THE JOURNAL OF Organic Chemistry®

VOLUME 44, NUMBER 1

JANUARY 5, 1979

Cycloadducts of Nitrosobenzene with Cyclic Dienones and Dienols

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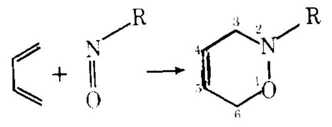
Received July 24, 1978

Nitrosobenzene adds regiospecifically to cyclohexadienones 3 and 4, the oxygen of the nitroso group being oriented toward the carbonyl group in the adduct. Addition to eucarvone, a cycloheptadienone, was slower but also regiospecific in the same sense. The hexamethylcyclohexadienone 5, however, gave both regioisomers in approximately equal amounts. Cyclohexadienols 13 and 14 add nitrosobenzene regiospecifically in two senses; the oxygen of the nitroso group is oriented toward the alcohol substituent, and the hydroxyl group is syn to the N–O bridge. The N–O orientation in addition to dienones and dienols is in accord with expectation from qualitative frontier orbital considerations, and the hydroxyl orientation in the dienol adducts may reflect hydrogen bonding in the transition state.

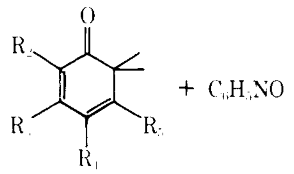
Various *C*-nitroso compounds readily form cycloadducts with conjugated dienes.[1,2] The products are 3,6-dihydro-1,2-oxazines 1, potentially useful synthetic intermediates with



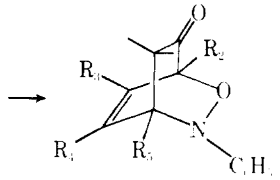
1

functionality at four contiguous carbon atoms since the C=C bond can be functionalized and the N–O bond can be reductively cleaved. These possibilities have been used, for example, in amino sugar synthesis.[3]

To extend the scope and synthetic utility of these reactions, we studied cyclic dienones and dienols as possible diene components in cycloadditions with nitroso compounds. We report here that such cycloadditions to nitrosobenzene proceed readily, often with high yield and high regioselectivity.



2, $R_2 = R_3 = R_4 = R_5 = H$
3, $R_2 = R_5 = H$; $R_3 = R_4 = CH_3$
4, $R_5 = H$; $R_2 = R_3 = R_4 = CH_3$
5, $R_2 = R_3 = R_4 = R_5 = CH_3$

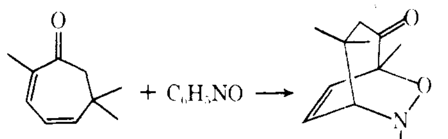


6
7 (51%)
8 (100%)
9 (and regioisomer **10**; 100%)

Results

Cyclohexadienones **2–5** were allowed to react at room temperature with nitrosobenzene in methylene chloride or carbon tetrachloride under a nitrogen atmosphere. Reactions were monitored by NMR and/or by disappearance of the green color of nitrosobenzene. The unsubstituted dienone **2**[4] gave NMR evidence of reaction, but new peaks possibly due to the adduct **6** quickly reached a maximum area when the solution still appeared to contain 75% starting material, and attempts to isolate an adduct were unsuccessful. Methyl substitution on the dienones enhanced their reactivity toward cycloaddition. Thus, the tetramethyldienone **3**[5] gave the crystalline adduct **7** (mp 62–63 °C) in 51% yield, and the pentamethyldienone **4**[6] gave a quantitative yield of **8** (mp 99–102 °C). Only a single regioisomer was obtained in each case, assigned structures **7** and **8** based on spectral and chemical evidence (vide infra). The fully methyl-substituted dienone **5**[7] also added nitrosobenzene quantitatively, but an approximately 1:1 mixture of **9** and its regioisomer **10** (N bonded to C_2 and O to C_5) was formed; only one isomer was isolated in pure form. Of all the dienones and dienols we report on here, only the reaction of **5** gave both regioisomers.

The only seven-membered ring dienone studied was eucarvone (**11**),[8] which reacted quantitatively to give adduct **12** (mp 56–57 °C).



11

12 (100%)

Cyclohexadienols reacted much more rapidly than the corresponding ketones. Thus, yields of **15** and **16** from **13** and

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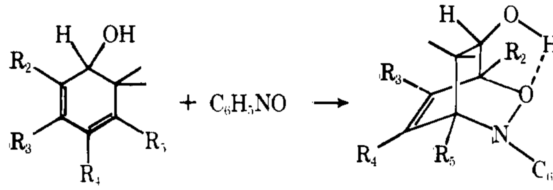
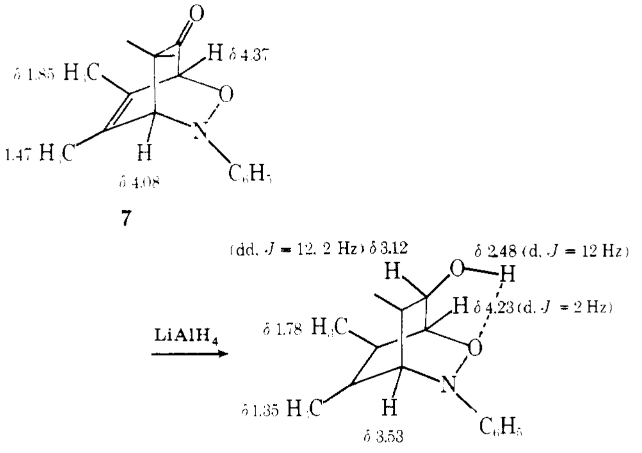


13, $R_2 = R_3 = R_4 = R_5 = H$ 15 (100%)
14, $R_2 = R_5 = H$; $R_3 = R_4 = CH_3$ 16 (100%)

14, respectively, were quantitative in a few minutes at room temperature. The crystalline adducts, unlike those from the corresponding ketones, did not readily dissociate on being warmed in an inert solvent (i.e., during recrystallization). Furthermore, the reactions were not only regiospecific with respect to the diene–nitrosobenzene orientation, but also with respect to the hydroxyl orientation; only the product with the hydroxyl group hydrogen bonded to the oxygen of the N–O bond was formed.

Structure Proof for Adducts 7 and 16. Lithium aluminum hydride reduction of ketone adduct 7 gave a nearly quantitative yield of the alcohol adduct 16. Consequently, the diene–nitrosobenzene orientation must be identical in the two adducts. Reduction of the carbonyl group in 7 occurs exclusively from the face opposite the N–O bridge; this stereochemistry was also observed (vide infra) in the reduction of 8.

