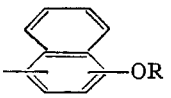
TABLE II

NAPHTHYL ALKAMINE ETHERS



	R′	R	Yield, %	B.p., °C.	Mm.	M.p., °C. hydrochloride	Formula	Calcd. C	Calcd. H	Analyses, % Found N	Found C	Found H	Found N
1	H	1-$CH_2CH_2CH_2N(C_2H_5)_2$	57.5	174–175	3.8		$C_{17}H_{23}NO$			5.44			5.55
2	H	2-$CH_2CH_2CH_2N(C_2H_5)_2$[a]	32	172	3.2	114–115	$C_{17}H_{23}NO$			5.42			5.52
							$C_{17}H_{23}NO\cdot HCl$	69.49	8.23		68.76	8.26	
3	4-OCH_3	1-$CH_2CH_2CH_2N(C_2H_5)_2$	31.4	203	4.4	167–170	$C_{18}H_{25}NO_2$	75.23	8.77		75.45	8.52	
4	H	1-$CH_2CHN(C_2H_5)_2$ (CH$_3$)	54	155–156	1.8		$C_{17}H_{23}NO$	79.34	9.01		79.60 79.48	8.67 8.73	

[a] Reference 1a b.p. 202° (18 mm.). [b] Reference *b*, Table I.

(0.005 mole), was dissolved in 25 ml. of dry xylene and stirred, while α-methylbenzylamine, 1.2 g. (0.01 mole), dissolved in dry xylene, was added dropwise. The solution was stirred and refluxed for 16 hours, the clear solution was washed with water and the xylene was dried. The addition of ethereal hydrogen chloride yielded a small amount of pasty material. Fresh dry ether was added three times and decanted. The paste slowly crystallized and the crude product melted at *ca.* 110°. A small portion was dissolved in a minimum amount of isopropyl alcohol and diluted with several volumes of dry ether. After standing four days at about 5°, the product crystallized. This material was recrystallized again and dried *in vacuo* at 56°; m.p. 114–115°.

Method B.—γ-Diethylaminopropyl 4-methoxynaphthyl ether: five and six-tenths grams of potassium hydroxide (0.1 mole) was dissolved in 150 ml. of ethyl alcohol by refluxing and 17.4 g. (0.1 mole) of 4-methoxy-1-naphthol[4] was added to the boiling solution. The solution became dark red almost at once and 14.9 g. (0.1 mole) of γ-diethylaminopropyl chloride (dissolved in a little alcohol) was dropped in rapidly. The mixture was then refluxed for 48 hours, cooled and filtered to remove the potassium chloride. The alcohol was removed under vacuum on the steam-bath and the residue was dissolved in dilute hydrochloric acid with cooling. The aqueous acid was then shaken once with ether and the layers were separated. The aqueous layer was made strongly basic with 40% sodium hydroxide and the oil which separated was extracted into ether and/or benzene. The organic layer was dried, the solvent removed under vacuum and the product was distilled. The red product boiled at 203° (4.4 mm.); $n^{24.5}D$ 1.5624.

(4) Prepared by M. Freifelder and G. R. Stone according to German Patent 234,411. The melting point of the purple compound was 123°. (The patent value is 131°.)

Acknowledgment.—The high pressure reactions were carried out by Morris Freifelder and G. R. Stone. All microanalyses were performed by E. F. Shelberg, Chief Microanalyst, and his staff.

NORTH CHICAGO, ILL. RECEIVED NOVEMBER 27, 1950

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Epimeric 20-Hydroxypregnene Derivatives[1]

BY RICHARD B. TURNER AND DOROTHY M. VOITLE

Catalytic hydrogenation of *i*-pregnenolone methyl ether followed by benzoylation and treatment with zinc acetate and acetic acid furnishes a mixture of 3β-acetoxy-20α- and 20β-benzoyloxy-Δ⁵-pregnene. Separation of the pure epimers can be accomplished by chromatography. These substances, on partial hydrolysis, afford the corresponding 3β-hydroxy derivatives, which yield the benzoates of Δ⁴-pregnene-20α-ol-3-one and Δ⁴-pregnene-20β-ol-3-one when subjected to Oppenauer oxidation. Lithium aluminum hydride reduction of Δ⁵-pregnene-3β-ol-20-one likewise yields a mixture of epimers, but separation of the products as the free diols or as the diacetates is impracticable. Earlier work of Marker on the conversion of pregnane-3α-ol-20-one into pregnane-20β-ol-3-one has been repeated and the intermediates have been isolated.

