Steroids and Related Studies. Part XVIII.[1] 3-Aza-A-homo-4a-eno[3,4-*d*]-tetrazole Steroid Analogues [2]

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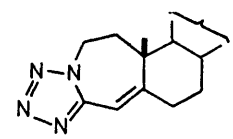
Treatment of (25*R*)-spirost-4-en-3-one with excess of hydrazoic acid in the presence of boron trifluoride gives (25*R*)-3-aza-A-homospirost-4a-eno[3,4-*d*]tetrazole. The latter has been degraded to 3-aza-A-homopregna-4a,16-dieno[3,4-*d*]tetrazol-20-one, the 16α,17α-epoxide of which yielded the 17α-hydroxy-16β-chloro-, bromo-, and thiocyanato-derivatives. The oxime of 3-aza-A-homopregna-4a,16-dieno[3,4-*d*]tetrazol-20-one, on rearrangement and hydrolysis, gave 3-aza-A-homoandrost-4a-eno[3,4-*d*]tetrazol-17-one.

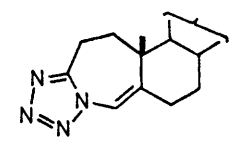
SINCE some steroids exhibit a depressant activity towards the central nervous system, and leptazol (pentamethylenetetrazole) has analeptic action, we considered that tetrazolo-steroids might have some effect on the nervous system. Some tetrazolo-steroids are claimed to possess antifertility and antispermatogenic activity,[3] but these results have not been substantiated.[4] We have investigated the synthesis of tetrazoles in the spirostan series, which we expected could then be degraded to the pregnane and androstane analogues.

(25*R*)-Spirost-4-en-3-one,[5] prepared from diosgenin by Oppenauer oxidation, was treated with hydrazoic acid in chloroform in the presence of boron trifluoride–ether complex. The product, elemental analysis of which showed that the tetrazole system had been formed, was considered to be either the 3-aza-steroid (A) or the 4-aza-system (B).

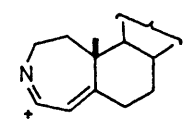
Only a few tetrazolo-steroids have been previously reported. Wu [6] prepared tetrazoles from 5α- and 5β-cholestan-3-one which were tentatively considered to have 3-aza-A-homo[3,4-*d*]tetrazole structures and showed u.v. absorption at 230 nm. From 17β-hydroxy-5α-androstan-3-one and 5α-cholestan-3-one Mechoulam [3,4] obtained mixtures of isomeric tetrazoles containing 3-aza-A-homo-[3,4-*d*]tetrazole and 4-aza-A-homo-[3,4-*d*]-tetrazole systems. Several tetrazoles have been prepared from αβ-unsaturated 4-en-3-ones; [3,4,7] these are thought to have the 3-aza-structure (A), and show a u.v. absorption maximum near 244 nm.[4] The formation of structures of type (A) is in agreement with the



(A)



(B)



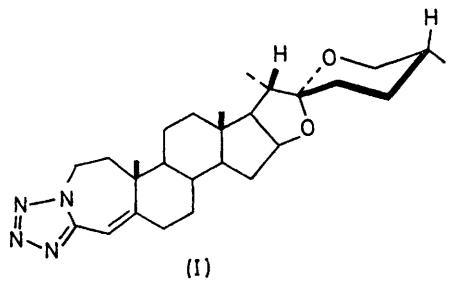
(C)

observation that Schmidt reactions of 4-en-3-ones or Beckmann rearrangements of their oximes generally yield lactams corresponding to the 3-aza-A-homo-4a-en-4-one system.[8–14] In the case of our tetrazole synthesis, the intermediate partial structure (C) in the Schmidt reaction [15] could react further with hydrazoic acid to give system (A).

