Tetrahedron Vol 28, pp. 2489 to 2506. Pergamon Press 1972. Printed in Great Britain

THE FISCHER-INDOLE CYCLIZATION OF PHENYLHYDRAZONES AND *N*-METHYLPHENYLHYDRAZONES OF SOME 6-SUBSTITUTED CHOLESTAN-3-ONES

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Abstract—The Fischer-indole cyclization of the phenylhydrazones and N-methylphenylhydrazones of 5α- and 5β-cholestan-3-one has been reinvestigated, and additional products characterized.

The Fischer-indole cyclization of the phenylhydrazones and N-methylphenylhydrazones of certain 6-substituted cholestan-3-ones was also investigated. Derivatives of cholest-2-eno[3,2-*b*]indole were the major products of the reaction of 5α- and 5β-cholestane-3,6-dione, although in the latter case, cyclization also occurred to give the cholest-3-eno[3,4-*b*]indole system. 6-Substituted cholest-3-eno[3,4-*b*]indole derivatives were obtained in good yield by the cyclization of the N-methylphenylhydrazones of 6β-acetoxy- and 6β-hydroxy-5β-cholestan-3-one.

A NUMBER OF STUDIES[1] have been made of the acid-catalysed Fischer-indole cyclization of the phenylhydrazones and N-methylphenylhydrazones of 3-oxo-steroids. The position of ring fusion of the resulting steroidal indole parallels the direction of enolization of the 3-oxo function and both are apparently governed by the stereochemistry at C-5. Mechanistically, the first step in the Fischer-indole cyclisation is considered[2] to be an hydrazone-enehydrazine equilibrium, and the parallel is therefore unexceptional. 5α-Cholestan-3-one is reported[3] to yield 5α-cholest-2-eno[3,2-*b*]indole (Ia) on cyclization of the phenylhydrazone, whereas 5β-cholestan-3-one is analogously converted into 5β-cholest-3-eno[3,4-*b*]indole (IIa). These structures have been unequivocally established by chemical degradation.[4]

A separate investigation reported below into the Fischer-indole cyclization of the phenylhydrazones of 6-substituted 3-oxo steroids resulted in the isolation of more than one isomeric product. This, together with the fact that enolization of 3-oxo steroids, particularly as shown for 5β-cholestan-3-one,[5] yields both 2- and 3-enol, prompted us to reinvestigate cyclization of the phenylhydrazones and *N*-methylphenylhydrazones of 5α- and 5β-cholestan-3-one in refluxing AcOH.

The product of reaction of 5α-cholestan-3-one with phenylhydrazine in AcOH was examined by gas liquid chromatography and was shown to consist essentially of two components, the major one being the previously reported[6] 5α-cholest-2-eno-[3,2-*b*]indole (Ia). The minor component (11·5%), which was separated in both cases on 1% OV-1 and OV-17, had retention times identical to an authentic sample of 5α-cholest-3-eno[3,4-*b*]indole (IIIa), synthesized by hydrogenation of the known cholesta-3,5-dieno[3,4-*b*]indole (Va).[7]

Separation of this mixture could not be readily achieved by chromatography on alumina or silica gel, but the product was found to consist of two crystalline components which could be separated by hand. The major component (plates) was shown by GLC to be pure 5α-cholest-2-eno[3,2-*b*]indole (Ia), whereas the other (needles) was shown to consist of an equimolar mixture of the indole (Ia) and 5α-cholest-3-eno[3,4-*b*]indole (IIIa). When the pure isomers Ia and IIIa were mixed in equal proportions and allowed to crystallize from EtOH, a single crystalline product was obtained, identical in physical and GLC characteristics to the needles obtained in the Fischer-indole cyclization. The nature of these products was further investigated by mass spectrometry using an LKB 900 combined gas chromatograph—mass spectrometer: spectra characteristic of the [3,2-*b*]- and [3,4-*b*]-systems were obtained.*

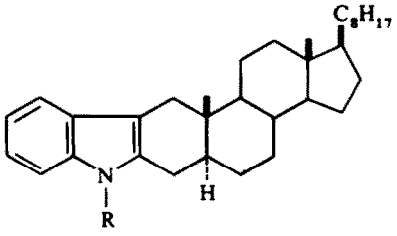
The N-methylphenylhydrazone of 5α-cholestan-3-one was analogously converted into 1′-methyl-5α-cholest-2-eno[3,2-*b*]indole[8] (Ib, 89·5%) and 1′-methyl-5α-cholest-3-eno[3,4-*b*]indole (IIIb, 10·5%) in refluxing AcOH; the methylindole (IIIb) was unambiguously prepared by cyclization of the N-methylphenylhydrazone of cholest-4-en-3-one followed by hydrogenation with Pd/C.[8] In the light of previous work, the proportion of [3,4-*b*]indole formed in this reaction is surprising, and indicates that in the hydrazone-enehydrazine equilibrium, a substantial proportion of the cholest-3-ene isomer is formed.

Similar considerations were found to apply to the reaction of 5β-cholestan-3-one with phenylhydrazine in refluxing AcOH. The major product (91%) was found to be the previously reported[9] 5β-cholest-3-eno[3,4-*b*]indole (IIa) while the GLC retention time and mass spectrum of the minor product (9%) indicates the structure to be that of the [3,2-*b*]indole IVa. In this case, the GLC separation was not so marked as with the 5α-isomers, and separation was achieved only on OV-17. The retention times of the four isomers Ia, IIa, IIIa and IVa were sufficiently different on this phase to permit GLC separation of mixtures of all four isomers.

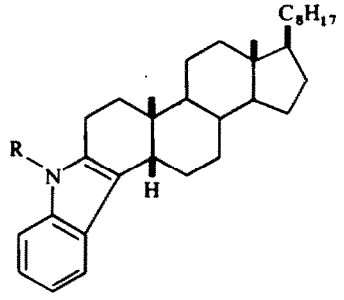
Reaction of N-methylphenylhydrazine with 5β-cholestan-3-one in refluxing AcOH also resulted in the formation of [3,2-*b*] and [3,4-*b*]indoles. Three products were observed on GLC, and these had retention times and mass spectra corresponding to 1′-methyl-5β-cholest-2-eno[3,2-*b*]indole (IVb), 1′-methyl-5β-cholest-3-eno[3,4-*b*]-indole[8] (IIb), and 1′-methylcholesta-3,5-dieno[3,4-*b*]indole[8] (V). Pure samples of the indoles IIb and V were isolated in 51 and 4% respectively by chromatography on alumina. The formation in small yield of compound V was previously noted[8] when the reaction was carried out in polyphosphoric acid.

1′-Methyl-5β-cholest-2-eno[3,2-*b*]indole (IVb) was unambiguously synthesized from the steroidal indole VI, formed by the cyclization of the N-methylphenylhydrazone of cholest-4,6-dien-3-one in AcOH. Catalytic hydrogenation with Pd/C in benzene gave as the major product the known 1′-methyl-5α-cholest-2-eno[3,2-*b*] indole (Ib), thus establishing the structure of the cyclized product as 1′-methylcholesta-2,4,6-trieno[3,2-*b*]indole; the [3,2-*b*] structure fully accords with previous evidence[10] regarding the enolization of cholesta-4,6-dien-3-one. The required 5β-isomer IVb was obtained as minor product (27%) of the hydrogenation.

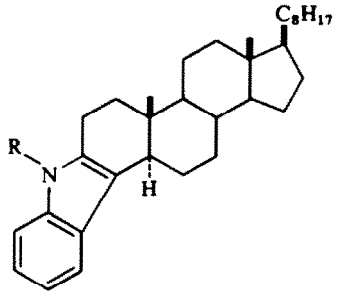
* The differences in the mass spectra of various isomeric steroidal indoles of this type have been investigated in collaboration with other workers and will be the subject of a further communication.



