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The preparation of 8-fluoro-t-butyl[2.2]metacyclophanes (5) are described. Dithia[3.3]metacyclophane (3) and [3.3]metacyclophane bis(sulphones) (4) were obtained as a mixture of transoid and cisoid conformers, but [2.2]metacyclophanes (5) were exclusively obtained as the transoid conformer after pyrolysis of the sulphones (4). AlCl₃–MeNO₃-catalyzed trans-t-butylation of 8-fluoro-16-methyl-5,13-di-t-butyl[2.2]metacyclophane (5a) in benzene under a variety of conditions failed to give 8-fluoro-16-methyl[2.2]metacyclophane (32) but, instead, the tetrahydropyrenes (33) and/or (34) were obtained depending upon the conditions used. Internally substituted [2.2]metacyclophanes were isomerized to the strainless [2.2]metacyclophanes and these were then oxidized to the tetrahydropyrene (33).

Recently we found that 8,16-dimethyl-2, 8,16-dihydroxy-, and 8,16-difuoro-[2.2]metacyclophanes⁴ can be prepared by AlCl₃–MeNO₃-catalyzed trans-t-butylation of the corresponding t-butyl derivative. These results suggest that 16-

substituted 8-fluoro[2.2]metacyclophanes might be prepared from the corresponding t-butyl derivatives by the similar manner.⁵ We report here the preparation of the title compounds and their treatment with AlCl₃–MeNO₃ catalyst in benzene solution.

Results and Discussion

Preparation.—A preparative route to the title compounds is summarized in Scheme 2.

The preparations of (1a)⁶ and (2a–b)² have already been described in earlier papers. Since, however, the chloromethylation of t-butylfluorobenzene afforded (1a) only in low yield, the preparation of 2,6-bis(bromomethyl)-4-t-butylfluorobenzene (15) was, instead, attempted.

1-Fluoro-2,6-dimethyl-4-t-butylbenzene (10), prepared in four steps from m-xylene, on bromination with 2.2 equivalents of NBS gave a mixture of mono- (14), di- (15), and tri-bromides (16); with 4.1 equiv. of NBS the tetrabromide (17) was obtained in 54% yield. Compound (12) was prepared from (10) by AlCl₃–MeNO₃-catalyzed trans-t-butylation in the presence of biphenyl (11) as an acceptor.⁶ In contrast to that of (10), bromination of (12) with 2.2 equiv. of NBS afforded a good yield of the desired compounds (1b).

The preparative route to compound (2c) is shown in Scheme 4. Direct preparation of (19) from (18) by bromination afforded a mixture of (19) and its isomer (20). The molar ratio of (19): (20) is 1:1, as estimated from n.m.r. spectral results.

Table 1. Chemical shifts (δ) of internal methyl protons of dithia[3.3]metacyclophanes (3), [3.3]metacyclophane bis(sulphones) (4), and [2.2]metacyclophanes (5).

<table>
<thead>
<tr>
<th>Compound</th>
<th>transoid</th>
<th>cisoid</th>
<th>transoid</th>
<th>cisoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3a)</td>
<td>1.47</td>
<td>2.40</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>(3b)</td>
<td>1.53</td>
<td>2.40</td>
<td>1.6</td>
<td>1</td>
</tr>
<tr>
<td>(3d)</td>
<td>1.56</td>
<td>2.40</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>(4a)</td>
<td>1.37</td>
<td>2.50</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>(4b)</td>
<td>1.34</td>
<td>2.55</td>
<td>1.6</td>
<td>1</td>
</tr>
<tr>
<td>(4d)</td>
<td>1.24</td>
<td>2.50</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>(5a)</td>
<td>0.63</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(5b)</td>
<td>0.59</td>
<td>0</td>
<td>1</td>
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</tr>
<tr>
<td>(5d)</td>
<td>0.63</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. The AlCl₃–MeNO₃ catalyzed reaction of 8-fluoro-16-methyl-5,15-di-t-butyl[2.2]metacyclophane (5a) in benzene*.

