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Studies Directed Toward the Total Synthesis of Novel Azasteroids. III. The Formation of a Hexahydroisoquinoline, Octahydroisoquinoline and a Decahydro-2H-benzo[a]quinolizine as Precursors to 8-Azasteroids. (1,2)

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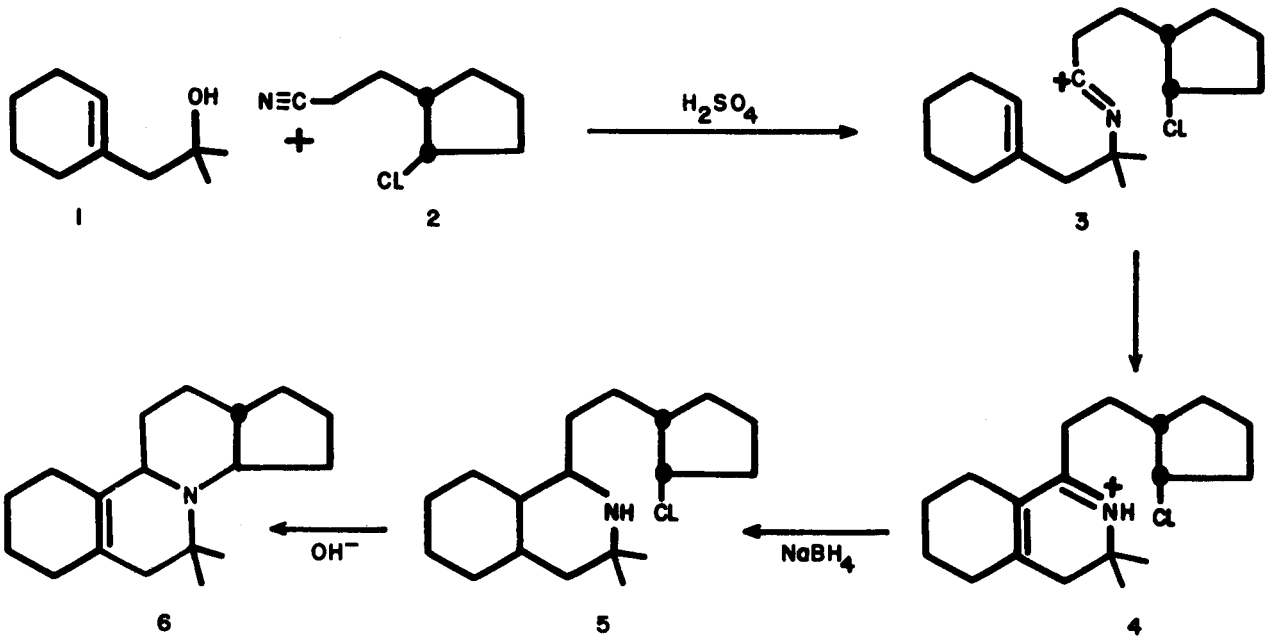
A plan of approach to novel 8-azasteroids was tested with suitable model compounds to determine its feasibility. The results of these experiments are described.

