Calixarenes. 3. Preparation of the 2,4-Dinitrophenyl and Camphorsulfonyl Derivatives of the Calix[8]arene from *p-tert*-Butylphenol

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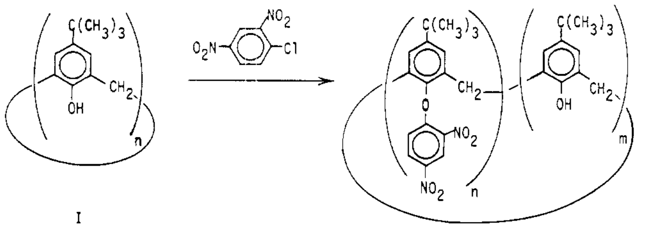
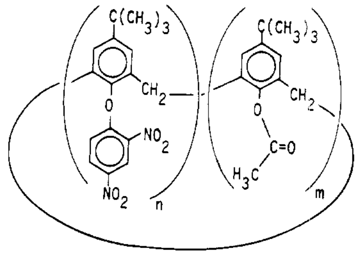
As part of a study of the chemistry of the calixarenes, which are cyclic oligomers obtained from the condensation of para-substituted phenols and formaldehyde,[1] the preparation of the 2,4-dinitrophenyl and camphorsulfonyl derivatives of a calixarene has been investigated. These derivatives are of interest because of the additional functionality that is introduced into the calixarene system and the increasingly diverse types of compounds that are thereby available for testing as complex-forming, polyfunctional catalysts. Also, the results of this study provide additional support for the cyclic octameric structure that has been assigned to the calixarene from *p-tert*-butylphenol and formaldehyde.[2,3]

Condensation of *p-tert*-butylphenol with formaldehyde in the presence of base under the conditions described in papers 1 and 2 of this series[2,4] affords, in greater than 90% yield, a high-melting compound to which a cyclic octameric structure has been assigned[2] (I, $n = 8$). When a pyridine solution of this compound is treated with an amount of 2,4-dinitrochlorobenzene corresponding to more than 1.0 equiv per phenolic residue, a product is obtained that can be separated by thin-layer chromatography into two isomers with almost identical properties but possessing different melting points and somewhat different ^{13}C NMR spectra. The analytical data for these compounds are compatible with a calixarene in which 75% of the hydroxyl hydrogens have been substituted by 2,4-dinitrophenyl groups, viz. II ($n = 3$, $m = 1$) or II ($n = 6$, $m = 2$). The excess dinitrophenylating reagent is removed quantitatively as *N*-(2,4-dinitrophenyl)pyridinium chloride. Treatment of the 2,4-dinitrophenylcalixarene (as a mixture) with a silylating agent fails to convert the free hydroxyl group(s) to a trimethylsilyloxy group(s), but treatment with acetyl chloride affords the acetoxy derivative III ($n = 3$, $m = 1$) or III ($n = 6$, $m = 2$). When I is treated with an amount of 2,4-dinitrochlorobenzene corresponding to 0.25 equiv per phenolic residue, a product is obtained that can be separated into a pair of compounds, one with properties compatible with structure II ($n = 1$, $m = 7$) and the other with properties compatible with structure II ($n = 1, m = 3$) or II ($n = 2$, $m = 6$). Treatment of the first of these compounds with an excess of 2,4-dinitrochlorobenzene yields the same mixture, described above, that is obtained directly from I and 2,4-dinitrochlorobenzene.



I

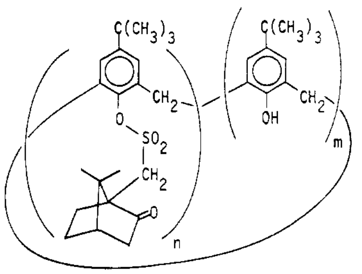
II-A (n=6, m=2)
II-B (n=1, m=7)
II-C (n=2, m=6)



III

On the assumption that the calixarene from which these 2,4-dinitrophenyl derivatives are prepared is a single, pure entity and on the assumption that the basic framework of this molecule remains intact throughout its reactions, the most rational interpretation of these results is that the calixarene is a cyclic octamer. Thus, the products obtained when an excess of reagent is used are designated as hexasubstituted octamers (II-A), and those obtained when a smaller amount of reagent is used are designated as monosubstituted (II-B) and disubstituted (II-C) octamers, respectively. Both the disubstituted and the hexasubstituted octamers can exist in four structurally different forms for which numerous conformers are possible.[5] Whether the pair of isomers designated as the hexasubstituted compounds are structural or conformational isomers is not known.

