CH_3): NMR ($CDCl_3$) aliphatic H's 3.30 (q, J = 7.5 Hz, 4 H), 2.71 (q, J = 7.5 Hz, 2 H), 2.11 (s, 3 H), 1.27 (t, J = 7.5 Hz, 3 H), 1.11 ppm (t, J = 7.5 Hz, 6 H); aromatic H's 7.20 (d, J = 9.5 Hz, 1 H), 6.85–6.65 ppm (m, three signals, 2 H). Irradiations at 3.30 ppm result in the sharpening of the peaks (6.85–6.65).

5-(*N,N*-Diethylamino)-2-butyl-3-propylbenzofuran (**9**, R = *n*-C_3H_7): NMR ($CDCl_3$) aliphatic H's 2.0–0.65 (m, 18 H), 2.57 and 2.70 (2 t, J = 7 Hz, 4 H), 3.32 ppm (q, J = 7 Hz, 4 H); aromatic H's, ABX spectrum, 7.25 (d, J = 8 Hz, 1 H), 6.83 (d, J = 1.5 Hz, 1 H), 6.73 ppm (dd, J = 8.5, 2.5 Hz, 1 H). Irradiations at 3.32 ppm result in the sharpening of the d (6.83) and the dd (6.73).

5-(*N,N*-Diethylamino)-2-isopropylidene-3-dimethyldihydro-2,-3-benzofuran (**11**): NMR ($CDCl_3$) aliphatic H's 3.23 (q, J = 7 Hz, 4 H), 1.10 (t, J = 7 Hz, 6 H), 1.52 (s, 6 H), 1.79 ppm (s, 6 H); aromatic H's, ABX spectrum, 6.73 (d, J = 9.5 Hz, 1 H), 6.56 (d, J = 2.5 Hz, 1 H), 6.52 ppm (dd, J = 9.5, 2.5 Hz, 1 H); ir (film) $\nu_{C=C}$ 1705 cm^{-1}.

5-(*N,N*-Diethylamino)-1,3-tetramethylbenzo-3a,7a-cyclopentanone (**12**): NMR ($CDCl_3$) aliphatic H's 3.42 (q, J = 7 Hz), 1.18 (t), 1.26 (s), 1.33 ppm (s) (18 H); aromatic H's 7.17 (d, J = 8.25 Hz, 1 H), 6.85–6.50 ppm (m, three signals, 2 H); ir (film) 1750 cm^{-1}.

6-Morpholino-2,3-tetramethylenebenzofuran (**16**, n = 2): mp 122–123°; NMR ($CDCl_3$) aliphatic H's 1.82 (m, 4 H), 2.62 (m, 4 H), 3.10 (m, 4 H), 3.82 ppm (m, 4 H); aromatic H's 7.27 (d, J = 8.5 Hz, 1 H), 6.96 (d, J = 2 Hz, 1 H), 6.85 ppm (dd, J = 8, 2 Hz, 1 H). Irradiations at 3.10 ppm result in the sharpening of the d (6.96) and of the dd (6.85). Irradiations at 2.62 ppm result in the sharpening of the d (7.27).

6-Morpholino-2,3-pentamethylene-2,3-benzofuran (**16**, n = 3): mp 109–110°; NMR ($CDCl_3$) aliphatic H's 1.80 (m, 6 H), 2.66 (m, 2 H), 2.88 (m, 2 H), 3.13 (m, 4 H), 3.86 ppm (m, 4 H); aromatic H's, ABX spectrum, 7.27 (d, J = 8 Hz, 1 H), 7.0–6.8 ppm (m, AB part, three signals, 2 H). Irradiation at 3.13 ppm results in the sharpening of the AB part. Irradiation at 2.66 ppm results in the sharpening of the X part of the spectrum.

Condensation of 17 (20 mmol) and 2 (40 mmol) in THF (260 cm^3) with $NaNH_2$ (40 mmol) and *t*-BuONa (20 mmol). Experimental conditions. Run 19, 25 then 50°; 2.5 then 24 hr; runs 20 and 21, 25 then 50°; 1 then 3 hr.

5-Methoxy-2,3-tetramethylenebenzofuran (**18**, R_1 = CH_3O): NMR ($CDCl_3$) aliphatic H's 1.80 (m, 4 H), 2.60 (m, 4 H), 3.75 ppm (s, 3 H); aromatic H's, ABX spectrum between 6.60 and 7.35 ppm.

2,3-Tetramethylenebenzofuran (**18**, R_1 = H): NMR ($CDCl_3$) m between 1.5 and 1.2 (4 H), m (2.3–3, 4 H), m (7–7.75, 4 H).

Acknowledgments. We are grateful to K. G. Taylor, visiting Professor in Nancy University, and the referees for discussing this manuscript, to Produits Chimiques Ugine Kuhlmann for financial support, and to M. Dorme (Laboratoire de Microanalyse, Paris VI) for the microanalyses.

Registry No.—**1**, 55039-58-2; **2** (n = 1), 55886-83-4; **2** (n = 2), 55886-84-5; **2** (n = 3), 55886-85-6; **2**(n = 4), 55886-86-7; **4** (n = 1), 55886-87-8; **4** (n = 3), 55886-88-9; **5** (n = 1), 55886-89-0; **5** (n = 2), 55886-90-3; **5** (n = 3), 55886-91-4; **5** (n = 4), 55886-92-5; **8** (R = CH_3), 55886-93-6; **8** (R = *n*-C_3H_7), 55886-94-7; **9** (R = CH_3), 55886-95-8; **9** (R = *n*-C_3H_7), 55886-96-9; **10**, 55886-97-0; **11**, 55886-98-1; **12**, 55886-99-2; **15**, 55039-67-3; **16** (n = 2), 55887-00-8; **16** (n = 3), 55887-01-9; **17** (R_1 = CH_3O; R_2 = R_3 = H), 623-12-1; **17** (R_1 = R_3 = H; R_2 = Cl), 541-73-1; **17** (R_1 = R_2 = H; R_3 = Cl), 95-50-1; **18** (R_1 = CH_3O), 7291-77-2; **18** (R_1 = H), 13130-19-3.

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High-Dilution Cyclization of Polyoxapentacosanodinitriles[1]

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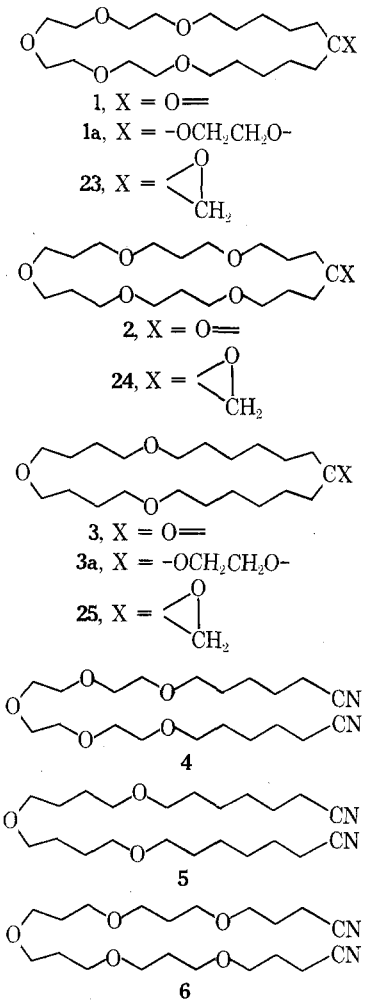
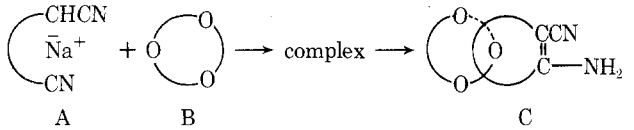
The syntheses of 7,10,13,16,19-pentaoxapentacosanodinitrile (**4**), 8,13,18-trioxapentacosanodinitrile (**5**), and 5,9,13,17,21-pentaoxapentacosanodinitrile (**6**), and the Ziegler-type cyclization of these nitriles by an improved method, are described. The cyclized products were converted into 7,10,13,16,19-pentaoxacyclotetracosanone (**1**), 8,13,18-trioxacyclotetracosanone (**3**), and 5,9,13,17,21-pentaoxacyclotetracosanone (**2**), respectively. From **1**, **2**, and **3** were prepared the amino alcohols 1-piperidinomethyl-7-10-13-16-19-pentaoxacyclotetracosanol (**26**), 1-piperidinomethyl-5,9,13,17,21-pentaoxacyclotetracosanol (**27**), and 1-piperidinomethyl-8,13,18-trioxacyclotetracosanol (**28**), respectively. By reduction of the ketonitrile obtained by the cyclization of **5**, there was obtained 2-aminomethyl-8,13,18-trioxacyclotetracosanol (**29**). The amino alcohols **26–29** were screened for biological activity with negative results.

