applying second-order corrections,[30] and then recomputing the distance between each line.

The light source, variable temperature equipment, and the sample tubes are as described previously.[4b] The temperature in the tube was calibrated with a thermocouple and accurate to ±5°. The photolyses were carried out in typical cases as follows.

For the photolysis of diacyl peroxides or acyl peresters[6] a small amount of the peroxide (*ca.* 100 mg) was dissolved in a relatively large volume (15:1) of cyclopropane or cyclopropane–ethane mixtures. For diacyl peroxides it was also possible to employ diethyl ether or ether–pentane mixtures as solvent to enable lower temperatures to be obtained before crystallization became a problem.

For photolytic reduction of alkyl halides,[3a] equal volumes of di-*tert*-butyl peroxide and triethylsilane were diluted with sufficient cyclopropane (and ethane) to give a final ratio of approximately 1:1:1:4. A correspondingly smaller amount of dibromoalkanes was used. The halide was usually the bromide, but chlorides could also be used. In the latter case, good spectra of alkyl radicals could only be observed at certain temperatures, above and below which the spectrum of triethylsilyl radicals was also observed. In some experiments the triethylsilane was replaced by tri-*n*-butylstannane and an alkyl iodide employed.

For the addition of chlorine atoms to alkenes, the samples contained a small amount of di-*tert*-butyl peroxide, a very small amount of anhydrous HCl, and roughly equal amounts of cyclopropane and ethane. Larger amounts of HCl lead to a dimunition of the intensity of the spectrum. In order to prevent premature thermal additions from occurring, the HCl was kept apart from the alkene by interposing a layer of cyclopropane during the preparation of the sample. The same procedure was used for HBr.

All samples were thoroughly degassed using a freeze–pump–thaw cycle. When spectra were weak or not observed, the amounts of the various components were varied to obtain optimum concentrations.

Materials. Di-*tert*-butyl peroxide was obtained from Shell Chemical Co., washed, and redistilled at reduced pressure prior to use. The β-chloro and β-bromopropionyl peroxides and peresters were prepared by a procedure described previously.[31] The γ-chloro and γ-bromobutyryl peroxides and peresters were synthesized by Mr. Y. D. Tang and the *tert*-butyl γ,γ,γ-trichlorobutyryl perester was kindly donated by Dr. L. K. Montgomery.

Triethylsilane, 1-bromo-3-fluoropropane, 1,3-diiodopropane, 1,1,1-trichloro-3-bromopropane, 1-bromo-4-chlorobutane, 1,5-diiodopentane, and 1,6-dibromohexane were obtained from Columbia Organic Chemicals Co. 1,2-Dibromoethane and 1-bromo-3-chloropropane were kindly donated by the Dow Chemical Co. 1,3-Dibromopropane, 1,4-dibromobutane, and 1,5-dibromopentane were obtained from Distillation Products industries (Eastman Kodak). 1-Bromo-2-chloroethane and *n*-propyl iodide were from Matheson Coleman and Bell, 1,4-diiodobutane came from City Chemical Co., 2-bromopropene was from J. T. Baker Co., 2,3-dibromopropene came from Aldrich Chemical Co., and 1,1,1-trifluoro-2-bromoethane was from Pierce Chemical Co. 1-Bromo-2-fluoroethane was prepared from 2-fluoroethanol (Columbia Organic Chemical Co.) and phosphorus tribromide; bp 71–73° (lit. 71–72°).[32]

The procedure for quantitative analysis of carbon dioxide, ethane, ethylene, and butane was described previously.[31]

Acknowledgment. We wish to thank the National Science Foundation for generous financial support, Mr. Y. D. Tang for samples of some of the peroxides, and Dr. L. K. Montgomery and Dr. T. Kawamura for helpful discussions.

(30) R. W. Fessenden, *J. Chem. Phys.*, 37, 747 (1962).

(31) J. K. Kochi, *J. Amer. Chem. Soc.*, **85**, 1958 (1963).

(32) F. W. Hoffman, *J. Org. Chem.*, **15**, 425 (1950).

Synthesis and Thermal Rearrangement of the 2-Azabicyclo[3.1.0]hex-3-ene Ring System[1]

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Contribution from the Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11790. *Received February 10, 1972*

Abstract: The 2-azabicyclo[3.1.0]hex-3-ene ring system has been prepared. Heating *N*-carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene in the gas phase at 285° gave only *N*-carbomethoxy-1,2-dihydropyridine. Studies on the 6,6-dideuterio derivative **17** and the results of an attempt to prepare the *N*-methyl derivative **25** suggest that a dipolar species analogous to **15** is involved in the thermal reactions of this ring system. In contrast, the thermal rearrangement of *N*-carbomethoxy-6-carbethoxy-2-azabicyclo[3.1.0]hex-3-ene gave dihydropyridine **30**. This result is not consistent with a dipole intermediate but is consistent with **5b** undergoing a cycloreversion to give **29** which cyclizes to the observed dihydropyridine. The thermal rearrangements of the 2-azabicyclo[3.1.0]hex-3-ene ring systems are discussed in terms of the ability of substituents at position 6 to interact with one of the highest occupied molecular orbitals of the cyclopropane ring.

Heterocycles can be related to carbocycles by either substituting unsaturated nitrogen (–N=) for unsaturated carbon (–CH=) or by substituting saturated nitrogen (–NH–) for saturated carbon ($–CH_2–$). Paquette and coworkers have, in recent years, synthesized the aza analogs of cyclooctatetraene, semibullvalene, and bullvalene which are representatives of the former type of substitution.[2] They have observed that these molecules display some fascinating chemistry and their studies have given chemists a more complete understanding of the chemical reactivity of unsaturated heterocyclic molecules.

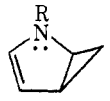
Substitution of saturated nitrogen (–NH–) for a saturated carbon ($–CH_2–$) is particularly interesting since the lone pair of electrons on nitrogen can interact with unsaturated centers. Heterocycles of this latter type have the ability to be more extensively conjugated and contain two additional π electrons compared to the analogous carbocyclic system.

The 2-azabicyclo[3.1.0]hex-3-ene ring system (**1**) can be related to bicyclo[3.1.0]hex-2-ene (**2**) in the above

(1) Portions of this work have been published in preliminary form: F. W. Fowler, *Angew. Chem., Int. Ed. Engl.*, **10**, 135 (1971); *Chem. Commun.*, 1359 (1969).

