Studies Directed toward the Total Synthesis of Azasteroids. I. 3,4-Cyclopenteno-5,6-dihydropyridines and 6,6-Tetramethylene-5,6-dihydro-1,3-oxazines[1-3]

A. I. MEYERS, J. SCHNELLER, AND N. K. RALHAN

Department of Chemistry, Louisiana State University, New Orleans, Louisiana

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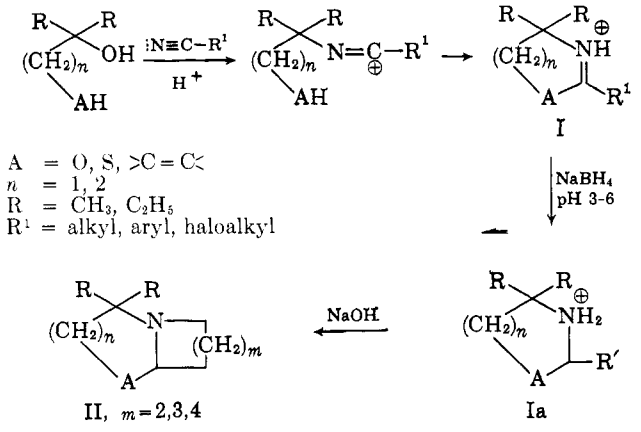
A study designed to obtain the azasteroid system by the condensation of suitably substituted nitriles with unsaturated tertiary alcohols in sulfuric acid has led initially to unexpected products identified as 2-substituted 6,6-tetramethylene-5,6-dihydro-1,3-oxazines (VII). The conditions favoring the formation of these products were found to be a function of the water activity in sulfuric acid. Decrease of the water activity led to exclusive formation of the desired azasteroidal precursor, a 3,4-cyclopenteno-5,6-dihydropyridine, presumably through the stabilized azocarbonium ion. The yield of the dihydropyridine was found to be quite low when the unsaturated alcohol XIIIb was employed (19%) but was increased to 76% when the corresponding glycol XVIII was the starting material. A study of the reduction products of the dihydropyridine was performed to test the feasibility of this ring system as a useful model in the steroid approach.

For several years, a study has been in progress which has extended the scope of the Ritter N-alkyl amide synthesis[4] to the preparation of a wide variety of N-heterocyclic compounds of the types I and II. The experimental conditions leading to I involved the treatment of a tertiary alcohol derivative containing an additional nucleophilic substituent with an alkyl or aryl nitrile in cold concentrated sulfuric acid. By employing β-, γ-, or δ-halonitriles with the tertiary alcohols, bicyclic bases II were produced by merely allowing the reaction to proceed to I followed by partial neutralization of the sulfuric acid solvent to a suitable pH (3–6) and adding sodium borohydride to obtain Ia. Alkaline treatment then gave II. The latter series of products were, therefore, produced in a single synthetic operation which did not require the isolation of intermediates I and Ia.



To date, this method has led to the convenient preparation of 5,6-dihydro-1,3-thiazines,[5] 5,6-dihydro-1,3-oxazines,[6,7] 2-thiazolines,[5,8] 5,6-dihydropyridines,[8] 1-pyrrolines,[8,9] and 1-azabicycloalkanes[10] in over-all yields of 40% or higher. The use of dinitriles[11] in this ring closure reaction led to α,ω-bis(N-heterocyclyl)alkanes derived from series I.

On the basis of the aforementioned studies, it soon became evident that this method could also be applied to the total synthesis of a variety of novel azasteroids if the proper starting materials could be obtained. A plan of approach (Chart I) was devised which required compounds containing relatively simple structural features. By treating *cis*-2-(2-cyanoethyl)chlorocyclohexane with the α-(1-cyclopentenyl)-*t*-alkanol in cold concentrated sulfuric acid, it was anticipated that the initial product would be the 3,4-cyclopentenodihydropyridine derivative III which could be reduced in a weakly acidic solution to the tetrahydropyridine IV. Further neutralization with sodium hydroxide would allow intramolecular alkylation to occur (presumably with some concurrent elimination) resulting in the racemic 9-azasteroid V possessing a *trans*-AB ring fusion. Examination of the structure of V indicates that it represents a molecule with several significant structural deviations from the natural steroids. This was of interest in view of the many recent efforts to modify the steroid nucleus in anticipation of enhanced biological activity.[12] Further modifications of V were considered as well as several other approaches which would place the nitrogen atom at any of the remaining ring junction positions. It was necessary, however, to test the feasibility of this scheme before proceeding to more complex structures.

A logical beginning to this approach appeared to be the study of the initial ring closure leading to the cyclopenteno-5,6-dihydropyridine III, using a simple nitrile. For this study, acetonitrile was chosen first to be followed by other nitriles of increasing complexity. The present paper will describe the results of reaction of simple nitriles with a cyclopentenyl-*t*-alkanol.

(1) A preliminary report of this study has already appeared; L. M. Trefonas, J. Schneller, and A. I. Meyers, *Tetrahedron Letters*, **22**, 785 (1961).

(2) Presented before the Organic Division at the Southeastern Regional Meeting of the American Chemical Society, Gatlinburg, Tenn., November 1–3, 1962.

(3) Supported by funds granted by the National Institutes of Health, RG-6248(C2).

(4) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045, 4048 (1948).

(5) A. I. Meyers, *J. Org. Chem.*, **25**, 1147 (1961).

(6) (a) A. I. Meyers, *ibid.*, **25**, 147 (1960); (b) E. J. Tillmanns and J. J. Ritter, *ibid.*, **22**, 839 (1957).

(7) A. I. Meyers, *ibid.*, **25**, 218 (1961).

(8) J. J. Ritter and A. I. Meyers, *ibid.*, **23**, 1918 (1958).

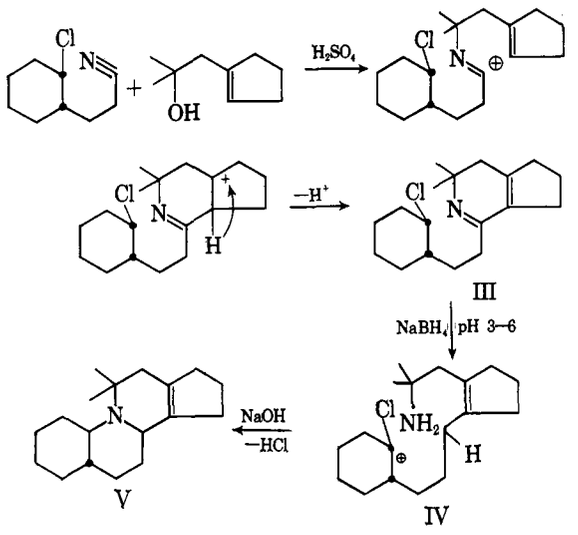
(9) A. I. Meyers, *ibid.*, **24**, 1233 (1959).