Syntheses of Δ⁴-pregnene-20α-ol-3-one[2,3] and of the corresponding 20β-hydroxy derivative from 3β-hydroxy-Δ⁵-norcholene-22-one and from 3β-hydroxy-Δ⁵-20-iso-norcholene-22-one, respectively, have recently been reported by Wieland and Miescher.[4] We have also had occasion to prepare these substances, as well as certain related pairs of C.20 epimers, and have employed a somewhat different procedure, for which Δ⁵-pregnene-3β-ol-20-one served as starting material. The results of this investigation are described in the present communication.

Δ⁵-Pregnene-3β-ol-20-one was first converted into *i*-pregnenolone methyl ether[5] (I), which was then hydrogenated over Raney nickel in alcohol solution. The resulting oily product was benzoylated directly and, after treatment with acetic acid and zinc acetate, furnished a mixture of 3β-acetoxy-20α-benzoyloxy-Δ⁵-pregnene (IIa) and 3β-acetoxy-20β-benzoyloxy-Δ⁵-pregnene (IIb), which could be readily separated by chromatography on alumina. The two C.20 epimers (IIa and IIb) were obtained from *i*-pregnenolone methyl ether in a combined yield of 80%, the ratio of IIb to IIa being about 3:2.

Configurations assigned to these substances are based on the following evidence. Saponification of the lower melting isomer (IIa) gave Δ⁵-pregnenediol-3β,20α (m.p. 182–183.5°), whereas hydrolysis of the higher melting derivative (IIb) yielded Δ⁵-pregnenediol-3β,20β (m.p. 211–211.5°).[4] The corresponding diacetates melted at 145.5–146° and at 138.5–140°,[6] respectively. Hydrogenation of the diacetate (m.p. 146°) derived from

(1) This work was supported by funds provided by the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

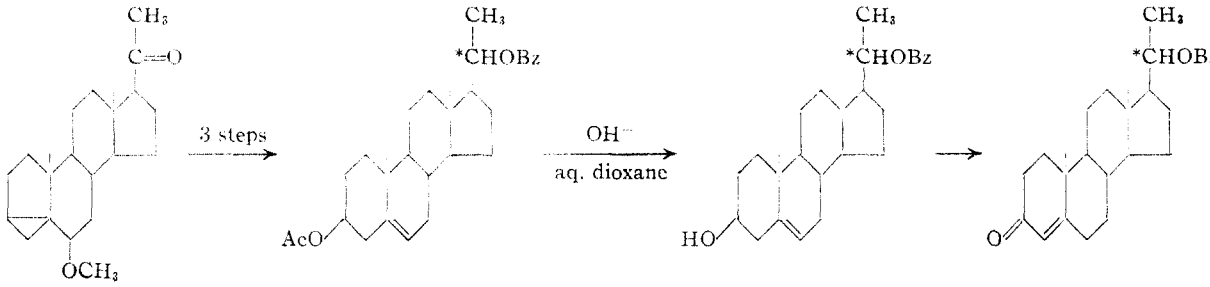
(2) A. Butenandt and J. Schmidt, *Ber.*, **67**, 2092 (1934).

(3) The designations 20α and 20β are used in the sense discussed by L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948); see also L. H. Sarett, THIS JOURNAL, **71**, 1165, 1169, 1175 (1949), and W. Klyne and D. H. R. Barton, *ibid.*, **71**, 1500 (1949).

(4) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(5) A. Butenandt and W. Grosse, *Ber.*, **70**, 1446 (1937).

(6) Wieland and Miescher (ref. 4) report a melting point of 125–126° for this compound.



IIa furnished the known allopregnanediol-3β,20α diacetate[7] melting at 165–167°. Similarly, allopregnanediol-3β,20β diacetate,[8] was obtained by hydrogenation of Δ⁵-pregnenediol-3β,20β diacetate (m.p. 140°) obtained from IIb.

Direct crystallization of the mixture of IIa and IIb, formed from *i*-pregnenolone methyl ether as previously described, afforded an apparently homogeneous substance, m.p. 132.5–133.5°, in about 70% yield. Comparison of the specific rotation (−47.6°) of this material with the specific rotations of pure samples of IIa (−14.5°) and of IIb (−88.8°) indicated that the product is an aggregate containing one molecule of IIa for each molecule of IIb, and it can in fact be prepared by crystallization of a mixture of equal parts of the two pure epimers.

