properties of the sulfonylureas drugs are related to an ability to assist the transport of calcium cations may suggest why an acidic group needs to be present in hypoglycemic [(acylamino)alkyl]benzoic acids.

Experimental Section

Melting points are uncorrected. IR and NMR were determined on Perkin-Elmer 157 and a Varian HA 100 spectrometer, respectively. Spectral data were consistent with the assigned structures and were supported by MS fragmentations from a Hitachi RMU-6E instrument. Where analyses are indicated only by symbols, elementary analyses are within ±0.4% of the theoretical values.

p-[2-(5-Chloro-2-methoxybenzamido)ethyl]benzoic Acid (2) (General Method A). A solution of 5-chloro-2-methoxybenzoyl chloride (545 mg, 2.66 mmol) in acetone (1 mL) was added dropwise with stirring to a solution of *p*-(2-aminoethyl)benzoic acid (560 mg, 2.55 mmol) in 2 N NaOH (3.2 mL) and acetone (4.0 mL) maintained at 0–5 °C. The ice bath was removed, and the mixture was stirred for 2 h. The mixture was diluted with H_2O (40 mL) and acidified with 2 N HCl to pH 3. The solid product was collected and crystallized from EtOH to give **2** (330 mg, 37%).

5-Chloro-2-methoxy-*N*-[2-(*p*-aminophenyl)ethyl]benzamide (11). A solution of $SnCl_2 \cdot 2H_2O$ (7.0 g, 32.4 mmol) in EtOH (10 mL) was added to a stirred suspension of **10** (2.7 g, 8.0 mmol) in EtOH (8 mL) and 11 N HCl (8 mL), and stirring continued for 24 h. The mixture was diluted with H_2O (50 mL) and made alkaline with 30%, w/w, NaOH. The mixture was extracted with $CHCl_3$, and the $CHCl_3$ was shaken with an excess of 2 N HCl. The acid layer was made alkaline with 30%, w/w, NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried ($MgSO_4$), and evaporated. Crystallization of the residue from *i*-PrOH–petroleum ether, bp 60–80 °C, gave 11 (355 mg, 14.5%).

5-Chloro-2-methoxy-*N*-[2-[*p*-(1-hydroxyethyl)phenyl]ethyl]benzamide (16). $NaBH_4$ (0.8 g, 21.6 mmol) was added in portions to a stirred suspension of **15**, (4.7 g, 14.2 mmol) in EtOH (100 mL). After 6 h, dilute HOAc was added, and the EtOH was evaporated. The residue was shaken with EtOAc and H_2O, and the EtOAc was dried ($MgSO_4$) before evaporation. The residue was crystallized from toluene–petroleum ether, bp 60–80 °C, to give **16** (3.3 g, 70%).

5-Chloro-2-methoxy-*N*-[2-(*p*-vinylphenyl)ethyl]benzamide (17). A solution of **16** (3.0 g, 9.0 mmol) and I_2 (100 mg, 0.39 mmol) in xylene (20 mL) was heated under reflux for 3 h. The cooled xylene was washed with $Na_2S_2O_3$ solution, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$), eluting with $CHCl_3$–EtOAc (40:1). Crystallization of the evaporated eluates from petroleum ether, bp 60–80 °C, gave **17** (1.1 g, 38.7%).

5-Chloro-2-methoxy-*N*-[2-(*p*-ethylphenyl)ethyl]benzamide (18). A solution of **17** (600 mg, 1.9 mmol) in EOH (20 mL) was hydrogenated at 1 atm over 5% Pd/C (100 mg) for 10 min. The catalyst was filtered and the EtOH was evaported. The residue was purified by preparative TLC on silica gel using 5% EtOAc in $CHCl_3$ as eluant. Evaporation of the eluates and crystallization of the residue from petroleum ether, bp 60–80 °C, gave **18** (300 mg, 49%).

Hypoglycemic Assay. Rats were fasted for 24 h. Compounds were ball milled in 0.5% Tween 80 overnight and dosed orally by gavage at 50 mg/kg to rats in groups of four. After 1 h, an oral glucose load (1 g/kg) was given by gavage. After an additional 1 h, blood samples were taken from the retro-orbital sinus under light ether anesthesia. Blood glucose levels were measured by a glucose oxidase method, and the effect of the compound on the ability of the rat to accommodate the glucose load was compared with control group rats given excipient. Compounds improving glucose tolerance by 15% or more were tested again in groups of six rats. The mean of the two results was taken, and if greater than 15%, the compound was considered active.

