Conversion of Barbaralone into Bicyclo[4.2.1]nona-2,4,7-trien-9-one by a Bromination–Reduction Sequence

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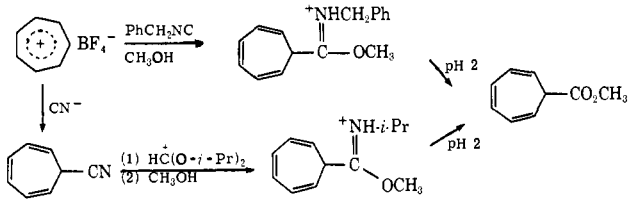
Abstract: Treatment of barbaralone with bromine affords the tetracyclic dibromide II, which is converted into barbaralone (I) and bicyclo[4.2.1]nona-2,4,7-trien-9-one (IV) upon treatment with sodium amalgam. The major product IV is formed *via* internal alkylation of the bromo enolate VIIb to the tetracyclic ketone XI, followed by retro Diels–Alder cleavage. Barbaralone is formed from the bromo enolate VIIa by an unusual rearrangement. An improved method for preparation of methyl cycloheptatrienecarboxylate is described starting with tropylium fluoroborate and an isonitrile.

In a preliminary report, we described the bromination of tricyclo[3.3.1.0^{2,8}]nona-3,6-dien-9-one (I, barbaralone) and some reactions of the major product, the tetracyclic dibromide II.[3] Minor amounts of the symmetrical isomer III were also isolated in addition to bicyclic dibromides. Treatment of the bicyclic dibromides or of the tetracyclic dibromide III with sodium amalgam resulted in conversion to barbaralone (I), but similar treatment of II was found to produce a mixture of ketones including I. We now report that the major reduction product is bicyclo[4.2.1]-nona-2,4,7-trien-9-one (IV), the result of an interesting sequence of rearrangements. Surprisingly, the other major product, barbaralone, is formed *via* ionic rearrangement and not by 1,4 fragmentation alone.

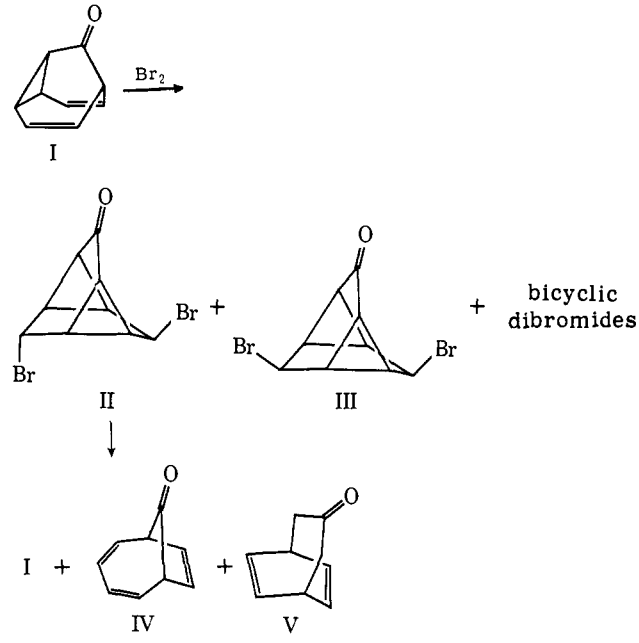
Starting Materials. Preparation of Methyl Cycloheptatrienecarboxylate. Barbaralone was prepared essentially according to the method of Doering, *et al.*,[4] *via* the diazo ketone derived from cycloheptatrienecarboxylic acid. The difficulties involved with preparation of the acid by decomposition of ethyl diazoacetate in benzene[5] prompted us to consider alternatives which would be less tedious on large scale. A simple procedure was found, involving the reaction of tropylium fluoroborate with benzyl isonitrile[6,7] in cold methanol, followed by hydrolysis of the intermediate imidate ester at pH 1–3.



A second, related method was developed *via* mild hydrolysis of cycloheptatrienyl cyanide. Treatment of the cyanide with diisopropoxycarbonium fluoroborate,[8] methanol, and dilute acid affords methyl cycloheptatrienecarboxylate. Both methods afford pure (>97%) product uncontaminated by double bond isomers, but the second route is somewhat more laborious.

