Reactions of a β-Hydroxy Nitrene. The Synthesis of B-Nor Steroids

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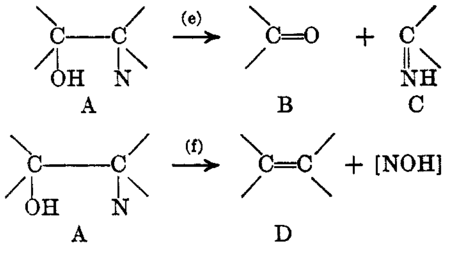
Photolysis of 5α-hydroxy-6β-azido steroids has been shown to proceed by two new pathways involving novel reactions of a postulated intermediate β-hydroxy nitrene. The first pathway involves carbonyl formation with C–C bond cleavage and the second olefin formation. The stereochemistry of the resulting B-nor steroids and other products has been determined and the mechanistic implications of these pathways considered.

Study of the products and mechanism of the pyrolysis[1,2] and photolysis[3,4] azides revealed that activated nitrenes[5] are probably intermediates in such reactions. Nitrenes are highly reactive species for which four routes[1-5] of decomposition have been documented. These are (a) 1,2-hydrogen shift to give imines (1,2-bond insertion); (b) hydrogen abstraction from solvent to yield amines; (c) internal 1,5-hydrogen shift *via* a diradical and subsequent cyclization to pyrrolidines;[3b,c] and (d) 1,3-bond insertion. We now wish to report two new pathways for the reaction of nitrenes modified by the presence of a β-hydroxyl. These are (e) carbonyl formation with C–C bond cleavage and imine formation (A → B + C) and (f) olefin formation by elimination of the elements of nitroxyl (A → D).



β-Hydroxynitrenes can be generated by photolysis of the corresponding azides. In the course of this work a synthesis of β-hydroxy azides from oxiranes and sodium azide was developed which is applicable in the presence of acid sensitive groups. Utilizing this method, the α-epoxide **1** (Scheme I) was converted during prolonged reflux in aqueous dioxane with sodium azide to the 5-hydroxy 6-azide **2**.

The stereochemistry of the epoxide opening, expected to be *trans* diaxial,[6] was established in the following manner. The configurations of C-5 and C-6 were determined separately, employing as a model the β-hydroxy azide **5**. The epoxide **4** was converted to azide **5**. Photolysis in 95% ethanol afforded as the major crystalline product an α-hydroxy ketone **9** which most likely arises *via* 1,2-hydrogen migration (route a, *vide supra*) followed by hydrolysis of the 6-imine by water. Acid hydrolysis gave the known A/B *trans*-dione **10**.[7] Since the photolysis of **5** to give a α-hydroxy ketone **9** involved a simple 1,2-hydrogen shift which does not affect the A/B ring junction, and further since the acid conditions employed to remove the 20-ketal group from **9** does not affect the A/B ring junction in such a 5-hydroxy-6-keto steroid,[8] the stereochemistry of **10** (known to be A/B *trans*), **9**, and **5** must be identical. In order to establish the configuration at C-6 in the 5α-hydroxy 6-azides, the nmr spectra (Table I) of the azides **2** and **5**, as well as additional models **12** and **13** (prepared from epoxide **11**) were examined. The position of the 6-H in all of these azides appeared at about 204 cps with a line width at one-half height of from 5 to 6 cps, characteristic of an equatorial proton (6α-H).[9] This then establishes the 6-azido group in **2**, **5**, **12**, and **13** as axial and in the β configuration. These stereochemical results are similar to those obtained by Ponsold[10] in the acid-catalyzed opening of oxiranes with azide ion.

The azide **2** was photolyzed until the starting material was no longer detectable by tlc (usually *ca.* 2 hr). Examination of the crude product by thin layer chromatography (tlc) revealed more than 10 products. Column chromatography on Florisil[11] afforded two crystalline compounds **6** and **7** in 8 and 20% yields, respectively. The structure of **7** was established by combustion analysis and comparison of its infrared and nmr spectra (Table I) with those of model compound **9**. In addition, acid hydrolysis afforded **8** which exhibited the expected absorption for a Δ^4-3,6-dione,[12,13] λ_{max} 250 mμ (ε 10,550). The similarity of rings C and D and side chains of **9** and **7** is evident from the positions of the C-18 and C-21 methyl resonances in the nmr (see Table I), showing that the presence of an oxygen function at the C-11 position of **2** during photolysis produced no anomalous reactions in the C or D ring. Calculation[14] of the approximate position of the 19-methyl resonance of compound **7**[14d] relative to the unsubstituted steroid gives a value of

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[1] P. A. S. Smith and J. H. Hall, *J. Am. Chem. Soc.*, **84**, 480 (1962), and references cited therein.

[2] G. Smolinsky, *ibid.*, **82**, 4717 (1960); **83**, 2489 (1961).

[3] (a) D. H. R. Barton and L. R. Morgan, Jr., *J. Chem. Soc.*, 662 (1962); (b) D. H. R. Barton and A. N. Starratt, *ibid.*, 2444 (1965); (c) R. M. Moriarty and M. Rahman, *Tetrahedron*, **21**, 2877 (1965).

[4] J. H. Boyer and F. C. Canter, *Chem. Rev.*, **54**, 1 (1954).

[5] L. Horner and A. Christmann, *Angew. Chem. Intern. Ed. Engl.*, **3**, 594 (1963).

[6] D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

[7] (a) M. Ehrenstein and M. T. Decker, *J. Org. Chem.*, **5**, 544 (1940); (b) L. Knof, *Ann.*, **657**, 171 (1962).

