modulation and a rf energy of 8996 MHz. The magnetic field was scanned from 1000 to 10 000 G.

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Registry No.—**1**, 161-36-4; **2**, 205-94-7; **3**, 832-80-4; **5**, 118-92-3; **6**, 57762-01-3; **8**, 57762-02-4; **9**, 789-24-2; **20**, 57762-03-5; **23**, 20302-14-1; **25**, 35377-95-8; *o*-dichlorobenzene, 95-50-1; decalin, 91-17-8; *N*-phenylmaleimide, 941-69-5.

References and Notes

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(5) Synthesis and the evidence for the structural assignment of **8** are reported in ref 3b. The structural details and the chemistry of **8** have not been studied as yet in these laboratories. The origin of the thermal stability of **8** is a question of substantial significance.
(6) For summary of progress in synthesis and determination of the properties of benzocyclopropenes see W. E. Billups, W. Y. Chow, and C. V. Smith, *J. Am. Chem. Soc.*, **96**, 1979 (1974); B. Halton, *Chem. Rev.*, **73**, 113 (1973), and references cited therein.
(7) Heating **1** slowly yields a transient red intermediate which might be **7**.
(8) (a) For discussion of the quantum mechanical symmetry aspects of dipolar intermediates which are structurally similar to **11–12**, see M. J. S. Dewar and K. Narayanaswami, *J. Am. Chem. Soc.*, **86**, 2422 (1964). (b) The possibility that **13** may exist as a diradical with different spin moments has been raised in ref 1.
(9) (a) Since only a single intense band is observed in the region scanned, the electronic and spin orbit coupling constants are very small or zero. (b) E. Wasserman, L. C. Snyder, and W. A. Yaeger, *J. Chem. Phys.*, **41**, 1763 (1964).
(10) S. Goldschmidt and K. Renn, *Ber.*, **55**, 628 (1922).
(11) (a) Irradiation of azobenzene in cumene produces **19**. Formation of **19** is believed to occur by abstraction of hydrogen from cumene by electronically excited azobenzene to produce cumyl and *sym*-diphenylhydrazyl radicals. Cumyl radical then attacks azobenzene to give **19**. (b) J. K. S. Wan, L. D. Hess, and J. N. Pitts, Jr., *J. Am. Chem. Soc.*, **86**, 2069 (1964).
(12) Molecular weights were determined with a vapor phase osmometer (Mechrolab 300 series).
(13) (a) Mixtures of **2** and **9** may be conveniently analyzed by integration of their respective methyne C–H NMR bands. (b) Separation of **2** and **9** may be effected by repeated crystallization from 60–90 °C ligroin (**2** is the more soluble) or by chromatography on silica gel (**2** is the more strongly retained).
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Diels–Alder Reactions Involving Heterocyclic Dienophiles. Synthesis of Substituted Hydroquinazolines and 1,3-Diazaspiro[4.5]decadienes

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A direct synthetic route to substituted 2-aminohydroquinazolines **6** (**b, c** and/or **d, f,** and **g**) and 2-amino-1,3-diazaspiro[4.5]-deca-1,7-dien-4-ones **5** (**b, c** and/or **d, e,** and **f**) is described. The key step is a Diels–Alder reaction between heterocyclic dienophiles **2** and **4** and a series of 1,3-dienes. Attempts to prepare **6b** from the readily available methyl orotate–1,3-butadiene adduct **7** resulted in a rearrangement, producing spiral compounds **5a** and **9**. The structure of the hydrobromide salt **12** of amine **5a** was determined by x-ray crystallographic analysis, confirming the structure assignments in the entire series.

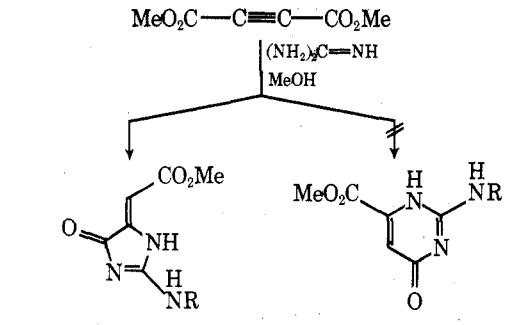
Our interest in the Diels–Alder reaction involving hydropyrimidine dienophiles stems from the possibility of utilizing the resulting hydroquinazoline adducts for the synthesis of biologically interesting analogues of the powerful nerve poison tetrodotoxin.[2] Carbomethoxyisocytosine **4** (Chart I) is an especially attractive candidate for the Diels–Alder reaction and, based on the original work of Ruhemann and Stapleton[3] in the ethyl ester series, appeared to be readily prepared by acetylation of the product, mp >345 °C, obtained by the condensation of dimethyl acetylenedicarboxylate with guanidine carbonate in methanol containing sodium methoxide.

Recently, Katner and Ziege[4] assembled uv evidence and some chemical evidence which seemed to require that the Ruhemann and Stapleton condensation afforded imidazoline **1** rather than isocytosine **3**. Katner and Ziege further showed that the original condensation product could be isomerized by hot sodium hydroxide followed by reesterification to a compound, mp 288–291 °C, to which they assigned the structure **3**. In this present paper we illustrate a new synthetic route to substituted 2-aminohydroquinazolines utilizing acetylated pyrimidone **4** as a dienophile. During the course of this work rearrangements were encountered which eventually required an x-ray crystallographic analysis in order to confirm the structure assignments in this entire series.

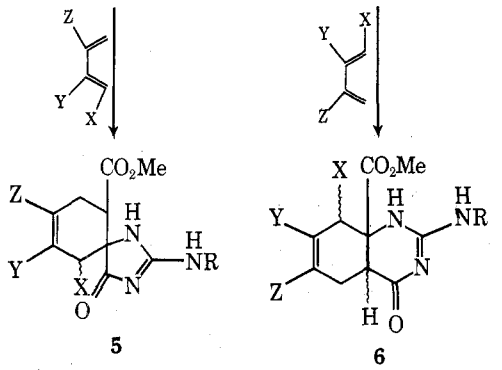
Results and Discussion

Acetylation of Katner and Ziege's mp 288–291 °C material **3** (correct structure assignment, see below) afforded acetyl derivative **4**.[4] Reaction of **4** with excess 1,3-butadiene[5] in THF at 195 °C for 2 days afforded hydroquinazoline **6b** in 9% yield as a 65:35 mixture of isomers at C-10. These substances were clearly (by NMR) isomeric to the butadiene adduct **5b**[2,5] derived in 72% yield from imidazoline **2**. Ammonium hydroxide–MeOH hydrolysis to crystalline **6a** followed by reacety-

