

# Preparation and Some Reactions of 3,5:8,10-Di-1,3-benzo[8](3,4)-1,2,5-thiadiazolocyclophane

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Titled 1,2,5-thiadiazolometacyclophane **1** was prepared *via* thia[2.3]cyclophane **5** which was obtained by the reaction of di(bromomethyl) **2** with sodium sulfide under phase-transfer-catalyzed conditions. Cyclophane **1** gave the corresponding pyrene derivatives by the oxidative transannular reaction in the reaction with brominating reagent. Reduction of **1** with lithium aluminum hydride followed by acetylation with acetic anhydride gave a 4:1-mixture of *cis*- and *trans*-diamide **11** and **12** with a trace amount of cyclophane-ring-cleaved product **13**. On the other hand, **13** was obtained as a major product in the reduction with metal sodium and diisobutylaluminum hydride.

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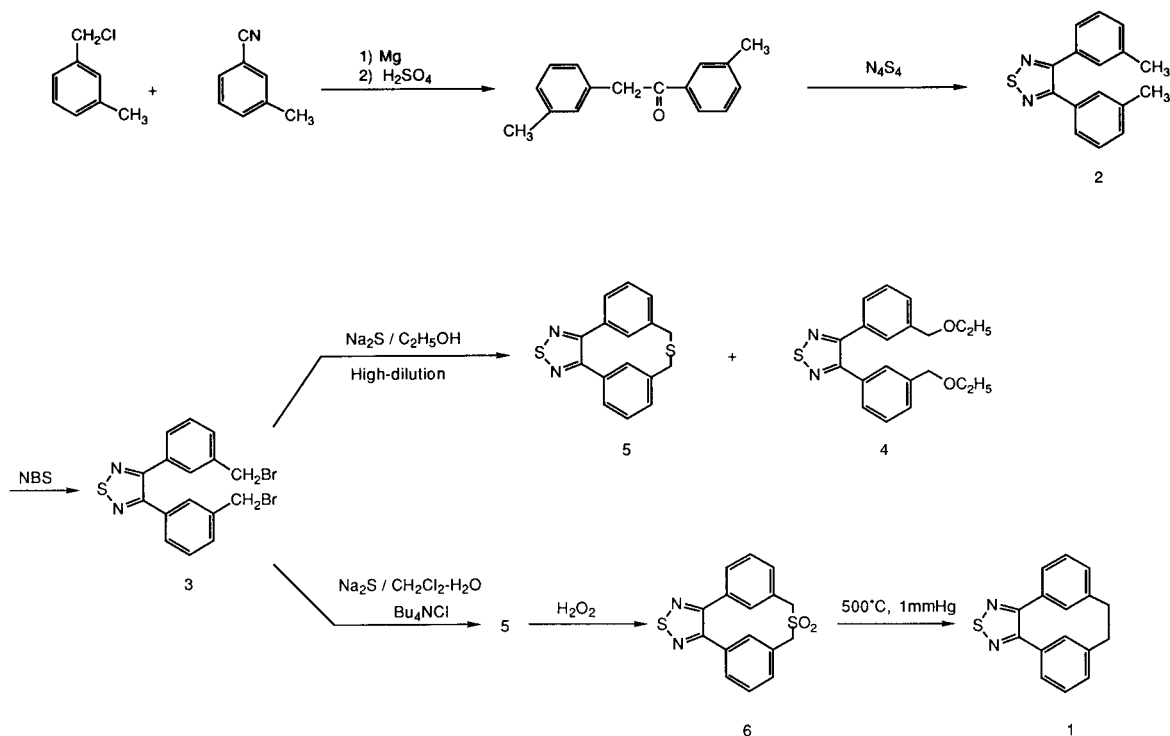
Previously, we prepared a series of [2<sup>3</sup>]cyclophane-1,2-diones [1] and -1,2-diacetoamides [2] by contraction of the 1,2,5-thiadiazole-ring which was incorporated in the bridge of the corresponding [2<sup>3</sup>]cyclophanes. As a continuation of the above, we now report the preparation of the titled [2<sup>2</sup>]metacyclophane **1** and some of its chemical properties.

