Conformations and "Nicotinic" Activities of Cyclic Analogues of Choline Aryl Ether

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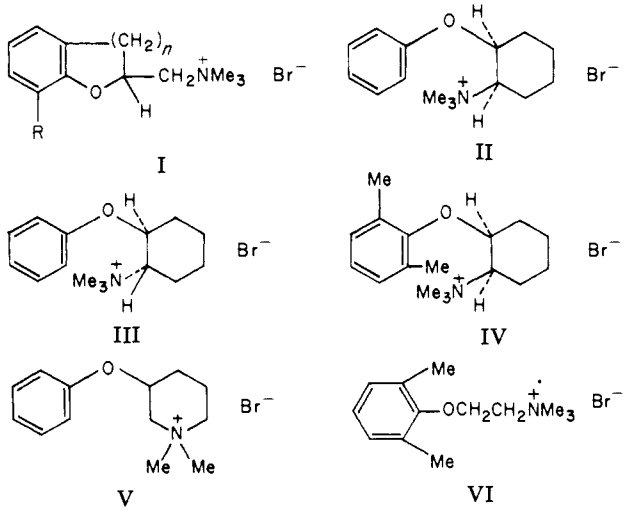
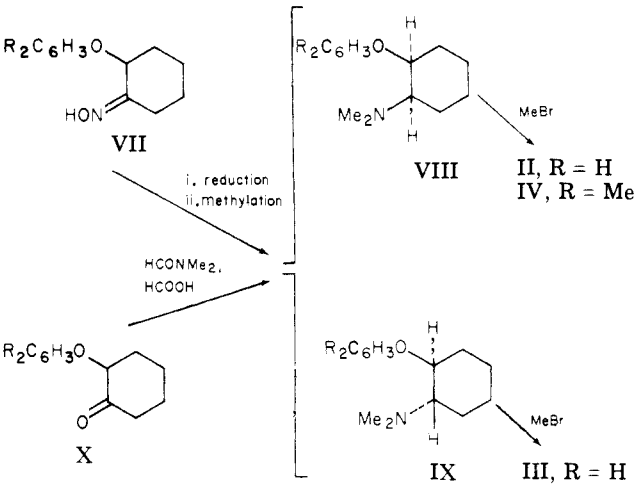
The synthesis of cis and trans isomers of *N,N,N*-trimethyl-2-phenoxycyclohexylammonium bromide, *cis-N,N,N*-trimethyl-2-(2',6'-xylyloxy)cyclohexylammonium bromide, and *N,N*-dimethyl-3-phenoxypiperidinium bromide is described. Their structures and conformations were determined by NMR and uv absorption spectroscopy, the minimum torsional angles about the aryl–oxygen bond being 20, 20, 80, and 27°, respectively. Since the piperidinium compound stimulates ganglia, it is concluded that either planarity of the aryl-O-C system is not essential for this type of activity or receptor interaction can involve appreciable bond distortion. The absence of ganglion-stimulant activity in the remaining compounds indicates the need for a transoid arrangement of the O-C-C-N^+ system.

In 1967 Clark and Williams,[1] using an ultraviolet spectroscopic method, determined the conformations of the ring systems of a series of oxygen heterocycles I (R = H, n = 1–3; R = Me, n = 1) in which the dihedral angle between the plane of the benzene ring and that containing the ether oxygen and its two adjacent carbon atoms is expected to be essentially fixed. From an examination of their biological properties, Clark et al.[2] concluded that a zero torsional angle is optimal for stimulation of ganglionic nicotinic receptors. A corollary of this conclusion is that a flexible nicotinic molecule such as choline phenyl ether which, from spectroscopic measurements, exhibits a time averaged angle of twist greater than zero adopts a conformation in which the phenyl–O–C system is planar when interacting with its receptor.