(10) A. I. Meyers and W. Y. Libano, *ibid.*, **26**, 1682, 4399 (1961).

(11) A. I. Meyers, *ibid.*, **25**, 2231 (1960).

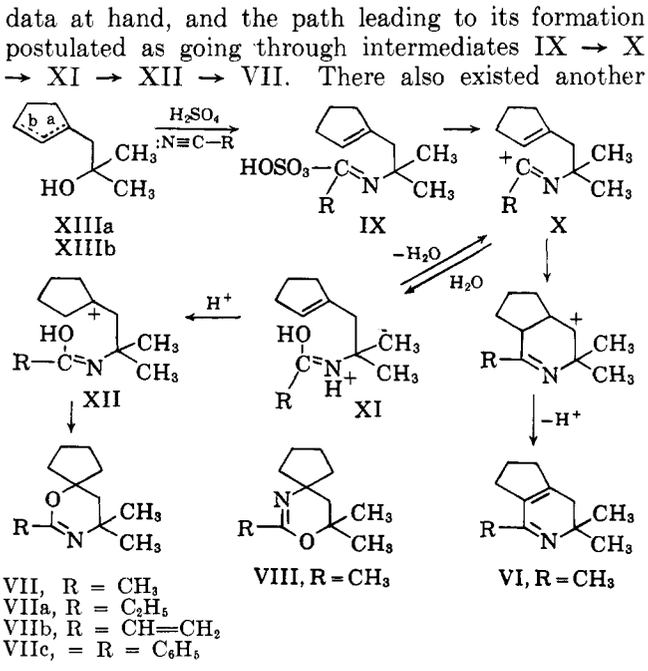
(12) To quote but a few: (a) C. W. Shoppee, *et al.*, *J. Chem. Soc.*, 1050 (1962), and earlier papers cited therein; (b) N. J. Doorenbos, *et al.*, *J. Org. Chem.*, **26**, 2546 (1961); (c) J. P. Kutney and R. A. Johnson, *Chem. Ind.* (London), 1713 (1961); (d) M. P. Cava and E. Moroz, *J. Am. Chem. Soc.*, **84**, 116 (1962); (e) J. Meinwald, G. G. Curtis and P. G. Gassmann, *ibid.*, **84**, 116 (1962); (f) B. J. Magerlein, R D. Birkenmeyer, and F. Kagen, *ibid.*, **82**, 1252 (1960); (g) P. B. Sallman, R. L. Elton, and R. M. Dodson, *ibid.*, **81**, 4435 (1959).

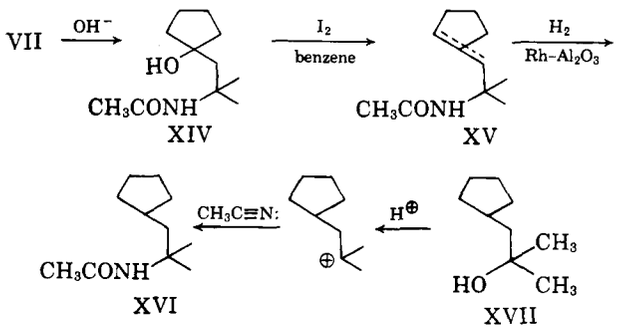
CHART I



Results and Discussion

When α-(1-cyclopentenyl)-*t*-butyl alcohol (XIIIa) was added to an ice-cold solution of acetonitrile in 96% sulfuric acid, extensive polymerization of the unsaturated alcohol resulted and no identifiable material was obtained. The fate of the entire program was altered, however, when the order of introducing the reactants was changed. Slow, dropwise addition of sulfuric acid to a cold solution of the alcohol in excess acetonitrile resulted in a basic product which exhibited a single strong band at 6.00 μ, yielded a pure picrate but did not show any signs of the C=C link which would be present in the cyclopentenodihydropyridine VI. Elemental analyses indicated that the compound possessed oxygen. The significant clue to the structure of the product was, however, the extremely strong absorption band at 6.00 μ which was reminiscent of the O—C=N stretching frequency observed by others[7,13] for dihydro-1,3-oxazines. On this basis a structure VII was advanced which was consistent with all the data at hand, and the path leading to its formation postulated as going through intermediates IX → X → XI → XII → VII. There also existed another possibility regarding the structure of the oxazine. If protonation of the double bond on the cyclopentenyl alcohol XIIIa occurred prior to that of the hydroxyl group, this would give rise to the isomeric oxazine VIII. Both of these structures would be consistent with all the data and their spectra would be indistinguishable. Evidence that VII was the correct structure was obtained by a degradation scheme which was initiated by alkaline hydrolysis of the oxazine to the hydroxyamide XIV, followed by dehydration with iodine to the unsaturated amides XV. Reduction, using rhodium catalyst, afforded a single saturated amide XVI. This amide was also prepared by the Ritter reaction[4] from α-cyclopentyl-*t*-butyl alcohol (XVII) and acetonitrile in sulfuric–acetic acid. The amides, as obtained from both routes were identical in every respect.[14]





The reaction was repeated using several other representative nitriles (VIIa–VIIc) all yielding the corresponding 2-substituted 6,6-tetramethylene-5,6-dihydro-1,3-oxazines. When the isomeric unsaturated alcohol, α-(3-cyclopentenyl)-*t*-butyl alcohol (XIIIb) was examined in this reaction, the products were identical to those obtained from the 1-cyclopentenyl alcohol and the yields were slightly higher (Table I) being accompanied by less polymeric material. By employing the the 3-cyclopentenyl alcohol, the reaction path leading to the oxazine, previously formulated, need not be altered other than considering an acid-catalyzed isomerization of the 3-olefin to the 1-olefin.

TABLE I

2-SUBSTITUTED 6,6-TETRAMETHYLENE-5,6-DIHYDRO-1,3-OXAZINES

Nitrile	% yield from α-substituted-*t*-butyl alcohol 1-Cyclopentenyl–	3-Cyclopentenyl–
Acetonitrile	41	63
Propionitrile	38	58
Acrylonitrile	29	57
Benzonitrile	39	72

The problem which now existed was to divert the sequence leading to oxazine formation to the desired cyclopentenopyridine derivative VI which is the necessary precursor in the proposed plan of approach to the azasteroid. It seemed reasonable that if the postulated reaction path (IX → X → XI → XII → VII) was essentially correct the equilibrium between X and XI was the critical factor in determining whether the oxazine or the pyridine would result. If reaction conditions could be arrived at which would decrease the ratio XI/X, this would then serve to enhance the formation

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 268.