In this paper the syntheses of 7,10,13,16,19-pentaoxacyclotetracosanone (**1**), 5,9,13,17,21-pentaoxacyclotetracosanone (**2**), and 8,13,18-trioxacyclotetracosanone (**3**), and derivatives thereof, are described. These compounds were desired as possible components of catena and rotaxane type compounds.[4] The novel catena compounds hoped for would be of interest for testing as to their pharmacological activity inasmuch as the two functional groups would be on different rings, e.g., hydroxyl on one ring, amino on the other, which by rotating could put the functions at different distances from each other. In previous examples of catena compounds, polymethylene chains were used almost exclusively in the construction of the desired large rings. We were interested in including oxygen atoms in the chain for three reasons: (a) the presence of oxygen atoms might make possible the attainment of yields of catenas and rotaxanes higher than those heretofore obtained by statistical methods;[5,6] (b) the resulting compounds would be more



likely to have solubility in aqueous biological systems than their polymethylene counterparts; and (c) the ability of oxygen atoms in cyclic ethers (crown ethers)[7] to complex with inorganic cations might make potential medicaments derived from such precursors of interest.

Thus, to elaborate on the function of the ether oxygens under (a) above, if one were to cyclize a long-chain dinitrile under Ziegler–Thorpe conditions the initial sodio derivative A might complex in the region of the oxygen atoms[7] of a suitably sized large ring B, so that when cyclization to the eneaminonitrile occurred a larger fraction of catena compound C would be formed than would be the case if the ring B did not contain any ether oxygens.



Although our attempts to prepare catena compounds by Ziegler–Thorpe cyclization of 7,10,13,16,19-pentaoxapentacosanodinitrile (**4**) and of 8,13,18,-trioxapentacosanodinitrile (**5**) in the presence of 7,10,13,16,19-pentaoxacyclotetracosanone ethylene ketal (**1a**) and 7,12,17-trioxacyclotetracosanone ethylene ketal (**3a**), respectively, failed, we made observations on the cyclization of the dinitriles, **4, 5,** and 5,9,13,17,21-pentaoxapentacosanodinitrile (**6**), which are of interest in connection with high-dilution techniques. These dinitriles were chosen because each would result eventually in a 24-member ring ketone, a size which a study of molecular models indicated could comfortably include a catena or rotaxane insert.

In the classic studies from the Ziegler laboratory detailed directions for the cyclization of dinitriles by strong bases (e.g., sodium methylanilide) by a high-dilution technique are given.[8,9] An elaborate apparatus was used; lengthy reaction periods (often 3–14 days) and careful attention to concentration factors were required if yields in the range of 70–80% of iminonitriles were to be obtained. Hydrolysis and decarboxylation to ketones was generally effected by refluxing with 70% H_2SO_4.

We have simplified the apparatus as shown in Figure 1.

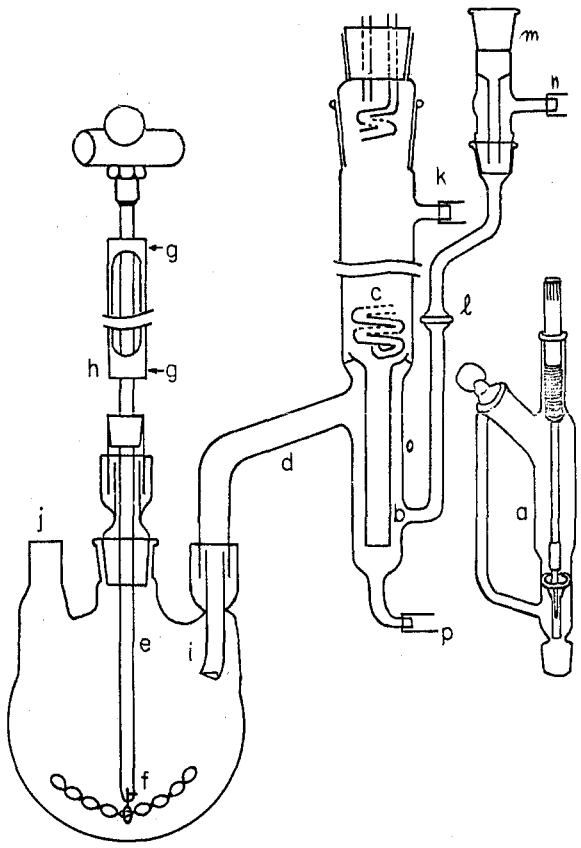


Figure 1.

The chief change lies in the replacement of the cumbersome mercury-controlled addition system[10] by a special addition funnel[11] a which delivers a dilute ethereal solution of the dinitrile as shown in b where it is further diluted with the ether condensed by the efficient copper-coiled condenser[12] c and swept into the reaction flask via return tube d. The use of mercury-sealed joints and stirrer was dictated by the experience of the Ziegler school in the publications of which such seals are always preferred to other methods of closure. The stirrer shaft e was constructed of $^3/_{16}$ in. stainless steel and was connected to a Hershberg wire stirrer[13] f (or a curved metal blade containing holes). The two ball bearings g which guide the shaft are contained in a one-piece hollowed metal holder h which ensures that the ball bearings remain firmly aligned during a lengthy reaction period. The ether returning to the reaction flask is delivered at i, a wide driptip which delivers the ether so that it does not first touch the walls of the flask. This device prevents the buildup of large clumps of insoluble complexes in this area as occurs when such a driptip is not used.[14]

For the cyclizations the main reaction flask was flamed and swept with dry nitrogen introduced through a tube at j and exited at opening k with a solid balljoint at l instead of the addition funnel a. After cooling under nitrogen, the solution of sodium *N*-methylanilide, prepared in another

Table I
Cyclization of Dinitriles

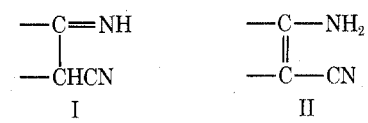
Expt	Dinitrile,[a] g	Ether,[b] ml	Total vol[c] of ether, l.	Time for addition[d]	EAN[e]	KN[f]
			4			
1	25.5	300	1.8	20	82.5	79
2	45.4	300	1.8	26	82	80[g]
3	61.4	400	2.8	24		82[g]
4	63.8	300	1.8	26	80	
5	61.4	400	2.8	6		82
6[h]	30.0	200	1.4	19	23	77[i]
7[h]	15.0	200	1.4	16	33	
8[h,j]	8.0	100	0.3	7	74	
			5			
9	59.3	400	2.5	36		79
10	55.5	500	3.0	72	83	
11	59.3	400	2.5	24	81	
12[h]	15.0	200	1.4	12	86	
13[h,k]	5.0	75		5[l]	60	
14[h,m]	12.0	80	0.3	6	86	
15[k]	6.3	200	2.0	16	78	
16[h,j]	8.0	100	0.3	5	44	
17[h,n]	15.0	100	0.385	10	79	
			6			
18	57.6	400	2.5	24	86	
19[h]	59.5	750	2.5	24	80	

