Synthesis and Pharmacological Evaluation of Some 6-Substituted 7-Methyl-1,4-dioxa-7-azaspiro[4.5]decanes as Potential Dopamine Agonists

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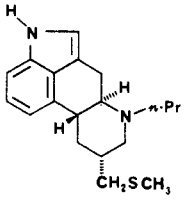
Three 7-methyl-1,4-dioxa-7-azaspiro[4.5]decanes that contained either the benzyl, 3-indolylmethyl, or 4-indolylmethyl group at the 6-position were synthesized via alkylation of the pyrrolidine enamine of the key intermediate, ethyl 3-oxopiperidine-1-carboxylate. The spirodecane derivatives were evaluated for in vivo central and peripheral dopamine agonist activity. None of the compounds displayed central nervous system activity; however, the 4-indolylmethyl analogue exhibited potent dopamine agonist activity in the cat cardioaccelerator nerve assay and possesses an ID_{50} of 0.095 μmol/kg compared to apomorphine, which possesses an ID_{50} of 0.0348 μmol/kg in the same assay.

The dopamine agonist activity of ergoline derivatives, e.g., pergolide (1), and aporphine derivatives, e.g., apomorphine (2), is well documented.[1] Considerable effort has been made by others to identify those structural features common to ergots and aporphines that confer a high degree of dopamine activity to compounds derived from these two structurally diverse heterocycles. It has been suggested[2] that the indole NH of ergots possessing dopamine agonist activity may be biologically equivalent to the "meta" OH of dopamine and perhaps the 11-OH of apomorphine when these compounds interact with dopamine receptors. Therefore, it seems reasonable that the pharmacological evaluation of a compound possessing both the substituted indole nucleus of ergots and the octahydrobenzo[*g*]quinoline moiety found in apomorphine will reveal interesting structure–activity relationships (SAR) pertinent to indole derivatives possessing dopamine activity. Toward this end, a project was initiated in this laboratory to prepare octahydroindolo[3,4-*f*,*g*]quinoline (3) and evaluate it for dopamine agonist activity.



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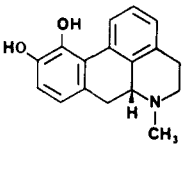

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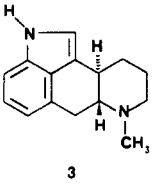

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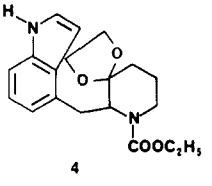

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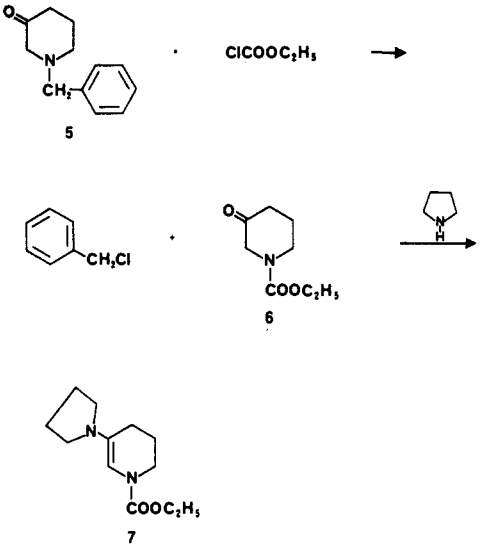
A key intermediate for the synthesis of 3 was envisaged to be the 6-(4-indolylmethyl)-1,4-dioxa-7-azaspiro[4.5]decane derivative (4). The unusual chemical stability of the spiro-ring system prompted us to submit derivatives of 4 for pharmacological evaluation. This report presents the synthesis and pharmacological evaluation of three 6-substituted 7-methyl-1,4-dioxa-7-azaspiro[4.5]decanes with in vivo dopamine agonist activity.

