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Steroidal Tetrazoles: Ring B Fused Tetrazoles in the Cholestane Series

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Abstract

Treatment of cholesta-3,5-dien-7-one (1) with excess of hydrazoic acid gave 4-oxo-7a-aza-B-homocholest-5-eno[7a,7-*d*]tetrazole (6) and the lactam (7). Similar reaction of 3α,5-cyclo-5α-cholestan-6-one (2) provided 6-aza-B-homo-3α,5-cyclo-5α-cholestano[6,7-*d*]tetrazole (8) along with the lactam (9). Under similar conditions the ketol (3) furnished the seco nitrile (11), a product of cleavage. The tetrazoles (12) and (13) were obtained from the ketones (4) and (5), respectively, together with the lactams (14) and (15).

Steroidal tetrazoles have become of interest in recent years because of their pharmacological potential.[1] Several papers have appeared recently describing the synthesis of tetrazoles mainly from steroidal 4-en-3-ones[2–5] and of 7a-aza-B-homocholest-5-eno[7a,7-*d*]tetrazol-3′β-yl acetate[5] using excess of hydrazoic acid. This paper is concerned with similar reaction of cholesta-3,5-dien-7-one (1), 3α,5-cyclo-5α-cholestan-6-one (2), 5-hydroxy-6-oxo-5α-cholestan-3β-yl acetate (3), cholest-5-en-7-one (4) and its 3β-chloro analogue (5). The formulated structures have been established on the basis of their spectral properties, chemical transformation and comparison with authentic samples where available.

There is no report in the literature of the synthesis of a tetrazole from conjugated dienones. Moreover, these dienones are known to give products of oxidation (as carbonyl group) with simultaneous insertion of nitrogen in the ring system when treated with hydrazoic acid.[6] The dienone (1) was treated with hydrazoic acid and boron trifluoride in benzene which furnished (6) and (7). The tetrazole (6) was identified by its characteristic infrared and ultraviolet spectra (Table 1). According to Mitsuhashi *et al.*,[6] hydrazoic acid can react with the C3–C4 double bond to produce either a 3-oxo group with the double bond migrating to C4–C5 or to a 4-oxo group with double bond at C5–C6. The tetrazole could then arise by further reaction with either the 7-oxo function or one at either C3 or C4. Confirmation

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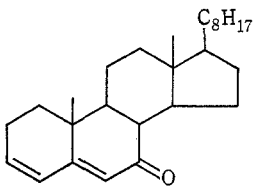
[2] Moural, J., and Syhora, K., *Collect. Czech. Chem. Commun.*, 1970, **35**, 2018.
[3] Singh, H., Mathur, R. B., and Sharma, P. P., *J. Chem. Soc., Perkin Trans.*, 1972, 990.
[4] Singh, H., Malhotra, R. K., and Parashar, V., *Tetrahedron Lett.*, 1973, 2587.
[5] Singh, H., Malhotra, R. K., and Luhadiya, N. K., *J. Chem. Soc., Perkin Trans.*, 1974, 1480.
[6] Mitsuhashi, K., Nomura, K., and Miyoshi, F., *Chem. Pharm. Bull.*, 1971, **19**, 1983.

of the keto tetrazole (6) structure was obtained from the n.m.r. spectrum which had a broad peak at δ 4·5 (1H) ascribable to N–C8–H (cf.[5]). The vinylic proton appeared at a much lower field (δ 7·53 s) and clearly looked a proton β to a carbonyl group. The minor product was found to be the keto lactam (7) by its comparison with an authentic sample.[6]

Table 1. Spectral data

Compound	N.m.r. (δ) C8–H	C6–H	C10–Me	I.r.[A] (cm^{-1})	U.v. (nm) (log ε)
(12)	4·22	6·55	1·23	1670, 1505, 1465, 1380	243 (4·10)
(13)	4·21	6·63	1·38	1660, 1505, 1470, 1380	240 (4·13)
(6)	4·50	7·53	1·23	1650, 1500, 1465, 1380	272 (4·42)

[A] C=C and tetrazole moiety.



