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THE PREPARATION OF 14β,18-CYCLOSTEROIDS FROM N-DESMETHYL-N(20)-CONENE DERIVATIVES AND 18-AMINOSTEROIDS[1,2]

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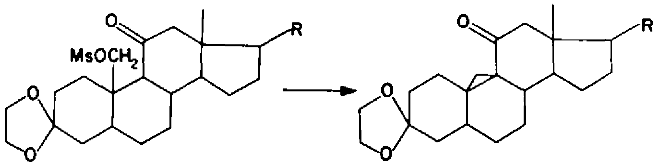
Abstract—14β,18-Cycloprogesterone (VI) was prepared by deamination of $\Delta^{4,20(N)}$-3-oxo-18,20-iminopregnadiene (III). Deamination of 18-amino-5α-pregnane-3β,20-diol (VII) afforded 14β,18-cyclo-5α-pregnane-3β,20-diol (VIII).

IN THE period of the last ten years, the steroid nucleus has been grossly modified in the course of the search for varied biological activities known to be associated with steroidal hormones. Recently, attention has been directed towards the preparation of structures in which the angular methyl groups have been functionalized.[3] These steroids with functionalized angular groupings also have been used to prepare other modified steroids in which the angular group is part of a cyclopropane ring. For example, an 11-oxo-19-mesylate derivative has been converted to a 9,19-cyclosteroid[4] and an 11-oxo-18-chloride has yielded a 12,18-cyclo material.[3] Also, 5,19-cyclosteroids have been prepared by solvolysis of Δ^5-19-tosyl derivatives[5] and by reduction of 3-oxo-Δ^4-tosyl derivatives with lithium in liquid ammonia.[6]



To prepare a 14,18-cyclosteroid by any of these processes would require an 18-hydroxy steroid containing functional groups in ring D and such precursors are not readily available. An alternate synthesis of such a cyclosteroid was suggested by earlier studies in this laboratory which were concerned with the reaction of angularly substituted groups on simple fused ring systems.[7] It was found that when

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[1] This work was supported in part by Grant No. CY-4284, U.S. Public Health Service.

[2] Preliminary communication in *Tetrahedron Letters* 453 (1962).

[3] For a summary of many of these modifications see V. Georgian, J. F. Kerwin, M. E. Wolff and F. F. Owings, *J. Amer. Chem. Soc.* **84**, 3594 (1962); and O. Halpern, R. Villotti and A. Bowers, *Chem. & Ind.* 116 (1963).

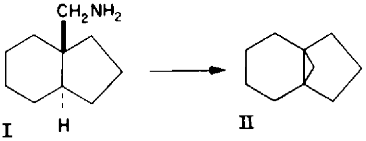
[4] H. Wehrli, M. S. Heller, K. Schaffner and O. Jeger, *Helv. Chim. Acta* **44**, 2162 (1961).

[5] J. J. Bonet, H. Wehrli and K. Schaffner, *Helv. Chim. Acta* **45**, 2615 (1962).

[6] L. H. Knox, E. Velarde and A. D. Cross, *J. Amer. Chem. Soc.* **85**, 2533 (1963).

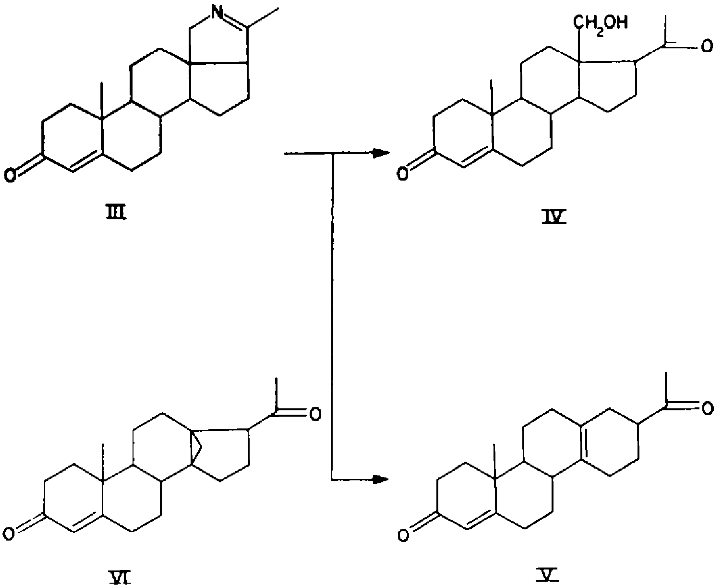
[7] W. G. Dauben, T. L. Westman and F. T. Bond, *Abstracts of* 141*st Meeting of the American Chemical Society* p. 29-O Washington, D.C., March 28 (1962).

