Heterocyclic Studies. 44. Thermal Rearrangement of 2-Acyl-1,2-diazabicycloheptenones

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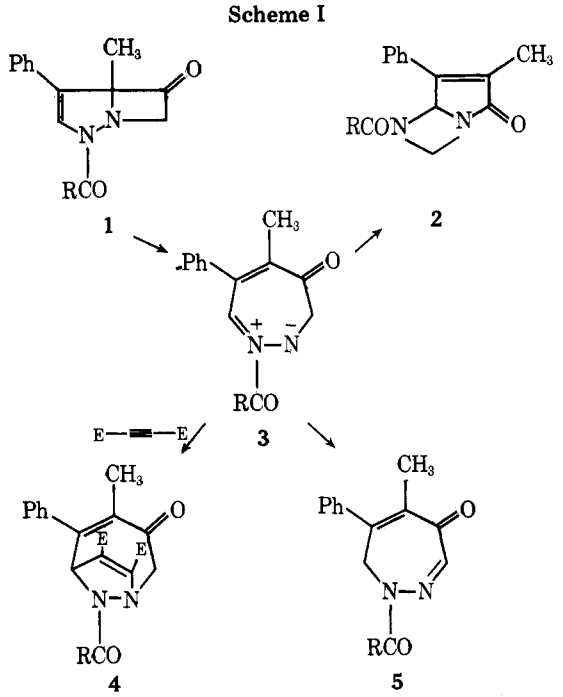
1-Acyl-2-(alkoxymethyl)tetrahydropyridazinones 8 are obtained from the bicyclic ketones 1 on heating in alcohol or alcohol–benzene mixtures and are suggested to arise by trapping of the intermediate **10**. A pathway from **10** to the bicyclic pyrrolinones 2 is suggested (Scheme II).

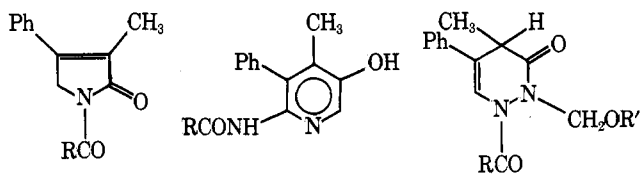
Some years ago we reported the transformation of the bicyclic ketones **1**, on warming, to the isomeric bicyclic pyrrolinones **2**.[3] It was subsequently found that the 1-acyl-1,7-dihydrodiazepinone **5a** is a minor product accompanying **2a**, and that heating **1** in the presence of acetylenedicarboxylic ester gives the adducts **4**.[4] The formation of **4** and **5** clearly point to the acyldiazepinium betaine **3** as an initial intermediate in the thermal reaction of **1**. We now present information about further steps in the unusual rearrangement to **2**.

Scheme I



a, R = CH_3
b, R = C_6H_5

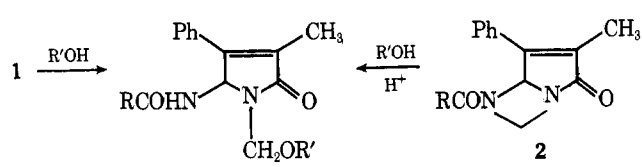
A clue to the pathway from **1** to **2** was obtained from a study of the reactions of the bicyclic ketones with alcohols. In methanol, **1a** and **1b** are converted to mixtures of the acylpyrrolinones **6** and 3-hydroxypyridines **7** as described in an earlier paper.[5] However, when the benzoyl ketone **1b** was heated in benzene containing 10% methanol, the major product in the mixture was different from those obtained in either solvent alone; the NMR spectrum indicated the presence of $CH_3OCH_2N<$ and $CH_3CH<$ groups.[6] A homologous product was then isolated as a crystalline solid from the reaction of **1b** in refluxing absolute ethanol, and the tetrahydropyridazinone structure **8b** (R′ = Et) was established by crystallographic analysis. The pyridine **7b** is a minor product in the reaction of **1b** in ethanol, but is formed in progressively larger amount, together with pyrrolinone **6b**, as the reaction temperature is lowered to 50 °C, or when traces of water are



a, R = CH_3
b, R = C_6H_5

present. Thus, even in 99% ethanol at 70 °C for 1 h, the product was a mixture of **7b** and (ca. 10%) **6b**, and contained little if any pyridazinone **8b**.