Partial hydrolysis of IIa and of IIb proceeded smoothly in aqueous dioxane solution in the presence of one equivalent of sodium hydroxide and gave the corresponding 3β-hydroxy-20α- and 20β-benzoyloxy-Δ⁵-pregnenes (IIIa and IIIb) in yields of better than 90%. Partial saponification with sodium hydroxide in methanol was less satisfactory. The odor of methyl benzoate could be detected in the reaction mixture, an observation that suggests the occurrence of base-catalyzed ester interchange in addition to hydrolysis. Since the base is not consumed in the ester interchange reaction, hydrolysis under these conditions can proceed beyond the desired point.

3β-Hydroxy-20α-benzoyloxy-Δ⁵-pregnene (IIIa) and 3β-hydroxy-20β-benzoyloxy-Δ⁵-pregnene (IIIb) were oxidized by the Oppenauer procedure and yielded, respectively, Δ⁴-pregnene-20α-ol-3-one benzoate (IVa) and Δ⁴-pregnene-20β-ol-3-one benzoate (IVb). The physical constants of the free keto-alcohols and of the corresponding acetyl derivatives from these substances are in substantial agreement with the values reported by Wieland and Miescher.[4]

As an alternative to the procedure described in the preceding paragraphs we have explored the reduction of Δ⁵-pregnene-3β-ol-20-one acetate[9] with lithium aluminum hydride. Although stereospecific reductions of carbonyl groups at C.11[10] and at C.17[11] by this reagent have been observed, pregnenolone acetate furnished a mixture of stereoisomeric diols, which, however, could not be separated by fractional crystallization. Chromatography of the corresponding diacetates yielded Δ⁵-pregnenediol-3β,20β diacetate, m.p. 138.5–140°, and a substance melting at 104–105.5°. Δ⁵-Pregnenediol-3β,20α diacetate could not be isolated. Subsequent investigation showed that the low melting product can be prepared by crystallization of equal amounts of the two epimeric diacetates, and it is hence presumably a molecular compound.

In 1937 Marker and his collaborators[7,12] described the preparation of pregnane-20β-ol-3-one from pregnane-3α-ol-20-one by a series of reactions involving hydrogenation (Pt), acetylation, partial hydrolysis, oxidation and, finally, hydrolysis of the resulting acetoxy ketone. The only intermediate isolated by these investigators was pregnanediol-3α,20β diacetate. In connection with the present work we have repeated Marker's experiments and have isolated the intermediate products. In addition, pregnane-20β-ol-3-one acetate was converted by bromination and dehydrobromination into an unsaturated ketone identical with Δ⁴-pregnene-20β-ol-3-one acetate (m.p. 161–162°) derived from IVb. Details of this work will be found in the experimental section.

Experimental[13]

3β-Acetoxy-20α(and 20β)-benzoyloxy-Δ⁵-pregnene (IIa and IIb).—*i*-Pregnenolone methyl ether (4.60 g.) was hydrogenated in 35 ml. of ethanol in the presence of nickel catalyst freshly prepared from 5.0 g. of Raney nickel alloy. After 3.5 hours 340 ml. of hydrogen had been absorbed (theory, 343 ml.) and no further reaction was observed. The catalyst was removed by filtration, and the product was taken into ether, washed with water and a saturated solution of sodium chloride, filtered through anhydrous sodium sulfate, and concentrated to dryness under reduced pressure.

The crude product was then dissolved in 25 ml. of dry pyridine, cooled in ice, and treated with 2.00 ml. of benzoyl chloride. After standing overnight at room temperature, the reaction mixture was diluted with water and extracted with ether. The ether layer was washed successively with dilute hydrochloric acid, water, dilute sodium hydroxide, and saturated sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed, and the residue was refluxed for 3 hours with 12.0 g. of zinc acetate and 250 ml. of glacial acetic acid. The solution was then concentrated under reduced pressure, diluted with water, and extracted with ether. The ether extract was finally washed, dried, and evaporated. On fractional chromatography over alumina, the residual oil furnished 3.15 g. of IIb, m.p. 169–171°, from the early eluates and 2.00 g. of a more strongly adsorbed product, IIa, m.p. 148–151°; combined yield, 5.15 g. (80% based on *i*-pregnenolone methyl ether).

