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CYCLOTETRAVERATRYLENE[a]

CHARACTERIZATION AND CONFORMATIONAL PROPERTIES

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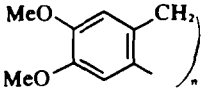
Abstract—The preparation and characterization of cyclotetraveratrylene (**6**) is described. Acid-catalyzed condensation of 3,4-dimethoxybenzyl alcohol or chloromethylation of bis(3,4-dimethoxyphenyl)methane both gave a mixture of cyclotriveratrylene (**2**) and **6** in approximately the proportion 5:1 respectively. The conformational mobility associated with the cyclododecatetraene ring of **6** was studied by variable temperature proton magnetic resonance spectroscopy over the temperature range 229–319°K. Activation parameters for the interconversion of "sofa" conformers **6A** were obtained: $F^{\ddagger}_{(T)}$ 12·8–13·7 (±0·3) kcal and $S^{\ddagger}$ *ca* −11 (±2) eu. The large negative entropy term is interpreted in terms of a rigid, transitional conformer, possibly the crown form **6B**.

The cycloveratrylenes (**1**) constitute a homologous series formed by coupling of a 3,4-dimethoxybenzyl unit in head-to-tail fashion at α and C-6 carbons. The lowest member of this series, 2,3,6,7-tetramethoxy-9,10-dihydroanthracene (cyclodiveratrylene), has been shown to undergo rapid inversion of the dibenzocyclohexane ring as judged



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from equivalence of the methylene protons (singlet at $\delta \simeq 3{\cdot}78$).[1] In contrast, cyclotriveratrylene (**2**) has been found to possess a rigid crown (C_{3v}) conformation,[2-4] in which the methylene carbons form truncated apex of a 3-sided pyramidal structure. No the inversion of this structure is observed even at temperatures approaching 200°.[5] The saddle conformation of cyclotriveratrylene, in which one of the benzo rings is displaced outwards and upwards, should be appreciably more flexible than the crown configuration **2**, according to molecular models. Although this flexible saddle conformer has never been detected for cyclotriveratrylene itself, it apparently is the favored conformer of ketone **3**.[6] When **3** is reduced with hydride, two conformationally isomeric alcohols result, the more stable of which possesses the crown conformation with the OH group exo, and the less stable has the flexible conformation.

Certain heterocyclic analogs of cyclotriveratrylene have also been prepared. The 2,5-dimethylthiophene analog **4** is conformationally mobile at −60°, the saddle conformer apparently being preferred in this case.[7] The indole trimer **5** has also been assigned a saddle conformation although the NMR of this compound changes little over the temperature range −25° to 100°.[8] A recently prepared oxa analog of the sym-tribenzocyclononene system was found to be conformationally flexible, with an inversion barrier between crown forms of *ca* 10 kcal/mole.[9]

Cyclotetraveratrylene (**6**) was first reported by Erdtman[2] as a byproduct in the chloromethylation of veratrole, which gives mainly the trimeric compound **2**. The tetramer is conveniently prepared by condensation of 3,4-dimethoxybenzyl alcohol (**7**) in acetic acid containing a small quantity of sulfuric acid.[10] The precipitated solid consists largely of a mixture of **2** and **6**, from which **6** may be isolated by fractional crystallization.

A rational synthesis of cyclotetraveratrylene, based upon the assumption that chloromethylation of bis(3,4-dimethoxyphenyl)methane (**10**) would afford principally **6**,[11] was also attempted. However, when **10**, prepared by treatment of guaiacol carbonate (**8**) with formaldehyde and sulfuric acid followed by methylation of the resulting bis(3-hydroxy - 4 - methoxy)phenylmethane **9**[12] with dimethyl sulfate, was subjected to chloromethylation conditions, trimer **2** and tetramer **6** were produced in the same proportion (*ca* 5:1) as was obtained

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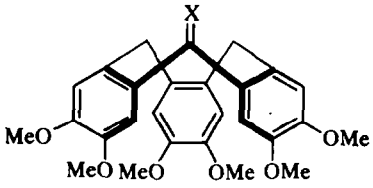

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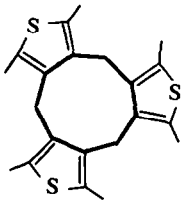
3: X = O



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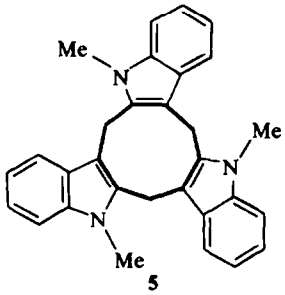

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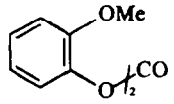
from the acid-catalyzed condensation of **7**. Presumably **10** undergoes a reverse Friedel–Crafts reaction to veratrole and 3,4-dimethoxybenzyl cation, which is then reassembled as the **2**/**6** mixture.