[8] W. J. Wechter and H. C. Murray [*J. Org. Chem.*, **28**, 755 (1963)] reported that these conditions are sufficiently mild so that a 20-keto steroid fails to enolize; a 5-hydroxy-6-ketone should be at least as stable.

[9] (a) A. Hassner and C. Heathcock, *ibid.*, **29**, 1350 (1964); (b) L. A. Freiberg, *ibid*, **30**, 2476 (1965).

[10] K. Ponsold, *Ber.*, **95**, 1727 (1962).

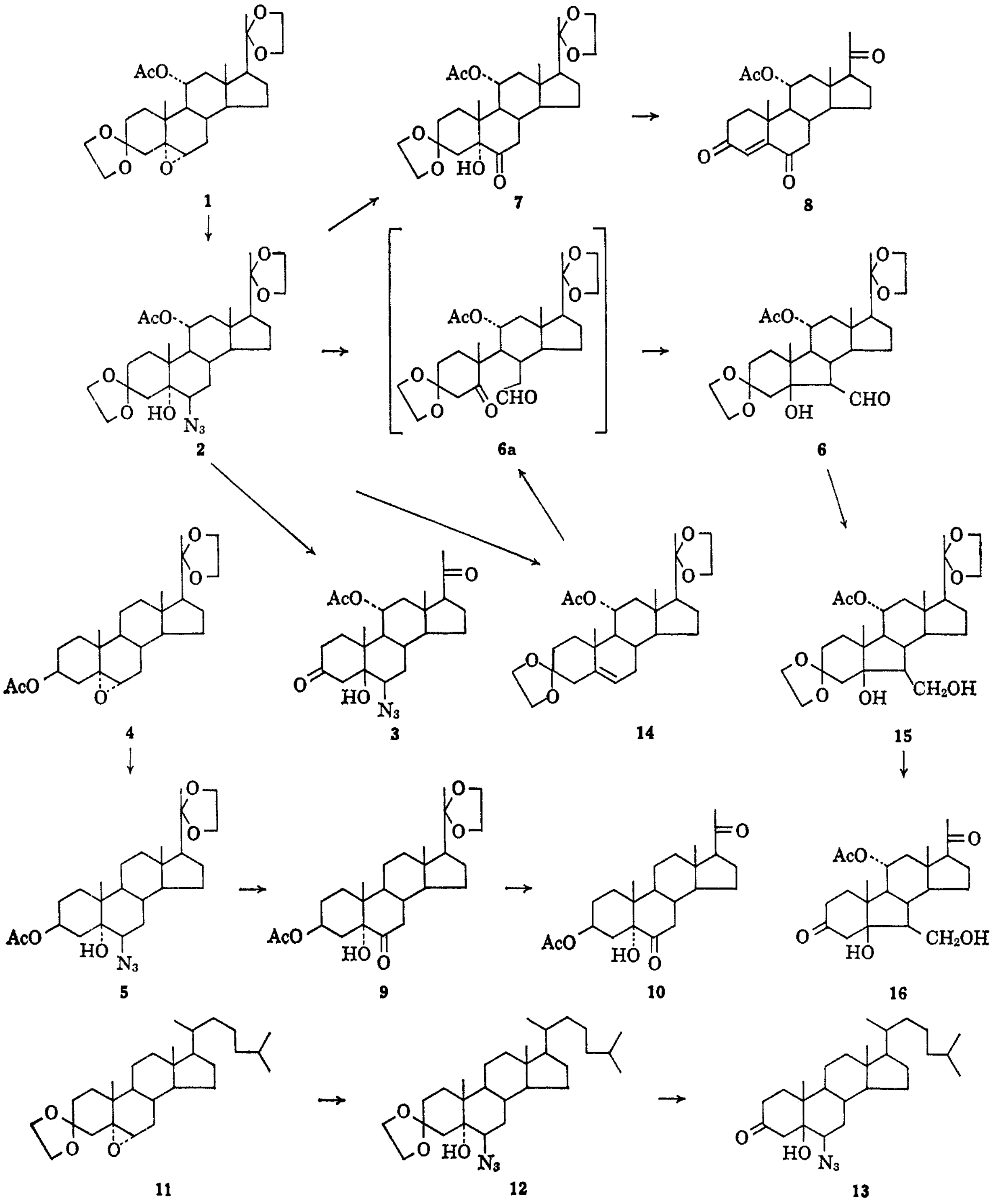
[11] A synthetic magnesium silicate manufactured by the Floridin Co., Warren, Pa.

[12] (a) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, Chapter 5; (b) L. Dorfman, *Chem. Rev.*, **50**, 47 (1953).

[13] 6-Ketoprogesterone exhibits λ_{max} 251 mμ (ε 10,575).

[14] (a) G. Slomp and F. MacKellar, private communication from these laboratories in which a catlog of over 2000 steroids has been prepared. (b) R. F. Zurcher, *Helv. Chim. Acta*, **44**, 1380 (1961); *ibid.*, 2045 (1963). (c) N. S. Bhacca and D. H. Williams, "Application of Nmr Spectroscopy in Organic Chemistry, Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964. (d) Employing a value of 38 cps for the 19-CH_3 for the unsubstituted steroid the following corrections, assumed to be additive, based on the above references[14a-c], were made: 20 ketal (+9 cps), 11α-OAc (+5.5 cps), 3-ketal-5α-OH (−2 cps), and 6-keto (+1.5 cps).

SCHEME I



52 cps in good agreement with the observed 19-methyl resonance of compound 7 at 52 cps.

