**RESUME AND DISCUSSION**

The synthetic and structural investigations carried on the preparation of new heterosteroids are discussed below under the heads: 6-Aza-B-homo-5\(_\alpha\)-cholestan-3,7-dione and Some Derivatives; Certain Tetrazolo[e-4,3-\(\beta\)]-3-aza-A-homo Steroid Analogs; and 4-Azaspirostans and Related Studies.

### 6-AZA-B-HOMO-5\(\alpha\)-CHOLESTANE-3,7-DIONE AND SOME DERIVATIVES

The objective of this study was to look into the synthesis of the title compound (31) and prepare analogs through reactions due to the 3-keto function. The compound (31) was prepared through a series of reactions starting with cholesteryl acetate.

Nitration of cholesteryl acetate (32) was carried out
according to the procedure of Anagnostopoulos and Fieser. \(^\text{88}\)

6-Nitro-5-cholesten-3\(\beta\)-yl acetate (33) was reduced with zinc and acetic acid to 6-oxo-5\(\alpha\)-cholestan-3\(\beta\)-yl acetate (34) \(^\text{89}\) and converted to its oxime (35) \(^\text{90}\) by treatment with hydroxylamine hydrochloride in pyridine.

The keto-oxime (35) on Beckmann rearrangement with thionyl chloride in benzene yielded 7-oxo-6-aza-\(\beta\)-homo-5\(\alpha\)-cholestan-3\(\beta\)-yl acetate (36), \(^\text{91}\) which on alkaline hydrolysis gave the 3\(\beta\)-hydroxy analog (37). \(^\text{92}\) The lactam (36)
had also been prepared by Schmidt reaction on the ketone

(34). The location of the nitrogen atom in (36) was
certified but the 50D-configuration was based on analogy.

For further information on the structure and stereochemistry of (36), the spectral studies have been carried out. The NMR spectrum of (36) in chloroform solution showed a doublet (J=5 cps) at \( \delta \) 3.92, and two broad peaks centered at \( \delta \) 5.32 and 6.53 each corresponding to a single proton; other proton signals appeared at higher field (\( \delta \) 7.6-9.3). After deuterium exchange by shaking with D2O for a few minutes, the peaks at \( \delta \) 3.92 disappeared and the broad peak at \( \delta \) 6.53 was transformed into a multiplet; obviously the former corresponds to N-H and the latter to 5-H. Had the N been at position-7 in the lactam, a two-proton signal coupled to N-H would have appeared.

The stereochemistry at the A/B ring junction in (36) can be deduced from the size of the coupling between 5-H and
the adjacent methylene protons. However, such couplings could not be determined by a first order analysis of the 5-H signal in (36) because it was a part of an ABM system.

6-Aza-B-homo-5γ-cholestane-3,7-dione (31) was prepared by chromic acid oxidation of (37). It showed infrared bands at 3425 (N-H stretching), 1730 (keto C=O stretching), and 1685 cm\(^{-1}\) (lactam C=O stretching). The NMR spectrum of the 3-ketone (31) supported the conclusion about the location of the N but the signal of the 5-H proton was again a multiplet and too complex for first order interpretation.

The 3-ketone (31) on treatment with pyridinium hydrobromide perbromide gave a monobromo derivative, the infrared spectrum of which showed bands at 3390 (N-H stretching), 1748 (keto C=O stretching), and 1670 cm\(^{-1}\) (lactam C=O stretching). The NMR spectrum of the monobromo derivative was very informative: a one-proton doublet (J=11 cps) at \(\tau\) 5.31 clearly indicated that it was a 4-bromo compound—the 2-bromo structure would have produced a quartet. The 5-H signal was a quartet (J=5 and 11 cps) which was simplified to a doublet (J=6, 20; J=11 cps) on deuterium exchange.

The size of coupling between 4-H and 5-H corresponds to Jaa, therefore the 4-bromo derivative and, (36) and (31) must belong to the 5γ-cholestane series. The infrared spectrum of (31) showed the ketocarbonyl absorption at 1730 cm\(^{-1}\) which was shifted to 1748 cm\(^{-1}\) in the 4-bromo
compound. This observation\textsuperscript{94} indicates that the bromo substituent is equatorial (A) and hence the bromo product from (31) is 4\textsuperscript{b}-bromo-6-aza-B-homo-5\textsuperscript{c}-cholestan-3,7-dione (38).

