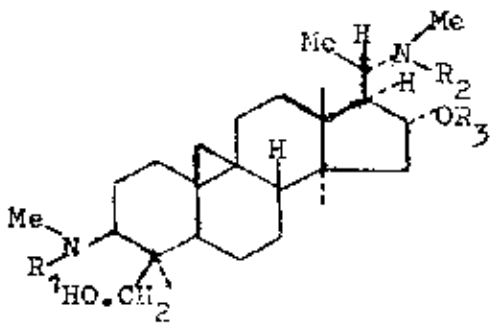
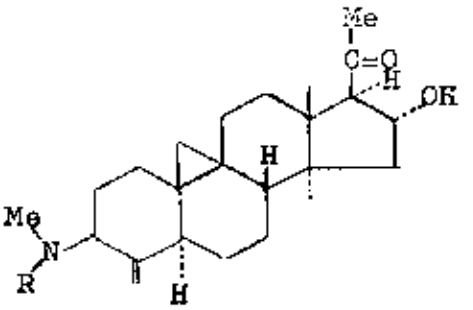
CHAPTER I

INTRODUCTION

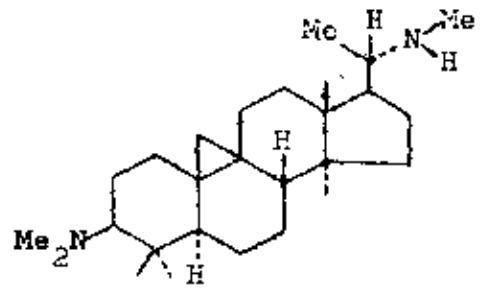
Extracts of Buxus plants have long been used in the treatment of disease, including malaria and skin diseases (85), and they have been investigated chemically for some time (42,86,99). Recent investigations on the alkaloids isolated from the leaves of Buxus sempervirens L., and the leaves and twigs of Buxus microphylla Sieb. et. Zucc. by Kupchan and Asbun (60), and Nakano and Terao (73) respectively have shown that they have the structures (I),(II),(III),and (IV).



(I) $R_1 = R_2 = H$ or Me
$R_3 = H$ or Bz



(II) R = H or Me



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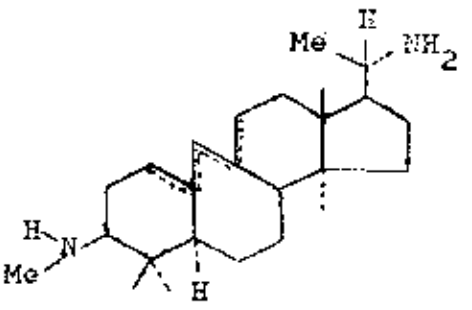


(IV)*

* The exact location of the conjugated diene chromophore in (IV) has not been settled.

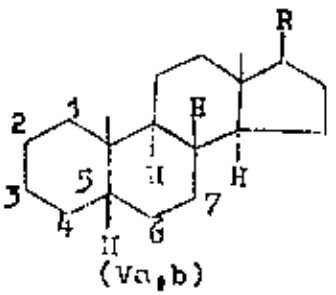
During the course of these investigations it became necessary to determine the configuration of the 3- amino group, and as there were no examples in the literature of configurational assignments of amino groups in similar environments, reference had to be made to the investigation of Haworth et al. (45,46,49) on the decomposition of steroidal trimethylammonium hydroxides to settle this stereochemical point.

Haworth et al. (45,46,49) have examined the Hofmann degradation of a number of steroidal trimethylammonium hydroxides; their results are summarized in Tables I and II.