Compound 6, also obtained from the photolysis of 2, proved to be a B-nor-5β-hydroxy-6β-carboxaldehyde. A preliminary structure of this product was formulated from its nmr spectrum and speculation as to the mechanism of its formation. The compound exhibits (*cf.* Table I) intact ketals, 11β-H, 18-, 19-, and 21-hydrogen resonances, acetate H, and a resonance and multiplicity characteristic of an aldehyde[15] adjacent to >CH at 584 cps (d, $J = 3$ cps). A comparison of the crude photolysis products with compound 6 by tlc indicated that compound 6 was not a direct product of the photolysis. It was postulated, therefore, that the keto aldehyde 6a (not isolated) is the direct photolytic product after hydrolysis of the imine by water. Subsequent aldol condensation was thought to have taken place during chromatography on Florisil.[11] Such condensations of steroid keto aldehydes to give B-nor-5β-hydroxy-6β-carboxaldehydes[16] are well documented. In order to confirm the structure of 6 and establish the probable intermediacy of 6a, this latter compound was synthesized by an alternate

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[15] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, Chapter 4, p 62.

[16] K. Tanabe, R. Hayoski, and R. Takasaki, *Chem. Pharm. Bull.* (Tokyo), **9**, 1, 12 (1961).

TABLE I
NMR SPECTRA[a]

Compound		18-H	19-H	21-H	Other
1	(epoxide)	42	68	71	
2	(azides)	49.5	71	75	6α-H, 204 cps, $W_{1/2}{}^{b}$ = 5 cps
5		46	68	76	6α-H, 204 cps, $W_{1/2}$ = 6 cps
12		55	65		6α-H, 204 cps, $W_{1/2}$ = 6 cps
13		54	78		6α-H, 204 cps, $W_{1/2}$ = 6 cps
7	(6 ketones)	47	52	75	
9		48	44.5	77	3α-H, 302 cps (br)
17	(2 → 5 epoxide)	47	68	76	2β- (or 1β-H), 257 cps (t, J = 5 cps)
6	(aldehyde)	56 (or 58)	58 (or 56)	76	CHO, 584 cps (d, J = 3 cps)
14	(olefin)	52	67	75	6-H, 325 cps (m)

[a] All nmr spectra were recorded on a Varian Model A-60 spectrometer in deuteriochloroform solution with tetramethylsilane (TMS) as internal standard. Peaks are reported as cycles per second (cps) downfield from TMS taken as 0 cps. [b] See ref 9.

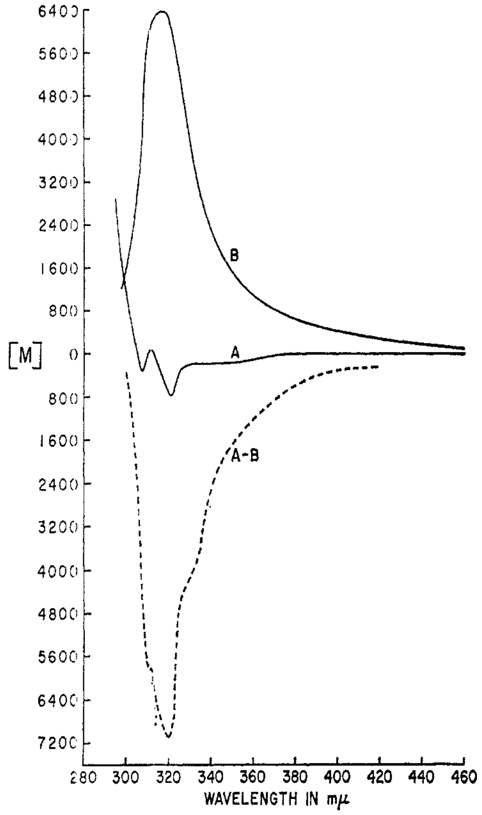


Figure 1.—The ORD spectrum of dione **16**.

route and without isolation converted to compound **6**. Ozonolysis of the olefin **14**, followed by isolation under "reducing" conditions, afforded the crude keto aldehyde **6a**. Chromatography of this material on Florisil[11] afforded an aldehyde which was identical with the photolysis product **6** by infrared, nmr, mixture melting point, and tlc. In this manner, not only the gross structure but also the stereochemistry of compound **6** was established. In analogous compounds of type **6a**, aldol condensation during chromatography has been shown to give B-nor-5-hydroxy-6β-carboxaldehydes.[16] The A/B ring junction, based on these earlier[16] assignments, was reconfirmed in the following manner. The aldehyde **6** was reduced to the alcohol **15**. Acid hydrolysis of **15** afforded the dione **16**. The optical rotatory dispersion (ORD) spectrum (Figure 1) of this dione exhibits a weak negative Cotton curve (curve A). When the contribution of the 20-ketone (curve B, pregnenolone) is subtracted, curve A-B exhibits a strong negative Cotton effect. This latter curve is characteristic of a closely related A/B-*cis*-B-nor 3-ketone, namely 5β-hydroxy-B-norcoprostan-3-one 6β-carboxylate;[17] the 3-keto-A/B-*trans* system exhibits a strong positive Cotton curve.[17]