Results and Discussion

Treatment of the dibromide II with 3% sodium amalgam in scrupulously dried benzene results in a mixture of volatile ketones in 80% yield. The products consist of barbaralone (I) (21% relative yield), an isomeric ketone IV (54%), bicyclo[3.2.2]nona-6,8-dien-3-one (V) (10%),[9] and two unidentified products



(13 and 2%). The major product IV is identical with a sample of authentic bicyclo[4.2.1]nona-2,4,7-trien-9-one prepared from cyclooctatetraene dianion.[10]

(1) Alfred P. Sloan Fellow, 1971–1973.

(2) We thank the Merck Company Foundation for an unrestricted grant in partial support of this work.

(3) E. Vedejs, *Tetrahedron Lett.*, 5045 (1969).

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(5) M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 2021 (1956).

(6) I. Ugi, W. Betz, and K. Offerman, *Chem. Ber.*, 97, 3008 (1964); I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem.*, 77, 492 (1965).

(7) In retrospect, the authors recommend (without actually having tried them) some of the less volatile, crystalline isonitriles instead of benzyl isonitrile. The reaction no doubt would proceed equally well, but (hopefully) without equally unfortunate olfactory consequences.

(8) R. F. Borch, *J. Org. Chem.*, 34, 627 (1969).

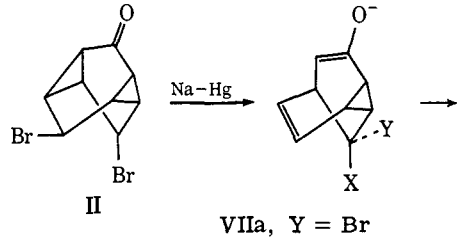
(9) J. A. Baker, A. M. Chalmers, W. W. Flood, D. D. MacNicol, A. B. Penrose, and R. A. Raphael, *Chem. Commun.*, 167 (1970).

(10) S. Winstein, *et al.*, unpublished results; we thank Dr. Mitsuru Sakai for the experimental procedure and spectral data.

In spite of all precautions, traces of proton donors must have been present in the reduction medium since V and the unidentified minor products contain two additional hydrogens compared to I or IV (mass spectral analysis). Treatment of barbaralone with sodium amalgam under similar conditions results in partial conversion into two dihydro derivatives which correspond in glpc retention times to the unknown minor products from II. However, V is not formed from sodium amalgam reduction of barbaralone or IV.

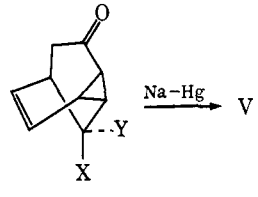
Sodium amalgam reduction of II in carefully dried tetrahydrofuran results in relatively more overreduction. If the reaction is worked up after a short time, it is evident that trace hydroxylic impurities also serve to trap a monobromo ketone VI (C_9H_9BrO) prior to complete reduction.

Using longer reaction times, the ketone V is formed at the expense of VI. The bromo ketone VI has no distinct uv maximum, so the carbonyl absorption at 5.93 μ in the infrared spectrum requires a bisected cyclopropyl ketone structure. The tricyclic structures VIa or VIb are consistent with this evidence, and also with the presence of two hydrogens at δ 5.9–6.1 in the nmr spectrum. The formation of VI is easily rationalized by reductive fragmentation of a cyclopropyl C–C bond to form the enolate VII which is converted into VI by an unknown proton source. Repetition of this process converts VI into V by reductive fragmentation of the remaining cyclopropane ring.

