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Synthesis of 4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane and Isolation of Atropisomeric Forms of the Tetraoxide

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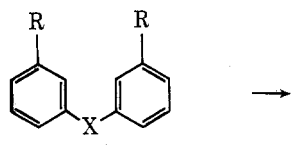
Unsuccessful attempts were made to synthesize a [5.1]metacyclophane by the Stevens rearrangement of the bissulfonium salts derived from the 2,6-dithia[7.1]metacyclophanes **9**, **10**, **11**, and **12**. Compound **15b** preferentially underwent a double Sommelet rearrangement in good yield to provide 4,4,9,17-tetramethyl-2,6-dithia[7.1]paracyclophane. The bissulfone derived by oxidation was shown to exist in atropisomeric forms **20** and **19**. These atropisomers, designated *syn*-**20** and *anti*-**19**, were isolated by preparative high-pressure liquid chromatography, and the activation energy of their interconversion to the 50:50 equilibrium mixture determined by the appropriate kinetic measurements.

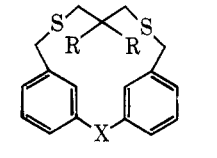
The chemistry of [2.2]metacyclophanes has been greatly extended using the ready synthetic access provided by the sulfur extrusion procedures of Boekelheide[1-3] and others.[4-6]

When our work commenced these procedures had been used exclusively to prepare [2.2]cyclophanes. It was not evident to us at that time whether they were more generally applicable. Only recently has the sulfone pyrolysis procedure of Vogtle[4] been shown to work well for the preparation of cyclophanes with bridges other than ethano between the aromatic rings.[7]

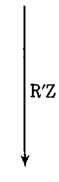
We chose to investigate whether the Stevens rearrangement procedure[1] could be used to prepare other metacyclophanes. In particular, we were interested in [5.1]metacyclophanes, whose aromatic rings are able to adopt the same relationship to one another as those of the dibenzsuberane system. The spatial relationship of the aromatic rings to one another in such bridged diarylmethanes is considered important in the design of antidepressant drugs.[8] A suitable starting material to explore this possibility, the diacid **1**, was readily available from the reaction of benzoic acid, paraformaldehyde, and concentrated sulfuric acid, using the procedure of Schöpff.[9,10] The diacid **1** was esterified, and the dimethyl ester **2** reduced with $LiAlH_4$ to give the known carbinol **3**.[11] This carbinol **3** was in turn converted to the dichloro compound **4**. When this dichloro compound **4** was treated with 1,3-propanedithiol in refluxing ethanolic sodium hydroxide under conditions designed to favor intramolecular reaction, a good yield (83%) of the 2,6-dithia[7.1]metacyclophane **9** was obtained. Chromic acid oxidation of the dichloro compound **4** yielded the corresponding benzophenone **5** which, on reaction with 1,3-propanedithiol under analogous conditions, yielded 2,6-dithia[7.1]metacyclophan-14-one (**10**). Conversion of both these metacyclophane derivatives **9** and **10** to their bissulfonium salts was effected by reaction with Meerwein's salt. Reaction of these sulfonium salts, under conditions described by Boekelheide[1] to favor the Stevens rearrangement, gave products **14a** and **14b**, respectively, based on their NMR spectra. These compounds **14a** and **14b** appeared to be derived from an initial Saytzeff elimination followed by the orbital

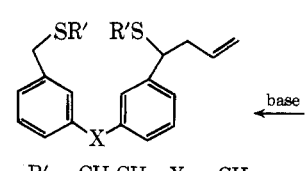


1, R = CO_2H; X = CH_2
2, R = CO_2CH_3; X = CH_2
3, R = CH_2OH; X = CH_2
4, R = CH_2Cl; X = CH_2
5, R = CH_2Cl; X = CO
6, R = CH_2SH; X = CO
7, R = CH_2SCN; X = CH_2
8, R = CH_2SH; X = CH_2

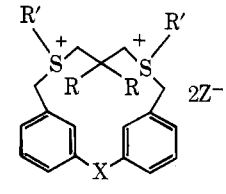


9, R = H; X = CH_2
10, R = H; X = CO
11, R = CH_3; X = CO
12, R = CH_3; X = CH_2





14a, R′ = CH_2CH_3; X = CH_2
14b, R′ = CH_2CH_3; X = CO

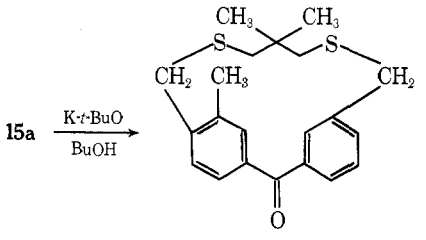


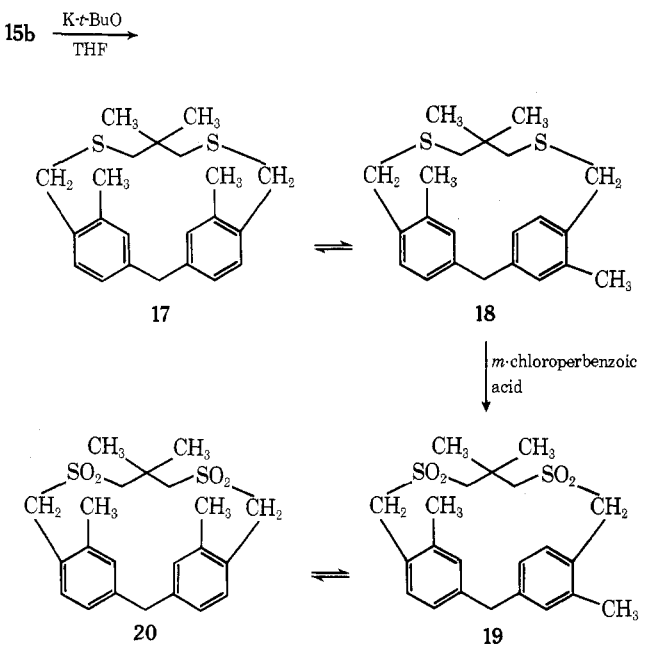
13, R = H; R′ = CH_2CH_3; X = CH_2; Z = BF_4
15a, R = R′ = CH_3; X = CO; Z = FSO_3
15b, R = R′ = CH_3; X = CH_2; Z = FSO_3

symmetry allowed rearrangement of the resulting allyl sulfonium ylide.[12]

The dichloro compounds **4** and **5** were converted by standard procedures to the dithiols **8** and **6**. Reaction of these dithiols **8** and **6** with 2,2-dimethyl-1,3-dibromopropane in 2-methoxyethanol containing sodium hydroxide provided the 4,4-dimethylmetacyclophanes **12** and **11** in moderate yields (55 and 48%, respectively). Conversion of these compounds **12** and **11** to the bissulfonium salts **15b** and **15a** was effected by magic methyl.

