Arylazo-steroids. Part III.† 3-, 7-, and 17-Arylazo-steroids

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A number of 3-arylazo-5α- and -5β-cholestanes have been synthesised, and also their 3-hydroperoxy-derivatives. The previously described 17-phenylazoandrost-5-en-3β-ol has been shown to have the 17β-configuration, and a number of derivatives with 17α-substituents have been synthesised. The preparation of a 7-hydroperoxy-7-phenylazo-5α-cholestan-3β-yl acetate is described. The ultraviolet and visible spectra of the above compounds are discussed. Comment is made on the reduction of phenylhydrazones with lithium aluminium hydride.

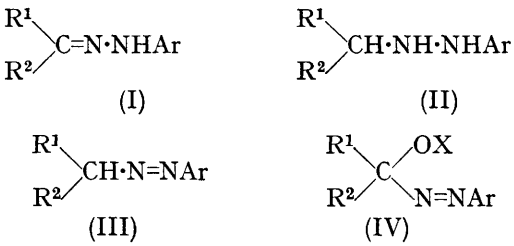
WORK on the optical rotatory dispersion spectra of arylazo-sugar derivatives,[1] in particular their remarkable solvent effects, suggested that the study of optically active arylazoalkanes would be of interest. An accessible route to arylazoalkanes (III) has been shown [2] to be the lithium aluminium hydride reduction of an aldehyde or ketone arylhydrazone (I), followed by oxidation of the arylhydrazino-product (II) with reagents such as mercuric oxide. Arylazo-derivatives with

† The papers by J. Buckingham and R. D. Guthrie, *J. Chem. Soc.* (*C*), 1967, 1700, 1703, are considered as Parts I and II.

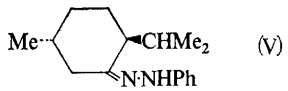
[1] E. O. Bishop, G. J. F. Chittenden, R. D. Guthrie, A. F. Johnson, and J. F. McCarthy, *Chem. Comm.*, 1965, 93.

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

geminal oxygen-containing substituents (IV) may be obtained by the oxidation of arylhydrazones with oxygen [3] or other oxidising agents.[4-6]



The easiest way to make an optically active compound of type (III) appeared to be to start with an optically active ketone, such as menthone.

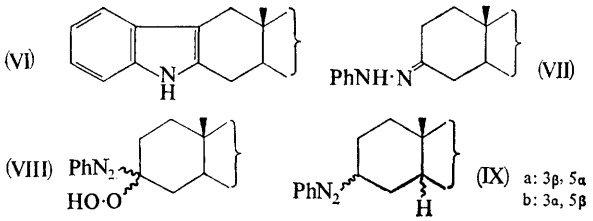


Menthone phenylhydrazone (V) has long been known,[7] but no attempt seems to have been made to reduce it. Treatment with boiling solutions of lithium aluminium hydride in ether or tetrahydrofuran gave colourless oils having infrared spectra almost identical with that of the starting material (which is a low-melting solid). It thus appeared that reduction of the hydrazone grouping in (V) proceeded with extreme slowness, if at all (presumably owing to steric hindrance from the neighbouring alkyl group), and is not a feasible route to arylazo-compounds of interest.

The other types of readily available optically active ketones are the steroid ketones, and so their conversion into phenylazo-steroids was studied. The synthesis of 6-phenylazo-steroid derivatives by other routes has already been described.[8,9]

3-*Phenylazo-steroids*.—By treating 5β-cholestan-3-one (coprostanone) with phenylhydrazine in hot acetic acid, Doree and Gardner [10] isolated a colourless crystalline solid, m.p. 191°, which had not the correct analysis for a phenylhydrazone. Later,[11] it was realized that this compound was an indolo-steroid; no genuine 5β-cholestan-3-one phenylhydrazone has since been reported. An indolo-steroid (VI) has similarly been prepared [12] from 5α-cholestan-3-one (cholestanone), but again there is no mention in the literature of an authentic phenylhydrazone.

Reaction of 5α-cholestan-3-one with phenylhydrazine in hot ethanol containing a little acetic acid, gave, on cooling, a white amorphous or microcrystalline solid, m.p. *ca.* 128°, which was the authentic phenylhydrazone (VII). Treatment with hot glacial acetic acid caused cyclisation to the known [12] indolo-steroid (VI) in good yield.



The phenylhydrazone (VII) in ether was autoxidised rapidly in air to give a yellow solution, from which two yellow crystalline phenylazo-hydroperoxides (VIII) could be isolated. The first, m.p. 144° (decomp.), was reasonably stable and could be obtained in 38% yield by direct recrystallisation of the autoxidation product. The second, isolated by chromatography (7% yield), m.p. 48° (decomp.), was too unstable for the determination of either elemental composition or an infrared spectrum, although an ultraviolet spectrum was obtained which showed the presence of the phenylazo-chromophore. The exact nature of this second compound remains in doubt, but it is probably the 3-epimer of the major product. *cis–trans*-Isomerism of the azo-group is thought unlikely, since the autoxidation was carried out in the dark; the two compounds did not appear to interconvert in solution.