These earlier studies gave no insight into the conformation of the choline fragment that is required for nicotinic activity since in the compounds tested free rotation about the (O)C–C(N)$^+$ bond was possible. We now report the synthesis, conformational analysis, and biological evaluation of four compounds, II–V, in which the conformational possibilities of the O–C–C–N^+ system are constrained by ring structures. Thus, in the cis and trans isomers of *N,N,N*-trimethyl-2-phenoxycyclohexylammonium bromide (II and III, respectively) and in *cis-N,N,N*-trimethyl-2-(2',6'-xylyloxy)cyclohexylammonium bromide (IV) the preferred conformation of the O–C–C–N^+ system is expected to be gauche (cisoid) and fully staggered (transoid) in *N,N*-dimethyl-3-phenoxypiperidinium bromide (V). A preliminary account of some of the results described has already appeared.[3]



Chemistry. In 1956 Winternitz[4] claimed to have obtained the pure cis isomer of *N,N*-dimethyl-2-phenoxycyclohexylamine (VIII, R = H) by methylation of the primary amine derived from the corresponding oxime (VII, R = H). In our hands this somewhat tedious procedure



gave a mixture of approximately 60% cis and 40% trans isomers (VIII and IX, respectively) which was separated using dry column chromatography on alumina. Quaternization yielded the required salts II and III. The Leuchart reaction, dimethylformamide and formic acid on 2-phenoxycyclohexanone (X, R = H), provided a more convenient route to the mixture of amines (VIII and IX, R = H).

The Leuchart reaction on 2-(2',6'-xylyloxy)cyclohexanone (X, R = Me) produced a single isomer, quaternization of which yielded the cis compound IV.

Biological Results. Intravenous administration of compound V (1.05 μmol/kg) to pithed rats produced a rise in the blood pressure similar in magnitude to that produced by 0.075 μmol/kg of phenocholine bromide. The response was abolished by pentolinium (4 μmol/kg iv). Of the other compounds, II and III produced slight increases in blood pressure (ca. 10 mmHg) at a dose level of 31 μmol/kg and compound IV (29 μmol/kg) produced no increase in blood pressure but antagonized the pressor response of phenocholine.

Table I shows the mean percentage reduction in the heights of the action potentials from rabbit isolated superior cervical ganglia produced by the test compounds, xylocholine and phenocholine. All the test compounds are similar in potency to xylocholine and all are considerably less potent than phenocholine. Only compound IV (11.6 μM) produced any reduction in the preganglionic action potential (10%).

Discussion

The assignment of a cis configuration to compounds II

Table I. Reduction in Ganglionic Action Potential (as Percentage of Control ± Standard Error of the Mean, $n = 3$) of Rabbit Isolated Superior Cervical Ganglia after Immersion for 15 min, at 34 °C, in Krebs Solution Containing Compounds in the Stated Concentrations and Gassed with 95% O_2-5% CO_2

Compd	Concn, M × 10^{-5}					
	0.17	0.33	0.67	1.33	1.7	2.67
II	34.5 ± 7.7	47 ± 13	72 ± 8.5	89.5 ± 3.3		
III	26.6 ± 9.3	43.8 ± 4.1	64.7 ± 4.1	85.3 ± 3.8		
IV	10.3 ± 5.3	27.1 ± 0.6	43.7 ± 3.8	69.7 ± 4.5		93.0 ± 6.1
V	23.3 ± 3.8	39.0 ± 4	56.3 ± 6.3	81 ± 6.4		
Xylocholine		17.7 ± 7.8	42 ± 12.7	64 ± 7.9		90.3 ± 3.6
Phenocholine		23.5 ± 1.2[a]	47.6 ± 5[a]		88.6 ± 6.9[a]	

[a] Percent reduction produced by stated concentration × 10^{-2}.