The structure of cyclotetraveratrylene (**6**) follows from spectral data as well as certain straigntforward transformations. The mass spectrum of **6** shows a molecular ion at *m*/*e* 600·2732, corresponding to $C_{36}H_{40}O_8$ and, as noted by Erdtman,[2] progressive degradation to trimer, dimer, and monomer units (*m*/*e* 449, 299, and 151 respectively) constitutes the major fragmentation pathway. The UV spectrum of **6** is similar to that of cyclotriveratrylene. However, comparison of the ambient temperature NMR spectra of **2** and **6** reveals a striking difference. Whereas the methylene protons of **2** appear as an AB quartet (δ 3·45 and 4·70, J = 14 Hz), the corresponding protons in **6** give rise to a broadened singlet (δ 3·59). In addition, OMe and aromatic protons occur as singlets (δ 3·78 and 6·60 respectively). Thus, the tetrabenzocyclododecane ring of **6** is endowed with a greater degree of flexibility than the 9-membered ring of **2**.

Demethylation of **6** with boron tribromide in chloroform gave the highly polar octahydroxy derivative **11** which exhibited NMR behavior (variable temperature) similar to **6**. Acetylation of **11** gave octaacetate **12**.

Conformational studies. The greater conformational mobility of the 12-membered ring of **6**, and hence the equivalence of methylene protons, provides an interesting contrast with the rigid conformation of **2**. In order for the methylene protons of **6** to become equivalent, they must be able to pass through the 12-membered ring (the benzo rings clearly cannot), each passage involving a pseudorotation at the methylene-bridge C atom. Successive pseudorotations of the four methylene groups will equilibrate all eight protons. This process is



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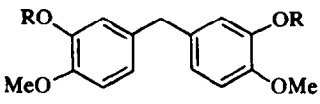

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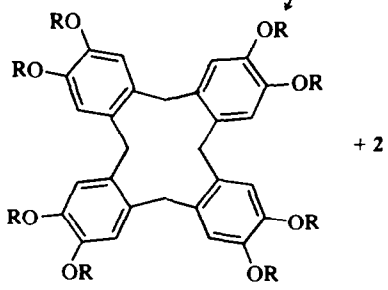
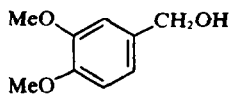
10: R = Me



6: R = Me
11: R = H
12: R = COMe



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evidently prohibited in the case of **2** by the severe hydrogen contacts generated. The activation barrier to the pseudorotation process for **6**, would appear from a molecular model to depend primarily upon the degree of angle distortion. In an effort to determine the parameters for this process, a variable temperature NMR study of **6** was undertaken.

Upon cooling a $CDCl_3$ solution of **6**, the singlet resonances or aromatic and OMe protons become broadened until at *ca* −50°, each is a well-defined pair of signals of equal area at δ 6·29, 6·88 and δ 3·65, 4·03 respectively. The methylene protons at this temperature appear as a pair of doublets (J = 16 Hz) at δ 3·27 and *ca* 3·8, partially obscured by OMe resonances. Peak separation ($\delta\nu_0$) under conditions of slow exchange was 36·3 and 23·1 Hz for aromatic and OMe protons respectively. For kinetic measurements,[15] it was found most convenient to use the line-width of the high-field signal of the aromatic pair at slow exchange (Fig 1). A plot of total line-width vs temperature gave the width (W*) of this peak without exchange broadening as 2·4 Hz and the width of the coalesced line as 1·8 Hz. The width of the aldehyde proton of acetaldehyde was used as reference and was 0·40 ± 0·02 Hz in the temperature range of the experiment. Intermediate values of W* were interpolated from a plot of W* vs log $\eta CHCl_3/T$, and corrected line-widths (W_{cor}) were found from the observed widths (W_{obs}) according to:

$$W_{cor} = W_{obs} - W^*.$$

Using Bovey's universal plot of line-width vs $\tau\Delta\omega$ for a collapsing doublet,[15] residence times (τ) and hence rate constants (k) were obtained for eight temperatures from W_{cor} values. The data are summarized in Table 1. A plot of log k vs 1/T gave a straight line with a slope (activation energy) of 10·9 ± 0·2 kcal/mole. Values of $F^{\neq}_{(T)}$ and $S^{\neq}$ were found from the Eyring formulation.