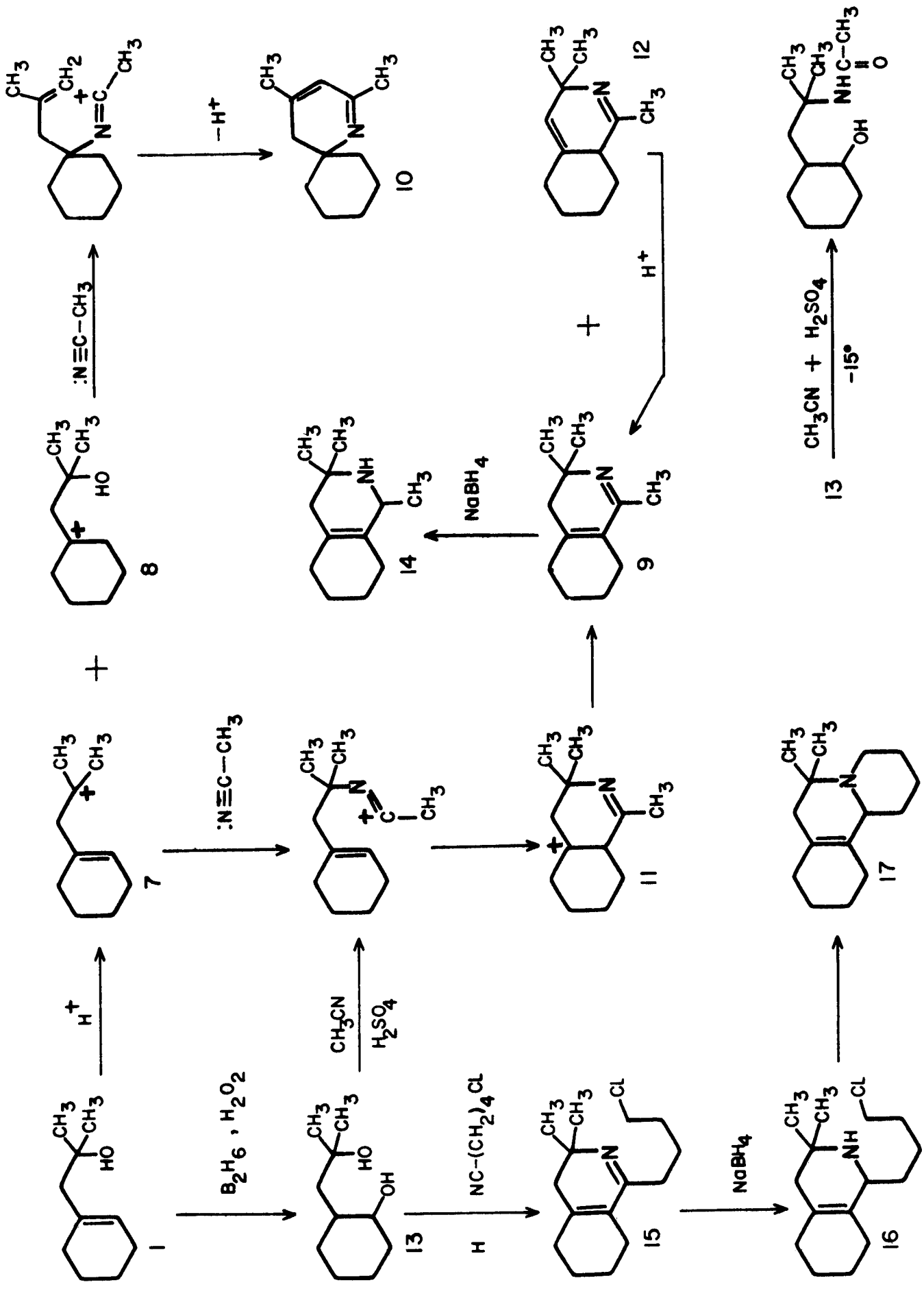
As part of an extensive program to utilize the Ritter reaction (4) and some of its recent extensions (5) in obtaining a variety of azasteroidal systems, a plan (Chart 1) was devised which might lead to 8-azasteroids from relatively simple starting materials. It was hoped that an appropriately substituted tertiary alcohol, α,α-dimethyl-1-cyclohexene-1-ethanol, **1**, and nitrile, *cis*-2-chlorocyclopentanepropionitrile, **2**, would condense in concentrated sulfuric acid *via* the azocarbonium ion (5) **3**, to the hexahydroisoquinoline, **4**. The plan then required that the sulfuric acid mixture be quenched in water, partially neutralized (*p*H 3), reduced with sodium borohydride, and cyclized with base to produce the racemic 8-azasteroid, **6**. The stereochemical study of the steroid would in this case be limited to the CD ring fusion which was expected to be *trans* if the intramolecular alkylation step proceeds in the usual manner (with inversion).