trans-8hydrindanylcarbinylamine (I) was allowed to react with nitrous acid,



I II

tricyclo[4.3.1.0^{1,6}]decane (II) was formed in 74% yield. The applicability of this type of reaction in the steroid series was open to question, however, since the reaction of $\Delta^{4,20(N)}$-3-oxo-18,20-iminopregnadiene (III) with nitrous acid in acetic acid had been studied by Jeger[8] and the only product reported was the unrearranged 18-hydroxyl derivative IV. In contrast to these results, Hora and Černý[9] had reported that under the same conditions, III gave only 1·5% of IV. The major product obtained in 69% yield possessed the same number of oxygen atoms as the starting material and the material was tentatively assigned the rearranged structure V.[10] The formation of this



III IV VI V

latter product was in line with the earlier result obtained by the Czech workers in their study of the deamination of 18-amino-5α-pregnane-3β,20-diol.[11] The D-homosteroid structure postulated for these rearranged materials was simply based on the analogy of the deamination reaction with the Demjanov rearrangement. The composition of the rearranged materials, however, did not rule out a cyclosteroid structure related to II since such a material is isomeric with V.

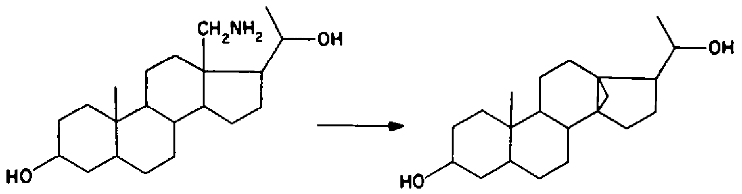
[8] F. Buzetti, W. Wicki, J. Kalvoda and O. Jeger, *Helv. Chim. Acta* **42**, 388 (1959).

[9] J. Hora and V. Černý, *Coll. Czech. Chem. Comm.* **26**, 2217 (1961).

[10] In the Belgian patent 585, 821, assigned to Ciba, Basel, it was reported that from this same reaction only 15·7% yield of 18-hydroxyprogesterone was obtained. It was also reported that there was obtained an oily material in 57% yield; this latter material which is most likely the same as the major product obtained by the Czech workers was not examined.

[11] V. Černý and F. Šorm, *Coll. Czech. Chem. Comm.* **25**, 2841 (1960).

The reaction of 18-amino-5α-pregnane-3β,20-diol (VII) with nitrous acid in acetic acid was reinvestigated and in agreement with Hora and Černý,[9] it was found that the major product was not an 18-hydroxy derivative of VII. The structure of the product was shown to be the cyclosteroidal diol VIII. The absence of an olefinic double bond in VIII was indicated by its low end absorption in the ultraviolet (ε_{205} 500) and the lack of vinyl proton absorption in its NMR spectrum. A structure such as V containing a tetrasubstituted double bond would be expected to exhibit an UV end absorption of about 8000.[12] The NMR spectrum of VIII possessed a pair of doublets centered at τ 9·49 and 9·89 (J = 4·5 cs). Such high field absorptions are characteristic of the two nonequivalent protons of a methylene group of a cyclopropane ring.[13] The finding of only doublets proved that the remaining two carbons of the cyclopropane ring were fully substituted. These data indicate the structure VIII for the major deamination product, thus making this material the first 14β,18-cyclosteroid to be prepared.[14]



VII VIII

The structure of the major deamination product for the reaction of the pyrroline III was also re-examined and it was shown that the material also possessed a similar 14β,18-cyclo structure VI since its NMR spectrum displayed the characteristic high field doublets (J = 6·0 cs) at τ 9·19 and 9·72. Thus, VI is 14β,18-cycloprogesterone.