Treatment of a pyridine solution of I with an amount of camphorsulfonyl chloride corresponding to 0.25 equiv per phenolic residue yields a pair of compounds which, if I is correctly formulated as an octamer, correspond to a monocamphorsulfonyl (IV-A) and a dicamphorsulfonyl derivative (IV-B), respectively. These compounds are of interest because of their possible use in studying the complexing characteristics of calixarenes, the assumption being that the rotatory behavior will depend on the extent



IV-A (n=1, m=7)
IV-B (n=2, m=6)

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[2] Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, *43*, 4905.

[3] Cornforth, J. W.; D'A Hart, P.; Nichols, G. A.; Rees, R. J. S.; Stock, J. A. *Br. J. Pharmacol.* **1955**, *10*, 73.

[4] Gutsche, C. D.; Muthukrishnan, R. *Tetrahedron* **1979**, 2213.

[5] There are four possibilities for cyclic sequences containing six units of one kind and two of another, viz., a–a–a–a–a–a–b–b, a–a–a–a–a–b–a–b, a–a–a–a–b–a–a–b, and a–a–a–b–a–a–a–b. The general formulas for compounds II-A, II-C, III, and IV-B are intended to embrace all of these possibilities.

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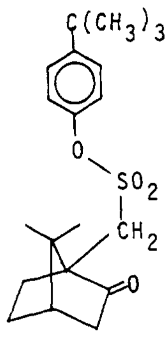

V

and nature of the complex formed. In this connection the circular dichroism of IV-A has been measured and compared with that of the camphorsulfonyl derivative of *p-tert*-butylphenol (V). When identical weight/volume concentrations of IV-A and V are used, V shows a large, almost symmetrical envelope with λ_{max} 294 nm (specific ellipticity 15°/cm, molecular ellipticity 55.20°/cm), whereas IV-A shows a much smaller, double-humped envelope with λ_{max} 294 nm (specific ellipticity 4.0°/cm, molecular ellipticity 60.12°/cm). Thus, the incorporation of the camphorsulfonyl moiety into a calixarene appears to alter its circular dichroic characteristics to some extent.

Experimental Section[6]

Hexakis(2,4-dinitrophenyl) Derivative of Calix[8]arene from *p*-*tert*-Butylphenol (II-A). A mixture containing 1.95 g (1.1 mmol) of I (mp 398–400 °C) and 2.44 g (12 mmol) of 2,4-dinitrochlorobenzene in 12 mL of pyridine was stirred under a blanket of nitrogen for 2 h at 115 °C. At the beginning of the reaction there was a small amount of solid phase, but after 30 min the solution had become clear. The reaction mixture was cooled, and the solid fraction was removed by filtration, dried, and recrystallized from ethanol to yield 0.84 g (3 mmol) of *N*-(2,4-dinitrophenyl)pyridinium chloride, mp 186–188 °C dec.

Anal. Calcd for $C_{11}H_8N_3O_4Cl$: C, 46.97; H, 2.84; N, 14.94. Found: C, 46.56; H, 3.15; N, 14.70.

Evaporation of the pyridine from the filtrate left a solid that was recrystallized from acetic acid to afford 2.47 g (73%) of an almost colorless powder, mp 235–237 °C, which appeared to be homogeneous by TLC analysis on silica with hexane–ethanol (7:3) as the developing agent but which showed a pair of very closely spaced spots with chloroform as the developing agent. When the crude product was recrystallized from carbon tetrachloride instead of acetic acid, material with mp 252–254 °C (shrinks at 218 °C) was obtained which, similarly, was shown by TLC to be a mixture. Therefore, preparative-scale TLC separation of the original mixture was employed, and this produced a higher melting compound (R_f 0.46) and a lower melting compound (R_f 0.50). Recrystallization of the higher melting compound from carbon tetrachloride yielded colorless crystals: mp 255–257 °C; IR (KBr) 3560 (br, non-H-bonded OH), 1540 and 1348 cm^{-1} (NO_2); IR ($CHCl_3$) 3560 cm^{-1} (s, non-H-bonded OH); UV$_{max}$ (CH_3CN) 218 nm (ϵ 84 960), 249 (36 100), 280 (43 145); ^{1}H NMR ($CDCl_3$) δ 8.64 (br s, 6, H-3 of Ar(NO_2)$_2$), 7.96 (br s, 6, H-5 of Ar(NO_2)$_2$), 7.0 and 6.51 (br s, 18, ArH and ArOH), 3.61 (br s, 16, CH_2), 1.18 (br s, 72, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 25.9 (19%, **C**$(CH_3)_3$), 31.0 (100%, C(**CH**$_3$)$_3$), 34.2 (24%, CH_2), 115.8 (25%, Ar), 122.0 (23%, Ar), 125.0 (18%, Ar), 126.9 (33%, Ar), 130.9 (35%, Ar), 141.0 (25%, Ar); osmometric mol wt ($C_6H_4Cl_2$, 100 °C) 2250 ± 100 (calcd 2292).

