limited amount of water was used, tiny crystals precipitated, m.p. 245–247°. It seemed likely that the lower melting form probably constituted the hydrated amino acid.

Purification attempts by means of copper salt formation were unsuccessful. Treatment of the acid with a dilute ferric chloride solution failed to give a red coloration characteristic of some amino acids.

Evidently the water of crystallization was held very tenaciously by the amino acid since the melting point of the material, 153–158°, was not altered after drying in the Abderhalden apparatus over phosphoric anhydride or under vacuum at the reflux temperature of *n*-butyl acetate for 2.5 days. Approximately the theoretical loss of one molecule of hydration was observed upon heating a small amount of the material in an oil-bath maintained at 175–180° for 25 minutes. The resulting dehydrated product, m.p. 247–248°, was analyzed.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.72; H, 5.82; N, 5.48.

By the use of bromine and sodium hydroxide 0.291 g. of 9-carboxamido-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid, m.p. 255–256°, was degraded to 0.231 g. of crude amino acid, m.p. 220–250° dec. Upon recrystallization from water the material decomposed at 240–245° and its decomposition point was not depressed when mixed with the amino acid prepared from the nitro acid. Both amino acids when treated with acetic anhydride gave a derivative soluble in 2.5% sodium hydroxide and insoluble in hydrochloric acid, m.p. 285–289°. No observable depression of the decomposition point was observed when they were mixed and further investigation was not undertaken.

Thirty-two milligrams of the amino acid from the Hofmann degradation was esterified with methanol acidified with sulfuric acid and gave 14.7 mg. of product from 170 mg. of starting material, m.p. 133–135° (39%). Recrystallization from methanol raised the melting point to 137–139°. Reduction of the adduct of 9-nitroanthracene and methyl acrylate gave the same amino ester and mixed melting points were not depressed.

Anal. Calcd. for $C_{18}H_{17}NO_2$: N, 5.00. Found: N, 4.95.

9-Anthramide and Allyl Alcohol.—From 6.3 g. of 9-anthramide and 30 g. of allyl alcohol which had been heated in a sealed tube at 170–175° for 17 hours was isolated 3.24 g. of material, m.p. 222–224° (40%), and 1.7 g., m.p. 146–147° (22%). A mixed melting point with 9,10-dihydro-9,10-ethano-12-methylol-9-carboxylic acid lactone[3] with the higher melting product gave no depression.

The lower melting product gave a poor analysis and was converted into material melting at 118–119° when refluxed with acetic anhydride. A mixed melting point with authentic 9-cyano-9,10-dihydro-9,10-ethanoanthracene-11-methanol acetate was 121–121.5°.

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BOULDER, COLO.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. VI. Synthesis of 3'-Acetyl-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene[1]

BY NORMAN A. NELSON,[1a] JOHN C. WOLLENSAK,[2] RODGER L. FOLTZ, JACKSON B. HESTER, JR., JOHN I. BRAUMAN, ROBERT B. GARLAND[3] AND GARY H. RASMUSSON[4]

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The preparation and determination of the configuration at the ring junction of an isomer of 3'-acetyl-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (VIII) is described. Conversion of VIII to 3'-oxo-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (Xa) (*cf.* 1-hydrindanone) was carried out under conditions which should not affect the ring junction, and equilibration of this material resulted in recovery of unchanged starting material. In view of the fact that *cis*-1-hydrindanone is more stable than *trans*-1-hydrindanone, the equilibration studies suggest that Xa and consequently VIII probably have the *cis* configuration at the ring junction.

In a previous paper[5] we reported the total synthesis of *dl*-18,19-dinorprogesterone[6] utilizing a tricyclic starting material representing the A, B and C rings of the final product. At the time the work was being carried out we were also investigating an approach to 18,19-dinorprogesterone involving the synthesis of a tricyclic intermediate representing the B, C and D rings to which ring A could be attached.[7] The present paper reports this work. The preparation of an isomer of 3'-acetyl-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (VIII) is described together with studies of the stereochemistry of its ring fusion. The five-membered ring of VIII was elaborated by methods similar to those described previously.[5,8]

Alkylation of 2-hydroxymethylene-6-methoxy-1-tetralone (I)[9] with sodium hydride and methallyl iodide in dimethylformamide solution[5] gave 74% of 2-methallyl-6-methoxy-1-tetralone (II). When the direct alkylation of 6-methoxy-1-tetra-

(1) Abstracted in part from the thesis of J. C. Wollensak, submitted to the Massachusetts Institute of Technology, 1958, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, and from the theses of J. B. Hester, Jr. (1955), R. L. Foltz (1956) and J. I. Brauman (1959) submitted in partial fulfillment of the requirements for the degree of Bachelor of Science.