The ^1H NMR spectra, shown partially on the structures,[9] were helpful in making a preliminary assignment of the N–O orientation. The coupling pattern fixed the low-field bridgehead proton (δ 4.23) in 16 adjacent to the CHOH of the saturated carbon bridge; the high-field bridgehead proton (δ 3.53) was a singlet. Kresze and Firl noted[10] that in the adducts obtained from *p*-chloronitrosobenzene and a rather large variety of 1,3-dienes, the proton adjacent to oxygen occurs at lower field than that adjacent to nitrogen. Consequently the N–O orientation should be as shown in 16. This assignment was confirmed by deuterium labeling. Starting with **3d** (3; R_2 = D, $R_3 = CD_3$, $R_4 = CH_3$, R_5 = H), the resulting **7d** lacked signals at δ 4.37 and 1.85 and the resulting **16d** lacked signals at δ 4.23 and 1.78.

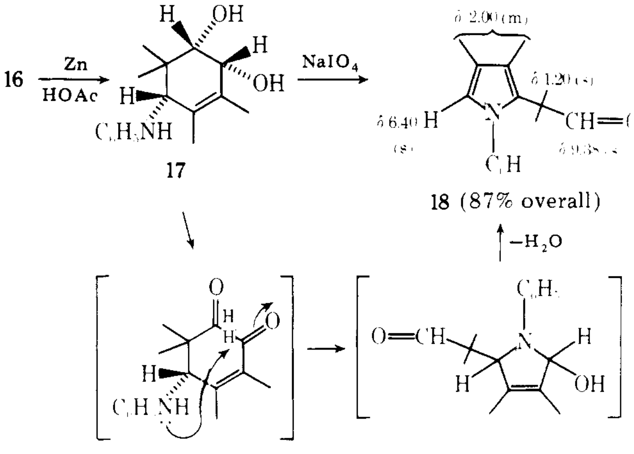


7

16

The chemical shifts of the two vinyl methyl groups in 16 (and in 7) are quite different from one another. Apparently, the methyl at the "N-end" of the molecule is substantially shielded by the *N*-phenyl group.[11]

The structure of 16 (except for O–H stereochemistry, which we discuss later) was also established by chemical degradation. Reduction with zinc and acetic acid followed by periodate oxidation gave the crystalline pyrrole aldehyde 18 in high yield. The structure of 18 was clear from its spectra. If the N–O bond were the other way around in 16, 18 could not have been formed by this reaction sequence.

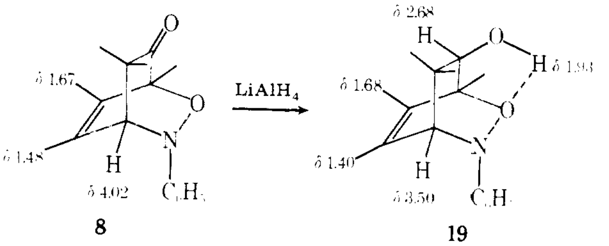


17

18 (87% overall)

Finally, the O–H stereochemistry in 16 is assigned on spectral grounds. The IR spectrum showed a strong intramolecular hydrogen bond OH stretch at 3576 cm^{-1}, unaffected by dilution. Also, comparison of 16 with a series of analogous alcohols (vide infra) shows that the chemical shift of the hydroxyl proton occurs at much lower field (δ 2.4 ± 0.4) when the hydroxyl is "over" the N–O bond than when it is "over" the C=C bond (δ 1.2 ± 0.1). A similar effect, though not quite as large, is seen with the C–H bond of the CHOH groups (δ 3.4 ± 0.1 when "over" the N–O bond, δ 3.0 ± 0.1 when "over" the C=C bond). These differences can reasonably be attributed to shielding by the C=C bridge and deshielding by the N–O bridge.

Structure of Adduct 8. The structure of 8 is based upon comparison of its NMR spectrum with that of 7, upon deuterium labeling, and upon comparison of the NMR spectrum of its reduction product 19 with that of 16. The bridgehead proton of 8 appeared at δ 4.02, comparable with the bridgehead proton adjacent to nitrogen in 7 (δ 4.08). When deuterium-labeled 4 with $R_3 = CD_3$ was used, the resulting labeled 8 (**8d**) lacked the low-field vinyl methyl signal at δ 1.67, consistent with its location toward the oxygen "end" of the N–O bond. Hydride reduction of 8 gave quantitatively a single crystalline alcohol 19, whose bridgehead proton appeared at δ 3.50, consistent with location adjacent to nitrogen (compare with 16). The upfield positions of the CHOH protons in 19 compared with 16 can be attributed to replacement of the bridgehead hydrogen by methyl; the chemical shift of the hydroxyl proton is only consistent with its location syn to the N–O bridge (vide supra; also see Table I).



8

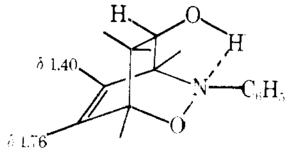
19

Adducts from Hexamethyldienone 5. Reaction of 5 with nitrosobenzene at room temperature for 30 min gave a quantitative yield of two adducts, 9 and its N–O regioisomer 10. Since these ketones could not be separated readily without dissociation problems, they were reduced directly with lithium aluminum hydride to a mixture of four isomeric alcohols. The alcohols were separated by chromatography on silica gel; three were obtained crystalline and the fourth as an oil. They were, in order of elution from the column, assigned structures 20–23. Two alcohols eluted quickly and can be assumed to have a

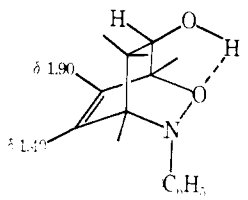
Table I. ^{1}H NMR Spectra of Bicyclic Alcohols[a,b]

compd	C_2	C_3[c]	C_4[c]	C_5	*gem*-dimethyls	O-H	CH-OH	arom
20	1.23	1.40	1.76	1.30	0.83, 1.08	2.98	2.98	6.64-7.18
21	1.40	1.90	1.40	1.23	0.87, 1.03	2.10[d]	2.90[d]	6.70-7.23
22	1.52	1.90	1.38	1.33	0.83, 1.15	1.18[e]	3.38[e]	6.65-7.30
23	1.26	1.40	1.92	1.33	0.80, 1.26	1.26[e]	3.45[e]	6.70-7.23
19	1.42	1.66	1.40	3.50	0.97, 1.27	1.93[d]	2.86[d]	6.60-7.35
16	4.23[f]	1.78	1.35	3.53	0.96, 1.25	2.48[d]	3.12[g]	6.72-7.33
15	4.42[h]	5.80-6.65[i]		3.86[j]	1.00, 1.30	2.42[k]	3.18[l]	6.80-7.35

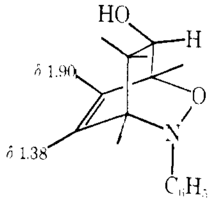
[a] Spectra were obtained in $CDCl_3$, chemical shifts are in δ relative to tetramethylsilane, *J* are in hertz, and all peaks had integrated areas appropriate to the structure. [b] The numbering C_2-C_5 refers to the substituent, H or CH_3, at that carbon atom in the starting cyclohexadienone or cyclohexadienol. [c] These peaks were quartets, $J = 0.8$-1.2 Hz. [d] Doublets, $J = 12$ Hz. [e] Doublets, $J = 9$ Hz. [f] d, $J = 2$ Hz. [g] dd, $J = 12$ and 2 Hz. [h] dt, $J = 6$ and 2 Hz. [i] m. [j] dd, $J = 6$ and 2 Hz. [k] s. [l] d, $J = 2$ Hz.