![Structural Diagram]

It may be noted that the bromination of 3-keto-5\textsuperscript{c}-steroids\textsuperscript{95} usually leads to the 2\textsuperscript{c}-derivatives. The preference for the 4\textsuperscript{c}-position for the bromine in (38) must be due to the altered nature of the B ring in (31).

The reaction of the bromoketone (38) with N-phenylthiourea gave a thiazolo product, which is given the structure 2\textsuperscript{b}'-phenylaminothiazolo[d-3,4]\textsuperscript{c}-6-aza-B-homo-5\textsuperscript{c}-cholestan-7-one (39). The NMR spectrum of (39) showed two one-proton

![Additional Diagram]
doublets ($J=6$ cps) at $\tau 3.9$ and $5.58$; on deuterium exchange the peak at the lower field due to the N-H signal disappeared and the other peak became a singlet. This corroborates the structure (39) instead of the alternate structure (40). The angular structure (39) further confirms that the precursor (38) has the bromine on C-4.

The treatment of the 3-ketone (31) with phenylhydrazine in acetic acid led to an indole for which the alternative structures (41) and (42) can be written. The NMR spectrum of

![Structure](image)

(41)  (42)

the product showed the 5-H proton signal as a broad peak at $\tau 6.28$ which became a complex multiplet after deuterium exchange. These observations establish the linear structure (41) for the indole. Although during bromination the 4-methylene in (31) was found to be more reactive, the indole with the angular structure (42) was not obtained in the Fischer-Indole synthesis.
It may be mentioned that Ban and Sato\textsuperscript{96} proved that the Fischer-Indole synthesis product from $5\alpha$-cholestan-3-one has the linear structure and the indole got from $5\beta$-cholestan-3-one has the angular structure. These findings are in accord with the earlier presumptions\textsuperscript{97,98} indicating linear and angular indolosteroid structures for the indoles obtained from $5\alpha$-3-ketones and $5\beta$-3-ketones on the basis of greater reactivity of 2-methylene and 4-methylene, respectively.

In the bromination of (31) it is the position 4 which is more reactive, in contrast to reactivity of position 2 in the formation of indolosteroid (41). For the anomaly no particular explanation can be given at this stage.

Next, the ketone (31) was submitted to Schmidt reaction through sodium azide in polyphosphoric acid system. There were obtained two dilactams, mp $> 300^\circ\text{C}$ (dec) and mp 282-283\textsuperscript{0} (dec), in 34\% and 11\% yields, respectively. The isomeric structures (43) and (44) are possible. Earlier, Doorenbos and Singh\textsuperscript{92} carried out the reaction and obtained only one
dilactam, mp > 300°, to which structure (43) was tentatively assigned; however, 5α-cholestan-3-one and 5β-cholestan-3-one oximes are known to have given a mixture of 3-aza-A-homo-4-oxo and 4-aza-A-homo-3-oxo lactams.

It has not been possible to draw clear distinction between structures (43) and (44). The NH signals for the higher melting isomer appear as one broad peak at $\tau 2.75$. The spectrum of the lower melting isomer showed two distinct peaks at $\tau 3.25$ and 3.75 for the NH signals. From considerations of symmetry, structure (44) may be assigned to the higher melting compound. The spectrum with two NH peaks is more in keeping with different environments for the NH protons if (43) is to be taken as the structure of the lower melting compound.

CERTAIN TETRAZOLO[e,4,3]-3-AZA-A-HOMO STEROID ANALOGS

Some steroids are known which have CNS-depressing activity. Leptazol, which is pentamethylenetetrazole, has analeptic action. It is possible that tetrazolosteroids may have one kind or the other of the CNS action. Some tetrazolosteroids are claimed to possess antifertility and anti-spermatogenic activity but these results could not be substantiated on further experimentation. Nevertheless, it was considered of interest to prepare different tetrazolosteroids which could be worthy of getting tested for biological actions. The synthesis of tetrazoles in the
spirostan series was thought of since these could then be degraded to the pregnane and androstane analogs.

Diosgenin, (25R)-5-spirosten-3β-ol (45) was considered to be an attractive starting material. The sapogenin (45) on Oppenauer oxidation yielded (25R)-4-spirosten-3-one (46).