A logical beginning to this approach would best involve the use of simple, readily available materials as models to test its feasibility. Since the preparation of the *cis*-chloronitrile, **2**, would require a cumbersome effort it was decided to utilize acetonitrile first to test the formation of the 1-methyl analog of **4**. When acetonitrile was treated with the olefinic alcohol in ice-cold sulfuric acid and the mixture allowed to remain overnight, there was obtained a mixture of two unstable oils which appeared as two closely overlap-

CHART I

PLAN OF APPROACH TO 8-AZASTEROID




B_2H_6, H_2O_2
H^+
CH_3CN
H_2SO_4
$NC-(CH_2)_4Cl$
$NaBH_4$
$:N\equiv C-CH_3$
$-H^+$
H^+
$CH_3CN + H_2SO_4$
-15°
$NaBH_4$

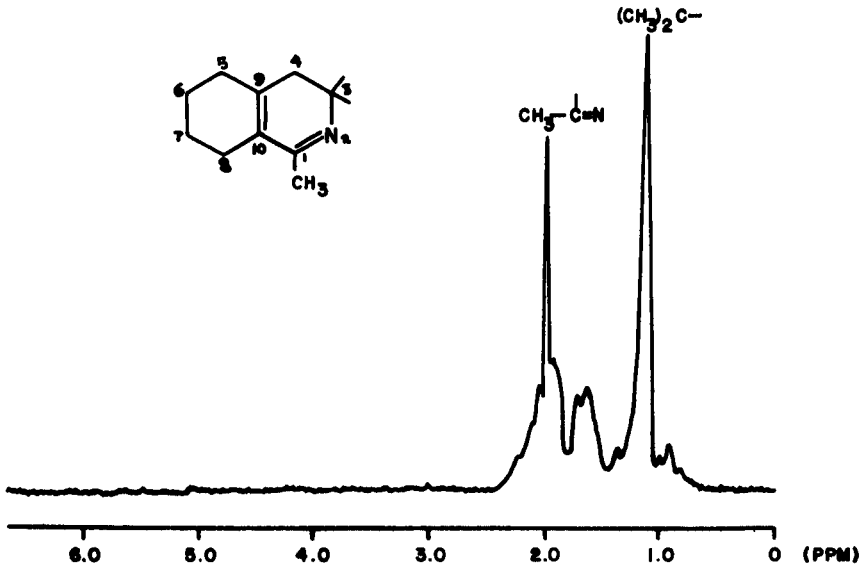


FIG. 1 NMR SPECTRUM TAKEN IN DEUTERIOCHLOROFORM AT 60 MC USING TMS AS INTERNAL STANDARD

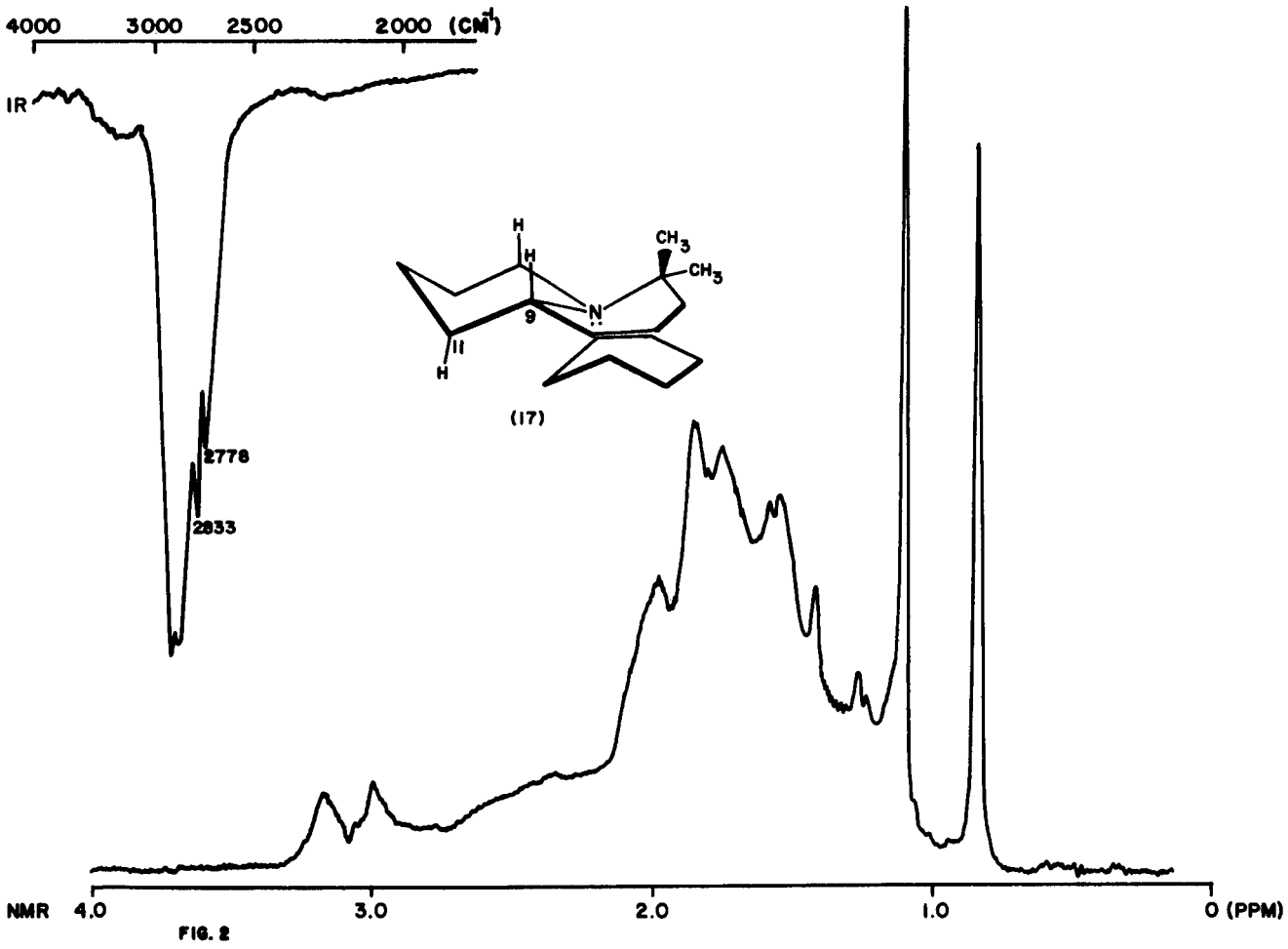


FIG. 2

ping peaks on a gas chromatogram. Attempts to completely resolve the peaks were never entirely successful. The infrared spectrum of the mixture indicated that there was present the conjugated C=N linkage (6) (6.29 μ), conjugated C=C linkage (6.00 μ), vinyl proton (11.90 μ) and no NH or OH groups. The ultraviolet spectrum exhibited a maximum at 258 mμ (ϵ 3950) indicative of the 1,3-diene system in 5,6-dihydropyridines (5). The nmr spectrum (neat and $CDCl_3$), exhibited a strong signal at 1.12 ppm (CH_3), doublet centered at 1.95 ppm (CH_3-C=C and CH_3-C=N-) and a vinyl proton signal at 5.69 ppm. The integrated counts on these proton signals indicated that the