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

(1) This investigation was supported in part by a research grant, CY-2999, from the National Cancer Institute, Public Health Service.

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(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).

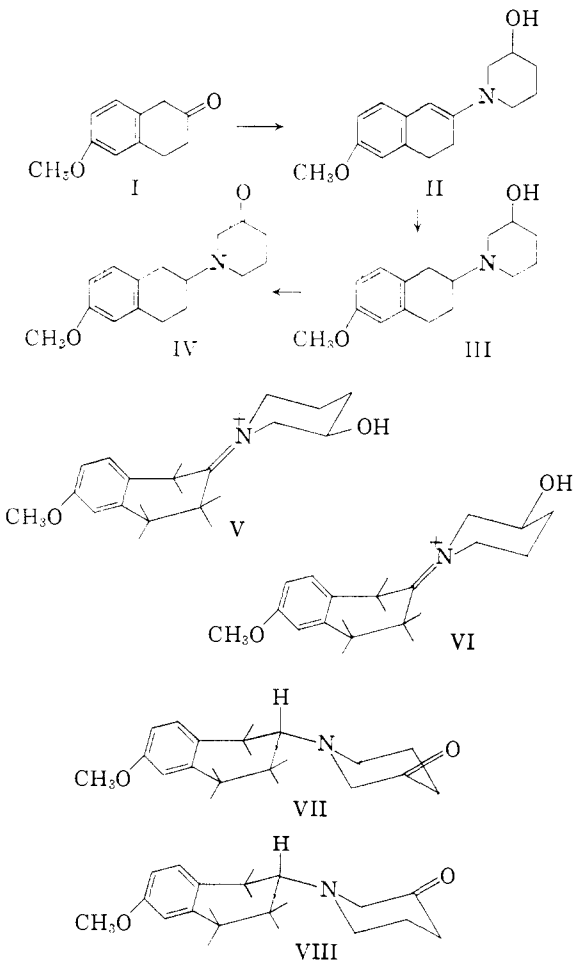
compound was prepared by two routes. Birch treatment[4] of 6-methoxy-2-naphthol with two molecular equivalents of sodium resulted in the selective reduction of the phenolic ring and gave 6-methoxy-2-tetralone in 70% yield. This ketone was also prepared in 56% yield through the oxidation of 6-methoxy-3,4-dihydronaphthalene using peracetic acid.[5]

The enamine II resulting from the condensation of 6-methoxy 2-tetralone and 3-hydroxypiperidine was hydrogenated in the presence of glacial acetic acid and Adams catalyst to give 2-(3-hydroxypiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (III) which was isolated and purified as its perchlorate derivative in an overall yield of 62%. The infrared and ultraviolet spectra of the unstable intermediate enamine II are in complete agreement with the structural assignment.

Treatment of the perchlorate of III with base regenerated the free amino alcohol which was oxidized with chromium trioxide to give 42% of 2-(3-ketopiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV) and 27% unchanged amino alcohol after chromatographic separation of the product on Florisil. The amino ketone IV is sensitive to air, but can be stored under a nitrogen atmosphere or as its stable perchlorate. Reduction of the amino ketone with lithium aluminum hydride gave an amino alcohol which was isolated as its perchlorate derivative in 61% yield. This salt proved to be identical with the perchlorate of III as indicated by their infrared and ultraviolet spectra, melting points and mixed melting point.

When considering the methods employed in the preparation of the amino alcohol III, one would expect a mixture of two racemates to be formed. For example, catalytic reduction of the racemic enamine II should occur with nearly equal ease from either side of the dihydronaphthalene ring. If this reduction is preceded by protonation of the enamine, the resulting immonium ion intermediate should exist in solution as conformations of types V and VI, which are diastereoisomers having essentially the same steric requirements for reduction. Therefore, nearly equal amounts of the two racemates of III should again be formed. Similarly the racemic amino ketone IV can exist in solution as four important conformations because of the location of the nitrogen atom. For example, structures VII and VIII represent two conformations for one of the enantiomers of the amino ketone.[6] Because of the mirror-image relationship of the carbonyl groups in the heterocyclic rings of VII and VIII, reduction of the ketone should give nearly equal amounts of two racemates, regardless of how stereospecific the reduction is. With these views in mind, we have attempted to establish the presence of two racemates in samples of the amino alcohol III. The only indication that the product is a mixture of isomers is the broad melting point range of the material. It should be noted that the perchlorate salt from which the amino alcohol was generated is sharp melting. Chromatographic purification of III on Florisil and paper chromatography of the material under a variety of conditions has failed to cause the separation of diastereoisomers.[7]