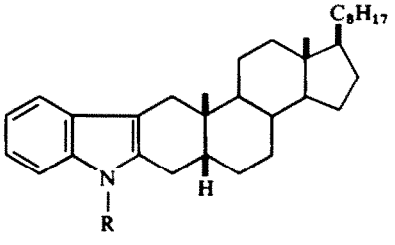
Ia R = H
Ib R = Me



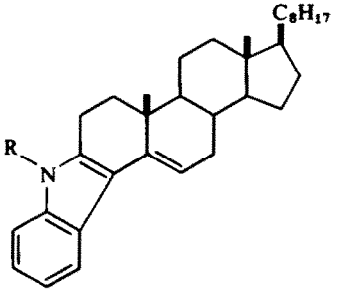
IIa R = H
IIb R = Me



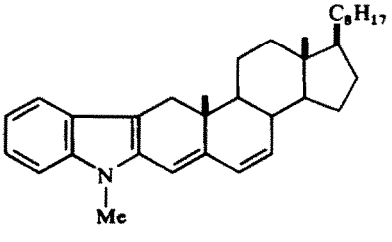
IIIa R = H
IIIb R = Me



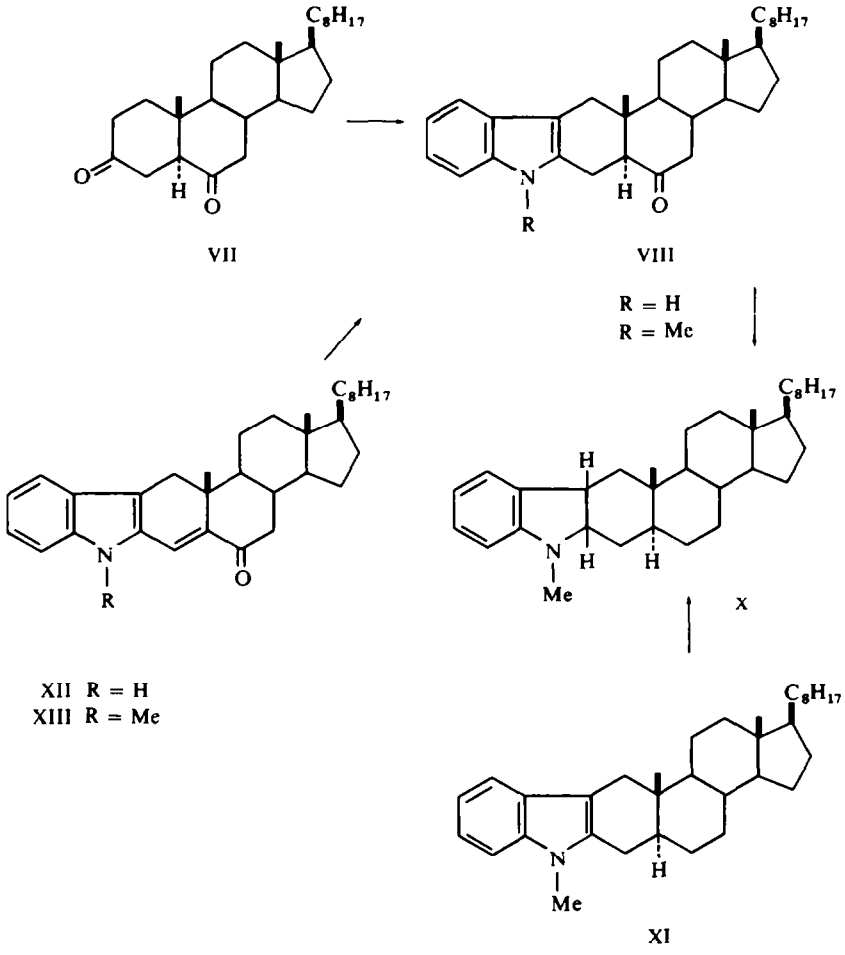
IVa R = H
IVb R = Me



Va R = H
Vb R = Me



VI



The cyclization of the *p*-benzyloxyphenylhydrazones of 5α- and 5β-cholestan-3-one was also undertaken. Each phenylhydrazone was prepared by reaction of the ketone with *p*-benzyloxyphenylhydrazone, and in both cases, only the major steroidal indole was isolated and characterized. Of particular interest, in view of the biological interest in 5-hydroxyindoles, is 5′-hydroxy-5α-cholest-2-eno[3,2-*b*]indole; this was obtained by cyclization of the *p*-benzyloxyphenylhydrazone of 5α-cholestan-3-one, followed by removal of the benzyl group by catalytic hydrogenation. A previous attempt to use the benzyloxy protecting group in the synthesis of fused 5-hydroxyindoles in the androstane series was unsuccessful,[11]

As part of an investigation[12] into rigid analogues of tryptamine and 5-hydroxytryptamine, the synthesis of 6-substituted cholest-3-eno[3,4-*b*]indoles was now undertaken with a view to converting these into the corresponding 6α- and 6β-amino derivatives. The cholest-2-eno[3,2-*b*]indole system is readily available, and the synthesis of the 6α- and 6β-amino derivatives was also undertaken for comparative biological evaluation.

The influence of a C-6 substituent on the direction of enolization in cholestan-3-ones is not fully documented, and efforts were first made to examine the cyclization of the monophenylhydrazones of 5α- and 5β-cholestane-3,6-dione; the greater reactivity of the carbonyl function at C-3 as compared with C-6 is such that the monohydrazone is formed preferentially at C-3.

5α-Cholestane-3,6-dione (VII) undergoes sulphonation[13] which has been observed to proceed in the direction of enolization,[14] to give the 2α-derivative, and with bromine in the presence of acetate ion the dione VII is converted into the 2-bromo derivative.[15,16] The reported formation[15,17] of 4,7-dibromocholest-4-ene-3,6-dione from both 5α- and 5β-cholestane-3,6-dione appears to be the result of an HBr-catalysed rearrangement following substitution at C-2. The expectation was, therefore, that cyclization of the monophenylhydrazone of 5α-cholestane-3,6-dione (VII) would lead to the formation of a cholest-2-eno[3,2-*b*]indole. Treatment of 5α-cholestane-3,6-dione (VII) with phenylhydrazine in refluxing AcOH led to the formation of a crystalline steroidal indole with ν_{max} 3470, 1700 cm^{-1} in 76% yield. This was assigned the structure 6-oxo-5α-cholest-2-eno[3,2-*b*]indole (VIII). Chemical evidence for this assignment was obtained from a study of the N-methyl derivative IX prepared by treatment of the dione VII with N-methylphenylhydrazine. Clemmensen reduction of the keto group in 6-oxo-5α-cholest-2-eno[3,2-*b*]*N*-methylindole (IX) led also to the reduction of the indole ring and is therefore in agreement with other reports:[18] the product is formulated as the indolenine X and is identical in all respects to the indolenine obtained from the reduction of 5α-cholest-2-eno[3,2-*b*]N-methylindole (XI) under the same conditions, but different from the corresponding reduction product of the isomeric 5α-cholest-3-eno[3,4-*b*]N-methylindole.

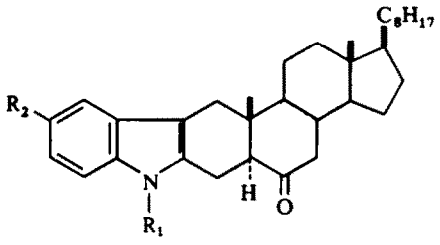
The steroidal indole VIII and its N-methyl derivative IX were unambiguously synthesized from cholest-4-ene-3,6-dione by cyclization of the known 3-monophenylhydrazone[19] and the mono-N-methylphenylhydrazone using polyphosphoric acid, followed by stereospecific hydrogenation of the C-4,5 double bond of the unsaturated steroidal indoles XII and XIII. In this case, cyclization to give a cholest-3-eno[3,4-*b*]indole is not possible.

A number of substituted cholest-2-eno[3,2-*b*]indoles were synthesised in this way from 5α-cholestane-3,6-dione using the appropriate phenylhydrazine, and details are given in Table I.

6-Oxo-5α-cholest-2-eno[3,2-*b*]indole (VIII) and its N-methyl analogue IX were converted into their oximes by reaction with hydroxylamine hydrochloride and NaOAc in refluxing EtOH. Stereospecific reduction of steroidal oximes with either Na in EtOH or LAH to give predominantly the equatorial and axial amines respectively is well established.[20] These methods were employed in the reduction of the oximes of steroidal indoles VIII and IX.

n-Amyl alcohol was found to be the best solvent for the reduction with Na, and crystalline hydrochloride salts of both 6α-amino-5α-cholest-2-eno[3,2-*b*]indole (XIV) and 6α-amino-5α-cholest-2-eno[3,2-*b*]N-methylindole (XV) were obtained by this method. With lower boiling solvents, little or no reduction occurred. Similarly, with LAH, reduction was incomplete using diethyl ether or THF as solvent. 6β-Amino-5α-cholest-2-eno[3,2-*b*]indole (XVI) and 6β-amino-5α-cholest-2-eno[3,2-*b*]N-methylindole (XVII) were eventually obtained as crystalline solids by reduction in refluxing di-*n*-butyl ether.