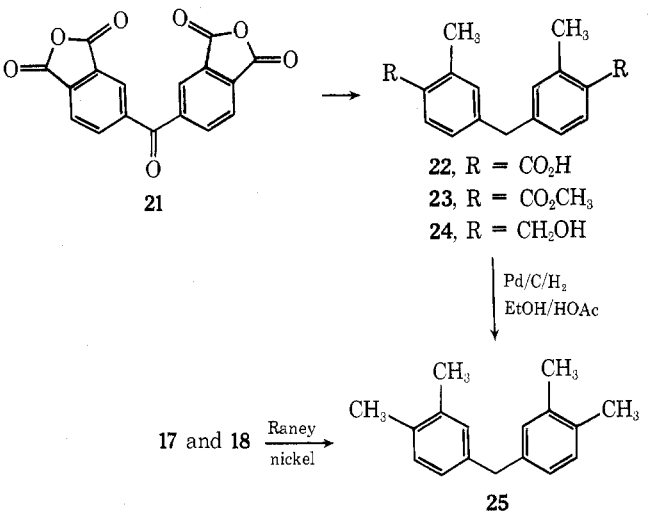
When the metacyclophanone bissulfonium salt **15a** was allowed to react under Stevens rearrangement conditions a multiplicity of products was obtained. With potassium *tert*-butoxide in *tert*-butyl alcohol a small amount of one crystalline product **16** was isolated and characterized. This compound **16** was derived from two further competing processes,





i.e., Sommelet rearrangement and transmethylation. On the other hand, reaction of the metacyclophane bissulfonium salt **15b** with potassium *tert*-butoxide in THF provided a good yield (85%) of an oil which was essentially homogeneous, based on TLC evidence. One product was obtained from this oil by direct crystallization. It was evident from the analytical and spectral data that this product was the paracyclophane derivative **18**, derived from a double Sommelet rearrangement of the bissulfonium salt **15b**. Of especial interest was the time-dependent nature of the NMR spectrum of compound **18**. On being allowed to remain in the NMR probe, the intensity of the singlet at δ 0.30 assigned to the *gem*-dimethyl group dropped, and two new singlets appeared, one at δ 0.52 and one above the Me_4Si signal at δ −0.22. Other changes also occurred in the low-field part of the spectrum. Examination of models and inspection of their symmetry properties suggested that the crystalline Sommelet product was the anti atropisomer **18** which, on solution, slowly equilibrated via bond rotation to a syn/anti mixture. The syn atropisomer **17**, in which the *gem*-dimethyl group is no longer symmetrical with respect to the aromatic rings, presumably favors a conformation with one of the methyl groups oriented within the ring. Such a conformation would permit shielding of this methyl group by the aromatic rings and thus account for a chemical shift above Me_4Si signal. Furthermore, it was then evident, based on the NMR spectrum, that the original oil from the reaction of the bissulfonium salt **15b** with potassium *tert*-butoxide was essentially a mixture of the syn and anti atropisomers **17** and **18**.

It seemed surprising that the bissulfonium salt **15b**, instead of undergoing a double Stevens rearrangement which would have given the relatively strain-free [5.1]metacyclophane, gave instead the highly rigid 4,4,9,17-tetramethyl-2,6-dithia[7.1]-paracyclophane **17/18**. Additional proof for the structural assignment was therefore sought. Desulfurization of the product mixture **17/18** using Raney nickel yielded a crystalline hydrocarbon whose melting point was essentially identical with that reported in the literature for 1,1′-methylenebis(3,4-dimethylbenzene) (**25**).[13] Unfortunately, the method of synthesis previously used to prepare this compound **25** was ambiguous. We therefore chose to synthesize the hydrocarbon **25** from the commercially available 3,3′,4,4′-benzophenone tetracarboxylic anhydride (**21**), which has the appropriate



carbon skeleton. High-pressure hydrogenation gave, surprisingly, a single diacid **22** whose structure was assigned from the NMR spectrum. The spectrum indicated that the molecule was symmetrical about the methylene group and the low-field aromatic proton, i.e., next to the carboxyl group, had an ortho coupling. The carboxyl groups of the diacid **22** were converted by standard procedures to methyl groups. The resulting crystalline hydrocarbon **25** was identical in all respects with that derived from the desulfurization of the dithia[7.1]-paracyclophanes **17** and **18**.

We made several attempts to obtain a pure sample of the syn paracyclophane **17** but the low energy barrier to interconversion of **17** and **18** created experimental problems. We therefore oxidized the mixture of atropisomers **17** and **18** to the corresponding bissulfones **20** and **19**. In a somewhat analogous case of the 3,13-dioxa-8-thia-2,14-dioxo[15]paracyclophane, oxidation to the sulfone increased the activation energy to internal rotation of the aromatic ring by nearly 3 kcal/mol.[14] In our case the increase in conformational stability now permitted separation of the syn and anti atropisomers **20** and **19** by means of preparative high-pressure liquid chromatography and their complete characterization. Assignment of the anti structure **19** to the higher melting atro-

Table I. Eyring/Arrhenius Plot Data

Temp, °C	$1/T$, K × 10^{-3}	k, s^{-1} × 10^{-4}	Ln k/T
70	2.914	0.740	−1.535
80	2.832	1.934	−1.442
90	2.754	5.673	−1.337

Table II. Thermodynamic Parameters for the Equilibration

E_a	25.2 ± 1.2 kcal/mol
$\Delta H^{\ddagger}$	24.5 ± 1.2 kcal/mol
$\Delta S^{\ddagger}$	−6.4 ± 3.5 eu

pisomer was possible from the NMR spectrum. The *gem*-dimethyl group was a singlet in contrast to the lower melting syn atropisomer **20** where it was a doublet. In neither case, though, were the chemical shifts of the methyl groups anomalous, and therefore the methyl groups are presumably oriented away from the center of the ring. Interrelationship between the sulfides and sulfones was obtained directly by oxidation of the crystalline *anti*-dithia[7.1]paracyclophane **18** to the higher melting anti bissulfone **19.**