(2) For a recent review of this work see L. A. Paquette, *Angew. Chem., Int. Ed. Engl.*, **10**, 11 (1971).

described manner. A reasonable synthesis to this ring system appeared to be the addition of a carbene or



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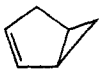
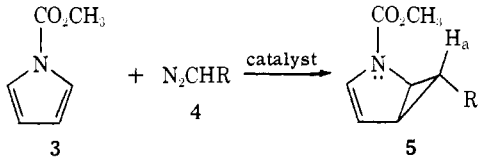


2

carbenoid to pyrrole. However, previous studies have shown that the copper-catalyzed decomposition of diazo compounds in the presence of pyrrole derivatives gave only substitution rather than addition products.[3] This result is not surprising and is related to the known property of pyrroles to behave as aromatic molecules rather than dienes. For example, it is well known that pyrrole, unlike furan, does not behave as a diene in the Diels–Alder reaction.[4] However, it is known that pyrroles with strong electron-withdrawing groups on nitrogen behave anomalously. *N*-Carbomethoxypyrrole does react with dienophiles to give Diels–Alder adducts.[5] Apparently, the carbonyl group interacts with the pair of electrons on nitrogen causing the pyrrole nucleus to behave more as a diene.

Following the suggestions of this earlier work, we have observed that the 2-azabicyclo[3.1.0]hex-3-ene ring system can be prepared by the decomposition of diazo compounds in the presence of *N*-carbomethoxypyrrole. These structures are based on their spectral data and elemental analysis (see Experimental Section).

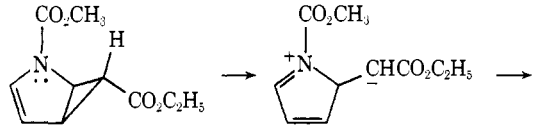


3 + N_2CHR (4) $\xrightarrow{\text{catalyst}}$ 5

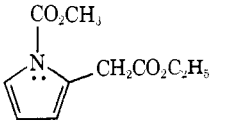
a, R = H
b, R = $CO_2C_2H_5$
c, R = *p*-$CH_3C_6H_4$

The assignment of endo stereochemistry to the cyclopropyl hydrogen at position H_a in **5b** and **c** is in accord with the known magnetic shielding effect of the double bond in the carbocyclic system.[6] This results in an upfield shift of this hydrogen in the nmr spectrum.

Unlike 2-azabicyclo[3.1.0]hex-3-ene **5a**, attempts to distill **5b** in the presence of the catalyst (CuBr) result



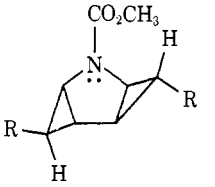
5b



6

in rearrangement to the 2-substituted pyrrole **6**. This result can be explained by postulating a zwitterionic structure which in the case of **5b** can be stabilized by the carbethoxy substituent.[7]

In addition to the monoadducts, diazo compounds **4a** and **4b** also gave smaller amounts of the *anti*-2-azatricyclo[4.1.0.0.^{3,5}]heptane ring, system **7**. Trace



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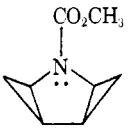


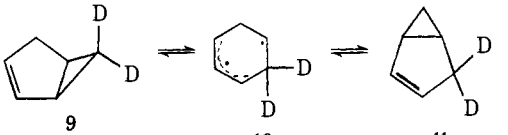
8

a, R = H
b, R = $CO_2C_2H_5$

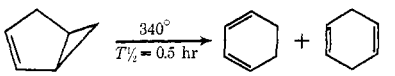
quantities of the *syn*-2-azatricyclo[4.1.0.0^{3,5}]heptane ring, system **8**, could also be isolated when diazomethane was used.

Since the use of diazomethane in the preparation of **5a** is a very hazardous procedure, we were led to try a more convenient carbenoid. *N*-Carbomethoxypyrrole is unreactive toward the Simmons–Smith reagent. Furakawa, *et al.*, have recently reported that a carbenoid useful for cyclopropane synthesis can be prepared from diethylzinc and methylene iodide.[8] Their data indicate that this is a more reactive species than the Simmons–Smith reagent. We have found that it can be used for the preparation of *N*-carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene from *N*-carbomethoxypyrrole.

The analogous carbocycle, bicyclo[3.1.0]hex-2-ene, is known to display interesting thermal rearrangements. At 255° it undergoes a degenerate vinylcyclopropane rearrangement[9] and at higher temperatures it isomerizes to a mixture of 1,3- and 1,4-cyclohexadienes.[10] These are formed in the ratio expected from their relative thermodynamic stabilities. The allylically stabilized diradical has been postulated as an intermediate in these reactions.[11]



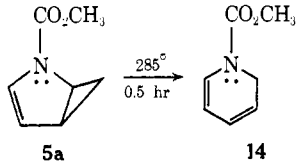
9 ⇌ 10 ⇌ 11



2 → 12 + 13

Heating **5a** in the gas phase at 285° for 0.5 hr results in the 1,2-dihydropyridine as the only detectable compound. Although this result is superficially similar to the carbocycle, three distinct differences are apparent. First, the temperature required to bring about the rearrangement is considerably lower for the heterocycle. The isomerization of the heterocycle is complete within

(3) C. W. Rees and C. E. Smithen, *Advan. Heterocycl. Chem.*, 3, 57 (1964).
(4) R. C. Bansal, A. W. McCulloch, and A. G. McInnes, *Can. J. Chem.*, 47, 2391 (1969), and references cited therein.
(5) N. W. Gabel, *J. Org. Chem.*, 27, 301 (1962).
(6) J. Warkentin, E. Singleton, and J. F. Edgar, *Can. J. Chem.*, 43, 3456 (1965).
(7) G. Cauquis, B. Divisia, and G. Reverdy, *Bull. Soc. Chim. Fr.*, 3031 (1971).
(8) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, 24, 53 (1968).
(9) W. von E. Doering and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, 2, 115 (1963).
(10) R. J. Ellis and H. M. Frey, *J. Chem. Soc. A*, 553 (1966).
(11) For a discussion on whether the diradical is an intermediate or a transition state see: M. R. Willcott and V. H. Cargle, *J. Amer. Chem. Soc.*, 91, 4310 (1969), and references cited therein.