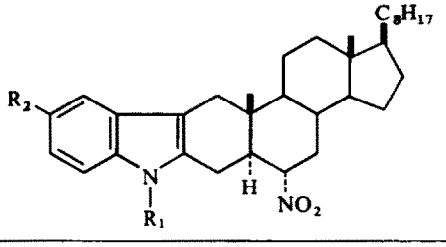
TABLE 1



R_1	R_2	Yield (%)	m.p.	Solvent of crystallization	Analysis Found (%)			Required (%)		
					C	H	N	C	H	N
CH_3	H	91	279–281°	EtOAc	83·8	10·1	—	83·8	10·1	—
CH_2Ph	H	74	198–201°	EtOAc	84·8	9·3	2·5	85·2	9·5	2·5
H*	OCH_2Ph	86	142–143°	EtOH	80·7	8·6	—	80·7	9·1	—
H	CH_3	80	245–247°	EtOH	84·0	10·0	—	83·7	10·1	—
H	Cl	71	253–255°	EtOH	77·5	9·0	—	78·0	9·1	—
H	OCOPh	79	234–237°	EtOAc/EtOH	80·9	8·7	—	80·9	8·7	—
CH_2Ph	OCH_2Ph	77	177–180°	EtOAc	84·0	8·9	—	84·2	8·9	—
CH_2Ph	OCH_3	84	192–193°	EtOAc/EtOH	83·2	9·4	—	82·9	9·3	—

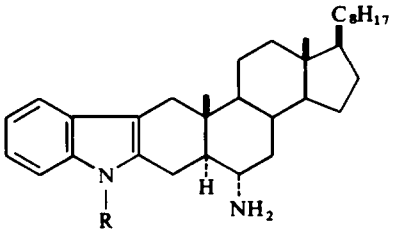
* characterized as the oxime.

TABLE 2

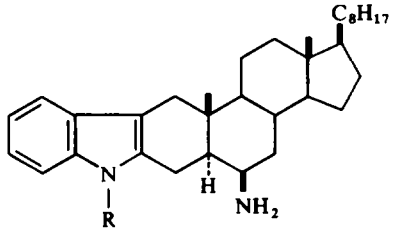


R_1	R_2	Yield (%)	m.p.	Solvent of crystallization	Analysis Found (%)			Required (%)		
					C	H	N	C	H	N
H	H	56	296–298°	EtOH	78·8	9·2	5·6	78·5	9·6	5·6
CH_3	H	85	225–227°	EtOAc	78·8	9·2	—	78·7	9·7	—
H	OCH_2Ph	85	246–249°	EtOH	78·8	8·8	4·7	78·6	8·9	4·6
CH_2Ph	H	73	187–190°	EtOAc/EtOH	80·9	9·0	—	80·7	9·2	—
H	OCH_3	68	251–254°	EtOH	75·9	9·4	—	76·3	9·4	—
H	CH_3	78	266–269°	EtOH	78·9	9·7	—	78·7	9·7	—
H	Cl	86	267–269°	EtOH	73·6	8·8	—	73·5	8·8	—
H	Br	64	274–276°	EtOH	67·6	8·1	—	67·9	8·1	—
H	I	62	288–290°	EtOH	63·0	7·7	—	62·9	7·5	—

An alternative but less successful approach to the synthesis of 6α-amino-5α-cholest-2-eno[3,2-*b*]indole (XIV), from the corresponding 6α-nitro derivative, was also investigated. Condensation of 6α-nitro-5α-cholestan-3-one[21] with phenylhydrazine and a number of substituted phenylhydrazines, followed by AcOH cyclization of the resulting hydrazones, led to the formation of a series of 6α-nitro-5α-cholest-2-eno[3,2-*b*]indoles (Table 2). All attempts to reduce the nitro group by catalytic hydrogenation were, however, unsuccessful. Reduction of 6α-nitro-5α cholest-2-eno[3,2-*b*]indole itself was effected in poor yield by the use of LAH, but the product, which formed an acetyl derivative with ν_{max} 3440, 3400 and 1660 cm^{-1}, was not fully characterized.



XIV R = H
XV R = Me



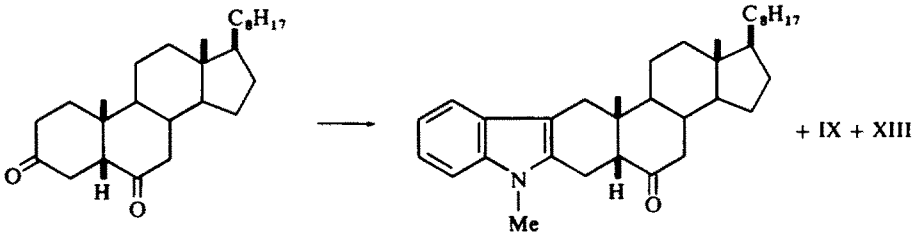
XVI R = H
XVII R = Me

Cyclization of the phenylhydrazones of 6-substituted 5β-cholestan-3-ones was now investigated as a route to the corresponding cholest-3-eno[3,4-*b*]indole derivatives. 5β-3-oxo steroids are known to exhibit dual enolization properties,[5] although cholest-3-eno[3,4-*b*]indole is the major product of the cyclization of the phenylhydrazone of 5β-cholestan-3-one.

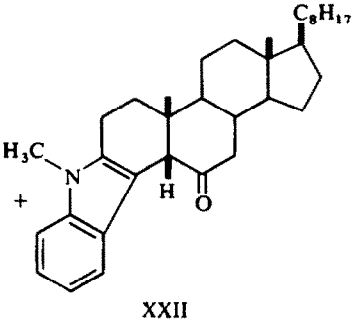
Exploratory investigations were first carried out with 5β-cholestane-3,6-dione, prepared from cholesterol via 3β,6β-dihydroxy-cholest-4-ene by a modified version of that previously reported.[22] Treatment of this diketone with phenylhydrazine in AcOH under the conditions previously described for the Fischer-indole cyclization resulted in the formation of a dark coloured complex mixture from which only the 3-monophenylhydrazone of cholest-4-ene-3,6-dione could be isolated in low yield. The reason for the formation of the unsaturated phenylhydrazone during this reaction is not clear, although dehydrogenations with the production of aromatic species have frequently been noted during Fischer-indole cyclizations catalysed by AcOH.[2,23] Furthermore, 4-oxo-1,2,3,4,5,6-hexahydrobenzo[a]carbazole (XVIII) is a minor product of the cyclization of the monophenylhydrazone of *trans*-1,5-dioxo-1,2,3,4,4a,5,6,7,8a-decahydronaphthalene (XIX).[24]

Failure to obtain a cholest-3-eno[3,4-*b*]indole by treatment of 5β-cholestane-3,6-dione (XX) with phenylhydrazine prompted us to investigate the reaction with N-methylphenylhydrazine in which fewer by-products might be anticipated. Reflux for five min in AcOH yielded a dark-coloured solution from which three crystalline products were isolated by repeated recrystallization or by chromatography on neutral alumina. 6-Oxo-5α-cholest-2-eno[3,2-*b*]N-methylindole (IX) was obtained