Chemistry

The synthetic strategy designed for the synthesis of 4 sought to take advantage of the electrophilic nature of a suitably 4-substituted indole and required a piperidine derivative that possessed a nucleophilic center at the 2-position to synthesize the key intermediate 9. Moreover, the 2-substituted 3-oxopiperidine derivative possesses an electrophilic center that could ultimately form a carbon–carbon bond with the nucleophilic 3-position of the indole moiety for the preparation of 3. A survey of the literature revealed that two compounds, 4-(bromomethyl)-1-tosylindole (8)[3] and the enamine of ethyl 3-oxopiperidine-1-carboxylate (7),[4] that met these requirements had been prepared previously. Though the alkylation of 7 was not reported,[4] precedent for this approach is provided by a report by Masamune et al.,[5] who studied the alkylation of the pyrrolidine enamine derivative of 1-acetyl-3-oxopiperidine. The Batcho–Leimgruber modification[6] of the Reissert indole synthesis reported by others[7,8] was used to prepare 4-(hydroxymethyl)-1-tosylindole from methyl 2-methyl-3-nitrobenzoate, and the former was then converted to 8 as reported by Oppolzer et al.[3] The method reported[4] for the preparation of 6 from 5 involved a catalytic N-debenzylation step followed by treatment of the crude product from this reaction with ethyl chloroformate to give the carbamate 6 (Scheme I). In our hands, 5, when

Scheme I. Preparation of Ethyl 3-(1-Pyrrolidinyl)-1,4,5,6-tetrahydropyridine-1-carboxylate



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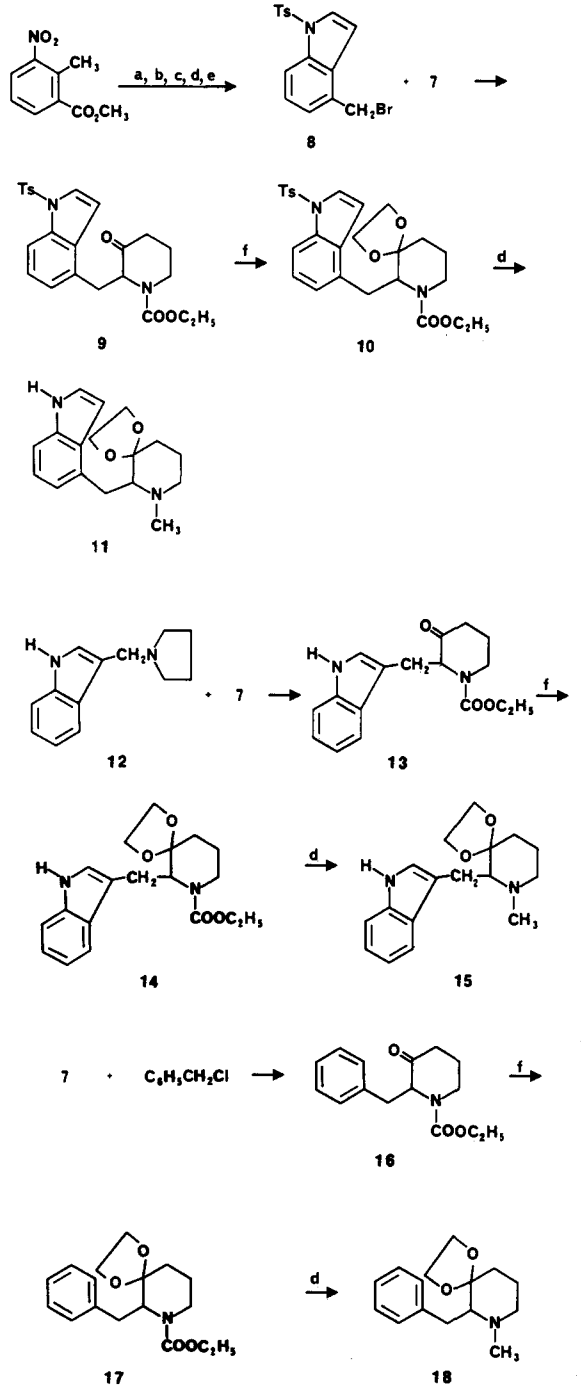
Scheme II. Preparation of 6-Substituted 7-Methyl-1,4-dioxa-7-azaspiro[4.5]decanes



