optical rotational data, and Charles Pidacks and associates for carrying out the partition chromatographies. Also we wish to acknowledge that the paper strip chromatographic assays were conducted by Robert H. Blank who also developed the systems herein described.

11-Alkylated Steroids. IV.[1] Synthesis and Reactions of Olefins Derived from 11β-Hydroxy-11-methyl-5β-pregnane-3,20-dione

WILLIAM J. WECHTER AND GEORGE SLOMP

Research Laboratories of The Upjohn Company, Kalamazoo, Mich.

Received May 3, 1961

The dehydration of 11β-hydroxy-1–methyl-5β-pregnane-3,20-dione yielded both the $\Delta^{9(11)}$- and Δ^{11}-11-methyl steroids. Employing these olefinic intermediates, the chemistry of C-ring altered steroids has been investigated. The structures of many of these products were elucidated by their NMR spectra and an interesting unshielding effect of allylic systems was observed.

Among recent reports on the reaction of methyllithium with 11-keto steroids[2a,2b,3] the preparation of 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (I), a potent central nervous system depressant,[4] was described. Prompted by the marked biological properties of this compound, the present work was undertaken as part of the continuing investigation of 11-alkylated steroids.

By the method of Drake, Fonken, and Howard[5] (*N*-bromoacetamide–pyridine–sulfur dioxide) 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (I) was dehydrated giving a mixture of 11-methyl $\Delta^{9(11)}$-5β-pregnene-3,20-dione (II) and 11-methyl-Δ^{11}-5β-pregnene-3,20-dione (III). The composition of this mixture was established by NMR spectroscopy as roughly 85% of the $\Delta^{9(11)}$ (II) and 15% of the Δ^{11}-pregnene (III).

Ozonolysis of the above mixture of the olefins yielded 46% of a neutral tetrone (IV) in addition to 3% of a polyketo acid (IVa) which was characterized only by its infrared spectrum. The 9,11-secotetrone (IV) gave upon treatment with base the expected aldol products (V and VI) characterized by a variety of chemical and physical methods including NMR, ultraviolet, infrared, and X-ray unit cell determination. While the isomeric triones V and VI differed in their physical constants and NMR spectra, they could not be distinguished. The other somewhat more remote possibilities for the structure of aldol products [structures (VII) and (VIII)] were incompatible with the ultraviolet spectrum of the α,β-unsaturated ketone system [$\lambda_{max}^{C_2H_5OH}$ 239 mμ (log ϵ 4.08)]. Construction of a Courtaud Model[6] of the isomeric C-homo steroid (IX) indicated that the unsaturated ketone system of this molecule could not become co-planar and since the ultraviolet and infrared spectra (γ_{max} 1715, 1650, and 1625 cm.$^{-1}$) were normal this possibility was unlikely. Further the C-homo possibility (IX) appeared highly unlikely since the 9,11-secobisketal (XXI) did not undergo aldol condensation. The NMR spectra of the aldol products, in addition to the two angular methyl absorptions[7] at 9.07 and 8.60 and at 9.12 and 8.62 τ,[8] showed methyls on double bonds as close doublets at 8.03 and 8.02 τ, respectively. The magnitude of the coupling constants (both 1.5 c.p.s.) was indicative of splitting through a double bond by an adjacent vinyl hydrogen which was present as a multiplet in the two condensation products at 4.10 or 4.19 τ, respectively. Structures VII, VIII, and IX lacked this configuration and were thus clearly eliminated.

In addition to the tetrone IV and keto acid IVa the 9α,11α-epoxide (X) derived from the original olefin was isolated from the ozonization mixture. The structure of this compound was established by three independent syntheses from the 11-methyl-$\Delta^{9(11)}$-olefin (II) employing separately trifluoroperacetic, chromic acid, and potassium permanganate as epoxidizing agents, all of which would be expected to attack the relatively unhindered backside (α-attack) of the molecule. Further evidence for this structural assignment was the inactivity of the epoxide towards perchloric acid in acetone. (9β,-11β-Epoxides are known to open hydrolytically

---

[1] This paper was presented at the Michigan–Toledo–South Bend Meeting-in-Miniature of the American Chemical Society, February 27, 1960. Since the original presentation of this paper, the chemistry of some 5α-11-methyl steroids has appeared [J. Elks, *J. Chem. Soc.*, 3333 (1960)].

[2] (a) H. J. Ringold, E. Batres, and J. A. Zedric, *Tetrahedron*, **4**, 165 (1958); (b) G. S. Fonken and J. A. Hogg, *ibid.*, **365** (1958).

[3] G. S. Fonken, *J. Org. Chem.*, **23**, 1075 (1958).