vinyl signal was approximately one-third of a proton and the methyl signal at 1.12 ppm equal to four protons. Since the methyl group signal must be a multiple of three if was concluded that the mixture was approximately 33% of 10 and 67% of 9. Both of these structures would be very similar with regard to their infrared and ultraviolet spectrum yet would be quite distinct in their nmr characteristics. The percentage of 9 and 10 in the mixture is also supported by the gas chromatographic analyses, whose peaks were extrapolated to total resolution. It should not, however, be very surprising to encounter such a mixture since the olefinic alcohol would, as expected, protonate at the ring carbon to give 8 with facility comparable to hydroxyl protonation to give 7 (7). Along with the mixture, 9 and 10, there was also obtained a significant degree of polymerization of the alcohol 1. It was found that the rate of alcohol addition, stirring, and size of the alcohol droplet during addition have a pronounced effect upon both the amount of polymer formed and the yields of heterocyclic bases. When the alcohol was added through an ordinary dropping funnel into the stirred cold (0-8°) sulfuric acid, no products were obtained, only extensive polymerization to rubbery insoluble tars. However, if the alcohol was added through a capillary tube (8) into a vigorously stirred cold (-10 to 0°) sulfuric acid solution containing acetonitrile, the amount of polymer recovered was only 50% as much as the previous run and the heterocyclic bases were obtained in 30% yield.