With the separate crystalline atropisomers **20** and **19** in hand, an estimate of the barrier to their interconversion, i.e., the internal rotation of one aromatic ring, was obtained from kinetic data. A preliminary estimate was made by studying the rate of convergence of the NMR spectra of compounds **19** and **20** when heated at 100 °C in DMF. The position of equilibrium was also established by this experiment as being, not surprisingly, 50:50. It is evident from models that whether the aromatic methyl groups are on the same or opposite sides of the ring there are no serious steric interactions. A more precise estimate of the activation energy to interconversion of compounds **19** and **20** was obtained by use of analytical high-pressure liquid chromatography to measure the rate of conversion of the higher melting anti atropisomer **19** to the equilibrium mixture at 70, 80, and 90 °C. From an Arrhenius and Eyring plot the appropriate activation parameters were obtained (Table II).

This type of isomerism, designated atropisomerism,[15] has long been known for hindered diphenyl derivatives.[16] In these cases, though, as in other cases of restricted rotation in diphenyls, the barrier to interconversion appears to be due to ortho/ortho′ substituent interaction.[17] In our case of the interconversion of compounds **19** and **20,** it appears to be, based on models, due to the transannular interaction of the ortho H atom with the methylene group between the sulfone and the *gem*-dimethyl group. Whatever the reason, the 2,6-dithia[7.1]paracyclophane ring system does appear to be capable of an unusual type of isomerism which permits isolation and characterization of stable atropisomers. Recently, several other examples of stable atropisomers have been provided by the work of Oki.[18]

The very elegant work of Mislow[19] may also be regarded as a logical extension of the stereochemical possibilities created by restricted rotation about carbon–carbon single bonds.

The failure of the Sevens rearrangement to provide the [1.5]metacyclophane[20] is understandable in the light of the radical pair mechanism proposed for the Stevens rearrangement.[21] This mechanism requires a homolytic cleavage in the ylide as the rate-determining step. Thus, both carbons of the new bond to be formed must be attached to stabilizing functionality, i.e., to facilitate ylide formation in one direction and homolysis in the other. The Stevens rearrangement is therefore well suited to the preparation of [2.2]cyclophanes where both carbon atoms of the new bond are benzylic. Its use in other situations seems extremely limited in view of these structural requirements and the other reaction pathways open to sulfonium salts on treatement with base, as is evident from our work.

Experimental Section[22]

3,3′-Methylenedi(benzyl alcohol) (3). This substance, mp 42–43 °C, was prepared by the $LiAlH_4$ reduction, by the procedure of LeBlanc,[11] of the dimethyl ester **2** of the diacid **1** obtained by the concentrated H_2SO_4 catalyzed condensation of paraformaldehyde and benzoic acid by the procedure of Schöpff.[9,10,23]

1,1′-Methylenebis(3-chloromethylbenzene) (4). Thionyl chloride (19 g, 0.16 mol) was added to benzene (100 ml) containing 3 drops of pyridine. 3,3′-Methylenedi(benzyl alcohol) (**3,** 15 g, 0.066 mol) dissolved in benzene was added slowly with stirring. The mixture was refluxed for 2 h. The benzene was removed. The residue was redissolved in ether. The ether solution was washed (10% aqueous $KHCO_3$, brine), dried ($MgSO_4$), and concentrated to dryness. The residue was distilled in vacuo. The main fraction was the bis(chloromethyl) compound **4** (11.65 g, 67% yield): bp 157–162 °C (0.2 mm); NMR δ 7.22 (s, 8), 4.50 (s, 4), 3.98 (s, 2); ir (film) 1604 (m), 1590 (m), 1488 (m), 1444 (s), 1264 (s), 700 cm^{-1} (s).

Anal. Calcd for $C_{15}H_{14}Cl_2$: C, 67.93; H, 5.32. Found: C, 68.05; H, 5.60.

2,6-Dithia[7.1]metacyclophane (9). 1,1′-Methylenebis(3-chloromethylbenzene) (**4,** 6.35 g, 24 mmol) was dissolved in an ethanol/benzene mixture (200 ml of a 4:1 mixture). Propane-1,3-dithiol (2.87 g, 26 mmol) and NaOH (2 g, 50 mmol) were dissolved in 95% ethanol (200 ml). Both solutions were added simultaneously and dropwise to refluxing ethanol (600 ml) under N_2. The addition took 2 h. The mixture was refluxed for a further 1 h. The solvents were removed in vacuo. The residue was dissolved in chloroform and water. The chloroform layer was separated, washed (brine), dried ($MgSO_4$), and concentrated to dryness. The waxy solid was recrystallized from 2-propanol/ether to give 2,6-dithia[7.1]metacyclophane (**9**): mp 92–94 °C (6.0 g, 83% yield); NMR δ 7.28–6.88 (m, 8), 3.94 (s, 2), 3.58 (s, 4), 2.12 (t, 4), 1.56–1.06 (m, 2); ir (Nujol) 1600 (m), 1580 (m), 1232 (m), 714 cm^{-1} (s); MS *m/e* 300 (M^+).

Anal. Calcd for $C_{18}H_{20}S_2$: C, 71.98; H, 6.71. Found: C, 72.42; H, 6.96.

2,6-Dimethyldithia[7.1]metacyclophane-2,6-bis(thiaonium tetrafluoroborate) (13). The dithia[7.1]metacyclophane **9** (1 g, 3.3 mmol) was dissolved in methylene chloride (5 ml). Triethyloxonium tetrafluoroborate (1.4 g, 7.3 mmol) was added as a solid with stirring. After 2 h at room temperature the methylene chloride was decanted from an insoluble gum which had separated. The gum was crystallized from ethanol to give the bissulfonium salt **13,** mp 168 °C dec (1.7 g, 97% yield).

Anal. Calcd for $C_{22}H_{30}B_2F_8S_2$: C, 49.64; H, 5.68. Found: C, 49.73; H, 5.85.