The α,β-unsaturated ketone (46) was reacted with chloroform solution of hydrazoic acid in the presence of boron trifluoride etherate. A product was obtained the elemental composition of which showed that tetrazole system had formed. The product so obtained could have either tetrazolo[e-4,3-3-aza-A-homo-4a-ene (B) or tetrazolo[e-3,4]-4-aza-A-homo-4a-ene (C) system.
There are known only a few cases of the preparation of tetrazolosteroids. Wu\textsuperscript{102} prepared the respective tetrazoles from 5α-cholestan-3-one and 5β-cholestan-3-one and these were tentatively considered to have tetrazolo[e-4,3-J-3-aza-A-homo structures. These tetrazoles were found to absorb at 230 nm. Mechoulam\textsuperscript{100,101} obtained from 17β-hydroxy-5α-androstan-3-one and 5β-cholestan-3-one mixtures of isomeric tetrazoles, having tetrazolo[e-4,3]-3-aza-A-homo and tetrazolo[e-3,4]-4-aza-A-homo functions. Several tetrazole preparations from \( \omega,\beta \)-unsaturated 4-en-3-one steroids are also known.\textsuperscript{100,101,103,104}

These are mentioned to have tetrazolo[e-4,3]-3-aza-A-homo-4a-ene (B) structure, and show maximum around 244 nm.\textsuperscript{101,104}

One could postulate the structure (B) for the tetrazole from the observation that 4-en-3-ones on Schmidt reaction or their oximes on Beckmann rearrangement generally yield lactams corresponding to 3-aza-A-homo-4a-en-4-one system.\textsuperscript{105-111}

These findings are of significance in speculating the structure of tetrazoles obtained from 4-en-3-ones.

Consider, for example, the sequence of getting (I) from (D) by Schmidt reaction.\textsuperscript{112} Evidently, for (I) to be the product, the reaction will be proceeding as shown. The entity (G) looks to be preferred rather than the other geometric isomer which is possible. The group migration takes place from the side opposite to the leaving \( \text{N}_2 \). The intermediate (H) thus formed can be precursor of (I). In the presence of excess hydrazoic acid one can visualize...
transformation of (H) to (B) through (J). This reasoning thus supports the structure (B) rather than (C) for the tetrazoles obtained from 4-en-3-ones.
As such, the product of reaction of compound (46) with excess hydrazoic acid can be considered to have structure (47). This showed a maximum at 244 nm (ε 17,780).

The NMR analysis provides a support for structure (47). The most revealing peak was the multiplet centered at τ 5.56 integrating for two protons. Dimaio and Permutti have reported that the NMR spectrum of the tetrazole system (K) exhibits a complex multiplet at τ 7.05 while that of (L) absorbs near τ 5.05. As an illustration they cited the case of the tetrazole (48) formed from cyclohexanone. Greco and Gray reported the tetrazole (49) to exhibit multiplet centered at τ 5.44. In light of these observations the multiplet centered at τ 5.56 for the compound (47) confirms the
structure, and excludes a system like (C) from consideration.

The infrared spectrum of (47) showed bands at 1640 cm\(^{-1}\) (C=C stretching), and 1520 and 1445 cm\(^{-1}\), which may be due to \(-\text{C=N-}\) and \(-\text{N=N-}\) stretching frequencies of the tetrazole system. Cervantes et al.\(^{135}\) have prepared tetrazoles of the type (M) which also show vibrations in the same region.

Tetrazolo[\(e-4,3\)]-3-aza-A-homo-(25\(R\))-\(4\)a-spirost\(en\) (47) was submitted to Marker degradation to obtain tetrazolo-\([e-4,3]-3\text{-aza-A-homo}-4a,16\text{-pregnadien}-20\text{-one}\) (50). The latter showed ultraviolet maximum at 240 nm (\(\varepsilon\) 25,120). The infrared spectrum indicated olefin-C-H stretching (3045 cm\(^{-1}\)), \(\alpha,\beta\)-unsaturated C=O stretching (1650 cm\(^{-1}\)), conjugated C=C stretching (1580 cm\(^{-1}\)), and vibrations at 1520 and 1435 cm\(^{-1}\). The NMR multiplet centered at \(\delta 5.55\) was also diagnostic as
discussed above. To further confirm the structure of (50), the mass spectrum was taken, which exhibited significant peaks at m/e 352 (Molecular ion M⁺; 77% of base peak), 337 (M⁺-CH₃; 30%), 309 (M⁺-CH₃CO; 48%), 164 (M⁺-C₁₃H₁₆O; 83%), and 43 (M⁺-C₁₉H₂₅N₄; base peak). The fragmentation as shown can account for the significant mass spectral peaks.