The problem which now existed was to circumvent the simultaneous formation of the isomeric base, 10. The reaction was repeated using acetonitrile and the corresponding glycol, 13, which was obtained in high yield from hydroboration of the cyclohexenyl alcohol, 1. The rationale in employing this substance was based mainly upon the fact that the tertiary hydroxyl group would protonate faster (leading to the carbonium ion) than the secondary hydroxyl group. This would then allow the nitrile to be attacked by an "isomerically pure" carbonium ion resulting only in the desired isoquinoline derivative, 9. The secondary hydroxyl group in 13 after prolonged contact in sulfuric acid would, presumably protonate, depart as the hydronium ion, leaving the carbonium ion in equilibrium with the olefinic linkage. When acetonitrile in cold sulfuric acid was treated with the glycol there was once again obtained a mixture of two products but not the same two previously mentioned. One product of this mixture was indeed 9 but the other was not the spirodihydropyridine, 10. The ultraviolet spectrum of the mixture showed a maximum at 255 mμ (ϵ 2200) and the infrared spectrum indicated conjugated C=N (6.29 μ), unconjugated C=N (6.05 μ), and vinyl proton (11.90 μ). Two picrates were isolated (127°, 147°) and gave identical analytical results. On this basis, the structures 9 and 12 were advanced for this binary mixture of bases. If these were correct, then it should be possible to isomerize 12 to 9 in acidic medium since the conjugation and tetrasubstitution of the olefinic linkage in 9 should provide the driving force (9). The reaction of the glycol and the acetonitrile was repeated in sulfuric acid and then allowed to remain for 18 hr. at room temperature in this solvent. There was isolated from this reaction, in 30% yield, a single product whose infrared spectrum exhibited only conjugated C=N (6.29 μ), no vinyl proton, and conjugated C=C (6.00 μ). The ultraviolet spectrum of 9 was in further support of the structure showing a maximum at 255 mμ (ϵ 4250). The nmr spectrum (Fig. 1) was also in complete agreement with the isoquinoline indicating two strong methyl signals, 1.12 ppm [$(CH_3)_2C$-] and 1.98 ppm (CH_3-C=N-) in the ratio 2:1. It can also be seen that there is no visible trace of vinyl proton signals in the 5-6 ppm region. Although the hexahydroisoquinoline was an unstable oil, turning from light yellow to deep red within an hour's exposure to air, it could be kept quite stable in a nitrogen atmosphere. An attempt to improve upon the 30% yield was made by performing the reaction in concentrated sulfuric acid at -5° to -20°. The degree of polymerization was further reduced but the major product obtained along with 9 was the hydroxyamide, 18; a product resulting from a simple Ritter reaction (4). It is obvious that the secondary hydroxyl group is not significantly removed under these conditions. The acquisition of this isoquinoline derivative gave initial support to the proposed plan of approach at least as far as the first ring closure was concerned.

The next step in the planned synthesis was the sodium borohydride reduction of the C=N linkage in aqueous acid solution. This has already been accomplished (5) in another series and therefore no serious difficulty was anticipated. The reduction went smoothly in aqueous acid (*p*H 3-5) and resulted in the octahydroisoquinoline, 14. That the reduction was specific for the C=N linkage and no C=C reduction and/or rearrangement occurred was adequately demonstrated by the infrared spectrum which was rather non-descript, indicating the absence of the C=N, -C=C-H, and conjugated C=C links. The N-H and C=C stretching modes were too weak to detect with certainty. The nmr spectrum was in complete agreement with the expected product indicating only a doublet for the C-1 methyl (1.20 ppm, J=1.6 c.p.s.) and a sharp signal for the C-3 *gem*-dimethyl groups (1.11 ppm). There was also present a multiplet of bands in the allylic region (1.8-2.1 ppm). A phenylthiourea derivative was readily prepared to further support the secondary amine structure.

