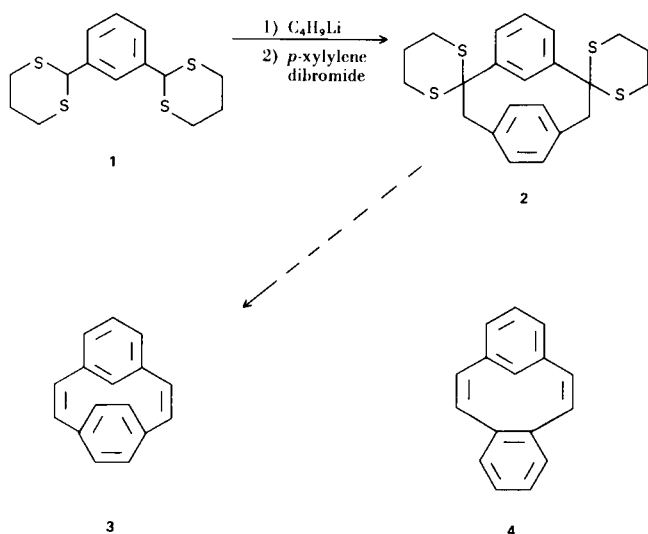


Conformational Effects Observed in an NMR Study of Some Thiacyclophanes (1,2)

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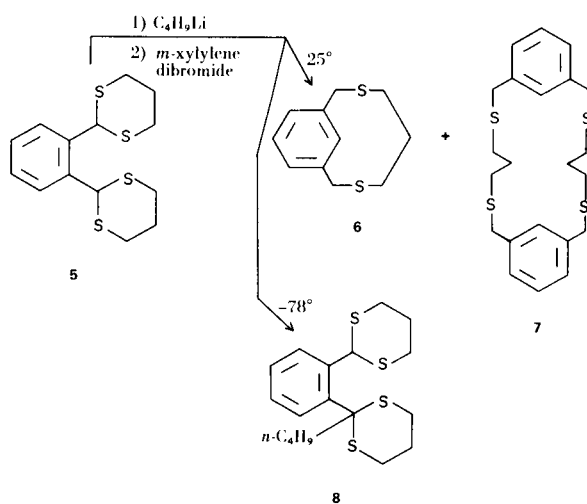
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Recently, we described a convenient synthesis of cyclophanes by the alkylation of aromatic bis-dithianes, such as **1**, with dihalides to give [2.2]metaparacyclophanes (**2**) as well as other cyclophanes (**3**). The further conversion of **2** to [2.2]metaparacyclophane-1,9-diene (**3**) occurred smoothly and the spectral properties of this molecule strongly suggest that the two benzene rings are perpendicular to each other with the "internal" hydrogen of the *meta*-bridged ring being inserted into the cavity of the π -cloud of the *para*-bridged ring. Since molecules having two aromatic π -clouds held perpendicular to each other are of inherent theoretical interest, we were led to explore this method of synthesis for the preparation of other molecules that might display this interesting property.

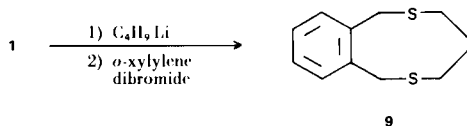


Examination of molecular models suggested that [2.2]-*orthometacyclophane*-1,9-diene (**4**) might also have the two aromatic π -clouds perpendicular to each other but in an edge-on relationship. For this reason we studied the reaction of *o*-phthalaldehyde bis(1,3-propanedithioacetal) (**5**) with *m*-xylylene dibromide as a possible route to **4**. Unexpectedly, though, the product of the reaction was not the desired [2.2]*orthometacyclophane*, but instead there was isolated [7](2,6)dithiametacyclophane (**6**) in 18% yield and its dimer **7** in 5% yield. The reaction path for the formation of **6** and **7** under these conditions is not

obvious but it would appear that decomposition of **5** had liberated propane-1,3-dithiol which had subsequently undergone reaction with the *m*-xylylene dibromide to give **6** and **7**. In the hope that this type of decomposition might be avoided at lower temperatures, the reaction was then tried at -78° instead of room temperature. The course of the reaction was indeed changed but now the sole product to be isolated was the *n*-butyl derivative **8**.