Acknowledgment. We thank Dr. D. C. N. Earl for the hypoglycemic assay data.

Registry No. **2**, 54870-28-9; **6**, 87262-53-1; **8**, 33924-49-1; **9**, 87262-54-2; **10**, 25921-64-6; **11**, 63484-38-8; **12**, 41859-64-7; **13**, 64353-00-0; **14**, 87262-55-3; **15**, 60531-37-5; **16**, 64507-35-3; **17**, 87262-56-4; **18**, 64353-17-9; **19**, 41859-81-8; 5-chloro-2-methoxybenzoyl chloride, 29568-33-0; *p*-(2-aminoethyl)benzoic acid, 1199-69-5.

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Novel Tetracyclic Spiropiperidines. 4.[1] Synthesis and Pharmacological Evaluation of Spiro- and 6,7-Dihydrospiro[benzo[*b*]pyrrolo[3,2,1-*jk*][1,4]benzodiazepine-2(1*H*),4′-piperidine]s

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A previously described series of 1-arylspiro[indoline-3,4′-piperidine]s was reported by us to possess significant antidepressant properties. This biological activity was found to be at a maximum among those compounds bearing an ortho substituent (e.g., NH_2 as in 1) in the pendant aryl ring. In order to explore further this "ortho effect", we synthesized cyclic analogues of type **3** and **4** in which the position of the *o*-NH_2-substituted aryl group is conformationally restricted and defined. When tested for antidepressant activity by tetrabenazine ptosis prevention in mice, it was found that restriction of rotation of the pendant *o*-aminophenyl group in these rigid analogues resulted in a loss of antidepressant properties. However, analgesic activity was retained and even improved by this molecular constraint.

We recently described the synthesis of a series of 1-arylspiro[indoline-3,4′-piperidine]s of formula I.[1] Some of the members of this class were shown to possess significant antidepressant activity, as measured by the in-

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(1) For paper 3 in this series, see Ong, H. H.; Profitt, J. A.; Fortunato, J.; Glamkowski, E. J.; Ellis, D. B.; Geyer III, H. M.; Wilker, J. F.; Burghard, H. *J. Med. Chem.* **1983**, *26*, 981.

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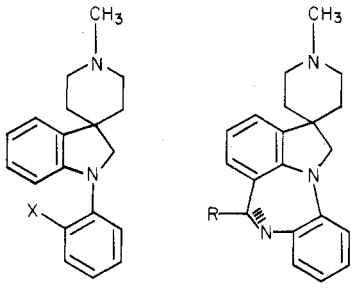


I II

hibition of tetrabenazine-induced ptosis in mice. This biological property was found to be at an optimum with those compounds carrying an ortho substituent in the pendant phenyl ring. The analogue bearing an *o*-amino moiety (X = NH_2) was one of the most potent within this subgroup. We thought it would be of interest to explore further this "ortho effect" by making the nitrogen of the amino group part of a relatively inflexible ring fused to the molecular framework of I. This would afford analogues of I in which the phenyl ring with its ortho substituent would no longer be able to rotate freely but instead would be frozen in a single, well-defined orientation with respect to the tricyclic portion of the molecule. Incorporation of such conformational/rotational restraints represents a promising approach toward achieving greater selectivity at receptor sites.[3] The synthesis of such rigid (cyclic) analogues, of formula II, and their pharmacological evaluation are the subject of this present study.

