Synthesis of Spiro[isobenzofuran-1(3*H*),4'-piperidines] as Potential Central Nervous System Agents. 5. Conformationally Mobile Analogues Derived by Furan Ring Opening

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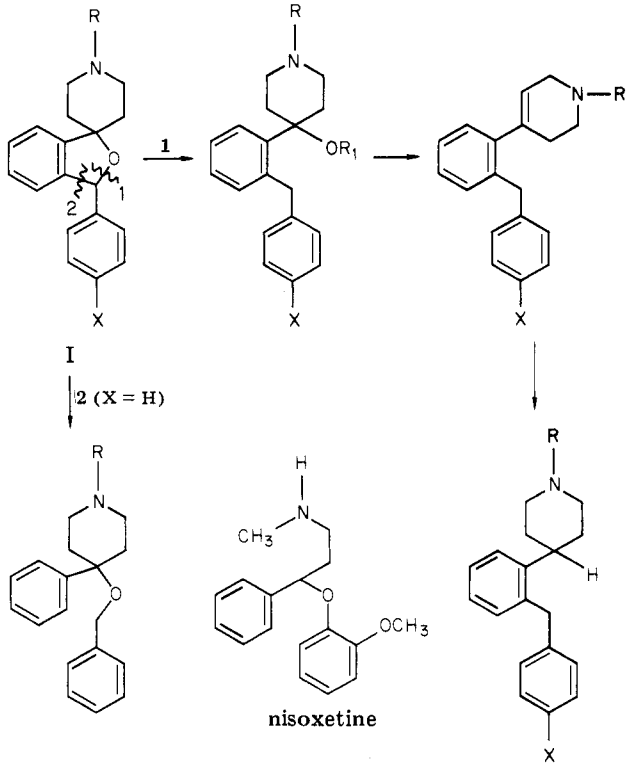
Synthesis and antitetrabenazine activity of 4-[2-(arylmethyl)phenyl]piperidines and 4-(benzyloxy)-4-phenylpiperidines, prepared as simplified and possibly more readily synthesized analogues of 3-phenylspiro[isobenzofuran-1(3*H*),-4'-piperidine], are reported. Several 4-[2-(arylmethyl)phenyl]piperidines display antitetrabenazine activity comparable to imipramine or amitriptyline but are two- to fourfold less active than analogous 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines]. Structure–activity relationships for 4-[2-(arylmethyl)phenyl]piperidines are generally similar to the profile established for 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines]. Significant antitetrabenazine activity is associated only with derivatives where the arylmethyl group is ortho to the piperidine ring. 4-(Benzyloxy)-4-phenylpiperidines and 4-[2-(arylmethyl)phenyl]-4-piperidinols and the corresponding methyl ethers and esters display weak to modest antitetrabenazine activity. 4-[2-(Arylmethyl)phenyl]-1,2,3,6-tetrahydropyridine derivatives, at best, exhibit modest antitetrabenazine activity, with the exception of 4-[2-(phenylmethyl)phenyl]-1,2,3,6-tetrahydropyridine which is approximately equipotent with amitriptyline. The results of these investigations allow certain speculations to be made with respect to the role of the furan ring in the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines] and antitetrabenazine activity.

We previously reported the synthesis, pharmacology, and biochemical properties of 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidine] derivatives.[3-12] Many of these compounds display potent antitetrabenazine activity and may be considered as potential antidepressant agents. The preparation of structurally simplified and thus possibly more readily synthesized analogues of these compounds prompted this investigation.

Correlation of the angular relationship between the aromatic rings of tricyclic antidepressants and potent in vitro inhibition of norephinephrine uptake was reported by Maxwell et al.[13,14] Molecular model studies of the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines] show that the 3-arylisobenzofuran moiety is a rigid system in which the 3-aryl group has rotational freedom and that good superimposition of the 3-phenylisobenzofuran moiety of 3-phenylspiro[isobenzofuran-1(3*H*),4'-piperidine] (HP 505, Scheme I, I, R = X = H) and the 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine nucleus of, for example, desipramine is possible. Hypothetical carbon–oxygen bond cleavage of the furan ring of the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidine] nucleus suggested a novel series of readily synthesized 4-[2-(arylmethyl)phenyl]-4-piperidinols (Scheme I). These piperidinols could be converted to ethers and esters or dehydrated to tetrahydropyridines, which could be reduced to piperidine derivatives. Significance of the ortho relationship of the arylmethyl moiety and the piperidine ring with respect to antitetrabenazine activity could be evaluated by synthesis of *m*- and *p*-(arylmethyl) analogues. In each series of these analogues, the (arylmethyl)phenyl moiety could adopt conformations in which the aromatic rings bear the angular relationship observed with the tricyclic antidepressants. Hypothetical cleavage of the indicated furan ring carbon–carbon bond suggested a series of 4-(benzyloxy)-4-phenylpiperidines which are structurally similar to both the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines] and the antidepressant nisoxetine[15] (Scheme I). Although these hypothetical ring cleavages suggested several series of conformationally mobile analogues, we hoped that some of these analogues would retain the potent antitetrabenazine activity associated with the more rigid 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidine] derivatives.