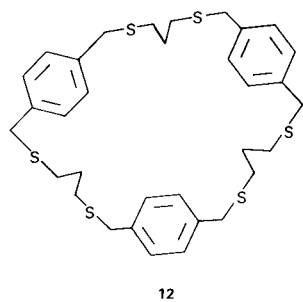
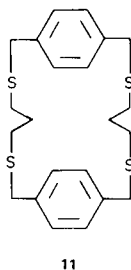
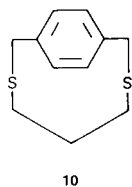
As an alternative path to **4**, the reaction of isophthalaldehyde bis(1,3-propanedithioacetal) (**1**) with *o*-xylylene dibromide was investigated. However, again, the product was not the desired [2.2]*orthometacyclophane* derivative but instead the [7](2,6)dithiaortho-cyclophane (**9**), together with polymeric by-products.



Although we were frustrated in our attempts to prepare **4**, it was of interest to prove the structures of **6** and **9** and to study their properties in greater detail. Treatment of *m*-xylylene dibromide with the dianion of propane-1,3-dithiol in tetrahydrofuran under high dilution conditions

gave **6** in 43% yield and **7** in 10% yield. Since the properties of **6** and **7**, as prepared in this way, are in full accord with those of the previous preparation, this independent synthesis provides full proof of structure (4). Similarly, treatment of *o*-xylylene dibromide with the dianion of propane-1,3-dithiol gave **9** in 67% yield (5).

To complete the series, *p*-xylylene dibromide was also treated with the dianion of propane-1,3-dithiol. However, in this case none of the desired [7](2,6)dithiaparacyclophane (**10**) was formed; only the dimer and trimer derivatives, **11** and **12**, were isolated and characterized.



NMR spectra.

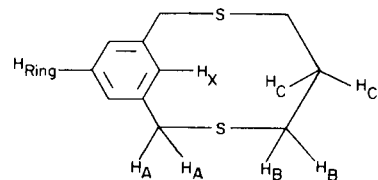
The nmr spectra of the various dithiacyclophanes are presented in Table I. The spectrum of **6** is clearly anomalous in that the signal for the $H_{C,C'}$ protons is shifted to higher field by about 1 ppm.

The reason for this anomaly becomes apparent from examination of molecular models. In the case of **6** the most probable conformations (Figure 1a and 1b) have the methylene protons $H_{C,C'}$ extending into the cavity of the aromatic π -electron cloud. Thus, the aromatic diamagnetic ring current is responsible for the upfield shift of these protons. However, for the other dithiacyclophanes **7**, **9**, **11** and **12**, each has at least one conformation in which the methylene protons are out of the region of the aromatic π -electron cloud (e.g. see Figure 1c).

In the room temperature nmr spectrum of **6**, the methylene protons H_C and $H_{C'}$ appear to be equivalent. This could not be so if the molecule existed entirely in one of the conformations indicated in Figure 1a or b. It appears

TABLE I

Proton Chemical Shifts of Dithiacyclophanes with designation of protons as shown below for **6** as a model. Spectra taken in deuteriochloroform at room temperature.



	H_X	H_{Ring}	H_A	H_B	H_C
6	2.34 (s)	2.6-3.0 (m)	6.17 (s)	7.41 (t)	9.55 (q)
7		2.81 (s)	6.37 (s)	7.65 (t)	8.40 (q)
9		2.74 (s)	6.22 (s)	7.42 (t)	8.0-8.3 (m)
11		2.82 (s)	6.39 (s)	7.78 (t)	8.45 (q)
12		2.79 (s)	6.40 (s)	7.62 (t)	8.1-8.6 (m)

then that the bridging atoms are inverting back and forth over the molecule at room temperature, and hence give an "average" chemical shift. It was thus supposed that one or more conformations of **6** might be "frozen-out" by cooling. Indeed, when the nmr spectrum of **6** was recorded at lower temperatures (Figure 2), a "freezing-out" process did occur. As the sample was cooled, the signal at τ 9.55, assigned to an averaging of protons $H_{C,C'}$, at first broadened and collapsed, then reappeared as two peaks centered at τ 8.29 and τ 10.21. The latter signal was assigned to the proton H_C which in conformation 1a is strongly shielded in the cavity of the π -electron cloud. In this spectrum the methylenic protons H_B and the ring-proton H_X now also show different signals. It does appear however that the benzylic protons H_A are still able to rotate sufficiently to allow equivalence.