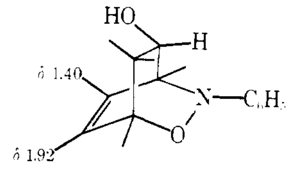
20 (40%)



21 (40%)



22 (10%)

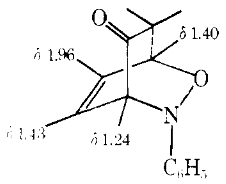


23 (10%)

strong intramolecular hydrogen bond (**20**, **21**), whereas the other two alcohols (**22**, **23**) eluted much more slowly. The O-H protons in **20** and **21** appeared at appreciably lower field (δ 2.98 and 2.10, respectively) than those in **22** and **23** (δ 1.18 and 1.26, respectively); conversely, the proton on the hydroxyl-bearing carbon appeared at lower field in **22** and **23** than in **20** or **21** (Table I). These shift differences support the assignment of the hydroxyl orientation based on chromatographic elution behavior.

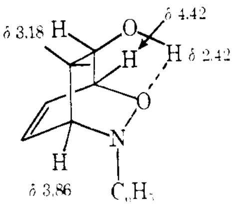
The N-O orientations were settled by deuterium labeling. When **5d** (**5** with a CD_3 group at C_3)[7] was used in place of **5**, the NMR spectra of **20** and **23** lacked the high-field vinyl methyl signal (δ 1.40) and those of **21** and **22** lacked the low-field vinyl methyl signal (δ 1.90). Since in **16**, whose structure was unequivocal from chemical degradation, these methyls were at the N and O "ends" of the molecule, respectively, the N-O orientation of **20-23** can safely be assigned as shown.

When the reaction of **5** with nitrosobenzene was carried out at reflux with 1,2-dichloroethane as solvent for 2 h, a crystalline adduct (mp 78-79 °C) was isolated in about 50% yield. It is assigned structure **10** on the grounds that when **5d** (labeled with CD_3 at C_3) was used, the vinyl methyl signal at δ 1.43 was absent in the NMR spectrum of the product. When **5-*d*$_6$** (labeled with CD_3 at C_3 and C_5) was used, the signals at δ 1.43 and 1.40 were absent. If the high-field vinyl methyl is at the *N*-phenyl "end" of the molecule, and the low-field bridgehead methyl is at the oxygen "end" of the N-O bond, then this ketone must have the N-O orientation shown in **10**.



10

Structure of 15. The N-O and OH orientation of this crystalline alcohol (mp 107-109 °C) could readily be assigned from the NMR spectrum, using correlations developed above. Coupling between the methine proton on the hydroxyl-bearing carbon and the low-field bridgehead proton establishes the N-O orientation, whereas the O-H chemical shift fixes its orientation (Table I). The similarity between the spectra of **15** and **16** lends confidence to the assignment.



15

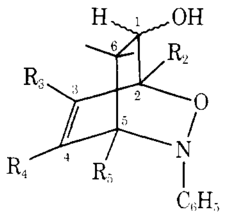
Structure Proof for Adduct 12. The chemical shift of the bridgehead proton in **12** is consistent with its location adjacent to the nitrogen of the N-O bridge, though its value is not conclusive. Therefore, a chemical proof of the N-O orientation was sought. Lithium aluminum hydride reduction of **12** gave a 1:1 mixture of two crystalline alcohols, **24** and **25**. The bridgehead protons in these alcohols appeared at δ 3.76 and 3.78, respectively (coupled with both vinyl protons), again consistent with location adjacent to nitrogen (compare with **16**). Reduction of these alcohols gave crystalline anilino diols **26** and **27**, each of which on periodate oxidation gave the same product, an oil assigned structure **28** on the basis of spectral properties. Its IR spectrum showed strong carbonyl bands at 1687 (α,β-unsaturated ketone) and 1715 cm^{-1} (aldehyde). The NMR spectrum was clear-cut, with an aldehyde triplet at δ 9.40 coupled to a methylene doublet at δ 2.18 ($J = 3$ Hz), a *gem*-dimethyl singlet at δ 1.18, an acetyl methyl at δ 1.77, and vinyl and aryl protons at δ 5.7-6.1 and 7.1-7.5, respectively, as well as peaks attributable to the methine and N-H protons. The retention of the anilino group in this product eliminates the alternative N-O orientation since this reaction sequence would have resulted in its loss as aniline.

^{13}C NMR Correlations. ^{13}C NMR spectra of the bicyclic alcohols were measured, and it was possible to assign most of the peaks uniquely. These assignments are summarized in Table II.

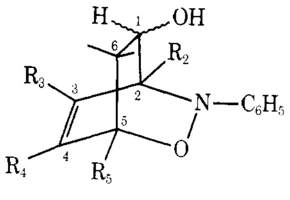
Discussion

The kinetic study[12] of the cycloaddition of 1,3-cyclohexadiene to a variety of substituted nitrosobenzenes showed that electron-withdrawing substituents on the dienophile increase the rate and that electron-donating substituents retard the rate. Consequently, nitrosobenzene falls into the familiar class

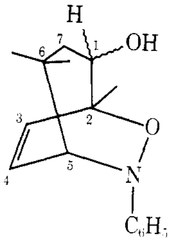
Table II. ^{13}C NMR Spectra of Bicyclic Alcohols[a]