Reaction of the Bissulfonium Salt 13 with NaH. The bissulfonium salt **13** (1.6 g, 3 mmol) was added to a slurry of sodium hydride (derived from washing 1.26 g of 57% NaH in oil, 30 mmol) under N_2. The mixture was stirred at room temperature for 24 h. Ice was added to decompose excess NaH. The mixture was partially concentrated in vacuo, and then extracted (ether). The combined extracts were washed (brine) and dried ($MgSO_4$). Removal of the ether gave a yellow oil [0.9 g, NMR δ 5.90–4.70 (m, ~2), 3.28 (d, <1)]. This material consisted mainly of compound **14a.**

3,3′-Bis(chloromethyl)benzophenone (5). 1,1′-Methylenebis(3-chloromethylbenzene) (**4,** 2.65 g, 0.01 mol) was dissolved in a 1:1 mixture of acetic anhydride and CCl_4 (40 ml). Chromic anhydride (2 g, 0.02 mol) was added with stirring at room temperature. After 3 h water (350 ml) was added. The mixture was extracted (ether). The ethereal extract was washed (10% aqueous $KHCO_3$, brine) and dried ($MgSO_4$). Removal of the ether gave a solid which was recrystallized from ether to give 3,3′-bis(chloromethyl)benzophenone (**5,** 1.8 g, 64% yield): mp 114–116 °C; ir (Nujol) 1660 (s), 1604 (m), 1310 (m), 1262 (m), 1186 (m), 702 cm^{-1} (s); uv (MeOH) 253 nm (ε 17 900).

Anal. Calcd for $C_{15}H_{12}Cl_2O$: C, 64.53; H, 4.33. Found: C, 64.45; H, 4.23.

3,3′-Bis(mercaptomethyl)benzophenone (6). 3,3′-Bis(chloromethyl)benzophenone (**5,** 10 g, 35.8 mmol) was dissolved in ethanol (200 ml). Thiourea (6.2 g, 81.5 mmol) was added and the mixture refluxed for 16 h. The reaction mixture was concentrated to half volume in vacuo and then diluted with ether. On standing a solid separated, which was collected. This solid (13.6 g, mp 163–8 °C) was refluxed in 10% aqueous NaOH (100 ml) for 3 h under N_2. The cooled solution was extracted (ether), made acid (2 N HCl), and reextracted (ether). The latter ethereal extracts were combined, washed (brine), and dried

($MgSO_4$). Removal of the ether yielded a solid which was recrystallized from ether to give 3,3′-bis(mercaptomethyl)benzophenone (**6**, 6.9 g, 70% yield): mp 95–96 °C; NMR δ 7.84–7.24 (m, 8), 3.78 (d, 4, J = 8 Hz), 1.82 (t, 2); ir (Nujol) 1644 (s), 1600 (s), 1580 (m), 1302 (s), 1290 (s), 1180 (m), 700 cm^{-1} (m); uv (MeOH λ_{max} 225 nm (ε 15 790).

Anal. Calcd for $C_{15}H_{14}OS_2$: C, 65.69; H, 5.15. Found: C, 65.75; H, 5.47.

2,6-Dithia[7.1]metacyclophan-14-one (10). 3,3′-Bis(chloromethyl)benzophenone (**5**, 1.6 g, 5.8 mmol) was dissolved in a 3:1 ethanol/benzene mixture (180 ml). This solution was added dropwise to refluxing ethanol (400 ml) to which was being added dropwise a solution of 1,3-propanedithiol (0.626 g, 6.0 mmol) and NaOH (0.48 g, 11.6 mmol) in 95% ethanol (180 ml). Addition of the two solutions took 1 h. The mixture was refluxed for a further 4 h. The solvents were removed in vacuo and the residue redissolved in methylene chloride. This solution was washed (2 N HCl, brine), dried ($MgSO_4$), and concentrated to dryness. The residue (1.6 g) was recrystallized from ethanol to give 2,6-dithia[7.1]metacyclophan-14-one (**10**, 1.41 g, 77% yield): mp 87–89 °C; NMR δ 8.0–7.20 (m, 8), 3.70 (s, 4), 2.56 (t, 4), 2.02–1.48 (quintet, 2); ir (Nujol) 1656 (s), 1600 (m), 1580 (m), 1314 (s), 1284 (s), 976 (m), 730 cm^{-1} (s); uv (MeOH) λ_{max} 253 nm (ε 14 120).

Anal. Calcd for $C_{18}H_{18}OS_2$: C, 68.78, H, 5.77. Found: C, 68.47; H, 6.00.

Attempted Stevens Rearrangement on 2,6-Dithia[7.1]metacyclophan-14-one (10). 2,6-Dithia[7.1]metacyclophan-14-one (**10**, 1 g, 2.2 mmol) was dissolved in methylene chloride (20 ml). With stirring at room temperature triethyloxonium fluoroborate (1.3 g, 6.8 mmol) was added. A thick gum slowly separated. The methylene chloride was removed. Tetrahydrofuran and NaH (0.72 g, 30 mmol) were added. The mixture was stirred for 16 h and concentrated to dryness and the residue was partitioned between methylene chloride and water. The methylene chloride layer was washed (water), dried ($MgSO_4$), and concentrated to dryness. The residue (1.2 g) was put onto an alumina column (neutral III) made up in hexane. A major fraction (360 mg) was eluted by benzene. This was concluded to be principally the rearranged Saytzeff elimination product **14b** based on spectral data: MS m/e 370 (M^+) 329 ($M - CH_2CH{=}CH_2$); NMR δ 7.75–6.9 (m, 8), 5.95–5.30 (m, 1), 5.17–4.72 (d of m, 2), 4.05–3.65 (m, 1), 3.72 (s, 2), 2.80–2.06 (sextet, 6), 1.38–0.95 (sextet, 6).

4,4-Dimethyl-2,6-dithia[7.1]metacyclophan-14-one (11). 3,3′-Bis(mercaptomethyl)benzophenone (**6**, 3 g, 11 mmol) was dissolved in 2-methoxyethanol (100 ml). This solution was added during 1.5 h to refluxing 2-methoxyethanol (800 ml), to which was being added at the same time a solution of sodium hydroxide (0.9 g, 22 mmol) and 2,2-dimethyl-1,3-dibromopropane (2.53 g, 11 mmol) in 2-methoxyethanol (100 ml). After completion of the addition refluxing was continued for a further 1.5 h. The 2-methoxyethanol was removed in vacuo and the residue partitioned between ether and water. The ethereal layer was washed (brine), dried ($MgSO_4$), and concentrated to dryness. The resulting oil (3.5 g) crystallized slowly and was recrystallized from ether to give 4,4-dimethyl-2,6-dithia[7.1]metacyclophan-14-one (**11**, 2.17 g, 58% yield): mp 103–105 °C; NMR δ 8.00–7.25 (m, 8), 3.70 (s, 4), 2.66 (s, 4), 1.00 (s, 6); ir (Nujol) 1672 (s), 1586 (m), 1320 (s), 746 cm^{-1} (s); uv (MeOH) 249 nm (ε 14 730).

