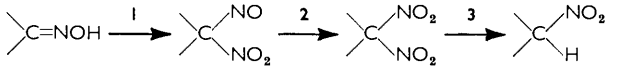
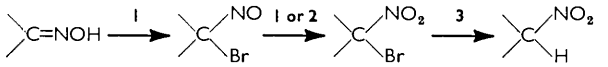
470. *Nitro-steroids. Part II.* A New Route to Nitro-steroids*

By J. R. Bull, Sir Ewart R. H. Jones, and G. D. Meakins

Our objective was a general method for preparing nitro-steroids, primarily required for spectrography. After unsuccessful attempts by oxidising oximes with peracids, a new general method, sequence (*A*), was developed and used to prepare 3-, 4-, 6-, 7-, and 17-nitro-steroids. Nitration of the oxime was followed by oxidation of the pseudo-nitrole to a *gem.*-dinitro-compound. Controlled hydrogenation of the latter resulted in reduction of one nitro-group and hydrogenolysis to mononitro-compounds. With the 4-, 6-, and 17-dinitro-compounds the α-group was removed selectively, and the 3-dinitro-compound afforded both α- and β-mononitro-products: reduction of the 7-derivative led, unexpectedly, to the 7α-mononitro-compound. In each epimeric pair of mononitro-compounds the equatorial isomer is the more stable, but the relative stabilities (equatorial/axial) vary with the position of substitution.

(A) 

Reagents: 1, HNO_3 (fuming). 2, H_2O_2–HNO_3. 3, Pt–H_2 (4 mols.).

(B) 

Reagents: 1, *N*-Bromosuccinimide. 2, H_2O_2–HNO_3. 3, $NaBH_4$.

The method of Patchett *et al.*[1] [sequence (*B*)] was early investigated with the oxime of 5α-cholestan-3-one (**5**). Although this route afforded 3β-nitro-5α-cholestane (**15**) the yield in the first stage was very low, in contrast with the method's satisfactory application to 17-oximes.

Steroid oximes react smoothly with chlorine to give deep blue, crystalline *gem.*-chloronitroso-compounds which can be oxidised to the chloronitro-derivatives.

Our original object in studying nitro-steroids was to determine whether the nitro-group was a suitable chromophore for applying the method of optical rotatory dispersion to structural problems. However, it became clear that they show interesting features in all

* Part I, W. A. Harrison, Sir Ewart R. H. Jones, G. D. Meakins, and P. A. Wilkinson, *J.*, 1964, 3210.

[1] A. A. Patchett, F. Hoffman, F. F. Giarrusso, H. Schwam, and G. E. Arth, *J. Org. Chem.*, 1962, **27**, 3822. We are grateful to Dr. A. A. Patchett for supplying us with details of his work before publication.

standard spectrographic techniques, and thus allow comparison of the nature of the information obtained from them. Studies of the optical rotatory dispersion (by Professor W. Klyne), circular dichroism (by Dr. G. Snatzke), nuclear magnetic resonance, infrared, and ultraviolet characteristics will be reported later:[2] we now describe the preparation of nitro-steroids and related compounds.

Wanting to obtain several epimeric pairs of nitro-steroids, we began our studies at position 3 of the cholestane nucleus. Although a general preparative method was so established, this site presents more difficulties than the others studied. Attempts to carry out nucleophilic substitution of the 3β-group of 5α-cholestan-3β-yl toluene-*p*-sulphonate (1) with silver or sodium nitrite were unsuccessful, as were similar attempts with cyclohexanes.[3] For example, treatment of the ester (1) with sodium nitrite in dry *N*-methylpyrrolidone (an experiment suggested by the work of Kornblum,[4] Henbest,[5] and their co-workers) afforded 5α-cholestan-3α-ol (3) (95%) and a trace of 5α-cholest-2-ene. The former may arise through an intermediate such as (4) which generates the 3α-alcohol during working up: this solvolytic displacement provides a convenient additional method for inverting the 3β-hydroxyl group.[6]

Monocyclic nitro-compounds have been obtained from oximes by treatment with peracids:[7] such oxidations of 3-hydroxyimino-5α-cholestane (5) failed to give 3-nitrocholestane. With peroxyacetic acid in chloroform or methylene dichloride complex mixtures were formed, and from the products obtained in either solvent two chloronitro-compounds were isolated in low yields. One, prepared by a second route described later was 3α-chloro-3β-nitro-5α-cholestane (6) while the second is almost certainly the 3α-nitro-isomer (7).

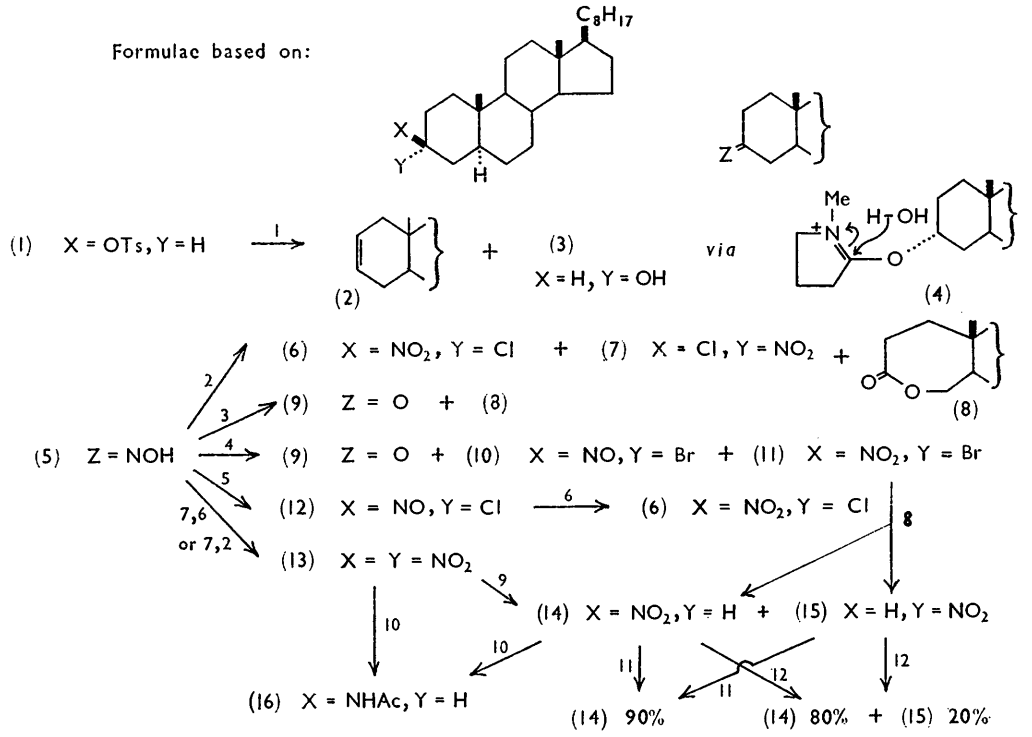
The origin of these compounds is uncertain. Hydrogen chloride, present in traces in the solvents, may be oxidised to chlorine which then reacts with the oxime. Alternatively, removal of a hydrogen atom from the oxime by the peracid may generate a free radical which abstracts chlorine from the solvent giving chloronitroso-compounds: these would then be oxidised to the chloronitro-products.

The use of peroxyacetic acid in a medium consisting largely of buffered acetonitrile gave mainly 5α-cholestan-3-one (9) and when the solvent was mainly acetic acid the ketone was accompanied by the derived lactone (8).[8] With trifluoroperoxyacetic acid in methylene chloride the oxime (5) gave a mixture from which the 3β-chloro-3α-nitro-compound (7) was isolated in 8% yield, but in view of the more promising route (*A*) discussed below different conditions were not investigated.

The less direct sequence (*B*) (see Summary) for converting oximes into nitro-compounds was introduced by Iffland and Criner[9] for simple aliphatic and alicyclic ketoximes, and modified by Patchett and his co-workers[1] in their preparation of 17β-nitroandrost-5-en-3β-yl acetate. Despite considerable experimentation the first step of this sequence was never successful with 3-hydroxyimino-5α-cholestane (5); the major product was invariably the parent ketone (8), and under the best conditions (using *N*-bromosuccinimide and potassium hydrogen carbonate in ether–water) the products were the bromonitroso-compound (10) (4%), the bromonitro-compound (11) (8%), and 5α-cholestan-3-one (9) (80%). Alternative procedures for obtaining the bromonitroso-compound from the oxime using bromine[10] or hypobromite[11,3] were similarly unsatisfactory. The bromonitro-compound (11) was

[2] Part III, in the press, and later Parts of this Series.
[3] A. T. Nielsen, *J. Org. Chem.*, 1962, **27**, 1993.
[4] N. Kornblum, R. A. Smiley, R. K. Blackwood, and O. C. Iffland, *J. Amer. Chem. Soc.*, 1955, **77**, 6269.
[5] H. B. Henbest and W. R. Jackson, *J.*, 1962, 954.
[6] F. C. Chang and R. T. Blickenstaff, *J. Amer. Chem. Soc.*, 1958, **80**, 2906; G. H. Douglas, P. S. Ellington, G. D. Meakins, and R. Swindells, *J.*, 1959, 1720.
[7] W. D. Emmons and A. S. Pagano, *J. Amer. Chem. Soc.*, 1955, **77**, 4557.
[8] V. Burckhardt and T. Reichstein, *Helv. Chim. Acta*, 1942, **25**, 1434.
[9] O. C. Iffland and G. X. Criner, *J. Amer. Chem Soc.*, 1953, **75**, 4047.
[10] O. Piloty, *Ber.*, 1898, **31**, 452.
[11] G. E. Foster, *J.*, 1899, 1141.

thus difficult to prepare, but its reduction with sodium borohydride proceeded smoothly to give a mixture of the 3β- and 3α-nitro-5α-cholestanes [(14) and (15)] in a 3 : 2 ratio.