The most stable conformation of **6** is the "sofa" form **6A** (C_{2h} symmetry). This conformer would be expected to have aromatic, methoxyl, and methylene protons divided into two equal sets, the methylene signals corresponding to intra- and extraannular protons. Upon warming, pseudorotations at the methylene bridge of the cyclododecatetraene ring interconvert "sofa" forms, probably via a crown conformation **6B** (C_{4v} or C_{2v} symmetry†). The large negative entropy of activation for this process implies that the transitional conformation **6B** is appreciably less flexible than **6A**.[16]

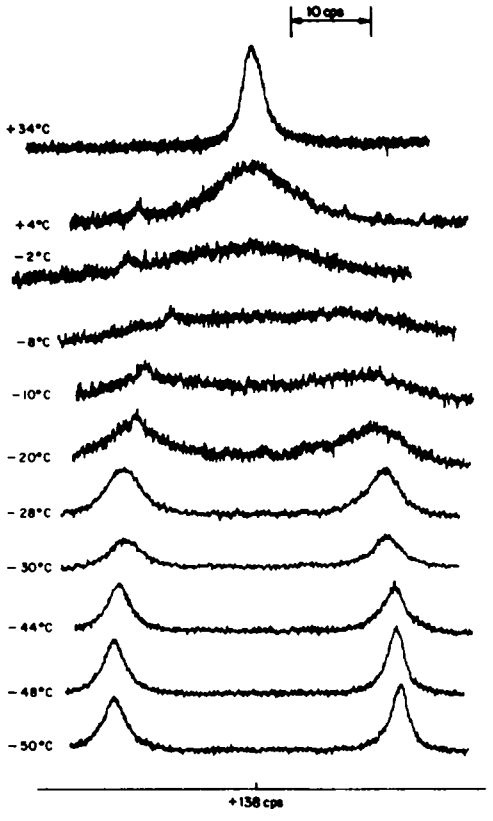
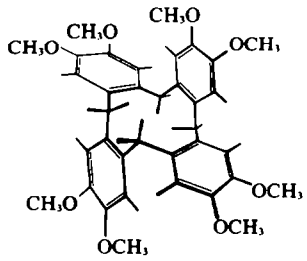


Fig 1. The aromatic proton resonance signal in the NMR spectrum of **6** at various temperatures. The chemical shift is relative to the aldehyde proton of acetaldehyde.

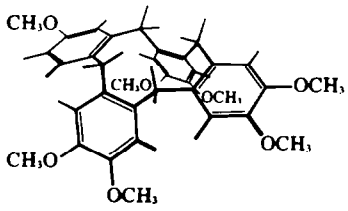
†The C_{2v} structure, formed by an inward movement of a pair of opposite benzene rings (and accompanied by the outward movement of the other pair), relieves a serious steric interaction of aromatic protons on adjacent rings.

Table 1. Activation parameters for conformational equilibration of **6**

$°K^T_K$	$\eta_{CHCl_3} \times 10^3$ poise	W_{obs} cps	W* cps	W_{cor} cps	$\tau\Delta\omega$ cycles	$k(1/2\tau)$ sec^{-1}	$F^{\neq}_{(T)}$	$S^{\neq}$
319	4·48	1·8 ± 0·1	—	—	—	—	—	—
307	4·92	3·1 ± 0·1	1·8	1·3	$1·5 \times 10^{-2}$	$1·2_1 \times 10^3$	13·7 ± 0·3	− 10·8 ± 1·7
277	6·69	11·4 ± 0·1	2·0	9·4	$9·8 \times 10^{-2}$	$1·8_5 \times 10^2$	13·3 ± 0·3	− 10·8 ± 1·8
271	7·16	20·0 ± 0·1	2·0	18·0	$2·1 \times 10^{-1}$	$8·5_6 \times 10$	13·4 ± 0·3	− 11·1 ± 1·8
253	9·0	9·2 ± 0·1	2·1	7·1	$6·8 \times 10^{-1}$	$2·6_7 \times 10$	13·1 ± 0·3	− 10·7 ± 1·9
245	10·2	4·7 ± 0·1	2·2	2·5	1·9	$9·5_3$	13·2 ± 0·3	− 11·5 ± 2·1
243	10·6	4·0 ± 0·1	2·2	1·8	2·5	$7·1_3$	13·2 ± 0·3	− 11·6 ± 2·1
229	13·5	3·0 ± 0·1	2·3	0·7	6·4	2·8	12·8 ± 0·3	− 10·5 ± 2·2
225	14·5	2·4 ± 0·1	2·4	—	—	—	—	—



6A



6B

EXPERIMENTAL

General procedures. M.ps were determined on a Kofler hot-stage and are uncorrected. IR spectra were recorded on either a Perkin–Elmer 137 or 237 spectrophotometer as mulls. The UV spectrum of **6** was recorded on a Cary 14 spectrophotometer. NMR spectra were measured on a Varian A-60 spectrometer with TMS as internal standard. Mass spectra and accurate mass determinations were measured on a AEC MS-9 spectrometer at 70 eV. Elemental analyses were carried out by Micro-Tech Laboratories, Inc., Stokie, Illinois.

