640. *Aza-steroids. Part VII.** 3-*Aza*-A-*homopregn*-4a-*ene and Related Compounds.*

By C. W. Shoppee, Ruth E. Lack, and B. C. Newman.

20,20-Ethylenedioxypregn-4-en-3-one oxime, by Beckmann rearrangement and hydrolysis of the 20-ketal group, gives 3-aza-A-homopregn-4a-ene-4,20-dione. Reduction of the 20-ketal derivative with lithium aluminium hydride gives 3-aza-A-homopregn-4a-en-20-one. Pregn-4-en-3-one oxime undergoes Beckmann rearrangement to give 3-aza-A-homopregn-4a-en-4-one.

Nuclear magnetic resonance spectroscopy has been used to distinguish between *anti*- and *syn*-forms of the above mentioned oximes and to clarify the relationship between the two reported forms of cholest-4-en-3-one oxime.

In a further attempt to prepare modified steroids with physiological activity of anti-hormonal type, we have prepared some 3-aza-A-homopregnane derivatives. This work has followed the recent syntheses of A-homo-lactams derived from Δ^4-3-ketones in the cholestane,[1,2] androstane,[2,3] and 17-substituted androstane [2,4] series.

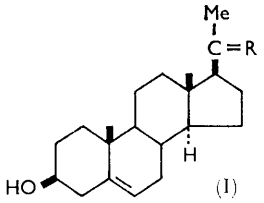
20,20-Ethylenedioxypregn-5-en-3β-ol (I; R = O·CH_2·CH_2·O) was prepared in 75% yield by a modification of the method employed in the preparation of the 3,3-ethylenedioxy-derivative of testosterone.[5] Oxidation of this ketal (I), with chromic acid in acetone [6] or ether,[7] resulted in hydrolysis of the 20-ketal group; the use of excess of chromium trioxide in pyridine [8] yielded mainly 20,20-ethylenedioxypregn-4-ene-3,6-dione (VI), whilst no reaction occurred with one equivalent of chromium trioxide in pyridine. Oppenauer oxidation of the ketal (I; R = O·CH_2·CH_2·O), however, gave an 80% yield of 20,20-ethylenedioxypregn-4-en-3-one (II; R = O·CH_2·CH_2·O), converted into the oxime (III; R = O·CH_2·CH_2·O) by treatment with alkaline hydroxylamine hydrochloride. Brief hydrolysis with toluene-*p*-sulphonic acid gave the 3-oxime of pregn-4-ene-3,20-dione (II; R = O).

Beckmann rearrangement of the oxime (III; R = O), containing 86% of the *anti*-isomer, with thionyl chloride at 10° [1] gave a 15% yield of 3-aza-A-homopregn-4a-ene-4,20-dione (IV; R = O) ($\lambda_{max.}$ 224 mμ; log ε 4·2) as the only product, whilst in dioxan [4]

* Part VI, Shoppee and Roy, *J.*, 1963, 3774.

[1] Shoppee, Krueger, and Mirrington, *J.*, 1962, 1050.
[2] Doorenbos and Singh, *J. Pharm. Sci.*, 1962, **51**, 318.
[3] Shoppee and Krueger, *J.*, 1961, 3641.
[4] Mazur, *J. Org. Chem.*, 1963, **28**, 248.
[5] Campbell, Babcock, and Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 4717.
[6] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39; Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548; Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.
[7] Brown and Garg, *J. Amer. Chem. Soc.*, 1961, **83**, 2952.
[8] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.