[a] *N,N*-Dimethylformamide dimethyl acetal. [b] H_2, Pd/C. [c] TsCl. [d] $LiAlH_4$. [e] $(C_6H_5)_3P$, CBr_4. [f] $HOCH_2CH_2OH$, TsOH.

subjected to similar conditions, gave equivocal results, and the catalytic hydrogenolysis step required long reaction times, which resulted in decomposition of the unstable 3-ketopiperidine. The slow rate of catalytic hydrogenolysis of 1-benzyl-3-oxopiperidines has been reported previously.[9] We found that **6** could be prepared in excellent yield by treating **5** sequentially with triethylamine and ethyl chloroformate in $CHCl_3$ at room temperature. The conversion of **6** to its enamine derivative and subsequent alkylation with **8** gave **9**. The product from the alkylation step resisted all efforts to obtain it in crystalline form; therefore, it was converted to its ethylene ketal (**10**), which could be crystallized readily and was obtained in analytically pure form. Treatment of **10** with $LiAlH_4$ in refluxing THF effected the reduction of the carbamate moiety to the *N*-methyl analogue, and under these conditions the tosyl-protecting group was cleaved to give **11**. The 3-indolylmethyl analogue (**15**) was prepared by treating the enamine **7** with 3-(1-pyrrolidinylmethyl)indole (**12**) to give **13** in a manner analogous to what has been reported[10] for the alkylation of the enamine of cyclohexanone with gramine. Compound **13** was converted directly to the ethylene ketal derivative (**14**), which after column chromatography could be obtained as a solid in analytically pure form. The benzyl analogues (**16**–**18**) were prepared as outlined in Scheme II and behaved chemically in a manner similar to that of the indolylmethyl derivatives.

Table I. Biological Potencies of 6-Substituted 7-Methyl-1,4-dioxa-7-azaspiro[4.5]decanes

compd	dose, μmol/kg, iv[a]	% inhibn of nerve stimulation	cat cardioaccelerator nerve: ID_{50}, μmol/kg
11	0.035	26 ± 19	0.095[b] (0.001–1.55)[c]
	0.105	48 ± 21	
	0.315	79 ± 11	
15	3.5	32 ± 17.4[d,e]	>4.0
18	0.46	22 ± 11.7	>4.0
	1.38	18 ± 2.0[e]	
	4.60	36 ± 12.3[d]	
apomorphine			0.0348 (0.027–0.045)[c]

[a] $N = 3$ for each concentration tested. [b] Inhibitory effect was reversed by intravenous administration of haloperidol, 50 μg/kg. [c] Confidence limits (95%) of the calculated ID_{50} dose. [d] Increased arterial pressure at this dose. [e] Increased heart rate slightly at this dose.

The ethylene ketal derivatives were subjected to a variety of conditions known to effect hydrolysis of this protecting group, and these studies revealed that the 1,4-dioxa-7-azaspiro[4.5]decane ring system is chemically very stable. For example, **11** was recovered unchanged in quantitative yield after stirring in 6 N HCl at 25 °C for 12 h. Also, **17** did not undergo detectable hydrolysis when stirred in refluxing 1 N HCl/THF for 1 h. Nichols and Barfknecht reported[11] that *n*-hexyl 1-methyl-5,5-diethoxypiperidine-3-carboxylate underwent ester hydrolysis without significant hydrolysis of the diethyl acetal moiety.

Results

The compounds **11**, **15**, and **18** were evaluated for in vivo dopamine agonist activity in the cat cardioaccelerator nerve assay[12] and in the rat rotation assay.[12] Compound **11** was also evaluated for its ability to displace [^{3}H]-spiroperidol (2 nM) from rat striatal tissue, and it was inactive in this assay.[13] None of the compounds screened produced rotational behavior in rats with unilateral lesions of the nigrostriatal projection at a dose of 4.0 mg/kg, nor did they antagonize apomorphine-induced rotations in rats in the same assay.

With cat in vivo experiments, the 4-indolylmethyl compound (**11**) exhibited a potency in the same molar range as that exhibited by the potent dopamine agonist, apomorphine, in the same assay. The effects of **11** on the cardioaccelerator nerve of the cat were blocked by the

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dopamine antagonist, haloperidol.