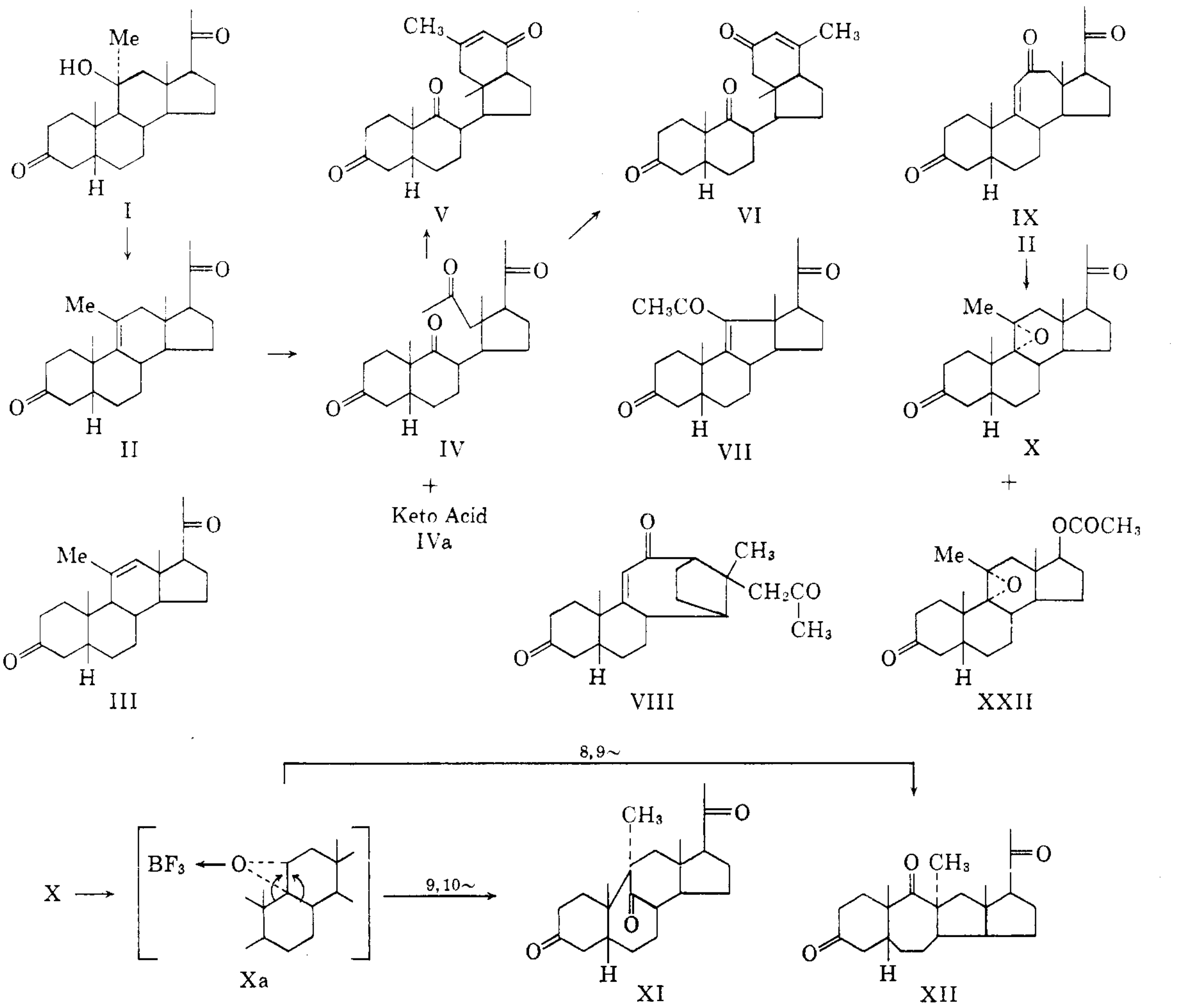
[4] P. H. Seay (The Upjohn Co.), private communication.

[5] A. Drake, A. Fonken, and R. B. Howard, British Patent 790,452.

[6] (a) Harley and Robinson, *Trans. Faraday Soc.*, **48**, 847 (1952); (b) Robinson and Ambrose, *ibid.*, 854 (1952); (c) Robinson, *Discussions Faraday Soc.*, **16**, 125 (1954).

[7] For Basic Steroid NMR assignments see J. N. Schoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

[8] These spectra were measured in a Varian A-60 spectrometer in $CDCl_3$ solution.



quite rapidly while the corresponding 9α,11α-epoxides are slow or unreactive.[9])

When treated with boron trifluoride etherate, the epoxide (X) rearranged sterospecifically to give in high yield a single new isomer. Such an acid-catalyzed rearrangement of the 9α,11α-epoxide (X) would initially be expected to occur by electrophillic attack on the epoxide oxygen by boron trifluoride (Xa) followed by axial opening[10,11] of the complex with concerted shift of the electron pair from either the 8,9 or 9,10 bond to the 11-position with the formation of a new ketone at C-9 to give trione XI or XII. The infrared spectrum of the boron trifluoride rearrangement product exhibited an abnormally low carbonyl absorption associated with the new ketone at 1683 cm.$^{-1}$ ($CHCl_3$). A model compound, the bicyclo[4.3.1]decan-10-one derivative (XIII) prepared by the method of Stork and Untch,[12] also exhibited an abnormal carbonyl frequency at 1685 cm.$^{-1}$ (neat). If the transition states leading to the formation of XI or XII resemble the products, then models indicate that XI* would be the transition state of lower energy since XII contains an energetically unfavorable *trans* fusion between two five-membered rings. Based on the above considerations, structure XI has tentatively been assigned to the rearrangement product.[13]

Treatment of the bicyclotrione (XI) with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene afforded the biscyclic ethylene acetal (XIV) in which it was apparent from the infrared spectrum (C=O at 1677 cm.$^{-1}$) that the new ketone had not reacted. This bisketal was converted readily to the original bicyclotrione XI upon mild acid hydrolysis.

