The conformers of all four compounds were modeled by using Moledit/Optimol.[30] The interatomic distances obtained for the conformers of cyclooctene **9** by modeling were compared to experimental distances derived from transient NOE methods and were found to be in good agreement for the equatorial hydroxy conformer (R = 0.957) but much less so for the axial hydroxy conformer (R = 0.482). This indicates that the equatorial hydroxy, axial methyl conformer of cyclooctene **9** predominates in solution, which is consistent with calculated energies of 29.9 kcal/mol (equatorial OH) and 33 kcal/mol (axial OH), although variable temperature studies show that interconversion between conformers is very facile (fast exchange regime at 300 K). The axial hydroxy conformer of cyclooctene 8 was indicated as the major conformer by the observation of a strong NOE between H5 and H4, and comparison of calculated and measured coupling constants for this conformer [$J_{H5,H6(syn)}$ = 10.1 Hz (obsd), 9.2 (calcd); $J_{H5,H6(anti)}$ = 6.2 Hz (obsd), 7.3 (calcd)]. This is in agreement with the energies calculated for the axial OH and the two possible skewed equatorial OH conformers of 8, which are 28.04, 29.41, and 30.1 kcal/mol, respectively, but interconversion between conformers is again rapid at 300 K. Interconversion between the conformers of the cycloheptenes **4** and **5** was also rapid at 300 K, and no conformational preference was observed. In dibenzo[a,d]cycloheptenes possessing bulkier 5-substituents, the axial conformer is favored.[31]

In conclusion, it is unlikely that conformation plays a significant role in determining the relative reactivities of the hydroxylamines **6** (X = OH), **28**, and **44** since, despite the strong bias observed in the conformational populations of the corresponding cyclooctenes **8** and **9**, conformational interconversion is not a rate limiting factor at relevant temperatures.

Acknowledgment. We thank Mr. R. Williams for NMR and mass spectra, Drs. K. Hoogsteen and J. P. Springer for X-ray crystallography, and Mrs. E. Brawn for typing the manuscript.

Registry No. **1**, 70449-94-4; **2**, 124812-64-2; **4**, 10354-00-4; **5**, 18259-45-5; **9**, 124813-06-5; **15a**, 4189-17-7; **15b**, 3973-55-5; **15c**, 124853-22-1; **15d**, 3979-65-5; **15e**, 42982-04-7; **15f**, 22046-29-3; **16e**, 124813-48-5; **16f**, 125303-39-1; **17e**, 124813-50-9; **18a**, 124813-45-2; **18b**, 124813-21-4; **18c**, 124813-10-1; **18d**, 124813-30-5; **18e**, 124813-51-0; **18f**, 117374-57-9; **19a**, 124813-43-0; **19b**, 124813-22-5; **19c**, 124813-11-2; **19d**, 124813-28-1; **20a**, 124813-44-1; **20b**, 124813-20-3; **20c**, 124813-12-3; **20d**, 124813-29-2; **20e**, 124813-53-2; **21**, 38240-87-8; **29**, 125299-78-7; **30** (isomer 1), 125409-20-3; **30** (isomer 2), 125409-22-5; **33a**, 124813-46-3; **33b**, 124813-23-6; **33c**, 124813-13-4; **33d**, 124813-31-6; **34b**, 124813-25-8; **34c**, 124813-15-6; **34d**, 124813-39-4; **34e**, 124813-54-3; **35**, 124812-98-2; **36**, 124812-90-4; **37**, 124813-60-1; **38**, 124812-92-6; **39**, 124812-91-5; **40**, 124812-89-1; **41**, 124812-97-1; **42**, 124812-99-3; **43**, 2975-65-7; **44**, 125303-41-5; **45**, 124813-57-6; **46**, 124813-01-0; **47**, 124813-37-2; **48** (isomer 1), 125409-21-4; **48** (isomer 2), 125409-23-6; **49**, 125303-40-4; **52**, 124812-96-0; I, 125303-42-6; II, 89442-08-0; 5-oxo-5,6-dihydrodibenzo[a,e]cyclooctene, 3111-86-2.

Supplementary Material Available: Tables of crystal data, fractional coordinates, bond distances, and bond angles of structure **2** (6 pages). Ordering information is given on any current masthead page.

(30) MSDRL Molecular Modelling Package, written by the Molecular Systems Group, MSDRL Rahway.

(31) Young, S. D.; Baldwin, J. J.; Cochran, D. W.; King, S. W.; Remy, D. C.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 339.

Transannular Reactions of 5-Azido- and 5-Nitronodibenzo[*a*,*e*]cyclooctatrienes and -dibenzo[*a*,*d*]cycloheptatrienes. Syntheses of Pavine and Homoisopavine Analogues

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Received August 18, 1989

Transannular cycloaddition reactions of substituted dibenzocyclooctenes and dibenzocycloheptenes have been used to prepare ring homologues of the uncompetitive *N*-methyl-D-aspartate receptor antagonist MK-801 (1) and its major hydroxylated metabolite. Controlled thermolysis of the 5-azidodibenzo[*a*,*e*]cyclooctene **5** yields the pentacyclic aziridine **14**. In contrast, thermolysis of the corresponding cycloheptene azide **8** results in ring expansion, forming the imine **17**. Aziridine ring opening reactions of **14** provide a regiospecific route to the 12-endo-substituted pavine alkaloid analogues **3** and **23–25**. Treatment of the dibenzo[*a*,*e*]cyclooctene-5-ol **13** and the corresponding cyclohepten-5-ol **32** with formaldoxime under acidic conditions gave isoxazolidines **27**, **28**, and **33**, probably via intramolecular cycloaddition of the lable nitrones **6** and **9**. Ring cleavage reactions of the isoxazolidines formed the exo-hydroxy-substituted homoisopavines **29** and **30** and the iminomethanocycloheptane **34**. The more facile transannular reactions of the cyclooctenes relative to the cycloheptene derivatives can be explained by the formation of less strained transition states in the cyclooctene cases.

