for 6 h with stirring. The mixture was filtered, extracted with ether, and dried over sodium sulfate. After concentration, 0.45 g (40%) of **19a** was obtained. **19a:** mp 217–218 °C (ethanol); IR (Nujol) 3140, 1660, 1600, 1580, 1550 cm^{-1}; mass spectrum (70 eV) *m/e* 225 (M^+); NMR (Me_2SO-d_6) δ 2.53 (s, 3 H, SCH_3), 7.37–7.87 (m, 3 H, aromatic), 8.10–8.33 (m, 1 H, aromatic), 11.63 (br, 1 H, NH).

Anal. Calcd for $C_{10}H_8NOSCl$: C, 53.22; H, 3.55; N, 6.21; S, 14.19; Cl, 15.74. Found: C, 53.07; H, 3.40; N, 6.21; S, 14.02; Cl, 15.52.

Bromination of 17. To a suspension of **17** (0.5 g, 2.6 mmol) and CuO (0.5 g) in ethanol (30 mL) was added bromine (1 g) at room temperature and the mixture was heated at 60 °C for 7 h with stirring. After cooling, the precipitate was filtered and washed with hot ethanol. The filtrate was concentrated to give 0.7 g (100%) of **19b:** mp 220–222 °C (ethanol); IR (Nujol) 3120, 1650, 1600, 1570, 1540 cm^{-1}; mass spectrum (70 eV) *m/e* 269 (M^+); NMR ($CDCl_3$) δ 2.66 (s, 3 H, SCH_3), 7.33–7.94 (m, 3 H, aromatic), 8.12–8.36 (m, 1 H, aromatic), 11.61 (br, 1 H, NH).

Anal. Calcd for $C_{10}H_8NOSBr$: C, 44.44; H, 2.96; N, 5.19. Found: C, 44.42; H, 2.81; N, 5.11.

Registry No.—**5a,** 64188-42-7; **5b,** 64188-40-5; **5c,** 64188-38-1; (*E*)-**6a,** 64188-36-9; (*Z*)-**6a,** 64188-34-7; (*E*)-**6b,** 64188-33-6; (*Z*)-**6b,** 64188-35-8; (*E*)-**6c,** 64188-32-5; (*Z*)-**6c,** 64188-56-3; (*E*)-**7a,** 64188-55-2; (*Z*)-**7a,** 64188-54-1; (*E*)-**7b,** 64188-53-0; (*Z*)-**7b,** 64188-52-9; (*E*)-**7c,** 64188-50-7; (*Z*)-**7c,** 64188-51-8; **8a,** 64188-49-4; **8b,** 64188-48-3; **9a,** 541-46-8; **9b,** 103-81-1; **10,** 64188-47-2; **11a,** 64188-46-1; **11b,** 64188-45-0; **12,** 28669-33-2; **13a,** 7182-10-7; **13b,** 2981-10-4; **15a,** 64188-44-9; **15b,** 64188-43-8; **16,** 64188-41-6; **17,** 64188-39-2; **18,** 491-30-5; **19a,** 64188-37-0; **19b,** 64201-56-5; aniline, 62-53-3; *p*-nitrophenylhydrazide, 100-16-3; phenylhydrazide, 100-63-0.

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Synthesis of *N*-Methyl-1-oxa-5-aza[10]paracyclophane: A Conformationally Restricted Analogue of Phenoxypropylamines[1a]

Ching Sui Yi,[1b] Louis C. Martinelli,[1c] and C. DeWitt Blanton, Jr.*

Department of Medicinal Chemistry, School of Pharmacy, University of Georgia, Athens, Georgia 30602

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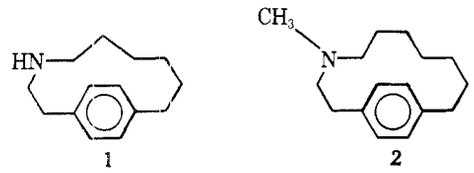
The synthesis of *N*-methyl-1-oxa-5-aza[10]paracyclophane (**4**) is reported; this represents the first example of this ring system being formed via an intramolecular halo–phenoxide reaction (ether synthesis). Attempts to synthesize phenoxyethylamine and phenoxypropylamine analogues by the acyloin reaction or by the intramolecular amine–ester reaction failed to yield the desired paracyclophanes.

Many compounds have been prepared as conformationally restricted analogues of phenethylamine in order to assess stereochemical requirements of the drug receptor.[2] These served as a stimulant for the recent publication[3] of the synthesis of 3-aza[10]paracyclophane (**1**) and *N*-methyl-3-aza[10]paracyclophane (**2**). In this paper, we are reporting the results of synthesis of conformationally restricted analogues **3** and **4** of adrenergic antagonists which contain the basic ar-



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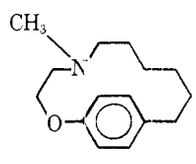

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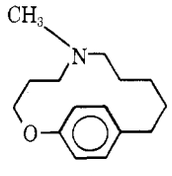


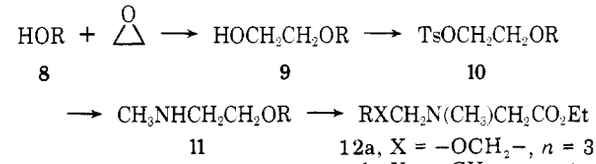
4

yloxyethylamine or aryloxypropylamine structure (e.g., phenoxybenzamine and propranolol).