In an effort to test the tentative structure XI, an attempt was made to exchange the possibly enolizable hydrogen at C-8 for deuterium. Bredt's rule[14] would eliminate the possibility of enolization of the bridgehead hydrogen at C-8 of trione XI. More recently Prelog[15] demonstrated by the synthesis of

---

[9] H. Heyman and L. F. Fieser, *J. Am. Chem. Soc.*, **73**, 5252 (1951).

[10] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4569 (1957).

[11] D. H. R. Barton, *Experientia*, **6**, 316 (1950).

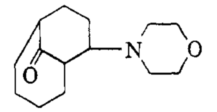
[12] G. Stork and K. Untch, private communication.

[13] The NMR spectrum which showed an intact pregnane side chain and three other methyl groups did not distinguish between structures XI and XII.

[14] J. Bredt, *Ann.*, **395**, 26 (1913); *ibid.*, **437**, 1 (1924).

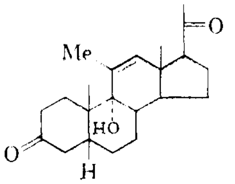
[15] V. Prelog, M. M. Wirth, and L. Ruzicka, *Helv. Chim. Acta*, **29**, 1425 (1946).

2-methylbicyclo[12.4.1]octadec-1-ene-18-one that if the ring system is sufficiently large, bridgehead double bonds (*i.e.*, cyclic *trans* double bonds) are indeed possible. In keeping with the proposed structure both the bisketal (XIV) and the bicyclo-[4.3.1]decan-10-one (XIII) failed to incorporate deuterium on prolonged reflux in alkaline deuteroethanol.

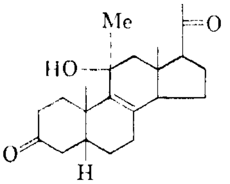


XIII

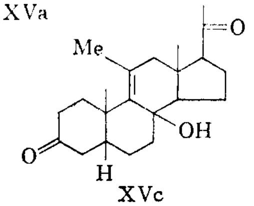
Treatment of the 11-methyl-$\Delta^{9(11)}$-pregnene (II) with *N*-bromoacetamide in aqueous acetone under acid or neutral conditions in an effort to prepare the corresponding bromohydrin gave unexpectedly a new alcohol which did not contain bromine. While this product would be expected to be an allylic alcohol, it could neither be oxidized by activated manganese dioxide nor by sodium dichromate. Thus, the new hydroxyl group was neither at C-12 nor attached to the methyl group at C-11. The remaining possibilities arising by direct allylic halogenation and hydrolysis or by simple allylic rearrangement of the primary product were the Δ^{11}-9-ol (XVa), Δ^{8}-11-ol (XVb) and $\Delta^{9(11)}$-8-ol (XVc). The NMR spectrum of the new alcohol clearly showed that a methyl group and no hydrogen atom was attached to the double bond systems. Structures XVa and XVb lacked this structural feature; therefore, XVc is the NBA product.



XVa

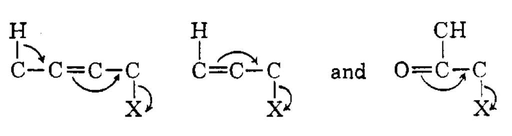


XVb



XVc

It was of interest to note the deshielding of the 11-methyl hydrogens by the introduction of the allylic hydroxyl group (XV *vs.* II). This downfield shift of about 0.35 τ was observed in several examples of allylic hydroxyl or halogen systems and may be due to a form of hyperconjugation such as

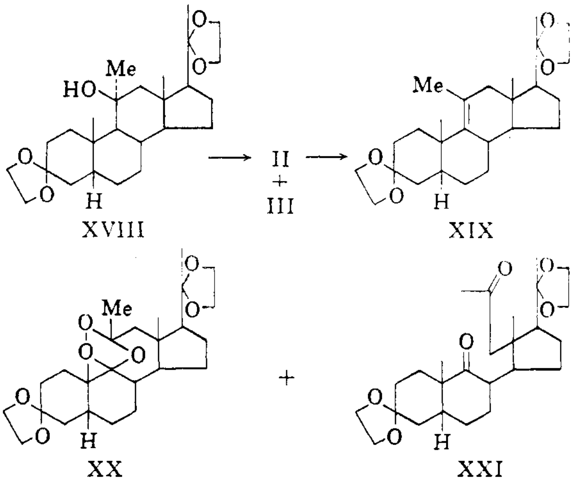


which decreases the electron density in the double bond. This effect has been observed in 17-hydroxy-20-ketopregnanes and in several 6-substituted 3-keto-Δ^4 steroids.[16]

Employing a large excess of catalyst the tetrasubstituted 11-methyl-$\Delta^{9(11)}$-pregnene (II) was reduced to the saturated diol XVI; assuming backside addition of hydrogen at C-9 and C-11, the methyl group at C-11 would have the β-configuration. This diol was in turn oxidized to 11β-methyl-5β-pregnane-3,20-dione XVII.