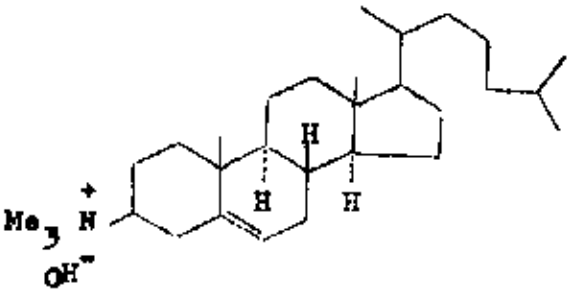
Table I

Hofmann Degradation of Axial Steroidal Bases

References	Quaternary hydroxide	Crude hydrocarbon (%)	Crude base recovered (%)
45,49	3α - Trimethyl -5α-cholestane ammonium hydroxide (Va)	79	17
45,49	3β -Trimethyl -5β -cholestane ammonium hydroxide (Va)	66	17
49	3α - Trimethyl -5α -pregnane ammonium hydroxide (Vb)	38	8
46	6β -Trimethyl -5α -cholestane ammonium hydroxide (Va)	73(Δ^5)	-



(Va,b)



(Va) R = $CHMe(CH_2)_3CHMe_2$

(Vb) R = Et

(VI)

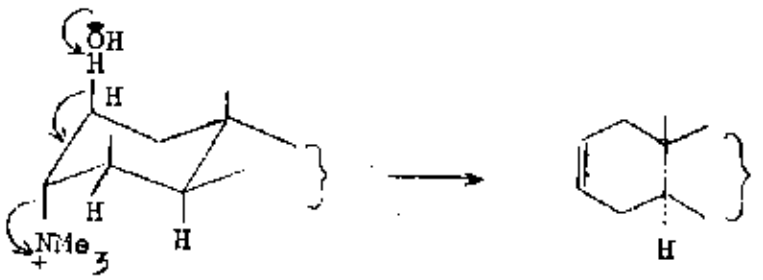
Table II

Hofmann Degradation of Equatorial Steroidal Bases

References	Quaternary hydroxide	Crude hydrocarbon (%)	Crude base recovered (%)
45,49	3β-Trimethyl-5α-cholestane ammonium hydroxide (Va)	4	92
45,49	3α-Trimethyl-5β-cholestane ammonium hydroxide (Va)	18	63
49	3β-Trimethyl-5α-pregnane ammonium hydroxide (Vb)	5	50
46	6α-Trimethyl-5α-cholestane ammonium hydroxide (Va)	8 ($\Delta^5 + \Delta^5$)	63
49	3β-Cholest-5-enyl-trimethyl-ammonium hydroxide (VI)	88	-

It can be seen from the above data that the main product resulting from the degradation of axial trimethylammonium hydroxides is the corresponding olefin; the equatorial epimer, however, affords only a little hydrocarbon, reversion to the tertiary steroidal base being the preferred course of reaction.

These results are consistant with a bimolecular elimination mechanism which requires a trans antiparallel arrangement of the participating centres (36). These 3α- substitution in the 5α - cholestane and 5α- pregnane salts (VII) satisfies this condition, the quaternary nitrogen and the axial hydrogens on the β-carbon atoms being trans and coplanar. However in the 3β-epimers, the dihedral angle of the quaternary nitrogen and the hydrogens attached to the β-carbon atoms is about 60°for a chair conformation (VIII), and almost 180° for a twist conformation (X). Since the former would be expected to be the preferred conformation, eg. lower steric compression, substitution rather than elimination should predominate (VIII → IX)(6,9).



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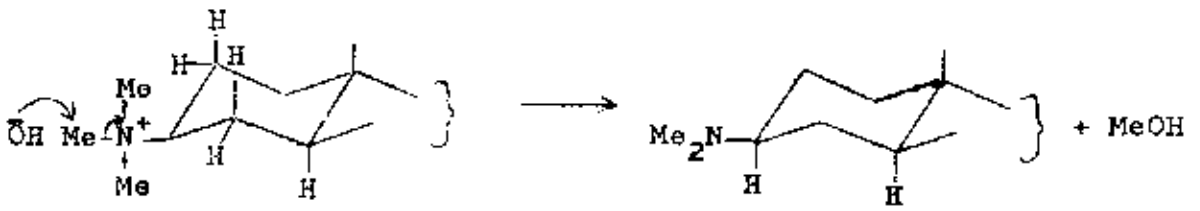
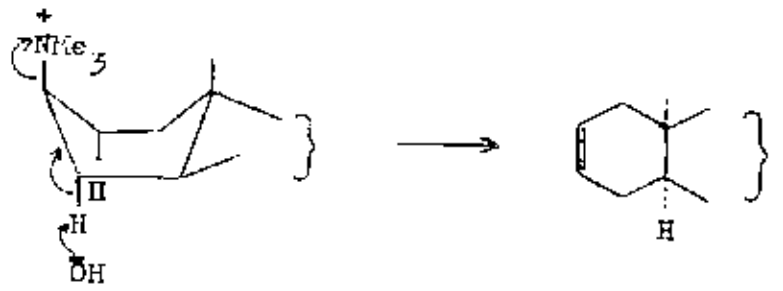
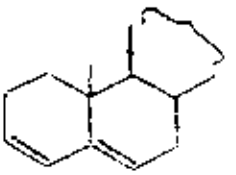


