

THE PREPARATION OF 14 $\beta$ ,18-CYCLO-PROGESTERONE FROM CONESSINE

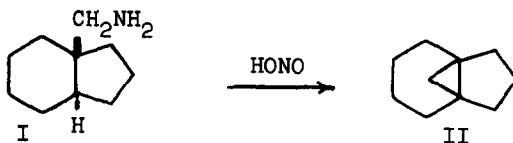
VIA N-DESMETHYL-4,N(20)-CONADIENE-3-ONE<sup>1</sup>

William G. Dauben and Paul Laug

Department of Chemistry, University of California, Berkeley 4, California

(Received 19 April 1962)

IN the course of the study of the reaction of angularly substituted groups on fused ring systems,<sup>2</sup> the reaction of trans-8-hydrindanylcarbinylamine (I) with nitrous acid was investigated.<sup>3</sup> It was found that 74 per cent of



tricyclo [4.3.1.0<sup>1,5</sup>] decane (II), 6 per cent of bicyclo [4.3.1] decane-1-ol, 16 per cent of 9-hydroxydecalin, and 4 per cent of octalins were formed. Similar results were obtained using trans-9-decalylcarbinyl amine.<sup>3</sup>

In 1960, Černý and Šorm<sup>4</sup> reported that when the related 18-aminopregnane-3 $\beta$ ,20-diol (III), derived from conessine, was allowed to react with nitrous acid the major product formed was 18-nor-D-homo- $\Delta^{13}$ -5 $\alpha$ -pregnene-3 $\beta$ ,20-diol (IV). Also, Buzetti, Wicki, Kalvoda and Jeger<sup>5</sup> deaminated the related pyrrolidine V and reported only the isolation of 18-hydroxyprogesterone (VI).

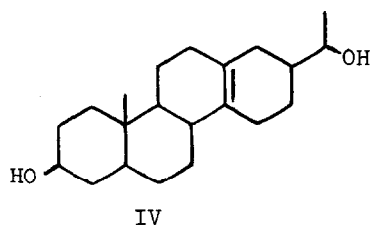
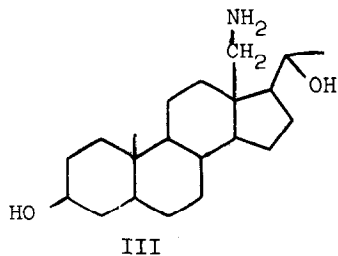
<sup>1</sup> This work was supported in part by Grant No. CY-4284, U.S. Public Health Service.

<sup>2</sup> W.G. Dauben and J.B. Rogan, *J. Amer. Chem. Soc.* **79**, 5002 (1957).

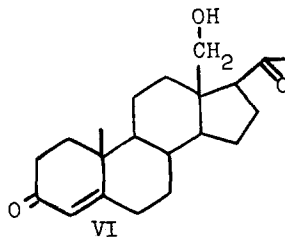
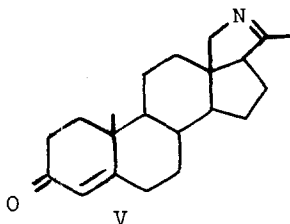
<sup>3</sup> W.G. Dauben, I.L. Westman and F.T. Bond, Abstracts of Papers presented at the 141st Meeting of the American Chemical Society, Washington, D.C., March 28, 1962, pp. 29-30.

<sup>4</sup> V. Černý and F. Šorm, *Coll. Czech. Chem. Comm.* **25**, 2841 (1960).

<sup>5</sup> F. Buzetti, W. Wicki, J. Kalvoda and O. Jeger, *Helv. Chim. Acta* **42**, 388 (1959).



