Some Dehydrogenation Reactions of Steroidal Arylhydrazones

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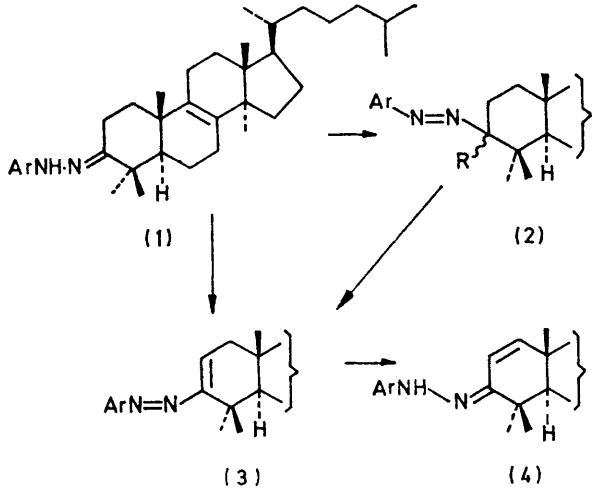
Arylhydrazones of 5α-cholestan-3-one and lanost-8-en-3-one are dehydrogenated by iodine and potassium t-butoxide, and by nitrobenzene or *p*-nitrobenzoic acid and potassium t-butoxide, to the 1,2-didehydro- or 1,2,4,5-tetradehydro-analogues respectively in high yield.

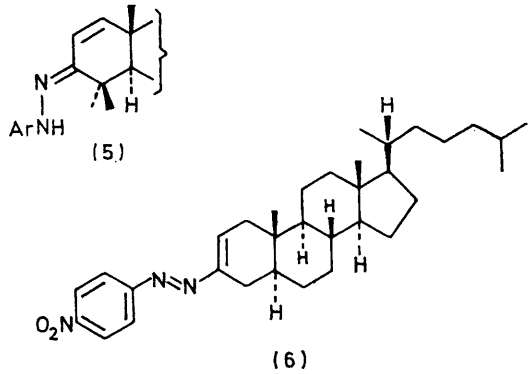
THE controlled ring A dehydrogenation of steroidal 3-ketones is generally carried out using dichlorodicyanoquinone [1] (DDQ) or selenium dioxide.[2] In a search for better reagents for this process, we have examined the



oxidation of arylhydrazones of 5α-cholestan-3-one and lanost-8-en-3-one. Aliphatic arylhydrazones are readily oxidised in the α-position by both radical and ionic processes. Thus reaction with oxygen gives the arylazo-hydroperoxide [3] [as (2; R = OOH)], and lead tetra-acetate gives the α-acyloxyarylazo-compounds [4] [as (2; R = OAc)].

In principle, oxidation by a reagent which does not add to the 3-position should furnish an azo-alkene intermediate (3). Isomerisation of the latter [5] would then afford the arylhydrazone [(4) and/or (5)]. We anticipated that the anion of (say) a *p*-nitrophenylhydrazone (1) would be oxidised readily by an electron-transfer process to give, with loss of a proton, the azo-alkene (3). Treatment of the latter with (say) potassium t-butoxide would give the more stable hydrazone by isomerisation. We decided to combine the two steps into one operation in the following way.