Now that the first two steps have been accomplished (Chart 1) with suitable models, the next step would have to involve a halogen-containing nitrile and a study of the ring closure (to ring C). Treatment of δ-chlorovaleronitrile with the glycol in sulfuric acid at room temperature overnight, dilution of the sulfuric acid mixture with water, reduction of 15 with sodium borohydride to the secondary amine, 16, followed by base-catalyzed intramolecular alkylation gave the tricyclic

steroidal precursor, 17, in 25% yield. The product was free of any isomeric bases and an examination of its nmr spectrum (Fig. 2) indicated it possessed the *gem*-methyl groups whose relative proximity to the olefinic bond results in a difference in degrees of shielding phenomena. The lowest field signal is due to the tertiary proton adjacent both to the nitrogen and the olefinic linkage. The stereochemical assignments given to 17 (Fig. 2) is based upon previous studies of related ring systems (5). The two sharp shoulder peaks at 2833 and 2778 cm^{-1} are correlated to the presence of a *trans*-diaxial arrangement of the two protons adjacent to the nitrogen electron pair. This correlation has been used by others (10) to establish the presence of a *trans*-quinolizidine system. Recently (5, 11), nmr techniques have been employed to supplement the infrared rule (12). It was shown that the *axial* tertiary proton adjacent to nitrogen gives rise to a signal at fields higher than 3.8 ppm whereas corresponding *equatorial* protons absorb at fields lower than 3.8 ppm. The tricyclic bases exhibits a strongly coupled proton signal (C-9) centered at 3.09 ppm (J=10 c.p.s.). The large coupling constant is due to the interaction with the adjacent methylene group (C-11). The magnitude of coupling constants is well-known (13) to be a function of the dihedral angle between protons on adjacent carbon atoms. It can readily be seen that the axial proton on C-9 is related to the axial proton on C-11 by a dihedral angle very close to 180°, whereas the dihedral angle between the equatorial protons on C-11 and C-9 are in the vicinity of 45°. The former angle (180°) results in a large degree of spin-spin coupling whereas the latter angle (45°) would give a small coupling constant. The result of both interactions appears as two widely separated (10 c.p.s.) poorly resolved multiplets.

The approach to 8-azasteroids via the route described in Chart 1 appears now to be sufficiently practical to warrant further studies utilizing authentic precursors. This work is currently in progress.

EXPERIMENTAL (14,15,16)

α-(1-Cyclohexenyl)-*tert*-butanol, **1.**

The addition of methyl magnesium iodide to an ethereal solution of 1-cyclohexenylacetone (17) under usual Grignard conditions gave an 82% yield of the unsaturated alcohol, b.p. 106° (17mm); n_D^{25} 1.4804 (lit. (18) 1.4804).

Trans-2-Hydroxy-α,α-dimethylcyclohexaneethanol, 13.

The hydroboration procedure of Brown and Zweifel (19) was employed as follows:

Diborane was prepared by the addition of 15.9 g. (0.43 mole) of sodium borohydride in 300 ml. diglyme to 125 g. of boron trifluoride-ethyl ether complex in 120 ml. diglyme. The diborane, thus generated, was carried into the reaction flask, previously flushed with nitrogen and containing 83.2 g. of cyclohexenyl-*tert*-butanol in 250 ml. tetrahydrofuran, with a stream of nitrogen gas. The nitrogen carrier gas was discontinued after several minutes and diborane was allowed, under its own pressure, to add to the olefinic solution. The addition of diborane was performed at 20-30° with constant stirring. When the addition was complete, the solution was stirred at room temperature overnight. Water was added (50 ml.) to the cold (0-10°) solution in a dropwise fashion followed by 100 ml. of 10% sodium hydroxide also at 0-10°. The reaction was then heated at 50° for 0.5 hr. followed by the dropwise addition of 100 ml. 30% hydrogen peroxide at room temperature. The resulting two layer system was separated and the aqueous layer extracted with ether. The extracts were combined with the separated organic layer and dried over magnesium sulfate. Removal of the solvent left a viscous oily residue, which distilled at 121-125° (1.5 mm); n_D^{22} 1.4725. The viscous colorless oil solidified on standing and was recrystallized from petroleum ether, m.p. 55-56°. The yield was 80 g. (86%). The infrared spectrum ($CHCl_3$) exhibited strong broad absorption in the 2.70-2.95 μ region (-OH). The nmr spectrum exhibited a single sharp signal at 1.95 ppm [$(CH_3)_2$-C], and broad signal at 5.65 ppm (both OH groups) which dissappeared upon the addition of deuterated water. The stereochemistry was shown to be *trans*, consistent with hydroboration additions (20) by the broad multiplet at 3.11 ppm (*H*-C-OH) typifying an axial proton (21).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.77; H, 11.63. Found: C, 70.14, H, 11.65.