(14) After the completion on this work, an X-ray crystallographic study on the hydrobromide of the spirooxazine was performed by Prof. L. M. Trefonas of this department. The result of this study also confirmed that VII was the correct structural assignment; *cf.* ref. 1.

of VI. It is presumably apparent from the equilibrium, X ⇌ XI that the water activity present in the solvent would determine which of these two species would predominate. Therefore, if the water activity in the acid could be diminished, this would increase the ion-solvating power of the solvent and decrease the ratio XI/X sufficiently to allow the reaction to proceed to the cyclopentenopyridine VI. Since the experimental conditions leading to the oxazine involved slow addition of twenty-five milliliters of sulfuric acid to a mixture of 0.25 mole of nitrile and 0.15 mole of the cyclopentenyl alcohol XIIIa, the water activity would be quite high during the initial stages of the acid addition. As the acid was added in excess, the water activity progressively decreased. This procedure led exclusively to the oxazine. Reversal of the order of addition, in which the same quantity of cyclopentenyl alcohol was added to the nitrile in twenty-five milliliters of sulfuric acid, gave, as previously mentioned, only polymeric products. The latter procedure, nevertheless, was still considered to be the only manner in which a minimum water activity could be maintained throughout the entire reaction period and shift the equilibrium in favor of X. This procedure was again applied but this time to the isomeric 3-cyclopentenyl alcohol XIIIb in the hope that polymerization would not be as extensive as in the previous case. It was observed that both XIIIa and XIIIb gave the same carbonium ion species in the sulfuric acid.[15]

The products obtained from the reaction included two basic fractions analyzed by gas chromatography to be a mixture containing 34% of the oxazine VII and 66% of a new substance possessing only the elements carbon, hydrogen, and nitrogen. The latter product was quite unstable, turning deep red after several hours' exposure to air. The ultraviolet spectrum of a freshly distilled sample exhibited a single peak, λ_{max} 263 mμ (ε 4260) typical of a 1,3-endocyclic conjugate system[16] in a six-membered ring. The infrared spectrum revealed a band of medium intensity at 6.00 μ and a strong, very sharp band at 6.25 μ indicative of the conjugated C=C and C=N stretching frequencies, respectively.[9,13] The n.m.r. spectrum (in deuteriochloroform) disclosed proton resonances which were all consistent with the structural assignment VI. That the C=C link was, in fact, located at the ring fusion was confirmed by: (a) the absence of the C=C—H stretching mode at 3.3 μ and the deformation modes at 11.9–12.4 μ; (b) the absence of a proton resonance signal at low field due to the C=C—H proton (lowest proton signal appeared at 7.6 τ); and (c) the high value of the λ_{max} since an exocyclic double bond would absorb at shorter wave length.[16]

By repeating the reaction of the 3-cyclopentenyl alcohol and acetonitrile in increasing amounts of sulfuric acid (such that the initial and final water activity was lowered) the *nearly exclusive formation* of the desired cyclopentenodihydropyridine was eventually achieved, thus validating the earlier postulate regarding intermediates X and XI (Table II).

(15) Dilute solutions (10^{-4} *M*) of each cyclopentenyl alcohol in concentrated sulfuric acid exhibited the same ultraviolet absorption spectrum, λ_{max} 303 mμ (ε 5500), which is characteristic of alkenyl carbonium ions; *cf.* N. C. Deno, H. G. Richey, Jr., J. D. Hodge, and M. J. Wisotsky, *J. Am. Chem. Soc.*, **84**, 1498 (1962).

(16) For an informative discussion of the ultraviolet maxima of alicyclic dienes and many leading references, *cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 15–21 (*cf.* E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, pp. 153–168).

TABLE II

FORMATION OF VI AND VII FROM α-(3-CYCLOPENTENYL)-*t*-BUTYL ALCOHOL AND ACETONITRILE AS A FUNCTION OF SULFURIC ACID CONCENTRATION[a]

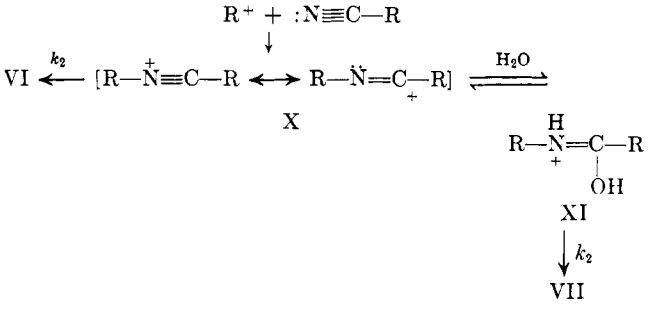
95.8% H_2SO_4 used initially[b]		Final % H_2SO_4[c]	Final water activity[d] (log *a*)	Total bases VI and VII	% Yield	
g.	ml.				VI	VII
46.0	25.0	90.5	−3.66	41	66	34
92.0	50.0	93.1	−4.10	36	89	11
138.0	75.0	94.0	−4.26	27	98.5	1.5
184.0	100.0	94.4	−4.33	20	99.5	0.5
276.0	150.0	94.8	−4.40	19	99.8	0.2

[a] Analysis of this mixture was conveniently accomplished by gas chromatography using a 7-ft. column containing Chromsorb P coated with 5% KOH and 20% silicon oil (DC-710); *cf.* E. D. Smith and R. D. Radford, *Anal. Chem.*, **33**, 1160 (1961). [b] Each run was performed using 0.15 mole of α-(3-cyclopentyl)-*t*-butyl alcohol which yielded upon protonation 0.15 mole of H_3O^+. [c] These values were obtained from the following expression:

$$\text{Final \% } H_2SO_4 = 100\% - \frac{\text{wt. of } H_2O \text{ in } 95.8\% \ H_2SO_4 + \text{wt. of } 0.15 \text{ mole } H_2O}{\text{wt. of } 95.8\% \ H_2SO_4 + \text{wt. of } 0.15 \text{ mole } H_2O} \times 100$$

[d] The values were obtained by graphical interpolation from the expression derived by N. C. Deno and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **76**, 245 (1954): $\log a_{H_2O} = \log X_{H_3O^+} + H_0 + 5.00$, and assuming that the activity coefficient of water is essentially constant between 83–99.8% sulfuric acid.