Anal. Calcd for $C_{124}H_{124}N_{12}O_{32}$: C, 64.92; H, 5.45; N, 7.20. Found: C, 64.76; H, 5.24; N, 7.21.

The lower melting compound was obtained as a colorless solid: mp 235–237 °C; IR, UV, and ^{1}H NMR virtually identical with those of the higher melting isomer described above; ^{13}C NMR ($CDCl_3$) δ 29.4 (33%), 29.7 (61%), 31.1 (100%), 31.45 (81%), 34.5 (16%), 95.8 (12%), 100.05 (12%), 116.1 (14%), 127.5 (25%), 129.05 (15%), 130.7 (12%), 140.9 (16%), 150.1 (15%), 150.3 (20%), 160.5 (11%).

Anal. Calcd for $C_{124}H_{124}N_{12}O_{32}$: C, 64.92; H, 5.45; N, 7.20. Found: C, 65.03; H, 5.56; N, 7.15.

Hexakis(2,4-dinitrophenyl)bis(acetyl) Derivative of Calix[8]arene from *p*-*tert*-Butylphenol (III). A 0.342-g (0.15-mmol) sample of II-A (mixture of isomers) was dissolved in 4 mL of pyridine and treated, under a blanket of nitrogen, with 0.5 mL of acetyl chloride. After 20 min the initially formed precipitate had completely dissolved, at which point the mixture was refluxed for 10 min. When the mixture was cooled and diluted with water, a precipitate formed which was separated by filtration and recrystallized from ethanol to yield 0.204 g (57%) of III as an almost colorless powder: mp 252–253 °C dec; IR (KBr) 3110 (H-3 stretch of Ar(NO_2)$_2$), 1770 (C═O), 1735 (sh, C═O), 1540 and 1350 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 8.64 (br s, 6, H-3 of Ar(NO_2)$_2$), 7.96 (br s, H-5 of Ar(NO_2)$_2$), 7.0 and 6.51 (br s, 22, ArH), 3.51 (br s, 16, CH_2), 2.16 (br s, 6, $COCH_3$), 1.16 (br s, 72, $C(CH_3)_3$).

Anal. Calcd for $C_{128}H_{128}N_{12}O_{34}$: C, 64.64; H, 5.39. Found: C, 64.59; H, 5.77.

Mono(2,4-dinitrophenyl) Derivative of Calix[8]arene from *p*-*tert*-Butylphenyl (II-B). A solution of 0.97 g (1.5 mmol) of I in 15 mL of pyridine was treated, under a blanket of nitrogen, with 0.606 g (3 mmol) of 2,4-dinitrochlorobenzene. The reaction mixture was heated 2 h at 115 °C and cooled, and the pyridine was removed under vacuum. The residue was dissolved in ether, and the ether solution was washed with water, aqueous sodium bicarbonate, water, dilute hydrochloric acid, and water. After being dried, the ether was removed, and the residue was recrystallized from 150 mL of acetic acid to yield 0.520 g of a product that showed a single spot on TLC analysis (R_f 0.6 with 2:3 ether–hexane): mp 268–273 °C dec; IR (KBr) 3560 (s, non-H-bonded OH), 3220 (br, H-bonded OH), 3060 (very weak, C–H stretch of Ar(NO_2)$_2$), 1540 and 1340 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 9.37 (br s, 6, H-bonded OH), 8.70 (m, 2, H-3 and H-5 of Ar(NO_2)$_2$), 7.23–6.88 (m, 16 [calcd 18], ArH), 3.90 (br s, 7 [calcd 8], CH_2), 3.53 (br s, 6, CH_2), 1.33 (s, 9, $C(CH_3)_3$ of the Ar(NO_2)$_2$-containing moiety), 1.24 (s, 63, $C(CH_3)_3$ of other ArH moieties).

Anal. Calcd for $C_{94}H_{114}N_2O_{12}\cdot{}^1/_2CH_3CO_2H$: C, 76.41; H, 7.77; N, 1.87. Found: C, 76.31; H, 7.78; N, 1.79.