The 6-benzyl (18) and 6-(3-indolylmethyl) (15) derivatives were synthesized and were evaluated for their ability to elicit dopamine agonist activity, to determine what effect varying the aromatic group at position 6 of 7-methyl-1,4-dioxa-7-azaspiro[4,5]decane would have on biological activity. As the data reveal (see Table I), both 15 and 18 are weak peripheral dopamine agonists in the cat cardioaccelerator nerve assay compared to 11, and at the doses required to elicit dopamine agonist activity, the former exhibit some adrenergic activity. These preliminary results suggest that the dopamine agonist activity of these derivatives is dependent on the nature of the aromatic group at position 6 of 7-methyl-1,4-dioxa-7-azaspiro[4,5]decane. Moreover, the difference in dopamine agonist activity displayed by 15 and 18 suggests that perhaps the 4-(2-aminoethyl)indole moiety may contribute more significantly to dopamine agonist activity than does the 3-(2-aminoethyl)indole moiety when present in this spirodecane ring system, and studies are currently in progress to explore the SAR of 1,4-dioxa-7-azaspiro[4.5]decanes in more detail.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries with a Thomas-Hoover melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer. Chemical shifts are reported in parts per million (δ) relative to Me_4Si. IR spectra were recorded with a Beckmann 4230 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and are within 0.4 of theoretical percentages. Common reagent-grade chemicals and starting materials were purchased from commercial sources and were used as received. All reactions were run under an inert atmosphere (N_2), and flash chromatography using SiO_2 as the stationary phase and C_6H_{12}/EtOAc (8:2) as the eluent was used to isolate compounds that could not be crystallized or vacuum distilled.

Ethyl 3-Oxopiperidine-1-carboxylate (6). To a stirred and cooled (ice bath) solution of 1-benzyl-3-piperidone hydrochloride hydrate (51 g, 0.226 mol), Et_3N (35 mL, 0.25 mol), and $CHCl_3$ (250 mL) was added dropwise $ClCO_2CH_2CH_3$ (24 mL, 27 g, 0.25 mol). After addition was complete, additional $ClCO_2CH_2CH_3$ (15 mL) was added to the flask, and the reaction was then stirred at 25 °C for 1 h. The $CHCl_3$ solution was washed with 1 N HCl, and the volatiles were evaporated to give 6 as an orange oil, which was distilled to yield 28 g (72%) of 6 after a forerun of benzyl chloride: bp 105 °C (1 mm) (lit.[4] bp 100–101 °C (0.3 mm) δ 1.27 (t, 3 H), 1.97 (m, 2 H), 2.4 (t, 2 H), 3.57 (t, 2 H), 3.92 (s, 2 H, and 4.08 (q, 2 H); IR (film) 1700, 1725 (sh) cm^{-1}.

Ethyl 2-[[4-(*p*-Tolylsulfonyl)indolyl]methyl]-3-oxopiperidine-1-carboxylate (9). A solution of 6 (3.6 g, 21 mmol), pyrrolidine (2.24 g, 31.5 mmol), and C_6H_6 (100 mL) was stirred at 25 °C for 1 h. Analysis by vapor-phase chromatography revealed that the reaction was almost complete, and then the flask was heated and 50 mL of C_6H_6 was distilled and collected in a Dean–Stark trap. A solution of 4-(bromoethyl)-1-(*p*-tolylsulfonyl)indole[3] (8) in CH_3CN (100 mL) was added to the flask in one portion, and an additional 50 mL of solvent was distilled from the flask with continued heating. TLC analysis of the reaction mixture after the second distillation of solvent revealed that no starting material remained, and after cooling, the volatiles were evaporated. The dark oil that remained was stirred with 5% $NaHCO_3$ at 80 °C for 30 min; then it was cooled, and the product was extracted from the aqueous layer with EtOAc. The organic layers were combined and dried (Na_2SO_4), and the volatiles were evaporated to give a dark oil, which was chromatographed to yield 6.69 g (77%) of 9 that would not crystallize: ^{1}H NMR (CCl_4) δ 0.5–4.2 (unresolved br m, 16 H), 4.62 (t, 1 H), and 6.5–7.9 (m, 9 H); IR (film) 1720 (sh), 1705 cm^{-1}.