Chart I



1, R = H (mp >345 °C) 3, R = H (mp 288-291 °C)
2, R = Ac 4, R = Ac



5 6

a, X = Y = Z = R = H
b, X = Y = Z = H; R = Ac
c, X = Y = H; Z = Me; R = Ac
d, X = Z = H; Y = Me; R = Ac
e, X = OAc; Y = Z = H; R = Ac
f, X = OAc; Y = H; Z = Me; R = Ac
g, X = OAc; Y = Me; Z = H; R = Ac

lation gave a 95:5 crystalline mixture, mp 96–99 °C, of hydroquinazolines **6b.**

Despite the rather low yield in the above Diels–Alder reaction we were encouraged to investigate other more highly substituted dienes since the reaction constituted a direct route to synthetically important 2-aminohydroquinazolines. Isoprene afforded a 64:36 mixture (by NMR) of adducts **6c** and/or **6d** in 20% yield. While we were unable to ascertain the position of the methyl group, thermal and base equilibration studies suggested that these two substances were C-10 isomers of one another. The reaction of isoprene with imidazoline **2,** on the other hand, proceeded much better, affording **5c** and/or **5d** in 79% yield. One pure isomer, mp 191.5–193.5 °C, could be obtained by MeOH–HCl hydrolysis of the mixture to the crystalline amino derivative, mp 245–248 °C, followed by reacetylation.

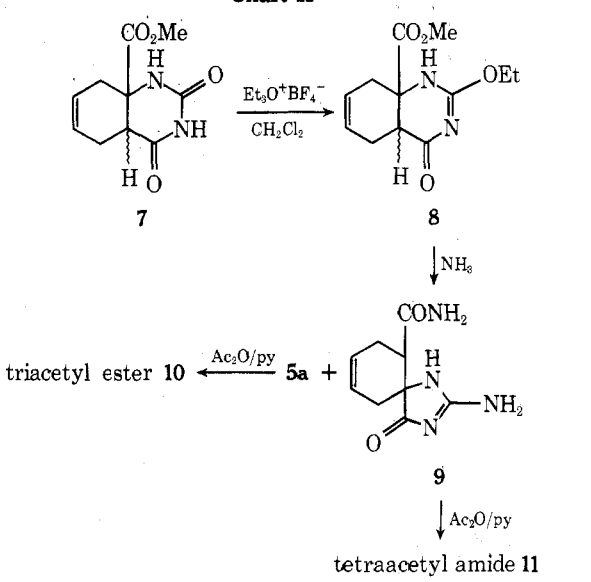
The first oxygenated diene investigated was 1-acetoxy-1,3-butadiene. Reaction with imidazoline **2** afforded a mixture of isomers rich in **5e** in 50% yield. Several recrystallizations were required to produce **5e,** mp 193–200 °C, and the NMR spectrum indicated the presence of the 9ξ-acetoxy isomer in the mother liquors. The orientation of the acetoxy group in this and subsequent oxygenated diene reactions followed from the multiplicity of H-10 in the NMR spectra of both the **5** and the **6** series of adducts (see Experimental Section).

Reasoning that the presence of an additional methyl group on the diene might enhance the regioselectivity of the Diels–Alder reaction we then turned to reactions with 1-acetoxy-3-methyl-1,3-butadiene.[7] With imidazoline **2** a mixture of isomers was produced which afforded **5f,** mp 220–228 °C, in 15% yield after crystallization. The reaction of the diene with pyrimidone **4** was particularly interesting since the resulting adducts **6f** have a substitution pattern amiable toward subsequent elaboration to tetrodotoxin. The Diels–Alder reaction, however, produced only in low yield a mixture of difficultly separable stereoisomers **6f,** though all possessed the correct regioorientation: isomer A, mp 222 °C; isomer B, mp 164–178 °C; isomer C, mp 184–186 °C. Base equilibration studies suggested that isomers A and C differ only in stereochemistry at C-10.

The Diels–Alder reaction between pyrimidone **4** and 1-acetoxy-2-methyl-1,3-butadiene[6] was also studied. Isomer A, mp 139–142 °C (**6g**), was obtained after chromatography as the major isomer in 5% yield, accompanied by lesser amounts of isomer B, mp 178–179 °C. Base equilibration studies suggested that these two substances differed only in stereochemistry at C-10. Small amounts of a third isomer could be detected in some chromatography fractions by NMR, but it was not possible to obtain a pure sample.

In view of the ready availability of hydroquinazoline **7**[2] (Chart II), prepared by a Diels–Alder reaction between 1,3-butadiene and methyl orotate, we sought to convert **7** into the corresponding 2-amino derivative **6a,** a seemingly straightforward task. Treatment of **7** with Meerwein's reagent (triethyloxonium tetrafluoroborate)[8] in dichloromethane gave the crystalline imino ether **8.** Reaction of **8** with ammonia in methanol[8] at 120 °C produced a mixture of ester amine **5a** and amide amine **9,** both of which could be prepared directly from **1** via the sequence acetylation, Diels–Alder reaction with 1,3-butadiene, treatment with ammonia in methanol. Moreover, several other substances, namely **5b, 10,** and **11,** could also be prepared starting with either **1** or methyl orotate adduct **7.**

Chart II

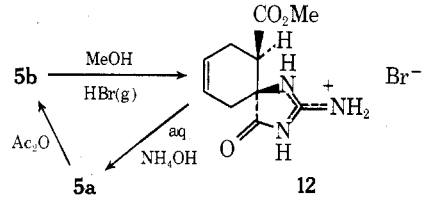


At this juncture it appeared conceivable that heterocycle **1** of mp >345 °C (see above) in fact possessed structure **3,** hence the direct correspondence of the butadiene adduct derived from the mp >345 °C material with the methyl orotate–butadiene adduct **7.** Alternatively, a rearrangement could have occurred at some point in the conversion of **7** into **5a** + **9.** In order to settle this important point unambiguously Diels–Alder adduct **5b,** mp 194–196 °C (**3,** ref 2), was converted into the crystalline amine hydrobromine salt **12** for x-ray crystallographic analysis by treatment with aqueous hydrogen bromide in methanol. Salt **12** afforded amino ester **5a** upon neutralizing a cold aqueous solution of **12** with ammonium hydroxide. Acetylation of **5a** produced in this way gave back starting Diels–Alder adduct **5b.**

