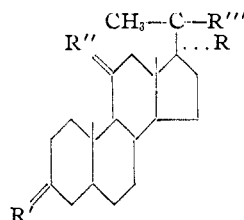


TABLE I

PHYSICAL CONSTANTS AND YIELD DATA:



R'	R''	R'''	Yield, %	M.p. °C. <sup>(a)</sup>	[α] <sub>D</sub> <sup>(b)</sup>	Empirical Formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	Recrystallization solvent
R = H									
	O		85	128.4-129.6	+ 55.1	C <sub>23</sub> H <sub>36</sub> O <sub>4</sub>	73.36 73.68	9.64 9.96	Methanol-water
			87	159.8-160.4	+ 67.1	C <sub>23</sub> H <sub>38</sub> O <sub>4</sub>	72.97 72.86	10.12 10.45	Methanol-water
		O	85	216.0-217.6 <sup>c</sup>	+132.9	C <sub>21</sub> H <sub>34</sub> O <sub>3</sub>	75.40 75.22	10.25 10.55	Methanol-water
	O		91	125.4-127.0	+ 53.9	C <sub>23</sub> H <sub>38</sub> O <sub>5</sub>	71.74 71.92	9.15 8.84	Methanol-water
			91	138.5-139.5	+ 61.0	C <sub>23</sub> H <sub>40</sub> O <sub>5</sub>	71.39 71.10	9.59 9.91	Methanol-water
O		O	85	174.0-175.0	+135.0	C <sub>21</sub> H <sub>32</sub> O <sub>3</sub>	75.86 75.68	9.70 9.79	Methanol-water
		O		178.8-179.6 <sup>d</sup>	+135.9	C <sub>23</sub> H <sub>36</sub> O <sub>4</sub>	73.36 73.64	9.64 9.84	Methanol-water
R = OH									
	O		94	149.6-150.4	+ 28.7	C <sub>23</sub> H <sub>38</sub> O <sub>5</sub>	70.37 70.33	9.25 9.55	Acetone-hexane
			100	179.0-180.5	+ 21.7	C <sub>23</sub> H <sub>38</sub> O <sub>5</sub>	70.01 70.00	9.71 9.50	Acetone-water
		O	95	224.0-227.0	+ 70.6	C <sub>21</sub> H <sub>34</sub> O <sub>4</sub>	71.96 71.73	9.78 9.57	Acetone-water
	O		93	182.5-183.5	+ 30.8	C <sub>23</sub> H <sub>38</sub> O <sub>6</sub>	69.09 69.38	8.81 9.13	Methanol-water
			96	181.0-182.4	+ 30.1	C <sub>23</sub> H <sub>40</sub> O <sub>6</sub>	68.77 68.97	9.24 9.56	Methanol
O		O	95	213.2-214.4	+ 69.6	C <sub>21</sub> H <sub>32</sub> O <sub>4</sub>	72.38 72.37	9.26 9.44	Methanol
		O		189.0-190.4	+ 82.7	C <sub>23</sub> H <sub>36</sub> O <sub>5</sub>	70.37 70.20	9.25 9.19	Methanol-water

<sup>a</sup> All m.p.s. are corrected. <sup>b</sup> All rotations in acetone, in a one-decimeter tube, at a concentration of ca. 1%. <sup>c</sup> Reported (ref. 8), m.p. 222-225°. <sup>d</sup> Reported (ref. 8) m.p. 182-184°, [α]<sub>D</sub>+147.5° (acetone).

of water was refluxed overnight. The solution was filtered hot, water added to incipient crystallization and the mixture was chilled and filtered; yield 9.6 g., m.p. 181.0-182.4°.

**Pregnan-11β,17α-diol-3,20-dione.**—A solution of 8.5 g. of the 11β-hydroxybisketal in 25 ml. of acetic acid and 10 ml. of water was warmed on the steam-bath for 0.5 hour. Water was added to induce crystallization and the mixture was chilled and filtered. There was formed 6.1 g. (95%) of di-one, m.p. 213.2-214.4°.