In isopropyl alcohol, the pyridazinone **8b** (R′ = *i*-Pr) was isolated as the major product from **1b** at 50 °C, but as the temperature was increased to 80 °C, another compound was formed in progressively larger amount. This substance was isolated by chromatography and identified as the 1-isopropoxymethyl pyrrolinone **9b** (R′ = *i*-Pr). Finally, the reaction



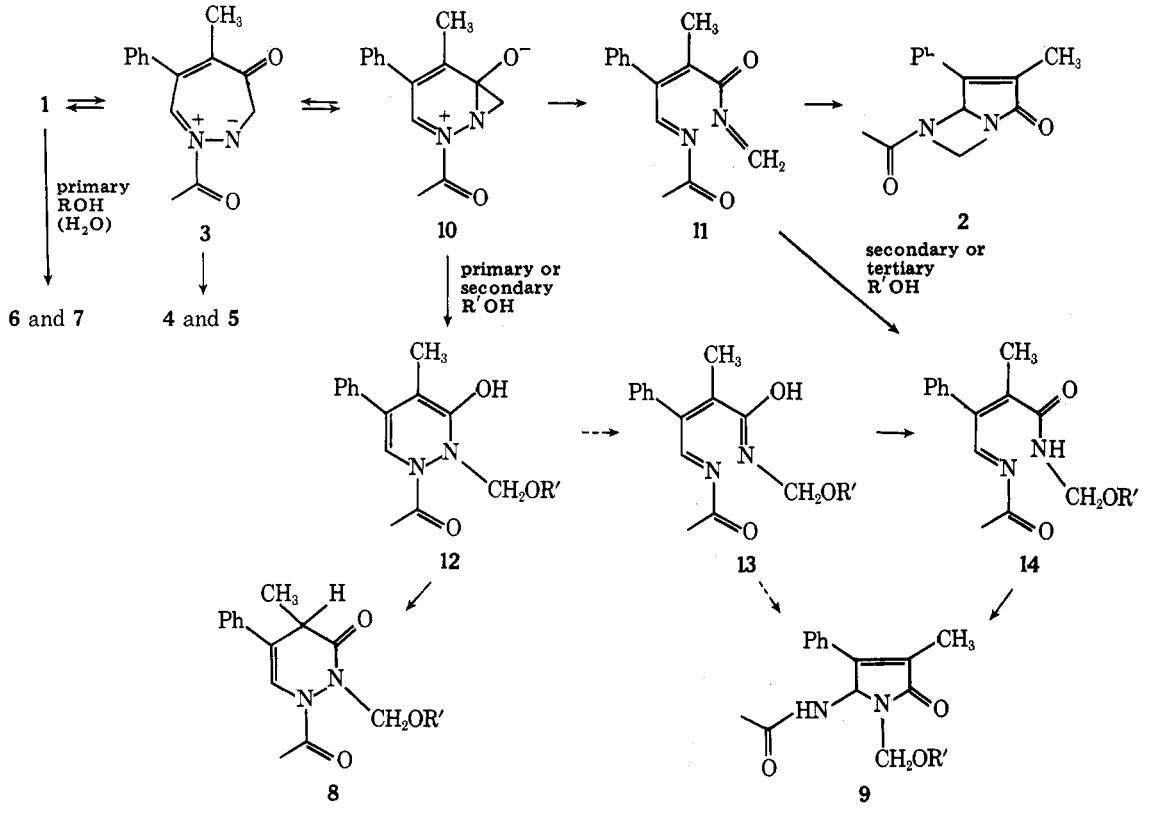
a, R = CH_3
b, R = C_6H_5

of **1b** in *tert*-butyl alcohol gave the pyrrolinone **9b** (R′ = *t*-Bu) as the principal product at 50 °C, with a minor amount of the pyridazinone **8b** (R′ = *t*-Bu). At 80 °C, only a trace of **8b** was present, and **9b** was isolated by direct crystallization.