Cyclotetraveratrylene (**6**). Following the procedure of Lindsey,[3b] a soln of freshly distilled (7) 0·0496 (8·34 g mole) in 45 ml glacial AcOH containing 0·5 ml conc H_2SO_4 was heated on the steam-bath for 0·25 h. During this time a pale green, flocculent ppt came down. When the mixture had cooled, the solid was collected by filtration and was washed with water and dried. This residue was taken up into hot benzene and the soln was allowed to cool slowly. In this way, the crystalline material deposited was found to consist of 1·22 g (16%) of **6** with *ca* 5% contamination by **2**. An analytically pure sample of **6** was obtained either by sublimation at 150° (0·05 mm) or by recrystallization from chloroform-benzene. The sublimed sample had m.p. 304–307° and the recrystallized sample had m.p. 319–321°. The two samples, which represented visibly different crystalline modifications, were identical in all other respects; λ_{max} ($CHCl_3$) 289 nm (ϵ 23,750) and 294 (24,520); IR 1605 and 1590 cm^{-1}. (Found: C, 71·82; H, 6·86. Calc. for $C_{36}H_{40}O_8$: C, 71·98; H, 6·71).

2, 3, 6, 7, 10, 11, 14, 15 - *Octahydroxytetrabenzo[adgj]cyclododecatetraene* (**11**). To a soln of **6** (170 mg; 0·284 mmole) in 20 ml $CHCl_3$ was added 1 ml BBr_3 and the mixture was heated under reflux for 1 h. The mixture was diluted with water and crude **13** was separated as a grey-white amorphous solid by filtration. Crystallization of this material from acetone-water afforded 117 mg (85%) of **13** as colorless prisms, m.p. >350°; IR 3600, 1615, and 895 cm^{-1}; NMR (d_6-acetone) δ 3·36 and 6·50 (broadened singlets, ratio 1:1)

2, 3, 6, 7, 10, 11, 14, 15 - *Octaacetoxytetrabenzo[adgj]cyclododecatetraene* (**12**). A mixture of **13** (124 mg; 0·254 mmole) in 15 ml dry pyridine containing 1 ml Ac_2O was warmed to reflux temp, during which the hydroxy compound was slowly dissolved. After 5 min under reflux, the soln was allowed to cool, and the partially crystalline solid which was deposited was collected by filtration. This material was sublimed at 150° (0·05 mm) to give 102 mg (49%) of **14** as fine needles, m.p. >350°; IR 1765 and 1215 cm^{-1}; mass *m/e* 824 (M^+). (Found: C, 63·97; H, 4·76. Calc. for $C_{44}H_{40}O_{16}$: C, 64·08; 4·89%).

Bis(3,4-dimethoxyphenyl)methane (**10**). To a stirred, ice-cold soln of guaiacol carbonate (27·4 g; 0·10 mole) in 100 ml dioxane was added 10 ml 36% aqueous formaldehyde soln followed (slowly) by 25 ml of conc H_2SO_4. The mixture was allowed to warm to room temp and was then set aside for 3 days. The mixture, containing a substantial quantity of solids was then diluted with water and the supernatant was decanted. The residue was washed once more with water followed by 10% Na_2CO_3 aq, and was then taken up into a soln of 25 g of KOH in 100 ml MeOH and 20 ml water. To this soln, cooled in ice, was added slowly and with stirring 25 ml of Me_2SO_4. After addition was complete, the mixture was stirred at room temp for 1 h and then filtered to remove a small quantity of solid (polymer). The filtrate was extracted with benzene and the benzene extract, after drying (Na_2SO_4), yielded a light brown, viscous oil. This material was taken up into warm EtOH and, upon standing for 48 h, the soln yielded 8·51 (30%) of **10**, m.p. 72–73° (lit[3b] 74°); NMR ($CDCl_3$) δ 3·85 (two barely resolved singlets, 14 H) and 6·78 (6 H, m); mass *m/e* 288 (M^+).

Chloromethylation of **10**. To an ice-cold, stirred soln of **10** (220 mg; 0·76 mmole) in 4 ml EtOH was added 3 ml of 36% aqueous formaldehyde soln followed (slowly) by 4 ml conc HCl. The mixture was allowed to warm to room temp and was stirred overnight. The mixture was diluted with 25 ml of water and the ppt was collected by filtration. The solid, after drying, afforded 88 mg of a mixture of **2** and **6**, which were separated by fractional crystallization from benzene to give 11 mg (after sublimation) of **6** and 53 mg of **2**, identified in each case by m.p., IR, and TLC comparison.