Crystals of the hydrobromide salt ($C_{10}H_{14}N_3O_3Br$) were found to be triclinic with a = 6.926 (2), b = 7.780 (2), c =

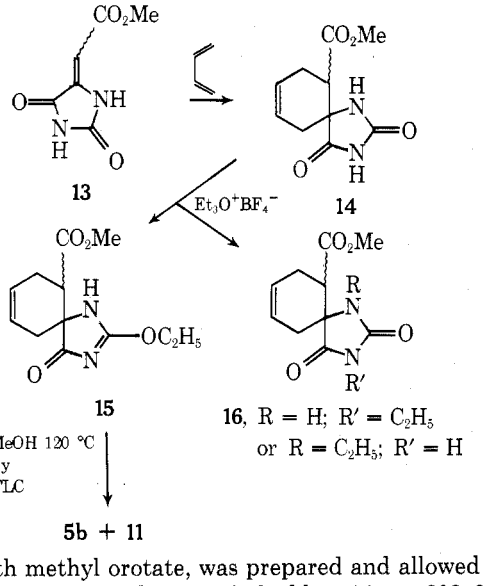
12.654 (5) Å, α = 109.68 (3), β = 94.65 (3), and γ = 93.67 (2)°. The measured crystal density (1.54 g/cm^3) indicated the presence of two molecules per unit cell (calculated density 1.58 g/cm^3). Intensity data (1066 reflections, of which 991 were "observed") out to 2θ = 100° (λ = 1.542 Å) were measured on an automatic diffractometer. The centric space group $P\bar{1}$ was confirmed by the solution of structure in which all nonhydrogen atoms were located by Patterson and Fourier methods. Least-squares refinements of all coordinates and isotropic temperature factors (anisotropic for Br^-) converged to R = 0.07. A final difference map showed only rather diffuse peaks corresponding to most of the hydrogen atoms. However, no attempt was made to determine their coordinates.

The salt was thus shown to possess the spiro structure **12**,



in which the two carbonyl groups are trans to one another about the cyclohexene ring. Each of the nitrogen atoms appears to be involved in a N–H···Br$^-$ hydrogen bond to a different Br$^-$ ion (N–Br$^-$ distances 3.28, 3.37, 3.44 Å).

In view of the x-ray analysis results it is clear that the Ruhemann and Stapleton condensation does in fact produce imidazoline **1**, consistent with Katner and Ziege's[4] conclusions, and that a rearrangement has taken place in our conversion of methyl orotate adduct **7** into **5a**. In order to determine at which stage the rearrangement occurred, the hydantoin **13**,[4]



isomeric with methyl orotate, was prepared and allowed to react with butadiene, producing spiral adduct **14**, mp 208–210 °C, isomeric with methyl orotate adduct **7**,[2] mp 186–188 °C (see Experimental Section). The nonidentity of **7** and **14**[9] rules out the possibility that methyl orotate is in "equilibrium" with hydantoin **13** under the Diels–Alder conditions and that the latter compound is the only one that reacts.

Spiral adduct **14** was then allowed to react with freshly prepared Meerwein's reagent, producing imino ether **15**, mp 141–142 °C (ethoxy quartet at δ 4.56), a substance clearly different from imino ether **8**, mp 109 °C (ethoxy quartet at δ 4.22). The nonidentity of **8** and **15** established[9] that the rearrangement involving **7** → **5a** did not occur at the stage of the reaction of **7** with Meerwein's reagent.

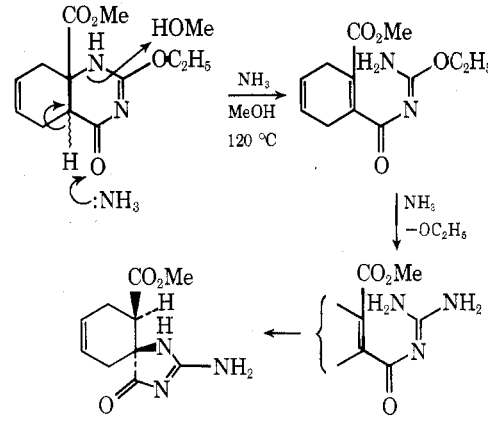
Reaction of **14** with an aged stock solution of Meerwein's reagent in CH_2Cl_2 afforded a crystalline isomer, mp 118–118.5 °C, which was assigned the *N*-ethyl structure **16** based on the appearance of the quartet of the ethyl group at δ 3.62. Rajabelee and Hanessian[10] have also observed N-alkylation in the reaction of Meerwein's reagent with certain nucleosides in CH_2Cl_2.

While **16** proved to be essentially inert to the ammonia–methanol reaction, spiral imino ether **15** led, as expected, to a mixture of spiral adduct **5b** and tetraacetylamide **11** after acetylation and preparative TLC of the reaction mixture.

Since it was conceivable that imino ether **8** reacted with ammonia to produce first the desired hydroquinazoline **6a** which then rearranged under the reaction conditions to spiral derivative **5a**, pure **6a** was separately subjected to the ammonia–methanol treatment. A good yield of starting **6a** together with some of the corresponding amide amine was recovered.

The above experiments, taken as a whole, indicate that the rearrangement **7** → **5a** might occur as shown in Scheme I.[11]

Scheme I



Experimental Section[12]

2-Acetamido-6-carbomethoxy-4(3*H*)-pyrimidone (4). A mixture of 20 g of 2-amino-6-carbomethoxy-4(1*H*)-pyrimidone (**3**), mp 279–281 °C dec (DMF), prepared according to the method of Davies et al.,[13] and Ac_2O (100 ml) was heated at 110 °C for 5 h and then cooled, affording crystals. Recrystallization from CH_3CN yielded 15.32 g (61%) of the title compound as a white, microcrystalline powder: mp 206–207 °C (lit.[4] mp 196–201 °C); NMR δ 2.21 (s, 3, acetyl), 3.92 (s, 3, MeO), 6.92 (s, 1, vinyl); mass spectrum *m/e* 211 (M^+), 183, 169.

Anal. Calcd for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; 19.90. Found: 45.48, H, 4.30; N, 19.71.

