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A NEW RING-CONTRACTION REACTION*

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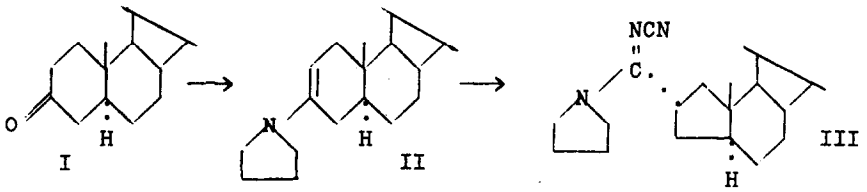
Methods available for ring contraction of cydic ketones under mild conditions are few in number and limited in scope (1). Reaction of cyanogen azide (2) with the enamines of cyclic ketones has been found to constitute a new and valuable method for effecting ring contractions, especially of steroid ring-A ketones.

The reaction sequence is exemplified by conversion of 5α-cholestan-3-one (Ia) tc an enamine (IIa), by the action of pyrrolidine in benzene with



azeotropic removal of water (3). Dropwise addition of a solution of cyanogen azide in ethyl acetate to a solution of the enamine in the same solvent at 20-30° is accompanied by evolution of nitrogen and the formation of 2α-(N-pyrrolidinylcyanoiminomethyl)-A-nor-5α-cholestane (IIIa), which is isolated in 70% yield by column chromatography [m.p. 222.5-224.5° (ethyl acetate); λ_{max}^{EtOH} 250 mμ, ϵ_{max} 17,000; $\nu_{max}^{CHCl_3}$ 2230 (C≡N), 1560 (C=N) cm^{-1}]. This procedure is especially convenient to use in the androstane and pregnane series, for the resulting cyanoamidines are sparingly soluble in the reaction medium and are isolated simply by filtration. Thus, 17β-hydroxy-5α-androstan-3-one (Ib) gives 2α-(N-pyrrolidinylcyanoiminomethyl)-A-nor-5α-androstan-17β-ol

*Steroid Syntheses with Cyanogen Azide. I.
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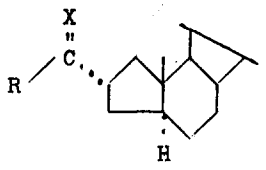
(IIIb) [80% yield; m.p. 261.5-263.5°], and 5α-pregnane-3,20-dione (Ic) gives 2α-(N-pyrrolidinylcyanoiminomethyl)-A-nor-5α-pregnan-20-one (IIIc) [60% yield; m.p. 198-203°].*

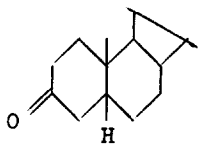
Assignment of structure to these 2-substituted A-norsteroids (III) is based on: hydrolysis of IIIa by excess, concentrated KOH in boiling ethanol to give a carboxylic acid which on esterification with methanol-sulfuric acid affords 2α-methoxycarbonyl-5α-cholestane (IV), identical to that obtained by the Favorski rearrangement of 2α-bromo-5α-cholestan-3-one (4); mild alkaline



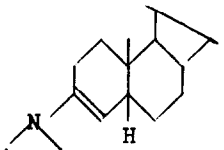
IV X = O; R = OCH_3
V X = O; R = N-pyrrolidinyl
VI X = H_2; R = N-pyrrolidinyl
VII X = $(CH_3)_2$; R = N-pyrrolidinyl

hydrolysis of IIIa by one equivalent of 1N NaOH in boiling ethanol to give an amide V [61% yield; m.p. 158-159.5°]; reduction of the cyanoamidine IIIb with lithium aluminum hydride to give 2α-(N-pyrrolidinylmethyl)-A-nor-5α-androstan-17β-ol (VI). Reaction of the cyanoamidine IIIb with excess methylmagnesium bromide in boiling benzene-ether is accompanied by replacement of the cyano-imino group by two methyl groups and formation of VII.