Similar results were obtained in the reaction of lead tetra-acetate [4] with 5α-cholestan-3-one phenylhydrazone (VII). The poorly crystalline product was shown to consist of two yellow components in approximately equal amounts by thin-layer chromatography; the R_F values were too similar to attempt a separation. The infrared spectrum of the mixture indicated that both components were azo-acetates, and they are again thought to be 3-epimers.

Lithium aluminium hydride reduction of the phenylhydrazone (VII) gave a colourless solid which rapidly turned yellow in air, affording 3β-phenylazocholestane (IXa) in 50% yield, the configuration of which was shown by its catalytic reduction, followed by acetylation, to give the known [13] 3β-acetamidocholestane. No trace of an isomeric yellow compound was detected in the product from the lithium aluminium hydride reduction.

A number of nuclear-substituted 5α-cholestan-3-one phenylhydrazones were also prepared (see Table 1). All were converted into the corresponding hydroperoxides by autoxidation, only the more stable isomers being characterised (see Table 2). Several were also converted into the corresponding 3β-arylazo-steroid by lithium aluminium hydride reduction followed by air or mercuric oxide oxidation (see Table 3). In one case (*p*-bromophenyl) the intermediate arylhydrazino-steroid

[3] Ref. 2 and references therein.
[4] D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, 1961, **83**, 747.
[5] J. T. Edwards and S. Samand, *Canad. J. Chem.*, 1963, **41**, 1638.
[6] M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc.* (*C*), 1967, 735.
[7] G. Plancher and O. Carrasco, *Atti. Accad. Lincei*, 1904, **13**, 632.
[8] J. Buckingham and R. D. Guthrie, *J. Chem. Soc.* (*C*), 1967, 1700.
[9] J. Buckingham and R. D. Guthrie, *J. Chem. Soc.* (*C*), 1967, 1703.
[10] C. Doree and J. A. Gardner, *J. Chem. Soc.*, 1908, **93**, 1625.
[11] C. Doree, *J. Chem. Soc.*, 1909, **95**, 638.
[12] C. Doree and V. A. Petrow, *J. Chem. Soc.*, 1935, 1391.
[13] C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1956, 1649.

was prepared by lithium aluminium hydride–lead chloride reduction [14,15] of the azo-compound; it was oxidised rapidly in solution back to the yellow azo-compound.

It is interesting that, among the hydroperoxides which were prepared, was that from cholestanone *p*-nitrophenylhydrazone. This result tends to support the finding [2] that butan-2-one *p*-nitrophenylhydrazone was autoxidised slowly in solution, contrary to O'Connor and Rosenbrook's [16] statement that it was resistant to 'tautomeric change'.

5α-Cholestan-3-one *N*-methylphenylhydrazone was also prepared; as expected, it showed no tendency to autoxidise.

Reaction of 5β-cholestan-3-one with phenylhydrazine, in a similar manner to that employed for the 5α-compound, gave a low-melting, easily-oxidised solid which was not characterised. Autoxidation of this product gave rise to two yellow compounds which, however, were very unstable and could not be obtained pure. Lithium aluminium hydride reduction of the crude phenylhydrazone, followed by spontaneous air-oxidation, afforded, after chromatographic purification, 3α-phenylazo-5β-cholestane (IXb) as a yellow gum which crystallised after several days. Again no trace of an epimeric phenylazo-compound was detected. This is in agreement with the reduction of 5β-cholestan-3-one oxime, which gave only 3α-amino-5β-cholestane, although the reduction of 5α-cholestan-3-one oxime with lithium

TABLE 1

5α-Cholestan-3-one arylhydrazones

Ar	M.p.[a]	$[\alpha]_D$	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
p-Br·C_6H_4	133—137°	−59·4°	71·3	9·4	5·0	$C_{33}H_{51}BrN_2$	71·3	9·25	4·9
p-Me·C_6H_4	125—128	−40·7	—	—	5·9	$C_{34}H_{54}N_2$	—	—	5·7
o-Me·C_6H_4	75—80	0	—	—	5·45	$C_{34}H_{54}N_2$	—	—	5·7
p-NO_2·C_6H_4	209—210	−132	76·0	9·8	8·3	$C_{33}H_{51}N_3O_2$	76·0	9·85	8·05
p-NH_2·SO_2·C_6H_4	223—225	+39·8 [b]	—	—	7·7	$C_{33}H_{53}N_3O_2S$	—	—	7·6
p-MeO·C_6H_4	~110	+34·0	—	—	5·4	$C_{34}H_{54}N_2O$	—	—	5·5
p-HO·OC·C_6H_4	182—197	+39·8	—	—	5·1	$C_{34}H_{52}N_2O_2$	—	—	5·4

[a] With decomposition. [b] Dioxan solution.