Scheme I



R = H, CH_3, $C_6H_5(CH_2)_n$; R_1 = H; CH_3, acyl;
X = H, F, CH_3O, HO

Chemistry. 2-Bromobenzophenone (**1a**), 3-bromobenzophenone (**1b**), 4-bromobenzophenone (**1c**), 2-bromo-4'-fluorobenzophenone (**1d**), and 2-bromo-4'-methoxybenzophenone (**1e**) were prepared by Friedel–Crafts aromatic ketone synthesis (Scheme II). Red phosphorous–hydriodic acid reduction of **1a–d** and triethylsilane–trifluoroacetic acid reduction of **1e** gave bromodiphenylmethanes **2a–e**. Low-temperature metallation of **2a–e** with *n*-butyllithium, addition of 1-methyl-, 1-benzyl-, or 1-phenethyl-4-piperidone, and aqueous quenching (method A) afforded piperidinols **3a–g** (Table

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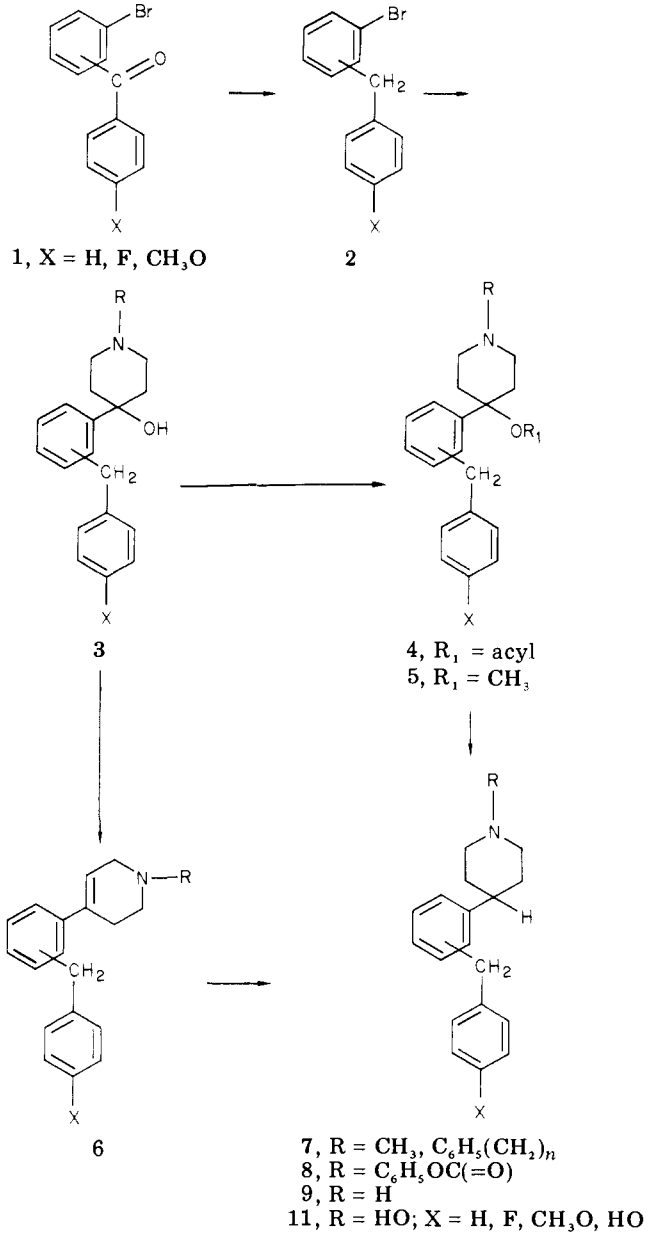
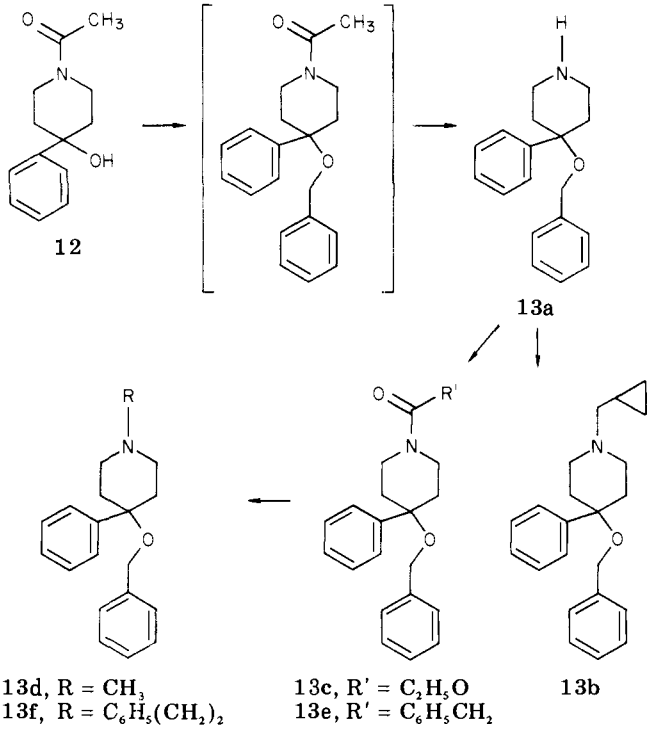
Scheme II