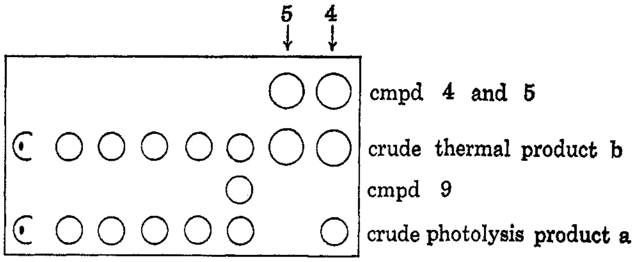
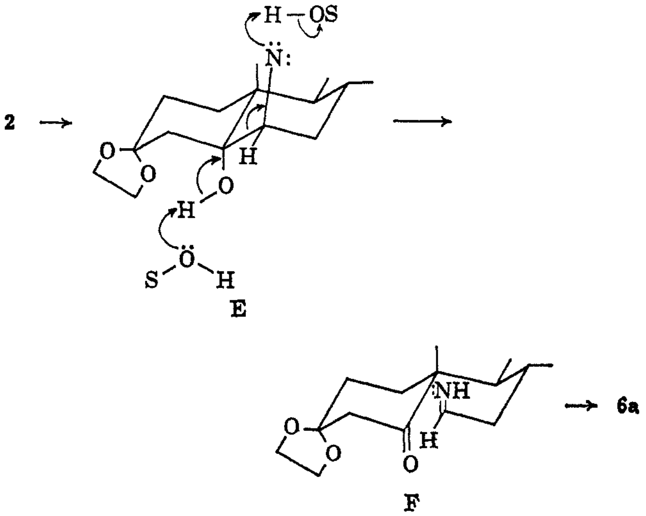


Figure 2.—Thin layer chromatography data.

Following from the structures of the photolysis products of **2**, detailed above for compounds **6** and **6a**, we have demonstrated reaction route e[18] for nitrenes. Assuming a low-energy reaction path, one can now speculate that the nitrene E from **2** rearranges to F as outlined, and is subsequently hydrolyzed by water. The proton transfer, owing to the *trans* relationship of N and O in the intermediate,[19] cannot be intramolecular.



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(17) L. Knof, *Ann.*, **656**, 183 (1962), and references cited therein.

(18) R. M. Moriarty and M. Rahman [*J. Am. Chem. Soc.*, **87**, 2520 (1965)] reported the photodecarboxylation of an α-azido acid, the course of which is very similar to reaction path e.

(19) While there may be some deviation from the ideal chair-chair conformation due to 1,3 interactions between the N and the 19-CH_3, as well as the 5-hydroxyl and 3-ketal, no permissible conformation would allow an intramolecular reaction.

Thus, it probably involves a concerted process mediated by solvent and at a low frequency by a second nitrene molecule. A mechanism involving hydrogen abstraction to give radical species which undergo the same over-all process involving single electron shifts can also be formulated. We prefer the ionic mechanism (E → F) since product **6** cannot be isolated when the reaction is carried out in benzene rather than ethanol. Although this is "negative evidence," such an indicated requirement for the presence of a Lewis base is certainly consonant with the ionic process.

It is of interest that the thermal decomposition of the azide **5** appears (by tlc, Figure 2) to give the same distribution of products as does the photolytic decomposition. This point is worthy of further investigation since presumably the thermal and photolytic products of azides are ordinarily different.[20]

If the photolysis of the azide **2** is carried out in benzene, a new product is isolated which does not appear (by tlc) to be a product of the photolysis in ethanol. This product is the olefin **14** which is identical with an authentic sample. The mechanism of this transformation of the nitrene is obscure, but formally involves reaction path f (*vide supra*). The presence of the theoretically co-produced oxidation product of ammonia, nitroxyl[21] or its hydrate, diammonium hydroxide was not investigated.

If either the azide **2** or the photolysis product **7** is subjected to irradiation for periods in excess of 12 hr, an insoluble product crystallizes from the photolysis mixture. The structure of this compound has not been established.[22]

Experimental Section

6β-Azido-5α,11α-dihydroxypregnane-3,20-dione Bis(cyclic ethylene ketal) 11-Acetate (2).—A 10.0-g sample of the epoxide **1**[24] and 5.0 g of sodium azide was dissolved in 200 ml of dioxane and 50 ml of water. The solution was heated at reflux under nitrogen for 5 days. The cool solution was treated with Darco G60 (2 g) and diluted to 500 ml with water. The solid product was filtered, washed with water and dried overnight at 60° under vacuum: yield, 9.19 g of crude; mp 164–230°. This material was adsorbed onto 275 g of Florisil in methylene chloride and eluted with 21 375-ml fractions of acetone–Skellysolve B over a gradient of from 5 to 20% acetone. Fractions 4–10 were combined and recrystallized from acetone to give 3.44 g of the azide, mp 184.5–185.5°. A sample was recrystallized two times for analysis: mp 184.5–185.5°, ν_{max} 3510, 2100, 1723, and 1250 cm.$^{-1}$

Anal. Calcd for $C_{27}H_{41}N_3O_7$: C, 62.41; H, 7.95; N, 8.09. Found: C, 62.43; H, 7.66; N, 8.19.

6β-Azido-5α,11α-dihydroxypregnane-3,20-dione 11-Acetate (3).—A 2.0-g sample of the above ketal **2** was dissolved with warming in 40 ml of ethanol and 2.0 ml of 3 *N* hydrochloric acid and the resulting solution was allowed to stand at room temperature overnight. The solution was then diluted to 125 ml with water which precipitated a gummy yellow solid. This material was separated and washed by decantation. The residue was crystallized from ethanol–water, mp 97–167° dec. Recrystallization from acetone–Skellysolve B afforded 640 mg of crystalline material, mp 206–207° dec. A sample was recrystallized once for analysis: mp 207.5–208.5°; infrared spectrum consistent with structure.