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THE SYNTHESIS OF (±)-THALPHENINE, THALIGLUCINE AND THALIGLUCINONE[1]

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Abstract—Photolysis of the phenolic tetrahydrobenzylisoquinoline **11** in basic solution yielded (±)-de-N-methylthalphenine (**14**). Quaternization with methyl iodide then afforded thalphenine iodide (*rac.* **1**) which upon Hofmann elimination supplied thaliglucine (**2**). Thaliglucinone (**3**) is obtained by oxidation of thaliglucine (**2**).

Of the more than one hundred aporphine alkaloids presently known, (+)-thalphenine (**1**), found in *Thalictrum polygamum* Muhl. (Ranunculaceae), is the only one to possess a methylenoxy bridge.[2] Since several syntheses of the aporphine skeleton are available, the main problem in the laboratory preparation of thalphenine revolved around the construction of the unusual methylenoxy bridge.[3]

Spangler and Boop had shown that an efficient route to the aporphines consisted of the intramolecular photocyclization of a 7 - hydroxy - 2' - bromotetrahydrobenzylisoquinoline in basic solution.[4] It was, therefore, reasoned that the 7 - hydroxy - 2' - bromotetrahydrobenzylisoquinoline **11** could be the required precursor for a synthesis of thalphenine (**1**). Irradiation of **11** in the presence of sodium hydroxide would then lead to the aporphine anion **12** which possessed the extra carbon at C-11 necessary for the eventual formation of the methylenoxy bridge.

An important observation from the literature was that the 2-chloromethylphenol **15** upon treatment with base was immediately converted to the unstable quinone methide **16** which could be trapped by styrene to yield the chroman **17**.[5] It was consequently a plausible assumption that the aporphine anion **12**, upon being formed, could be readily converted to the homologous quinone methide **13** which in turn would undergo rapid bond isomerization to de-N-methylthalphenine (**14**).

In order to test the above hypothesis, it was necessary first to prepare the required 7-hydroxy-2'-bromotetrahydrobenzylisoquinoline **11**. Friedel–Crafts alkylation of the known methyl 2-bromo-4,5-methylenedioxyphenylacetate[6] with chloromethyl methyl ether using zinc chloride in chloroform[7] led to a crystalline product which was assigned the chloromethyl ester structure **5**. The alternate structure **4** for the product could be discarded since refluxing **5** in sodium hydroxide followed by acidification did not lead to a lactonic product, while a structure such as **4** would indeed have been expected to generate a δ-lactone under such conditions.

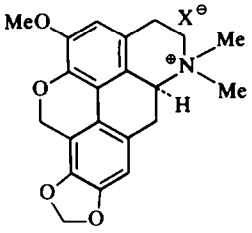
The compound obtained from the treatment of the chloromethyl ester **5** with methanolic sodium hydroxide was the methoxymethyl ether **6**. The acid chloride of **6** was then utilized in the N-acylation of 3 - methoxy - 4 - benzyloxy - β - phenethylamine[8] to produce the crystalline amide **7**.

The next three steps in the synthesis followed essentially classical lines. The colorless imine hydrochloride salt **8** was obtained through Bischler–Napieralski cylization of **7** using PCl_5 in chloroform at room temperature. Liberation of the free base and reaction with methyl iodide then supplied the imine methiodide salt **9** which was reduced with sodium borohydride to the tetrahydrobenzylisoquinoline **10**.

The selective hydrolysis of the benzyloxy protective group in **10** while keeping the methoxymethyl ether linkage intact was brought about at room temperature using equal volumes of ethanol and conc HCl, so that the 7 - hydroxy - 2' - bromotetrahydrobenzylisoquinoline **11** was obtained as an oil in 73% yield from **10**.

Photolysis of **11** to the aporphine system was achieved in 34% yield when the following experimental conditions were satisfied: (a) the precursor **11** had to be purified prior to irradiation; this was usually accomplished by column chromatography over neutral alumina, (b) the photolysis was sensitive to oxidation and was carried out in a closed, degased, system at 0°, and (c) a low, rather than high, pressure mercury lamp was utilized.