<table>
<thead>
<tr>
<th>Run</th>
<th>Catalyst [(5a)] (mol/mol)</th>
<th>Time (h)</th>
<th>Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3</td>
<td>2</td>
<td>(33) (82)</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>2.5</td>
<td>(33) (80), (34) (6)</td>
</tr>
<tr>
<td>3</td>
<td>2.6</td>
<td>3</td>
<td>(34) (97)</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>1.5</td>
<td>(34) (96)</td>
</tr>
<tr>
<td>5</td>
<td>1.3</td>
<td>0.25</td>
<td>(34) (90)</td>
</tr>
</tbody>
</table>

* The reaction temperature was 25 °C. The isolated yields are shown. ⁶ AlCl₃ is used as a catalyst.

Therefore, (19) was prepared by the alternative route shown in Scheme 4. The trans-t-butylation of (23) in the presence of AlCl₃, AlBr₃, and AlI₃ or de-t-butylation in boiling 85% H₃PO₄ failed to give the expected compound (24). However, the trans-t-butylation of (19), which was prepared from (22), gave (25) in good yield.

Mitchell and Boekelheide⁷ reported that reaction of 2,6-bis(chloromethyl)toluene (27) and (2c) afforded a mixture of the transoid and cisoid conformers (28) and (29) respectively. In contrast we found that⁸ reaction of 2,6-bis(chloromethyl)-4-t-butyltoluene (30) and (2a) afforded exclusively the transoid conformer (31). The n.m.r. spectra of (3) and (4) prepared in the
present work show that they are a mixture of transoid and cisoid
conformers, the molar ratio of which seems dependent upon the
5- and 13-substituents (see Table 1). The data show that the
molar ratios of the transoid and cisoid conformers of (3) and (4)
are almost equivalent, an indication that there is no exchange
between the two during the oxidation of (3) to (4). On pyrolysis,
compound (4) gave the less strained transoid conformer of (5)
exclusively, the syn conformer not being detected by n.m.r.
spectroscopy. AlCl₃-MeNO₂-catalyzed trans-t-butylation of

(5a) in benzene under a variety of conditions failed to give the
expected compound 8-fluoro-16-methyl[2.2]metacyclophane
(32), 5°-4-t-butylbenzene (35) and the tetrahydropyrenes
(33) and/or (34) being formed instead (see Scheme 6 and Table 2).
Mild conditions gave compound (33) as the sole product whilst
more severe gave compound (34) a result which suggests that
(33) might be an intermediate in the formation of (34). Indeed,
(34) was also obtained in good yield when (33) was treated with
AlCl₃-MeNO₂; oxidation of (34) with DDQ in benzene led to
2-methylpyrene (36). Similar catalytic treatment of (5b) also afforded (33) (79%) while (5d) gave only (34) (84%) AlCl₃-MeNO₂ catalyzed reaction of (5b) and (5d) also afforded (33) and (34), and a schematic representation of the path for this set of reactions is shown in Scheme 7. Although two routes, a and b (see Scheme 7) may be envisaged for the formation of (34) from (5a), route b may be ruled out because (i) the AlCl₃-MeNO₂ catalyzed reaction of (5a) under mild conditions afforded (33) exclusively and (ii) isomerization of (5b) to give strainless (5e) is more likely than a route via (5d) and the strained compound (37). Indeed, catalytic treatment of (5e) in benzene gave compound (33) (86%) as expected on the basis of earlier reported observations.

A mechanism for the formation of (33) from (5e) is tentatively

Scheme 3. Reagents and conditions: i, 4-methyl-2,6-di-t-butylphenol,
AlCl₃-MeNO₂ (quart); ii, HNO₃ (75%); iii, Fe-HCl (89%); iv, NaNO₂,
HBF₄, heat (47%); vi, AlCl₃, CS₂, Ph-P (11); vii, NBS (2.2 equiv.),
CCl₄; viii, NBS (4.1 equiv.), CCl₄ (54%); ix, NBS (2.2 equiv.), CCl₄
(80%).

Scheme 2. Reagents and conditions: i, KOH-EtOH, high dilution; ii, m-
CPBA, CHCl₃ (ca. 100%); iii, 500 °C, 3 mmHg.

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**Scheme 4.** Reagents and conditions: i, Br₂, Fe; ii, HNO₃, H₂SO₄ (77%); iii, Fe–HCl (60%); iv, Ac₂O, AcOH (98%); v, AlCl₃; vi, AlBr₃; vii, AlCl₃; viii, H₃PO₄, heat; ix, NaNO₂; x, CuBr, HBr (62%); xi, AlCl₃, benzene (83%); xii, thiourea; xiii, NaOH (92%).

