Tetrakis(isopropylthio)-1,4-difluorobenzene (14): mp 64–66 °C; NMR (60 MHz) δ 3.65 (septet, 1 H), 1.25 (d, 6 H); mass spectrum, *m/e* 410 (100%, M), 368 (31.5, M – C_3H_6), 326 (31.5, M – $2C_3H_6$), 284 (34, M – $3C_3H_6$), 242 (44, M – $4C_3H_6$).

Hexakis(isopropylthio)benzene (15): yellow, mp 113–115 °C; NMR (60 MHz) δ 3.75 (septet, 1 H), 1.2 (d, 6 H); mass spectrum, *m/e* 522 (100%, M), 480 (8.4, M – C_3H_6), 438 (11, M – $2C_3H_6$), 396 (23, M – $3C_3H_6$), 354 (32, M – $4C_3H_6$), 312 (33, M – $5C_3H_6$), 270 (11, M – $6C_3H_6$).

Pentakis(isopropylthio)thiophenol (16): yellow, mp 68–70 °C; NMR (90 MHz) δ 6.85 (s, 1 H, this proton exchanges with D_2O), 3.75 (septet, 2 H), 3.65 (septet, 1 H), 3.6 (septet, 2 H), 1.25 (d, 12 H), 1.15 (d, 12 H), 1.1 (d, 6 H); mass spectrum, *m/e* 480 (100%, M), 438 (13, M – C_3H_6), 396 (19, M – $2C_3H_6$), 354 (38, M – $3C_3H_6$), 312 (63.5, M – $4C_3H_6$), 270 (26, M – $5C_3H_6$).

1,2,4,5-Tetrakis(ethylthio)benzene (19): mp 65–67 °C; NMR (90 MHz) δ 7.2 (s, 1 H), 2.95 (q, 4 H), 1.35 (t, 6 H).

2,4,5-Tris(ethylthio)thiophenol (20): bp 130–134 °C (0.01 mm); NMR (90 MHz) δ 7.35 (s, 1 H), 7.15 (s, 1 H), 4.4 (s, 1 H, this proton exchanges with D_2O), 2.4 (q, 4 H), 2.35 (q, 2 H), 1.3 (t, 3 H), 1.25 (t, 3 H), 1.2 (t, 3 H).

Hexakis(ethylthio)benzene (21): bp 148–149 °C (0.01 mm); NMR (90 MHz) δ 3.05 (q, 2 H), 1.2 (t, 3 H).

Pentakis(ethylthio)thiophenol (22): bp 147–148 °C (0.01 mm); NMR (90 MHz) δ 6.85 (s, 1 H, this proton exchanges with D_2O), 3.05 (q, 4 H), 2.95 (q, 6 H), 1.2 (t, 6 H), 1.15 (t, 6 H), 1.1 (t, 3 H).

Hexakis(methylthio)benzene (27): mp 88–90 °C (lit.[14] mp 88–90 °C); NMR (60 MHz) δ 2.5 (s).

Pentakis(methylthio)thiophenol (28): mp 95–97 °C; NMR (90 MHz) δ 6.8 (s, 1 H, this proton exchanges with D_2O), 2.6 (s, 6 H), 2.55 (s, 3 H), 2.5 (s, 6 H).

1,2,4-Tris(isopropylthio)benzene[13] (**6**), 1,2,4,6-tetrakis(isopropylthio)benzene[13] (**10**), *p*-bis(ethylthio)benzene[13] (**18**), *p*-chlorophenyl methyl sulfide[1] (**23**), *p*-bis(methylthio)benzene[13] (**24**), *p*-chlorophenyl isopropyl sulfide[1], obtained from **25**, and *p*-(isopropylthio)phenyl methyl sulfide[1], obtained from **26**, have physical and spectroscopical properties identical with those reported in the literature.

Acknowledgment. Financial support from the CNR, Rome, is gratefully acknowledged.

Registry No. 5, 74542-66-8; **6**, 70415-95-1; **7**, 74542-67-9; **8**, 74542-68-0; **9**, 74542-69-1; **10**, 70416-07-8; **11**, 74525-22-7; **12**, 74525-70-4; **13**, 2570-41-4; **15**, 74542-72-6; **16**, 74542-73-7; **18**, 17661-83-5; **19**, 4115-58-6; **20**, 74542-74-8; **21**, 70648-34-9; **22**, 74542-75-9; **23**, 123-09-1; **24**, 699-20-7; **25**, 106-54-7; **26**, 1122-97-0; **27**, 58468-22-7; **28**, 70648-33-8; HMPA, 680-31-9; Me_2CHSNa, 20607-43-6; EtSNa, 811-51-8; MeSNa, 5188-07-8; 1,2,3-$C_6H_3Cl_3$, 87-61-6; 1,2,4-$C_6H_3Cl_3$, 120-82-1; 1,3,5-$C_6H_3Cl_3$, 108-70-3; 1,3,5-$C_6H_3Br_3$, 629-39-1; 1,2,3,4-$C_6H_2Cl_4$, 634-66-2; 1,2,4,5-$C_6H_2Cl_4$, 95-94-3; 1,2,4,6-$C_6H_2Cl_4$, 634-90-2; C_6HCl_5, 608-93-5; C_6Cl_6, 118-74-1; C_6F_6, 392-56-3; *p*-$C_6H_4Cl_2$, 106-46-7; C_6H_5SMe, 100-68-5; C_6H_5SH, 108-98-5; *p*-chlorophenyl isopropyl sulfide, 7205-62-1; **7** sulfone, 74542-76-0; **8** sulfone, 74542-77-1.