2-Acetamido-7- and/or -8-methyl-10β-carbomethoxy-1β,3-diazaspiro[4.5]deca-1,7-dien-4-one (5c and 5d) and 2-Amino-7- or -8-methyl-10β-carbomethoxy-1β,3-diazaspiro[4.5]deca-1,7-dien-4-one (5c or 5d, R = H). A 127-ml pressure reactor fitted with a glass liner was charged with 2.00 g of dienophile **2**, mp ~280 °C, 6.8 g of isoprene, and 42 ml of THF, sealed, and then heated at 140 °C for 65 h. Concentration of the resulting yellow solution and trituration of the gummy residue with hot MeOH gave from the MeOH fraction a yellow solid which was chromatographed over silica gel. Elution with 10% EtOAc in hexane afforded 1.76 g (79%) of a white foam. Two recrystallizations from EtOAc afforded a mixture of **5c** and **5d**: mp 178–182 °C; mass spectrum *m/e* 279 (molecular ion), 220.

Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.13; N, 15.05. Found: C, 55.79; H, 6.09; N, 15.05.

One pure isomer could be obtained as follows. A 580-mg sample, mp 173–180 °C, of the mixture was hydrolyzed by a 18-h reflux period in 30 ml of MeOH containing 0.5 ml of concentrated HCl. The solvent was removed under vacuum, the residue was dissolved in water and centrifuged, and then the solution was basified to pH 8, affording 345 mg (70%) of white crystals, mp 212–240 °C. Three recrystallizations from water afforded a pure sample of 2-amino-7- or -8-methoxy-10β-carbomethoxy-1β,3-diazaspiro[4.5]deca-1,7-dien-7-one as white stars: mp 245–248 °C; NMR (Me_2SO-d_6) δ 1.68 (bs, 3, allylic Me),

2.1–3.0 (m, 5, allylics and H-10), 3.52 (s, 3, MeO), 5.44 (bs, 1, vinyl); mass spectrum *m/e* 237 (M^+), 178.

Anal. Calcd for $C_{11}H_{15}N_3O_3$: C, 55.68; H, 6.37. Found: C, 55.83; H, 6.35.

A 2.17-g sample, mp 220–236 °C, of this last substance was treated with 1.09 g of Ac_2O dissolved in 25 ml of pyridine and allowed to stand at 25 °C for 19 h. Removal of the solvents and recrystallization of the residue from EtOAc afforded 1.67 g (65%) of white crystals, mp 191–193 °C. Recrystallization from EtOAc afforded the analytical specimen as white needles: mp 191.5–193.5 °C; NMR δ 1.78 (bs, 3, allylic Me), 2.1–3.4 (m, 5, allylics and H-10), 2.49 (s, 3, *N*-acetyl), 3.65 (s, 3, MeO), 5.3–5.6 (bs, 1, vinyl); mass spectrum *m/e* 279 (M^+).

Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.13. Found: 56.07; H, 6.06.

2-Acetamido-6ξ-acetoxy-10β-carbomethoxy-1β,3-diazaspiro[4.5]deca-1,7-dien-4-one (5e). The pressure reactor was charged with 2.00 g of dienophile **2**, 50 ml of THF, and 3.00 g of 1-acetoxybuta-1,3-diene,[6,14] sealed, and then heated at 140 °C for 40 h. Evaporation of the solvent, chromatography of the residue over silica gel, and elution with EtOAc–benzene (1:4) afforded 1.5 g (50%) of a foam (*m/e* 323.110; calcd 323.111) rich in **5e**. Three recrystallizations from EtOAc–hexane produced pure **5e** as a white, microcrystalline powder: mp 193–200 °C; NMR δ 2.14 (s, 3, acetoxy), 2.42 (s, 3, *N*-acetyl), 2.4–2.9 (m, 2, allylics), 3.3–3.5 (d of d, 1, H-10), 3.75 (s, 3, MeO), 5.45 (d, J = 2 Hz, 1, H-6), 5.5–6.2 (m, 2, vinyls), 8.7–9.0 (bs, 1, NH).

Anal. Calcd for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.26; N, 13.00. Found: C, 52.31; H, 5.30; N, 13.24.

The structure assignment was confirmed by hydrogenation of a 50-mg sample of **5e** over 30 mg of 5% Pd/C in 10 ml of EtOAc. After filtration, the solvent was evaporated, affording 32 mg of crystalline dihydro derivative: mp 182–186°; mass spectrum *m/e* 325.125 (calcd 325.127). In the NMR spectrum the C-10 proton appeared at δ 3.10 as a triplet whereas the C-6 proton appeared at δ 5.40 as a doublet of doublets.

An NMR spectrum of the original mother liquors of **5e** indicated that some of the 9ξ-acetoxy isomer was also produced in the reaction.

1-Acetoxy-3-methylbuta-1,3-diene.[7] A mixture of 10.43 g of KOAc and 40.1 ml of Ac_2O was refluxed under N_2 for 30 min with stirring. Then 11.774 g of 3-methylcrotonaldehyde[15] was added over a 20-min period and reflux was continued for 30 min after the addition. After cooling to 25 °C an equal volume of water was added, and the mixture was transferred to a separatory funnel and then extracted with hexane (4 × 60 ml). The hexane extract was washed with water, saturated $NaHCO_3$, and brine and dried (Na_2SO_4). Fractional distillation at reduced pressure afforded 12.45 g (71%) of the title compound, bp 66–68.5 °C (29 mm) [lit.[7] bp 69 °C (40 mm)].

2-Acetamido-8-methyl-6ξ-acetoxy-10β-carbomethoxy-1β,3-diazaspiro[4.5]deca-1,7-dien-4-one (5f). The pressure reactor was charged with 2.00 g of dienophile **2**, 50 ml of THF, and 1.0 g of 1-acetoxy-3-methylbuta-1,3-diene, sealed, and heated at 140 °C for 48 h. Evaporation of the solvent, chromatography of the residue over silica gel, and elution with EtOAc–benzene (1:9) afforded 660 mg of a white foam, rich in **5f** but also containing another isomer (by NMR). Crystallization from EtOAc–hexane produced 450 mg (15%) of **5f** as a white, microcrystalline powder: mp 220–228 °C; NMR δ 1.84 (bs, 3, allylic Me), 2.10 (s, 3, acetoxy), 2.45 (s, 3, *N*-acetyl), 2.4–3.0 (m, 2, allylics), 3.4 (d of d, 1, H-10), 3.70 (s, 3, MeO), 5.4–5.6 (m, 2, vinyl and H-6); mass spectrum *m/e* 337.129 (calcd, 337.127), 294, 277, 212.