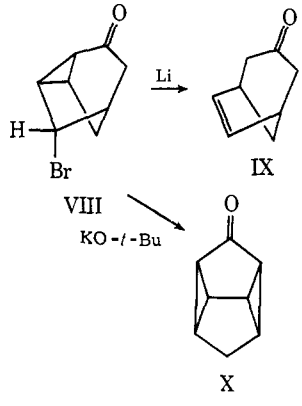


II

VIIa, Y = Br
X = H
b, X = Br; Y = H



VI

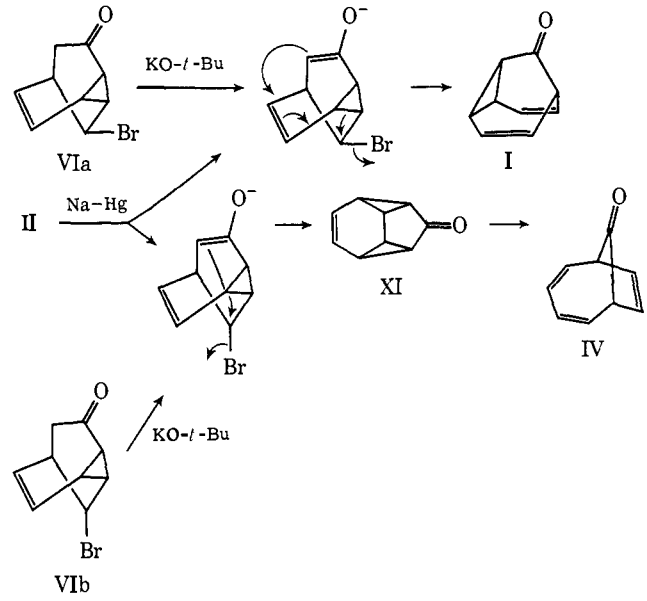


X

LeBel and Liesmer have described the closely related reductive fragmentation of the bromo ketone VIII to IX upon treatment with lithium.[11] Also these authors have found that potassium *tert*-butoxide converts VIII into a tetracyclic ketone X by internal alkylation of the enolate. On the basis of this precedent, it appeared likely that the enolate VII might also afford the analogous tetracyclic ketone XI which would then rearrange to IV by retro Diels–Alder reaction.[12,12a]

However, treatment of the bromo ketone VI (isolated from sodium amalgam reduction) with potassium *tert*-butoxide affords no trace of IV, and barbaralone (I) is the *sole* volatile product (66% yield). This surprising result can be explained if the stereochemistry VIa is assigned to the bromo ketone. Backside displacement of bromide by enolate carbon is not possible in VIa and the tetracyclic ketone XI would not be expected. An interesting rationale for conversion of VIa into barbaralone is illustrated in Scheme I. We note that the

Scheme I



VIb

orbital interactions which convert VIa into barbaralone are completely analogous to the six-electron rearrangement suggested by Schleyer and Barborak and Winstein and Grutzner to account for the degeneracy of barbaralyl cation.[13]

Assuming that initial reductive cleavage of II produces both VIIa and VIIb, it is possible to account for the formation of I, IV, and V. Unfortunately, all attempts to trap VIIb as the bromo ketone VIb from deliberately "wet" sodium amalgam reductions failed due to extensive overreduction. More useful results were obtained from brief (30–45 sec) treatment of II with zinc dust in acetic acid.[14] Under these conditions, the products include barbaralone (8%), V (2%), VIa

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(12a) NOTE ADDED IN PROOF. The formation of IV from the enolate of 7-bromobicyclo[4.3.0]nona-2,4-dien-8-one has been rationalized similarly *via* XI: L. A. Paquette, R. H. Meisinger, and R. E. Wingard, Jr., *J. Amer. Chem. Soc.*, 94, 2155 (1972).

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(14) Longer reduction times favor the conversion of bromo ketones VI into V and a reduced bromo ketone which no longer contains a cyclopropane ring. This substance is tentatively assigned the structure 9-bromobicyclo[3.3.1]non-6-en-3-one on the basis of nmr, ir, and mass spectra. This product was not detected from Na–Hg reductions.

(72%), and a new bromo ketone assigned the structure VIb (7%). The infrared and nmr spectra of VIb and VIa are closely analogous with the exception that one of the methylene hydrogens of the syn bromo ketone VIa is deshielded by δ *ca.* 0.5 compared to the corresponding signal of VIb, in agreement with the assigned stereochemistry.

Treatment of VIb with potassium *tert*-butoxide affords bicyclo[4.2.1]nona-2,5,7-trien-9-one (IV) as the sole volatile product. This reaction reconfirms the stereochemistry assigned to VIa and VIb, and also provides the necessary experimental support for Scheme I.

In summary, reductive cleavage of II with reducing metals affords both possible enolates VIIa and VIIb. In the absence of a proton donor, VIIa rearranges to barbaralone while VIIb undergoes internal alkylation to form XI. Retro Diels–Alder reaction is well established in closely related systems,[12] and affords the major product IV. In the presence of proton donors, VIIa and VIIb are converted into the bromo ketones VIa and VIb which in turn are subject to further reduction to V.