**Scheme 5.** Reagents and conditions: i, Br₂, Fe; ii, HNO₃, H₂SO₄ (77%); iii, Fe–HCl (60%); iv, Ac₂O, AcOH (98%); v, AlCl₃; vi, AlBr₃; vii, AlCl₃; viii, H₃PO₄, heat; ix, NaNO₂; x, CuBr, HBr (62%); xi, AlCl₃, benzene (83%); xii, thiourea; xiii, NaOH (92%).

**Scheme 6.** Reagents and conditions: i, AlCl₃–MeNO₂, benzene.
anhydride (130 g) was added gradually at 25 °C a mixture of nitric acid (68 g), acetic acid (43 g) and acetic anhydride (43 g). After this addition, the reaction mixture was poured into a large amount of ice–water and extracted with benzene. The benzene solution was washed with 10% aqueous NaOH and water, dried (Na$_2$SO$_4$), and evaporated under reduced pressure to leave a residue which was recrystallized from ethanol to give (8) (112 g, 75%) as pale yellow prisms, m.p. 85–86 °C (lit.,$^9$ m.p. 85 °C).

**Preparation of 2,6-Dimethyl-4-t-butylaniline (9).**—A mixture of compound (8) (86.7 g, 0.42 mol), iron powder (81 g), concentrated HCl (30 ml), ethanol (40 ml), and water (250 ml) was stirred and heated under reflux for 28 h after which time the iron powder was filtered off. The filtrate was extracted with benzene and the extract washed with water, dried (Na$_2$SO$_4$), and evaporated under reduced pressure to leave a residue which was distilled under reduced pressure to give (9) (65.8 g, 89%) as colourless oil, b.p. 89–91 °C at 1 mmHg. $\nu_{\text{max}}$ (NaCl) 3 450, 3 375, 3 000, 2 950, 2 840, 1 615, 1 515, 1 488, 1 350, 1 210, 1 120, 1 025, 860, and 725 cm$^{-1}$; $\delta_{\text{H}}$(CDCl$_3$) 1.26 (9 H, s), 2.12 (6 H, d, J 2 Hz), 3.34 (2 H, br s, exchanged by D$_2$O), 6.92 (2 H, s); m/z 177 (M$^+$). (Found: C, 81.2; H, 11.2. C$_{12}$H$_{14}$N requires C, 81.30; H, 10.80%).

**Preparation of 1-Fluoro-2,6-dimethyl-4-t-butylbenzene (10).**—To a solution of the amine (9) (50.1 g, 0.28 mol) in tetrahydrofuran (95 ml) cooled in an ice–NaCl bath was added first HBF$_4$ (42%) (447 ml) and then saturated aqueous NaNO$_2$ (11 g). The resulting crystalline precipitated was filtered off, washed with 5% HBF$_4$ solution and methanol, and dried in vacuo. Subsequently it was heated under reflux in toluene for 5 h, to afford after evaporation under reduced pressure of the solvent a residue which was distilled under reduced pressure to give (10) as pale yellow oil (24.2 g, 46%), b.p. 70–71 °C at 4 mmHg; $\nu_{\text{max}}$(NaCl) 2 980, 2 890, 1 490, 1 365, 1 320, 1 295, 1 210, 870, 815, and 725 cm$^{-1}$; $\delta_{\text{H}}$(CDCl$_3$) 1.26 (9 H, s), 2.22 (6 H, d, J 2 Hz), and 6.94 (2 H, d, J 2 Hz); m/z 179 (M$^+$) (Found: C, 80.1; H, 9.6. C$_{12}$H$_{17}$F requires C, 79.96; H, 9.51%).