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### 11-Oxygenated Steroids. IV. The Selective Reduction of Steroidal 11,20-Diketones with Sodium Borohydride<sup>1</sup>

BY EUGENE P. OLIVETO AND E. B. HERSHBERG

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The selective reducing action of sodium borohydride toward steroidal diketones has been re-

(1) For the previous paper in this series, cf. E. P. Oliveto, T. Clayton and E. B. Hershberg, *This Journal*, **75**, 486 (1953).

ported previously.<sup>2</sup> Heymann and Fieser<sup>2a</sup> observed that gentle reduction of 3,11-diketocholic acid with this reagent gave an 85% yield of crude 3-( $\alpha$  and  $\beta$ )-hydroxy-11-keto-cholic acid, and Elisberg, Vanderhaeghe and Gallagher<sup>2b</sup> reduced etiocholan-3,17-dione to a mixture of 70% of etiocholan-3 $\alpha$ -ol-17-one and 15% of etiocholan-3 $\beta$ -ol-17-one. Similarly, lithium borohydride has been observed<sup>3</sup> to reduce cortisone acetate 3-monosemicarbazone in part to Reichstein's Substance U ( $\Delta^4$ -pregnen-17 $\alpha$ ,20 $\beta$ ,21-triol-3,11-dione)-3-semicarbazone, although the authors believed that this selective reduction was associated with the decreased solubility of the product since they noted partial separation of material during the reaction. The present work describes the action of sodium borohydride on two other steroidal 11,20-diketones.

In an attempt to prepare pregnan-3 $\alpha$ ,11 $\beta$ ,20 $\beta$ -triol (IV, R = H) a solution of pregnan-3 $\alpha$ -ol-11,20-dione (I, R = H) and sodium borohydride in aqueous methanol was allowed to react at room temperature. A product, first believed to be the desired compound IV, separated almost immediately. The infrared spectrum, however, indicated the presence of a six-membered ring ketone and the material was tentatively identified as pregnan-3 $\alpha$ ,20 $\beta$ -diol-11-one (II, R = H).

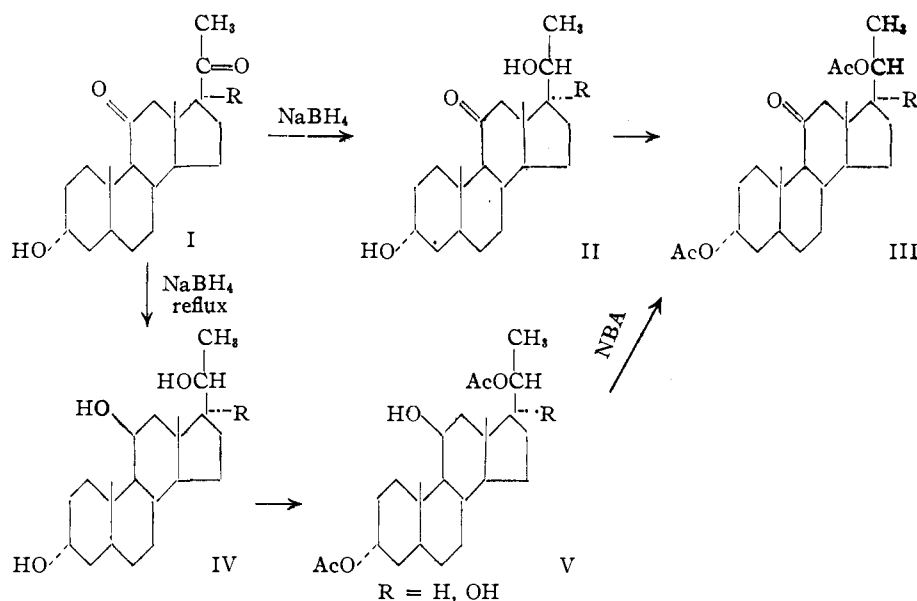
When the reaction was repeated on pregnan-3 $\alpha$ ,17 $\alpha$ -diol-11,20-dione (I, R = OH), no crystals separated, but the product obtained by dilution with water still contained a six-membered ring ketone and was assigned the structure pregnan-3 $\alpha$ ,17 $\alpha$ ,20 $\beta$ -triol-11-one (II, R = OH).

The proof of structure of these compounds was accomplished as follows: The 11,20-diketones (I) were reduced completely to the corresponding 11 $\beta$ ,20 $\beta$ -diols (II) by refluxing overnight with sodium borohydride in aqueous methanol. The alcohols were then acetylated, producing the diacetates (V). These were oxidized in high yield by means of N-bromoacetamide to the 11-keto-3 $\alpha$ ,20 $\beta$ -diacetates (III), which have been prepared previously<sup>4</sup> through a different route by Sarett.

