MeI according to the procedure of Gaj and Moore[23] and had mp 195–198° (EtOH); mass spectrum (70 eV) *m/e* 285 (M), 284 (M − 1, $C_8H_{16}INO_2$), 228 (M − 57, $C_5H_{11}INO$), 224 (M − 61, $C_6H_{11}IN$), 183 (M − 102, C_3H_4IO), 158 (M − 127, $C_8H_{16}NO_2$), 155 (M − 100, C_3H_4IO), 142 (M − 143, CH_3I), 141 (M − 144, CH_2I), 85 (M − 200, $C_4H_5O_2$). *Anal.* ($C_8H_{16}INO_2$) C, H, I, N.

1-Chloro-2,3-dihydroxy-2-methylpropane.—Performic acid oxidation[21,22] of 3-chloro-2-methylpropene afforded 35% of product with bp 53–55° (0.75 mm). *Anal.* ($C_4H_9ClO_2$) C, H, Cl.

***cis,trans*-2,4-Dimethyl-4-chloromethyl-1,3-dioxolane** was prepared in 44% yield from 1-chloro-2,3-dihydroxy-2-methylpropane and paraldehyde in refluxing C_6H_6 with azeotropic removal of H_2O and had bp 29–32° (0.5 mm), lit.[24] 148–151° (760 mm). Glpc (10% Carbowax column, 110° isothermal, He 30 ml/min) revealed two major peaks with retention times of 9 and 10 min; nmr (neat, Me_4Si as internal reference), 2-H τ 4.88 and 4.93 (two overlapping quartets), 2-CH_3 and 4-CH_3 8.65–8.70 (overlapping), remaining multiplet at 5.82–6.60. *Anal.* ($C_6H_{11}ClO_2$) C, H, Cl.

***cis,trans*-2,4-Dimethyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide (V)** was obtained in 37% yield from *cis,trans*-2,4-dimethyl-4-chloromethyl-1,3-dioxolane and Me_2NH in C_6H_6 followed by quaternization with MeI[1] and had mp 185–187° (EtOH), lit.[24] 139–140°; nmr (CD_3CN, Me_4Si as internal reference), $N^+(CH_3)_3$ τ 6.74 (singlet), 4-CH_3 8.47, 2-CH_3 8.67 (doublet).

Biological Section.—Muscarinic activities were determined using the rat ileum preparation as described previously.[1,20]

(23) B. J. Gaj and D. R. Moore, *Tetrahedron Lett.*, 2155 (1967).

(24) E. Gryszkiewicz-Trochimowski, O. Gryszkiewicz-Trochinowski, and R. Levy, *Bull. Soc. Chim. France*, 610 (1958), have reported this melting point for material derived from the dioxolane obtained through the $SnCl_4$-catalyzed reaction of MeCHO and 2-chloromethyl-2-methylethylene oxide.

Derivatives of 2-Azabicyclo[2.2.2]octane. III. Substituted Phenylsulfonylcarbamoyl Derivatives

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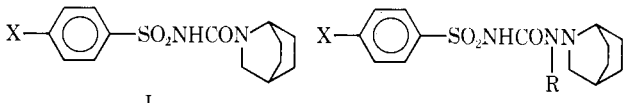
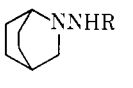
Continuing our studies[1] on the replacement of simple amine functions in clinically effective drugs by the bicyclic 2-azabicyclo[2.2.2]octane moiety[2] we have prepared the title compounds as potential hypoglycemic agents. Compounds of formulas I and II (Table I)