The Michael addition of 6-methoxy-1,2,3,4-tetrahydroisoquinoline to 2-cyclohexenone gave 2-(3-ketocyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IX) in 94% yield. Reduction of this amino ketone with lithium aluminum hydride proceeded in a stereospecific manner giving a 94.5% yield of 2-(*cis*-3-hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xa). The assignment of the configuration of Xa as *cis* is based on analogy with the reduction of other 3-substituted cyclohexanones with this reagent[8] and on the appearance of infrared absorption bands at 3670 and 3340 cm.$^{-1}$ in dilute (0.01 *M*) solutions of Xa in carbon tetrachloride. *trans*-3-Aminocyclohexanols, being incapable of intramolecular hydrogen bonding, have no absorption band near 3300 cm.$^{-1}$ in dilute solutions.[9]



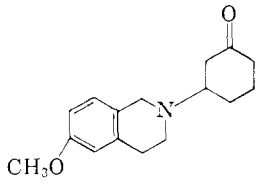
(4) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(5) *Cf.* W. Salzer, *Z. physiol. Chem.*, **274**, 39 (1942). In our preparation, the intermediate oxidation product rearranges during distillation to give the β-tetralone directly.

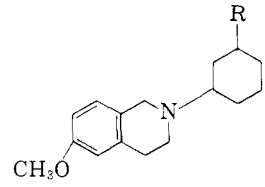
(6) The change from conformation VII to VIII can be pictured as involving rotation of the piperidone ring 180° about the C_2-nitrogen bond together with a chair to chair conformational inversion and nitrogen inversion.

(7) We are indebted to Dr. Mike Daskalakis and Miss Jean Steele of G. D. Searle and Company for some of the papergram experiments.

(8) See, for example, (a) E. L. Eliel and R. S. Ro, THIS JOURNAL, **79**, 5992 (1957), and (b) H. L. Goering and C. Serres, Jr., *ibid.*, **74**, 5908 (1952).



IX

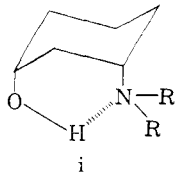


Xa, R = *cis*-OH
b, R = *cis*-$OSO_2C_6H_4CH_3$
c, R = *trans*-$OCOCH_3$
d, R = *trans*-OH

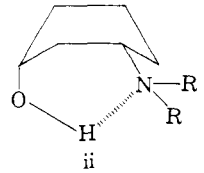
The catalytic reduction of 3-alkyl-substituted cyclohexanones usually affords a mixture of *cis*- and *trans*-substituted cyclohexanols, the *trans* isomer of which can be obtained by elution chromatography or by fractional crystallization of derivatives.[8a,10] In an attempt to obtain the *trans*-amino alcohol Xd, the amino ketone IX was reduced under a variety of conditions using Adams catalyst. Fractional crystallization or elution chromatography of the products failed to separate the isomers. Acetylation of the reduction product and elution chromatography of the acetates also resulted in an incomplete separation of isomers as indicated by a comparison of the infrared spectra of the first and last fractions of the acetate band from the chromatogram.