XIX XVIII



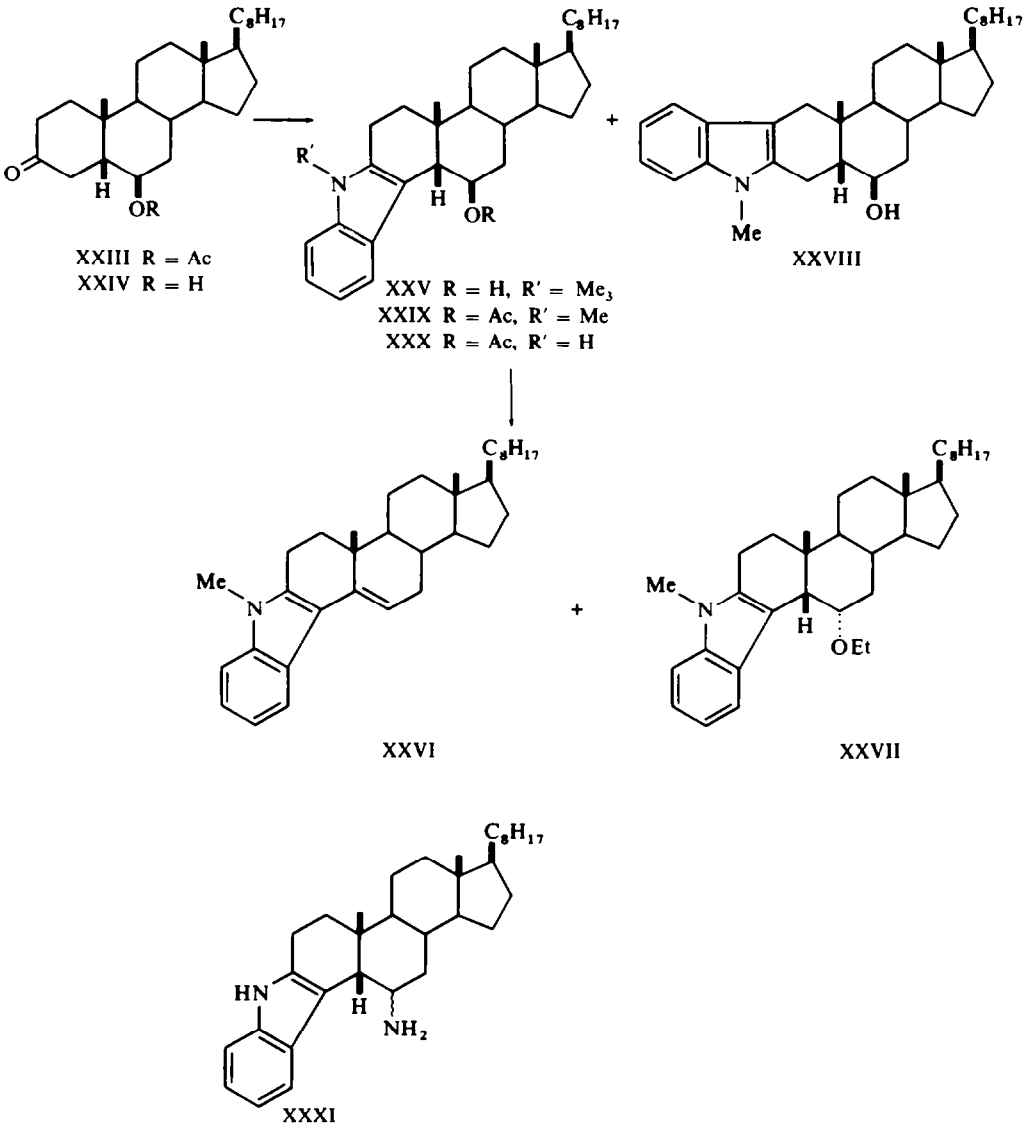
XX XXI + IX + XIII



XXII

in 16% yield and identified by comparison with an authentic sample. An isomer, isolated in 33% yield, was shown to be the 5β analogue XXI by epimerization to the 5α-derivative IX with HCl in AcOH. A third and minor product was the previously reported 6-oxocholesta-2,4-dieno[3,2-*b*]N-methylindole (XIII).

Repetition of this cyclization followed by epimerization at C-5 of the crude mixture with HCl led to the isolation of the 5α-isomer IX in 65% yield, the unsaturated ketone XIII in 12% yield, and a third product later shown unambiguously to be the required 6-oxo-5β-cholest-3-eno[3,4-*b*]N-methylindole (XXII) in 10% yield. The formation of the [3,2-*b*] isomer as the major product of this reaction demonstrates that under these conditions enolization involves predominantly C-2 rather than C-4 as in 5β-cholestan-3-one itself. The controlling factor in the enolization of 5β-cholestan-3-ones is said to be a steric one,[5] and it has been shown, for example, that the introduction of an 11β-hydroxyl substituent results in the formation of a higher proportion of C-2 enol relative to C-4 enol than in 5β-cholestan-3-one itself.[25] Epimerization at C-5 must occur either in the hydrazone or in 6-oxo-5α-cholest-2-eno[3.2-*b*]N-methylindole (XXI) as 5β-cholestane-3,6-dione is stable in AcOH under the reaction conditions employed.



The failure to obtain a reasonable quantity of a 6-oxo-5β-cholest-3-eno[3,4-*b*]-indole from 5β-cholestane-3,6-dione prompted us to investigate the cyclization of the phenylhydrazones of 6β-hydroxy- and 6β-acetoxy-5β-cholestan-3-one: the 6-oxo function could be generated later by oxidation of the alcohol, a method previously described[12] for the synthesis of the analogous 1,2,3,4-tetrahydrocarbazole derivatives.

6β-Acetoxy-5β-cholestan-3-one (XXIII) was prepared from 5β-cholestane-3β,6β-diol by a previously reported method,[26] the 6β-hydroxy derivative XXIV, originally characterized as a gum, was obtained in crystalline form by hydrolysis of the acetate XXIII with NaOH in EtOH followed by crystallization from petrol. The reaction of 6β-hydroxy-5β-cholestan-3-one (XXIV) with phenylhydrazine in AcOH gave a

non-crystalline product; evidence for the formation of a hydroxy cholesteno-indole was obtained from the IR spectrum (ν_{max} 3600, 3475 cm^{-1}) but crystalline material could not be isolated even on repeated chromatography. Two crystalline products were, however, obtained from the reaction of hydroxy-ketone XXIV with N-methylphenylhydrazine. The major product, separated by chromatography on neutral alumina, was shown to be 6β-hydroxy-5β-cholest-3-eno[3,4-*b*]N-methylindole (XXV) by elimination of the 6β-hydroxyl group as the tosylate to give authentic cholesta-3,5-dieno[3,4-*b*]N-methylindole[8] (XXVI); a second product of the elimination in EtOH was 6α-ethoxy-5β-cholest-3-eno[3,4-*b*]N-methylindole (XXVII).

The minor product of the reaction of the hydroxyketone XXIV with N-methylphenylhydrazine was characterized as 6β-hydroxy-5β-cholest-2-eno[3,2-*b*]N-methylindole (XXVIII) by oxidation with CrO_3 in pyridine to give 6-oxo-5α-cholest-2-eno[3,2-*b*]N-methylindole (IX) epimerization at C-5 presumably having occurred during the oxidation procedure. The possibility of the product XXVIII being the 5α-isomer was eliminated by comparison with an authentic sample of this compound prepared either by the reduction of 6-oxo-5α-cholest-2-eno[3,2-*b*]N-methylindole (IX) with LAH, the 6β-hydroxy being predominantly formed,[27] or by reaction of 6β-hydroxy-5α-cholestan-3-one[27,28] with N-methylphenylhydrazine in AcOH. Further evidence for the stereochemical assignment was provided by the NMR spectrum. Band width measurements and chemical shift values of the 19-methyl signals are both in agreement with this compound being the 5β-isomer; details are given below.

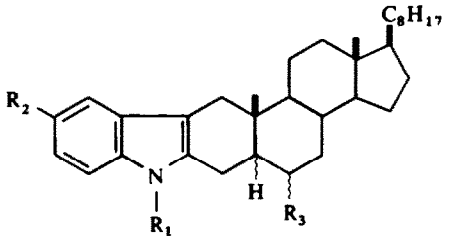
The major product (87%) of the reaction of 6β-acetoxy-5β-cholestan-3-one (XXIII) with N-methylphenylhydrazine in AcOH was also the [3,4-*b*]isomer (XXIX). Confirmation for this structure was obtained by basic hydrolysis of the 6β-acetoxyl group to give a product which was identical in all respects with a sample of authentic 6β-hydroxy-5β-cholest-3-eno[3,4-*b*]N-methylindole (XXV). The alcohol XXV can in turn be converted into the acetate XXIX by treatment with Ac_2O. Unlike the 6β-hydroxy compound XXIV, 6β-acetoxy-5β-cholestan-3-one (XXIII) also underwent a Fischer indole cyclization with phenylhydrazone to yield a crystalline product in 44% yield: this was assigned the structure 6β-acetoxy-5β-cholest-3-eno[3,4-*b*]-indole (XXX) by analogy with the N-methylphenylhydrazine reaction.

With the successful construction of the desired 6-substituted cholesteno[3,4-*b*]-indole system, it remained to introduce a 6-amino function to complete the synthesis of the tryptamine analogue (XXXI). The intention was to oxidise the 6β-hydroxyl group to the ketone, and to reduce the oxime prepared from this ketone with Na in amyl alcohol and LAH to give the isomeric 6α-amino and 6β-amino derivatives respectively. In the event, this proved impossible. Oxidation of 6β-hydroxy-5β-cholest-3-eno-[3,4-*b*]N-methylindole (XXV) could not be effected by means of the Oppenauer oxidation, used so successfully in the oxidation of the analogous 3-hydroxy-1,2,3,4-tetrahydrocarbazole;[12] the alcohol (XXV) was recovered from a variety of reaction conditions, and the lack of reactivity is assumed to be due to steric inhibition of the formation of the cyclic intermediate. Oxidation to the ketone (XXII) was achieved in low yield with CrO_3 and pyridine at 0°, and the sample was identical in all respects to that obtained from the reaction of 5β-cholestane-3,6-dione and N-methylphenylhydrazine. Both the position and half-height band width of the 19-Me signal in the NMR spectrum were consistent with this compound possessing the 5β-stereochemistry. An even poorer yield of 6-oxo-5β-cholest-3-eno[3,4-*b*]indole was obtained

by hydrolysis and oxidation of 6β-acetoxy-5β-cholest-3-eno[3,4-*b*]indole (XXX). The low yield at this stage together with the difficulty experienced in oxime formation made this route to the 6-amino derivatives unattractive, and the approach was discontinued.