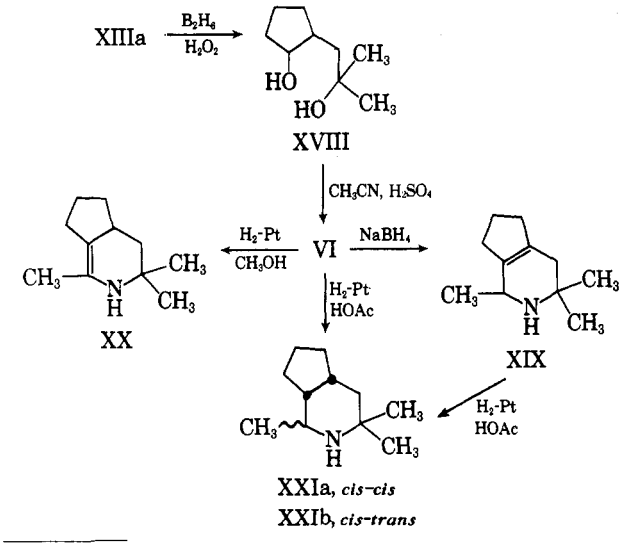
It is evident from Table II that the azocarbonium ion X appears to be particularly favored in sulfuric acid concentrations above 93% since the pyridine VI is clearly the predominant product. More convincing evidence is indicated by the change in final water activity in the range 90–95% sulfuric acid which is *decreased by at least a factor of five.* The initial water activity would be much lower during the initial stages of the alcohol addition where the acid concentration is essentially 96% (log a_{H_2O} 4.62). This decrease in water activity would tend to enhance the ion-solvating power of the solvent and increase the amount of X in the following equilibrium.



The results in Table II need not necessarily imply that the equilibrium lies heavily in favor of *X* at lower water activities since the rate constants k_1 and k_2 may be very different, that is to say, k_2 may be much greater than k_1, due to the fact that the azocarbonium ion is a much stronger acid than a proton and may add to the olefinic double bond at a much faster rate. Therefore, only appreciable (but not necessarily predominant) concentrations of *X* would be required for cyclopentenopyridine formation. The existence of the azocarbonium

ion species has been postulated[17] in the past as an intermediate both in the Schmidt reaction and the Beckmann rearrangement where concentrated sulfuric acid was employed. The rate of the Beckmann rearrangement was found to parallel the ion-solvating properties of the solvent medium.[18] Recently, Hill[19] has found that in some instances the Beckmann rearrangement, performed in concentrated sulfuric acid is actually a Ritter-type reaction,[5] where the nitrile formed *in situ* from the oxime, recombines with the carbonium ion, presumably to the azocarbonium ion. Subsequent dilution with water destroys this intermediate and yields the N-alkylamide.

Since the relatively low yield of I was accompanied by extensive polymerization of the cyclopentenyl alcohol in 96% sulfuric acid, the reaction was repeated in 98 and 100% sulfuric acid to determine if the quantity of water present in the acid performed any significant function regarding the polymerization. After four attempts in each acid medium, the yield of the pyridine and the quantity of polymerization was essentially unchanged. These results were considered to be due to the olefinic bond and dehydration to some diene species which extensively underwent acid-catalyzed polymerization. On this basis it was thought desirable to employ a starting compound which did not possess a double bond but one which could be converted to an olefin *in situ* during the course of the reaction. This technique has already been reported[20] to be advantageous in the formation of Δ^{-1} pyrrolines, prepared from ditertiary glycols and nitriles in much higher yields than those produced from the corresponding dienes.[21] By treating α-(1-cyclopentenyl)-*t*-butyl alcohol (XIIIa) with diborane according to the procedure of Brown and Zweifel[22] an 86% conversion to the glycol XVIII was realized. No trace of any isomeric product could be found during gas chromatographic analysis. The ultraviolet spectrum of this glycol in 96% sulfuric acid (10^{-5} *M*) was identical to that of both cyclopentenyl alcohols XIIIa and XIIIb [λ_{max} 303 mμ (ϵ 5400)] indicating that all three compounds gave identical carbonium ion species under these conditions. Addition of this glycol to a cold solution of acetonitrile in 98% sulfuric acid resulted in 76% yield of the cyclopentenodihydropyridine VI. The conditions under which this experiment was performed were identical to those employing the cyclopentenyl alcohol, yet the amount of polymerization was considerably less. This much more satisfactory procedure for obtaining the cyclopentenodihydropyridine then led to a study of the second step in the proposed steroid synthesis, that of reduction of the C=N link. The latter reduction would have to be carried out in acidic solution in order that the desired intermediates would react in the proper sequence. By adding an equimolar quantity of sodium borohydride to a solution of VI in dilute mineral acid solution, a quantitative reduction leading to XIX occurred. That the product was pure and free of any isomers was adequately demonstrated by gas chromatography. The infrared spectrum was very nondescriptive, showing only C—H stretching and long wavelength ring vibrations. The N—H group did not appear very distinctly in the spectrum, yet its presence was confirmed by a Zerewitinoff determination. The intensity of the stretching frequency of the tetrasubstituted C=C link was too weak to be detected.



The reduction using sodium borohydride was repeated on the dilution product of the glycol–acetonitrile–sulfuric acid mixture. After adjusting the quenched reaction mixture to pH 3.5 and adding sodium borohydride, the product thus obtained was identical to that prepared in the aforementioned experiment. Thus, it appeared that *for simple nitriles, at least, the first two operations of the proposed azasteroid synthesis were feasible.*

Further studies on the behavior of the cyclopentenopyridine toward reduction were undertaken in an effort to obtain an insight into the type of products which might be expected in the more complex steroid system.

Reduction of VI in absolute methanol using a platinum catalyst resulted in a very rapid uptake of one equivalent of hydrogen. An examination of the infrared spectrum of the product revealed that the C=N link was no longer present although this reduction method is known[23] not to reduce this group except when acetic acid is employed as the solvent. However, had the reduction occurred at the C=N link then the product would have been XIX. A mixture of the hydrochlorides of the reduced base (m.p. 195°) and that of XIX (m.p. 213°) gave a large depression in melting point. The position of the double bond (XX) was eventually confirmed by the enamine–imine tautomerism described by Leonard and Gash[24] where an absence of a band at 6.0–6.3 μ in the spectrum of the free base gave two sharp bands at 6.20 μ (C=N$^+$H) and 6.30 μ ($^+NH_2$) in the spectrum of its hydrosulfate salt.[25]

Repeating the catalytic reduction of I, in acetic acid, resulted in the absorption of two equivalents of hydro-

(17) (a) P. A. S. Smith, *J. Am. Chem. Soc.*, **70**, 320 (1948); (b) A. W. Chapman and C. C. Howis, *J. Chem. Soc.*, 806 (1933); (c) A. W. Chapman, *ibid.*, 1550 (1934).

