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.); $n^{30}\mathrm{D}$ 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.); $n^{30}\mathrm{D}$ 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.); $n^{30}\mathrm{D}$ 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]

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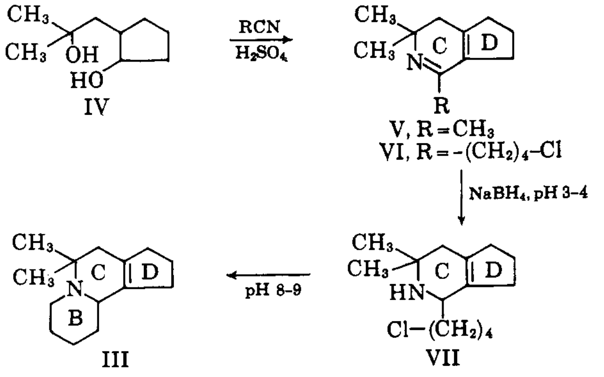
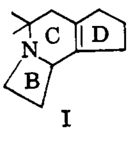
Received April 11, 1963

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.

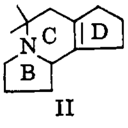
The plan of approach for preparing azasteroids as described in an earlier publication[3] has now resulted in further related systems whose ease of preparation and structural features are of interest. These products (I–III) are results of a study whose main purpose was to determine the feasibility of 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.



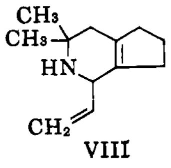
By treating α-(2-hydroxycyclopentyl)-*t*-butyl alcohol (IV) with δ-chlorovaleronitrile in cold concentrated sulfuric acid, there was obtained the cyclopentanodihydropyridine VI which was not isolated but reduced directly with sodium borohydride in weakly acidic solution. Attempts to isolate the cyclopentenopiperidine 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,



I



II



VIII

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[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.