This sequence of reactions not only proves the course of the partial reduction of these 11,20-diketones, but also establishes that sodium borohydride reduces a 20-carbonyl group predominantly to the

20 $\beta$ -hydroxy configuration. It is interesting to note, however, that the yields, both on partial (I  $\rightarrow$  II) and complete (I  $\rightarrow$  IV) reduction in the series when R = OH, are significantly lower than when R = H. This may be another example<sup>5</sup> of the influence of the 17-substituent on the course of the reduction of a 20-carbonyl group.

No attempt was made to establish conditions of time, temperature and concentration necessary to obtain the optimum yields of the 11-keto compounds (II) by selective reduction of the 20-carbonyl group in I.



#### Experimental<sup>6</sup>

**Pregnan-3 $\alpha$ ,11 $\beta$ ,17 $\alpha$ ,20 $\beta$ -tetrol (IV, R = OH).**—This compound has been prepared previously in 74% yield<sup>7</sup> in these laboratories by the reduction of pregnan-3 $\alpha$ ,17 $\alpha$ -diol-11,20-dione with sodium borohydride.

Its 3,20-diacetate (V, R = OH) prepared by the action of acetic anhydride and pyridine on IV (R = OH) melted at 111.0–112.2° solidified and remelted at 186.2–187.5°,  $[\alpha]_D^{25} +67.7^\circ$  (acetone). It crystallized from aqueous methanol as the monohydrate.

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{40}\text{O}_6 \cdot \text{H}_2\text{O}$ : C, 66.05; H, 9.31. Found: C, 65.81; H, 9.07.

**Pregnan-3 $\alpha$ ,11 $\beta$ ,20 $\beta$ -triol (IV, R = H).**—In a manner similar to the preparation of IV (R = OH), pregnan-3 $\alpha$ ,11 $\beta$ ,20 $\beta$ -triol was prepared from pregnan-3 $\alpha$ -ol-11,20-dione by refluxing overnight with sodium borohydride. The triol, obtained in 85% yield, had m.p. 233–235°,  $[\alpha]_D^{25} +38.9^\circ$  (dioxane).

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{38}\text{O}_3$ : C, 74.94; H, 10.78. Found: C, 75.10; H, 10.56.

The 3,20-diacetate (V, R = H) melted at 119.0–120.4°,  $[\alpha]_D^{25} +67.8^\circ$  (acetone).

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{40}\text{O}_5$ : C, 71.39; H, 9.59. Found: C, 71.07; H, 9.84.

**Pregnan-3 $\alpha$ ,20 $\beta$ -diol-11-one (II, R = H).**—A solution of 2 g. of sodium borohydride in 5 ml. of water was added at room temperature to a solution of 1 g. of pregnan-3 $\alpha$ -ol-11,-

(5) P. L. Julian, F. W. Meyer, W. J. Karpel and W. Cole, *ibid.*, **73**: 1982 (1951).

(6) All melting points are corrected. All rotations were taken in a 1-decimeter tube at a concentration of about 1%. We are indebted to Mr. Edwin Conner, Mrs. Alice Barrella, Mrs. Elizabeth McEntire and Miss Joan Mustachio for the analytical and rotational data, and to Dr. William Tarpley, Miss Betty Blasko and Miss Cecelia Vitiello for the infrared data.

(7) H. Herzog, M. Jevnik, P. Perlman, A. Nobile and E. B. Hershberg, *THIS JOURNAL*, **75**, 266 (1953).

(2) (a) H. Heymann and L. F. Fieser, *THIS JOURNAL*, **73**, 5252 (1951); (b) E. Elisberg, H. Vanderhaeghe and T. F. Gallagher, *ibid.*, **74**, 2814 (1952).

(3) N. L. Wendler, Huang-Minlon and M. Tishler, *ibid.*, **73**, 3818 (1951).

(4) (a) L. H. Sarett, *ibid.*, **70**, 1690 (1948); (b) L. H. Sarett, *ibid.*, **71**, 1169 (1948).

20-dione in 15 ml. of methanol. Almost immediately, crystals began to form. After allowing the mixture to stand overnight, the precipitate was collected with suction; yield 0.8 g., m.p. 230–232°. The analytical sample, crystallized once more from aqueous methanol, melted at 231.4–232.6°,  $[\alpha]_D +31.2^\circ$  (acetone), reported<sup>4a</sup> m.p. 236–238°.