On the basis of available evidence it is not possible to determine whether direct 1,4 elimination of bromine is also involved as a route to barbaralone from II. Barbaralone is formed in low yield from zinc–acetic acid reduction of II under conditions where the enolate intermediates are protonated rapidly, so it appears that 1,4 elimination of bromine can compete with reductive cyclopropane cleavage α to the carbonyl group. However, there is little reason to believe that zinc–acetic acid reduction of II is a good model for sodium–amalgam reduction under aprotic conditions. The two reducing media produce differing ratios of VIIa:VIIb (10:1 for zinc–acetic acid, *ca.* 2:3 for Na–Hg in benzene) and may differ in mechanistic details as well.

Experimental Section

Nmr spectra were obtained with a Varian HA-100 instrument; mass spectra were obtained with the MS-9 spectrometer; melting points were determined with a hot stage-microscope apparatus and are corrected.

Methyl Cycloheptatrienecarboxylate. A. From Tropylium Fluoroborate and Benzyl Isonitrile. Tropylium fluoroborate (160 g) was stirred vigorously with acetonitrile (600 ml, distilled from CaH_2) and absolute methanol (100 ml) at 0°. Benzyl isonitrile[6] (95 g) was added dropwise over 1.5 hr at 0° and the dark brown reaction mixture was stirred an additional 30 min. Aqueous 10% hydrochloric acid (200 ml) was then added and the mixture was stirred 1 hr at 0°. The mixture was then diluted with water (1 l.) and extracted several times with pentane. A pentane-insoluble, dark brown organic layer separated during the extraction and was discarded. The pentane extracts were washed once with water, dried over sodium sulfate, and evaporated under the aspirator, and the residue was distilled, bp 44° (0.15 mm), to yield methyl cycloheptatrienecarboxylate (84 g, 69% based on isonitrile) as the only significant volatile fraction.

B. From Cycloheptatrienylcyanide and Isopropoxycarbonium Fluoroborate.[8] Tropylium fluoroborate was dissolved in water and treated with excess sodium cyanide in a good hood. Cycloheptatrienyl cyanide separated as a red-brown liquid. The crude product was diluted with ether, dried over $MgSO_4$, and decolorized with Norit, and the ether was evaporated to yield the cyanide as a pale yellow oil.

The cyanide (123 g, 1.05 mol) was added dropwise to a solution of dry methylene chloride (30 ml) and isopropoxycarbonium fluoroborate (prepared according to the method of Borch[8] from 690 g of isopropyl orthoformate) at −20° and stirred 30 min after addition was complete. The solution was then allowed to warm to 25° and was stirred 1.5 hr. Vigorous gas evolution was observed during this period. The solution was then poured into methanol (200 ml), cooled to 0°, and combined with aqueous 15% HCl. After 45 min at 0°, the product was worked up as described above to yield methyl cycloheptatrienecarboxylate (120–140 g, 75–88%, depending on the quality of isopropoxycarbonium fluoroborate).

Bromination of Barbaralone (I).[4] To a solution of barbaralone (0.51 g, 3.9 mmol) in dichloromethane (20 ml, cooled to −78°) was added dropwise a solution of bromine (630 mg, 3.9 mmol) in dichloromethane (5 ml). The addition required 20 min, and the reaction was allowed to stir for an additional 30 min. The triasteranone dibromide (II) was crystallized from the crude product using benzene–chloroform to yield 0.8 g, 70%. The mother liquors contain three additional compounds, previously identified as isomers of II.[3] Triasteranone dibromide (II) was a white solid: mp 149°; ir ($CHCl_3$) 5.93 μ; nmr ($CDCl_3$) 2.0–2.7 (m, 6 H), 4.94 (m, 1 H), 5.93 (br s, 1 H).