Anal. Calcd for $C_{15}H_{19}N_3O_6$: C, 53.41; H, 5.63; N, 12.46. Found: C, 53.64; H, 5.73; N, 12.67.

3,4,5,8,9,10ξ-Hexahydro-2-acetamido-9β-carbomethoxyquinazolen-4-one (6b) and 3,4,5,8,9,10ξ-Hexahydro-2-amino-9β-carbomethoxyquinazolen-4-one (6a). The pressure reactor was charged with 2.0 g of dienophile **4**, mp 206–207 °C, 50 ml of THF, and 8 ml of 1,3-butadiene, sealed, and heated at 195 °C for 48 h. Concentration of the resulting yellow solution and trituration of the gummy residue with hot MeOH gave, from the MeOH fraction, 2.9 g of a yellow solid which was chromatographed over silica gel. Crude **6b** (300 mg), obtained by elution with EtOAc–benzene (1:9), was subjected to preparative TLC (acetone–$CHCl_3$, 7:3), affording 200 mg (9%) of **6b** as an oily 65:35 mixture (by NMR) of C-10 isomers: mass spectrum *m/e* 265 (M^+), 250, 233, 211, 206.

A crystalline sample of **6b** was obtained as follows. A solution of 107 mg of the 65:35 mixture, 6 ml of MeOH, and 1 ml of concentrated NH_4OH was refluxed under N_2 for 45 min and then cooled, affording 27 mg (30%) of amino ester **6a** (mostly one isomer): mp 253 °C dec; mass spectrum *m/e* 223 (M^+), 164, 147, 122.

An 11-mg sample of **6a** was acetylated with Ac_2O–pyridine (1:1) producing, after chromatography over silica gel and two recrystallizations from EtOAc–hexane, 5 mg of crystalline **6b** as a 95:5 mixture of isomers: mp 96–99 °C; mass spectrum *m/e* 265.106 (calcd 265.106); NMR (predominant isomer) δ 2.21 (s, acetyl), 2.2–2.8 (m, allylics), 3.04 (m, H-10), 3.70 (s, MeO), 5.72 (m, vinyls).

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.31; H, 5.37; N, 15.92.

3,4,5,8,9,10ξ-Hexahydro-2-ethoxy-9β-carbomethoxyquinazolen-4-one (8). Methyl orotate–butadiene adduct 7[2] (185 mg), mp 186–188 °C (exhibits polymorphism, also mp 201–203 °C[2]), was stirred in CH_2Cl_2 (25 ml) at 10 °C with excess triethyloxonium fluoroborate for 2 days. The solution was then washed with 5% $NaHCO_3$ and brine, and then dried (Na_2SO_4) and evaporated. Chromatography of the residue over silica gel and elution with EtOAc–benzene (1:19) yielded an oil which crystallized from benzene–hexane, affording 139 mg (67%) of analytically pure **8**: mp 109 °C; NMR δ 1.28 (t, $-CH_2CH_3$), 2.0–2.9 (m, allylics), 3.12 (m, H-10), 3.76 (s, MeO), 4.22 (q, $-CH_2CH_3$), 5.64 (m, vinyls); mass spectrum *m/e* 252 (M^+), 198, 193, 170, 165.

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.15; H, 6.43; N, 11.16.

1,4,5,8,9,10ξ-Hexahydro-2-acetamido-6- and/or -7-methyl-9β-carbomethoxyquinazolen-4-one (6c or 6d). The pressure reactor was charged with 2.00 g of dienophile **4**, mp 206–207 °C, 50 ml of THF, and 8 ml of isoprene, sealed, and heated at 195 °C for 48 h (optimum conditions). Evaporation of the solvent, trituration of the residue with MeOH, and evaporation of the MeOH fraction gave 2 g of a residue which was chromatographed over silica gel. Elution with EtOAc–benzene (1:9) afforded 520 mg (20%) of a 64:36 mixture (by NMR) of two of the title compounds: mass spectrum *m/e* 279 (M^+), 264, 225, 220. Thermal and base equilibration studies[16] suggested that these two substances were likely isomeric at C-10. Two recrystallizations from EtOAc–hexane produced an analytical sample of a 9:1 mixture as a white powder: mp 120–130 °C; NMR (major isomer) δ 2.24 (s, 3, *N*-acetyl), 2.3–2.6 (m, 4, allylics), 3.22 (t, 1, H-10), 3.80 (s, 3, MeO), 5.20–5.50 (m, 1, vinyl).

Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.13. Found: C, 56.16; H, 6.34.

1,4,5,8,9,10ξ-Hexahydro-2-acetamido-6-methyl-8ξ-acetoxy-9β-carbomethoxyquinazolen-4-one (6f). The pressure reactor was charged with 2.00 g of dienophile **4**, 42 ml of THF, and 4.0 g of 1-acetoxy-3-methylbuta-1,3-diene, sealed, and heated at 170–190 °C for 48 h. Removal of the solvent left a thick, brown oil which was chromatographed over silica gel (50 g). The column was such that the eluent was continuously distilled and the distillate returned to the top of the column. Continuous elution (1 h) with benzene and then EtOAc–benzene (1:9) (1 h) afforded polymeric material. Continued elution for 3–5 h brought off an isomeric mixture of two adducts. Crystallization from ethyl acetate–hexane afforded 90 mg (2%) of isomer A: mp 222 °C dec; NMR δ 1.78 (bs, allylic Me), 2.10 (s, acetoxy), 2.26 (s, *N*-acetyl), 2.50 (m, allylics), 3.08 (d of d, H-10), 3.70 (s, MeO), 5.58 (m, vinyl), 5.84 (d, H-8); mass spectrum *m/e* 337 (M^+), 322, 294, 278, 262; uv (EtOH) max 254 nm (ε 6440).

Anal. Calcd for $C_{15}H_{19}N_3O_6$: C, 53.40; H, 5.67; N, 12.45. Found: C, 53.64; H, 5.84; N, 12.57.

From rechromatography of the combined mother liquors from several runs, it was possible to isolate crystalline isomer B: mp 164–178 °C; NMR δ 1.58 (s, allylic Me), 2.01 (s, acetoxy), 2.26 (s, *N*-acetyl), 2.40 (m, allylics), 3.20 (d of d, H-10), 3.76 (s, MeO), 5.50 (m, vinyl and H-8); mass spectrum *m/e* 337 (M^+), 322, 294, 278, 262, 254.