I II

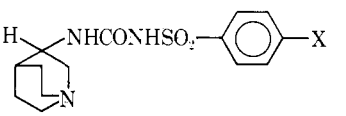


IIIa, R = H
b, R = $C_6H_5CH_2$
c, R = *p*-$ClC_6H_4CH_2$
d, R = Me

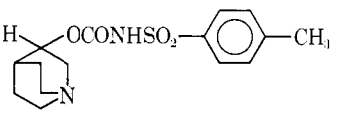
were prepared by the condensation of isoquinuclidine or a 2-aminoisoquinuclidine with a substituted phenylsulfonyl isocyanate or a substituted phenylsulfonyl carbamate ester according to known procedures. 2-Aminoisoquinuclidine (IIIa) was prepared by LAH reduction of the 2-nitroso compound. Complete conversion of the latter and maximum yield of IIIa was obtained if the reduction was carried out for prolonged periods of time in the presence of a large excess of LAH. Catalytic hydrogenation of the 2-nitroso compound using PtO_2, 5% Pd–C, or Raney Ni catalysts in a variety of solvents invariably gave excellent yields of isoquinuclidine.

Condensation of IIIa with benzaldehyde or *p*-chlorobenzaldehyde gave the benzylidene derivatives which were reduced (LAH in THF)[3] to the substituted benzyl compounds IIIb and IIIc, respectively. The 2-methylamino derivative IIId was prepared from the 2-formyl compound by reduction (LAH).[3a]

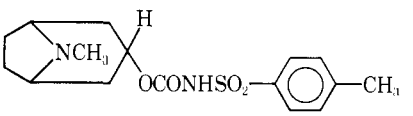
In addition, the sulfonylurea derivatives IV, prepared from 3-aminoquinuclidine, the sulfonyl carbamates derived from 3-quinuclidinol (V), 3-tropinol (VI), and 3-tropinone oxime (VII) were prepared.



IVa, X = CH_3
b, X = Cl



V



VI

VII

These compounds, listed in Table II, were inactive in the hypoglycemic screen.

The hypoglycemic potency[4] of these compounds was determined in normal mice and in diazoxide-induced hyperglycemic mice.[5] The activities of compounds of formulas I and II were compared with known hypoglycemic agents. At the screening dose of 160 mg/kg orally in normal mice, **2** (Table I) and 1-(*p*-chlorophenylsulfonyl)-3-propylurea were equally potent for periods of 1–3 hr after treatment. Compound **1** and 1-(*p*-tolylsulfonyl)-3-butylurea were equally effective at the 1-hr bleeding period but **1** was of lower potency at the 3-hr period.

Compound **4** (Table I) was the most potent compound in this series. On a milligram basis, **4** was

(1) For preceding papers in this series see F. J. Villani, and C. A. Ellis, *J. Med. Chem.*, **9**, 185, 264 (1966).

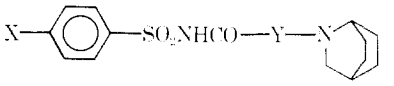
(2) Throughout this work the common name, isoquinuclidine, is used.

(3) Contrary to the results from other laboratories on the reduction of similar types of compounds, the benzylidene derivatives of this ring system resisted catalytic hydrogenation or $NaBH_4$ reduction; LAH in Et_2O gave variable results. See, for example, (a) M. J. Kalm, *J. Med. Chem.*, **7**, 427 (1964); (b) J. H. Biel, A. E. Drukker, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway, and A. Horita, *J. Amer. Chem. Soc.*, **81**, 2805 (1959).

(4) The biological data herein reported were obtained by Miss A. Gulbenkian and Dr. I. Tabachnick of the Biological Research Division of the Schering Corporation.

(5) I. Tabachnick, A. Gulbenkian, and F. Seidman, *Diabetes*, **13**, 408 (1964).

