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Chemistry of the 3a,7a-Dihydro-1H-indole Esters. Aromatization by Bromine†

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A series of tetramethyl 1-substituted benzyl-3a,7a-dihydro-1H-indole-2,3,3a,4-tetracarboxylates were prepared and their reactions with bromine were examined. The initial reaction seemed to be the formation of the intermediate *N*-bromo quartnery ammonium bromide. This intermediate underwent aromatization with loss of the 3a-methoxycarbonyl group. Bromine replaced the *N*-substituent of the *p*-methoxybenzyl compound and addition of bromine occurred across the C_6–C_7 double bond of the indole ring. Bromination of the benzyl ring and aromatization occurred for the *m*-methoxybenzyl compound.

Although bromine has a strong potential as an oxidizing agent, it has not been employed for the process of aromatization of dihydrobenzenes (eg. 1,3-cyclohexadiene or 1,4-cyclohexadiene to benzene) because addition would take place rather than dehydrogenation. Indeed, there are only a few examples of using bromine for the purpose of aromatization of nitrogen containing heterocyclic compounds.[1,2] Iodine was used for the conversion of cyclohexenones into anisols.[3]

As a part of our continuing investigation on the chemistry of 3a,7a-dihydroindole esters (**2**) which were prepared from *N*-substituted pyrroles (**1**) and dimethyl acetylenedicarboxylate (DMAD)[4,5] we reexamined the aromatization reaction of **2** by bromine. We suggested previously the formation of *N*-bromo quarternary ammonium ion (**3**) in the process of aromatization of 2.[4] It could be justified by formation of the *N*-bromodihydroindole (**2i**) from the unsubstituted compound aromatization of *N*-substituted dihydroindole esters (**2**). The aromatization of *N*-substituted dihydroindole esters (**2**). The chemistry involved here may well reflect the reactivity of the tertiary amine with electrophilic reagents. The fate of **3** may give insight to the relative reactivity of the substituted benzyl groups.

Results and Discussion

At first, substituted benzylpyrroles (**1c-i**) were prepared by the reaction of 2,5-diethoxytetrahydrofuran and the corresponding benzylamines.[6] The 1:2 adducts (**2c-h**) were prepared by refluxing the pyrroles (**1c-h**) with DMAD in anhydrous ether for 40-90 h and the solid precipitates were isolated and recrystallized from methanol. Reaction time, yields and melting points of the compounds are listed in Table 1. Note the *p*-methoxybenzylpyrrole (**1g**) gave the highest yield (80%) while the *m*-methoxy compound (**1f**) gave the lowest yield (20%). *p*-Nitrobenzylpyrrole (**1i**) did not react.

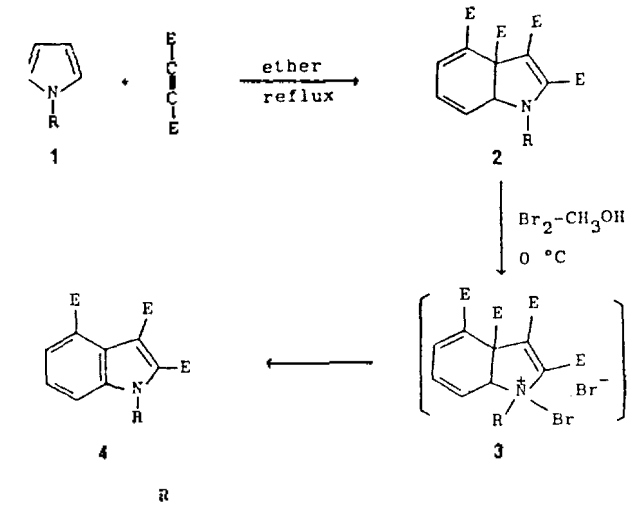
When the 3a, 7a-dihydroindole esters (**2**) were treated with bromine in methanol at 0 °C, aromatization took place but the yield of **4** varied depending on the substituents as shown in the Table 1. Similarly, the *N*-methyl compound (**2b**)[7] underwent almost quantitative aromatization. However, with *N*-benzyl (**2c**) or substituted benzyl compounds (**2d-h**) the aromatization reaction was not complete even in the presence of three-fold excess of bromine. The UV spectra of the reaction mixtures and the TLC examination indicated that con-