Sodium Amalgam Reduction of Triasteranone Dibromide (II). General Method. Triasteranone dibromide (II) (0.1 g) was added to a rapidly stirred mixture of freshly made 3% sodium amalgam (2 g) and solvent (5 ml), dried in a special apparatus. Two three-neck flasks were joined by a glass tube, and each flask was also fitted with a stopcock and an argon flow system. In one flask was placed dry solvent and excess lithium aluminum hydride. In the other flask was placed the required sodium amalgam. With positive argon flow, the solvent was distilled over into the flask containing the amalgam, cooled to −50°. The argon flow was reversed, and the solvent distilled back into the cooled solvent flask. This cycle was repeated three times, and then 5 ml of solvent was distilled into the amalgam flask. The dibromide II was then added and the mixture was stirred vigorously for the desired time. Excess ether was added, the solution was decanted from the mercury residue and passed through a short path (3 in.) silica gel column with ether (100 ml), and the solvent was removed *in vacuo*. The residue was analyzed by glpc on a 10-ft 20% Carbowax column at 160°. The products included barbaralone (I, retention time 18 min), bicyclo[4.2.1]nona-2,4,7-trien-9-one (IV, retention time 7.6 min), bicyclo[3.2.2]nona-6,8-dien-3-one (V, 6.8 min), and two unidentified overreduction products (retention time <7 min) in relative yields as follows:

Solvent	Time, hr	Yields (%) of I	IV[10]	V[9]	Over-reduction
Benzene	5	21	54	10	15
THF	1.5	20	50	12	18

The overall yield of volatile products was *ca.* 80% from reductions in benzene.

Reduction of Barbaralone with Na–Hg. Barbaralone was treated with sodium amalgam according to the general method in dry THF for 18 hr. According to glpc analysis, two products were formed, identical in retention time with the unidentified minor products from reduction of II. The two products were collected by preparative glpc and subjected to mass spectral analysis. Both were found to have *m/e* 134, corresponding to incorporation of two hydrogens. Both substances are ketones (carbonyl at 5.8 μ), presumably derived from reductive cyclopropane cleavage.

Isolation of *syn*-9-Bromotricyclo[3.3.0.0^{2,8}]non-6-en-3-one (VIa). Dibromide II (0.07 g, 24 mmol) was reduced with sodium amalgam as before. After 1 hr, the reaction was worked up and the crude product was separated by preparative layer chromatography (plc) over silica gel (Brinkman PF 254) with $CHCl_3$ eluent. Two uv-active bands were collected, the faster (R_f 0.5) yielding IV (12 mg, 39%) and the slower (R_f 0.4) yielding VIa (12 mg, 24%).

VIa: mp 63°; ir ($CHCl_3$) 5.92 μ; nmr ($CDCl_3$, δ) 2.1–2.4 (mult overlapping a broad singlet at 2.32, 4 H), 2.8–3.1 (mult, 2 H), 4.45 (br singlet, 1 H), 5.8–6.1 (mult, 2 H); exact mass found for C_9H_9OBr, 213.98127 ± 0.0018 (calcd, 213.98175).

Conversion of VIa into Barbaralone with Base. A solution of VIa (0.022 g, 0.1 mmol) in *tert*-butyl alcohol (1 ml) was treated with commercial potassium *tert*-butoxide (11 mg, 0.1 mmol) for 1 hr at room temperature. The mixture was then diluted with ether, washed with water, and dried over $MgSO_4$, and the solvent was evaporated under the aspirator. Analysis by glpc indicated barbaralone (66% yield) as the sole volatile product. In the absence of base, VIa was found to be stable in *tert*-butyl alcohol under these conditions.

Zinc–Acetic Acid Reduction of II. *anti*-9-Bromotricyclo[3.3.0.0^{2,8}]non-6-en-3-one (VIb). The dibromide II (0.47 g, 1.6 mmol) was added to a stirred suspension of zinc dust (0.21 g, 3.2

mmol) in glacial acetic acid (5 ml) at 16°. After 45 sec the mixture was filtered, the residue was washed well with ether, and the ether layer was washed to neutrality with aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$, evaporated, and separated by plc over silica gel using 20% acetone in hexane as eluent (two developments). The following zones were collected: R_f 0.7, 0.021 g of barbaralone and V (8 and 2% yield, respectively, by nmr analysis); R_f 0.5, 0.245 g of VIa (72%); R_f 0.4, 0.023 g of *anti*-9-bromotricyclo[3.3.0.$0^{2,8}$]non-6-en-3-one (VIb) (7%); mp 142–143°; ir ($CHCl_3$) 5.95 μ; nmr ($CDCl_3$, δ) 2.2–2.4 (mult, 5 H), 2.9 (br singlet, 1 H), 4.7 (br singlet, 1 H), 5.92 (doublet of doublets, J = 7 and 9 Hz, 1 H), 6.2 (doublet of multiplets, J = 9 Hz, 1 H); exact mass found for C_9H_9OBr, 213.98308 ± 0.0018 (calcd, 213.98175).