1,3,3-Trimethyl-3,4,5,6,7,8-hexahydroisoquinoline, **9.**

The glycol, 13, (17.2 g.; 0.10 mole) was added in small portions to a vigorously stirred solution of 5.0 g. (0.12 mole) of acetonitrile in 96% sulfuric acid at 0-5°. The addition was complete within two hours and then the temperature was not allowed to rise above 5°. Stirring was continued for an additional two hours and then the ice bath removed and the mixture stirred overnight at room temperature. After dilution of the deep red solution in water, the color became light yellow and was extracted several times with chloroform to remove insoluble polymers. The aqueous solution was carefully neutralized with 35% sodium hydroxide, keeping the temperature below 40° by external cooling. The oil which separated was taken up in ether, the solutions then dried overnight with potassium carbonate under a nitrogen atmosphere. After removal of the solvent, the residue was distilled and gave 5.3 g. (30%) of a light yellow oil, b.p. 72° (1.5 mm), n_D^{24} 1.5070. The infrared spectrum indicated strong absorption at 6.00 μ (conjugated C=C), 6.29 μ (conjugated C=N). Ultraviolet maximum (ethanol) at 255 mμ, ε 4250. The compound was rapidly decomposed upon exposure to air turning from light yellow to deep red within an hour.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.36; H, 10.73; N, 7.91. Found: C, 81.09; H, 10.86; N, 7.91.

The picrate (ethanol) melted at 127°.

Anal. Calcd. for $C_{18}H_{22}N_6O_7$: C, 53.20; H, 5.42; N, 13.79. Found: C, 53.38; H, 5.50; N, 14.00.

1,3,3-Trimethyl-1,2,3,4,5,6,7,8-octahydroisoquinoline, **14.**

A solution of 6.1 g. of the hexahydroisoquinoline in 50 ml. of 0.5M hydrochloric acid was adjusted to *p*H 3.5, and a solution of 1.6 g. of sodium borohydride in 20 ml. water was added dropwise with stirring. The *p*H was maintained between the limits of 3-4 by the periodic addition of 0.5M sulfuric acid. The solution was stirred at room temperature for two hours, made alkaline and extracted with ether. After drying the ethereal solution with potassium carbonate and removing solvent, there was obtained 5.9 g. of a colorless oil, b.p. 70° (0.8mm); n_D^{25} 1.4904. The infrared spectrum showed a weak band at 3.05 μ (NH) and no absorption between 3.5-6.9 μ. The nmr spectrum ($CDCl_3$) exhibited a strong signal at 1.11 ppm [$(CH_3)_2C$-] and a doublet at 1.20 ppm (CH_3-CH-).

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.46; H, 11.73; N, 7.82. Found: C, 80.60; H, 11.61; N, 7.63.

The phenylthiourea (from ethanol) melted at 172-174°.

Anal. Calcd. for $C_{18}H_{26}N_2S$: S, 10.19; N, 8.92. Found: S, 9.99; N, 8.94.