Anal. Calcd for $C_{23}H_{33}N_3O_5$: C, 64.10; H, 7.71; N, 9.74. Found: C, 64.30; H, 7.52; N, 9.66.

6β-Azido-3β,5α-dihydroxypregnan-20-one Cyclic Ethylene Ketal 3-Acetate (5).—3β-Hydroxy-5α,6α-epoxypregnan-20-one cyclic ethylene ketal 3-acetate[25] (12.0 g) and sodium azide (5 g) was added to 250 ml of dioxane–water (4:1). The resulting mixture was heated to reflux under nitrogen for 5.5 days. The solution was then diluted to 1.5 l. with water and extracted with five 100-ml portions of methylene chloride. The combined extracts were washed with water, saturated sodium chloride solution, dried (Na_2SO_4), and taken to dryness under reduced pressure. The residue was adsorbed onto a column of 600 g of Florisil which was in turn eluted with 6 l. of 7.5% acetone in Skellysolve B, followed by 6 l. of 20% acetone in Skellysolve B. The crystalline fractions were combined and recrystallized from acetone to give 8.56 g, mp 178–179.5° dec. A sample was recrystallized once for analysis: mp 179.5–181.0° dec; ν_{max} 3380, 2100, and 1695 cm.$^{-1}$

Anal. Calcd for $C_{25}H_{30}O_5N_3$: C, 65.05; H, 8.52; N, 9.10. Found: C, 65.29; H, 8.92; N, 9.05.

5,11α-Dihydroxy-3,20-dioxo-B-nor-5β-pregnane-6β-carboxaldehyde 11-Acetate Cyclic 3,20-Bis(ethylene acetal) (6), and 5,11α-Dihydroxy-5α-pregnane-3,6,20-trione 11-Acetate Cyclic 3,-20-Bis(ethylene ketal) (7).—The azide (**2**) (3.0 g) dissolved in 700 ml of 95% ethanol was irradiated with a 200-w Hanovia lamp under a cover of nitrogen for 1 hr. [The disappearance of starting material was followed by tlc (silica gel G, 1:1 cyclohexane–ethyl acetate). At this time there was little residual starting material and several new species were present as determined by detection on the tlc plates with 50% sulfuric acid and heat.] The solvent was removed under reduced pressure and the residue adsorbed onto a chromatographic column (150 g of Florisil). The products were eluted during 30 fractions of 250 ml each over a gradient of from 2 to 20% acetone in Skellysolve B. Fractions 5–10 (1.21 g) were combined and recrystallized from acetone–Skellysolve B to give colorless needles, 800 mg, mp 173.5–176.5°. The sample was recrystallized twice from ethanol and three times from acetone–Skellysolve B to give pure 5,11α-dihydroxy-5α-pregnane-3,6,20-trione 11-acetate cyclic 3,-20-bis(ethylene ketal): mp 179.0–180.0°; ν_{max} 3515, 1720, and 1250 cm^{-1}.

Anal. Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19. Found: C, 65.68; H, 8.06.

Fractions 12–15 (240 mg) were combined and recrystallized from acetone–Skellysolve B giving hairlike clusters, 160 mg, mp 156–160°. A sample was recrystallized from acetone–Skellysolve B for analysis [mp 157–160°; ν_{max} 3530, 2750, 1715 (sh), 1725 and 1250 cm^{-1}] to give 5,11α-dihydroxy-3,20-dioxo-B-nor-5β-pregnane-6β-carboxaldehyde 11-acetate cyclic 3,20-bis(ethylene ketal).

Anal. Calcd for $C_{29}H_{40}O_8$: C, 65.83; H, 8.00. Found: C, 66.19; H, 8.27.

5,11α-Dihydroxy-3,20-dioxo-B-nor-5β-pregnane-6β-carboxaldehyde 11-Acetate (7) by Ozonolysis of 11α-Hydroxy-Δ⁵-pregnene-3,20-dione Cyclic 3,20-Bis(ethylene ketal) 11-Acetate (14).—To a saturated solution (about 0.04 *N*) of ozone in methylene chloride at −78° was added compound **14** (4.6 g, 10 moles)

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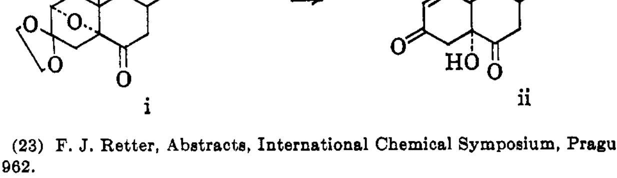
(20) W. Kirmse, *Angew. Chem.*, **71**, 537 (1959).

(21) R. J. Meyer, "Gmelin's Handbuch Der Anorganischen Chemie," Vol. IV, Verlag Chemie, Berlin, 1936, p 855.

(22) This solid has been tentatively assigned structure i, based on the following preliminary evidence; elemental analysis and acid hydrolysis to a trione whose ultraviolet spectrum is characteristic of a Δ^1-3-ketone and whose elemental and infrared analysis are consistent with tentative structure ii. The nmr spectrum of i (Table I) exhibits a triplet centered at 257 cps (J = 5 cps) indicative of an ether oxygen (no OH by infrared) flanked by a single carbon bearing two hydrogens. These data are consistent with an oxygen bridge from C-5 to C-1 or C-2 assuming no deep seated skeletal rearrangement. Such a C-2 to C-5 ether bridge has been reported[23] to be a product of the light-catalyzed oxidation of progesterone in carbon tetrachloride to 2,5-epoxypregnane-3,6,20-trione. Consequently, we favor the 2,5-epoxide structure for i.



i

ii

(23) F. J. Retter, Abstracts, International Chemical Symposium, Prague, 1962.