The discovery that antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamic acid receptor can prevent neuronal damage in animal models of cerebral ischemia[1] has stimulated attempts to identify novel ligands that interact with this receptor. In the accompanying paper, we described the synthesis of the dibenzocyclooctanimine **1**,[2] a ring homologue of the prototype non-competitive NMDA antagonist MK-801 (**2**).[3] Compound **1** was obtained from spontaneous ring closure of the unstable hydroxylamine **4**, a process that proceeded regioselectively, affording the bicyclo[4.2.1] system exclusively (Chart I).

The isomeric bicyclo[3.3.1] compound **3** possesses the ring system found in pavine alkaloids, and several routes to this structural class have been developed.[4] However,

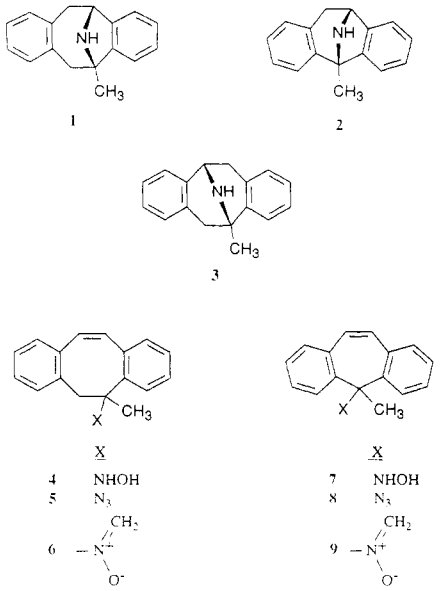
(1) Foster, A. C.; Gill, R.; Woodruff, G. N. *J. Neurosci.* **1988**, *8*, 4745 and references cited therein.

(2) Leeson, P. D.; et al. *J. Org. Chem.*, preceding paper in this issue.

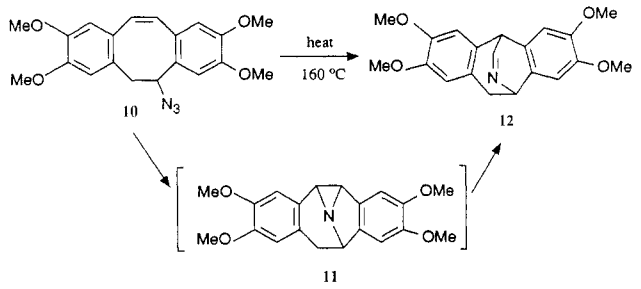
(3) Kemp, J. A.; Foster, A. C.; Wong, E. H. F. *Trends Neurosci.* **1987**, *10*, 294.

0022-3263/90/1955-2103$02.50/0

Chart I



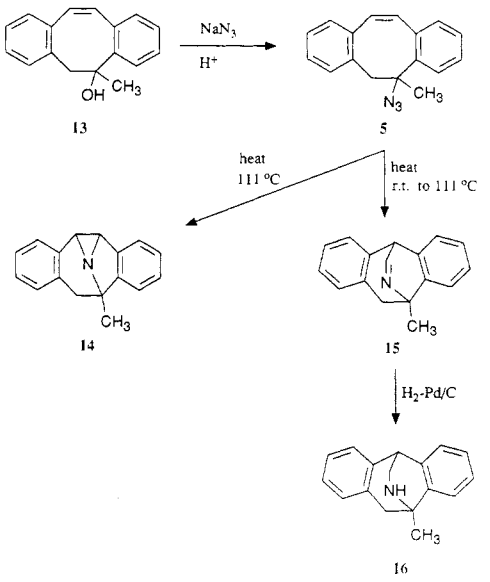
Scheme I



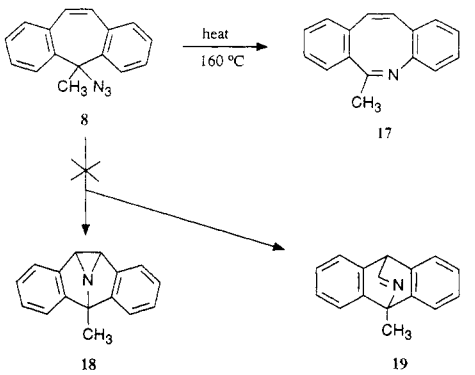
approaches involving transannular ring closure have given inconsistent results,[5] the only successful method to date being the mercury(II)-mediated cyclization of a 5-(dimethylamino)cyclooctene.[6] Herein we disclose the synthesis of compound **3**, and related iminomethano-bridged dibenzocycloalkanes, by means of transannular cycloaddition reactions of substituted dibenzocyclooctenes carrying azido (**5**) and nitrono (**6**) functionality.[7] The significantly greater rate of transannular cyclization found for the cyclooctenehydroxylamine **4** relative to the corresponding cycloheptene (**7**)[2,8] suggested the importance of geometrical factors influencing relative transition state stabilities. Studies of the relative abilities of the two ring systems to undergo transannular cyclization reactions are extended in this paper by comparisons of the reactions of **5** and **6** with the corresponding dibenzocycloheptenes **8** and **9**. Notably, thermolytic reactions of the azides **5** and **8** were found to proceed via different pathways involving transannular cycloaddition and Schmidt rearrangement, respectively.

