

THERMAL AND PHOTOLYTIC REARRANGEMENT OF 4-AZIDO- $\Delta^{4,6}$ -  
3-KETOSTEROIDS TO 5 $\beta$ -CYANO-A-NOR- $\Delta^6$ -3-KETOSTEROIDS

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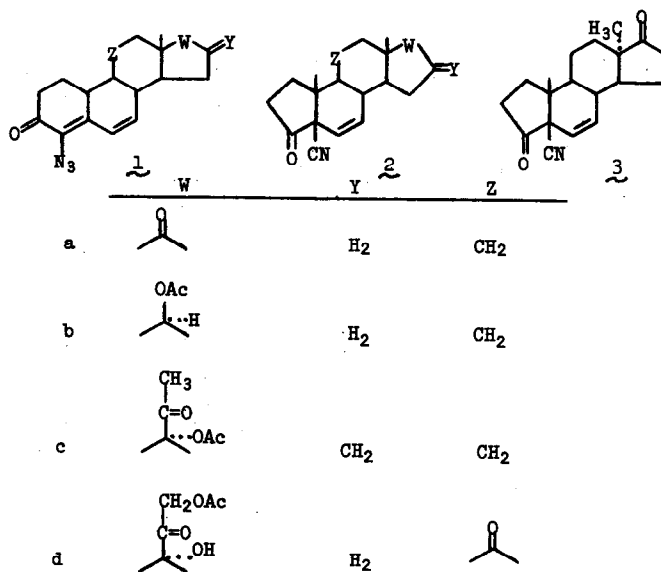
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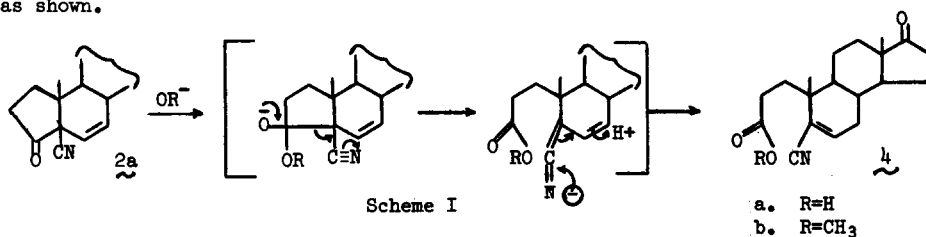
Thermal and photolytic transformations of cyclic organic azides to cyanides with concomitant ring contraction have been described<sup>2</sup>. We now report the application of this transformation to 4-azido- $\Delta^{4,6}$ -3-ketosteroids, and the utilization of X-ray crystallographic analysis in establishing the structures of the resultant A-nor-5-cyano-3-ketosteroids.

Exposure of 4-azido-4,6-androstadiene-3,17-dione (1a)<sup>3</sup> in refluxing toluene to a 250-Watt photoflood lamp for 3.5 hr afforded 5 $\beta$ -cyano-A-nor-6-androstene-3,17-dione (2a)<sup>4</sup> in 74% yield. Similarly 1b<sup>3</sup> gave the A-nor-testosterone analog 2b; 1c<sup>3</sup> gave the 16-methylene-17 $\alpha$ -acetoxyprogesterone analog 2c; and 1d<sup>3</sup> gave the A-nor-6-dehydrocortisone acetate analog 2d in comparable yields.

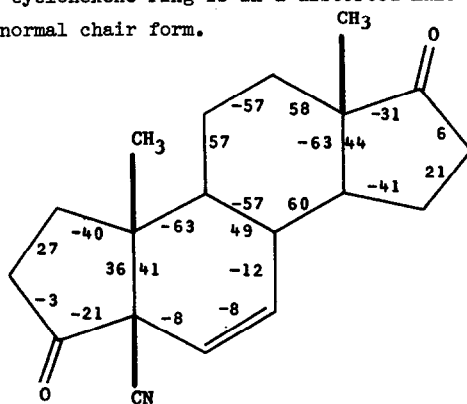


The formation of 2a was shown to occur thermally at the reflux temperature of the designated solvent (toluene, 5 hr, 74%; benzene, 10 hr, 60% and 8% recovered 1a; cyclohexene, 20 hr, 72%; absolute ethanol, 20 hr, 69%; cyclohexane, 22 hr, 78% and pyridine, 16 hr, 73%) or photochemically at 10-12° (toluene, 3500Å, 5 hr, 69%; 3000Å, 5 hr, 46%). At the shorter wavelength, additionally, 25% of the 13α-epimer (3) of 2a was obtained.

Compound 2a displayed the following characteristics:  $[\alpha]_D^{25} +101.9^\circ$  (dioxane),  $\nu_{\max}$  (Nujol) 2230 (CN), 1757 and 1745  $\text{cm}^{-1}$  (3- and 17-carbonyls of cyclopentane rings),  $\delta$  0.93 (13-CH<sub>3</sub>), 1.33 (10-CH<sub>3</sub>), 5.90 (6H, 7H)<sup>5</sup>. The infrared spectrum indicated a non-conjugated 5-membered ring A ketone, and the pmr spectrum supported the presence of a non-conjugated double bond ( $\Delta^6$ ). The proximity of the cyano group to the 3-carbonyl function was established by cleavage of 2a, with sodium hydroxide in aqueous ethanol and with sodium methoxide in methanol, into the seco acid derivative 4a and the methyl ester 4b, respectively. The formation of the  $\Delta^5$  conjugated cyano compound 4b [ $[\alpha]_D^{25} +7.1^\circ$  (dioxane),  $\lambda_{\max}$  207 nm,  $\epsilon$  11,600 (isooctane),  $\delta$  6.23 (6-H, d, d 5.5, 2.0 Hz)] according to Scheme I is consistent with the placement of the cyano group and the double bond as shown.