TABLE 2

3-Arylazo-3-hydroperoxy-5α-cholestanes

Ar	M.p.[a]	$[\alpha]_D$	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N	U.v. data [b]
p-Br·C_6H_4	151—152°	+24·6°	67·6	8·65	4·8	$C_{35}H_{51}BrN_2O_2$	67·45	8·75	4·8	285 (17,500), 411 (213)
p-Me·C_6H_4	152—153	+28·4	78·3	10·5	5·4	$C_{34}H_{54}N_2O_2$	78·1	10·4	5·4	285 (16,150), 403 (218)
o-Me·C_6H_4	125—126	+25·3	78·2	10·6	5·4	$C_{34}H_{54}N_2O_2$	78·1	10·4	5·4	279 (17,700), 414 (211)
p-NO_2·C_6H_4	138—139	+31·0	71·3	9·3	7·5	$C_{33}H_{51}N_3O_4$	71·6	9·3	7·6	284 (20,300), 425 (264)
p-NH_2·SO_2·C_6H_4	157	+53·3	67·4	8·8	7·3	$C_{33}H_{53}N_3O_4S$	67·4	9·1	7·15	271 (17,450), 418 (200)
p-MeO·C_6H_4	153	+55·0	75·8	10·0	5·2	$C_{34}H_{54}N_2O_3$	75·8	10·1	5·2	308 (18,500), 399 (325)
p-HO·OC·C_6H_4	174	+56·9	73·8	9·4	5·1	$C_{34}H_{52}N_2O_4$	73·9	9·5	5·1	274 (18,500), 417 (220)

[a] With decomposition. [b] $\lambda_{max.}(\varepsilon)$ ($CHCl_3$).

TABLE 3

3β-Arylazo-5α-cholestanes

Ar	M.p.	$[\alpha]_D$	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N	U.v. data [a]
p-Br·C_6H_4	179—180°	+28·7°	71·2	9·4	5·0	$C_{33}H_{51}BrN_2$	71·3	9·25	4·9	276 (17,750), 407 (223)
p-Me·C_6H_4	153—154	+33·9	83·3	11·0	5·8	$C_{34}H_{54}N_2$	83·2	11·1	5·7	277 (16,050), 402 (266)
o-Me·C_6H_4	112—113	+23·9	83·3	11·1	5·8	$C_{34}H_{54}N_2$	83·2	11·1	5·7	271 (8900) 407 (226)
p-MeO·C_6H_4	166—167	+32·4	80·6	10·8	5·5	$C_{34}H_{54}N_2O$	80·6	10·7	5·5	301 (14,450), 396 (321)

[a] $\lambda_{max.}(\varepsilon)$ ($CHCl_3$).

[14] G. A. Olah, *J. Amer. Chem. Soc.*, 1959, **81**, 3165.

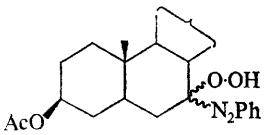
[15] G. J. F. Chittenden and R. D. Guthrie, *J. Chem. Soc.*, 1963, 2358.

[16] R. O'Connor and W. Rosenbrook, *J. Org. Chem.*, 1961, **26**, 5208.

aluminium hydride gave a mixture of 3α- and 3β-amino-5α-cholestane.[13] The 3α-configuration of (IXb) was proved by catalytic reduction over platinum, followed by acetylation, to give the known [13] 3α-acetamido-5β-cholestane.

Following some preliminary optical rotatory dispersion measurements, it was thought desirable to prepare a 3-phenylazo-steroid in which the phenylazo-group was subject to restricted rotation by nearby substituents. The readily available 4,4-dimethylcholest-5-en-3-one was therefore converted into its crystalline phenylhydrazone, but this compound could not be reduced by lithium aluminium hydride in ether.

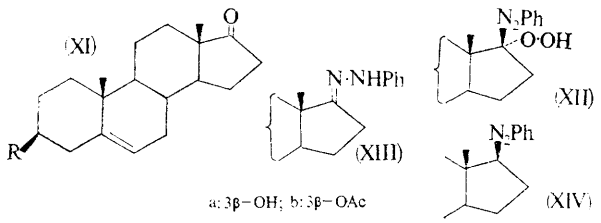
7-Phenylazo-steroids.—The preparation of steroids bearing phenylazo-substituents was continued by the reaction of 7-oxocholestan-3β-yl acetate with phenylhydrazine. This did not give a crystalline product, but on autoxidation a highly crystalline hydroperoxide (X) was obtained in good yield.



(X)

17-Phenylazo-steroids.—Chaplin, Hey, and Honeyman,[17] in attempting to prepare a steroid having an indolo-ring fused to ring D, heated dehydroepiandrosterone (XIa) with phenylhydrazine in acetic acid. The product which they obtained was, however, neither a phenylhydrazone nor an indolo-steroid, but was yellow and was considered to be the phenylazo-hydroperoxide (XIIa).

By reaction of dehydroepiandrosterone with phenylhydrazine in ethanol containg a little acetic acid, they were able to obtain impure dehydroepiandrosterone

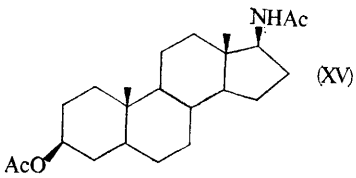


phenylhydrazone (XIIIa), and found that it readily oxidised in air to the crystalline yellow hydroperoxide (XIIa). Similar results were obtained when dehydroepiandrosterone acetate (XIb) was used as the starting material; the phenylhydrazone (XIIIb) could be isolated by rapid work-up, avoiding contact with air, and it readily oxidised to the acetate hydroperoxide (XIIb).