The alkoxymethylpyrrolinones **9** were identified by comparison with samples prepared by alcoholysis of the bicyclic pyrrolinone **2**. This reaction, which was a key step in the structure elucidation of **2**,[3] occurs slowly on heating **2** in alcohols and very rapidly in the presence of acid. It was supposed initially that the pyrrolinones **9b**, R′ = *i*-Pr and *t*-Bu, arose in the reactions of **1b** by ring opening of the bicyclic pyrrolinone **2b**. However, this process was shown not to be the major source of the alkoxymethylpyrrolinone from **1b** in *tert*-butyl alcohol, since the reaction of **2b** with *tert*-butyl alcohol is much slower than that of **1b** under the same conditions. After a mixture of **1b** and **2b** was heated in *tert*-butyl alcohol solution at 60 °C for 24 h, the NMR spectrum showed nearly complete reaction of **1b**, with formation of **9b**, and only minor loss of **2b**.

Qualitatively similar behavior was observed with the acetyl ketone **1a** in alcohols, but the reaction mixtures were complicated by the presence of the dihydrodiazepinone **5a**. (In the thermal reactions of **1a** and **1b** in benzene, **5a** and **5b** amount to about 35 and 10% of the product, respectively.[4])

Scheme II



In refluxing isopropyl alcohol, the acetyl ketone **1a** was converted to the pyridazinone **8a** (R′ = *i*-Pr) and 15–20% of **5a**; **8a** was not obtained in crystalline form and was characterized only by NMR. The reaction mixture from **1a** in refluxing *tert*-butyl alcohol was complex, and probably contained **8a** and **9a** (R′ = *t*-Bu). In benzene containing 10% *tert*-butyl alcohol, NMR showed a mixture of **2a**, **5a**, and **9a** (R′ = *t*-Bu). The mixture was not separated; **9a** (R′ = *t*-Bu) was identified by the correspondence of eight distinctive NMR peaks with those of a sample prepared from **2a**.

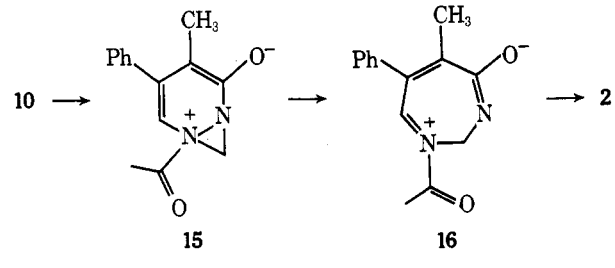
Discussion

The succession of products obtained from the ketones **1** with alcohols of decreasing nucleophilic power suggests the trapping of a series of increasingly reactive intermediates which lead eventually, if not intercepted, to the rearrangement product **2**. One sequence that seems consistent with the data is shown in Scheme II.

In the most polar media, methanol and aqueous ethanol, the ketones undergo reactions at 50–60 °C or below that are more rapid than the ring opening to **3**. These reactions, which will be described in more detail in a later paper, lead to the previously described products **6** and **7**. At 50 °C and above, reactions proceeding via **3** become progressively more important, particularly in less polar media.

Compounds **4** and **5** (Scheme I) provide evidence for the initial intermediate **3**, formed by 6π electrocyclic ring opening of **1**. A second bicyclic valence isomer available from **3** is **10**. Nucleophilic attack by primary or secondary alcohols at the three-membered ring of **10** would lead, via the enol **12**, to the pyridazinone **8**. In the absence of a reactive nucleophile, collapse of **10** could give the acyclic intermediate **11**. The CON=CH_2 system of **11** would be highly electrophilic, perhaps sufficiently so to undergo addition of sterically hindered alcohols, giving **14** and thence the pyrrolinones **8**. Finally, when generated in an unreactive medium, recyclization of **11** would give the end product **2**.