Iodination[6] of the *p*-nitrophenylhydrazone of lanost-8-en-3-one (1; Ar = *p*-$O_2N{\cdot}C_6H_4$) in the presence of potassium t-butoxide proceeded smoothly to give, in 85% yield, the *E*-*p*-nitrophenylhydrazone of lanosta-1,8-dien-3-one [7] (4; Ar = *p*-$O_2N{\cdot}C_6H_4$), identified by comparison with authentic material. The intermediates [presumably as (2) and (3)] could be detected by t.l.c., but because of the short reaction time (5 min) no attempt was made at their isolation. 5α-Cholestan-3-one *p*-nitrophenylhydrazone was similarly treated with two successive additions of 1 equiv. each of potassium t-butoxide and iodine to give the *p*-nitrophenylhydrazone of cholesta-1,4-dien-3-one in 85% yield. This process offers, therefore, an efficient alternative to the DDQ and selenium dioxide procedures. If these iodinations were proceeding *via* capture of the hydrazone anion [to give (2; R = I)], then the equivalent proton capture would afford the tautomeric phenylazoalkanes. In order to check this, the purple anion of the *p*-nitrophenylhydrazone of 5α-cholestan-3-one was generated in 1,2-dimethoxyethane under anaerobic conditions and quenched with aqueous 10% acetic acid. Two products were identified in addition to starting material. These were 3-*p*-nitrophenylazo-5α-cholest-2-ene (6) (8%), and the isomeric *p*-nitrophenylhydrazone of 5α-cholest-1-en-3-one (12%).



The first was identified spectroscopically, in particular *via* the characteristic u.v. spectrum [3] and the presence of one vinylic proton signal in the n.m.r. spectrum at τ 3·0, which showed multiplet splitting and not the relatively simple splitting pattern expected of a 4-ene.[8] The

[1] (*a*) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 1960, 14; (*b*) D. Burn, V. Petrow, and G. Weston, *J. Chem. Soc.*, 1962, 29; (*c*) A. B. Turner and H. Ringold *J. Chem. Soc.* (*C*), 1967, 1720; (*d*) A. B. Turner, *ibid.*, 1968, 2568.

[2] Ch. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, 1956, **39**, 734.

[3] A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, 1965, 2788.

[4] D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, 1961, **83**, 747.

[5] *Cf.* A. Hassner and P. Catsoulalos, *Chem. Comm.*, 1967, 121.

[6] (*a*) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 1962, 470; (*b*) J. Schantl, *Tetrahedron Letters*, 1970, 3785; (*c*) 1971, 153.

[7] D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 1957, 2907.

[8] *Cf.* N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 85.

former compound (6) could be isomerised into the arylhydrazone by further treatment under the reaction conditions.

This unexpected oxidative process was carefully repeated under conditions of rigorous exclusion of oxygen, and oxidation was again observed. The nitro-group of the arylhydrazone must therefore have been the oxidant.[9] The oxidation was repeated in the presence of potassium t-butoxide and an excess (15 equiv.) of nitrobenzene to give a 92% yield of the *p*-nitrophenylhydrazone of cholesta-1,4-dien-3-one. Similarly, lanost-8-en-3-one *p*-nitrophenylhydrazone gave a quantitative yield of the *E*-form of lanosta-1,8-dien-3-one *p*-nitrophenylhydrazone (4; Ar = *p*-$O_2N{\cdot}C_6H_4$) identical with the product of iodine oxidation.

This oxidation procedure is very efficient, but the work-up in the presence of an excess of nitrobenzene proved troublesome. Consequently, the oxidation was repeated using *p*-nitrobenzoic acid as oxidant. 5α-Cholestan-3-one *p*-nitrophenylhydrazone in the presence of an excess of potassium t-butoxide and *p*-nitrobenzoic acid gave a 90% yield of cholesta-1,4-dien-3-one *p*-nitrophenylhydrazone. Here the work-up is simplified (base extraction if needed), and this is the preferred method. Other nitroaryl oxidants (*p*-dinitrobenzene and *p*-nitrobenzenesulphonic acid) were tried, but proved less efficient.

Unexpectedly, the oxidation of lanost-8-en-3-one *p*-nitrophenylhydrazone under these conditions gave the less stable *Z*-form of lanosta-1,8-dien-3-one *p*-nitrophenylhydrazone (5), m.p. 167—170°, (*cf.* *E*-form, m.p. 178—181°) with very similar spectral properties to the *E*-form, but with a shift of *ca.* 0·2 p.p.m. to higher field of the H-1 and H-2 signals in the n.m.r. spectrum, and a small hypsochromic shift in the u.v. spectrum.