[a] In all runs only redistilled dinitrile and about a tenfold excess of sodium *N*-methylanilide were used. [b] Milliliters of ether used to dissolve dinitrile. [c] The total final volume of ether includes the ether used for *b* and also that involved in making and transferring the condensing agent, sodium *N*-methylanilide. [d] Time in hours for addition of dinitrile. After addition complete refluxing continued for 1–5 hr. [e] Yield of crude ethyleneaminonitrile (EAN) usually was equal to the weight of starting dinitrile. Portions on vacuum distillation usually yielded 70–85% of pure distilled EAN. When percent is given this means distilled EAN. [f] The overall yield of distilled ketonitrile from dinitrile without purification of EAN. [g] Typical of several runs in which little variation in yield of KN was noted. [h] Run in appropriately sized conventional three-necked flask by direct addition of dinitrile solution (NHDA, not high dilution apparatus). [i] Percent of polymer. [j] Potassium *N*-methylanilide used. The preparation from KH[42] and *N*-methylaniline was more inconvenient than that for the sodio derivative. [k] NHDA experiment with about 3–4 equiv of $[(CH_3)_3SI]_2NNa$[43] as condensing agent. [l] Refluxed 10 hr after addition. [m] About one-half the concentration of sodium *N*-methylanilide was used, e.g., 4–5 mol/mol of dinitrile. [n] Only about 2 equiv of condensing agent per mole of **5** (about ⅕ of amount recommended earlier[16]).

conventional three-neck flask, was forced in by nitrogen pressure through a tube inserted at j. The addition funnel a (with flow rate previously calibrated) was then attached to an adapter m attached at l and the openings k and n connected by a T-tube (not shown) opening to the atmosphere through a drying tube (not shown). The ethereal solution of the dinitrile was added to a after a rapid rate of reflux of ether had been maintained for enough time to fill the body of the mixing chamber o to the overflow point. The opening p at the bottom of the mixing chamber was closed by a pinch clamp at q (not shown).

A solution of the dinitrile in ether was added slowly to a well-stirred rapidly refluxing solution of an excess of sodium methylanilide in ether freshly prepared by treating sodium with *N*-methylaniline in the presence of isoprene.[15,16] Much importance was attached to very slow addition (often 72 hr or more) of the solution of dinitrile in ether to the sodium *N*-methylanilide reagent solution in order that high yields might result.[15] We have found that **4, 5,** and **6** are cyclized in high yields even when addition of the dinitriles is made in as short a time as 6 hr (see Table I) and in certain cases when conventional apparatus is used instead of the high-dilution setup as outlined in Figure 1. Perhaps these results are due to conformational factors which make intramolecular cyclization more facile when oxygen atoms are present in the chains.[17,18]

In the work of Ziegler and coworkers[8] the cyclized products from dinitriles were assumed to have the β-iminonitrile structure I. In the cases of **4a, 5a,** and **6a,** we believe that the ethyleneaminonitrile structure II is at hand. Our



I II

evidence lies in the fact that the nitrile bands in the infrared for **4a, 5a,** and **6a** are sharp single lines near 4.6 μm[19] whereas the nitrile band in the starting dinitriles are sharp bands near 4.4 μm. If the structure I were at hand we would expect the CN band to occur near 4.4 μm.

The hydrolyses of the cyclized products to yield cyclic ketones had been carried out by refluxing with strong sulfuric acid solutions.[15,16] Because of the oxygen atoms in the rings of our compounds, we worked out an improved stepwise procedure under milder conditions, as shown in Scheme I (shown only for compounds derived from **4**).

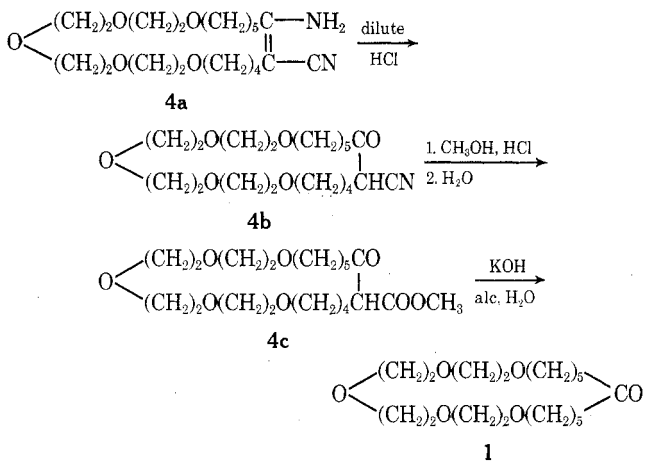
The syntheses of **4** and **5** were carried out as shown in Scheme II.

Interestingly, the best yields of **8** and **11** were obtained when the dimesylate **7** or the dichloride **10** was added to the solution (held near 100°) formed by treating 3 equiv of sodium with excess diol as solvent. The conversion of the dimesylates **9** and **12** to dinitriles **4** and **5** was better effected in benzene by using phase-transfer catalysis[20] than by reaction with potassium cyanide in aqueous DMSO.

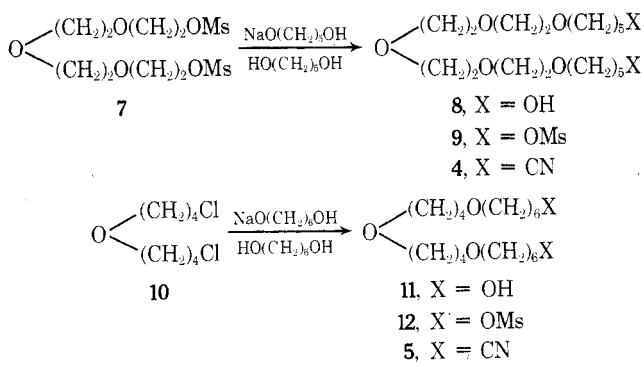
The synthesis of **6** was carried out as shown in Scheme III.

The conversion of 1,3-propanediol to **13** was carried out essentially as described.[21] Methanolysis of **13** using a cationic exchange resin afforded **14** in almost quantitative

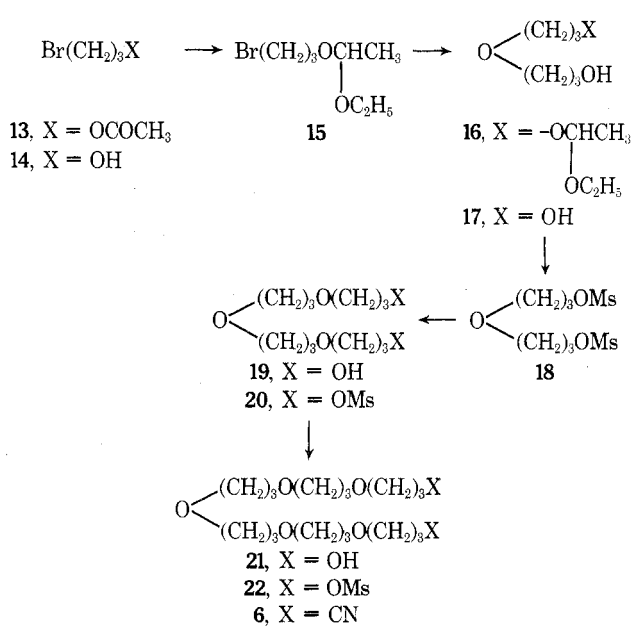
Scheme I



Scheme II

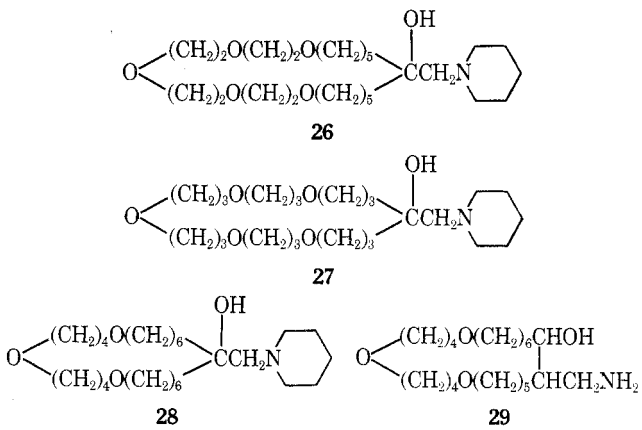


Scheme III



yield. The conversion of **14** to **17** has previously been accomplished in 57% yield.[22] We have improved this by proceeding through the intermediate[23] **15**, which was added to a solution formed by treating sodium with excess 1,3-propanediol to form **16**. Hydrolysis of **16** yielded **17** in 70% overall yield from **14**. The remaining steps were carried out essentially as in the syntheses of **4** and **5**.