Interestingly enough, the product of the photolysis was (±)-de-N-methylthalphenine (**14**), so that species **12** and **13** were never isolated. Quaternization of **14** with methyl iodide led to (±)-thalphenine iodide (*rac.* **1**), identical in terms of TLC R_f values, and UV and NMR spectra with a sample of the natural product.[2] (±)-De-N-methylthalphenine (**14**) was most probably formed in this study via the intermediacy of the quinone methide **13**. As mentioned earlier, such a



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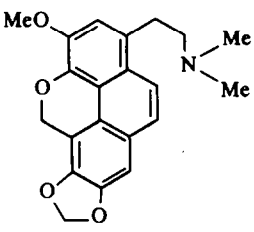

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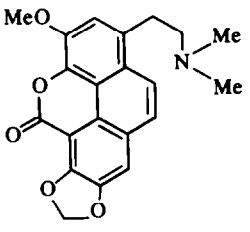

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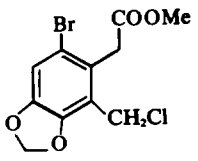

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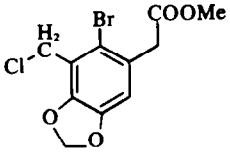

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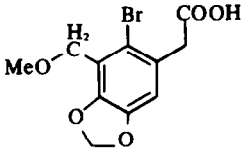

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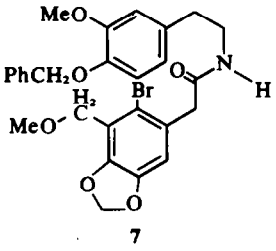

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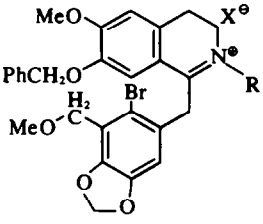

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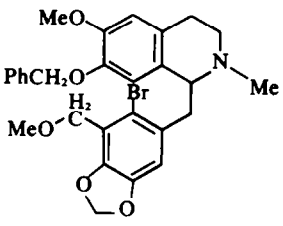

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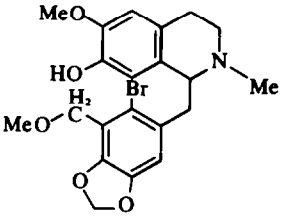

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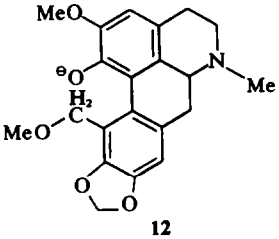

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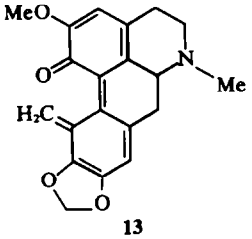

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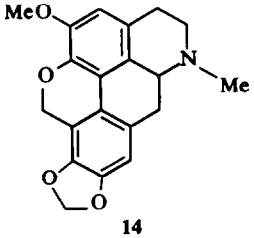

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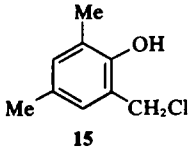

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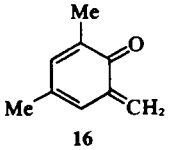

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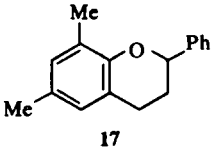

17

transformation bears strong similarity to the production of the chroman **17** from the ortho-quinone methide **16** and styrene. However, the possibility of an intramolecular S_N2 attack by the phenoxide anion in species **12**, with methoxide anion as the leaving group, cannot be totally excluded.

Two optically inactive alkaloids related to thalphene (**1**) are thaliglucine (**2**) and thaliglucinone (**3**), also found in *Thalictrum* species.[2,9] In the present study, base catalyzed Hofmann elimination of (±)-thalphenine (*rac.* **1**) gave rise to thaliglucine (**2**), identical in all respects with the natural product. Since dichromate oxidation of thaliglucine (**2**) is known to lead to thaliglucinone (**3**),[9] the sequence under consideration also represents a synthesis of the latter base.

EXPERIMENTAL

Standard experimental procedures. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis. M.ps are uncorrected. The NMR data were recorded at 60 MHz in $CDCl_3$ unless indicated otherwise; TMS was the internal reference. Mass spectra were obtained on an AEI MS-902 spectrometer. All TLC was on Merck Silica Gel-254 plates.

Methyl 2 - bromo - 3 - chloromethyl - 4,5 - methylenedioxyphenylacetate (**5**). A soln of methyl 2 - bromo - 4,5 - methylenedioxyphenylacetate (6·77 g; 247 mmol), and $ZnCl_2$ (6·77 g) and chloromethyl methyl ether (6·77 g, 85 mmol) in 226 ml $CHCl_3$ was stirred at room temp for 65 h. The $CHCl_3$ soln was filtered, and the solvent evaporated. The solid residue was recrystallized from MeOH, 5·29 g (67% yield), colorless needles, m.p. 111–111·5°. (Found: C, 41·21; H, 3·26. Calcd. for $C_{11}H_{10}O_4BrCl$: C, 41·08; H, 3·13%).