Thermolytic Reactions of the Azides 5 and 8. During an unsuccessful attempt to prepare the alkaloid pavine, Jung and Miller[5] showed that thermolysis of the

Scheme II



Scheme III

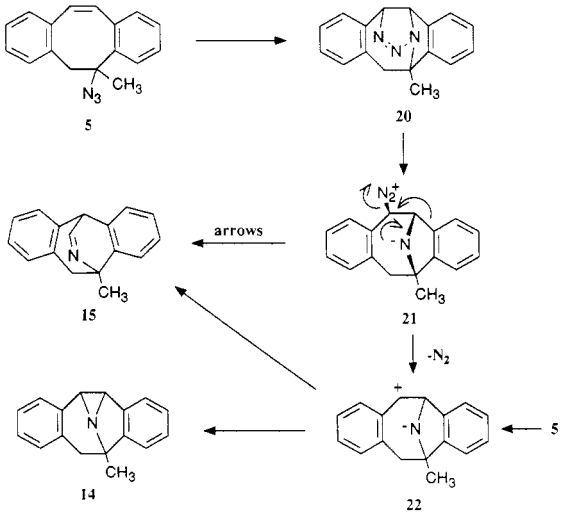


azide **10** at 160 °C for 36 h resulted in skeletal rearrangement, affording dehydroisopavine (**12**). The strained pentacyclic aziridine **11** was proposed as a possible labile intermediate (Scheme I). We had shown that the related aziridine **14** is a stable and isolable compound,[2] but a practical synthesis of **14** was required in order to explore ring opening reactions. This was accomplished by thermolysis of the azide **5** (Scheme II). Treatment of the dibenzo[*a*,*e*]cyclooctene alcohol **13** with hydrazoic acid resulted in smooth conversion to the required azide **5**. Compound **5** was characterized spectroscopically, but proved to be thermally unstable, being slowly converted at room temperature to the expected rearrangement product, the dehydroisopavine derivative **15**.[5] The structure **15** was confirmed by catalytic hydrogenation to the known compound **16**, an isopavine analogue that in common with **2** possesses anticonvulsant activity.[9]

When a solution of the azide **5** in toluene was heated from room to reflux temperature, compound **15** was formed as the major product, but the aziridine **14** was clearly also present in low yield. Thermolysis conditions were optimized to increase the yield of **14**. Dropwise addition of a toluene solution of **5** to excess refluxing toluene gave the desired aziridine **14** in 90% yield. Attempts to effect thermolytic conversion of the purified aziridine **14** to the dehydroisopavine **15** were unsuccessful, showing that **14** is not an intermediate in the thermal conversion of **5** to **15**.

(4) Gozler, B. In *The Alkaloids*; Brossi, A.; Ed.; Academic: New York, 1987; Vol. 31, p 317.
(5) Jung, M. E.; Miller, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 1984.
(6) Nomoto, T.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1982**, 1113.
(7) Preliminary communications: (a) Carling, R. W.; Leeson, P. D. *Tetrahedron Lett.* **1988**, *29*, 6985. (b) Leeson, P. D.; James, K.; Baker, R. *J. Chem. Soc., Chem. Commun.* **1989**, 433.
(8) Lamanec, T. R.; Bender, D. R.; DeMarco, A. M.; Karady, S.; Reamer, R. A.; Weinstock, L. M. *J. Org. Chem.* **1988**, *53*, 1768.
(9) Russel, J. H. British Patent 1,146,109, 1969.

Scheme IV

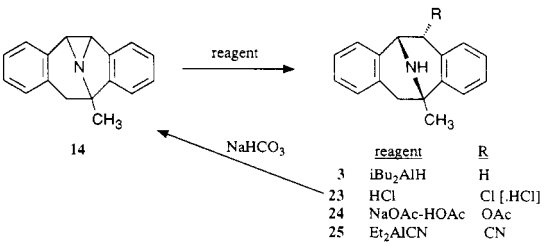


In contrast to the facile thermolysis reactions of the dibenzocyclooctene azide **5**, the corresponding cycloheptene azide **8** proved to be stable in refluxing toluene, and higher temperatures were needed to induce reaction. However, in refluxing mesitylene (160 °C), conversion to an unstable but isolable cyclic imine **17** occurred, presumably as a result of a classical Schmidt-type ring expansion[10] (Scheme III). Neither the known aziridine **18**[11] nor the possible rearrangement product **19** were isolated, suggesting that the pathway leading from the dibenzocyclooctene azide **5** to **14** and **15** is excluded in the case of the lower homologue **8**.

A feasible mechanism accounting for the formation of both **14** and **15**, and for the observed temperature dependence on the product ratio, is shown in Scheme IV. Intramolecular azide–olefin cycloaddition[12] would be expected to give **20** as the least strained of the two possible triazolines. Triazolines are often unstable and have been demonstrated in many cases to undergo conversion to both aziridines and rearranged imines, probably via betaine intermediates.[13] Thus, the betaine **21** is a likely intermediate, in which the ideal antiperiplanar arrangement of migrating aryl and leaving diazonium groups would be expected to result in facile rearrangement, giving the dehydroisopavine **15**. The exo configuration of the leaving group in **21** precludes formation of the aziridine **14** via an intramolecular SN2 reaction. However, **14** would be formed from internal collapse of the zwitterion **22** resulting from unimolecular loss of N_2 from **21**. The appearance of higher yields of **14** at elevated temperatures may be explained by an increased rate of conversion of **21** to **22**. An alternative[5] but less well precedented pathway for formation of **22** from **5** is direct displacement of N_2 by intramolecular nucleophilic attack of the azide by the cyclooctene double bond. Mechanisms requiring the intermediacy of the nitrene[5] derived from **5** seem less likely, since the rearrangement to **15** occurs at room temperature, and even the highest temperature employed (refluxing toluene, 111 °C) is considerably less than that normally required (>160 °C) for conversion of alkyl azides to nitrenes.[10]

(10) Scriven, E. J. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
(11) (a) Britcher, S. F.; Lyle, T. A.; Thompson, W. J.; Varga, S. L. Eur. Pat. Appl. 0264 183 A1, 1988. (b) Larsen, R. D.; Davis, P.; Corley, E. C.; Reider, P. J.; Lamanec, T. R.; Grabowski, E. J. J. *J. Org. Chem.* **1990**, *55*, 299.
(12) Padwa, A. In *1,3-Dipolar Cycloadditions*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. II, p 316.
(13) Kadaba, P. K. *Adv. Heterocycl. Chem.* **1984**, *37*, 217.