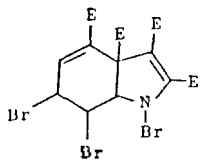
Table 1. The Yields and Melting Points of 3a,7a-Dihydroindoles (2) and Indoles (4)

Compd	Reaction time, h	Yield, %	mp, °C
2a [a]	96	6	162–165
2b	41	80	145–147[b]
2c	40	68	133.5–135[c]
2d	47	78	141–142.5
2e	89	48	154–155
2f	89	20	60.5–61
2g	72	80	104–107
2h	96	53	136–138.5
4b		98	120–121.5
4c		70	114
4d		20	108
4e		50	142–144
4f		38	127–130
4g		23	157.5–159

[a]All values are from ref. 4. [b]Lit.[7] 146°C, [c]Lit.[7] 135°C.

†This paper is dedicated to professor Hak Sook Lyu of Yonsei University on his 60th birthday.




5

Scheme I

siderable amount of the starting materials were present.

An interesting phenomenon was the loss of *p*-methoxybenzyl group and the formation of the tribromo compound (**5**) from **2g**. The identical compound has been isolated from the reaction of **2a** with bromine.[4] The formation of **5** may support the rationale shown in the Scheme I.

The key step in the oxidation seemed to be the nucleophilic attack of the lone pair of electrons on the nitrogen atom on bromine. The more basic the lone pair of electrons, caused by the inductive effect due to the substituents, the easier intermediate **3** is formed. Once the intermediate **3** forms, aromatization may take place with the loss of the 3a-$COOCH_3$ group although the fate of it has not been determined. The possibility of cleavage of *p*-methoxybenzyl group from **2g** due to methanol or any acidic impurity which may catalyze the cleavage was ruled out not only because **2g** was recrystallized from methanol but also added HCl did not cause any change of the compound under the similar reaction condition of aromatization.

Comparison of the spectra of **2** and **4** is interesting. Note the AB pattern at about δ 4.25 in the NMR spectra of **2**, due to the geminal coupling of CH_2 protons. The patterns became a singlet and shifted down field to δ 5.77 in **4**. Apparently, the aromatization of the indole skeleton causes the change in the chemical shift and shape of the peak. The average value of the UV absorption of **2** is 275 nm while that of **4** is 310 nm.

The mass spectra of **2** and **4** have base peak **m/e** values corresponding to the substituted benzyl cations. However, the loss of 91 mass units is as intense as the base peak in **2**, which is probably due to fragments such as CH_3OCO and CH_3OH. Similar fragmentation is almost insignificant in **4**.

Reaction of **2f** with bromine gave **4f**. Aromatization of the dihydroindole moiety and bromination of the benzyl ring took place under the general reaction conditions employed for conversion of **2** to **4**. This is expected because the CH_3O group is a strongly activating group in aromatic bromination. The mass spectrum of **4f** shows a fragment corresponding to $Br(CH_3O)C_6H_6H_3CH_2^+$ at *m/e* 199 and 201 with relative intensities of 31.2% and 31.6%, respectively. The position of the substitution seemed to be *para* to the CH_3O group and *ortho* to the CH_2 group. However, the NMR spectrum of **4f** shows an interesting chemical shift for the protons on the benzene ring. A doublet at δ 5.57 (J = 3 Hz) is quite unusual for the proton of this kind. The calculated δ values for the protons of 4-bromo-3-methoxybenzylamine are 6.71, 6.77, and 7.40 for 2-, 6-, and 5-H, respectively.[5] The δ values for the 2-bromo-5-methoxybenzylamine protons are 6.71, and 7.40 for 6-, 4-, and 3-H, respectively. Therefore, the peaks at 5.57, 6.78 (*dd*, J = 3 and 8 Hz), and 7.37 (*d*, J = 8 Hz) can be assigned as the chemical shifts due to 6'-, 4'-, and 3'-H, respectively. An explanation for the unusual δ 5.57 shift could be attributed to a particular conformation relative to either the C=O of 2-$COOCH_3$ or the indole ring putting this proton into the shielding cone. If the position of the substitution is *ortho* to the CH_3O group and *para* to the CH_2 group, the chemical shift value of 6'-H would also be significantly off from the calculated one. The λ_{max} value in the UV spectrum (312 nm) also confirmed that the bromination took place on the phenyl ring rather than on the indole skeleton. Bromination apparently occurred after the aromatization, otherwise **2g** might have given similar bromination products.