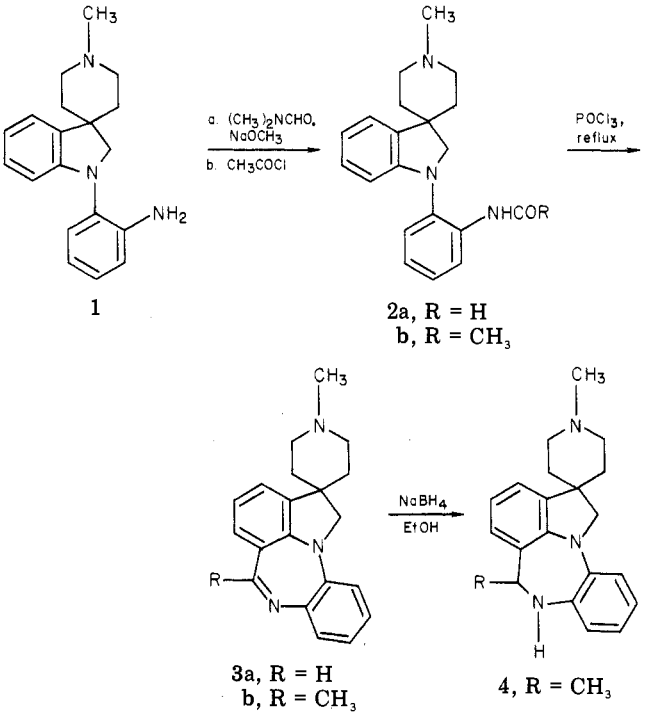
Chemistry. The target compounds were synthesized according to the procedure shown in Scheme I. The preparation of the starting material **1** was reported by us in a previous publication.[1] The amino group of **1** was formylated by heating with dimethylformamide in the presence of sodium methoxide. The dimethylformamide served both as solvent and as a convenient formylating agent. In addition, the amino group was acylated with acetyl chloride to afford amides of type **2**. These amides served as the immediate precursors to a Bischler–Napieralski cyclization reaction. When the amides **2** were refluxed in phosphorus oxychloride, cyclodehydration took place, resulting in the construction of a seven-membered central ring.[4] This provided the first class of rigid analogues, depicted by formula **3**.

The imino bond in the central ring was reduced with sodium borohydride in ethanol to provide a somewhat less rigid analogue, **4**. The absence of the unsaturated imino linkage in the central ring reduces coplanarity and confers a degree of conformational mobility to this ring.

Biological Activity. The target heterocycles were evaluated for biological activity in a variety of pharmacological screens. The expected antidepressant activity was determined by measuring their ability to prevent tetrabenazine (TBZ) induced ptosis in mice.[5] Tetrabenazine causes behavioral depression in mice with concomitant ptosis, in a manner similar to reserpine. The great majority of antidepressant agents are known to antagonize these effects, and the degree of inhibition correlates well with clinical efficacy.[6] The test procedure was described previously in a report from these laboratories.[5b] The results obtained in this animal model are shown in Table I. None of the rotationally restricted analogues **3a,b** or **4** demonstrated any significant activity in inhibiting tetrabenazine-induced ptosis. This result is in marked contrast to the potent activity [ED_{50} = 4.0 (ip) 1.9 (po) mg/kg] observed for the reference compound **1**, in which the pendant phenyl ring, with its *o*-amino substituent, is not conformationally restricted and may rotate freely about the N_1–Ph bond.

The novel cyclic congeners were also tested for other possible effects on the central nervous system. Potential anxiolytic activity was assessed by inhibition of pentylenetetrazol lethality.[7] The prevention of amphetamine

Scheme I



1 2a, R = H; b, R = CH_3 3a, R = H; b, R = CH_3 4, R = CH_3

Table I. Biological Activity[a]

no.	TBZ ptosis,[b] mg/kg, ip	PQW Writhing: [b] ED_{50}, mg/kg, sc
1	ED_{50} = 4.0 (3.5-4.6) ED_{50} (po) = 1.9 (1.2-2.7)	11.6 (10.5-12.8)
3a	20% @ 20	12.1 (10.6-14.1)
3b	50% @ 20	4.7 (4.3-5.0)
4	20% @ 20	9.73 (8.4-11.0)

[a] See Biological Activity section in the text and references cited therein for the testing procedures. [b] A linear regression analysis was used to determine the ED_{50} values and the 95% confidence intervals, which are in parentheses.

(2) Present address: McNeil Laboratories, Spring House, PA.

(3) Among the many references that could be cited are: (a) Burns, P.; Crooks, P. A.; Heatley, F.; Costall, B.; Naylor, R. J.; Nohria, Y. *J. Med. Chem.* **1982**, *25*, 363. (b) Cannon, J. G.; Crockatt, D. M.; Long, J. P.; Maixner, W. *Ibid.* **1982**, *25*, 1091. (c) Cannon, J. G.; Long, J. P.; Bhatnagar, R. *Ibid.* **1981**, *24*, 1113. (d) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Blount, J. F.; Todaro, L.; Berger, L.; Davidson, A. B.; Boff, E. *Ibid.* **1981**, *24*, 1026.