(1a) Research Laboratories of the Upjohn Company, Kalamazoo, Michigan.

(2) Public Health Service Research Fellow of the National Cancer Institute, 1955–1958.

(3) National Science Foundation Fellow, 1953–1955; William S. Knudsen Fellow, 1955–1956.

(4) National Science Foundation Fellow, 1958–1959.

(5) N. A. Nelson and R. B. Garland, THIS JOURNAL, **79**, 6313 (1957).

(6) Two reports have since appeared on the preparation of *d*-18,19-dinorprogesterone; see W. F. Johns, *ibid.*, **80**, 6456 (1958), and G. Stork, H. N. Khastgir and A. J. Solo, *ibid.*, **80**, 6457 (1958).

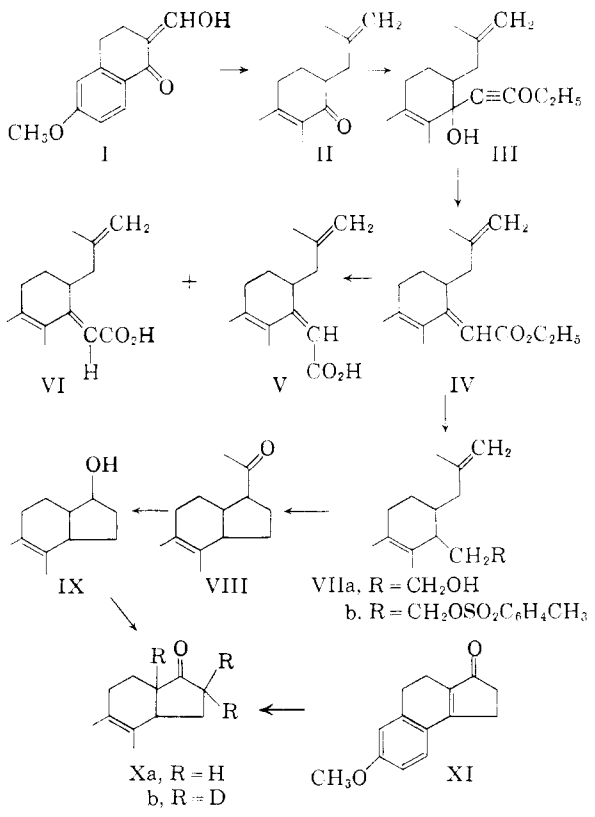
(7) Methods by which ring A could be attached have already been described; see, for example, G. Stork, H. J. E. Loewenthal and P. C. Mukharji, *ibid.*, **78**, 501 (1956), and L. J. Chinn and H. L. Dryden, Jr., Abstracts of Papers presented at the Chicago Meeting of the American Chemical Society, September 7–12, 1958, p. 14-O.

(8) (a) L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth, THIS JOURNAL, **75**, 2112 (1953); (b) G. E. Arth, G. I. Poos, R. M. Lukes, F. M. Robinson, W. F. Johns, M. Feurer and L. H. Sarett, *ibid.*, **76**, 1715 (1954); (c) W. F. Johns, R. M. Lukes and L. H. Sarett, *ibid.*, **76**, 5026 (1954).

(9) D. K. Banerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *ibid.*, **78**, 3769 (1956).

lone[10] was attempted using sodium amide and methallyl iodide in ether solution, the yield of II was only 25%. Treatment of II with ethoxyacetylenemagnesium bromide gave the oily acetylenic carbinol III which, on treatment with dilute sulfuric acid, gave a mixture of ethyl *cis*- and *trans*-2-methallyl-6-methoxy-1-tetralidenacetates (IV) in an over-all yield of 81%. In one run the mixture of esters was saponified and the resulting acids were fractionally crystallized giving 47.5% of *cis*-2-methallyl-6-methoxy-1-tetralidenacetic acid (V) and 17% of the corresponding *trans* isomer VI. The structural assignments are based on the ultraviolet spectra of the isomers, the *trans* isomer absorbing more intensely and at longer wave lengths.[11]

Reduction of the unsaturated esters IV to 1-(β-hydroxyethyl)-2-methallyl-6-methoxytetralin (VIIa) using sodium and ethanol proceeded in 69% yield to give what was probably a mixture of *cis* and *trans* isomers. The crude alcohol was converted to 1-(β-tosyloxyethyl)-2-methallyl-6-methoxytetralin(VIIb) in 88% yield. Attempted separation of the isomers of the tosylate VIIb by elution chromatography was unsuccessful. It was possible to obtain 27% of a crystalline isomer from the oily tosylate by direct crystallization. The solution infrared spectra of the crystalline and oily tosylates are very similar, indicating that the oily product was chiefly one isomer. Therefore, in subsequent reactions, the tosylate was purified only by chromatography before use.