Experimental

Melting points were determined on a MEL-TEMP apparatus and are uncorrected. Infrared and ultraviolet-visible spectra were recorded on Perkin-Elmer models 783 and 552-S spectrophotometers, respectively. NMR spectra were recorded on a JEOL FX-90Q spectrometer using TMS as internal standard. Mass spectra were obtained on an AEI MS-30 spectrometer at 70 eV and 200 °C. Elemental analyses were performed by M-H-W Laboratories, Phoenx, Arizona.

Starting Materials. 2,5-Diethoxytetrahydrofuran and substituted benzylamines were purchased from Aldrich Chemical Co. DMAD (Aldrich Chemical Co.) was distilled prior to use.

Compounds **1c-i** were prepared by adapting Elming's procedure.[6] The yields and bp (mm Hg) are as follows: **1c**: 65%, 129 °C (10); **1d**: 78%, 99-105 °C (2.5) **1e**: 46%, 104 °C (0.9); **1f**: 90%, 85 ° C (1.0): **1g**: 57%, 109 °C (0.3); **1h**: 16%, mp 159-162 °C; **li**: 63%, 98-102 °C (2.5). Compounds **2a** and **2b** were prepared by literature methods.[4,7]

Procedure 1 - Dihydroindole Esters. Illustrative Procedure: Tetramethyl 3a,7a-Dihydro-1-(4-methylphenyl)-methyl-1H-indole-2,3,3a,4-tetracarboxylate (2d). A solution of **1d** (3.42 g, 20.0 mmole) and DMAD (5.68 g, 40.0 mmole) in anhydrous ether (30 *ml*) was refluxed for 47 h. Upon cooling the solution in a freezer (-5 °C) overnight pale yellow precipitate formed which was collected by filtration and recrystallized from methanol to give **2d** (7.10 g, 78%), mp 141-142.5 °C: IR (KBr) 1740, 1715, 1570, 1430, 1260,

1140, 840, 787 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (*s*, 3 H, CH_3), 3.64, 3.75, 3.78, and 3.87 (all *s*, 3 H each, $COOCH_3$), an AB pattern centered at 4.13 and 4.37 (2 H, CH_2, J = 16.0 Hz), 4.82 (*d*, 1 H, 7a-H, $J_{7a,7}$ = 3.0 Hz), 5.80 (*dd*, 1 H, 7-H, $J_{7,7a}$ = 3.0 Hz, $J_{7,6}$ = 9.0 Hz), 6.19 (*dd*, 1 H, 6-H, $J_{6,5}$ = 6.0 Hz), 6.96 (*d*, 1 H, 5-H, $J_{5,6}$ = 6.0 Hz), 7.11 (*s*, 4 H, C_6H_3); UV (MeOH) λ_{max} 239 nm (ε 6500), 245 (6800), 251 (7800), 257 (9800), 275 (15900), 295 infl (6000); mass spectrum, *m/e* 455 (13.9, M$^+$), 364 (100, M$^+$ – CH_3OCO, CH_3OH), 105 (100, $CH_3C_6H_4CH_2^+$).

Anal. Calcd for $C_{24}H_{25}NO_8$ (455.47): C, 63.29; H, 5.53; N, 3.08. Found: C, 63.23; H, 5.32; N, 3.11.

Tetramethyl 1-Benzyl-3,7a-dihydro-1H-indole-2,3,3a,4-tetracarboxylate (2c). The Acheson procedure,[7] which used no solvent, gave 36% yield. Our procedure increased the yield to 68%: IR (KBr) 1745, 1736, 1663, 1570, 1485, 1431, 1345, 1262, 1200, 1122, 1070, 1028, 945, 841, 786, 760, 740, 701, 680 cm^{-1}; NMR ($CDCl_3$) δ 3.60, 3.69, 3.75, and 3.80 (all *s*, 3H each, $COOCH_3$), and AB pattern centered at 4.11 and 4.36 (2 H, CH_2, J = 15.0 Hz), 4.78 (*d*, 1 H, 7a-H, $J_{7a,7}$ = 3.0 Hz), 5.77 (*dd*, 1 H, 7-H, $J_{7,7a}$ = 3.0 Hz, $J_{7,6}$ = 9.0 Hz), 6.18 (*dd*, 1 H, 6-H, $J_{6,7}$ = 9.0 Hz, $J_{6,5}$ = 6.0 Hz), 6.96 (*d*, 1 H, 5-H, $J_{5,6}$ = 6.0 Hz), 7.27 (*s*, 5 H, C_6H_5); UV (MeOH) λ_{max} 239 nm (ε 3900), 245 (4200), 251 *(5000)*, 257 (6400), 275 (10700), 295 infl (6000); *mass spectrum*, *m/e* (%) 411 (15.4 M$^+$), 350 (100, M$^+$–CH_3OCO, CH_3OH), 91 (100, $C_6H_5CH_2^+$).