Chemistry of Heterocyclic Compounds. 55. Synthesis and Conformational Studies of Substituted 1,2-Diaryl- and Heteroarylbenzenes. Synthesis of Benzopyridinocyclophanes[1a]

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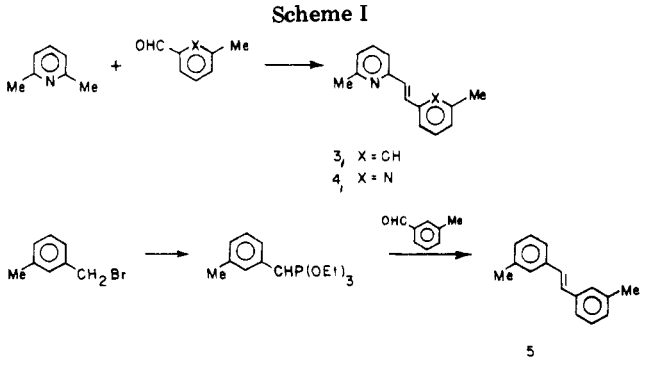
Received May 29, 1980

The syntheses of 1,2-bis(3-methylphenyl)-, 1-(6-methyl-2-pyridyl)-2-(3-methylphenyl)-, and 1,2-bis(6-methyl-2-pyridyl)benzenes are described. The aryl and heteroaryl olefins were brominated and didehydrobrominated to give the corresponding acetylenes, which were treated with α-pyrone to generate the respective ortho-substituted benzenes. The methyl substituents were oxidized with potassium permanganate to give, after esterification, the diesters. 1,2-Bis(6-methyl-2-pyridyl)benzene was α-brominated and cyclized with sodium sulfide to give the thiacyclophane **25**. The barrier for ring inversion of **25** was ascertained by VT NMR to be $\Delta G^* = 12.5$ kcal/mol at 245 K. Attempts to determine the rotational barriers of **11** and **12** were unsuccessful; however, a ΔG^* of 10 kcal/mol was estimated for **13**.

Recently, we successfully prepared a series of poly(2-pyridyl)phenylbenzenes and proposed that if the barrier to free rotation was appreciably high, configurational isomers could be isolated.[2] For example, 1,2-bis(2-pyridyl)tetraphenylbenzene (**1**) could exist in either a cis (β,β) or trans (α,β) form and thus hexakis(2-pyridyl)-benzene should exist as eight nonsuperimposable isomers, including one enantiomeric pair.

Gust et al.[3] have recently reported the synthesis of the related substituted hexaarylbenzenes (**2**) and then demonstrated that **2a** can be separated by column chromatography into stable geometrical isomers. The close similarity in methyl and methoxy group resonances can be detected by ^1H NMR. Hexaarylbenzene **2b** was also partially separated into geometrical isomers and subsequently isomerized at 217.5 °C to give an equilibrium

Scheme I

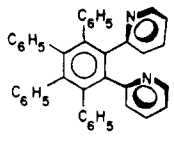


(1) (a) Previous paper in this series: Newkome, G. R.; Kawato, T.; Benton, W. H. *J. Org. Chem.* **1980**, *45*, 626. (b) Taken in part from the Ph.D. Theses of J.M.R. (1979) and J.M.R. (1974).

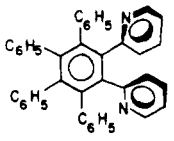
(2) Newkome, G. R.; Islam, N. B.; Robinson, J. M. *J. Org. Chem.* **1975**, *40*, 3514.

(3) (a) Gust, D. *J. Am. Chem. Soc.* **1977**, *99*, 6980. (b) Gust, D.; Patton, A. *Ibid.* **1978**, *100*, 8175. (c) Patton, A.; Dirks, J. W.; Gust, D. *J. Org. Chem.* **1979**, *44*, 4749.

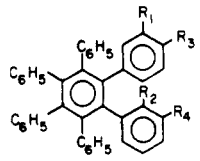
0022-3263/80/1945-4380$01.00/0



β,β-1

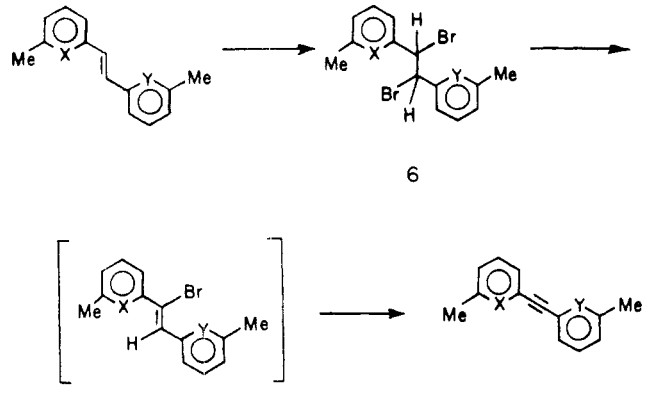


β,α-1



2a, R_1 = OMe; R_2 = Me; R_3 = R_4 = H
b, R_1 = R_2 = Me; R_3 = R_4 = H
c, R_1 = R_2 = H; R_3 = R_4 = Me

Scheme II



6

7

8, X = N; Y = CH
9, X = Y = N
10, X = Y = CH

isomer ratio of 0.6 ($\Delta G^{\ddagger}_{491K}$ = 38 kcal/mol). At 0 °C, the NMR spectrum of the methyl groups of **2c** showed two distinct peaks (equal intensity) separated by 1.7 Hz and at 21 °C, coalescence of these two methyl peaks to a singlet occurred ($\Delta G^{\ddagger}_{294K}$ = 16.4 kcal/mol).

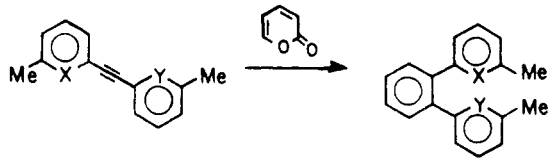
In light of the added hindrance caused by the numerous aryl or heteroaryl groups,[2] we now describe the synthesis and conformational properties of 1,2-bis(3-methylphenyl)-, 1-(6-methyl-2-pyridyl)-2-(3-methylphenyl)-, and 1,2-bis-(6-methyl-2-pyridyl)benzenes.

Results and Discussion

I. Synthetic Aspects. A. Aryl and heteroaryl olefins were synthesized by adaptations of a procedure previously outlined (Scheme I).[4] The 2-pyridyl olefins (**3** and **4**) were easily prepared by base condensation of the activated (2-pyridyl)methyl moiety with an appropriate aldehyde. In the case of *m*-xylene, the benzylic protons were not of sufficient acidity to utilize this procedure; therefore, via a modified Wittig procedure, (3-methylphenyl)methylenetriethoxyphosphorane,[5] prepared from 3-methylbenzyl bromide and triethylphosphite, was added to 3-methylbenzaldehyde to give **5** in 94% yield.