(24) G. B. Spero, J. C. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956).

(25) S. Rakhit, R. Deghenghi, and C. R. Engle, *Can. J. Chem.*, **41**, 703 (1963).

dissolved in 20 ml of the same solvent. The resulting solution was stirred at −78° for 0.5 hr whereupon the blue solution faded. Zinc dust (10 g) and 40 ml of acetic acid were then added and the suspension was allowed to come to room temperature during 2 hr. The solid was filtered and the filtrate was washed consecutively with water and aqueous sodium bicarbonate, dried (Na_2SO_4), and then taken to dryness under reduced pressure. The residue was taken up in acetone and the unreacted starting material was allowed to crystallize (1.5 g recovered). The solid was filtered, taken to dryness redissolved in methylene chloride, adsorbed onto a column of Florisil (300 g), and eluted with a gradient of from 2 to 15% acetone in Skellysolve B taking 40 250-ml fractions. Employing tlc, the fractions were examined with compound **6** as a control. Fractions 10–16 apparently contained the desired material, thus they were combined and crystallized from acetone–Skellysolve B to give 380 mg (20% based on recovered starting material) of the desired product, mp 156–160° dec.

This product was identical by tlc, infrared, and nmr analysis with the aldehyde **6** and the melting point was not depressed upon admixture with the authentic material.

Anal. Calcd for $C_{29}H_{40}O_8$: C, 65.83; H, 8.19. Found: C, 65.84; H, 8.35.

11α-Hydroxy-6-ketoprogesterone Acetate (8).—A 800-mg sample of the ketone **7** from the above photolyses was dissolved in 10 ml of acetone and treated with 10 drops of 3 *M* hydrochloric acid overnight at room temperature. The solution was diluted to 50 ml with water and the acetone removed under reduced pressure and the product was extracted into methylene chloride. The extracts were washed consecutively with water, saturated sodium chloride solution, and dried (Na_2SO_4). The methylene chloride solution was adsorbed onto 75 g of Florisil and the product was eluted over 20, 100-ml fractions employing a gradient of from 5 to 15% acetone–Skellysolve B followed by 17 additional fractions to 30% acetone. Fractions 26–34 (336 mg) were combined and recrystallized from acetone–Skellysolve B to give 242 mg of a light yellow crystalline solid, mp 178.0–180.5°. A sample was recrystallized for analysis: mp 180.0–181.5°; ν_{max} 1730, 1690, 1603, and 1235 cm^{-1}; λ_{max} 250 mμ (10,550).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.36; H, 7.85.

3β,5α-Dihydroxypregnane-6,20-dione 20-Cyclic (Ethylene ketal) 3-Acetate (9). A. Photolytic.—A sample of the azide (**5**) (2.5 g) in 250 ml of ethanol (95%) was irradiated at 27° with a 200-w Hanovia mercury arc and the disappearance of starting the material was followed by tlc (silica gel G, 1:1 ethyl acetate–cyclohexane). The reaction was terminated after 75 min and the alcohol was removed under reduced pressure. The residue exhibited **8**, distinguishable by tlc (50% sulfuric acid spray/heat). This residue was taken up in methylene chloride and adsorbed onto 150 g of Florisil chromatographic column. The column was eluted over a gradient of from 2 to 10% acetone–petroleum ether during 25 250-ml fractions. Fractions 13–18 contained 356 mg of the product which afforded 190 mg of material, mp 238.5–242.0° dec. A sample was recrystallized for analysis: mp 240.0–242.5°; ν_{max} 3405, 1732, 1709, and 1700 cm.$^{-1}$

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.77; H, 8.70.

B. Thermal.—A small sample (10 mg) of the azide (**5**) was heated over a free flame above its melting point for 1 min. This product was taken up in methylene chloride and examined by tlc [silica gel G, ethyl acetate–cyclohexane (35:65%)]. The products of the thermal decomposition proved to have identical mobilities with those produced by the photolysis A except that the relative intensities of the spots varied for decompositions A and B.

3β,5α-Dihydroxypregnane-6,20-dione 3-Acetate (10).—The crude chromatographed product **9** from preparation A above (*ca.* 760 mg) was taken up in 15 ml of 67% acetic acid with warming, then allowed to stand for 18 hr at room temperature. The solution was diluted with 25 ml of water, then taken to dryness under reduced pressure. The residue in benzene was adsorbed onto 75 g of neutral activity I alumina and eluted with 30, 50-ml portions of solvent over a gradient of from 6 to 50% ether in benzene, four fractions of 100% ether, followed by 20 fractions over a gradient of from 0 to 10% methanol in benzene. Fractions 46 and 47 (590 mg) were rechromatographed on 50 g of silica gel. The column was eluted with 128 5-ml fractions of 1:1 ethyl acetate–chloroform. Fractions 15–21 were combined and recrystallized from acetone giving 97 mg of the product, mp 217.5–219.0°. This material was recrystallized twice: mp 218.5–219.5° (224.5–225.5° corrected) (lit.[7a,b] mp 222.5–224° and 226.5–227.0°); infrared spectrum consistent with structure.

6β-Hydroxymethyl-5β-11α-dihydroxy-B-nor-pregnane-3,20-dione Bis(cyclic ethylene ketal) 11-Acetate (15).—The above aldehyde (250 mg) in 7 ml of THF was treated with 50 mg of sodium borohydride in 4 ml of water at room temperature for 10 min. One drop of acetic acid was added, followed by 10 ml of water. The THF was then removed under reduced pressure and the crystalline solid was isolated and washed well with water to give 215 mg: mp 164–166°; infrared spectrum consistent with structure. Tlc on silica gel G (1:1 ethyl acetate–cyclohexane, indicated a single major product detectable with permanganate–periodate spray.