Reduction of either hydroperoxide (XIIa) or (XIIb) with lithium aluminium hydride in ether yielded the phenylazo-steroid (XIVa), which was characterised as its 3-acetate (XIVb). The constitution of these compounds was shown by their characteristic ultraviolet and visible spectra and by the isomerisation of (XIVb) into dehydroepiandrosterone acetate phenylhydrazone (XIIIb) on treatment with perchloric acid. The configuration of the phenylazo-group in both (XIV) and their hydroperoxides (XII) remained unknown.

Repetition of the above work gave results identical with those previously obtained,[17] and the structures proposed for the phenylazo-compounds (XII) and (XIV) are substantiated. In fact, the initial product from the lithium aluminium hydride reduction of the hydroperoxides (XII) appears to be the phenylhydrazino-compound, since, immediately after working-up the reduction product, a colourless solution was obtained, which rapidly turned yellow in air, and on evaporation and recrystallisation the phenylazo-steroid (XIVa) was obtained.

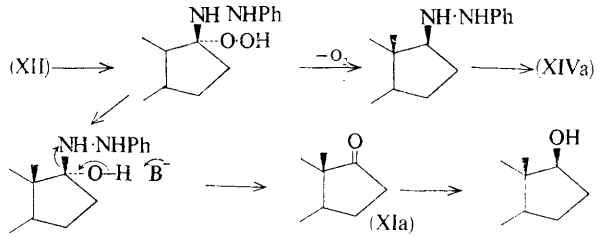
The 17-phenylazo-group in (XIV) was shown to have the β-configuration by catalytic reduction of (XIVa) followed by acetylation to give 17β-acetamido-5α-androstan-3β-yl acetate (XV), identical with a sample



(XV)

obtained by catalytic hydrogenation of the known [18] 17-acetamidoandrost-5-en-3β-yl acetate. Although the saturated *NO*-diacetyl derivative (XV) is described in the literature,[19] its mode of preparation (by the Beckmann rearrangement of a 20-keto-steroid oxime) did not conclusively establish its configuration.

When the lithium aluminium hydride reduction of (XIIb) was carried out under conditions somewhat different from those employed by Chaplin, Hey, and Honeyman [17] (using more concentrated reactants), the isolated product was not (XIVa) but instead androst-5-ene-3β,17β-diol, characterised as the diacetate. Presumably the phenylazo-hydroperoxide (XII) is first



reduced to the phenylhydrazino-hydroperoxide (XVI), which is then capable either of a unimolecular decomposition (predominating under low base conditions) or of a base-catalysed process leading to dehydroepiandrosterone (XI), subsequent reduction of which produces the 17β-alcohol.

Support for the above mechanism was provided by the reduction of 7ξ-phenylazo-7ξ-hydroperoxycholestan-3β-

[17] A. F. Chaplin, D. H. Hey, and J. Honeyman, *J. Chem Soc.*, 1959, 3194.

[18] C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.*, 1959, 345.
[19] J. Schmidt-Thomé, *Chem. Ber.*, 1955, **88**, 895.

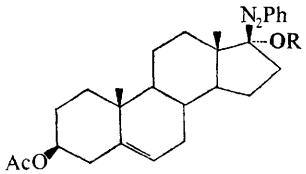
yl acetate (X), from which a 12% yield of 3β-hydroxycholestan-7-one was isolated. This ketone is known to be somewhat resistant to lithium aluminium hydride reduction.[20]

The optical rotatory dispersion spectra, which will be fully discussed in a later paper,[21] indicated that the phenylazo-group in the hydroperoxides (XII) also has the 17β-configuration, as expected from their mode of preparation, in which attack of oxygen presumably takes place preferentially from the less hindered face of the molecule.

An attempt was made to prepare the phenylazo-steroid (XIVa) by the alternative route involving lithium aluminium hydride reduction of the phenylhydrazone (XIIIb), but this was unsuccessful, the phenylhydrazone being recovered [as the hydroxperoxide (XIIa)] in 59% yield.

This result, taken in conjunction with those previously obtained, makes it evident that the lithium aluminium hydride reduction of phenylhydrazones to phenyl alkylhydrazines is subject to fairly severe steric restrictions, and in the steroid field is confined, among the examples studied, to the arylhydrazones of 5α- and 5β-cholestan-3-one.

Other derivatives with geminal oxygen-containing functional groups were prepared by procedures involving attack of various reagents on dehydroepiandrosterone acetate phenylhydrazone (XIIIb). Lead tetra-acetate in methylene chloride [4] gave the azo-acetate (XVII), while in the presence of methanol or ethanol [6] the alkoxy-compounds (XIX) and (XX) were obtained



(XVII) R = COMe
(XVIII) R = COPh
(XIX) R = Me
(XX) R = Et

instead. Benzoyl peroxide [5] oxidised the phenylhydrazone to the benzoyloxy-compounds (XVIII). Yields in these reactions were poor to moderate. Like the hydroperoxides (XII) and the phenylazo-steroids (XIV), these compounds are thought to have the 17β-phenylazo-configuration from the shape of their o.r.d. curves [21] and their mode of preparation.

