pension of prereduced platinum oxide under hydrogen gas at 1 atm pressure is injected the magenta-colored photoproduct (430 mg) dissolved in methylene chloride (50 mL). The hydrogen uptake at room temperature ceases after approximately 2 h with 2.0 equiv of gas being consumed. The catalyst was separated and the filtrate was washed repeatedly (3×) with sodium bicarbonate solution. The organic layer was separated, dried ($K_2CO_3$), and evaporated under vacuum. The residue was recrystallized from pentane yielding 280 mg (85%) of 8 as a slightly yellow crystalline solid: mp 145–146 °C; IR (KBr) 3400, 3000, 2850, 1600, 1490, 1440, 1320, 1080, 760, 735, 720, 690 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.3 (m, 5 H), 7.2–6.4 (m, 4 H), 5.8 (s, 1 H), 3.4 (m, 2 H), 2.5–1.4 (m, 15 H); MS 333 ($M^+$) (very weak), 332 ($M^+ - 1$) (very strong).

Anal. Calcd for $C_{23}H_{27}NO$: C, 82.8; H, 8.2; N, 4.2. Found: C, 82.6; H, 8.0; N, 4.1. Stirring a solution of the above yellow compound in 2 N hydrochloric acid at 60 °C for 48 h gave only recovered starting material with no indication of hydrolysis.

**Registry No.**—**4b**, 63609-66-5; **5**, 63609-67-6; **8**, 63609-68-7; 3-methyl-2,1-benzisoxazole, 4127-53-1; *tert*-butyl alcohol, 75-65-0; 3-phenyl-2,1-benzisoxazole, 5176-14-7; 2,1-benzisoxazole, 271-58-9.

## References and Notes


(1) P. Claus et al., *Pure Appl. Chem.*, **33**, 339 (1973).
(2) The apparent rate difference was due to the wavelength of the longest absorption band of the salt which was found to be responsible for the photochemistry discussed. Larger groups at the N or 3 positions in **1** increased the wavelength according to the following order: phenyl > methyl > hydrogen and adamantyl > *tert*-butyl > methyl.
(3) The addition of more basic salts such as NaCN, $NaN_3$, or NaOAc results in a dark addition reaction yielding 3-substituted 2,1-benzisoxazolines.[4]
(4) R. A. Olofson, R. K. VanderMeer, and S. Stournas, *J. Am. Chem. Soc.*, **93**, 1543 (1971).
(5) Minor amounts of ortho substitution also occur (see Table II).
(6) Th. Doppler, H. J. Hanson, and H. Schmid, *Helv. Chim. Acta*, **55**, 1730 (1972).
(7) R. C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forsch.*, **18**, 1 (1971).
(8) (a) P. v. R. Schleyer, E. Funke, and S. Liggero, *J. Am. Chem. Soc.*, **91**, 3965 (1969); (b) *ibid.*, **95**, 8207 (1973).
(9) The same reduction product was obtained using $NaBH_4$, indicating C–O or C–N bond hydrogenolysis was not occurring. Also, the $^{13}C$ NMR spectrum of **4** shows two resonances at low field, one at 211.6 (N=$C^+$) and 198.4 (C=O) ppm from $Me_4Si$. **1h**, a model for **4c**, does not exhibit any resonance below 170 ppm.
(10) If the arylazonium ion **3** is indeed a viable intermediate, then the solvolysis of *N*-chloro-*N*-phenyl-1-adamantanamine should give the 4-*N*-phenyl-3-azahomoadamantene. This route is being pursued. For analogous system, see ref 13.
(11) R. K. VanderMeer, Ph.D. Thesis, Pennsylvania State University, State College, Pa., 1972.
(12) All melting points are uncorrected. IR spectra were obtained with a Perkin-Elmer 137 spectrophotometer and NMR spectra with a Varian T-60 spectrometer using $Me_4Si$ as internal standard. UV spectra were taken with a Cary 17 spectrophotometer.
(13) P. Kovacic, J. Liu, E. Levi, and P. Roskos, *J. Am. Chem. Soc.*, **93**, 5801 (1971).
(14) For other reports on the synthesis of 3-homoadamantene, see: B. L. Adams and P. Kovacic, *J. Am. Chem. Soc.*, **97**, 2829 (1975); H. Kwart and J. Slutsky, *J. Org. Chem.*, **41**, 1429 (1976).


# A Reinvestigation of the Synthesis of *cis*-1,2,3,4,4a,10a-Hexahydro[1,4]benzodioxino[2,3-*c*]pyridine and a Synthesis of *meso*-2,3,4,5,5a,11a-Hexahydro-1*H*-[1,4]benzodioxino[2,3-*d*]azepine


Neville Finch,* Louis Blanchard, and L. H. Werner

*Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901*


*Received April 25, 1977*

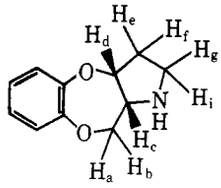

A reinvestigation of the reaction of 1-benzyl-3,4-dibromopiperidine (**2**) with the disodium salt of catechol (**1**) was made. *cis*-2-Benzyl-1,2,3,4,4a,10a-hexahydro[1,4]benzodioxino[2,3-*c*]pyridine (**5**), previously described by Coulson[2] and Berthold,[3] was formed along with a slightly greater amount of the undescribed *cis*-1-benzyl-1,2,3,3a,10,10a-hexahydro[1,5]benzodioxepino[3,2-*b*]pyrrole (**4**). A rationale in accord with previous observations on substitution reactions of 3-substituted piperidines[4] is provided for the stereospecific but not regiospecific outcome. Reaction of the disodium salt of catechol (**1**) with *cis*-hexahydro-1-methylsulfonyl-4,5-bis(methylsulfonyloxy)azepine (**12**) and removal of the *N*-methylsulfonyl group from the product **13** provided access to the previously undescribed *meso*-2,3,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (**14**). The cis configuration of the ring junction in **14** was proven by conversion to the *d*-camphorsulfonamide **15** and demonstration that on removal of the *d*-camphorsulfonyl group the original meso compound **14** was regenerated, rather than an enantiomer.