From the difference in chemical shifts of H_C and $H_{C'}$ at -95° ($\Delta\nu_{CC'}=196$ Hz) and the temperature of collapse ($T_C = -50^\circ$). The energy of the barrier to change this conformation is calculated (6) as $\Delta G=10.2$ kcal/mole (7).

On further cooling of the sample we observe further changes in the nmr spectrum indicating contributions from still another conformation. This could correspond to a conformation such as that shown in Figure 1b, in which the proton H_C must now extend still further into the cavity of the π -electron cloud, as evidenced by its upfield shift to τ 11.36. The barrier to inversion of this conformation ($\Delta\nu_{CC'}=254$ Hz; $T_C = -80^\circ$) is calculated as $\Delta G=8.7$ kcal/mole. It is also observed that below -75° the benzylic protons H_A are now no longer equivalent, and the energy of the barrier to interconvert these protons is $\Delta G=10.1$ kcal/mole ($\Delta\nu=17$ Hz; $T_C = -75^\circ$).

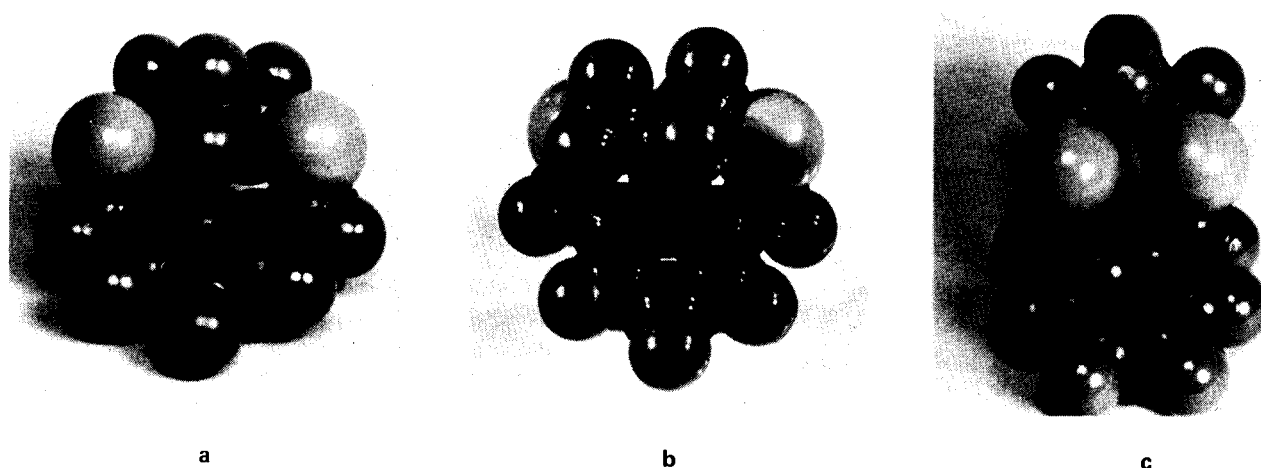


Figure 1. Fisher-Taylor-Hirschfelder molecular models of two conformations of [7](2,6)dithiametacyclophane (**6**), a and b, and a conformation of [7](2,6)dithiaortho-cyclophane (**9**), c.