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(6) Benesova, O.; Nahunek, K. *Psychopharmacologia* **1971**, *20*, 337.

aggregation toxicity was used to detect neuroleptic activity.[8] Again, none of the rigid analogues displayed any noteworthy activity in these animal models.

Potential analgesic activity was determined by measuring the inhibition of phenyl-*p*-benzoquinone-induced writhing (PQW) in mice.[9] Table I reveals that the PQW activity of reference compound **1** was retained and even enhanced in its rigid analogues **3a,b** and **4**.

From these results, it may be concluded that the antidepressant properties of molecule **1** are strongly dependent upon the ability of the ortho-substituted phenyl ring to assume a rotational conformation other than that represented by the rigid analogues described in this report. Apparently, the potential analgesic properties of these pentacyclic molecules are not limited by such rotational considerations.

Experimental Section

The structures of all novel compounds were confirmed by their IR (Perkin-Elmer 457 grating spectrophotometer) and NMR (JEOL C-60HL) spectra. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL. Extraction solutions were dried over anhydrous sodium sulfate and concentrated on a Buchi Rotavapor-R. Chromatographic purifications were carried out with silica gel 60 as the solid phase (70–230 mesh), from EM Laboratories, Inc., Elmsford, NY. The final yields reported in this section represent analytically pure products. No effort was made to optimize yields.

***N*-[2-[1′-Methylspiro[3*H*-indole-3,4′-piperidin]-1(2*H*)-yl]phenyl]formamide Hydrochloride (2a).** A stirred mixture of 15.0 g (0.041 mol) of 2-[1′-methylspiro[3*H*-indole-3,4′-piperidin]-1(2*H*)-yl]benzenamine dihydrochloride (**1**)[1] and 75 mL of dimethylformamide was heated under N_2 to 90 °C, when 8.6 g (0.164 mol) of sodium methoxide was added. After this addition, the reaction temperature was raised to 110–115 °C and maintained at that temperature for 40 min. The resulting dark brown mixture was allowed to cool to 90 °C and then poured onto 800 mL of ice/water. The crude formamide was filtered, washed well with water, and then dissolved in 350 mL of $CHCl_3$. The $CHCl_3$ solution was extracted with H_2O, and the extract was dried and concentrated to give 11.8 g (90% crude yield). This material was dissolved in 175 mL of ether, filtered, and added to a stirred solution of 400 mL of ethereal hydrogen chloride at ice-bath temperature. The resulting salt was filtered, washed with ether, and dried to afford 12.1 g. Recrystallization from methanol–ether provided 8.2 g of pure **2a**, mp 287.5 °C dec. The overall yield was 56%. Anal. ($C_{20}H_{23}N_3O$·HCl) C, H, N.

***N*-[2-[1′-Methylspiro[3*H*-indole-3,4′-piperidin]-1(2*H*)-yl]phenyl]acetamide Oxalate (2b).** An ice-cold slurry of 6.81 g (0.019 mol) of 1·2HCl in 100 mL of CH_2Cl_2 was treated dropwise with a solution of 8.4 mL (0.059 mol) of triethylamine in 50 mL of CH_2Cl_2. Then a solution of 1.5 mL (0.021 mol) of acetyl chloride in 50 mL of CH_2Cl_2 was added dropwise. After stirring overnight, the reaction mixture was washed twice with H_2O, once with 10% NaOH, and again with H_2O. The organic phase was dried and concentrated to afford 7.6 g. This crude amide was dissolved in 50 mL of ether and filtered, and then the filtrate was treated with a solution of 2.03 g of oxalic acid in 50 mL of ether. An additional 200 mL of ether was added to maximize precipitation of the product. The resulting salt was filtered, washed with ether, and recrystallized from 2-propanol to afford 3.63 g (45% overall yield) of pure **2b**, mp 170 °C dec. Anal. ($C_{21}H_{25}N_3O$·$C_2H_2O_4$) C, H, N.