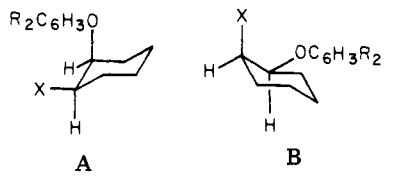
Table II. Position and $W_{1/2}$ Values for the NMR Peaks of the (O)CH Proton in Tertiary Amines VIII (R = H or Me) and IX (R = H) and the Derived Metho Bromides II-IV[a]

Compd	τ	$W_{1/2}$, Hz
VIII, R = H	5.3	7
IX, R = H	5.7	22
VIII, R = Me	5.37[b]	10[b]
II	4.93	7
III	5.2	c
IV	4.84	7

[a] Tertiary amines were recorded in CCl_4 solution and quaternary salts in D_2O. [b] Recorded in $CDCl_3$. [c] Obscured by H_2O absorption.

and IV and trans to compound III rests upon the NMR absorption of the (O)CH protons of the quarternary salts and their tertiary amine precursors (Table II). Coe et al.[5] have shown that in a series of phenoxycyclohexylamines the signal for the (O)CH proton occurs at a lower value for the cis isomers than for the trans and that the width of the signal at half-height ($W^1/_2$) varies between 6 and 8.5 Hz for the cis isomer and is approximately 17 Hz for the trans structures.

Compound III is thus expected to be predominantly in the diequatorial conformation but compounds II and IV are believed to be dynamic equilibrium mixtures of the two possible conformations A and B (X = $^+NMe_3$).



A B

Brownstein and Miller[6] have shown that increased coupling with a consequent increase in $W^1/_2$ occurs when a molecule is in a fixed conformation. The NMR of the cis-tertiary amine VIII (R = Me) at different temperatures showed an increase of the $W^1/_2$ value of the (O)CH signal from ca. 10 Hz at room temperature to ca. 23 Hz at −60°. Some indication of the preferred fixed conformation at −60° may be inferred from the movement of the (O)CH proton signal from τ 5.37 at room temperature to ca. 5.07 at −60°. Since Eliel[7] has shown that axial protons absorb at higher fields than equivalent equatorial protons, it seems likely that the preferred fixed conformation of tertiary amine VIII (R = Me) will be A (X = NMe_2) and that a parallel situation will obtain with quaternary salts II and IV.

The pressor response to compound V which is blocked by pentolinium and occurs in the pithed rat clearly shows this compound is capable of stimulating ganglionic nicotinic receptors. By analogy with previous work, therefore,[1,2] it would be expected to be able to adopt a zero torsional angle about the aryl–oxygen bond when interacting with its receptor. The other compounds tested are capable of interacting with these nicotinic receptors since they produce blockade, at approximately similar concentrations, in the isolated superior cervical ganglion preparation. They show no marked ganglion stimulant properties, however, and would therefore not be expected to be able to achieve a zero torsional angle.

In calculating the "angles of twist" of chroman and related compounds, Clark and Williams[1] applied no correction for ring fusion. If a similar procedure is adopted for compounds II–V, "angles of twist" of 48, 48, 72, and 50°, respectively, are obtained. The closeness of three of these values to 45° suggests that free rotation may be possible in compounds II, III, and V, making planarity of the Ar–O–C system a possibility. However, inspection of molecular models shows that such planar conformations can only be achieved if bond distortion is permitted. Furthermore, the calculated "angle of twist" for compound IV is smaller than would be expected from a comparison with that of xylocholine, which has been shown by x-ray crystallography to be 86°.[8] It is probable therefore that the angles calculated above are all too small and that a correction for the nonsteric effects of chain branching at the carbon adjacent to the oxygen should be applied. An estimate of the nonsteric effects of the ring structure may be made by considering the changes in molecular extinction coefficient which occur on the stepwise substitution of methyl groups into the methoxyl group of anisole. The first methyl leads to an increase of 359 whereas the second and third produce decreases of 18 and 1466, respectively, the expected electron-donating effects being overridden by the effects of steric hindrance.[9] If the nonsteric, absorption-promoting effect of each methyl is 359, then the total steric effect of the isopropyl group in isopropyl phenyl ether may be estimated as 377 (359 + 18) absorption units. It seems reasonable to assume that the steric hindrance in phenoxycyclohexane is similar to that in isopropyl phenyl ether, and since the molecular extinction coefficient at 273 nm of phenoxycyclohexane in *n*-hexane is 1432, the theoretical absorbance of this compound in the absence of steric hindrance may be estimated at 1809 (1432 + 377). This is 230 absorbance units greater than that of anisole in which free rotation about the phenyl–oxygen bond is possible. It is suggested that the difference (−230) is a suitable correction to apply for the saturated ring structures. Applying this correction we obtain time-averaged "angles of twist" of 53, 53, 84, and 56° and minimum possible angles, determined graphically using the expression $\epsilon_{corr}/\epsilon_0 = {}^1/_2[1 - (\sin\theta')/(\pi - 2\theta')]$, of 20, 20, 80, and 27°, respectively, for compounds II–V. The calculated "angle of twist" of 84° for compound IV is very close to the known angle of 86° for xylocholine.