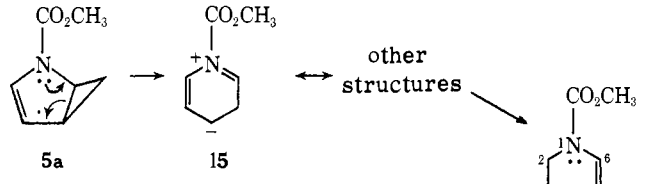


5a 14

0.5 hr at 285° whereas the carbocycle has a half-life of 0.5 hr at 340°. Secondly, lowering the temperature to 240° results in only incomplete conversion to dihydropyridine. None of the isomeric aziridine, the product of a vinylcyclopropane rearrangement, could be detected. Finally, none of the presumably more stable 1,4-dihydropyridine is formed.[12]

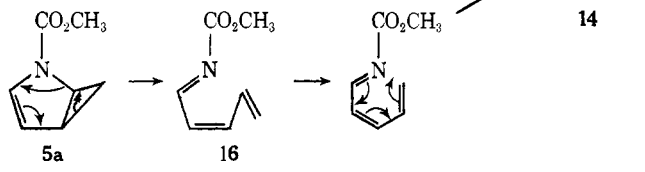
Two reasonable and distinct mechanisms can be postulated for the thermal isomerization of **5a**. It could ring expand to dipole **15** which can then undergo a hydrogen shift to give the dihydropyridine **14**. Alternatively, **5a** could undergo a $2_\pi + 4_\pi$ cycloreversion to give the acyclic imine **16** which could cyclize to the dihydropyridine **14**.[13] This mechanism was recently proposed for the thermal rearrangement of a highly substituted 2-azabicyclo[3.1.0]hex-3-ene structure.[14]

Mechanism I



5a 15 14

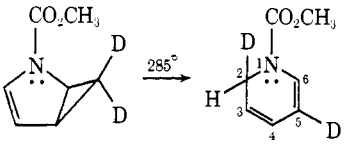
Mechanism II



5a 16

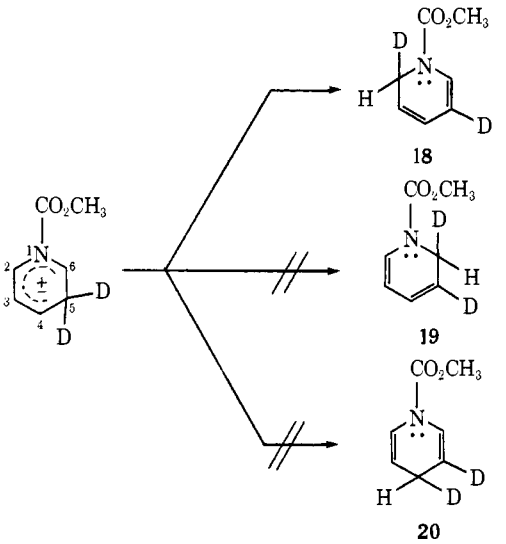
These two mechanisms should, in principle, be distinguishable by labeling **5a** with deuterium at position 6. If mechanism I is operative then deuterium will be incorporated in **14** at positions 2 (or 6) and 5 depending upon whether a hydrogen shift in dipole **15** occurs from position 5 to 2 or 6. If mechanism II is correct, then deuterium will only be incorporated in position 2 of dihydropyridine **14**.

The prerequisite deuterium labeled compound was prepared using the carbenoid derived from methylene-d_2 iodide and diethylzinc. Pyrolysis of **17** gave a product whose nmr spectrum is only consistent with dihydropyridine **18**. The upfield olefinic hydrogen at position 5 normally present in **14** is completely absent and the nmr integration shows the presence of only one hydrogen at position 2. Other features of the nmr spectrum consistent with the above assignment are the appearance of the hydrogen at postion 6 as a broad singlet and the hydrogens at positions 3 and 4 appearing as an AB system with the upfield portion further coupled (see Experimental Section).



17 18

There are potentially two 1,2-dihydropyridines, **18** and **19**, that could be produced from the dideutero dipole. This dipole is electronically analogous to cycloheptatriene and a hydrogen shift from position 5 to position 6 or 4 to give **19** or **20** is electronically analogous to a 1,7-hydrogen shift in cycloheptatriene.[15] A 1,7-hydrogen shift is forbidden from orbital symmetry arguments.[16] Dihydropyridine **19** and the presumably more stable 1,4-dihydropyridine **20** are not formed. Only the 1,2-dihydropyridine **18** is observed. This is the dihydropyridine that would result by a hydrogen shift from position 5 to position 2. This is analogous to a 1,5-hydrogen shift in cycloheptatriene and is allowed from orbital symmetry considerations.

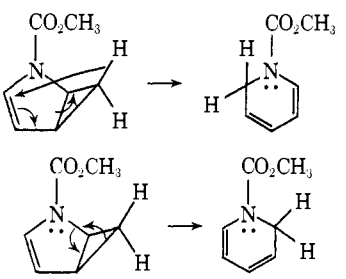


18 19 20

The assumption of a dipole intermediate (mechanism I) adequately rationalizes the differences in reactivity between the carbocycle **2** and the heterocycle **1**. The more facile thermal rearrangement of the heterocycle as compared to the carbocycle is explicable in terms

(12) We have recently observed that the *N*-methyldihydropyridines can be equilibrated using strong base, the 1,4-dihydropyridine being the more stable isomer.

(13) Mechanisms I and II could be concerted or nonconcerted processes. For simplicity, we have considered these mechanisms in terms of discrete steps. Mechanism I could also be concerted. The hydrogen shift could occur simultaneously with the cyclopropane ring opening. Mechanism II could also be represented as a concerted reaction. The orbital symmetry allowed process would be a 1,3-sigmatropic shift with inversion at C-6.



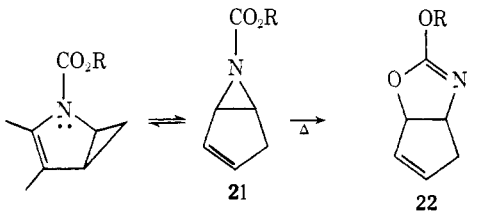
(14) J. F. Biellmann and M. P. Goeldner, *Tetrahedron*, 27, 2957 (1971).

(15) R. W. Murray and M. L. Kaplan, *J. Amer. Chem. Soc.*, **88**, 3527 (1966).

(16) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag-Chemie, Weinheim/Bergstr., Germany, 1970.

of greater stability, with respect to the ground state, being associated with the more extensively delocalized heterocyclic intermediate **15** compared to the analogous carbocyclic diradical **10**.