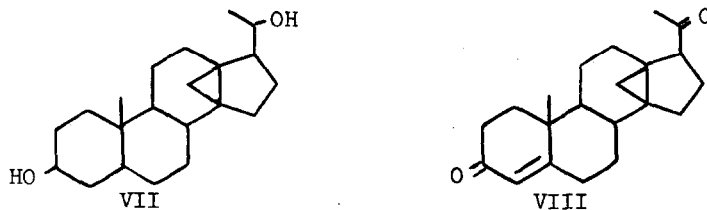
Hora and Černý<sup>6</sup> reinvestigated the reaction of the pyrroline V and found that VI was only a minor product, the major product being a material to which was assigned the 18-nor-D-homo structure analogous to IV.



In view of our results with the simple model compounds being so different from those reported both by Černý and by Jeger, we have also studied the reaction of nitrous acid with the 18-amino derivative III and the pyrroline V. In agreement with Černý, it was found that the major product was not an 18-hydroxy derivative of a diol or dione but a simple diol or dione. However, these latter materials did not possess the 18-nor-D-homo structure suggested by Černý but were found to be cyclopropane compounds related to II.

The diolamine III upon reaction with sodium nitrite in aqueous acetic acid yielded 35-45 per cent of 14 $\beta$ ,18-cyclo-pregnane-3 $\beta$ ,20-diol (VII), m.p. 170.0-171.5<sup>o</sup>,  $[\alpha]_D^{20}$  -4<sup>o</sup> (lit.<sup>4</sup> m.p. 170.5-172.0<sup>o</sup>,  $[\alpha]$  0<sup>o</sup>). The absence of a double bond was indicated by the low end absorption in the ultraviolet

<sup>6</sup> J. Hora and V. Černý, Coll. Czech. Chem. Comm. **26**, 2217 (1961).

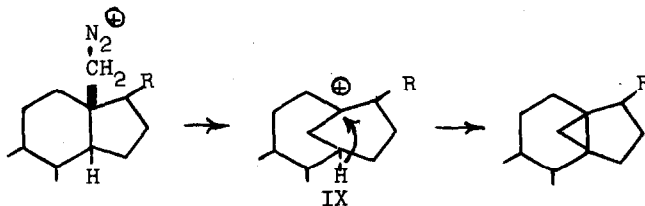


( $\epsilon_{205}^{500}$ ) and the lack of vinyl proton absorption in the NMR spectrum.

The presence of the cyclopropane ring was established by the presence in the NMR spectrum of a pair of doublets centered at 9.49 $\tau$  and 9.89 $\tau$  ( $J = 4.5$  cps).<sup>7</sup>

The pyrroline V was similarly treated with sodium nitrite in aqueous acetic acid and there was obtained 40-50 per cent of 14 $\beta$ ,18-cyclo-progesterone (VIII), m.p. 104-105°,  $[\alpha]_D +140^\circ$  (lit.<sup>6</sup> m.p. 104-105°,  $[\alpha]_D +147^\circ$ ). The NMR spectrum of VIII possessed a pair of doublets centered at 9.19 $\tau$  and 9.72 $\tau$  ( $J = 6$  cps).

It is suggested that the cyclopropane ring is formed by an intramolecular alkylation reaction involving the equivalent of the carbonium ion IX, the alkylation being facilitated by the spatial proximity of carbons 1 and 5 in the bicyclic ion.<sup>8</sup>



These results with angularly substituted aminomethyl groups on compounds derived from the steroidal amine, conessine, taken in conjunction

<sup>7</sup> The absorption of the nonequivalent protons of the cyclopropyl methylene group in tricyclo [4.3.1.0] decane was two doublets centered at 9.62 $\tau$  and 9.84 $\tau$  ( $J = 5$  cps).

<sup>8</sup> A similar bridging reaction of the cyclodecyl carbonium ion to form decalin has been reported by Cope, McLean and Nelson [*J. Amer. Chem. Soc.* **77**, 1648 (1955)].

with the results obtained with the simple hydrindane and decalin derivatives, clearly establish the generality of this deamination reaction and its utilization for the synthesis of tricyclo [4.3.1.0] decane systems.