The formation of a cyclopropane ring in the deamination of a simple primary amine has been shown to occur only to the extent of 10%.[15] The formation of such a ring system in 50–70% yield from a substituted neopentyl type amine, however, is quite exceptional since neopentylamine, itself, gives rise to no cyclopropane derivative on deamination.[15] In the deaminations involving angular aminoethyl groups, the first step in the reaction most likely is a Wagner-Meerwein rearrangement to form the bridgehead carbonium ion IX. Collapse of such a carbonium ion to form an olefin would be retarded since the resulting double bond would be highly strained by being at a bridgehead. On the other hand, alkylation of the carbonium ion by the other bridgehead carbon atom with concomitant loss of a proton would be facilitated by

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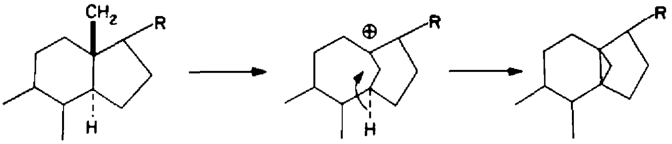
[12] R. A. Micheli and T. H. Applewhite, *J. Org. Chem.* **27**, 345 (1962).

[13] The absorption of nonequivalent protons of the methylene group of the cyclopropane ring in tricyclo[4.3.1.$0^{1,6}$]-decane was two doublets centered at τ 9·62 and 9·84 (J = 5·0 c/s).[7] Similar doublets have been reported in Δ^{23}-cycloartene-3β-25-diol by R. McCrundle and C. Djerassi (*Chem. & Ind.* 1311 (1961)), in 12,18-cyclosteroids,[3] and in 5,19-cyclosteroids.[6]

[14] After our preliminary publication[3] of these results, J. Hora, V. Černý, and F. Šorm, *Tetrahedron Letters* 501 (1962), *Coll. Czech. Chem. Comm.* **27**, 2771 (1962), independently established the 14β,18-cyclosteroid structures for the deamination products. The isomeric 17,18-cycloprogesterone has been reported by K. Heusler, J. Kalveda, P. Wieland, G. Anner and A. Wettstein, *Helv. Chem. Acta* **45**, 2575 (1962).

[15] P. S. Skell and I. Starer, *J. Amer. Chem. Soc.* **82**, 2971 (1960); M. C. Silver, *ibid.* **82**, 2971 (1960); M. C. Silver, *ibid.* **83**, 3482 (1961).



IX

the spacial proximity of the two carbon atoms. An analogous bridging reaction of the cyclodecyl carbonium ion to form decalin has been reported by Cope *et al.*[16] It is interesting to note that in the bicyclo[4.3.1]decyl carbonium ion IX, the equivalent of a cyclononane ring is held by the one carbon bridge in the conformation which makes a transannular reaction most favored.

EXPERIMENTAL[17]

Dihydroconessine series[18]

5,6-Dihydroconessine. The preparation of this compound has been described previously using a Pd-C catalyst.[19,20] In our hands, this catalyst gave impure product and the use of Pt as a catalyst was preferable.