(7) R. E. Marker, *et al.*, THIS JOURNAL, **59**, 2291 (1937).

(8) R. E. Marker, *et al.*, *ibid.*, **59**, 614 (1937).

(9) The acetyl derivative was employed in order to avoid initial precipitation of an insoluble complex.

(10) Observation of L. H. Sarett.

(11) A. C. Ott and M. F. Murray, Abst. A. C. S. 118th Meeting, Chicago (1948).

(12) R. E. Marker and O. Kamm, THIS JOURNAL, **59**, 1373 (1937).

(13) All melting points are corrected. We are indebted to Mr. S. M. Nagy, M. I. T., for microanalyses. Specific rotations, unless otherwise specified, were measured in chloroform solution.

Recrystallization of IIa from dilute methanol gave a pure sample, m.p. 153–153.5°, $[\alpha]_D$ −14.5° (*c*, 1.38).

Anal. Calcd. for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68. Found: C, 77.24; H, 8.78.

The analytical sample of IIb was obtained by recrystallization from methanol and melted at 172.5–173°, $[\alpha]_D$ −88.8° (*c*, 1.49).

Anal. Calcd. for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68. Found: C, 77.30; H, 8.69.

In a separate experiment in which chromatography was omitted, a product (m.p. 132.5–133.5°; *anal.* C, 77.28, H, 8.60; $[\alpha]_D$ −47.6°) was isolated by direct crystallization from methanol. The same substance could be obtained by crystallization of a mixture of equal parts of the pure isomers IIa and IIb from the same solvent.

Hydrolysis of 3β-acetoxy-20α-benzoyloxy-Δ⁵-pregnene (IIa) with methanolic sodium hydroxide yielded **Δ⁵-pregnenediol-3β,20α**, which, after several recrystallizations from dilute ethanol and thorough drying, melted at 183–184°, $[\alpha]_D$ −53.5° (*c*, 1.12). Treatment of the diol with acetic anhydride and pyridine afforded **Δ⁵-pregnenediol-3β,20α diacetate**, m.p. 145.5–146.5°, $[\alpha]_D$ −53.8° (*c*, 1.76). The diacetate, on hydrogenation (Pt), furnished **allopregnanediol-3β,20α diacetate**,[7] m.p. 165–167°, $[\alpha]_D$ ±0° (*c*, 1.14).[14]

Hydrolysis of 3β-acetoxy-20β-benzoyloxy-Δ⁵-pregnene (IIb) followed by crystallization of the product from dilute ethanol gave **Δ⁵-pregnenediol-3β,20β**, m.p. 211–211.5°, $[\alpha]_D$ −64.3 (*c*, 1.15). This substance was converted into **Δ⁵-pregnenediol-3β,20β diacetate**, m.p. 138.5–140°, $[\alpha]_D$ −36.0° (*c*, 1.61), on treatment with acetic anhydride and pyridine. A mixed melting point with the corresponding 20α epimer (m.p. 145.5–146.5°) was depressed to 105–108°. Recrystallization of a mixture of equal parts of the two diacetates gave material melting at 104–105°. Catalytic hydrogenation of the 3β,20β-diacetate (Pt) yielded **allopregnanediol-3β,20β diacetate**,[8] m.p. 142–143°, $[\alpha]_D$ + 22.8° (*c*, 1.53).

Partial Hydrolysis of 3β-Acetoxy-20α-benzoyloxy-Δ⁵-pregnene (IIa).—To a solution of 1.95 g. of IIa in 50 ml. of purified[15] dioxane, 10 ml. of water and 3.00 ml. of 1.01 *N* sodium hydroxide solution was added. The turbid solution was stirred overnight at room temperature. At the end of this time an additional 5 ml. of water and 1.70 ml. of 1.01 *N* sodium hydroxide solution were added. Stirring was continued overnight, and the resulting clear solution was then diluted with a large volume of water and thoroughly extracted with ether. The ether extracts were combined, washed with water and a saturated solution of sodium chloride, filtered through anhydrous sodium sulfate, and concentrated to dryness. Crystallization from dilute methanol furnished 1.64 g. (91%) of **3β-hydroxy-20α-benzoyloxy-Δ⁵-pregnene** (IIIa) as the **hemihydrate**, m.p. 158–160°. The analytical sample, m.p. 159.5–160.5°, was prepared by several recrystallizations from dilute methanol.