Ultraviolet and Visible Spectra.—All of the compounds showed the expected pair of bands. As for simple phenylazo-alkanes [2] and for phenylazo-sugars,[22] these were the $\pi \longrightarrow \pi^*$ at 267—270 mμ (ε 10,000) and the $n \longrightarrow \pi^*$ band at about 405 mμ (ε 100—200). The shifts to longer wavelength on passing from an arylazo-compound to the corresponding arylazo-hydroperoxide were similar to those recorded [2] for simpler compounds, and were greater for the $\pi \longrightarrow \pi^*$ band; the magnitudes of these shifts were independent of the substituent in the benzene ring. The effect of the substituent on the actual band positions paralleled those reported [22] for arylazo-sugars.

The 17-phenylazo-ethers (XIX) and (XX) were found to have anomalous $n \longrightarrow \pi^*$ bands as shown in Table 4,

TABLE 4

Visible spectra of some 17-phenylazo-steroids; $\lambda_{max.}$ (mμ) in $CHCl_3$

(XIV)	(XII)	(XVII)	(XVIII)	(XIX)	(XX)
404	411	407	407	423	423

being at longer wavelength than the esters (XVII) and (XVIII) on the parent azo-compound (XIV). The ultraviolet spectra of some simple azo-ethers have been recorded,[6] but not their visible spectra. Professor R. O. C. Norman has now kindly determined the position of the $n \longrightarrow \pi^*$ band for these compounds, and the results (Table 5) are seen to be analogous to the steroid

TABLE 5

Visible spectra of some azo-ethers and -esters *

$Ph_2CR{\cdot}N{=}NPh$	$\lambda_{max.}$ (mμ)
R = OBz	401
R = OMe	417
R = OEt	417
$ArPhC(OAc){\cdot}N{=}NPh$	
Ar = m-$NO_2{\cdot}C_6H_4$	400

* R. O. C. Norman, personal communication.

series though the band positions are slightly shifted. At present we have no explanation to offer for this difference between azo-ethers and azo-esters.

EXPERIMENTAL

All evaporations were carried out using a rotary evaporator. Ultraviolet spectra were determined for chloroform solutions unless otherwise stated. Optical rotations were determined for chloroform solutions at 23°. Thin-layer chromatography was on silica (Merck). The identity of compounds was proved where necessary by mixed m.p., infrared spectrometry, and thin-layer chromatography. Lead tetra-acetate (85%) was washed with light petroleum and dried *in vacuo* immediately before use.

5α-Cholestan-3-one Phenylhydrazone (VII).—The ketone (0·50 g.), in boiling ethanol (15 ml.) containing acetic acid (1 ml.), was treated with phenylhydrazine (0·5 ml.). After 10 min. a little water was added, the solution was cooled to room temperature, and the product collected, washed with ethanol, and dried, to yield *5α-cholestan-3-one phenylhydrazone* (VII) (0·61 g, 99%), m.p. 128°, $[\alpha]_D$ −18·1° (*c* 0·45), $\nu_{max.}$ 3280, 1600, and 1500 cm.$^{-1}$ (Found: N, 5·9. $C_{33}H_{52}N_2$ requires N, 5·9%).

The product (359 mg.), when boiled under reflux in acetic acid (15 ml.) for 20 min. and cooled, gave a colourless crystalline precipitate of 2,3-indolo-5α-cholestane (VI) (240 mg., 69%), m.p. 180·5—182° (from chloroform–ethanol), $[\alpha]_D$ +62·4° (*c* 0·35) (lit.,[12] m.p. 180—181°).

The phenylhydrazone (VII) (0·90 g) was autoxidised in ether solution during 20 min. The ether was removed and the product recrystallised from ethyl acetate–light petroleum, affording yellow feathery needles (0·36 g., 38%) of

[20] K. Morita, *Bull. Chem. Soc. Japan*, 1959, **32**, 414.
[21] J. Buckingham and R. D. Guthrie, unpublished work.
[22] G. J. F. Chittenden and R. D. Guthrie, *J. Chem. Soc.*, 1964, 1045.

3ξ-*hydroperoxy*-3ξ-*phenylazo*-5α-*cholestane* (VIII) (isomer A), m.p. 144° (decomp.), $[\alpha]_D$ +36·0° (*c* 0·33), $\lambda_{max.}$(MeOH) 274 and 415 mμ (ε 8740 and 167) (Found: C, 78·0; H, 10·1; N, 5·5. $C_{33}H_{52}N_2O_2$ requires C, 77·9; H, 10·3; N, 5·5%).

The mother-liquors from the above preparation were evaporated and the residue chromatographed on a p.l.c. plate (some decomposition took place during the separation). Two yellow bands were obtained; that having the lower R_F yielded, after extraction of the yellow material with cold ether and careful recrystallisation of the product from warm aqueous ethanol, 3ξ-*hydroperoxy*-3ξ-*phenylazo*-5α-*cholestane* (VIII) (isomer B), as yellow platelets (65 mg., 7%), m.p. 48° (decomp.), $\lambda_{max.}$ 271·5 and 409 mμ (ε 13,300 and 155). An analytical sample decomposed on keeping *in vacuo* overnight.