The methallyl side chain of VIIb was converted to an acetonyl group by oxidation with a mixture of osmium tetroxide and periodic acid.[5,12] Ring closure of the intermediate 1-(β-tosyloxyethyl)-2-acetonyl-6-methoxytetralin with sodium ethoxide in ethanol gave 18% of a crystalline isomer of 3′-acetyl 1′,2′:1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (VIII). In a similar run using potassium *t*-butoxide in *t*-butyl alcohol for the ring closure, a 13% yield of the crystalline tricyclic ketone VIII was obtained.

We then turned our attention to the determination of the configuration at the ring junction of the crystalline isomer of VIII. In naturally occurring steroids the C–D ring fusion is *trans*.[13] In order to determine the configuration it was necessary to convert VIII to the tricyclic ketone Xa by a method which would not affect the ring junction, and then subject the ketone to basic equilibration. If an isomeric ketone was formed in high yield, it could be concluded that an epimerization had occurred to give the thermodynamically more stable *cis*-3′-oxo-1′,2′:1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (Xa). If no isomerization occurred, then compound Xa, and consequently compounds VIII and IX, should have *cis* ring fusions.

While no information is available on the relative stabilities of the *cis* and *trans* isomers of Xa, we believe that the *cis* isomer is more stable on the following basis.[14] Linstead, in his reveiw[15] on carbocyclic compounds, indicated that the *cis* isomer of 1-hydrindanone is more stable than the *trans* isomer by a factor of about 10. The greater stability of *cis*-1-hydrindanone involves in part the smaller deformation caused by bringing adjacent equatorial and axial bonds together in the attachment of the 5-membered ring than in bringing two equatorial bonds together to form the *trans* isomer.[14a] Similar arguments can be used for predicting the most stable attachment of a 5-membered ring to the 1,2-positions of tetralin. The alicyclic ring of tetralin (*cf.* cyclohexene)[16] can exist in a half-chair or half-boat conformation in which the substituent bonds at the α-positions have quasi-axial or quasi-equatorial conformations[17] and the substituent bonds at the β-positions have axial or equatorial conformations. From an inspection of molecular models it is clear that the attachment of a 5-membered ring to the α,β-positions of tetralin (as in Xa) involving either quasi-equatorial–

(10) Prepared from 2-methoxynaphthalene by the method of G. Stork, THIS JOURNAL, **69**, 576 (1947).

(11) This is in accordance with observations of the ultraviolet spectra of *cis*- and *trans*-α-ethylcinnamic acids and *cis*- and *trans*-α-ethylbenzalacetophenones; see H. O. House and D. J. Reif, *ibid.*, **79**, 6491 (1957).

(12) R. Pappo, D. S. Allen, Jr., R. U. Lemieux and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

(13) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, N. Y., 1959.

(14) For excellent discussions and reviews pertaining to the relative stabilities of *cis* and *trans* isomers of the hydrindane type see (a) E. L. Eliel and C. Pillar, THIS JOURNAL, **77**, 3600 (1955); (b) G. Quinkert, *Experientia*, **13**, 381 (1957); (c) ref. 13, pp. 212–216.

(15) R. P. Linstead, *Ann. Repts.*, **32**, 305 (1935).

(16) See D. H. R. Barton, R. C. Cookson, W. Klyne and C. W. Shoppee, *Chemistry & Industry*, 21 (1954), for a discussion on the stereochemistry of cyclohexene and its derivatives including tetralin.

(17) L. P. Kuhn, THIS JOURNAL, **74**, 2492 (1952), has adduced evidence indicating that the two α-positions in the half-chair conformation of tetralin are not equivalent. However, this information does not affect the conclusions regarding the relative stabilities of the *cis* and *trans* isomers of X.

axial or quasi-axial–equatorial bonds to give a *cis* ring fusion requires less deformation of the system than that of *cis*-1-hydrindanone. Similarly, an attachment of a 5-membered ring involving quasi-equatorial–equatorial bonds to give the *trans* isomer causes greater deformation of the ring system than that found in the unstable *trans*-1-hydrindanone. A consideration of other nonbonded interactions[18] in the *cis* and *trans* conformations of Xa enhances the argument that the *cis* isomer should be more stable than the *trans*.