Anal. Calcd for $C_{20}H_{22}OS_2$: C, 70.16; H, 6.48. Found: C, 70.39; H, 6.60.

Attempted Stevens Rearrangement of 4,4-Dimethyl-2,6-dithia[7.1]metacyclophan-14-one (11). 4,4-Dimethyl-2,6-dithia[7.1]metacyclophan-14-one (**11**, 0.8 g, 2.34 mmol) was dissolved in methylene chloride (30 ml) and cooled to −60 °C. Methyl fluorosulfonate (0.6 g, 5.15 mmol) in methylene chloride (5 ml) was added with stirring and the mixture allowed to warm to room temperature. Ethyl acetate (30 ml) was added. A solid **15a** (1.1 g, mp 125–127 °C) separated and was collected. The bulk of this precipitate (0.98 g, 1.7 mmol) was added to a solution of potassium *tert*-butoxide (1 g, 8.9 mmol) in *tert*-butyl alcohol (40 ml). The mixture was stirred at room temperature for 66 h. The *tert*-butyl alcohol was removed in vacuo, and the residue partitioned between water and ether. The ether was washed (brine), dried ($MgSO_4$), and removed. The residue (0.45 g) was subjected to preparative TLC (silica GF/benzene). The major band (200 mg) was eluted as a crystalline compound. This material was recrystallized to give compound **16**: mp 137–138 °C; NMR δ 7.92 (pr of t, J = 7 Hz), 7.52–6.90 (m, 7), 3.78 (q, 2, J = 13 Hz), 3.62 (s, 2), 2.44 (s, 3), 2.30 (q, 4, J = 13 Hz), 0.90 (s, 3), 0.82 (s, 3); ir (Nujol) 1680 (s), 1576 (m), 1276 (s), 1172 (m), 712 cm^{-1} (m); uv λ_{max} (MeOH) 251 nm (ε 12 800); MS m/e 356 (M^+).

Anal. Calcd for $C_{21}H_{24}OS_2$: C, 70.76; H, 6.79. Found: C, 70.59; H, 6.49.

1,1′-Methylenebis(3-thiocyanomethylbenzene) (7). 1,1′-Methylenebis(3-chloromethylbenzene) (**4**, 10.6 g, 0.04 mol) was added along with potassium thiocyanate (8.8 g, 0.088 mol) to 95% ethanol (200 ml). The mixture was refluxed for 4 h. A solid slowly separated. The ethanol was removed. The residue was dissolved in methylene chloride. The methylene chloride solution was washed (water), dried ($MgSO_4$), and removed in vacuo. The resulting solid was recrystallized from methanol to give 1,1′-methylenebis(3-thiocyanomethylbenzene) (**7**, 9.6 g, 77% yield): mp 60–62 °C; NMR δ 7.35–7.00 (m, 8), 4.02 (s, 4), 3.94 (s, 2); ir (Nujol) 2148 (s), 1600 (m), 1586 (m), 1254 (m), 708 (s), 700 cm^{-1} (s).

Anal. Calcd for $C_{17}H_{14}N_2S_2$: C, 65.80; H, 4.55; N, 9.03. Found: C, 66.02; H, 4.75; N, 8.73.

4,4-Dimethyl-2,6-dithia[7.1]metacyclophane (12). 1,1′-Methylenebis(3-thiocyanomethylbenzene) (**7**, 21.1 g, 0.068 mol) was dissolved in ether and added to ether containing $LiAlH_4$ (5.0 g, 0.135 mol). The mixture was refluxed for 2 h and added to excess saturated potassium sodium tartrate solution. The resulting solids were removed by filtration and washed with ether. The ethereal layer was separated, washed (brine), dried ($MgSO_4$), and concentrated to dryness. The resulting oil (17.7 g, 0.068 mol, 100% yield) crystallized slowly in the refrigerator: NMR δ 7.08 (s, 8), 3.88 (s, 2), 3.62 (d, 4, J = 7 Hz), 1.66 (t, 2, J = 7 Hz). The crude dithiol 8 was dissolved in 2-methoxyethanol (100 ml) and added to a solution of NaOH (5.4 g, 0.136 mol) in 2-methoxyethanol (200 ml). This solution was added dropwise to refluxing 2-methoxyethanol (1500 ml) to which 1,3-dibromo-2,2-dimethylpropane (15.64 g, 0.068 mol) dissolved in 2-methoxyethanol (250 ml) was being added at the same rate. After addition was completed (5 h), the mixture was refluxed for a further 4 h and allowed to stand overnight. 2-Methoxyethanol was removed in vacuo. The residue was partitioned between ether and water. The ethereal layer was separated, washed (brine), dried ($MgSO_4$), and concentrated to dryness. The residue was recrystallized from ether to give 4,4-dimethyl-2,6-dithia[7.1]metacyclophane (**12**, 10.8 g, 48% yield): mp 100–102 °C; NMR δ 7.40–6.90 (m, 8), 3.94 (s, 2), 3.56 (s, 4), 2.18 (s, 4), 0.88 (s, 6); ir (Nujol) 1602 (m), 1590 (m), 1282 (m), 1224 (m), 920 (m), 716 (s), 704 cm^{-1} (s).

Anal. Calcd for $C_{20}H_{24}S_2$: C, 73.14; H, 7.37. Found: C, 73.32; H, 7.23.

2,4,4,6-Tetramethyl[7.1]metacyclophane-2,6-bis(thiaonium fluorosulfonate) (15b). 4,4-Dimethyl-2,6-dithia[7.1]metacyclophane (**12**, 410 mg, 1.25 mmol) was dissolved in methylene chloride (2 ml) and the solution cooled to −50 °C. Methyl fluorosulfonate (330 mg, 2.75 mmol) in cooled methylene chloride (3 ml) was added dropwise with stirring. After stirring for 1 h to room temperature, ethyl acetate (3 ml) was added. The crystalline precipitate (607 mg, 87% yield) of the bissulfonium salt **15b**, mp 190 °C dec, was collected.