In our search for novel drugs, we have been investigating tricyclic systems which incorporate the 2-substituted 1,4-benzodioxan moiety.[1] One system of this type had previously been reported, i.e., the 1,2,3,4,4a,10a-hexahydro[1,4]benzodioxino[2,3-*c*]pyridine (**7**).[2] This synthesis of compound **7** had been subsequently repeated by another group.[3] Nevertheless, as the formation of a single product from the reaction of 1-benzyl-3,4-dibromopiperidine and the disodium salt of catechol seemed surprising, we investigated the reaction product more closely. The distillate described by Coulson[2] behaved as a single compound under a variety of GLC conditions, yet the yield, which was described by neither of the previous workers,[2,3] of crystalline *N*-benzylbenzodioxinopyridine hydrochloride **5** was in our hands too low for this distillate to be really homogeneous.

We next examined the distillate obtained following catalytic debenzylation of the initial product. Coulson[2] reported a 92% yield of the benzodioxinopyridine **7** hydrochloride from this distillate, but did not provide a yield for the conversion of this hydrochloride to the free base **7**. Berthold,[3] who undoubtedly had prepared a pure sample of the benzodioxinopyridine **7**, based on TLC and NMR evidence, provided a yield for neither process. Examination by GLC, after silylation, of the distillate obtained from our debenzylation experiment now clearly showed that this was a 56:44 mixture, with the benzodioxinopyridine **7** being the minor product.

The main product proved to be isomeric with the benzodioxinopyridine **7** and from NMR data it was determined to be *cis*-1,2,3,3a,10,10a-hexahydro[1,5]benzodioxepino[3,2-*b*]pyrrole (**6**). The cis stereochemistry of the ring junction was assigned from the magnitude and the solvent dependency of the coupling constant of the ring-junction protons, which suggested different mixtures of rapidly inconverting conformations (see Table I). Such conformational mobility is better

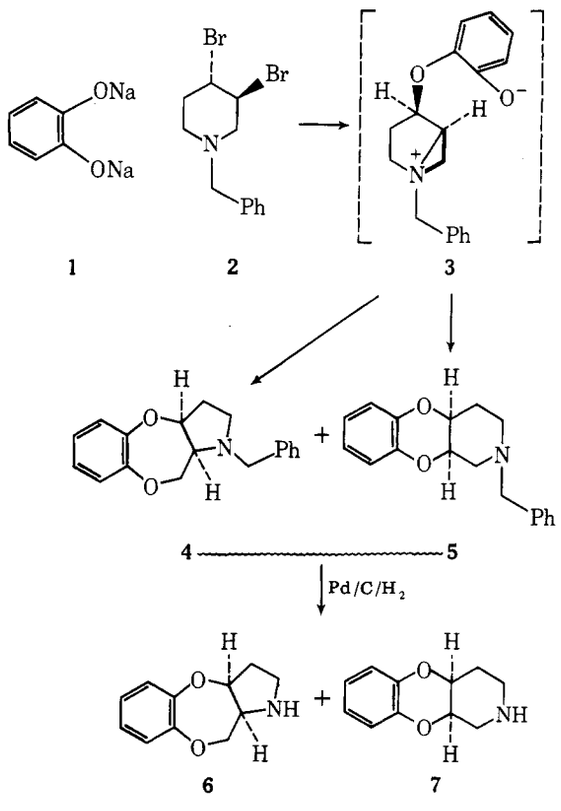
**Table I**



| In $CDCl_3$ | $H_a$ | $H_b$ | $H_c$ | $H_d$ | $H_e$ | $H_f$ | $H_g$ | $H_i$ |
|---|---|---|---|---|---|---|---|---|
| Chemical shift $\delta$ | 4.24 | 4.22 | 3.43 | 4.61 | 2.01 | 2.01 | 2.88 | 3.19 |
| Appearance | d | d | d of d of d | q | t of d | t of d | d of t | d of t |
| Coupling constants | $J_{ac}$ = 8.4 Hz | $J_{bc}$ = 6.2 Hz | $J_{ca}$ = 8.4 Hz<br>$J_{cb}$ = 6.2 Hz<br>$J_{cd}$ = 4 Hz | $J_{de} \simeq J_{df} \simeq J_{dc} \simeq$ 4 Hz | $J_{eg} \simeq J_{ei} \simeq J_{fg} \simeq J_{fi} \simeq$ 6.5 Hz<br>$J_{ed} \simeq J_{fd} \simeq$ 4.0 Hz | | $J_{gi} \simeq$ 11 Hz<br>$J_{ge} \simeq J_{gf} \simeq$ 6.5 Hz | $J_{ig} \simeq$ 11 Hz<br>$J_{if} \simeq J_{ie} =$ 6.5 Hz |
| In $C_6D_6$ | | | | | | | | |
| Chemical shift $\delta$ | 4.31 | 3.99 | 3.14 | 4.43 | 1.52 | 1.89 | 2.49 | 2.95 |
| Appearance | d of d | d of d | d of d of d | d of d of d | d of t of d | d of d of d of d | d of d of d | d of t |
| Coupling constants | $J_{ab}$ = 11.5 Hz<br>$J_{ac}$ = 10 Hz | $J_{ba}$ = 11.5 Hz<br>$J_{bc}$ = 5.8 Hz | $J_{ca}$ = 10 Hz<br>$J_{cb}$ = 5.8 Hz<br>$J_{cd}$ = 5.1 Hz | $J_{de}$ = 5.8 Hz<br>$J_{dc}$ = 5.1 Hz<br>$J_{df}$ = 2.2 Hz | $J_{ef}$ = 13.4 Hz<br>$J_{ed}$ = 5.8 Hz<br>$J_{ei} \simeq J_{eg} \simeq$ 8 Hz | $J_{fe}$ = 13.4 Hz<br>$J_{fi}$ = 8 Hz<br>$J_{fg}$ = 5 Hz<br>$J_{fd}$ = 2.2 Hz | $J_{gi}$ = 11 Hz<br>$J_{ge}$ = 8 Hz<br>$J_{gf}$ = 5 Hz | $J_{ig}$ = 11 Hz<br>$J_{ie} \simeq J_{if} \simeq$ 8 Hz |