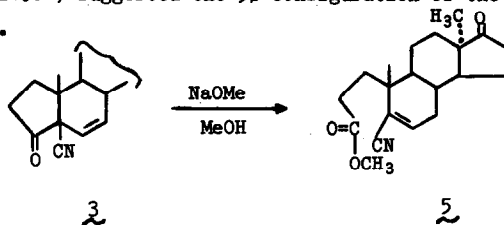


Assignment of the  $\beta$ -configuration to the cyano grouping in 2a was established unequivocally by X-ray analysis, which also confirmed the total structure. Crystals of 2a belong to the orthorhombic system, space group  $P2_12_12_1$ , with  $a = 11.70(1)$ ,  $b = 12.89(1)$ ,  $c = 10.89(1)$  Å,  $Z = 4$ . The structure was solved by direct phase determining procedures using MULTAN<sup>6</sup> and refined by full-matrix least-squares calculations (anisotropic C, N, O; fixed H contributions) to  $R = 0.107$  over 1282 visually estimated reflections from photographic data. The cyclopentanone rings both adopt envelope conformations, the cyclohexene ring is in a distorted half-chair form, and the cyclohexane ring approximates a normal chair form.



Endocyclic torsion angles (deg.) in 2a.

Compound 3 [ $[\alpha]_D -23.0^\circ$  (dioxane)] was converted with NaOMe in MeOH to the epimer (5) [ $[\alpha]_D -117.7^\circ$  (dioxane)] of 4b. The large levorotatory change observed with 3 *vis a vis* 2a suggested the presence of a 13 $\alpha$ -methyl<sup>7</sup> and the equivalence of rotational difference between 3 to 2a ( $124.9^\circ$ ) and 5 to 4b ( $124.8^\circ$ ) suggested the 5 $\beta$ -configuration of the cyano group in 3. <sup>13</sup>CMR confirmed this assignment<sup>8</sup>.



The azide transformation may be considered to proceed by one of several mechanistic possibilities<sup>2</sup>. For example, one may consider the rearrangement as proceeding *via* a seco-ketenimine intermediate, or through an azirine, or through a nitrene intermediate. However, most reactions of the nitrene type occur at higher temperatures than is required for the ready thermolytic conversion of our  $\Delta^{4,6}$ -4-azido compounds, and we have not observed a product which might result from the intermolecular reaction of a nitrene and solvent. We have, however, no convincing evidence to distinguish a preferred sequence.

In any event, this reaction proceeds in high yield to give the A/B cis-fused cyano product, and seems to require the 4-azido- $\Delta^{4,6}$ -diene system for this type of facile transformation. Thus, under similar reaction conditions, 6-azido-6-dehydro-17 $\alpha$ -acetoxyprogesterone<sup>9</sup> afforded no cyano product, and 6,7-dihydro 1c<sup>10</sup> afforded a product mixture which may have contained at most a small amount of a cyano component<sup>11</sup>. These latter reactions are under further investigation.

Acknowledgments. We thank J. Korpi for technical assistance in the preparation of 2d.

#### Notes and References

1. Schering Postdoctoral Fellow, 1968-1969.
2. See, for example, a) W. Weyler, Jr., D.D. Pearce, and H.W. Moore, *J. Amer. Chem. Soc.*, **95**, 2603 (1973), b) H.W. Moore and W. Weyler, Jr., *J. Amer. Chem. Soc.*, **93**, 2812 (1971), c) D. Knittel, H. Hemetsberger, R. Leipert, and H. Weidmann, *Tetrahedron Lett.*, 1459 (1970), d) H.W. Moore, *Chem. Soc. Reviews*, **2**, 415 (1973).
3. H.L. Herzog, J. Korpi, E.L. Shapiro, G. Teutsch, and L. Weber, *J.C.S., Chem. Comm.*, 72 (1973). 1b was prepared commencing with the  $\Delta^6$ -testosterone-17-acetate as in the manner of formation of 1a.
4. Satisfactory analytical and spectral data have been obtained for all new compounds.
5. NMR spectra were determined with a Varian A60-A or a Varian XL-100 spectrometer in CDCl<sub>3</sub> using TMS as the internal standard.
6. G. Germain, P. Main, and M.M. Woolfson, *Acta Cryst.*, **A27**, 368 (1971).
7. J.P.L. Bots, *Rec. trav. chim.*, **77**, 1010 (1958).

8. Subsequently, correlation of  $^{13}\text{C}$  nmr data revealed that cmr may also be applied to cis/trans ring juncture determination of compounds of this type, and will be the subject of a future publication by E.M. Smith, E.L. Shapiro, R. Brambilla, H.L. Herzog, and J. Meinwald.
9. G. Teutsch, L. Weber, G. Page, E.L. Shapiro, H.L. Herzog, R. Neri, and E.J. Collins, J. Med. Chem., 16, 1370 (1973).
10. Prepared in the manner described for the 19-nor series in the U.S. Patent 3,780,070 (Dec. 18, 1973).
11. A weak infrared absorption at  $2230\text{ cm}^{-1}$  was present which could be ascribed to a cyano absorption. However, attempted isolation of a component bearing this function was not successful.