Conversion of VIb into IV with Base. The procedure for treatment of VIa with potassium *tert*-butoxide was followed using 0.005 g of VIb. By glpc analysis, IV was formed as the only volatile product, confirmed by peak enrichment.

Thermal Isomerization of 3,6-Dideuterio- and 1,2,7,8,9,9-Hexadeuterio-*cis*-bicyclo[6.1.0]nona-2,4,6-triene[1,2]

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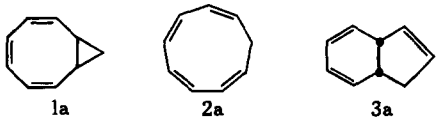
Abstract: Two deuterium-labeled analogs of *cis*-bicyclo[6.1.0]nona-2,4,6-triene have been synthesized and rearranged thermally to the corresponding *cis*-3a,7a-dihydroindenes. The labeling results show that a number of mechanistic formulations, "allowed" in terms of orbital symmetry theory and seemingly plausible, are not operative. Theoretical analysis leads to the conclusion that the rearrangement of bicyclo[6.1.0]nona-2,4,6-triene to dihydroindene may occur through the valence isomers bicyclo[5.2.0]nona-2,5,8-triene and *c,c,c,c*-cyclononatetraene, without intervention of any diradical intermediates.

Vogel and his collaborators synthesized *cis*-bicyclo[6.1.0]nona-2,4,6-triene (**1a**) in 1961,[4–6] and discovered its rearrangement to *cis*-3a,7a-dihydroindene (**3a**). Cyclononatetraene (**2a**) was one proposed intermediate.



1a **2a** **3a**

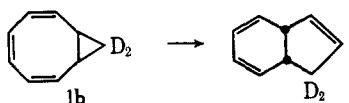
The comparative ease with which C-9-substituted derivatives of bicyclo[6.1.0]nona-2,4,6-triene may be synthesized has contributed to a rapid compilation of further instances of the conversion.[7–12] Some but not all[12] of these rearrangements may be related mechanistically to the parent hydrocarbon isomerization.

The same synthetic considerations, however, also contributed to a sustained absence of examples of the conversion of [6.1.0] systems having substitution at any of the other eight carbon atoms.

This paper outlines the current status of the mechanistic problems associated with the thermal isomerization of triene **1a** to *cis*-dihydroindene, describes the synthesis of 3,6-dideuterio- and 1,2,7,8,9,9-hexadeuteriobicyclo[6.1.0]nona-2,4,6-triene, demonstrates in two independent ways the stereochemical course of the rearrangements of these hydrocarbons, and concludes that an orbital symmetry-disallowed yet state-conservative and energetically concerted isomerization from a folded conformer of bicyclo[5.2.0]nona-2,5,8-triene to *c,c,c,c*-cyclononatetraene is the key step in the overall rearrangement process.

A subsequent manuscript will detail our theoretical approach to this and related thermal rearrangements, in which seemingly implacable conflicts between orbital symmetry theory and stereochemical and kinetic fact are resolved.[13]

Background. Following the initial observation of the bicyclo[6.1.0]nonatriene to *cis*-dihydroindene conversion it was shown that 9,9-dideuteriobicyclo[6.1.0]nonatriene (**1b**) rearranged to 1,1-dideuterio-*cis*-dihydroindene (**3b**).[14]



1b **3b**

The intervention of *c,c,c,c*-cyclonona-1,3,5,7-tetraene as an intermediate, suggested among other possibilities in the initial report[4] of the rearrangement, was supported by the finding that *anti*- and *syn*-9-methyl-*cis*-bicyclo[6.1.0]nonatriene and 9-methyl-*c,c,c,c*-cyclonona-1,3,5,7-tetraene all give the same or nearly the same

(1) This work was supported by the Cities Service Oil Co., the DuPont Co., and the National Science Foundation.

(2) Preliminary reports: J. E. Baldwin and A. H. Andrist, *J. Amer. Chem. Soc.*, 93, 4055 (1971); J. E. Baldwin, R. K. Pinschmidt, Jr., and A. H. Andrist, Autumn Meeting of the Chemical Society, York, Sept 1971, Abstract No. A23.

(3) National Institute of General Medical Sciences Predoctoral Fellow, 1968-1971.

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