In order to obtain a pure sample of 2-(*trans*-3-hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xd) the pure *cis*-amino alcohol was epimerized *via* the tosylate and acetate. Treatment of the *cis*-amino alcohol Xa with *p*-toluenesulfonyl chloride in pyridine gave 2-(*cis*-3-tosyloxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xb) in 78% yield. Displacement of the tosylate group with Walden inversion was carried out using tetraethylammonium acetate in acetone[11] and gave 42% of 2-(*trans*-3-acetoxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xc) which was directly reduced with lithium aluminum hydride to 2-(*trans*-3-hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xd) in 83% yield. As expected, dilute solutions (0.01 *M*) of the *trans*-amino alcohol showed an unassociated hydroxyl absorption band at 3670 cm.$^{-1}$, but no hydrogen bonded hydroxyl band near 3300 cm.$^{-1}$.

(9) R. R. Burford, F. R. Hewgill and P. R. Jefferies [*J. Chem. Soc.*, 2937 (1957)] have reported the occurrence of free hydroxyl absorption bands near 3620 cm.$^{-1}$ and intramolecular bonded hydroxyl bands near 3320 cm.$^{-1}$ for *cis*-3-aminocyclohexanol and some *N*-alkyl derivatives. The intramolecular hydrogen bonding has been viewed as arising from a diaxial conformation i. An alternative explanation would involve hydrogen bonding between an axial hydroxyl group and the equatorial nitrogen substituent of a boat conformation (ii). Conformation ii should become more important with increase in size of the amino substituent.



i



ii

(10) See, for example, S. Winstein and N. J. Holness, THIS JOURNAL, **77**, 5562 (1955); E. L. Eliel and C. A. Lukach, *ibid.*, **79**, 5986 (1957).

(11) *Cf.* A. C. Cope and H. E. Johnson, *ibid.*, **79**, 3889 (1957); A. C. Cope and B. C. Anderson, *ibid.*, **79**, 3892 (1957); A. C. Cope, M. Brown and H. E. Petree, *ibid.*, **80**, 2852 (1958).

Experimental[12]

6-Methoxy-2-tetralone (I). (A) From 6-Methoxy-2-naphthol.—In accord with the procedure of Birch,[4] 20.0 g. of 6-methoxy-2-naphthol[13] in 225 ml. of liquid ammonia and 21.5 ml. of *t*-butyl alcohol was reduced by the addition of 5.3 g. of sodium over a period of 10 minutes with stirring. The ammonia was removed as completely as possible in a stream of nitrogen before adding ether (100 ml.) and ice and water (125 ml.). The aqueous layer was extracted with ether (under nitrogen), and the ether layers were combined and washed with water, dried and concentrated. Distillation of the residue yielded 25.9 g. (64%) of 6-methoxy-2-tetralone (I), b.p. 111–114.5° (0.2 mm.) [lit.[5] b.p. 135° (0.8 mm.)], m.p. 35.5–36° (lit.[14] m.p. 36°), λ_{max}^{EtOH} 279 mμ (ε 2,040), $\nu_{max}^{CCl_4}$ 1718 cm.$^{-1}$(s, unconj. carbonyl); and 2.6 g. (6%) of additional product, b.p. 111–125° (0.2 mm.).

(B) From 6-Methoxy-3,4-dihydronaphthalene.—A cold solution of 15 g. of sodium acetate and 155 g. of 40% commercial peracetic acid was added with stirring to a cold solution of 104 g. of 6-methoxy-3,4-dihydronaphthalene[15] in 800 ml. of methylene chloride at such a rate that the temperature of the mixture remained below 0°. When the addition was completed, the mixture was stirred at −5° for 3 hours, then washed with 2 l. of 2 *N* sodium hydroxide solution, water and dried. Concentration of the solution gave a viscous residue which was distilled giving 65.5 g. of crude product, b.p. 160–165° (0.4 mm.). Redistillation of this material gave 64 g. (56%) of 6-methoxy-2-tetralone (I), b.p. 126–130° (0.3 mm.). The infrared spectra of this product and the product described in part A were essentially the same.