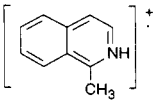
Scheme V



The mechanism depicted in Scheme IV can also account for the formation of dehydroisopavine (**12**) from the azide **10**[5] (Scheme I). However, the thermolysis reactions of **5** contrast with those of the tetramethoxy derivative **10**, where the aziridine **11** was not isolated. The increased migratory aptitude of the electron-rich dimethoxyaryl moiety in **10** may be responsible. The more facile reactivity of **5** relative to **10** is probably due to the presence in **5** of the 5-methyl substituent, which would be predicted to enhance the rate of transannular ring closure, as was found in the cyclization reactions of the hydroxylamines **4**[2] and **7**[8] compared with their 5-desmethyl derivatives.

Synchronous formation of both new N–C bonds is believed to be obligatory in azide–olefin cycloaddition.[12] Inspection of molecular models reveals that this condition is readily met for formation of the triazoline **20** from the cyclooctene azide **5**. In contrast, the required transition state in the cycloheptene azide **8** cannot be achieved without energetically penalizing molecular distortion. Consequently **8** undergoes the alternative Schmidt-type reaction observed (Scheme III). The relative reactivities of **5** and **8** are in accord with the differences in rates of cyclization of the corresponding hydroxylamines **4** and **7**. The more rapid ring closure of the cyclooctene derivative **4** relative to the cycloheptene **7** was shown by molecular modeling studies to be consistent with formation of a less strained transition state.[2]

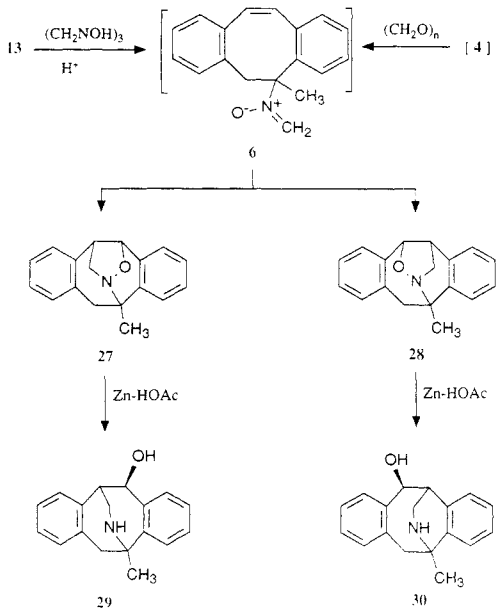
Cleavage Reactions of Aziridine 14. Ring cleavage reactions of aziridine **14** occurred readily only under conditions where the nitrogen atom was protonated or coordinated to a Lewis acid, the products in all cases being the thermodynamically preferred bicyclo[3.3.1]pavine analogues (Scheme V). Thus treatment of **13** with hydrogen chloride in ethyl acetate at room temperature gave the 12-endo chloride **23** as the hydrochloride salt. Attempts to isolate the free base from **23** resulted in ring closure, giving **14**. Sodium acetate in acetic acid gave the 12-endo acetate **24** and diethylaluminum cyanide gave the nitrile **25**. The target derivative **3** was obtained by cleavage of **14** with diisobutylaluminum hydride in toluene at 80 °C. The structures **3** and **23–25** were deduced by ^1H NMR and nuclear Overhauser spectroscopy. Compound **3** was spectrally distinct from the bicyclo[4.2.1] isomer **1**, the appearance of the isoquinolinium ion **26** in the mass spectrum being diagnostic for the pavine structure.[4] The regioselective ring cleavage reactions of **14** probably proceed by concerted SN2-like mechanisms, since 12-exo-substituted products were not detected.



26

Transannular Formation of Isoxazolidines 27, 28, and 33. The nitrone intermediates **6** and **9** were prepared in situ from the corresponding alcohols (**13**, Scheme VI;

Scheme VI

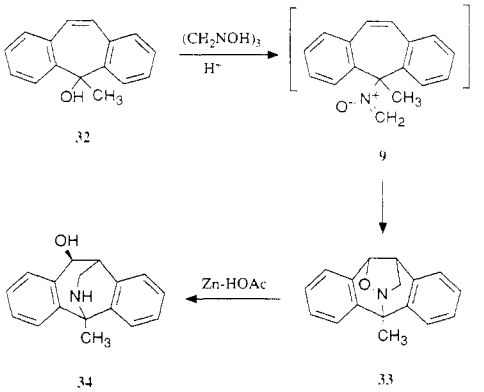


32, Scheme VII). Treatment of **13** with formaldoxime trimer under nonaqueous acidic conditions at room temperature resulted in a mixture of the isoxazolidines **27** and **28** in a combined yield of 79%, with the former being favored by a factor of 2.2:1 (Scheme VI). The reaction most reasonably proceeds via the nitrone **6** since in situ capture of the transient hydroxylamine **4**[2] with formaldehyde gave a similar ratio of adducts (1.7:1) although the yield was lower (41%). It has been shown that the regioselectivity observed in intramolecular nitrone cycloadditions is dependent on both angle strain in the transition state and entropic effects.[14] Carbon to carbon bond formation is believed to precede carbon to oxygen linkage, and since closure to a six-membered ring should be kinetically favored,[14] adduct **28** would be predicted to be the preferred product. Because **27** is actually the more abundant isomer, this must be formed through a lower energy transition state. The possibility of an alternative pathway involving intermolecular cycloaddition of **13** with formaldonitrone (**31**),[15] followed by ring closure, seems less

31

likely since formaldoxime apparently undergoes cycloaddition reactions only with highly activated dipolarophiles under more forcing conditions.[16] Whichever mechanism applies, a transannular cyclization must occur and the lower yield (9%, not optimized) of isoxazolidine **33** obtained from reaction of the dibenzo[*a*,*d*]cyclohepten-5-ol **32** (Scheme VII) is probably a consequence of greater angle strain in the transition state. Reductive cleavage of the isoxazolidines **27** and **28** gave the exo-hydroxy-substituted homoisopavine derivatives **29** and **30** which are homologues of the major human metabolite of **2**.[11,17] Similarly,

Scheme VII



cleavage of **33** gave the iminoethanodibenzocycloheptene[18] **34**.