A solution of 18·74 g (0·053 mole) conessine in 280 ml glacial acetic acid was added to a suspension of prehydrogenated Pt catalyst (generated from 1·87 g PtO) in 94 ml glacial acetic acid. The mixture was shaken with H_2 at room temp. and atm. press. for 30 hr (one mole equiv. H_2 was absorbed). The catalyst was removed by filtration, the filtrate concentrated (red. press.) to a small volume, and poured into NH_4OH aq. The precipitated material was removed by ether extraction and the ethereal solution washed with water and dried (Na_2SO_4). The ether was removed (red. press.) and the residual solid recrystallized from aqueous acetone, yield 16·0 g (85%), m.p. 104·5–106·0°, $[\alpha]_D$ +45° (*c* 1·4) [Lit.[19,20] m.p. 105·0–105·5°, $[\alpha]_D$ +46°]. By varying the rate of crystallization polymorphic forms of the compounds which melt at 71° and 97° could be obtained.

18-Amino-5α-pregnane-3β,20-diol (VII). The diolamine VII was prepared from 5,6-dihydroconessine following the procedure of Černý and Šorm.[11] The crude material was recrystallized 4 times from aqueous methanol. The pure compound showed a double m.p., first melting at 173–174°, then resolidifying and remelting at 220–225°. The $[\alpha]_D$ was +3·5° (THF, *c* 1·3) [Lit.[11] m.p. 242–244°, $[\alpha]_D$ +3°]. (Found: C, 74·84; H, 10·90; N, 3·99. Calc. for $C_{21}H_{37}O_2N$ (335·51): C, 75·15; H, 11·12; N, 4·18%).

14β,18-Cyclo-5α-pregnane-3β,20-diol (VIII). A solution of 170 mg (0·51 mmole) VII in 10 ml glacial acetic acid and 5 ml water was cooled to 0° and an ice-cold solution of 630 mg (9·1 mmoles) $NaNO_2$ in 4·5 ml water added. The resulting solution was allowed to stand for 7 hr at 0°, for 17 hr at 25°, and then diluted with water. The mixture was extracted with methylene chloride, the organic extract washed with $KHCO_3$ aq. followed by water, and dried (Na_2SO_4). The solvent was evaporated (red. press.) and the resulting brown solid chromatographed on alumina. Elution with benzene–ether (9:1) gave an oily product in 25% yield and was not examined further. Elution with benzene–ether (4:1) afforded 86 mg (53%) crude 14β,18-cyclo-5α-pregnane-3β,20-diol. The product was recrystallized from aqueous methanol and aqueous acetone to yield white plates, m.p. 170·0–171·5°, $[\alpha]_D$

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[16] A. C. Cope, D. C. McLean and N. A. Nelson, *J. Amer. Chem. Soc.*, **77**, 1628 (1955).

[17] The m.ps were determined in evacuated sealed capillary tubes and the temps are corrected. Unless otherwise stated, optical rotations and IR spectra were measured in chloroform solution. The NMR spectra were observed in deuterochloroform, using TMS as an internal standard. All chromatographies were conducted with Woelm neutral alumina (Act. III). All analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

[18] The reaction sequence in this series has been described, in detail, by Černý and Šorm.[11] Experimental procedures will only be given where it is essential to show the exact conditions of the reaction and/or the properties of the product.

[19] E. S. Späth and O. Hromatka, *Ber. Dtsch. Chem. Ges.* **63**, 126 (1930).

[20] R. D. Haworth, J. McKenna and G. W. Whitfield, *J. Chem. Soc.* 3127 (1949).

−4° (c, 1·3) [Lit.[11] m.p. 170·5–172·0°, [α]$_D$ 0°]. The IR spectrum displayed maxima at 3650, 3480 and 3030 cm^{-1}. (Found: C, 79·31; H, 10·59. Calc. for $C_{21}H_{34}O_2$ (318·48): C, 79·19; H, 10·76%).

Conessine series[21]

N,N′-Dicyanoconimine. A solution of 15·06 g (43·2 mmoles) conessine in 1·5 l. benzene was dried by distillation of 170 ml. benzene. A solution of 9·3 g (88 moles) cyanogen bromide in 170 ml dry benzene was added and the solution allowed to stand 2 hr at 50°. The precipitate was removed by filtration and the filtrate concentrated (red. press.). The residue was crystallized from methanol, yield 3·63 g, m.p. 170·0–171·5° [α]$_D$ +63° (c, 1·2). The mother liquors were chromatographed on alumina and elution with hexane–benzene (1:1) and with benzene gave an additional 3·11 g dicyano compound, m.p. 169·0–171·5°, total yield 41·5% [Lit.[8] m.p. 170–171°, [α]$_D$ 65°].