Anal. Calcd. for $C_{28}H_{38}O_3 \cdot {}^1/_2H_2O$: C, 77.92; H, 9.11; H_2O, 2.09. Found: C, 78.13; H, 9.09; H_2O, 1.85 (by loss in weight on drying).

The unsolvated product was obtained after careful drying in a Fischer pistol and melted at 161–162°, $[\alpha]_D$ −11.8° (*c*, 1.69).

Anal. Calcd. for $C_{28}H_{38}O_3$: C, 79.58; H, 9.06. Found: C, 79.28; H, 9.15.

Partial Hydrolysis of 3β-Acetoxy-20β-benzoyloxy-Δ⁵-pregnene (IIb).—A solution of 2.96 g. of IIb in aqueous dioxane was hydrolyzed with 7.00 ml. of 1.01 *N* sodium hydroxide solution, added in two portions as described in the preceding experiment. The product was crystallized from methylene chloride–petroleum ether; yield 2.55 g. (95%), m.p. 177–179°. After several recrystallizations from ether–petroleum ether, the melting point was raised to 183–184°, $[\alpha]_D$ −99.5° (*c*, 1.32).

Anal. Calcd. for $C_{28}H_{38}O_3$: C, 79.58; H, 9.06. Found: C, 79.35; H, 8.93.

Oppenauer Oxidation of 3β-Hydroxy-20α-benzoyloxy-Δ⁵-pregnene (IIIa).—The anhydrous hydroxybenzoate (1.50 g.) was refluxed overnight with 1.50 g. of aluminum *t*-butoxide in 20 ml. of dry benzene and 25 ml. of cyclohexanone. The mixture was then cooled and acidified with acetic acid, and the solvents were removed in a current of steam. The residue was acidified with dilute hydrochloric acid and extracted with ether. The ether solution was finally washed, dried and evaporated. Crystallization from methylene chloride–petroleum ether furnished 1.30 g. (87%) of material melting at 161–164°.

The analytical sample, m.p. 165.5–167°, $[\alpha]_D$ +79.0° (*c*, 1.20), was obtained after three recrystallizations from ethanol.

Anal. Calcd. for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found: C, 79.97; H, 8.72.

The material was hydrolyzed by refluxing for 3 hours with aqueous alcoholic sodium hydroxide in a nitrogen atmosphere, and furnished **Δ⁴-pregnene-20α-ol-3-one**, m.p. 161–162°, $[\alpha]_D$ +98.6° (*c*, 1.88), from which the corresponding acetate, m.p. 138.5–139.5°, $[\alpha]_D$ +87.0° (*c*, 2.24) was obtained by acetylation with acetic anhydride and pyridine.

Oppenauer Oxidation of 3β-Hydroxy-20β-benzoyloxy-Δ⁵-pregnene (IIIb).—Oxidation of the hydroxybenzoate (1.80 g.) melting at 184° was carried out as described above. Direct crystallization of the reaction product was troublesome, and the material was accordingly chromatographed on alumina. The yield of Δ⁴-pregnene-20β-ol-3-one benzoate melting at 137.5–138.5° was 1.46 g. (81%). Recrystallization from dilute methanol afforded the analytical sample, m.p. 138.5–139.5°, $[\alpha]_D$ +103° (*c*, 1.45).

Anal. Calcd. for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found: C, 79.82; H, 8.75.

Δ⁴-Pregnene-20β-ol-3-one, m.p. 174–175°, $[\alpha]_D$ +90.4° (*c*, 2.17), was obtained by hydrolysis in a nitrogen atmosphere. The corresponding 20β-acetyl derivative melted at 161–162°, $[\alpha]_D$ +129° (*c*, 1.96).

Lithium Aluminum Hydride Reduction of Pregnenolone Acetate.—Δ⁵-Pregnene-3β-ol-20-one acetate (700 mg.) in 20 ml. of anhydrous ether was treated with 20 ml. (excess) of 0.214 molar lithium aluminum hydride in ether. After 20 minutes the excess reducing agent was decomposed with ice, the ether was evaporated, and the product filtered and treated with methanolic sodium hydroxide to hydrolyze any residual 3-acetate. Attempts to obtain a pure substance by crystallization of the hydrolysis product were unsuccessful. The material was therefore acetylated and chromatographed on alumina. Δ⁵-Pregnenediol-3β,20β diacetate, m.p. 138.5–140°, was obtained from the early eluates. A second product, m.p. 104–105.5°, was isolated from later fractions. This substance, however, did not yield a crystalline hydrogenation product, and could be obtained by crystallization of a mixture of equal parts of the two diacetates epimeric at C.20 (see above). No other crystalline components could be isolated.