In summary, the results reported here and in the previous paper[2] show that transannular cyclization and cycloaddition reactions of 5-substituted dibenzo[*a*,*e*]cyclooctenes **4**, **5**, and **6** are more facile than those of the corresponding dibenzo[*a*,*d*]cycloheptenes **7**, **8**, and **9**. This difference can be accounted for by formation of less strained transition states in the transannular reactions of the cyclooctene derivatives.

Experimental Section

General methods are described in the preceding paper.[2]

5-Azido-5-methyl-5,6-dihydrodibenzo[*a*,*e*]cyclooctatriene (5). To a solution of 5-hydroxy-5-methyl-5,6-dihydrodibenzo[*a*,*e*]cyclooctatriene (**13**)[2] (7.08 g, 0.03 mol) in dichloromethane (80 mL) was added sodium azide (5.85 g, 0.09 mol), followed by the dropwise addition of dichloroacetic acid (10 mL) in dichloromethane (20 mL). When the addition was complete, saturated sodium hydrogen carbonate solution was added until the solution was basic, and the organic layer was separated, dried (Na_2SO_4), filtered, and evaporated to dryness to leave a clear oil (7.4 g, 95%): NMR (60 MHz, $CDCl_3$) δ 1.60 (3 H, s, CH_3), 3.40 (2 H, m, CH_2), and 6.60–7.95 (10 H, m, ArH); ν_{max} 2100 cm^{-1} (azide). The azide could not be further characterized by spectroscopy or combustion analysis due to significant conversion to the dehydroisopavine **15** at room temperature.

2,3:6,7-Dibenzo-1-methyl-9-azatricyclo[3.3.1.$0^{8,9}$]nona-2,6-diene (14). To refluxing toluene (100 mL) under nitrogen was added a solution of **5** (3.5 g) in toluene (100 mL) over a period of 0.25 h. The cooled solution was concentrated in vacuo to give a solid residue, which was recrystallized from diethyl ether/hexane to give the title compound (2.8 g, 90%), mp 132 °C, which was identical in all respects with a sample prepared previously.[2]

12,13-Didehydro-10,11-dihydro-10,5-iminomethano-10-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (15). A solution of 5-azido-5-methyl-5,6-dihydrodibenzo[*a*,*e*]cyclooctatriene (**5**) (3.5 g) in toluene (70 mL) was heated from room to reflux temperature over a period of 0.25 h, then cooled and concentrated in vacuo to leave a residue, which was purified by chromatography on silica gel, using 2% methanol in dichloromethane as eluent, to give the title compound (2.78 g, 90%), mp 91 °C: ^1H NMR (360 MHz, $CDCl_3$) δ 2.00 (3 H, s, CH_3), 2.91 (1 H, d, J = 17.6 Hz, 11-H_{eq}), 3.18 (1 H, d, J = 17.6 Hz, 11-H_{ax}), 4.55 (1 H, d, J = 4.1 Hz, 5-H), 6.80–7.50 (8 H, m, ArH), and 8.53 (1 H, d, J = 4.1 Hz, 13-H); MS m/e 233 (M^+). Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.28; H, 6.59; N, 5.83.

10,11-Dihydro-10,5-iminomethano-10-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene Hydrochloride (16). A solution of **15** (0.1 g) in absolute ethanol (10 mL) was shaken under a hydrogen atmosphere at 50 psi in the presence of 10% palladium on charcoal

(14) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497.
(15) Adeney, P. D.; Bouma, W. J.; Radon, L.; Rodwell, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 4069.
(16) Ochiai, M.; Obayashi, M.; Morita, K. *Tetrahedron* **1967**, *23*, 2641.
(17) (a) Karady, S.; Corley, E. G.; Abramson, N. L.; Weinstock, L. M. *Tetrahedron Lett.* **1989**, *30*, 2191. (b) Thompson, W. J. *J. Med. Chem.* In press.
(18) Previous approaches to this ring system: (a) Walker, G. N.; Alkalay, D.; Engle, A. R.; Kempton, R. J. *J. Org. Chem.* **1971**, *36*, 466. (b) Dobson, T. A.; Davis, M. A. *Can. J. Chem.* **1971**, *49*, 1027. (c) Majeed, A. J.; Patel, P. J.; Sainsbury, M. *J. Chem. Soc., Perkin Trans. I* **1985**, 1195.

catalyst (0.3 g) for 1 h. After this time the catalyst was removed by filtration and the solvent evaporated in vacuo to give a residue, which was purified by chromatography on silica gel, using 5% methanol in dichloromethane as eluent, to give the free base of the title compound[9] (0.072 g, 71%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.70 (3 H, s, CH_3), 1.79 (1 H, br s, NH), 3.06 (1 H, d, J = 17.5 Hz, 11-H_{eq}), 3.34 (1 H, d, J = 17.5 Hz, 11-H_{ax}), 3.35 (1 H, dd, J = 11.2 and 5.0 Hz, 13-H_{ax}), 3.62 (1 H, d, J = 11.2 Hz, 13-H_{eq}), 3.92 (1 H, d, J = 5.0 Hz, 5-H), and 6.96–7.35 (8 H, m, ArH); irradiation of 5-H (δ 3.92) produced NOE effects to both ring systems and irradiation of the methyl group (δ 1.70) gave a NOE to only one aromatic spin system as assigned by COSY. The free base (0.07 g) was dissolved in ethyl acetate (1 mL) and a 5 M solution of hydrogen chloride in ethyl acetate (0.5 mL) was added. The hydrochloride salt was collected by filtration, washed with diethyl ether, and dried to give the title compound (0.056 g, 64%), mp 260 °C: MS m/e 235 (M^+), 234, 206, 191, 178, 165, 144 (100), 115, 103, 91, 77. Anal. Calcd for $C_{17}H_{17}N$·HCl: C, 75.13; H, 6.68; N, 5.15. Found: C, 74.92; H, 6.72; N, 5.08.

