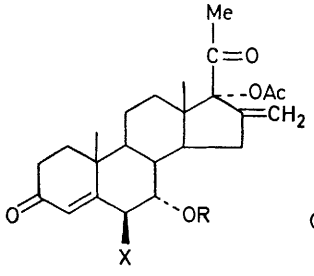
Efficient Synthesis and Mechanisms of Formation of 4-Azido-, 4-Thiocyanato-, and 4-Isothiocyanato-3-oxo-$\Delta^{4,6}$-steroids

By H. L. HERZOG, J. KORPI, E. L. SHAPIRO,* G. TEUTSCH, and L. WEBER
(*Schering Corporation, 86 Orange Street, Bloomfield, New Jersey* 07003)

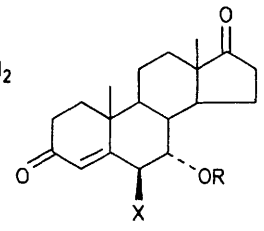
Summary Processes for the preparation of 4-azido-, 4-thiocyanato-, and 4-isothiocyanato-3-oxo-$\Delta^{4,6}$-steroids are presented; possible mechanisms of formation are suggested.

IN view of the potentiating effect of 6-halogeno-substitution on progestational activities, we have sought the corresponding 6-pseudohalogeno-derivatives.[1]



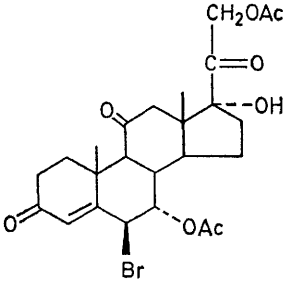
(1)

a; X = Br, R = MeCO
b; X = N_3, R = $MeSO_2$

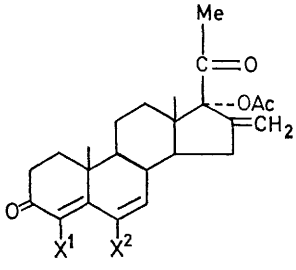


(2)

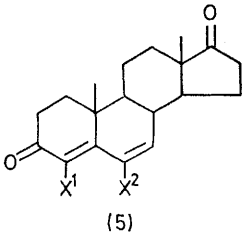
c; X = N_3, R = MeCO
d; X = SCN, R = H



(3)

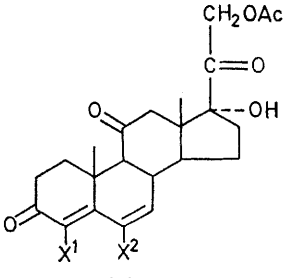


(4)



(5)

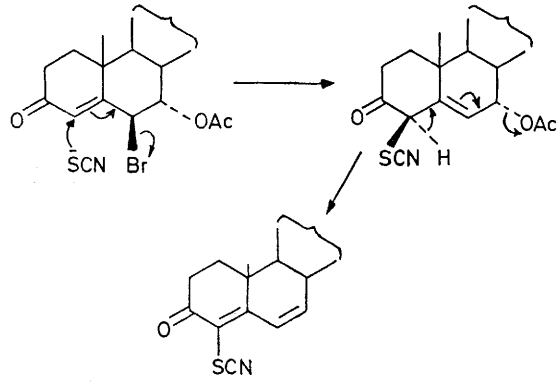
a; X^1 = N_3, X^2 = H
b; X^1 = SCN, X^2 = H



(6)

c; X^1 = NCS, X^2 = H
d; X^1 = H, X^2 = N_3
e; X^1 = H, X^2 = SCN

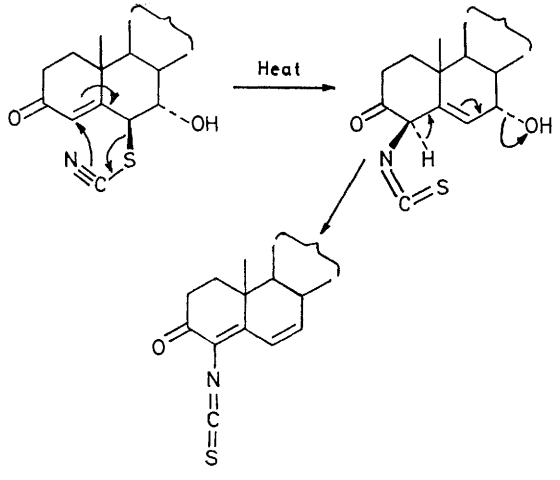
Reaction of the 6β-bromo-7α-acetoxy-progestin (**1a**)[1] [or its C_{19} counterpart (**2a**)][2b] with NaN_3 in DMF or DMSO at 25° for 3 h surprisingly† gave the 4-azido-$\Delta^{4,6}$-product (**4a**)