Since the acyloin reaction is perhaps the most important method for preparing paracyclophanes,[4] the first approach studied attempted to synthesize an oxazaparacyclophane (**3**) by utilizing the appropriate diester (**12a**) in an acyloin reaction (Scheme I). The diester was obtained in a straightforward manner through Friedel–Crafts acylation[5] of anisole by succinic anhydride. The keto acid **5** was reduced by the Clemmensen method,[6] and the resulting acid **6** was treated with 48% hydrobromic acid. The phenolic acid **7** was esterified[7] and the phenolic ester **8** reacted with ethylene oxide followed by tosylation and amination to give the amino ester **11.** Alkylation with ethyl bromoacetate resulted in the diester **12a.** However, under normal acyloin reaction conditions,[9] this diester failed to undergo the cyclization reaction. Only starting material and a polymeric substance were isolated from the reaction mixture.

Recently, Wu and co-workers[3b,8] found that a diester (**12b**) with an ester group one carbon length away from the nitrogen atom would not cyclize in the acyloin reaction. However, with

Scheme I[a]



$RXCH_2N(CH_3)(CH_2)_2CO_2Et$

13a, X = $-CH_2-$, n = 3
b, X = $-OCH_2-$, n = 3

[a] R = $-Ph(CH_2)nCO_2Et$, n = 3, 4.

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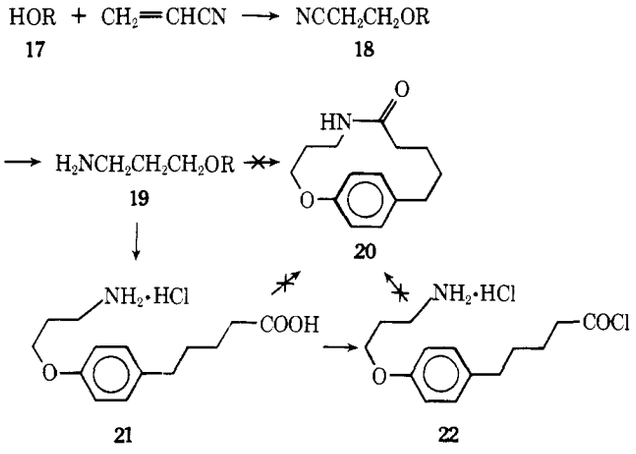
Scheme II[a]



[a] R = -Ph(CH2)4CO2CH3.

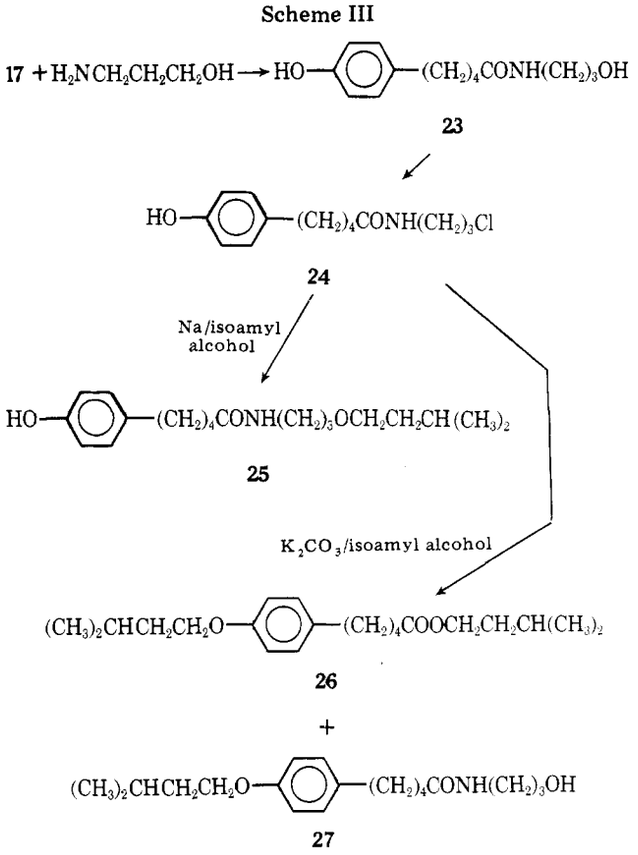
diester **13a** the acyloin reaction gave the cyclized product which was utilized to prepare the paracyclophane **2.** Replacing ethyl bromoacetate by ethyl bromopropionate (Scheme I) gave diester **13b** with the ester group two carbon lengths away from the nitrogen atom. This diester (**13b**) still failed to undergo the normal acyloin reaction. Addition of trimethylchlorosilane (Me_3ClSi)[10] to the reaction process also failed to produce any cyclized product.

Since the important acyloin reaction failed, other intramolecular reactions were considered. The second attempt involved the intramolecular amine–ester reaction (Scheme II). The synthetic route for the synthesis of **17** was similar to that described in Scheme I, except glutaric anhydride was used instead of succinic anhydride. Michael reaction of the phenolic ester **17** with acrylonitrile, followed by catalytic hydrogenation, gave the amino ester **19.** Refluxing the amino ester **19** in xylene or Dowtherm-A for 5 days gave a small amount of polymeric intermolecular amide as indicated by TLC and IR. Most of the amino ester was recovered without change. These results suggested a modification of the ester group in an attempt to obtain a more reactive moiety.

First, the ester was converted to the acid **21.** In order to facilitate reaction of the amino group with the carboxyl group, an attempt to form a mixed anhydride at the carboxylic acid moiety was studied. This was done by using dicyclohexylcarbodiimide (DCC)[11] or 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate[12] as in peptide-synthesis techniques. But, due to the limited solubility of the amino acid **21** in acetonitrile or methylene chloride, the reaction was unsuccessful. Similar results were obtained when the acyl halide moiety **22** replaced the carboxylic acid group.