B. Aryl and Heteroaryl Acetylenes. Bromination of these olefins (**3**–**5**) gave the respective dibromides (**6**, Scheme II), which were not purified but were subjected directly to a hot alcoholic sodium hydroxide solution, giving (60–95%) the desired acetylenes (**8**–**10**). In certain cases, the intermediary vinylic bromides (e.g., **7**) were isolated, as a minor side product; however, subsequent treatment of these vinyl bromides with hot potassium *tert*-butoxide or potassium amide in liquid ammonia gave the corresponding acetylenes in high yields. Didehydrobromination reactions have been realized during the preparation of **9** (X = Y = N); thus before the synthesis of pyridyl acetylenes is attempted, a previous paper should be consulted.[4] Bis(2-pyridyl)acetylene can also be synthesized in average yields by a procedure described by Teitel et al.[7a] or by the treatment of 2-bromo- or 2-iodopyridines with bis(triphenylphosphine)palladium dichloride–cuprous iodide in diethylamine[7b,c] or triethylamine[7d] under very mild conditions.

C. Diaryl and Heteroarylbenzenes. Substituted benzenes have been smoothly prepared by the Diels–Alder reaction of the appropriate acetylene with α-pyrone.[8] Acetylene **9** and the less activated acetylene **8** were treated with α-pyrone at 220 °C for 9 and 72 h, respectively, to give the corresponding heteroarylbenzenes (**12** and **11**),



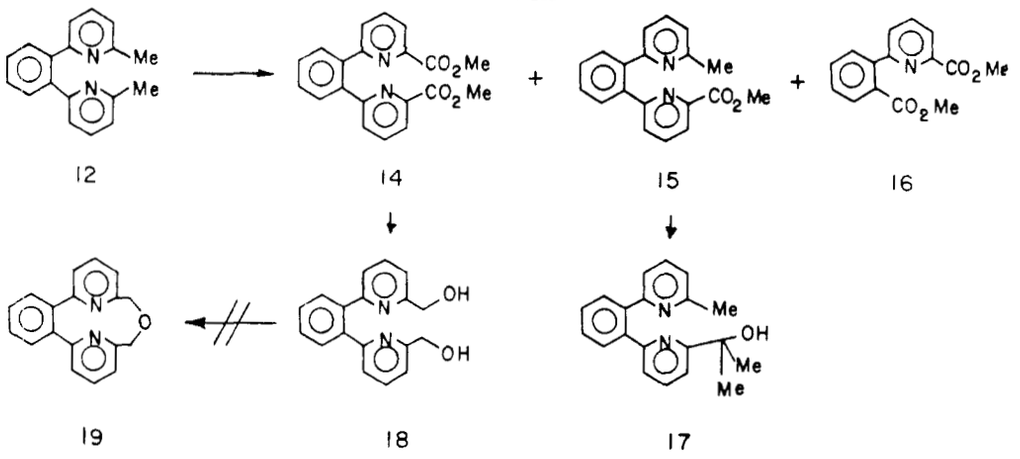
11, X = N; Y = CH
12, X = Y = N
13, X = Y = CH

whereas **10** and α-pyrone were subjected to 300–320 °C in a steel bomb for 5 days to ensure high yields of **13**. Without added hydroquinone, the yields of the ortho-substituted benzenes were lowered, and intractable materials were formed.

1,2-Bis(6-methyl-2-pyridyl)benzene (**12**) was oxidized with aqueous potassium permanganate to give, after Fischer esterification, a mixture of unchanged starting material, the desired diester **14** (42%), the monoester **15** (26%), and the unsymmetrical diester **16** (Scheme III), which was isolated in variable yields depending upon the severity of the reaction conditions. Prolonged oxidative conditions resulted in increased decomposition of a pyridyl nucleus. Traces of diethyl 2,6-pyridinedicarboxylate and -phthalate can be isolated from the rigorous oxidation of **12**; however, these products were minimized when the described oxidative conditions were used. Treatment of **15** with 2 equiv of methyllithium gave **17** (74%); however,

(4) Newkome, G. R.; Koppersmith, D. L. *J. Org. Chem.* **1973**, *38*, 4461.
(5) Wheeler, O. H.; De Pabon, H. N. B. *J. Org. Chem.* **1965**, *30*, 1473.
(6) Coleman, G. H.; Holst, W. H.; Maxwell, R. D. *J. Am. Chem. Soc.* **1936**, *58*, 2310.
(7) (a) Teitel, T.; Collin, P. J.; Sasse, W. H. F. *Aust. J. Chem.* **1972**, *25*, 171. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (c) Edo, K.; Yamanaka, H.; Sakamoto, T. *Heterocycles* **1978**, *9*, 271. (d) Roper, J. M. Ph.D. Dissertation, Louisiana State University, 1979.
(8) Alder, K.; Rickert, H. *Chem. Ber.* **1973**, *70*, 1354. Reed, J. E.; Schilling, C. L., Jr.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.* **1969**, *34*, 2188.

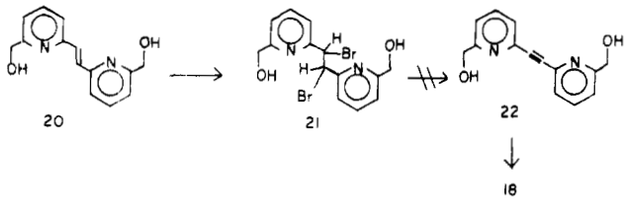
Scheme III



with a large excess of methyllithium, diminished yields of **17** were realized probably due to competitive intramolecular reactions arising from the carbanion generated from abstraction of an acidic (6-pyridyl)methyl proton.

Diester **14** was easily reduced with excess sodium borohydride in methanol to give the corresponding diol **18**, which possesses a very limited solubility in most common organic solvents and failed to give the cyclic ether **19** upon treatment with either HBr[9] or hot (150 °C) phosphoric acid.