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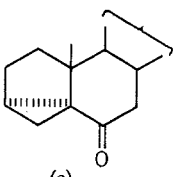
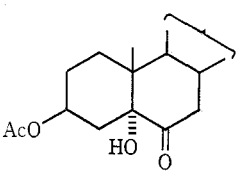


(2)



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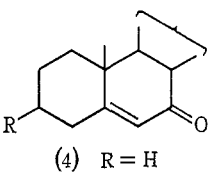
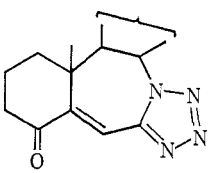
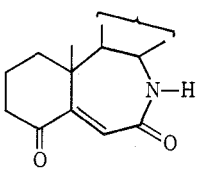


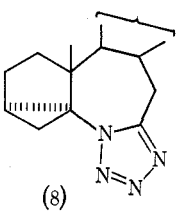
(4) R = H
(5) R = Cl



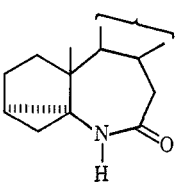
(6)



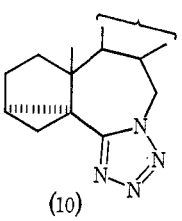
(7)



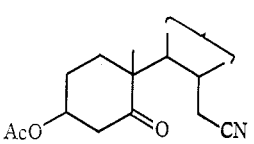
(8)



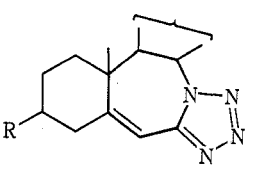
(9)



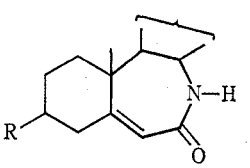
(10)



(11)



(12) R = H
(13) R = Cl



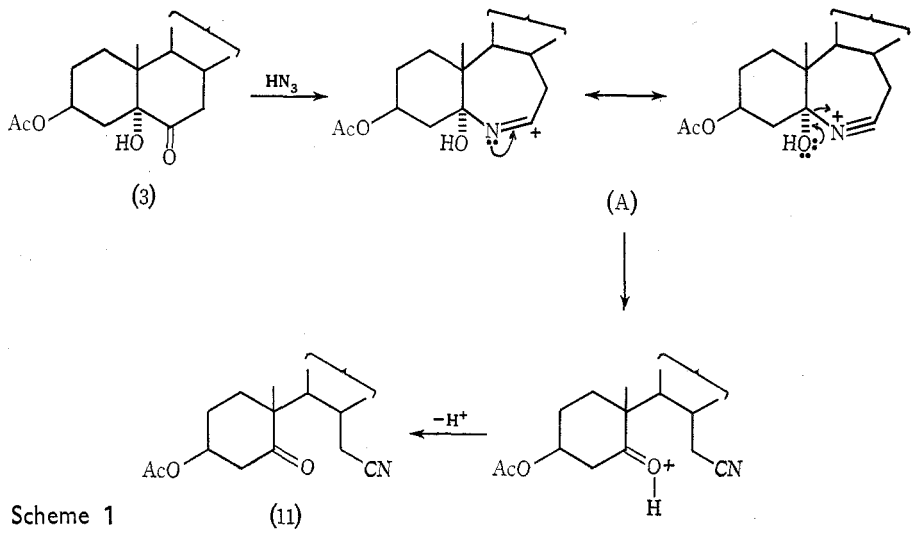
(14) R = H
(15) R = Cl

The study was extended to 6-oxo steroids. When (2) was treated with hydrazoic acid–boron trifluoride, it gave the tetrazole (8) as the major product along with the lactam (9).[7] The structure (8) was supported by the n.m.r. spectrum in preference to the alternative structure (10); the signal at δ 3·36 (2H) was ascribed to N=C–C7a–H_2

[7] Ahmad, M. S., Shafiullah, and Mushfiq, M., *Tetrahedron Lett.*, 1970, 2739.

(cf.[8]). In the alternative structure (10) these protons are expected to appear at relatively lower field. No signal for vinylic protons was observed which supported the fact that the cyclopropane ring remained unaffected. However, it is pertinent to mention that the cyclopropane protons did not appear in the region 0–0·6.[9] It is reasonable to believe that because of the electron-withdrawing tetrazole system, these protons merged with the methyl or methylene signals.