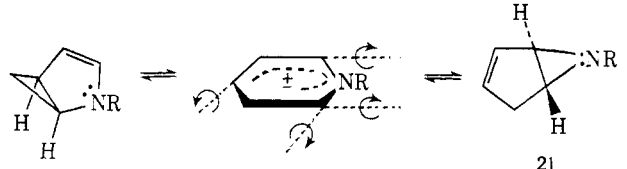
Since the previous results indicate that the activation energy for formation of the intermediate in the vinylcyclopropane rearrangement is lower in the case of the heterocycle than the analogous carbocycle, the absence of the aziridine **21** is interesting. It could



21 22

be argued that the aziridine **21** is less stable than the isomeric cyclopropane and its equilibrium concentration is too small to detect. We do not believe this explanation is correct. Aziridine **21** is probably never being formed. Lwowski has shown that the pyrolysis of an analogous aziridine (R = C_2H_5 rather than CH_3) gives only the oxazoline and not the analogous dihydropyridine or cyclopropane.[17] If the aziridine was formed in our system we believe we should observe the oxazoline.

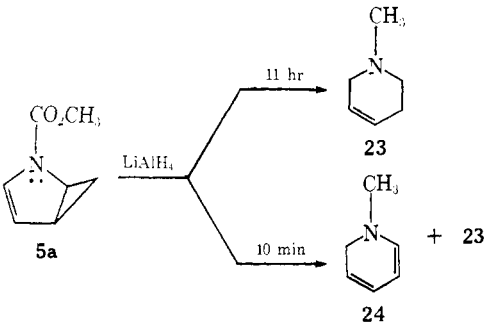
The interconversion of the dipole **15** with the cyclopropane **5a** involves six π electrons and is thermally allowed only if it occurs in a disrotatory fashion. However, the interconversion of the dipole with the aziridine involves four electrons and is thermally allowed if it occurs in a conrotatory fashion. Conrotatory closure of dipole **15** would produce a trans fused aziridine which would be expected to be very unstable. Also, disrotatory ring closure of dipole **15** to the cis fused aziridine would be a violation of orbital symmetry considerations and should be unfavorable as compared to the allowed process leading to the cyclopropane.



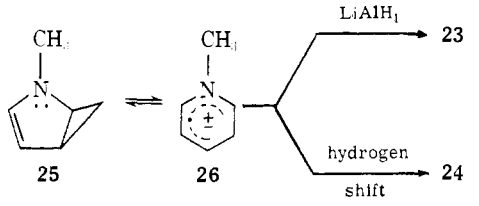
5a, R = CO_2CH_3 15 21

The previous discussion clearly indicates that the presence of the lone pair of electrons on nitrogen alters considerably the chemistry of heterocycle **5a** compared to carbocycle **2**. Since the carbomethoxy group decreases the availability of the lone pair on nitrogen it would be anticipated that the presence of an alkyl group or hydrogen on nitrogen would enhance the reactivity of the 2-azabicyclo[3.1.0]hex-3-ene ring system.

An attempt to reduce carbamate **5a** to the *N*-methyl derivative with lithium aluminum hydride for 11 hr gave only the tetrahydropyridine **23**. If the reduction was carried out for only 10 min then a mixture of the *N*-methyl-1,2-dihydropyridine **24** and **23** is produced. We have further shown that dihydropyridine **24** is not reduced to tetrahydropyridine **23** under these reaction conditions. These results in conjunction with the previously observed thermal behavior of the 2-azabicyclo-



[3.1.0]hex-3-ene ring system suggest that the carbamate function is initially reduced to the *N*-methyl derivative **25**. Since the lone pair of electrons on nitrogen can interact very strongly with the π system it would not be surprising if **25** would ring open rapidly to dipole **26** even at low temperatures. In the absence of lithium aluminum hydride (short reaction time) dipole **26** can slowly undergo a hydrogen shift during the work-up to give dihydropyridine **24**. However, if lithium aluminum hydride is present then dipole **26** or even **25** can be further reduced to the tetrahydropyridine **23**.



The above result suggests that the 2-azabicyclo[3.1.0]-hex-3-ene ring system will not be stable at room temperature unless there are electron-withdrawing groups present on the nitrogen atom. This is in contrast to the sulfur and oxygen systems which are known and stable at room temperature.[18] These results further indicate that the lone pair on nitrogen can interact more effectively with unsaturated carbon than either oxygen or sulfur.

The thermal rearrangement of **5b** follows an interesting course. Heating **5b** *under the same conditions as* **5a** gave a product to which we have assigned structure **30**.

The nmr spectrum ($CDCl_3$) at room temperature was very complex. In addition to the absorptions for the ethyl group it showed a multiplet at τ 2.87–3.27 (1 H) and 3.77–4.98 (4 H). The methoxyl absorption appeared as two unequally intense singlets. If the nmr spectrum was taken in DMSO-d_6 at 100° then the low-field multiplet collapses into a doublet (τ 3.28, J = 8.0 Hz). Another doublet (J = 5.5 Hz) appears at τ 4.78 superimposed on the multiplet. We attribute these absorptions to hydrogens at positions 2 and 3. The methoxy absorptions also collapse into a singlet.

The temperature dependence of this spectrum is undoubtedly due to hindered rotation of the carbamate function. We have previously observed this phenomenon on **5a**[1] and hindered rotation has also been observed in related carbamates.[19]

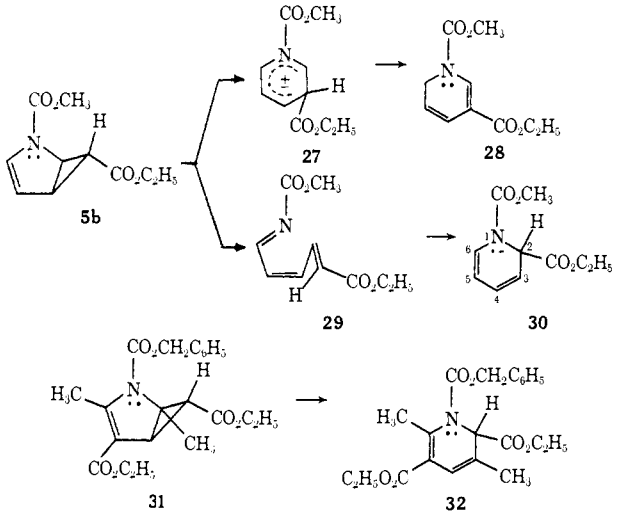
Dihydropyridine **30** is inconsistent with mechanism I which would have produced dihydropyridine **28**.