The phenylhydrazone (VII) (3 g.), suspended in dry ether (100 ml.), was added as quickly as possible to a solution of lithium aluminium hydride (3 g.) in ether (300 ml.) boiling under nitrogen. After 4 hr. the solution was worked up by cautious addition of water to give a colourless ether solution, which was then stirred overnight with yellow mercuric oxide (20 g.). Evaporation of the filtered solution and recrystallisation of the product from ethyl acetate–methanol gave the bright yellow 3β-*phenylazo*-5α-*cholestane* (IXa) (1·5 g., 50%), m.p. 139—140° (with birefringent effects), $[\alpha]_D$ +22·0° (*c* 0·32), $\lambda_{max.}$ 269 and 404 mμ (ε 10,300 and 180) (Found: C, 83·0; H, 11·0; N, 6·15. $C_{33}H_{52}N_2$ requires C, 83·1; H, 11·0; N, 5·9%).

The product (IXa) (595 mg.), in absolute ethanol–cyclohexane (1 : 1) (50 ml.), was hydrogenated for 17 hr. at 55 atm. and 80°, over Raney nickel. The catalyst was removed, the filtrate evaporated, and the residue acetylated with acetic anhydride in pyridine, to give 3β-acetamido-5α-cholestane (from light petroleum) (259 mg., 48%), m.p. 242—244°, $[\alpha]_D$ +9·5° (*c* 0·46) {lit.,[13] m.p. 245—246°, $[\alpha]_D$ +12° (*c* 0·1)}.

The 5α-cholestan-3-one arylhydrazones listed in Table 1 were prepared in a manner similar to that described for the above phenylhydrazone.

The 3β-arylazo-5α-cholestane derivatives and their hydroperoxides, described in Tables 3 and 2 respectively, were prepared in a way similar to that described above for the phenyl derivatives.

5α-*Cholestan*-3-*one* N-*Methyl*-N-*phenylhydrazone*.—This crystallised from ethanol (poor recovery) as feathery needles, m.p. 139—140°, $\lambda_{max.}$ 266 mμ (ε 9200) (Found: C, 83·1; H, 11·15; N, 5·9. $C_{34}H_{54}N_2$ requires C, 83·2; H, 11·1; N, 5·7%).

N-(p-*Bromophenyl*)-N′-(3β-*cholestanyl*)*hydrazine*.—To a solution of lithium aluminium hydride (0·4 g.) in ether (50 ml.), containing lead chloride (5 mg.) boiling under nitrogen, was added a suspension of 3β-(*p*-bromophenylazo)-5α-cholestane (750 mg.) in ether (100 ml.). After boiling under reflux for 19 hr. the solution was worked up in the usual way, and the pale yellow product recrystallised from a small volume of light petroleum, to give 0·45 g. (60%) of almost colourless needles of the *product*, m.p. 128—129° and 176—178°, $[\alpha]_D$ −7·0° (*c* 0·32), $\lambda_{max.}$ 290 mμ (ε 3410) (shoulder on end-absorption) (Found: C, 71·2; H, 9·5; Br, 14·4; N, 4·9. $C_{33}H_{53}BrN_2$ requires C, 71·1; H, 9·6; Br, 14·3; N, 5·0%). From the colourless mother-liquors, which had been left to stand overnight, were isolated bright yellow needles of the *p*-bromophenylazo-compound, m.p. and mixed m.p. 178—179°.

5β-*Cholestan*-3-*one Phenylhydrazone*.—The ketone[23] (2·2 g.), in boiling ethanol (50 ml.), was treated with phenylhydrazine (2 ml.) and acetic acid (4 ml.) under reflux for 30 min. The cooled solution was then poured into ice–water (300 ml.), and the pale yellow precipitate, collected, washed, and dried. After 4 hr., the partly decomposed solid (3·0 g.) was added in small portions to a solution of lithium aluminium hydride (2 g.) in dry ether (200 ml.) under nitrogen. The solution, after boiling under reflux for 2 hr. and standing overnight, was worked up in air, to give a yellow oil which was chromatographed on Florisil (250 g.). Elution with light petroleum–benzene (9 : 1) removed a yellow product, which was further purified by p.l.c. (benzene development) to give a yellow gum, that crystallised on standing under acetone at −15° for several days, affording 3α-*phenylazo*-5β-*cholestane* (IXb) (0·80 g., 30%), as bright yellow prisms, m.p. 72·5—75·5°, $\lambda_{max.}$ 267·5 and 404·5 mμ (ε 11,250 and 167) (Found: C, 83·0; H, 10·9; N, 6·1. $C_{33}H_{52}N_2$ requires C, 83·1; H, 11·0; N, 5·9%).

The product was reduced in acetic acid–cyclohexane with Adams catalyst followed by acetylation of the product in pyridine, to give crude 3α-acetamido-5β-cholestane (83%) (from aqueous acetone), m.p. about 185°; further recrystallisations from, alternately, chloroform–light petroleum and aqueous acetone, afforded the pure material, m.p. 215—217°, $[\alpha]_D$ +54·4° (*c* 0·22) {lit.,[13] m.p. 217—218°, $[\alpha]_D$ +48° (*c* 0·92)}.