The Perchlorate of 2-(3-Hydroxypiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (III).—A solution of 13.3 g. of 3-hydroxypiperidine[16] and 23.1 g. of 6-methoxy-2-tetralone in 200 ml. of toluene was prepared under a nitrogen atmosphere and heated under reflux for 22 hours, the water formed during the course of the reaction being removed by means of a Dean–Stark apparatus. Distillation of the toluene, finally under reduced pressure, gave a pale yellow residue whose ultraviolet spectrum [λ_{max}^{EtOH} 294 mμ (ε 14,450)] is consistent with the structure of 2-(3-hydroxypiperidyl)-6-methoxy-3,4-dihydronaphthalene (II). The crude enamine II was dissolved in 150 ml. of cold glacial acetic acid and hydrogenated using 1.0 g. of Adams catalyst and an initial pressure of 31 p.s.i. The hydrogenation stopped when 78% of the theoretical amount of hydrogen had been absorbed. Removal of the catalyst and most of the acetic acid (reduced pressure) gave an oily residue which was diluted with water and washed with either. The aqueous layer was then made strongly basic with sodium hydroxide and the product extracted with ether. The ether extract was dried over potassium carbonate and then concentrated under reduced pressure to give 20.4 g. (60%) of crude 2-(3-hydroxypiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (III) as a viscous pale yellow oil, $\nu_{max}^{CCl_4}$ 3400 cm.$^{-1}$ (w-broad, hydroxyl), λ_{max}^{EtOH} 279 (ε 2,080) and 287.5 mμ (ε 1,900).

Chromatographic purification of the crude amino alcohol III (0.940 g.) using Florisil (100 g., 100–200 mesh) and an ether–methanol mixture (9:1) as the eluent gave 0.754 g. of a light yellow oil whose infrared spectrum is superimposable over that of the crude amino alcohol. To a portion of the chromatographed amino alcohol (0.670 g.) in 25 ml. of cold ether was added dropwise with swirling a 1:1 mixture of 70% perchloric acid and absolute ethanol until the mixture was distinctly acidic. Filtration of the mixture gave 0.844 g. (91%) of white crystals. The analytical sample of the

(12) Melting points and boiling points are uncorrected. The infrared spectra were determined with a Baird 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.

(13) H. E. French and K. Sears, THIS JOURNAL, **70**, 1279 (1948).

(14) (a) J. W. Cornforth, R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 689 (1942); (b) G. P. Crowley and R. Robinson, *ibid.*, 2001 (1938).

(15) W. S. Johnson, J. M. Anderson and W. E. Shelberg, THIS JOURNAL, **66**, 218 (1944); see also R. B. Woodward and R. H. Eastman, *ibid.*, **66**, 674 (1944).

(16) C. H. Kao, *J. Chem. Eng. China*, **15**, 80 (1948); *C. A.*, **44**, 3993 (1950).

perchlorate of 2-(3-hydroxypiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene was crystallized from absolute ethanol and had m.p. 205.5–206.5°, λ_{max}^{EtOH} 279 (ε 2,095) and 287 mμ (ε 1,958).

Anal. Calcd. for $C_{16}H_{24}ClNO_6$: C, 53.11; H, 6.69; Cl, 9.80; N, 3.87. Found: C, 53.21; H, 6.72; Cl, 9.95; N, 3.91.

In another run involving 19.3 g. of 6-methoxy-2-tetralone, the ethereal extract of the crude amino alcohol was dried and treated with perchloric acid as described above giving 24.4 g. (62%) of the perchlorate of III, m.p. 200.5–202.5°. Recrystallization of the product gave 21.0 g. of material which melted at 202.5–203.5°.

Attempts to obtain a sharp-melting sample of the free amino alcohol III were unsuccessful. Samples of the material which had been purified by chromatography or by short path distillation (using a heating bath at 150° and a pressure of 0.001 mm.) crystallized on standing over a period of weeks and melted over a range of 70–82°.