Anal. Calcd for $C_{15}H_{19}N_3O_6$: C, 53.40; H, 5.67; N, 12.45. Found: C, 53.20; H, 5.72; N, 12.38.

Continued elution of the first column with ethyl acetate–benzene (3:17) and crystallization from EtOAc–hexane afforded isomer C in low variable yield: mp 184–186 °C; NMR δ 1.76 (s, allylic Me), 2.12 (s, acetoxy), 2.28 (s, *N*-acetyl), 2.3 (m, allylics), 3.26 (t, H-10), 3.76 (s, MeO), 5.31 (m, vinyl), 5.84 (m, H-8); mass spectrum *m/e* 337 (M^+), 322, 293, 278, 262, 254; uv (EtOH) max 254 nm (ε 9600).

Anal. Calcd for $C_{15}H_{19}N_3O_6$: C, 53.40; H, 5.67; N, 12.45. Found: C, 53.41; H, 5.68; N, 12.46.

1,4,5,8,9,10ξ-Hexahydro-2-acetamido-7-methyl-8ξ-acetoxy-9β-carbomethoxyquinazolen-4-one (6g). The pressure reactor was charged with 2.0 g of dienophile **4**, 42 ml of THF, 100 mg of hydroquinone, and 6 ml of 1-acetoxy-2-methylbuta-1,3-diene,[6,14] sealed, and heated at 170–180 °C for 48 h. Two runs were combined and allowed to stand at 25 °C for 1 day, affording 1.04 g, mp 207–210 °C, of starting **4**. The mother liquor was chromatographed over 70 g of silica gel using a solvent recycling column. After a 1-h elution with benzene, a 3.75-h elution with EtOAc–benzene (1:19), and a 2.5-h elution with EtOAc–benzene (1:9), a 3.75-h elution with EtOAc–benzene (3:19) produced 768 mg of foam, which by NMR was predominantly isomer A (R_f 0.6, EtOAc) with some isomer B (R_f 0.5, EtOAc) present. Crystallization from EtOAc–hexane afforded 269 mg (4%) of isomer A, mp 139–144 °C. Mother liquors afforded an additional 44 mg.

Recrystallization from EtOAc–hexane gave the analytical sample: mp 139–142 °C; NMR δ 1.76 (bs, allylic Me), 2.11 (s, acetoxy), 2.21 (s, *N*-acetyl), 2.3–2.7 (m, allylics), 2.97 (d of d, H-10), 3.70 (s, MeO), 5.72 (m, vinyl), 5.88 (bs, H-8); mass spectrum *m/e* 337 (M^+), 322, 294, 278, 261, 219, 218; uv (EtOH) max 255 nm (ε 6460), 207 (14 300).

Anal. Calcd for $C_{15}H_{19}N_3O_6 \cdot \frac{1}{4}$EtOAc: C, 53.48; H, 5.89; N, 11.69. Found: C, 53.82; H, 6.00; 11.65.

The next fraction, eluted for 3.25 h with EtOAc–hexane (1:4), was 634 mg of a solid foam which by TLC was a mixture of isomer A, isomer B, and starting **4**. The mother liquors of the previous fraction, this fraction, and fractions from other runs enriched in isomer B were rechromatographed. Crude crystalline isomer B was thus obtained and further purified by preparative TLC over silica gel. Recrystallization from EtOAc–hexane afforded 28 mg of pure isomer B as rocklike prisms: mp 178–179 °C; NMR δ 1.67 (bs, allylic Me), 2.16 (s, acetoxy), 2.25 (s, *N*-acetyl), 2.2–2.5 (m, allylics), 3.26 (bt, H-10), 3.77 (s, MeO), 5.70 (m, vinyl), 5.87 (bs, H-8).

Anal. Calcd for $C_{15}H_{19}N_3O_6$: C, 53.41; H, 5.68; N, 12.46. Found: C, 53.32; H, 5.73; N, 12.23.

2-Amino-10β-carbamido-1β,3-diazaspiro[4.5]deca-2,7-dien-4-one (9) and Its Tetraacetyl Derivative (11). A. From Ethoxy Compound 8. A solution of 140 mg of ethoxy compound **8** in 40 ml of MeOH saturated with NH_3 was heated in a bomb at 120 °C for 2 h. The solution was then evaporated and the residue was leached with $CHCl_3$ (solution A, see next experiment), leaving 47 mg of a white solid. Crystallization from MeOH gave amide amine **9** as a MeOH solvate: mp 254 °C dec; mass spectrum *m/e* 208 (M^+), 191, 164.

Anal. Calcd for $C_9H_{12}N_4O_2 \cdot \frac{1}{4}$MeOH: C, 51.38; H, 6.06; N, 25.92. Found: C, 51.09; H, 5.71; N, 26.24.

A 23-mg sample of amide amine **9** derived from **8** was stirred for 12 h at 25 °C with 4 ml of Ac_2O–pyridine (1:1) and then evaporated and chromatographed over silica gel. Elution with EtOAc–benzene (1:19) gave a thick oil which crystallized from EtOAc–hexane, affording 13 mg of tetraacetyl amide **11**: mp 173–175 °C; NMR δ 2.36 (s, acetyl), 2.43 (bs, two acetyls), 2.59 (s, acetyl), 2.2–2.8 (m, allylics), 3.50 (d of d, H-10), 5.88 (m, vinyls); mass spectrum *m/e* 376 (M^+), 334, 292, 277.

Anal. Calcd for $C_{17}H_{20}N_4O_6$: C, 54.25; H, 5.36; N, 14.88. Found: C, 54.02; H, 5.36; N, 14.92.

B. From Diels–Alder Adduct 5b. Adduct **5b**, mp 194–196 °C (**3**, ref 2), was converted into amino ester **5a**, mp 258–259 °C (**5**, ref 2), with HCl in MeOH.[2] A 100-mg sample of **5a** was treated in a bomb with 40 ml of MeOH saturated with NH_3 at 120 °C for 10 h. Removal of the solvent and trituration with $CHCl_3$ left a residue which upon crystallization from MeOH–$CHCl_3$ yielded 16 mg of amide amine **9**, mp 251–253 °C dec, identical by mixture melting point with that derived from **8**. Similarly acetylation of **9** derived from **5b** afforded slightly impure tetraacetyl amide **11** identical by NMR with that prepared from **8**.