Ethyl 6-[[4-(*p*-Tolylsulfonyl)indolyl]methyl]-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (10). A mixture of 9 (6.6 g, 14.5 mmol), $HOCH_2CH_2OH$ (6 mL), $TsOH{\cdot}H_2O$ (0.1 g), and C_6H_6 (150 mL) was heated to reflux, and the water that formed was removed with a Dean–Stark trap. After 12 h, the reaction was allowed to cool, and the solution was washed successively with 5% $NaHCO_3$ and saturated NaCl and dried (Na_2SO_4). Evaporation of the volatiles gave an oil that solidified, and the solid was recrystallized from EtOAc to yield 5.5 g (77%) of 10 as thick needles: mp 152–155 °C; ^{1}H NMR (CCl_4) δ 0.2–4.4 (unresolved br m, 21 H), and 6.67–7.87 (m, 9 H); IR (KBr) 1680 cm^{-1}. Anal. ($C_{26}H_{30}N_2O_6S$) C, H, N.

6-(4-Indolylmethyl)-7-methyl-1,4-dioxa-7-azaspiro[4.5]decane (11). A mixture of 10 (4.23 g, 8.5 mmol), $LiAlH_4$ (0.975 g, 25.7 mmol), and THF (50 mL) was heated at reflux, 12 h, and after cool (ice bath), saturated Na_2SO_4 was added dropwise cautiously to the mixture with stirring until the suspended solid became white. The solution was filtered, and the filter cake was washed with several portions of hot THF. The volatiles of the combined filtrates were evaporated to give an oil, which soon solidified. The solid was recrystallized from EtOAc to yield 1.86 g (76%) of colorless cubes: mp 181–186 °C: ^{1}H NMR ($CDCl_3$/$(CD_3)_2SO$) δ 1.5–1.9 (br m, 4 H), 2.2–2.3 (m and s, 4 H), 2.75 (m, 1 H), 3.0–3.2 (m, 3 H), 4.0 (s, 4 H), 6.6–7.2 (m, 5 H), and 7.63 (br s, 1 H, exchanges with D_2O). Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

Ethyl 6-(3-Indolylmethyl)-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (14). A mixture of 6 (1.71 g, 10 mmol), pyrrolidine (1.2 mL, 1.02 g, 14.4 mmol), and C_6H_6 was stirred for 30 min at 25 °C; then the mixture was heated to reflux and 15 mL of solvent was collected in a Dean–Stark trap. After the flask had cooled, the volatiles were evaporated, and then 3-(pyrrolidin-1-ylmethyl)indole (2.0 g, 10 mmol) in CH_3CN (25 mL) was added to the flask, and this mixture was heated to reflux. After 48 h, additional 6 (1.0 g) was added to the flask and refluxed for 24 h. The mixture was cooled and 1 N HCl (25 mL) was added to the flask, and this mixture was then stirred for 1 h at 25 °C. The product was extracted from the aqueous layer with EtOAc, and the combined organic layers were washed with 5% $NaHCO_3$ and saturated NaCl and dried (Na_2SO_4). Evaporation of the volatiles gave a red oil that resisted all attempts to crystallize it. This oil was used in the next step without further purification. A solution of crude 13, $HOCH_2CH_2OH$ (3.0 g, 50 mmol), and $TsOH{\cdot}H_2O$ (0.03 g) was warmed (80 °C) on the rotary evaporator until H_2O ceased to distill from the flask. Purification of the crude oil by chromatography gave an oil that crystallized from EtOAc/C_6H_{12} to yield 3.25 g (94%) of 14 as off-white clusters: mp 122–125 °C ^{1}H NMR ($CDCl_3$) δ 0.4–1.1 (2 m, 3 H), 1.8 (m, 4 H), 2.8–3.2 (m, 3 H), 3.2–4.8 (m and br s, 8 H), 6.8–7.6 (m, 5 H), and 8.3 (br s, 1 H); IR (KBr) 3300, 2950, 1675 cm^{-1}. Anal. ($C_{19}H_{24}N_2O_4$) C, H, N.