Several alternatives to the steps in Scheme II can be considered. Thus an acyclic enol **13**, which could arise by ring opening of **12**, would provide another plausible path to **9**. In an attempt to test this possibility, the pyridazinone **8b** (R′ = Et) was heated under reaction conditions in which **9** is formed from **1**, but no reaction was observed. An alternative pathway from **10** to **2** involves intermediates **15** and **16**, but further



comment on these or other possibilities is not justified by the present data. The sequence involving intermediates **10** and **11** provides a rational basis for the products observed, and is clearly an improvement over our earlier speculations on the formation of **2**.[3]

Crystallography. Crystals of **8b** (R′ = Et) are orthorhombic, space group $P2_12_12_1$, with a = 13.911 (25), b = 14.184 (12), c = 19.630 (16), and Z = 8. The intensity data were collected on a Hilger-Watts diffractometer (θ–2θ scans, Ni-filtered Cu Kα radiation, pulse height discrimination). The size of the crystal used for data collection was 0.1 × 0.3 × 0.5 mm. Of the 2976 reflections with $\theta < 57°$, 2346 had intensities which were significantly greater than background. The structure was solved by a multiple solution procedure.[7] The first E map calculated revealed all of the atoms of one molecule and half of the atoms of the other molecule in the asymmetric unit. The remaining atoms were found on an electron density map based on these atoms. Full-matrix least squares was used for the initial refinement in which all atoms had isotropic temperature factors. For the anisotropic refinement, block diagonal least squares was used in which the matrix was partitioned into two blocks. A difference map calculated at the conclusion

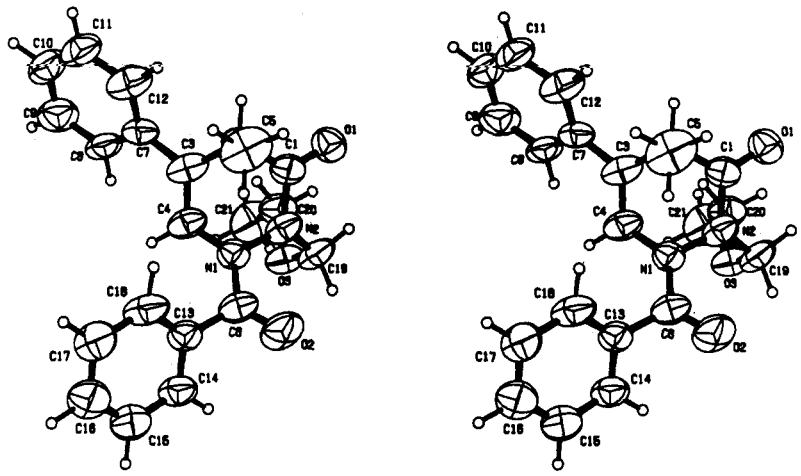


Figure 1. ORTEP projection of **8b** (R′ = Et).

of the anisotropic refinement of the heavier atoms had peaks at reasonable positions for many of the hydrogen atoms. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms, which were held fixed at their calculated positions. The final unweighted and weighted discrepancy indices are $R = 0.088$ and $wR = 0.099$ for the 2346 observed reflections. The final difference map has no peaks greater than ± 0.5 eÅ^{-3}. The final atomic coordinates are tabulated in supplementary pages (see paragraph at end of paper regarding supplementary material). A stereoscopic view of the structure is shown in Figure 1. There are two independent molecules in the unit cell. One molecule (primed) is related to the other (unprimed) by a noncrystallographic pseudoglide plane.

$$x' = x - (0.006 \pm 0.007)$$
$$y' = y + (0.270 \pm 0.007)$$
$$z' = -z - (0.011 \pm 0.010)$$

The relatively high R values are attributed to the fact that a suitable single crystal was not available. The specimen used for data collection was cut from a multiple crystal, and may not have been a true single crystal. Despite the high R values, the correctness of structure **8b** (R′ = Et) is supported by several lines of evidence. All bond lengths (std dev 0.015 Å) and bond angles (std dev 1.0°) are consistent with the structure. Prominent peaks were found for the hydrogen atoms at C(2) and C(4) in both independent molecules. Finally, the R factors for the isotropic refinement of two other trial structures were higher than those for structure **3**. The results of the three isotropic refinements were (a) N(1), N(2), N(1)′, N(2)′ as nitrogens, $R = 0.166$, $wR = 0.181$; (b) N(1), C(4), N(1)′, C(4)′, as nitrogens and N(2), N(2)′ as carbons, $R = 0.169$, $wR = 0.183$; (c) N(2), C(4), N(2)′, C(4)′ as nitrogens and N(1), N(1)′ as carbons, $R = 0.171$, $wR = 0.185$.

Experimental Section

NMR spectra designated FT 90 MHz were recorded on a Bruker HFX 90 instrument; other NMR spectra were obtained with Perkin-Elmer R-12B or Varian A-60A spectrometers.