N-[2-(Hydroxycyclohexyl)-1,1-dimethylethyl]acetamide, **18.**

A solution of 5.0 g. (0.12 mole) of acetonitrile in 150 ml. 98% sulfuric acid was cooled to -15° and 17.2 g. (0.1 mole) of the glycol, 13, added in portions with efficient stirring. After the addition was complete, the mixture was kept overnight at 0° and then poured into a mixture of ice and water. No rubbery polymers appeared at this stage and the solution after being extracted with chloroform was neutralized with 30% sodium hydroxide. The alkaline solution was extracted with ether and the ether extracts were dried with potassium carbonate. Removal of the solvent gave a residue consisting of a mixture (22) of hexahydroisoquinolines, 9 and 12, in about 20% yield and 12.1 g. of a glassy solid which could not be crystallized. Passage through an alumina column resulted in a colorless glass which exhibited infrared maxima at 2.9 μ (OH), 3.1 μ (NH), 6.0 μ (Amide I), 6.6 μ (Amide II).

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.60; H, 10.80; N, 6.58. Found: C, 66.91; H, 10.89; N, 6.44.

1,3,4,5,6,7,8,9,10,11-decahydro-6,6-dimethyl-2H-benzo[a]quinolizine, **17.**

In a 250-ml. three-necked flask equipped with a mechanical stirrer, dropping funnel and thermometer was placed 150 ml. of concentrated sulfuric acid. The acid was cooled to 0-2° and 14.7 g. of δ-chlorovaleronitrile was added during 0.5 hr. maintaining the temperature below 5°. After the addition was complete there was added in portions, with vigorous stirring, very small solid portions of the glycol, 13. After all the glycol had been added (17.2 g. in 3 hr.) the ice bath was removed and the reaction stirred overnight at room temperature under a nitrogen atmosphere. The solution was then poured over chipped ice and the resulting brown mixture extracted with chloroform to remove all insoluble tars. The aqueous acid solution was then cooled in an ice bath and neutralized to *p*H 7-8 with 35% sodium hydroxide maintaining the temperature below 40°. The solution was then adjusted to *p*H 3-4 and reduced by the addition of sodium borohydride solution (7.5 g. in 100 ml. water containing a drop of 35% sodium hydroxide for stabilization). The *p*H was kept within the limits 3-5 during the 30 minute addition of the borohydride solution. After stirring at room temperature for 1-2 hours the solution was made alkaline to *p*H 8-10 and stirred overnight. The alkaline solution was extracted with ether and the extracts dried with sodium sulfate. After removal of the solvent, the residue was distilled and gave 3.7 g. (17%) of a colorless oil, b.p. 130-5° (6 mm), n_D^{24} 1.5107. The infrared spectrum showed complex absorption at 3.5-3.6 μ (C-H stretching *trans*-diaxial to nitrogen) and no absorption from 3.6 μ- 6.9 μ. The nmr spectrum is shown in Fig. 2. Gas chromatographic analysis exhibited a single symmetrical peak at 200°C (22).

Anal. Calcd. for $C_{15}H_{25}N$: C, 82.21; H, 11.40; N, 6.39. Found: C, 82.07; H, 11.36; N, 6.33.

The picrate (from ethanol) melted at 179°.

Anal. Calcd. for $C_{21}H_{28}N_4O_7$: N, 12.50. Found: 12.56.

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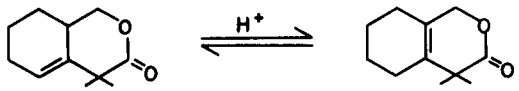

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(14) All melting points and boiling points are uncorrected.

(15) Microanalyses performed by Galbraith Laboratories, Knoxville, Tenn.

(16) All nmr spectra taken on a Varian A-60 instrument. For these measurements we thank Mr. Gordon Boudreaux, United States Department of Agriculture, Southern Regional Research Laboratory, New Orleans, La.

(17) Obtained from Columbia Organic Chemicals, Columbia, S. C., and Aldrich Chemical Co., Milwaukee, Wisconsin. Samples from both sources contained 7-10% of the conjugated carbonyl isomer which could not be completely separated by distillation. The Grignard reaction was performed on samples which contained, after repeated distillations, 3-4% of the conjugated isomer and the resulting alcohol was readily purified.

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