The oxidation of 3′-acetyl-1′,2′:1,2-cyclopentano - 1,2,3,4 - tetrahydro - 6 - methoxynaphthalene with perbenzoic acid followed by saponification of the product gave a 36% yield of 3′-hydroxy-1′,2′:1,2-cyclopentano - 1,2,3,4 - tetrahydro - 6 - methoxynaphthalene (IX) together with 18% recovery of the starting material. The oxidation of the tricyclic alcohol IX to the corresponding ketone Xa had to be carried out in such a manner as to avoid enolization of the ketone. The procedure described by Djerassi, Engle and Bowers[19] was employed and first applied to cholesterol as a model since the product of this reaction, Δ^5-cholestene-3-one, is highly susceptible to enolization and rearrangement. Treatment of cholesterol under mild conditions with chromic acid in acetone gave the expected Δ^5-cholestene-3-one as the major product together with a small amount of Δ^4-cholestene-3-one as determined from the infrared spectrum of the product. The same oxidation conditions were then applied to the alcohol IX and gave a 75% yield of a single crystalline ketone. This isomer of Xa was subjected to equilibration, first by passage of it through a column of basic alumina,[20] and second by treatment of it with methanolic sodium methoxide solution. In the first case the starting material was recovered in 95% yield and in the second, recovery of Xa amounted to 48%.

At this point a larger sample of the same isomer (shown by comparison of infrared spectra and a mixed melting point determination) of 3′-oxo-1′,2′:1,2-cyclopentano-1,2,3,4-tetrahydro - 6 - methoxynaphthalene(Xa) was prepared in 94% yield by reduction[5,20] of the tricyclic unsaturated ketone XI[21] with sodium in liquid ammonia. Since the reaction mechanism involved in the conversion of XI to Xa proceeds through an enolate anion, it is probable that the product represents the most stable isomer. However, to establish conclusively that equilibration of the ketone had occurred, a sample of Xa was treated with a solution of sodium methoxide in deuterated methanol. A mass spectrometric analysis of the product showed that 77% of the ketone had exchanged 3 hydrogen atoms for deuterium, indicating that enolization and equilibration at the bridgehead had definitely occurred. A mixture of the undeuterated and deuterated ketones (Xa from IX, and Xb) showed no melting point depression.

To confirm further the contention that the oxidation conditions used in the conversion of IX to Xa did not promote enolization, the mixture of deuterated ketones (containing 77% of Xb) was subjected to the same oxidation conditions. For the purpose of the experiment, isopropyl alcohol was oxidized to acetone with chromic acid in the presence of the deuterated ketones. The infrared spectrum of the recovered ketone (83%) was identical (20 peaks) to the sample of deuterated ketone used, thus confirming that the conditions of oxidation did not result in any appreciable enolization.[22]

From other analogies,[16] one would expect that the sodium–alcohol reduction of IV would give the *trans* isomer of 1-(β-hydroxyethyl)-2-methallyl-6-methoxytetralin(VIIa) in preponderant amount. While this may actually have been the case, the quasi-equatorial and quasi-axial nature of the substituent bonds in the 1-position of the product (VIIa) would not be conducive to a clean stereospecific reduction. A further loss of *trans* isomers may have occurred in the cyclization of VIIb to the tricyclic ketone VIII since, in this reaction, the *cis* isomer of VIIb can react easily giving an essentially strainless product, while the *trans* isomer would give a strained product and should therefore, be less prone to cyclize and more susceptible to side reactions.

As this work was nearing completion the earlier observations[5] on the biological inactivity of 18,19-dinorprogesterone was verified by other workers[6] and, as a consequence, further work on this problem concerning the isolation of *trans* isomers was stopped.

Experimental[23]

2-Methallyl-6-methoxy-1-tetralone (II). (A) From 6-Methoxy-1-tetralone.—Sodium amide was prepared from 3.5 g. of sodium and 150 ml. of anhydrous liquid ammonia containing a crystal of ferric nitrate. The reaction mixture was diluted with 50 ml. of ether and warmed to remove the excess ammonia. The mixture was cooled (0°), a solution of 26.4 g. of 6-methoxy-1-tetralone[10] in 200 ml. of ether was added, and the resulting mixture was refluxed for 5 hours before distilling most of the ether to remove traces of ammonia. To the cooled reaction mixture was added 50.7 g. of methallyl iodide[8a] in 200 ml. of ether, and after refluxing the mixture for 4 hours it was poured into ice-water and extracted with ether. The ether extract was washed, dried and concentrated to give 35 g. of a dark oil which was chromatographed on 800 g. of Merck acid-washed alumina using hexane–ethyl acetate eluents. The first band of oily material eluted (16.3 g.) appears to be the dialkylated derivative while the second band eluted yielded on crystallization from pentane 8.70 g. (25%) of 2-methallyl-6-methoxy-1-tetralone, m.p. 54.7–55.2°, $\nu_{max}^{CCl_4}$ 1670(s, conj. carbonyl) and (s, terminal methylene) 893 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.00; H, 7.99.