A 0.15-g (0.035-mmol) sample of II-B, prepared as described above, and 0.2 g (0.98 mmol) of 2,4-dinitrochlorobenzene were dissolved in 3 mL of dry pyridine and heated at 115 °C for 2 h under a blanket of nitrogen. The pyridine solution was cooled, the *N*-(2,4-dinitrophenyl)pyridinium chloride was removed by filtration, the pyridine was evaporated from the filtrate, and the residue was crystallized from aqueous acetic acid to yield 0.19 g (79%) of II-A, mp 235–237 °C, consisting of the mixture of isomers described above.

Bis(2,4-dinitrophenyl) Derivative of Calix[4]arene from *p*-*tert*-Butylphenol (II-C). The mother liquor from the acetic acid recrystallization of II-B, described above, deposited 0.64 g (26%) of material upon standing. Purification by silica gel chromatography (4:1 chloroform–pentane) followed by crystallization from 95% ethanol–chloroform gave II-C as a colorless solid: mp 228–230 °C dec; IR (KBr) 3520 (s, non-H-bonded OH), 3350 (br, H-bonded OH), 1540 and 1350 cm^{-1} (NO_2); ^{1}H NMR ($CDCl_3$) δ 8.58 (br s, 2, H-3 of Ar(NO_2)$_2$), 7.83 (br s, 8, OH and H-5 of Ar(NO_2)$_2$), 7.1–6.55 (m, 18, ArH), 3.58–2.87 (br s, 16, CH_2), 1.25 (s, 18, $C(CH_3)_3$), 1.21 (s, 18, $C(CH_3)_3$), 1.16 (s, 18, $C(CH_3)_3$), 1.00 (s, 18, $C(CH_3)_3$).

Anal. Calcd for $C_{100}H_{116}N_4O_{16}\cdot{}^3/_4CHCl_3$: C, 70.43; H, 6.80; N, 3.26. Found: C, 70.70; H, 7.07; N, 3.04.

Further concentration of the acetic acid mother liquor produced another 0.47 g (19%) of a mixture which did not yield pure materials by chromatographic separation.

Mono(camphorsulfonyl) Derivative of Calix[8]arene from *p*-*tert*-Butylphenol (IV-A). A mixture of 1.3 g (1 mmol) of I and 0.5 g (2 mmol) of camphorsulfonyl chloride (mp 62–64 °C)[6]

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(6) Melting points were determined on samples in evacuated and sealed capillary tubes. The IR, ^{1}H NMR, and ^{13}C NMR spectra were obtained on a Perkin-Elmer 457, a Hitachi Perkin-Elmer R-24B, and a JEOL FX-100 instrument, respectively. Microanalyses were carried out by Industrial Testing Laboratories, St. Louis, Mo.

in 10 mL of dry pyridine was heated at 115 °C for 3 h under a blanket of nitrogen. The solution was cooled, the pyridine was removed by evaporation under vacuum, and the residue was washed with two 50-mL portions of ether. The ether-insoluble residue consisted of 0.34 g (26%) of unreacted I. Thin-layer chromatography on silica gel of the ether-soluble fraction (1.04 g) yielded a lower melting and a higher melting compound. The lower melting compound (R_f 0.7; $CHCl_3$) was recrystallized from pentane to give IV-A as a colorless solid: mp 197–199 °C dec; IR (KBr) 3430 (br, weakly H-bonded OH), 1750 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.15–6.55 (m, 16, ArH), 4.25–3.15 (m, 25, $ArCH_2Ar$, ArOH, and SO_2CH_2), 2.1 (br s, $COCH_2$), 1.5–1.1 (m, 72, $C(CH_3)_3$), 1.0 (m, 11, CH_2 and CH in camphor).

Anal. Calcd for $C_{98}H_{126}O_{11}S$: C, 77.88; H, 8.34; S, 2.12. Found: C, 77.70; H, 8.47; S, 2.12.

Bis(camphorsulfonyl) Derivative of Calix[8]arene from *p-tert*-Butylphenol (IV-B). The higher melting compound from the thin-layer chromatography described above was recrystallized from hexane–ethanol to give a colorless solid: dec 210–214 °C without melting; IR (KBr) 3450 (br, weakly H-bonded OH), 1750 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 6.97 (br s, 16, ArH), 4.1–3.6 (br d, 16, $ArCH_2Ar$), 2.5–1.8 (m, 18, CH_2 and CH of camphor), 1.3–0.5 (m, 80, $C(CH_3)_3$ and CH_3).

Anal. Calcd for $C_{108}H_{140}O_{14}S_2$: C, 75.17; H, 8.12. Found: C, 75.09; H, 8.16.

Acknowledgment. This research was supported by Grant GM-23534 from the National Institutes of Health.