(VIII) (IX)



(X)

An exception to the above findings is the decomposition of 3β-cholest-5-enyl - trimethylammonium hydroxide (VI). This compound furnishes a large quantity of cholesta-3, 5-diene (XI) even though the quaternary nitrogen is equatorial. This result can be interpreted either in terms of an E1cB mechanism involving the acidic allylic β- hydrogen at the 4 - position, a relaxation of the rigidity of the system, or more likely an E_1 mechanism promoted trans-annularly by the 5 - 6 unsaturation (5).



(XI)

The olefins resulting from the degradation of the 6 - substituted 5α-cholestanyl trimethylammonium hydroxides do not conform with the Hofmann rule (52) of orientation which states

that when more than one olefin may be formed from a tetraalkyl-ammonium or trialkylsulphonium salt, the olefin bearing the smallest number of alkyl groups will predominate.

The 6α-equatorial salt gave a small quantity of cholest-5-ene by a cis elimination and the 6β-axial salt underwent a normal trans - elimination with Saytzeff orientation even though C_7 possessed a suitably oriented axial hydrogen atom. The latter result (46) has been related to the considerable non-bonded interaction between the axial 10 -methyl group and the 6-β quaternary nitrogen and 4-methylene groups, and a recent rate study (28) of the degradation of 5α-cholestan -6β -yl-trimethyl iodide and the tris-trideuteromethyl analogue has suggested that the observed isotope effect (k_H/k_D = 1.6) is best described as steric in origin. Deformation of ring B is not responsible for these anomolous results as is shown by nuclear magnetic resonance; the half-intensity width of the 6α-H multiplet of the trimethylammonium salt in deuteriochloroform is ~9 cps which is consistant with an equatorial hydrogen in a chair conformation.

Recently, Gent and McKenna (46) have made a kinetic study of the Menschutkin reaction methyl iodide with a series of 3 -(tertiary amino) steroids, and have concluded that equatorial bases have lower energies of activation and lower " frequency factors" than their axial epimers; the difference is probably mainly due to the greater degree of solvation possible with intermediate complexes derived from the less hindered amine (40).

McKenna et al. (62,69) have also determined the approximate first order rate constants for the quaternisation of epimeric 3,6 and 7 dimethylaminocholestanes with methyl iodide, and the degradation of the corresponding trimethylammonium hydroxides. They have suggested that the differences resulting from varying the position and conformation of the amino group in the cholestane nucleus are due mainly to changes in steric compression. Their results are shown in the Table III.

Table III

Isomer	K_q	K_{hc}	K_b
3β	2×10^{-2}	1.5×10^{-7}	6.0×10^{-7}
3α	2×10^{-3}	6.5×10^{-6}	1.5×10^{-6}
6α	2×10^{-4}	4×10^{-7}	6×10^{-6}
6β	8×10^{-6}	$> 10^{-2}$	-
7α	2×10^{-6}	2.5×10^{-4}	2×10^{-5}

The nitrous acid deamination of primary aminosteroids has also been the subject of stereochemical investigation. Shoppee et al. (88,90) have found that the deamination of epimeric 2,3,4,6, and 7 amino steroids follows a strict stereochemical pattern; saturated equatorial amines yield the appropriate equatorial alcohols with retention of configuration, in quantitative yields, whilst axial saturated steroidal amines afford the appropriate axial alcohol with retention of configuration,

unaccompanied by the epimeric alcohols, but accompanied by much elimination, the olefins produced conforming to the Saytzeff rule. Their results are shown in Tables IV and V.