TABLE I



No.	X	Y	Method	Yield, %	Mp, °C	Formula	Analyses
1	CH_3		A	45	183–185[a]	$C_{15}H_{20}N_2O_3S$	C, H
2	Cl		B	23	237–238[b]	$C_{14}H_{17}ClN_2O_3S$	C, H, N
3	CH_3	NH	B	43	199–201[b]	$C_{15}H_{21}N_3O_3S$	C, H, N
4	Cl	NH	B	57	204–205[b]	$C_{14}H_{18}ClN_3O_3S$	C, H, N
5	Cl	N-CH_3	B	50	173–174[b]	$C_{15}H_{20}ClN_3O_3S$	C, H, N
6	CH_3	N-$CH_2C_6H_5$	A	52	112–113[c]	$C_{22}H_{27}N_3O_3S$	C, H, N
7	Cl	N-$CH_2C_6H_5$	B	59	178–179[b]	$C_{21}H_{24}ClN_3O_3S$	H, N; C[d]
8	CH_3	N-*p*-$ClCH_2C_6H_4$	B	49	152–153[c]	$C_{22}H_{26}ClN_3O_3S$	C, H, N
9	Cl	N-*p*-$ClCH_2C_6H_4$	B	85	166–168[b]	$C_{21}H_{23}Cl_2N_3O_3S$	C, H, N

[a] Recrystallized from C_6H_6–petroleum ether. [b] Recrystallized from $CHCl_3$–petroleum ether. [c] Recrystallized from MeOH–H_2O. [d] C: calcd, 58.11; found, 58.67.

TABLE II

No.	Method	Yield, %	Mp, °C	Formula	Analyses
IVa	A	31	157–160	$C_{15}H_{21}N_3O_3S$[a]	C, H, N
IVb	B	39	199–200	$C_{14}H_{18}ClN_3O_3S$[a]	C, H, N
V	B	50	292–294	$C_{15}H_{20}N_2O_4S$[a]	C, H, N
VI	A		170–172[b]		
VII	A	51	166–170	$C_{16}H_{21}N_3O_4S$[c]	C, H, N

[a] Recrystallized from MeCN–H_2O. [b] Isolated with 0.5MeCN of crystallization. *Anal.* ($C_{34}H_{47}N_5O_8S_2$) H, N; C: calcd, 56.88; found, 56.27. [c] Recrystallized from C_6H_6.

10–12 times as potent as **2** in the normal mouse and about 5–7 times as potent as 1-(hexahydro-1H-azepin-1-yl)-3-(*p*-tolylsulfonyl)urea. Compound **4** had a moderate duration of action. The corresponding *p*-methyl derivative, **3**, was approximately one-third as potent as **4**.

In the diazoxide-induced hyperglycemia in mice, having blood glucose levels in the range of 550–650 mg/100 ml, oral administration of 1 mg/kg each of **2** and **4** lowered the blood glucose values to 419 and 228 mg/100 ml, respectively, after 1 hr.

Substitution of the 2-amino in II by Me or $PhCH_2$ gives compounds of very low hypoglycemic potency. Previous investigators[6] have observed a similar effect by Me substitution in the 1-aminohexamethylenimine group of antidiabetic agents. The *p*-chlorobenzyl compound (**9**, Table I) shows a mild hyperglycemic effect at a dose of 500 mg/kg in the mouse screen.

Experimental Section[7]

2-Nitrosoisoquinuclidine.—To a solution of 242 g of isoquinuclidine (2.2 moles) in 178 ml of concentrated HCl and 88 ml of H_2O was added dropwise a solution of $NaNO_2$ (178 g) in 300 ml of H_2O with stirring at 75–80°. Additional quantities of 2 *N* HCl were added during the addition to keep the solution acid. The mixture was stirred at this temperature for 3 hr and allowed to cool. The product was filtered and air dried and was sufficiently pure for the next step, yield 198 g (64%). An analytical sample was recrystallized from hexane, mp 140–142°. *Anal.* ($C_7H_{12}N_2O$) C, H, N.

2-Aminoisoquinuclidine (IIIa).—In a typical experiment, 42 g (0.3 mole) of the 2-nitroso compound in 800 ml of Et_2O was added dropwise to a refluxing stirred suspension of LAH (17.1 g, 0.45 mole) in 800 ml of Et_2O, heated with stirring for 19–22 hr, and processed as usual to give 30.6 g (82.5%) of product having mp 80–82°. The hydrochloride, mp 190–192°, was recrystallized from EtOH–Et_2O. *Anal.* ($C_7H_{14}N_2 \cdot HCl$) H; C: calcd, 51.68; found, 52.28; N: calcd, 17.22; found, 16.56.