Finally, the intramolecular halo–ether reaction was considered for the synthesis of an oxazaparacyclophane. The phenolic halide **24** was prepared by amination of the phenolic ester **17** with 3-amino-1-propanol, followed by treatment with thionyl chloride (Scheme III). When the phenolic halide was subjected to the intramolecular halo–phenoxide reaction,[13] ether **25** was isolated in 80% yield. A possible explanation is that isoamyl alcohol reacts with sodium to form the alkoxide anion instead of the phenoxide anion, and the alkoxide anion displaced the halogen. Therefore, potassium carbonate was used to modify the reaction condition in an attempt to achieve a selective reaction with only the phenolic moiety (Scheme III). However, two products were isolated from the reaction mixture. Compound **27** was the major product (60% yield), whereas **26** was isolated in a maximum yield of only 5%. Possible explanations for the reaction products involve the presence of the amide proton on phenolic halide **24.**

Scheme III

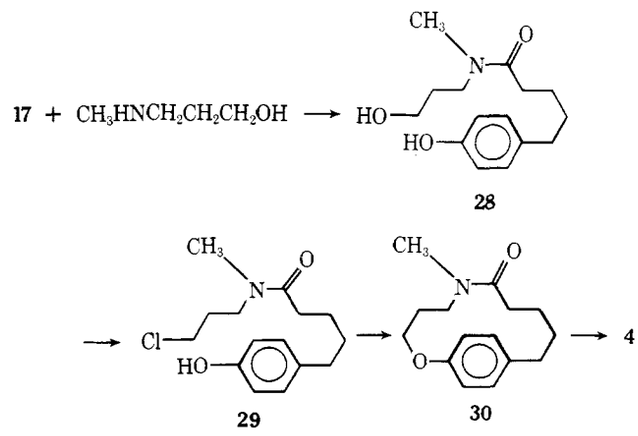


Structural assignment for compounds **25** and **27** was based on the IR and NMR spectrum and elemental analysis. Structural assignment for **26** was based on the IR and NMR spectrum only. Compound **27** gave a positive chromic anhydride test[14] and a negative bromine in water test,[14] indicating the presence of an alcoholic group and not a phenolic group.

To solve the amide proton problem, the phenolic halide **29** (Scheme IV) was prepared by amination of the phenolic ester **17** with *N*-methyl-3-amino-1-propanol, followed by treatment with thionyl chloride. When compound **29** was subjected to the high dilution intramolecular halo–phenoxide reaction, a yellowish thick oil was obtained. Chromatographic separation provided the lactam **30.** Lithium aluminum hydride reduction gave the desired product, *N*-methyl-1-oxa-5-aza[10]paracyclophane (**4**).

Structural assignments for **30** and **4** were confirmed by IR, NMR, and MS. Compound **4** gave the correct elemental analysis. The NMR spectra also provided further evidence for the paracyclophane. The open-chain phenolic alcohol **28** and

Scheme IV



phenolic halide **29** showed two methyl peaks at δ 2.89, 3.0 and δ 2.85, 3.0, respectively, representing the anti and syn conformers with the anti conformer dominating approximately 2:1. After cyclization, the lactam **30** also showed two methyl peaks at δ 2.88 and 3.0, but with equal intensity as expected. The NMR temperature-dependent studies showed these two methyl peaks coalesced at 70 °C. On cooling, the single peak separated again. This suggests that at room temperature the rotation about the central C–N bond of the disubstituted amide **30** is hindered, and two resonance peaks were observed. When the temperature was increased to 70 °C, the energy barrier about the C–N bond was overcome and coalescence occurred. The methylene protons at positions 3, 8, and 9 of compound **4** are shifted to δ 1.3 compared to 1.6 of the open-chain compounds **28** and **29.** This also suggests that protons are shielded by the aromatic ring as is the character of paracyclophanes.[15]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 467 grating spectrophotomer. The NMR spectra were determined on a Hitachi Perkin-Elmer R20 A high-resolution NMR spectrometer using tetramethylsilane (Me_4Si) as internal reference. Mass spectra were determined on a Dupont 21-490 mass spectrometer, Department of Biochemistry, University of Georgia. Elemental analyses were determined by Atlantic Microlab, Inc., Atlanta, Georgia. TLC were performed on Eastman Chromatogram sheets, Type 6060 (silica gel).

β-Anisoylpropionic acid (**5**) was prepared from anisole and succinic anhydride, mp 145–146 °C (lit. mp 144.5–146.5 °C).[5] Reduction of **5** by the Clemmensen method[6] gave γ-(*p*-methoxyphenyl)butyric acid (**6**), mp 56–58 °C (lit. mp 56 °C).[5] The keto acid **6** was treated with 48% hydrobromic acid to yield γ-(*p*-hydroxyphenyl)butyric acid (**7**), mp 104–106 °C (lit. mp 110–111 °C).[16] γ-Anisoylbutyric acid (**14**) was prepared from anisole and glutaric anhydride, mp 137–138 °C (lit. mp 139 °C).[16] Reduction of **14**[6] gave δ-(*p*-methoxyphenyl)valeric acid (**15**), mp 111 °C (lit. mp 116 °C).[16] Treatment of **15** with hydrobromic acid gave δ-(*p*-hydroxyphenyl)valeric acid (**16**), mp 114–116 °C (lit. mp 117–119 °C).[17] These starting materials were obtained in 75–95% yield.