1-Benzoyl-2-ethoxymethyl-4-methyl-5-phenyl-1,2,3,4-tetrahydropyridazin-3-one (8b, R′ = Et). A solution of 3.0 g of **1b** in 15 ml of absolute ethanol was refluxed for 7.5 h and then evaporated to a yellow gum; the NMR spectrum indicated the presence of mainly **8b** and a minor amount of **7b**. The gum crystallized after addition of ether to give 1.1 g of colorless solid; an additional 0.4 g of solid was obtained on further crystallization from ethanol. Recrystallization from aqueous ethanol gave slender rods: mp 110–112 °C; δ ($CDCl_3$) (90 MHz FT) 1.14 (t, J = 7.0 Hz), 1.51 (d, J = 7.3 Hz), 3.44 (q, J = 7.0 Hz), 3.72 (dd, J = 1.2, 7.3 Hz) [H-4], 4.99 (d, J = 11 Hz) and 5.58 (d, J = 11 Hz) [AB NCH_2O], 7.19–7.69 ppm (m).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.73; H, 6.32; N, 8.02.

A sample crystallized slowly from ethanol at 38–30 °C and was used for crystallographic analysis.

Isopropoxymethylpyridazinone 8b (R′ = *i*-Pr). A solution of 160 mg of **1b** in 15 ml of 2-propanol was kept in a 50 °C bath for 4 days and evaporated to a yellow syrup which crystallized after standing for 12 h. Recrystallization from 2-propanol plus water gave 69 mg of **7b** (R = *i*-Pr) as colorless crystals: mp 123–124 °C; δ ($CDCl_3$) (90 MHz FT) 1.09 (d, J = 6.1 Hz) and 1.14 (d, J = 6.0 Hz) [nonequivalent isopropyl CH_3 groups], 1.52 (d, J = 7.2 Hz), 3.57 (septet, J = 6.1 Hz), 3.70 (dd, J = 1.3 and 7.3 Hz) [H-4], 4.95 (d), and 5.64 (d, J = 11 Hz) [NCH_2O], 7.2–7.69 ppm (m).

Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.98; H, 6.29; N, 7.83.

5-Benzamido-1-isopropoxymethyl-3-methyl-4-phenyl-3-pyrrolin-2-one (9b, R′ = *i*-Pr). The bicyclic pyrrolinone **2b** (50 mg) was suspended in 1 ml of 2-propanol and 1 drop of concentrated HCl was added. The solid rapidly dissolved; after 2 min, 3 ml of water was added. The resulting crystalline solid was collected and recrystallized from 2-propanol to give 300 mg of **9b** (R′ = *i*-Pr) as colorless needles: mp 176–117 °C; δ ($CDCl_3$) 1.15 [d, J = 5.9 Hz, $(CH_3)_2CH$–], 2.10 (s, CH_3), 3.75 (septet, J = 5.9 Hz), 4.75 (d, J = 10 Hz), and 5.03 (d, J = 10 Hz) [NCH_2O], 6.7–7.2 (m, H-5 and NH), 7.2–8.0 ppm (m).

Anal. Calcd for $C_{22}H_{24}O_3N_2$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.63; H, 6.81; N, 7.78.

9b (R′ = *i*-Pr) from 1b. A solution of 300 mg of **1b** in 15 ml of 2-propanol was refluxed for 7 h and then evaporated to a yellow syrup. The NMR spectrum showed a mixture of **8b** and **9b** in a ratio of 2:1. A portion of this syrup was chromatographed on a 20 × 20 cm silica gel plate with $CHCl_3$ as eluent. The pyridazinone **8b** was present in a band just below the solvent front. A central band containing **9b** was scraped from the plate and extracted to give 30 mg of **9b** as colorless needles, mp 173–175 °C.