The foregoing considerations support structure (I) for

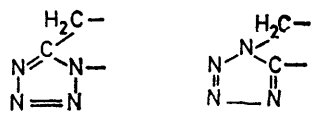
[1] Part XVII, H. Singh and S. Padmanabhan, *Indian J. Chem.*, in the press.
[2] H. Singh, R. B. Mathur, V. V. Parashar, and P. P. Sharma, Abstracts of Papers, XXIIIrd International Congress of Pure and Applied Chemistry, Boston, 1971, p. 77.
[3] R. Mechoulam, U.S.P. 3,182,069 (*Chem. Abs.*, 1965, **63**, 8452).
[4] R. Mechoulam, *Israel J. Chem.*, 1968, **6**, 909.
[5] R. E. Marker, T. Tsukamoto, and D. L. Turner, *J. Amer. Chem. Soc.*, 1940, **62**, 2525.
[6] M. T. Wu, D.Sc. Thesis, Tohoku University, 1961.
[7] J. Moural and K. Syhora, Czech. Pat. 123,697 (*Chem. Abs.*, 1968, **69**, 36,371).
[8] R. H. Mazur, *J. Org. Chem.*, 1963, **28**, 248.
[9] C. W. Shoppee, R. Lack, R. N. Mirrington, and L. R. Smith, *J. Chem. Soc.*, 1965, 5868.
[10] H. Singh and T. K. Kaw, *Indian J. Chem.*, 1965, **3**, 522.
[11] C. W. Shoppee and G. Krüger, *J. Chem. Soc.*, 1961, 3641.
[12] N. J. Doorenbos and H. Singh, *J. Pharm. Sci.*, 1962, **51**, 418.
[13] F. Kohen, *Chem. and Ind.*, 1966, 1378.
[14] H. Singh, V. V. Parashar, and M. L. Psahn, *Indian J. Pharm.*, 1969, **31**, 28.
[15] E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, New York, 1959, p. 624.

the product of the reaction of (25*R*)-spirost-4-en-3-one with excess of hydrazoic acid, which showed $\lambda_{max.}$ 244 nm



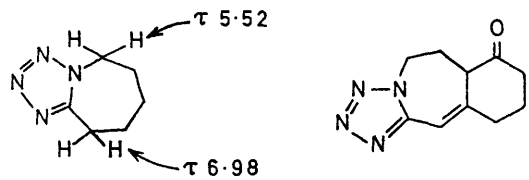
(I)

(log ε 4·25). The n.m.r. spectrum agreed with this assignment, showing a two-proton multiplet centred at τ 5·56. DiMaio and Permutti [16] have reported that the spectrum of the tetrazole system (D) exhibits a complex



(D) (E)

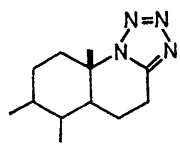
multiplet at τ 7·05 whereas that of (E) shows a signal near τ 5·05, and cited the tetrazole (II), formed from cyclohexanone, as an example. Greco and Gray [17] reported



(II) (III)

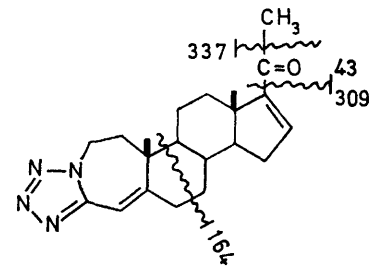
the tetrazole (III) to exhibit a multiplet centred at τ 5·44.

The i.r. spectrum of compound (I) showed bands at 1640 (C=C stretch), and at 1520 and 1445 cm^{-1}, which may be due to C=N and N=N stretching frequencies of the tetrazole system. Cervantes *et al.*[18] have prepared tetrazoles of type (F) which show vibrations in the same region.



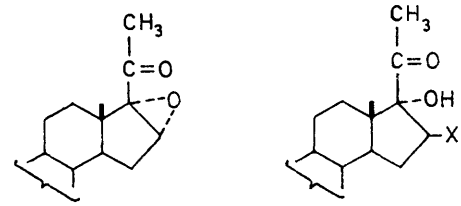
(F)

3-Aza-A-homospirost-4a-eno[3,4-*d*]tetrazole (I) was submitted to a Marker degradation to give 3-aza-A-homopregna-4a,16-dieno[3,4-*d*]tetrazol-20-one (IV), identified by its electronic, vibrational, and the n.m.r. spectra (multiplet at τ 5·55). The mass spectrum exhibited peaks at *m/e* 352 (M^+, 77%), 337 ($M^+ - CH_3$, 30%), 309 ($M^+ - CH_3{\cdot}CO$, 48%), 164 ($M^+ - C_{13}H_{16}O$, 83%), and 43 ($M^+ - C_{19}H_{25}N_4$; 100%), interpretable in terms of the cleavages indicated.