Reagents (for this and following series): 1, *N*-Methylpyrrolidone (+$NaNO_2$), 2, AcO_2H–$CHCl_3$ (or CH_2Cl_2). 3, AcO_2H–MeCN (or AcOH). 4, *N*-Bromosuccinimide–$KHCO_3$. 5, Cl_2. 6, H_2O_2–HNO_3. 7, HNO_3 (fuming) at 40°. 8, $NaBH_4$. 9, Pt–H_2 (4 mols.). 10, Pt–H_2 (complete reduction) then Ac_2O. 11, KOH–EtOH (refluxing) then AcOH at 0°. 12, $NaHCO_3$–EtOH (refluxing).

Chlorination of the oxime (5) with chlorine in ether gave the deep blue, beautifully crystalline chloronitroso-compound (12) in 84% yield.* This and similar compounds described later are stable indefinitely in the solid state: in solution they are fairly easily oxidised to the chloronitro-compounds [as (6)] and are photochemically transformed,[2] but, surprisingly, no evidence was obtained of the formation of colourless dimers. To complete a route to 3-nitro-5α-cholestane required removal of the chlorine atom: unfortunately no selective reduction could be achieved with sodium borohydride, aluminium amalgam, chromous chloride, or by various hydrogenation procedures. [The configurations of the halogeno-nitroso- and -nitro-compounds prepared in this work are based on the assumption that addition of halogen occurs on the less hindered (α) face of the steroid nucleus.[13] The structures shown are confirmed by the n.m.r. results.[2]]

In considering other types producible by suitable addition reactions with oximes, we turned to *pseudo*-nitroles [$>C(NO)NO_2$]. These are normally prepared from secondary nitro-compounds with nitrous acid, the classical Victor Meyer reaction, but an alternative, nitration of oximes, has long been known.† One of the first *pseudo*-nitroles obtained

* The formation of chloronitroso-products from steroid di- and tri-ketones has now been reported by Hüttenrauch.[12]

† Much of the literature on the systems $>C(NO_2)X$, where X = Hal, NO, and NO_2, was published before about 1905: several features of this early work [14] are being re-examined.[2]

[12] R. Hüttenrauch, *Arch. Pharm.*, 1961, **294**, 366.

[13] For references see L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publ. Corp., New York, 1959, pp. 14, 98.

[14] It is well summarised by T. W. J. Taylor and W. Baker in N. V. Sidgwick's "The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937.

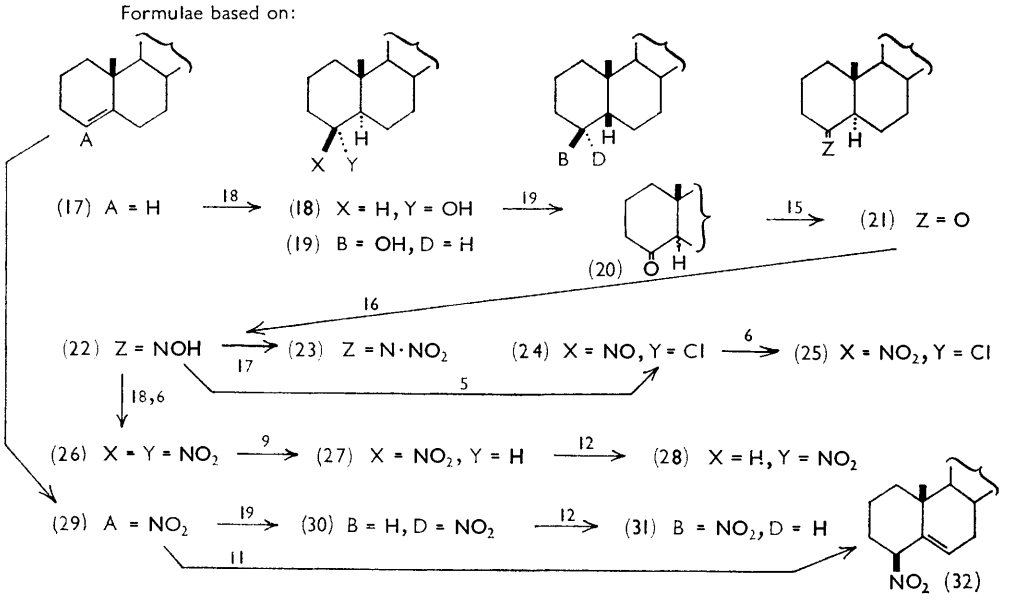
thus,[15] from camphoroxime, was oxidised in air to the *gem.*-dinitro-compound and this, rather interestingly, was studied by optical rotatory dispersion and circular dichroism techniques.[16] *gem.*-Dinitro-compounds have also been prepared by methods [14] which do not involve *pseudo*-nitroles, one variation being the treatment of the salt of a mononitro-compound with a mixture of silver nitrate and inorganic nitrites in neutral or alkaline media.[17] Although no systematic study of the reduction of *gem.*-dinitro-compounds has been recorded it seemed feasible (see later) that one of the nitro-groups might be removed by controlled hydrogenation. Trials with 3,3-dinitro-5α-cholestane (13) showed that selective reduction was possible, and sequence (*A*) (see Summary) was then developed as a general method for preparing nitro-steroids.

The slow addition of purified fuming nitric acid to a solution of the 3-oxime (5) in refluxing methylene dichloride produced a blue solution of the *pseudo*-nitrole; oxidation to the dinitro-compound (13) was expedited by hydrogen peroxide. With this oxime the yield of dinitro-compound (23%) was much lower than those of the other dinitro-compounds described here. Under the milder conditions (described later) which sufficed to convert other steroid oximes into dinitro-compounds the 3-oxime was largely unchanged. Catalytic reduction of the dinitro-compound (13) gave a variety of products depending on the extent of hydrogenation. However, by stopping the reaction after the absorption of the theoretical four mol. of hydrogen a good yield (90%) of the 3-nitro-5α-cholestanes [(14) and (15), in about equal proportions] was obtained. The 3α-epimer (15) was separated by fractional crystallisation, and when this compound, or the mixture obtained in the reduction, was refluxed with ethanolic potassium hydroxide and the solution carefully acidified at 0° the 3β-nitro-compound (14) was obtained. The almost exclusive formation of the 3β-isomer arises from kinetic control during protonation of the *acid*-salt: on treatment with sodium hydrogen carbonate in boiling ethanol, conditions of thermodynamic control,[18] both the α- and the β-nitro-compounds gave a mixture in which the 3β : 3α ratio was 4 : 1. Complete catalytic reduction of the dinitro-compound (13) followed by acetylation afforded an amide (25% yield) which was shown to be the 3β-isomer (16) [19] by a similar preparation from the 3β-nitro-compound (14).

The remaining description is mainly confined to topics not already covered in the discussion of the 3-series, and to instances in which the behaviour differed markedly from that already described. To obtain the starting material for work at position 4, cholest-4-ene (17) was hydroborated to give an alcoholic fraction containing 5α-cholestan-4α-ol (18) (58%) and a 5β-cholesten-4-ol [42%, almost certainly the 4β-compound (19)]. [Previously [20] only 5α-cholestan-4α-ol (60% yield) was reported.] After chromic oxidation the 5α- and 5β-cholestan-4-ones could be separated, but the 5α-isomer (21) was more readily obtained (64% from cholest-4-ene) by alkaline isomerisation of the ketone mixture.[21] Conversion of the derived oxime (22) into the *gem.*-dinitro-compound (26) proceeded satisfactorily under milder conditions than for the 3-oxime (5). In initial experiments, formation of a by-product, $C_{27}H_{46}N_2O_2$ was a difficulty. Its infrared spectrum indicated the presence of a nitro-group (absorption at 1569 cm.$^{-1}$) and contained a medium-intensity band at 1629 cm.$^{-1}$ which, in view of the molecular formula, was attributed to a polarised C=N system. The nitrimine [22] structure (23) was confirmed by preparing the compound (82% yield) from the oxime (22). Formation of the nitrimine during the nitration of the