(18) For example, the extent of eclipsing in the 5-membered ring, interaction of the hydrogen atoms at positions 5′ and 8, etc.

(19) C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(20) *Cf.* A. J. Birch, H. Smith and R. E. Thornton, *J. Chem. Soc.*, 1339 (1957).

(21) A. J. Birch, J. A. K. Quartey and H. Smith, *ibid.*, 1768 (1952).

(22) The possibility that the initial oxidation product of IX was, in fact, the *trans* isomer of Xa, and that it underwent a particularly facile epimerization to the *cis* isomer in the reaction, has not been rigorously excluded.

(23) Melting points and boiling points are uncorrected. The infrared spectra were determined with a Baird (model B) or Perkin–Elmer (model 21) spectrophotometer fitted with a sodium chloride prism. In reporting infrared spectra, (s) denotes strong, (m) medium and (w) weak absorption. Ultraviolet spectra were determined with a Cary recording spectrophotometer (model 11 MS). The microanalyses were performed by Dr. S. M. Nagy and his associates. We are indebted to Prof. K. Biemann and Dr. J. Seibl for mass spectrometric analyses which were determined with a CEC 21-103 instrument with a heated inlet at 140°.

The last material eluted from the column was 7.12 g. of 6-methoxy-1-tetralone.

(B) From 2-Hydroxymethylene-6-methoxy-1-tetralone.—A mixture of 110.2 g. of 2-hydroxymethylene-6-methoxy-1-tetralone [m.p. 69–70.5° or 96.8–98° (lit.[9] 68–69°)],[24] 13.1 g. of sodium hydride and 1100 ml. of purified dimethylformamide was stirred under a nitrogen atmosphere for 30 minutes. The red reaction mixture was then cooled to 0° and 176.4 g. of methallyl iodide was added, causing an immediate precipitation of sodium iodide. After stirring the mixture for 4 hours, 93 g. of potassium hydroxide in 140 ml. of water was added to the neutral solution. The mixture was concentrated *in vacuo* to about 500 ml. and then diluted with 2500 ml. of water and 500 ml. of ether. The ether layer was separated, washed with saturated sodium chloride solution, dried and concentrated *in vacuo*. The residue was passed through 300 g. of Alcoa F-20 alumina using an eluent of 5% ethyl acetate in hexane. Evaporation of the solvent gave 92 g. (74%) of crude 2-methallyl-6-methoxy-1-tetralone, m.p. 48.2–52.2°, raised to 52.4–54.6° on one recrystallization from hexane.

***cis*- and *trans*-2-Methallyl-6-methoxy-1-tetralideneacetic Acids (V and VI).**—A solution of 34 g. of ethoxyacetylene[25] and 200 ml. of ether was added slowly with stirring to a solution of ethylmagnesium bromide prepared from 9.7 g. of magnesium turnings, 44.5 g. of ethyl bromide and 400 ml. of ether. The brown oil which formed over a 2-hour period was dissolved by the addition of 300 ml. of benzene. The solution was cooled to 5° while 52 g. of 2-methallyl-6-methoxy-1-tetralone in 120 ml. of benzene was added. The mixture was stirred at room temperature for 6 hours before pouring it into ice-water and extracting the product with ether. The ether extract was washed with water, dried and concentrated *in vacuo* to give the crude acetylenic carbinol which was converted without further purification to the unsaturated esters (*cis*- and *trans*-IV).

To a solution of the acetylenic carbinol in 600 ml. of tetrahydrofuran was added 34 ml. of 10% aqueous sulfuric acid. The mixture was stirred at room temperature for 5 hours, 0.5 *N* sodium bicarbonate was added to neutralize the acid and most of the tetrahydrofuran was distilled *in vacuo*. The product was extracted with ether and the ether extract was washed with water, dried and concentrated *in vacuo*. Distillation of the residue through a short Vigreux column gave 54.7 g. (81%) of a mixture of ethyl *cis*- and *trans*-2-methallyl-6-methoxy-1-tetralideneacetates, b.p. 144–154° (mostly at 152–154°) (0.024 mm.), $n^{28}D$ 1.5560–1.5553.

