The infrared spectrum (Nujol slurry) had peaks at 3.05 μ and 3.15 μ (N—H), and a peak at 6.05 μ (C=O). The NMR spectrum had a P^{31} chemical shift of +2.7 p.p.m. and a minor resonance at +5.1 p.p.m. (15.9% solution in acetone).

The reaction of S-methyl diethoxyphosphinylthiolformate with sodium iodide. A solution of *S*-methyl diethoxyphosphinylthiolformate (10.61 g., 50 mmoles) and sodium iodide (7.49 g., 50 mmoles) in tetrahydrofuran (100 ml.) was stirred in a dry atmosphere at 25° for 9.5 hr. The reaction mixture contained solid. The mixture was cooled to 0°. The solid was filtered, was washed with ether, and was dried at 60°/20 mm. for 1 hr. to yield *O*-ethyl *O*-sodium carbomethylthiophosphonate (9.50 g., 46 mmoles, 92%), m.p. 205°–210°. The hydroscopic product was recrystallized twice from hot acetone to yield white crystals, 7.17 g., m. p. 205–207°.

Anal. Calcd. for $C_4H_8NaO_4PS$: C, 23.31; H, 3.91; P, 15.03; S, 15.56. Found: C, 23.19; H, 3.61; P, 15.29; S, 15.74.

The infrared spectrum (potassium bromide) had a peak at 6.17 μ with a shoulder at 6.13 μ (C=O). The NMR spectrum had a P^{31} chemical shift of +3.2 p.p.m.

The reaction of sodium diisopropylphosphonate with carbon disulfide followed by reaction with methyl iodide. Sodium diisopropyl phosphonate was prepared in the usual manner. A solution of sodium diisopropylphosphonate (0.2 mole) in tetrahydrofuran (200 ml.) was added to well stirred carbon disulfide (76 g., 1 mole) at 2–8° over 15 min. The solution became deep red colored. Methyl iodide (30 g., 0.21 mole) was added to the stirred solution at 5° during 5 min. The reaction mixture was stirred for an additional 5 min. at 5°. The homogeneous dark-red mixture was poured into ice water (750 ml.). The organic phase was extracted into ether (300 ml.). The ether phase was washed with water (4 × 500 ml.). The organic phase was dried, (magnesium sulfate), filtered, and evaporated to yield an oil. The oil was distilled through a 10-in. vacuum jacketed Vigreux column to yield a main fraction, a dark red-colored liquid, *S*-methyl diisopropoxyphosphinyldithioformate (30.8 g., 0.12 mole, 60%), b.p. 116–117°/0.4 mm., n_D^{25} 1.5168.

Anal. Calcd. for $C_8H_{17}O_3PS_2$: C, 37.49; H, 6.69; P, 12.09; S, 25.02. Found: C, 37.75; H, 7.07; P, 11.88; S, 24.72.

The NMR spectrum had a P^{31} chemical shift of +4.2 p.p.m.

The reaction of sodium diisopropyl phosphonate with carbon disulfide followed by reaction with p-chlorobenzyl chloride. In this experiment the sodium hydride (50.9% dispersion in mineral oil) (4.8 g., 0.1 mole) was freed of mineral oil by washing with hexane (3 × 300 ml.). The supernatant liquor was removed by means of nitrogen pressure by filtering through a dip tube having a frittered glass tip. The sodium diisopropyl phosphonate (0.1 mole) was prepared in tetrahydrofuran (100 ml.) in the usual manner. The tetrahydrofuran solution of the sodium diisopropyl phosphonate was added to carbon disulfide (38 g., 0.5 mole) as before. A solution of *p*-chlorobenzyl chloride (14.5 g., 0.09 mole) in tetrahydrofuran (100 ml.) was added to the reaction mixture at 1–3° over 5 min. The reaction mixture was stirred in a nitrogen atmosphere at room temperature for 19 hr. The mixture was then refluxed for 1 hr. Ether was added to the mixture. The mixture was washed with water (3 × 500 ml.). The organic phase was dried, (magnesium sulfate), filtered and evaporated *in vacuo* at 80° to yield a dark red oil. The oil was evacuated at 80°/0.1 mm. for 1 hr. and then at room temperature at 0.1 mm. for 20 hr. to yield a deep red oil, *S*-*p*-chlorophenyl diisopropoxyphosphinyldithioformate (27.4 g., 0.075 mole, 83%).