accommodated by a cis ring junction. Furthermore, if one assumes trans addition of bromine to the precursor *N*-benzyltetrahydropyridine to give *trans*-1-benzyl-3,4-dibromopiperidine (**2**), then an intermediate aziridinium ion **3** would be obtained from the reaction with catechol disodium salt **1**. This, in turn, leads to both the *cis*-benzodioxinopyridine **7** as well as the *cis*-benzodioxepinopyrrole **6**. We therefore conclude that previous reports[2,3] suggesting that a single product **5** is obtained from the reaction of *trans*-3,4-dibromopiperidine **2** and the disodium salt of catechol (**1**) are in error. Approximately equal amounts of the previously described *cis*-benzodioxinopyridine **5** and the undescribed *cis*-benzodioxepinopyrrole **4** are formed. Thus, the substitutions are stereospecific but not regiospecific, in accord with related work on 3-substituted piperidines by Hammer[4] (Scheme I).

Scheme I

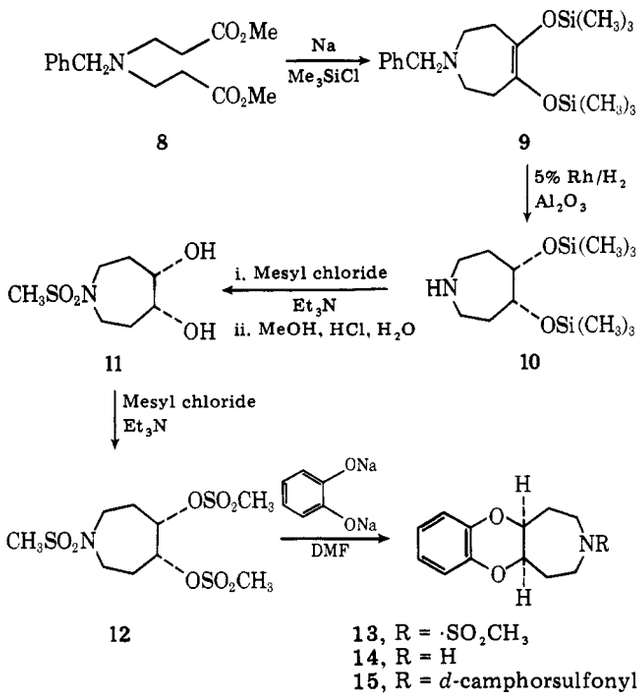


We redirected our efforts at a benzodioxanyl system which, by virtue of symmetry, would not be beset with problems of regiospecificity at the substitution step, and yet by choice of the appropriate synthetic route would still permit control of the stereochemistry. The obvious choice was the previously undescribed 2,3,4,5,5a,11a-hexahydro[1,4]benzodioxino-[2,3-*d*]azepine (**14**). An appropriate starting material was readily available via the acyloin reaction of methyl 3-[*N*-benzyl-*N*-(2-carbomethoxyethyl)amino]propionate (**8**) under silylating conditions.[5,6]

Catalytic reduction of the disilyl enol ether **9** yielded the dihydro disilyl ether **10**. Reaction of this disilyl ether **10** in methylene chloride with mesyl chloride and triethylamine, followed by an acid workup, provided *cis*-hexahydro-4,5-dihydroxy-1-methylsulfonylazepine (**11**) in approximately 70% overall yield from the acyloin product **9**.

Attempts to improve the overall yield of this process concentrated on the catalytic hydrogenation step. GC/MS analysis of the product mixture provided an excellent insight into the nature of the side reactions (see Table II). The major side reaction was reduction of the aromatic ring of the benzyl group rather than its hydrogenolysis. Other side reactions were debenzylation without reduction of the enol ether and solvolysis of this product. Several catalysts and solvents were investigated, but none could surpass the almost 80% overall yield for the two processes of debenzylation and enol ether reduction achieved by excess 5% rhodium on alumina in ethyl acetate.

Scheme II




The large proportion of catalyst is essential to achieve this yield but the catalyst can be reactivated and reused.

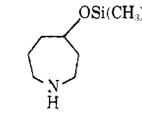
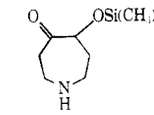
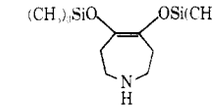
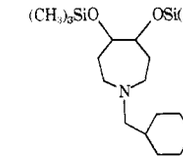
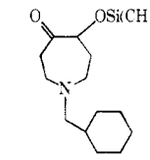
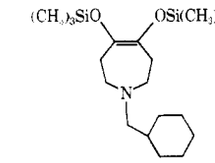
The dihydroxy-*N*-methylsulfonylazepine (**11**) was a single stereoisomer and this was initially assigned as cis based on the synthesis. The trimesyl derivative **12** was formed by reaction in methylene chloride with mesyl chloride and triethylamine. We were unable to find conditions to proceed in one step from the hydrogenated bis(silyl ether) **10** to the trimesyl derivative **12** in good yield. The two-step procedure proved, in our hands, to be the better process. Reaction of the trimesyl derivative **12** with the disodium salt of catechol (**1**) in dimethylformamide gave a 70% yield of the crystalline *meso*-1,2,4,5,5a,11a-hexahydro-3-methylsulfonyl[1,4]benzodioxino[2,3-*d*]azepine (**13**). Removal of the *N*-methylsulfonyl group by treatment overnight with Red-al in benzene yielded the parent *meso*-2,3,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (**14**).

