reported for the *gaseous* state at 298° K.[6] The large experimental error precludes any definite conclusion, but the data do suggest that despite a concerted and seemingly effective effort to maintain their samples in the liquid state, Allinger and Coke may have had an appreciable fraction of their samples in the gaseous state at the temperatures used. Perhaps the high pressures developed during the equilibrations, when the samples were heated well above their boiling points, can account for some of the difference.

As predicted in the literature,[5,6] *trans*-hydrindane is the more stable isomer at room temperature, due to a more favorable enthalpy. At higher temperatures (above 466° K.[5]) the *cis* form is more stable because of a more favorable entropy. The conformational implications of these facts have been considered in detail.[5,6,9]

Experimental

Preparation of the Hydrindanes.—One liter of commercial indene and 40 g. of 5% palladium on charcoal were placed in a 4-l. bomb. Hydrogen pressure of 1000–2000 p.s.i. and a temperature of 160° were maintained for 24 hr. Distillation of the crude product through a 100-cm. column filled with Podbielniak "Heli-Pak" packing gave 600 g. of material boiling at 159–166°. The remainder of the product was primarily indane (b.p. 177°).

The hydrindane mixture obtained from the hydrogenation product, containing approximately 70% *cis* isomer, was used for approaching the equilibria from the *cis*-rich side. *trans*-Rich material was made by equilibrating a 100-g. portion of the hydrogenation product mixture with 10 g. of aluminum bromide at room temperature overnight. Distillation of this product through the 100-cm. packed column gave 75 g. of material containing more than 80% *trans* isomer.

The pure isomers were prepared only in small quantities. Two careful distillations of 50 g. of the hydrogenation mixture through the 100-cm. packed column gave 3 g. of material boiling at 166° (755 mm.), which was shown by gas chromatographic analysis to be greater than 99.5% pure *cis* isomer. Two similar distillations of 50 g. of the mixture containing 70% *trans*-hydrindane gave 2 g. of material boiling at 159° (760 mm.). Gas chromatographic analysis showed that this material was better than 98% pure *trans*-hydrindane.

Equilibration.—Sample mixtures were prepared by stirring 15 ml. of either *cis*- or *trans*-rich hydrindane with freshly powdered aluminum bromide at room temperature for 5 min. Aliquots (2–3 ml.) of this aluminum bromide-saturated hydrindane solution were then pipetted into 5-ml. Pyrex ampoules and sealed. The samples were then placed in the desired temperature-controlled environment for the equilibration period, which ranged from 1 day at the higher temperatures to several weeks at the lower temperatures. The concentration of indane necessary to retard fragmentation and yet allow equilibration at a reasonable rate was a very critical factor in carrying out these equilibrations. This had to be determined by trial and error for each temperature, which ultimately required the preparation and analysis of approximately 200 samples. The concentrations of indane required varied from zero for the 251° K. sample to 6–7% for the 320° K. sample. Equilibrations at 251 and 277° K. were carried out in rooms closely regulated at those temperatures. Although fluctuations of 2° occurred, the equilibrations were so slow that the average temperatures can be used. At 300.0 and 320.3° K., the samples were immersed in oil baths regulated to ±0.05°. Individual samples were removed and analyzed regularly to follow the progress of each group of *cis*- or *trans*-rich samples toward equilibrium. This assured that the equilibrium was approached from both sides at each temperature. When an ampoule was opened, the sample was pipetted immediately into a test tube containing 10 ml. of cold water and mixed thoroughly to destroy the catalyst. The hydrindane layer was then pipetted off, dried with 0.5 g. of anhydrous potassium carbonate, and centrifuged.

Analysis.—The gas chromatographic analyses were carried out on a Perkin–Elmer Vapor Fractometer using a 300-ft. Golay "R" column at a temperature of 100° and helium pressure of 20 p.s.i. The separation was complete, and the retention times were 8.4 min. (*trans*) and 9.3 min. (*cis*). The product of the retention time and the peak height was taken as the measure of each peak. The number thus obtained for the *trans* peak was then divided by the corresponding number for the *cis* peak to get the ratio of *trans*- to *cis*-hydrindane. Two standard samples were carefully prepared and analyzed ten times each. These data showed that a correction factor of 0.942 for the *trans*- to *cis*-hydrindane ratio was required. This factor was applied to the results of all analyses.

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(9) *Cf.* also W. B. Moniz and J. A. Dixon, *J. Am. Chem. Soc.*, **83**, 1671 (1961).