(18) For numerous references pertaining to this system, *c.f.* J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 338, 339.

(19) R. K. Hill and O. J. Chartyk, *J. Am. Chem. Soc.*, **84**, 1064 (1962).

(20) A. I. Meyers and J. J. Ritter, *ibid.*, **23**, 1918 (1958).

(21) E. J. Tillmanns, Ph.D. thesis, New York University, 1954.

(22) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2550 (1961).

(23) (a) P. J. A. Demoen and P. A. J. Janssen, *ibid.*, **81**, 6283 (1959); (b) A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1920 (1958).

(24) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(25) Protonation of α,β-unsaturated amines in concentrated sulfuric acid was reported to give a mixture of 1- and 3-protonated amines; *cf.* R. L. Hinman and E. B. Whipple, *ibid.*, **84**, 2536 (1962).

gen and the production of two saturated bases, XXIa and XXIb. Analysis of this mixture by gas chromatography revealed that the ratio of products was 98 ± 0.5% to 2 ± 0.5%. Confirmation that the two peaks observed in the gas chromatogram were indeed those of two geometric isomers XXIa and XXIb and that the 98:2 ratio of peak areas was not a single compound and some impurity, the reduction products of XIX were examined under identical instrument conditions. This revealed approximately a 50:50 mixture of two saturated bases whose retention times were identical to the two products obtained by direct reduction of VI.

The high degree of stereoselectivity observed in the reduction of VI in acetic acid could lead to the assumption that the major product is the *cis–cis* isomer XXIa, and the minor product, the *cis–trans*. The reduction of 3,4-cyclopentenopyridine under the same conditions have been reported to yield exclusively 3,4-*cis*-cyclopentanopiperidine.[26] The validity of this analogy can be questioned if the presence of the methyl group in the dihydropyridine are considered important with respect to their effect upon direction of hydrogen addition. However, if the reduction of the tetrahydropyridine XIX in acetic acid involves *cis* addition then the resulting two products would be the *cis–cis* and the *cis–trans*. This fact is borne out upon gas chromatographic analysis of the products whose peaks are completely superimposable over those of the products from reduction of VI. Considering the possibility that the reduction of the dihydropyridine involved 1,4-addition then the tetrahydropyridine XX would presumably have to be an intermediate. This implies that the subsequent hydrogen addition would result in a *trans*-ring fusion as well as the *cis*-fusion.[27] Reduction of XX in acetic acid proceeded very slowly (fifty hours) and gave rise to a 55:45 mixture of bases of which the former was identical to XXIa, the latter *different* from XXIb.

This result is to be compared with the reduction of dihydropyridine VI in acetic acid which was complete within one hour. It is, therefore, difficult to account for the existence of XX as an intermediate in the reduction of the dihydropyridine. A further study has begun to substantiate these stereochemical results as well as the configuration of the 2-methyl group in XXIa and XXIb.

The present study has demonstrated that the first two steps of the planned azasteroid synthesis, (1) ring closure to the dihydropyridine and (2) borohydride reduction in acidic medium, were successful for simple nitriles. The next step, intramolecular alkylation to form the B ring remains to be examined. A study was therefore undertaken to employ halonitriles in this approach and the results are reported in the subsequent article.[28]

Experimental[29,30]

2,4,4-Trimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (VII).—To a cold mixture of 21.5 g. (0.15 mole) of α-(2-cyclopentenyl)-*t*-butyl alcohol and 13.2 ml. (0.25 mole) of acetonitrile was added dropwise with stirring 25 ml. of 95.8% sulfuric acid. The mixture was kept below 10° during the addition of the acid which took about 0.5 hr. Due to the viscous nature of the resulting dark red solution an additional 25 ml. of concentrated sulfuric acid was added all at once and stirring continued for an additional 2 hr. at 8–12°. The reaction mixture was poured over 200 g. of chipped ice and stirred well. After standing at room temperature for several hours the aqueous acid solution was extracted three times with 75-ml. portions of chloroform. Upon neutralization with 35% sodium hydroxide an oil appeared which was taken up with ether and dried over potassium carbonate. Distillation of the residue from the ethereal solution gave 15.8 (63%) g. of a colorless oil, b.p. 77–79° (4 mm.); $n^{30}D$ 1.4694; $\lambda_{max}^{CCl_4}$ 6.00 (O—C=N).

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.92; H, 10.49; N, 7.73. Found: C, 73.12; H, 10.34; N, 7.75.

The **picrate** (from ethanol) melted at 154–155°.

The **hydrobromide** (from ethanol–ethyl acetate) melted at 173–174°.

2-Ethyl-4,4-dimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (VIIa).—The method of preparation was similar to that of VII. After removal of the ether there was obtained a colorless oil (58%), b.p. 65–67° (1 mm.); $n^{30}D$ 1.4719.

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.80; H, 10.77; N, 7.18. Found: C, 73.98; H, 10.65; N, 7.14.

The **picrate** (from ethanol) melted at 105–106°.

2-Vinyl-4,4-dimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (VIIb) was prepared in the usual manner yielding a colorless oil (57%), b.p. 68° (1 mm.); $n^{30}D$ 1.4848.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.68; H, 9.85; N, 7.25. Found: C, 74.46; H, 9.84; N, 7.09.

The **picrate** (from ethanol) melted at 156–158°.

2-Phenyl-4,4-dimethyl-6,6-tetramethylene-5,6-dihydro-1,3-oxazine (VIIc).—This compound was obtained as a brown solid after removal of the ether. Various attempts at recrystallization were fruitless. The pure oxazine (72%) was obtained by elution chromatography on a Florisil column using 20% petroleum ether–80% benzene as the eluent, m.p. 67–68°.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 79.10; H, 8.65; N, 5.77. Found: C, 79.11; H, 8.71; N, 5.62.

The **picrate** (from ethanol) melted at 143–144°.

α-(3-Cyclopentenyl)-*t*-butyl alcohol (XIIIb) was prepared (89%) by treating 3-cyclopentenylacetone[31] with methylmagnesium bromide in diethyl ether, b.p. 80–82° (10 mm.); $n^{30}D$ 1.4645.

Anal. Calcd. for $C_9H_{16}O$: C, 77.14; H, 11.42. Found: C, 76.90; H, 11.23.

α-(1-Cyclopentenyl)-*t*-butyl alcohol (XIIIa) was prepared (85%) by the action of methylmagnesium bromide on 1-cyclopentenylacetone (Aldrich Chemical Co.) in diethyl ether, b.p. 52–53° (0.5 mm.); $n^{30}D$ 1.4640.