Assuming that the diol **11**, from which this compound **14** was derived, was cis, one could assign the cis stereochemistry to the B/C ring fusion of hexahydroazepinobenzodioxin **14** because it was presumably derived by $S_N2$ processes. Nevertheless, we chose to confirm the assignment by conversion of **14** to the *N*-*d*-camphorsulfonamide **15**. This compound **15** was recrystallized to constant melting point and rotation. A CD curve was obtained on this material and a Cotton effect was observed at 290 nm. Removal of the *N*-*d*-camphorsulfonyl group by Red-al in refluxing benzene yielded an optically inactive material **14**, identical in all respects with the hexahydrobenzodioxinoazepine **14**, from which we had started. Therefore, the hexahydrobenzodioxinoazepine **14** is a meso compound and hence rings B and C are cis fused.

## Experimental Section[7]

***cis*-2-Benzyl-1,2,3,4,4a,10a-hexahydro[1,4]benzodioxino-[2,3-*c*]pyridine (5) and *cis*-1-Benzyl-1,2,3,3a,10,10a-hexahydro-[1,5]benzodioxepino[3,2-*b*]pyrrole (4).** 1-Benzyl-3,4-dibromopiperidine hydrobromide[2] (128 g, 0.31 mol) was treated with $K_2CO_3$ (75 g, 0.54 mol) as a solution in water (200 mL). The mixture was extracted with ether. The ethereal extract was dried ($Na_2SO_4$) and concentrated to dryness in vacuo. The residue **2** (102.4 g, 0.31 mol) was dissolved in DMF (150 mL) and added dropwise during 30 min to a slurry of catechol disodium salt (**1**) obtained by adding sodium methoxide (33.5 g, 0.62 mol) to a solution of catechol (34.2 g, 0.31 mol) in DMF (600 mL) under $N_2$, heating for 15 min to 100 °C, and then cooling to room temperature. Upon completion of the addition, the reaction mixture, under $N_2$, was heated at 145–150 °C for 12 h and allowed to stand at room temperature for a further 6 h. The DMF was removed in vacuo. The residue was partitioned between water and benzene. The benzene extracts were washed (water, 1 N NaOH, water), dried ($Na_2SO_4$), and concentrated to dryness in vacuo. The residue was distilled. A forerun (bp 92–183 °C/0.2 mm, 6.0 g) was discarded. The main fraction (bp 184–188 °C/0.2 mm, 31.97 g, 0.114 mol, 37%) consisted to the extent of 80% of an inseparable mixture of compounds **4** and **5**. (GLC retention time 28.1 min on a Supelco 80/100 support with a 12% UCW 98 coating at 180 to 300 °C on a 35 °C/min program.)

Table II

| Retention time, min | % of total | Mol ion *m/e* | Proposed structure from fragmentation |
|---|---|---|---|
| 1.8 | 2.0 | 187 |  **10** |
| 4.5 | 77.8 | 275 | |
| 5.2 | 2.5 | 201 |  |
| 6.8 | 5.9 | 273 |  |
| 14.3 | 0.7 | 371 |  |
| 14.6 | 5.0 | 297 |  |
| 14.8 | 5.0 | 369 |  |

***cis*-1,2,3,4,4a,10a-Hexahydro[1,4]benzodioxino[2,3-*c*]pyridine (7) and *cis*-1,2,3,3a,10,10a-Hexahydro[1,5]benzodioxepino[3,2-*b*]pyrrole (6).** The mixture of compounds **4** and **5** (31.9 g, 0.114 mol) was dissolved in glacial acetic acid (125 mL) and hydrogenated in a Parr apparatus over 10% Pd/C (3.3 g) for 6 h (45 to 35 psi). The catalyst was removed and the filtrate concentrated in vacuo. The residue was partitioned between water and $CH_2Cl_2$. The aqueous phase was made basic (6 N NaOH). The $CH_2Cl_2$ extracts were washed (saturated NaCl solution) and dried ($Na_2SO_4$), and the $CH_2Cl_2$ was removed in vacuo. The residue was distilled. A forerun (0.76 g, bp 105–108 °C/0.2 mm) and a main fraction (bp 109–114 °C/0.2 mm, 11.74 g, 0.061 mol, 53%) were collected and they partially crystallized on cooling. The main fraction consisted of 56% of compound **6** (11.4 min) and 44% of compound **7** (11.9 min) (GLC; silylation by 10% Regisil and run on a Supelco 80/100 support with a 2% OV-25 coating at 140 °C). The forerun and main fraction were dissolved in hot hexane (50 mL). On cooling, the hexahydrobenzodioxinopyridine **7** separated as a crystalline solid, 4.82 g, mp 96–98 °C (lit.[2] 99–101 °C, lit.[3] 96–97 °C). An analytical sample had: mp 98–99 °C; NMR $\delta$ 6.88 (s, 4), 4.24 (m, 2); IR (Nujol) 1584 (m), 1484 (s), 1130 (m), 1044 (m), 846 (m), 770 (s), 732 (s) $cm^{-1}$; TLC ($CHCl_3/HCO_2H$ 9:1 on alumina) $R_f$ 0.45; GLC (silylated by 10% Regisil) 11.9 min on a Supelco 80/100 support with a 2% OV-20 coating at 140 °C.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.13; H, 7.12; N, 7.14.