Thus the observed ganglion stimulant property of compound V appears to contradict the contention that a zero "angle of twist" of the Ar–O–C system is necessary

for ganglion stimulant activity. However, the possibility of overriding the inherent steric hindrance to planarity on interaction with the receptor cannot be excluded. Although compounds II, III, and V have similar "angles of twist" in the Ar–O–C system, the arrangement of the (O)C–C(N) system in V is transoid whereas this system must be cisoid in compound II. NMR evidence shows compound III to be diequatorial and hence also to be cisoid. It is suggested therefore that the transoid conformation of the (O)C–C(N) system favors ganglion stimulant activity in the aryl ethers investigated. This conformation is different from that of Chothia and Pauling[10] who, from x-ray crystallographic observations on choline esters, postulated a cisoid arrangement for acetylcholine when activating nicotinic receptors.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 257 and ultraviolet spectra on a Unicam SP800A spectrophotometer. NMR spectra were determined on a Varian 60- or 100-MHz spectrometer at the SRC Physico-Chemical Measurement Unit at Harwell and microanalyses were carried out by Mr. J. A. Stewart of the University of Leeds microanalytical laboratory. The spectra of all compounds were consistent with the assigned structures.

***N,N*-Dimethyl-2-phenoxycyclohexylamine (VIII and IX, R = H).** 2-Phenoxycyclohexanone[4] (X, R = H; 26.3 mmol) in 90% formic acid (2.4 g) was added over 10 min to dimethylformamide (65.7 mmol) in 90% formic acid (0.8 g) at 140°. The mixture was heated at 150–160° for 6 h, cooled, basified with sodium hydroxide solution, and extracted with ether. The amine was taken into dilute hydrochloric acid, made alkaline with sodium hydroxide, and extracted into ether. Distillation yielded the required cis–trans mixture (11.0 mmol, 42%): bp 103–105° (0.7 mm); NMR (CCl_4) τ 7.96 (6 H, s, Me_2N), 7.2–7.9 [~9 H, m, $(CH_2)_4$ + CH(N)], 5.7 [~0.36 H, m, $W_{1/2}$ = 22 Hz, CH(O) of trans isomer], 5.3 [~0.64 H, m, $W_{1/2}$ = 7 Hz, CH(O) of cis isomer], 2.5–3.5 (5 H, m, aromatic H).

Separation of Cis and Trans Isomers. a. Thin-Layer Chromatography. Good separations were obtained on alumina (0.01-in. layer on glass, activated at 120° for 40 h) using the following solvent systems: (i) petroleum spirit (bp 60–80°) (98 vol)–absolute ethanol (98%) + 0.880 ammonia (2%) (2 vol); (ii) petroleum spirit (bp 60–80°) (94 vol)–acetone (98%) + 0.880 ammonia (2%) (6 vol). Isomers showed as dark brown spots on spraying with equal parts of 1% iodine solution and 28% sulfuric acid. R_f values: cis isomer, system i 0.28; system ii 0.48; trans isomer, system i 0.47; system ii 0.57.

b. Dry Column Chromatography. A 38 × 1.75 in. glass column was packed to a height of 30 in. with alumina which had been activated at 200° for 48 h and then partially deactivated with 5% water. The mixture of isomers (1–1.5 g) was dissolved in ether (10 ml) and mixed with alumina of the same activity (10 g) and the ether removed in a rotary film evaporator. The amine–alumina mixture was poured on top of the prepared alumina column and was then overlayed with a further 3-in. layer of alumina. The column was developed with diethyl ether and the eluate, collected in 25-ml fractions, and monitored by thin-layer chromatography.