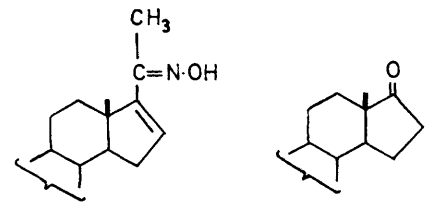


(IV)

Treatment of compound (IV) with alkaline hydrogen peroxide gave an epoxide considered to have structure (V), by analogy with similar epoxidations of the 16-en-20-one system.[19-21] The corresponding halogenohydrins were obtained by treating the epoxide (V) with hydrochloric and hydrobromic acids; the 16β-halogeno-17α-hydroxy-structures (VI) and (VII) were assigned by analogy with the products of similar reactions.[21-23]



(V) (VI) R=Cl (VII) R=Br (VIII) R=SCN



(IX) (X)

Similarly, the product of interaction of the epoxide and potassium thiocyanate in glacial acetic acid [24] is considered to have structure (VIII), $\nu_{max.}$ 2135 cm^{-1} (C≡N).

[16] G. DiMaio and V. Permutti, *Tetrahedron*, 1966, **22**, 2059.
[17] C. V. Greco and R. P. Gray, *Tetrahedron*, 1970, **26**, 4329.
[18] A. Cervantes, P. Crabbé, J. Iriarte, and G. Rosenkranz, *J. Org. Chem.*, 1968, **33**, 4294.
[19] E. Batres, T. Cardenas, J. A. Edwards, G. Monroy, O. Mancera, C. Djerassi, and H. J. Ringold, *J. Org. Chem.*, 1961, **26**, 871.
[20] E. S. Rothman and M. E. Wall, *J. Amer. Chem. Soc.*, 1959, **81**, 411.
[21] B. Löken, S. Kaufmann, G. Rosenkranz, and F. Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 1738.
[22] B. Ellis, D. Patel, and V. Petrow, *J. Chem. Soc.*, 1958, 800.
[23] G. R. Allen, jun., and M. J. Weiss, *J. Amer. Chem. Soc.*, 1959, **81**, 4968.
[24] T. Komeno, *Chem. and Pharm. Bull. (Japan)*, 1960, **8**, 680.

Beckmann rearrangement of the oxime (IX) [prepared from the ketone (IV)] with phosphoryl chloride in pyridine, followed by acid hydrolysis, gave 3-aza-A-homoandrost-4a-eno[3,4-*d*]tetrazol-17-one (X).

EXPERIMENTAL

Optical rotations were measured for solutions in chloroform. U.v. and i.r. spectra were obtained for solutions in methanol and for potassium bromide discs, respectively. T.l.c. was carried out on silica gel G (Merck) and plates were developed by exposure to iodine vapour. Anhydrous sodium sulphate was employed as drying agent.

(25R)-3-*Aza*-A-*homospirost*-4a-*eno*[3,4-d]*tetrazole* (I).—A stirred solution of sodium azide (100 g) in water (250 ml) was cooled to 0° and chloroform (500 ml) was added, followed dropwise by concentrated sulphuric acid (93 ml) during 30 min at 0—5°. The mixture was stirred for a further 30 min with the temperature kept below 5°. The chloroform layer was separated and dried.