1′-Methylspiro[benzo[*b*]pyrrolo[3,2,1-*jk*][1,4]benzodiazepine-2(1*H*),4′-piperidine] Dihydrochloride (3a). A stirred mixture of 10.0 g (0.031 mol) of **2a** (as the free base) and 75 mL of phosphorus oxychloride was heated under N_2 for 1 h at 100 °C. Excess phosphorus oxychloride was then distilled off at aspirator pressure, and the residue was boiled and triturated with 200 mL of absolute EtOH. The resulting solid was filtered and washed with EtOH and then with ether to afford 7.99 g of crude product as the dihydrochloride salt. This was purified further as follows. The crude salt was dissolved in 300 mL of H_2O and enough NH_4OH was added to make the solution alkaline. The product free base was extracted into 300 mL of CH_2Cl_2, and this solution was washed twice with H_2O, dried, and concentrated to give 4.59 g. This material was dissolved in a solution of 50 mL of ether and 20 mL of CH_3OH, then added to 150 mL of ethereal hydrogen chloride kept at ice-bath temperature, and stirred well. The precipitated salt was collected, washed well with ether, and dried to furnish 4.95 g (42% overall yield) of pure **3a**, mp >310 °C. Anal. ($C_{20}H_{21}N_3$·2HCl) C, H, N.

6,1′-Dimethylspiro[benzo[*b*]pyrrolo[3,2,1-*jk*][1,4]benzodiazepine-2(1*H*),4′-piperidine] Dihydrochloride (3b). A stirred mixture of 34.2 g (0.102 mol) of **2b** (as the free base) and 200 mL of phosphorus oxychloride was refluxed for 5 h under N_2 and then kept at room temperature overnight. Excess phosphorus oxychloride was removed at aspirator pressure, and the residue was triturated with hexane and collected. This crude salt was dissolved in 800 mL of EtOH, and 800 mL of 10% NaOH was added. The solution was filtered, the filtrate was concentrated, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic phase was separated, washed with H_2O, dried, and concentrated. The resulting free base was dissolved in 350 mL of EtOH, and the stirred solution was treated dropwise with 175 mL of ethanolic hydrogen chloride. After 2 h at 0 °C, the product was filtered, washed with ether, and dried to give 20.8 g. Recrystallization from CH_3OH–ether afforded 18.8 g (47% overall yield) of pure **3b**, mp 302 °C. Anal. ($C_{21}H_{23}N_3$·2HCl) C, H, N.

6,7-Dihydro-6,1′-dimethylspiro[benzo[*b*]pyrrolo[3,2,1-*jk*][1,4]benzodiazepine-2(1*H*),4′-piperidine] Dihydrochloride (4). A stirred mixture, under N_2, of 60.1 g (0.190 mol) of **3b** (as the free base) in 450 mL of absolute EtOH was cooled to 0 °C and then 30 g of sodium borohydride was added in portions over a 2-h period. After stirring overnight at room temperature, the mixture was cooled to 0 °C and treated cautiously with 625 mL of H_2O. The volume of the mixture was reduced by one-half on the rotary evaporator, and the resulting solid was collected. This material was dissolved in 400 mL of $CHCl_3$, and the solution was washed with 10% NaOH, twice with H_2O, dried, and concentrated to give 78 g. A 14.2-g portion of this crude product was dissolved in 150 mL of CH_2Cl_2 and adsorbed onto a chromatography column containing 750 g of silica gel packed in ether. The column was eluted first with ether, followed by increasing percentages (25% per step) of CH_2Cl_2 in ether, and then with increasing percentages (1% per step) of CH_3OH in CH_2Cl_2. This brought forth 5.31 g (48% overall yield) of pure product (free base) using 16% CH_3OH in CH_2Cl_2. This material was dissolved in 30 mL of 2:1 CH_2Cl_2/ether, and the solution was added to 150 mL of ethereal hydrogen chloride, kept at 0 °C and stirred vigorously. This provided 6.44 g of pure **4**, mp 293 °C dec. The overall yield to this product was 47%. Anal. ($C_{21}H_{25}N_3$·2HCl) C, H, N.

Acknowledgment. The authors express their appreciation to Marc N. Agnew and Peter Kranack for determining the IR and NMR spectra. We also gratefully acknowledge Helene Skidanow for her help in the preparation of this manuscript.

(7) The testing methodology was described in Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Spaulding, T. C.; Wilker, J. C.; Geyer III, H. M.; Kruse, H. *J. Med. Chem.* **1980**, *23*, 494.

(8) Chance, M. R. A. *J. Pharmacol. Exp. Ther.* **1946**, *87*, 214, and the modification used in our laboratories reported in ref 7.

(9) Siegmund, E.; Cadmus, R.; Lu, G. *Proc. Soc. Exp. Biol. Med.* **1957**, *95*, 729, and the modification described in ref 7.