In order to investigate the possibility that amino alcohols having a crown ether type[7] feature in a large ring might have interesting physiological activity, we prepared 1-piperidinomethyl-7,10,13,16,19-pentaoxacyclotetracosanol (**26**) from **1**, 1-piperidinomethyl-5,9,13,17,21-pentaoxacyclotetracosanol (**27**) from **2**, and 1-piperidinomethyl-8,13,18-trioxacyclotetracosanol (**28**) from **3**, by conversions of the ketones to epoxides[24] **23**, **24**, and **25**, respectively, followed by reaction of these with piperidine. In addition, 2-cyano-8,13,18-trioxacyclotetracosanone (**5b**) was reduced with $LiAlH_4$ to yield 2-aminomethyl-8,13-18-trioxacyclotetracosanol (**29**). The four compounds, **26–29**, were



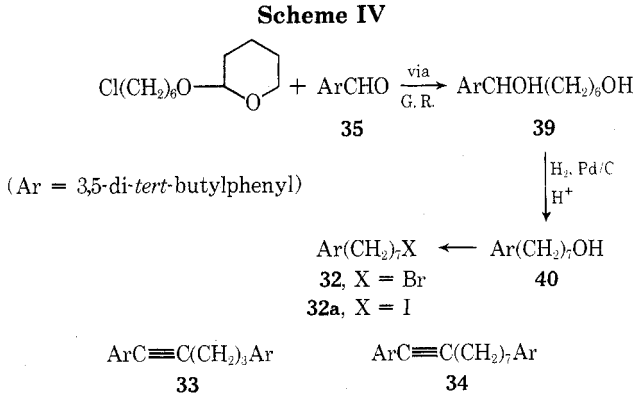
screened at the Upjohn Co.[25] Compounds **26**, **27**, and **29** were screened at Merck Sharp and Dohme.[26] Unfortunately, no activity was found in any of the tests used.[25,26]

A few experiments were run in which the sodium and lithium salts of 3,5-di-*tert*-butylphenylacetylene[27] (**30**) were condensed with 3-(3,5-di-*tert*-butylphenyl)propyl bromide (**31**) (and iodide, **31a**), and 7-(3,5-di-*tert*-butylphenyl)heptyl bromide (**32**) (and iodide, **32a**) in the presence of **1a**. Although the alkylation reactions proceeded well to yield 1,5-di(3,5-di-*tert*-butylphenyl)-1-pentyne (**33**) and 1,9-di(3,5-di-*tert*-butylphenyl)-1-nonyne (**34**), respectively, both in the presence and absence of **1a**, no evidence for the formation of appreciable amounts of rotaxanes was obtained.

The bromide **31** was prepared from the mesylate **36a** of 3-(3,5-di-*tert*-butylphenyl)propanol (**36**), which was prepared by the steps 3,5-di-*tert*-butylbenzaldehyde (**35**)[27] → methyl 3-(3,5-di-*tert*-butylphenyl)-3-hydroxypropanoate[27] → methyl 3-(3,5-di-*tert*-butylphenyl)acrylate (**37**) → methyl 3-(3,5-di-*tert*-butylphenyl)propanoate (**38**) → **36**.

The bromide **32** and the iodide **32a** were synthesized as shown in Scheme IV.

Scheme IV



Experimental Section[28]

Dimesylate of 3,6,9-Trioxa-1,11-undecanediol (7). To a cooled, stirred solution of 194 g (1 mol) of tetraethylene glycol[29] in 1 l. of benzene containing 253 g (2.5 mol) of distilled triethylamine in a 3-l. flask[30] was added dropwise during 2 hr a solution of 286 g (2.4 mol) of methanesulfonyl chloride in 50 ml of benzene. The

temperature during addition and for 3 hr more was held at 5–7°. The solid was suction filtered and washed twice with 300 ml of 1:1 benzene–CH_2Cl_2. The filtrate and washings were combined and concentrated to dryness on a rotary evaporator. A CH_2Cl_2 solution of the residue was washed with ice water (3 × 100 ml) and saturated salt solution (2 × 45 ml) and was dried over $MgSO_4$. After complete removal of the CH_2Cl_2 on a rotary evaporator there was obtained 325 g (93%) of crude dimesylate **7**. This crude product was further purified by stirring vigorously with dry ether (150 ml), which was then decanted to leave 320 g (91.6%) of **7** as a yellow oil suitable for conversion into **8**.

6,9,12,15,18-Pentaoxa-1,23-tricosanediol (8).* To 1404 g (13.5 mol) of redistilled 1,5-pentanediol, bp 137–138° (12 mm), held at 95–100° under N_2 in a 3-l. flask[30] by a heating mantle was added 62 g (2.7 mol) of sodium in small clean chunks. The reaction temperature was maintained at 105–110° by the rate of addition of the sodium (about 2 hr needed without any external heating by the mantle which was kept in place). As soon as the last sodium had reacted, a solution of 315 g (0.9 mol) of **7** was added during 90 min without external heating (temperature in the 100–105° range) and the resulting viscous, homogeneous reaction mixture was held at 100° for 20 hr. This hot solution was poured into 1.5 l. of acetone and to the resultant cooled solution was added about 450 ml of dry ether saturated at room temperature with dry HCl until the pH was 6–7 (external testing). The solid was removed by filtration and washed with dry acetone (2 × 1 l.). The filtrate and washings were concentrated on a rotary evaporator and the residue was rapidly vacuum distilled in a modified Claisen flask[31] to yield 280 g (87.5%), bp 220–250° (0.5 mm), after recovery of the excess 1,5-pentanediol which was reused as obtained in other similar runs. Redistillation[32] afforded 230 g (74% overall) as a center cut, bp 235–240° (0.5 mm), of **8**.[33] This material was analytically pure.

7,10,13,16,19-Pentaoxapentacosanodinitrile (4).* By the same method as described above for **7**, 220 g of **8** was converted into 305 g (97%) of crude **9** [271 g (87%) of purified **9**]. A well-stirred mixture of 195 g of KCN, 300 ml of water, 300 ml of benzene, 5 g of Aliquat 336,[20] and 261 g of pure **9** was held at reflux for 5–6 hr, cooled, diluted with water to dissolve salts, and worked up as usual using CH_2Cl_2–benzene extraction. Distillation afforded 83% of **4**, bp 230–250° (1 mm). Redistillation yielded 70% (overall) of analytically pure **4**, bp 240–247° (1 mm), ir 4.42 μm. The boiling point recorded for various runs varied somewhat because it was advantageous to heat the Claisen neck externally in order to expedite distillation of the high-boiling material.[32]

7,12,17-Trioxa-1,23-tricosanediol (11).* In a typical run the solution at 80–90° formed by treating 75.9 g of sodium with 2124 g of 1,6-hexanediol, bp 132° (9 mm), at 100° was treated with 299 g of **10**,[34] bp 92–94° (1 mm), during 1 hr. After stirring at 80–90° for 14 hr the mixture was diluted with sufficient acetone and ether to facilitate filtration (in this case 400 ml of acetone and then 300 ml of ether). After a work-up similar to that for **8** there was obtained 365 g (67%) of **11**, bp 215–225° (0.3 mm). A center cut was taken for analysis.

8,13,18-Trioxapentacosanodinitrile (5).* In a manner similar to that described for the preparation of **7**, 385 g of **11** in 800 ml of benzene containing 260 g of triethylamine was treated with 283 g of methanesulfonyl chloride in 300 ml of benzene to yield crude mesylate **12*** in 98% yield. A small portion was crystallized from hexane–ether to yield pure **12**, mp 50–51°. Conversion of 600 g of **12** into **5** was carried out as described for **4** by heating at reflux with 390 g of KCN, 200 ml of water, and 400 ml of benzene containing 10 g of Aliquat 336[20] for 5 hr. After two distillations there was obtained 300 g (68%) of a center cut of **5**, bp 244–249° (0.3 mm), ir 4.44 μm, as a pale yellow oil.

3-Bromo-1-propanol (14). 3-Bromo-1-propyl acetate (**13**), bp 55–60° (1 mm), was obtained in 67% yield essentially as described.[21] A solution of 120 g of **13** in 600 ml of methanol containing 50 g of ion exchange resin[35] was held at reflux for 6 hr. The resin was removed by filtration and the filtrate was distilled to yield 92 g (98%) of **14**, bp 60–64° (1 mm).