[15] L. Wolff, *Annalen*, 1895, **288**, 32; W. Charlton, J. C. Earl, J. Kenner, and A. A. Luciano, *J.*, 1932, 30.
[16] S. Mitchell and R. R. Gordon, *J.*, 1936, 853.
[17] R. B. Kaplan and H. Schechter, *J. Amer. Chem. Soc.*, 1961, **83**, 3535.
[18] H. E. Zimmerman and T. E. Nevins, *J. Amer. Chem. Soc.*, 1957, **79**, 6559.
[19] D. P. Dodgson and R. D. Haworth, *J.*, 1952, 67.
[20] S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, 1959, **24**, 1034.
[21] N. L. Allinger, M. A. Da Rouge, and R. B. Hermann, *J. Org. Chem.*, 1961, **26**, 3626.
[22] S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J.*, 1958, 4614; J. P. Freeman, *J. Org. Chem.*, 1961, **26**, 4190; T. H. Wieland and D. Grimm, *Ber.*, 1963, **96**, 275.

oxime was suppressed by using carefully purified nitric acid, and the yield of dinitro-compound (22) was correspondingly improved. [With the 3-oxime (5) the presence of



Reagents: 5,6,9,11, and 12—see above. 13, B_2H_6 then H_2O_2–NaOH. 14, CrO_3–$COMe_2$. 15, KOH–MeOH. 16, H_2NOH. 17, HNO_2. 18, HNO_3 (fuming) at 0 to −5°. 19, Pt–H_2 (*ca.* 2·5 mol.).

nitrous acid during nitration would lead to regeneration of the ketone (8) rather than nitrimine formation.[22]] Controlled hydrogenation of 4,4-dinitro-5α-cholestane (22) afforded selectively the 4β-nitro-compound (27), converted into the more stable 4α-epimer (28) (90% yield) with sodium hydrogen carbonate.

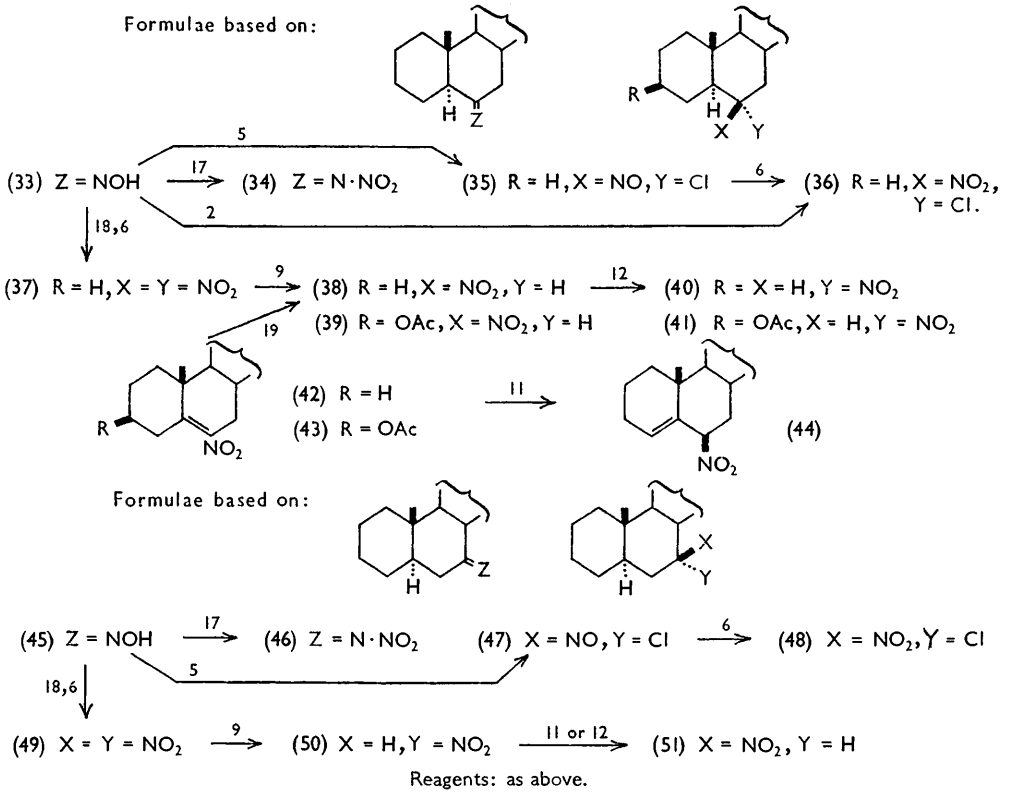
In an attempt to prepare the 4-nitro-compounds by an alternative method, 4-nitrocholest-4-ene (29) [23,24] was partially hydrogenated over platinum. During the hydrogenation of this and other conjugated nitro-compounds an uptake of 2 to 2·5 mol. of hydrogen was necessary fully to reduce the ethylenic bond. After chromatographic purification a third 4-nitrocholestane was obtained (10% yield), and converted quantitatively by sodium hydrogen carbonate into a fourth 4-nitrocholestane. The third nitro-compound is thus 4α-nitro-5β-cholestane (30) and the fourth 4β-nitro-5β-cholestane (31), formulations fully confirmed spectrographically. Treatment of 4-nitrocholest-4-ene with hot ethanolic potassium hydroxide followed by careful acidification afforded a non-conjugated nitro-compound for which structure (32) follows by analogy with similar work [25,26] and spectrographic examination.[2]

The oxime (33) of 5α-cholestan-6-one gave the *gem.*-dinitro-compound (37), the nitrimine (34), and the chloronitroso- and chloronitro-derivatives [(35) and (36)]: the last was also obtained by treating the oxime (33) with peroxyacetic acid in chloroform. Reduction of the dinitro-compound (37) to 6β-nitro-5α-cholestane (38) proceeded in high yield as did isomerisation of the latter to the 6α-nitro-compound (40). In this series the mononitro-compounds were obtained by an alternative route in which controlled hydrogenation of 6-nitrocholest-5-ene (42) [23] and 6-nitrocholesteryl acetate (43) [27,28] afforded the 6β-nitro-5α-compounds (38) and (39). Isomerisation of the 3β-acetoxy-6β-nitro-compound (39)

[23] A. Windaus, *Ber.*, 1920, **53**, 488.
[24] D. H. R. Barton and W. J. Rosenfelder, *J.*, 1951, 1048.
[25] A. Bowers, M. B. Sanchez, and H. J. Ringold, *J. Amer. Chem. Soc.*, 1959, **81**, 3702.
[26] W. A. Harrison, E. R. H. Jones, G. D. Meakins, and P. A. Wilkinson, *J.*, 1964, 3210.
[27] A. Windaus, *Ber.*, 1903, **36**, 3752.
[28] C. E. Anagnostopoulos and L. F. Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 532.

to the 6α-isomer (41) * established that the 3β-group did not influence the direction of the hydrogenation. The rearrangement of 6-nitrocholest-5-ene with strong alkali (first carried out by Mitui [29]) was repeated to give a product for which structure (44) follows from analogous work.[25,26]

Work at position 7 is summarised in formulæ (45) to (51). Although the dinitro-compound (49) was a glass, gas–liquid chromatography and spectrographic examination



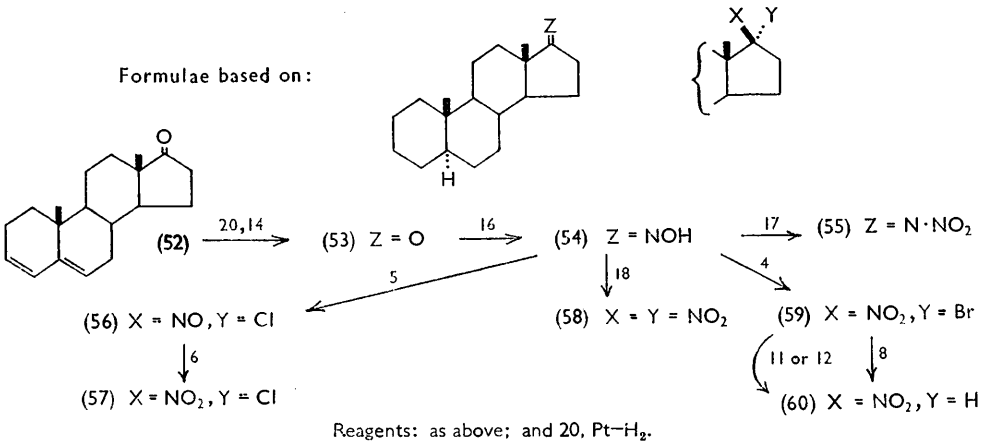
did not indicate the presence of impurities, and it gave the well-crystalline 7α-nitro-derivative (50) in 80% yield.

Since the main synthetic method (*via* the *gem.*-dinitro-compounds) was developed after obtaining poor yields with the *N*-bromosuccinimide sequence [9] in the 3-series it was of interest to compare the two routes in preparing nitro-derivatives of 5α-androstan-17-one.[30] [This ketone (53) was most conveniently prepared from dehydroepiandrosterone by dehydration to the 3,5-diene (52),[31] hydrogenation, and then mild oxidation to reconstitute the 17-oxo-group from the small proportion of 17-alcohol formed in the reduction: the alternative procedure involves the more difficult hydrogenation of the 3β-hydroxy-Δ^5-system as the first stage.] Conversion of the oxime (54) to the bromonitro-compound (59) and to 17β-nitro-5α-androstane (60) closely resembled the corresponding sequence described by Patchett *et al.*[1] Controlled reduction of the dinitro-derivative (58) also gave the 17β-nitro-compound (60), the overall yield of which from the oxime was 60% by

* Several nitro-steroids, including compounds (14) and (41), have recently been prepared by Professor A. Hassner and his collaborators, who kindly supplied specimens for comparison with ours. The close correspondence in properties, including the infrared spectra, established the identity of samples of compounds (14) and (41) prepared by the different routes.