A portion of the crystalline solid was converted to the hydrochloride salt, which was recrystallized from 2-propanol/ether to give the crude hydrochloride of the hexahydrobenzodioxinopyridine **7**, mp 213–214 °C (lit.[2] 216–220 °C, lit.[3] 206–209 °C); recrystallization from 2-propanol gave the analytical sample, mp 234–235 °C.

Anal. Calcd for $C_{11}H_{13}NO_2$·HCl: C, 58.02; H, 6.20; N, 6.15. Found: C, 57.97; H, 6.25; N, 6.50.

The hexane mother liquors from crystallization of the hexahydrobenzodioxinopyridine **7** were concentrated in vacuo. The residue (6.88 g) was dissolved in 2-propanol and treated with dry HCl in ethyl acetate. The crude hydrochloride of the hexahydrobenzodioxepinopyrrole **6** (5.13 g), mp 194–202 °C, could not be purified by recrystallization based on TLC evidence ($CHCl_3/HCO_2H$ 9:1 on alumina, $R_f$ of **6** 0.60; $R_f$ of **7** 0.45). Therefore, a portion (3.1 g) of the crude hydrochloride **6** was chromatographed on thick-layer plates (silica gel GF) eluted by $CHCl_3$/MeOH, 9:1. A center cut (1.0 g; $R_f$ 0.60) was reconverted to the hydrochloride **6** (0.94 g), mp 203–205 °C. Recrystallization from 2-propanol, with light charcoaling, gave the analytically pure hydrochloride of **6** (0.61 g): mp 207–208 °C; NMR ($Me_2SO$) $\delta$ 7.02 (s, 4), 4.86 (q, 1), 4.58 (m, 2), 4.12 (sextet, 1); IR (Nujol) 1580 (m), 1488 (s), 1248 (s), 766 (s) $cm^{-1}$.

Anal. Calcd for $C_{11}H_{13}NO_2$·HCl: C, 58.02; H, 6.20; N, 6.15. Found: C, 58.13; H, 6.20; N, 5.81.

A portion of the hydrochloride (0.3 g) was dissolved in water, made basic (2 N NaOH), and extracted ($CH_2Cl_2$). The extracts were dried ($Na_2SO_4$) and the methylene chloride was removed. The residue (0.25 g) yielded the crystalline hexahydrobenzodioxepinopyrrole **6**: mp 45–47 °C; NMR[8] see Table I; IR (melt) 1572 (m), 1480 (s), 1286 (s), 1242 (s), 1032 (m), 744 (s) $cm^{-1}$.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.82; H, 6.59; N, 7.16.

**1-Benzyl-2,3,6,7-tetrahydro-4,5-bis(trimethylsilyloxy)azepine (9).** Sodium (68.5 g, 2.97 mol) was powdered under toluene. Chlorotrimethylsilane (355 g, 3.27 mol) was added to the well-stirred sodium sand under $N_2$ in toluene. To this mixture was added 10–20% of a solution of methyl 3-[*N*-benzyl-*N*-(2-carbomethoxyethyl)amino]-propionate[9] (**8**) (201 g, 0.74 mol) in toluene (200 mL). With stirring, the reaction was initiated by gentle heating. Upon initiation, heating was discontinued and the reaction was controlled by ice-bath cooling. Reflux was maintained by addition of the remaining diester **8** during ca. 45 min. Heating was applied upon completion of addition, and the mixture was refluxed for a further 1.5 h. The mixture was cooled and passed through Filtercel. The filtrate was washed (aqueous $NaHCO_3$) and dried ($Na_2SO_4$), and the toluene was removed in vacuo. The residue was distilled over a little $CaCO_3$. A forerun (3.8 g) was discarded. The bulk of the material was mainly 1-benzyl-2,3,6,7-tetrahydro-4,5-bis(trimethylsilyloxy)azepine **9** (bp 144–160 °C/0.1–0.4 mm, 208.6 g, 0.574 mol, 77%); MS *m/e* 363 ($M^+$), 348 ($M - CH_3$), 274 [$M - OSi(CH_3)_3$]. A portion was redistilled. The main fraction, bp 151–153 °C/0.2 mm, was the pure *N*-benzylbis(silyloxy)azepine **9**: NMR $\delta$ 7.30 (s, 5), 3.56 (s, 2), 2.62 (m, 2), 2.32 (m, 2); IR (film) 1684 (w), 1246 (s), 1200 (s), 1094 (m), 890 (s), 836 (s), 726 (m), 694 (m) $cm^{-1}$; GLC on Chrom WHP 60/80 with a 5% DC-550 coating at 200 °C, 96%, 6.3 min.

Anal. Calcd for $C_{19}H_{33}NO_2Si_2$: C, 62.75; H, 9.15; N, 3.83. Found: C, 63.19; H, 9.39; N, 4.34.

This silylated acyloin **9** has a limited shelf life and is best reduced immediately following distillation.

***cis*-Hexahydro-4,5-bis(trimethylsilyoxy)-1*H*-azepine (10).** The *N*-benzylbis(silyloxy)azepine **9** (100 g, 0.275 mol) was dissolved in ethyl acetate (500 mL) and hydrogenated over 5% rhodium on alumina (40 g) in the presence of $CaCO_3$ (5 g) at 50 psi and 50–55 °C in a Parr apparatus. The hydrogenation was stopped after uptake of two times theory ($\Delta p$ 92 psi). The solids were removed by filtration and the ethyl acetate in vacuo. The residue (74.3 g) was distilled over $CaCO_3$. The major fraction was mainly *cis*-hexahydro-4,5-bis(trimethylsilyloxy)-1*H*-azepine (**10**), bp 107–118 °C/C 2 mm (60.1 g, 0.218 mol, 79%): NMR $\delta$ 3.90 (t, 2), 2.84 (q, 4), 1.76 (m, 4), 1.56 (s, exchangeable, 1); IR (film) 2930 (m), 1254 (s), 1108 (s), 1060 (s), 1008 (m), 834 (s), 748 (m) $cm^{-1}$; GLC on Supelco 80/100 with a 10% Sp 2250 coating at 150 to 300 °C programmed at 35 °C/min, 79%, 5.0 min. The nature of the other 21% of material was investigated by GC/MS on an LKB 9000 instrument, using a glass column with a 3% OV-17 coating temperature programmed from 50 to 250 °C at 8 °C/min.[10]

From the mass spectral fragmentation patterns, all but three peaks representing a total of 1.1% could be identified (Table II).