Ethyl γ-(*p*-Hydroxyphenyl)butyrate (8). To the solution of **7** (180 g, 1 mol) in 700 mL of absolute ethanol was added 1 mL of concentrated hydrochloric acid. The mixture was refluxed in a Soxhlet extractor filled with a 3-Å molecular sieve[7] for 12 h. Ethanol was removed in vacuo and the residue was poured into 300 mL of water and extracted with two 200-mL portions of chloroform. The chloroform layer was dried over sodium sulfate and concentrated on the rotary evaporator. The residual liquid was distilled under reduced pressure to yield 190 g (91.3%) of colorless liquid: bp 125 °C (0.005 mm); IR (neat) 3450, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3 H, ethyl CH_3), 1.95 (m, 2 H, β-CH_2), 2.21 and 2.55 (2 t, 4 H, α- and γ-CH_2's), 4.14 (q, 2 H, ethyl CH_2), 6.8 and 7.04 (2, d, 4 H, aromatic H's), 7.41 (s, 1 H, phenol).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 68.97; H, 7.81.

Ethyl γ-[*p*-(2-Hydroxyethoxy)phenyl]butyrate (9). A mixture of **8** (4.16 g, 0.2 mol), potassium carbonate (27.6 g, 0.2 mol), and 300 mL of absolute ethanol was refluxed for 2 h. After cooling, the reaction mixture was placed in an ice–salt bath and 25 g (0.55 mol) of ethylene oxide was added. The whole mixture was warmed slowly to room temperature and stirred for 36 h under a closed system. After filtration, the alcohol was removed in vacuo to yield a highly viscous liquid (quantitative); IR (neat) 3490, 1748 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3 H, ethyl CH_3), 1.88 (m, 2 H, β-CH_2), 2.19 and 2.56 (2 t, 4 H, α- and γ-CH_2's), 3.91 (s, 4 H, OCH_2CH_2O), 4.1 (q, 2 H, ethyl CH_2), 6.8 and 7.09 (2 d, 4 H, aromatic H's).

A phenylurethane derivative[18] of **9** was prepared: mp 82–84 °C.

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.78; H, 6.80; N, 3.77.

Ethyl γ-[*p*-(2-*p*-Toluenesulfonoxyethoxy)phenyl]butyrate (10). To a solution of **9** (50 g, 0.2 mol) in 200 mL of dry pyridine was added *p*-toluenesulfonyl chloride (38 g, 0.21 mol), at or below 0 °C, over a period of 20 min. The mixture was stirred at 0 °C for 4 h and then poured into 300 mL of cold 6 N hydrochloric acid and extracted two times with 300-mL portions of ether. After removing the ether, the crude thick liquid (70.5 g, 87%) was used without further purification: IR (neat) 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.21 (t, 3 H, ethyl CH_3), 1.92 (m, 2 H, β-CH_2), 2.39 (s, 3 H, $ArCH_3$), 2.2–2.62 (m, 4 H, α- and γ-CH_2's), 4.1 (q, 2 H, ethyl CH_2), 4.09 and 4.32 (m, 4 H, OCH_2CH_2O), 6.68 and 7.06 (2 d, 4 H, aromatic H's), 7.3 and 7.82 (2 d, 4 H, tosyl aromatic H's).

Ethyl γ-[*p*-(2-*N*-Methylaminoethoxy)phenyl]butyrate (11). In a 1-L round-bottomed flask was placed 40.6 g (0.1 mol) of **10,** 400 mL of aqueous 40% methylamine solution, and 400 mL of chloroform. The mixture was stirred vigorously for 2 days at room temperature and poured into a separatory funnel. The chloroform layer was separated and the water layer extracted two times with 100-mL portions of chloroform. The combined chloroform layer was dried over magnesium sulfate and removed in vacuo. The residual liquid was distilled under reduced pressure to yield 13.1 g (50%) of slightly yellow liquid: bp 140 °C (0.01 mm); IR (neat) 3370, 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H, ethyl CH_3), 1.9 (m, 2 H, β-CH_2), 2.4 and 2.79 (m, 4 H, α- and γ-CH_2's), 2.48 (s, 3 H, NCH_3), 3.95 (s, 1 H, NH), 4.05 (q, 2 H, ethyl CH_2), 6.8 and 7.1 (2 d, 4 H, aromatic H's).

The hydrochloride salt was prepared by dissolving **11** in ether followed by treatment with hydrogen chloride gas. The salt was collected by filtration: mp 136–138 °C.

Anal. Calcd for $C_{15}H_{23}NO_3$·HCl: C, 59.69; H, 8.02; N, 4.64; Cl, 11.75. Found: C, 59.83; H, 8.03; N, 4.78; Cl, 11.62.

Ethyl γ-[*p*-(2-*N*-Methyl-*N*-carboethoxymethylaminoethoxy)phenyl]butyrate (12a). To a solution of **11** (22 g, 0.093 mol) and dicyclohexylmethylamine (DCMA) (6.2 g, 0.083 mol) in 100 mL of benzene was added 14.4 g (0.085 mol) of ethyl bromoacetate (a precipitate was deposited within 5 min from the stirred mixture). The mixture was refluxed at 80 °C for 6 h, and the precipitate was then removed by filtration. The benzene layer was washed two times with 20 mL of water and removed in vacuo. The yellowish residual liquid was distilled under reduced pressure to yield 23.5 g (80.6%) of diester: bp 180–182 °C (0.075 mm); IR (neat) 2900, 2905, 1750, 1255, 830 cm^{-1}; NMR ($CDCl_3$) δ 1.22 and 1.24 (2 t, 6 H, ethyl CH_3's), 1.88 (m, 2 H, β-CH_2), 2.5 (s, 3 H, NCH_3), 2.25 and 2.58 (m, 4 H, α- and γ-CH_2's), 3.4 (s, 2 H, NCH_2COO), 4.06 (t, 2 H, $ArOCH_2$), 4.09 and 4.11 (2 q, 4 H, ethyl CH_2's), 6.82 and 7.1 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.94; H, 8.31; N, 3.98. Found: C, 64.80; H, 8.35; N, 3.92.