2 - Bromo - 3 - methoxymethyl - 4,5 - methylenedioxyphenylacetic acid (**6**). A mixture of **5** (5 g; 0·0155 mol) in 175 ml of 1N NaOH and 175 ml MeOH was stirred and refluxed for 50 min. The soln was washed with ether and acidified with 2N HCl. Heating on a steam bath for 30 min and then standing at room temp for 2 h gave a ppt which was extracted with ether. The soln was dried ($MgSO_4$) and evaporated to give 3·02 g colorless crystals (EtOAc), 64% yield, m.p. 161–162°; NMR (DMSO-d_6) δ 3·3 (3H, s, OCH_3), 3·69 (2H, s, CH_2COOH), 4·45 (2H, s, CH_3OCH_2), 6·10 (2H, s, OCH_2O), 7·00 (1H, s, ArH). (Found: C, 43·54; H, 3·77. Calcd. for $C_{11}H_{11}O_5Br$: C, 43·58; H, 3·65%).

N - β - (3 - Methoxy - 4 - benzyloxyphenylethyl) - 2' - bromo - 3' - methoxymethyl - 4',5' - methylenedioxyphenylacetamide (**7**). Powdered PCl_5 (6·5 g) was added in portions to **6** (6·5 g; 21·4 mmol) in 130 ml $CHCl_3$. The soln was stirred at room temp for 3 h and then dropped directly with stirring into a two layer mixture made from 3-methoxy-4-benzyloxy-β-phenethylamine hydrochloride (6·27 g; 21·4 mmol) and Na_2CO_3 (19·5 g) in 150 ml $CHCl_3$ and 150 ml water. The mixture was stirred for an additional 90 min. The $CHCl_3$ layer was washed with dil HCl, water, and then dried. Evaporation of the solvent left a residue which was recrystallized from EtOH, 7·5 g, 65% yield, m.p. 163–164°. (Found: C, 59·40; H, 5·07. Calcd. for $C_{27}H_{28}NO_6Br$: C, 59·78; H, 5·20%).

1 - (2' - Bromo - 3' - methoxymethyl - 4',5' - methylenedioxybenzyl) - 6 - methoxy - 7 - benzyloxy - 3,4 - dihydroisoquinoline hydrochloride (**8**). The above amide **7** (3·0 g; 5·55 mmol) and 3·0 g PCl_5 in 30 ml $CHCl_3$, were stirred at room temp overnight. Evaporation to half volume and addition of ether gave a ppt which was collected and recrystallized from MeOH to give 2·43 g colorless crystals in 78% yield, m.p. 219–221°. (Found: C, 56·39; H, 5·03. Calcd. for $C_{27}H_{27}NO_5BrCl$. 1 MeOH: C, 56·72; H, 5·27%).

1 - (2' - Bromo - 3' - methoxymethyl - 4',5' - methylenedioxybenzyl) - 6 - methoxy - 7 - benzyloxy - 3,4 - dihydro - 2 - methylisoquinolinium iodide (**9**). The aforementioned hydrochloride salt **8** (3·0 g; 5·35 mmol) together with Na_2CO_3 (8 g) in 40 ml water and 100 ml $CHCl_3$, was shaken for 10 min in a separatory funnel. The $CHCl_3$ layer was separated, washed with water, and dried. Evaporation of the solvent gave the imine which was taken into 60 ml MeOH and 24 ml MeI. After two days in a closed flask the solvent was evaporated. The methiodide salt was recrystallized from MeOH–ether, 2·76 g yellow crystals, 77% yield, m.p. 213–214°. This material was pure enough to use in the next step.

1 - (2' - Bromo - 3' - methoxymethyl - 4',5' - methylenedioxy) - 2 - methyl - 6 - methoxy - 7 - benzyloxy - 1,2,3,4 - tetrahydrobenzylisoquinoline (**10**). To the immonium iodide salt **9** (3·18 g; 4·8 mmol) in 150 ml EtOH cooled with ice water, was added in portions 1·5 g $NaBH_4$. The mixture was then stirred for 20 min at 0°. The solvent was removed and the residue taken up in $CHCl_3$ and water. The $CHCl_3$ layer was separated, washed with water, and dried. Evaporation left a residue which was chromatographed over neutral alumina. Elution with $CHCl_3$–EtOAc (4:1) supplied 1·92 g colorless oil, 74% yield; NMR δ 2·44 (3H, s, N–CH_3), 3·42 (3H, s, CH_2OCH_3), 3·85 (3H, s, $ArOCH_3$), 4·61 (2H, s, CH_3OCH_2), 4·90 (2H, s, $PhCH_2$), 5·87 and 5·91, J_{gem} = 1·2 Hz (2H, q, O–CH_2O), 6·35 (1H, s, ArH), 6·60–6·62 (2H, 2s, ArH), and 7·35 (5H, s, C_6H_5).