The NMR spectra of many of the cholesteno-indoles reported in this paper were examined. In all cases, the aromatic indole protons appear, as expected, in the 2τ to 3·5τ region, and the methylene protons of the steroidal skeleton and C-17 side chain result in the large envelope between 7τ and 9·5τ.[29] The signal from the C-21 Me group, split into a doublet by the C-20 proton, occurs at 9·14τ (*J* 6 Hz) and the C-26 and C-27 Me signals, superimposed but split into a doublet by the C-25 proton, are visible at 9·17 (*J* 6 Hz). In the cholesteno-indoles reported, the C-18 Me signal is fairly constant around 9·3τ, but the position of the C-19 Me signal varies considerably (Tables 3 and 4). This value is, in fact, characteristic of

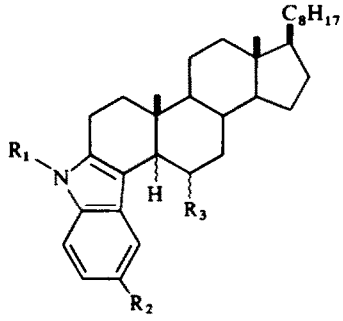
TABLE 3



R_1	R_2	R_3	C-5	C-18	C-19		R_1
					τ	$\Delta W_{\frac{1}{2}}$	
H	H	H	α	9·31	9·22	0·8	—
Me	H	H	α	9·31	9·23	0·8	6·48
H	OCH_2Ph	H	α	9·30	9·20	—	—
H	OH	H	α	9·30	9·21	—	..
Me	H	α-NO_2	α	9·28	9·14	—	6·47
H	CH_3	α-NO_2	α	9·30	9·19	—	—
Me	H	=O	α	9·31	9·30	—	6·46
H	CH_3	=O	α	9·34	9·34	—	—
H	Cl	=O	α	9·31	9·31	—	—
Me	H	β-OH	β	9·30	8·63	—	6·43
Me	H	=O	β	9·36	8·96	—	6·47d.

the stereochemistry of the A/B ring junction as previously shown in other steroidal systems.[30] In the 5β-series, the C-19 Me signal appeared downfield of the C-21 Me signal at around 8·8τ, whereas in the 5α-series, it usually appeared upfield of this Me signal and just downfield of the C-19 Me in the 9·2τ region. This property proved useful in determining the stereochemistry at C-5 of several of the compounds reported, notably 6-oxo-5β-cholest-3-eno[3,4-*b*]N-methylindole (XXII).

TABLE 4



R_1	R_2	R_3	C-5	C-18	C-19		R_1	C-5
					τ	$\Delta W_{\frac{1}{2}}$		
H	H	H	α	9·32	9·19	—	—	—
Me	H	H	α	9·32	9·21	—	6·50	—
H	H	H	β	9·36	8·90	0·45	—	7·20
Me	H	H	β	9·34	8·89	0·6	6·49	7·18
Me	H	β-OCOCH$_3$	β	9·39	8·79	0·4	6·43	6·69
Me	H	β-OH	β	9·33	8·80	—	6·42	7·12 m
Me	H	=O	β	9·34	8·93	0·2	6·41	6·58

The half-height band width of the C-19 Me signal was used as a second criterion for A/B ring-fusion stereochemistry. It has been shown[31] that in the 5α series, the protons of C-19 Me group are coupled to the 1α, 5α, and 9α protons and hence C-19 Me signal appears broader than in the 5β series where coupling can only occur with the 9α proton. The values for various cholestano-indoles are also given in Tables 3 and 4; the stereochemistry assigned to 6-oxo-5β-cholest-3-eno[3,4-*b*]N-methylindole (XXII) is supported by these measurements.

EXPERIMENTAL

GLC results were obtained at 270° with a Perkin–Elmer F11 gas chromatograph fitted with 6 foot glass columns packed with either 1% OV-1 or 1% OV-17 on Gas Chrom Q (100–120 mesh). Nitrogen at 40 ml/min. was used as the carrier gas. Retention data are expressed using Kováts retention indices, and the yields of each product eluted from the column are expressed as percentages of the total steroidal indole fraction. Experience with these reactions has shown almost quantitative conversion of the saturated 3-oxo-steroids into indolic material.

Mass spectrometric results were obtained with an LKB 9000 gas chromatograph-mass spectrometer fitted with a 3 foot glass column packed with 1% OV-17 on Gas Chrom Q (100–120 mesh) and kept at 270°. Mass spectra were recorded at 70 ev. with the accelerating voltage 3·5 kv., and the ion-source temperature 290°. High resolution data were obtained with a CEC 21-110B spectrometer. Melting points were determined with a Koffler hot stage microscope and infrared data were recorded with a Perkin–Elmer 237 spectrometer.

Reaction of 5α-cholestan-3-one with phenylhydrazine. 5α-Cholestan-3-one (1·0 g) and phenylhydrazine (0·32 ml) in AcOH (10 ml) were heated under reflux for 5 min. GLC analysis of the mixture (1 μl) on 1% OV-1 and 1% OV-17 columns showed it to contain 5α-cholest-2-eno[3,2-*b*]indole (Ia, 88·5%), retention

indices 4070 (1% OV-1) and 4560 (1% OV-17), and 5α-cholest-3-eno [3,4-*b*]indole (IIIa, 11·5%), retention indices 4090 (1% OV-1) and 4645 (1% OV-17). The product was allowed to crystallize from the cooled mixture and was recrystallized from EtOH. Samples of two crystalline forms were separated by hand and examined by GLC. The major component (plates) was shown to be 5α-cholest-2-eno[3,2-*b*]indole, m.p., 178–181° (lit.[6]. 180–181); $M^+ = 459$. The needle-shaped crystals m.p., 171–180° contained 5α-cholest-2-eno[3,2-*b*]indole and 5α-cholest-3-eno[3,4-*b*]indole in equal proportions; $M^+ = 459$ (both components). Further recrystallization of the product from EtOH yielded GLC pure 5α-cholest-2-eno-[3,2-*b*]indole (1·0 g, 85%), m.p. 179–181°; $\nu_{max}(CHCl_3)$ 3475 cm.$^{-1}$

5α-Cholest-3-eno[3,4-b]*indole* (IIIa). Cholesta-3,5-dieno [3,4-*b*]indole (Va) was synthesized from cholest-4-en-3-one and phenylhydrazine.[8] It had m.p. 193–196° (lit.[7], 195°). This was hydrogenated over 10% Pd/C to *5α-cholest-3-eno*[3,4-b]*indole* (40%), m.p. 170–174° (Found: C, 85·8; H, 10·8. $C_{33}H_{49}N$ requires: C, 86·2; H, 10·8%), ν_{max} ($CHCl_3$) 3475 cm.$^{-1}$.

Mixed crystals of 5α-cholest-2-eno[3,2-b]*indole* (1a) *and 5α-cholest-3-eno*-[3,4-*b*]*indole* (IIIa). 5α-Cholest-2-eno[3,2-*b*]indole (1·0 mg) and 5α-cholest-3-eno[3,4-*b*]indole (1·0 mg) were dissolved in hot EtOH (0·5 ml) and the mixture was cooled. The resulting needle-shaped crystals (1·5 mg, 75%) had m.p. 171–180°. No m.p. depression was observed on admixture with the needles obtained from the reaction of 5α-cholestan-3-one with phenylhydrazine and the GLC characteristics of the two samples were identical.

Reaction of 5α-cholestan-3-one with N-*methylphenylhydrazine.* 5α-Cholestan-3-one (1·0 g) was reacted with N-methylphenylhydrazine in AcOH as described above. GLC analysis of the product showed the presence of 1-methyl-5α-cholest-2-eno[3,2-*b*]indole (Ib, 89·5%), retention indices 4080 (1% OV-1) and 4540 (1% OV-17), $M^+ = 473$; and 1′-methyl-5α-cholest-3-eno[3,4-*b*]indole (IIIb, 10·5%), retention indices 4125 (1% OV-1) and 4630 (1% OV-17), $M^+ = 473$. The product was allowed to precipitate from the mixture and was recrystallized from EtOAc to give 1′-methyl-5α-cholest-2-eno[3,2-*b*]indole (1·1 g, 88%), m.p. 212–214° (lit.[8]. 215–217°).

1′-Methyl-5α-cholest-3-eno[3,4-b]*indole* (IIIb). This was prepared by the method described by Warnhoff and NaNonggai[8] and had m.p. 192–194° (lit.[8], 194–196°).