## Results and Discussion.

### 1. Preparation.

Shortened preparative route of 3,4-di-*m*-tolyl-1,2,5-thiadiazole (**2**) [2] was developed as Scheme 1. Compound **2** was brominated as previously reported and di(bromomethyl) **3** was treated with sodium sulfide in ethanol under

Scheme 1



highly diluted conditions. The solvent reacted with **3**, giving di(ethoxymethyl) **4** in 57% yield as a major product, with a small amount of the expected thia[2.3]cyclophane **5** (8% yield). Compound **5** was obtained in 40% yield under phase-transfer-catalyzed conditions (methylene chloride/water/tetrabutyl-ammonium fluoride). Oxidation of **5** gave sulfone **6** (91% yield) which was pyrolyzed at 500° *in vacuo* (0.5 Torr), giving the desired **1** (75% yield). Anti-conformation of **1** and **5** was established by the characteristic up-field shift of inner protons of benzene ring, 5.50 and 6.12 ppm, respectively.

## 2. Transannular Reaction Giving Pyrene Derivatives.

Transannular reaction to pyrene derivative is the characteristic feature of [2<sup>2</sup>]metacyclophane derivatives. Cyclophane **1** is susceptible towards oxidative transannular reaction (Scheme 2). On treatment with bromine in the presence of iron powder in carbon tetrachloride, **1**, gave 4,5-dihydropyreno[4,5-*c*]-1,2,5-thiadiazole (**7**) in 37% yield. The reaction of **1** with bromine in the dark in carbon tetrachloride afforded a 2:1-mixture of unchanged **1** and pyreno[4,5-*c*]-1,2,5-thiadiazole (**8**). When the reaction was carried out under irradiation of a tungsten lamp, the ratio of **1**:**8** in the reaction mixture was 1:7. The reaction with

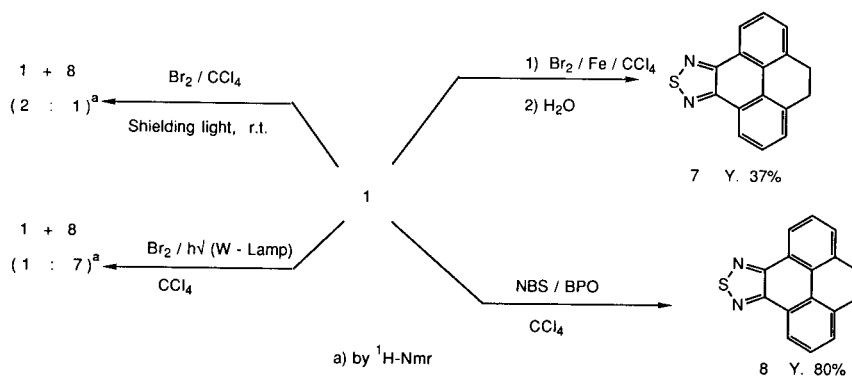
*N*-bromosuccinimide in the presence of benzoyl peroxide gave **8** in 80% yield.

Treatment of **1** with nitric acid at 0° in acetic anhydride gave a 3:1-mixture of **1** and **7**.

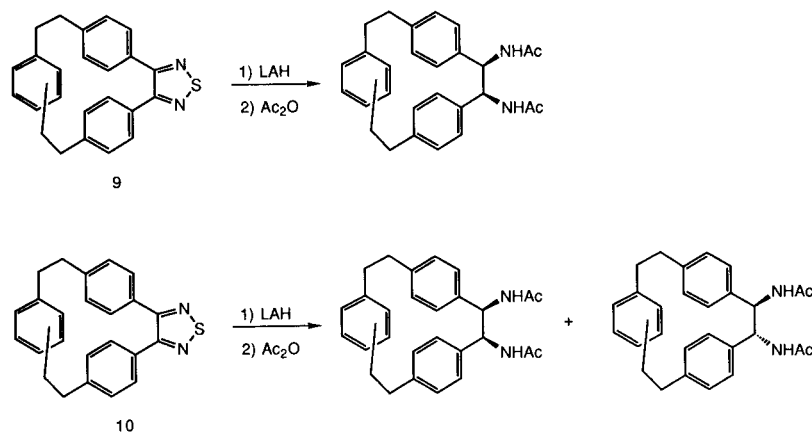
## 3. Reduction.