***tert*-Butoxymethylpyrrolinone 9b, R′ = *t*-Bu.**[8] A solution of 1.0 g of **2b** in 50 ml of *tert*-butyl alcohol was refluxed for 6 h. After evaporation of the alcohol, the residual yellow oil crystallized on addition of ether. Recrystallization from ether gave 610 mg of white needles of **9b** (R′ = *t*-Bu): mp 171–172 °C; ν^{KBr} 3400, 1725, 1660 cm^{-1}; δ ($CDCl_3$) 1.21 (s, *t*-Bu), 2.11 (d, J = 0.6 Hz, 3-CH_3), 4.80 (J = 9 Hz) and 5.00 (J = 9 Hz) [AB NCH_2O], 6.85 and 6.95 (multiplets, H-5 and NH), 7.27–7.95 ppm (m, 10).

Anal. Calcd for $C_{23}H_{26}O_3N_2$: C, 72.99; H, 6.93. Found: C, 72.95; H, 6.83.

Reaction of Acetyl Ketone 1a in Isopropyl Alcohol. Following the general procedure used to examine the products from **1a** and **1b** by NMR, a solution of 35 mg of **1a** in 1.5 ml of *i*-PrOH was refluxed (16 h) and evaporated to an oil in vacuo. CCl_4 was added and evaporated three times and the NMR spectrum in $CDCl_3$ was then recorded. Peaks for **8a** (R = *i*-Pr): δ 1.10 (d, J = 6.2 Hz) and 1.15 (d, J = 6.2 Hz) [nonequivalent isopropyl CH_3], 1.40 (d, J = 7.5 Hz), 3.76 (center of symmetrical six-line multiplet), 5.07 (d, J = 11 Hz), 5.70 (d, J = 11 Hz) [AB NCH_2O], 7.55 (s, aryl). Peaks for **5a:** δ 1.95 (s), 2.48 (s), 5.00 (s). The ratio of peak heights indicated a ratio of **8a/5a** of ~8:1.

***tert*-Butoxymethylpyrrolinone 9a (R′ = *t*-Bu).** A sample of **2a**[4] was prepared by refluxing a solution of 210 mg of bicyclic ketone **1a** in toluene for 50 min. After evaporation, crystals of **5a** were obtained from the yellow oil by treatment with ether. After removal of two crops

of **5a**, the residual oil, 126 mg, which could not be crystallized, had the NMR spectrum of **2a**[4] [δ 1.90 (d, J = 1.5 Hz), 2.10 (s), 5.10 (d, J = 10 Hz), 5.88 (m), 5.92 (d, J = 10 Hz), 7.5–7.9 (m)] with only a trace of **5a**. A solution of this oil in 2 ml of *tert*-butyl alcohol was heated for 16 h at 70 °C and was then evaporated. Crystals formed slowly from ether. Repeated recrystallization from ether gave colorless needles of **9a** (R′ = *t*-Bu): mp 177–178 °C; δ 1.30 (s, *t*-Bu), 2.0 (d, J ~0.4 Hz, 3-CH_3), 2.11 (d, $COCH_3$), 4.80 (d, J = 9.5 Hz) and 5.05 (d, J = 9.5 Hz) [$-OCH_2N$], 6.1 and 6.9 (both apparent doublets, NH and H-5, 7.6 (s, C_6H_5).

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.38; H, 7.66; N, 8.88.

Registry No.—**1a**, 5109-37-5; **1b**, 5109-45-5; **2a**, 36004-91-8; **2b**, 10137-20-9; **5a**, 36004-94-1; **8a** (R′ = *i*-Pr), 59729-10-1; **8b** (R′ = Et), 59729-11-2; **8b** (R′ = *i*-Pr), 59729-12-3; **9a** (R′ = *t*-Bu), 59729-13-4; **9b** (R′ = *i*-Pr), 59729-14-5; **9b** (R′ = *t*-Bu), 59729-15-6.

Supplementary Material Available. Table of atomic coordinates (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Visiting professor at University of Delaware from University of the Witwatersrand, Johannesburg, South Africa.
(2) Hoffmann-La Roche Inc.
(3) J. M. Eby and J. A. Moore, *J. Org. Chem.*, **32**, 1346 (1967).
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(5) J. A. Moore, R. L. Wineholt, F. J. Marascia, R. W. Medeiros, and F. J. Creegan, *J. Org. Chem.*, **32**, 1353 (1967).
(6) This experiment was carried out by R. T. Taylor.
(7) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A.*, **27**, 368 (1971).
(8) This experiment was carried out by C. M. Kopay.