In a similar small scale run involving 5.0 g. of 2-methallyl-6-methoxy-1-tetralone there was obtained 6.11 g. of the mixture of esters. The esters were saponified by stirring them with a mixture of 135 ml. each of methanol and water and 19 g. of potassum carbonate for 17 hours at room temperature and for 5 hours under reflux. Most of the methanol was distilled and the resulting aqueous solution was washed with ether, then acidified with sodium dihydrogen phosphate. The crude product (extracted with ether) was crystallized from methanol yielding as a first crop 1.01 g. (17%) of *trans*-2-methallyl-6-methoxy-1-tetralideneacetic acid (VI), m.p. 125.5–126.1°, which on further recrystallizations melted at 127.1–127.8°, λ_{max}^{EtOH} 300 mμ (ε 16,660).

Anal. Calcd. for $C_{17}H_{19}O_3$: C, 75.25; H, 7.06. Found: C, 75.17; H, 7.37.

The mother liquor from the above crystallization upon standing at −4° gave 2.80 g. (47.5%) of *cis*-2-methallyl-6-methoxy-1-tetralideneacetic acid (V), m.p. 107–108°. The analytical sample melted at 107.8–108.6°, λ_{max}^{EtOH} 295.5 mμ (ε 9,550).

Anal. Calcd. for $C_{17}H_{19}O_3$: C, 75.25; H, 7.06. Found: C, 74.91; H, 7.17.

1-(β-Tosyloxyethyl)-2-methallyl-6-methoxytetralin (VIIb).—To a solution of 32.48 g. of ethyl 2-methallyl-6-methoxy-1-tetralideneacetate in 300 ml. of absolute ethanol heated to reflux was added 23.5 g. of sodium with efficient stirring over a 15-minute period. The stirring was stopped momentarily a number of times to prevent excessive foaming. The sodium was consumed in about 45 minutes and then 150 ml. of ethanol and 150 ml. of water were added successively. The mixture was heated for an additional 2 hours before distilling most of the alcohol and extracting the product with ether. The ether extract was washed with water, dried and concentrated *in vacuo* to give a residue which was distilled through a short Vigreux column yielding 19.4 g. (69%) of 1-(β-hydroxyethyl)-2-methallyl-6-methoxytetralin (presumably a mixture of *cis* and *trans* isomers), b.p. 137–144° (0.15 mm.), $n^{29}D$ 1.5452–1.5553, for successive fractions; $\nu_{max}^{CCl_4}$ 3660(w), 3450(broad) and 1040(s, alcohol), 1645(w) and 890(s, terminal methylene), 1608(s), 1580(w) and 1500(s, aromatic ring) cm.$^{-1}$ and no ester carbonyl absorption. The fractions were combined and used directly in the next step.

To a cold solution of 3.62 g. of 1-(β-hydroxyethyl)-2-methallyl-6-methoxytetralin in 25 ml. of anhydrous pyridine was added with stirring 3.28 g. of *p*-toluenesulfonyl chloride. The solution was allowed to stand in the refrigerator for 24 hours, then 10% sodium bicarbonate solution was added and the mixture was stirred for 10 minutes. The product was extracted with ether and the ether extract was washed, dried and concentrated giving 5.6 g. of a yellow oil which was chromatographed on 300 g. of Davison silica gel wet-packed with 15% ether in hexane. Elution with 25% ether in hexane gave 5.06 g. (88%) of the oily tosylate.

In an earlier run the infrared spectra of the first and last fractions of the tosylate band were identical, indicating that no fractionation of *cis* and *trans* isomers was occurring. The tosylate fractions of that run were combined (1.69 g.) and crystallized twice from methanol giving 0.45 g. of 1-(β-tosyloxyethyl)-2-methallyl-6-methoxytetralin (VIIb), m.p. 48–49°, raised to 51.2–51.4° on further recrystallizations; $\nu_{max}^{CCl_4}$ 1365(s), 1188(s) and 1178(s, sulfonate grouping), 1643(w) and 890(s, terminal methylene) cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}O_4S$: C, 69.55; H, 7.30; S, 7.73. Found: C, 69.50; H, 7.49; S, 7.85.

Since the infrared spectrum of the crystalline product was essentially the same (very slight differences in the intensities of three bands) as the spectrum of the chromatographed product above, the oily tosylate was used without further purification.