After each run the column material was removed, allowed to air dry, and then repacked into the column. The separation efficiency of the alumina increased with usage.

Synthetic mixtures prepared from the "pure" isomers containing 1% of one isomer and 99% of the other could be separated readily by thin-layer chromatography.

***cis*- and *trans*-*N,N,N*-Trimethyl-2-phenoxycyclohexylammonium Bromides (II and III).** The purified cis (5.0 mmol) and trans (2.0 mmol) isomers VIII and IX (R = H) were quaternized with methyl bromide to yield the required cis (4.15 mmol, 82%) and trans (1.73 mmol, 86%) quaternary salts.

Cis isomer II: NMR (D_2O) τ 8.7 [4 H, m, $(CH_2)_2$], 7.96 [4 H, m, $(CH_2)_2$], 6.95 (9 H, s, $^+NMe_3$), 6.5 [1 H, t, CH(N)], 4.93 [1 H, m (apparent singlet), $W_{1/2}$ = 7 Hz, CH(O)], 2.6–3.2 (5 H, m, aromatic H); λ_{max} (H_2O) ~263 nm (sh) (ϵ 954), 269 (1214), 275.5 (975). Anal. ($C_{15}H_{24}BrNO$) C, H, N, Br.

Trans isomer III: NMR (D_2O) τ 8.9–7.6 [8 H, m, $(CH_2)_4$], 6.9 (9 H, s, $^+NMe_3$), 6.36 [1 H, m, CH(N)], 5.2 [m, CH(O)– partially obscured by water peak], 2.6–3.2 (5 H, m, aromatic H); λ_{max} (H_2O) ~264 nm (sh) (ϵ 979), 269.5 (1222), 276 (996). Anal. ($C_{15}H_{24}BrNO$) C, H, N, Br.

2-(2',6'-Xylyloxy)cyclohexanone (X, R = Me). 2,6-Xylenol (0.6 mol), sodium wire (0.6 mol), and *tert*-butyl alcohol (500 ml) were stirred and heated until the sodium dissolved. 2-Chlorocyclohexanone (0.6 mol) was then added over 1 h and heating continued for a further 3 h. Ether (300 ml) was added to the cooled reaction mixture and the ethereal solution extracted with 8% sodium hydroxide solution (3 × 100 ml). The ether and *tert*-butyl alcohol were evaporated and the residue was distilled. The fraction, bp 126–140° (0.5 mm), crystallized on cooling and was recrystallized from petroleum spirit (bp 40–60°) to yield X (R = Me): 0.19 mol; 31%; mp 48–49°; NMR (CCl_4) τ 7.81 (6 H, s, CH_3), 7.16–8.6 [8 H, m, $(CH_2)_4$], 5.9 [1 H, t, (ArO)CH], 3.18 (3 H, m, aromatic H). Anal. ($C_{14}H_{18}O_2$) C, H.

***cis*-*N,N*-Dimethyl-2-xylyloxycyclohexylamine (VIII, R = Me).** 2-(2,6-Xylyloxy)cyclohexanone (X, R = Me; 91 mmol) in formic acid (9 g) was added over 15 min to dimethylformamide (0.50 mol) in formic acid (9 g) at 165° (bath temperature); the mixture was heated under reflux for 5 h, cooled, and extracted with dilute hydrochloric acid. The acid extract was washed with ether and made alkaline with sodium hydroxide and the amine taken into ether. Distillation yielded the required amine: 25.8 mmol; 28%; bp 104–106° (0.3 mm); NMR (CCl_4) τ 7.8–8.9 [8 H, m, $(CH_2)_4$], 7.72 [12 H, two overlapping s, Ar $(Me)_2$ + NMe_2], 7.58 [1 H, m, CH(NMe)], 5.61 [1 H, partially resolved m, $W_{1/2}$ = 10 Hz, (O)CH], 3.2 (3 H, m, aromatic H). Anal. ($C_{16}H_{25}NO$) C, H, N.