[29] P. Mitui, *Bull. Agric. Chem. Soc., Japan*, 1940, **16**, 144.
[30] J. Elks and C. W. Shoppee, *J.*, 1953, 241.
[31] W. J. C. Ross, *J.*, 1945, 25.

Patchett's method and 45% by the nitration route. The bromosuccinimide sequence has a further advantage in that ethylenic bonds need not be protected during either

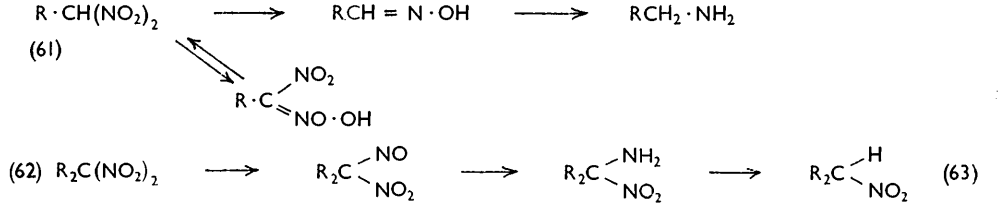


Reagents: as above; and 20, $Pt-H_2$.

stage. However, the vital consideration is that formation of the bromonitroso-intermediate should occur more quickly than the competing hydrolysis of the oxime. Further work is in progress to define the structural features which determine the relative rates of these reactions.

The 17β-nitro-compound (60) was recovered unchanged after the usual treatment with sodium hydrogen carbonate or with potassium hydroxide. This provides independent evidence for the nitro group's configuration since the 17β-isomer would be expected to predominate under conditions of either thermodynamic or kinetic control.

The preparation of nitro-steroids described here is based upon the selective reduction of one nitro-group from a *gem.*-dinitro-system. Some precedent is found in early work by Ponzio [32] who observed that reduction of *gem.*-dinitro-compounds of type (61) gave oximes



or primary amines. Although there is no direct evidence for the intermediate stages in the present reduction, which starts with dinitro-compounds (62) derived from ketones, the simple formulation (62) ⟶ (63) seems reasonable.

In four of the five dinitro-compounds reduced (positions 3, 4, 6, 7, and 17) the C–N cleavage is highly stereospecific. With the 4, 6, and 17 compounds the product is the β-mononitro-derivative, as expected, since the nitro-group which remains is protected from attack by its proximity to one of the angular methyl groups. In the case where reduction gives a mixture of mononitro-compounds (position 3) the protection is absent. From its resemblance to the 3-dinitro-compound the 7-isomer would be expected to give both the 7-mononitro-compounds: 7α-nitrocholestane was, however, the sole product obtained.

The epimerisations with sodium hydrogen carbonate described above were primarily aimed at the preparation of the more stable (3β, 4α, 6α, 7β, and 17β) nitro-steroids. However, the composition of the mixtures produced by such treatment provides a measure of the relative stabilities of the epimers. Analysis of the mixtures by gas–liquid chromatography was not very satisfactory, the separation between epimers being small, and in the

[32] G. Ponzio, *J. prakt. Chem.*, 1902, [ii], **65**, 197.

infrared spectra the resemblance between epimers made it impossible to detect a small amount of one epimer in the presence of a far greater proportion of the other. Nevertheless, the percentages of the equatorial epimers in the equilibrium mixtures (approached from both sides) could be reliably estimated as 3β = 80; 4α and 6α > 90; 7β = 70; 17β > 90%. With the 3-compounds it is reasonable to suppose that the 4 : 1 ratio represents the " natural " relative stabilities of equatorial and axial nitro-groups, since neither epimer is subject to unusual interactions. With the 4- and 6-compounds the axial isomers are involved in severe non-bonded repulsions with the 19-methyl groups, and are consequentially destabilised. In the 7-series it is the equatorial (7β) group which suffers the additional interactions, primarily that involving the $C_{(15)}$-methylene, and a lower equatorial percentage results. The situation at position 17 is less clear since it is possible that the conformation of ring D differs in the two isomers.[33,2]

Experimental

Preparations common to several series are described first: then those which apply only to some, and isolated experiments are described last. Several of the oxidation procedures are potentially dangerous and *safety precautions* are necessary.

M. p.s were determined on a Kofler hot-stage apparatus and are corrected. Rotations were determined in chloroform at 20° with a Bendix–Ericcson automatic polarimeter. Ultraviolet spectra were recorded for ethanol solutions with a Cary 14M spectrometer, and infrared spectra for carbon tetrachloride or carbon disulphide solutions with a Perkin-Elmer model 237 spectrometer: for most compounds spectrographic data will be reported elsewhere.[2] Neutral alumina was prepared by stirring P. Spence material (grade H) with an excess of ethyl acetate for 2 days, filtration, washing repeatedly with hot water, and heating at 250° for 2 days. Silica gel was B.D.H. chromatographic grade. Light petroleum had b. p. 60—80°.

Oximes.—*6-Hydroxyimino-5α-cholestane* (**33**). A solution of 5α-cholestan-6-one (13 g.),[34] hydroxylamine hydrochloride (6 g.), and hydrated sodium acetate (12 g.) in ethanol (450 c.c.) was refluxed for 45 min. After addition of water the product was collected, washed with water, and dried to give the 6-oxime (12·8 g.), m. p. 204—206° (needles from ethyl acetate), $[\alpha]_D$ −11° (*c* 0·5), $\nu_{max.}$ 3560, 3230, and 1665 cm.$^{-1}$ (lit.,[35] m. p. 195°).

Similar preparations gave the 3-oxime (**5**), m. p. 197—201° (from acetone), $[\alpha]_D$ +21° (*c* 1·0) (lit.,[36] m. p. 199°); 4-oxime (**22**), m. p. 219—222° (from chloroform–methanol), $[\alpha]_D$ +114·5° (*c* 1·1) (lit.,[37] m. p. 205—207°); 7-oxime (**45**), m. p. 133—135° (prisms from ethyl acetate), $[\alpha]_D$ −116° (*c* 1·0) (lit.,[38] m. p. 134—135°); *17-hydroxyimino-5α-androstane* (**54**), m. p. 177—179° (plates from acetone–methanol), $[\alpha]_D$ +18° (*c* 1·0) (Found: C, 78·7; H, 10·8; N, 4·7. $C_{19}H_{31}NO$ requires C, 78·8; H, 10·8; N, 4·8%), $\nu_{max.}$ 3595, 3300, and 1676 cm.$^{-1}$.

gem.-*Dinitro-compounds.*—*6,6-Dinitro-5α-cholestane* (**37**). A mixture of fuming nitric acid (200 c.c., d. 1·5) and sulphuric acid (200 c.c.) was distilled at atmospheric pressure in an apparatus protected from moisture, the first 100 c.c. of distillate being collected. Before nitration this process was repeated, urea (100 mg. for 10 c.c. of acid) was added, and the acid used immediately.

Fuming nitric acid (10 c.c.) was added cautiously during 10 min. to a stirred solution of the 6-oxime (**33**) (1 g.) in dry ether (40 c.c.) at −5°. The blue colour which developed during the addition intensified after a further 20 min. at −5°. The temperature was then allowed to rise slowly to 15° during 30 min. and maintained at 15° for a further 30 min., stirring being continued throughout. Hydrogen peroxide (5 c.c., 100 vol.) was added cautiously, and after the blue colour had disappeared (5—10 min.) the mixture was diluted with water and extracted with ether. The ether solution was washed with water, aqueous sodium hydrogen carbonate, aqueous ferrous sulphate, and water, and then dried. Evaporation at 40°/15 mm. gave material which was dissolved in light petroleum and chromatographed on neutral alumina (60 g.). Elution with light petroleum–benzene (9 : 1; 500 c.c.) afforded the *dinitro-compound* (**37**) (0·57 g., 50%)

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[36] J. O. Ralls, *J. Amer. Chem. Soc.*, 1938, **60**, 1744.
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which crystallised from ethyl acetate as needles, m. p. 122—123°, solidifying at 124° to plates, m. p. 126—127°, $[\alpha]_D$ +36° (*c* 0·5) (Found: C, 70·1; H, 10·0; N, 5·85. $C_{27}H_{46}N_2O_4$ requires C, 70·1; H, 10·0; N, 6·1%).

Elution with benzene (250 c.c.) gave 5α-cholestan-6-one (0·23 g., m. p. and mixed m. p. 96—98°), and ether–methanol (19 : 1; 250 c.c.) eluted the 6-oxime (33) (0·16 g.), m. p. 203—205°.

