 3β-*Chlorocholest*-5-*ene*. The chloride (3 g) in THF (100 ml) was treated with 0·1N chromous chloride (132 ml) under reflux for 6 hr. Recovery gave the starting material (2·95 g), m.p. 97–98°, $[\alpha]_D$ −27° (*c*, 7·5).

(vi) 3β-*Hydroxy*-5α-*chloro*-6β-*nitrocholestane in the presence of excess thiol*. The alcohol (0·25 g, 0·0005 mole) and butan-1-thiol (0·037 mole) in THF (100 ml) were heated with 0·1N chromous chloride (21 ml; 0·0022 equiv) under reflux. Recovery gave the starting material (0·248 g; 96·3%) mixed m.p. with starting material no depression. IR spectrum consistent with starting material.

(vii) 3β-*Hydroxy*-5α-*chloro*-6β-*nitrocholestane in the presence of thiol and excess chromous chloride*. The alcohol (2 g, 0·0042 moles) and n-butane thiol (4 ml, 0·037 mole) in THF (400 ml) were heated with 0·1N chromous chloride (482 ml, 0·05 mole) for 3 hr. Recovery gave the oxime of 3β,5α-dihydroxycholestan-6-one (1·3 g), m.p. 227–229° identified by IR, mass spectrum and mixed m.p.

(viii) 6-*Nitrocholesterylacetate in the presence of excess thiol*. 6-Nitrocholesteryl acetate (1·5 g) and butan-1-thiol (3 ml) in THF (100 ml) were treated with 0·1N chromous chloride (242 ml) under reflux for 3 hr. Recovery gave the starting material (1·3 g) identified by IR and mixed m.p.

Preparation of the oximes

(i) 3β-acetoxy-5α-hydroxycholestan-6-one (2 g) in EtOH (50 ml) was treated with hydroxylamine hydrochloride (0·6 g) and pyridine (0·7 ml) overnight. The mixture was poured into ice water, extracted with ether. The extract was washed, dried and evaporated to give a residue which was separated by preparative TLC on silica in 30% AcOEt–light petroleum. The oxime of 3β-acetoxy-5α-hydroxycholestan-6-one crystallized from moist MeOH as needles, m.p. 146–150°. The slower running fraction was the oxime of 3β,5α-dihydroxycholestan-6-one which crystallized from moist MeOH as fine needles, m.p. 227–229°.

(ii) Cholesteryl chloride (3·6 g) was stirred for 3 days with formic acid (20 ml): 30% H_2O_2 (10 ml). The soln was made just alkaline to litmus with KOHaq, diluted with water (200 ml) and stirred for 24 hr with ether. The soln was extracted with ether. The extract was dried and evaporated to give 3β-chlorocholestan-5α,6β-diol which crystallized from MeOH–ether as needles (2·5 g), m.p. 88–90°.

The alcohol (0·7 g) in acetone (25 ml) was stirred with 8N CrO_3 (0·5 ml) for 45 min. The soln was diluted and extracted with ether. Evaporation of the solvent gave 3β-chloro-5α-hydroxycholestan-6-one (0·45 g) which crystallized from aqueous MeOH as needles, m.p. 179 180°.

The chloro-ketone (50 mg) in EtOH (15 ml) was treated with hydroxylamine hydrochloride (100 mg) and pyridine (0·2 ml) at room temp for 24 hr. The soln was poured into water, filtered and the oxime (30 mg) crystallized from MeOH as needles, m.p. 185 187° identical to the oxime VIII obtained in the above reduction.