Azasteroids. III.[1] 3-Aza-A-homo Androgens

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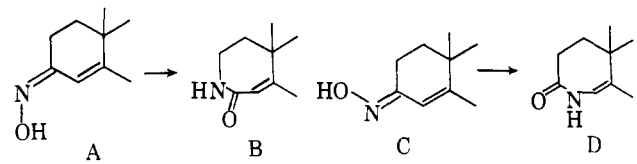
The continuing search for modified steroids with hormonal or antihormonal activity is currently emphasizing structures with hetero atoms incorporated in the polycyclic nucleus.[2–4] Our own interest has been in azasteroids[1,5] which are particularly attractive since they are potentially available from any ketosteroid *via* oxime and Beckmann rearrangement. The present report concerns work leading to A-homo derivatives of testosterone and 17α-methyltestosterone.

Beckmann rearrangement of an α,β-unsaturated ketoxime may give either an α,β-unsaturated lactam or an enamine lactam depending on the stereochemistry of the starting oxime. Thus, *syn*-oxime A leads to lactam B while *anti*-oxime C should give lactam D assuming no change in configuration of the oxime during the reaction.



The structure of the lactam may be determined by the position of the ultraviolet maximum,[6] lactams of type B showing a maximum around 220 mμ while those of type D absorb maximally around 240 mμ. Some steroid A-homolactams derived from Δ⁴-3-ketones have been described[7–9] and all seem to be of type B. It would also be useful to have a simple method for distinguishing between *syn*- and *anti*-α,β-unsaturated oximes both for purposes of structure assignment and for determination of homogeneity. We felt that nu-

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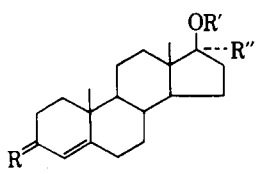
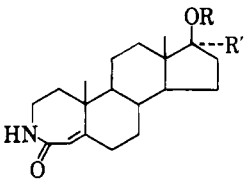
(2) T. L. Jacobs and R. B. Brownfield, *ibid.*, **82**, 4033 (1960).
(3) M. Gut and M. Uskokovic, *J. Org. Chem.*, **26**, 1943 (1961).
(4) N. J. Doorenbos and C. L. Huang, *ibid.*, **26**, 4106 (1961).
(5) R. H. Mazur, *J. Am. Chem. Soc.*, **81**, 1454 (1959).
(6) R. H. Mazur, *J. Org. Chem.*, **26**, 1289 (1961).
(7) C. W. Shoppee and G. Krueger, *J. Chem. Soc.*, 3641 (1961).
(8) C. W. Shoppee, G. Krueger, and R. N. Mirrington, *ibid.*, 1050 (1962).
(9) N. J. Doorenbos and H. Singh, *J. Pharm. Sci.*, **51**, 418 (1962).

clear magnetic resonance spectroscopy might serve this purpose due to the expected shift in the vinyl proton position caused by the proximity of the hydroxyl group in the *syn*-oxime A. Some precedent was found in the observation of Phillips[10] that *syn*- and *anti*-aldoximes showed different chemical shifts of the aldehyde proton. We confirmed this premise very simply as we had at hand the isomers of isophorone oxime of known configuration.[6] Thus, the n.m.r. spectrum[11] of *syn*-isophorone oxime showed a downfield shift of the vinyl proton of 42 c.p.s. relative to the *anti*-oxime. The same effect was observed with our steroid Δ^4-3-ketoximes (43 c.p.s. downfield shift for *syn*-I, 42 c.p.s. for *syn*-II) and, in addition, the 19-methyl peak was shifted downfield 2–3 c.p.s. in the *syn* isomer relative to the *anti* isomer. Subsequent to our findings, the same results were reported by Slomp.[12] Thus, combination of n.m.r. and ultraviolet spectra permit assignment of configurations to unsaturated ketoximes and their Beckmann rearrangement products and, within limits, allow percentage composition of mixtures to be determined.