Tetramethyl 1-(4-Chlorophenyl)methyl-3a,7a-dihydro-1H-indole-2,3,3a,4-tetracarboxylate (2e). IR (KBr) 1746, 1720, 1660, 1573, 1486, 1433, 1410, 1345, 1263, 1200, 1140, 1122, 1092, 1070, 1018, 945, 928, 838, 805, 786 cm^{-1}; NMR ($CDCl_3$) δ 3.67, 3.77, 3.80, and 3.86 (all *s*, 3 H each, $COOCH_3$), an AB pattern centered at 4.14 and 4.38 (2 H, CH_2, J = 16.0 Hz), 4.83 (*d*, 1 H, 7a-H, $J_{7a,7}$ = 3.0 Hz), 5.80 (*dd*, 1 H, 7-H, $J_{7,7a}$ = 3.0 Hz, $J_{7,6}$ = 9.0 Hz), 7.22 (*dd*, 1 H, 6-H, $J_{6,7}$ = 9.0 Hz, $J_{6,5}$ = 6.0 Hz), 7.03 (*d*, 1 H, 5-H, $J_{5,6}$ = 6.0 Hz), an AB pattern centered at 7.22 and 7.39 (4 H, C_6H_4, J = 8.6 Hz); UV (MeOH) λ_{max} 239 nm (ε 5700), 245 (6000), 251 (7000), 259 (9100), 274 (14600), 295 infl (8100); mass spectrum, *m/e*(%) 475 (1.5 M$^+$), 384 (66, M$^+$–CH_3OCO, CH_3OH), 125 (100, $ClC_6H_4CH_2^+$).

Anal. Calcd for $C_{23}H_{22}ClNO_8$ (475.88): C, 58.05; H, 4.66; Cl, 7.45; N, 2.94. Found: C, 57.93; H, 4.53; Cl, 7.58; N, 2.99.

Tetramethyl 3a,7a-Dihydro-1-(3-methoxyphenyl)-methyl-1H-indole-2,3,3a,4-tetracarboxylate (2f). IR (KBr) 1746, 1731, 1661, 1572, 1491, 1435, 1348, 1272, 1212, 1198, 1170, 1148, 1123, 1071, 1036, 930, 839, 787 cm^{-1}; NMR (DMSO-d_6) δ 3.45 (*s*, 3 H, OCH_3), 3.53, 3.64, 3.75, and 3.78 (all *s*, 3 H each, $COOCH_3$), an AB pattern centered at 4.24 and 4.40 (2 H, CH_2, J = 16 Hz), 4.72 (*d*, 1 H, 7a-H, $J_{7a,7}$ = 3.0 Hz), 6.08 (*dd*, 1 H, 7-H, $J_{7,7a}$ = 3.0 Hz, $J_{7,6}$ = 9.0 Hz), 6.36 (*dd*, 1 H, 6-H, $J_{6,7}$ = 9.0 Hz, $J_{6,5}$ = 6.0 Hz), 6.70–7.40 (*m*, 5 H 5-H and C_6H_4); UV (MeOH) λ_{max} 239 nm (*e* 5400), 245 (5600), 251 (6600), 257 (8600), 275 (15000), 295 infl (7900); mass spectrum, *m/e* (%) 471 (1.3 M$^+$), 380 (12.5, M$^+$–CH_3OCO, CH_3OH), 121 (100, $CH_3OC_6H_4CH_2^+$).

Anal. Calcd for $C_{24}H_{25}NO_9$(471.47): C, 61.14; H, 5.34; N, 2.97. Found: C, 61.15; H, 5.32; N, 3.02.