The tetrazolopregnane analog (50) was next converted to its oxime (51) showing infrared bands at 3285 (bonded O-H stretching), 1630, 1560 and 1490 cm⁻¹. The oxime (51) on Beckmann rearrangement with phosphoryl chloride in pyridine, followed by acid hydrolysis, gave the product (52), exhibit-
ing infrared bands at 1730 (C=O stretching), 1635, 1515 and 1440 cm\(^{-1}\).

The oxime (53) was prepared from the ketone (52). The infrared spectrum of (53) exhibited bands at 3400, 1635, 1520, and 1430 cm\(^{-1}\). The oxime on Beckmann rearrangement with thionyl chloride in dioxan yielded the lactam (54).

The infrared spectrum indicated \(\text{N-H stretching (3425 and 3125 cm}^{-1})\), lactam C=O stretching (1660 cm\(^{-1}\)), and bands at 1535 and 1450 cm\(^{-1}\).

That the lactam system is as in (54) and not corresponding to the alternative function 17-aza-17a-oxo, has been confirmed by synthesis of (54) from authentic 17a-aza-D-homo-4-androstene-3,17-dione (H. Singh and V. V. Parashar, unpublished data).
Tetrazolo[e-4,3] 3-aza-A-homo-4a,16-pregnadien-20-one (50), obtained from diosgenin through tetrazolo[e-4,3]-3-aza-A-homo-(25R,4α)-spirosten (47), was also used to prepare certain analogs involving reactions with the 16-en-20-one system.

The treatment of (50) with alkaline hydrogen peroxide gave an epoxide, the UV absorption maximum being at 242 nm. The epoxide is considered to have structure (55), in analogy with the known 16β,17α-oxido stereochemical disposition in the case of similar epoxidations of the 16-en-20-one function. The infrared spectrum of (55) showed vibrations at 1698 (C=O stretching), 1645 (C=C stretching), 1520 and 1440 cm⁻¹.

The respective halohydrins (56) and (57) were obtained by reacting (55) with hydrochloric and hydrobromic acids, respectively. The opening of the oxido system giving 16β-halo-17α-hydroxy analogs (56 and 57) is depicted on the basis of
earlier records\textsuperscript{118-120} of the same type. Similarly the product of interaction between the epoxide and potassium thiocyanate in glacial acetic acid\textsuperscript{121} is considered to have structure (58). The infrared spectra of (56), (57) and (58) were satisfactory. The spectrum of (58) showed a band at 2135 cm\(^{-1}\) indicating C=\(\equiv\)N stretching of the thiocyanato group.

\textbf{4-}AZASPIROSTARS AND SOME RELATED STUDIES

For this phase of investigation, the secketo acid,
5-oxo-3,5-seco-4-nor-(25R)-spirostan-3-oic acid (59), was required. It was prepared by oxidation of (25R)-4-spirosten-3-one (46) with periodate-permanganate reagent of Lemieux and von Rudloff.\textsuperscript{122-125} Earlier the same reagent had been used to prepare 5-oxo-3,5-seco-4-norcholestan-3-oic acid from 4-cholesten-3-one\textsuperscript{126} and 3\beta-acetoxy-9-oxo-9,12-seco-11-nor-(25R)-5\alpha-spirostan-12-oic acid from 3\beta-acetoxy-(25R)-5\alpha-spirost-9(11)-en-12-one.\textsuperscript{127}

The infrared spectrum of secoketo acid (59) showed vibrations at 2930, 2895, 2870 and 2850 cm\(^{-1}\), falling in the region corresponding to C-H and bonded O-H stretchings, and 1720 and 1705 which are assigned to C=O stretchings.