Table IV

Nitrous Acid Deamination of Axial Amines

Reference	Amine	Substitution product	Elimination product
88	2β-Amino-5α-cholestane	2α-ol (0%) 2β-ol (21%)	$\Delta^1 + \Delta^2$ (75%)
90	3α-Amino-5α-cholestane	3α-ol (45%) 3β-ol (0%)	Δ^2 (54%)
90	3β-Amino-5β-cholestane	3α-ol (0%) 3β-ol (46%)	Δ^3 (50%)
90	3α-Amino-cholest-5-ene	-	cholesta-3, 5-diene (70%)
90	3β-Hydroxy-6β-amino-5α-cholestane	-	Δ^5 (95%)
88	4β-Amino-5α-cholestane	-	Δ^4 (92%)
90	6β-Amino-5α-cholestane	-	$\Delta^5 + \Delta^6$ (?) (99%)
88	7α-Amino-5α-cholestane	7α-ol (36%) 7β-ol (0%)	Δ^7 (61%)

Table V

Nitrous Acid Deamination of Equatorial Amines

Reference	Amine	Substitution product	Elimination product
88	2α-Amino-5α-cholestane	2α-ol (96%) 2β-ol (0%)	-
90	3β-Amino-5α-cholestane	3α-ol (0%) 3β-ol (99%)	-
90	3α-Amino-5β-cholestane	3α-ol (92%) 3β-ol (0%)	-
90	3β-Amino-cholest-5-ene	3α-ol (0%) 3β-ol (100%)	-
90	3β-Hydroxy-6α-amino-5α-cholestane	6α-ol (98%) 6β-ol (0%)	-
88	4α-Amino-5α-cholestane	4α-ol (82%) 4β-ol (0%)	-
90	6α-Amino-5α-cholestane	6α-ol (97%) 6β-ol (0%)	-
88	7β-Amino-5α-cholestane	7α-ol (0%) 7β-ol (95%)	-

Shoppee's findings are at variance with the observations of Huckel (54,56) who has investigated a large number of substituted cyclohexylamines and found that both axial and equatorial amino compounds on deamination afford alcohols with concurrent inversion and retention of configuration. White and Batchelor (101) have recently reinvestigated the nitrous acid deamination of 3α-and 3β-aminocholestanes under a variety of conditions and have found that in each case retention and inversion of configuration occurs; their results, which are shown in Table VI, being in line with Huckel's findings.

Table VI

The Nitrous Acid Deamination of 3α-and 3β-Amino-5α-cholestanes

Configuration of amino group	Solvent	Acetates			Alcohols			Olefin (%)
		Yield (%)	Ret. (%)	Inv. (%)	Yield (%)	Ret. (%)	Inv. (%)	
3β, eq.	HOAc	53	66	34	41	90	10	5
3α, ax.	HOAc	15	60	40	9	89	11	38
3β, eq.	50%HOAc*	29	61	39	43	65	35	25
3α, ax.	50%HOAc	19	-	-	13	61	39	45

* containing 25% of dioxane.

They have also computed the total alcohol formed in the deamination in 50% acetic acid based on the acetate and alcohol isolated and compared their results with those reported by Shoppee (90). This data is tabulated in Table VII.

Table VII

Comparison of Deamination in 50% Acetic Acid

Reference	Configuration of amino group	Total alcohols			Olefin (%)
		Yield (%)	Ret. (%)	Inv. (%)	
101	3β, eq.	69	64	36	25
90	3β, eq.	99	99	0	0
101	3α, ax.	30	60.6	39.7	45
90	3α, ax.	45	45	0	54

Shortly after Batchelor and White (101) reported their findings on the deamination of 3-amino-5α-cholestanes, Shoppee *et al.* (93) published the results of their reinvestigation of these reactions. They have used thin-layer chromatography for the detection of the products of the reaction and gas-liquid chromatography for estimating the proportions of the products. Their results as shown in Table VIII and IX support the findings of White and Batchelor (101), and prove that deamination of steroidal amines occurs with predominant, though not exclusive, retention of configuration.