the yield of the same ε-lactam (IV; R = O) was increased to 58%. This result supports the observation by Mazur [4] that the product from the Beckmann rearrangement, with thionyl chloride in dioxan, of the oximes of unsaturated ketones is not necessarily related configurationally to the starting oxime.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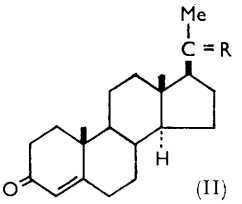
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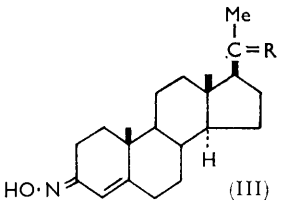
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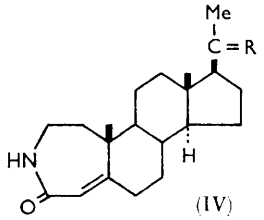
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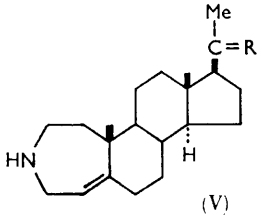
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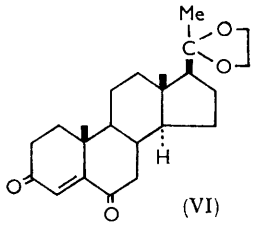
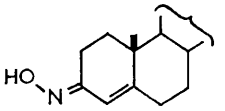

(VI)

Ketalisation of the 20-keto-group in (IV; R = O), followed by prolonged reduction with lithium aluminium hydride in ether or tetrahydrofuran and hydrolysis of the ketal group, gave 3-aza-A-homopregn-4a-en-20-one (V; R = O) characterised as the *N*-acetyl derivative.

Pregnenolone (I; R = O) gave pregn-5-en-3β-ol (I; R = H_2) by a modified Wolff–Kishner reduction [9] under nitrogen,[3] and this was converted by Jones's oxidation [6] into pregn-5-en-3-one, which readily rearranged when treated with oxalic acid in ethanol [10] to pregn-4-en-3-one (II; R = H_2). This ketone, also obtained in 82% yield by Oppenauer oxidation of pregn-5-en-3β-ol (I; R = H_2), gave the oxime (III; R = H_2), which, after recrystallisation from methanol, contained 67% of the *anti*-isomer. Beckmann rearrangement of this oxime with thionyl chloride [1] gave 3-aza-A-homopregn-4a-en-4-one (IV; R = H_2) in 35% yield as the only product.

Slomp and Wechter [11] and Mazur,[4] using nuclear magnetic resonance spectroscopy, established a method of distinguishing between the *anti*- (X) and *syn*- (Y) isomers of the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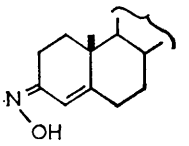
anti


(Y)

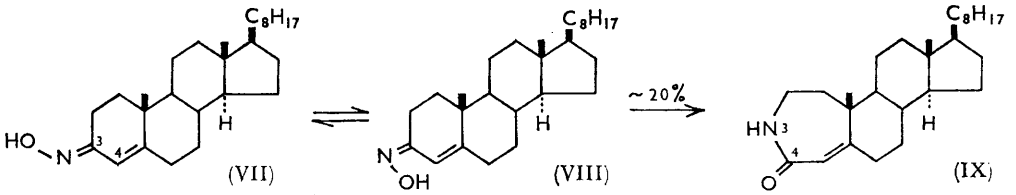
syn

oximes derived from αβ-unsaturated ketones in the steroid series by examining the chemical shift of the vinyl proton caused by the proximity of the hydroxyl group in the *syn*-oxime (Y). The nuclear magnetic resonance spectrum of the 3-oxime of pregn-4-ene-3,20-dione (III; R = O) showed peaks at τ 3·52 (*syn*) and 4·23 (*anti*) in a ratio corresponding to 86% of *anti*, after recrystallisation from methanol. The ratio of *anti*-form (X) to *syn*-form (Y) varied with recrystallisation from different solvents but neither isomer could be obtained pure.