**Bromination of Compound (10) with NBS: Typical Procedure.**—A solution of compound (10) (2.0 g, 11.1 mmol), NBS (8.1 g, 45.5 mmol), and benzoyl peroxide (500 mg) in CCl$_4$ (300 ml) was heated under reflux for 4 h after which the mixture was cooled to room temperature. The precipitated succinimide was filtered off and the filtrate evaporated under reduced pressure to leave a residue which was recrystallized from hexane to give (17) (2.89 g, 54%) as pale yellow prisms, m.p. 132–133 °C; $\nu_{\text{max}}$(KBr) 2 970, 2 870, 1 660, 1 470, 1 360, 1 275, 1 210, 1 150, 1 090, 975, 880, 815, 750, 695, and 660 cm$^{-1}$; $\delta_{\text{H}}$(CDCl$_3$) 1.37 (9 H, s), 6.85 (2 H, s), and 7.76 (2 H, d, J 7 Hz); m/z 491, 493, 495, 497, and 499 (M$^+$) (Found: C, 29.15; H, 2.75. C$_{12}$H$_{13}$Br$_4$ requires C, 29.07; H, 2.64%).

When bromination of (10) with 2.1 equiv. of NBS was carried out under similar conditions to those described above, a mixture of (10), (14), (15), and (16) was obtained as described in the text. The molar ratios of the products was estimated by n.m.r. spectral analysis of the mixture.

**Preparation of 1-Fluoro-2,6-dimethylbenzene (12).**—To a solution of compound (10) (2.0 g, 11.1 mmol) and biphenyl (8.55 mmol) in CS$_2$ (15 ml) was added AlCl$_3$ (0.5 g, 3.75 mmol). The mixture was then stirred at room temperature for 1.5 h after which it was poured into a large amount of ice–water and extracted with methylene chloride; the extract was washed with water, dried (Na$_2$SO$_4$), and evaporated under reduced pressure to leave a residue which was distilled under reduced pressure to give (12) (1.24 g, 89.9%) as a colourless oil, b.p. 165–167 °C at 760 mmHg (lit.,$^{10}$ b.p. 85 °C at 115 mmHg).

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**Experimental**

All m.p.s and b.p.s are uncorrected. N.m.r. spectra were determined at 100 MHz with a Nippon DENSHI JEOL FT-100 n.m.r. spectrometer with SiMe$_4$ as an internal reference, and i.r. spectra were measured as KBr pellets or a liquid film on NaCl plates in a Nippon Bunko 1R-202 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct inlet system through g.c.

**Preparation of 1,3-Dimethyl-2-nitro-5-t-butylbenzene (8).**—To a solution of compound (7)$^8$ (117 g, 0.72 mol) in acetic

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**Scheme 8.**

Reagents and conditions: i, AlCl$_3$-MeNO$_2$, benzene (73%); ii, AlCl$_3$-MeNO$_2$, benzene (83%); iii, DDQ, benzene (80%).

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Proposed reaction pathways described above.

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**Scheme 9.**

Reagents and conditions: i, AlCl$_3$-MeNO$_2$, benzene (73%); ii, AlCl$_3$-MeNO$_2$, benzene (83%); iii, DDQ, benzene (80%).
Preparation of 1,3-Bis(bromomethyl)-2-fluorobenzene (1b).—A solution of compound (12) (3.0 g, 24.2 mmol), NBS (9.48 g, 53.2 mmol), and benzoyl peroxide (500 mg) in CCl₄ (300 ml) was treated and worked up as described above, to afford (1b) (5.46 g, 80%) as colourless prisms (from hexane), m.p. 90—91.5 °C (lit.,¹¹ m.p. 90—91.5 °C).

Bromination of 4-t-Butyltoluene (18) with Bromine.—Although bromination of (18) with bromine under the reported conditions¹² afforded the desired 2-bromo-4-t-butyltoluene in good yield, similar bromination of (18) with 2 mol equiv. of bromine gave a mixture of (19) and (20), which was inseparable by distillation and column chromatography (silica gel). The molar ratio and the determination of the structures of both products were carried out by n.m.r. spectral analysis.