Reaction of (3) in the usual manner gave (11) as the only isolable product. From the spectral properties and comparison with an authentic sample, it was identified as 3β-acetoxy-5-oxo-5,6-secocholestan-6-onitrile (11).[10] The Schmidt reaction of 6-ketones or the Beckmann rearrangement of corresponding oximes gives 6-aza lactams and on this basis ion (A) can be postulated as the intermediate leading to (11) (Scheme 1). Further reaction of hydrazoic acid with (11) does not occur possibly because its approach to the C 5-oxo function is blocked by the bulky α-substituent.[10]



Scheme 1 (11)

Treatment of the ketones (4) and (5) with hydrazoic acid–boron trifluoride in benzene led to the formation of the tetrazoles (12) and (13), respectively, in major amounts. The identity of (12) and (13) was established on the basis of their elementary analyses, spectral properties (i.r., u.v., n.m.r., Table 1) and chemical conversion. The minor products were found to be the lactams (14)[11] and (15).[12]

Experimental

All melting points are uncorrected. I.r. spectra were obtained with a Perkin–Elmer 237 spectrophotometer in KBr and u.v. spectra in 95% EtOH with a Beckman DK 2 spectrophotometer. N.m.r. spectra were run in $CDCl_3$ in a Varian A60 instrument with $SiMe_4$ as the internal standard. Rotations were determined in $CHCl_3$. Thin-layer chromatographic plates were coated with silica gel. A 20% aqueous solution of perchloric acid was used as spraying agent. Light petroleum refers to a fraction of b.p. 60–80°.

[8] DiMaio, G., and Permutti, V., *Tetrahedron*, 1966, **22**, 2059.
[9] Tadanier, J., and Cole, W., *J. Org. Chem.*, 1962, **27**, 4624.
[10] Ahmad, M. S., Pillai, N. K., and Chaudhry, Z. H., *Aust. J. Chem.*, 1974, **27**, 1537.
[11] Shoppee, C. W., Akhtar, M. I., and Lack, R. E., *J. Chem. Soc.*, 1964, 3392.
[12] Ahmad, M. S., Shafiullah, and Islamuddin, *Indian J. Chem.*, 1974, **12**, 1323.

Preparation of Hydrazoic Acid Solution

The hydrazoic acid solution was prepared according to Moural and Syhora.[2] Sodium azide (4 g) was dissolved in water (20 ml) and to this was added benzene (30 ml) at 0°. Sulphuric acid (4 ml) was then added dropwise with shaking over a period of 30 min at 0–5°; shaking was continued for an additional 30 min and the organic layer was separated, dried and filtered. This solution of hydrazoic acid (about 30 ml) was made up to 50 ml by addition of benzene and was used in the reactions with ketones.

*4-Oxo-7a-aza-*B*-homocholest-5-eno[7a,7-*d*]tetrazole (6)*

To a cooled solution of hydrazoic acid in benzene as prepared above was added boron trifluoride etherate (1·5 ml, freshly distilled) and to this was added a solution of (1)[13] (2 g) in benzene (25 ml) over a period of about 5 h and the mixture was allowed to stand at room temperature for 30 h. Benzene was removed by distillation under reduced pressure and the residue dissolved in ether. The ethereal solution was washed with water, sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. After evaporation of the solvent, an oil (1·8 g) was obtained which was chromatographed over silica gel (30 g) and eluted in 20 ml portions. Elution with chloroform gave the *tetrazole* (6) (200 mg), recrystallized from light petroleum–ether, m.p. 117°; $[\alpha]_D$ −180° (Found: C, 73·6; H, 9·6; N, 12·7. $C_{27}H_{42}N_4O$ requires C, 73·9; H, 9·5; N, 12·7%). N.m.r. δ 7·53, s, C6–H; 4·5, br, C8–H; 2·5, m, C3–H_2; 1·23, s, C10–Me; 0·76, s, C13–Me; 0·96, 0·85 (remaining methyls). Further elution with chloroform–ether (4 : 1) gave (7) (60 mg), recrystallized from ether, m.p.[6] and m.m.p. 184°.