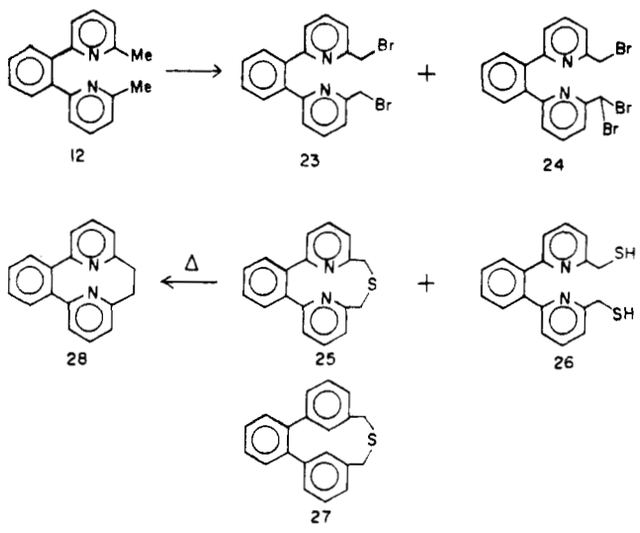
An alternate procedure was devised starting with diol **20**,[10] which upon bromination gave (80%) the crystalline dibromide **21**; however, all attempts to transform **21** into



the desired acetylene **22** failed. Variation of the reaction conditions did not result in acetylene formation, but rather variable yields of olefin **20** were recovered, as a result of a facile debromination reaction.

In order to generate the corresponding thiacyclophane, we brominated **12** with *N*-bromosuccinimide in benzene with AIBN as initiator.[11] Although bromination products were plentiful, the symmetrical dibromo compound **23** was isolated (7%) along with a tribrominated product **24** (Scheme IV). Vögtle's procedure[11] works best for arylmethyl substitution, whereas for the heteroaryl methyls the yields of desired products are low, at best, and generally contaminated with polybrominated products. Treatment of **23** with an ethanolic solution of sodium sulfide hydrate at reflux gave (8%) the cyclized pyridinophane **25** along with the very air-sensitive dithiol **26**. The spectral data for **25** are consistent with the cyclic structure in that the NMR shows a distinct spike at δ 3.83 for the α-methylene groups (Figure 1) and a doublet at δ 7.03 for the 5-pyridyl hydrogen. At diminished (<240 K) temperatures, the singlet is transformed (243 K) into an eventual AB system. The barrier for ring inversion[12]

Scheme IV



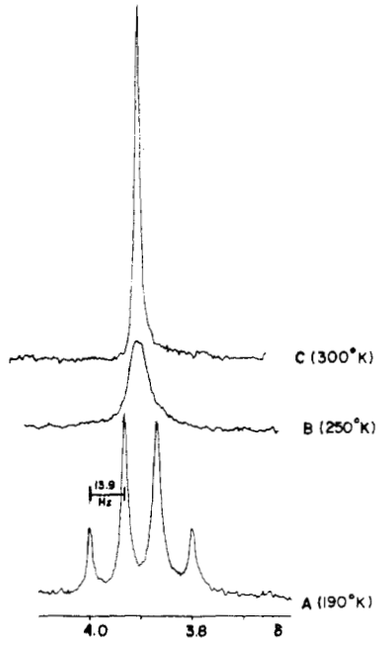


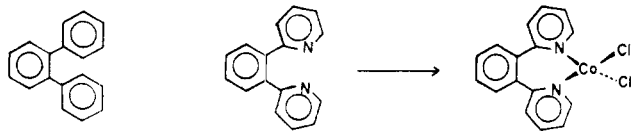
Figure 1. VT NMR spectrum of cyclophane **25** run in CD_2Cl_2 at 200 MHz: A at 27 °C, B at −23 °C, C at −83 °C.

($\Delta G^{\ddagger}_{245K}$ = 12.5 kcal/mol) determined in dichloromethane is reasonable, albeit slightly higher than anticipated, when compared to $\Delta G^{\ddagger}_{280K}$ = 13.1 kcal/mol for **27**.[13]

(9) Wittig, G.; Davis, P.; Koenig, G. *Chem. Ber.* **1951**, *84*, 627.
(10) Baker, W.; Buggle, K. M.; McOmie, J. F. W.; Watkins, D. A. M. *J. Chem. Soc.* **1958**, 3594.
(11) F. Vögtle, *Synthesis* **1977**, 273.
(12) Sakamoto, K.; Oki, M. *Tetrahedron Lett.* **1973**, 3989 and references cited therein.

Limited sample size of **25** and **23** prevented the subsequent conversion of **25** to **28** in isolatable amounts by sulfur extrusion reactions with triethyl phosphite and photochemical irradiation. The mass spectral data suggest that desulfuration is the primary fragmentation route due to the intense $M^+ - 33$ (32) signals. Further studies are being conducted to prepare **28** and related cyclophanes.

II. Further Rotational Aspects of the Di(hetero)arylbenzenes. In 1937, Clews and Lonsdale[14] reported the X-ray crystal structure of 1,2-diphenylbenzene (**29**) and



29 30 31

concluded that (a) neither phenyl group can be orthogonal to the central ring, and (b) the most likely structure of **29** has the two phenyl rings rotated about 50° in the same direction from the plane of the central ring. Electron-diffraction studies have supported the noncoplanarity as demonstrated by X-ray data and have further indicated that in the gas phase the phenyl rings oscillate no more than ±15° from the orthogonal orientation.[15]

Simple biphenyl has been shown to possess a low (2–5 kcal/mol) rotational barrier as calculated with a semiempirical π-electron procedure[16] or 4.9 kcal/mol via the CNDO/2 method.[17] The crystal structure of hexaphenylbenzene has similarly shown the phenyl rings to be rotated from +62° to +71° from the plane defined by the central ring,[18] whereas, electron-defraction studies[19] in the gas phase have afforded a 90 ± 10° interplanar angle. The barrier to rotational or isomeric interconversion of two adjacent phenyl rings possessing an *o*-methyl group in hexaarylbenzene has been shown to be ca. 38 kcal/mol, whereas with a neighboring *m*-methyl or -methoxy group the value is ca. 16 kcal/mol.[3a]

At ambient temperature, the NMR spectrum of **13** showed a sharp singlet at δ 2.45 for the methyl groups. At reduced temperatures, the singlet broadened, and at −80 °C, two broad singlets of approximately equal intensity were detected. The two peaks were separated by 1.5 Hz at 200 MHz. When the sample was warmed, the singlets broaden, coalesce, and regress to the singlet. Line-shape analyses of the temperature-dependent spectra gave a $\Delta G^{\ddagger}_{210K} \simeq 10$ kcal/mol. This is in approximate agreement with a prediction of Gust[3c] in which the barrier to 1,2-diarylbenzene isomerization is low and indicative of a relatively minor steric influence exerted by the *m*-methyl substituents. Substituents in the 3- and 6-positions of the central ring should exert a considerable buttressing effect on the rotational barriers of the *o*-aryl rings.