Preparation of 2,6-Diamino-4-t-butyltoluene (22).—A mixture of compound (21)¹³ (30 g, 126 mmol), iron powder (4.4 g), concentrated HCl (18.1 ml), and water (200 ml) was treated and worked up as described in the reduction of compound (8), to afford (22) (13.5 g, 60%) as colourless prisms (from hexane), m.p. 96—97 °C; vₖₑₑₑ(KBr) 3430, 3380, 3290, 3100, 2960, 2870, 1650, 1630, 1590, 1460, 1450, 1350, 1330, 1270, 1260, 1160, 1150, 1080, 1070, 940, 820, 810, 710, and 660 cm⁻¹; δₙ(CDCl₃) 1.22 (9 H, s), 1.93 (3 H, s), 3.31 H, 14 H, br s, disappeared with D₂O, and 6.20 (2 H, s); m/z 177 (M⁺). (Found: C, 74.25; H, 10.55; N, 15.5. C₁₁H₁₈N₂ requires C, 74.11; H, 10.18; N, 15.71%).

Preparation of 2,6-Diacetamido-4-t-butyltoluene (23).—A solution of compound (22) (10 g, 56 mmol) in acetic acid (15 ml) and acetic anhydride (150 ml) was stirred for 15 min at room temperature and then heated for 30 min on water-bath, before it was poured into a large amount of ice-water. The precipitated crystals were filtered off, washed with water, and recrystallized from ethanol to give (23) (14.4 g, 98%) as colourless prisms, m.p. > 300 °C; vₖₑₑₑ(KBr) 3230, 3040, 2960, 2870, 1650, 1610, 1530, 1475, 1425, 1400, 1365, 1290, 1270, 1210, 1130, 1035, 970, 930, 870, 815, 730, and 700 cm⁻¹; δₙ(CDCl₃) 1.21 (9 H, s), 1.94 (3 H, s), 2.01 (6 H, s), 7.11 (2 H, s), and 9.30 (2 H, s), exchangeable with D₂O; m/z 261 (M⁺). (Found: C, 68.85; H, 8.6; N, 10.55. C₁₅H₂₀N₂O₂ requires C, 68.67; H, 8.45; N, 10.68%).

Preparation of 2,6-Dibromo-4-t-butyltoluene (19) from compound (22).—To concentrated H₂SO₄ (75 ml) was added first NaNO₂ (7.5 g) at 70 °C and then a solution of compound (22) (8.2 g, 46 mmol) in acetic anhydride (45 ml). This solution was then added gradually to a solution of CuBr₂ (6.7 g, 46.5 mmol) in concentrated hydrobromic acid (140 ml) < 40 °C. After cessation of N₂ evolution the reaction mixture, was poured into water, steam distilled, and the distillate extracted with benzene.

The extract was washed with 10% aqueous NaOH and water, dried (Na₂SO₄), and evaporated under reduced pressure to leave a residue which was distilled under reduced pressure to give (19) (8.7 g, 62%) as a colourless oil, b.p. 100—112 °C at 2.5 mmHg; vₖₑₑₑ(NaCl) 2960, 2870, 1590, 1530, 1450, 1380, 995, 870, 730, and 690 cm⁻¹; δₙ(CDCl₃) 1.27 (9 H, s), 2.51 (3 H, s), and 7.46 (2 H, s); m/z 304, 306, and 308 (M⁺). (Found: C, 42.6; H, 4.4. C₁₈H₁₄Br₂ requires C, 42.93; H, 4.61%).

Preparation of 2,6-Dibromotoluene (25).—A mixture of compound (19) (5.0 g, 16.3 mmol) and AlCl₃ (2.2 g, 16.5 mmol) in benzene (40 ml) was stirred at room temperature for 6 h after which the mixture was poured into a large volume of water and extracted with ether. The ether solution was washed with water, dried (Na₂SO₄), and evaporated under reduced pressure to leave a residue which was distilled under reduced pressure to give (25) (3.38 g, 83%) as a colourless oil, b.p. 123—125 °C at 23 mmHg (lit.,¹⁴ 122 °C at 23 mmHg). t-Butylbenzene formation was detected by g.c. analysis of the reaction mixture.
Preparation of Trisubstituted 8-Fluoro[2.2]metacyclophanes (5) from (3).—The preparation of compounds (3), (4), and (5) were described in a previous report.2 The yields are summarized in Scheme 2.

6,15,18-Trisubstituted 9-Fluoro-2,11-dithia[3.3]metacyclophane (5e) from (4e).—The preparation of compounds (3e), (4e), and (5e) were described in a previous report.2 The yields are summarized in Scheme 2.

References

1. 1982, 46, 1543.

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