6-(3-Indolylmethyl)-7-methyl-1,4-dioxa-7-azaspiro[4.5]decane (15). A solution of 14 (2.5 g, 7.3 mmol) in THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.55 g, 14.5 mmol) in THF (25 mL). After addition was complete, the mixture was heated at reflux for 24 h. The reaction was cooled, and H_2O (0.55 mL), 15% NaOH (0.55 mL), and H_2O (1.65 mL) were added sequentially. The mixture was filtered, and the filtrate was evaporated to give an oil that solidified. Recrystallization of the solid from EtOAc yielded 0.7 g (34%) of 15 as cubes: mp 207 °C; ^{1}H NMR ($CDCl_3$/$(CD_3)_2SO$) δ 1.3–1.9 (m, 4 H), 2.2 (s and m, 4 H), 2.6–3.2 (m, 4 H), 3.9 (s, 4 H), and 6.8–7.6 (m, 5 H). Anal. ($C_{17}H_{22}N_2O_2$) C, H, N.

Ethyl 2-Benzyl-3-oxopiperidine-1-carboxylate (16). A solution of pyrrolidine (1.0 g, 1.2 mL, 15 mmol), 6 (1.71 g, 10 mmol), and C_6H_6 (25 mL) was stirred at 25 °C for 30 min. The solution was then heated to reflux and solvent was collected in a Dean–Stark trap until no more H_2O was formed. The remaining volatiles were evaporated, and benzyl chloride (1.26 g, 11 mmol) in CH_3CN (25 mL) was added to the crude enamine 7, and this mixture was stirred at reflux for 48 h. After the mixture cooled, 1 N HCl (50 mL) was added to the flask, and the product was extracted from the aqueous layer with Et_2O. The Et_2O layers were combined and evaporated, and the red oil that remained was distilled to yield 1.3 g (50%) of 16 as a light yellow oil: bp 155–160 °C (0.3 mm); ^{1}H NMR (CCl_4) δ 0.9–1.4 (2 t, 3 H), 2.4–2.6 (m and t, 4 H), 2.9–3.2 (d and m, 3 H), 3.6–4.2 (m, 3 H), 4.6 (t, 1 H), and 7.08 (br s, 5 H); IR (film) 1720 (sh), 1700 cm^{-1}. Anal. ($C_{14}H_{19}NO_3$) C, H, N.

Ethyl 6-Benzyl-1,4-dioxa-7-azaspiro[4.5]decane-7-carboxylate (17). A solution of 16 (1.4 g, 5.4 mmol), $HO(CH_2)_2OH$ (1.05 g, 17 mmol), and $TsOH{\cdot}H_2O$ was warmed (80 °C)

with stirring. After 5 min, C_6H_6 was added to the flask and the solution was heated to reflux. When water that formed during the reaction ceased to collect in the Dean–Stark trap, the solution was allowed to cool and was washed successively with 1 N HCl, 5% $NaHCO_3$, and saturated NaCl. The volatiles were evaporated, and the oil that remained was combined with the crude oil from a previous reaction. The crude product was distilled to yield 1.7 g (89%) of 17 as a clear liquid: bp 150–155 °C (0.3 mm); ^{1}H NMR ($CDCl_3$) δ 0.8–1.2 (m, 3 H), 1.6–2.0 (m, 4 H), 2.8–3.1 (m, 3 H), 3.6–4.6 (m, 8 H), and 7.2 (s, 5 H); IR (film) 2960, 2900, 1700 cm^{-1}. Anal. ($C_{17}H_{23}NO_4$) C, H, N.