Preparation of 3α-Acetoxy-20β-hydroxypregnane.—Pregnane-3α-ol-20-one acetate (1.35 g.) was dissolved in 10 ml. of acetic acid and hydrogenated in the presence of 200 mg. of prereduced platinum oxide catalyst. When the absorption of hydrogen was complete, the catalyst was removed by filtration, and the filtrate was diluted with ether and washed with water. The ethereal solution was dried, concentrated, and diluted with petroleum ether. The product weighed 1.14 g. (85%) and melted at 129–133°. Several recrystallizations from ether–petroleum ether furnished a pure sample, m.p. 136.5–137°, $[\alpha]_D$ +28.8° (*c*, 2.12).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.56. Found: C, 75.98; H, 10.63.

The 20β-benzoate, prepared as a derivative and crystallized from methanol, melted at 89–90.5° with effervescence and contained half a molecule of methanol of crystallization.

Anal. Calcd. for $C_{30}H_{42}O_4 \cdot {}^1/_2CH_3OH$: C, 75.89; H, 9.19. Found: C, 75.91; H, 9.35.

Treatment of 3α-acetoxy-20β-hydroxypregnane with hydrogen chloride in methanol gave the free diol, m.p. 233.5–234.5°, $[\alpha]_D$ +12° (*c*, 0.86 in ethanol). Acetylation furnished **pregnanediol-3α,20β diacetate**,[7] m.p. 111–112°, $[\alpha]_D$ +52.7° (*c*, 1.76).

Preparation of 3α-Hydroxy-20β-acetoxypregnane Hemietherate.—**Pregnanediol-3α,20β diacetate** (900 mg.), obtained in nearly quantitative yield by acetylation of the 3-monoacetate (see above), was dissolved in 25 ml. of dioxane

(14) W. Klyne and D. H. R. Barton (footnote 8) report a specific rotation of −0.3° for this substance.

(15) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 369.

and treated with 1.50 ml. of 0.963 *N* NaOH solution. Water was added to turbidity, and the reaction mixture was stirred for 8 hours at room temperature. An additional 0.80 ml. of 0.963 *N* NaOH solution was then added, and the reaction mixture was allowed to stand overnight at room temperature. The product was isolated by dilution with water and ether extraction, and after crystallization from ether–petroleum ether gave a substance (885 mg., 87%) melting at 115–117° with effervescence. The melting point was raised to 118–119° (effervescence) by several recrystallizations from ether–petroleum ether.

Anal. Calcd. for $C_{23}H_{38}O_3 \cdot {}^1/_2C_4H_{10}O$: C, 75.14; H, 10.85; ether, 9.28. Found: C, 74.93; H, 10.57; ether, 8.45 (by loss in weight).

The compound could not be satisfactorily crystallized from any other common solvent; removal of the solvent of crystallization led to the formation of an oil, $[\alpha]D$ +44.8° (*c*, 2.12).

Preparation of Pregnane-20β-ol-3-one Acetate.—The hemietherate (260 mg.), obtained above, was dissolved in 5.00 ml. of acetic acid and treated with 3.00 ml. of 1.40 *N* chromic acid in dilute acetic acid. After standing overnight, the solution was diluted with water and extracted with ether. The ether extract was washed, dried, and evaporated. Crystallization of the residue from dilute methanol gave 225 mg. (87%) of ketone, m.p. 136.5–137.5°. The analytical sample melted at 138–138.5°, $[\alpha]D$ +51.0° (*c*, 2.20).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.72; H, 10.28.

Hydrolysis with 1% methanolic potassium hydroxide furnished pregnane-20β-ol-3-one,[7] m.p. 179–180°, $[\alpha]D$ +14.9° (*c*, 1.34).