4-Oxa-1,7-heptanediol (17). To a stirred solution at 100–105° formed by treating 17.7 g of sodium with 380 g of 1,3-propanediol, bp 110° (12 mm), was added during 1 hr 148 g of **15** formed from 104 g of **14** as described.[23] The mixture was held at 100–105° for 10 hr and then acidified with concentrated HCl until neutral (pH 7, external testing). After adding 50 g of resin[35] and 81 g of water the mixture was refluxed for 24 hr. The solids were removed by filtration and rinsed with ethanol. Distillation of the combined filtrate and washings yielded 100.5 g (70% from **14**) of **17**, bp 90–95° (0.5 mm).[36]

4,8,12-Trioxa-1,15-pentadecanediol (19).* The diol **17** was converted into its dimesyl derivative **18** essentially as described for the preparation of **7**. Then **18** was converted, in 77% overall yield from **17**, into **19**, bp 158–165° (0.5 mm), by adding to excess 1,3-propanediol containing its sodium salt as described for the preparation of diols **8** and **11**.

4,8,12,16,20-Pentaoxa-1,23-tricosanediol (21).* The diol **19** was converted via its dimesyl derivative **20** into **21** essentially as described above in analogous examples. Overall yields of **21**, bp 220–228° (0.5 mm), were about 78%.

5,9,13,17,21-Pentaoxapentacosanodinitrile (6).* The dimesylate **22** was prepared as described above for **7** and the crude product was converted in 82% overall yield to **6**, bp 230–238° (0.5 mm) (twice distilled), ir 4.45 μm.

General Description of Ziegler-Type High-Dilution Cyclizations. Sodium sand was prepared in a 3-l. flask[30] by melting clean sodium under freshly distilled xylene and then stirring rapidly while cooling. In general about 10 g-atom of sodium was used per mole of dinitrile. The xylene was forced out with pure dry nitrogen and the sodium sand was rinsed with dry ether (all ether was freshly distilled from Grignard reagent[37]). In a typical run a solution of 102 g (1.5 mol) of distilled isoprene (undistilled isoprene was also used) and 209 g (1.95 mol) of distilled *N*-methylaniline in 50–300 ml of dry ether was added dropwise during 1 hr to a *gently* stirred suspension of the sand prepared from 34.5 g (1.5 g-atom) of sodium under 300 ml of ether. To the resulting suspension of sodium *N*-methylanilide was added about 2 l. of ether to effect solution. This was then transferred by N_2 pressure into the high-dilution apparatus (Figure 1).[38] To this *vigorously* (about 3 l. of ether per hour) refluxing solution was added a solution of 57.6 g (0.15 mol) of **4** in 400 ml of ether during 24 hr.[39] After addition of **4**, the refluxing was continued for 2 hr. Water[40] was then added until the exothermic reaction was over and then 300 ml more to aid in obtaining clean layers.[41] After the usual work-up[28] (no acid wash) the *N*-methylaniline, bp ca. 65° (0.2 mm), was removed by distillation (heating bath in the range 100–200°) and the residue was weighed. In a typical case the weight of crude residue equaled the weight of starting dinitrile. Small amounts were vacuum distilled to yield analytical samples. In the present case a center cut of 2-amino-8,11,14,17,20-pentaoxacyclotetracosenonitrile (**4a**),* bp 235–240° (0.5 mm), ir 4.58 μm, was taken for analysis and spectral data.

The remainder of crude **4a** was shaken with 2 l. of 6 *N* HCl for 30 min. After dilution with 2 l. of water, the ketonitrile was isolated as usual to yield 49.3 g (85.6% based on **4**) of 2-cyano-7,10,13,16,19-pentaoxacyclotetracosanone (**4b**),* bp 210–213° (0.5 mm). In general conversions of crude ethyleneaminonitriles (EAN) to pure distilled ketonitriles (KN) ran well over 90%. In the preferred procedure, the crude EAN were converted directly into KN.

By similar procedures **5** was converted into 2-amino-9,14,19-trioxacyclotetracosenonitrile (**5a**),* bp 225–230° (0.3 mm), ir 5.62 μm, and 2-cyano-8,13,18-trioxacyclotetracosanone (**5b**),* bp 205–210° (0.2 mm), and **6** into 2-amino-6,10,14,18,22-pentaoxacyclotetracosenonitrile (**6a**),* bp 235–240° (0.6 mm), ir 4.58 μm, and 2-cyano-5,9,13,17,21-pentaoxacyclotetracosanone (**6b**),* bp 210–213° (0.5 mm).

Perusal of Table I allows a number of observations to be made regarding Ziegler-type cyclizations. Evidently the presence of oxygen atoms makes the yield of cyclized product less sensitive to dilution factors and to time of addition of the dinitrile solution to the condensing agent (expt 1–5 for **4** and 9–11 for **5**) than is the case with dinitriles of the general formula $NC(CH_2)_nCN$.[16] Experiments 5 and 14 show that even if the time of addition is cut to 6 hr high yields of eneaminonitriles can be obtained. Indeed, experiments in which solutions of dinitrile were added directly to solutions containing condensing agent without use of high-dilution apparatus afforded acceptable yields of EAN in the cases of **5** and **6** (expt 12, 14, 19). However, this technique did not work well in the case of **4**; as much polymer was obtained under these conditions (expt 6, 7). A few experiments demonstrated that condensing agents (expt 8, 16, $C_6H_5NKCH_3$,[42] expt 13, 15, $[(CH_3)_3Si]_2NNa$[43]) other than sodium *N*-methylanilide can be used successfully.

Conversion of β-Ketonitriles 4b, 5b, and 6b into Cyclotetracosanones, 1, 2, and 3. In the best of many experiments, 147.5 g of distilled **4b** was stirred with 2740 ml[44] of methanol saturated with dry HCl at 25–30° for 4 hr. Most of the methanol was removed on a rotary evaporator and 500 ml of water was added to the residue. An ether–CH_2Cl_2 extract of the product was washed with saturated salt solution, and the crude residue, after removal of organic solvents, weighed 144.6 g. This crude keto ester was held at reflux

in a solution containing 217 g of KOH and 720 ml of water in 720 ml of ethanol for 17 hr. After a conventional work-up, vacuum distillation afforded 109 g (88%) of **1**,* bp 192–210° (0.4 mm). The use of phosphoric acid in dilute acetic acid, which proved successful in a previous case,[19a] did not work nearly as well with our ethyleneaminonitriles, nor did any of several other hydrolytic methods mentioned.[19a]

In a typical experiment, 98.4 g of **6b** and 2 l. of saturated methanolic HCl were stirred for 5 hr and worked up as described above to yield 106 g of crude keto ester. A portion was distilled to yield pure methyl 2-keto-6,10,14,18,22-pentaoxacyclotetracosanylcarboxylate (**6c**),* bp ca. 225° (0.4 mm). A solution of the remaining crude **6c** in 1 l. of 50% alcohol containing 160 g of KOH was refluxed for 20 hr and worked up as usual to yield 65 g (71% from **6b**) of **2**,* bp 190–198° (0.5 mm).

The ketonitrile **5b** was converted into methyl 2-keto-9,14,19-trioxacyclotetracosanylcarboxylate (**5c**) as described above for **4c**. A portion of **5c**,* bp 232–235° (0.3 mm), was taken for analysis. A solution of 105 g of crude **5c** in 1.1 l. of 50% alcohol containing 159 g of KOH was refluxed for 8 hr. After the usual work-up there was obtained 69 g (76%) of pure **3**,* bp 195–197° (0.3 mm).

Ethylene Ketals of 1 and 3. In a typical experiment a solution of 10.8 g of **1**, 2.8 g of ethylene glycol, and 200 mg of *p*-toluenesulfonic acid in 250 ml of benzene was held at reflux for 5 hr with removal of water by azeotropic distillation. Solid K_2CO_3 (20 g) was stirred in for 2 hr. After a conventional work-up there was obtained 11.0 g (91%) of **1a**,* bp 230–235° (0.5 mm). In a similar experiment involving 10.5 g of **3** and 3.0 g of ethylene glycol there was obtained 10.6 g (90%) of **3a**,* bp 202–205° (0.3 mm).