6β-Hydroxymethyl-5β,11α-dihydroxy-B-nor-pregnane-3,20-dione 11-Acetate (16).—The bisketal (**15**) above (100 mg) was taken up in 3 ml of 67% acetic acid–water with warming. After 1 hr the reaction mixture was diluted to 10 ml with water and chilled in an ice bath. The product crystallized as white needles, mp 212–213.2°. Tlc on silica gel (1:3 cyclohexane–ethyl acetate) indicated only a single spot (detected with hot 50% H_2SO_4): infrared ν_{max} 3380, 1725, 1702, 1240, and 1028 cm^{-1}; ORD (dioxane) negative Cotton curve, characteristic of an A/B *cis*-ring junction (see Figure 1).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.01; H, 8.63.

Photolysis of 6β-Azido-5α,11α-dihydroxypregnane-3,20-dione, Cyclic Bis-3,20-(ethylene ketal) 11-Acetate in Benzene Solution.—A 1.65-g sample of the azide was dissolved in 260 ml of benzene and irradiated as described above. After 1.5 hr, tlc indicated that the starting material (as described above) was in very low concentration. At this time the irradiation was stopped and the benzene was removed under reduced pressure. The product was adsorbed onto a column of 175 g of Florisil and eluted over a gradient of from 1 to 7.5% acetone–petroleum ether during 25 375-ml fractions. Fractions 9–12 contained 57 mg of crystalline material which upon recrystallization from acetone–petroleum ether gave a material, mp 179.5–182°, which was identified by infrared and nuclear magnetic resonance analysis as the known[22] Δ^5 compound (**14**). Admixture with an authentic sample exhibited no melting point depression. Fractions 15–20 contained 569 mg (34%) of the 5-hydroxy 6-ketone (**7**) *vita infra*. This material was identical with an authentic sample by infrared analysis and exhibited no melting point depression upon admixture with the authentic sample.

Synthesis of the Proposed Transannular Epoxide (i). A. By Prolonged Photolysis of the Azide 3.—A 1.0-g portion of the azide **3** dissolved in 220 ml of 95% ethanol was irradiated in a quartz cell employing a 200-w Hanovia mercury vapor lamp at 27° for 12 hr. The solid which precipitated was filtered, washed with ethanol, and dried, giving 120 mg, mp 292–295° dec. This material was recrystallized twice for analysis from acetone: mp 298° dec; ν_{max} 1705, 1720, and (sh) 1750 cm^{-1}; no OH; ultraviolet analysis negative. These data are consistent, along with the nmr (Table I), with structure i.

Anal. Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19. Found: C, 65.94; H, 8.73.

B. By Irradiation of 5α,11α-Dihydroxypregnane-3,6,20-trione Cyclic 3,20-Bis(ethylene ketal) 11-Acetate (7).—A 200-mg sample of the dihydroxy ketone (**7**) was dissolved in 140 ml of ethanol and photolyzed for 2 hr as described above. At this time a white crystalline solid had separated. The crystalline material was isolated, washed with a small amount of ethanol, and air dried, mp 279–284° dec. This material was identical with the 12-hr photolysis product (**14**) assigned tentatively the structure 11α-hydroxy-2α,5α-epoxypregnane-3,6,20-trione cyclic 3,20-bis(ethylene ketal) 11-acetate. Identical by tlc, the product exhibited no melting point depression upon admixture with an authentic sample of i. The mother liquors were taken to dryness and examined by tlc (1:1 ethyl acetate-cyclohexane, silica gel G) and found not to contain any aldehyde **6** but rather starting material and additional product on comparison with authentic samples.

C. Attempted Synthesis from 5β,11α-Dihydroxy-3,20-dione-B-nor-5β-pregnane-6β-carboxaldehyde Cyclic 3,20-Bis(ethyl acetal) 11-Acetate (6).—A 100-mg sample of the aldehyde (**6**) dissolved in 140 ml of ethanol was photolyzed as described above for 2 hr. The solvent was then removed under reduced pressure and the residue was examined by tlc as described in the previous experiment. In this manner starting material, two new and unknown substances and no epoxide i or dihydroxy ketone **7** were detected.

Acid-Catalyzed Hydrolysis and Rearrangement of the Proposed Transannular Epoxide to the Proposed 5α,11α-Dihydroxy-4-pregnane-3,6,20-trione 3,20-Bis(cyclic ethylene acetal) 11-Acetate (ii).—The photolysis product (i) above (120 mg) was suspended in 15 ml of methanol, the solution heated on a steam bath, and treated with 1 ml of 3 *N* hydrochloric acid (dropwise). The solution was allowed to come to room temperature overnight. The solution was then diluted to 30 ml with water and the alcohol was removed under reduced pressure. The residual semisolid was separated and crystallized fractionally (decant from oil) from acetone–Skellysolve B, mp 171.5–174°. A single recrystallization provided an analytical sample: ν_{max} 3070 (bonded OH), 1737, 1675, 1608, and 1245 cm^{-1}; λ_{max} 231 mμ (11,550).

Anal. Calcd for $C_{23}H_{30}O_6$: C, 67.71; H, 8.09. Found: C, 68.63; H, 7.51.