II). Alternatively, Grignard addition (method B) of **2a** to 1-benzyl-4-piperidone at low temperature provided key intermediate **3f** in comparatively good yield. This synthesis, in principle, provides a route which avoids the relative expense and potential hazards associated with *n*-butyllithium for large-scale work. Hydrogenolysis of **3f** (method C) afforded secondary amine **3h** which was converted to *N*-formyl derivative **3i** by refluxing with ethyl formate (method D). Treatment of **3a,b,f** with excess acetyl chloride (method E) provided esters **4a–c** (Table II). Treatment of the potassium salt of **3i** with excess iodomethane afforded methyl ether **5a** (method F, Table II). Reduction of the formyl group of **5a** with $LiAlH_4$ (method G) provided tertiary amine **5b**, whereas alkaline hydrolysis (method H) gave secondary amine **5c**. Acid-catalyzed dehydration of **3a–h** afforded tetrahydropyridines **6a–h** (method I, Table III). Catalytic reduction and/or hydrogenolysis of **4b,c** and **6a,c–e,g–h** gave piperidines **7a–e,g** and **9a** (methods J, K, and O; Table I). N-Dealkylation of **7a–e** with phenyl chloroformate (method M) provided carbamates **8a–e**, which were hydrolyzed (method N) to **9a–e** (Table I). Phenolic derivatives **7f** and

Scheme III



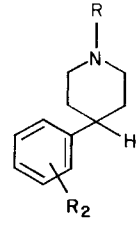
9f were prepared by cleavage of methyl ethers **7e** and **9e** with 48% hydrobromic acid (method L). *N*-Hydroxy derivative **11** was prepared by benzoyl peroxide oxidation (method P) of **9a** to give *N*-benzoyloxyamine **10**, which was hydrolyzed (method Q) to **11** (Table I). 4-(Benzyloxy)-4-phenylpiperidines (Table IV) were prepared by treatment of **12** with sodium hydride and benzyl bromide, followed by alkaline hydrolysis to afford **13a** (method S, Scheme III). N-Alkylation of **13a** with cyclopropylmethyl chloride gave **13b** (method T), while acylation (method U) with ethyl chloroformate or phenylacetyl chloride afforded **13c** and **13e**, which were reduced with $LiAlH_4$ (method G) to tertiary amines **13d** and **13f**, respectively.

Results and Discussion

Tetrabenazine methanesulfonate induces a reserpine-like behavorial depression with concomitant ptosis which is antagonized by antidepressant agents. Since drugs may produce antitetrabenazine activity by different mechanisms, such as inhibition of norepinephrine uptake or monoamine oxidase, comparison of structurally different compounds only with respect to antitetrabenazine activity may not be valid unless evidence of a similar mechanism of action is also provided. The 3-arylspiro[isobenzofuran-1(3*H*),4′-piperidine] derivatives are potent inhibitors of in vitro norepinephrine uptake by rat brain synaptosomes with IC_{50} values ranging between 10^{-6} and 10^{-8} M.[7,8] Preliminary studies with **9a** also demonstrate potent in vitro inhibition of norepinephrine uptake by rat brain synaptosomes, and the activity of **9a** is approximately equipotent to HP 505 (I, R = X = H).[7,16] Neither HP 505 nor **9a** has any significant effect on rat brain mitochondrial monoamine oxidase at 1×10^{-8}–10^{-4} M.[11,16] These preliminary biochemical data for **9a** support a common mechanism of action with the 3-arylspiro[isobenzofuran-1(3*H*),4′-piperidines], and comparison of antitetrabenazine data at least for the more active compounds of this paper would appear valid.