It was found [2] that, in the reduction of 1,2,5-thiadiazolo[2<sup>3</sup>]cyclophanes **9** and **10** with lithium aluminum hydride, *meta*-cyclophanes **9** was reduced in only a *cis*-manner, while *para*-cyclophanes **10** gave a mixture of the *cis*- and *trans*-diamine, although the formation of *cis*-diamine is predominant (Scheme 3). Reduction of strained meta[2.2]cyclophane **1** was investigated and the results are given in Scheme 4. When **1** was reduced with lithium aluminum hydride at 0° and the reduction mixture was acetylated with acetic anhydride, a 4:1-mixture of *cis*- and *trans*-diamide, **11** and **12**, was obtained in 30% yield. A trace amount of cyclophane-ring cleaved product **13** was formed in this reduction. The cleavage of the carbon-carbon bond of [2.2]metacyclophane skeleton of **1** occurred when **1** was treated with sodium in dry ethanol, giving **13** in 18% yield, together with unchanged **1** in 10% yield. Also, reduction of **1** with diisobutylaluminum hydride in toluene at 0° afforded **13** and **11** in 49% and 7% yield,

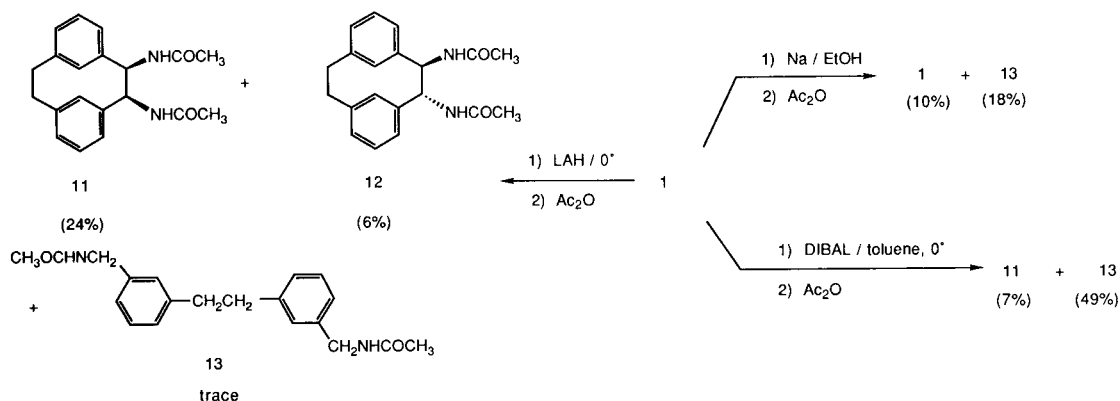
Scheme 2



Scheme 3



Scheme 4



respectively, Formation of **13** reflects the strain of anti-[2.2]metacyclophane.

The structures of **11** and **12** was determined on the basis of their <sup>1</sup>H-nmr spectra. In *cis*-diamide **11**, two acetoamide groups are unequivalent: the signals of two methyl groups were observed at 2.03 and 2.07 ppm, and two amide NH signals at 5 and 8 ppm, respectively. Methine and methylene protons in equatorial positions of [2.2]metacyclophane ring are deshielded by benzene ring and observed at 5.51 and 3.15 ppm, respectively, while those in axial position appeared at 4.35 and 2.13 ppm, respectively. The difference of chemical shift values between two amide protons in axial and equatorial position, respectively, was similarly reasoned.

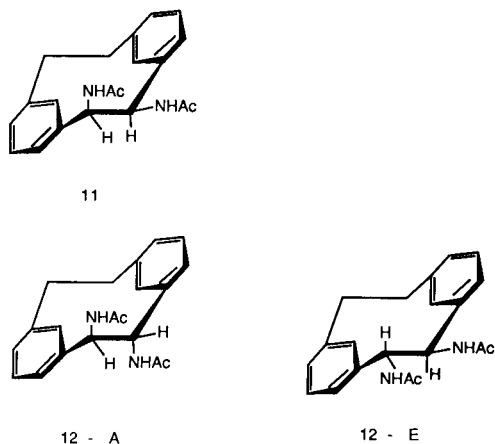


Figure 1. Conformation of 11 and 12

In *trans*-diamide **12**, two conformers, **12-A** and **12-E** (Figure 1), may be expected isolable at room temperature, since ring-inversion of anti-[2.2]metacyclophane *via* the *syn*-isomer is a high energy process; in **12-A**, two acetylamino groups are situated in the axial positions, while in **12-E** those do in equatorial ones. Two methyl signals of *trans*-**12** were observed at 1.95 ppm as a single

peak. Chemical shift values of methine proton (5.25 ppm) is close to the one on axial position of *cis*-**11**. Therefore, the structure of **12**, is assigned as **12-A**.

Since *trans*-**12-E** has the bulky substituent in equatorial positions and seems thermodynamically more stable than *cis*-**11** and *trans*-**12-A**, thermal conversion of a mixture of **11**- and **12-A** was investigated at 270°, giving a small amount of cyclophane-ring opened **13**, together with a complex mixture of unidentified decomposition products.

## EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-apparatus and a Mitamura-riken MELT-THERMO and are uncorrected. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system. The <sup>1</sup>H-nmr spectra were recorded on a JEOL FX-100 NMR spectrometer using tetramethylsilane as an internal standard in deuteriochloroform unless otherwise stated. The ir spectra were measured on a Nippon-bunko A-102 spectrophotometer as a potassium bromide pellets. Column chromatography was carried out on silica gel (Wako gel, C-300).

1,2-Di(*m*-tolyl)ethanone [3].

An ether solution of 3-methylbenzylmagnesium chloride was prepared by adding dropwise an ether solution (80 ml) of  $\alpha$ -chloro-*m*-xylene (11.1 g) to an ether suspension (80 ml) of magnesium turnings (1.10 g) at 0° for 8 hours under nitrogen atmosphere. To this solution was added to dropwise an ether solution (80 ml) of *m*-tolunitrile (4.21 g) and the mixture was stirred at for overnight, poured into dilute hydrochloric acid, and extracted with benzene and methylene chloride. The combined extract was dried and the solvents were evaporated *in vacuo* to leave the residue which was distilled under reduced pressure (3 Torr) at 95-100° (bath temperature). The residue in the distilling flask was chromatographed using a 95:5-mixture of hexane and ethyl acetate as an eluent, giving 1,2-di(*m*-tolylethanone) (3.44 g). This compound was obtained as a yellow oil; <sup>1</sup>H-nmr;  $\delta$  2.31 (s, 3H), 2.39 (s, 3H), 4.20 (s, 2H), 6.98-7.90 (m, 8H); ms: *m/e* 224 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>16</sub>O: C, 85.68; H, 7.19. Found: C, 85.75; H, 7.20.

Preparation of **5**. (1) Under High Dilution Conditions.

To a degassed ethanol (2.4 l) at reflux was added dropwise at a simultaneous rate, each from a separately dropping funnel, a solution of **3** (3.00 g) in a mixture of benzene and ethanol (60 ml) and a solution of sodium sulfide nonahydrate (2.00 g) in a mixture of ethanol and water (60 ml) for 26 hours. After the addition was completed, the mixture was refluxed for 2 hours. The solvent was evaporated and the residue was extracted with methylene chloride (250 ml). The extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*, leaving the residue which was extracted with hot hexane. The extract was condensed and chromatographed using a 9:1-mixture of hexane and ethyl acetate as an eluent to give **5** (82 mg, 4%) and **4** (1.43 g, 57%).

#### 3,4-Di(*m*-ethoxymethylphenyl)-1,2,5-thiadiazole (**4**).

This compound was obtained as pale yellow oil; <sup>1</sup>H-nmr: δ 1.19 (t, J = 7 Hz, 6H), 3.48 (q, J = 7 Hz, 4H), 4.45 (s, 4H), 7.00-7.58 (m, 8H); ms: m/e 354 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>S: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.33; H, 6.46; N, 7.55.

#### 2-Thia-4,6-1,3-benzo[6.0](3,4)-1,2,5-thiadiazolometacyclophane (**5**).

This compound was obtained as colorless prisms (ethanol), mp 150-152°; <sup>1</sup>H-nmr: δ 3.60 (s, 4H), 6.12 (br s, 2H), 7.36-7.56 (m, 6H); ms: m/e 296 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>S: C, 64.84; H, 4.08; N, 9.45. Found: C, 64.61; H, 4.22; N, 9.45.

#### (2) Under Phase Transfer Conditions.

To a vigorously stirred mixture of sodium sulfide nonahydrate (340 mg), tetrabutylammonium fluoride trihydrate (112 mg), water (17 ml), and methylene chloride (17 ml) was added dropwise a solution of **3** (500 mg) in methylene chloride (17 ml) for 30 minutes at room temperature. After the addition was finished, the mixture was stirred at room temperature for 2.5 hours. The organic layer was separated, washed with water (30 ml x 2), dried over magnesium sulfate, and evaporated *in vacuo* to leaving the residue. It was triturated with benzene and insoluble materials were filtered. The filtrate was condensed and chromatographed using benzene as an eluent, giving colorless solid, which, on recrystallization from hexane, afforded **5** (140 mg, 40%).