Reaction of 5β-cholestan-3-one with phenylhydrazine. 5β-Cholestan-3-one (1·0 g) was reacted with phenylhydrazine in AcOH and a sample (1 μl) of the product was examined by GLC as described above. The two components were identified as 5β-cholest-2-eno[3,2-*b*]indole (IVa, 8%), retention index 4450 (1% OV-17), M^+=459; and 5β-cholest-3-eno[3,4-*b*]indole (IIa, 92%), retention index 4470 (1% OV-17), M^+=459. No separation could be obtained with a 1% OV-1 column (retention index of both components 3960). After precipitation from the mixture the product was recrystallized from EtOH to give 5β-cholest-3-eno[3,4-*b*]indole (0·7 g, 59%), m.p. 190–194° (lit.[9], 192°), $\nu_{max}(CHCl_3)$ 3475 cm.$^{-1}$

Reaction of 5β-cholestan-3-one with N-*methylphenylhydrazine.* 5β-Cholestan-3-one (1·0 g) and N-methylphenylhydrazine were reacted in AcOH as described above and a sample (1 μl) of the product was examined by GLC. The following compounds were identified: 1′-methyl-5β-cholest-2-eno[3,2-*b*]indole (IVb), 10·8%), retention index 4380 (1% OV-17), M^+=473; 1′-methyl-5β-cholest-3-eno[3,2-*b*]indole (IIb, 81·2%) retention indices 3940 (1% OV-1, no separation from IVb) and 4425 (1% OV-17), M^+=473, and 1′-methylcholesta-3,5-dieno[3,4-*b*]indole (Vb, 5·6%), retention indices 4155 (1% OV-1) and 4690 (1% OV-17), M^+=471. The mixture was poured into water and the product was chromatographed on neutral alumina (grade 3). Elution with light petroleum (b.p. 60–80°) and recrystallization of the residue from EtOAc/EtOH gave 1′-methyl-5β-cholest-3-eno-[3,4-*b*]indole (0·57 g, 51%), m.p. 150–154° (lit.[8], 151–153°). Further elution with a 1:1 mixture of light petroleum (b.p. 60–80°) and benzene gave 1′-methylcholesta-3,5-dieno-[3,4-*b*]indole (0·04 g, 4%), m.p. 222–224° identical with an authentic sample.

1′-Methylcholesta-2,4,6-trieno[3,2-b]*indole* (VI). Cholesta-4,6-diene-3-one (1·0 g) and N-methylphenylhydrazine (0·32 ml) in AcOH (10 ml) were heated under reflux for 5 min. and cooled. The resulting crystalline precipitate was washed with AcOH and recrystallized twice from EtOAc/EtOH to give *1′-methylcholesta-2,4,6-trieno*-[3,2-b]*indole* (0·35 g, 29%), m.p. 187–191° (Found: C, 86·7; H, 10·1. $C_{34}H_{47}N$ requires C, 86·9; H, 10·1%), M^+=469, $\nu_{max}(CHCl_3)$ 1605, 1470 cm.$^{-1}$

Hydrogenation of 1′-methylcholesta-2,4,6-trieno[3,2-b]*indole.* 1′-Methylcholesta-2,4,6,trieno[3,2-*b*]indole (0·35 g) in benzene (20 ml) was hydrogenated over 10% Pd/C (0·02 g) until the uptake of hydrogen ceased (30 min). After removal of the catalyst, GLC analysis of the solution indicated the presence of *1′-methyl-5β-cholest-2-eno*[3,2-b]*indole* (27%), M^+=473; and 1′-methyl-5α-cholest-2-eno[3,2-*b*]indole (73%), M^+=473. The solvent was removed and the residue was recrystallized from EtOAc to give 1′-methyl-5α-cholest-2-eno[3,2-*b*]indole (0·2 g, 65%), m.p. 212–214°. This showed no m.p. depression on admixture with an authentic sample, and the IR and MS of the two samples were identical. The residue from the mother

liquors of this recrystallization was chromatographed on neutral alumina (grade 1). Elution with light petroleum (b.p. 60–80°) yielded, as the first fraction, a white solid which was recrystallized from EtOH to give 1'-methyl-5β-cholest-2-eno[3,2-*b*]indole (1·5 mg, 0·35%), m.p. 195–197° (Found M^+=473·4027; calculated for $C_{34}H_{51}N$, M^+=473·4022. GLC analysis of further fractions from the column indicated progressive contamination of this compound by the 5α-isomer.

1'-*Methylcholesta*-3,5-*dieno*[3,4-b]*indole* (Vb). This was prepared by the method described by Warnhoff and NaNonggai[8] and had m.p. 222–224° (lit.[8]. 221–223°).

5'-*Benzyloxy*-5α-*cholest*-2-*eno*[3,2-*b*]*indole*. This was prepared in 68% yield from 5α-cholestan-3-one and *p*-benzyloxyphenylhydrazine by the method described above for the synthesis of the unsubstituted steroidal indoles. The *indole* had m.p. 176–177° from EtOH. (Found: C, 84·8; H, 9·7. $C_{40}H_{55}NO$ requires C, 84·9; H, 9·8%).

5'-*Benzyloxy*-5β-*cholest*-3-*eno*[3,4-*b*]*indole*. The *indole* was prepared in 78% yield from 5β-cholestan-3-one and *p*-benzyloxyphenylhydrazine, and had m.p. 136–138° from EtOH. (Found: C, 84·9; H, 10·0. $C_{40}H_{55}NO$ requires C, 84·9; H, 9·8%).

5'-*Hydroxy*-5α-*cholest*-2-*eno*[3,2-*b*]*indole*. 5'-Benzyloxy-5α-cholest-2-eno[3,2-*b*]indole (2·0 g) in EtOH (200 ml) was hydrogenated over 10% Pd/C (0·2 g) until the uptake of hydrogen ceased (13 hr). The catalyst was removed and the solution concentrated. 5'-*Hydroxy*-5α-*cholest*-2-*eno*[3,2-b]*indole* (1·2 g, 71%) separated from the cooled solution and was recrystallized from EtOH. It had m.p. 256–263° (decomp.), (Found: C, 83·4; H, 10·5. $C_{33}H_{49}NO$ requires C, 83·3; H, 10·4%); ν_{max} 3590, 3475 cm^{-1}.

6-*Oxo*-5α-*cholest*-2-*eno*[3,2-b]*indole* (XIII). Phenylhydrazine (2·7 g) was added to a solution of 5α-cholestane-3,6-dione (10·0 g) in glacial AcOH, and the mixture heated under reflux for 10 min. The *indole* (8·9 g, 76%) was isolated by dilution with water, filtration and recrystallization from EtOH and had m.p. 269–272°. (Found: C, 84·2; H, 10·2; N, 2·8. $C_{33}H_{47}NO$ requires C, 83·7; H, 10·0; N, 3·0%).

Compounds listed in Table 1 are prepared by this method using the appropriately substituted phenylhydrazine.

1'-*Methyl*-2,3-*dihydro*-5α-*cholest*-2-*eno*[3,2-b]*indole* (X). (a) A mixture of 1'-methyl-5α-cholest-2-eno-[3,2-*b*]indole[8] (0·10 g) and amalgamated Zn[33] (0·59 g) in AcOH (10 ml) was heated under reflux for 4 days. The mixture was then filtered, poured into water, and the product (0·09 g) filtered, washed with water, dried and chromatographed on neutral alumina (grade 1). Elution with a 10:1-mixture of light petroleum (b.p. 60–80°) and benzene gave the 2,3-*dihydro-indole* (0·028 g, 28%), m.p. 136–138° from EtOH. (Found: C, 85·7: H, 11·0. $C_{34}H_{53}N$ requires C, 85·8; H, 11·2%). (b) Clemmensen reduction of 1'-methyl-6-oxo-5α-cholest-2-eno[3,2-*b*]indole under conditions identical to those described in (a) gave a 10% yield of the dihydro-indole X, m.p. 136–138°.

1'-*Methyl*-3,4-*dihydro*-5α-*cholest*-3-*eno*[3,4-*b*]*indole*. 1'-Methyl-5α-cholest-3-eno[3,4-*b*]indole[8] (0·10 g) was reduced with Zn and AcOH employing the conditions described above for the [3,2-*b*] isomer. 1'-*Methyl*-3,4-*dihydro*-5α-*cholest*-3-*eno*[3,4-*b*]*indole* (0·027 g, 27%) was obtained by chromatography on alumina, and had m.p. 177–179°. (Found: C, 85·3; H, 11·6. $C_{34}H_{53}N$ requires C, 85·8; H, 11·2%). On admixture with the product from the reduction of 1'-methyl-6-oxo-5α-cholest-2-eno[3,2-*b*]indole, a m.p. depression was observed.

6-*Oxocholesta*-2,4-*dieno*[3,2-*b*]*indole* (XII). Cholest-4-ene-3,6-dione 3-monophenylhydrazone[19] (3·87 g) was heated gently with polyphosphoric acid (8 g) to initiate reaction. When the reaction appeared to be complete, the mixture was cooled, diluted with water, and the product extracted with ether. Removal of the ether by distillation yielded the *indole* (1·32 g, 36%) with m.p. 283–285° from EtOH. (Found: C, 84·0; H, 9·8. $C_{33}H_{45}NO$ requires C, 84·0; H, 9·6%); ν_{max} 3480, 1670, 1600 and 1555 cm^{-1}.

Hydrogenation at room temperature and atmospheric pressure of indole XII (1·32 g) in EtOAc (50 ml) with PtO gave a sample (0·42 g, 32%) with m.p. 270–272° from EtOH, identical with 6-oxo-5α-cholest-2-eno[3,2-*b*]indole (VIII) prepared by reaction of 5α-cholestane-3,6-dione with phenylhydrazine.