Antitetrabenazine activity was determined for each series of compounds and the results are presented in Tables I–IV. Data for previously reported[3,4] 3-aryl-

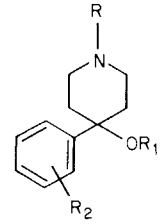
Table I. 4-[(Arylmethyl)phenyl]piperidines[a] and Spiro[isobenzofuran-1(3*H*),4'-piperidine] Analogues



compd	R	R_2	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]	tetrabenazine ptosis:[f] ED_{50}, mg/kg ip (mouse) 4-[(arylmethyl)-phenyl]-piperidines	tetrabenazine ptosis:[f] ED_{50}, mg/kg ip (mouse) spiro[isobenzofuran-1(3*H*),4'-piperidines][g]
7a	CH_3	2-$C_6H_5CH_2$	**6a**	J	220–222	55	J	$C_{19}H_{23}N$·HCl	C, H, Cl	2.5 (1.9–3.3)	1.1 (0.6–1.8)
7b	CH_3	3-$C_6H_5CH_2$	**4b**	K	162–164	27	F	$C_{19}H_{23}N$·$C_2H_2O_4$	C,[h] H, N	>20	
7c	CH_3	4-$C_6H_5CH_2$	**6c**	J	130–133	35	F	$C_{19}H_{23}N$·$C_2H_2O_4$	C, H, N	>20	
7d	CH_3	2-(4-FC_6H_4)CH_2	**6d**	J	183–186	46	J	$C_{19}H_{22}FN$·HBr	C, H, N, F	4.9 (4.3–5.6)	1.4 (1.1–1.7)
7e	CH_3	2-(4-$CH_3OC_6H_4$)CH_2	**6e**	J	182–185	43	C	$C_{20}H_{25}NO$·HBr	C, H, N	⩾20	1.1 (0.9–1.4)
7f	CH_3	2-(4-HOC_6H_4)CH_2	**7e**	L	229–232	51	F	$C_{19}H_{23}NO$	C, H, N	>20	1.0 (0.3–1.7)
7g	$C_6H_5(CH_2)_2$	2-$C_6H_5CH_2$	**6g**	J	220–225	39	F-H	$C_{26}H_{29}N$·HBr	C, H, N	10.8 (9.1–13.5)	>20
9a	H	2-$C_6H_5CH_2$	**6h, 8a, 4c**	J, N, O	207–209	50, 92, 63	J	$C_{18}H_{21}N$·HCl	C, H, N	1.7 (1.4–2.0)	0.5 (0.3–0.7)
9b	H	3-$C_6H_5CH_2$	**8b**	N	176–179	35	J	$C_{18}H_{21}N$·HCl	C, H, N	>20	
9c	H	4-$C_6H_5CH_2$	**8c**	N	168–172	20	J	$C_{18}H_{21}N$·HCl	C, H, N	>20	
9d	H	2-(4-FC_6H_4)CH_2	**8d**	N	227–231	23	J	$C_{18}H_{20}FN$·HBr	C, H, N, F	1.5 (1.2–1.8)	0.6 (0.4–0.7)
9e	H	2-(4-$CH_3OC_6H_4$)CH_2	**8e**	N	246–248	40	G	$C_{19}H_{23}NO$·HCl	C, H, N	7.1 (6.4–7.9)	2.6 (2.2–3.1)
9f	H	2-(4-HOC_6H_4)CH_2	**9e**	L	217–221	34	F	$C_{18}H_{21}NO$	C, H, N	1.2 (0.97–1.4)	0.7 (0.5–0.9)
11	HO	2-$C_6H_5CH_2$	**10**	Q	142–147	67	G	$C_{18}H_{21}NO$	C, H, N	7.3 (6.2–8.9)	1.4 (1.2–1.7)
8a	$C_6H_5O_2C$	2-$C_6H_5CH_2$	**7a**	M	120–122	62	J	$C_{25}H_{25}NO_2$	C, H, N	>20	
8b	$C_6H_5O_2C$	3-$C_6H_5CH_2$	**7b**	M	48–51	15	I	$C_{25}H_{25}NO_2$	C, H, N	nt	
8c	$C_6H_5O_2C$	4-$C_6H_5CH_2$	**7c**	M	72–77	40	J	$C_{25}H_{25}NO_2$	C, H, N	nt	
8d	$C_6H_5O_2C$	2-(4-FC_6H_4)CH_2	**7d**	M	107–110	49	F	$C_{25}H_{24}FNO_2$	C, H, N	nt	
8e	$C_6H_5O_2C$	2-(4-$CH_3OC_6H_4$)CH_2	**7e**	M	116–119	49	F	$C_{26}H_{27}NO_3$	C, H, N	nt	
10	$C_6H_5CO_2$	2-$C_6H_5CH_2$	**9a**	P	102–103	9	G	$C_{25}H_{25}NO_2$	C, H, N	nt	
imipramine										1.3 (0.9–1.7)	
desipramine										0.8 (0.6–0.9)	
amitriptyline										1.9 (1.6–2.1)	