The relationship of the compounds was confirmed spectrophotometrically *via* aqueous base equilibration. The *Z*-form, after acidification of the basic medium, gave a product with a spectrum identical with that of the *E*-form.

We consider that these oxidations of *p*-nitrophenylhydrazone anions by *p*-nitrobenzoic acid must involve two one-electron transfers from the anion to the nitro-group of the *p*-nitrobenzoic acid coupled with proton loss.

EXPERIMENTAL

Unless otherwise stated, the following procedures were adopted in the experiments described. M.p.s were determined on a Kofler hot-stage apparatus. Rotations were measured in chloroform. I.r. spectra were recorded on solutions in chloroform or carbon tetrachloride or on Nujol mulls. U.v. spectra were measured in ethanol. N.m.r. spectra were measured in deuteriochloroform with tetramethylsilane as internal standard.

Reactions were followed by t.l.c. on silica GF_{254} plates. Preparative t.l.c. (p.l.c.) was carried out on 0·05 × 20 × 20 cm (small) or 0·1 × 20 × 60 cm (large) plates of the same material. Organic solvent extracts of aqueous solutions were dried with anhydrous sodium sulphate. Petroleum refers to that fraction with b.p. 60—80 °C.

5α-Lanost-8-en-3-one p-*Nitrophenylhydrazone* (1; Ar = *p*-$O_2N{\cdot}C_6H_4$).—5α-Lanost-8-en-3-one (1·55 g) in ethanol (15 ml) containing acetic acid (1 ml) and water (0·3 ml) was heated to boiling and *p*-nitrophenylhydrazine (0·55 g) was added. The solution was heated at reflux under nitrogen for 30 min, cooled, and filtered to give the p-*nitrophenylhydrazone* (1; Ar = *p*-$O_2N{\cdot}C_6H_4$) (1·98 g, 97%), m.p. 144—146° (from EtOH), $[\alpha]_D^{25}$ +13·4° (*c* 0·167), $\nu_{max.}$ 3300, 2950, 1600, 1338, 1272, 1120, and 856 cm^{-1}, $\lambda_{max.}$ 250 (ε 10,500) and 395 nm (23,800), τ 1·29, 2·98 (4H, q, *J* 9 Hz, ArH), and 2·24 (1H, s, NH), *m/e* 561 (M^+), 546, 531, 410, and 260 (100%) (Found: C, 77·0; H, 9·9; N, 7·5. $C_{36}H_{35}N_3O_2$ requires C, 76·7; H, 9·8; N, 7·4%).

5α-Lanosta-1,8-dien-3-one E-p-*Nitrophenylhydrazone* (4; Ar = *p*-$O_2N{\cdot}C_6H_4$).—5α-Lanost-8-en-3-one *p*-nitrophenylhydrazone (1; Ar = *p*-$O_2N{\cdot}C_6H_4$) (50 mg) was added to 1,2-dimethoxyethane (5 ml) containing potassium t-butoxide (70 mg) under argon. Iodine (22·5 mg) was added quickly and after 10 min at room temperature, the solution was quenched with aqueous 5% acetic acid (10 ml). The suspension was extracted with benzene (3 × 15 ml), washed with water (2 ml), and dried and the solvent was removed to give the E-p-*nitrophenylhydrazone* (4; Ar = *p*-$O_2N{\cdot}C_6H_4$) (59 mg, 85%), m.p. and mixed m.p. 178—181° (from EtOH), $[\alpha]_D^{25}$ +14·1° (*c* 0·09), $\nu_{max.}$ 3350, 1600, 1530, 1510, 1310, 1270, 1115, and 860 cm^{-1}, $\lambda_{max.}$ 240 (ε 9000), 295 (4500), 328 (4000), and 404 nm (25,000), τ 1·85, 2·91 (4H, q, *J* 9 Hz, ArH), 2·07 (1H, m, NH), 3·26, and 3·68, (2H, q, *J* 10 Hz, H-1, H-2) (Found: C, 77·1; H, 9·4; N, 7·4. $C_{36}H_{53}N_3O_2$ requires C, 77·2; H, 9·5; N, 7·5%).