Dehydration of 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione, bis(cyclic ethylene acetal) (XVIII) with *N*-bromoacetamide-pyridine-sulfur dioxide[5] gave after chromatography on Florisil an intractable gum. Hydrolysis of the ketal functions of this material gave a mixture of unsaturated diones which when crystallized slowly gave two crystal types. These crystals were separated by hand and on repeated recrystallization gave both the pure 11-methyl-Δ^{11}-(III) and 11-methyl-$\Delta^{9(11)}$ diones (II).

Subsequently, the 11-methyl-$\Delta^{9(11)}$-bisketal (XIX) was prepared from 11-methyl-$\Delta^{9(11)}$-dione (V). Ozonolysis of this bisketal (XIX) in ethyl acetate gave principally the 11-methyl-9,11-ozonide (XX) (characterized by its carbon hydrogen analysis and infrared spectrum as well as its ability to liberate iodine from an acid sodium iodide solution). Formation of stable ozonides from hindered double bonds are well known.[17] The isolation of the ozonide from the bisketal (XIX) contrasts with the formation of the 9,11-seco derivative IV on onization of the parent dione (II) and may result from running the former compound in neutral and the latter compound in an acidic solvent. In fact, a small amount of the 9,11-secodione (XXI) was isolated from the ozonization of the ketal (XIX). As mentioned above, this material, in which the 3- and 20-keto groups were protected as their ketals, did not undergo aldol condensation under conditions identical to those employed with II and this fact lent further support to the structure of the aldol condensation products.



---

[16] These shifts will be the subject of a future publication.

Experimental[18]

11-Methyl-5β-pregn-9(11)-ene-3,20-dione (II).—11β-Hydroxy-11-methyl-5β-pregnane-3,20-dione[3] (I) (110 g., 0.27 mole) was dissolved in 500 ml. of dry pyridine and treated with 51 g. (0.27 mole) of *N*-bromoacetamide (NBA) for 15 min. at room temperature. The solution was then chilled to ice temperature and a stream of sulfur dioxide gas passed over the reaction mixture until the deep red color produced was bleached to a light yellow. The resulting solution was poured into 4 l. of ice water and the product allowed to crystallize giving 105 g. of crude crystalline solid. This material was recrystallized from ethyl acetate–petroleum ether (b.p. 50–70°) giving 25.1 g., m.p. 142–146°, and a second crop, 15.5 g., m.p. 123–159°. An analytical sample was obtained by several recrystallizations from ethyl acetate–petroleum ether (b.p. 50–70°), m.p. 143–144°; $[\alpha]_D$ 129° (acetone); NMR, 7.89 (21-H), 8.17 (11-CH_3), 8.56 (19-H), and 9.47 τ (18-H).

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.68; H, 9.94.

11-Methyl-5β-pregn-11-ene-3,20-dione (III).—A sample of the crude dehydration product (above) was crystallized slowly (several weeks) from pure ethyl acetate and two different crystalline materials (prisms and bars) were separated by hand. The higher melting compound (III) was recrystallized from ethyl acetate for analysis, m.p. 171.8–178.5° (Kofler). The infrared spectrum of this material was considerably different from that of the $\Delta^{9(11)}$-dione (II), exhibiting at C=C absorption at 1625 cm.$^{-1}$; NMR, 4.02 (12-H), 7.89 (21-H), 8.17 (11-CH_3), 8.94 (19-H), and 9.34 τ (18-H).

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.03; H, 9.70.

11-Methyl-9,11-*seco*-5β-pregnane-3,9,11,20-tetrone (IV).—A sample of 2.6 g. (7.5 mmoles) of 11-methyl-5β-pregn-9(11)-ene-3,20-dione was dissolved in a mixture of 50 ml. of ethyl acetate and 30 ml. of glacial acetic acid. The solution was chilled to −10° and ozone passed in at the rate of 0.3 mmole/min. for 50 min. (15 mmoles). At the end of this period 10 ml. of water and 2 ml. of 30% hydrogen peroxide was added and the resulting solution allowed to stand over a week-end at room temperature. The solution was diluted with 3 volumes of water and 50 ml. of ether added. The reaction mixture was washed free of acetic acid with water, followed by dilute sodium hydroxide solution. Upon acidification of the basic extract a small amount of white solid precipitated (78 mg., 3%) which was identified as an acid by its infrared spectrum, ν_{max} 3380 and 1705 trailing to a shoulder at 1640 cm.$^{-1}$.