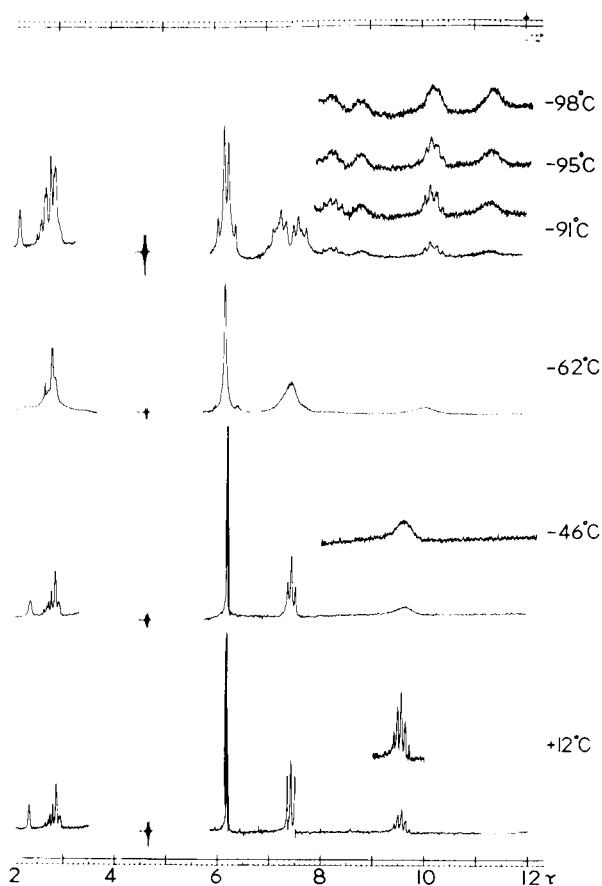


Figure 2. NMR spectra of [7](2,6)dithiametacyclophane **6** in deuteriomethylene chloride, measured using a Varian HA-100 MHz spectrometer.

The magnitude of the upfield shift of the Proton HC at -98° when compared to the corresponding protons of the other cyclophanes **7**, **9**, **11** and **12** is *ca.* 3 ppm. This represents one of the largest chemical shifts obtained in a *metacyclophane* in which protons experience a shielding effect due to the proximity of the aromatic π -electron cloud (3,8,9).

On examination of models of the cyclophanes **7**, **9**, **11** and **12** it was expected that these would also show temperature dependant nmr spectra. However, samples cooled to -100° showed no change in their spectra. It can thus be concluded that there is no such restricted movement of the bridging atoms in these compounds, as is present in the ten-membered ring of **6**.

EXPERIMENTAL

All evaporations were carried out under reduced pressure. Extracted reaction mixtures were dried with magnesium sulfate. Chromatography was carried out on silica gel (on a 50x4.7 cm column unless otherwise stated). Petrol used for elution was redistilled 30-60° petroleum ether. Melting point determinations were taken on a Mel-Temp apparatus and are uncorrected. NMR spectra were taken in deuteriochloroform using a Varian HA-100 MHz spectrometer.

o-Phthalaldehyde Bis(1,3-propanedithioacetal) (**5**).

A solution of *o*-phthalaldehyde (13.4 g., 0.10 mole), propane-1,3-dithiol (31 g., 0.222 mole) and *p*-toluenesulphonic acid (600 mg.) in 500 ml. of benzene was boiled under reflux using a Dean Stark trap for 2 hours. The reaction became a deep purple. After the solution was cooled, the benzene was evaporated and the product extracted with chloroform. The extracts were washed well with water and then dried and evaporated. The residue was taken up in benzene and boiled with charcoal for a few minutes. After

filtration through celite and concentration of the filtrate, colourless crystals of product deposited. Recrystallization from benzene-hexane mixture containing some methanol (to remove any thiol) yielded colourless crystals 24.2 g. (77%) of **5**, m.p. 156-157°; nmr, a multiplet at τ 2.3-2.9 (4H, ArH), a singlet at 4.31 (2H, Ar-CH<), a multiplet at 6.7-7.3 (8H, -S-CH₂-), and a multiplet at 7.7-8.3 (4H, -CH₂-). Mass spectrum, peaks at M^+/e 314 (76%), 208 ($M^+-C_3H_6S_2$: 91%), and 134 ($M^+-C_6H_{12}S_3$: 100%)

Anal. Calcd. for C₁₄H₁₈S₄: C, 53.50; H, 5.77; S, 40.72. Found: C, 53.53; H, 5.63; S, 40.59.

Reaction of **5** with *m*-Xylylene Dibromide.

a) Room Temperature.

A solution, prepared by adding 26 ml. of a 1.6 molar solution of *n*-butyllithium in hexane (0.042 mole) to the bis-dithiane **5** (6.28 g., 0.020 mole) in dry tetrahydrofuran (600 ml.) was added simultaneously with a solution of *m*-xylylene dibromide (5.28 g., 0.020 mole) in dry tetrahydrofuran (600 ml.) through two Hershberg dropping funnels during 12 hours to rapidly stirred dry tetrahydrofuran (1 l., under nitrogen in a 3 l. three-necked Morton flask). After the mixture had been stirred at room temperature for 24 hours, it was boiled under reflux for 1 hour, cooled and concentrated. The residue was taken up in chloroform, washed with water and then passed through a short magnesium sulfate column to remove polymer. After concentration of the eluate, the residue was dissolved in a 1:4 mixture of methylene chloride-petroleum ether and chromatographed over silica gel. Concentration of the eluate gave a white solid which, after recrystallization from a benzene-cyclohexane mixture, gave 750 mg. (18%) of **6** as colourless needles, m.p. 105-106°; nmr, a singlet at τ 2.34 (1H, ArH), a multiplet at 2.6-3.0 (3H, ArH), a singlet at 6.17 (4H, Ar-CH₂-), a triplet centered at 6.41 (4H, -S-CH₂-, J=7.5 Hz), and a quintuplet at 9.55 (2H, -CH₂-, J=7.5 Hz); mass spectrum, parent molecular ion M^+/e 210 (57%), and a major fragmentation peak at 104 ($M-C_3H_6S_2$, 100%).