4,4-*Dimethylcholest*-5-*en*-3-*one Phenylhydrazone*.—The ketone,[24] on reaction with phenylhydrazine in the usual way, afforded the phenylhydrazone (83%) as colourless needles from ethyl acetate–light petroleum, m.p. 166—178° (decomp.), $[\alpha]_D$ −93·5° (*c* 0·25), $\lambda_{max.}$ 274·5 mμ (ε 22,000) (Found; C, 83·65; H, 10·7; N, 5·8. $C_{35}H_{54}N_2$ requires C, 83·6; H, 10·8; N, 5·6%).

The product (500 mg.) in ether (200 ml.) was treated with lithium aluminium hydride (0·5 g.) under reflux for 18 hr. The solution was worked up as quickly as possible and the product crystallised from light petroleum to give unchanged starting material (180 mg., 36%) (infrared spectrum, t.l.c.). The remainder of the product apparently consisted (t.l.c.) of further quantities of starting material and its autoxidation products, by comparison with authentic samples.

Reaction of 3β-*Acetoxycholestan*-7-*one with Phenylhydrazine*.—The acetate[25] (755 mg.), in boiling ethanol (30 ml.), was treated during 1 hr. with phenylhydrazine (0·4 ml.) and acetic acid (1 ml.). Addition of water to the cooled solution precipitated an oil. The product was extracted into ether, and the ether layer washed with water, dried, allowed to autoxidise, and evaporated under reduced pressure, to give yellow needles of 7ξ-*hydroperoxy*-7ξ-*phenylazocholestan*-3β-*yl acetate* (X) (from light petroleum) (750 mg., 82%), m.p. 129·5° (decomp.), $[\alpha]_D$ −280° (*c* 0·37), $\lambda_{max.}$ 275 and 413 mμ (ε 13,200 and 155) (Found: C, 74·3; H, 9·5; N, 5·0. $C_{35}H_{54}N_2O_4$ requires C, 74·2; H, 9·6; N, 4·9%).

The product (350 mg.) was reduced exactly as described for 17α-hydroperoxy-17β-phenylazoandrost-5-en-3β-yl acetate by Chaplin *et al.*[17] The product, a yellow oil, was dissolved in hot methanol, and the solution was left to stand overnight, during which period it turned dark red. On concentration of the solution at room temperature in a

[23] H. Grasshof, *Z. physiol. Chem.*, 1934, **223**, 249.
[24] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1957, 1131.
[25] O. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503.

current of air, a nearly colourless semicrystalline mass was deposited, which was twice recrystallized (charcoal) from aqueous methanol, to give 3β-hydroxycholestan-7-one (30 mg., 12%), m.p. 167—169°.

Catalytic Reduction of 17β-*Phenylazoandrost-5-en-3β-ol* (XIVa).—The steroid [17] (435 mg.), in cyclohexane–ethanol (1 : 1) (50 ml.), was added to a suspension of pre-reduced Adams catalyst (250 mg.) in cyclohexane (20 ml.) containing acetic acid (5 ml.). The suspension took up 6·0 moles of hydrogen during 85 min. The filtered, colourless solution was evaporated, and the residue acetylated in pyridine overnight, to give 17β-acetamidoandrostan-3β-yl acetate (XV) (51%) (from chloroform–light petroleum), m.p. 194—196°, identical with the sample obtained below.

An authentic sample was obtained as follows: 17β-acetamidoandrost-5-en-3β-yl acetate [18] (m.p. 193—195°) (lit.,[18] m.p. 196°) (530 mg.) in methanol (50 ml.) and acetic acid (20 ml.) was hydrogenated for 3·5 hr. over pre-reduced Adams catalyst (150 mg.), to give the product (XV) (470 mg., 88%), m.p. 194—196° $[\alpha]_D$ −35·5° (*c* 0·58) (lit.[19] m.p. 195—196°).

Attempted Lithium Aluminium Hydride Reduction of Dehydroepiandrosterone Acetate Phenylhydrazone (XIIIb).—(*a*) The phenylhydrazone [17] (707 mg.), suspended in ether (50 ml.), was added slowly to a solution of lithium aluminium hydride (400 mg.) in ether (100 ml.), boiling under nitrogen. After 3·5 hr. the solution was worked up under nitrogen to give a colourless gum rapidly turning yellow in air. The product was dissolved in ether (100 ml.) and allowed to autoxidise in air for 3 hr. Evaporation of the ether and recrystallisation of the residue from ethyl acetate–light petroleum then afforded 17α-hydroperoxy-17β-phenylazoandrost-5-en-3β-ol (XII) (0·41 g., 59%), m.p. 153—154° (decomp).

(*b*) Reduction in tetrahydrofuran solution gave the same isolated product (XII) in 36% yield.