The neutral ozonolysis product, contained in the ether extract, was dried over sodium sulfate and the solvent distilled, yielding a light brown oil. This material was chromatographed on 150 g. of Florisil. Fractions eluted with 10% acetone–petroleum ether yielded a small amount of white crystalline material and a colorless oil weighing 1.3 g. (46%). The infrared spectrum of this oil (ν_{max} 1720 cm.$^{-1}$, broad and very strong) was consistent with the tetrone structure. Owing to the physical state of the product, it was not characterized further.

Products of the Aldol Condensation of 11-Methyl-9,11-seco-5β-pregnane-3,9,11,20-tetrone (V and VI).—A solution of 1.3 g. of 11-methyl-9,11-seco-5β-pregnane-3,9,11,20-tetrone in 10 ml. of methanol was treated with 3 ml. of 25% sodium methoxide for 3 hr. The solution was diluted with several volumes of water and the organic product extracted into ether. After washing several times with water and drying over sodium sulfate, the ether solution was evaporated to dryness yielding a semicrystalline oil; yield 650 mg. (53%). This material was adsorbed onto 65 g. of Florisil.

Acetone (10%) in petroleum ether eluted a white crystalline material, m.p. 181–187° dec. The combined fractions were recrystallized for analysis from ethyl acetate–petroleum ether giving colorless diamond shaped crystals,[19] m.p. 188.8–190.6°. The infrared was consistent with the assigned structure (V or VI) $\lambda_{max}^{C_2H_5OH}$ 239 mμ (log ε 4.08), $[\alpha]_D^{CHCl_3}$ −71° ν_{max} 1715, 1650, and 1625 cm.$^{-1}$, NMR[8] 9.12, 8.62 (18- and 19-H), 8.03 ($CH_3C{=}CH$ doublet, J = 1.5 c.p.s) and 4.19 τ (vinyl H, quartet).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.10; H, 8.12.

Earlier fractions employing the same solvent system yielded upon recrystallization from ethyl acetate–petroleum ether a small amount of crystalline material, m.p. 148.2–150.0°. Admixture with the above material exhibited a considerable melting point depression. The isomeric trione (VI) exhibited $\lambda_{MAX}^{C_2H_5OH}$ 239 mμ (log ε 4.08), ν_{max} 1715, 1650, and 1725 cm.$^{-1}$, $[\alpha]_D$ +32°, NMR: 9.07, 8.60 (18- and 19-H), 8.02 ($CH_3{-}C{=}CH$ doublet J = 1.5 c.p.s.) and 4.11 τ (vinyl H, quartet).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.17; H, 8.87.

Oxidation of II with Trifluoroperacetic Acid.—To a solution of 2.0 g. of II in 100 ml. of methylene chloride was added 50 g. of disodium hydrogen phosphate and then with vigorous stirring *ca.* 18 mmoles of trifluoroperacetic acid (freshly prepared) in 10 ml. of methylene chloride. The mixture was stirred for 1 hr. at room temperature when 100 ml. of water was added. The methylene chloride solution was separated, washed once with water, and dried (Na_2SO_4), filtered, and evaporated to dryness. The product was taken up in hot ethyl acetate and allowed to crystallize giving 480 mg., m.p. 181–192°. Three recrystallizations from ethyl acetate afforded 17β-hydroxy-11-methyl-9α,11α-epoxy-5β-androstan-3-one 17-acetate (XXII), m.p. 204–207°, ν_{max} 1740 sh., 1723, and 1695 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.31; H, 8.61.

The mother liquors were combined, evaporated to dryness, and chromatographed on 50 g. of Florisil.

A 5% acetone–petroleum ether mixture eluted 290 mg. (14%) of a white solid. Four recrystallizations from ethyl acetate afforded 11-methyl-9α,11α-epoxy-5β-pregnane-3,20-dione (X), m.p. 168–169°, ν_{max} 1710 sh., 1703, 1675 sh. and 1650 cm.$^{-1}$ sh.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.56; H, 9.14.

Ozonization of II.—A large quantity (40 g.) of II was ozonized as described earlier. Chromatography on 2 kg. of Florisil afforded 3 g. (eluted with 8% acetone in petroleum ether) of a solid. Recrystallization of this material from ethyl acetate gave an epoxide whose infrared spectrum and melting point (167–169°) were identical with the epoxide (X). Admixture with an authentic sample showed no melting point depression.

Permanganate Oxidation of II.—To a solution of 2 g. of II in 200 ml. of 95% acetic acid, 80 ml. of a 5% potassium permanganate solution was added dropwise at 10°. After 1 hr. in an ice bath the reaction mixture was treated with 6.4 g. of sodium bisulfite in 30 ml. of water followed by 400 ml. of water. The aqueous solution was extracted three times with 100-ml. portions of ether. The combined ether extracts were washed with sodium bicarbonate solution, dried (Na_2SO_4), decanted, and evaporated to dryness under reduced pressure. The resulting yellow oil was adsorbed onto 100 g. of Florisil and eluted with 10% acetone–

---

[17] P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

[18] The NMR spectra were measured except where noted with a Varian 4300-2 spectrometer in deuterochloroform solution operating at 40 Mc. and calibrated against internal tetramethylsilane using the audio frequency side band technique [J. P. Arnold and W. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951)]. Chemical shifts are expressed in tau units.