Cholesta-1,4-dien-3-one p-*Nitrophenylhydrazone*.—5α-Cholestan-3-one *p*-nitrophenylhydrazone (101 mg) in dry, oxygen-free 1,2-dimethoxyethane (6 ml) was treated under argon sequentially with iodine (49 mg) and potassium t-butoxide (44 mg), then after 20 min with potassium t-butoxide (44 mg) and iodine (49 mg), and finally after a further 5 min with an excess of potassium t-butoxide (150 mg). The solution was stirred for 30 min and quenched with aqueous 5% acetic acid (10 ml). Extraction with benzene and filtration of the extract through a 5 cm column of alumina (grade III), gave the p-*nitrophenylhydrazone* (86 mg, 85%) m.p. 178—180° (from EtOH–$MeNO_2$), $[\alpha]_D^{25}$ +10·8° (*c* 0·104), $\nu_{max.}$ 3350, 1600, 1530, 1510, 1320, 1270, 1110, and 850 cm^{-1}, $\lambda_{max.}$ 248 (ε 8000) and 420 nm (30,000), τ 1·87, 2·91 (4H, q, *J* 9 Hz, ArH) and 3·45—3·90 (3H, m, H-1, H-2, H-4), *m/e* 517 (M^+, 100%) (Found: C, 76·8; H, 8·9; N, 7·9. $C_{33}H_{47}N_3O_2$ requires C, 76·6; H, 9·1; N, 8·1%).

3-p-*Nitrophenylazo-5α-cholest-2-ene* (6) *and* 5α-*Cholest-1-ene-3-one* p-*Nitrophenylhydrazone*.—Anhydrous 1,2-dimethoxyethane (10 ml) was distilled under argon into a flask containing stirred 5α-cholestan-3-one *p*-nitrophenylhydrazone (90 mg). Potassium t-butoxide (300 mg) was added and the purple solution stirred for 3 min at room temperature before the addition of aqueous 10% acetic acid (10 ml). Ether extraction afforded a mixture which was separated by p.l.c. (solvent EtOAc–petroleum, 1 : 4). The least polar component was 3-p-*nitrophenylazo-5α-cholest-2-ene* (6) (7 mg), m.p. 168—169° (from EtOH), $[\alpha]_D^{26}$ +60°, (*c* 0·44), $\nu_{max.}$ 1640, 1610, 1590, 1538, 1350, and 870 cm^{-1}, $\lambda_{max.}$ 328 nm (ε 25,000), τ 1·74, 2·22 (4H, q, *J* 9 Hz, ArH), and 3·0 (1H, m, H-2), *m/e* 519 (M^+, 100%) and 489 (Found: C, 76·2; H, 9·4; N, 8·0. $C_{33}H_{49}N_3O_2$ requires C, 76·2; H, 9·5; N, 8·1%).

The next most polar component was 5α-*cholest-1-en-3-one*

[9] *Cf.* F. G. Holliman, B. A. Jeffery, and D. J. H. Brock, *Tetrahedron*, 1963, **19**, 1841.

p-*nitrophenylhydrazone* (11 mg), m.p. 215—217° (from EtOH), mixed m.p. 217—220° with an authentic sample, $\nu_{max.}$ 3350, 1590, 1530, 1510, 1330, 1310, 1260, 1110, and 860 cm^{-1}, $\lambda_{max.}$ 237 (ε 3900), 289 (3600), 321 (3200), and 402 nm (13,000), τ 1·85, 2·87 (4H, q, *J* 8 Hz, ArH), 2·28 (1H, m, NH), 3·53, and 3·83 (2H, q, *J* 10 Hz, H-1, H-2), *m/e* 519 (M^+, 100%) (Found: C, 76·1; H, 9·3; N, 8·0. $C_{33}H_{49}N_3O_2$ requires C, 76·2; H, 9·5; N, 8·1%).