6-Benzyl-7-methyl-1,4-dioxa-7-azaspiro[4.5]decane (18). A solution of 17 (1.7 g, 5.6 mmol) in THF (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.5 g, 13 mmol) in THF (5 mL). After addition was complete, the mixture was heated at reflux for 12 h; then H_2O (0.5 mL), 15% NaOH (0.5 mL), and H_2O (1.5 mL) were added successively to the cooled flask. The solution was filtered, and the volatiles were evaporated to give an oil, which was distilled to yield 1 g (72%) of 18 as a yellow liquid: bp 120–125 °C (0.3 mm); ^{1}H NMR ($CDCl_3$) δ 1.5.1.9 (m, 4 H), 2.2–2.4 (m and s, 4 H), 2.6–2.9 (m, 4 H), 3.9 (s, 4 H), and 7.2 (s, 5 H). Anal. ($C_{15}H_{21}NO_2$) C, H, N.

Pharmacology. Methods. Cat Cardioaccelerator Nerve Assay. Cats were anesthetized by injection of pentobarbital sodium (30 mg/kg) into the thoracic cavity, and the surgical and experimental procedure was the same as has been published.[12] Experimental compounds were administered intravenously in doses of 0.33 log intervals.

Rotation Assay. Male Sprague–Dawley rats with 6-hydroxydopamine unilateral denervation of the nigrostriatal projection were used to test compounds for circling behavior.[12] Compounds were administered at a dose of 4.0 mg/kg and were also evaluated for their ability to antagonize apomorphine (0.25 mg/kg) induced rotations.

Dopamine Receptor Binding Studies. A method of Seeman et al.[13] was employed using [^{3}H] spiroperidol (2 nM) and rat striatal tissue.

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Synthesis and Biological Activity of Benzothiazolo[3,2-*a*]quinolone Antibacterial Agents

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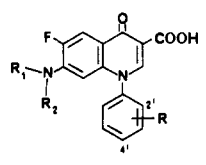
A new class of heterocyclic compounds with potent antibacterial activity, namely, 2-substituted amino-3-fluoro-5,12-dihydro-5-oxobenzothiazolo[3,2-*a*]quinoline-6-carboxylic acids, is described. The compounds are conformationally restricted analogues of 7-substituted amino-6-fluoro-1-aryl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids. Compounds 7 and 10, having a 4-methylpiperazinyl and a piperazinyl substitution at the 2-position, respectively, possess in vitro antibacterial activities comparable to norfloxacin (15). Compound 8, which has a 4-acetylpiperazinyl substitution at the 2-position, is active against Gram-positive organisms and nearly inactive against Gram-negative organisms. An efficient and short synthesis of this novel heterocyclic system via an intramolecular nucleophilic displacement cyclization reaction is reported.

In an earlier paper,[1] we reported the synthesis and antibacterial activity of 7-substituted amino-6-fluoro-1-aryl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids (1), which possess a 1-(substituted phenyl)-1,4-dihydro-4-oxopyridine-3-carboxylic acid moiety. These potent antibacterial agents belong to 4-quinolones, a class of compounds that has attracted increasing attention as a source of new antibacterial agents.[2,3] The mode of action of this class of compounds is the inhibition of bacterial DNA gyrase.[4]



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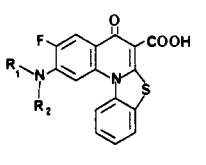

2

The optimization of substituents in the field of quinolone antibacterials has recently been reported. Quantitative structure–activity relationship (QSAR) analysis of a set of N-1 allyl and alkyl derivatives suggested an optimum STERIMOL length of 4.2 Å, corresponding approximately to an ethyl group.[5] This generalization obviously does not include aryl substituents, as shown by the high activity reported for N-1 phenyl analogues.[1] The purpose of this work was to determine the effect on antibacterial activity of forcing the N-1 phenyl substituent into rigid planar conformation. This may provide further insight into the importance of the spatial characteristics of 1-phenyl substitution. 5-Oxo-1,2-dihydro-5*H*-thiazolo[3,2-*a*]quinoline-4-carboxylic acid derivatives have recently been reported to be good antibacterial agents.[6] This indicates that substitution of a sulfur atom at the 2-position of 1,4-dihydro-4-oxoquinoline-3-carboxylic acid derivatives can lead to active compounds. Hence, a conformationally restricted rigid analogue formed by bridging the phenyl and quinolone rings by a sulfur atom would

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(4) Cozzarelli, N. R. *Science (Washington, DC)* **1980**, *207*, 953.
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