Similar preparations gave the *4,4-dinitro-compound* (26) (45%), m. p. 133—135° (rods from ethyl acetate–methanol), $[\alpha]_D$ (*c* 0·4) (Found: C, 69·95; H, 10·0; N, 5·95); *7,7-dinitro-compound* (49) (48%) as a glass, $[\alpha]_D$ 0° (*c* 1·0) (Found: C, 69·7; H, 9·85; N, 5·8); *17,17-dinitro-compound* (58) (48%), m. p. 188—190° (rods from ethyl acetate–methanol), $[\alpha]_D$ +70° (*c* 0·5) (Found: C, 65·3; H, 8·8; N, 8·0. $C_{19}H_{30}N_2O_4$ requires C, 65·1; H, 8·6; N, 8·0%).

The *3,3-dinitro-compound* (13) was prepared in two ways: (*a*) Fuming nitric acid (25 c.c.) was added during 5 min. to a refluxing solution of the 3-oxime (5) (5 g.) in methylene dichloride (250 c.c.). After 40 min., hydrogen peroxide (10 c.c., 100 vol.) was added cautiously and the refluxing continued for 1 hr. more. Working up and chromatography as above gave *3,3-dinitro-5α-cholestane* (1·31 g., 23%), m. p. 147—148° (rods from ethyl acetate–methanol), $[\alpha]_D$ +34° (*c* 0·9) (Found: C, 70·0; H, 10·0; N, 6·2. $C_{27}H_{46}N_2O_4$ requires C, 70·1; H, 10·0; N, 6·1%).

(*b*) The oxime (5) (2 g.) in methylene dichloride (50 c.c.) was added during 10 min. to a refluxing mixture of fuming nitric acid (10 c.c.) and methylene dichloride (100 c.c.) and the refluxing continued for a further 20 min. A solution containing peroxyacetic acid [10 c.c. of a solution prepared by adding acetic anhydride (11·3 c.c.) dropwise to a mixture of 85% hydrogen peroxide (4 c.c.) and chloroform (25 c.c.) at −5°] was added slowly to the boiling mixture which was then refluxed for 1 hr. After the addition of water the organic layer was separated and washed successively with water, aqueous sodium hydrogen carbonate, water, aqueous ferrous sulphate, and water. The 3,3-dinitro-compound (0·71 g., 31%), m. p. 147—148°, was isolated by elution with light petroleum–benzene (19 : 1) from neutral alumina as above.

Hydrogenolysis of gem.*-Dinitro-compounds.*—*6β-Nitro-5α-cholestane* (38). A solution of the 6,6-dinitro-compound (37) (0·75 g.) in ethyl acetate (30 c.c.) was shaken in hydrogen with pre-reduced Adams catalyst (150 mg.) at 20°. After the absorption of 4 mol. of hydrogen (*ca.* 150 c.c.) the reduction was stopped, the filtered solution was evaporated, and the residue chromatographed on silica gel (75 g.). Elution with light petroleum–benzene (4 : 1; 500 c.c.) gave the *6β-nitro-compound* (0·60 g.), m. p. 100—102°. After two crystallisations from ethyl acetate the product was obtained as needles, m. p. 106—107°, $[\alpha]_D$ −23° (*c* 0·54) (Found: C, 77·7; H, 11·3; N, 3·4. $C_{27}H_{47}NO_2$ requires C, 77·6; H, 11·3; N, 3·35%). Elution with ether gave the 6-oxime (35) (43 mg.), m. p. 200—204°, identified by infrared examination.

Similar reduction of the 4,4-dinitro-compound (26) (0·75 g.) gave *4β-nitro-5α-cholestane* (27) (0·64 g.), m. p. 115—116° (plates from methanol), $[\alpha]_D$ +83° (*c* 0·5) (Found: C, 77·3; H, 11·4; N, 3·4%), and the 4-oxime (22) (27 mg.), m. p. 214—218° undepressed by admixture with authentic material. The 7,7-dinitro-compound (49) (483 mg.) gave *7α-nitro-5α-cholestane* (50) (352 mg.), m. p. 119—120° (rods from ethyl acetate), $[\alpha]_D$ −11° (*c* 0·5) (Found: C, 77·8; H, 11·4; N, 3·3%). 17,17-Dinitro-5α-androstane (58) (650 mg.) gave *17β-nitro-5α-androstane* (60) (537 mg.) which crystallised from ethyl acetate as plates and sublimed at 140° forming rods, m. p. 158—159°, $[\alpha]_D$ +49° (*c* 1·0) (Found: C, 74·7; H, 10·1; N, 4·65. $C_{19}H_{31}NO_2$ requires C, 74·7; H, 10·2; N, 4·6%).

3,3-Dinitro-5α-cholestane (13) (1·15 g.) afforded a mixture of the 3-nitro-5α-cholestanes (0·93 g.), m. p. 125—140°, $[\alpha]_D$ +25° (*c* 0·5) (Found: C, 77·6; H, 11·3; N, 3·35%) and the 3-oxime (5) (65 mg.). Examination of the mixture of 3-nitro-compounds by g.l.c. gave two barely separated peaks of equal intensity. Chromatography on silica did not separate the products, and the melting-range of the mixture was unchanged by sublimation at 140°/0·1 mm. Fractional crystallisation from acetone gave *3α-nitro-5α-cholestane* (15) (120 mg.) as plates, m. p. 157—160°, $[\alpha]_D$ +26° (*c* 1·2) (Found: C, 77·5; H, 11·3; N, 3·8. $C_{27}H_{47}NO_2$ requires C, 77·6; H, 11·3; N, 3·35%). Evaporation of the combined mother-liquors afforded a mixture, m. p. 116—128°, which was treated with potassium hydroxide as described later.

Reaction of Oximes with Chlorine.—*6α-Chloro-6β-nitroso-5α-cholestane* (35). Dry chlorine was passed through a solution of the 6-oxime (33) (500 mg.) in ether (100 c.c.) at 20° for 10 min. in the dark. Removal of the solvent and the excess of chlorine at 30°/10 cm. and two crystallisations of the residue from ethyl acetate afforded the *chloronitroso-compound* (35) as blue plates (356 mg.), m. p. 105—106°, $[\alpha]_D$ +218° (*c* 1·0) (Found: C, 74·2; H, 10·85; Cl, 8·0; N, 3·5. $C_{27}H_{46}ClNO$ requires C, 74·35; H, 10·6; Cl, 8·1; N, 3·2%).

Similar preparations gave the 3-*chloronitroso-compound* (12) (84%), m. p. 146—148° (blue rods from ethyl acetate), $[\alpha]_D$ +216° (*c* 0·9) (Found: C, 74·0; H, 10·7; N, 3·25%); 4-*compound* (24) (72%), m. p. 84—85° (blue rods from ethyl acetate), $[\alpha]_D$ −93° (*c* 0·5) (Found: C, 73·9; H, 10·5; Cl, 8·3; N, 3·3%); 7-*compound* (47) (70%), m. p. 68—72° (blue blades from ethyl acetate), $[\alpha]_D$ +58° (*c* 0·55) (Found: C, 74·15; H, 10·6; Cl, 8·1; N, 3·4%); 17-*compound* (56) (89%), m. p. 108—109° (blue hexagonal rods from acetone–methanol), $[\alpha]_D$ +822° (*c* 0·1) (Found: C, 70·6; H, 9·7; Cl, 10·85; N, 4·2. $C_{19}H_{30}ClNO$ requires C, 70·5; H, 9·3; Cl, 10·9; N, 4·3%).

Oxidation of Chloronitroso-compounds.—6α-*Chloro*-6β-*nitro*-5α-*cholestane* (36). Fuming nitric acid (4 c.c.) was added during 1 min. to a vigorously stirred mixture of the 6-chloronitroso-compound (35) (1 g.) in chloroform (50 c.c.) and hydrogen peroxide (5 c.c., 100 vol.) at 20°. A brisk exothermic reaction took place during the addition. Stirring was continued until the mixture became colourless (*ca.* 20 min.), chloroform (50 c.c.) was added, and the organic layer separated, washed repeatedly with water, dried, and evaporated at 20 mm. The residue was adsorbed from light petroleum on neutral alumina (50 g.). Elution with light petroleum (650 c.c.) afforded the 6-*chloronitro-compound* (36) (593) mg.) which crystallised from ethyl acetate–methanol as needles, m. p. 120—121°, solidifying at 122° to plates, m. p. 123—124°, $[\alpha]_D$ +20° (*c* 1·0) (Found: C, 71·4; H, 10·3; Cl, 8·0; N, 3·2. $C_{27}H_{46}ClNO_2$ requires C, 71·7; H, 10·3; Cl, 7·8; N, 3·1%).

Similar oxidations gave the 3-*chloronitro-compound* (6) (84%), m. p. 175—175·5° (blades from ethyl acetate), $[\alpha]_D$ +30° (*c* 1·0) (Found: C, 71·8; H, 10·5; Cl, 7·8; N, 3·3%); 4-*compound* (25) (68%), m. p. 130—132° (rods from ethyl acetate), $[\alpha]_D$ +23·5° (*c* 0·6) Found: C, 71·6; H, 10·0; Cl, 7·9; N, 3·3%); 7-*compound* (48) (50%), m. p. 58—61° (leaflets from acetone), $[\alpha]_D$ +26° (*c* 0·6) (Found: C, 71·6; H, 10·15; Cl, 7·75; N, 3·2%); 17-*compound* (57) (56%), double m. p. 122—123° and 128—129° (from ethyl acetate–methanol), $[\alpha]_D$ +26° (*c* 0·6) (Found: C, 71·6; H, 10·15; Cl, 7·75; N, 3·2. $C_{27}H_{46}ClNO_2$ requires C, 71·7; H, 10·3; Cl, 7·8; N, 3·1%).