Anal. Calcd. for C₁₁H₁₄S₂: C, 62.84; H, 6.71; S, 30.44. Found: C, 62.79; H, 6.75; S, 30.37.

Further elution of the column with a 3:2 methylene chloride-petroleum ether mixture gave recovery of 503 mg. (10%) of **5**. Then elution with pure methylene chloride gave 186 mg. (5%) of **7**, after recrystallization from a benzene-hexane mixture, as colourless crystals, m.p. 120.5-121.0°; nmr, a singlet at τ 2.81 (8H, ArH), a singlet at 6.37 (8H, Ar-CH₂-), a triplet at 7.65 (8H, -S-CH₂-, J=7.0 Hz), and a quintuplet at 8.40 (4H, -CH₂-, J=7.0 Hz); mass spectrum, parent molecular ion M^+/e 420 (100%) with major fragmentation peaks at 208 (67%) and 105 (80%).

Anal. Calcd. for C₂₂H₂₈S₄: C, 62.84; H, 6.71; S, 30.44. Found: C, 62.87; H, 6.78; S, 30.39.

b) Low Temperature.

To a solution of 6.28 g. of **5** in 1.5 l. of dry tetrahydrofuran there was added 27.5 ml. of a 1.6M solution of *n*-butyllithium in hexane and the mixture was stirred at -78° under nitrogen for 30 minutes. The yellow solution was stirred for 30 minutes and then a solution of 5.28 g. of *m*-xylylene dibromide in 25 ml. of dry tetrahydrofuran was added with vigorous stirring. After an additional hour at -78°, the solution was warmed to room temperature and concentrated. The residue was taken up in chloroform, washed with water, dried, and the chloroform extract concentrated. The residual oil was then taken up in 50% benzene-petroleum ether mixture and chromatographed over silica gel. Concentration of the main eluate fraction left an oil which, after recrystallization from a hexane-cyclohexane mixture, gave 2.1 g. (28%) of **8** as

white crystals, m.p. 142-143°; nmr, two multiplets at τ 1.8-2.3 and 2.5-2.8 (4H, ArH), a singlet at 2.58 (1H, Ar-CH-S-), a multiplet at 6.8-7.5 (8H, -S-CH₂-), a multiplet at 7.5-8.3 (8H, -CH₂-), and a multiplet at 8.5-9.5 (5H, -CH₂-CH₃); mass spectrum, parent molecular ion M^+/e 370 (53%) with major fragmentation peaks at 295 ($M^+-C_3H_7S_1$ 100%) and 264 ($M^+-C_3H_6S_2$, 72%).

Anal. Calcd. for C₁₈H₂₆S₄: C, 58.37; H, 7.08; S, 34.56. Found: C, 58.56; H, 6.97; S, 34.49.

Reaction of **1** with *o*-Xylylene Dibromide.