#### 2-Thia-4,6-1,3-benzo[6.0](3,4)[1,2,5]thiadiazolometacyclophane 2,2-Dioxide (**6**).

After a mixture of **5** (0.95 g) and 30% aqueous hydrogen peroxide (1.9 ml) in acetic acid (15 ml) was heated in oil bath at 50-60° for 7 hours, precipitates were filtered and washed with hexane, giving **6** as colorless crystalline powder (0.96 g, 91%). This compound had mp 295-303° dec; ir: ν 1306, 1111; <sup>1</sup>H-nmr: δ 4.16 (br s, 4H), 6.25 (br s, 2H), 7.29-7.80 (m, 6H); ms: m/e 328 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>: C, 58.52; H, 3.68; N, 8.53. Found: C, 58.36; H, 3.76; N, 8.46.

#### 3,5:8,10-Di-1,3-benzo[8(3,4)[1,2,5]thiadiazolocyclophane (**1**).

Pyrolysis was conducted under reduced pressure (0.5 mm Hg) in an apparatus described previously [4]. After **6** (0.90 g) was pyrolyzed at 500° for 10 minutes, the pyrolysate was extracted with methylene chloride (80 ml). The extract was evaporated *in vacuo*, leaving a residue which, on chromatography with benzene as an eluent, gave crude **1**. Recrystallization from hexane afforded **1** (0.54 g, 75%) as colorless prisms. The compound had mp

150-151°; <sup>1</sup>H-nmr: δ 1.90-2.28 (m, 2H), 3.02-3.40 (m, 2H), 5.50 (br s, 2H), 7.08-7.60 (m, 6H); MS: m/e 264 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>S: C, 72.70; H, 4.57; N, 10.60. Found: C, 72.69; H, 4.70; N, 10.45.

#### 4,5-Dihydropyreno[4,5-c][1,2,5]thiadiazole (**7**).

A 3% solution (6.2 g) of bromine in carbon tetrachloride was added dropwise at room temperature to a mixture of **1** (50 mg) and iron powder (43 mg) in carbon tetrachloride (15 ml) and the whole mixture was stirred at room temperature for 4 hours. Precipitates were collected by filtration and extracted with methylene chloride. The extract was evaporated *in vacuo* and the residue was triturated with water, extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated *in vacuo* to leave the residue, which, on recrystallization from hexane, afforded **7** as colorless prisms (17 mg, 37%). This compound had mp 118-120°; <sup>1</sup>H-nmr: δ 4.18 (s, 4H), 7.31-7.58 (m, 4H), 8.40 (dd, J = 5 and 2.5 Hz, 2H); ms: m/e 262 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>S: C, 73.26; H, 3.84; N, 10.68. Found: C, 72.92; H, 3.94; N, 10.52.

#### Pyreno[4,5-c][1,2,5]thiadiazole (**8**).

After a mixture of **1** (50 mg), N-bromosuccinimide (180 mg), and benzoyl peroxide (22 mg) in carbon tetrachloride was heated at reflux for 3 hours, it was poured into 5% aqueous sodium bicarbonate (10 ml) and extracted with methylene chloride. The extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to leave the residue, which, on recrystallization from hexane, afforded **8** as pale yellow needles (39 mg, 80%). This compound had mp 221-223°; <sup>1</sup>H-nmr: δ 7.80-8.16 (m, 6H), 8.70 (dd, J = 5 and 2.5 Hz, 2H); ms: m/e 260 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>8</sub>N<sub>2</sub>S: C, 73.83; H, 3.10; N, 10.76. Found: C, 73.50; H, 3.48; N, 10.37.

#### Reduction of **1** with Lithium Aluminum Hydride.

After a mixture of **1** (200 mg) in tetrahydrofuran (10 ml) was added dropwise at 0° to a mixture of lithium aluminum hydride (86 mg) in dry tetrahydrofuran (10 ml), the reaction mixture was stirred at room temperature under nitrogen for 5.5 hour. To it, ethyl acetate (10 ml), then 4 drops of water were added dropwise with an external ice-cooling. Precipitates were filtered by the aide of celite and washed with methylene chloride (50 ml). The filtrate and washing were combined, dried over magnesium sulfate and evaporated *in vacuo* to leave the residue. To it was added acetic anhydride (2 ml) and the mixture was stirred at room temperature overnight. A precipitated solid was collected by filtration and washed with chloroform, giving **13** (3 mg). Evaporation of the washing afforded **11** (36 mg).

Water (50 ml) was added to the filtrate and the mixture was stirred at room temperature overnight, neutralized with sodium bicarbonate, extracted with methylene chloride (100 mg x 2). The extract was dried over magnesium sulfate and evaporated *in vacuo*, leaving the residue, which was triturated with hot benzene, giving a 3:2-mixture (by <sup>1</sup>H nmr) of **11** and **12** (57 mg).