Conversion of Pregnane-20β-ol-3-one Acetate into Δ⁴-Pregnene-20β-ol-3-one Acetate.—The 20β-acetoxy ketone (1.94 g.) obtained by the procedure described above was dissolved in 25 ml. of acetic acid and treated with 5.38 ml. of a 1.10 molar solution of bromine in acetic acid. After the reaction was complete, water was added, and the mixture was extracted with ether. The ether extract was then washed successively with sodium thiosulfate solution, dilute sodium hydroxide, and saturated sodium chloride. After drying over anhydrous sodium sulfate, the solution was concentrated and diluted with petroleum ether. The crystalline product that separated weighed 1.55 g. and melted at 161–163.5° (dec.). Recrystallization of a small sample gave material that melted sharply at 164–165° (dec.). Analysis for bromine was high, however, and the substance was evidently contaminated by products of higher bromination.

The crude crystalline product was refluxed for 7 hours with 30 ml. of dry pyridine, and after crystallization from ether–petroleum ether material was obtained that melted at 148.5–152°; yield 370 mg. Four recrystallizations from ether–petroleum ether afforded a pure sample, m.p. 157–158°, that did not depress the melting point of Δ⁴-pregnene-20β-ol-3-one acetate derived from IVb.

CAMBRIDGE 38, MASS. RECEIVED NOVEMBER 16, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

β-Erythroidine. III. A Study of the Hofmann Decomposition of Dihydro-β-erythroidine[1]

BY V. BOEKELHEIDE AND EUGENE AGNELLO

The Hofmann decomposition of dihydro-β-erythroidine has been found to yield an oxygen-free degradation product of molecular formula $C_{15}H_{19}N$. Oxidation experiments and infrared data have provided evidence that this degradation product contains a terminal methylene group and an ortho disubstituted benzene ring. A partial structure is suggested for the $C_{15}H_{19}N$ product.

In a previous communication[1] the behavior of β-erythroidine toward various acidic reagents was reported. In order to understand this behavior and to formulate the observed isomerizations on a rational basis, it was necessary that conclusive evidence be obtained regarding the carbon skeleton present in β-erythroidine. Of the various degradative procedures that one might apply to the molecule, the Hofmann method of exhaustive methylation appeared to be the most promising and was the first to be investigated. The present paper reports the initial results of this work.

Although Folkers and Koniuszy have stated that β-erythroidine possesses a nitrogen atom common to two rings,[2,3] experimental details supporting this have not yet appeared. In agreement with their results, though, we found in a preliminary study that the alkaloid could be carried through two stages of the Hofmann decomposition without loss of the nitrogen atom.[4] However, the results of this study were such as to indicate that a less highly unsaturated molecule might be better suited for carrying through the extended series of degradation steps necessary for complete removal of the nitrogen atom. Because the preparation of tetrahydro-β-erythroidine is complicated by the formation of stereoisomers whereas that of dihydro-β-erythroidine is not,[5] the dihydro derivative was chosen for study.

The reduction of β-erythroidine using Raney nickel catalyst in the presence of aqueous base proceeded smoothly to give dihydro-β-erythroidine in fairly good yield.[5] After purification by recrystallization of its hydrobromide salt, the dihydro derivative was converted, *via* its methiodide, to a crystalline methohydroxide base, m.p. 178–180° dec. When this base was heated at 170 to 190° in a molecular still, decomposition occurred and there were collected two fractions: a clear mobile oil boiling at 170–190° at 20 mm. and a thick viscous oil boiling at 190° at 0.05 mm. The two fractions formed in roughly equivalent amounts and both were characterized as tertiary amines.

The composition of the higher boiling oil, as indicated by analysis of its methiodide, was in agreement with that to be expected for a normal methine base formed by loss of a molecule of water. On the other hand the lower boiling oil appeared to be the result of a much more deep-seated de-

(1) Aided by a grant from the National Foundation for Infantile Paralysis. For the preceding paper, see Sauvage and Boekelheide, THIS JOURNAL, **72**, 2062 (1950).

(2) Folkers and Koniuszy, *ibid.*, **61**, 3053 (1939).

(3) Folkers and Koniuszy, Abstracts of Papers 97th Meeting of the American Chemical Society, April, 1939, Division of Organic Chemistry, page 17.

(4) Sauvage and Boekelheide, unpublished work.

(5) (a) Folkers and Koniuszy, U. S. Patent 2,370,651, March 6, 1945; (b) Major and Folkers, U. S. Patent, 2,280,837, April 28, 1942; (c) Folkers and Koniuszy, British Patent 596,976, Jan. 15, 1948.