2-Amino-10β-carbomethoxy-1β,3-diazaspiro[4.5]deca-2,7-dien-4-one (5a) and Its Triacetyl Derivative 10. The $CHCl_3$ solution A, obtained in the previous experiment, was evaporated, affording 58 mg of a mixture of amide amine **9** and ester **5a**. A second crop, 26 mg, mp 255–257 °C dec, was obtained which was mostly ester **5a** (by TLC). While the melting point of this last substance compared well with that of **5a**, mp 258–259 °C, prepared from adduct **5b** (see previous experiment), identity of the two samples of **5a** was best demonstrated by acetylation (Ac_2O–pyridine, 1:1) to the triacetyl derivative **10**. Thus the 26-mg sample of **5a** derived from **8** afforded, after chromatography (silica gel), elution with EtOAc in benzene (1:19), and crystallization from EtOAc–hexane, 16 mg of triacetyl derivative **10**: mp 118–121 °C; NMR δ 2.36 (bs, two acetyls), 2.56 (s, acetyl), 2.0–2.8 (m, allylics), 3.30 (d of d, H-10), 3.66 (s, methoxy), 5.80 (m, vinyls); mass spectrum *m/e* 349 (M^+), 307, 276, 265.

Anal. Calcd for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 54.96; H, 5.54; N, 12.07.

Reaction of Amino Ester 6a with Ammonia in Methanol. A mixture of 40 ml of MeOH saturated with NH_3 and 17 mg of **6a**, mp 251–252 °C, was placed in a pressure reactor and heated at 120 °C for 2.5 h. After removal of the solvent, the residue was treated with 2 ml of Ac_2O–pyridine (1:1) and stirred at 25 °C for 22 h. Removal of the solvent under vacuum afforded 24 mg of a yellow solid which was purified by preparative TLC over silica gel using EtOAc–$CHCl_3$ (1:1). There was obtained 16 mg (79%) of acetyl ester **6b** which crystallized upon standing (mp 96–99 °C dec). The NMR spectrum was identical with that of the predominant isomer in the originally obtained mixture of **6b** (see above).

2-Amino-10β-carbomethoxy-1β,3-diazaspiro[4.5]deca-2,7-dien-4-one Hydrobromide Salt (12). A solution of 284 mg of adduct **5b**, mp 205–206 °C (**3**, ref 1), 25 ml of MeOH, and 1.2 ml of concentrated HBr (48%) was allowed to stand at 25 °C for 3 days and then the volatiles were removed under vacuum. Fresh MeOH was twice added and evaporated and then the residue was dissolved in EtOAc and seeded, affording 197 mg (60%) of chunky prisms: mp 177–178 °C; NMR (D_2O) δ 2.2–3.1 (m, allylics), 3.40 (d of d, H-10), 3.71 (s, MeO), 5.86 (m, vinyls).

Anal. Calcd for $C_{10}H_{14}N_3O_3Br$: C, 39.49; H, 4.64; N, 13.82. Found: C, 39.47; H, 4.66; N, 13.97.

This sample was analyzed by x-ray crystallographic analysis (see Discussion).

10-Carbomethoxy-1,3-diazaspiro[4.5]dec-7-ene-2,4-dione (14). A mixture of 2.5 g of hydantoin **13**, mp 252–254 °C [prepared from imidazoline **1** (**2**, ref 1) by treatment with boiling H_2SO_4–MeOH[4]], 8 ml of butadiene, 42 ml of dry THF, and 10 mg of hydroquinone was heated in a bomb at 185 °C for 46 h. The resulting dark yellow liquid was decanted and the gummy residue was washed with hot $CHCl_3$ followed by hot MeOH. All solutions were combined, concentrated, and then diluted with hot MeOH to precipitate hydrocarbon polymer. After repetition of the procedure three times, the solution was concentrated and diluted with $CHCl_3$. Starting hydantoin **13**, 260 mg, mp 248–251 °C dec, separated out upon standing. The mother liquor was evaporated to dryness and the residue taken up in EtOAc and allowed to stand. Filtration yielded 1.28 g of crude product, crystallization of which from EtOAc afforded 950 mg (28%) of adduct **14** as a white powder, mp 204–207 °C. Recrystallization from EtOAc–hexane afforded the analytical specimen of **14**: mp 208–210 °C; NMR δ 2.1–2.9 (m, allylics), 3.0–3.3 (m, H-10), 3.68 (s, MeO), 5.6–5.9 (m, vinyls), 6.3 (bs, NH), 8.3 (bs, NH).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.65; H, 5.41; N, 12.39.

10-Carbomethoxy-2-ethoxy-1,3-diazaspiro[4.5]deca-2,7-dien-4-one (15). To 193 mg of **14**, mp 206–208 °C, was added 10 ml of a freshly prepared CH_2Cl_2 solution which was 1.0–1.6 M in triethyloxonium fluoroborate and the resulting mixture was stirred at 10 °C for 18 h. The solution which formed upon warming to 25 °C was diluted with 20 ml of CH_2Cl_2 and washed with ice-cold saturated K_2CO_3. The CH_2Cl_2 layer was separated from the emulsion, washed with brine, and dried (Na_2SO_4). Evaporation gave 121 mg of a colorless oil which was taken up in benzene–hexane. After 2 days crystals separated out. Recrystallization from benzene–hexane gave 26 mg (12%), mp 138–143 °C. A second recrystallization afforded the analytical specimen of *O*-ethoxy derivative **15** as white stars: mp 141–142 °C; NMR δ 1.40 (t, CH_2CH_3), 2.0–2.9 (m, allylics), 3.11 (d of d, H-10), 3.66 (s, MeO), 4.56 (q, CH_2CH_3), 5.78 (m, vinyls), 5.98 (bs, NH).

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.18; H, 6.40; N, 11.15.

10-Carbomethoxy-1- or -3-ethyl-1,3-diazospiro[4.5]dec-7-ene-2,4-dione (16). A 100-mg sample of **14** was allowed to react with triethyloxonium fluoroborate in CH_2Cl_2 essentially as in the last experiment, except that an aged stock solution of the fluoroborate was employed. Crystallization of the crude product from EtOAc yielded 75 mg (67%) of **16** as colorless prisms, mp 120–122 °C. Three recrystallizations from EtOAc–benzene afforded the analytical sample as white stars: mp 118–118.5 °C; mass spectrum *m/e* 252.109 (calcd, 252.111); NMR δ 1.25 (t, CH_2CH_3), 2.0–2.9 (m, allylics), 3.15 (d of d, H-10), 3.62 (q, CH_2CH_3), 3.65 (s, MeO), 5.79 (m, vinyls), 5.98 (bs, NH).