Tetramethyl 3a,7a-Dihydro-1-(4-methoxyphenyl)-methyl-1H-indole-2,3,3a,4-tetracarboxylate (2g). IR (KBr) 1745, 1725, 1665, 1614, 1566, 1515, 1490, 1463, 1430, 1345, 1260, 1198, 1143, 1120, 1068, 1040, 1023, 966, 941, 927, 902, 840, 822, 788, 763, 744 cm^{-1}; NMR ($CDCl_3$) δ 3.63 (*s*, 3 H, OCH_3), 3.72, 3.76, 3.81 and 3.84 (all *s*, 3 H each, $COOCH_3$), an AB pattern centered at 4.09 and 4.29 (2 H, CH_2, J = 17.0 Hz), 4.80 (*d*, 1 H, 7a-H, $J_{7a,7}$ = 3.0 Hz), 5.77 (*dd*, 1 H, 7-H, $J_{7,7a}$ = 3.0 Hz, $J_{7,6}$ = 9.0 Hz), 6.18 (*dd*, 1 H, 6-H, $J_{6,7}$ = 9.0 Hz, $J_{6,5}$ = 6.0 Hz), 6.97 (*d*, 1 H, 5-H, $J_{5,6}$ = 6.0 Hz) overlapped by an AB pattern centered at 6.84 and 7.15 (4 H, C_6H_4, J = 9.0 Hz); UV (MeOH) λ_{max} 238 nm (ε 7100), 245 (6800), 251 (7500), 257 (9300), 275 (15700), 295 infl (8500); mass spectrum, *m/e* (%) 471 (8.2, M$^+$), 380 (15.9, M$^+$), 380 (15.9, M$^+$–CH_3OCO, CH_3OH), 121 (100, $CH_3OC_6H_4CH_2^+$).

Anal. Calcd for $C_{24}H_{25}NO_9$ (471.47): C, 61.14; H, 5.34; N, 2.90. Found: C, 61.09; H, 5.35; N, 3.00.

Tetramethyl 3a,7a-Dihydro-1-(2-methylphenyl)-methyl-1H-indole-2,3,3a,4-tetracarboxylate (2h). IR (KBr) 1743, 1722, 1662, 1581, 1546, 1435, 1477, 1349, 1267, 1216, 1200, 1173, 1141, 1125, 1069, 766, 743 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (*s*, 3H, CH_3), 3.63 (*s*, 3H) and 3.80 (*s*, 9 H, all $COOCH_3$), an AB pattern centered at 4.23 and 4.43 (2 H, CH_2, J = 14.0 Hz), 4.83 (*d*, 1 H, 7a-H, $J_{7a,7}$ = 2.5 Hz), 5.[illegible] (*dd*, 1 H, 7-H, $J_{7,7a}$ = 2.5 Hz, $J_{7,6}$ = 9.0 Hz), 6.25 (*dd*, 1 H, 6-[illegible], $J_{6,5}$ = 9.0 Hz, $J_{6,5}$ = 6.0 Hz), 6.98 (*d*, 1 H, 5-H, $J_{5,6}$ = 6.0 Hz) [illegible].18 (*s*, 4 H, C_6H_4); UV (MeOH) λ_{max} 277 nm (ε 18000), 295 infl (9700); mass spectrum, *m/e* (%) 455 (0.1, M$^+$$CH_3O$), 364 (60.8, M$^+$–$CH_3OCO$, CH_3OH), 105 (100, $CH_3C_6H_4CH_2^+$).

Anal. Calcd for $C_{24}H_{25}NO_8$ (455.47): C, 63.29; H, 5.53; N, 3.08. Found: C, 63.35; H, 5.57; N, 3.13.

Procedure of 2-Aromatization by Bromine. Illustrative Procedure: Trimethyl 1-(4-Methylphenyl)methyl-1H-indole-2,3,4-tricarboxylate (4d). Compound **2d** (0.46 g, 1.00 mmole)was dissolved in methanol (20 *mL*) and cooled to 0 °C. Bromine (0.15 *mL*, 2.93 mmole) was added. The solution was stirred at 0 °C for 2 h and kept in a refrigerator (5°C) overnight to give a white solid, which was collected by filtration and washed with cold methanol. After drying under vacuum **4d** was obtained, 0.08 g (20%), mp 108 °C: IR (KBr) 1722, 1703, 1601, 1570, 1516, 1495, 1460, 1432, 1260, 1250, 1222, 1193, 1172, 1050, 1012, 945, 909, 868, 810 cm^{-1}; NMR ($CDCl_3$) δ 2.27 (*s*, 3 H, CH_3), 3.87, 3.94, and 3.99 (all *s*, 3 H each, $COOCH_3$), 5.76 (*s*, 2 H, CH_2), an AB pattern centered at 6.92 and 7.18 (4 H, C_6H_4, J = 9.0 Hz), 7.33 (*dd*, 1 H, 6-H, $J_{6,7}$ = 9.0 Hz, $J_{6,5}$ = 8.0 Hz), 7.56 (*dd*, 1 H, 7-H, $J_{7,6}$ = 9.0 Hz, $J_{7,5}$ = 1.6 Hz), 7.88 (*dd*, 1 H, 5-H, $J_{5,6}$ = 8.0 Hz, $J_{5,7}$ = 1.6 Hz); UV (MeOH) λ_{max} 248 nm infl (ε 5200), 254 infl (5900), 258 infl (4400), 272 infl (3400), 310 (17500); mass spectrum, *m/e* (%) 395 (3.0, M$^+$), 363 (13.6), 331 (13.1), 304 (1.8), 105 (100, $CH_3C_6H_4CH_2^+$).