3'-Acetyl-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (VIII).—To a solution of 1.10 g. of crude 1-(β-tosyloxyethyl)-2-methallyl-6-methoxytetralin, 20 ml. of purified tetrahydrofuran and 2.5 ml. of pyridine was added 2 ml. of 0.115 *M* osmium tetroxide in tetrahydrofuran. The mixture was stirred briefly before adding a solution of 1.48 g. of periodic acid dihydrate in 5 ml. of water. The stirring was continued for 5 hours at room temperature, then 3 g. of sodium sulfite in 20 ml. of water was added slowly with cooling. The mixture was stirred for an additional 2 hours, the product was then extracted with ether and the ether extract was washed, dried thoroughly and concentrated *in vacuo*. The residue was dissolved in 10 ml. of absolute ethanol and a solution prepared from 72 mg. of sodium and 10 ml. of ethanol was added. The mixture was allowed to stand at room temperature overnight. The reaction mixture was diluted with 150 ml. of water, extracted with chloroform and the chloroform extract was washed, dried and concentrated to give 0.61 g. of a residue which was chromatographed on 50 g. of Merck alumina using 3% ethyl acetate in hexane as eluent. Fractions containing the ketonic product were combined (330 mg.) and crystallized from hexane yielding 115 mg. (18% from VIIb) of the tricyclic ketone VIII, m.p. 44–45°; the analytical sample melted at 46.0–47.5°, $\nu_{max}^{CCl_4}$ 1707(s, carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.70; H, 8.31.

3'-Oxo-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (Xa). (A) From 3'-Acetyl-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (VIII).—A mixture of 102 mg. of the methyl ketone VIII, 3.00 ml. of 0.286 *M* perbenzoic acid in benzene and 3 mg. of *p*-toluenesulfonic acid was allowed to stand at 4–6° for 40 hours and was then poured into 10% potassium bicarbonate solution and extracted with ether. Concentration of the ether extract gave an oil which was heated under reflux for 2 hours (nitrogen atmosphere) in a mixture of 5 ml. of methanol and 1.5 ml. of 40% potassium carbonate solution. The reaction mixture was cooled, extracted with ether, and the ether extract was washed, dried and concentrated *in vacuo* giving a yellow oil which was chromatographed on 10 g. of Merck alumina. Elution with benzene gave 18 mg. of unchanged 3'-acetyl-1',2':1,2-cyclopentano-1,2,3,4-tetrahy-

(24) The infrared solution spectra of the high and low melting forms are identical.

(25) E. A. Braude and O. H. Wheeler, *J. Chem. Soc.*, 320 (1955).

dro-6-methoxynaphthalene, microstage m.p. 44–45°, and elution with 50% ether in benzene gave 33 mg. (36%) of **3'-hydroxy-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (IX)**, microstage m.p. 48–51°, ν_{max}^{KBr} 3400(s) and 1041(s, hydroxyl) cm.$^{-1}$.

To a cold solution of 61.6 mg. of the alcohol IX in 9.5 ml. of acetone (distilled from potassium permanganate and anhydrous potassium carbonate) was added rapidly with stirring 0.080 ml. of a chromium trioxide solution (made from 26.75 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid diluted to 100 ml. with distilled water). The reaction was carried out under a nitrogen atmosphere and after exactly 5 minutes at 14°, the green reaction mixture was poured into 40 ml. of cold water. The product was extracted with ether and the ether extract was washed, dried and concentrated. The oily residue was crystallized from pentane giving 46 mg. (75%) of 3'-oxo-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene, microstage m.p. 58–62°, $\nu_{max}^{CCl_4}$ 1742 (s, carbonyl) cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.51; H, 7.58.

Thirty milligrams of the product was passed slowly through a column of 10 g. of Alcoa F-20 alumina, eluting with ether. The product was crystallized from petroleum ether giving 28.5 mg. (95%) of material, microstage m.p. 61.5–63.5° (mixed m.p. with original oxidation product, undepressed), the infrared spectrum is essentially the same as that of the original oxidation product.