Anal. Calcd. for $C_9H_{16}O$: C, 77.14; H, 11.42. Found: C, 77.03; H, 11.35.

2,6,6-Trimethyl-3,4-cyclopenteno-5,6-dihydropyridine (VI).

A. From α-(3-Cyclopentenyl)-*t*-butyl Alcohol (XIIIb).—To a cold solution of 4.1 g. of acetonitrile in 150 ml. of 95.8% sulfuric acid was added with stirring, 12.6 g. of α-(3-cyclopentenyl)-*t*-butyl alcohol at 5–7° during a period of 2 hr. After addition was complete the dark mixture was stirred for 3 hr. at 7–12° and then poured over 500 g. of chipped ice. The tarry material which appeared was removed by extraction with chloroform and the dark aqueous solution was made strongly basic by the careful addition of 35% sodium hydroxide. The red oil which then appeared was taken up in ether and dried with potassium carbonate. Distillation of the ether residue gave 2.9 g. (19%) of a light yellow oil which grew progressively darker when allowed to remain in contact with air; b.p. 61.5° (0.4 mm.); $n^{30}D$ 1.4925; λ_{max}^{EtOH} 263 mμ, (log ε 3.63); $\lambda_{max}^{CCl_4}$ 6.00 μ (C=C), 6.25 (—C=N).

Anal. Calcd. for $C_{11}H_{17}N$: C, 80.99; H, 10.42; N, 8.58. Found: C, 81.06; H, 10.38; N, 8.61.

The **picrate** (from ethanol) had m.p. 144°.

Anal. Calcd. for $C_{17}H_{20}N_4O_7$: C, 52.10; H, 5.11; N, 14.29. Found: C, 52.06; H, 5.16; N, 14.10.

B. From α-(2-Hydroxycyclopentyl)-*t*-butyl Alcohol (XVIII).—The glycol (16.0 g.) was added slowly to a solution of 5.5 ml. of acetonitrile in 150 ml. of 98% sulfuric acid at 3–5° with good mechanical stirring. The solution took on color much more

(26) V. Prelog and V. Meltzer, *Helv. Chim. Acta*, **29**, 1170 (1946); G. G. Ayerst and K. Shofield, *J. Chem. Soc.*, 4097 (1958); K. Jewers and J. McKenna, *ibid.*, 1575 (1960).

(27) A referee has pointed out that Dreiding models of XX indicate that if the heterocyclic ring exists in the quasi chair form then a *trans*-ring fusion would predominate, whereas a quasi boat form would give the *cis*-product.

(28) A. I. Meyers and N. K. Ralhan, *J. Org. Chem.*, **28**, 2950 (1963).

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

(30) Microanalyses were performed by Alfred Bernhardt, Mulheim (Ruhr), West Germany.

(31) We wish to thank the Lilly Research Laboratories, Indianapolis, Ind., for a generous sample of this material.

slowly than experiments using the unsaturated alcohol. After the addition of the glycol was complete, however, the solution was a golden yellow. Stirring was continued at 5–7° for an additional 2 hr. and then the mixture poured on 350–400 g. chipped ice. The remainder of the procedure was identical with that described previously. Distillation of the ethereal residue gave 12.1 g. (76%) of VI.

Hydroboration of α-(1-Cyclopentenyl)-*t*-butyl Alcohol to the Glycol XVIII.—All reactants were distilled on the day of use. The apparatus employed consisted of a diborane generator containing 133 g. (0.89 mole) of boron trifluoride–ethyl ether complex and 120 ml. of diglyme into which a solution of 15.0 g. (0.43 mole) of sodium borohydride in 300 ml. of diglyme was slowly added. A slow stream of dry nitrogen continuously carried the diborane into a reaction flask containing 75 g. (0.54 mole) of α-(1-cyclopentenyl)-*t*-butyl alcohol dissolved in 250 ml. of tetrahydrofuran. The addition of diborane was complete within 3 hr., and the reaction mixture was allowed to remain at room temperature overnight. After adding 100 ml. of 10% sodium hydroxide at 0°, the mixture was heated to 50° for 1 hr. and cooled to room temperature, at which point 100 ml. of 30% hydrogen peroxide was cautiously added. An exothermic reaction ensued which was easily controlled by the rate of peroxide addition. The two layers which appeared were separated and the aqueous layer extracted several times with equal volumes of ether. Combination and drying of the organic layers gave a clear colorless solution. Removal of the mixture of solvents and distillation of the residue gave 73 g. (86%) of a viscous colorless oil, b.p. 110–112° (0.5 mm.); $n^{27}D$ 1.4735; infrared spectrum exhibited strong –OH (3.0 μ).

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.29; H, 11.39. Found: C, 68.09; H, 11.20.

2,6,6-Trimethyl-3,4-cyclopenteno-1,2,5,6-tetrahydropyridine (XIX). A. By Direct Reduction of VI.—A solution of 6.5 g. (0.04 mole) of I in 300 ml. of 0.25 *N* hydrochloric acid was adjusted to pH 3.5, and a solution of 1.48 g. (0.04 mole) of sodium borohydride in 30 ml. of 0.5% sodium hydroxide was added slowly maintaining the pH range of the solution between 3 and 4. After stirring for an additional hour at pH 4, the solution was neutralized and extracted with ether to remove the reduced base. Distillation of the dried ethereal extract resulted in 6.2 g. of a colorless oil, b.p. 53–55° (0.5 mm.); $n^{30}D$ 1.4810.

Anal. Calcd. for $C_{11}H_{19}N$: C, 80.00; H, 11.51; N, 8.49. Found: C, 80.21; H, 11.49; N, 8.39.

The **hydrochloride**, prepared by passing dry hydrogen chloride into an ethereal solution of the base and recrystallizing the crude salt with methanol–ethyl acetate, melted at 213°.

Anal. Calcd. for $C_{11}H_{20}NCl$: C, 65.51; H, 9.94; N, 6.98; Cl, 17.55. Found: C, 65.59; H, 9.92; N, 6.99; Cl, 17.47.

B. From α-(2-Hydroxycyclopentenyl)-*t*-butyl Alcohol and Acetonitrile.—The initial procedure is identical to that described for the formation of VIb, up to and including the chloroform extraction. The electrodes of a pH meter were inserted into the aqueous acid solution and the pH adjusted to 3–4 by the addition of sufficient 30% sodium hydroxide. The total volume of solution was approximately 800 ml. A solution containing 3.7 g. (0.1 mole) of sodium borohydride in 50 ml. of 0.5% sodium hydroxide was added dropwise to the weakly acidic solution keeping the pH between the range 3–4 by concurrent addition of 6 *N* sulfuric acid. After completion of the addition, stirring was maintained for 1.5 hr. and then the solution was neutralized. Extraction with ether, drying, and distillation resulted in 11.8 g. (72%) of the unsaturated base XIX.