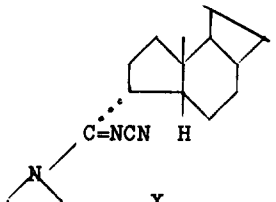
This new ring-contraction method also serves as a route to 3-substituted A-norsteroids. For example, 17β-hydroxy-17α-methyl-5β-androstan-3-one (VIII) gives, via the Δ^3-enamine (5), 17α-methyl-3α-(N-pyrrolidinylcyano-iminomethyl)-A-nor-5β-androstan-17β-ol (X) [68% yield]. Assignment of



VIII



IX



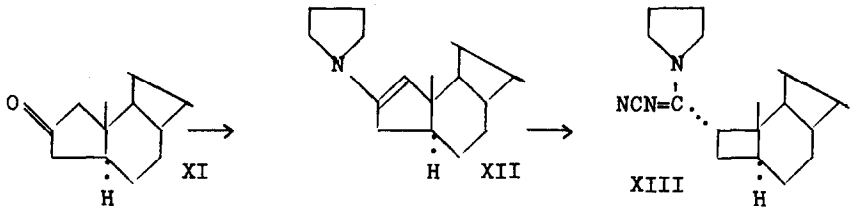
X

configuration to the 3α-substituent is based primarily on C-19 nmr chemical shifts of X in $CDCl_3$ and benzene (6) and will be described in a subsequent publication.

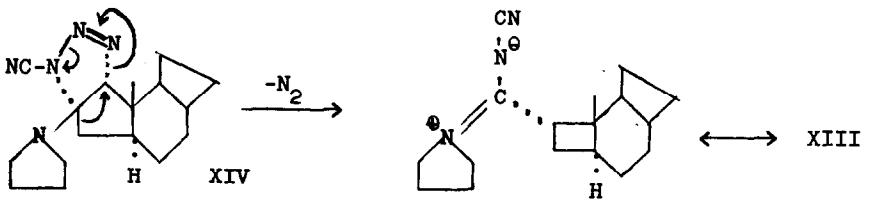
*All new compounds had correct elemental analyses and infrared and nmr spectra were consistent with assigned structures.

Contraction of a cyclopentane to a cyclobutane ring involves a significantly greater increase in strain than does contraction of a cyclohexane to a cyclopentane ring. Perhaps for this reason there are relatively few methods known for effecting contractions to cyclobutane rings (7). It is therefore of special interest that the enamine-cyanogen azide ring contraction reaction can be applied to the synthesis of an A-dinorsteroid (8).

Conversion of 17β-acetoxy-A-norandrostan-2-one (XI) to its enamine (XII) can be accomplished under forcing conditions by heating at reflux a

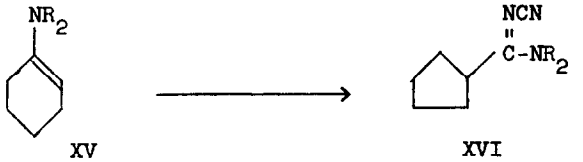


xylene solution of the ketone with excess pyrrolidine in a Soxhlet extractor, the thimble of which is filled with CaC_2 as a desiccant. After 20 hrs., conversion to enamine XII is essentially complete. Reaction of an ethyl acetate solution of enamine XII with cyanogen azide followed by chromatography of the product on alumina gives a glass having λ_{max} 1560 cm^{-1} (C=N), and a U.V. extinction coefficient corresponding to a 60% yield of crude cyanoamidine XIII. Crystallization from ether gives pure 2α-(N-pyrrolidinylcyanoimino-methyl)-A-dinor-5α-androstan-17β-ol acetate (XIII) in 10% yield [m.p. 162-163°]. Assignment of the Δ^1 structure to the intermediate enamine is based on the known direction of enolization of A-nor-2-ketones (9); assignment of structure to the A-dinorsteroid XIII rests on analogy and the spectral data cited above, whereas assignment of configuration depends on the likelihood of back-side approach (10) by N_3CN on XII to form an unstable triazoline XIV precursor to XIII. An unstable triazoline (11) intermediate was clearly indicated



by the fact that addition of N_3CN to a solution of enamine XII in ethyl acetate at 20-30° was not accompanied by the usual evolution of nitrogen but rather by precipitation of a sparingly soluble, colorless substance which, though too unstable to be characterized or isolated, underwent decomposition with loss of nitrogen and formation of cyanoamidine XIII when warmed to about 40-45°.

Application of the cyanogen azide-enamine rearrangement to non-steroid ketones has been examined briefly. Addition of cyanogen azide to 1-dimethylaminocyclohexene (XVa) or 1-morpholinocyclohexene (XVb) in acetonitrile at



XV XVI

-10° gives the corresponding cyclopentanecarboxamidines, XVIa (R = CH_3) [m.p. 98-100°], and XVIb (R_2 = C_4H_8O) [m.p. 125-127°] in 80-90% yields.*

A detailed account of the use of this valuable method of ring contraction for the preparation of unusual A-norsteroids will be given in future publications.

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