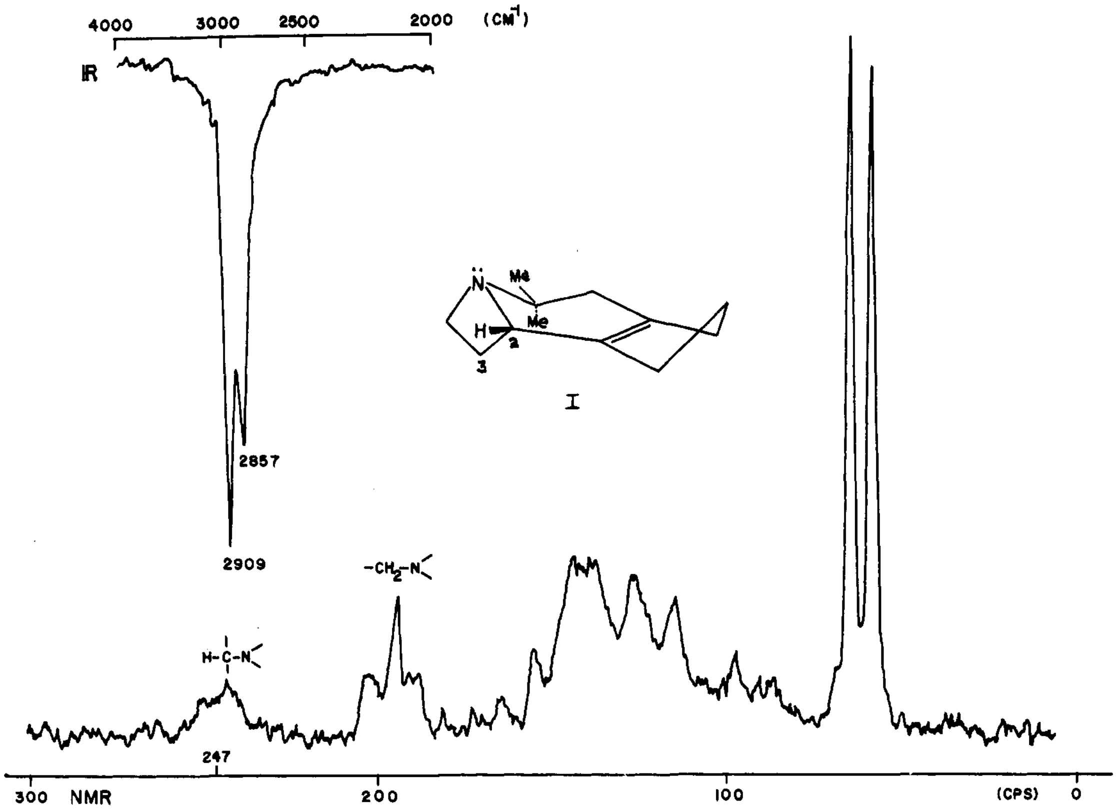

Fig. 1.—Infrared spectra were determined in carbon tetrachloride. N.m.r. spectra were performed on Varian A60 instrument using deuteriochloroform as a solvent and tetramethylsilane as an internal standard.

under essentially the same conditions, it was convenient to prepare the B-nor II and the bis-B-nor I derivatives from γ-chlorobutyronitrile and β-chloropropionitrile, respectively.

Isolation and purification of II presented no difficulty whatsoever, but I could not be purified by simple distillation or even careful fractionation. Gas chromatographic analysis of the distillate containing I indicated two close but well resolved peaks in the ratio 10.5:89.5. The component present in the smaller amount was believed to be the vinyl derivative VIII, which was finally removed by chromatography on a Florisil column. The vinyl derivative VIII undoubtedly was a product of elimination during the intramolecular ring closure.

The structures of I–III are supported by the absence of any infrared absorption bands in the region 3.5–6.9 μ. The tetrasubstituted double bond in these systems does not show any significant absorption in the 6-μ region. Ozonolysis of III, however, gave a basic compound which exhibited strong carbonyl bands at 5.90 μ.

The absence of the N–H stretching bands in the 3-μ region, the negative Zerewitinov determination, and the lack of deuterium exchange (n.m.r.) all supported the bridgehead nitrogen structure. The tetrasubstituted double bond is supported by its very weak infrared stretching band in the 6-μ region, the absence of a vinyl proton n.m.r. signal (lowest field signal, 247 c.p.s.), and the production of a basic product possessing strong carbonyl absorption at 5.9 μ. Attempts to reduce the double bond at the CD ring fusion under a variety of conditions were fruitless. The use of platinum, palladium, and rhodium in various solvents as well as pressures and temperatures ranging from 60 to 1500 p.s.i. and 25 to 180°, respectively, also failed to bring about reduction. The technique employing diborane and a carboxylic acid[5] under several different experimental conditions resulted in complete recovery of the starting material. Similar observations have been reported[6] in the attempted hydroboration of highly hindered double bonds in steroids.

The stereochemical assignments of the tricyclic bases, I–III, with respect to C-2 were made with the aid of the C–H stretch region (2700–2900 cm.$^{-1}$) and their n.m.r. spectra (Fig. 1). It can be seen that the infrared spectrum of III exhibits two sharp bands on the low frequency side of the major C–H absorption. These bands (2747 and 2825 cm.$^{-1}$) have been correlated with the presence of at least two α hydrogens *trans*-diaxial to the unshared electron pair on the bridgehead nitrogen.[7–10] The infrared spectrum of II also exhibits the two bands below 2900 cm.$^{-1}$ which indicates that the two α protons are in a *trans*-diaxial arrangement with the bridgehead nitrogen. Examination of the spectrum of I shows a rather simple C–H absorption and no distinct bands below 2857 cm.$^{-1}$. This, based on the preceding correlations, would place the proton at C-2 in a *cis* position relative to the electron pair. It is highly unlikely that the BC ring fusion in I would be other than *cis*. If I–III are represented in their most favored conformation, then the proton at C-2 should exhibit the characteristic axial and equatorial chemical shifts for a proton flanked both by a nitrogen atom and an olefinic linkage. Since it is well known that the equatorial protons produce n.m.r. signals at lower fields than their

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[5] H. C. Brown and K. Murray, *J. Am. Chem. Soc.*, **81**, 4108 (1959).