Table VIII

Deamination of 3β-Amino-5α-cholestane (3β-NH_2, eq.)

Solvent	Temp. (°c)	Acetates			Alcohols			Olefin (%)
		Yield (%)	Ret. (%)	Inv. (%)	Yield (%)	Ret. (%)	Inv. (%)	
HOAc	20	59	61	39	32	94	6	9
50%HOAc + 25% Dioxane	-20	44	39	61	34	82	18	22
50%HOAc + 25% Dioxane	20	36	45	55	41	83	17	23
50%HOAc + 50% Dioxane	~20	34	45	55	53	89	11	13

Table IX

Deamination of 3α-Amino-5α-cholestane (3α-NH_2, ax.)

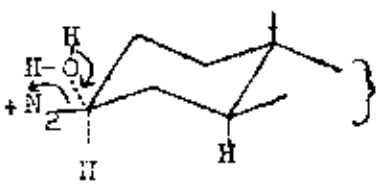
Solvent	Temp. (°c)	Acetates			Alcohols			Olefin (%)
		Yield (%)	Ret. (%)	Inv. (%)	Yield (%)	Ret. (%)	Inv. (%)	
HOAc	20	19	45	45	~0	0	0	81
50%HOAc	~20	6	50	50	7	57	43	83
50%HOAc	20	3	50	50	40	95	5	57
50%HOAc	0	20	50	50	-	-	-	80

Several theories have been proposed to account for the almost exclusive retention of configuration which occurs in the deamination of steroidal amines.

Cram et al. (3,22,26,31,33,44,81,82) have postulated the idea of forming a "high energy", "hot" or "unsolvated" carbonium ion on deamination. The ion RN_2^+ is supposed to break down almost as soon as it is formed in a reaction which is so rapid that neither solvent assistance or neighbouring group participation are required. The nitrogen molecule is expelled without serious energy drain on the rest of the molecule, to leave a relatively high energy carbonium ion. Its stereochemical fate is controlled by the relative proximity of solvent molecules to the equatorial or axial faces of the carbonium ion once the nitrogen molecule has left. However, this hypothesis fails to explain why diasteriomeric amines in cyclic systems generally yield different sets of products. Streitweiser (97)

has also objected to these views; he has proposed an E_2 decomposition of RN_2^+ with a solvent molecule as the diazonium ion decomposes by processes requiring low activation energies. An E_2 mechanism is claimed to afford a more satisfactory account of the deamination of alicyclic systems and allylic amines (83).

Shoppee et al. (90) consider that carbonium ions are not involved in the deamination of steroidal amines which have rigid ring structures. They have suggested that the reaction must involve the interaction of water with the diazonium cation in a pyrimidal S_N2 transition state (XII,XIII). An immediate objection to this explanation became apparent when it was shown that the olefin formed conformed with the Saytzeff rule of elimination, whereas elimination from the diazonium cation should have been governed by the Hofmann rule.



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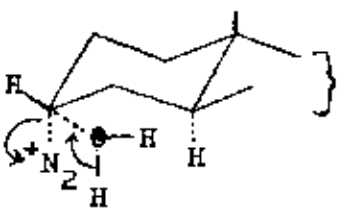
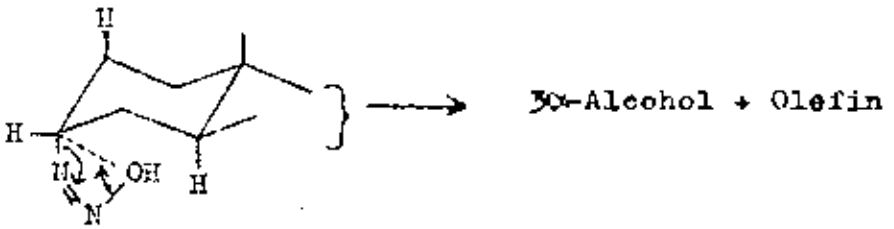


(XIII)

Austin and Howard (2) have suggested an alternative reaction path way which is analogous to substitution by the S_N1 mechanism (XIV). They argue that this mechanism, which involves the diazohydroxide, would lead directly to the alcohol with retention of configuration. In addition, such a mechanism is consistant with Shoppee's observation that elimination is

Saytzeff-controlled; the olefin is formed by fragmentation of the non-polar diazohydroxide (XV) and is not derived from the polar diazonium cation.