SCHEME 1

[or (**5a**)]‡ (*ca.* 60%). In each case a small amount of the isomeric 6-azide [(**4d**) or (**5d**), respectively] was also formed.§ Thermally induced allylic rearrangement (60°) of the 6β-azido-7α-acetoxy-compound (**1c**) [or (**1b**)] in DMF or dioxan also yielded the 4-azido-$\Delta^{4,6}$-product (**4a**)

Similarly, (**1a**) [or (**2a**)] afforded only the 4-thiocyanato-$\Delta^{4,6}$-product (**4b**) [or (**5b**)] in 75—85% yield from reaction with KSCN in DMF for 2—4 days at 25°. The corresponding 4-isothiocyanate (**4c**) [or (**5c**)] was prepared in good yield by the thermally induced allylic rearrangement of the 6β-thiocyanate (**1d**) [or (**2d**)][2b,5] in DMF, benzene, or



SCHEME 2

† Ref. 3 reports a 6α-azido-3-oxo-Δ^4-steroid, obtained from the 6β-bromo-analogue with azide ion, and a similar transformation has been effected by H. Reimann of these laboratories.
‡ Satisfactory analytical and spectral data have been obtained for all new compounds.
§ Refs. 2 and 4 report the preparation of 6-azido-3-oxo-$\Delta^{4,6}$-steroids by other processes.

toluene. The mode of attachment (through S or N) at C-4 was assigned, apparently unambiguously, by i.r. analysis.[6]

The results obtained with the asymmetric triatomic unit in the thiocyanate–isothiocyanate series appear to define unambiguously the pathway of reaction of (**1a**) with nucleophiles 'N_3^-' and 'SCN^-'. (See Scheme 1).

This follows since the 4-thiocyanate cannot arise out of 6-thiocyanate by thermally induced allylic rearrangement by the presently understood mechanism (Scheme 2). This presumption was tested for the azido-series by exposing the 6β-azido-7α-acetoxy compound (**1c**) (the hypothetical intermediate in the neighbouring group-assisted displacement of the 6β-bromo-substituent by azide ion) to the reaction conditions under which (**4a**) had been formed from (**1a**). The 6-azido-Δ^6-product (**4d**) (11%) but no (**4a**) was formed thereby establishing that allylic rearrangement is not a significant pathway to (**4a**) under these conditions (25°C). However, 6β-azido-7α-acetoxy-compounds cannot be excluded as intermediates in the formation of the 6-azido-$\Delta^{4,6}$-products [(**4d**) and (**5d**)] from the corresponding 6β-bromides.

In summary, the 4-substituted products reported here which were derived from (**1a**) [and (**2a**)] arise by S_N2' attack of the nucleophile (regiospecifically directed by the 7α-acetate) and those which were derived from (**1b**—**d**) [or (**2d**)], arise by S_Ni' rearrangement.

Application of these findings to the corticoid series has also afforded (**6a**) and (**6b**) from (**3**).

(*Received, 23rd October* 1972; *Com.* 1799.)

[1] E. L. Shapiro, L. Weber, H. Harris, C. Miskowicz, R. Neri, and H. L. Herzog, *J. Medicin. Chem.*, 1972, **15**, 716, and references therein cited.
[2] (a) Belg. P. 770,378 (1972); (b) G. Teutsch, L. Weber, G. Page, E. L. Shapiro, and H. L. Herzog, in preparation.
[3] K. Ponsold and G. Schubert, *J. prakt. Chem.*, 1969, **311**, 445.
[4] G. Drefahl, K. Ponsold, and G. Schubert, *J. prakt. Chem.*, 1969, **311**, 919.
[5] (a) K. Ponsold and G. Schubert, *Z. Chem.*, 1968, **8**, 465, have reported the 16-demethylene analogue of (**1d**); (b) E. L. Shapiro, U.S.P. 3,673,233 (1972).
[6] L. Luskin, G. E. Gantert, and W. E. Craig, *J. Amer. Chem. Soc.*, 1956, **78**, 4965.