This variation in the ratio of *anti*- to *syn*-isomers appears to be due to fractional crystallisation rather than to interconversion of the isomers, since the pure *anti*-oxime of cholest-4-en-3-one [1] (VII) (m. p. 62°/152°; τ 4·23) was unchanged when recrystallised from solvents

[9] Huang-Minlon, *J. Amer. Chem. Soc.*, 1949, **71**, 3301.
[10] Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4377.
[11] Slomp and Wechter, *Chem. and Ind.*, 1962, 41.

of different polarity. The oxime of cholest-4-en-3-one (m. p. 152°) previously reported as the *syn*-isomer [1] (VIII) is a mixture of *syn* (τ 3·52) and *anti* (τ 4·23) in the ratio 2 : 3. It is curious that the pure *anti*-oxime (VII) on attempted Beckmann change in benzene with



p-acetamidobenzenesulphonyl chloride gave <13% of the ε-lactam (IX), possibly by partial conversion into the mixture of *syn*- (VIII) and *anti*-oxime (VII) constituting the so-called "B"-form; the "B"-form, by Beckmann rearrangement in pentane with thionyl chloride, likewise gave only the ε-lactam (IX), expected from the *syn*-oxime (VIII), in ~20% yield. The failure of the pure *anti*-oxime (VII) to undergo Beckmann change with thionyl chloride alone to give the 3-oxo-4-aza-isomer of (IX) may be connected with the presence of some degree of double-bond character in the 3,4-bond.

Experimental

For general experimental directions, see *J.*, 1958, 3458. $[\alpha]_D$'s are for chloroform solutions. Ultraviolet absorption spectra were measured for ethanol solutions in a Perkin-Elmer model 4000Å spectrophotometer, and infrared absorption spectra were determined in carbon tetrachloride (unless otherwise specified) on a Perkin-Elmer model 221 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian D.P. 60 instrument at 60 Mc./sec. with deuteriochloroform as solvent and tetramethylsilane as internal reference.

20,20-*Ethylenedioxypregn-5-en-3β-ol* (I; R = O·CH_2·CH_2·O).—Pregn-5-en-3β-ol-20-one (4 g.) was treated under nitrogen with ethylene glycol (600 ml.) and toluene-*p*-sulphonic acid (100 mg.) at 125—135° while ethylene glycol (500 ml.) was slowly distilled off at 14 mm. After 2 hr. the mixture was cooled and neutralised with a saturated solution of sodium hydrogen carbonate. The *product* (3·4 g.) had m. p. 166—169° (from methanol), $[\alpha]_D$ −32° (*c* 1·6) [Found (after repeated azeotropic distillation with toluene): C, 76·7; H, 10·3. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%].

Oxidation of 20,20-*Ethylenedioxypregn-5-en-3β-ol.*—(*a*) The ketal (I; R = O·CH_2·CH_2·O) (200 mg.) was treated with a standard solution of chromic acid [a solution of pure chromium trioxide (26·73 g.) in concentrated sulphuric acid (23 ml.) diluted with water to a volume of 100 ml.[6]] under nitrogen for 5 min. The usual isolation procedure gave a crude material, probably a mixture of pregn-5-en-3β-ol-20-one and pregn-5-ene-3,20-dione. Treatment of the ketal (I; R = O·CH_2·CH_2·O) with chromic acid in ether [7] also resulted in hydrolysis of the 20-ketal group.

(*b*) The ketal (I; R = O·CH_2·CH_2·O) (400 mg.) in pyridine (5 ml.) was slowly added to a suspension of finely powdered chromium trioxide (760 mg.) in pyridine (15 ml.), with cooling. After 3 days, water (200 ml.) was added and the product was extracted with ether. The product (350 mg.) was chromatographed on silica gel (30 g.). Elution with ether–pentane (1 : 1) yielded 20,20-*ethylenedioxypregn-4-ene-3,6-dione* (V) (170 mg.) as yellow needles (from ether–pentane), m. p. 194—197°, $[\alpha]_D$ −27°, $\lambda_{max.}$ 253 mμ (log ε 4·0), $\nu_{max.}$ 1691 cm.$^{-1}$ (Found: C, 74·3; H, 8·8. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·65%).