Anal. Calcd for $C_{22}H_{30}F_2O_6S_4$: C, 47.46; H, 5.43. Found: C, 47.50; H, 5.55.

4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane (17/18). The bissulfonium salt **15** (460 mg, 0.83 mmol) was added to a solution of potassium *tert*-butoxide (250 mg, 1.66 mmol) in dry tetrahydrofuran (60 ml) with stirring. Stirring was continued for 30 min at room temperature. The tetrahydrofuran was removed in vacuo. The residue was dissolved in methylene chloride. The solution was washed (water, brine), dried ($MgSO_4$), and concentrated to dryness. The residue (253 mg, 85% recovery) partially crystallized. Recrystallization from ethanol/benzene gave *anti*-4,4,9,17-tetramethyl-2,6-dithia[7.1]paracyclophane (**18**, 80 mg, 27% yield): mp 150–151 °C; NMR δ 7.10–6.76 (m, 6), 3.74 (s, 2), 3.62 (q, 4, J = 14 Hz), 2.24 (s, 6), 1.36 (q, 4, J = 13 Hz), 0.30 (s, 6); ir (Nujol) 1602 (m), 1156 (s), 816 (m), 740 (m), 718 cm^{-1} (s); uv λ_{max} (MeOH) 248 nm (ε 680); MS m/e 356 (M^+).

Anal. Calcd for $C_{22}H_{28}S_2$: C, 70.73; H, 7.92. Found: C, 71.07; H, 7.53.

On warming the NMR solution (45–50 °C), the most striking change is the diminution of the signal at δ 0.30 and the appearance of two new singlets at δ 0.52 and −0.22. Other more complex changes take place in the lower field part of the spectrum.

Desulfurization of 4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane (17/18). The dithia[7.1]paracyclophane **17/18** (188 mg, 0.53 mmol) was refluxed in ethanol (180 ml) with Raney nickel suspension (20 ml) for 18 h. The Raney nickel was removed and the filtrate concentrated to dryness. The residue (72 mg, 61% recovery) was analyzed by VPC on a Chromosorb (AW-DMCS) column with a UCW-98 coating. Three peaks were obtained, retention time 2.6 (8.2%), 3.9 (86.6%), 7.1 min (5.2%). The retention time 3.9 min material was identified by comparison with authentic 1,1′-methylenebis(3,4-dimethylbenzene). The residue was distilled in a short tube in a hot block at 0.2 mm. The bulk of the material distilled to give a colorless liquid (42 mg) which slowly crystallized on cooling. This was recrystallized from petroleum ether (40–60 °C)/ethanol to give 1,1′-methylenebis(3,4-dimethylbenzene) (12 mg, **25**): mp (34–35 °C (lit.[13] 35–36 °C); no depression of melting point on admixture with material prepared by unambiguous synthesis (see below); identical NMR and mass

spectra.

Synthesis of Authentic 1,1′-Methylenebis(3,4-dimethylbenzene) (25). 3,3′,4,4′-Benzophenone tetracarboxylic dianhydride (**21**, Aldrich, 6 g, 18.6 mmol) was dissolved in a 1:1 mixture of ethanol and acetic acid (120 ml). Pd/C catalyst (7 g, 10%) was added and the mixture hydrogenated in a Parr apparatus at 55 °C for 3 h at 45 psi. A fall in pressure was observed. The catalyst was removed and the filtrate concentrated to dryness. The residue was dissolved in ether and extracted with 10% aqueous $KHCO_3$ solution (three times). The bicarbonate washings were acidified and reextracted (ether). Removal of the ether gave a solid (4.7 g), mp 236–239 °C. This solid was suspended in methanol (50 ml), concentrated H_2SO_4 (3 ml) was added, and the mixture was refluxed for 4 h. The methanol was removed. The residue was dissolved in ether, washed (water, 10% $KHCO_3$, and brine), dried ($MgSO_4$), and concentrated to dryness. The residue (4.2 g) was distilled. The main fraction was dimethyl 4,4′-methylenebis(*o*-toluate) (**23**): bp 173 °C (0.2 mm) (3.8 g, 65% yield, based on the bis anhydride); NMR δ 7.80 (d, 2, J = 9 Hz), 7.20–6.90 (m, 4), 3.92 (s, 2), 3.84 (s, 6), 2.55 (s, 6); ir (film) 1724 (s), 1612 (m), 1572 (m), 1440 (s), 1260 (s), 1200 (s), 1082 (s), 780 cm^{-1} (m); uv (MeOH) λ_{max} 237 nm (ε 20 370), 284 (2790).

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.07; H, 6.71.

The dimethyl ester **23** (3.8 g, 12.2 mmol) was dissolved in ether (20 ml) and added to a slurry of $LiAlH_4$ (1.5 g) in ether (100 ml). The mixture was refluxed for 2 h. The excess $LiAlH_4$ decomposed with saturated potassium sodium tartrate. The mixture was filtered through Celite. The Celite was washed with ether. The ethereal filtrate was dried ($MgSO_4$) and concentrated to dryness. The residue (3.03 g, 97% yield) crystallized on standing. A portion (~⅓) was recrystallized from 2-propanol to give 1,1′-methylenebis(3-methyl-4-hydroxymethylbenzene) (**24**): 0.91 g; mp 93–95 °C; NMR δ 7.25–6.80 (m, 6), 4.44 (s, 4), 3.80 (s, 2), 2.50 (s, 2 exch), 2.16 (s, 6); ir (Nujol) 3350–3250 (s), 1040 (s), 1020 (s), 846 (m), 822 (m), 750 cm^{-1} (m).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.69; H, 8.02.

The dibenzyl alcohol **24** (3 g, 11.7 mmol) was dissolved in a 1:1 mixture of ethanol/acetic acid (80 ml). Pd/C (3 g, 10%) was added and the mixture hydrogenated in a Parr apparatus at 55 °C and 42 psi for 5 h. The mixture was passed through Celite. The filtrate was concentrated to dryness and the residue (1.8 g, 69%) distilled in a short-path apparatus. The principal fraction, bp 108 °C (0.2 mm), was 1,1′-methylenebis(3,4-dimethylbenzene) (**25**): mp 34–35.5 °C (petroleum ether/ethanol) (lit.[13] mp 35–36 °C); NMR δ 6.94 (s, 6), 3.84 (s, 2), 2.20 (s, 12); ir (film) 1612 (m), 1576 (m), 1502 (s), 1452 (s), 1384 (m), 1018 (m), 998 (m), 826 (m), 802 (s), 750 cm^{-1} (s).