[a] All compounds exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yield of analytically pure material; yields were not optimized. [d] A = acetone; B = acetonitrile; C = chloroform; D = cyclohexane; E = dimethyl sulfoxide; F = absolute ethanol; G = 95% ethanol; H = ether; I = hexane; J = 2-propanol; K = methanol; L = toluene. [e] Analytical results within ±0.4% of theoretical values unless otherwise noted. [f] nt = not tested. Compounds 8b–e and 10 were prepared as intermediates. [g] Refer to structure I, Scheme I, where X represents the aromatic substituent indicated for the corresponding 4-[(arylmethyl)phenyl]piperidine. The synthesis, pharmacology, and biochemical properties of 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines] was previously reported (ref 3–12). [h] C: calcd, 70.96; found, 70.52.

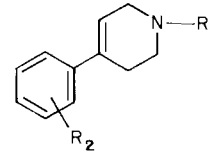
Table II. 4-[(Arylmethyl)phenyl]-4-piperidinols[a]



compd	R	R_1	R_2	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]	tetrabenazine ptosis:[f] ED_{50}, mg/kg ip (mouse)
3a	CH_3	H	2-$C_6H_5CH_2$	2a	A	163-165	58	L	$C_{19}H_{23}NO$	C, H, N	18.0 (13.6-27.5)
3b	CH_3	H	3-$C_6H_5CH_2$	2b	A	88-92	20	D	$C_{19}H_{23}NO$	C, H, N	>20
3c	CH_3	H	4-$C_6H_5CH_2$	2c	A	119-121	28	D	$C_{19}H_{23}NO$	C, H, N	>20
3d	CH_3	H	2-(4-FC_6H_4)CH_2	2d	A	142-144	29	I	$C_{19}H_{22}FNO$	C, H, N	8.2 (7.5-9.1)
3e	CH_3	H	2-(4-$CH_3OC_6H_4$)CH_2	2e	A	142-144	25	J	$C_{20}H_{25}NO_2$	C, H, N	>20
3f	$C_6H_5CH_2$	H	2-$C_6H_5CH_2$	2a	A, B	190-191	56, 40	B	$C_{25}H_{27}NO\cdot HCl$	C, H, N, Cl	>20
3g	$C_6H_5(CH_2)_2$	H	2-$C_6H_5CH_2$	2a	A	135-138	46	L	$C_{26}H_{29}NO$	C, H, N	>20
3h	H	H	2-$C_6H_5CH_2$	3f	C	226-227[g]	76	J	$C_{18}H_{21}NO\cdot HCl$	C, H, N, Cl	5.4 (4.0-8.2)
3i	HCO	H	2-$C_6H_5CH_2$	3h	D	171-174	68	K	$C_{19}H_{21}NO_2$	C, H, N	nt
4a	CH_3	CH_3CO	2-$C_6H_5CH_2$	3a	E	205-206	71	F	$C_{21}H_{25}NO_2\cdot HCl$	C, H, N, Cl	>20
4b	CH_3	CH_3CO	3-$C_6H_5CH_2$	3b	E	188-189	45	F-H	$C_{21}H_{25}NO_2\cdot HCl$	C, H, N	>20
4c	$C_6H_5CH_2$	CH_3CO	2-$C_6H_5CH_2$	3f	E	193-194	60	J	$C_{27}H_{29}NO_2\cdot HCl$	C, H, N, Cl	>20
5a	HCO	CH_3	2-$C_6H_5CH_2$	3i	F	93-96	37	F-H	$C_{20}H_{23}NO_2$	C, H, N	nt
5b	CH_3	CH_3	2-$C_6H_5CH_2$	5a	G	238-239	62	F	$C_{20}H_{25}NO\cdot HCl$	C, H, N, Cl	>20
5c	H	CH_3	2-$C_6H_5CH_2$	5a	H	87-89	77	D	$C_{19}H_{23}NO$	C, H, N	7.8 (6.9-8.8)

[a-f] See corresponding footnotes to Table I. [g] Decomposition.