Ethyl γ-[*p*-(2-*N*-Methyl-*N*-β-carboethoxyethylaminoethoxy)phenyl]butyrate (13b). This compound was prepared by the same procedure as compound **12a.** The only difference was the use of ethyl bromopropionate instead of ethyl bromoacetate. A light yellow liquid was obtained in 75–80% yield: bp 208–210 °C (0.02 mm); IR (neat) 2940, 2860, 2800, 1730, 1612, 825 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 6 H, ethyl CH_3's), 2.36 (s, 3 H, NCH_3), 1.95–2.8 (m, 12 H, all CH_2's except $ArOCH_2$), 4.05 (t, 2 H, $ArOCH_2$), 4.1 (q, 4 H, ethyl CH_2's), 6.8 and 7.11 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.49; H, 8.61; N, 3.88.

Methyl δ-(*p*-Hydroxyphenyl)valerate (17). This compound was prepared (91%) in the same manner as compound **8,** except methanol was used instead of ethanol: mp 38 °C; bp 155 °C (0.025 mm); IR (neat) 3400, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (m, 4 H, β- and γ-CH_2's), 2.4 (m, 4 H, α- and δ-CH_2's), 3.65 (s, 3 H, CH_3), 6.85 and 7.0 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.16; H, 7.77.

Methyl δ-[*p*-(2-Cyanoethoxy)phenyl]valerate (18). In a 50-mL round-bottomed flask were placed **17** (5.2 g, 0.025 mol) and a small piece of sodium metal in 30 mL of benzene. The mixture was refluxed for 3 h. After cooling to room temperature, 2.5 g, (0.05 mol) of acrylonitrile was added dropwise and the mixture refluxed for 10 h. The reaction mixture was poured carefully into 50 mL of cold 3 N hydrochloric acid and extracted with two 50-mL portions of ether. The ether layer was dried over magnesium sulfate and removed in vacuo to yield a slightly yellow oil (4.2 g, 64%). The crude product was used directly for catalytic hydrogenation without further purification: TLC ($CHCl_3$), R_f 0.45; IR (neat) 2255, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (m, 4 H, β- and γ-CH_2's), 2.0–2.5 (m, 6 H, α- and δ-CH_2's and CH_2CN), 3.6 (s, 3 H, CH_3), 3.9 (t, 2 H, $ArOCH_2$), 6.75 and 7.03 (2 d, 4 H, aromatic H's).

Methyl δ-[*p*-(3-Aminopropyloxy)phenyl]valerate Hydrochloride (19). A mixture of **18** (5.25 g, 0.025 mol), 10 mL of concentrated hydrochloric acid, 1 g of 10% palladium-on-carbon, and 250 mL of methanol was subjected to hydrogenation on a Parr apparatus; initial pressure was 53 psi. After shaking for 2 h, the pressure had dropped to 51 psi and remained constant thereafter. The solution was filtered and the methanol removed in vacuo. The crude product (3.8 g, 66%) was washed several times with ether to yield a white powder

(50%): mp 161–163 °C, TLC ($CHCl_3$), R_f 0.15; IR (KBr) 1740 cm^{-1}; NMR (Me_2SO-d_6) δ 1.5–2.5 (m, 10 H, α-, β-, γ-, and δ-CH_2's and $NCCH_2C$), 2.95 (t, 2 H, NCH_2), 3.58 (s, 3 H, CH_3), 4.02 (t, 2 H, $ArOCH_2$), 6.86 and 7.12 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{15}H_{23}NO_3$·HCl: C, 59.69; H, 8.02; N, 4.64; Cl, 11.75. Found: C, 59.52; H, 8.05; N, 4.70; Cl, 11.86.

δ-[p-(3-Aminopropyloxy)phenyl]valeric Acid Hydrochloride (21). A mixture of **19** (18 g, 0.06 mol) in 150 mL of 6 N hydrochloric acid was refluxed for 12 h. After cooling, the product was collected by filtration and recrystallized from water (14 g, 81.4%): mp 184–187 °C; IR (KBr) 1700 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}NO_3$·HCl: C, 58.43; H, 7.71; N, 4.87; Cl, 12.32. Found: C, 58.54; H, 7.77; N, 4.82; Cl, 12.22.

δ-[p-(3-Aminopropyloxy)phenyl]valeryl Chloride Hydrochloride (22). To a mixture of **21** (10 g, 0.037 mol) in 50 mL of benzene was added 4.2 g (0.04 mol) of thionyl chloride. The reaction mixture was refluxed for 1 h. After cooling, the crude product was filtered. However, the acyl chloride was unstable and hydrolyzed to the corresponding acid within 2 h: mp 144–146 °C; IR (KBr) 1815 cm^{-1}.

***N*-(3-Hydroxypropyl)-δ-(p-hydroxyphenyl)valeramide (23).** A mixture of phenolic ester **17** (20.8 g, 0.1 mol) and 3-amino-1-propanol (15 g, 0.2 mol) was placed in a 200-mL round-bottomed flask and heated at 130 °C for 10 h. Approximately 3 mL of methanol was collected in a Dean–Stark apparatus. The excess 3-amino-1-propanol was removed by distillation under reduced pressure to yield quantitatively a dark-brown thick oil, which decomposed on micromolecular distillation. Without further purification, compound **23** was converted to the corresponding alkyl halide **24** in the following reaction: TLC (chloroform/acetone) R_f 0.2; IR (neat) 3300, 1640 cm^{-1}; NMR (pyridine-d_5) δ 1.5–1.9 (m, 6 H, β- and γ-CH_2's and $NCCH_2C$), 2.1–2.48 (m, 4 H, α- and δ-CH_2's), 3.45 (t, 2 H, NCH_2), 3.72 (t, 2 H, CH_2O), 7.0 (s, 4 H, aromatic H's).