(17) A. Mishra, S. N. Rice, and W. Lwowski, *J. Org. Chem.*, 33, 481 (1968).

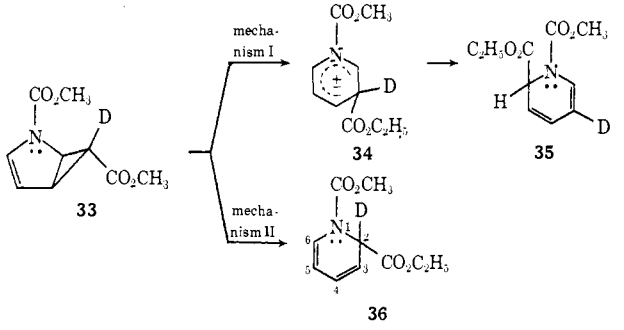
(18) E. Müller, H. Kessler, H. Fricke, and H. Suhr, *Tetrahedron Lett.*, 16, 1047 (1963).

(19) K. Hojo and S. Masamune, *J. Amer. Chem. Soc.*, **92**, 6690 (1970).

However, this structure is consistent with mechanism II and with the product that Biellmann and Goeldner[14] obtained from the pyrolysis of homopyrrole **31**. This 2-azabicyclo[3.1.0]hex-3-ene also has a carbethoxy substituent at position 6.



Dihydropyridine **30** would be produced if a carbethoxy rather than a hydrogen shift occurred from dipole **27**. However, this possibility was ruled out by preparing the labeled dihydropyridine **33** and subjecting it to the same reaction conditions. Dihydropyridine **35** would be produced if a carbethoxy shift was



occurring from dipole **34**. The nmr spectrum shows no deuterium incorporation β to the nitrogen. The nmr spectrum does show the absence of the doublet centered at τ 4.78 (hydrogen at carbon 2 in **30**) and the appearance of the hydrogen at carbon 3 as a doublet. We believe these data are only consistent with dihydropyridine **36**.

This dramatic effect of the carbethoxy group on the mechanism of the thermal rearrangement of the 2-azabicyclo[3.1.0]hex-3-ene ring system can be understood in terms of recent discussions of substituent effects on the cyclopropane ring.[20] If there is a π-electron acceptor, such as a carbonyl group, attached to the cyclopropane then the lowest unoccupied orbital of this π-electron acceptor can interact with the antisymmetric component of the occupied degenerate Walsh orbital pair in cyclopropane. This interaction removes electron density from the cyclopropane ring and therefore it weakens the bonding between positions 1 and 6 and 5 and 6 but strengthens the bond between positions 1 and 5. Since the carbethoxy group is a π-electron acceptor, the 6-carbethoxy substituted 2-azabicyclo[3.1.0]hex-3-ene (**5b**) should have a stronger 1–5 bond than the hydrogen-substituted structure **5a** and thus ring opening to the dipole should be more favorable for **5a** than **5b**. Ring opening of the 2-azabicyclo[3.1.0]hex-3-ene ring system to the acyclic structure **38** requires breaking of the 5–6 bond. This bond should be weaker in **5b** as compared to **5a** and ring opening to give **38** should be more favorable for **5b** than for **5a**. We believe that the combination of the above two effects is responsible for the dramatic substituent effect on the thermal rearrangement of the 2-azabicyclo[3.1.0]hex-3-ene ring system. The magnitude and precise nature of this effect will have to await further study.

Although our studies have been carried out on a heterocycle the results certainly have implications that are applicable to the analogous carbocycle (bicyclo[3.1.0]hex-2-ene). It is probable that thermal rearrangement of the parent system to 1,3- and 1,4-cyclohexadiene can be interpreted in terms of a diradical.[10] However, this work indicates that the thermal rearrangements of bicyclo[3.1.0]hex-2-enes with electron-withdrawing substituents at the 6 position, such as 6,6-dicarbomethoxybicyclo[3.1.0]hex-3-enyl acetate,[21] are proceeding through 2 + 4 cycloreversions.

Experimental Section[22]

Reaction of *N*-Carbomethoxypyrrole with Diazomethane. Essentially the same procedure was used as has previously been reported by Doering and Roth[23] except that the diazomethane was generated by adding 40 g of Diazald to a solution of 50 ml of 35% KOH and 100 ml of 2-(2-methoxyethoxy)ethanol. Passing the diazomethane in N_2 through 5.00 g of *N*-carbomethoxypyrrole and 0.60 g of CuCl produced a 39% yield of *N*-carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene (**5a**): nmr ($CDCl_3$) τ 3.60 (s, br, $W_{1/2}$ = 9 Hz, 1 H), 4.53–4.70 (m, 1 H), 5.83–6.28 (m, 1 H), 6.22 (s, 3 H), 7.75–8.00 (m, 1 H), 8.98–9.37 (m, 1 H), and 9.83–10.08 (m, 1 H); ir (neat) 3086 (olefinic and cyclopropyl hydrogens), 1705 (C=O), and 1592 cm^{-1} (C=C); mass spectrum (70 eV) *m/e* (rel intensity) 139 (35), 138 (65), 94 (100), 80 (58), 59 (50), and 27 (75). The analytical sample was purified by preparative vpc (on a 5 ft × 0.25 in. column of 3% SE-30 on Varport 30) at 100°, 50 ml of He/min, and retention time = 3.38 min.

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.69; H, 6.45; N, 10.12.

A 12% yield of *N*-carbomethoxy-2-azatricyclo[3.1.0.0^{3,5}]heptane (**7a**) was also obtained: nmr ($CDCl_3$) τ 6.25 (s, 3 H), 6.95 (s, br, $W_{1/2}$ = 15 Hz, 2 H), 8.07–8.47 (m, 2 H), and 9.03–9.47 (m, 4 H); ir (neat) 3095 (cyclopropyl hydrogens) and 1705 cm^{-1} (C=O). The analytical sample was purified by preparative vpc at 100°, 50 ml of He/min, and retention time = 5.38 min (5 ft × 0.25 in. column of 3% SE-30 on Varport 30).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24. Found: C, 62.50; H, 7.17.