[6] W. J. Wechter, *Chem. Ind.* (London), 294 (1959); M. Nussim and F. Sondheimer, *ibid.*, 400 (1960).

[7] F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

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[9] E. Wenkert and D. Roychaudhuri, *ibid.*, **78**, 6417 (1956).

[10] W. E. Rosen, *Tetrahedron Letters*, No. **14**, 481 (1961).

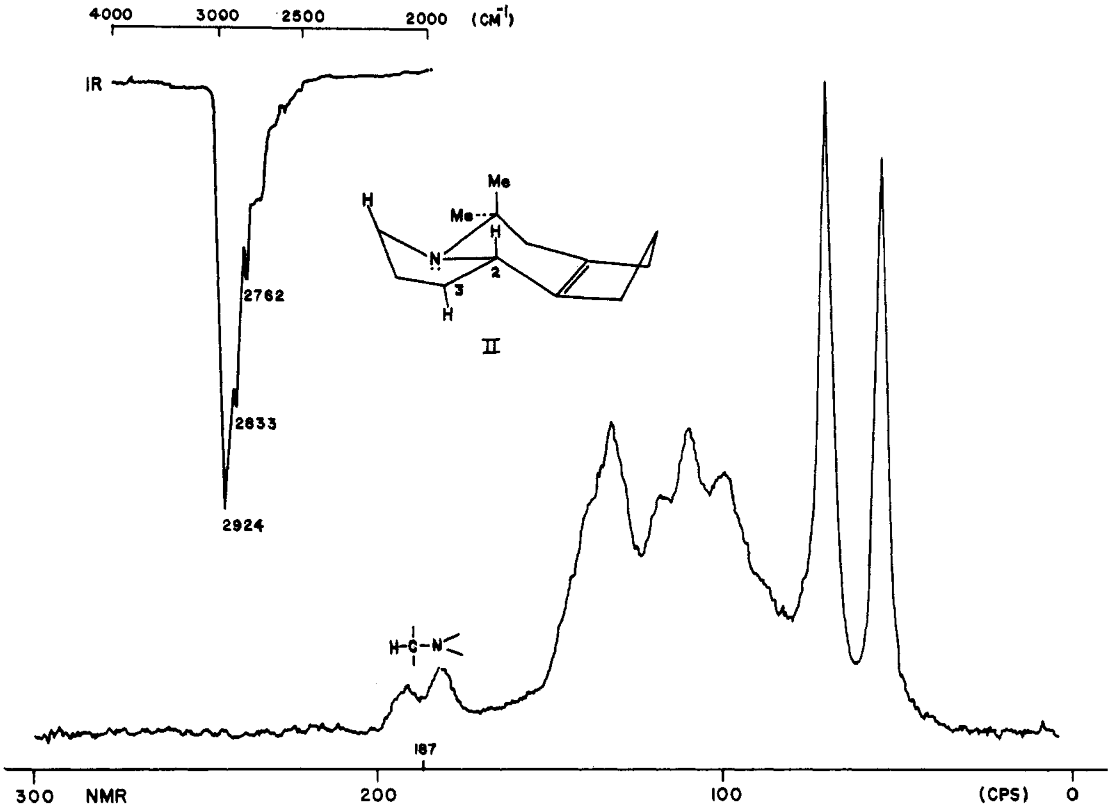

Fig. 2.—See caption to Fig. 1.