(*c*) 20,20-Ethylenedioxypregn-5-en-3β-ol (3·1 g.) in refluxing acetone (25 ml.) and benzene (33 ml.) was treated with a hot solution of aluminium isopropoxide (2·8 g.) in benzene (18 ml.) for 8 hr. The crude product, extracted with benzene, was purified by chromatography on alumina (95 g.). Elution with ether–benzene (1 : 1) gave 20,20-*ethylenedioxypregn-4-en-3-one* (2·5 g.), m. p. 189—191° (from methanol), $[\alpha]_D$ +102° (*c* 1·0), $\lambda_{max.}$ 241 mμ (log ε 4·15), $\nu_{max.}$ 1677 cm.$^{-1}$ (Found: C, 77·1; H, 9·6. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·55%).

20,20-*Ethylenedioxypregn-4-en-3-one Oxime* (III; R = O·CH_2·CH_2·O).—The ketal (II; R = O·CH_2·CH_2·O) (1·55 g.) was treated with a solution of hydroxylamine hydrochloride (1·6 g.) and potassium hydroxide (6·4 g.) in methanol (70 ml.) at 65° for 1 hr. The usual isolation

procedure afforded the *oxime* (1·25 g.), m. p. 192—195°, $[\alpha]_D$ +155° (*c* 1·0), $\lambda_{max.}$ 241 mμ (log ε 4·33), $\nu_{max.}$ 3600, 1632 (C=N) cm.$^{-1}$ (Found: C, 74·0; H, 9·6; N, 3·4. $C_{23}H_{35}NO_3$ requires C, 73·95; H, 9·45; N, 3·75%).

Pregn-4-ene-3,20-dione 3-Oxime (III; R = O).—A solution of the ketal (III; R = O·CH_2·CH_2·O) (1·25 g.) in methanol (100 ml.) was treated with toluene-*p*-sulphonic acid (200 mg.) at 65° for 10 min. After removal of methanol by distillation, the product was extracted with chloroform–ether (1 : 2), washed with saturated sodium hydrogen carbonate solution, and isolated by evaporation. The *oxime* (770 mg.) had m. p. 241—244° (from methanol), $[\alpha]_D$ +194° (*c* 1·65), $\lambda_{max.}$ 240 mμ (log ε 4·34), $\nu_{max.}$ ($CHCl_3$) 3582, 1689 (C=O), 1627 (C=N) cm.$^{-1}$ (Found: C, 76·9; H, 9·2; N, 4·0. $C_{21}H_{34}NO_2$ requires C, 76·55; H, 9·5; N, 4·25%). This oxime was a mixture of *syn* (τ 3·52) and *anti* (τ 4·23) isomers in the ratio 3 : 17.

3-Aza-A-homopregn-4a-ene-4,20-dione (V; R = O).—(*a*) The oxime (III; R = O) (400 mg.) was added during 15 min. to thionyl chloride (5 ml.) at 10°, and the mixture was poured into 4N-potassium hydroxide (45 ml.) previously heated to 90°. The crude product, extracted with chloroform, was chromatographed on alumina (12 g.). Elution with chloroform–ether (1 : 1) afforded unchanged oxime (III; R = O) (180 mg.), whilst elution with chloroform afforded the required *dione* (58 mg.), m. p. 264—266° (from acetone), $[\alpha]_D$ +95° (*c* 1·2), $\lambda_{max.}$ 224 mμ (log ε 4·20), $\nu_{max.}$ 3420, 1699 (C-20=O), 1647 (C-4=O), 1605 (C=C) cm.$^{-1}$ (Found: C, 76·45; H, 9·25. $C_{21}H_{31}NO_2$ requires C, 76·55; H, 9·5%).

(*b*) A solution of the oxime (III; R = O) (2·34 g.) in dioxan (200 ml.) was treated with thionyl chloride (30 ml.) at 10°. After 1 hr. at 20°, the solution was poured into saturated potassium hydrogen carbonate solution, and the product extracted with chloroform and chromatographed on silica gel (190 g.). Elution with methanol–ethyl acetate (1 : 49) afforded the lactam (V; R = O) (1·35 g.).