5-Aza-6-methyldibenzo[*a*,*e*]cyclooctatetraene (17). The azide 8[19] (0.68 g) was dissolved in mesitylene (30 mL) and the solution heated at 160 °C for 20 h under an atmosphere of nitrogen. After this time the solvent was removed under vacuum and the residue purified by chromatography on silica gel with 15% ethyl acetate in hexane as eluent, to give, as a colorless oil, the title compound **17** (0.18 g, 30%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.32 (3 H, s, CH_3), 6.95 (2 H, s, ArCH=CHAr), 7.26 (1 H, m, ArH), 7.34–7.49 (6 H, m, ArH), and 7.60 (1 H, dd, J = 10.2 and 2.4 Hz, ArH); exact mass m/e found 219.1028, $C_{16}H_{13}N$ requires 219.10408.

5-Methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,11-imine (3). To a solution of the aziridine **14** (0.232 g, 0.01 mol) in dry toluene (10 mL) was added a solution of diisobutylaluminum hydride in toluene (2 mL of a 1.6 M solution, 0.03 mol), and the reaction mixture was heated at 80 °C for 4 h. Water (10 mL) was added to the cooled solution and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo to leave a residue, which was purified by chromatography on silica gel to give the title compound as a colorless, crystalline solid (0.2 g, 85%): mp 84–85 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.65 (3 H, s, CH_3), 1.76 (1 H, br s, NH), 2.83 (1 H, d, J = 16.0 Hz, 12-H_{eq}), 2.91 (1 H, d, J = 16.2 Hz, 6-H_{ax}), 3.04 (1 H, d, J = 16.2 Hz, 6-H_{ax}), 3.46 (1 H, dd, J = 16.0 and 5.6 Hz, 12-H_{ax}), 4.53 (1 H, d, J = 5.6 Hz, 11-H) and 6.89–7.29 (8 H, m, ArH); irradiation of the methyl group (δ 1.65) gave a NOE to one aromatic ring and irradiation of 11-H (δ 4.53) gave a NOE to the other aromatic ring system as determined by COSY NMR spectroscopy; MS m/e 235 (M^+), 234, 144 (100), 115, 91. Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.53; H, 7.47; N, 5.84.

12-*endo*-Chloro-5-methyl-5,6,11,12-tetrahydrodibenzo-[*a*,*e*]cycloocten-5,11-imine Hydrochloride (23). To a solution of the aziridine **14** (0.116 g, 0.005 mol) in dry ethyl acetate (2 mL) was added a 5 M solution of hydrogen chloride in ethyl acetate (1 mL), and the reaction mixture was stirred for 1 h at room temperature. The solid produced was filtered, washed with diethyl ether, and dried under high vacuum to give the title compound (0.12 g, 78%): mp 245–250 °C; ^{1}H NMR (360 MHz, DMSO) δ 1.93 (3 H, s, CH_3), 3.16 (1 H, d, J = 17.3 Hz, 6-H_{eq}), 3.45 (1 H, d, J = 17.3 Hz, 6-H_{ax}), 5.27 (1 H, d, J = 5.0 Hz, 11-H), 6.29 (1 H, d, J = 5.0 Hz, 12-H), and 7.10–7.58 (8 H, m, ArH); irradiation of the methyl group (δ 1.93) and 12-H (δ 6.29) gave NOE's to the same aromatic ring system as determined by COSY analysis; MS m/e 269 (M^+). Anal. Calcd for $C_{17}H_{16}ClN$·HCl: C, 66.68; H, 5.60; N, 4.57. Found: C, 66.42; H, 5.50; N, 4.43.

12-*endo*-Acetoxy-5-methyl-5,6,11,12-tetrahydrodibenzo-[*a*,*e*]cycloocten-5,11-imine (24). To a solution of the aziridine **14** (0.27 g, 0.0016 mol) in glacial acetic acid (3 mL) was added sodium acetate (0.25 g, 0.003 mol), and the reaction mixture was heated at reflux for 2 h under an atmosphere of nitrogen. The excess acetic acid was removed in vacuo and the residue partitioned between ethyl acetate (10 mL) and saturated sodium hydrogen carbonate solution (10 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum to leave a residue, which was recrystallized from ethyl acetate/hexane to give the title compound as a colorless solid (0.25 g, 74%): mp 149 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.51 (3 H, s, CH_3), 2.11 (3 H, s, CH_3COO), 2.81 (1 H, d, J = 16.3 Hz, 6-H_{eq}), 2.92 (1 H, d, J = 16.3 Hz, 6-H_{ax}), 4.52 (1 H, d, J = 5.9 Hz, 11-H), 6.27 (1 H, d, J = 5.9 Hz, 12-H), and 6.83–7.42 (8 H, m, ArH); irradiation of the 5-methyl group (δ 1.51) and 12-H (δ 6.27) gave NOE's to the same aromatic ring system as assigned by COSY analysis; MS m/e 293 (M^+). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.67; H, 6.59; N, 4.76.

12-*endo*-Cyano-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5,11-imine (25). To a solution of the aziridine **14** (0.116 g, 0.005 mol) in dry toluene (2 mL) at room temperature under nitrogen was added diethylaluminum cyanide (1 mL of a 1 M solution in toluene) in one portion. The reaction mixture was stirred at room temperature for 1 h and then heated at 80 °C for 0.5 h. Water (5 mL) and ethyl acetate (5 mL) were added to the cooled solution and the organic layer was separated, washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel with 20% ethyl acetate in dichloromethane as eluent and the product obtained was recrystallized from diethyl ether/hexane to give the title compound as a colorless solid (0.088 g, 66%): mp 155–156 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.64 (3 H, s, CH_3), 2.93 (1 H, d, J = 16.4 Hz, 6-H_{eq}), 3.06 (1 H, d, J = 16.4 Hz, 6-H_{ax}), 4.65 (1 H, d, J = 4.8 Hz, 11-H), 4.72 (1 H, d, J = 4.8 Hz, 12-H), and 6.93–7.52 (8 H, m, ArH); irradiation of the methyl group (δ 1.64) and 12-H (δ 4.72) gave NOE's to the same aromatic ring system as assigned by COSY analysis; MS m/e 260 (M^+). Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.02; H, 6.08; N, 10.68.