Registry No. I (n = 8), 68971-82-4; II-B (n = 1, m = 7), 71370-09-7; IV-A (n = 1, m = 7), 71370-10-0; 2,4-dinitrochlorobenzene, 97-00-7; N-(2,4-dinitrophenyl)pyridinium chloride, 4185-69-7; camphorsulfonyl chloride, 21286-54-4.

Studies on the Synthesis of α-Functionalized Quinols: Synthesis of Jacaranone

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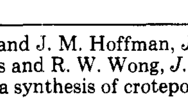
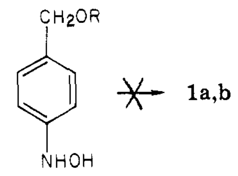
The potential of quinols and protected quinols[1] as synthetic intermediates prompted us to study the preparation and reactivity of quinols substituted in the α position (**1**). We have prepared and characterized three such α-substituted quinols, including the natural product jacaranone (**1e**).[2]



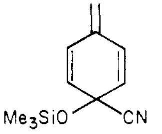
1a, X = OH
b, X = $O_2CC_6H_5$
c, X = SC_6H_5
d, X = $OCH_2C_6H_5$
e, X = CO_2CH_3

The classical preparation of quinols[3] by acid-catalyzed hydrolysis of para-substituted phenylhydroxylamines failed completely when applied to [p-(hydroxymethyl)phenyl]hydroxylamine (**2a**) or to its benzoate (**2b**), affording polymeric material in each case.

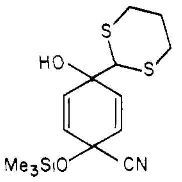


2a, R = H
b, R = COC_6H_5

Addition of unsubstituted Grignard or alkyllithium reagents to the protected cyanohydrin of benzoquinone followed by deprotection of the carbonyl affords quinols in good yield.[4] Therefore, we attempted to effect the 1,2-addition of α-substituted carbanions to the protected dienone **3**.



3



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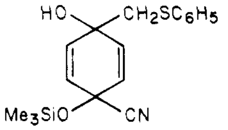
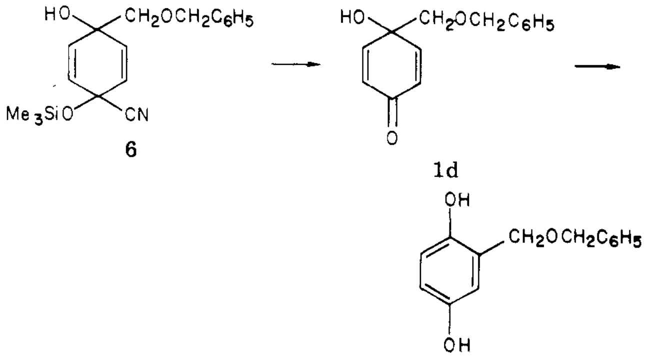


5

A number of substituted alkyllithium reagents added efficiently to the carbonyl of dienone **3**. Thus, 2-lithio-1,3-dithane[5] reacted with **3** at −90 to −100 °C to give a 95% yield of crude adduct **4**, from which a single isomer[6] was obtained in 30% yield overall on recrystallization.

Likewise [(phenylthio)methyl]lithium added to dienone **3** to give a quantitative yield of the crude adduct **5**. Deprotection of the masked carbonyl with silver fluoride[4] gave the quinol **1c** in 61% yield.

Addition of [(benzyloxy)methyl]magnesium chloride[7] to dienone **3** gave only 11% of the 1,2-adduct **6**; p-cyanophenol, presumably the product of one-electron reduction of the dienone, was identified as one of the byproducts from this reaction. Adduct **6** was obtained in good yield, however, when dienone **3** was added to [(benzyloxy)-



6
1d
7

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[1] (a) D. A. Evans and J. M. Hoffman, *J. Am. Chem. Soc.*, **98**, 1983 (1976); (b) D. A. Evans and R. W. Wong, *J. Org. Chem.*, **42**, 350 (1977). (c) See also the Ichihara synthesis of crotepoxide which uses a protected quinone: K. Oda, A. Ichihara, and S. Sakamura, *Tetrahedron Lett.*, 3187 (1975).

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[3] S. Goodwin and B. Witkop, *J. Am. Chem. Soc.*, **79**, 179 (1957).

[4] D. A. Evans, J. M. Hoffman, and L. K. Truesdale, *J. Am. Chem. Soc.*, **95**, 5822 (1973).

[5] D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).

[6] We found that several of the isomeric mixtures of Me_3SiCN protected quinols were separable by fractional crystallization; for our purposes, here, however, separation offered no advantage, and deprotection was generally performed on the mixture of isomers.

[7] B. Castro, *Bull. Soc. Chim. Fr.*, 1533 (1967).