A Symmetrical Diazaditwistane. 2,9-Dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane

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The facile synthesis of 2,9-dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane (**3**), a unique and symmetric diazaditwistane, from *endo*-7,11-dicyano-4,9-dimethyl-4,9-diazatricyclo[6.2.2.0^{2,7}]dodeca-11-ene (**2**) via an intramolecular hydride transfer is reported. Spectral evidence and deuterium labeling studies confirming the structure of **3** and its mode of formation are presented.

In connection with studies directed toward the development of bioactive molecules with functional groups in unique and fixed three-dimensional relationships, an examination of the chemistry of Diels–Alder adduct **1** and its reduction product **2**, both of which have been recently prepared by Liberatore, Casini, and Carelli,[1] was begun. During the course of these studies, we have discovered that **2**, when heated in polar, protic solvents, undergoes a facile rearrangement to afford **3** (2,9-dicyano-5,11-dimethyl-5,11-diazatetracyclo[6.2.2.0^{2,7}.0^{4,9}]dodecane), which is a substituted, diaza analogue of the recently reported ditwistane system.[2] Formation of **3** was first noted when **2** was refluxed in water. It was isolated in 55% yield by filtration and shown to be isomeric with **2** by means of mass spectral and elemental analyses. Subsequent large-scale preparations of **3** in 81% yield have been carried out in methanol at 150 °C. The ir spectrum of **3** displayed one band at 2240 cm^{-1} ($CHCl_3$) indicative of saturated nitrile, and no double bond stretching absorptions were present in the spectrum. The ^1H and ^{13}C NMR spectra of **3** provided the basis for its structural assignment. In 1 N DCl the ^1H NMR spectrum revealed nine protons distributed in a ratio of 2:1:3:1:1:1, starting from high field, none of which occurred in the vinyl region. Since mass spectral and elemental analyses confirmed a molecular formula of $C_{14}H_{18}N_4$ for **3**, we concluded that it must be highly symmetrical in nature. The proton spectrum is summarized in Table I. The *N*-methyl resonance appeared as a singlet at 3.08 ppm, and the remainder of the proton spectrum could be interpreted by a first-order analysis, with second-order effects contributing to line broadening. The presence of the following groups was indicated: CH_3N, $NCHCH_2$, and NCH_2CH. The ^{13}C NMR spectrum, summarized in Table II, suggested the presence of seven types of carbon atoms. In addition to the five already indicated, a nitrile carbon and a carbon attached to four other carbons were detected. Assignments were confirmed by off-resonance decoupling experiments. The highly symmetrical nature was again indicated in this spectrum. Based on the accumulated data, structure **3** has been assigned to the new product. It contains a C_2 axis of symmetry and exists as an enantiomeric pair. Resolution of **3** has been achieved via its dibenzoyl-D-tartrate salt. Details of this procedure are reported in the Experimental Section.

A reasonable reaction path for the formation of **3** involves an intramolecular hydride transfer in **2** as indicated, which proceeds through a dipolar transition state or through a discrete zwitterionic intermediate, which subsequently affords **3**. The proposed reaction path requires that the piperidine ring in **2** adopt a boatlike conformation prior to hydride transfer. Models suggest that this, the subsequent hydride transfer, and the final ring closure involve no severe distortions of the molecular framework. The latter two transformations occur over six-atom frameworks. This and the ability of the substituents to stabilize the developing charges in the intermediate or transition state account for facility of the reaction.

Consistent with the proposed intramolecular reaction path, no deuterium incorporation resulted when the reaction was run in D_2O. Also, it was noted that the reaction proceeded at comparable rates in water (100 °C), methanol (150 °C), and ethylene glycol (160 °C), much more slowly in 1-butanol (118 °C), hardly at all in *tert*-butyl alcohol (150 °C) and dimethyl sulfoxide (150 °C), and not at all in diglyme (125 °C) and xylene (140 °C). The requirement for a polar, protic solvent is consistent with the proposed ionic nature of the reaction path. In acetic acid (115 °C) and 50% aqueous acetic acid (105 °C) the reaction proceeded at one-quarter of its rate in water, suggesting that acid catalysis does not facilitate the reaction. Although we have not been able to find a direct analogy for this specific type of hydride-transfer reaction in the literature,