Anal. Calcd. for $C_{14}H_{20}ClO_3PS_2$: C, 45.83; H, 5.49; P, 8.44; S, 17.48. Found: C, 45.98; H, 5.75; P, 8.14; S, 17.77.

The NMR spectrum (neat) had P^{31} chemical shifts of +4.2 p.p.m., 0.0 p.p.m. and −16.1 p.p.m. The peak at +4.2 p.p.m. accounted for >95% of the combined areas under the peaks.

Acknowledgment. The author wishes to thank Mr. John Pustinger and Dr. Gail Birum for their valuable assistance in this work. He wishes to thank Mr. John W. Cooper for the infrared spectra and Messrs. William S. Coakley, Robert E. Dorsett and John E. Strobel for the NMR data.

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Steroids. II. 4-Aza-5-cholesten-3-one and 4-Aza-5-pregnene-3,20-dione[1,2]

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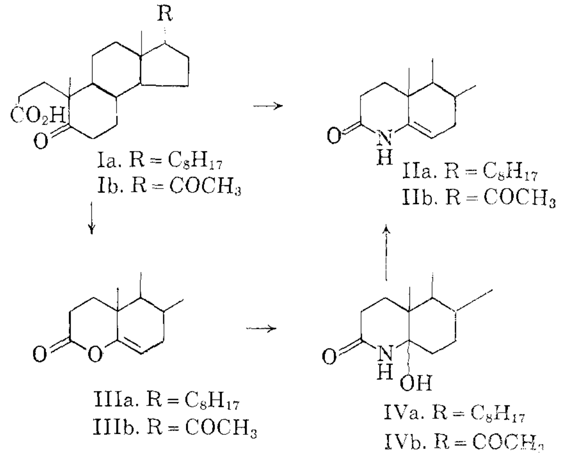
Received September 28, 1960

The synthesis of 4-aza-5-cholesten-3-one (IIa), m.p. 252–253°, from 3,5-seco-4-norcholestan-5-on-3-oic acid (Ia) by reaction with ammonia at 140° has been reported by our laboratory.[5] Wildi[6] described a similar preparation for this compound. Recently the synthesis of IIa with a much lower melting point, m.p. 189°, by the reaction of ammonia with 4-oxa-5-cholesten-3-one (IIIa) at 25° was announced.[7] The reported spectra of these compounds were similar and it was thought that they might be different crystalline forms.

The procedure of Uskoković and Gut[7] was



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(1) For paper I in this series see R. E. Havranek and N. J. Doorenbos, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 328 (1960).

(2) This work was supported by Research Grant CY-4132 from the National Cancer Institute, National Institutes of Health.

(3) Sterling-Winthrop Research Fellow, 1958–59.

(4) H. A. B. Dunning Research Fellow, 1959–60.

(5) N. J. Doorenbos and C. L. Huang, Abstract, 136th National A.C.S. Meeting, 30-O, Atlantic City, September 1959.

(6) R. S. Wildi, U. S. Patent **2,897,202**, July 28, 1959.

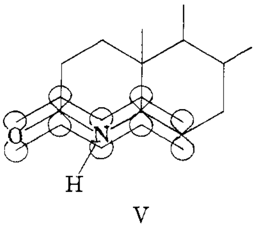
(7) M. Uskoković and M. Gut, *Helv. Chim. Acta*, **42**, 2258 (1959).

repeated in this laboratory. The high yield reported was approached only after allowing the reaction to proceed for one week. As the reaction time was shortened, increased amounts of IIIa were recovered. The product of this reaction, m.p. 190–192°, was shown to be 4-azacholestan-5ξ-ol-3-one (IVa) and not IIa as reported.[7] The structure was established by analysis and spectra. The 5-hydroxy derivative (IVa) was easily dehydrated to IIa by acid catalysts at 25° or by heating above 100°. Perhaps the previous investigators had dehydrated IVa to IIa by drying at 100° before determining the analysis and spectra.