***cis*-*N,N,N*-Trimethyl-2-xylyloxycyclohexylammonium Bromide (IV).** Methyl bromide (74 mmol) was added to *N,N*-dimethyl-2-xylyloxycyclohexylamine (VIII, R = Me) (6.3 mmol) and dry acetone (30 ml) in a 50-ml ampule cooled in solid CO_2. The sealed ampule was stored at room temperature for several days. The required quaternary salt was isolated and recrystallized from dry acetone and ethyl alcohol: yield 5.55 mmol; 88%; NMR (D_2O) τ 8–9 [8 H, m, $(CH_2)_4$], 7.8 [6 H, s, (Ar)Me], 6.8 [9 H, s, $^+N(Me)_3$], 6.5 [1 H, m, CH(N)], 4.62 [1 H, br s, $W_{1/2}$ = 7 Hz, CH(O)], 3.15 (3 H, m, aromatic H); λ_{max} (H_2O) 267 nm (ϵ 471), ~274 (sh) (ϵ 380). Anal. ($C_{17}H_{28}BrNO$) C, H, N, Br.

***N,N*-Dimethyl-3-phenoxypiperidinium Bromide (V).** *N*-Methyl-3-phenoxypyridinium bromide[11] (11.2 mmol) in ethanol was hydrogenated (24 h) at 3 atm over Adams platinum oxide (0.3 g), the catalyst removed, the alcohol evaporated, and the residue, after making alkaline with 8% sodium hydroxide solution, extracted with ether. The dried (Na_2CO_3) ethereal solution was evaporated to dryness and the residue, in dry acetone (30 ml), quaternized with methyl bromide (63.2 mmol) as described above. Recrystallization from a mixture of dry acetone, ethanol, and ether gave the required quaternary bromide (5.6 mmol, 50%): λ_{max} (H_2O) ~264 nm (sh) (ϵ 879), 269 (1084), 275.5 (865). Anal. ($C_{13}H_{20}BrNO$) C, H, N, Br.

Biological Methods. Blood Pressure of Pithed Rats. Male rats (180–250 g), anesthetized with urethane (1.8 g/kg ip), were artificially respired (3 ml/s) via a tracheal cannula and pithed by using the approach through the orbit.[12] Blood pressure was recorded from the carotid artery on a Devices recorder. Drugs were administered in normal saline via a jugular vein.

Atropine sulfate (14 μmol/kg) was administered to block muscarinic responses and standard responses to 0.38–0.48 μmol/kg of phenocholine bromide were obtained before administering the test substances.

Isolated Superior Cervical Ganglion Preparation. New Zealand white rabbits of either sex were anesthetized with urethane (8–12 mg/kg, 12% w/v solution) injected into the lateral ear vein. The right superior cervical ganglion together with short lengths of the pre- and postganglionic nerves was excised and set up for recording as described previously[2] except that after preamplification with a Tektronix Type RM122 low-level preamplifier the action potentials were recorded on a Tektronix 502A oscilloscope fitted with a Telford Type C110 oscilloscope camera. Stimulation of the preganglionic nerve was by means of a Grass S8 stimulator using single pulses of 5-μs duration and supramaximal voltage (15–30 V) via an isolation unit.

Each compound was tested on three different nerve–ganglion preparations and the effect of the highest concentration of each compound used on the preganglionic nerve action potential was measured.