Reaction Conditions Leading to Mixture of VI and VII.—This is a typical experiment in which the quantity of sulfuric acid employed led to a mixture of both products (Table II). To a solution of 8.2 g. of acetonitrile in 50 ml. of 95.8% sulfuric acid was added 24.6 g. (0.19 mole) of α-(3-cyclopentenyl)-*t*-butyl alcohol over a period of 2 hr. at 5–7°. After stirring for an additional 3 hr. the products were isolated in the usual manner. The infrared spectrum exhibited strong bands at 6.00 (—O—C=N and C=C) and 6.25 μ (conjugated C=N). Injection of 2.0 μl. of this mixture into the gas chromatograph at 145° on a Chromosorb P column coated with 5% potassium hydroxide and 20% silicon oil (DC-710)[32] gave two symmetrical peaks in the ratio 11% VII to 89% VI. These peaks were identified by employing pure samples of VI and VII under identical instrument conditions.

Alkaline Hydrolysis of VII to XIV.—A suspension of 6.0 g. of VII in 100 ml. of 30% sodium hydroxide was refluxed for 16 hr. and then extracted with ether. The removal of the ether left a viscous colorless oil, $\lambda_{max}^{CCl_4}$ 2.76 μ (–OH), 2.91 (NH), 5.89 (amide I), 6.61 (amide II).

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.45; H, 10.55; N, 7.05. Found: C, 66.60; H, 10.48; N, 6.90.

Dehydration of XIV to XV was accomplished by adding 0.05 g. of iodine to a solution of 5.4 g. of XIV in 100 ml. of benzene and removing the water in an azeotrope trap. After heating for 24 hr. the solution was filtered and the benzene evaporated *in vacuo*. The residue was washed with 0.1 *N* hydrochloric acid and then with water and dried, m.p. 84–92°. Attempts to separate the unsaturated amides by chromatography on alumina were not entirely successful, and the mixture was analyzed as such.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.92; H, 10.49; N, 7.73. Found: C, 73.05; H, 10.41; N, 7.70.

Hydrogenation of the Mixture of Unsaturated Amides to XVI.—A solution of 75 mg. of the amide mixture in 10 ml. of methanol containing 50 mg. of 5% rhodium on alumina[33] was subjected to 45 lb. hydrogen pressure for 20 min. at room temperature. Removal of the catalyst and evaporation of the solvent gave 65 mg. of colorless crystals, m.p. 73–75°.

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.15; H, 11.48; N, 7.65. Found: C, 72.03; H, 11.33; N, 7.71.

α-Cyclopentyl-*t*-butyl alcohol was obtained quantitatively by hydrogenating a mixture consisting of 7.6 g. of α-(1-cyclopentenyl)-*t*-butyl alcohol, 75 ml. of methanol, and 0.5 g. 5% rhodium-on-alumina. The reduction, performed at room temperature under 40 lb. pressure, was complete within 2 min. After removal of the catalyst and solvent, there was obtained 7.5 g. of a colorless liquid, b.p. 59–60° (0.5 mm.); $n^{30}D$ 1.4536. The 3.25-μ band (C=C—H) was absent in the infrared spectrum.

Anal. Calcd. for $C_9H_{18}O$: C, 76.15; H, 12.68. Found: C, 76.00; H, 12.77.

Preparation of XVI *via* the Ritter Reaction.—A solution of 4.8 g. (0.034 mole) of α-cyclopentyl-*t*-butyl alcohol, 15 ml. of glacial acetic acid, and 2.0 ml. of acetonitrile in 20 ml. of concentrated sulfuric acid was allowed to stand in a stoppered flask at room temperature for 16 hr. The dark solution was then poured over 300 g. of chipped ice, which gave rise to a viscous oil which was extracted with ether, and dried with magnesium sulfate. Evaporation of the solvent left a tacky solid which could not be purified by recrystallization. Chromatography on alumina using petroleum ether as the eluent gave a light yellow solid, m.p. 50–65°. The crude amide was dissolved in 6 *N* hydrochloric acid and the solution extracted with chloroform until all the color was removed. Upon neutralization of the aqueous solution, a colorless powdery precipitate appeared, which after thorough washing and drying melted at 73–74°. A mixture of this product with that obtained by the reduction of XV, gave no depression in the melting point. Furthermore, the infrared spectra of both compounds were completely superimposable.

Reduction of VI to XX in Methanol.—A solution of 3.0 g. (0.018 mole) of VI in 30 ml. of absolute methanol containing 0.5 g. of platinum oxide was hydrogenated at 42 lb. at 25°. The absorption of 0.018 mole of hydrogen was complete within 15 min. Removal of the catalyst by filtration and concentration of the solution yielded an oil which distilled at 74° (3.5 mm.); $n^{30}D$ 1.4793. Examination of the product by gas chromatographic analysis (10% DC-710 silicon oil, 5% potassium hydroxide on Chromosorb P at 145°) indicated a single product. The infrared spectrum (carbon tetrachloride) exhibited very weak bands at 3.10 (NH) and 6.00 μ (C=C). The infrared spectrum in chloroform containing a drop of concentrated sulfuric acid exhibited medium bonds at 6.19 ($C=\overset{+}{N}H$) and 6.31 μ ($>\overset{+}{N}H_2$), indicative of the 3- and 1-protonated enamine.[10]

Anal. Calcd. for $C_{11}H_{19}N$: C, 80.00; H, 11.51; N, 8.48. Found: C, 79.94; H, 11.45; N, 8.45.

The **hydrochloride** melted at 194° (methanol–ethyl acetate).

Anal. Calcd. for $C_{11}H_{20}NCl$: C, 65.51; H, 9.94; Cl, 17.55. Found: C, 65.21; H, 10.05; Cl, 17.53.

Reduction of VI to XXIa and XXIb in Acetic Acid.—A solution of 3.0 g. (0.018 mole) of VI in 30 ml. of acetic acid containing

(32) We wish to thank Dr. E. D. Smith, University of Arkansas, Graduate Institute at Little Rock, for suggesting this column to us for use with basic compounds.

(33) Engelhard Industries, Newark, N. J.