The more polar components were unchanged starting hydrazone (50 mg) and a number of uncharacterised highly polar substances.

Isomerisation of 3-p-*Nitrophenylazo-5α-cholest-2-ene* (6).—3-*p*-Nitrophenylazo-5α-cholest-2-ene (6) was treated with potassium t-butoxide under identical conditions to those of its formation except that 30 min was allowed before the solution was quenched. Work-up as before gave 5α-cholest-1-en-3-one *p*-nitrophenylhydrazone, identical with the sample previously isolated.

Cholesta-1,4-*dien*-3-*one* p-*Nitrophenylhydrazone* via *Oxidation by a Nitro-group*.—(*a*) 5α-Cholestan-3-one *p*-nitrophenylhydrazone (104 mg) in 1,2-dimethoxyethane (10 ml) containing nitrobenzene (350 mg) was stirred under argon with potassium t-butoxide at room temperature for 30 min. The solution was quenched with aqueous 10% acetic acid (10 ml) and extracted with ether. The residue after evaporation of ether was chromatographed over a silica column (15 g) in ether–hexane (1 : 19). Elution was continued until all the nitrobenzene had been removed. Elution with ether–hexane (1 : 9) gave cholesta-1,4-dien-3-one *p*-nitrophenylhydrazone (95 mg), identical by m.p., t.l.c., i.r., u.v., and n.m.r. with authentic material.

(*b*) 5α-Cholestan-3-one *p*-nitrophenylhydrazone (105 mg) in 1,2-dimethoxyethane (10 ml) containing *p*-nitrobenzoic acid (350 mg) was treated with potassium t-butoxide (700 mg) as before for 60 min at room temperature under argon. The reaction was quenched with aqueous 5% acetic acid (20 ml) and the solid was filtered off and recrystallised from nitromethane to give cholesta-1,4-diene-3-one *p*-nitrophenylhydrazone (91 mg), identical with an authentic specimen as before.

5α-*Lanosta*-1,8-*dien*-3-*one* p-*Nitrophenylhydrazone* (4; Ar = *p*-$O_2N{\cdot}C_6H_4$) via *Oxidation by a Nitro-group*.—(*a*) 5α-Lanost-8-en-3-one *p*-nitrophenylhydrazone (110 mg) was oxidised as above with nitrobenzene (350 mg) to give the *E*-form of 5α-lanosta-1,8-dien-3-one *p*-nitrophenylhydrazone (4; Ar = *p*-$O_2N{\cdot}C_6H_4$) (110 mg), m.p. 179—180°, identical with the sample obtained by iodine oxidation.

(*b*) The anion of 5α-lanost-8-en-3-one *p*-nitrophenylhydrazone (114 mg) was oxidised as above with *p*-nitrobenzoic acid under argon to give the *Z*-form of lanosta-1,8-dien-3-one *p*-nitrophenylhydrazone (5; Ar = *p*-$O_2N{\cdot}C_6H_4$), almost isomerically pure, m.p. 167—170° (*E*-form; m.p 178—181°), $\nu_{max.}$ 3370, 1600, 1510, 1330, 1265, 1110, and 850 cm^{-1}, τ 1·92, 2·98 (4H, q, *J* 9 Hz, ArH), 3·48, and 3·94, (2H, q, *J* 10 Hz, H-1, H-2), *m/e* 559 (M^+), 529, 408, and 191 (100%), $\lambda_{max.}$ 257, 282, 320, and 399 nm, $\lambda_{max.}$ (NaOH–HCl) 235, 297, 327, and 405 nm, identical with that of the *E*-form.

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