All attempts to ascertain the rotational barriers of **11** and **12** were unsuccessful. The NMR spectrum of either **11** or **12** was unchanged from +40 to −90 °C; the methyl groups remained constant as singlets over this temperature range. In **17**, the *gem*-dimethyl moiety was a spike from +40 to −90 °C, indicative of facile isomerization of the pyridyl groups. The possibility of fortuitous superimposable peaks cannot be totally eliminated; however, different solvents did not separate the signals. The complexation of **30** with cobalt(II) chloride in anhydrous ethanol quantitatively gave complex **31**, indicative of a facile heteroaryl ring isomerization at 25 °C. The crystalline complex **31** is stable to air but upon hydrolysis can be reverted back to the free ligand. A similar complex of **11** was prepared, but due to the steric size of the 6-methyl substituents attempted purification regenerated the free ligand.

Currently, further studies are in progress to ascertain the minimal hindrance necessary to secure diastereomeric isomers.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Beckman IR-7 spectrophotometer. Unless otherwise noted, ^{1}H NMR spectra were recorded in deuteriochloroform solution (10%, w/v) with Me_4Si as internal standard (δ 0) on either a Varian A-60 A or a Bruker WP200 spectrometer. For preparative thick-layer chromatography, 2-mm Brinkmann silica gel PF-254-366 plates were used and eluted with the stipulated solvents. Elemental analyses were performed by Mr. R. Seab in these laboratories.

α-Pyrone was prepared from malic acid in two steps, according to published procedures.[20]

A. 1,2-Bis(3-methylphenyl)benzene. *trans*-3,3′-Dimethylstilbene (5). A mixture of (3-methylphenyl)methylenetriethoxyphosphorane (32.0 g, 0.133 mol), prepared (90%) from triethyl phosphite and 3-methylbenzyl bromide,[5] and 3-methylbenzaldehyde (16 g, 0.133 mol) was added dropwise to a stirred suspension of oil-free sodium hydride (4 g) in *N,N*-dimethylformamide (100 mL) and benzene (50 mL). The mixture was refluxed for 2 h, cooled, and diluted with water. The organic layer was separated and the aqueous layer extracted with ether. The combined organic extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo, giving 26.0 g (94%) of *trans*-3,3′-dimethylstilbene: mp 55–56 °C (cyclohexane) (lit.[21] mp 55.1–56.2 °C); NMR δ 2.35 (s, C_{arom} CH_3, 6H), 7-7.4 (m, C_{arom} H, vinyl H, 10 H).

Bis(3-methylphenyl)acetylene (10). To a solution of *trans*-3,3′-dimethylstilbene (24 g, 0.115 mol) in chloroform (100 mL) was added bromine (18.5 g, 0.115 mol) in chloroform (100 mL) dropwise over 1 h. The mixture was stirred for 4 h, and then the solvent was removed in vacuo, affording the crude dibromide: mp 150–160 °C (lit.[6] mp 166.5–167 °C); 40 g.

The crude dibromide was dissolved in anhydrous methanol, excess alcoholic sodium hydroxide was added, and the solution was refluxed for 24 h under nitrogen. The solvent was removed in vacuo, ice–water was added, and the crude product was extracted with ether, dried, and concentrated, affording 15.2 g (66%) of the acetylene **10**. Recrystallization from hexane afforded an analytical sample: mp 73–74 °C (lit.[6] mp 73.5–74 °C); NMR δ 2.31 (s, C_{arom} CH_3, 6 H), 7.1–7.4 (m, C_{arom} H, 8 H); Raman (neat) 2212 (C≡C), 1596, 1577, 1222, 1168, 1126, 997 cm^{-1}.

The intermediate vinyl bromide was isolated from the mother liquors: NMR δ 2.15, 2.25 (2 s, C_{arom} CH, 6 H), 7.1–7.4 (m, C_{arom} H, vinyl H, 7 H). The crude material (3 g) was dissolved in anhydrous *tert*-butyl alcohol (30 mL), and excess potassium *tert*-butoxide was added. The mixture was refluxed for 12 h and worked up as previously described above. Recrystallization of the residual solid afforded additional acetylene **10**: mp 71–73 °C (hexane); 2.1 g.

1,2-Bis(3-methylphenyl)benzene (13). A solution of bis(3-methylphenyl)acetylene (1.0 g, 4.85 mmol), α-pyrone (2.0 g, 20 mmol), and hydroquinone (100 mg) in redistilled xylene (25 mL) was heated to 300–320 °C for 5 days in a stainless-steel bomb.

(13) Hammerschmidt, E.; Vögtle, F. *Chem. Ber.* **1980**, *113*, 1125. Personal communication from F. Vögtle, Feb 1979.
(14) Clews, C. J. B.; Lonsdale, K. *Proc. R. Soc. London, Ser. A* **1937**, *161*, 493. Also see: Trotter, J. *Acta Crystallogr.* **1961**, *14*, 1135.
(15) Karle, I. L.; Brockway, L. O. *J. Am. Chem. Soc.* **1944**, *66*, 1974.
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The solvent and unchanged α-pyrone were removed in vacuo, and the residue was chromatographed (thick layer), eluting with hexane to afford **13** as a colorless oil: 490 mg (40%); bp 170–173 °C (1.4 mm); NMR δ 2.24 (s, $C_{arom}CH_3$, 6 H), 6.7–7.2 (m, C_{arom} H, 8 H), 7.32 (s, C_{arom} H, 4 H).

Anal. Calcd for $C_{20}H_{18}$: C, 92,98; H, 7.02. Found: C, 92.86; H, 7.05.