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Sulfamylurea Hypoglycemic Agents. 6. High-Potency Derivatives

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Synthetic methods for a series of novel sulfamylurea derivatives have been developed. The hypoglycemic activity of simple 1-piperidinosulfonylureas is greatly enhanced by attaching an acylaminoethyl function in the 4 position of the piperidine ring. Optimum activity is achieved when the acyl radical is 5-chloro-2-methoxybenzoyl, 2-methoxynicotinyl, 5-chloro-2-methoxynicotinyl, 1,2-dihydro-1-methyl-2-ketonicotinyl, 2,3-ethylenedioxybenzoyl, quinoline-8-carbonyl, or 6-chloroquinoline-8-carbonyl. Optimal substituents on the terminal urea nitrogen are cyclohexyl, bicycloheptenylmethyl, and in certain cases propyl, 7-oxabicycloheptanylmethyl, and adamantyl. One of these compounds (81, gliamilide) was found to be well tolerated in man and it displayed a very short plasma half-life.

Previous publications from these laboratories[1] have shown that sulfamylureas and sulfamylsemicarbazides, especially those which contain a piperidine ring, display hypoglycemic activity similar to the sulfonylureas chlorpropamide and tolbutamide. The dramatic potency enhancement achieved by attachment of an acylaminoalkyl chain to the benzene nucleus of tolbutamide[2] prompted us to investigate the effect of a similar structural modification in the sulfamylurea series.

Chemistry. The synthesis of the 4-(5-chloro-2-methoxybenzamidoalkyl)piperidinosulfonylureas was initially approached as outlined in Scheme I. The coupling products of 2-methoxy-5-chlorobenzoyl chloride and 4-(2-aminoethyl)pyridine or 4-aminomethylpyridine were reduced under carefully controlled conditions to avoid loss of the aromatic chlorine. The resulting piperidine derivatives were converted by heating with sulfamide in 1,2-dimethoxyethane[1a] to the corresponding sulfamide derivatives. Treatment of these as the sodium salts with isocyanates or 3-substituted 1,1-diphenylureas[1a] gave the sulfamylureas listed in Tables I and II.

Subsequently, our interest shifted to the preparation of a wide variety of acylaminoethylpiperidinosulfonylureas and it became apparent that a versatile synthetic route to these compounds required 4-(2-aminoethyl)piperidinosulfonamide (**160**) as an intermediate. The most successful synthesis of **160** is depicted in Scheme II. Reaction of 4-(2-aminoethyl)pyridine with phthalic anhydride gave the phthalimide derivative **157** in excellent yield. Reduction of **157** to the piperidine derivative **158** was straightforward. After considerable experimentation pyridine was found to be the solvent of choice for converting **158** to the sulfonamide derivative **159**. Removal of the phthalimido group with anhydrous hydrazine followed by hydrochloric acid gave **160** in good overall yield.

Compound **160** was acylated using aqueous or nonaqueous acid chloride procedures, reactions with acid anhydrides, or EEDQ[3] couplings to afford the sulfonamide derivatives listed in Table VII. With a few exceptions (compounds **118** and **120**) no attempt was made to maximize yields.

Several procedures were investigated for the conversion of these sulfonamides to sulfamylureas. Reaction of a sulfonamide and an appropriate amine with carbonyldiimidazole, or reaction of a sulfonamide with ethyl chloroformate, forming a carbamate, followed by aminolysis (Scheme III) gave good yields of the desired products only in certain cases. However, two previously applied methods[1a] were found to be advantageous and generally applicable: conversion of the sulfonamides to the sodium salts with NaH in DMF, followed by reaction with an isocyanate or a 3-substituted 1,1-diphenylurea. The first method was used whenever the isocyanate of a desired amine was commercially available. Again, with the exception of compound **81**, no attempt was made to maximize yields.

Pharmacology. All compounds were tested in groups of five or six unanesthetized male rats of the Charles River strain (200–250 g), fasted 18–24 h prior to the experiment. The drugs were administered intraperitoneally at the doses indicated (5–25 mg/kg), and blood samples were taken from the tail vein prior to dosing and 1 h after drug administration. Blood glucose was determined using the ferricyanide reduction micromethod on a Technicon Autoanalyzer. Hypoglycemic activity is reported as percent drop in blood glucose at 1 h after dosing relative to a saline-treated control group. Statistical significance was ascertained by Student's t test.[4] Chlorpropamide is