15, 16, 19, 21, 22



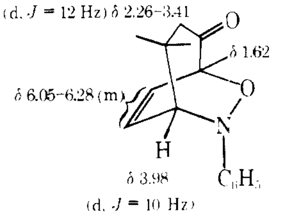
20, 23



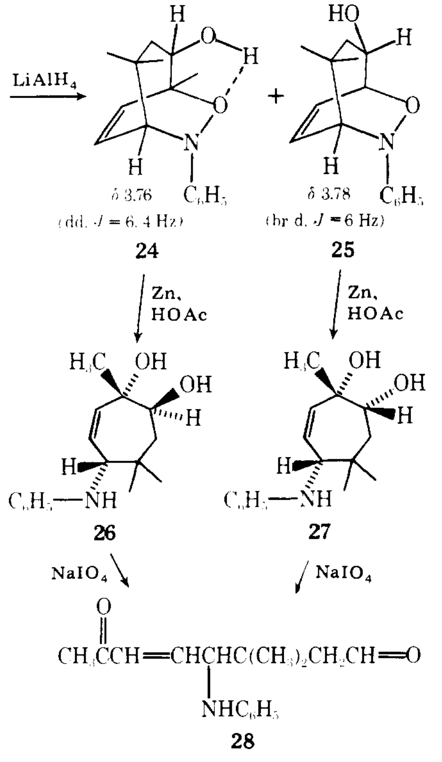
24, 25

compd	1	2	3	4	5	6	gem	R_2	R_3	R_4	R_5	aryl[b]
15	73.85	76.26	127.71	132.50	67.51	34.65	24.56, 29.91					152.12, 121.86, 117.00, 128.43
16	74.04	81.34	126.89	132.63	73.85	35.35	21.54, 29.12		14.41[d]	18.26		152.71, 121.83, 117.13, 128.29
19	76.78	80.93	128.91	132.83	73.54	35.65	21.83, 29.25	16.58	11.87[d]	18.90		152.79, 121.63, 117.04, 128.24
21	77.86	78.69	130.78	134.06	67.62	39.42	17.96,[c] 28.36	17.29[c]	12.78[d]	15.73[c]	16.02[c]	149.45, 125.19, 124.81, 127.49
22	81.61	77.95	129.95	134.54	68.14	41.83	20.77, 25.13	18.85[c]	14.02[d]	15.66[c]	16.08[c]	149.63, 124.81, 124.48, 127.38
20	77.62	66.00	128.26	135.97	81.62	40.47	19.23,[c] 27.82	14.20[c]	14.17[d]	15.36[c]	18.42[c]	148.48, 125.37, 124.16, 127.61
23	80.99	65.77	128.34	135.50	80.69	43.03	20.08,[c] 24.49	14.17[c]	15.26[d]	15.04[c]	18.88[c]	148.91, 125.29, 124.65, 127.51
24	73.16	77.69	129.02	132.35	70.25	35.80[e]	28.76, 30.14	23.54				152.88, 121.55, 117.36, 128.33
25	74.06	78.64	129.21	129.95	68.69	32.67[e]	25.77, 31.68	23.25				152.81, 121.13, 116.85, 128.49

[a] The numbering system is based on the numbering of the dienol or dienone from which the adduct was prepared, as indicated in the structures above. [b] Aryl carbons are listed in the sequence ipso, para, and ortho–meta, with the last two not being distinguished. [c] Assignment of these methyls may be interchanged. [d] Established by deuterium label. [e] The methylene carbon in the three-carbon bridge is at δ 44.78 in **24** and δ 44.96 in **25**.



12

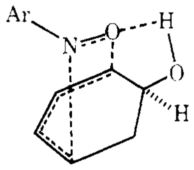


$$\underset{\displaystyle NHC_6H_5}{CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH{=}CH\underset{|}{C}HC(CH_3)_2CH_2CH{=}O}$$

of electron-demanding dienophiles. Its enhanced rate of reaction with cyclohexadienols **13** and **14** as compared with the corresponding cyclohexadienones **2** and **3**, respectively, which we observed and the greater stability of the dienol adducts vis-à-vis the dienone adducts are therefore quite reasonable.

The orientation of nitrosobenzene cycloadditions has been discussed at length,[2b] and both steric and electronic factors can be involved. Our results show that the addition is highly regioselective in the case of dienones and dienols, with the oxygen of the nitroso group being oriented toward the diene carbon which bears the carbonyl or CHOH substituent. The only exception occurred with **5**, where both regioisomers **9** and **10** were formed in approximately equal amounts. In this case, steric factors may be involved since both termini of the diene moiety are methyl substituted. The high regioselectivity in all other cases can be rationalized using approximate frontier orbital theory. The most important interactions are between the HOMO of the dienone or dienol and the LUMO of the nitrosobenzene. Coefficients are expected to be largest for these orbitals at C_5 of the dienone or dienol and on the nitrogen of the nitroso group,[13] accounting for the formation of a C_5–N and C_2–O bond in the cycloaddition products.

The high regioselectivity of the hydroxyl groups in the dienol adducts **15** and **16** is striking. The syn orientation of the hydroxyl group and the N–O bridge in the product may be a



reflection of some hydrogen bonding between the two oxygens in the transition state. A similar factor may be involved in the highly regioselective hydride reduction of the dienone adducts **7** and **8**. This regioselectivity, which is absent, however, in the hydride reduction of the eucarvone adduct **12**, must be favored by the geometry of the bicyclo[2.2.2] ring system.

If the regioselectivity demonstrated here with nitrosobenzene can be obtained with other *C*-nitroso compounds with modifiable or removable groups on the nitrogen (i.e., chloronitroso compounds or nitrosyl cyanide), then the reactions we have described with dienones and dienols may have considerable synthetic utility. These possibilities are being explored.

Experimental Section

^{1}H NMR spectra were recorded with a Varian Model A-60 or T-60 spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained with a Varian CFT-20 spectrometer. IR spectra were obtained with a Unicam Model SP-200 or Perkin-Elmer Model 137 spectrometer and were calibrated (polystyrene). UV spectra were measured with a Unicam Model SP-800 ultraviolet spectrophotometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 mass spectrometer at 70 eV. Elemental analyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, Mich., or by Clark Microanalytical Laboratory, Urbana, Ill. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected.

***N*-Phenyl-7-oxa-8-aza-3,3,5,6-tetramethylbicyclo[2.2.2]oct-5-en-2-one (7).** A solution of dienone **3**[5] (1.5 g, 10 mmol), nitrosobenzene (1.07 g, 10 mmol, Aldrich Chemical Co.; if not green, recrystallize from ethanol; store in freezer), and methylene chloride (20 mL) was stirred at room temperature until the green color disappeared (about 4 h). The solvent was removed at room temperature (rotary evaporator), and the residual dark, viscous oil was dissolved in a minimum volume of pentane. The solution, cooled overnight in a refrigerator, deposited 1.35 g (51%) of crystals, which on recrystallization from pentane gave light yellow **7**: mp 62–63 °C; IR (Nujol) 1720 (s), 1600 (w), 1595 (m), 1220 (m), 1020 (w), 903 (m), 770 (s), 700 (s) cm^{-1}; NMR (CCl$_4$) δ 1.08 (s, 3 H), 1.40 (s, 3 H), 1.47 (q, 3 H, J = 1.2 Hz), 1.85 (q, 3 H, J = 1.2 Hz), 2.7–3.2 (m, 5 H), 4.08 (s, 1 H), 4.37 (s, 1 H).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.59; H, 7.56; N, 5.44.