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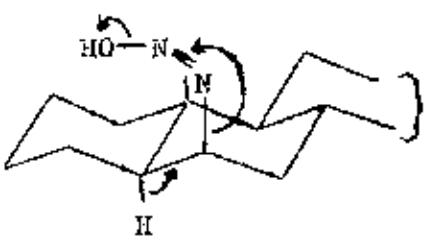

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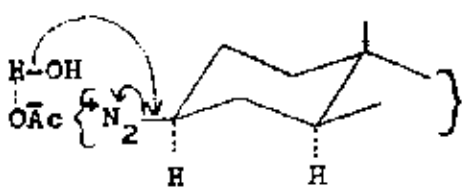
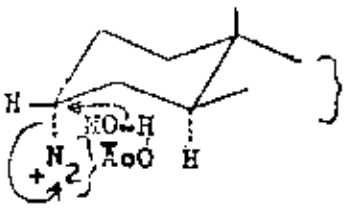


(XVI)

Recently, Shoppee et al. (93) have suggested an internal S_N1 substitution of the solvated diazonium ion pair (XVI,XVII), leading to products with retained configuration. They regard processes (XVI,XVII) as the more probable ones, and they suggest that the work of Cohen and Jankowski (27) on trans-2-amino-trans-decalin (XVIII) provides strong supporting evidence for their mechanism.

A study of the deamination of 3-amino-4,4-dimethylcholest-5-enes and 4,4-dimethyl-5α-cholestanes could prove valuable in testing the validity of carbonium ion intermediates in the deamination of steroidal amines. These systems are known to



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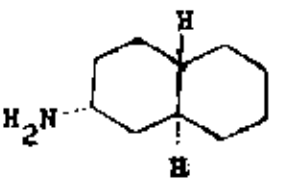
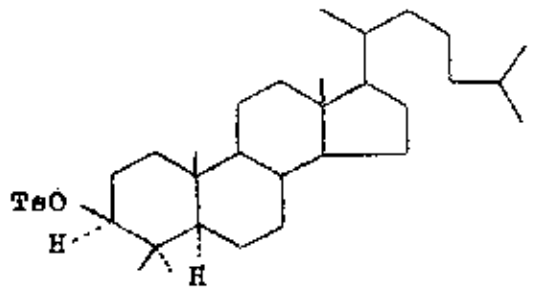


(XVIII)

readily undergo rearrangements; thus, 4,4-dimethyl-5α-cholestanyl toluene-p- sulphonate (XIX)(15,91) and 4,4,14α-trimethyl-5α-cholest-8-en-3β-yl-toluene-p-sulphonate (91)(XX) afford hydrocarbons of the type (XXI) as well as the alcohols of the type (XXII,XXIII) on solvolysis. The formation of these products is readily understood in terms of carbonium ion rearrangements, the driving force being the release of the steric compression in ring A. Solvolysis of the epimeric 3α-toluene-p- sulphonates (91) furnishes a different set of products (XXIV,XXV,XXVI); Nametkin rearrangement, which involves the shift of the 4β-methyl group to C_3, occurs in this system rather than Wagner Meerwein rearrangement (ring contraction from six to five membered ring) as occurs with the 3β-epimers.