1-Piperidinomethyl-8,13-18-trioxacyclotetracosanol (28).* In a 250-ml flask[30] was placed 1.6 g of a sodium hydride suspension (57%) in mineral oil. By washing several times under N_2 with petroleum ether the mineral oil was removed. To the NaH was added 20 ml of THF and 20 ml of dimethyl sulfoxide (DMSO). Heating at 65–70° was maintained until no more hydrogen was evolved (45–55 min). About 20 ml of THF was added and the mixture was cooled to −5°, when 6.6 g of trimethylsulfonium iodide in 20 ml of DMSO was added during 2 min followed by a solution of 5.6 g of **3** in 25 ml of DMSO. After stirring at −5° for 15 min the solution was held at 20–25° for 45 min. After a conventional work-up there was obtained 5.5 g (94.5%) of the epoxide of 1-methylene-8,13,18-trioxacyclotetracosane (**25**),* bp 190–193° (0.4 mm). A solution of 5.4 g of **25** in 70 ml of freshly distilled piperidine was held at reflux for 24 hr. Most of the piperidine was vacuum distilled, the brown residue was distilled, and the distillate was treated with about 1 g of activated charcoal (Darco G-60) in CH_2Cl_2. Distillation afforded 5.7 g (86%) C of **28** as a pale yellow oil, bp 215–220° (0.4 mm).

1-Piperidinomethyl-7,10,13,16,19-pentaoxacyclotetracosanol (26).* In a similar way 5.04 g of **1** was converted into 4.25 g (81%) of the epoxide of 1-methylene-7,10,13,16,19-pentaoxacyclotetracosane (**23**),* purified by molecular distillation[45] at 125–135° for analysis, bp 205–207° (0.2 mm). On heating with piperidine as above there was obtained 3.1 g (63%) of twice distilled[45] center cut of **26**, bath temperature about 140°, pressure not accurately recorded.

1-Piperidinomethyl-5,9,13,17,21-pentaoxacyclotetracosanol (27).* In a manner entirely similar to that described for the synthesis of **28**, 14.4 g of **2** was converted into the epoxide **24**, which was converted directly into 13.0 g (75% overall) of **27**, bp 225–230° (0.3 mm).

2-Aminomethyl-8,13,18-trioxacyclotetracosanol (29).* In a typical experiment a solution of 8.0 g of **5b** in 100 ml of 1:1 ether–THF was added to a suspension of 2 g of $LiAlH_4$ in 100 ml of 1:1 ether–THF. After stirring for 15 hr the mixture was worked up (including 20% sodium potassium tartrate in the aqueous phase) to yield 5.0 g (62%) of **29**, bp 225–227° (0.2 mm).

3-(3,5-Di-*tert*-butylphenyl)propanol (36).* Methyl 3-(3,5-di-*tert*-butylphenyl)-3-hydroxypropanoate was prepared from **35** and methyl bromoacetate as described.[27] In the best of several experiments a solution of 29.2 g of β-hydroxy ester in 100 ml of benzene containing 5 g of resin[35] was refluxed into a Dean-Stark trap for about 19 hr, when the formation of a cloudy distillate had ceased. A conventional work-up afforded 23.6 g (86%) of methyl 3-(3,5-di-*tert*-butylphenyl)acrylate (**37**),* bp 134–137° (0.5 mm). In another experiment similar to this except that boron trifluoride etherate (2 ml) replaced the resin and 10 g of molecular sieves[46] was included in the reaction mixture, a 44% yield of **37** was obtained and a 28% yield of dimethyl 3,5-di-(3,5-di-*tert*-butylphenyl-)-4-oxaheptanedioate (**41**),* mp 157.5–158.5°. Catalytic hydrogenation of the acrylate over 5% Pd/C in ethyl acetate for 90 min produced methyl 3-(3,5-di-*tert*-butylphenyl)propanoate (**38**),* bp 121–124° (0.5 mm), in 92% yield. Reduction of **38** (undistilled product from reduction of **37**) in THF yielded **36**, bp 119–121° (0.4 mm), in 93% overall yield from **37**. The mesylate **36a**,* mp 69–72°, was obtained in 94% yield. By treatment of 19.8 g of **36a** in toluene containing Aliquat 336[20] with aqueous sodium bromide there was obtained 20.3 g (82%) of **31**,* bp 120–121° (0.4 mm). This bromide, **31**, was also produced in high yield by reaction of **36** with CBr_4 and $(C_6H_5)_3P$ as described.[47] The iodide **31a**, bp 124–129° (0.4 mm), *m/e* 358, was also similarly prepared in high yield but was not analyzed because of rapid discoloration. The **31a** used in chemical reactions was always freshly prepared.

1,5-Di-(3,5-di-*tert*-butylphenyl)-1-pentyne (33).* The sodium hexamethyldisilazane prepared from 1.69 g of hexamethyldisilazane[48] and sodium amide in 75 ml of dry benzene was treated with a solution of 2.14 g of **30** in 10 ml of diglyme and 15 ml of benzene. During the addition of **30** a white precipitate appeared. A solution of 3.11 g of **31** in 15 ml of benzene was then added during 25 min and the mixture was refluxed for 12 hr. The product, 4.41 g, isolated as usual, was chromatographed over 60 g of silica gel to yield 3.1 g (72%) of **33**, mp 114–116°, using Skellysolve B. The analytical sample, obtained with little loss by recrystallization from ethanol, melted at 118.5–119.5°. In a similar preparation, except that **31a** was used instead of **31**, a 74% yield of **33** was obtained.

Attempts to Prepare a Rotaxane. In several similar experiments about 12 g of **1a** was added after the preparation of the sodium salt of **30** and the benzene was removed by distillation. Freshly distilled iodide **31a** was then added to the viscous residue during 5 min at 25°. Then about 2 ml of benzene was added whereupon an exothermic reaction occurred (40°). The benzene was then distilled and the mixture was heated at 70° for 66 hr. After isolation as usual the entire product was chromatographed over 350 g of silica gel. From the fractions eluted with Skellysolve B there was recovered appreciable amounts of **30**, **31a**, and **33**, followed by 1.1 g of a fraction which on mass spectrographic analysis showed a peak at *m/e* 849, that expected for the rotaxane. However, further attempts at chromatography of this fraction failed to yield a pure rotaxane. When the lithium salt of **30** was used (prepared with butyllithium) results similar to those described above were obtained.

1-(3,5-Di-*tert*-butyl)phenyl-1,7-heptanediol (39).* A solution of 45 g of 6-(tetrahydropyranyloxy)hexyl chloride, bp 125–128° (4.5 mm), prepared in 85% yield essentially as described,[49] in 50 ml of THF was added during 1 hr to 6.8 g of Mg in 100 ml of THF after about 2 g of ethylene dibromide[50] had been used to activate the Mg. After refluxing for 2 hr and cooling to room temperature a solution of 25 g of **35**[25] in 50 ml of THF was added rapidly and the resulting mixture was held at reflux for 2 hr. After the usual work-up 30 g (80%) of **39**, bp 204–206° (0.5 mm), suitable for further work, was obtained. After a small sample had stood for 2 weeks it crystallized to yield the analytical sample, mp 79–80°, on recrystallization from petroleum ether (bp 90–100°).

7-(3,5-Di-*tert*-butylphenyl)heptanol (40).* A mixture of 62 g of **39**, 300 ml of pure methanol, 1 ml of concentrated H_2SO_4, and 0.5 g of 5% Pd/C was hydrogenated under 50 psi of H_2 for 10 hr to yield 56 g (95%) of **40**, bp 158–160° (0.9 mm). When pure **39** was used the major part of the reduction was complete within 30 min.