Formation of Nitrimines.—6-*Nitrimino*-5α-*cholestane* (34). A solution of sodium nitrite (1 g.) in water (4 c.c.) was added at 0° to a solution of the 6-oxime (33) (400 mg.) in ether–glacial acetic acid (1 : 1; 50 c.c.). After 2 hr. water was added, and the product was isolated with ether and chromatographed on silica gel (50 g.). Elution with light petroleum (500 c.c.) gave the 6-*nitrimine* (34) (276 mg.), m. p. 76—81°, which after two crystallisations from acetone–methanol had m. p. 84—87°, $[\alpha]_D$ −13° (*c* 0·4) (Found: C, 75·6; H, 10·8; N, 6·6. $C_{27}H_{46}N_2O_2$ requires C, 75·3; H, 10·8; N, 6·5%).

Similar preparations gave the 4-*nitrimine* (23) (82%), m. p. 189—191° (needles from ethyl acetate), $[\alpha]_D$ +107° (*c* 0·5) (Found: C, 75·25; H, 10·6; N, 6·6%), $\nu_{max.}$ 1569, 1321, 1312 (NO_2) and 1629 (C=N) cm.$^{-1}$; 7-*nitrimine* (46) (79%), m. p. 94—97° (from ethyl acetate), $[\alpha]_D$ −105° (*c* 1·0) (Found: C, 75·0; H, 10·6; N, 6·4); 17-*nitrimine* (55) (57%), m. p. 110—112° (rods from ethyl acetate), $[\alpha]_D$ +19° (*c* 0·5) (Found: C, 71·3; H, 9·3; N, 8·4; $C_{19}H_{30}N_2O_2$ requires C, 71·7; H, 9·5; N, 8·8%).

Treatment of Nitro-compounds with Sodium Hydrogen Carbonate.—A boiling solution of the nitro-compound (100—500 mg.) in ethanol–water (9 : 1; 100 c.c.) was saturated with sodium hydrogen carbonate and the mixture refluxed for 12 hr. After concentration at 20 mm. to about half-volume the mixture was worked up by the addition of water and extraction with ether. The infrared spectrum of the product was recorded in order to establish the proportions of the epimeric nitro-compounds present, before crystallisation as described below.

3α-Nitro-5α-cholestane (15) (100 mg., key infrared band for estimation at 1363 cm.$^{-1}$) and 3β-nitro-5α-cholestane (14) (100 mg., preparation described later, key infrared band at 1377 cm.$^{-1}$) both gave a mixture, m. p. 85—105°, $[\alpha]_D$ +24° (*c* 0·5), in which the 3β : 3α ratio was 4 : 1. Two crystallisations of the products from ethyl acetate gave the 3β-compound (14) (40 mg.), double m. p. 98—99° and 108—110°, identical with an authentic specimen described later. 4β-Nitro-5α-cholestane (27) (325 mg.) afforded 4α-*nitro*-5α-*cholestane* (28) (300 mg.), m. p. 124—125° (rods from ethyl acetate—methanol), $[\alpha]_D$ +23° (*c* 0·5) (Found: C, 77·8; H, 11·5; N, 3·2. $C_{27}H_{47}NO_2$ requires C, 77·6; H, 11·3; N, 3·35%). 4α-Nitro-5β-cholestane (30) (120 mg., preparation described later) gave 4β-*nitro*-5β-*cholestane* (31), m. p. 88—89° (plates from ethyl acetate–methanol), $[\alpha]_D$ +43° (*c* 0·5) (Found: C, 77·6; H, 11·3; N, 3·35%). The material obtained from 6β-nitro-5α-cholestane (38) (450 mg.) crystallised from aqueous ethanol to give 6α-*nitro*-5α-*cholestane* (40) (413 mg.) as plates m. p. 138—139°, $[\alpha]_D$ +45° (*c* 1 : 1) (Found: C, 77·6; H, 11·1; N, 3·5%). 6β-Nitro-5α-cholestan-3α-yl acetate (39) (450 mg.) afforded material

(435 mg.) containing at least 90% of the 6α-isomer (41): two crystallisations of the material from methanol yielded the 6α-*nitro-compound* as needles (231 mg.) which changed at 110° to prisms, m. p. 128—129°, $[\alpha]_D$ +38° (*c* 0·6) (Found: C, 73·1; H, 10·3; N, 2·8. $C_{29}H_{49}NO_4$ requires C, 73·2; H, 10·4; N, 2·9%). 7α-Nitro-5α-cholestane (50) (150 mg.) gave a mixture containing 7β- and 7α-compounds in a ratio of 7 : 3. Several crystallisations of the product from acetone–methanol afforded the 7β-nitro-compound (51) (45 mg.), double m. p. 74—75° and 95—97°, identical with an authentic specimen described later. 17β-Nitro-5α-androstane (60) (100 mg.) was recovered unchanged (92 mg., m. p. 157—159°, $[\alpha]_D$ +50°) after treatment with sodium hydrogen carbonate.

Treatment of Nitro-compounds with Potassium Hydroxide.—A solution of the nitro-compound (100 mg.) in 0·4% ethanolic potassium hydroxide (20 c.c.) was refluxed under nitrogen for 3 hr., cooled to 0°, and acidified by dropwise addition of glacial acetic acid (0·2 c.c.). [In larger scale experiments the nitro-compound (1 g.) was treated with 0·4% ethanolic potassium hydroxide (100 c.c.) and the mixture concentrated at 20 mm. to half-volume before being cooled and acidified.] The material obtained by dilution with water and extraction with ether was crystallised as described below.

3α-Nitro-5α-cholestane (15) (100 mg.), 3β-nitro-5α-cholestane (14) (100 mg., obtained initially from the 3α-nitro-compound), and a mixture of epimers [0·5 g., m. p. 116—128° obtained in the reduction of the 3,3-dinitro-compound (13) described earlier] were separately treated in this way. Crystallisation of the products from ethyl acetate–methanol gave in each case the 3β-*nitro-compound* (14) (87–93%) as plates, m. p. 98—99°, solidifying at 101° to plates, m. p. 109—110°, $[\alpha]_D$ +23° (*c* 1·0) (Found: C, 77·3; H, 11·3; N, 3·1. $C_{27}H_{47}NO_3$ requires C, 77·6; H, 11·3; N, 3·35%).

4-Nitrocholest-4-ene (29) (450 mg., preparation described later) gave material (420 mg.) which was absorbed from light petroleum on silica gel (50 g.). Elution with light petroleum–benzene (4 : 1; 400 c.c.) afforded 4β-*nitrocholest-5-ene* (32) (305 mg.) which after two crystallisations from ethyl acetate–methanol was obtained as leaflets (110 mg.), m. p. 149—151°, $[\alpha]_D$ +85·5° (*c* 0·4) (Found: C, 78·1; H, 10·7; N, 3·8. $C_{27}H_{45}NO_2$ requires C, 78·0; H, 10·9; N, 3·4%), $\nu_{max.}$ 1549 (NO_2), 1660 and 840 (Δ^5) cm.$^{-1}$. 6-Nitrocholest-5-ene (42) (1·1 g., preparation described later) gave 6β-nitrocholest-4-ene (44) (0·56 g.), m. p. 113·5—115° (needles from ethyl acetate), $[\alpha]_D$ −67° (*c* 0·5) (Found: C, 78·4; H, 11·3; N, 3·4. Calc. for $C_{27}H_{45}NO_2$: C, 78·0; H, 10·9; N, 3·4%) (lit.,[29] m. p. 113°), $\nu_{max.}$ 1548 (NO_2), 1665 and 851 (Δ^4) cm.$^{-1}$.

The product from 7α-nitro-5α-cholestane (50) (200 mg.) was dissolved in benzene and filtered through silica gel (25 g.). Evaporation and crystallisation of the residue from acetone–methanol afforded 7β-*nitro-5α-cholestane* (51) (110 mg.) as prisms melting at 74—75° and solidifying at 76° to give rods, m. p. 96—97°, $[\alpha]_D$ +50° (*c* 0·5) (Found: C, 77·2; H, 11·1; N, 3·3. $C_{27}H_{47}NO_2$ requires C, 77·6; H, 11·3; N, 3·3%). Treatment of 17β-nitro-5α-cholestane (60) (100 mg.) with potassium hydroxide gave starting material (90 mg.), m. p. and mixed m. p. 156—159°.

Nitration of Olefins.—The following procedure closely resembles that developed by Anagnostopoulos and Fieser [28] for nitrating cholesteryl acetate. Of the ten experiments carried out with cholest-5-ene six were successful, but in the other four the reaction mixture became deep brown and no pure product could be isolated. With cholesteryl acetate and cholest-4-ene the results reported were reproducible.