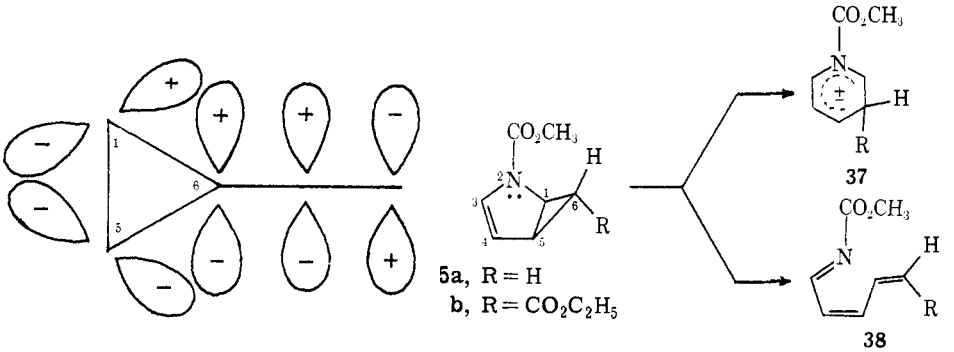
Larger quantities of the above products could be purified by combining several runs and distilling the mixture through an 8-in. spinning band column. The fraction bp 86–89° (13 Torr) proved to be *N*-carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene (**5a**) and the fraction bp 105–110° (13 Torr) proved to be mainly *anti*-*N*-carbomethoxy-2-azatricyclo[4.1.0.0^{3,5}]heptane (**7a**) contaminated with a small amount of *syn*-*N*-carbomethoxy-2-azatricyclo[4.1.0.0^{3,5}]heptane (**8**). These were separated by preparative vpc at 100°, 50 ml of He/min, and retention time = 6.6 (anti) and 8.2 min (syn); mp 70–72° from hexane. The nmr spectrum ($CDCl_3$) of the syn isomer showed τ 6.28 (s, 3 H), 6.17–6.60 (m, 2 H), 8.00–8.37 (m, 2 H), and 9.17–

(20) R. Hoffmann, *Tetrahedron Lett.*, 2907 (1970); see also H. Gunther, *ibid.*, 5173 (1970); M. J. S. Dewar and D. H. Lo, *J. Amer. Chem. Soc.*, **93**, 7201 (1971).

(21) J. A. Berson and R. C. Solomon, *ibid.*, **93**, 4620 (1971).

(22) Melting points are uncorrected. The microanalyses were performed by either Galbraith Laboratories, Knoxville, Tenn., or by A. Bernhardt Microanalytisches Laboratorium, West Germany. The infrared spectra were recorded using a Perkin-Elmer Model 257. The nmr spectra were recorded using a Varian A-60 nmr spectrophotometer. The mass spectra were recorded using a Hitachi Perkin-Elmer RMU7.

(23) W. von Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).



9.58 (m, 4 H); ir (KBr) 3098, 3078 (cyclopropyl hydrogens), and 1685 cm^{-1} (C=O).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.84; H, 7.26; N, 9.00.

Reaction of *N*-Carbomethoxypyrrole with Ethyl Diazoacetate. To 8.40 g of *N*-carbomethoxypyrrole and 0.40 g of CuBr at 90–95° was added 7.76 g of ethyl diazoacetate **4b** over 45 min. The reaction mixture stood at 90–95° for an additional 30 min. Unreacted pyrrole was removed by distillation, bp 69° (18 Torr). Distillation of the residue gave 2.4 g (17%) of *N*-carbomethoxy-6-carbethoxy-2-azabicyclo[3.1.0]hex-3-ene (**5b**): bp 104–107° (1.0 Torr); nmr (CCl_4) τ 3.47 (d, br, 1 H, J = 4.5 Hz), 4.52–4.70 (m, 1 H), 5.90 (q, J = 7.5 Hz, 2 H, OCH_2CH_3), 5.57–5.88 (m, 1 H), 6.22 (s, 3 H, OCH_3), 7.12–7.38 (m, 1 H), 8.73 (t, J = 7.5 Hz, 3 H, OCH_2CH_3), and 9.08 (t, 1 H, J = 2.0 Hz); ir (neat) 3120, 3060 (vinyl and cyclopropyl hydrogens), 1720 (C=O), and 1590 (C=C) cm^{-1}; mass spectrum (70 eV) *m/e* (relative intensity) 211 (12), 138 (100), 94 (76), 59 (57), and 52 (38).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20. Found: C, 56.59; H, 6.23.

A 5% yield of *N*-carbomethoxy-4,7-dicarbethoxy-2-azatricyclo-[4.1.0.0^{3,5}]heptane (**7b**) was obtained by passing the residue from the distillation through 90% of Fischer activity 1 Al_2O_3 with 200 ml of ether. Removal of the ether gave a yellow oil which crystallized on standing. Recrystallization from pentane–ether gave the analytical sample: mp 97–98°; nmr (CCl_4) τ 5.83 (q, 4 H, J = 7.5 Hz, OCH_2CH_3), 6.28 (s, 3 H, OCH_3), 6.60 (d, br, 2 H, J = 7 Hz), 7.52–7.78 (m, 2 H), 8.17–8.30 (m, 2 H), and 8.72 (t, 6 H, J = 7.5 Hz, OCH_2CH_3); ir (KBr) 3090, 3063 (cyclopropyl hydrogens), and 1712 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44. Found: C, 56.36; H, 6.21.

6-(*p*-Methylphenyl)-*N*-carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene (5c). The procedure was similar to that previously reported by Goh, Closs, and Closs.[24] To 2.25 g of $ZnBr_2$ was added 1.84 g of *N*-carbomethoxypyrrole and 3 ml of pentane. The reaction was cooled in an acetone–ice cold bath and 1.92 g of *p*-tolyldiazomethane was added cautiously over 15 min. The reaction was then filtered and the solvent removed *in vacuo* to give 4.49 g of an orange oil. Nmr analysis indicates this mixture contains 10% of **5c**. This was isolated using preparative thin-layer chromatography (20 cm × 20 cm × 1.5 mm silica gel) and eluting with 10% ether–benzene (v/v), R_f = 0.5): mp 102.0–102.5° (from ether–pentane); nmr ($CDCl_3$) τ 3.18 (center of AB, 4 H, aromatic), 3.45–3.72 (m, 1 H), 4.51–4.70 (m, 1 H), 5.79–6.17 (m, 1 H), 6.33 (s, 3 H), 7.43–7.72 (m, 1 H), 7.15 (s, 3 H), and 8.58–8.75 (m, 1 H); ir (CCl_4) 1714 (C=O) and 1587 cm^{-1} (C=C).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 72.99; H, 6.66. Found: C, 73.33; H, 6.59.