7-(3,5-Di-*tert*-butylphenyl)heptyl Bromide (32) and Iodide (32a). The mesylate of 30 g of **40** was prepared in a conventional way in benzene using triethylamine and converted into **32**, bp 160–162° (0.5 mm), in 91% overall yield by using phase transfer catalysis[18] and aqueous sodium bromide. Similarly the iodide **32a**, bp 188–194° (1.5 mm), was obtained in 82% overall yield. Because both the bromide and iodide discolored on standing no analyses were performed. However, NMR data [$CDCl_3$, $(CH_3)_4Si$, δ 0] were consistent with data expected from **32**, δ 1.29 [s, 28, $(CH_3)_3C$ and $(CH_2)_5$], 2.50 (t, 2, J = 7 Hz, $ArCH_2$), 3.25 (t, 2, J = 7 Hz, CH_2Br), 6.68 (d, 2, J = 2 Hz, ArH), and 7.12 (t, 1, J = 2 Hz, ArH); and **32a**, δ 1.29 [s, 28, *t*-Bu and $(CH_2)_5$], 2.50 (t, 2, J = 7 Hz, $ArCH_2$), 3.10 (t, 2, J = 7 Hz, CH_2I), 6.85 (d, 2, J = 2 Hz, ArH), and 7.12 (t, 1, J = 2 Hz, ArH). Freshly distilled samples of **32** and **32a** were used in all alkylation experiments.

1,9-Di-(3,5-di-*tert*-butylphenyl)-1-nonyne (34).* In the best of several experiments in which solvent (DMSO, diglyme, HMPA) and cation (Na, Li) were varied, a solution of 2.14 g of **30** in 10 ml of hexane at 0° was treated with 5.3 ml of 1.9 *M* butyllithium in hexane. The white precipitate which formed dissolved after adding 10 ml of THF. To this solution was added 3.67 g of **32** in 20 ml of hexamethylphosphoramide, freshly distilled from CaH_2. The mixture was held at room temperature and worked up as usual to yield 3.6 g (72%) of **34**, isolated by chromatography as an oil. Hydroge-

nation over 5% Pd/C in ethyl acetate afforded 1,9-di(3,5-di-*tert*-butylphenyl)nonane (**42**),* mp 45–46°. In all attempts to obtain a rotaxane compound by treating Na and Li salts of **30** with **32** or **32a** in the presence of **1a**, no fractions were obtained which showed the presence of a rotaxane when subjected to mass spectrographic analysis.

Registry No.—**1**, 55333-55-6; **1a**, 55333-56-7; **2**, 55333-79-4; **3**, 55333-80-7; **3a**, 55333-81-8; **4**, 55333-82-9; **4a**, 55333-83-0; **4b**, 55333-84-1; **5**, 55333-85-2; **5a**, 55333-86-3; **5b**, 55333-87-4; **5c**, 55333-88-5; **6**, 55333-89-6; **6a**, 55333-90-9; **6b**, 55333-91-0; **6c**, 55333-92-1; **7**, 55400-73-2; **8**, 55333-93-2; **9**, 55400-71-0; **10**, 6334-96-9; **11**, 55333-94-3; **12**, 55333-95-4; **13**, 592-33-6; **14**, 627-18-9; **15**, 34399-67-2; **17**, 2396-61-4; **18**, 55333-96-5; **19**, 30242-05-8; **20**, 55333-97-6; **21**, 55333-98-7; **22**, 55333-57-8; **23**, 55333-58-9; **24**, 55333-59-0; **25**, 55333-60-3; **26**, 55333-61-4; **27**, 55333-62-5; **28**, 55333-63-6; **29**, 55333-64-7; **30**, 36720-94-2; **31**, 55333-65-8; **31a**, 55333-66-9; **32**, 55333-67-0; **32a**, 55333-68-1; **33**, 55333-69-2; **34**, 55333-70-5; **35**, 17610-00-3; **36**, 55333-71-6; **36a**, 55333-72-7; **37**, 55333-73-8; **38**, 55333-74-9; **39**, 55333-75-0; **40**, 55333-76-1; **41**, 55333-77-2; **42**, 55333-78-3; methanesulfonyl chloride, 124-63-0; 1,5-pentanediol, 111-29-5; 1,6-hexanediol, 629-11-8; 1,3-propanediol, 504-63-2; 6-(tetrahydropyranyloxy)hexyl chloride, 2009-84-9.

References and Notes

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(13) Reference 11, p 308.
(14) A referee pointed out that an alternate apparatus has been described: D. W. Karle, Ph.D. Thesis, University of South Carolina, 1965, CU Microfilms No. 65-7233.
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(25) The screening tests were the following.

Acute Hypotensive. Two rats are given a single dose of the test compound orally. Mean arterial pressure is measured directly from the aorta through a chronic indwelling cannula, prior to and 4 and 24 hr after dosing. Variations in average pressure at the three time periods are evaluated statistically.

Antidiabetic. The test compound is administered orally to rats at a dosage of 100 mg/kg. Immediately prior to giving the test material the animals are injected subcutaneously with 100 mg of glucose. The rats are bled two hours later via the jugular vein and blood sugar concentrations determined. Results are expressed as a ratio (T/C) of blood glucose values of test animals to controls. [See G. C. Gerritsen and W. E. Dulin, *J. Pharmacol. Exp. Ther.*, **150**, 491 (1965)].

Anti-inflammatory Hind Paw Edema. The test compound is administered orally, and its effect on the reduction of the local inflammatory edema produced by injection of carageenin in the right paw of the rat is expressed as per cent inhibition of edema formation and as potency relative to a standard such as aspirin. [See E. M. Glenn, B. J. Bowman, W. Kooyers, T. Koslowske, and M. L. Myers, *J. Pharmacol. Exp. Ther.*, **155**, 157 (1967)].

Antiviral-Cell Culture. Test compounds are added to infected (RNA and DNA viruses) and control cell cultures which are subsequently examined for cell toxicity and/or antiviral activity, scored in terms of relative diameter of cell lysis protection.

Antiviral in Vivo. The compound is administered to mice, intraperitoneally, 100 mg/kg before and after intranasal infection with encephalomyocarditis (EMC) virus. A three-stage sequential system is used to classify the compound as active or inactive on the basis of mortality in groups of animals.

CNS Preliminary Screen. The compound is administered intraperitoneally to a group of mice at a dose of 100 mg/kg. Observations, 30 min after dosing, are made on spontaneous effects and autonomic symptoms. Then nicotine sulfate is injected intravenously and observations on convulsions and lethality are recorded.

Apomorphine Antagonism. The ability of the test compound administered intraperitoneally to inhibit cage climbing in mice induced by 2.5 mg/kg dose of apomorphine is expressed in terms of seconds (out of a 60-sec test period) in which the mice did show the climbing response.

Diuretic. Fasted male rats are given a 40 mg/kg oral dose of the test compound, and urine volume is measured for 5 hr after administration. [See L. L. Skaletzky, B. E. Graham, and J. Szmuszkovicz, *J. Med. Chem.*, **12**, 977 (1969)].

Serum Lipids. The test compound is administered orally in two divided doses in a 20-hr period following the injection of Triton WR-1339 to fasted rats. At 43 hr after the Triton injection, blood is collected, and serum cholesterol and triglycerides are determined. Values are reported in relation to those in 30 control animals. [See P. E. Schurr, J. R. Schultz, and T. M. Parkinson, *Lipids*, **7**, 68 (1972)].

Cholesterol–Lipoprotein. The test compound is administered orally to groups of rats prefed a diet which elevates blood lipids. After four days of compound treatment, the animals are fasted overnight, blood collected, and individual serum samples analyzed for total cholesterol and heparin-precipitable lipoprotein. Values are reported in terms of ratios to corresponding levels in control animals. [See A. Tinsho, I. Shimizu, T. Takenawa, H. Hikuchi, and T. Rukjo, *J. Pharm. Soc. Jpn.*, **92**, 879 (1972)].

Signed by Paul W. O'Connell, Ph.D., Head, Biological Screening Office, the Upjohn Co., Kalamazoo, Mich.

(26) The screening tests were as follows.

Compounds **26**, **27**, and **29** were screened rather extensively in a series of in vitro tests for antimicrobial activity. These include a standard in vitro assay, by an agar tube dilution method, for an assortment of gram-positive and gram-negative bacteria and fungi considered important in human disease; plus other antibacterial and antifungal activities in vitro for organisms of industrial significance, e.g., for the pulp, paper, and paint industries.