B. 1-(3-Methylphenyl)-2-(6-methyl-2-pyridyl)benzene (11). *trans*-1-(6-Methyl-2-pyridyl)-2-(3-methylphenyl)ethene (3). A mixture of lutidine (20 g, 187 mmol), 3-methylbenzaldehyde (10 g, 83.2 mmol), and acetic anhydride (20 mL) was refluxed for 12 h. The volatile unchanged starting materials were removed in vacuo, and the residue was distilled, affording the crude olefin [bp 140–160 °C (0.5 mm)], which was fractionally redistilled to give **3** as a pale yellow oil: 11.2 g (64%); bp 156–157 °C (0.75 mm); NMR δ 2.29 (s, $C_{arom}CH_3$, 3 H), 2.52 (s, 6-CH_3 pyr, 3 H), 6.8–7.8 (m, C_{arom} H, pyr H, and vinyl H, 9 H).

Anal. Calcd for $C_{15}H_{15}N$: C, 86.10; H, 7.22; N, 6.69. Found: C, 85.96; H, 7.27; N, 6.72.

(3-Methylphenyl)(6-methyl-2-pyridyl)acetylene (8). Olefin **3** was brominated as described above; mp 189–192 °C. Further purification was not attempted.

A mixture of the crude dibromide (12 g) and potassium *tert*-butoxide (10 g) in anhydrous *tert*-butyl alcohol (10 mL) was refluxed for 12 h under nitrogen. The solvent was removed, ice–water was added slowly, and the crude product was extracted with dichloromethane, dried, and concentrated to give 5.65 g (70%) of the crude acetylene **8**. Recrystallization from cyclohexane afforded an analytical sample: mp 60–61 °C; NMR δ 2.32 (s, $C_{arom}CH_3$, 3 H), 2.55 (s, 6-CH_3 pyr, 3 H), 6.9–7.7 (m, C_{arom} H and pyr H, 7 H); IR ($CHCl_3$) 2216 (C≡C), 1603, 1587, 1572, 1568, 1487, 1454 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}N$: C, 86.93; H, 6.32; N, 6.75. Found: C, 87.01; H, 6.24; N, 6.73.

1-(3-Methylphenyl)-2-(6-methyl-2-pyridyl)benzene (11). A mixture of **8** (2.0 g, 9.7 mmol), α-pyrone (2.0 g, 21 mmol), and hydroquinone (50 mg) in redistilled *o*-dichlorobenzene (50 mL) was refluxed for 72 h under nitrogen. The solvent was removed in vacuo, and the residue was distilled, affording **11** as a colorless oil: 2.0 g (80%); bp 168–170 °C (1.3 mm); NMR δ 2.22 (s, $C_{arom}CH_3$, 3 H), 2.48 (s, 6-CH_3 pyr, 3 H), 6.6–7.7 (m, C_{arom} H, pyr H, 11 H).

Anal. Calcd for $C_{19}H_{17}N$: C, 87.98; H, 6.61; N, 5.40. Found: C, 87.82; H, 6.62; N, 5.26.

C. 1,2-Bis(2-pyridyl)benzenes. 1,2-Bis(2-pyridyl)benzene. A solution of bis(2-pyridyl)acetylene[4] (250 mg, 1.39 mmol; lit.[4] mp 69–71 °C), α-pyrone (220 mg, 2.29 mmol), and redistilled nitrobenzene (5 mL) was refluxed for 9 h under nitrogen. The mixture was cooled, suspended in ether, and extracted with 5% hydrochloric acid. The extract was basified with sodium carbonate and then extracted with methylene chloride. The organic layer was dried over sodium sulfate and concentrated in vacuo to afford an oil, which was chromatographed (thick layer), eluting with cyclohexane–ethyl acetate (1:1) to give 53 mg (21%) of the unchanged acetylene and 171 mg (53%) of 1,2-bis(2-pyridyl)benzene (**30**). Recrystallization from cyclohexane afforded colorless flakes: mp 123–123.5 °C; NMR δ 6.8–8.0 (m, C_{arom} H, 10 H), 8.5–8.8 (t, 6-H of pyr, 2 H); IR (Nujol) 1580, 1555, 1414, 1145, 799, 757, 749 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 83.06; H, 5.08; N, 12.05.

An ethanolic solution of 1,2-bis(2-pyridyl)benzene was treated with a stoichiometric amount of $CoCl_2$, warmed, and concentrated in vacuo, affording a blue complex, which was recrystallized from 2-propanol to give **31** as blue crystals, mp >300 °C. Warming of the cobalt(II) complex with H_2O for 10 min regenerates the starting ligand, mp 120–122 °C (cyclohexane).

1,2-Bis(6-methyl-2-pyridyl)benzene (12). A solution of bis(6-methyl-2-pyridyl)acetylene[4] (**9**; 2.0 g, 9.62 mmol, lit.[4] mp 138–139 °C), α-pyrone (2.0 g, 21 mmol), hydroquinone (20 mg), and redistilled *o*-dichlorobenzene (20 mL) was refluxed for 48 h under nitrogen. The solvent was removed in vacuo to give a dark residue, which was distilled, affording **12** as a nearly colorless oil: 1.4 g (56%); bp 110–114 °C (0.2 mm); NMR δ 2.49 (s, 6-CH_3 pyr, 6 H), 6.82 (d, 5-H of pyr, J = 8.5 Hz, 2 H), 6.98 (d, 3-H of pyr, J = 8.5 Hz, 2 H), 7.35 (t, 4-H of pyr, J = 8.5 Hz, 2 H), 7.52 (m, 4,5-H of Ph, 2 H), 7.35 (m, 3,6-H of Ph, 2 H); IR (neat) 1580, 1445, 1300, 1160, 998, 802, 760 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 82.86; H, 6.37; N, 10.54.

1,2-Bis[6-(carbomethoxy)-2-pyridyl]benzene (14). An aqueous solution (1 L) of **12** (4.89 g, 18.8 mmol) and potassium permanganate (3.3 g, 21 mmol) was vigorously stirred at 80 °C under nitrogen for 6 h. Additional potassium permanganate (3.3 g, 21 mmol) was added three times over 18 h. The hot solution was filtered through Celite, cooled, and extracted with ether, removing unchanged starting material (1 g, 21%).