20,20-Ethylenedioxy-3-aza-A-homopregn-4a-en-4-one (V; R = O·CH_2·CH_2·O).—The lactam (V; R = O) (1 g.) was treated in nitrogen with ethylene glycol (200 ml.) and toluene-*p*-sulphonic acid (40 mg.) at 135—145° while ethylene glycol (150 ml.) was slowly distilled off at 10 mm. After 1 hr., the mixture was cooled and neutralised with a saturated solution of sodium hydrogen carbonate, and the product extracted with chloroform. Chromatography on alumina (50 g.) and elution with chloroform–ether (1 : 1) afforded the *product* (880 mg.) m. p. 260—261° (from methanol), $[\alpha]_D$ +26° (*c* 1·7), $\lambda_{max.}$ 220 mμ (log ε 4·22), $\nu_{max.}$ ($CHCl_3$) 3342, 1657, 1651, 1645, 1606 cm.$^{-1}$ (Found: C, 73·55; H, 9·2. $C_{23}H_{35}NO_3$ requires C, 73·95; H, 9·45%).

20,20-Ethylenedioxy-3-aza-A-homopregn-4a-ene (VI; R = O·CH_2·CH_2·O).—The ketal (V; R = O·CH_2·CH_2·O) (950 mg.) was treated with lithium aluminium hydride (4·5 g.) in ether (1·5 l.) at 36° for 90 hr. After the excess of the reagent had been decomposed with ice–water, the ethereal solution was decanted, the residual inorganic material extracted with ether, and the combined ethereal solutions dried briefly and evaporated. The resultant oil was chromatographed on alumina (25 g.). Elution with ether afforded amorphous 20,20-ethylenedioxy-3-aza-A-homopregn-4a-ene (290 mg.), showing no absorption at 220 mμ and no N–H stretching band at 3400 cm.$^{-1}$; it was not analysed at this stage. Elution with chloroform–ether (1 : 1) afforded unchanged starting ketal (60 mg.).

3-Aza-A-homopregn-4a-en-20-one (V; R = O).—A solution of the ketal (VI; R = O·CH_2·CH_2·O) (290 mg.) in methanol (30 ml.) was treated with toluene-*p*-sulphonic acid (20 mg.) at 65° for 10 min. After removal of methanol by distillation, the product was extracted with ether, and the extract washed with a saturated solution of sodium hydrogen carbonate. Evaporation afforded an oil which was chromatographed on alumina (8·5 g.). Elution with chloroform–ether (1 : 3, 1 : 1) and with chloroform afforded the *ketone* as a non-crystallisable oil (120 mg.), $\nu_{max.}$ (Nujol) 1710 (C-20=O) cm.$^{-1}$. The *N*-acetyl derivative, prepared by use of acetic anhydride–pyridine at 20° for 15 hr., after chromatography on alumina and elution with chloroform–ether (1 : 3), was amorphous and was distilled at 200°/0·1 mm., to afford a glass.

Pregn-5-en-3β-ol (I; R = H_2).—Pregn-5-en-3β-ol-20-one (I; R = O) (6 g.) was heated under nitrogen with diethylene glycol (150 ml.) and hydrazine hydrate (15 ml.) at 135—145° for 1 hr. The solution was then heated to 190° to drive off excess hydrazine and water, and cooled, potassium hydroxide (15 g.) was added, and the mixture reheated at 180—200° for 3 hr. The product, extracted with ether, afforded pregn-5-en-3β-ol (5·4 g.), m. p. 132—133° (from methanol) (lit.,[9] 133—134°); no C=O band at 1700 cm.$^{-1}$.