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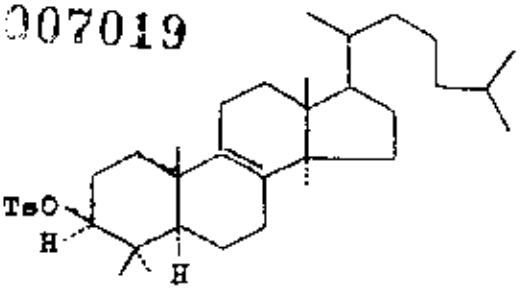
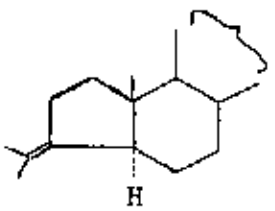


(XX)

(Ts = Tosyl = p-$MeC_6H_4SO_2$)



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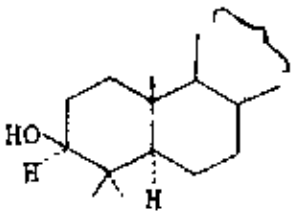

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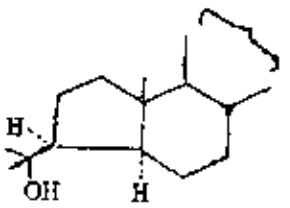

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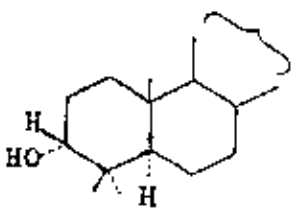

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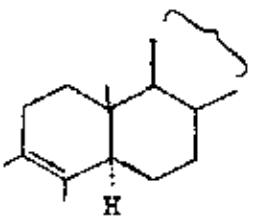

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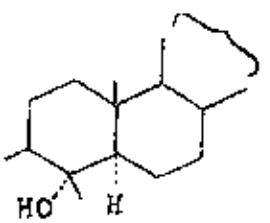
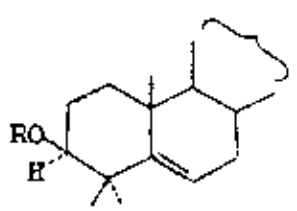
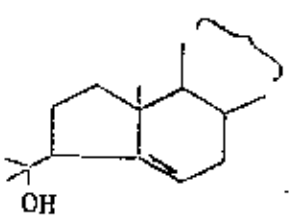


(XXVI)

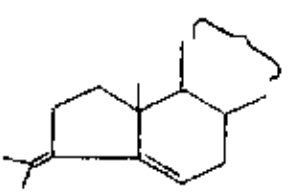
3α-and 3β-Toluene-p-sulphonates of 4,4-dimethylcholest-5-ene have also been subjected to solvolysis. The 3β-epimer (XXVII) (48,72) yields (XXIX) and (XXX) as the major and (XXVIII) and (XXXI) as the minor products. On the other hand, the 3α-epimers (92) afford the corresponding 3α-alcohol, 3β,4β-dimethylcholest-5-en-4α-ol (XXXII), and 3,4-dimethylcholesta-3,5-diene (XXXIII).



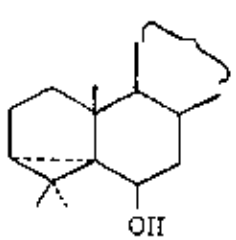
(XXVII) R = Ts
(XXVIII) R = H



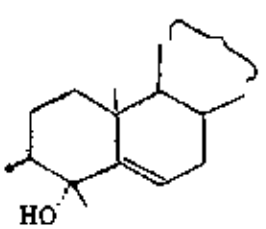
(XXIX)



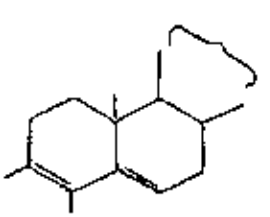
(XXX)



(XXXI)



(XXXII)



(XXXIII)

In addition to the mechanistic value which could be derived from a study of the 3-amino-4,4-dimethylcholest-5-ene and 4,4-dimethyl-5α-cholestane; the results could prove useful in the future for determining the configuration of the amino group in alkaloids of the type found in the Buxus family.

The purpose of our investigation is to synthesize the epimeric 3-amino-4,4-dimethylcholest-5-enes and the 4,4-dimethyl-5α-cholestanes and determine their configurations as the first step towards determining the steric course of the deamination of these amines.