The **picrate** was recrystallized from EtOH, mp 177–180°. *Anal.* ($C_7H_{14}N_2 \cdot C_6H_3N_3O_7$) C, H, N.

2-Benzylideneaminoisoquinuclidine.—A solution of 25.2 g (0.2 mole) of 2-aminoisoquinuclidine and 21.2 g (0.2 mole) of benzaldehyde in 300 ml of EtOH containing 1 ml of HOAc was heated on a steam bath under reflux for 3 hr. The solution was concentrated to one-half volume, poured into H_2O, and steam distilled to remove excess PhCHO. The residue was extracted (Et_2O) and the ether was dried (Na_2SO_4) and concentrated to a yellow solid, mp 34–35° (from petroleum ether (bp 30–60°)), yield 33 g (79%). *Anal.* ($C_{14}H_{18}N_2$) C, H, N.

Similarly, the ***p*-chlorobenzylidene** compound was prepared in 73% yield, mp 99–100° (from hexane). *Anal.* ($C_{14}H_{17}ClN_2$) C, H, N.

2-Benzylaminoisoquinoquinuclidine (IIIb).—To a refluxing solution of 14.7 g (0.39 mole) of LAH in 800 ml of THF was added a solution of 27 g (0.13 mole) of the benzylidene derivative in 200 ml of THF. The mixture was heated under reflux for 18 hr and decomposed, and the product was isolated as usual, bp 112–119° (0.1 mm), yield 17.1 g (61%). *Anal.* ($C_{14}H_{20}N_2$) C, H, N.

2-(*p*-Chlorobenzylamino)isoquinuclidine (IIIc) was obtained by the same method, bp 143–150° (0.25 mm), yield 60%. *Anal.* ($C_{14}H_{19}ClN_2$) H, N; C: calcd, 67.05; found, 66.24.

2-Methylaminoisoquinuclidine (IIId).—The 2-formamido derivative was prepared using ethyl formate:[8a] mp 113–115° from hexane, yield 63%. *Anal.* ($C_8H_{14}N_2O$) C, H, N. Reduction of this compound with LAH in THF as above gave the methylamino compound which was converted to HCl salt, mp 151–153°. *Anal.* ($C_8H_{16}N_2 \cdot HCl$) C, H, N.

Condensation Method A.—To a solution of 5.5 g (0.05 mole) of isoquinuclidine in 150 ml of xylene was added slowly a solution of 10 g of *p*-toluenesulfonyl isocyanate[8] in 100 ml of xylene and the mixture was heated on a steam bath for 30 min and cooled. The product was filtered and recrystallized.

Condensation Method B.—Ethyl *p*-toluenesulfonylcarbamate and ethyl *p*-chlorophenylsulfonylcarbamate were prepared in the usual manner.[9] The carbamate esters (0.08 mole) were dissolved in PhMe and dried by azeotropic distillation using a Dean-Stark H_2O separator. 2-Aminoisoquinuclidine (0.08 mole) in 200 ml of PhMe was similarly dried and was added dropwise to the warm PhMe solution of the carbamate ester. The mixture was stirred and heated under reflux for 3 hr and cooled. The precipitated solid was filtered, suspended in H_2O, and acidified with 5% HCl. The product was filtered, air dried, and recrystallized.

(6) J. B. Wright and R. E. Willette, *J. Med. Chem.*, **5**, 815 (1962).

(7) Melting points were obtained on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Microanalyses were obtained by the Physical-Analytical Department of Schering Corp. Where analyses are indicated only by the symbols of the elements analytical results obtained for these elements were within 0.4% of the theoretical values.

(8) (a) H. Krzikalla, German Patent 817,602 (1951); *Chem. Abstr.*, **47**, 2206 (1953); (b) J. W. McFarland, C. F. Gerber, and W. M. McLamore, *J. Med. Chem.*, **8**, 871 (1965).

(9) F. J. Marshall and M. W. Segal, *J. Org. Chem.*, **23**, 927 (1958).