2,3:6,7-Dibenzo-1-methyl-9-aza-10-oxatricyclo[3.3.2.1]-undeca-2,6-diene (27) and 2,3:6,7-Dibenzo-1-methyl-9-aza-10-oxatricyclo[4.2.2.1]undeca-2,6-diene (28). Sodium acetate (2.1 g, 0.026 mol) and dichloroacetic acid (3.2 mL, 0.039 mol) were dissolved in dichloromethane (3.2 mL) at room temperature with rapid stirring, and after a period of 1 h a solution of formaldoxime hydrochloride (1.16 g, 0.0086 mol) in dichloromethane (10 mL) was added. After a further 0.5 h, the alcohol **13** (1 g, 0.0043 mol) was added to the reaction mixture, and stirring was continued for 14 h. Sodium hydroxide solution (1 N, 30 mL) was added followed by dichloromethane (30 mL), and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under vacuum to give a residue, which was purified by chromatography on silica gel using 20% ethyl acetate in hexane as eluent, to give initially compound **27** (0.62 g, 55%): mp 168–170 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.88 (3 H, s, CH_3), 2.73 (1 H, d, J = 16.7 Hz, 8-H_{eq}), 3.38 (1 H, dd, J = 12.2 and 7.3 Hz, 11-H_{ax}), 3.61 (1 H, d, J = 16.7 Hz, 8-H_{ax}), 3.99 (1 H, d, J = 12.2 Hz, 11-H_{eq}), 4.13 (1 H, dd, J = 7.7 and 7.3 Hz, 5-H), 5.38 (1 H, d, J = 7.7 Hz, 4-H), and 6.66–7.16 (8 H, m, ArH); irradiation of 8-H_{ax} (δ 3.61) produced a NOE to 11-H_{eq} (δ 3.99) as well as 8-H_{eq} (δ 2.73); MS m/e 263 (M^+). Anal. Calcd for $C_{18}H_{17}NO$·0.1H_2O: C, 81.54; H, 6.54; N, 5.28. Found: C, 81.33; H, 6.54; N, 5.16. Further elution gave **28** (0.27 g, 24%): mp 126–127 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.73 (3 H, s, CH_3), 2.62 (1 H, d, J = 14.9 Hz, 8-H_{eq}), 3.13 (1 H, d, J = 10.6 Hz, 11-H_{eq}), 3.55 (1 H, dd, J = 10.6 and 4.1 Hz, 11-H_{ax}), 3.85 (1 H, dd, J = 6.8 and 4.1 Hz, 4-H), 3.96 (1 H, d, J = 14.9 Hz, 8-H_{ax}), 5.56 (1 H, d, J = 6.8 Hz, 5-H), and 6.69–7.07 (8 H, m, ArH); irradiation of 8-H_{eq} (δ 2.62) gave a NOE only to 8-H_{ax} (δ 3.96) and irradiation of 8-H_{ax} (δ 3.96) gave a NOE only to 8-H_{eq} (δ 2.62); MS m/e 263 (M^+). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.04; H, 6.55; N, 5.29.

12-*exo*-Hydroxy-5,11-iminomethano-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctenecacetic Acid (29). Compound **27** (0.13 g) was dissolved in glacial acetic acid (10 mL) and zinc dust (0.26 g) was added. The reaction mixture was heated with stirring at 65 °C under an atmosphere of nitrogen for 8 h, then cooled, filtered, and concentrated in vacuo. The crude product was purified by chromatography on silica gel using 7.5% methanol in dichloromethane as eluent to give the title compound as a colorless solid (0.128 g, 71%): mp 167–169 °C; ^{1}H NMR (360 MHz, DMSO) δ 1.77 (3 H, s, CH_3), 1.98 (3 H, s, CH_3CO_2H), 2.83 (1 H, d, J = 16.4 Hz, 6-H_{eq}), 2.54–3.63 (3 H, m, 11-H, 14-H_{eq}, 14-H_{ax}), 3.67 (1 H, d, J = 16.4 Hz, 6-H_{ax}), 4.88 (1 H, d, J = 6.4

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Hz, 12-H), and 6.78-7.25 (8 H, m, ArH); MS *m/e* 265 (M^+). Anal. Calcd for $C_{18}H_{19}NO{\cdot}CH_3CO_2H{\cdot}0.1H_2O$: C, 73.41; H, 7.15; N, 4.28. Found: C, 73.32; H, 7.15; N, 4.24.

11-*exo*-Hydroxy-5,12-iminomethano-5-methyl-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctenacetic Acid (30). Compound **28** (0.1 g) was dissolved in glacial acetic acid (5 mL) and zinc dust (0.2 g) was added. The reaction mixture was heated at 65 °C under an atmosphere of nitrogen for 14 h, then cooled, filtered, and concentrated in vacuo. The crude product was purified by chromatography on silica gel using 30% methanol in dichloromethane as eluent to give, as a colorless solid, the title compound (0.107 g, 87%): mp 185 °C dec; ^{1}H NMR (360 MHz, DMSO) δ 1.57 (3 H, s, CH_3CO_2H), 1.87 (3 H, s, CH_3), 2.70 (1 H, d, J = 14.5 Hz, 6-H_{eq}), 2.79 (1 H, dd, J = 12.8 and 8.1 Hz, 14-H_{ax}), 3.27 (1 H, d, J = 14.5 Hz, 6-H_{ax}), 3.40 (1 H, m, 12-H), 3.54 (1 H, d, J = 12.8 Hz, 14-H_{eq}), 4.79 (1 H, d, J = 6.4 Hz, 11-H), and 6.89-7.12 (8 H, m, ArH); MS *m/e* 265 (M^+). Anal. Calcd for $C_{18}H_{19}NO{\cdot}CH_3CO_2H$: C, 73.82; H, 7.12; N, 4.30. Found: C, 74.06; H, 7.06; N, 4.39.