6-*Nitrocholest-5-ene* (42).—Fuming nitric acid (15 c.c., freshly purified) was added dropwise during 10 min. to a stirred solution of cholest-5-ene (2·5 g.) in ether (30 c.c., distilled from phosphoric oxide and stored over sodium) at −5°. After 25 min. at −5° the temperature was slowly raised to 10°, and stirring continued until brown fumes appeared above the liquid. (The total reaction time was *ca.* 1·5 hr.) Dilution with water, extraction with ether, and crystallisation from methanol gave 6-nitrocholest-5-ene (1·4 g.) as plates, m. p. 117—120°. After a further crystallisation from ethyl acetate–methanol the product had m. p. 120—121·5°, $[\alpha]_D$ −85·5° (*c* 0·6), $\lambda_{max.}$ 2610 Å (ε 2780), $\nu_{max.}$ 1520 cm.$^{-1}$ (lit.,[23] m. p. 117—118°).

Cholesteryl acetate (2·5 g.) was nitrated and the product crystallised twice from methanol to give 6-nitrocholesteryl acetate (43) (1·8 g.), m. p. 104—105°, $[\alpha]_D$ −80° (*c* 0·8), $\lambda_{max.}$ 2610 Å (ε 2850), $\nu_{max.}$ 1735, 1232, and 1034 (OAc), and 1525 (NO_2) cm.$^{-1}$ {lit.,[28] m. p. 103—104°, $[\alpha]_D$ −80°, $\lambda_{max.}$ 2580 Å (ε 1940)}.

The product from cholest-4-ene (17) (2·5 g.) was adsorbed from light petroleum on silica gel (150 g.). Elution with light petroleum (250 c.c.) gave cholest-4-ene (210 mg.), m. p. and mixed

m. p. 78—80°. The material eluted with benzene (600 c.c.) crystallised from acetone to give 4-nitrocholest-4-ene (29) (1·49 g.), m. p. 68—70°, $[\alpha]_D$ +78° (*c* 0·4) (Found: C, 77·8; H, 10·9; N, 3·45. Calc. for $C_{27}H_{45}NO_2$: C, 78·0; H, 10·9; N, 3·4%), $\lambda_{max.}$ 2620 Å (ε 2700), $\nu_{max.}$ 1645 (C=C) and 1520 (NO_2) cm.$^{-1}$ (lit.,[23] m. p. 70°).

Hydrogenation of Unsaturated Nitro-compounds.—*6β-Nitro-5α-cholestane* (38). A solution of 6-nitrocholest-5-ene (42) (2·15 g.) in ethyl acetate (50 c.c.) was shaken in hydrogen with pre-reduced Adams catalyst (200 mg.). After the absorption of 2 mol. of hydrogen (*ca.* 235 c.c.) the reduction was stopped, the filtered solution was evaporated, and the residue absorbed from light petroleum on silica gel (200 g.). Elution with light petroleum–benzene (3 : 1; 800 c.c.) gave 6β-nitro-5α-cholestane (1·45 g.), m. p. 102—104°, identified by mixed m. p. and comparison of infrared spectra with an authentic specimen described earlier.

The hydrogenation of 6-nitrocholesteryl acetate (1·4 g.) over pre-reduced Adams catalyst (200 mg.) was stopped after the absorption of *ca.* 135 c.c. of hydrogen and the product was chromatographed on silica gel (100 g.). Elution with light petroleum–benzene (4 : 1; 1200 c.c.) afforded *6β-nitro-5α-cholestan-3β-yl acetate* (39) (0·71 g.) which crystallised from methanol as plates melting at 113—115° and solidifying at 115° to prisms, m. p. 136—138°, $[\alpha]_D$ −49° (*c* 0·6) (Found: C, 73·5; H, 10·4; N, 2·8. $C_{29}H_{49}NO_4$ requires C, 73·2; H, 10·4; N, 2·9%). Crystallisation from ethyl acetate gave the higher-melting form, also obtained by seeding the melt from the lower-melting form.

A similar reduction of 4-nitrocholest-4-ene (29) (1·5 g.) was stopped after the absorption of 200 c.c. of hydrogen and the product was chromatographed on silica gel (200 g.). Elution with light petroleum–benzene (9 : 1, 500 c.c.) afforded a product (0·376 g.) which was twice crystallised from ethyl acetate to give *4α-nitro-5β-cholestane* (30) (0·14 g.) as rods, m. p. 144—146°, $[\alpha]_D$ −48° (*c* 0·4) (Found: C, 77·5; H, 11·3; N, 3·1. $C_{27}H_{47}NO_2$ requires C, 77·6; H, 11·3; N, 3·35%).

Ketones.—*5α-Cholestan-4-one* (20). Cholest-4-en-3-one (20 g.) was reduced with lithium aluminium hydride, the product acetylated, and the mixture of 3-acetoxycholest-4-enes (20 g.) so obtained was reduced with lithium (3 g.) in ethylamine (300 c.c.) [39] to give cholest-4-ene (17) (10·3 g.), m. p. 79—81°, $[\alpha]_D$ +65° (*c* 0·6) (lit.,[39] m. p. 83—84°, $[\alpha]_D$ +73°). Lithium aluminium hydride (4·5 g.) in dry ether (250 c.c.) was added during 20 min. to a solution of cholest-4-ene (15 g.) and boron trifluoride–ether complex (20 c.c.) in ether (300 c.c.) at 20°, the mixture being stirred in an atmosphere of nitrogen. After 1 hr. moist ether was added cautiously and the mixture was then shaken with saturated aqueous sodium sulphate (200 c.c.). The material obtained from the ether layer was dissolved in tetrahydrofuran (100 c.c.), and to the vigorously stirred solution 4N-sodium hydroxide (100 c.c.) and then hydrogen peroxide (100 c.c. 100 vol.) were added. After 2 hr. at 20° water was added and the material (14·9 g.) isolated with ether was absorbed from light petroleum on neutral alumina (400 g., deactivated by treatment with 40 c.c. of water). Elution with light petroleum (500 c.c.) gave cholest-4-ene (2 g.), m. p. and mixed m. p. 78—80°. Ether (1 l.) eluted crystalline material (12·8 g.), m. p. 160—185°, $\nu_{max.}$ 3620 cm.$^{-1}$. This was shown by g.l.c. to contain 58% of 5α-cholestan-4α-ol (18) (peak intensified after adding authentic material to the mixture) and 42% of a compound which was almost certainly 5β-cholestan-4β-ol (19), as indicated by the next stage. The mixture, dissolved in acetone–benzene (6 : 1; 700 c.c.), was oxidised with 8N-chromic acid (15 c.c.) to give a product which was dissolved in benzene and filtered through neutral alumina (400 g.). Removal of solvent afforded crystalline material (12·5 g.), m. p. 80—105°, $\nu_{max.}$ 1712 (CO) cm.$^{-1}$.

A portion (1 g.) of this product was crystallised several times from acetone to give 5α-cholestan-4-one (21) as plates, m. p. 98—100°, $[\alpha]_D$ +28° (*c* 0·9). Fractional crystallisation of the material obtained from the combined mother-liquors afforded 5β-cholestan-4-one as needles, m. p. 108—111°, $[\alpha]_D$ +35° (*c* 1·0) (Shoppee *et al.*[40] report m. p. 109°, $[\alpha]_D$ +40°), thus establishing the presence of a 5β-cholestan-4-ol in the mixture (m. p. 160—185°) produced by hydroboration.

The material recovered from these crystallisations and the bulk (11·5 g.) of the ketone mixture were combined and refluxed for 2 hr. with 3% methanolic potassium hydroxide (500 c.c.). Standard working up gave 5α-cholestan-4-one (9·7 g.), m. p. 98—100° (from acetone–methanol), $[\alpha]_D$ +28° (*c* 0·5) (lit.,[41] m. p. 99—99·5°, $[\alpha]_D$ +29·5°).

[39] A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J.*, 1957, 1969.
[40] C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Summers, *J.*, 1959, 630.
[41] L. Ruzicka, R. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, 1944, **27**, 727.

5α-*Cholestan*-6-*one*.—Hydroboration of cholest-5-ene (17 g.) followed by oxidation of the product with 8N-chromic acid as above gave material which was chromatographed on neutral alumina (350 g.). (In this series the treatment with potassium hydroxide was omitted.) Elution with light petroleum gave cholest-5-ene (2·05 g., m. p. and mixed m. p. 90—93°), and elution with benzene afforded 5α-cholestan-6-one (13·1 g.), m. p. 98—100° $[\alpha]_D$ −7° (*c* 0·93) (lit.,[34] m. p. 98°, $[\alpha]_D$ −7°). Ether–methanol (19 : 1; 300 c.c.) eluted 5α-cholestan-6α-ol (0·93 g.), m. p. and mixed m. p. 126—128° (lit.,[20] 128—129°).