Deuterated **3** was prepared by refluxing **3** (1 g, 7 mmol) in methanol-*d* (50 mL) containing sodium methoxide (1.25 g) for 24 h under nitrogen. The methanol was evaporated in vacuo, and the residue was extracted with hot benzene. The benzene extract was washed with water, dried (MgSO$_4$), and evaporated to give **3d** which lacked the ^{1}H NMR signals at δ 2.02 (C$_3$ methyl) and 5.68 (C$_2$ vinyl proton). Adduct **7d** obtained from this dienone lacked ^{1}H NMR signals at δ 1.85 and 4.37, and the signal at δ 1.47 sharpened to a singlet.

***N*-Phenyl-7-oxa-8-aza-3,3,5,6-tetramethylbicyclo[2.2.2]oct-5-en-2-ol (16).** Dienone **3** (1.5 g, 10 mmol) in anhydrous ether (80 mL) was added to a slurry of lithium aluminum hydride (0.2 g, 5 mmol) in anhydrous ether (40 mL) at 0 °C. After 2 h of stirring at 0 °C, standard workup[14] gave a quantitative yield of dienol **14** which was dissolved in 20 mL of ice-cold methylene chloride and treated directly with nitrosobenzene (1.07 g, 10 mmol). Reaction was complete in 2 h at 0 °C (green color absent) and was quantitative. Removal of the solvent at reduced pressure and recrystallization of the residue from pentane gave pure **16**, mp 98–99 °C. The adduct could also be sublimed (90–100 °C, 0.1 torr) without dissociation: IR (Nujol) 3330 (s), 1597 (m), 1130 (m), 1065 (s), 964 (w), 833 (s), 765 (s), 730 (s), 700 (s) cm^{-1}; ^{1}H NMR, see Table I; treatment with D$_2$O caused the peak at δ 2.48 to disappear, and that at δ 3.12 collapsed to a broad singlet; ^{13}C NMR, see Table II.

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.04; H, 8.13; N, 5.34.

Starting with **3d**, the resulting **16d** lacked the doublet of δ 4.23 and quartet at δ 1.78, and the quartet at δ 1.35 sharpened to a singlet.

Reduction of 7. A solution of **7** (0.26 g 1 mmol) in ice-cold ether (25 mL) was added rapidly to an ice-cold stirred slurry of lithium aluminum hydride (0.5 g) in ether (20 mL). After 30 min at 0 °C, standard workup[14] gave a quantitative yield of **16** (identical melting point, IR, NMR). An NMR spectrum of the crude product gave no evidence for any epimeric alcohol.

2-Methyl-2-[*N*-phenyl-3′,4′-dimethyl-2′-pyrryl]propanal (18). To a solution of **16** (1.3 g, 5 mmol) in glacial acetic acid (15 mL) was added 5 g of zinc powder, and the mixture was stirred at 50 °C for 6 h. The cooled mixture was diluted with ether and filtered to remove the excess zinc. The ether and most of the acetic acid were removed under reduced pressure, water (25 mL) was added, and the solution was neutralized with concentrated ammonium hydroxide and extracted with ether. The ether extract was washed with water, dried (MgSO$_4$), and evaporated to give 1.26 g of a brown oil (crude **17**): IR (neat) 3450–3550 cm^{-1} (s); NMR (CDCl$_3$) δ 0.90, 1.07, 1.32, and 1.72 (s, 3 H each), 3.22–4.30 (br m, 6 H), 6.53–7.17 (m, 5 H, arom).

To a solution of the crude diol **17** (1.25 g, 5 mmol) in absolute ethanol (20 mL) was added at room temperature a solution of sodium metaperiodate (1.1 g, 5 mmol) in water (8 mL). Within 10 min a white precipitate deposited from the previously clear solution. After 30 min of stirring at room temperature, the mixture was filtered and the clear filtrate was evaporated under reduced pressure to give a semisolid residue which was diluted with water (5 mL) and extracted with ether. The ether extract was washed with water, dried (MgSO$_4$), and evaporated to give crude **18** as a dark viscous oil (1.09 g, 87%). Vapor phase chromatography (10 ft × 0.25 in. SE-30 column, 220 °C, He rate 85 mL/min, retention time 12 min) gave pure **18**: mp 59–60 °C; IR (neat) 2720 (w), 1715 (s), 1600 (m), 1500 (s), 1464 (m), 1402 (s), 1375 (s), 1220 (m), 1110 (m), 920 (w), 788 (s), 760 (s) cm^{-1}; NMR (CDCl$_3$) δ 1.20 (s, 6 H), 2.00 (m, 6 H), 6.40 (m, 1 H), 7.32 (m, 5 H), 9.38 (s, 1 H).

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.44; H, 7.97; N, 5.75.

***N*-Phenyl-7-oxa-8-aza-1,3,3,5,6-pentamethylbicyclo[2.2.2]oct-5-en-2-one (8).** A solution of **4**[6] (1.08 g, 6 mmol) and nitrosobenzene (0.74 g, 6.3 mmol) in carbon tetrachloride (15 mL) gave, after 30 min at room temperature and removal of the solvent at reduced pressure, a quantitative yield of **8**: mp 99–102 °C (30–60 °C petroleum ether); IR (Nujol) 1720 (s), 1590 (m), 1210 (w), 1030 (m), 800 (w), 765 (s), 720 (w), 700 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.13, 1.45, and 1.48 (s, 3 H each), 1.48 and 1.67 (q, 3 H each, J = 1.2 Hz), 4.02 (s, 1 H), 6.90–7.05 (m, 5 H).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.35; H, 7.82; N, 5.18. Found: C, 75.24; H, 7.80; N, 5.16.

From **4d** (**4** with a CD$_3$ group at C$_3$), prepared from **4**, methanol-*d*, and sodium methoxide,[7] the resulting **8d** lacked the quartet at δ 1.67 and the peak at δ 1.48 sharpened to a 6 H singlet.

***N*-Phenyl-7-oxa-8-aza-1,3,3,5,6-pentamethylbicyclo[2.2.2]oct-5-en-2-ol (19).** Lithium aluminum hydride reduction of **8** (as described for **7**) gave a quantitative yield of **19**: mp 113–114 °C (pentane); IR (Nujol) 3300 (s), 1598 (s), 1205 (m), 1170 (m), 1140 (m), 1060 (s), 1035 (m), 1000 (w), 920 (m), 820 (m), 780 (s), 700 (s) cm^{-1}; ^{1}H NMR, see Table I; with D$_2$O, the peak at δ 1.93 disappeared and the peak at δ 2.86 collapsed to a broad singlet; ^{13}C NMR, see Table II.

Alcohols 20–23. Nitrosobenzene (1.12 g, 10.5 mmol) was added to a solution of **5**[7] (1.78 g, 10 mmol) in carbon tetrachloride (25 mL), and the mixture was allowed to stand at room temperature for 30 min. Removal of the solvent under reduced pressure gave a quantitative yield of an approximately 1:1 mixture of adducts **9** and **10** (NMR). Attempts to resolve the mixture by various chromatographic techniques were thwarted due to dissociation back to **5** and nitrosobenzene (green color).