2,3:6,7-Dibenzo-1-methyl-8-aza-9-oxatricyclo[3.2.2.1]deca-2,6-diene (33). Sodium acetate (11.08 g, 0.135 mol) and dichloroacetic acid (16.8 mL, 0.203 mol) were dissolved in dichloromethane (17 mL) at room temperature with rapid stirring, and after 1 h formaldoxime hydrochloride (6.1 g, 0.045 mol) in dichloromethane (20 mL) was added. After a further 0.5 h, 5-hydroxy-5-methyldibenzo[*a*,*d*]cycloheptene (**32**)[8] (5 g, 0.0225 mol) was added to the reaction mixture and stirring was continued for 14 h. A sodium hydroxide solution (1 N, 100 mL) was added followed by dichloromethane (100 mL), and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a residue, which was purified by chromatography on silica gel, using 20% ethyl acetate in hexane as eluent, to give as a colorless foam **33** (0.49 g, 9%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.18 (3 H, s, CH_3), 2.63 (1 H, d, J = 9.8 Hz, 10-H_{eq}), 3.57 (1 H, dd, J = 9.8 and 4.3 Hz, 10-H_{ax}), 4.19 (1 H, dd, J = 6.5 and 4.3 Hz, 5-H), 5.57 (1 H, d, J = 6.5 Hz, 4-H), and 6.92-7.31 (8 H, m, ArH); MS *m/e* (CI) 250 (M^+). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.92; H, 6.17; N, 5.18.

11-*exo*-Hydroxy-5,10-iminomethano-5-methyl-5*H*-10,11-dihydrodibenzo[*a*,*d*]cycloheptene (34). Compound **33** (0.24 g) was dissolved in glacial acetic acid (25 mL) and zinc dust (0.48 g) was added. The reaction mixture was stirred and heated at 70 °C under an atmosphere of nitrogen for 36 h, then cooled, filtered, and concentrated in vacuo. The residue was partitioned between dichloromethane (50 mL) and sodium hydroxide solution (1 N, 50 mL) and the organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and evaporated under vacuum. The crude product was purified by chromatography on silica gel with 10% methanol in dichloromethane as eluent to give the title compound as a colorless solid (0.08 g, 33%): mp 261-264 °C; ^{1}H NMR (360 MHz, DMSO) δ 1.85 (3 H, s, CH_3), 2.87 (1 H, dd, J = 11.2 and 3.7 Hz, 12-H_{ax}), 3.19 (1 H, dd, J = 4.1 and 3.7 Hz, 10-H), 3.68 (1 H, d, J = 11.2 Hz, 12-H_{eq}), 4.71 (1 H, d, J = 4.1 Hz, 11-H), 5.58 (1 H, br, NH), and 7.08-7.41 (8 H, m, ArH); MS *m/e* found 251.13310, $C_{17}H_{17}NO$ requires 251.13101. Anal. Calcd for $C_{17}H_{17}NO{\cdot}0.9H_2O$: C, 76.32; H, 7.08; N, 5.24. Found: C, 75.98; H, 6.67; N, 5.02.

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Registry No. (±)-**3**, 125299-69-6; (±)-**5**, 125299-73-2; **8**, 89442-07-9; (±)-**13**, 120903-19-7; (±)-**14**, 125299-74-3; (±)-**15**, 125299-75-4; (±)-**16**, 125299-77-6; (±)-**16**·HCl, 34697-36-4; **17**, 125357-78-0; (±)-**23**·HCl, 125357-79-1; (±)-**24**, 125299-76-5; (±)-**25**, 125357-80-4; (±)-**27**, 120903-20-0; (±)-**28**, 120903-20-0; (±)-**29**·HOAc, 125411-78-1; (±)-**30**·HOAc, 125411-79-2; **32**, 18259-45-5; (±)-**33**, 125357-81-5; (±)-**34**, 125357-82-6.

Stereoselectivity in the Ortho Ester Claisen Rearrangements of the *E* and *Z* Isomers of γ-(1,3-Dioxan-4-yl)allyl Alcohols†,[1]

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The *E* and *Z* isomers of (2*R*,4*S*,5*R*)-5-hydroxy-4-(3-hydroxy-1-propenyl)-2-methyl-1,3-dioxane (**3Z** and **3E**), which were derived from 4,6-*O*-ethylidene-D-glucose (**1**), and their 5-*O*-*tert*-butyldimethylsilyl derivatives (**5Z**) and (**5E**) served as substrates for Claisen rearrangements with triethyl orthoacetate. The rearrangement employing **5Z** proceeds with moderate to high levels of diastereoselectivity. The chemically determined stereochemical assignments of the newly introduced stereogenic centers in the rearrangement products reveal that the diastereomer with an *R* configuration is the major rearrangement product. The results of the Claisen rearrangement of **5Z** with triethyl orthopropionate are also described.

Recent reports from these laboratories have described an efficient approach to the stereoselective quaternization of a skeletal carbon of some aldohexoses by means of the ortho ester Claisen (Johnson-Claisen) rearrangement.[2] Furthermore, the utility of the rearrangement product was demonstrated through the total syntheses of various natural products.[3] In the course of our ongoing investigations on the Claisen rearrangement of carbohydrate-derived enantiomeric allyl alcohols, we have studied the Claisen rearrangements of (2*R*,4*S*,5*R*)-5-hydroxy-4-(3-hydroxy-1-propenyl)-2-methyl-1,3-dioxane (**3Z** and **3E**) and their 5-*O*-*tert*-butyldimethylsilyl derivatives **5Z** and **5E** with triethyl orthoacetate and with triethyl orthopropionate.

Compared with our previous results which showed highly stereoselective Claisen rearrangement of bicyclic substrates

† This paper is dedicated to Professor Kenneth L. Rinehart in honor of his 60th birthday.

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