***N*-(3-Chloropropyl)-δ-(p-hydroxyphenyl)valeramide (24).** In the same flask of the above reaction, compound **23** was placed in an ice–salt bath. Thionyl chloride (25 mL) was added dropwise over a period of 1 h. After warming to room temperature, stirring was started and continued overnight. The reaction mixture was poured into 300 mL of ice water and extracted with two 200-mL portions of methylene chloride. The methylene chloride extract was then passed through a silica gel column, using the same solvent as eluent, to yield a yellow thick liquid (13 g, 48.3%): TLC (chloroform/acetone) R_f 0.6; IR (neat) 3300, 1630 cm^{-1}; NMR (acetone-d_6) δ 1.59–2.49 (m, 10 H, α-, β-, γ-, and δ-CH_2's and $NCCH_2C$), 3.37 (t, 2 H, NCH_2), 3.57 (t, 2 H, CH_2Cl), 6.7 and 6.97 (2 d, 4 H, aromatic H's), 7.5 (s, 1 H, phenol); mass spectrum *m/e* 269 (M^+, calcd 269).

Anal. Calcd for $C_{14}H_{20}NO_2Cl$: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.58; H, 7.55; N, 5.12; Cl, 13.02.

***N*-(3-Isoamyloxypropyl)-δ-(p-hydroxyphenyl)valeramide (25).** All glassware was dried overnight in an oven (ca. 150 °C) before use. A 3-L Morton flask was fitted with high-dilution apparatus[19] and a high-speed stirrer[20] with a constant flow of dry nitrogen.[21] Isoamyl alcohol[23] (1.6 L) was charged into the Morton flask and distilled into the high-dilution flask (ca. 0.8 L). Freshly cut sodium metal (6.4 g, 0.28 mol) was transferred and stirred (ca. 10 000 rpm) to make a fine suspension. The phenolic halide **24** (18.7 g, 0.07 mol) in 300 mL of isoamyl alcohol was added dropwise over a period of 10 h to the stirring (ca. 9000 rpm) and refluxing sodium suspension. After the addition was completed, refluxing was continued for 1 h and then the mixture was cooled in an ice–water bath. Acetic acid (10 mL) was added dropwise with moderate stirring, followed by 500 mL of water (under nitrogen flow). Isoamyl alcohol was separated, dried over sodium sulfate, and then removed in vacuo. The residue was purified by silica gel column chromatography, using ether as eluent, to yield a slightly yellow thick oil (17.8 g, 80%): IR (neat) 3320, 2950, 2870, 1650, 1100, 820 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 6.0 Hz, isopropyl CH_3's), 1.36–2.6 (m, 13 H, α-, β-, γ-, and δ-CH_2's, CH, and $NCCH_2COCCH_2C$), 3.25–3.55 (m, 6 H, $NCH_2CCH_2OCH_2$), 6.78 and 7.02 (2 d, 4 H, aromatic H's), 8.71 (s, 1 H, phenol).

Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 70.36; H, 9.02; N, 3.94.

A phenylurethane derivative[18] of **25** was prepared: mp 99–102 °C.

Anal. Calcd for $C_{26}H_{36}N_2O_4$: C, 70.88; H, 8.24; N, 6.36. Found: C, 70.75; H, 8.25; N, 6.37.

Isoamyl δ-(p-Isoamyloxyphenyl)valerate (26) and *N*-(3-Hydroxypropyl)-δ-(p-isoamyloxyphenyl)valeramide (27). The procedure employed for the preparation of compound **25** was used, except potassium carbonate (4 equiv) was employed as the base. The crude product was purified by chromatography on a silica gel column: Fraction 1, petroleum ether eluate, contained silicon or grease; fraction 2, chloroform eluate, gave compound **26** (5%); fraction 3, acetone eluate, gave compound **27** (60%).

Compound **26:** IR (neat) 2960, 2870, 1742, 1240, 815 cm^{-1}; NMR ($CDCl_3$) δ 0.92 and 0.96 (2 d, 12 H, J = 6.0 Hz, isopropyl CH_3's), 1.56–2.57 (m, 14 H, CH and all CH_2's except $ArOCH_2$ and $COOCH_2$), 3.97 and 4.1 (2 t, 4 H, $ArOCH_2$ and $COOCH_2$), 6.8 and 7.1 (2 d, 4 H, aromatic H's).

Compound **27:** mp 55–56 °C; IR (KBr) 3300, 2920, 1635, 1240, 800 cm^{-1}; NMR (acetone-d_6) δ 0.95 (d, 6 H, J = 6.0 Hz, isopropyl CH_3's), 1.55–2.53 (m, 13 H, CH and all CH_2's except $ArOCH_2$ and NCH_2CCH_2O), 3.25 (t, 2 H, NCH_2), 3.95 (t, 2 H, $ArOCH_2$), 6.8 and 7.1 (2 d, 4 H, aromatic H's).

Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99, H, 9.72; N, 4.36. Found: C, 70.72; H, 9.72; N, 4.32.