The crude ketone mixture was reduced by a 4–5-fold excess of lithium aluminum hydride in ether (200 mL) at 0 °C, followed by standard workup.[14] The resulting alcohol mixture (quantitative yield) was chromatographed on silica gel (60 g) using 4:1 hexane–ether as eluent. The products, in order of elution, had the following properties. For **20**: viscous liquid; IR (neat) 3480 cm^{-1}; ^{1}H NMR, see Table I; D$_2$O decreased the area of the peak at δ 2.98 to 1 H; ^{13}C NMR, see Table II; mass spectrum, *m/e* (relative intensity) 287 (4), 200 (8), 77 (100). M_r Calcd for $C_{18}H_{25}NO_2$: 287.18851. Found: 287.18793. For **21**: mp 108–109 °C (hexane); IR (KBr) 3330 cm^{-1}; ^{1}H NMR, see Table I; with D$_2$O, the peak at δ 2.10 disappeared and the peak at δ 2.90 collapsed to a broad singlet; ^{13}C NMR, see Table II; mass spectrum, *m/e* (relative intensity) 287 (12), 200 (100), 77 (33). M_r Calcd for $C_{18}H_{25}NO_2$: 287.18851. Found: 287.18820. For **22**: mp 113–115 °C (hexane); IR (KBr) 3450 cm^{-1}; ^{1}H NMR, see Table I; with D$_2$O, the peak at δ 1.18 disappeared and the peak at δ 3.38 collapsed to a broad singlet; ^{13}C NMR, see Table II; mass spectrum, *m/e* (relative intensity) 287 (10), 200 (100), 77 (45). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77. Found: C, 75.19; H, 8.80. For **23**: mp 128–129 °C (hexane); IR (KBr) 3440 cm^{-1}; ^{1}H NMR, see Table I; with D$_2$O, the peak at δ 1.26 vanished and the peak at δ 3.45 collapsed to a broad singlet; ^{13}C NMR, see Table II; mass spectrum, *m/e* (relative intensity) 287 (10), 200 (100), 77 (98). M_r Calcd for $C_{18}H_{25}NO_2$: 287.18851. Found: 287.18878. The yields of **20–23** were 40, 40, 10, and 10%, respectively.

Use of **5d**[7] (CD$_3$ at C$_3$) gave **20d** and **23d** lacking the signal at δ 1.40, and the signals at δ 1.76 and 1.92, respectively, sharpened to singlets; for **21d** and **22d**, the signal at δ 1.90 was absent and that at δ 1.40 or 1.38, respectively, sharpened to a singlet.

***N*-Phenyl-7-aza-8-oxa-1,3,3,4,5,6-hexamethylbicyclo[2.2.2]-oct-5-en-2-one (10).** A solution of **5**[7] (1.78 g, 10 mmol) and nitrosobenzene (1.07 g, 10 mmol) in 1,2-dichloroethane (25 mL) was refluxed for 2 h. Removal of the solvent at reduced pressure left a brown viscous oil which was dissolved in petroleum ether (30–60 °C) and cooled overnight in a refrigerator. Two crops of crystals were collected, yielding 1.82 g (65%) of **10**: mp 78–79 °C; IR (Nujol) 1720 (s), 1640 (w), 1590 (m), 1392 (s), 1300 (w), 1220 (m), 1120 (w), 1090 (m), 1080 (m), 1035 (m), 950 (w), 815 (w), 788 (s), 707 (s) cm^{-1}; NMR (CCl_4) δ 0.97, 1.11, 1.24, and 1.40 (s, 3 H each), 1.43 and 1.96 (q, 3 H each, *J* = 1.2 Hz), 7.00–7.06 (m, 5 H).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.85; H, 8.25; N, 4.92.

Use of **5d** (CD_3 at C_3)[7] gave **10d** lacking the quartet at δ 1.43, and the signal at δ 1.96 sharpened to a singlet. Use of **5-*d*₆** (CD_3 at C_3 and C_5) gave **10-*d*₆** lacking signals at δ 1.43 and 1.40, with the signal at δ 1.96 sharpened to a singlet.

Lithium aluminum hydride reduction of **10** (as described for **7**) gave mainly **20** (NMR), contaminated with another isomer, presumably **23**.

Reaction of 6,6-Dimethyl-2,4-cyclohexadienone (2) with Nitrosobenzene. A solution of **2**[4] (0.61 g, 5 mmol) and nitrosobenzene (0.59 g, 5.5 mmol) in carbon tetrachloride (10 mL) was monitored by ^{1}H NMR. A new set of peaks including a singlet at δ 1.30 grew in quickly, but then ceased to increase in area (the *gem*-dimethyl group of **2** appears as a singlet at δ 1.16). Removal of the solvent and workup of the residue did not yield any adduct **6** (the new singlet may have been due to **6** or dimers of **2**).

***N*-Phenyl-7-oxa-8-aza-3,3-dimethylbicyclo[2.2.2]oct-5-en-2-ol (15).** Dienone **2**[4] (10 mmol) was reduced quantitatively with excess lithium aluminum hydride in ether at 0 °C by standard procedures, and the resulting crude dienol **13** was treated directly with 1.05 equiv of nitrosobenzene in carbon tetrachloride (15 mL) at room temperature. Reaction was complete in less than 15 min (NMR) and gave a quantitative yield of a single adduct **15**: mp 107–109 °C (3:1 hexane–ethyl acetate); IR (KBr) 3500 cm^{-1}; ^{1}H NMR, see Table I; in D_2O, the peak at δ 2.42 vanished; ^{13}C NMR, see Table II; mass spectrum, *m/e* (relative intensity) 231 (22), 184 (100).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.78; H, 7.34.

***N*-Phenyl-8-oxa-9-aza-1,4,4-trimethylbicyclo[3.2.2]non-6-en-2-one (12).** A solution of eucarvone[8] (7.5 g, 0.05 mol) and nitrosobenzene (5.35 g, 0.05 mol) in methylene chloride (150 mL) was stirred at room temperature for 10 h, by which time the green color was discharged. Evaporation of the solvent under reduced pressure, dissolution of the residual oil in pentane, and cooling overnight in a refrigerator afforded a near quantitative yield of **12**: mp 56–57 °C; IR (Nujol) 1705 (s), 1655 (s), 1595 (m), 1375 (s), 1240 (m), 1180 (m), 1090 (s), 1020 (s), 862 (s), 770 (s), 700 (s) cm^{-1}; UV λ_{max} (CH_3OH) 285 sh (ε 162), 244 (7558), 208 (10 400); ^{1}H NMR ($CDCl_3$) δ 1.07, 1.45, and 1.62 (s, 3 H each), 2.26 and 3.41 (d, 1 H each, *J* = 12 Hz), 3.98 (d, 1 H, *J* = 10 Hz), 6.05–6.28 (m, 2 H), 6.92–7.40 (m, 5 H). The peak at δ 2.26 was further split into a doublet, *J* = 1 Hz, and the peak at δ 3.98 was further split into multiplets. ^{13}C NMR ($CDCl_3$) δ 206.18 (carbonyl), 152.83 (C_1 phenyl), 122.18 (C_4 phenyl), 117.36 and 128.59 ($C_{2,3}$ phenyl), 129.14 and 132.62 (vinyl carbons), 53.77 (methylene, confirmed by deuterium substitution), 82.63 (bridgehead adjacent to carbonyl), 71.41 (other bridgehead), 39.48 (quaternary carbon with *gem*-dimethyl), 26.30 and 29.91 (*gem*-dimethyl), 19.95 (bridgehead methyl).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.86; H, 7.60; N, 5.55.