Anal. Calcd for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 91.25; H, 9.10.

***anti*-4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane 2,2,6,6-Tetraoxide (19).** The crystalline *anti*-dithia[7.1]paracyclophane **18** (100 mg, 0.28 mmol) was dissolved in methylene chloride (50 ml). *m*-Chloroperbenzoic acid (260 mg of 85%, i.e., 1.33 mmol) was added with stirring at room temperature. The mixture was stored overnight at −7 °C. The precipitated *m*-chlorobenzoic acid was removed. The filtrate was washed (10% aqueous $KHCO_3$ solution, water), dried ($MgSO_4$), and concentrated to dryness. The solid residue (118 mg) was rapidly recrystallized from ethanol to give the *anti*-dithia[7.1]paracyclophane tetraoxide **19**: mp 256–257 °C; NMR (DMF) δ 7.36–6.96 (m, 6), 4.28 (q, 4, J = 14 Hz), 3.91 (s, 2), 2.36 (s, 6), 2.27 (s, 4), 1.28 (s, 6); ir (Nujol) 1608 (w), 1308 (s), 1292 (s), 1134 (s), 850 cm^{-1} (m); uv λ_{max} (MeOH) 251 nm (ε 7 200); MS *m/e* 420 (M^+).

Anal. Calcd for $C_{22}H_{28}O_4S_2$: C, 62.82; H, 6.71. Found: C, 62.92; H, 6.63.

***syn*-4,4,9,17-Tetramethyl-2,6-dithia[7.1]paracyclophane 2,2,6,6-Tetraoxide (20).** The crystalline *anti*-dithia[7.1]paracyclophane **18** (1 g, 2.8 mmol) was equilibrated to a syn/anti mixture by refluxing overnight in chloroform. The chloroform was removed and the residue oxidized by *m*-chloroperbenzoic acid as described above for the anti isomer. The resulting residue (1.1 g) of a mixture of syn and anti isomers of the tetraoxide was separated by preparative high-pressure liquid chromatography on a Waters Model ALC 100 with a Model 6000 pump. An 8 ft × 0.375 in. column of Woelm neutral III alumina N 18 with a 75:25 mixture of 25% water saturated isooctane and THF as the mobile phase. Portions (100 mg) of the syn/anti mixture were injected with a 2-ml loop injector. Separation and isolation required five recycles at a flow rate of 4 ml/min (~22 h total). Detection was by means of uv absorption (254 nm). From several such portions, fractions containing the pure fast and slow isomers were combined. The fast isomer was recrystallized from ethanol to give the *anti*-4,4,9,17-tetramethyl-2,6-dithia[7.1]paracyclophane 2,2,6,6-tetraoxide, mp 256–257 °C, identical with the material prepared from the crystalline *anti*-dithia[7.1]paracyclophane by mixture melting point, NMR, and retention time in high-pressure liquid chromatography. The slower moving isomer was recrystallized from ethanol to give *syn*-4,4,9,17-tetramethyl-2,6-dithia[7.1]paracyclophane 2,2,6,6-tetraoxide (**20**): mp 230–232 °C; NMR (DMF) δ 7.20 (s, 6), 4.39 (q, 4, J = 14 Hz), 3.94 (s, 2), 2.30 (q, 4, J = 14 Hz), 1.33 (s, 3), 1.28 (s, 3); ir (Nujol) 1608 (w), 1308 (s), 1288 (s), 1122 (s), 846 cm^{-1} (m); uv (MeOH) λ_{max} 252 nm (ε 7310); MS *m/e* 420 (M^+).

Anal. Calcd for $C_{22}H_{28}O_4S_2$: C, 62.82; H, 6.71. Found: C, 62.45; H, 6.59.

Equilibration of the *syn*- and *anti*-Dithia[7.1]paracyclophane Tetraoxides 19/20. The deuterated DMF solution of both syn and anti isomers was heated overnight at 100 °C. The spectra resulted from either isomer were identical and consisted of a 1:1 mixture. Solutions (0.5%) in dioxane of the pure syn and anti isomers were prepared. These solutions were heated overnight in vials in temperature-controlled silicone oil baths at 70, 80, and 90 °C. After freezing aliquots of these solutions, their composition was determined by high-pressure liquid chromatography under conditions employed for the kinetic studies below. Peak area was estimated as the peak height times width at half height. Within the limits of error of this procedure (±1%) each of the six vials contained a 1:1 syn/anti mixture. Thus, neglecting the small differences in ε in the uv spectrum, the equilibrium constant K can be assumed to be unity over this temperature range.

Kinetic Measurements. A Waters Model 202/401 liquid chromatograph, equipped with a Model 6000 pump and uv detector for 254 nm, was employed. A 6 ft × 0.125 in. column was packed with HC-Pellumina (Reeve Angel) and eluted with 25% water saturated isooctane/tetrahydrofuran (75:25). The flow rate was maintained at 1.5 ml/min at 1500 psi. Septum injection was used. The anti isomer had a retention time of 18 min, the syn isomer a retention time of 26 min. Baseline separation was achieved at 20-μg levels. Solutions (0.5%) of the anti isomer in *p*-dioxane were heated in reaction vials, equipped with Teflon septa, in constant-temperature silicone oil baths at 70, 80, and 90 ± 0.5 °C. Aliquots were removed at appropriate times and frozen immediately in a dry ice bath. Samples (4 μl) of these aliquots were analyzed. Peak areas were estimated by multiplying peak height by the width at half height. The shapes of the curves obtained from both isomers were similar. A plot of log [1 − 2 (% of syn)/(% of anti)] vs. time was made for each temperature. The linear regression equations were estimated by the least-squares method. The validity of the equations were checked by testing the significance of the slopes. In all cases the probability (p <0.001) indicated that the relation could be expressed as linear. The resulting data (Table I) were used via Eyring and Arrhenius plots to derive the thermodynamic parameters for the process (Table II).[24]