To this solution (450 ml) of hydrazoic acid in chloroform at 0°, boron trifluoride–ether complex (6·8 ml) was added with shaking. A solution of (25*R*)-spirost-4-en-3-one (12 g) in chloroform (225 ml) was then added during 5 h at 0°. The mixture was kept for 20 h at room temperature (20—25°), then filtered, and the residue was washed with chloroform (50 ml). The chloroform layers were combined, washed free of acid with water, dried, and evaporated. The residue crystallised from methanol to give the *tetrazole* (I) (6·6 g, 50%), m.p. 281—283° (decomp.); $[\alpha]_D^{20}$ −72·1° (*c* 1·19); $\lambda_{max.}$ 244 nm (log ε 4·25); $\nu_{max.}$ 1640, 1520, and 1445 cm^{-1} (Found: C, 71·6; H, 8·85; N, 12·2. $C_{27}H_{40}N_4O_2$ requires C, 71·65; H, 8·9; N, 12·3%).

3-*Aza*-A-*homopregna*-4a,16-*dieno*[3,4-d]*tetrazol*-20-*one* (IV).—In a sealed tube the tetrazole (I) (6·4 g) and acetic anhydride (44 ml) were heated in an oil-bath (bath temp. 100° (±10°)) for 1·5 h. The cooled mixture was poured into a large excess of water and the supernatant liquid was decanted. The brown oily residue was washed with water, dissolved in glacial acetic acid (60 ml), and treated with chromium trioxide (2·8 g) in 90% acetic acid (60 ml), with the temperature kept near 15°. The mixture was stirred occasionally during 2 h at 20—25°, then ethanol (95%) was added to destroy the excess of chromium trioxide. A large volume of water was added and the precipitate was extracted with ether (5 × 150 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated. To a solution of the yellow residue in acetone (72 ml) was added sodium hydroxide (3·25 g) in water (24 ml). The mixture was refluxed for 40 min, cooled, and diluted with water; the precipitate was filtered off, washed thoroughly with water, dried, and crystallised from methanol to yield the *tetrazole* (IV) (1·7 g, 34%), m.p. 234—237°; $[\alpha]_D^{20}$ +75·6° (*c* 1·08); $\lambda_{max.}$ 240 nm (log ε 4·40); $\nu_{max.}$ 3045, 1650, 1580, 1520, and 1435 cm^{-1} (Found: C, 71·55; H, 8·05; N, 15·8. $C_{21}H_{28}N_4O$ requires C, 71·55; H, 8·0; N, 15·9%).

16α,17α-*Epoxy*-3-*aza*-A-*homopregn*-4a-*eno*[3,4-d]-20-*one* (V).—A solution of compound (IV) (4 g) in methanol (140 ml) cooled to 0° was treated successively with cold aqueous 4N-sodium hydroxide (4 ml) and hydrogen peroxide (30%; 10 ml). After 24 h at 5—7° the mixture was poured into an excess of cold water. The crystalline product that separated was filtered off, washed with water, and dried to yield the *epoxide* (V) (350 mg, 84%), m.p. 261—265° (from methanol); $\lambda_{max.}$ 242 nm (log ε 4·35); $\nu_{max.}$ 1698, 1645, 1520, and 1440 cm^{-1} (Found: C, 67·9; H, 7·6; N, 15·0. $C_{21}H_{28}N_4O_2$ requires C, 68·45; H, 7·65; N, 15·2%).

16β-*Chloro*-17α-*hydroxy*-3-*aza*-A-*homopregn*-4a-*eno*[3,4-d]-*tetrazol*-20-*one* (VI).—A solution of the epoxide (V) (200 mg) in glacial acetic acid (5 ml) saturated with dry hydrochloric acid gas was set aside at room temperature for 2·5 h, then poured into a large volume of water. The separated solid was filtered off, washed free of acid with water, and crystallised from aqueous methanol to give the *chlorohydrin* (VI) (140 mg, 64%), m.p. 225—226° (decomp.); $\lambda_{max.}$ 242·5 nm (log ε 4·36); $\nu_{max.}$ 3370, 1720, 1640, 1520, and 1440 cm^{-1} (Found: C, 62·35; H, 7·45; Cl, 8·9; N, 14·0. $C_{21}H_{29}ClN_4O_2$ requires C, 62·25; H, 7·2; Cl, 8·75; N, 13·85%).