Anal. Calcd for $C_{22}H_{21}NO_6$ (395.47): C, 66.82; H, 5.35; N, 3.54. Found: C, 66.65; H, 5.30; N, 3.54.

Trimethyl 1-Benzylindole-2,3,4-tricarboxylate (4c).[7] Spectral data absent in the literature are presented: IR (KBr) 1705, 1598, 1510, 1491, 1440, 1351, 1272, 1250, 1230, 1211, 1190, 1164, 1118, 1070, 1042, 1022, 998, 929, 900, 862, 810, 775, 765, 743, 722, 690 cm^{-1}; NMR ($CDCl_3$) δ 3.86, 3.92 and 3.98 (all *s*, 3 H each, $COOCHl_3$), 5.78 (*s*, 2 H, CH_2), 6.90–7.90 (*m*, 8 H, 5-, 6-, 7-H and C_6H_5); UV (MeOH) λ_{max} 242 nm (ε13800), 249 (10900), 255 (7800), 261 (4800), 309 (22500); mass spectrum, *m/e* (%) 381 (5.8, M$^+$), 349 (21.5, M$^+$–CH_3OH), 317 (9.6, M$^+$-2CH_3OH), 290 (3.9), 91 (100, $C_6H_5CH_2^+$).

Trimethyl 1-(4-Chlorophenyl)methyl-1H-indole-2,3,4-tricarboxylate (4e). IR (KBr) 1721, 1710, 1518, 1492, 1462, 1434, 1370, 1351, 1282, 1255, 1228, 1198, 1175, 1152, 1126, 1089, 1053, 1015, 991, 942, 910, 870, 836, 745 cm^{-1}; NMR ($CDCl_3$) δ 3.88, 3.94, and 3.99 (all *s*, 3 H each, $COOCH_3$), 5.77 (*s*, 2 H, CH_2), an AB pattern centered at 6.97 and 7.24

(4 H, C_6H_4, J=9.5 Hz), 7.35 (*dd*, 1 H, 6-H, $J_{6,7}$=9.0 Hz, $J_{6,5}$=7.5 Hz), 7.54 (*dd*, 1 H, 7-H, $J_{7,5}$=1.8 Hz, $J_{7,6}$=9.0 Hz), 7.88 (*dd*, 1 H, 5-H, $J_{5,6}$=7.5 Hz, $J_{5,7}$=1.8 Hz); UV (MeOH) λ_{max} 221 nm (ε 27600), 245 infl (7100), 255 infl (4000), 278, infl (3300), 312 (13500); mass spectrum, *m/e* (%) 415 (3.9, M^+), 383 (23.7, M^+-CH_3OH), 351 (6.1, M^+-2CH_3OH), 324 (3.3), 125 (100, $ClC_6H_{CH_2}^+$).

Anal. Calcdl for $C_{21}H_{18}ClNO_6$ (415.83): C, 60.66; H, 4.36; Cl, 8.52; N, 3.37. Found: C, 60.52; H, 4.26; Cl, 8.34; N, 3.33.