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Registry No. —**3,** 59054-28-3; **4,** 59054-29-4; **5,** 59054-30-7; **6,** 59054-31-8; **7,** 59054-32-9; **8,** 59054-33-0; **9,** 59054-34-1; **10,** 59054-35-2; **11,** 59054-36-3; **12,** 59054-37-4; **13,** 59054-39-6; **14a,** 59054-40-9; **14b,** 59054-41-0; **15a,** 59054-43-2; **15b,** 59054-45-4; **16,** 59070-05-2; **17,** 59054-46-5; **18,** 59121-41-4; **19,** 59054-47-6; **20,** 59121-42-5; **21,** 2421-28-5; **23,** 59054-48-7; **24,** 59054-49-8; **25,** 726-05-6; thionyl chloride, 7719-09-7; propane-1,3-dithiol, 109-80-8; triethyloxonium tetrafluoroborate, 368-39-9; thiourea, 62-56-6; 2,2-dimethyl-1,3-dibromopropane, 5434-27-5; methyl fluorosulfonate, 421-20-5; potassium thiocyanate, 333-20-0.

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Indolizidines, α-Arylthiohemiaminals, and α-Arylsulfonylhemiaminals from a Quinolizidine Enamine and an Arenesulfonyl Chloride[1]

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The treatment of the quinolizidine enamine 6-dehydrodeoxynupharidine (**1**) with *p*-toluenesulfonyl chloride in benzene solution produces the following compounds: *p*-tolyl disulfone (**2**); *p*-tolyl disulfide (**3**); 7β-(*p*-tolylthio)-deoxynupharidin-6-ol (**4**); 7α-(*p*-tolylthio)-7-epideoxynupharidin-6-ol (**5**); 7β-(*p*-toluenesulfonyl)deoxynupharidin-6-ol (**6**); 7α-(*p*-toluenesulfonyl)-7-epideoxynupharidin-6-ol (**7**); and two epimeric indolizidinecarboxaldehydes, **8** and **9**, which arise by skeletal rearrangement. All of the products are isolated except for one of the epimeric indolizidines, **8**. Gross structures assigned are consistent with spectral evidence and elemental analyses. The C-7 configuration in the α-thiohemiaminals **4** and **5** is determined by circular dichroism and the configuration at the same center in the α-sulfonylhemiaminals **6** and **7** is established by chemical correlation with **4** and **5**. The C-3 configuration and the stereochemistry of the ring fusion in the isolated indolizidinecarboxaldehyde, 5α-(3-furyl)-3β,10β-dimethylindolizidine-3α-carboxaldehyde (**9**), is ascertained through infrared studies of the primary alcohol, **14**, obtained from **9** by reduction. Primary alcohol **14** gives Bohlmann infrared bands, indicating the trans-fused indolizidine ring system, and infrared bands revealing the intramolecular hydrogen bonding of the primary alcohol to the nitrogen. The rationale for product formation is based on *p*-toluenesulfonyl chloride acting as an ambident electrophile.

We wished to prepare a group of α-arenesulfonylhemiaminals for the purpose of comparing their metal hydride reductions with those of α-arylthiohemiaminals. Therefore we carried out the reaction of *p*-toluenesulfonyl chloride with 6-dehydrodeoxynupharidine (**1**). No less than eight products, including *p*-tolyl disulfone (**2**), *p*-tolyl disulfide (**3**), and three pairs of diastereomers, result from this reaction which takes the unusual course, outlined in Scheme I, in producing the rearranged indolizidines **8** and **9** and the α-thiohemiaminals **4** and **5** in addition to affording the desired and expected α-sulfonylhemiaminals **6** and **7**. Because of the unusual course of this reaction we wish to present the evidence for the formation of the six compounds **4–9**; the procedures for the isolation of five of them (**4–7** and **9**); and the structure determination of **4–7** and **9** as the principal topics of this paper. *p*-Tolyl disulfone (**2**)[2,3,4] and *p*-tolyl disulfide (**3**)[5,6] have long been known and their identification needs no further treatment beyond what is given in the Experimental Section. Finally a brief discussion regarding product formation is presented. The features of α-sulfonyl- and α-thiohemiaminal reductions will be treated in a separate paper at a later date.

The Indolizidines. Although only one of the two indolizidine aldehydes, **9**, could be isolated for study, there was evidence that both diastereomers **8** and **9** were formed. Thus the ^1H NMR of a chromatographic fraction showing two spots on TLC revealed a pair of singlets at δ 0.92 and 1.07, the lower field signal being the more intense. These signals were attributed to C-11, the methyl group attached to C-3 of **8** or **9**. Moreover the same spectrum exhibited a pair of aldehyde protons at δ 9.04 and 9.79 whose integrated intensities were in the ratio of 8:1.

Chromatographic refinement of this same fraction gave the pure diastereomer **9** but failed to separate the minor diastereomer **8** in a state completely free of **9**. The ^1H NMR of **9** revealed the C-8 methyl (C-10) doublet at δ 0.91, the C-5 proton double doublet at δ 3.36, and the 3-furyl multiplets at δ 6.36 and 7.26, the last two signals representing three protons. Consequently neither the furan ring nor ring A of the starting enamine had been altered since these ^1H NMR characteristics agree with those of the corresponding protons[7,8] in deoxynupharidine and 7-epideoxynupharidine (**1**, 6,7β- and 6,7α-dihydro, respectively). This conclusion was supported by the ^{13}C NMR spectrum, which exhibited the C-10 quartet at 18.5 ppm, the C-8 doublet at 37.0 ppm, and the C-9 doublet at 67.5 ppm in addition to the normal 3-furyl signals at 109.8, 127.0, 140.0, and 142.9 ppm, all in accord with the ^{13}C chemical shifts of corresponding carbons in deoxynupharidine and 7-epideoxynupharidine.[9]

The appearance of the ir absorption at 5.79 μm and the ^1H NMR singlet at δ 9.04 indicated the presence of the aldehyde function. The aldehyde group must be attached to a quaternary carbon which also bears the second methyl group since the latter appears at δ 1.07 as a singlet. The quaternary carbon was linked to the nitrogen since the higher field singlet in the ^{13}C NMR appeared at 70.5 ppm. The second carbon attached to nitrogen gave the 67.5-ppm doublet as already mentioned above. The third carbon attached to nitrogen, as yet unaccounted for, appeared as a doublet at 52.9 ppm and was assigned to C-5. Therefore, of the total 15 carbons indicated by