(B) From 3'-Oxo-1',2':1,2-cyclopenteno-3,4-dihydro-6-methoxynaphthalene (XI).—Approximately 400 ml. of liquid ammonia was treated with 1 g. of sodium for 15 minutes before distilling about 300 ml. of the dried solvent through polyethylene tubing into the reaction flask fitted with a stirrer and Dry Ice-cooled condenser protected from the atmosphere by a sodium hydroxide drying tower. To the flask was added with stirring 0.754 g. of sodium followed in 10 minutes by the rapid addition of 3.22 g. of 3'-oxo-1',2':-1,2-cyclopenteno-3,4-dihydro-6-methoxynaphthalene[21] dissolved in the minimum amount of anhydrous ether. After 30 minutes, the deep green solution was treated with an excess of solid ammonium chloride and the ammonia was evaporated using a water-bath and a stream of nitrogen. When the volume of liquid reached about 200 ml., more anhydrous ether was added and the evaporation was continued until the solution came to room temperature. Water was added to dissolve the inorganic material and the ether layer and ether extracts of the aqueous layer were combined washed, dried and concentrated to a yellow oil which solidified. Recrystallization of the solid from petroleum ether gave 3.05 g. (94%) of 3'-oxo-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (**Xa**) in two crops, m.p. 64–65°. The infrared spectrum of this material is identical with that of the product described in part (A), and a mixed melting point determination of the two materials was not depressed.

Epimerization Studies of 3'-Oxo-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (Xa). (A) Under Base-catalyzed Conditions.—To a solution of sodium methoxide from 5 ml. of deuterated methanol (prepared by fractional distillation of an equimolar mixture of methyl oxalate and deuterium oxide) and 95 mg. of sodium was added 144 mg. of the ketone Xa. The mixture was allowed to stand for 50 minutes in a nitrogen atmosphere and was then acidified with 2 ml. of deuterated acetic acid (prepared from equimolar amounts of acetic anhydride and deuterium oxide) and concentrated under reduced pressure. An ether solution of the residue was washed, dried and concentrated yielding 108 mg. (75%) of deuterated 3'-oxo-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (Xb), microstage m.p. 63.5–65° (microstage mixed m.p. with undeuterated material Xa, 63–64.5°), $\nu_{max}^{CCl_4}$ 2140(w, CD stretching) cm.$^{-1}$. A mass spectrometric analysis of the product showed molecular ion peaks corresponding to 77% trideuterated, 21% dideuterated and 2% monodeuterated material, thereby indicating that extensive enolization had occurred at the epimerizable center alpha to the carbonyl function.

(B) Under Simulated Oxidation Conditions.—Oxidation of 20.2 mg. of isopropyl alcohol in the presence of 77.4 mg. of the deuterated 3'-oxo-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (Xb) (described in part A above) using the same concentrations of reagents and other conditions (see above) as were used in the oxidation of 3'-hydroxy-1',2':1,2-cyclopentano-1,2,3,4-tetrahydro-6-methoxynaphthalene (IX) to Xa, gave 64.3 mg. (83%) of unchanged deuterated ketone Xb, microstage m.p. 62.5–64°. The infrared spectrum of the product was identical (20 peaks) with that of the starting deuterated ketone and distinctly different in the fingerprint region from undeuterated ketone, thus illustrating that little if any enolization of Xb occurred during the oxidation.

CAMBRIDGE 39, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. VII. Synthesis of Tricyclic Analogs Containing Nitrogen[1]

BY NORMAN A. NELSON,[1a] RICHARD S. P. HSI, JAMES M. SCHUCK AND LEO D. KAHN

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The preparation of some tricyclic nitrogen-containing analogs of D-homoestrone and D-homoestradiol is described. The condensation of 6-methoxy-2-tetralone and 3-hydroxypiperidine yielded an enamine which was reduced to 2-(3-hydroxypiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (III). The chromic acid oxidation of III gave 2-(3-ketopiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV). The Michael addition of 6-methoxy-1,2,3,4-tetrahydroisoquinoline to 2-cyclohexanone gave 2-(3-ketocyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IX) which was reduced with lithium aluminum hydride to 2-(*cis*-3-hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xa). Epimerization of the *cis*-amino alcohol Xa *via* the tosylate and acetate gave 2-(*trans*-3-hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xd).

As part of a program on the synthesis of azasteroids[2] we have undertaken the preparation of some nitrogen-containing analogs of 18-nor-D-homoestrone and 18-nor-D-homoestradiol which lack ring C. This paper describes the synthesis of 2-(3-ketopiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV), 2-(3-ketocyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IX) and the corresponding amino alcohols. Similar tricyclic analogs lacking nitrogen have been reported to possess biological activity.[3]

The principal step in the approach to the analogs III and IV lay in the coupling of 3-hydroxypiperidine and 6-methoxy-2-tetralone (I). The latter

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(1a) Research Laboratories of the Upjohn Company, Kalamazoo, Michigan.

(2) N. A. Nelson, J. E. Ladbury and R. S. P. Hsi, THIS JOURNAL, **80**, 6633 (1958).

(3) F. C. Novello and M. E. Christy, *ibid.*, **75**, 5431 (1953).