A solution of 5.28 g. of *o*-xylylene dibromide in 700 ml. of dry tetrahydrofuran and a solution prepared by adding 38 ml. of a 1.1M solution of *n*-butyllithium in hexane to 6.28 g. of isophthalaldehyde bis(1,3-propanedithioacetal) in 700 ml. of dry tetrahydrofuran were added dropwise simultaneously through two separate Hershberg funnels over a period of 6 hours to 1 l. of rapidly stirred boiling tetrahydrofuran under a nitrogen atmosphere. After addition was complete, the mixture was stirred an additional 12 hours, cooled, and concentrated under reduced pressure. The residue was extracted with chloroform, washed with water, dried, and the chloroform extract was concentrated. The residue was taken up in petroleum ether and chromatographed over silica gel. The first eluate fraction gave 400 mg. of the starting dibromide. Then, using a 5% benzene-petroleum ether mixture for elution, there was isolated 168 mg. (4%) of **9** as white needles; m.p. 88.0-88.5° after recrystallization from a cyclohexane-hexane mixture; nmr, a singlet at τ 2.74 (4H, ArH), a singlet at 6.22 (4H, Ar-CH₂-S-), a triplet at 7.42 (4H, -CH₂-S-, J=5.5 Hz), and a multiplet at 8.0-8.3 (2H, -CH₂-); mass spectrum, parent molecular ion M^+/e 210 (75%) with major fragmentation peaks at 135 ($M^+-C_3H_7S$, 100%) and 104 ($M^+-C_3H_6S_2$, 25%).

Anal. Calcd. for C₁₁H₁₄S₂: C, 62.84; H, 6.71; S, 30.44. Found: C, 62.58; H, 6.63; S, 30.33.

Formation of Cyclophanes **6**, **7**, **9**, **11** and **12** by Reaction of Propane-1,3-dithiol with Xylylene Dibromides.

a) *o*-Xylylene Dibromide.

To a solution of 1.08 g. of propane-1,3-dithiol in 600 ml. of dry tetrahydrofuran there was added 14 ml. of a 1.6M solution of *n*-butyllithium in hexane. This prepared solution was then added dropwise through a Hershberg funnel to 1 l. of vigorously stirred tetrahydrofuran while simultaneously through a second Hershberg funnel there was added dropwise a solution of 2.64 g. of *o*-xylylene dibromide in 600 ml. of tetrahydrofuran. When addition was complete, the mixture was stirred an additional 30 hours at room temperature. After concentration, the residue was taken up in methylene chloride and washed successively with water, 0.1N aqueous hydrochloric acid, and water. The dried methylene chloride extract was then concentrated; the residue was taken up in a 30% methylene chloride-petroleum ether mixture and chromatographed over silica gel. The main eluate fraction gave 1.414 g. (67%) of white needles, m.p. 88.0-88.5°, after recrystallization from a cyclohexane-hexane mixture. A comparison of these crystals with **9**, as previously prepared, showed them to be identical in all respects.

b) *m*-Xylylene Dibromide.

Following the same procedure as described under (a) but using *m*-xylylene dibromide, we isolated 910 mg. (43%) of **6** as colourless needles, m.p. 105-106°, identical in all respects with the specimen of **6** prepared previously. In addition there was isolated 419 mg. (10%) of **7**, as colourless needles, m.p. 123-124°, identical in all

respects with the specimen of **1** prepared previously.

c) *p*-Xylylene Dibromide.

The procedure as described in (a) was used with *p*-xylylene dibromide. From the first eluate fraction there was isolated 660 mg. (31%) of **11** as colourless needles, m.p. 151-152°, after recrystallization from a cyclohexane-hexane mixture; nmr, singlet at τ 2.82 (8H, ArH), singlet at 6.39 (8H, Ar-CH₂-S-), a triplet at 7.78 (8H, -S-CH₂-, J=7.5 Hz), and a quintuplet at 8.45 (4H, -CH₂-, J=7.5 Hz); mass spectrum, parent molecular ion M^+/e 420 (36%) with major fragmentation peaks at 210 (45%) and 106 (100%).

Anal. Calcd. for C₂₂H₂₈S₄: C, 62.84; H, 6.71; S, 30.44. Found: C, 62.58; H, 6.59; S, 30.24.

Elution with methylene chloride then gave 190 mg. (9%) of **12** as colourless crystals, m.p. 120.5-121.0°, after recrystallization from a benzene-hexane mixture; nmr, a singlet at τ 2.79 (12H, ArH), a singlet at 6.40 (12H, Ar-CH₂-), a triplet at 7.62 (12H, -S-CH₂-, J=7.0 Hz), and a multiplet at 8.1-8.6 (6H, -CH₂-); mass spectrum, parent molecular ion M^+/e 630 (100%) with major fragmentation peaks at 420 (76%), 210 (193%), and 208 (234%).

Anal. Calcd. for C₃₃H₄₂S₆: C, 62.84; H, 6.71; S, 30.44. Found: C, 62.58; H, 6.75; S, 30.17.

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Received July 22, 1969

Eugene, Oregon 97403