The aqueous layer was evaporated to dryness. The residue was suspended in anhydrous methanol (50 mL), saturated with HCl gas, and refluxed for 18 h. After the solvent had been concentrated in vacuo, the residue was suspended in dilute sodium carbonate and extracted with cloroform. The combined chloroform extract was dried over magnesium sulfate and concentrated in vacuo to afford an oil, which was chromatographed (thick layer), eluting once with ethyl acetate–cyclohexane (1:3) to give a trace of **12** (20 mg), 1-[6-(carbomethoxy)-2-pyridyl]-2-(6-methyl-2-pyridyl)-benzene [**15**; 1.52 g (26%); NMR δ 2.47 (s, 6-CH_3 pyr, 3 H), 3.93 (s, 6-CO_2CH_3 pyr, 3 H), 7.0–8.3 (C_{arom} H, m, 10 H)], and 1,2-bis[6-(carbomethoxy)pyridyl]benzene[**14**; 2.68 g (42%); mp 128–129 °C (ethyl acetate–cyclohexane); NMR δ 3.91 (s, 6-CO_2CH_3 pyr, 6 H), 7.0–8.3 (m, C_{arom} H, 10 H); IR (Nujol) 1700 (C=O, ester), 1580, 1440, 1320, 1280, 1230, 1135, 1115, 988, 834, 783, 770, 755 cm^{-1}].

Anal. Calcd for $C_{20}H_{16}N_2O_4$ (diester): C, 68.95; H, 4.63; N, 8.04. Found: C, 68.67; H, 4.62; N, 8.04.

Anal. Calcd for $C_{19}H_{16}N_2O_2$ (monoester): C, 74.94; H, 5.31; N, 9.21. Found: C, 75.01; H, 5.26; N, 9.21.

The amount of recovered starting material and the varied percentage of esters were directly related to the oxidant and general reaction conditions. With a large excess of oxidant, further oxidation of **12** occurred, affording, after esterification, methyl 2-[6-(carbomethoxy)-2-pyridyl]benzoate (**16**): mp 90–91 °C; NMR δ 3.70 (s, $C_6H_4CO_2CH_3$, 3 H), 3.96 (s, $C_5H_3NCO_2CH_3$, 3 H), 7.3–8.2 (m, aryl H, 7 H).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.84; N, 5.17. Found: C, 66.41; H, 4.80; N, 5.28.

1-[6-(2-Hydroxypropyl)-2-pyridyl]-2-(6-methyl-2-pyridyl)benzene (17). The monoester **15** (490 mg, 1.61 mmol) dissolved in anhydrous ether (50 mL) was added dropwise to an excess of methylmagnesium bromide (Foote, 2.8 M, THF–benzene) at 0 °C under nitrogen. The mixture was stirred for 30 min at 30 °C, cooled, and quenched with a cold saturated ammonium chloride solution. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo, affording a pale yellow oil which was chromatographed (thick layer), eluting with cyclohexane–ethyl acetate (7:3) to afford **17** as a low-melting solid: mp 69–70 °C; 360 mg (74%); NMR δ 1.35 (s, CMe_2OH, 6 H), 2.40 (s, pyr CH_3, 3 H), 6.4–6.8 (br OH, 1 H, exchanged with D_2O), 6.8–7.7 (m, C_{arom} H, 10 H); IR (KBr) 3300 (OH), 1580, 1320, 1285, 1135, 770, 750 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.90; H, 6.63; N, 9.21. Found: C, 78.85; H, 6.59; N, 9.28.

1,2-Bis[6-(hydroxymethyl)-2-pyridyl]benzene (18). A methanol solution of **14** (921 mg, 2.64 mmol) was treated with excess sodium borohydride (568 mg, 15.0 mmol) added in small portions over 30 min. The reaction was then refluxed overnight and cooled, and acetone (5 mL) was added. The volatiles were removed in vacuo and the residue refluxed with a 10% sodium carbonate solution for 2 h under nitrogen. After concentration to dryness, the residue was continuously extracted with hot methylene chloride. Filtration of the combined *hot* extract through Celite gave, upon concentration, 898 mg of crude diol **18**, mp 179–184 °C. Recrystallization from ethanol gave 200 mg (26%) of the beige crystalline diol: mp 198–199.5 °C; NMR (Me_2SO-d_6) δ 4.44 (s, pyr CH_2, 4 H), 5.28 (br s, OH, 2 H), 6.75–7.80 (m, C_{arom} H, 10 H); IR (Nujol) 3270 (br, OH), 1575, 1560, 1295, 1160, 1050, 813, 772, 776 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.12; H, 5.59; N, 9.41.

1,2-Bis[6-(hydroxymethyl)-2-pyridyl]-1,2-dibromoethane (21) was prepared by the bromination of **20**[10] by the above procedure: 77% yield; mp 185–190 °C.

Attempted Preparation of Bis[6-(hydroxymethyl)-2-pyridyl]acetylene (22). To a vigorously stirred, refluxing solution of potassium hydroxide in methanol was added **21** in ca. 50-mg quantities, and the mixture was then refluxed for 30 min. The mixture was concentrated in vacuo to give an off-white solid residue, which was slurried in ice–water, filtered, and recrystallized from ethyl acetate to give 59–72% of pure starting olefin **20**, mp 139–140 °C. No acetylenic proudcts were isolated from this reaction sequence.

1,2-Bis[6-(bromomethyl)-2-pyridyl]benzene (23). A stirred benzene (100 mL) solution of **12** (2.8 g, 10.7 mmol) and azobisisobutyronitrile (50 mg) was treated with *N*-bromosuccinimide (4.6 g, 26 mmol) and illuminated with a 150-W lamp. After the mixture was refluxed for 12 h, the red suspension was extracted with a 10% aqueous solution of sodium carbonate (100 mL) and water (100 mL) and then concentrated in vacuo to afford a red oily residue (5.21 g), which was column chromatographed (silica gel), eluting with ethyl acetate to afford a mixture, 3.81 g. Rechromatography (thick layer) of this mixture, eluting with ethyl acetate–cyclohexane (1:4), afforded two major fractions.

Fraction A gave 1-[6-(bromomethyl)-2-pyridyl]-2-[6-(dibromomethyl)-2-pyridyl]benzene (**24**) as a semisolid: 243 mg; NMR ($CDCl_3$) δ 4.39 (s, CH_2Br, 2 H), 6.48 (s, $CHBr_2$, 1 H), 7.05–7.80 (m, arom H, 10 H); mass spectrum (70 eV), *m/e* (relative intensity) 497 (M^+, 4.4), 417 ($M^+ - 80$, 70.6), 257 ($M^+ - 240$, 30.2), 217 ($M^+ - 280$, 100), 191 (26).