Pregn-4-en-3-one (II; R = H_2).—(*a*) Pregn-5-en-3β-ol (I; R = H_2) (940 mg.) in acetone (200 ml.) was treated with standard chromic acid reagent[6] (3·1 ml.) for 5 min. at 15° under

nitrogen. After addition of water, the product was extracted with ether and the material chromatographed on silica gel (50 g.). Elution with ether–pentane (1 : 9) afforded *pregn-5-en-3-one* (470 mg.), m. p. 116—127° (from methanol), $[\alpha]_D$ +4° (*c* 1·0), no ultraviolet absorption at 240 mμ, $\nu_{max.}$ 1723 cm.$^{-1}$ (Found: C, 84·1; H, 10·95. $C_{21}H_{32}O$ requires C, 83·95; H, 10·75%). Pregn-5-en-3-one (150 mg.) was then treated with hydrated oxalic acid (15 mg.) and ethanol (1·2 ml.) at 78° for 10 min. The product was extracted with ether, washed with saturated sodium hydrogen carbonate solution, and chromatographed on alumina (4·5 g.). Elution with ether–benzene (1 : 50, 1 : 20) afforded *pregn-4-en-3-one* (75 mg.), m. p. 102—104° (from pentane), $[\alpha]_D$ +121° (*c* 1·3), $\lambda_{max.}$ 241 mμ (log ε 4·20), $\nu_{max.}$ 1678 cm.$^{-1}$ (Found: C, 83·75; H, 10·9%).

(*b*) Pregn-5-en-3β-ol (I; R = H_2) (2 g.) was treated with acetone (19 ml.), benzene (40 ml.), and aluminium isopropoxide (2·1 g.) at 85° for 8 hr. The product was extracted with chloroform and chromatographed on alumina (60 g.); elution with benzene and ether–benzene (1 : 99—1 : 9) afforded pregn-4-en-3-one (1·44 g.).

Pregn-4-en-3-one Oxime (III; R = H_2).—A solution of pregn-4-en-3-one (II; R = H_2) (1·02 g.) in pentane (75 ml.) was shaken with a methanolic solution of hydroxylamine acetate (10 ml.; 20%) (prepared by titrating molar quantities of hydroxylamine hydrochloride and sodium acetate, adding methanol, and removing sodium chloride by filtration) for 3 hr. at 20°. The solvents were distilled off and the product extracted with ether, to afford the *oxime* (880 mg.), m. p. 161—164° (from methanol), $[\alpha]_D$ +194° (*c* 1·2), $\lambda_{max.}$ 240 mμ (log ε 4·28), $\nu_{max.}$ 3603, 1636, 1631 cm.$^{-1}$ (Found: C, 79·8; H, 10·3. $C_{21}H_{33}NO$ requires C, 79·9; H, 10·5%). This oxime was a mixture of *syn* (τ 3·53) and *anti* (τ 4·21) isomers in the ratio 1 : 2.

3-Aza-A-homopregn-4a-en-4-one (V; R = H_2).—The oxime (III; R = H_2) (400 mg.) was added during 10 min. to thionyl chloride (4 ml.) at 10°. The mixture was added to 4N-potassium hydroxide previously heated to 90°. The product was extracted with chloroform–ether (1 : 3) and chromatographed on alumina (12 g.). Elution with chloroform–ether (1 : 50—1 : 1) afforded pregn-4-en-3-one oxime (120 mg.). Elution with chloroform–ether (1 : 1) afforded the ε-lactam (165 mg.), which by re-chromatography on alumina (7·5 g.) and elution with chloroform afforded *3-aza-A-homopregn-4a-en-4-one* (138 mg.), m. p. 228—231° [from acetone–ether (1 : 1)], $[\alpha]_D$ +34° (*c* 0·85), $\lambda_{max.}$ 223 mμ (log ε 4·18), $\nu_{max.}$ ($CHCl_3$) 3420, 1644, 1603 (C=C) cm.$^{-1}$ (Found: C, 80·0; H, 10·75. $C_{21}H_{33}NO$ requires C, 79·95; H, 10·55%).

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