1'-*Methyl*-6-*oxocholesta*-2,4-*dieno*[3,2-b]*indole* (XIII). N-methylphenylhydrazine (1·2 g) was added to a warm solution of cholest-4-ene-3,6-dione (3·98 g) in glacial AcOH (30 ml) and the mixture heated under reflux for 10 min. The *indole* crystallized from the solution on cooling; after recrystallization from EtOAc, it had m.p. 231–236° (1·5 g, 31%). (Found: C, 83·7; H, 9·9; N, 3·3. $C_{34}H_{47}NO$ requires: C, 84·1; H, 9·8; N, 2·9%); ν_{max} 1665, 1580 and 1535 cm^{-1}.

The indole XIII was hydrogenated employing the conditions described above for 6-oxocholesta-2,4-dieno[3,2-*b*]indole. 1'-Methyl-6-oxo-5α-cholest-2-eno[3,2-*b*] indole. m.p. 280–282° was obtained, identical in all respects to a sample of this compound prepared by the reaction of N-methylphenylhydrazine with 5α-cholestane-3,6-dione.

6-Hydroxyimino-5α-cholest-2-eno[3,2-b]indole. 6-Oxo-5α-cholest-2-eno[3,2-*b*]indole (5·0 g)was heated under reflux in EtOH aq with excess hydroxylamine hydrochloride and NaOAc for 8 hr. The EtOH was removed by distillation under reduced pressure, and the cooled solution poured into water. The resulting precipitate was filtered off, washed with water and recrystallized from MeOH to give the *oxime* (4·1 g, 80%), m.p. 240–243°. (Found: C, 80·5; H, 9·7. $C_{33}H_{48}N_2O$ requires C, 81·0; H, 9·9%).

The oxime of 1′-methyl-6-oxo-5α-cholest-2-eno[3,2-*b*]indole was similarly prepared in 93% yield and had m.p. 217–220° from MeOH. (Found: C, 81·1; H, 10·0. $C_{34}H_{50}N_2O$ requires C, 81·2; H, 10·0%).

6α-Amino-1′-methyl-5α-cholest-2-eno[3,2-b]indole hydrochloride. Na was added to a refluxing solution of 6-hydroxyimino-1′-methyl-5α-cholest-2-eno[3,2-*b*]indole (0·50 g) in *n*-amyl alcohol (50 ml) over 3 hr. Heating was continued for a further 1 hr, and the solution was then poured into water. The product was extracted with ether, and treated with an excess of 2N HCl. Crystals of the *hydrochloride* (0·37 g, 72%) had m.p. 251° (decomp.) from MeOH. (Found: C, 77·9; H, 10·2. $C_{34}H_{53}N_2Cl$ requires C, 77·7; H, 10·2%).

6β-Amino-5α-cholest-2-eno[3,2-b]indole (XVI). 6-Hydroxyimino-5α-cholest-2-eno[3,2-*b*]indole (0·10 g) in di-*n*-butyl ether (4·0 ml) was heated under reflux with an excess of LAH for 1½ hr. Excess LAH was destroyed by cautious addition of wet ether, followed by NaOH aq. The product was extracted with ether, and the ether solution washed with water and dried (Na_2SO_4). Distillation of the ether and crystallization from EtOH gave the *amine* (0·06 g, 63%), m.p. 132–135°. (Found: C, 83·2; H, 10·4. $C_{33}H_{50}N_2$ requires: C, 83·3; H, 10·6%).

6β-Amino-1′-methyl-5α-cholest-2-eno[3,2-b]indole (XVII). The *amine* was prepared in 66% yield from 6-hydroxyimino-1′-methyl-5α-cholest-2-eno[3.2-*b*]indole by the method described above for the preparation of 6β-amino-5α-cholest-2-eno[3,2-*b*]indole, and had m.p. 104–107°. (Found: C, 83·3; H, 10·4. $C_{34}H_{52}N_2$ requires C, 83·3; H, 10·7%).

6α-Nitro-5α-cholest-2-eno[3,2-b]indole. A solution of 6α-nitro-5α-cholestan-3-one[21] (4·3 g) and phenylhydrazine (1·1 g) in AcOH (20 ml) was heated under reflux for 15 min. The *indole* crystallized from solution on cooling; after recrystallization from EtOH, it had m.p. 296–298° (2·8 g, 56%). (Found: C, 78·8; H, 9·2; N, 5·6. $C_{33}H_{48}N_2O_2$ requires C, 78·5; H, 9·6; N, 5·6%), ν_{max} 3480 and 1555 cm^{-1}.

5β-Cholestane-3β,6β-diol. 3β,6β-Dihydroxy-cholest-4-ene[34] (5·0 g) was hydrogenated at 55° and atmospheric pressure in EtOH (50 ml) over PtO (0.35 g) until the uptake of hydrogen ceased. Further quantities of 3β,6β-dihydroxycholest-4-ene were added until 56·5 g had been hydrogenated. The catalyst was removed by filtration and the solvent distilled; recrystallization from EtOH gave the diol (50 g, 88%), m.p. 196–198° (Lit.[22] 198–200°).

5β-Cholestane-3,6-dione (XX). Oxidation of 5β-cholestane-3β,6β-diol (6.75 g) with CrO_3 in AcOH aq by the method described by Prelog and Tagmann[22] gave 5β-cholestane-3,6-dione (5·23 g, 78%), m.p. 172–175° (lit.[22] 170–174°).

Reaction of 5β-cholestane-3,6-dione with N-methylphenylhydrazine. (a) 5β-Cholestane-3,6-dione (0·20 g) and N-methylphenylhydrazine (0·064 ml) were heated under reflux in AcOH (2 ml) for 5 min, and the mixture poured into water. The products were extracted with $CHCl_3$ and the solution washed with water and dried (Na_2SO_4). Removal of $CHCl_3$ form by distillation at reduced pressure gave a brown oil which was chromatographed on neutral alumina (grade 1). Elution with a 1:1-mixture of light petroleum (b.p. 60–80°) and benzene, and recrystallization of the product from EtOAc, gave 1′-methyl-6-oxo-5α-cholest-2-eno[3,2-*b*]indole, m.p. 279–280° (0·036 g, 16%), identical in all respects with an authentic sample prepared from 5α-cholestane-3,6-dione as described above. Further elution with a 10:1-mixture of benzene and $CHCl_3$ gave a yellow oil which crystallized from EtOH; this product was identified as 1′-methyl-6-oxocholesta-2,4-dieno[3,2-*b*]indole, m.p. 235–238°, by comparison with an authentic sample prepared from cholest-4-ene-3,6-dione. Elution with a 5:1-mixture of benzene and $CHCl_3$ followed by recrystallization of the product from MeOH gave *1′-methyl-6-oxo-5β-cholest-2-eno[3,2-b]indole*, m.p. 179–180° (0·082 g, 33%), ν_{max} 1710 cm^{-1}. (Found: C, 83·8; H, 9·65. $C_{34}H_{49}NO$ requires C, 83·8; H, 10·1%).

(b) 5β-Cholestane-3,6-dione (0·20 g) and N-methylphenylhydrazine (0·064 g) in glacial AcOH (4 ml) were heated under reflux for 5 min. Conc HCl acid (5 drops) was added and heating was continued for a further 1 min. The hot solution was poured into water and the products extracted as in the previous experiment. Chromatography on neutral alumina (grade 1) gave three products; elution with a 1:1-mixture of light petroleum (b.p. 60–80°) and benzene gave 1′-methyl-6-oxo-5α-cholest-2-eno[3,2-*b*]indole (65%), whereas elution with a 3:5 mixture of light petroleum and benzene gave *1′-methyl-6-oxo-5β-cholest-3-eno[3,4-b] indole* (0·024 g, 10%), m.p. 208–210 from EtOH; ν_{max} 1605, 1710 cm^{-1}. (Found: C, 83·8; H, 10·2. $C_{34}H_{49}NO$ requires C, 83·8; H, 10·1%). Elution with benzene gave 1′-methyl-6-oxocholesta-2,4-dieno[3,2-*b*]indole (12%).

6β-*Hydroxy*-5β-*cholestan*-3-*one* (XXIV). 6β-Acetoxy-5β-cholestan-3-one[26] (7·0 g) was heated under reflux in EtOH with a solution NaOH (2.5 g) in EtOH (70 ml) and water (25 ml) for 1 hr. Water (100 ml) was added and the EtOH removed by distillation at reduced pressure. The product was extracted with ether, washed with water and dried (Na_2SO_4). Removal of the ether gave a gum which was crystallized from light petroleum (b.p. 40–60°) to give colourless plates of 6β-*hydroxy*-5β-*cholestan*-3-*one* (4.6 g, 73%), m.p. 92–93° and 116–117°. (Found: C, 80·7; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·6; H, 11·5%).