We have made the surprising observation that in the present work, the Beckmann product is not necessarily related configurationally to the starting oxime according to the accepted mechanism of the rearrangement. The conditions we employed (thionyl chloride in dioxane) apparently led to a thermodynamically controlled product for the α,β-unsaturated oximes. In both cases, only one lactam (the 3-aza-Δ^{4a}-4-ketone) could be isolated which would be the isomer expected from the *syn*-oxime. However, n.m.r. showed testosterone propionate oxime (I) to be a mixture of *syn* and *anti* isomers containing only about 10% *syn*. 17α-Methyltestosterone acetate oxime (IV) was the pure *anti* compound with no detectable amount of *syn*-oxime present. Unexpectedly, 17α-methyltestosterone oxime (II) was a 1:1 mixture of *syn* and *anti* forms, presumably a molecular complex. It is not possible to say whether the conditions of the rearrangement caused isomerization of the starting oximes or whether the reaction proceeded through an intermediate having little or no configurational stability. In any case, our results suggest the need for caution in relating the stereochemistry of oximes with the structure of derived lactams.





I. R = NOH, R′ = C_2H_5CO, R″ = H
II. R = NOH, R′ = H, R″ = CH_3
III. R = O, R′ = CH_3CO, R″ = CH_3
IV. R = NOH, R′ = CH_3CO, R″ = CH_3
V. R = C_2H_5CO, R′ = H
VI. R = R′ = H
VII. R = CH_3CO, R′ = CH_3
VIII. R = H, R′ = CH_3

The general synthetic scheme involved protection of the 17-hydroxyl group as an ester, formation of the oxime, Beckmann rearrangement to a seven-membered lactam and saponification of the 17-ester. Testosterone propionate gave the oxime I which was rearranged to the lactam V and hydrolyzed to 3-aza-17β-hydroxy-A-homo-4a-androsten-4-one (VI). 17α-Methyltestosterone acetate (III) *via* oxime IV yielded lactam VII and, after saponification, 3-aza-17β-hydroxy-17-methyl-A-homo-4a-androsten-4-one (VIII).

Experimental[13]

Testosterone Propionate Oxime (I).—Commercial testosterone propionate U.S.P. (6.88 g., 0.02 mole) and 2.08 g. (0.03 mole) of hydroxylamine hydrochloride were dissolved in 50 ml. of pyridine. Two milliliters of water was added to give a clear solution which was heated 1 hr. on the steam bath. The solution was poured into 500 ml. of water, the crude oxime filtered, washed with water, and dried to yield 7.03 g. (98%) of compound I, m.p. 165–175°. Crystallization from 95% ethanol gave long needles, m.p. 170–176°. Recrystallization from methanol raised the m.p. to 177–183° (lit.,[14] m.p. 167–170°); n.m.r.[11,15] 348 c.p.s. (*anti*), 391 c.p.s. (*syn*), area ratio about 9:1.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.41; H, 9.04; N, 4.15.

17α-Methyltestosterone Oxime (II).—The above procedure was followed using 27.42 g. (0.09 mole) of 17α-methyltestosterone and 8.35 g. (0.12 mole) of hydroxylamine hydrochloride in 250 ml. of pyridine; yield of crude II, 28.39 g. (100%), sinter 208°, m.p. 212–215°. Crystallization from methanol gave thick prisms, m.p. 224–228° (lit.,[16] m.p. 198–202°); n.m.r. 348 c.p.s. (*anti*), 390 c.p.s. (*syn*), area ratio about 1:1.

Anal. Calcd. for $C_{20}H_{31}NO_2$: C, 75.68; H, 9.84; N, 4.41. Found: C, 75.51; H, 9.81; N, 4.48.

17α-Methyltestosterone Acetate (III).—17α-Methyltestosterone (50.0 g.) and 4.0 g. of *p*-toluenesulfonic acid monohydrate were dissolved in 800 ml. of isopropenyl acetate and about 300 ml. distilled over a period of 5 hr. During the last 0.75 hr. the head temperature was constant at 96°. The cooled solution was washed twice with 2 *N* potassium bicarbonate, dried over sodium sulfate, and the solvent removed under vacuum.

A portion of the viscous residue (8.55 g., 0.022 mole) in 180 ml. of methanol was treated with 8.80 ml. (0.044 mole) of 5 *M* potassium carbonate and water added until the solution became homogeneous (40 ml. required). The solution was heated 5 min. under reflux, concentrated under vacuum to about 100 ml. and 200 ml. of water added to give the desired 17α-methyltestosterone acetate as needles, 6.62 g. (87%), m.p. 164–167°. Two crystallizations from ethanol raised the melting point to 174.5–176°; $[\alpha]^{23.5}D$ +85° (*c* 1, chloroform); λ_{max}^{MeOH} 240 mμ, ϵ 16,800 [lit.,[17] m.p. 172–173°; $[\alpha]^{20}D$ +88° (chloroform)].