Table III. 4-[(Arylmethyl)phenyl]-1,2,3,6-tetrahydropyridines[a]



compd	R	R_2	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]	tetrabenazine ptosis:[f] ED_{50}, mg/kg ip (mouse)
6a	CH_3	2-$C_6H_5CH_2$	3a	I	55-57	71	E	$C_{19}H_{21}N$	C, H	8.8 (8.0-9.6)
6b	CH_3	3-$C_6H_5CH_2$	3b	I	174-177	58	F-H	$C_{19}H_{21}N\cdot HBr$	C, H, N	>20
6c	CH_3	4-$C_6H_5CH_2$	3c	I	194-198	48	J	$C_{19}H_{21}N\cdot HBr$	C, H, N	>20
6d	CH_3	2-(4-FC_6H_4)CH_2	3d	I	192-196	39	J	$C_{19}H_{20}FN\cdot HBr$	C, H, N	8.0 (7.1-9.1)
6e	CH_3	2-(4-$CH_3OC_6H_4$)CH_2	3e	I	149-152	57	J	$C_{20}H_{23}NO\cdot HBr$	C, H	>20
6f	$C_6H_5CH_2$	2-$C_6H_5CH_2$	3f	I	216-223	54	J	$C_{25}H_{25}N\cdot HCl$	C, H, Cl	>20
6g	$C_6H_5(CH_2)_2$	2-$C_6H_5CH_2$	3g	I	98-100	56	I	$C_{26}H_{27}N$	C, H, N	>20
6h	H	2-$C_6H_5CH_2$	3h	I	73-75	64	I	$C_{18}H_{19}N$	C, H	2.1 (1.8-2.5)

[a-f] See corresponding footnotes to Table I.

Table IV. 4-(Benzyloxy)-4-phenylpiperidines[a]

compd	R	starting material	method	mp,[b] °C	yield,[c] %	recrystn solvent[d]	formula	anal.[e]	tetrabenazine ptosis:[f] ED_{50}, mg/kg ip (mouse)
13a	H	12	R, S	216–218	69	F–H	$C_{18}H_{21}NO \cdot HCl$	C, H, N, Cl	10.1 (8.7–11.4)
13b	c-$C_3H_5CH_2$	13a	T	231–232	44	F–H	$C_{22}H_{27}NO \cdot HCl$	C, H, N, Cl	6.3 (5.8–6.8)
13c	$C_2H_5O_2C$	13a	U	82–85	73	I	$C_{21}H_{25}NO_3$	C, H, N	>20
13d	CH_3	13c	G	214–216	81	A	$C_{19}H_{23}NO \cdot HCl$	C, H, N, Cl	6.2 (5.6–6.7)
13e	$C_6H_5CH_2CO$	13a	U	122–125	82[h]	F	$C_{26}H_{27}NO_2$	C, H, N	nt
13f	$C_6H_5(CH_2)_2$	13e	G	87–90	67	F	$C_{26}H_{29}NO$	C,[g] H, N	>20

[a-f] See corresponding footnotes to Table I. [g] C: calcd, 84.06; found, 83.54. [h] Crude.

spiro[isobenzofuran-1(3*H*),4'-piperidines] and for the reference standards imipramine, desipramine, and amitriptyline are included in Table I. Antitetrabenazine structure–activity relationships for piperidines **7–9** and **11** (Table I) are generally similar to relationships observed with the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines].[3,4] Thus, optimal activity appears to be associated with analogues where the nitrogen substituent is a hydrogen (**9a**) or a small alkyl group (**7a**). A larger nitrogen substituent (**7g** vs. **7a**) and N-hydroxylation (**11** vs. **9a**) lead to reduced activity. A basic nitrogen appears to be required for activity, as carbamate **8a** is essentially inactive. Significant antitetrabenazine activity is associated only with derivatives in which the phenylmethyl moiety is ortho rather than meta or para with respect to the piperidine ring (**7a** vs. **7b,c**; **9a** vs. **9b,c**). Selection of aromatic substituents (**F**, OCH_3, and OH) was based on the observed activity of the corresponding 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines].[3] Tertiary amine derivatives with these substituents (**7d–f**) display reduced antitetrabenazine activity in comparison with **7a**, whereas the activity of secondary amine analogues is equipotent (**9d**), decreased (**9e**), and slightly enhanced (**9f**) in comparison with **9a**. The fact that an aromatic substituent frequently does not influence antitetrabenazine activity of tertiary and secondary amines in a similar manner was also reported for 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines].[3] Piperidines **7a** and **9a,d,f** display antitetrabenazine activity comparable to imipramine or amitriptyline but are two- to fourfold less potent than the analogous 3-arylspiro-[isobenzofuran-1(3*H*),4'-piperidines].

Piperidinols **3**, esters **4**, and ethers **5** (Table II) generally display weak antitetrabenazine activity, with the exception of **3d,h** and **5c** which exhibit modest activity. Benzyl ethers **13** (Table IV), at best, display modest activity, with tertiary amine **13d** being approximately twice as potent as secondary amine **13a**. Tetrahydropyridines **6** (Table III) also, at best, exhibit modest activity, with the exception of secondary amine **6h** which is comparable to amitriptyline.