[19] A single crystal X-ray study was carried out by J. W. Shell of The Upjohn Co. This compound was found to crystallize in the orthorhombic system with unit cell dimensions; a = 11.53 Å.; b = 20.32 Å.; and c = 8.04 Å. The unit cell contains 4 molecules (d = 1.206) and is consistent with either structure V or VI.

petroleum ether to give 350 mg. of a solid. Recrystallization from petroleum ether–acetone, followed by ethyl acetate gave X (50 mg.) identical by m.p. 168–169° (no depression in melting point when admixed with an authentic sample) and infrared spectrum to the epoxide X obtained above.

A second material eluted with 8% acetone–petroleum ether and recrystallized from petroleum ether–acetone to yield 120 mg. of prisms, m.p. 204–210°, containing a hydroxyl group by infrared analysis. An additional recrystallization afforded 8-hydroxy-11-methyl-5β-pregn-9(11)-ene-3,20-dione (XV).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.92; H, 9.60.

Chromic Acid Oxidation of II.—A 1.0-g. sample of II was dissolved in 10 ml. of glacial acetic acid and treated with a solution of 750 mg. of chromic anhydride in 10 ml. of 90% acetic acid overnight at room temperature. The semisolid material which precipitated on dilution with 200 ml. of water collected and recrystallized from ethyl acetate–petroleum ether to give 50 mg. of a white crystalline solid, m.p. 158–162°, whose infrared spectrum was identical with that of the previous isolated epoxide X.

Attempted Acid Hydrolysis of 11-Methyl-9α,11α-epoxy-5β-pregnane-3,20-dione (X).—A 50-mg. sample of X was dissolved in 5 ml. of warm ethanol and 1 ml. of 0.8 *N* perchloric acid. The solution after standing at room temperature overnight, was warmed briefly on the steam bath and was diluted with water to give 40 mg. (80% recovery) of starting material X, m.p. 161–166°.

4,11-Methanocyclopenta[*h*]benzocyclononane-8,13-dione, 1,2,3,3a,6a,7,8,9,10,10a-decahydro-1-(1-oxoethyl)-10aβ,-11α,12aβ-trimethyl (XI).—A solution of 200 mg. of epoxide (X) in 20 ml. of benzene and 3 ml. of ether containing a few drops of boron trifluoride etherate was allowed to stand 3.5 hr. at room temperature and was then washed with sodium bicarbonate solution and water, dried (Na_2SO_4), and adsorbed onto 10 g. of Florisil. Fractions eluted with a 10% acetone–petroleum ether mixture contained 152 mg. (75%) of a trione. Recrystallization from petroleum ether–acetone afforded an analytical sample of an isomeric trione (XI), m.p. 189.5–192° (Kofler), infrared, ν_{max} 1700, 1683, (ratio 2:1) and 1638 cm.$^{-1}$; NMR: 7.94 (21-H), 8.32 (11-CH_3), 8.59 (19-H) and 9.24τ (18-H).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.90; H, 9.33.

Deuterium Exchange with Bicyclo[4.3.1]decan-10-one, 7-Morpholino.—A 1.0-g. sample of the bicyclo ketone (XIII) dissolved in 5.0 ml. of deuteroethanol containing about 200 mg. of sodium ethoxide and the solution heated to reflux for 72 hr. The cooled solution was diluted with 5 ml. of deuterium oxide and the product extracted into methylene chloride. The extracts were washed three times with saturated sodium chloride solution, dried over sodium sulfate, and the solvent removed under reduced pressure. The residual brown gum was distilled through a short path still (105°/75 μ) giving a colorless liquid whose infrared spectrum was identical with that of the starting material.

Anal. Calcd. for $C_{14}H_{23}O_2N$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.25; H, 9.73; N, 5.88.

Anal. Calcd. for $C_{14}H_{21}O_2ND_2$: Excess D, 8.72. Found: Excess D, 0.28.

Preparation of the 3,20-Bis(cyclic Ethylene Acetal) (XIV).—The trione (XI) (380 mg., 1.1 mmoles) was heated to reflux in 30 ml. of benzene containing 2 ml. of ethylene glycol and a few milligrams of *p*-toluenesulfonic acid employing a water trap. After 18 hr. the solution was cooled and washed consecutively with sodium bicarbonate solution, water and saturated sodium chloride solution, dried over sodium sulfate, and adsorbed onto 20 g. of Florisil. Acetone (2%)–petroleum ether eluted the bisketal which was recyrstallized once from petroleum ether for analysis, m.p. 180.2–183.8° (Kofler); ν_{max} 1677 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 71.88; H, 9.23.