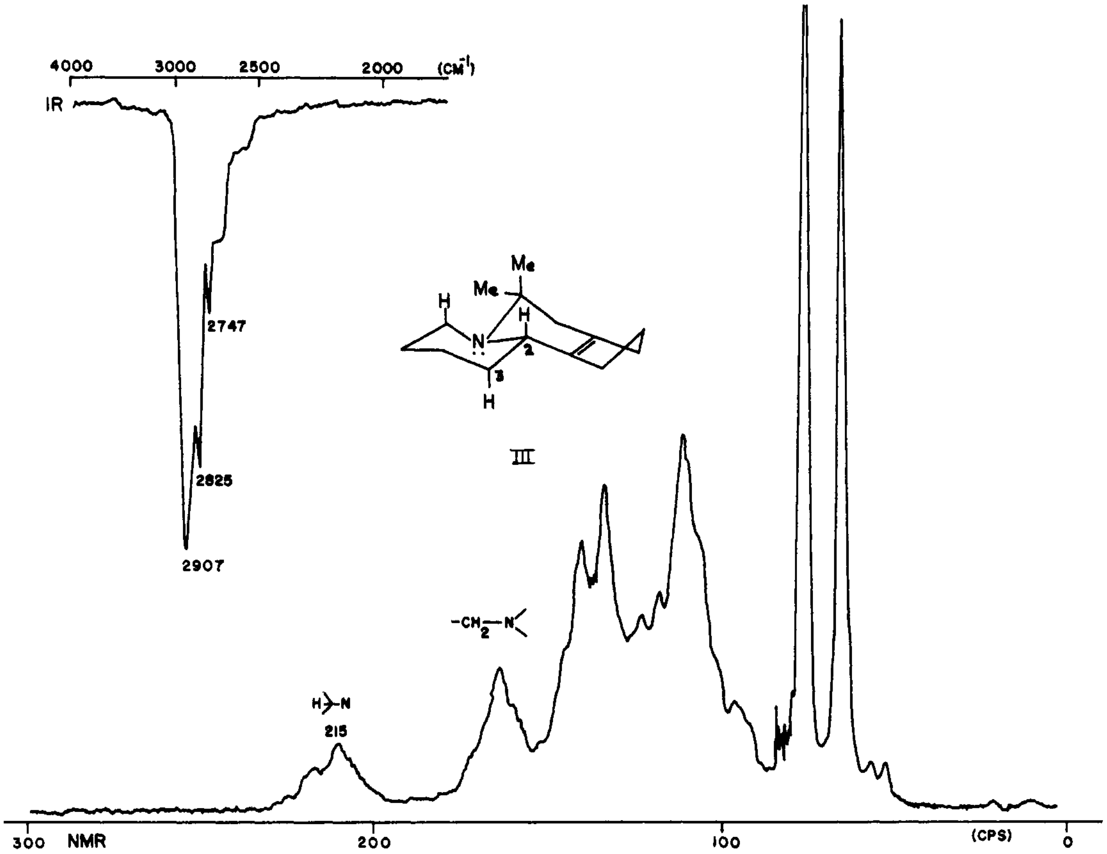

Fig. 3.—See caption to Fig. 1.

axial counterparts,[11] it is clear from Fig. 1 that the low field signal for I (247 c.p.s.) represents an equatorial C-2 proton, whereas the higher field signal in II (187 c.p.s.) and III (215 c.p.s.) reflect the presence of an axial C-2 proton. It also is seen that the C-2 proton signal in II and III is strongly coupled ($J_{\mathrm{H_2H_3}}$II = 10 c.p.s. and $J_{\mathrm{H_2H_3}}$III = 8.6 c.p.s.) and in I the poorly resolved C-2 proton signal appears to be similarly coupled ($J_{\mathrm{H_2H_3}}$III

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(11) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1959, p. 116.