2-(3-Ketopiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV).—An aqueous solution of 4.16 g. of the perchlorate of the amino alcohol III was basified with sodium hydroxide solution and extracted with ether to give, on evaporation of the solvent, a quantitative yield of the free amino alcohol. To a solution of this material in 400 ml. of purified acetone at 9° under a nitrogen atmosphere was added in one portion with efficient stirring 7 ml. of a chromium trioxide solution (26.72 g. of chromium trioxide and 23 ml. of concentrated sulfuric acid made up to 100 ml. with water).[17] After the mixture had been stirred at 9–12° for 30 minutes, a solution of 12 g. of sodium carbonate in 100 ml. of water was added and stirring was continued for 15 minutes. The inorganic salts were allowed to settle and the aqueous acetone solution was decanted and filtered. The inorganic salts were washed with ether and the washings were likewise decanted and filtered. The filtrates were combined and concentrated under reduced pressure at a bath temperature below 40° to give a milky mixture which was extracted with ether. The ether extract was washed with saturated sodium chloride solution, dried and concentrated to give 2.80 g. of a mixture of the amino alcohol III and amino ketone IV [$\nu_{max}^{CCl_4}$ 3400(w) and 1720(s) cm.$^{-1}$].

This material was chromatographed on 150 g. of Florisil (100–200 mesh). Ether eluted 1.25 g. (42%) of 2-(3-ketopiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (IV) which crystallized on standing under a nitrogen atmosphere (the product is sensitive to air). A sample dried (25°, 0.05 mm.) for analysis had m.p. 73–77°, λ_{max}^{EtOH} 279 (ε 2,180) and 287.5 mμ (ε 2,020), $\nu_{max}^{CCl_4}$ 1720 cm.$^{-1}$ (s, carbonyl).

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.85; H, 8.10; N, 5.32.

Further elution of the Florisil with an ether–methanol mixture (9:1) gave 0.80 g. (27% recovery) of 2-(3-hydroxypiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (III) which was converted in 90% yield to its perchlorate, m.p. 199–200°, raised to 204.5–205.5° after recrystallization from absolute ethanol.

A portion (340 mg.) of the amino ketone IV was treated with ethanolic perchloric acid to give 440 mg. (94%) of the **perchlorate of 2-(3-ketopiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene**, m.p. 184–186°. The analytical sample was crystallized from an acetone–ether mixture and had m.p. 193.5–194°, ν_{max}^{KBr} 1730 cm.$^{-1}$ (s, carbonyl).

Anal. Calcd. for $C_{16}H_{22}ClNO_6$: C, 53.41; H, 6.16; N, 3.89. Found: C, 53.36; H, 6.22; N, 3.87.

Reduction of 2-(3-Ketopiperidyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene.—To a slurry of 344 mg. of lithium aluminum hydride in 25 ml. of ether was added rapidly a solution of 235 mg. of the amino ketone IV in 100 ml. of ether and 10 ml. of tetrahydrofuran. The mixture was stirred and refluxed for 1 hour under a nitrogen atmosphere and was then hydrolyzed.[18] Filtration of the solids gave a filtrate which was chilled and treated with ethanolic perchloric acid to give 289 mg. of the perchlorate of the amino alcohol III, m.p. 193–200°. Recrystallization of the material from absolute ethanol gave 200 mg. (61%) of colorless plates, m.p. 203.5–204°, which did not depress the melting point of the amino alcohol perchlorate sample described above.

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

(18) V. M. Micovic and M. L. Mihailovic, *ibid.*, **18**, 1190 (1953).

2-Cyclohexenone.—To a mixture of dihydroanisoles prepared[19] from the Birch reduction of 90 g. of anisole was added 90 g. of tetrahydrofuran, 120 ml. of water and 27 ml. of concentrated hydrochloric acid. The mixture was heated under reflux for 15 minutes, then cooled to 0°, saturated with solid potassium carbonate and extracted with ether. The ether extract was dried and concentrated to give a residue which on distillation gave 54.0 g. (68%) of 2-cyclohexenone, b.p. 51–52° (7 mm.), $n^{28}D$ 1.4821 [lit.[20] b.p. 70° (26 mm.), λ_{max}^{EtOH} 225 mμ (ε 11,270)]. The products from a number of runs were found to be 86–95% pure (ultraviolet spectral analyses), the remainder of the material being 3-cyclohexenone and anisole. Essentially pure 2-cyclohexenone could be obtained by fractional distillation of the crude product using a Podbielniak column, b.p. 75° (29 mm.), $n^{25}D$ 1.4849, λ_{max}^{EtOH} 225 mμ (ε 10,900).