Reduction of 12. Lithium aluminum hydride (0.5 g) reduction of **12** (1.3 g, 5 mmol) in 200 mL of ether at 0 °C for 2 h followed by the usual workup[14] gave a mixture of **24** and **25** (1:1) in quantitative yield. This mixture could be resolved either by fractional crystallization, **24** being much more soluble in hexane than **25**, or by chromatography on silica gel with 4:1 hexane–ether as eluent. For **24**: mp 79–80 °C; IR (KBr) 3440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98, 1.37, and 1.53 (s, 3 H each), 1.62–1.75 (m, 2 H), 2.60 (d, 1 H, *J* = 11 Hz), 3.56 (dt, 1 H, *J* = 11 and 5 Hz), 3.76 (dd, 1 H, *J* = 6 and 4 Hz), 5.90–6.10 (m, 2 H), 6.75–7.30 (m, 5 H); with D_2O, the peak at δ 2.60 vanished and that at δ 3.56 collapsed to a triplet, *J* = 5 Hz; ^{13}C NMR, see Table II; mass spectrum, *m/e* (relative intensity) 259 (40), 77 (100). M_r Calcd for $C_{16}H_{21}NO_2$: 259.15720. Found: 259.15723. For **25**: mp 159–160 °C; IR (Nujol) 3250 (s), 1600 (m), 1230 (m), 1055 (s), 1035 (s), 1020 (s), 850 (s), 760 (s), 700 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03, 1.27, and 1.57 (s, 3 H each), 1.17 (dd, 1 H, *J* = 14 and 10 Hz), 1.56 (d, 1 H, *J* = 6 Hz), 1.73 (dd, 1 H, *J* = 14 and 6 Hz), 3.60 (dt, 1 H, *J* = 10 and 6 Hz), 3.78 (brd, 1 H, *J* = 6 Hz), 5.78 (dd, 1 H, J = 10 and 2 Hz), 6.03 (dd, 1 H J = 10 and 6 Hz), 6.45–7.30 (m, 5 H); with D_2O, the peak at δ 1.56 vanished and that at δ 3.60 collapsed to a dd, *J* = 10 and 6 Hz; ^{13}C NMR, see Table II. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.14; H, 8.10; N, 5.37.

Reduction of 24 and 25. To a solution of **25** (1.30 g, 5 mmol) in glacial acetic acid (55 mL) was added 5 g of zinc dust, and the mixture was stirred at 55 °C for 14 h. The cooled mixture was extracted with ether, the ether extract was filtered and evaporated (reduced pressure), and the residue was diluted with water and neutralized with concentrated ammonium hydroxide. The neutral mixture was extracted with ether, and the ether extract was washed with water, dried ($MgSO_4$), and evaporated to give a quantitative yield of **27**: mp 118–119 °C (ether); IR (Nujol) 3400 (m), 3260 (m), 1600 (s), 1520 (m), 1325 (w), 1100 (m), 1055 (w), 1020 (w), 950 (m), 760 (m), 700 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07, 1.10, and 1.37 (s, 3 H each), 1.72 (d, 2 H, *J* = 6 Hz), 2.85 (br s, 2 H), 3.65–4.00 (m, 3 H), 5.15–5.85 (m, 2 H), 6.42–7.23 (m, 5 H).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.37; H, 8.77; N, 5.30.

Similar reduction of **24** gave a quantitative yield of **26**: mp 95–96 °C; IR (Nujol) 3380 (m), 3260 (m), 1600 (s), 1310 (w), 1260 (m), 1140 (m), 1030 (s), 900 (s), 760 (s), 730 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02, 1.12, and 1.38 (s, 3 H each), 1.60–2.37 (m, 3 H), 3.47–3.75 (br, 4 H), 5.63–5.66 (m, 2 H), 6.50–7.23 (m, 5 H).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N. 5.36. Found: C, 73.31; H, 8.87; N, 5.23.

Oxidation of 26 and 27. To a solution of **27** (261 mg, 1 mmol) in methanol (30 mL) was added a solution of 0.45 g (2 mmol) of sodium metaperiodate in 5 mL of water. The mixture was stirred at room temperature for 3 h, after which the precipitated sodium iodate was filtered off and the clear filtrate was evaporated at reduced pressure. The residue, diluted with water, was extracted with methylene chloride. The extracts were washed with water, dried ($MgSO_4$), and evaporated to give a brown oil which was chromatographed on silica gel (5 g). The first fraction (105 mg) was a yellow oil (**28**): IR (neat) 3050 (m), 1718 (s), 1690 (s), 1600 (s), 1185 (s), 1050 (w), 770 (m), 690 (s) cm^{-1}; NMR (CCl_4) δ 9.40 (t, 1 H, *J* = 3 Hz). The product was contaminated with other products, and a purer sample was obtained in comparable yield by analogous oxidation of **26**: NMR (CCl_4) δ 1.18 (s, 6 H), 1.77 (s, 3 H), 2.18 (d, 2 H, *J* = 3 Hz), 5.77–6.10 (m, 2 H), 7.1–7.5 (m, 5 H), 9.40 (t, 1 H, *J* = 3 Hz).

Acknowledgment. We express appreciation to the National Institutes of Health (GM16997), the National Science Foundation (CHE76-08534), and the 3M Co. for financial support of this research.

Registry No.—**2**, 21428-63-7; **3**, 14069-95-5; **4**, 16395-18-9; **5**, 3854-96-4; **7**, 68070-79-1; **8**, 68070-80-4; **9**, 68070-81-5; **10**, 68070-82-6; **12**, 68070-83-7; **13**, 51983-44-9; **14**, 14069-97-7; **15**, 68070-77-9; **16**, 68070-76-8; **17**, 68070-84-8; **18**, 68070-85-9; **19**, 68070-75-7; **20**, 68070-73-5; **21**, 68070-74-6; **22**, 68108-28-1; **23**, 68108-29-2; **24**, 68070-78-0; **25**, 68108-30-5; **26**, 68070-86-0; **27**, 68108-31-6; **28**, 68070-87-1; nitrosobenzene, 586-96-9; eucarvone, 503-93-5.