= 7.5 c.p.s.). The variation in spin–spin coupling constants has been correlated with the magnitude of the dihedral angle between two adjacent carbon atoms[12] and particularly in rigid ring systems.[13–15] Since in I–III the pair of C-3 protons will have at least one member whose dihedral angle with the C-2 proton will be in the vicinity of 150–180°, then this would account for the large coupling constants.[16]

The remainder of the n.m.r. spectrum for each of the tricyclic bases indicate the expected chemical shifts for the particular protons as well as the proper integrated proton counts

Experimental[17,18]

α-(2-Hydroxycyclopentyl)-*t*-butyl alcohol [b.p. 113–115° (0.55 mm.)] was prepared as previously described.[1]

2,2-Dimethylcyclopenteno[*d*]-1-azabicyclo[4.4.0]decane (III).—To a cold (0–3°) solution of 9.05 g. (0.077 mole) of δ-chlorovaleronitrile in 150 ml. of 98% sulfuric acid was added, dropwise, 11.06 g. (0.70 mole) of α-(2-hydroxycyclopentyl)-*t*-butyl alcohol (IV). The addition of the glycol was performed while efficient stirring was maintained, and the temperature of the mixture was kept below 10°. The time required for the complete addition of the glycol under these conditions was approximately 1.5 hr. The deep reddish-colored reaction mixture was slowly poured over 500 g. of chipped ice in a 2-l. beaker.[19] The aqueous acid solution was extracted several times with chloroform to remove insoluble polymeric material and then partially neutralized (pH 2–4) with 35% sodium hydroxide. The temperature was maintained below 40° during the neutralization with the aid of external cooling. The electrodes of a pH meter (Beckman Zeromatic) were inserted into the solution and the acidity adjusted to pH 3–4 by the addition of 4 *M* sulfuric acid and 6 *M* sodium hydroxide which were contained in burets situated above the beaker. The clear solution was cooled to room temperature and a freshly prepared solution of sodium borohydride (2.66 g., 30 ml. of water, and one drop of 35% sodium hydroxide) was added dropwise while stirring was supplied by a magnetic stirrer. The pH of the reaction, during the borohydride addition was constantly kept within the limits of pH 3–4 by the periodic addition of the sulfuric acid or the sodium hydroxide. The sodium borohydride addition was complete after 1 hr. at 25°. The solution was allowed to stir at room temperature overnight and then made acidic to pH 1 and stirred for 1 hr. which destroyed the excess sodium borohydride. After adding 300 ml. of water, the pH was again adjusted to 8–8.5 and allowed to stir for 5 hr. The oil which had separated was extracted with ether and dried over potassium carbonate. Removal of the ether on a steam bath and distillation of the residual oil gave 6.6 g. (46%) of the tricyclic base, b.p. 100–102° (1.0 mm.); $n^{30}D$ 1.5062. The infrared spectrum (carbon tetrachloride) showed only strong absorption at 3.4 (CH), 6.9 μ (CH_2 bending), and ring skeletal vibrations above 8 μ.

Anal. Calcd. for $C_{14}H_{23}N$: C, 81.94; H, 11.22; N, 6.83. Found: C, 81.71; H, 11.07; N, 6.81.

The **picrate** from methanol, melted at 191–193°.

Anal. Calcd. for $C_{20}H_{26}N_4O_7$: C, 55.30; H, 6.13; N, 12.90. Found: C, 55.08; H, 6.23; N, 12.83.

2,2,-Dimethylcyclopenteno[*d*]-1-azabicyclo[4.3.0]nonane (II).—A cold solution of 7.93 g. (0.077 mole) of γ-chlorobutyronitrile in 150 ml. of 98% sulfuric acid was treated with 11.06 g. (0.070 mole) of α-(2-hydroxycyclopentyl)-*t*-butyl alcohol as described previously. Distillation of the residue from the ethereal extracts afforded 7.2 g. (54%) of a light yellow oil, b.p. 73° (0.25 mm.); $n^{30}D$ 1.5025. The infrared spectrum (carbon tetrachloride) exhibited only CH stretching, CH_2 bending, and skeletal vibrations.