Further attempts to purify the bis(trimethylsilyloxy)-1*H*-azepine **10** were not rewarding. The mixture was directly mesylated.

***cis*-Hexahydro-4,5-dihydroxy-1-methylsulfonylazepine (11).** The bis(trimethylsilyloxy)-1*H*-azepine (**10**) (75.6 g, 0.275 mol) was dissolved in methylene chloride (600 mL) and cooled in an ice bath. Triethylamine (115 mL, 0.83 mol) was added. Methanesulfonyl chloride (43 mL, 0.55 mol) was added dropwise during 30 min with cooling (ice bath). The mixture was allowed to warm to room temperature after a further 30 min. The reaction was poured onto ice–water. The methylene chloride was separated, washed (water, aqueous $NaHCO_3$), dried ($Na_2SO_4$), and removed in vacuo. The residue was dissolved in methanol (300 mL) and water (5 mL), and concentrated HCl (9 mL) was added to cleave the silyl groups. After 45 min, ether (75 mL) was added and the mixture cooled (ice bath). The *cis*-hexahydro-4,5-dihydroxy-1-methylsulfonylazepine **11** crystallized. It was collected, washed, and dried: mp 170–173 °C (45.1 g, 0.215 mol, 78%); NMR ($Me_2SO$) $\delta$ 4.36 (exchangeable, 2), 3.74 (m, 2), 3.22 (t, 4), 2.82 (s, 3), 2.0–1.5 (m, 4); IR (Nujol) 3360–3280 (s), 1130 (s), 958 (s), 868 (s), 708 (m) $cm^{-1}$; TLC ($CHCl_3/CH_3OH$ 9:1 on silica gel GF) $R_f$ 0.40.

Anal. Calcd for $C_7H_{15}NO_4S$: C, 40.17; H, 7.22; N, 6.69. Found: C, 39.95; H, 7.32; N, 6.18.

***cis*-Hexahydro-1-methylsulfonyl-4,5-bis(methylsulfonyloxy)azepine (12).** The 4,5-dihydroxy-1-methylsulfonylazepine (**11**) (10.5 g, 0.050 mol) was dissolved in $CH_2Cl_2$ (200 mL) containing triethylamine (26 mL, 0.19 mol), and the solution was cooled in an ice bath. Methanesulfonyl chloride (14.3 g, 0.125 mol) was added dropwise with stirring. The ice bath was removed and the mixture stirred overnight at room temperature. It was poured into ice–water. The methylene chloride layer was washed (dilute acid, water), dried ($Na_2SO_4$), and concentrated in vacuo. The residue was dissolved in ethyl acetate (50 mL) and allowed to stand overnight in the ice box. The *cis*-hexahydro-1-methylsulfonyl-4,5-bis(methylsulfonyloxy)-azepine (**12**), mp 137–138 °C (13.4 g, 0.037 mol, 74%), crystallized out: NMR ($Me_2SO$) $\delta$ 5.06 (t, 2), 3.56–3.08 (m + s at 3.26, 10), 2.92 (s, 3), 2.36–1.92 (m, 4); IR (Nujol) 1314 (s), 1178 (s), 1146 (s), 928 (s), 914 (s), 768 (m) $cm^{-1}$; TLC ($CHCl_3/CH_3OH/HCO_2H$ 85:5:10 on silica gel GF) $R_f$ 0.50.

Anal. Calcd for $C_9H_{19}NO_8S_3$: C, 29.58; H, 5.24; N, 3.83. Found: C, 29.83; H, 5.15; N, 3.70.

***meso*-1,2,4,5,5a,11a-Hexahydro-3-methylsulfonyl[1,4]benzodioxino[2,3-*d*]azepine (13).** Catechol (28 g, 0.253 mol) was dissolved in DMF (1.5 L) under $N_2$. To the well-stirred solution was added potassium *tert*-butoxide (57 g, 0.506 mol). The mixture was warmed to 100 °C (oil bath) for 15 min. After cooling to room temperature, the bis(methylsulfonyloxy)azepine **12** (92.2 g, 0.253 mol) was added as a solution in DMF. The mixture was heated at 140 °C for 12 h and allowed to stand at room temperature for 6 h. The DMF was removed in vacuo. The residue was shaken between water/ethyl acetate. The ethyl acetate was washed (cold 1 N NaOH and water), dried ($Na_2SO_4$) and removed in vacuo. The purple residue (78.9 g) was dissolved in ethanol (400 mL) and filtered. On cooling the filtrate, crude *meso*-1,2,4,5,5a,11a-hexahydro-3-methylsulfonyl[1,4]benzodioxino[2,3-*d*]azepine (**13**), mp 139–146 °C (46.8 g, 0.165 mol, 65%), was collected. Recrystallization from ethanol gave an analytical sample: mp 157–9 °C; NMR $\delta$ 6.84 (s, 4), 4.40 (m, 2), 3.86–3.00 (m, 4), 2.80 (s, 3), 2.50–1.60 (m, 4); IR (Nujol) 1594 (m), 1492 (s), 1314 (s), 1260 (s), 1138 (s), 1070 (s), 952 (m), 894 (m), 766 (s), 758 (s) $cm^{-1}$; TLC ($CHCl_3$ on silica gel GF) $R_f$ 0.30.

Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.10; H, 6.05; N, 4.94. Found: C, 55.44; H, 6.19; N, 5.00.

***meso*-2,3,4,5,5a,11a-Hexahydro[1,4]benzodioxino[2,3-*d*]azepine (14).** Crude *N*-methylsulfonyl[1,4]benzodioxinoazepine **13** (37.1 g, 0.131 mol) was dissolved in benzene (200 mL) and added during 15 min to a well-stirred solution of Red-al (Aldrich Chemical Co.) (191 mL of a 70% solution, 0.66 mol) in benzene (250 mL). The mixture was refluxed for 4 h and then allowed to stand overnight at room temperature. The reaction was quenched (350 mL of 4 N NaOH) and stirred for 15 min. The aqueous layer was separated, washed (two times with ether), and discarded. The combined ether washes and benzene layer were in turn washed (water), dried ($Na_2SO_4$), and concentrated in vacuo. The residue (28 g) was dissolved in ethyl acetate (300 mL) and treated with dry HCl in ethyl acetate. The crude hydrochloride of *meso*-2,3,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (**14**), mp 227–228 °C (22.03 g, 0.091 mol, 69%), was collected. It was recrystallized from 2-propanol/ether to give an analytical sample: mp 230–231 °C; NMR ($Me_2SO$) $\delta$ 6.92 (s, 4), 4.56 (t, 2), 3.42–3.06 (m, 4), 2.36–1.96 (m, 4); IR (Nujol) 1594 (m), 1492 (s), 1266 (s), 1250 (s), 1042 (m), 758 (m), 746 (m) $cm^{-1}$; TLC ($CHCl_3/CH_3OH$ 9:1 on silica gel GF) $R_f$ 0.10; MS *m/e* 205 ($M^+$).

Anal. Calcd for $C_{12}H_{15}NO_2HCl$: C, 59.62; H, 6.67; N, 5.80. Found: C, 59.86; H, 6.93; N, 5.59.

The hydrochloride of compound 14 was dissolved in water, made basic (6 N NaOH), and extracted ($CH_2Cl_2$). The methylene chloride extracts were washed (water), dried ($Na_2SO_4$), lightly charcoaled and concentrated in vacuo. The residual oil crystallized on standing, mp 60–63 °C. This material was recrystallized from ether/hexane to give the *meso*-2,3,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine **14**: mp 64–65 °C; NMR δ 6.86 (s, 4), 4.40 (t, 2), 3.40–2.40 (m, 4), 2.40–1.50 (m, 4); IR (Nujol) 3220 (m), 1594 (m), 1492 (s), 1264 (s), 1028 (m), 964 (m), 842 (m), 776 (m), 740 (m) $cm^{-1}$.

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.51; H, 7.47; N, 6.89.

**Dextrorotatory *meso*-3-[(2-Oxo-10-bornanyl)sulfonyl]-1,2,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (15).** To a cooled (ice bath) and well-stirred solution of the hexahydrobenzodioxinoazepine **14** (1.6 g, 0.0078 mol) in ethyl acetate (25 mL) was added diisopropylethylamine (1.3 g, 0.01 mol) and *d*-10-camphorsulfonyl chloride (1.96 g, 0.0078 mol). The ice bath was removed and the mixture stirred overnight. Additional ethyl acetate (75 mL) was added to dissolve a precipitate. The solution was washed (2 N HCl, water, saturated $NaHCO_3$, water) and dried ($Na_2SO_4$), and the ethyl acetate was removed in vacuo. The crystalline residue (3.07 g) was recrystallized from ethanol to give dextrorotatory *meso*-3-[(2-oxo-10-bornanyl)sulfonyl]-1,2,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (**15**), mp 153.5–155 °C (2.67 g, 0.0064 mol, 64%). Two further recrystallizations from ethanol gave material, mp 154.5–155 °C. There was no change in rotation, $[\alpha]^{25}_D$ +24.92° (*c* 14.645 mg/mL, $CHCl_3$): NMR ($Me_2SO$) δ 6.86 (s, 4), 4.46 (m, 2), 1.04 (s, 3), 0.82 (s, 3); IR (Nujol) 1740 (s), 1590 (m), 1492 (s), 1323 (s), 1269 (s), 1137 (s), 756 (s), 748 (s) $cm^{-1}$; CD in $CH_3OH$ (*c* 1 mg/mL)[10] single Cotton effect $[\theta]_{288}$ 3000. [*N,N*-Dimethyl-*d*-camphorsulfonamide CD in $CH_3OH$ (*c* 1 mg/mL) Cotton effect $[\theta]_{288}$ 3200.]

Anal. Calcd for $C_{22}H_{29}NO_5S$: C, 62.98; H, 6.97; N, 3.34. Found: C, 63.28; H, 7.26; N, 3.35.

**Conversion of the *d*-Camphorsulfonamide 15 to the Benzodioxinoazepine 14.** The *d*-camphorsulfonamide **15** (1.6 g, 0.00382 mol) in benzene (15 mL) was added to Red-al (Aldrich Chemical Co.) (7.7 mL, 0.0267 mol) in benzene (5 mL). The mixture was refluxed for 4.5 h, cooled, and treated with 4 N NaOH (20 mL) for 15 min. The aqueous layer was separated, washed ($Et_2O$), and discarded. The ether washes and the benzene were in turn washed (2 N NaOH, water), dried ($Na_2SO_4$), and concentrated in vacuo. The residue (0.98 g, theory 0.78 g) was partially crystalline. It was dissolved in ether and the crystalline material (0.2 g) removed by filtration. The filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate (10 mL) and treated with dry HCl in ethyl acetate. The crystalline precipitate (0.36 g), mp 233–234 °C, did not give a mixture melting point depression with the previously obtained *meso*-2,3,4,5,5a,11a-hexahydro[1,4]-benzodioxino[2,3-*d*]azepine hydrochloride (**14**). A CD spectrum of the hydrochloride obtained from the above described reduction showed no optical activity in the scanning range (230–400 nm in $CH_3OH$, *c* 1 mg/mL). A portion of this hydrochloride **14** was converted to the free base **14** as described previously. This free base, mp 59–63 °C, was identical (NMR, IR) with the *meso*-2,3,4,5,5a,11a-hexahydro[1,4]benzodioxino[2,3-*d*]azepine (**14**) previously obtained.