***N*-Methyl-*N*-(3-hydroxypropyl)-δ-(p-hydroxyphenyl)valeramide (28).** The procedure described for preparing compound **23** was employed, except that *N*-methyl-3-amino-1-propanol was used instead of 3-amino-1-propanol. The crude thick oil product (quantitative yield) decomposed on micromolecular distillation. Compound **28** was converted to the halide **29** without further purification: IR (neat) 3280, 2935, 1618, 1050, 818 cm^{-1}; NMR (acetone-d_6) δ 1.7 (m, 6 H, β- and γ-CH_2's and $NCCH_2C$), 2.45 (m, 4 H, α- and δ-CH_2's), 2.89 and 3.0 (2 s, 3 H, NCH_3), 3.45 (t, 2 H, NCH_2), 3.5 (t, 2 H, CH_2O), 6.76 and 7.04 (2 d, 4 H, aromatic H's).

***N*-Methyl-*N*-(3-chloropropyl)-δ-(p-hydroxyphenyl)valeramide (29).** The procedure described for preparing compound **24** was used. The crude product (40%) was purified by silica gel column chromatography using methylene chloride as eluent to yield a thick brown oil (30%): IR (neat) 3220, 2920, 1605, 1225, 818, 635 cm^{-1}; NMR (acetone-d_6) δ 1.6 (m, 6 H, β- and γ-CH_2's and $NCCH_2C$), 2.4 (m, 4 H, α- and δ-CH_2's), 2.85 and 3.0 (2 s, 3 H, NCH_3), 3.45 (t, 2 H, NCH_2), 3.55 (t, 2 H, CH_2Cl), 6.76 and 7.0 (2 d, 4 H, aromatic H's).

A phenylurethane derivative[18] of **29** was prepared: mp 126 °C.

Anal. Calcd for $C_{22}H_{27}N_2O_3Cl$: C, 65.58; H, 6.76; N, 6.95; Cl, 8.80. Found: C, 65.40; H, 6.78; N, 7.00; Cl, 8.84.

***N*-Methyl-6-keto-1-oxa-5-aza[10]paracyclophane (30).** This compound was prepared in the same general setup as compound **25** above. Xylene[24] (1.6 L) was charged into the Morton flask and distilled into the high-dilution flask (ca. 0.8 L). Freshly cut sodium metal (4 g, 0.17 mol) was transferred and stirred (ca. 10 000 rpm) to make a fine suspension. The phenolic halide **29** (13.1 g, 0.046 mol) in 500 mL of xylene was added dropwise over a period of 12 h to the stirring and refluxing sodium suspension. After the addition was completed, refluxing was continued for another hour and then the mixture was cooled in an ice bath. Acetic acid (10 mL) was added dropwise with moderate stirring, followed by 500 mL of water. The xylene layer was separated from a separatory funnel. The aqueous layer was basified by sodium hydroxide (ca. pH 8.5) and extracted with two 300-mL portions of chloroform. The combined xylene and chloroform layers were dried over sodium sulfate and concentrated on the rotary evaporator to yield a gummy material. This residual product was transferred to a silica gel column. Fractions 1 and 2, methylene chloride eluate, contained grease and some unknown open-chain material. Fraction 3, acetone eluate, gave the lactam **30** (1.5 g, 20%). Fraction 4, methanol eluate, gave an unidentified polymeric material (ca. 50%). The product from fraction 3 (paracyclophane, **30**) decomposed on micromolecular distillation.[25] Therefore, compound **30** was used in the following reaction directly: IR (neat) 2923, 2850, 1630, 1240, 1050, 820 cm^{-1}; NMR (acetone-d_6) δ 1.61 (m, 6 H, $C_{3,8,9}$ CH_2's), 2.4 (m, 4 H, $C_{7,10}$ CH_2's), 2.88 and 3.0 (2 s, 3 H, NCH_3), 3.51 (t, 2 H, C_4 CH_2), 3.94 (t, 2 H, C_2 CH_2), 6.8–7.1 (m, 4 H, aromatic H's); mass spectrum *m/e* 247 (M^+, calcd 247).

***N*-Methyl-1-oxa-5-aza[10]paracyclophane (4).** In a 100-mL three-necked round-bottomed flask was placed lithium aluminum hydride (150 mg, 3.94 mmol) and 50 mL of THF[26] under a constant flow of nitrogen. Lactam **30** (350 mg, 1.41 mmol) in 30 mL of THF was added to the mixture. The reaction mixture was refluxed for 8 h and then cooled in an ice bath. Excess reagent was decomposed by slow addition of 2 mL of water in 20 mL of THF followed by 0.5 mL of 10% sodium hydroxide solution. The mixture was filtered to remove the inorganic material and the filtrate was evaporated in vacuo. The residue was passed through a silica gel column, using ether as eluent. The ether gave a crude product (100 mg, 30%) which was recrystallized from acetone to yield a white powder (65 mg): mp 125–126 °C; IR (KBr) 2920, 2795, 1510, 1240, 805 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (m, 6 H, $C_{3,8,9}$ CH_2's), 2.2 (s, 3 H, NCH_3), 2.3 (m, 4 H, $C_{7,10}$ CH_2's), 2.45 (m, 4 H, $C_{4,6}$ CH_2's), 3.99 (t, 2 H, C_2 CH_2), 6.72 and 6.96 (2 d, 4 H, aromatic H's); mass spectrum *m/e* 233 (M^+, calcd 233).

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.93; N, 5.99. Found: C, 76.99; H, 9.94; N, 5.98.