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.67; H, 10.99; N, 7.33. Found: C, 81.62; H, 10.84; N, 7.28.

The **picrate**, from ethanol, melted at 188°.

Anal. Calcd. for $C_{19}H_{24}O_7N_4$: N, 13.33. Found: N, 13.32.

2,2-Dimethylcyclopenteno[*d*]-1-azabicyclo[4.2.0]octane (I).—This was obtained in essentially the same manner as described for III by treating a cold solution of 6.45 g. (0.77 mole) of β-chloropropionitrile in 150 ml. of 98% sulfuric acid with 11.06 g. (0.070 mole) of α-(2-hydroxycyclopentyl)-*t*-butyl alcohol. Removal of the ether left an oily residue which, although carefully fractionated [65–67° (1.0 mm.)], gave two peaks[20] in the ratio 89.5:10.5. A picrate, formed from this mixture, melted at 214° after two recrystallizations from ethanol. The infrared spectrum of the mixture exhibited a slight $C{=}CH_2$ stretching band at 3.25 μ and the corresponding bending frequency at 10.2 and 10.9 μ. This minor component was then assigned the structure VIII. The mixture (0.75 g.) was added to a Florisil column and eluted with petroleum ether–diethyl ether solvent pairs. The pure tricyclic base I was obtained (0.55 g.) and exhibited a single peak upon gas chromatographic analysis which corresponded to the 89.5% peak in the original mixture. The infrared spectrum showed the complete absence of the bands attributed to the vinyl derivative. The yield of I was 50%.

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.36; H, 10.73; N, 7.91. Found: C, 81.25; H, 11.02; N, 7.72.

The **picrate**, from methanol, melted at 214°.

Anal. Calcd. for $C_{18}H_{22}N_4O_7$: N, 13.80. Found: N, 14.05.

Attempted Reduction of II by Hydroboration–Propionic Acid.—A solution of 5.0 g. of II in 50 ml. of anhydrous tetrahydrofuran was treated with diborane generated from another flask containing 3.5 g. of sodium borohydride and 20 g. of boron trifluoride-ethyl ether complex in 50 ml. of diglyme. After standing overnight the tetrahydrofuran was removed by distillation, and the residue was treated with 5.0 ml. of propionic acid and heated to 150° for 3 hr. The mixture was cooled, neutralized, and extracted with ether. The residue from the ethereal extract was distilled, b.p. 80° (0.5 mm.), amounting to 4.2 g. The picrate, infrared spectrum, and the refractive index were identical with the starting material.

Ozonolysis of II.—A solution of 2.0 g. of II in 100 ml. of dichloromethane was cooled in an ice bath and subjected to a stream of ozone for 2 hr. Work-up of the ozonized mixture gave a tarry mixture which was for the most part basic and whose infrared spectrum (carbon tetrachloride) showed a strong carbonyl absorption at 5.90 μ. Attempts to purify this substance were fruitless.

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[12] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

[13] K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).

[14] A. D. Cross, *ibid.*, **84**, 3207 (1962).

[15] D. J. Collins, J. J. Hobbs, and S. Sternhell, *Tetrahedron Letters*, No. **10**, 623 (1963).

[16] The n.m.r. spectra were determined both at 60 and 24 Mc. to ensure that these signals were coupling values rather than chemical shifts. We thank Dr. R. E. Glick, Florida State University, who determined this using the Varian HR-60 instrument.

[17] All melting points and boiling points are uncorrected.

[18] Microanalyses were performed by Alfred Bernhardt, Mulheim (Ruhr), West Germany.

[19] The following two reactions—*i.e.*, the sodium borohydride reduction and the intramolecular alkylation—were carried out in this vessel.

[20] Analyzed on a 6-ft. column coated with 10% Dow Corning 710 and 5% potassium hydroxide on Chromsorb P.