Conimine. A mixture of 7·51 g (19·4 mmoles) N,N′-dicyanoconimine, 135 g (2·4 moles) KOH, 540 ml methanol, and 85 ml water was heated under reflux for 48 hr. A 200 ml portion of the solvent was removed by distillation, the resulting mixture filtered, and the filtrate cooled to 0°. The fine white needles which formed were separated and washed with water, m.p. 130–132°, yield 6·15 g (96%). A sample was recrystallized from aqueous methanol, m.p. 131·5–133·5°, [α]$_D$ −26° (c, 1·02) [Lit.[8] m.p. 131–132°, [α]$_D$ −29°].

N,N′-*Dichloroconimine.* To a stirred, ice-cold solution of 5·97 g (18·1 mmoles) conimine in 600 ml dry ether, 4·83 g (36·2 mmoles) freshly prepared N-chlorosuccinimide suspended in 600 ml dry ether was added slowly. The stirring was continued for an additional 30 min without cooling and the clear solution was washed 3 times with water and dried (Na_2SO_4). The ether was removed (red. press.) and the residue recrystallized from benzene–methanol, yield 5·89 g (81·5%), [α]$_D$ +31·5° (c, 1·41) [Lit.[8] [α]$_D$ +29°]. The white needles upon heating in a sealed capillary turned to yellow and brown between 105–220°, sintered at 230°, and decomposed at 250°.

N-*Desmethyl*-4,N(20)-*conadiene*-3-*one* (III). A solution of 5·66 g (14·2 mmoles) N,N′-dichloroconimine in 660 ml dry methanol containing sodium methoxide (prepared by allowing 6.6 g (0·29 g atom) Na to dissolve in the solvent) was slowly heated to reflux and then allowed to reflux 30 min. The solvent was removed (red. press.) at bath temp. 30–35° and the residual solid was dissolved in 500 ml 2N H_2SO_4. The acid solution was allowed to stand 12 hr and then basified with conc. NH_4OH aq. The mixture was extracted with a mixture of methylene chloride–ether and the organic extract washed with water and dried. The solvent was removed (red. press.) and the solid residue chromatographed on alumina. The pyrroline III was eluted with benzene and was recrystallized from benzene–hexane, yield 786 g (17%), m.p. 178–183° (dec). A sample was recrystallized from acetone–hexane, m.p. 183–185°, [α]$_D$ +92° (c, 0·75) [Lit.[8] m.p. 181–182°, [α]$_D$ +84°].

14β,18-*Cycloprogesterone* (VI). A solution of 748 mg (2·4 mmoles) pyrroline III in 93 ml 4:1 acetic acid–water was treated at 0° with a solution of 1·5 g (21·7 mmoles) $NaNO_2$ in 18 ml water and allowed to stand 24 hr at 0°. The reaction mixture was processed as described for the preceding deamination and the product chromatographed. A 1:1 mixture of hexane–benzene eluted 386 mg (50%) 14β,18-cycloprogesterone which was recrystallized from acetone–hexane, m.p. 103–104°, [α]$_D$ +140° (c, 0·96) [Lit.[8] m.p. 104–105°, [α]$_D$ +147°]. (Found: C, 80·86; H, 8·97. Calc. for $C_{21}H_{28}O_2$ (312·44): C, 80·73; H, 9·03%). The IR spectrum showed bands at 1615, 1650, 1695 and 3010 cm^{-1}.

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[21] The synthesis of N-desmethylconane-4,N(20)-diene-3-one has been reported by Jeger *et al.*[8] but no experimental details or yields were given.