2-(3-Ketocyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IX).—To a solution of 16.5 g. of cyclohexeneone (95% pure) and 50 ml. of ethanol was added 26.6 g. of 6-methoxy-1,2,3,4-tetrahydroisoquinoline.[21] The reaction mixture warmed appreciably and was kept at 50° for 35 minutes. Most of the solvent was removed by distillation under reduced pressure and the residue was diluted to a volume of 100 ml. with ether. Cooling this solution gave two crops of the amino ketone IX amounting to 39.6 g. (94%), m.p. 74–75°, λ_{max}^{EtOH} 279 (ε 2,130) and 287.5 mμ (ε 2,000) and a shoulder at 218 mμ (ε 10,650), $\nu_{max}^{CCl_4}$ 1705 cm.$^{-1}$ (s, carbonyl). A different crystallographic form of this substance was obtained from benzene–hexane solvent, m.p. 84.5–85.5°.

Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.99; H, 8.36; N, 5.58.

2-(*cis*-3-Hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xa).—A solution of 25.9 g. of 2-(3-ketocyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (IX) in 25 ml. of purified tetrahydrofuran was added over a 45-minute period with stirring to a solution of 1.9 g. of lithium aluminum hydride in 200 ml. of ether. At the end of the addition 200 ml. of ether was added and the resulting mixture was stirred for 30 minutes before consecutively adding 1.9 ml. of water (with caution), 1.9 ml. of 15% sodium hydroxide solution and 6 ml. of water.[18] The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was crystallized from 50 ml. of ether giving 21.5 g. of the amino alcohol, m.p. 92–94.5°, and a second crop amounting to 3.1 g., m.p. 90–94.5° (total yield 94.5%). The analytical sample of 2-(*cis*-3-hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline was recrystallized from ethanol–water, m.p. 99–99.8°, λ_{max}^{EtOH} 278.5 (ε 2,050) and 287 mμ (ε 1,910) and a shoulder at 217 mμ (ε 10,050); $\nu_{max}^{CCl_4}$ (10% solution) 3670 (w, unassociated hydroxyl), 3350 (m, broad, associated hydroxyl) and two bands characteristic of the *cis*-amino alcohol at 1006(w) and 960(m) cm.$^{-1}$, $\nu_{max}^{CCl_4}$ (0.01 *M*, 1-cm. cell) 3670 (m, unassociated hydroxyl) and 3340 cm.$^{-1}$ (m, intramolecular hydrogen bonded hydroxyl).[9]

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.83; N, 5.36. Found: C, 73.25; H, 8.82; N, 5.58.

2-(*cis*-3-Tosyloxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xb).—A solution of 15.0 g. of 2-(*cis*-3-hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 25 ml. of anhydrous pyridine and 12.0 g. of *p*-toluenesulfonyl chloride was prepared at 0° under a nitrogen atmosphere and the mixture was allowed to stand for 42 hours at about 5°. Ice-water (50 ml.) was added to the mixture followed by 25 ml. of saturated aqueous sodium bicarbonate solution. The resulting mixture was diluted with water and extracted with ether and with benzene. The organic layers were combined, dried and concentrated at room temperature under reduced pressure finally at 0.1 mm.). An ether solution (200 ml.) of the residue was treated with Norit, filtered and cooled giving 15.9 g. of crude product, m.p. 92–95°, and 2.7 g., m.p. 91.5–94°. Recrystallization of the tosylate from cyclohexane gave an analytically pure sample of Xb, m.p. 95–96°, $\nu_{max}^{CCl_4}$ 1370(s), 1190(s) and 1180 cm.$^{-1}$ (s, sulfonate group).

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Anal. Calcd. for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.04; N, 3.37. Found: C, 66.69; H, 7.00; N, 3.53.