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.93; H, 9.21.

17α Methyltestosterone Acetate Oxime (IV).—Crude III (29.74 g., 0.086 mole) was converted to the oxime by the procedure of the first example using 12.0 g. (0.172 mole) of hydroxylamine hydrochloride in 300 ml. of pyridine. The oxime was purified by chromatography on silica gel and the desired product eluted with 20% ethyl acetate in benzene. Crystallization from ethyl acetate–cyclohexane gave the oxime IV as feathery needles, 17.43 g. (56%), m.p. 157–159°; $[\alpha]^{24}D$ +100° (*c* 1, methanol); λ_{max}^{MeOH} 240 mμ, ϵ 20,800; n.m.r. 348 c.p.s. (*anti*).

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.46; H, 9.35; N, 3.75.

3-Aza-17β-propionoxy-A-homo-4a-androsten-4-one (V).—Compound I (14.40 g.) in 350 ml. of purified dioxane was cooled to 10° and 15 ml. of thionyl chloride added with stirring at such a rate that the temperature remained below 15°. After 1 hr. at room temperature, the solution was stirred vigorously and 350 ml. of 2 *N* potassium bicarbonate added. The mixture was extracted with ethyl acetate, the organic layer washed twice with 5%

(10) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958).

(11) N.m.r. spectra were determined on a Varian A-60 spectrometer in deuteriochloroform at 10% concentration using tetramethylsilane as an internal standard. The positions of the peaks are reported in cycles per second downfield from the standard.

(12) G. Slomp and W. J. Wechter, *Chem. Ind.*, (London), 41 (1962).

(13) We would like to thank R. T. Dillon and associates for analyses and spectra. Analytical samples were dried overnight at room temperature under high vacuum. Melting points were not corrected. Column chromatography was carried out by M. Winkler, R. Furkert, N. Bilek, and C. Nuernberg (direction E. G. Daskalakis).

(14) Merck Index, 7th ed., Merck and Co., Inc., 1960, p. 1019.

(15) Under the same conditions, *anti*-isophorone oxime[6] had a vinyl proton peak at 356 c.p.s., *syn*-isophorone oxime[6] at 398 c.p.s.

(16) Merck Index, 7th ed., Merck and Co., Inc., 1960, p. 684.

(17) B. Pelc, *Collection Czech. Chem. Commun.*, **25**, 309 (1960).

sodium sulfate, dried over sodium sulfate, and the solvent distilled. The residue was chromatographed on silica gel. Elution with ethyl acetate and subsequent crystallization from aqueous methanol yielded the lactam V as plates, 7.14 g. (50%), m.p. 238–239°; $[\alpha]^{27}D$ +14° (*c* 1, methanol); λ_{max}^{MeOH} 220 mμ, ε 16,500.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.17; H, 9.04; N, 4.02.

3-Aza-17β-hydroxy-A-homo-4a-androsten-4-one (VI).—Compound V (1.08 g., 0.003 mole) in 50 ml. of methanol was treated with 3.0 ml. of 4 *N* lithium hydroxide and the solution allowed to stand 4 hr. at room temperature. Neutralization with acetic acid, dilution with 50 ml. of water, and concentration under vacuum to approximately 50 ml. gave the desired lactam VI as needles, 0.91 g. (100%), m.p. 278–281°. Crystallization from ethanol raised the m.p. to 288–291°; $[\alpha]^{24}D$ +23° (*c* 0.5, chloroform); λ_{max}^{MeOH} 221 mμ, ε 17,700.

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 74.95; H, 9.65; N, 4.73.

17β-Acetoxy-3-aza-17-methyl-A-homo-4a-androsten-4-one (VII).—Oxime IV (3.59 g., 0.01 mole) in 80 ml. of purified dioxane was stirred with 1.44 ml. (0.02 mole) of thionyl chloride for 1 hr. at room temperature. The work-up was essentially as described for compound V. Chromatography of the crude product on silica gel and elution with 50% ethyl acetate in benzene yielded lactam VII, 2.13 g. (59%), m.p. 250–252°. Crystallization from 50% ethanol gave needles, m.p. 253–254°; $[\alpha]^{25}D$ +2° (*c* 1, methanol); λ_{max}^{MeOH} 220 mμ, ε 17,200.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.66; H, 9.26; N, 3.93.