Separation of **11** and **12** were done by fractional recrystallization from benzene.

#### *N,N'*-Diacetyl-*eq,ax*-1,2-diamido-[2.2](1,3)(1,3)cyclophane (**11**).

This compound was obtained as colorless needles (benzene),

mp 248-250°; ir: 3326, 3254, 1653  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$ :  $\delta$  2.03 (s, 3H), 2.07 (s, 3H), 1.90-2.40 (m, 2H), 2.90-3.40 (m, 2H), 4.19 (dd, J = 1.5 and 1.5 Hz, 1H), 4.35 (dd, J = 5 and 3 Hz, 1H), 4.40 (dd, J = 1.5 and 1.5 Hz, 1H), 5.26 (br d, J = 5 Hz, 1H, deuterium oxide-exchanged), 5.52 (dd, J = 5 and 3 Hz, 1H), 6.88-7.40 (m, 6H), 7.65 (br d, J = 5 Hz, 1H, deuterium oxide-exchanged); ms: m/e 322 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$ : C, 74.51; H, 6.88; N, 8.68. Found: C, 74.44; H, 6.81; N, 8.43.

#### *N,N'*-Diacyl-ax,ax-1,2-diamino-[2.2](1,3)(1,3)cyclophane (**12**).

This compound was obtained as colorless prisms (benzene), mp 320-330°; ir: 3324, 1650  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$ :  $\delta$  1.95 (s, 6H), 2.00-2.25 (m, 2H), 3.00-3.25 (m, 2H), 4.32 (dd, J = 1.5 and 1.5 Hz, 2H) 5.05-5.50 [(br m, 4H) which appeared at 5.25 (s, 2H) after exchanged with deuterium oxide, 6.88-7.40 (m, 6H)]; ms: m/e 322 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$ : C, 74.51; H, 6.88; N, 8.68. Found: C, 74.69; H, 7.18; N, 8.99.

#### *N,N'*-Diacyl-1,2-di(*m*-aminomethylphenyl)ethane (**13**).

This compound was obtained as colorless needles (nitrobenzene), mp 330-342° (decomp.); ir: 3300, 1650  $\text{cm}^{-1}$ ; MS: m/e 324 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2$ : C, 74.05; H, 7.46; N, 8.64. Found: C, 73.82; H, 7.12; N, 8.65.

#### Reduction of **1** with Sodium in Ethanol.

Sodium (3.00 g) was added, in small portions, to a refluxing solution of **1** (200 mg) in ethanol (80 ml) for 4 hours and the mixture was heated at reflux for one hour. The mixture was poured into water (100 ml) and extracted with methylene chloride (100 ml x 2). The extract was dried over magnesium sulfate and evaporated *in vacuo* to leave the residue. Acetic anhydride (2 ml) was added to it and the whole mixture was stirred at room temperature overnight. The precipitate **13** (43 mg, 18%) was collected by filtration. The filtrate was poured into water (50 ml) and

stirred at room temperature overnight. It was neutralized with sodium bicarbonate, extracted with methylene chloride (100 ml x 2). The extract was dried over magnesium sulfate and evaporated *in vacuo*, leaving the residue, which, on chromatography using methylene chloride as an eluent, giving **1** (20 mg, 10%).

#### Reduction of **1** with Diisobutylaluminium Hydride.

To a stirred mixture of **1** (200 mg) in toluene (13 ml), a 1 mole solution (4 ml) of diisobutylaluminium hydride in toluene was added at 0° under nitrogen atmosphere and the mixture was stirred at 0° for 4 hours. To it, benzene (30 ml), sodium fluoride (2.30 g), and water (0.65 ml) was added at 0° and the mixture was vigorously stirred at room temperature for one hour. It was filtered with aide of celite and washed with hot chloroform (100 ml). The filtrate and washings were combined and the organic layer was separated, dried over magnesium sulfate, and evaporated *in vacuo*. The resultant tarry material was dissolved in acetic anhydride and the mixture was stirred at room temperature overnight. The precipitated **13** (120 mg, 49%) was collected by filtration. The filtrate was poured into water (50 ml) and stirred at room temperature overnight. It was neutralized with sodium bicarbonate, extracted with methylene chloride (100 ml x 2). The extract was dried over magnesium sulfate and evaporated *in vacuo*, leaving the residue, which, on recrystallization from benzene, afforded **11** (19 mg, 7%).

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