Reaction of Dehydroepiandrosterone Acetate Phenylhydrazone (XIIIb) *with Oxidising Agents.*—(a) *With lead tetra-acetate.*[4] The phenylhydrazone (XIIIb) [17] (0·77 g.), in dry methylene chloride (15 ml.), was treated with lead tetra-acetate (2 g.) in dry methylene chloride (15 ml.) under nitrogen at room temperature for 30 min. A yellow colour developed and a white precipitate appeared. The solution was then boiled under reflux for 5 min., excess of water was added, and the solution filtered through Celite. The organic layer was separated, washed with sodium hydrogen carbonate solution, and water, dried, and evaporated, to yield an orange oil, a light petroleum solution of which crystallised on chilling. Recrystallisation of the solid from light petroleum afforded 17α-*acetoxy*-17β-*phenylazoandrost-5-en-3β-yl acetate* (XVII) (0·16 g.), as small yellow crystals, m.p. 212—214° (decomp.), $[\alpha]_D$ −5·9° (*c* 0·36, $\lambda_{max.}$ 272 and 407 mμ (ε 11,400 and 199) (Found; C, 73·1; H, 7·7; N, 6·0. $C_{29}H_{38}N_2O_4$ requires C, 72·8; H, 8·0; N, 5·85%). Chromatography of the mother-liquors over silica afforded a further quantity (0·24 g.) of product; total yield 0·40 g. (46%).

(b) *With lead tetra-acetate–methanol.*[6] The phenylhydrazone (XIIIb) (0·68 g.) was treated as in the previous experiment, except that the solution contained absolute methanol (35 ml.) as well as methylene chloride, and the solution was worked up after 20 min. at room temperature without boiling under reflux. Crystallisation of the product from methanol afforded 17α-*methoxy*-17β-*phenylazoandrost-5-en-3β-yl acetate* (XIX) (115 mg., 16%), as yellow needles, m.p. 192—192·5°, $[\alpha]_D$ −108° (*c* 0·31), $\lambda_{max.}$ 271·5 and 422·5 mμ (ε 12,000 and 137) (Found: C, 74·35; H, 8·25; N, 6·0. $C_{28}H_{38}N_2O_3$ requires C, 74·6; H, 8·5; N, 6·2%).

(c) *With lead tetra-acetate–ethanol.*[6] The reaction was carried out as in (b) except that ethanol was used instead of methanol. The product could not be crystallised directly but was purified by p.l.c. (development with ether–benzene, 1 : 9), the bright yellow, fast-running band being cut out. Crystallisation from ethanol then afforded 17α-*ethoxy*-17β-*phenylazoandrost-5-en-3β-yl acetate* (XX) (150 mg., 20%), as yellow needles, m.p. 157—158°, $\lambda_{max.}$ 270 and 422·5 mμ (ε 12,500 and 152) (Found: C, 74·95; H, 8·6; N, 6·0. $C_{29}H_{40}N_2O_3$ requires C, 75·0; H, 8·7; N, 6·0%). A further crystallisation, from aqueous methanol, caused a depression and broadening of the melting-point over about 50°, but did not affect the chromatographic purity. The other products from the reaction were not investigated.

(d) *With benzoyl peroxide.*[5] The phenylhydrazone (XIIIb) (0·80 g.), in benzene (25 ml.), was treated with freshly recrystallised benzoyl peroxide (356 mg., 1·2 equiv.) in benzene (25 ml.) under nitrogen at room temperature overnight. On evaporation of the solution at 40° an orange oil was obtained which was purified as in (c). Recrystallisation of the product from chloroform–light petroleum gave yellow needles of 17α-*benzoyloxy*-17β-*phenylazoandrost-5-en-3β-yl acetate* (XVIII) (0·15 g., 17%), m.p. 231—232·5°, $[\alpha]_D$ −64·4° (*c* 0·31), $\lambda_{max.}$ 273 and 407 mμ (ε 14,500 and 234) (Found: C, 75·5; H, 7·4; N, 4·9. $C_{34}H_{40}N_2O_4$ requires C, 75·5; H, 7·5; N, 5·2%).

Lithium Aluminium Hydride Reduction of 17α-*Hydroperoxy*-17β-*phenylazoandrost-5-en-3β-yl Acetate* (XIIb).—(*a*) Reduction according to Chaplin, Hey, and Honeyman [17] gave results identical with those reported by those authors.

(*b*) The hydroperoxide (XIIb) (4·08 g.), in dry ether (200 ml.), was added slowly to a solution of lithium aluminium hydride (3 g.) in ether (200 ml.), boiling under nitrogen. After 3 hr. at reflux the solution was allowed to stand at room temperature overnight, then worked up as usual. The product, a white solid, was suspended in ether (100 ml.) and shaken in air, affording a pale yellow solution and a white insoluble residue which was recrystallised three times (charcoal) from ethanol–acetone–light petroleum, to give androst-5-ene-3β,17β-diol (0·55 g., 21%), m.p. 184—185° (lit.,[26] 182—183°); diacetate, m.p. 164° (lit.,[26] 165—166°).

Attempted Reduction of Menthone Phenylhydrazone (V).—Menthone phenylhydrazone (8·5 g.) [7] was treated with lithium aluminium hydride (3 g.) in boiling ether (300 ml.). After 5 hr. the ether was distilled off and replaced with tetrahydrofuran, after which the solution was boiled under reflux for a further 64 hr. On working up, a pale yellow oil (8·1 g.) was obtained which had an infrared spectrum similar to that of the starting material.

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[26] L. Ruzicka and A. Wettstein, *Helv. Chim. Acta,* 1935, **18**, 1264.