5α-*Androstan*-17-*one* (53).—A solution of 3β-hydroxyandrost-5-en-17-one (20 g.) in dry benzene (150 c.c.) was refluxed for 30 min. with phosphoric oxide (30 g.). The liquid was decanted and filtered through neutral alumina (300 g.) with benzene (11). Evaporation afforded androsta-3,5-dien-17-one (52) (10·7 g.), m. p. 90—91° (plates from methanol), $[\alpha]_D$ −69° (*c* 0·5), $\lambda_{max.}$ 2340 Å (ε 21,480) and 2280 Å (ε 19,900) (lit.,[42] m. p. 87—89°, $[\alpha]_D$ −21°). A solution of this material (10·5 g.) in ethyl acetate–acetic acid (10 : 1; 110 c.c.) containing 60% perchloric acid (0·05 c.c.) was hydrogenated over pre-reduced Adams catalyst (0·5 g.) until the rate of absorption was slow (uptake *ca.* 2400 c.c. in 3 hr.). The product was dissolved in acetone (500 c.c.) and treated with 8N-chromic acid (8 c.c.). Standard manipulation gave material which was dissolved in benzene and filtered through neutral alumina (250 g.). The crystalline product (9·2 g.), m. p. 109—118°, $\nu_{max.}$ 1745 cm.$^{-1}$ was shown by g.l.c. to contain 95% of 5α-androstan-17-one (53) (peak intensified by admixture with authentic material) and 5% of 5β-androstan-17-one (see below). Fractional crystallisation of the product from methanol gave 5α-androstan-17-one (7·3 g.) as plates, m. p. 117—119° $[\alpha]_D$ +96° (*c* 1·0) (lit.,[30] m. p. 118—119°). The residues from the earlier crystallisations were combined and crystallised repeatedly from methanol to give 5β-androstan-17-one (60 mg.) as needles, m. p. 99—101°, $[\alpha]_D$ +97° (*c* 0·5), $\nu_{max.}$ 1745 cm.$^{-1}$ whose infrared spectrum was identical with that of authentic material.[43]

Reaction of Oximes with N-*Bromosuccinimide*.—*Using* 17-*hydroxyimino*-5α-*androstane* (54). A solution of the oxime (0·5 g.) in dioxan (10 c.c., freshly purified) and a mixture of *N*-bromosuccinimide (1 g.) and potassium hydrogen carbonate (0·5 g.) in dioxan–water (1 : 2; 15 c.c.) was shaken vigorously for 48 hr. at 20°. (A blue colour which developed after 1 hr. faded gradually during this time.) Dilution with water and extraction with ether gave material which was chromatographed on silica gel (50 g.). Light petroleum eluted 17α-*bromo*-17β-*nitro*-5α-*androstane* (59) (329 mg.), m. p. 129—130° (prisms from ethyl acetate–methanol), $[\alpha]_D$ +7° (*c* 0·5) (Found: C, 59·1; H, 7·8; N, 3·5; Br, 20·4. $C_{19}H_{30}BrNO_2$ requires C, 59·4; H, 7·9; Br, 20·8; N, 3·6%). Elution with benzene (100 c.c.) gave 5α-androstan-17-one (53) (61 mg.), m. p. and mixed m. p. 117—119°.

Sodium borohydride (50 mg.) was added in portions to a stirred solution of the bromonitro-compound (60) (100 mg.) in tetrahydrofuran–water (5 : 1; 12 c.c.). The product was filtered through silica gel (10 g.) with benzene (60 c.c.) to give 17β-nitro-5α-androstane (59) (64 mg.), m. p. 157—159° (from ethyl acetate), identical with authentic material described earlier.

Using 3-*hydroxyimino*-5α-*cholestane* (5). A solution of the oxime (1 g.) in ether (40 c.c.) and a suspension of *N*-bromosuccinimide (1·2 g.) in water (25 c.c.) containing potassium hydrogen carbonate (0·8 g.) was stirred vigorously for 6 hr. at 20°. The material obtained from the ether layer was chromatographed on neutral alumina (50 g.). Elution with light petroleum (100 c.c.) gave 3α-*bromo*-3β-*nitroso*-5α-*cholestane* (10) (48 mg.), m. p. 140—142° (blue blades from ethyl acetate), $[\alpha]_D$ −12° (*c* 0·4) (Found: C, 67·4; H, 10·5; N, 3·0; Br, 16·6. $C_{27}H_{46}BrNO$ requires C, 67·0; H, 10·3; Br, 16·5; N, 2·9%). {When heated slowly in air this compound melted at 134—136° and solidified at 138° to give the bromonitro-compound [(11), see below] as colourless rods, m. p. 169—172°.} Elution with light petroleum–benzene (19 : 1; 200 c.c.) afforded 3α-*bromo*-3β-*nitro*-5α-*cholestane* (11) (81 mg.), m. p. 173—176° (rods from ethyl acetate), $[\alpha]_D$ +36° (*c* 0·5) (Found: C, 65·3; H, 9·7; Br, 15·7; N, 2·5. $C_{27}H_{46}BrNO_2$ requires C, 64·9; H, 9·9; Br, 16·0; N, 2·8%). Light petroleum–benzene (1 : 1; 350 c.c.) eluted 5α-cholestan-3-one (8) (8·5 mg.), m. p. and mixed m. p. 127—130°.

Treatment of the 3-oxime (5) (1 g.) as described above for the 17-oxime (54) gave the bromonitroso-compound (10) (32 mg.), the bromonitro-compound (11) (66 mg.) and cholestanone (8) (611 mg.). Reduction of the bromonitro-compound (11) (50 mg.) with sodium

[42] G. Rozenkranz, S. Kaufmann, and J. Romo, *J. Amer. Chem. Soc.*, 1949, **71**, 3689.
[43] K. Dobriner, E. R. Katzenellenbogen, and R. N. Jones, "Infrared Absorption Spectra of Steroids," Interscience Publishers, New York, 1953.

borohydride yielded material (35 mg., m. p. 103—112°) shown by g.l.c. to contain 3β- and 3α-nitro-5α-cholestane [(14) and (15)] in a 3 : 2 ratio.

Conversion of 5α-*Cholestan*-3β-*yl Toluene*-p-*sulphonate* (1) *into* 5α-*Cholestan*-3α-*ol* (3).—The tosyl derivative (2 g.) in dry *N*-methylpyrrolidone (150 c.c.) was heated at 90° with dry sodium nitrite (2·6 g.) for 36 hr. Dilution with water, extraction with ether, and chromatography on neutral alumina gave 5α-cholest-2-ene (2) (40 mg., m. p. and mixed m. p. 69—70°, eluted with light petroleum) and 5α-cholestan-3α-ol [1·38 g., eluted with ether–methanol (19 : 1)], m. p. 186—187°, $[\alpha]_D$ +24° (*c* 0·8), identified by its infrared spectrum.

Peroxyacetic Acid Oxidation of 3-*Hydroxyimino*-5α-*cholestane* (5).—A solution of the oxime (2·5 g.) in chloroform (50 c.c.) was added during 5 min. to a refluxing solution of peroxyacetic acid in chloroform [25 c.c. of a solution prepared by adding acetic anhydride (11·3 c.c.) to a mixture of 85% hydrogen peroxide (4 c.c.) and chloroform (25 c.c.) at 0°]. The solution, which gradually became pale blue, was refluxed until colourless (*ca.* 70 min.). After standard working up (including destruction of peracid by washing with ferrous sulphate solution) the product (2·15 g.) was chromatographed on a neutral alumina (100 g.). Elution with light petroleum (600 c.c.) gave 3β-*chloro*-3α-*nitro*-5α-*cholestane* (7) (201 mg.), m. p. 135—136° (rods from ethyl acetate–methanol), $[\alpha]_D$ +27° (*c* 1·2) (Found: C, 71·65: H, 10·2; Cl, 8·1; N, 3·2. $C_{27}H_{46}ClNO_2$ requires C, 71·7; H, 10·3; Cl, 7·8; N, 3·1%) followed, in the next 750 c.c., by 3α-chloro-3β-nitro-5α-cholestane (6) (129 mg.), m. p. and mixed m. p. 173—175°, $[\alpha]_D$ +30° (*c* 0·8). Benzene (500 c.c.) eluted 3-oxo-4-oxa-A-homo-5α-cholestane (8) (1·12 g.), m. p. 185—187° (needles from acetone), $[\alpha]_D$ +9° (*c* 0·7) (Found: C, 80·95; H, 11·35. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%), $\nu_{max.}$ 1742 cm.$^{-1}$ [lit.,[7] m. p. 186—187°, $[\alpha]_D$ +1·2° (±2°)].

Complete Reduction of 3,3-*Dinitro*-5α-*cholestane* (13).—A solution of the dinitro-compound (500 mg.) in ethyl acetate (25 c.c.) was hydrogenated over Adams catalyst (150 mg.) until reduction stopped (*ca.* 7 mol. of hydrogen were absorbed in 12 hr.). A solution of the product in ether (50 c.c.) was refluxed with acetic anhydride (2 c.c.) for 4 hr. The material so obtained was crystallised repeatedly from ethanol to give 3β-acetamido-5α-cholestane (16) (124 mg.) as plates, m. p. 238—245°, $[\alpha]_D$ +8° (*c* 0·6) (Found: C, 80·7; H, 11·8; N, 3·2. Calc. for $C_{29}H_{51}NO$: C, 81·05; H, 12·0; N, 3·3%), $\nu_{max.}$ 3250, 3080, and 1638 cm.$^{-1}$ (lit.,[19] m. p. 245—246°, $[\alpha]_D$ +12°).

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