The synthesis of 4-aza-5-pregnen-3,20-dione (IIb) from 4-oxa-5-pregnen-3,20-dione (IIIb) was also reported.[7] The reaction intermediate, 4-aza-5ξ-hydroxypregnane-3,20-dione (IVb) was isolated and reported to have the same melting point as IIb, m.p. 288–289°. 4-Aza-5-pregnene-3,20-dione (IIb) had been prepared previously in this laboratory and it was felt that IVb should have a lower m.p. than IIb. 4-Aza-5ξ-hydroxypregnane-3,20-dione (IVb) was prepared as described[7] and found to have a melting point of 212–214°. IVb was readily dehydrated to IIb by acid catalysts at 25° or by heating above 100°.

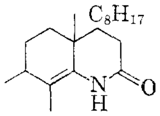
The melting points of IVa and IVb must be taken with care since they rapidly lose water at their melting point. The samples were prepared for analysis by drying for twelve hours at 25°/0.1 mm.

The methods used to convert IVa into IIa and IVb into IIb suggest that the 5,6-double bond is more stable than the 4,5-double bond in these lactams. Differences in resonance stabilization of these isomers might account for these observations. The 5-ene could have three pentacentric molecular orbitals (V), as a result of the filled *p*-orbital of nitrogen with the adjacent unsaturated atoms, whereas the 4-ene could have only two tetracentric molecular orbitals.

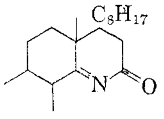


V

In comparison, it should be noted that Tsuda and Hayatsu[8] were able to isomerize 15-aza-D-homo-5α-cholest-8(14)-en-3β-ol-16-one benzoate (VI) into 15-aza-D-homo-5α-cholest-14-en-3β-ol-16-one benzoate (VII) by treatment with hydrochloric acid. VI is probably less stable for steric reasons. The double bond is exocyclic to two six-membered rings including a rather rigid ring B.



VI



VII

EXPERIMENTAL[9]

4-Aza-5-cholesten-3-one (IIa). 3,5-Seco-4-norcholestan-5-on-3-oic acid[10] (4.0 g., 0.010 mole) was dissolved in 200 ml. of concd. aqueous ammonium hydroxide and heated in a pressure vessel under a nitrogen atmosphere at 200° for 6 hr. The mixture was cooled, filtered, and dried to yield 3.80 g. (99%) of 4-aza-5-cholesten-3-one (IIa), m.p. 250–253°. One crystallization from acetone-ethanol yielded 3.56 g. of an analytical sample, m.p. 255–256° (reported m.p. 249–250°[6]; m.p. 189°[7]); $[\alpha]^{29}_D$ −82°; λ_{max} 233 mμ, log ε 4.13; infrared 2.95 (NH stretching), 3.15 (NH, H-bond), 5.96 (C=C), and 6.04 μ (C=O) (reported $[\alpha]_D$ −77°; λ_{max} 233 mμ, log ε 4.13).[7]

Anal. Calcd. for $C_{26}H_{43}ON$: C, 80.98; H, 11.24; N, 3.63. Found: C, 81.29; H, 11.55; N, 3.48.

4-Aza-5ξ-hydroxycholestan-3-one (IVa). IVa was prepared from 4-oxa-5-cholesten-3-one[10] (IIIa) by the procedure of Uskoković and Gut.[7] The following data were obtained on the product after drying for 12 hr. at 25°/0.1 mm.[11]: m.p. m.p. 190–192° dec.; $[\alpha]^{29}_D$ +86°; no peaks above 210 mμ in the ultraviolet; infrared 2.77 (OH stretching), 2.95 (OH, H-bond), and 6.02 μ (C=O).

Anal. Calcd. for $C_{26}H_{45}O_2N$: C, 77.36; H, 11.24; N, 3.47. Found: C, 77.75; H, 10.94; N, 3.73.

Thermal dehydration of IVa. A 100-mg. sample of IVa was heated in a nitrogen atmosphere at 250° for 1 min. Bubbles of water vapor could be observed for about 10 seconds. A solid residue, m.p. 244–247°, was obtained upon cooling. One crystallization from acetone-ethanol yielded a crystalline solid, m.p. 255–256°, which was shown to be identical to IIa by mixed melting point and a comparison of spectra.