16β-*Bromo*-1[illegible]*droxy*-3-*aza*-A-*homopregn*-4a-*eno*[3,4-d]-*tetrazol*-20-*one* [illegible] .—Compound (V) (250 mg) was dissolved in glacial [illegible]etic acid (6·2 ml) and treated with a solution of hydrobromic acid in glacial acetic acid (30%; 6·5 ml) during 70 min at room temperature. The product that separated on pouring the mixture into cold water was washed with water, dried, and crystallised from methanol to give the *bromohydrin* (VII) (150 mg, 49%), m.p. 207—208° (decomp.); $\lambda_{max.}$ 243 nm (log ε 4·26); $\nu_{max.}$ 1720, 1645, 1530, and 1450 cm^{-1} (Found: C, 55·25; H, 6·4; Br, 17·3; N, 11·7. $C_{21}H_{29}BrN_4O_2$ requires C, 56·1; H, 6·5; Br, 17·8; N, 12·45%).

17α-*Hydroxy*-16β-*thiocyanato*-3-*aza*-A-*homopregn*-4a-*eno*-[3,4-d]*tetrazol*-20-*one* (VIII).—A mixture of the epoxide (V) (200 mg), potassium thiocyanate (800 mg), and glacial acetic acid (6 ml) was heated on a steam-bath for 5 h, cooled, and poured into an excess of cold water. The separated solid was filtered off, washed successively with water, aqueous sodium hydrogen carbonate solution, and water, dried, and crystallised from methanol–ether to yield the *thiocyanate* (VIII) (120 mg, 52%), m.p. 248—249° (decomp.); $\lambda_{max.}$ 242·5 (log ε 4·20); $\nu_{max.}$ 2135, 1710, 1640, 1520, and 1445 cm^{-1} (Found: C, 61·6; H, 6·9; N, 16·05; S, 7·4. $C_{22}H_{29}N_5O_2S$ requires C, 61·75; H, 6·85; N, 16·4; S, 7·5%).

3-*Aza*-A-*homopregna*-4a,16-*dieno*[3,4-d]*tetrazol*-20-*one Oxime* (IX).—A solution of compound (IV) (1·5 g) and hydroxylamine hydrochloride (0·56 g) in pyridine (13 ml) was heated on a steam-bath for 3 h. The mixture was poured into water and the precipitated oxime was coagulated on a steam-bath. The product was filtered off, washed free of pyridine with hot water, dried, and crystallised from aqueous methanol to yield the *oxime* (IX) (1·1 g, 70%), m.p. 212—213°; $[\alpha]_D^{20}$ +111·4° (*c* 1·16); $\lambda_{max.}$ 240 nm (log ε 4·50); $\nu_{max.}$ 3285, 1630, 1560, and 1490 cm^{-1} (Found: C, 68·65; H, 7·95; N, 18·8. $C_{21}H_{29}N_5O$ requires C, 68·65; H, 7·95; N, 19·05%).

3-*Aza*-A-*homoandrost*-4a-*eno*[3,4-d]*tetrazol*-17-*one* (X).—A solution of phosphoryl chloride (6·0 ml) in dry pyridine (18 ml) was added dropwise during 30 min to a stirred solution of the oxime (IX) (1·5 g) in dry pyridine (15 ml), with the temperature kept between −10 and 0°. The mixture was stirred for a further 3 h below 0° and added gradually to a mixture of conc. hydrochloric acid (45 ml) and ice (45 g), with the temperature kept below 20°. The resulting mixture was kept at room temperature for 30 min, diluted with an equal volume of water, and extracted with chloroform. The extract was washed with water, dried, and evaporated to leave a brown syrup, which was purified by passage through alumina in benzene. Crystallisation from acetone–ether

gave the *product* (X) (450 mg, 34%), m.p. 220—222°; $[\alpha]_D^{20}$ +104·0° (*c* 1·27); $\lambda_{max.}$ 242·5 nm (log ε 4·20); $\nu_{max.}$ 1730, 1635, 1515, and 1440 cm^{-1} (Found: C, 69·85; H, 7·85; N, 17·25. $C_{19}H_{26}N_4O$ requires C, 69·9; H, 8·05; N, 17·15%).

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