The oxime (60) of the secoketo acid was prepared and this showed infrared bands for bonded O-H stretching (3240, 3110 cm\(^{-1}\)), C=O stretching (1705 cm\(^{-1}\)), and C=N stretching (1640 cm\(^{-1}\)).
When the secoketo acid (59) was refluxed with benzylamine and the reaction mixture processed, there was obtained the enamine lactam (61). The structure was apparent from its ultraviolet maximum at 236 nm ($\lambda_{max} = 236$ nm). The infrared spectrum indicated C-H stretching of the phenyl group ($3025$ cm$^{-1}$), lactam C=O stretching ($1670$ cm$^{-1}$), C=C stretching ($1640$ cm$^{-1}$), C=C stretching in the phenyl group ($1610, 1580, 1490, 1460, 1400$ cm$^{-1}$), and C-H out-of-plane bending of the phenyl group ($756, 713$ cm$^{-1}$).
Various 4-aza-5-en-3-one lactams in the cholestane, pregnane, and androstane series are already known.\textsuperscript{128-135} 4-Aza-5-sitosten-3-one has also been prepared.\textsuperscript{136}

To prepare saturated 4-aza-3-oxo lactam system, the secoketo acid (59) was submitted to Leuckart reaction. On chromatographic resolution the product resolved into two lactams: mp 318-321\degree (dec), yield 20\%, infrared bands at 3170 (bonded N-H stretching), 1655 cm\(^{-1}\) (lactam C=O stretching); mp 299-302\degree (dec), yield 14\%, infrared bands at 3260, 3185 (bonded N-H stretching), 1670 cm\(^{-1}\) (lactam C=O stretching). The elemental composition of both the lactams was same.

There could be a possibility of getting two isomeric lactams (62) and (63), considering that the stereochemistry of the spiroketal system will remain unaffected under the Leuckart reaction conditions. Leuckart reaction is known to be sensitive to steric effects\textsuperscript{137,138} which with
5α-cholestan-3-one gives the β-amino derivative. With this background at hand, Edward and Morand in fact prepared 4-aza-5α-cholestan-3-one, as the sole product from 5-oxo-3,5-seco-4-norcholestan-3-oic acid by this reaction. The configuration at 5 was shown to be definitely α. In analogy with this the lactam obtained from (59) should have been only (62), in which the linkage between positions 4 and 5 would have equatorial disposition (N). When the oxime (60) was reduced with sodium and ethanol, there was obtained only one lactam, mp 318-321° (dec), yield 47%, the infrared of which was superimposable on that of the higher melting lactam obtained by Leuckart reaction with (59). As the chemical conversions usually give the more thermodynamically stable product, the compound obtained by sodium-ethanol reduction of (60) and the major entity, mp 318-321° (dec), got from (59) directly, are assigned the A/B-trans configuration (62). The Leuckart reaction product melting at 299-302° (dec) may be tentatively given the structure (63).

It may be mentioned that the lactam obtained by sodium-ethanol reduction of 5-oximino-3,5-seco-4-nor-
cholestan-3-oic acid (60) was proved to be the lactam 4-aza-5α-cholestan-3-one (62).

The lactams (62) and (63) were reduced with lithium aluminium hydride to the amines (64) and (65), the lactam carbonyl stretchings in which were completely absent. The acetyl derivatives (66) and (67) were prepared, which showed amide C=O stretchings at 1650 cm⁻¹ and 1640 cm⁻¹, respectively.

With the experimental information in hand, it is not possible to commit definite configurations at position 5 in the products (62-67).

The marker degradation of (62) yielded 4-aza-5α-pregn-16-ene-3,20-dione (68), showing ultraviolet maximum at 237.5 nm for the 16-en-20-one function. The infrared bands were at 3210 (bonded N-H stretching), 1667 (unresolved 20-
and 3-carbonyl stretchings), and 1587 cm\(^{-1}\) (C=C stretching).

CONCLUDING REMARKS

During these investigations on the synthesis of 6-aza-B-homo-5α-cholestane-3,7-dione and derivatives, certain tetrazolo[5,4,3-b-4,3]β-3-aza-A-homo steroid analogs, and 4-aza-steroids, a number of interesting chemical features have been noted, some of which have been appropriately elucidated. A few of the points evidently need further studies to support the conclusions derived with the data in hand.

The heterosteroid compounds obtained are worthy of getting tested for their biological activity. Some of these have been synthesized in larger quantities for the purpose. Certain selected tetrazolosteroids prepared have already been given for testing of their antifertility activity at the Department of Pharmacology, Postgraduate Institute of
Medical Education and Research, Chandigarh.

It is possible to prepare several other synthetic analogs from the heterosteroid systems described.