Hydrolysis of XIV.—A sample of pure XIV (35 mg.) in 4 ml. of acetone and 2 ml. of 1 *N* sulfuric acid stood overnight at room temperature and then diluted with water to give large needles, 20 mg. (73%). Recrystallization from acetone–water afforded XI, m.p. 188–190°, identical by infrared spectrum with the sample described above.

Deuterium Exchange of XIV.—A 100-mg. sample of XIV in 2 ml. of deuteroethanol (100%) in which *ca.* 100 mg. of pure sodium had been dissolved, was heated to reflux for about 72 hr. The solution was diluted with 2 ml. of 99.87% deuterium oxide. The product was allowed to crystallize as short, colorless needles which were collected by filtration, washed with 1 ml. of deuterium oxide, and dried to give 95 mg. (95%), m.p. 178–183°. This material was recrystallized once from petroleum ether for analysis giving 75 mg., m.p. 180–181.5° (Kofler).

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32; D, 0 00. Found: C, 72.22; H, 9.40; D, 0.00.

8-Hydroxy-11-methyl-5β-pregn-9(11)-ene-3,20-dione (XV).—To a solution of 330 mg. (0.001 mole) of 11-methyl-5β-pregn-9(11)-ene-3,20-dione (II) in 25 ml. of acetone was added a solution of 274 mg. of *N*-bromoacetamide (0.002 mole) in 6 ml. of water. After a short induction period, the solution became light orange and was allowed to stand overnight at room temperature in the dark. The solution which was treated with sodium bisulfite solution to destroy the excess hypobromite afforded colorless needles upon addition of water. The crude product, 180 mg., m.p. 187.5–196.0°, contained a fractional amount (2.95%) of bromine which was not entirely removed by recrystallization from ethanol–water. It was then treated with zinc in 95% ethanol containing two drops of acetic acid. The product which precipitated on the addition of water was free of bromine and exhibited an infrared spectrum virtually identical to that of the material before the zinc treatment; m.p. 208–212.8° dec.; ν_{max} 1722, 1645, and 900 cm.$^{-1}$; NMR: 7.81 (11-CH_3), 7.92 (21-H), 8.54 (19-H), and 9.46 τ (18-H). This material was identical to the minor product obtained from the potassium permanganate oxidation of II above.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.92; H, 9.60. Found: C, 76.63; H, 9.79.

Dichromate Oxidation of XV.—A solution of XV (200 mg., 0.58 mmole) in 1 ml. of glacial acetic acid and 200 mg. of sodium dichromate dihydrate in 1 ml. of glacial acetic acid were mixed, shaken overnight at room temperature, chilled in the refrigerator, and then poured over ice and water. The product was collected, dissolved in methylene chloride, and chromatographed on 15 g. of Florisil. No α,β-unsaturated ketone was detected by ultraviolet. Only starting material and a new alcohol, m.p. 154–156°, were isolated. The new alcohol is tentatively considered to be an epoxide since it contained an additional atom of oxygen and exhibited only end absorption in the ultraviolet.

11β-Methyl-5β-pregnane-3,20-dione (XVII).—A 1.0-g. sample of 11-methyl-5β-pregn-9(11)-ene-3,20-dione in 100 ml. of acetic acid containing 5.0 g. of platinum oxide was shaken overnight in an atmosphere of hydrogen at about 40 p.s.i. The catalyst was collected on a Celite bed and the filtrate evaporated to dryness under reduced pressure. The residual gum, which gave a very weak tetranitromethane test, was taken up in 25 ml. of acetic acid and treated with 1.0 g. of chromic acid in 5 ml. of 90% acetic acid for 1 hr. The reaction mixture was poured over ice and water and the product extracted with methylene chloride. The combined extracts were washed with sodium bicarbonate solution, water and dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The solid residue was adsorbed onto 50 g. of Florisil and eluted with 10% acetone–petroleum ether to give 907 mg. (90%) which was recrystallized four times from petroleum ether for analysis, m.p. 155–156.5°, ν_{max} 1710 sh. and 1703 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.51; H, 10.80.

11-Methyl-5β-pregn-9(11)-ene-3,20-dione-3,20-bis(cyclic Ethylene Acetal) (XIX).—A solution of 5.0 g. (0.0158 mole) of 11-methyl-5β-pregn-9(11)-ene-3,20-dione (II), 50 mg. of *p*-toluenesulfonic acid, and 5 ml. of ethylene glycol in 70 ml. of benzene was heated to reflux overnight and the water collected in a Dean-Stark water separator. The reaction mixture was cooled, washed with sodium bicarbonate solution, water, and dried (Na_2SO_4), evaporated to about 10 ml., and adsorbed onto 225 g. of Florisil. Fractions eluted with 2% acetone–petroleum ether contained 5.52 g. (83.5%) of crude bisketal. Crystallization from petroleum ether afforded 4.1 g. (68%) of colorless prisms, m.p. 132–135°. A portion of this material was recrystallized once for analysis, m.p. 134–135°.