3-Aza-17β-hydroxy-17-methyl-A-homo-4a-androsten-4-one (VIII).—Acetate VII (3.59 g., 0.01 mole) in 225 ml. of methanol containing 22.4 g. (0.40 mole) of potassium hydroxide was allowed to stand 48 hr. at room temperature. The solution was neutralized with acetic acid, diluted with 400 ml. of water, and concentrated under vacuum to approximately 400 ml. to give the hydroxylactam VIII, 3.08 g. (97%), m.p. 287–290°. Crystallization from 50% methanol yielded needles, m.p. 291–293°; $[\alpha]^{25}D$ −3° (*c* 1, methanol); λ_{max}^{MeOH} 221 mμ, ε 17,100.

Anal. Calcd. for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.76; H, 9.88; N, 4.52.

The Epoxidation of Certain α,β-Unsaturated Ketones with Sodium Hypochlorite

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The epoxidation of α,β-unsaturated carbonyl compounds[1] and of 1,4-naphthoquinones[2] may be effected by means of hydrogen peroxide in alkaline medium. In most such cases the reactions are run under homogeneous conditions, whereby an organic solvent such as methanol, ethanol, or dioxane is employed if the unsaturated compound is not soluble in water. The anion of *t*-butyl hydroperoxide has also been found to convert α,β-unsaturated ketones to the corresponding epoxides.[3] The hypochlorite ion has also been used as an epoxidizing agent, wherein it presumably behaves analogously to the hydroperoxide and alkylhydroperoxide ions. Thus, 1,4-naphthoquinone has been converted to 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone by reaction with aqueous calcium hypochlorite under heterogeneous conditions.[4] The epoxides of some α,β-unsaturated aldehydes were isolated, in low yield, from the products of the reactions of the carbonyl compounds with sodium hypochlorite.[5] *trans*-Dibenzoylethylene oxide has been prepared by the hypochlorite oxidation of the unsaturated diketone in dioxane,[6] although no report of the yield was included.

While alkaline hydrogen peroxide is an excellent reagent for the epoxidation of most α,β-unsaturated carbonyl compounds, there are certain advantages to be realized in the use of sodium hypochlorite or calcium hypochlorite solutions for the same purpose. It was ascertained in this work that an ordinary commercial hypochlorite bleach solution is quite satisfactory and, consequently, provides a much less expensive and less hazardous reagent than concentrated hydrogen peroxide. In the course of an investigation, now in progress, dealing with the reactions of unsaturated carbonyl compounds with hypochlorites and related substances, it was found that the epoxidation is particularly effective when conducted in pyridine solution. The basicity of the solvent precludes the necessity of using another base, such as sodium hydroxide, in conjunction with a water-miscible organic solvent, such as dioxane.[6] Both benzalacetophenone and *trans*-dibenzoylethylene have been epoxidized with the sodium hypochlorite–pyridine reagent. The reactions are rapid and the yields almost quantitative.

The heterogeneous reaction of 1,4-naphthoquinone with aqueous calcium hypochlorite[4] results in a high yield of the corresponding epoxide. However, the reaction requires about twenty-four hours at room temperature for completion. In an effort to reduce the reaction time epoxidation under homogeneous conditions was indicated. The reaction of 1,4-naphthoquinone with aqueous sodium hypochlorite in dioxane led to the formation of the epoxide in 71% yield, after a reaction time of only a few minutes. When pyridine was used in place of dioxane the oxidation apparently proceeded beyond the epoxide stage, since no epoxide could be isolated. Instead, a brown solid, of as yet undetermined structure, was produced. In dioxane, to which dilute sodium hydroxide had been added, the reaction of 1,4-naphthoquinone with aqueous sodium hypochlorite resulted in the formation of about a 50% yield of the epoxide and other colored products. 2-Methyl-1,4-naphthoquinone behaves similarly to 1,4-naphthoquinone. In dioxane, the epoxide is produced in good yield, whereas in the more basic solvents (pyridine, or dioxane plus sodium hydroxide) red-brown solid products are formed.

It is of interest to note that in at least three instances claims to have epoxidized 1,4-naphthoquinone or 2-methyl-1,4-naphthoquinone with hypochlorous acid, according to Zincke's procedure, have been made.[7] As was pointed out previously, the reagent actually employed by Zincke was calcium hypochlorite. In order to verify these assertions, the reactions of 1,4-naphthoquinone and of 2-methyl-1,4-naphthoquinone with hypochlorous acid were investigated. In the case

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