Methiodide salt, m.p. 199–201° (MeOH): (Found: C, 50·94; H, 5·06; I, 18·35; and N, 2·04. Calcd. for $C_{29}H_{33}NO_5IBr$: C, 51·04; H, 4·87; I, 18·59; N, 2·05%).

1 - (2' - Bromo - 2' - methoxymethyl - 4',5' - methylenedioxy - 2 - methyl - 6 - methoxy - 7 - hydroxy - 1,2,3,4 - tetrahydrobenzylisoquinoline (**11**). The amine **10** (0·49 g; 0·91 mmol) in 45 ml EtOH, was mixed with 45 ml conc HCl, and allowed to stand at room temp under N_2 in a closed flask for one week. The soln was cooled in an ice-bath, made slightly basic with conc NH_4OH, and extracted with $CHCl_3$. The organic layer was dried and evaporated to give 0·39 g of an oil. Chromatography over neutral alumina and elution with $CHCl_3$, ether and MeOH (2:2:1) furnished 0·30 g of an oil (73%) pure enough to be used in the next transformation; NMR δ 2·41 (3H, s, N–CH_3), 3·41 (3H, s, CH_3–O–CH_2), 3·84 (3H, s, $ArOCH_3$), 4·60 (2H, s, CH_3–O–CH_2), 5·96 (2H, s, OCH_2O), 6·45 (1H, s, ArH), 6·60 (1H, s, ArH), 6·68 (1H, s, ArH).

Low resolution mass measurement, *m/e* 448 and 450 (0·24) $(M–H)^+$, 418 and 420 (0·24) $(M–MeO)^+$, 355 (0·95) $(M–Br–Me)^+$, 192 (100).

High resolution mass measurement for base peak: Found: *m/e* 192·1019. Calcd. for $C_{11}H_{14}NO_2$: *m/e* 192·1024.

(±)-De-N-methylthalphenine (**14**). A soln of **11** (0·075 g; 0·164 mmol) and NaOH (0·19 g) in 9 ml MeOH and 1 ml water was degassed by evacuating the liquid N_2 cooled soln several times, and photolyzed with a low pressure UV-Products mercury lamp at 0° for about 3½ h. The product was submitted to TLC separation on alumina plates, Alphate-FT-22, using $CHCl_3$–EtOAc (8:1). De-N-methylthalphenine, 19 mg, 34% yield, was thus obtained and crystallized from MeOH, m.p. 179–180°; NMR δ 2·50

(3H, s, NCH_3), 3·85 (3H, s, OCH_3), 4·90 and 5·45, J_{gem} = 14 Hz (2H, q, Ar–O–CH_2Ar), 5·94 and 5·98, J_{gem} = 1 Hz(2H, q, OCH_2O). 6·50 (1H, s, ArH), 6·63 (1H, s, ArH); λ_{max}^{EtOH} 221, 233sh, 278sh, 286, 312 and 323sh (log ϵ 4·49, 4·34, 3·86, 3·98, 4·07 and 4·05). (Found: C, 70·80; H, 5·88, Calcd. for $C_{20}H_{19}NO_4$: C, 71·20; H, 5·67%).

(±)-*Thalphenine iodide* (rac. **1**). The racemate **14** (45 mg) was dissolved in 25 ml ether, 4 ml MeOH and 2 ml MeI. The flask was stoppered under N_2 at, and the mixture allowed to stand for one day. Evaporation and recrystalization from MeOH provided 55 mg, 86% yield, of colorless crystals m.p. 193–194°. (Found: C, 51·87; H, 5·13. Calcd. for $C_{21}H_{22}NIO_4$·MeOH: C, 51·67; H, 5·12%). TLC R_f 0·41 in $CHCl_3$–MeOH (4:1), identical with (+)-thalphenine iodide. The NMR spectrum in DMSO-d_6 corresponded to that for the natural product.[2]

Thaliglucine (**2**). Racemic thalphenine iodide (38·8 mg) in 15 ml MeOH and 15 ml 3N KOH was heated at 45–55° for 6 h. The soln was evaporated to half volume and extracted with $CHCl_3$. The organic layer was dried and evaporated. Recrystallization from MeOH gave 24·1 mg (85%) of methine crystals, m.p. 121–122°, identical with the natural product.[2,9] Comparisons were in terms of TLC R_f values, UV, NMR and mass spectra.

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