0.45 g. of platinum oxide was reduced under a pressure of 45 lb. at 25°. The absorption of 0.036 mole of hydrogen was complete in 1 hr. The catalyst was removed and the solution neutralized with sodium hydroxide and extracted with ether. Distillation of the ether residue gave 2.8 g. of a colorless oil, b.p. 67–68° (1.5 mm.); $n^{30}D$ 1.4710. A sample injected into the gas chromatograph exhibited one strong peak (98%) and a small fore peak (2%). The mixture upon elemental analyses gave the following results.

Anal. Calcd. for $C_{11}H_{21}N$: C, 79.04; H, 12.57; N, 8.38. Found: C, 78.99; H, 12.48; N, 8.37.

A Zerewitinoff determination of active hydrogen gave 0.55% H (calcd., 0.61%).

The **hydrochloride** of the mixture, after a single recrystallization from methanol–ethyl acetate, melted sharply at 289° (sublimed at 240° at 1 atm.).

Anal. Calcd. for $C_{11}H_{22}NCl$: C, 64.86; H, 10.81; Cl, 17.44. Found: C, 65.10; H, 11.20; Cl, 17.80.

Hydrogenation of XIX to the Mixture XXIa and XXIb.—A solution of 6.0 g. of the tetrahydropyridine in 60 ml. of acetic acid and 1.5 g. of platinum oxide was hydrogenated at 60 lb. at 25° for 48 hr. After this period of time the theoretical uptake of hydrogen was complete. Removal of the catalyst, neutralization of the solution, and extraction with ether gave 5.8 g. of a colorless oil, b.p. 74–77° (3 mm.); $n^{30}D$ 1.4703; the analytical results were in accord with the calculated values. Gas chromatographic examination indicated that the sample was composed of two peaks in the ratio of 49.1% to 50.9%. Injection of the acetic acid reduction product of I under identical instrument conditions revealed that it was the same as one of the two reduction products of V. An attempt to separate the hydrochlorides of XXIa and XXIb was successful insofar as obtaining one of the isomers in a pure state, m.p. 289°. The other isomer could not be obtained without contamination, m.p. 235–260°.

N-2,6,6-Tetramethyl-3,4-cyclopentanopiperdine.—A solution of 4.0 g. of 2,6,6-trimethyl-3,4-cyclopentanopiperdine (XXIa) in 50 ml. of 98% formic acid and 30 ml. of 37% formalin solution was heated overnight on a steam bath. Upon cooling the solution was poured into 200 ml. of 25% sodium hydroxide and the resulting mixture extracted with ether. Distillation of the ethereal residue gave a colorless oil, b.p. 79° (1 mm.); $n^{30}D$ 1.4796.

Anal. Calcd. for $C_{12}H_{23}N$: C, 79.55; H, 12.70; N, 7.75. Found: C, 79.63; H, 12.59; N, 7.81.

The **methiodide** recrystallized from methanol–carbon tetrachloride, melted at 253°.

Anal. Calcd. for $C_{13}H_{26}NI$: C, 48.37; H, 8.05; I, 39.36. Found: C, 48.16; H, 8.17; I, 38.99.

Studies Directed toward the Total Synthesis of Azasteroids. II. Cyclopenteno[*d*]-1-azabicycloalkanes as Precursors to Azasteroids[1,2]

A. I. MEYERS AND N. K. RALHAN

Department of Chemistry, Louisiana State University, New Orleans, Louisiana

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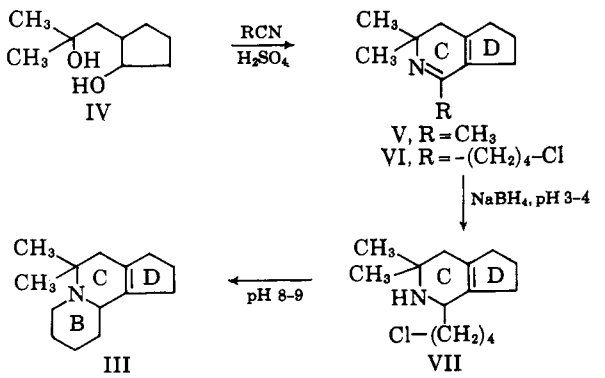
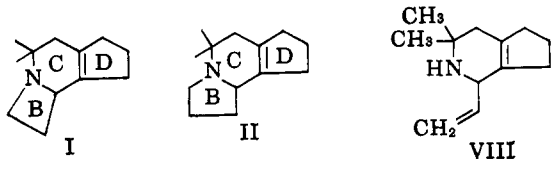
A study designed to obtain azasteroids by their total synthesis *via* a novel route has led to three new tricyclic bases, 2,2-dimethylcyclopenteno[*d*]-1-azabicyclo[4.2.0]octane (I), 2,2-dimethylcyclopenteno[*d*]-1-azabicyclo[4.3.0]nonane (II), and 2,2-dimethylcyclopenteno[*d*]-1-azabicyclo[4.4.0]decane (III). These systems were prepared from a single synthetic operation involving the appropriate chloroalkyl nitrile and α-(2-hydroxycyclopentyl)-*t*-butyl alcohol. The mechanism for the formation of these ring systems is consistent with previous studies which have led to related compounds.

The plan of approach for preparing azasteroids as described in an earlier publication[3] has now resulted in further related systems whose ease of preparation and structural features are of interest. These products (I–III) are results of a study whose main purpose was to determine the feasibility of applying the nitrile–glycol[4] condensation to the total synthesis of azasteroids. In a previous paper[3] the preparation of the model precursor (V, R = CH_3) was accomplished using acetonitrile. This product would ultimately represent the CD ring moiety of the azasteroid. In order to add the B ring it would be necessary to effect an intramolecular alkylation on the piperidine derivative VII using the appropriate halonitrile.



By treating α-(2-hydroxycyclopentyl)-*t*-butyl alcohol (IV) with δ-chlorovaleronitrile in cold concentrated sulfuric acid, there was obtained the cyclopentanodihydropyridine VI which was not isolated but reduced directly with sodium borohydride in weakly acidic solution. Attempts to isolate the cyclopentenopiperidine VII were never completely successful with regard to its purity, and, therefore, it was treated directly with base resulting in the steroidal precursor, III. When the entire sequence was performed without attempting isolation at any of the stages, a 46% yield of III based upon the glycol IV was obtained. The product, a light yellow oil, was found to be free of contaminants after a single distillation. By employing other chloronitriles,



(1) Presented before the Division of Organic Chemistry, 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963.

(2) This work supported by a grant from the National Institutes of Health (RG-6248).

(3) A. I. Meyers, J. Schneller, and N. K. Ralhan, *J. Org. Chem.*, **28**, 2944 (1963).

(4) A. I. Meyers and W. Y. Libano, *ibid.*, **26**, 1682, 4399 (1961), and earlier references cited therein.