Acid catalyzed dehydration of IVa. Samples of IVa were dehydrated by treatment with hydrochloric acid in acetic acid or boron trifluoride in acetic anhydride at room temperature. The latter experiment was an attempt to acetylate the hydroxyl group. The identity of the product in each of these reactions was established by mixed melting point and a comparison of spectra.

4-Aza-5-pregnene-3,20-dione (IIb). 3,5-Seco-4-norpregnan-5-on-3-oic acid[12] (Ib) (10.0 g., 0.03 mole) was dissolved in 260 ml. of absolute ethanol, which had been saturated previously with dry ammonia gas at 0°. The solution was heated in a sealed reaction vessel at 150° for 11 hr. The white crystalline solid which separated on cooling was filtered and crystallized from ethanol-ether to yield 6.0 g. (64%) of 4-aza-5-pregnene-3,20-dione (IIb), m.p. 295–296°; $[\alpha]^{25}_D$ −34°; λ_{max} 233 mμ, log ε 4.13; infrared 2.95 (NH stretching), 3.15 (NH, H-bond), 5.87 (ketone C = O), 5.96 (C=C), and 6.03 μ (lactam C=O); (reported m.p. 288–289°; $[\alpha]^{21}_D$ −4°; λ_{max} 233 mμ, log ε 4.13).[7]

Anal. Calcd. for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.31; H, 9.59; N, 4.33.

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(8) K. Tsuda and R. Hayatsu, *J. Am. Chem. Soc.*, **78**, 4107 (1956).

(9) Melting points were taken on a Thomas-Hoover m.p. apparatus and are uncorrected. Specific rotations were determined on 1% solutions in chloroform. Ultraviolet data were obtained with a Spectracord on solutions in 95% ethanol. Infrared data were obtained with an Infracord using chloroform solutions. Analyses were obtained from Drs. Weiler and Strauss, Oxford, England. The steroid intermediates were furnished by the National Service Center for Cancer Chemotherapy.

(10) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950).

(11) A portion of this sample was dried an additional 12 hr. under these conditions without a further loss in weight.

(12) C. C. Bolt, *Rec. trav. chim.*, **T70**, 940 (1951).

4-Aza-5ξ-hydroxypregnane-3,20-dione (IVb). IVb was prepared from 4-oxa-5-pregnen-3,20-dione[13] (IIIb) by the procedure of Uskoković and Gut.[7] The following data were obtained on this product after drying for 12 hr. at 25°/0.1 mm.[11]: m.p. 212–214° dec.; $[\alpha]_D^{28}$ + 171°; no peaks in the ultraviolet above 210 mμ; infrared 2.77 (OH stretching), 2.95 (OH, H-bond), 5.87 (ketone C=O), and 6.03 μ (lactam C=O); (reported m.p. 288–289°; $[\alpha]_D^{21}$ +173°).[7]

Anal. Calcd. for $C_{20}H_{31}O_3N$: C, 72.03; H, 9.37; N, 4.20. Found: C, 72.51; H, 9.25; N, 4.09.

Dehydration of IVb. IVb was dehydrated to IIb by the same procedures described above for IVa. The identity of the product, IIb, in each of these procedures was established by mixed melting point and a comparison of spectra.

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[13] M. Gut, *Helv. Chim. Acta*, 36, 906 (1953).

Steroids. III. Synthesis of Some 3-Aza-A-homocholestanes by the Beckmann and Schmidt Rearrangements in Polyphosphoric Acid[1,2]

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Received September 28, 1960

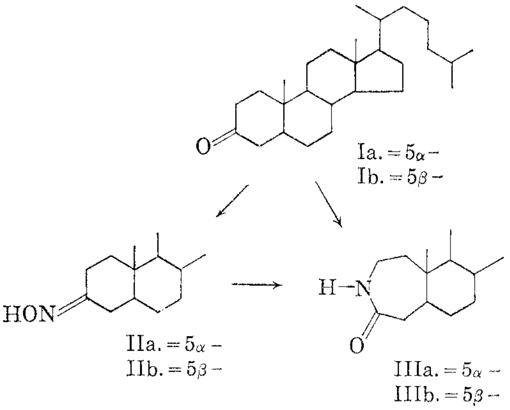
The great value of steroids in modern medicine and the interesting pharmacological properties of steroid alkaloids have brought about an increasing interest in aminosteroids and azasteroids. Over thirty papers and patents on azasteroids alone have appeared.[3]