These compounds were also tested in a standard anthelmintic assay in which they were administered for varying periods of time to laboratory rodents harboring commonly available parasites (flukes, nematodes, etc.) of specific ages. They were tested for coccidiosis activity by administering mixed with feed to groups of chickens harboring an infection of *Eimeria* over a standard length of time.

In vitro antiviral testing was carried out by adding the compounds to cells infected with a representative of DNA or RNA virus such as herpes, adeno, polio, para-influenza, or rhinovirus.

Compound **29** was examined in a special in ova procedure against a transplantable tumor, the assay being designed to pick up activity against both the primary tumor and metastasis of the tumor.

As you know, of all the testing mentioned above, the single positive result was with **26**, which showed some in vitro activity against rhinoviruses. We have attached no significance to the finding.

Signed by Norman G. Brink, Ph.D., Director of University Relations, Merck Sharp and Dohme Research Laboratories, Rahway, N.J.

(27) M. S. Newman and L. F. Lee, *J. Org. Chem.*, **37**, 4468 (1972).
(28) (a) All melting and boiling points are uncorrected. Melting points were taken with a Thomas-Hoover capillary melting apparatus. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich., and Galbraith Laboratories, Knoxville, Tenn. Infrared (ir) absorption spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on an A-60 NMR spectrophotometer, Varian Associates, Palo Alto, Calif. A Varian Aerograph A90-P3 was used for gas–liquid chromatographic (GLC) analyses. Silica gel, 100–200 mesh, purchased from Matheson Coleman and Bell and Woelm activity grade I alumina were used for column chromatography. The phrase "worked up as usual" means that the reaction mixture was extracted with ether–benzene and the organic solution was washed successively with water and saturated sodium chloride solution and dried by filtering through a bed of anhydrous magnesium sulfate, and the solvent was removed in vacuo on a rotary evaporator. (b) All compounds marked with an asterisk gave analytical results within 0.3% of the theoretical: Ed.
(29) Tetraethylene glycol (Aldrich Chemical Co.) was fractionated to yield a constant-boiling fraction, bp 198° (14 mm).
(30) All reactions were carried out in three-necked flasks fitted with pressure

equalizing addition funnels, reflux condenser, and appropriate mechanical stirrers.
(31) The side arm of such flasks varied from 6 to 8-in. depending on the size of the flask. All parts were at 0.5–0.75 in. i.d.
(32) Heating of the pot in such distillations was best accomplished by means of a molten salt bath (equimolar $NaNO_2$, KNO_3) with the external liquid level up to the narrow neck of the Claisen flask. Near the end of the distillation the refluxing distillate in the side arm was easily forced over by use of a heat gun or a Bunsen burner played gently over the side arm.
(33) The conditions described led consistently to better yields than others in which lower temperatures and other solvents were used.
(34) K. Alexander and L. E. Schniepp, *J. Am. Chem. Soc.*, **70**, 1839 (1948).
(35) Analytical grade cation exchange resin, AG-50W-X_4, 200–400 mesh, obtained from Bio-Rad Laboratories.
(36) A boiling point of 148–162° (15 mm) is given in ref 20.
(37) A suitable apparatus is described in M. S. Newman, "An Advanced Organic Laboratory Course", Macmillan, New York, N.Y., 1972, p 110.
(38) Any unreacted sodium was not transferred to the high-dilution flask. In many runs an undetermined amount of sodium failed to react. However, since such a large excess of sodium *N*-methylanilide was used, the yield of product did not seem to be affected.
(39) To determine the setting of the plunger in the addition funnel[11] the drop rate (in this case, 1 drop in 3–3.5 sec) was determined by calibration.
(40) In larger runs (and when much solid was present on walls in some runs) it was preferable to use 50% alcohol during the first stages of quenching.
(41) If polymer had formed in a reaction, it separated at this stage and could be removed by filtration.
(42) A suspension of KH in mineral oil was used as obtained from AIFA Products, Beverly, Mass. No isoprene was used.
(43) The use of sodium bis(trimethylsilyl)amide for preparation of sodio derivatives of nitriles has been described by C. Kruger, *J. Organomet. Chem.*, **9**, 125 (1967), and references cited therein.
(44) An increase in volume is noted on saturation of CH_3OH with HCl, e.g., 900 ml of CH_3OH yields 1250 ml of methanolic HCl.
(45) For a description of the apparatus used see ref 36, p 102.
(46) Linde 4A, Ventron, Beverly, Mass.
(47) J. Hooz and S. S. H. Gilliani, *Can. J. Chem.*, **46**, 86 (1968).
(48) U. Wannagat and H. Niederprum, *Chem. Ber.*, **94**, 1540 (1961).
(49) A. Fournet, R. Achard, and J. Morel, *C. R. Acad. Sci.*, **260**, 5054 (1965).
(50) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).

Mechanism and Stereochemistry of Oxetane Reactions. II. High Syn Stereoselectivity in the Oxetane Ring Opening of 6-Phenyl-7-oxabicyclo[4.2.0]octane under Acidic Conditions. Comparison with the Analogous Reactions of the Corresponding Oxirane

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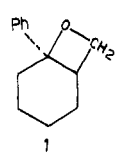
The direction and the stereochemistry of some oxetane ring opening reactions of 6-phenyl-7-oxabicyclo[4.2.0]octane (1) have been determined and compared with those of the corresponding oxirane (2). The reactions of 1 give mixtures of the syn and anti addition products, of the olefin 6 and of the unsaturated alcohol 9. Unexpectedly, some of the addition products are not stable under the reaction conditions and show facile epimerization at the tertiary carbon. The true kinetic product ratios were therefore obtained by extrapolation. The results reveal significant variation in the stereoselectivity and in the yields and ratios between the trichloroacetolysis and the solvolysis reactions of 1. A comparison of the reactions of 1 and 2 shows a much larger amount of nonaddition products in the case of oxetane 1 and marked differences in the syn stereoselectivity. The observed data can be explained by means of a mechanism involving transition states or intermediates with a high degree of carbocation character.

Whereas the stereochemistry of the ring opening of oxirane derivatives has received much attention and has been extensively investigated,[1,2] almost no data are available on that of their higher homologs, the oxetanes.[3] Although the structure and hybridization of orbitals in oxetanes and oxiranes are fundamentally different, the reactivity of the two systems is similar, especially under acidic conditions: the lesser degree of ring strain in oxetanes can be compensated by the greater electron donor capability of the ring oxygen atom.[3]

Previous work carried out in these laboratories on the stereochemistry of the ring opening of substituted oxiranes in acidic media has shown that these reactions are strongly influenced by several factors, such as structure, conformation, and configuration of the epoxide, solvent, type of reagent, etc. In order to get a better insight into the reactivity of the oxetane system and to establish how the stereochemical behavior of the ring opening of small-ring heterocycles can be modified depending on the size of the ring, we have undertaken a study of 6-phenyl-7-oxabicyclo[4.2.0]octane (1), a homolog of the oxirane 2 which has been thoroughly investigated and characterized.[2a,b,g,4,5] Furthermore, protonated oxetanes have been often suggested as intermediates in the Prins reaction,[6] so that a knowledge of the stereochemistry of oxetane ring opening under acidic conditions



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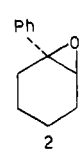

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could offer a good tool for a better understanding of the debated mechanism of the Prins reaction.

Oxetane 1 has been prepared by conversion of the cis diol 3 into the tosylate 4, which on treatment with potassium *tert*-butoxide afforded 1 (Chart A). The structure of 1 was confirmed by its ir and NMR spectra: presence of an ir band at 10.3 μ[7] and a NMR signal at δ 4.45 due to the methylene protons of the oxetane ring.[8]

It was first necessary to define the regiochemistry of the ring opening of 1. In fact, whereas the attack of the nucleophile on the benzylic carbon of 1 can afford both cis and trans products, the attack on the oxetane methylenic carbon can give, evidently, only cis products. The acid-catalyzed solvolysis of 1 in anhydrous methanol gave mixtures of the two methyl ethers 7 and 8 and of small amounts of the olefin 6 and the unsaturated alcohol 9; the methyl ether 5 arising from a nonbenzylic attack of the nucleophile was not detected and less than 0.2% of it could have been present. The conversion of 1 was very rapid (it had com-