Registry No.—**4**, 64201-22-5; **6**, 4521-28-2; **7**, 7021-11-6; **8**, 62889-58-1; **9**, 64201-23-6; **9** phenylurethane, 64201-24-7; **10**, 64201-25-8; **11**, 64201-26-9; **11** HCl, 64201-27-0; **12a**, 64201-28-1; **13b**, 64201-29-2; **17**, 64201-30-5; **18**, 64201-31-6; **19**, 64201-32-7; **21**, 64201-33-8; **22**, 64201-34-9; **23**, 64201-35-0; **24**, 64201-36-1; **25**, 64201-37-2; **25** phenylurethane, 64201-38-3; **26**, 64201-39-4; **27**, 64201-40-7; **28**, 64201-41-8; **29**, 64201-42-9; **29** phenylurethane, 64201-43-0; **30**, 64201-44-1; ethylene oxide, 75-21-8; *p*-toluenesulfonyl chloride, 98-59-9; ethyl bromoacetate, 105-36-2; ethyl bromopropionate, 539-74-2; acrylonitrile, 107-13-1; 3-amino-1-propanol, 156-87-6; isoamyl alcohol, 123-51-3; *N*-methyl-3-amino-1-propanol, 42055-15-2; xylene, 1330-20-7.

References and Notes

(1) (a) Presented at the 173rd National Meeting of the American Chemical Society, New Orleans, La., March 1977, Abstract ORGN 14; (b) Taken in part from the thesis submitted by C. S. Yi to the Graduate School of the University of Georgia in partial fulfillment of the requirements for the Ph.D. degree, May, 1977; (c) Present address: School of Pharmacy, Creighton University, Omaha, Nebraska 68178.
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(19) (a) Von Fritz Vogtle, *Chem.-Ztg.*, **96**, 396 (1972); (b) G. W. H. Potter, *Chem. Ind. (London)*, 1159 (1971).
(20) High-speed stirring was performed using a Labline Stir-O-Vac assembly (catalog No. 1280) coupled to a variable-speed motor (catalog No. 1285).
(21) Dry, oxygen-free nitrogen was obtained by passing through a column of drierite and then bubbling through a solution of benzophenone ketyl in xylene which was prepared from benzophenone and a sodium potassium alloy.[22]
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(23) Isoamyl alcohol was distilled from anhydrous calcium chloride, bp 128–129 °C.
(24) Xylene was refluxed with sodium overnight and then distilled, bp 138–140 °C.
(25) Compound **30** taken directly from the column did not give acceptable elemental analysis: Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.00; H, 8.76; N, 5.03.
(26) Tetrahydrofuran was distilled from LAH, bp 68 °C.

Chemistry of Heterocyclic Compounds. 26. Synthesis and Reactions of Multiheteromacrocycles Possessing 2,6-Pyrazino Subunits Connected by Carbon–Oxygen and/or –Sulfur Linkages[1]

George R. Newkome* and Ashutosh Nayak

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

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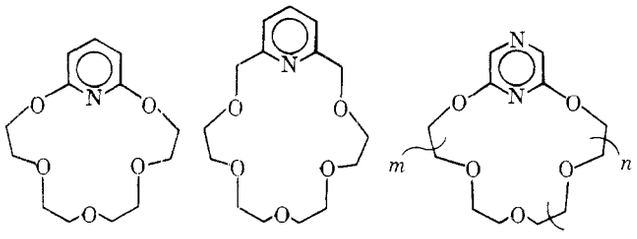
2,6-Dichloropyrazine (**4**) was treated with numerous glycol dianions, as well as the dianions of bis(2-mercaptoethyl) sulfide and bis(2-mercaptoethyl) ether, affording in most cases heteromacrocyclic ethers. Various expected uncyclized products were isolated and characterized. Quaternization of the N-4 position of the pyrazine ring was exclusively realized with these macrocycles. Diquaterization was accomplished with the 2:2-macrocycle **11**, and a new series of 1,3,5-cyclophanes (e.g., **40**) was generated from **5**.

Recently we described the preparation and characterization of carbon–oxygen bridged 2,6-pyridino macrocycles in which the bridging oxygens are directly attached to the pyridine nucleus (e.g., **1**).[2] This class of macrocycle[3] resulted from direct nucleophilic substitution of a ring halide by an alkoxide fragment and differs structurally and chemically from the macrocyclic class which possess a methylene group between the bridged heteroatoms and subring (e.g., **2**).[4] We herein describe the application of this procedure to the incorporation of the 2,6-pyrazino subunit into a "crown ether" (**3**) and the chemistry of these difunctional subheterocyclic rings.



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In light of potential pharmaceutical and pesticidal interest in substituted pyrazines, numerous nonmacrocyclic 2,6-disubstituted pyrazines have been synthesized from the readily available 2,6-dihalopyrazine by nucleophilic substitution. Conditions for substitution of the 2- (or 6-) halides from 2,6-dihalopyrazines by alkoxide,[5] hydroxide,[5b–d] cyanide,[5b] amines,[5b,h,l,6] alkylsulfides,[5c,7] phenoxide,[8] sulfanilamide,[5g,9] alkyl,[10] and aryl[10] have been described. Based on the above chemical substitution studies and the π-electron density calculations in the pyrazine ring,[11] 2,6-dinucleophilic substitution on the pyrazine ring should be equally, or slightly more, facile to that of our previously studied pyridine cases.[2] Although the literature contains several examples of 1,2- and 1,3-diazine subunits incorporated into macrocyclic rings, prepared also by different procedures,[3] there are, to the best of our knowledge, no examples of the 2,6-pyrazino moiety incorporated in a "crown ether" ring.[12]

A. Pyrazine Macrocycles with Carbon–Oxygen Bridges. 1. Diethylene Glycol. Reaction of 2,6-dichloropyrazine (**4**) with diethylene glycol dianion, generated in situ from diethylene glycol and 2 equiv of oil-free sodium hydride,

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