Reaction of 6β-*hydroxy*-5β-*cholestan*-3-*one with* N-*methylphenylhydrazine*. 6β-Hydroxy-5β-cholestan-3-one (4.4 g) and N-methylphenylhydrazine (1·42 ml) in glacial AcOH (44 ml) were heated under reflux for 5 min and the mixture poured into water. The resulting yellow precipitate (5·30 g) was filtered, washed with water, dried, and chromatographed on neutral alumina (grade 3). Elution with light petroleum (b.p. 60–80°) and with a 20:1 mixture of light petroleum and benzene gave small quantities of unidentified crystalline materials. Further elution with a 5:1-mixture of light petroleum and benzene, followed by crystallization of the product from MeOH, gave 6β-*hydroxy*-1′-*methyl*-5β-*cholest*-3-*eno*[3,4-b]*indole* (1·47 g, 27%), m.p. 164–166°, ν_{max} 3600, 1480 and 1000 cm^{-1}. (Found: C, 83·0; H, 10·6. $C_{34}H_{51}NO$ requires C, 83·3; H, 10·5%). Elution with a 1:1-mixture of light petroleum and benzene, followed by recrystallization of the product from MeOH, gave 6β-*hydroxy*-1′-*methyl*-5β-*cholest*-2-*eno*[3,2-b]*indole* (0·41 g, 8%), m.p. 185–187°, ν_{max} 3600, 1480 cm^{-1}. (Found: C, 83·4; H, 10·5. $C_{34}H_{51}NO$ requires C, 83·3; H, 10·5%).

Elimination of the 6β-*hydroxyl group from* 6β-*hydroxyl*-1′-*methyl*-5β-*cholest*-3-*eno*[3,4-b]*indole* (XXV). 6β-Hydroxy-1′-methyl-5β-cholest-3-eno[3,4-*b*]indole (0·04 g) and TSOH (0·24 g) were dissolved in pyridine (1·5 ml) and kept at room temperature overnight. The mixture was diluted with water, and the product isolated by extraction with $CHCl_3$. Removal of the solvent yielded a gum which gave, on crystallization from EtOH, 6α-*ethoxy*-1′-*methyl*-5β-*cholest*-3-*eno*[3,4-b]*indole* (0·024 g, 56%), m.p. 153–155°. (Found: C, 83·5; H, 10·2. $C_{36}H_{55}NO$ requires C, 83·5; H, 10·7%).

Repetition of this reaction followed by heating under reflux the crude gum in 2,4,6-collidine for four hr gave, on pouring into water, a brown solid (0·025 g) which when crystallized from EtOAc proved to be identical in all respects to an authentic sample of 1′-methylcholesta-3,5-dieno[3,4-*b*]indole (0·007 g, 18%), m.p. 220–222° (lit.,[8] 221–223°).

Oxydation of 6β-*hydroxy*-1′-*methyl*-5β-*cholest*-2-*eno*[3,2-b]*indole*. 6β-Hydroxy-1′-methyl-5β-cholest-2-eno[3,2-*b*]indole (0·05 g) in pyridine (0·5 ml) was added to a complex of CrO_3 oxide (0·025 g) in pyridine (0·25 ml) and the mixture kept at 0° overnight, poured into water, and the product extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with 2N HCl, $NaHCO_3$ solution, and water, and dried (Na_2SO_4). Removal of the $CHCl_3$ gave a yellow oil which was separated by chromatography on neutral alumina (grade 1). Elution with a 1:1-mixture of light petroleum (b.p. 60–80°) and benzene, followed by recrystallization of the product from EtOAc, gave 1′-methyl-6-oxo-5α-cholest-2-eno[3,2-*b*]indole, m.p. 281–282°, identical in all respects with a sample prepared as described above from 5α-cholestane-3,6-dione.

6β-*Hydroxy*-1′-*methyl*-5α-*cholest*-2-*eno*[3,2-b]*indole*. (a) 1′-Methyl-6-oxo-5α-cholest-2-eno[3,2-*b*]indole (0·1 g) in THF (10 ml) was heated under reflux with LAH (0·04 g) for 30 min. Excess LAH was decomposed with water, and the product extracted with $CHCl_3$ to give *the alcohol* (0·074 g, 74%), m.p. 206–208° from EtOH. (Found: C, 83·2; H, 10·3. $C_{34}H_{51}NO$ requires C, 83·3; H, 10·5%).

(b) 6β-Hydroxy-5α-cholestan-3-one[27,28] (0·035 g) and N-methylphenylhydrazine (0·012 ml) in glacial AcOH (2·0 ml) were heated under reflux for 5 min and cooled. The product was filtered, washed with AcOH, and recrystallized from EtOH to give *the alcohol* (0·03 g, 70%), m.p. 206–209°.

A m.p. depression was observed on admixture of a sample prepared by method (a) or (b) with the 5β-isomer (m.p. 185–187°) prepared by the reaction of 6β-hydroxy-5β-cholestan-3-one with N-methylphenylhydrazine.

6β-*Acetoxy*-1′-*methyl*-5β-*cholest*-3-*eno*[3,4-b]*indole* (XXIX). 6β-Acetoxy-5β-cholestan-3-one (3·0 g) and N-methylphenylhydrazine (1·0 ml) were refluxed in AcOH (25 ml) for 5 min, and the hot solution poured into water. The resulting pale yellow precipitate was filtered, and chromatographed on neutral alumina (grade 3). Elution with light petroleum (b.p. 60–80°) and crystallization of the product from MeOH gave *the acetoxy-indole* (2·8 g, 78%), m.p. 148–154°, ν_{max} 1720, 1470 and 1250 cm^{-1}. (Found: C, 81·3; H, 10·0. $C_{36}H_{53}NO_2$ requires C, 81·3; H, 10·1%).

Hydrolysis of this product (2·78 g) in EtOH (200 ml) by heating under reflux with a solution of NaOH (2·75 g) in water (6·5 ml) for 1 hr gave, on crystallisation from EtOH, 1′-methyl-6β-hydroxy-5β-cholest-3-eno[3.4-*b*]indole, identical in all respects with a sample prepared from 6β-hydroxy-5β-cholestan-3-one and N-methylphenylhydrazine.

6β-Acetoxy-5β-cholest-3-eno[3,4-b]indole (XXX). 6β-Acetoxy-5β-cholestan-3-one (3.5 g) and phenylhydrazine (0·85 ml) were heated under reflux in glacial AcOH (35 ml) for 5 min, cooled, and the solution poured into water. The resulting solid was chromatographed on neutral alumina (grade 3). Elution with a 1:1-mixture of light petroleum (b.p. 60–80°) and benzene, followed by recrystallization of the product from MeOH, gave *the indole* (1·8 g, 44%), m.p. 110°. (Found: C, 81·2; H, 9·8. $C_{35}H_{51}NO_2$ requires C, 81·2; H, 9·9%).

1'-Methyl-6-oxo-5β-cholest-3-eno[3,4-b]indole (XXII). 6β-Hydroxy-1'-methyl-5β-cholest-3-eno[3,4-*b*] indole (1·47 g) in pyridine (10 ml) was added to a complex of CrO_3 (0·43 g) in pyridine (3 ml) and the mixture kept at 0° overnight, poured into water, and the product extracted with $CHCl_3$. Distillation of $CHCl_3$ gave a brown oil which was chromatographed on neutral alumina (grade 3). Elution with a 10:1-mixture of light petroleum (b.p. 60–80°) and benzene, and recrystallization of the product from EtOH, gave *the ketone* (0·39 g, 27%), m.p. 206–210°. (Found: C, 83·8; H, 10·2. Calc. for $C_{34}H_{49}NO$, C 83·8; H, 10·1%). There was no m.p. depression on admixture with a sample of the ketone (m.p. 208–210°) prepared by reaction of 5β-cholestane-3,6-dione and N-methylphenylhydrazine as described above.

6-Oxo-5β-cholest-3-eno[3,4-b]indole. 6β-Hydroxy-5β-cholest-3-eno[3,4-*b*]indole (1·0 g) was oxidised by the method described above for the 1'-methyl analogue. Crystallization from EtOH gave *6-oxo-5β-cholest-3-eno[3,4-b]indole* (0·10 g, 10%) m.p. 192–195°, ν_{max} 3470, 1710, 1260 cm^{-1}. (Found: C, 83·4; H, 9·85. $C_{33}H_{47}NO$ requires C, 83·6; H, 10·0%).

Acknowledgements—One of us (D.J.H.) thanks the M.R.C. for a studentship. We are grateful to Dr. C. J. W. Brooks, Department of Chemistry, Glasgow University, for use of the F11 gas chromatograph and LKB 900 mass spectrometer, and to Miss Pamela Crain, Institute for Lipid Research, Baylor College of Medicine, Houston, Texas, for the high resolution mass measurement.

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