Trimethyl 1-(2-Bromo-5-methoxyphenyl)methyl-1H-indole-2,3,4-tricarboxylate (4f). IR (KBr) 1736, 1718, 1709, 1600, 1571, 1522, 1452, 1443, 1433, 1370, 1346, 1292, 1260, 1220, 1195, 1170, 1128, 1054, 1010, 805, 755, 745 cm^{-1}; NMR (DMSO-d_6) δ 3.51 (*s*, 3 H, OCH_3), 3.79, 3.84, and 3.89 (all *s*, 3 H each, $COOCH_3$), 5.57 (*d*, 1 H, 6'-H, $J_{6',4'}$=3.0 Hz), 5.74 (*s*, 2 H, CH_2), 6.78 (*dd*, 1 H, 4'-H, $J_{4',3'}$=9.0 Hz, $J_{4',6'}$=3.0 Hz), 7.37 (*d*, 1 H, 3'-H, $J_{3',4'}$=9.0 Hz), 7.5-7.7 (*m*, 3 H, 5-, 6-, and 7-H); UV (MeOH) λ_{max} 249 nm (ε 6000), 255 (4000), 261 infl (2600), 310 (15600); mass spectrum, *m/e* (%) 491 (7.4 M^++2), 489 (7.4, M^+), 460 [10.8, (M^++2)-CH_3O], 459 [17.2, (M^++2)-CH_3OH], 458 (11.9, M^+-CH_3O), 457 (15.8, M^+-CH_3O), 379 (25.5), 378 (100, M^+-CH_3OH, Br), 201 (32.5, $^{81}Br(CH_3O)C_6H_3CH_2^+$), 199 (31.2, $^{79}Br(CH_3O)C_6H_3CH_2^+$).

Anal. Calcd for $C_{22}H_{20}BrNO_7$ (490.32): C, 53.89; H, 4.11; N, 2.86. Found: C, 54.26; H, 4.19; N, 2.93.

Reaction of 2g with Bromine. Following procedure 2 a 90% yield of the tribromo compound **5** was isolated, mp 176-179 °C (lit.[4] mp 172-175 °C) and spectral data agreed with the literature.[4]

Trimethyl 1-(2-Methylphenyl)methyl-1H-indole-2,3,4-tricarboxylate (4h). IR (KBr) 1750, 1715, 1686, 1652, 1583, 1433, 1331, 1284, 1245, 1220, 1140, 1006, 822, 791, 762 cm^{-1}; NMR ($CDCl_3$) δ 2.47 (*s*, 3 H, CH_3), 3.87, 3.98 and 4.03 (all *s*, 3 H each, $COOCH_3$), 5.73 (*s*, 2 H, CH_2), 6.22 (*dd*, 1 H, 6'-H, $J_{6'-5'}$=8.0 Hz, $J_{6',4'}$=2.0 Hz), 6.8-8.0 (*m*, 6 H, 5-, 6-, 7-H and 3'-, 4'-, 5'-H); UV (MeOH) λ_{max} 244 nm infl (ε 8100) 255 infl (4800), 310 (16200); mass spectrum, *m/e* (%) 395 (17.9, M^+), 365 (41.7), 364 (100, M^+-CH_3O), 363 (31.2), 348 (11.5), 105 (94.2, $CH_3C_6H_3CH_2^+$).

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The Synthesis of *p*-Nitrocalix[4]arene

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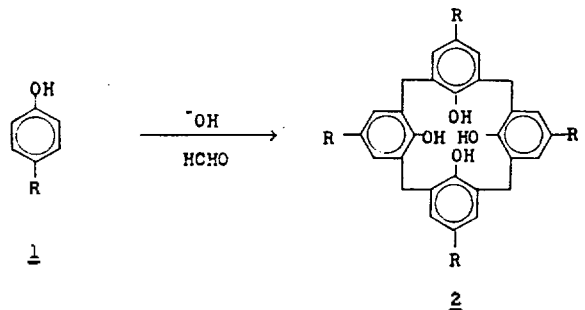
Methods for the preparation of *p*-nitrocalix[4]-arene via the direct substitution reaction of the *p-tert*-butylcalix[4]arene which is readily available with high yield from the base-induced direct condensation reaction procedure are described.

Introduction

Attempts to construct in vitro systems that mimic the in vivo catalytic activity of enzymes have led chemists to give increase attention to compounds that contain cavities of sufficient diameter and depth to form host-guest complexes. Calixarenes, which are [1$_n$] metacyclophanes comprising cyclic arrays of phenolic residues attached by methylene groups at the positions *"ortho"* to the hydroxyl groups, are members of a small group of organic compounds that are basketlike in shape[1] and possess the potential for forming host-guest complexes in which the guest resides in a cavity completely within a single host molecule.

Since the interesting prospects for enzyme model building



Scheme I