*6-Aza-*B*-homo-3α,5-cyclo-5α-cholestano[6,7-*d*]tetrazole (8)*

The ketone (2)[14] (2 g) was treated with hydrazoic acid–boron trifluoride etherate in the manner described for (1). The *tetrazole* (8) which crystallized out from the reaction mixture was filtered and recrystallized from light petroleum (500 mg), m.p. 137°; $[\alpha]_D$ −210° (Found: C, 76·4; H, 10·5; N, 12·9. $C_{27}H_{44}N_4$ requires C, 76·4; H, 10·3; N, 13·2%). ν_{max} 3030 (cyclopropane),[15] 1525, 1460, 1365 cm^{-1} (C=N, N=N). N.m.r. δ 3·36, 2H, C7a–H_2; 0·96, s, C10–Me; 0·66, s, C13–Me; 0·91, 0·81 (remaining methyls). The filtrate was stripped of the solvent under reduced pressure and the oil thus obtained was chromatographed over silica gel (30 g) and fractions of 15 ml were collected. Elution with benzene–ether (2 : 1) gave (8) (100 mg), m.p. and m.m.p. 137°. Further elution with benzene–ether (1 : 1) gave the lactam (9) (30 mg) which recrystallized from light petroleum, m.p.[7] and m.m.p. 198°.

3β-Acetoxy-5-oxo-5,6-secocholestan-6-onitrile (11)

The ketone (3)[16] (2 g) on treatment with hydrazoic acid–boron trifluoride etherate and subsequent workup gave (11) as the only isolable product which crystallized from ethanol (900 mg), m.p.[10] and m.m.p. 95°.

*7a-Aza-*B*-homocholest-5-eno[7a,7-*d*]tetrazole (12)*

Reaction of (4)[17] (2 g) with hydrazoic acid–boron trifluoride etherate in the usual manner gave an oil which was chromatographed over silica gel. Elution with light petroleum–benzene (4 : 1) gave the unchanged ketone (4) (40 mg), m.p. and m.m.p. 128°. Further elution with benzene–ether (2 : 1) afforded the *tetrazole* (12) (150 mg) which recrystallized from light petroleum–ether, m.p. 114°; $[\alpha]_D$ −110° (Found: C, 76·9; H, 10·6; N, 13·2. $C_{27}H_{44}N_4$ requires C, 76·4; H, 10·3; N, 13·2%). ν_{max} 1670 (C=C), 1505, 1465, 1380 cm^{-1} (C=N, N=N). N.m.r. δ 6·55, s, 1H, C6–H; 4·22, br, 1H, N–C8–H; 1·23, s, C10–Me; 0·81, s, C13–Me; 1·0, 0·91 (remaining methyls); λ_{max} 243 nm ($\log\varepsilon$ 4·10). Continued elution with the same solvent system gave the lactam (14), which recrystallized from light petroleum–ether, m.p.[11] and m.m.p. 210°.

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3β-Chloro-7a-aza-B-homocholest-5-eno[7a,7-d]tetrazole (13)

Reaction of (5)[18] (2 g) with hydrazoic acid–boron trifluoride etherate was performed in the usual manner to provide a semisolid material (*c.* 2 g). This was chromatographed over silica gel (40 g) and fractions of 30 ml were collected. Elution with chloroform gave *tetrazole* (13) (1·3 g) which recrystallized from light petroleum–ether, m.p. 172°; $[\alpha]_D$ −50° (Found: C, 70·6; H, 9·6; N, 12·0. $C_{27}H_{43}ClN_4$ requires C, 70·5; H, 9·3; N, 12·2%). ν_{max} 1660 (C=C), 1505, 1470, 1380 cm^{-1} (C=N, N=N). N.m.r. δ 6·63, s, 1H, C6–H; 4·21, br, 1H, N–C8–H; 3·81, br, 1H, $W_{h/2}$ 22 Hz, Cl–C3α–H; 1·38, s, C10–Me; 0·80, s, C13–Me; 1·0, 0·92, 0·83 (remaining methyls); λ_{max} 240 nm (log ε 4·13). Further elution with chloroform–ether (9 : 1) gave (15) (30 mg), m.p.[12] and m.m.p. 169°.

Sodium/Pentyl Alcohol Reduction of (13)

The tetrazole (13) (200 mg) was dissolved in warm pentyl alcohol (10 ml) and to this solution sodium metal (1 g) was added in small portions with intermittent heating during 30 min. The solution was kept warm for an additional period of 2 h. When all the metal had dissolved, the reaction mixture was poured into cold water and worked up in the usual manner followed by column chromatography over silica gel (6 g). Elution with benzene–ether (2 : 1) gave (12), m.p. and m.m.p. 114°.

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