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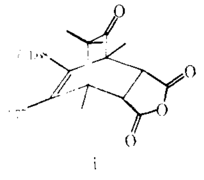

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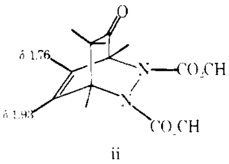

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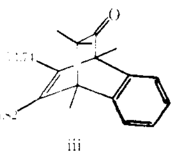

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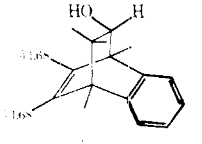
moconjugation between the carbonyl group and the double bond since it is wiped out when the carbonyl group is reduced (iv and v, A. C. Gripper Gray and H. Hart, loc. cit.). The substantial reversal of these shifts in **7** and **8** and the marked difference in the vinyl methyls in alcohols **16, 19, 20, 21, 22,** and **23** must be ascribed to the N–O bridge and/or shielding by the *N*-phenyl group.



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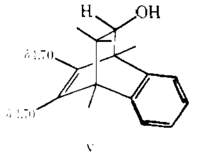

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Permethylnaphthacene

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Received July 25, 1978

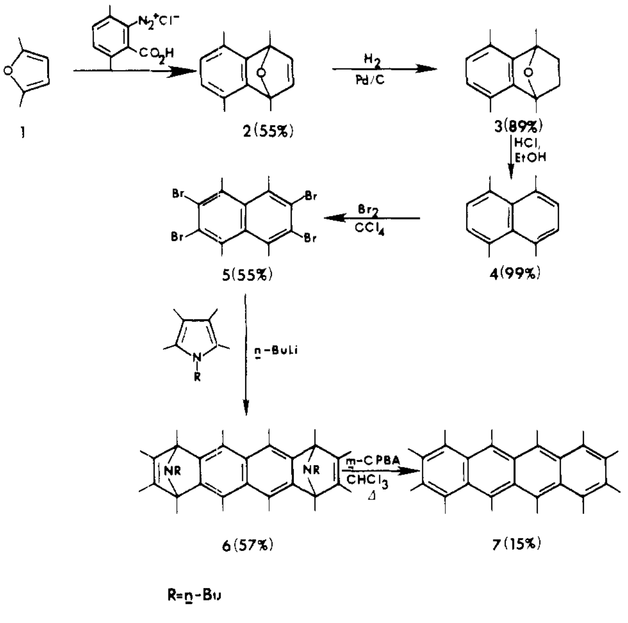
Dodecamethylnaphthacene, a compound with six peri interactions between methyl groups, has been synthesized in three steps from 1,4,5,8-tetramethylnaphthalene. A key step involves a bis or double aryne cycloaddition.

Permethylarenes present a synthetic challenge for several reasons. As a consequence of "peri" interactions, they are highly strained and the synthetic scheme must include strategy for making the acceptance of this strain palatable. They also readily isomerize to nonaromatic isomers in acid or base, so these reagents must be avoided or used with care in the final steps.[1] We have developed syntheses for octamethylnaphthalene,[2] decamethylanthracene,[3] and other highly substituted arenes[4] which introduce the "peri" interaction in a step which also aromatizes one of the rings, thus offering the transition state some compensation for the strain.

We wish to describe here the extension of this strategy to the synthesis of dodecamethylnaphthacene. An interesting feature of the synthesis is the use, in effect, of a bisaryne. The synthesis is outlined in Scheme I (yields are of isolated materials).

The first three steps represent an improved synthesis of the known[5] 1,4,5,8-tetramethylnaphthalene (**4**). 3,6-Dimethylbenzyne, generated from the diazonium carboxylate,[2] gave adduct **2** with 2,5-dimethylfuran in 55% yield.[6] Catalytic hydrogenation to **3** and dehydration to **4** proceeded in excellent yield.

Scheme I



Bromination of **4** in CCl_4 at 0–5 °C with iodine as the catalyst gave the ring-brominated product **5** in fair yield.[7] The NMR spectrum of **5** had a single peak at δ 2.70. *o*-Dibromoarenes have been used as aryne precursors,[8] and **5** was envisioned as a bisaryne precursor[9,10] which could supply the two central rings of permethylnaphthacene. Treatment of a mixture of **5** and *N*-*n*-butyltetramethylpyrrole with *n*-butyllithium gave a reasonable yield of a crystalline adduct **6**. The stereochemical relationship between the two nitrogen bridges is not known, but only a single isomer was obtained. The NMR spectrum of **6** had three singlets of equal area (12 H) for the three sets of methyl groups (δ 2.50, 1.89, and 1.70), consistent with the symmetry of a bisadduct. Some monoadduct may have been present, but was not isolated. The final step, elimination of the nitrogen bridges, could be accomplished only in poor yield by oxidation with *m*-chloroperbenzoic acid and thermal elimination of the *N*-oxide.[11]

Dodecamethylnaphthacene (**7**) is a reddish-orange crystalline hydrocarbon, mp 265–266 °C, with a rich electronic spectrum, the longest wavelength maximum being at 537 nm. Its ^1H NMR spectrum has three equal singlets at δ 2.98, 2.66, and 2.32, which can be assigned to the three sets of methyls as one proceeds from the center of the molecule to the ends. The methyl carbons in the ^{13}C NMR spectrum also had very different chemical shifts (δ 28.55, 22.57, and 16.32).

Dodecamethylnaphthacene is sensitive to traces of acid. Solutions in chloroform gradually develop new peaks in the ^1H NMR spectrum due to an isomer; this isomer turns up among the products of most reactions attempted with **7**. It can be obtained by treating a methylene chloride solution of **7** with a drop of trifluoroacetic acid (TFA). The red solution becomes blue-violet and then yellow and gives on workup the colorless crystalline isomer assigned structure **8**. The NMR spectrum shows doublets for the vinyl protons at δ 5.47 and 5.73 (J = 2.4 Hz), a methine quartet at δ 4.60, and a methyl doublet at δ 1.23 (J = 7.1 Hz), as well as a series of peaks for the aryl methyl groups. This facile isomerization is similar to that observed previously with other polymethylarenes containing double "peri" interactions.[1,3]

Solutions of dodecamethylnaphthacene are also sensitive to oxidation.[12] Irradiation of a carbon disulfide solution of **7** that was exposed to the air with a quartz iodine lamp gave (in addition to **8**) an endoperoxide **9** and other products. Attempts to photoisomerize **7** to a Dewar isomer (as occurs with decamethylanthracene[3]) by irradiating degassed benzene solutions led to products not yet identified.

0022-3263/79/1944-0007$01.00/0