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 75.15; H, 10.13.

Ozonization of 11-Methyl-5β-pregn-9(11)-ene-3,20-dione, Bis(cyclic Ethylene Acetal).—A solution of 11-methyl-5β-pregn-9(11)-ene-3,20-dione-3,20-bis(cyclic ethylene acetal) (5.52 g., 0.013 mole) in 100 ml. of ethyl acetate was treated at −20° to 10° over a 20-min. period with 1.33 g. (0.0277 mole) of 2% ozone in oxygen. The solution was diluted with 100 ml. of *t*-butyl alcohol and 1 ml. of 30% hydrogen peroxide in 10 ml. of water and was allowed to stand overnight at room temperature. The resulting solution was extracted with ether and the combined ether extracts washed consecutively with water, 5% alkali solution, water, and dried over anhydrous sodium sulfate. The basic extracts were acidified and yielded a negligible amount of solid. The dry ether solution was evaporated under reduced pressure and the residue chromatographed on 250 g. of Florisil. A 5% acetone–petroleum ether mixture eluted 1.578 g. of a crystalline ozonide, several recrystallizations from petroleum ether gave colorless prisms, m.p. 149–151°. This material liberates iodine from acid potassium iodide solution. The infrared spectrum is compatible with the assigned structure and exhibits a multitude of absorption bands in the C—O region.

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 67.08; H, 8.80.

Further elution with 5–10% acetone in petroleum ether afforded 2.771 g. of a gum whose infrared spectrum was consistent with that of the expected dione XXI; γ_{max} 1720 cm.$^{-1}$ (very strong and broad). This material was not characterized further since it could not be crystallized.

Acknowledgment.—The authors wish to thank J. W. Shell for the X-ray unit cell determination, W. A. Struck and associates for rotatory dispersion measurements and microanalyses, and M. F. Grostic for infrared as well as J. L. Stafford for ultraviolet spectra. The assistance of J. C. Babcock and G. S. Fronken, in the preparation of this manuscript, is gratefully acknowledged.

Structures Related to Morphine. XXIV.[1] Further Application of the Stevens Rearrangement in the Synthesis of Diastereoisomeric 6,7-Benzomorphans from 3-Ethyl-4-methyl- and 4-Ethyl-3-methylpyridines

S. E. FULLERTON, J. H. AGER, AND E. L. MAY

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health,
Public Health Service, Department of Health, Education, & Welfare, Bethesda, Maryland

Received February 1, 1962

Sodium borohydride reduction of 3-ethyl-1,4-dimethyl- and 4-ethyl-1,3-dimethylpyridinium halides (I) has given good yields of the tetrahydropyridines (II). Quaternization of II with *p*-methoxybenzyl chloride and Stevens rearrangement of the resultant III with phenyllithium leads in part to the 2-*p*-methoxybenzyltetrahydropyridines (IV) which have also been prepared from I *via* the Freund reaction (using *p*-methoxybenzylmagnesium chloride) and subsequent sodium borohydride or catalytic reduction. Cyclization of IV with 48% hydrobromic acid results in the formation of diastereoisomeric (at C-9) benzomorphans (V, VI) in a ratio of about 10:1, respectively. Also isolated in low yield in the cyclization of IVb was an isomeric compound which may have the indano rather than the tetrahydronaphthaleno type structure. Compounds Va and Vb have been converted to open nitrogen analogs (VIIa and VIIb desired also for pharmacological study), and Va has been degraded to 1-ethyl-7-methoxy-2-methylnaphthalene (VIII). Both V and VI are potent analgesics, VIa (racemate) exceedingly so, with about forty times the activity of morphine.

In previous communications[2] it has been shown that 3,4-lutidine and 3,4-diethylpyridine may be converted to corresponding diastereoisomeric (at C-9) pairs of 5,9-dialkyl-6,7-benzomorphans by the Grewe morphinan synthesis or by a more practicable sequence involving the Stevens rearrangement.[3] More recently[1] we have demonstrated unequivocally that the 5,9-dialkyl groups of the predominant isomers (designated α) are in *cis* juxtaposition for the hydroaromatic ring. The ratio of α to β (lesser) isomer was approximately 12:1 in the dimethyl series and 8:1 with the diethyl homologs.[4] In contrast to the dimethyl series, the α and β diethyl compounds exhibited pronounced infrared spectral differences which could be utilized in their separation and identification.[2] Further

---

(1) Paper XXIII, S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem*, **27**, 2144 (1962).

(2) (a) J. H. Ager and E. L. May, *ibid.*, **27**, 245 (1962). (b) E. L. May and J. H. Ager, *ibid.*, **24**, 1432 (1959).

(3) E. M. Fry and E. L. May, *ibid.*, **26**, 2592 (1961).

(4) As noted before (*cf.* ref. 2) these dialkylbenzomorphans possess marked neuropharmacologic properties and show a pronounced separation of activity and physical dependence capacity in animal species. Peak analgesic activity and thereapeutic ratio were shown by the β-diethyl compound.