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.30; H, 6.43; N, 11.20.

Reaction of Imino Ether 15 with Ammonia in Methanol. A mixture of 40 ml of MeOH saturated with NH_3 and 26 mg of **15**, mp 138–143 °C, was placed in a pressure reactor and heated at 120 °C for 3 h. After removal of the solvent the residue was treated with 2 ml of Ac_2O–pyridine (1:1) and stirred for 15 h at 25 °C. Removal of the solvent under vacuum and chromatography of the residue over silica gel yielded 12 mg (44%) of spiro adduct **5b** which crystallized upon standing (mp 199–202 °C). The NMR spectrum was identical with that of authentic **5b**. Also obtained from the chromatography was 9 mg (24%) of crude amide **11** (see above), identified on the basis of its NMR spectrum.

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Registry No.—**2**, 33532-78-4; **3**, 21615-64-5; **4**, 21615-58-7; **5a**, 58734-95-5; **5b**, 33532-79-5; **5c** (R = Ac), 58734-96-6; **5c** (R = H), 58734-97-7; **5d** (R = Ac), 58734-98-8; **5d** (R = H), 58734-99-9; **5e**, 58735-00-5; **5f**, 58735-01-6; *cis*-**6a**, 58735-02-7; *trans*-**6a**, 58735-03-8; *cis*-**6b**, 58735-04-9; *trans*-**6b**, 58735-05-0; *cis*-**6c**, 58735-06-1; *trans*-**6c**, 58735-07-2; *cis*-**6d**, 58747-69-6; *trans*-**6d**, 58735-08-3; **6f**, 58735-09-4; **6g**, 58735-10-7; **7**, 21615-63-4; **8**, 58735-11-8; **9**, 58735-12-9; **10**, 58735-13-0; **11**, 58735-14-1; **12**, 58747-70-9; **13**, 939-85-5; **14**, 58735-

15-2; **15**, 58735-16-3; **16**, 58735-57-2; isoprene, 78-79-5; 1-acetoxybuta-1,3-diene, 1515-76-0; 1-acetoxy-3-methylbuta-1,3-diene, 17616-47-6; KOAc, 127-08-2; 3-methylcrotonaldehyde, 107-86-8; ammonia, 7664-41-7.

Supplementary Material Available. A table of the atomic coordinates and temperature factors from this analysis (1 page). Ordering information is given on any current masthead page.

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Molecular Geometry Studies. Crystal and Molecular Structure of a 7-Spirocyclopropylbicyclo[2.2.1]heptene Anhydride[1]

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The molecular geometry of the bridge spirocyclopropyl anhydride (1) has been determined. There are no unusual bond lengths or bond angles which would make it especially unstable. The molecular packing suggests a weak intermolecular oxygen carbon–carbon π bond interaction between half of the molecules in the crystal. The agreement between x-ray crystallographic data and LIS measurements is excellent.

The conformation of molecules with internal strain, which includes derivatives of the bicyclo[2.2.1]heptane series, is of continuing interest.[3] Because these molecules are rigid their molecular geometry is presumably unchanged in the solid state and in solution. Hence, a knowledge of the conformation in the solid state is essential to both an understanding of specific chemical transformations and for substantiating theoretical work.

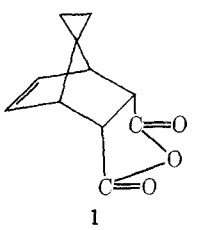
The addition of spiro substituents at the bridge position, as in the anhydride [3′aα,4′α,7′α,7′aα]-3′a,4′,7′,7′a-tetrahydrospiro[cyclopropane-1,8′-[4,7]methanoisobenzofuran]-1′,3′-dione (1), imposes further restrictions or "strain" on the bicyclo[2.2.1]heptane system.

Justification for the determination of the structure of anhydride **1** by x-ray crystallography was threefold:

(1) The structure determination of a bicyclo[2.2.1]heptane system containing a 7-spiro hydrocarbon substituent has not previously been reported. The only compound containing a spiro cyclopropylcyclopentyl grouping whose molecular geometry has been determined is spiro[bicyclo[4.1.0]hepta-2,4-diene-7,1′-(1*H*)indene].[4]

(2) To recognize if any unusual features in the endo anhydride **1**, including the cyclopropyl group, are present which would explain its facile rearrangement to the corresponding exo isomer under less stringent thermal requirements than the corresponding rearrangement of the parent compound 5-bicyclo[2.2.1]heptene-2,3-*endo*-dicarboxylic anhydride (**2**) to 5-bicyclo[2.2.1]heptane-2,3-*exo*-dicarboxylic anhydride (**3**). Interest in this area derives from a series of kinetic studies on the mechanism of the endo–exo transformation.[5]

(3) Previous NMR–LIS[6] work on anhydride **1** used idealized bond angles and bond lengths for computational results.[5] The PDIGM program provided the location of the complexation site between the shift reagent $Eu(fod)_3$ and the functional group based on the shift data obtained for specific hydrogens.[7,8] Comparison of actual vs. idealized bond length–bond angle values was deemed necessary if a systematic approach using NMR–LIS work to determine molecular geometry is meaningful.



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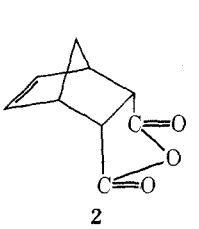

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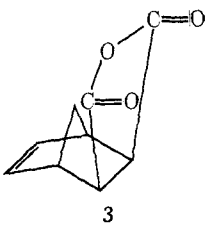

3

Discussion

The anhydride **1** crystallizes in an orthorhombic space group, $P2_12_12_1$, the same as the unsubstituted anhydrides **2** and **3**.[3a,c] Crystal data are given in Table I.

A major difference between **1** and **2** and **3** is the presence of two molecules in the asymmetric unit in **1**. Consequently two sets of molecular dimensions are available and are designated as molecule A and molecule B of anhydride **1**. The $C_{11}H_{10}O_3$ molecule is shown in Figure 1 and a stereoscopic view of the asymmetric unit in Figure 2.

Bond distances are givein in Table II, bond angles in Table III, and torsion angles calculated according to the convention of Klyne and Prelog[9] are given in Table IV.

The molecular geometry of the anhydride presents few unusual features. Characteristic bond lengths and bond angles are observed including the long carbon–carbon bonds (C_1–C_2,