Although structural modification may affect pharmacokinetic and/or pharmacodynamic properties of a drug, data for **9a** and HP 505 (I, R = X = H) permit some speculations as to the role of the furan ring of the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines] in antitetrabenazine activity. As mentioned, HP 505 and **9a** are approximately equipotent with respect to in vitro inhibition of norepinephrine uptake. However, the approximately threefold difference observed with respect to antitetrabenazine activity suggests that the furan ring is required for optimal in vivo activity, possibly due, a priori, to favorable effects on the pharmacokinetic properties of the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines]. This rationalization would imply that the furan ring has little significance with respect to receptor interaction but that further molecular modification of the furan ring by synthesis of isosteric analogues may afford even more potent compounds by favorably modifying pharmacokinetic properties. Synthesis of such isosteric analogues is in progress. Work is also in progress to ascertain whether the pharmacological and biochemical profiles of piperidines **7a** and **9a,d,f** and tetrahydropyridine **6h** offer potential advantages over the 3-arylspiro[isobenzofuran-1(3*H*),4'-piperidines], and these studies will be the subject of a future report.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^1H NMR (Jeolco C60HL; tetra-

methylsilane) spectra. Melting points were taken on a Thomas-Hoover capillary melting point apparatus. All melting and boiling points are uncorrected. Elemental analyses were performed by Micro Tech Laboratories, Skokie, Ill. Results are within ±0.4% of theoretical values unless otherwise noted in the tables. Organolithium reagents were obtained from Alfa Chemical Co. Reactions with organometallic reagents were maintained under a dry nitrogen atmosphere. Solvents dried over molecular sieves were employed for reactions requiring anhydrous solvents.

Bromodiphenylmethane Derivatives 2a–e. 2-,[17] 3-,[18] and 4-bromobenzophenone[19] (**1a–c**), prepared by Friedel–Crafts aromatic ketone synthesis, were reduced with red phosphorous–47% hydriodic acid[20] to afford 2-, 3- and 4-bromodiphenylmethane[21] (**2a–c**), respectively. 2-Bromobenzhydrol and 2-bromobenzhydryl methyl ether, available from the synthesis of the spiro[isobenzofuranpiperidines],[3] were also reduced with red phosphorous–47% hydriodic acid to **2a**. 2-Bromo-4′-fluorobenzophenone[22] (**1d**), prepared in similar manner as **1a–c**, was reduced with red phosphorous–hydriodic acid to afford 2-bromo-4′-fluorodiphenylmethane (**2d**), bp 117 °C (0.3 mm). 2-Bromo-4′-methoxybenzophenone[23] (**1e**) was reduced with triethylsilane–trifluoroacetic acid[24] to provide 2-bromo-4′-methoxydiphenylmethane (**2e**), bp 104 °C (0.2 mm).

1-Methyl-4-[2-(phenylmethyl)phenyl]-4-piperidinol (3a). Method A. A stirred, chilled (−40 °C) solution of **2a** (18.5 g, 0.075 mol), 70 mL of anhydrous tetrahydrofuran, and 18 mL of anhydrous hexane was treated over 20 min with 38 mL of 2.2 M *n*-butyllithium in hexane. After total addition, the dark-colored solution was stirred for 50 min at −45 °C, followed by the addition of a solution of 8.84 g (0.078 mol) of 1-methyl-4-piperidone and 25 mL of anhydrous tetrahydrofuran over 25 min. After total addition, the solution was stirred for 1.5 h at −50 °C, warmed to 0 °C, and quenched by the addition of 25 mL of water. The resultant suspension was diluted with 200 mL of water and 500 mL of hexane. The aqueous phase was removed and the organic phase containing the suspended material was washed twice with water. Collection of the product and recrystallization from toluene afforded 12.3 g (58%) of **3a** as colorless crystals. Properties of **3a** and of **3b–g**, prepared in a similar manner from the corresponding bromodiphenylmethane and piperidone derivatives, are included in Table II.

1-Benzyl-4-[2-(phenylmethyl)phenyl]-4-piperidinol Hydrochloride (3f). Method B. 2-(Phenylmethyl)phenylmagnesium bromide was prepared in the usual manner from 29.66 g (0.12 mol) of **2a**, 2.92 g (0.12 g-atom) of magnesium turnings, and 40 mL of anhydrous tetrahydrofuran. The dark solution was diluted with 40 mL of anhydrous tetrahydrofuran and was treated at −43 to −37 °C with a solution of 18.92 g (0.1 mol) of 1-benzyl-4-piperidone and 30 mL of anhydrous tetrahydrofuran. After total addition, the solution was stirred for 2 h at ambient temperature and then quenched by the addition of 20 mL of water (exothermic). The supernatant was decanted and the gelatinous precipitate was washed three times with 100-mL portions of methylene chloride. The combined organic phase was concentreated to an oil, which was diluted with 400 mL of methylene chloride and washed twice with 150-mL portions of 5% hydrochloric acid solution. The dried (Na_2SO_4), filtered organic phase was concentrated to an oil, which crystallized. Recrystallization from 250 mL of acetonitrile afforded 15.9 g (40%) of **3f** as colorless crystals. Properties of **3f** are included in Table II.