*Anal.* Calcd. for  $C_{21}H_{34}O_5$ : C, 75.40; H, 10.25. Found: C, 75.32; H, 10.15.

This compound was not identical with that obtained by refluxing I (R = H) with sodium borohydride overnight, for the infrared spectrum disclosed that a carbonyl group in a six-membered ring was still present in the former.

The 3,20-diacetate melted at 156.2–157.0°,  $[\alpha]_D +69.3^\circ$  (acetone).

There was no hydroxyl peak present in the infrared spectrum and no m.p. depression was obtained on admixture with an authentic sample<sup>8</sup>; reported<sup>4a</sup> m.p. 160.5–161.0°.

*Anal.* Calcd. for  $C_{26}H_{38}O_5$ : C, 71.74; H, 9.15. Found: C, 72.05; H, 9.37.

**Pregnan-3 $\alpha$ ,17 $\alpha$ ,20 $\beta$ -triol-11-one (II, R = OH).**—When pregnan-3 $\alpha$ ,17 $\alpha$ -diol-11,20-dione (I, R = OH) was allowed to react at room temperature overnight with sodium borohydride in aqueous methanol, no crystals formed and only pregnan-3 $\alpha$ ,11 $\beta$ ,17 $\alpha$ ,20 $\beta$ -tetrol was isolated in good yield. If the reaction was halted at the end of three hours by the addition of water and extraction with chloroform, it was possible to obtain a 55% yield of pregnan-3 $\alpha$ ,17 $\alpha$ ,20 $\beta$ -triol-11-one, m.p. 218–220°, after recrystallization of the chloroform residue from aqueous methanol. The analytical sample, crystallized once more, had a m.p. of 219.0–220.6°,  $[\alpha]_D +36.0$  (acetone), reported<sup>4b</sup> m.p. 220°,  $[\alpha]_D +38^\circ$ .

*Anal.* Calcd. for  $C_{21}H_{34}O_4$ : C, 71.95; H, 9.79. Found: C, 72.07; H, 10.01.

The infrared spectrum indicated the presence of a carbonyl group in a six-membered ring.

The 3,20-diacetate had a m.p. of 245.0–246.2°,  $[\alpha]_D +72.7^\circ$  (acetone) and did not depress the m.p. of an authentic sample<sup>8</sup>; reported<sup>4b</sup> m.p. 249–250°.

*Anal.* Calcd. for  $C_{26}H_{38}O_6$ : C, 69.09; H, 8.81. Found: C, 68.98; H, 8.99.

**Oxidation of Pregnan-3 $\alpha$ ,11 $\beta$ ,20 $\beta$ -triol 3,20-Diacetate (V, R = H).**—To a solution of 1.0 g. of V (R = H) in 10 ml. of acetone was added a solution of 635 mg. of N-bromoacetamide in 2 ml. of water and the mixture was placed in a refrigerator at 5° for 1 hour. The excess oxidizing agent was destroyed by the addition of 1 g. of sodium sulfite in 5 ml. of water; then excess water was added to precipitate the product completely; yield 0.95 g. of III (R = H), m.p. 159–160°. One crystallization from methanol raised the m.p. to 160.4–161.0°,  $[\alpha]_D +69.3^\circ$  (acetone).

This product gave no m.p. depression on admixture with pregnan-3 $\alpha$ ,20 $\beta$ -diol-11-one 3,20-diacetate obtained above, and the infrared spectra were identical.

*Anal.* Calcd. for  $C_{25}H_{36}O_6$ : C, 71.74; H, 9.15. Found: C, 71.43; H, 9.44.

**Oxidation of Pregnan-3 $\alpha$ ,11 $\beta$ ,17 $\alpha$ ,20 $\beta$ -tetrol 3,20-Diacetate (V, R = OH).**—In an analogous fashion, 1.0 g. of V (R = OH) was oxidized to the corresponding 11-ketone III (R = OH) with N-bromoacetamide; yield 0.89 g., m.p. 235–238°. One crystallization from methanol raised the m.p. to 245.2–246.2°,  $[\alpha]_D +72.1^\circ$  (acetone).

This product gave no m.p. depression on admixture with pregnan-3 $\alpha$ ,17 $\alpha$ ,20 $\beta$ -triol-11-one 3,20-diacetate obtained above, and the infrared spectra were identical.