Reaction of *N*-Carbomethoxypyrrole with Diethylzinc and Methylene-d_2 Iodide. To a deoxygenated 50-ml round-bottomed flask fitted with a serum cap, condenser, magnetic stirrer, and ice bath was added 2.0 ml (0.0191 mol) of diethylzinc. To this was added a degassed mixture of 7.776 g (0.0288 mol) of methylene-d_2 iodide and 9.503 g (0.0762 mol) of *N*-carbomethoxypyrrole through the serum cap over a period of 5 min. The exothermicity of the addition was determined by the rate of bubbling in an oil bubbler tube. After 15 min the ice bath was removed, while stirring and inert gas flow continued. After 4 days the reaction mixture was poured into 50 ml of 1:1 ether–water. The layers were separated and the water layer is washed twice with ether, the ether layers being combined. The organic phase was dried with $MgSO_4$ and filtered, and ether removed *in vacuo*. The reaction mixture was then distilled (room temperature (0.05 mm)) and then further purified by glc (10 ft, 5% SE-30 on ABS 50–60, column temperature 130°). Yields (based on $ZnEt_2$) by glc triangulation are, *N*-carbomethoxy-6,6-dideuterio-2-azabicyclo[3.1.0]hex-3-ene (**17**), 45%, nmr (neat) τ 3.77 (d, br, 1 H, J = 4.0 Hz), 4.69–4.88 (m, 1 H), 6.23 (d, br, 1 H, J = 6 Hz), 6.40 (s, 3 H), 7.98 (d of d, br, 1 H, J = 6 Hz, J' = 2.5 Hz); *N*-carbomethoxy-α-dideuteriomethylpyrrole, 35%, nmr ($CDCl_3$) τ 2.71–2.89 (m, 1 H), 3.81–4.15 (m, 2 H), 6.12 (s, 3 H), 7.60 (s, br, 1 H); *N*-carbomethoxy-4,4,7,7-tetradeuterio-2-azatricyclo[4.1.0.0^{3,5}]heptane, trace amounts, nmr ($CDCl_3$, room temperature) τ 6.34 (s, 3 H), 6.22–7.20 (m, 2 H), 8.33 (d, 2 H, J = 6.0 Hz).

Reaction of *N*-Carbomethoxypyrrole with Diethylzinc and Methylene Iodide. The procedure followed was analogous to that using methylene-d_2 iodide.

Pyrolysis of *N*-Carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene (5a). To a 314-ml Pyrex tube was added 145 mg of **5a**. The reaction vessel was evacuated (0.5 Torr) and heated to 285° for 0.5 hr. Cooling gave a quantitative yield of *N*-carbomethoxy-1,2-dihydropyridine **14** as an unstable colorless liquid: nmr ($CDCl_3$) τ 3.47 (d, br, J = 7.5 Hz, 1 H), 4.12–4.85 (m, 2 H), 4.88–5.18 (m, 1 H), 5.77 (d of d, J = 3.5 and 2.0 Hz, 2 H), and 6.37 (s, 3 H); ir (neat) 1715 (C=O), 1610, and 1588 cm^{-1} (C=C). The product was further characterized by conversion to a Diels–Alder adduct with *N*-phenylmaleimide: mp (from pentane–ethyl acetate) 130–131°; nmr ($CDCl_3$) τ 2.17–3.00 (m, 5 H), 3.48–3.72 (m, 2 H), 4.57–4.97 (s, br, $w_{1/2}$ = 12 Hz, 1 H), 6.32 (s, 3 H), and 6.45–7.17 (m, 5 H); ir (neat) 1777 and 1700 (C=O) and 1597 cm^{-1} (C=C).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16. Found: C, 65.21; H, 5.33.

Pyrolysis of *N*-Carbomethoxy-6-carbethoxy-2-azabicyclo[3.1.0]-hex-3-ene (5b) with CuBr. A mixture of **5b** (0.122 g) and CuBr (0.01 g) was sealed in an nmr tube and heated for 8 hr at 150°. Nmr analysis shows only ethyl *N*-carbomethoxypyrrole-2-acetate (**6**) which was purified by vpc (SE-30 at 150°): nmr (CCl_4) τ 8.63–8.87 (t, 3 H), 6.22 (s, 2 H), 6.13 (s, 3 H), 5.67–6.10 (m, 2 H), 3.88–3.97 (d, 2 H), 2.72–2.87 (t, 1 H); ir (neat) 1750 (C=O), 1580–1590 (w), 1498 (s), 1445 (vs) cm^{-1} (C=C).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.82; H, 6.36; N, 6.84.

Pyrolysis of *N*-Carbomethoxy-6,6-dideuterio-2-azabicyclo[3.1.0]-hex-3-ene (17). The procedure followed for the pyrolysis of **17** was analogous to that used for **5a**. Cooling gave a quantitative yield of 2,5-dideuterio-*N*-carbomethoxy-1,2-dihydropyridine (**18**): nmr ($CDCl_3$) τ 3.29 (s, br, 1 H), 4.12 (d, 1 H, J = 10.0 Hz), 4.50 (d of d, 1 H, J = 10.0 Hz, J' = 3.5 Hz), 5.57–5.77 (m, br, 1 H), 6.23 (s, 3 H).

Gas Pyrolysis of *N*-Carbomethoxy-6-carbethoxy-2-azabicyclo-[3.1.0]hex-3-ene (5b). To a 314-ml Pyrex tube was added 175 mg of **5b**. The vessel was evacuated (10^{-3} Torr) and heated to 300° for 1 hr. Cooling gave 130 mg (75%) of *N*-carbomethoxy-2-carbethoxy-1,2-dihydropyridine: nmr (DMSO-d_6, 100°, TMS external reference) τ 3.28 (d, J = 8.0 Hz, 1 H), 4.78 (d, J = 5.5 Hz, 1 H), 4.69–5.07 (m, 1 H), 5.99 (q, J = 7.0 Hz, 2 H), 6.40 (s, 3 H), 8.98 (t, J = 7.0 Hz, 3 H); ir (CCl_4) 1747, 1723 (C=O), and 1644 cm^{-1} (C=C).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.86; H, 6.20. Found: C, 56.97; H, 6.41.