The Beckmann and Schmidt rearrangements have offered two convenient methods for introducing a heterocyclic nitrogen into the steroid ring system. Many azasteroids have been prepared by the Beckmann rearrangement using a variety of solvents and such catalysts as tosyl chloride,[4-9] thionyl chloride,[10,11] phosphorus pentachloride,[4,5] p-acetylaminobenzenesulfonyl chloride,[7] and p-aminobenzenesulfonyl chloride.[12,13]

The Schmidt rearrangement has been applied to a few steroid ketones[4,5] with sulfuric acid being used as the catalyst in the presence of a suitable organic solvent.

The yields obtained by these methods have been variable and often below 60%. Recently Conley[14] reported polyphosphoric acid to be superior to other catalysts in the Beckmann and Schmidt rearrangements. Polyphosphoric acid is a mild catalyst and a good solvent for most organic compounds.

In 1957, a general study of heterocyclic steroids was begun in this laboratory. In order to obtain a preliminary evaluation of the usefulness of polyphosphoric acid for the synthesis of azasteroids, two azasteroids were synthesized by the Beckmann and Schmidt rearrangements using both polyphosphoric acid and more conventional methods. The azasteroids selected were 3-aza-A-homocholestan-4-one (IIIa) and 3-aza-A-homocoprostan-4-one (IIIb) since they may be prepared from readily available ketones. Shoppee and Sly[11] prepared these azasteroids by the Beckmann rearrangement of cholestan-3-one oxime (IIa) and coprostan-3-one oxime (IIb), using thionyl chloride as the catalyst and dioxane as the solvent. The crude yields, after purification by chromatography, were 63% for IIIa and 36% for IIIb. These chromatographed fractions were subjected to sublimation and repeated crystallizations in order to obtain analytically pure products. We obtained similar results with this procedure.



Ia. = 5α –
Ib. = 5β –

IIa. = 5α –
IIb. = 5β –

IIIa. = 5α –
IIIb. = 5β –

In this laboratory, it has been demonstrated that azasteroids may be prepared in high yield by either the Beckmann or Schmidt rearrangements, if polyphosphoric acid is used as the catalyst. No solvent was needed since polyphosphoric acid is a good solvent for cholestan-3-one (Ia) and coprostan-

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[1] For paper II in this series see N. J. Doorenbos, C. L. Huang, C.R. Tamorria, and M. T. Wu, *J. Org. Chem.*, 26, 2546 (1961).

[2] (a) This work was supported by Research Grant CY-4132 from the National Cancer Institute, U. S. Public Health Service; (b) presented at the 1960 A.A.A.S. meeting in New York City, December 29.

[3] Chien Li Huang, Ph.D. thesis, University of Maryland, 1960.

[4] S. Hara, *Pharm. Bull.* (*Japan*), 3, 209 (1955).

[5] S. Hara, *Yakugaku Zasshi*, 78, 1027 (1958).

[6] S. Hara, *Yakugaku Zasshi*, 78, 1030 (1958).

[7] S. Kaufmann, *J. Am. Chem. Soc.*, 73, 1779 (1951).

[8] R. H. Mazur, *J. Am. Chem. Soc.*, 81, 1454 (1959).

[9] K. Tsuda and R. Hayatsu, *J. Am. Chem. Soc.*, 78, 4107 (1956).

[10] B. M. Regan and F. N. Hayes, *J. Am. Chem. Soc.*, 78, 639 (1956).

[11] C. W. Shoppee and J. C. Sly, *J. Chem. Soc.*, 3458 (1958).

[12] H. Heusser, J. Wohlfahrt, M. Muller, and R. Anliker, *Helv. Chim. Acta*, 38, 1399 (1955).

[13] R. Anliker, M. Muller, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, 38, 1404 (1955).

[14] R. T. Conley, *J. Org. Chem.*, 23, 1330 (1958).