*Anal.* Calcd. for  $C_{25}H_{36}O_6$ : C, 69.09; H, 8.81. Found: C, 68.84; H, 9.00.

(8) Kindly supplied by Dr. L. H. Sarett.

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## Complexes of Boron Trifluoride with Amides

BY EARL L. MUETTERTIES<sup>1</sup> AND EUGENE G. ROCHOW

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Systems of boron trifluoride with formamide, acetamide and dimethylformamide have been

(1) Procter and Gamble Fellow in Chemistry, Harvard University, 1951–1952.

investigated. Each of the amides was found to add one mole of boron trifluoride; however, only the complex with dimethylformamide was sufficiently stable and non-reactive to allow purification. The lower reactivity and higher thermal stability of this particular complex is attributed to the greater basic strength of the nitrogen and to the absence of a hydrogen atom on the nitrogen.

### Experimental

**Reagents.**—Matheson tank boron trifluoride was subjected to a series of bulb-to-bulb vacuum distillations and was found to be spectroscopically free of silicon tetrafluoride.

Du Pont "stabilized" tetrahydrofuran was refluxed over sodium hydroxide for 24 hours and distilled. The distillate was refluxed over lithium aluminum hydride for seven hours and was again distilled.  $BF_3 \cdot O(CH_2)_4$  was prepared by passing boron trifluoride into tetrahydrofuran at 0° until there was no further take-up of the gas. The crude etherate was distilled collecting the fraction boiling at 58° and 1.2 mm.

Paragon "99%" formamide was triply distilled at 4 mm. pressure. The distillate however retained a slight odor of hydrogen cyanide. Eastman Kodak acetamide was distilled and the fraction boiling at 221–223° and atmospheric pressure was recrystallized from chloroform. The water in du Pont "Technical" dimethylformamide was removed by azeotropic distillation with benzene and then the amide was distilled. The fraction boiling at 152° and atmospheric pressure was collected.

**Dimethylformamide-Boron Trifluoride.**—Nine-hundredths of a mole of dimethylformamide was dissolved in 20 g. of tetrahydrofuran, and this was slowly added to a stirred solution of 0.1 mole of boron trifluoride-tetrahydrofuran etherate in 10 g. of tetrahydrofuran at 0°. After the addition was complete, most of the solvent was removed at reduced pressure. The solid material then was recrystallized from tetrahydrofuran. Fluorine was determined by the lead chlorofluoride method after the complex had been decomposed by base.<sup>2</sup>

*Anal.* Calcd. for  $C_3H_7ONBF_3$ : C, 25.57; H, 5.01; F, 40.45. Found: C, 25.54; H, 5.29; F, 39.81, 39.46, 39.98.

Dimethylformamide boron trifluoride melts at 58–59° (uncor.) and distils at 100° and 0.1 mm. Samples purified by vacuum distillation had sharper melting points than those purified by recrystallization from tetrahydrofuran or ethanol. The carbonyl band of the amide at 5.9  $\mu$  was not shifted in the infrared spectrum of the complex. The complex was immediately decomposed by water. The specific conductance of a 0.01 M solution, 30 millimhos, did not change significantly with time. Moreover, addition of nitron acetate to a fresh solution gave an immediate and large precipitation of nitron fluoborate. In contrast to its reactivity toward water, the complex was quite stable toward boiling ethanol. A half-gram sample of the compound was dissolved in 75 cc. of ethanol and the solution was refluxed for three days, after which time the complex was almost completely recovered. The stability of this complex of a tertiary amine toward heat and alcohols could well be due to the absence of a hydrogen atom on the nitrogen atom, disallowing dehydrohalogenation.

**Formamide and Acetamide Complexes.**—Attempted preparations of the addition compounds of formamide and acetamide with boron trifluoride in solution failed to produce crystalline material; only oils were obtained. To establish the stoichiometry of the reactions, boron trifluoride was added to a weighed sample of the amide in a vacuum system. When no further decrease in the pressure of the system took place, the reaction tube was evacuated and weighed.

	Formamide		Acetamide	
Amide, mmoles	6.68	3.62	6.84	6.89
BF <sub>3</sub> , mmoles	6.80	3.57	6.72	6.92
Mole fr. BF <sub>3</sub> /amide	1.018	0.986	0.985	1.001

The results clearly indicate the existence of one-to-one

(2) J. I. Hoffman and G. E. F. Lundell, *Bur. Stand. J. Res.*, **3**, 581 (1929).