**Acknowledgments.** We acknowledge the support and encouragement of Dr. Max Wilhelm and helpful discussions with Professor Peter Yates. We thank Miss Ruth Behnke for the NMR spectra, Miss Natalie Cahoon for IR spectra, Mr. S. Brody for GLC analyses, Mr. B. Korzun for TLC analyses, Mrs. B. Warren for MS spectra, and Mr. G. Robertson for microanalyses.

**Registry No.**—**1**, 7664,47-3; **2**, 63588-62-5; **2** hydrobromide, 63588-74-9; **4**, 63588-63-6; **5**, 27350-82-9; **6**, 63588-64-7; **6** HCl, 63588-65-8; **7**, 27354-40-1; **7** HCl, 27507-46-6; **8**, 793-19-1; **9**, 63588-66-9; **10**, 63588-67-0; **11**, 63588-68-1; **12**, 63588-69-2; **13**, 63588-70-5; **14**, 63588-71-6; **14** HCl, 63588-72-7; **15**, 63588-73-8; chlorotrimethylsilane, 75-77-4; methanesulfonyl chloride, 124-63-0; *d*-10-camphorsulfonyl chloride, 21286-54-4.

## References and Notes

(1) A. R. Martin, S. K. Mallick, and J. F. Caputo, *J. Org. Chem.*, **39**, 1808 (1974).
(2) C. J. Coulson and K. R. H. Wooldridge, *J. Chem. Soc. C*, 2830 (1969).
(3) R. Berthold, P. Niklaus, A. P. Stoll, and F. Troxler, *Helv. Chim. Acta*, **53**, 1128 (1970).
(4) C. F. Hammer, S. R. Heller, and J. H. Craig, *Tetrahedron*, **28**, 239 (1972).
(5) K. Rühlmann, H. Seefluth, and H. Becker, *Chem. Ber.*, **100**, 3820 (1967).
(6) J. J. Bloomfield, D. C. Owsley, and J. M. Netke, *Org. React.*, **23**, 259 (1976).
(7) Melting points were determined in a Thomas-Hoover melting-point apparatus and are uncorrected. NMR spectra were obtained on a Varian A60 in $CDCl_3$ unless otherwise stated. Infrared spectra were obtained on a Perkin-Elmer 21 or 521 instrument and mass spectra on an AE1 MS902 at 70 eV. The CD curves were obtained on a JEOLCO ORD/UV-5 instrument by Mrs. H. P. Yuan.
(8) We thank Dr. R. Rodebaugh of Central Research, CIBA-GEIGY Corp., Ardsley, N.Y., for these spectra and their interpretation. They were obtained on a Varian CFT-20 instrument.
(9) E. Rouvier, J. C. Giacomoni, and A. Cambon, *Bull. Soc. Chim. Fr.*, 1717 (1971).
(10) We are indebted to Dr. J. Karliner, Central Research, CIBA-GEIGY Corp., Ardsley, N.Y., for the GC/MS study and the CD determinations.

# Synthesis of a New Series of Macrocyclic Polyether–Diester Ligands[1]

Garren E. Maas, Jerald S. Bradshaw,* Reed M. Izatt, and James J. Christensen

*Departments of Chemistry and Chemical Engineering and Contribution No. 117 from the Thermochemical Institute, Brigham Young University, Provo, Utah 84602*

*Received May 27, 1977*

A new series of macrocyclic polyether–diester ligands (**1–11**) have been prepared by treating various oligoethylene glycols and sulfur-containing oligoethylene glycols with diglycolyl and thiodiglycolyl dichlorides. The compounds prepared were: 1,4,7,10,13-pentaoxacyclopentadecane-2,6-dione (**1**), 1,4,7,10,13,16-hexaoxacyclooctadecane-2,6-dione (**2**), 1,4,7,10,16-pentaoxa-13-thiacyclooctadecane-2,6-dione (**3**), 1,4,7,13-tetraoxa-10,16-dithiacyclooctadecane-2,6-dione (**4**), 1,4,7,10,13,16,19-heptaoxacycloheneicosane-2,6-dione (**5**), their 4-thia analogues **7, 8, 9, 10,** and **11**, respectively, and 1,7,10-trioxa-4-thiacyclododecane-2,6-dione (**6**). We have also prepared the potassium thiocyanate complex of **2** (**12**).

The synthesis and unique cation complexing characteristics of a number of cyclic polyethers were first reported by Pedersen[2] a decade ago. Since that time, a large number and variety of macrocyclic compounds have been prepared[3] and their cation complexing properties have been studied extensively.[4–11] It was originally postulated[2] and since confirmed by measurement of stability constants[10] that a qualitative relationship exists between complex stability and the ratio of cation diameter to ligand cavity diameter. It has become increasingly evident, however, that the stability of these complexes depends significantly on other cation and ligand parameters. For example, $K^+$ and $Ba^{2+}$ have nearly identical ionic radii (1.33 and 1.34 Å, respectively),[12] and on the basis of electrostatics alone, one would predict that the stability order $Ba^{2+} > K^+$ would be found for complexes where the ligand cavity would accommodate these cations. Although