Fraction B afforded 1,2-bis[6-(bromomethyl)-2-pyridyl]-benzene (**23**) as a sensitive semisolid: 297 mg (7%); NMR δ 4.39 (s, CH_2Br, 4 H), 6.95–7.80 (m, arom H, 10 H); mass spectrum (70 eV), *m/e* (relative intensity) 418 (M^+, 12), 339 ($M^+ - 79$, 98), 337 ($M^+ - 81$, 89), 218 ($M^+ - 200$, 100), 191 (23).

Preparation of Cyclophane 25. An ethanol (25 mL) solution of **23** (300 mg, 0.72 mmol) and an ethanol (25 mL) solution of sodium sulfide nanohydrate (173 mg, 0.72 mmol) were each added at an equimolar rate to a refluxing ethanol solution under nitrogen. After 22 h, the solution was concentrated in vacuo to afford a red solid residue, which was slurried in dichloromethane (20 mL) and filtered. The filtrate was concentrated to afford 233 mg of product which was chromatographed (thick layer), eluting three times with ethyl acetate–cyclohexane (1:4), to give two major fractions.

Fraction A gave the pyridinophane **25** as a colorless solid: 17 mg (8%); mp 162–166 °C dec; NMR δ 3.83 (s, CH_2S, 4 H), 7.03 (d, 5-H of pyr, J = 7 Hz, 2 H), 7.45–7.75 (m, arom H, 10 H); mass spectrum (70 eV), *m/e* (relative intensity) 290 (M^+, 23), 258 ($M^+ - 32$, 33), 257 ($M^+ - 33$, 100), 243 ($M^+ - 47$, 9), 242 ($M^+ - 48$, 12), 228 ($M^+ - 62$, 14), 217 (13.5), 204 (24), 182 (17), 149 (9), 128 (11).

Anal. Calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4,86; N, 9.65. Found: C, 74.18; H, 4.62; N, 9.61.

Fraction B afforded 1,2-bis[6-(mercaptomethyl)-2-pyridyl]-benzene (**26**) as an air-sensitive solid: 18 mg (8%), mp 171–181 °C dec; NMR δ 2.25 (br s, exchanged with D_2O, SH, 2 H), 7.17 (d, 3-H of pyr, J = 2.0 Hz, 2 H), 7.40–7.85 (m, arom H, 6 H); mass spectrum (70 eV), *m/e* (relative intensity) 324 (M^+, 5.3), 322 ($M^+ - 2$, 38), 257 ($M^+ - 67$, 100), 243 ($M^+ - 81$, 12), 229 ($M^+ - 95$,19), 204 ($M^+ - 120$, 25), 191 (10), 128 (15).

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Registry No. **3**, 74844-02-3; **5**, 35286-92-1; **6** (X = Y = CH), 74844-03-4; **6** (X = N; Y = CH), 74844-04-5; **7** (X = Y = CH), 74844-05-6; **8**, 74844-06-7; **9**, 42296-34-4; **10**, 2765-16-4; **11**, 74844-07-8; **12**, 74844-08-9; **13**, 73818-74-3; **14**, 74844-09-0; **15**, 74844-10-3; **16**, 74844-11-4; **17**, 74844-12-5; **18**, 74844-13-6; **20**, 74844-14-7; **21**, 74844-15-8; **23**, 74844-16-9; **24**, 74868-62-5; **25**, 74844-17-0; **26**, 74844-18-1; **30**, 74764-52-6; **31**, 74844-94-3; (3-methylphenyl)-methylenetriethoxyphosphorane, 74844-19-2; 3-methylbenzaldehyde, 620-23-5; α-pyrone, 504-31-4; lutidine, 27175-64-0; bis(2-pyridyl)-acetylene, 28790-65-0; cobalt chloride, 7646-79-9.

A One-Step Conversion of Cholest-4-en-3-one to 24-Hydroxychol-4-en-3-one

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Cholest-4-en-3-one has been converted in one step to 24-hydroxychol-4-en-3-one in 17% yield of crystalline material. The elimination of carbons 25–27 and the introduction of the primary alcohol group at C-24 are accomplished with CF_3CO_3H–H_2SO_4 at 0 °C.

The purpose of the present program is to selectively oxidize the saturated side chain of cholesterol, sitosterol, and campesterol. This would provide routes to steroids with modified side chains as well as routes to steroids of pharmaceutical value similar to the routes starting with deoxycholic acid, diosgenin, and stigmasterol.[1] The first success was the conversion of cholesterol to chol-5-ene-3β,24-diol in 14% yield in essentially three steps.[2] A further improvement is now reported.

It would be desirable to eliminate protecting groups, and it has now been found possible to do this with cholestenone (cholest-4-en-3-one). The method depends on suppressing the reactivity of enone systems toward CF_3CO_3H by adding H_2SO_4. Model studies showed that CF_3CO_3H–H_2SO_4 oxidized isooctane faster than isophorone (3,5,5-trimethylcyclohex-2-en-1-one). However, 3-methylcyclohex-2-en-1-one and mesityl oxide (4-methylpent-3-en-2-one) reacted faster than isooctane despite the suppressing effect of the H_2SO_4. All three ketones reacted faster than isooctane in the absence of H_2SO_4. The H_2SO_4 is believed to act by a combination of protonation of the enone and hydrogen bonding of H_3O^+ to the enone. Both effects reduce the reactivity of the enone toward the electrophilic CF_3CO_3H. The oxidations with CF_3CO_3H exhibit acid catalysis, but it is not known how this affects relative rates.

The conversion shown in the following equation was accomplished in 20–25% yields as determined by GC (gas chromatography) analysis and in 17% yield as measured by the amount of pure crystalline material. This conversion is the most effective yet reported for selectively oxidizing the saturated side chain, and it achieves this without the use of protecting groups.

The side products are more polar than I. Hexane extracts of the diluted reaction mixture contained 0.5 g of material from 1.0 g of cholestenone and included all of I. Further extraction with diethyl ether gave an additional 0.2–0.3 g of material which was shown by NMR to contain

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