Reduction of 5a with $LiAlH_4$. To 500 mg of $LiAlH_4$ in 30 ml of ether cooled in an ice bath was added 475 mg of **5a**. The reaction mixture was allowed to warm to room temperature and stirred for 11 hr. The excess hydride was decomposed by cooling the mixture in an ice bath and cautiously adding 2.5 ml of 20% NaOH. The

(24) S. H. Goh, L. E. Closs, and G. L. Closs, *J. Org. Chem.*, 34, 25 (1969).

mixture was stirred for 0.75 hr and the inorganic salts were filtered. The ethereal solution was dried with $MgSO_4$ and removal of the solvent gave 230 mg of *N*-methyl-1,2,3,6-tetrahydropyridine (**23**): nmr (CCl_4) τ 4.12–4.63 (m, 2 H, CH=CH), 7.08–7.27 (m, 2 H), 7.42–8.02 (m, 4 H), and 7.77 (s, 3 H, NCH_3). The nmr spectrum was identical with that prepared by the $NaBH_4$ reduction of *N*-methylpyridinium iodide.[25]

Initiating a similar reaction as above but shortening the reaction time to 10 min rather than 11 hr led to *ca.* 30% of **23** and 70% of **24** by nmr analysis. An authentic sample of *N*-methyl-1,2-dihydropyridine was prepared by the reduction of *N*-carbomethoxy-1,2-dihydropyridine (**14**)[26] and by the method of Fry.[27]

Preparation of α-Diazoacetic Acid-α-*d* Ethyl Ester. To a round-bottomed flask with magnetic stirrer was added 20.1 g of D_2O, 1.147 g of triethylamine, and 22.8 g of α-diazoacetic acid ethyl ester. The mixture was stirred for 2.5 hr and the organic material was extracted with anhydrous ether. The ether was removed by rotary evaporation and the organic phase was added to 20.7 g of D_2O and 1.14 g of triethylamine and stirring was continued for 3.5 hr, whereupon organic material was reextracted with anhydrous ether, dried over calcium sulfate, removed from the ether by rotary evaporation, and distilled (25° (0.05 mm)) to yield 16.9 g of $N_2CDCO_2C_2H_5$ (98.1% D by nmr).

Reaction of *N*-Carbomethoxypyrrole with α-Diazoacetic Acid-α-*d* Ethyl Ester. The reaction procedure was identical with that using α-diazoacetic acid ethyl ester, yielding a 17% yield of *N*-carbomethoxy-6-carbethoxy-*6-d*-2-azabicyclo[3.1.0]hex-3-ene (**33**): nmr (DMSO-d_6) τ 3.27 (d, J = 4.0 Hz), 4.25–3.25 (m, 1 H), 5.65 (d, J = 7.0 Hz, 1 H), 5.81 (q, J = 7.0 Hz, 2 H), 6.17 (s, 3 H) 7.11 (d of d, J = 7.0 Hz, J' = 3.0 Hz, 1 H), 8.74 (t, J = 7.0 Hz, 3 H).

Pyrolysis of *N*-Carbomethoxy-6-carbethoxy-*6-d*-2-azabicyclo-[3.1.0]hex-3-ene (33). The conditions of pyrolysis were identical with those for **5b** yielding upon cooling *N*-carbomethoxy-2-carbethoxy-*2-d*-1,2-dihydropyridine (**37**): nmr (DMSO-d_6, TMS external reference) τ 3.28 (d, J = 7.5 Hz, 1 H), 3.89–4.23 (m, 1 H), 4.30–4.65 (m, 1 H), 4.64 (d, J = 9.0 Hz, 1 H), 4.71–5.08 (m, 1 H), 5.98 (q, J = 7.0 Hz, 2 H), 6.38 (s, 3 H) 8.97 (t, J = 7.0 Hz, 3 H).

Acknowledgment. Financial support for this work was provided by the National Science Foundation (GP-20099) and the Research Foundation of the State University of New York. We thank Professor Robert Kerber for informative discussions and Dr. David Christman for recording the mass spectra.

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(26) Frank W. Fowler, *J. Org. Chem.*, **37**, 1321 (1972).
(27) E. M. Fry, *ibid.*, **29**, 1647 (1964).

The Total Synthesis of Kasugamycin[1]

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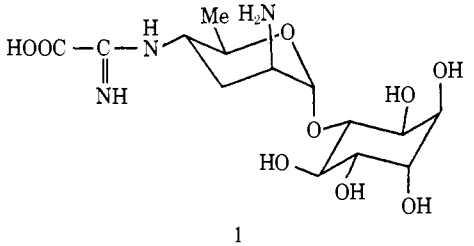
Contribution from the Institute of Microbial Chemistry, Shinagawa-ku, Tokyo, Japan, and Basic Research Laboratories, Toray Industries, Inc., Kamakura, Japan. *Received November 8, 1971*

Abstract: Kasuganobiosamine (**15d**) has stereoselectively been synthesized in ten steps, starting from 3,4-dihydro-6-methyl-2*H*-pyran-2-one (**2**). The key step involves the nitrosyl chloride addition to dihydropyran derivatives, *i.e.*, **2** → **3** and **12** → **13**, showing that the addition reaction is generally useful for the syntheses of the deoxyamino sugar moieties of kasugamycin, spiramycin, and tolypomycin Y. The displacement and resolution of **13** have been carried out by the reaction with 1D-1,2:5,6-di-*O*-isopropylidene-*chiro*-inositol, yielding the product stereochemically conforming with natural kasuganobiosamine (D-**15d**), which is successfully crystallized in a pure state without any other procedure for the separation of the diastereoisomers. The selective α-glycosidation in the synthesis of *dl*-methylkasugaminide (**15c**) has been determined by X-ray crystallographic study.

Kasugamycin (**1**), found in 1965,[4] is an antibiotic produced by *Streptomyces kasugaensis* and is



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useful for the prevention of rice blast, being an ideal agricultural chemical with low toxicity to humans, animals, and plants. A therapeutic effect on *Pseudomonas* infection in humans has also been confirmed.[5]

The structure was established in 1966 by chemical[6] and X-ray crystallographic[7] studies which had led to assignment of the 1D-3-*O*-(2-amino-2,3,4,6-tetradeoxy-4-oxalamidino-α-D-*arabino*-hexopyranosyl)-*chiro*-inositol for kasugamycin.

The structural features characteristic of **1** include the following: (i) the 2-amino group is in an axial orientation, different from the 2-amino groups of other antibiotics such as streptomycin, kanamycin, neomycin, and paromomycin which are oriented equatorially,[8] (ii) a unique group of an amidine carboxylic acid in equatorial orientation, (iii) the presence of the α linkage between the 2-amino 2-deoxysugar residue and D-*chiro*-inositol.

In this paper, we report the stereoselective total synthesis of kasugamycin (**1**). There seem to be two main approaches to the synthesis of the amino sugar moiety of antibiotics. One is to start with carbohydrates

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