6β-Azido-5α-hydroxycholestan-3-one Cyclic Ethylene Ketal (12).—A sample of epoxide **11**[26] containing some β isomer (5.15 g, mp 101–112°) dissolved in dioxane (100 ml) was treated with sodium azide (1.4 g) and *p*-toluene sulfonic acid (100 mg), dissolved in water (25 ml), and the solution heated to reflux for 7 days. The dioxane was distilled under reduced pressure and the residue suspended in water (200 ml). The product was extracted into methylene chloride. The combined extracts were washed with water, saturated sodium chloride solution, and dried (Na_2SO_4). The methylene chloride solution was adsorbed onto a column of Florisil (350 g) and eluted over a linear gradient of from 2 to 10% acetone–petroleum ether during 25, 400-ml fractions. Fractions 3–5 proved by tlc (silica gel G, 25% ethyl acetate–cyclohexane) to be a mixture of the azide and epoxide. These fractions (3.83 g) were adsorbed onto a 4.0 × 42 cm column of silica gel made up with cyclohexane and the column eluted with 25, 50-ml portions of ethyl acetate–cyclohexane (1:3). Fractions 7–10 (1.17 g) were combined and recrystallized from acetone–methanol, 1.05 g of azide, mp 89.5–91°. A sample was recrystallized for analysis with no change in melting point: ν_{max} 3460, 2080, 1190, 1170, 1100, and 1025 cm^{-1}.

Anal. Calcd for $C_{29}H_{49}N_3O_3$: C, 71.41; H, 10.31; N, 8.62. Found: C, 71.29; H, 10.05; N, 8.80.

6β-Azido-5α-hydroxycholestan-3-one (13).—The above ketal (**21**) (700 mg) dissolved in 15 ml of acetic acid with warming and further treated with 2 ml of water. The solution, after standing overnight at room temperature, was diluted with 50 ml of water, whereupon a solid precipitated. The product was isolated, washed with water, and recrystallized from acetone to give 530 mg, mp 180–182° dec. The sample was recrystallized three times from acetone for analysis: mp 182.5–184.0°; λ_{max}^{EtOH} 228 mμ (ε 1050); ORD (dioxane) $[M]_{372.5,min}$ −1001°, $[M]_{317.5,max}$ −97°, $[M]_{470}$ −702°; infrared spectrum consistent with structure.

Anal. Calcd for $C_{27}H_{45}N_3O_2$: C, 73.09; H, 10.22; N, 9.47. Found: C, 72.86; H, 10.41; N, 9.55.

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[26] G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

Stereoisomerism of 5-(α-Hydroxy-α-2-pyridylbenzyl)-7-(α-2-pyridylbenzylidene)-5-norbornene-2,3-dicarboximide, a Selective Rat Toxicant[1,2]

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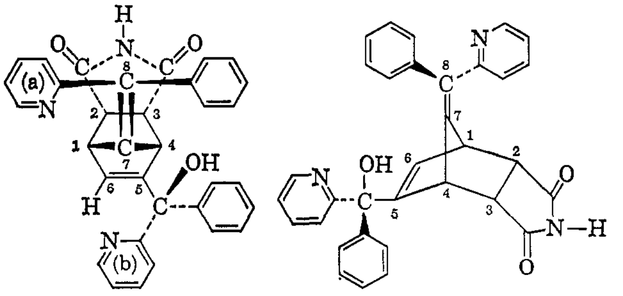
The eight possible racemates of norbormide **2**[2] were isolated and characterized. Assignments of stereochemistry are presented in Table I. The *endo–exo* assignments were based on (1) the preponderance of *endo* isomers from the Diels–Alder synthesis, (2) the thermal isomerization of *endo* to *exo* isomers, and (3) the downfield location in the nmr spectra of the resonance peaks of the 2,3-protons of *endo* isomers relative to the corresponding peaks of the *exo* isomers. The *cis–trans* assignments are based on the relative positions of the 1- and 4-proton peaks, the *trans* isomer having the 1-proton peak downfield. Photochemical isomerization indicated that *trans* to *cis* was the preferred conversion and demonstrated which *endo* (or *exo*) isomers had the same configurations of substituents on the carbinol carbon. These assignments based on chemical and spectral data have been confirmed by an independent X-ray study which also permitted *erythro–threo* designations to be made for the four *endo* isomers.

The selective toxicity of norbormide **2**[2] to members of the genus *rattus* has been reported.[3a] It is not lethal to any of the other 38 species of mammals (including ten rodent species), fish, or fowl tested, generally at 100 times the dose lethal to rats.[3b] The observation[3a] that a very considerable difference in rat toxicity existed among several of the isomers which comprise norbormide led us to obtain all of the isomers and investigate them in detail.

Chart I



trans–endo–erythro-orbormide (**2**)

Two representations of a norbormide isomer are illustrated in Chart I. The molecule has four elements of dissymmetry which give rise to eight racemates. There are five asymmetric carbon atoms: the carbinol carbon and atoms 1–4. Owing to the restriction of *cis* bridging across atoms 1 and 4 and the *cis* fusion of the imide at C-2 and C-3, each of these pairs is equivalent to one asymmetric carbon. Thus, three asymmetric

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[1] Presented in part before the Division of Medicinal Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

[2] Norbormide is the common name of the mixture of stereoisomers of 5-(α-hydroxy-α-2-pyridylbenzyl)-7-(α-2-pyridylbenzylidene)-5-norbornene-2,3-dicarboximide (**2**).

[3] (a) A. P. Roszkowski, G. I. Poos, and R. J. Mohrbacher, *Science*, **144**, 412 (1964); (b) A. P. Roszkowski, *J. Pharmacol. Exptl. Therap.*, **149**, 288 (1965).