2-(*trans*-3-Hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xd).—A solution of 3.5 g. of 2-(*cis*-3-tosyloxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 5.0 g. of tetraethylammonium acetate monohydrate[22] in 50 ml. of acetone (purified by refluxing reagent grade acetone in the presence of calcium oxide and potassium permanganate for 2 hours before distilling it) was refluxed for 60 hours. Distillation of the solvent gave a residue which was treated with water and extracted with benzene. The dried extract was concentrated under reduced pressure giving 1.0 g. (42%) of crude 2-(*trans*-3-acetoxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xc) which was dissolved in anhydrous ether.

The ether solution of Xc was added with stirring to 0.5 g. of lithium aluminum hydride in 200 ml. of ether. The mixture was stirred at room temperature for 1 hour and the product isolated as described above.[18] Crystallization of the product from hexane gave 760 mg. of the *trans*-amino alcohol, m.p. 111.5–113°. The analytical sample was crystallized from hexane, m.p. 112–113°; $\nu_{max}^{CCl_4}$ (10% solution) 3680 (w, unassociated hydroxyl), 3400 (m-broad, associated hydroxyl) and an absorption band characteristic of the *trans*-amino alcohol at 980 cm.$^{-1}$ (m), $\nu_{max}^{CCl_4}$ (0.01 *M* solution, 1-cm. cell) 3670 cm.$^{-1}$ (unassociated hydroxyl) and no absorption band attributable to hydrogen bonding from 3600–3100 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.83; N, 5.36. Found: C, 73.64; H, 9.01; N, 5.50.

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

Steroidal Hormone Analogs. VIII. Amino Acid Analogs of Some Artificial Estrogens[1]

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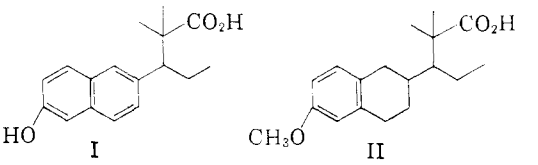
The condensation of 1,2,3,4-tetrahydro-2-naphthylamine with acetone cyanohydrin gave N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyronitrile which was hydrolyzed to N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid (Vb). Pyrolysis of the tetramethylammonium salt of Vb gave methyl N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyrate (Vc). 1,2,3,4-Tetrahydro-6-methoxy-2-naphthylamine, prepared from 6-methoxy-2-tetralone *via* the oxime, was carried through a similar series of reactions yielding N-2-(1,2,3,4-tetrahydro-6-methoxynaphthyl)-α-aminoisobutyric acid and the corresponding methyl ester. Attempts to introduce substituents on the nitrogen of Vb or Vc were unsuccessful.

Several isomers of doisynolic acid represent highly active artificial estrogens which are closely related to the naturally occurring estrogens.[3] Further structural simplifications of this type of hormone are represented in the biologically active allenolic acids I[4] and II,[5] the former of which (Horeau's acid) has been used clinically. In continuing our work on azasteroids,[6,7] we were interested in incorporating a nitrogen atom into the skeleton of these compounds to determine what effect this would have on their biological properties. In addition, some of the nitrogen-containing analogs, being complex α-amino acids, could conceivably possess biological properties not associated with hormone activity. This paper describes the preparation of the α-amino acids Vb and Vd related to II.



I II

At the outset of our work we wished to establish as a model experiment that cyclohexylamine could be converted to N-cyclohexyl-α-aminoisobutyric acid since the latter compound possesses the amino acid function of the hormone analogs Vb and Vd. The reaction of cyclohexylamine with acetone cyanohydrin, using the general procedure of Jacobson,[8] gave N-cyclohexyl-α-aminoisobutyronitrile (IIIa) in quantitative yield. Hydrolysis of the nitrile with concentrated hydrochloric acid following the directions of Steiger[9] gave N-cyclohexyl-α-aminoisobutyric acid (IIIb) after its isolation from the hydrochloride through the use of lead carbonate as described by Cocker and Lapworth.[10]

We next investigated the synthesis of N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid (Vb) from 2-tetralone since this amino acid is of interest for biological testing *per se*, and the

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