4-[2-(Phenylmethyl)phenyl]-4-piperidinol Hydrochloride (3h). Method C. A suspension of 4.0 g (0.01 mol) of **3f**, 1.0 g of 10% palladium on carbon catalyst, and 110 mL of 2-propanol was hydrogenated on a Parr apparatus at 72 °C and 50 psi for 1 h, followed by shaking for 1.5 h at ambient temperature. The suspension was filtered and the filter cake was washed with methanol. Evaporation of the combined filtrates and recrystallization of the residue from 2-propanol afforded 2.4 g (76%) of **3h** as colorless crystals, mp 226–227 °C dec. The free base was prepared by treatment of a methanolic solution of **3h** with 5% sodium hydroxide solution. The crude free base precipitated and was collected by vacuum filtration. Recrystallization from methanol–water afforded the free base as colorless crystals, mp 151–152 °C.

1-Formyl-4-[2-(phenylmethyl)phenyl]-4-piperidinol (3i). Method D. A stirred solution of 5.0 g (0.019 mol) of **3h** free base, 70 mL of ethyl formate, and 80 mL of absolute ethanol was heated overnight under reflux. Evaporation of the solvents and recrystallization of the residue from methanol afforded 3.8 g (68%) of **3i** as colorless crystals. Properties of **3i** are included in Table II.

4-Acetoxy-1-methyl-4-[2-(phenylmethyl)phenyl]piperidine Hydrochloride (4a). Method E. Treatment of 1.4 g (0.005 mol) of **3a** with 4.0 mL of acetyl chloride, with stirring and cooling, afforded a suspension of crystalline material. The suspension was allowed to stand for 96 h at ambient temperature, followed by collection of the solid material and washing with anhydrous ether. Recrystallization from absolute ethanol afforded 1.3 g (71%) of **4a** as colorless crystals. Properties of **4a** and of **4b,c**, prepared in similar manner, are included in Table II.

1-Formyl-4-methoxy-4-[2-(phenylmethyl)phenyl]piperidine (5a). Method F. A stirred mixture of 13.6 g (0.046 mol) of **3i**, 340 mL of anhydrous toluene, and 2.9 g (0.075 g-atom) of potassium metal (nitrogen atmosphere) was heated under reflux for a few minutes and cooled. Methyl iodide (66.7 g, 0.47 mol) was added, followed by stirring overnight at 83 °C. The cooled mixture was cautiously quenched with water, followed by washing the organic phase with water. The dried (Na_2SO_4) organic phase was evaporated to an oil, which crystallized. Recrystallization from absolute ethanol–ether afforded 4.0 g of colorless crystals. Workup of the mother liquor afforded an additional 1.2 g of product, giving a total yield of 5.2 g of **5a** as colorless crystals. Properties of **5a** are included in Table II.

1-Methyl-4-methoxy-4-[2-(phenylmethyl)phenyl]piperidine Hydrochloride (5b). Method G. A solution of 4.0 g (0.013 mol) of **5a** and 300 mL of anhydrous ether was added dropwise to a stirred suspension of 0.68 g (0.017 mol) of $LiAlH_4$ and 100 mL of anhydrous ether under nitrogen with exclusion of moisture. The mixture was stirred overnight at ambient temperature and was cautiously quenched with water. The mixture was filtered, the phases were separated, and the aqueous phase was extracted with ether. The combined organic phase was dried (Na_2SO_4) and evaporated to an oil, which was converted to the hydrochloride salt with ethereal hydrogen chloride. Recrystallization from absolute ethanol afforded 2.7 g (62%) of **5b** as colorless crystals. Properties of **5b** are included in Table II. Properties of **13d,f**, prepared by refluxing a mixture of 0.084 mol of **13c,e**, respectively, 0.025 mol of $LiAlH_4$, and 120 mL of anhydrous tetrahydrofuran for 3 h, are included in Table IV.

4-Methoxy-4-[2-(phenylmethyl)phenyl]piperidine (5c). Method H. A stirred solution of 1.16 g (0.0037 mol) of **5a**, 3.3 g (0.059 mol) of potassium hydroxide pellets, and 25 mL of methanol was heated under reflux for 2 h. The cooled solution was diluted with water and extracted with ether. The organic phase was dried (K_2CO_3), filtered, and evaporated to an oil. Recrystallization from cyclohexane afforded 0.70 g (77%) of **5c** as colorless crystals. Properties of **5c** are included in Table II.

1-Methyl-4-[2-(phenylmethyl)phenyl]-1,2,3,6-tetrahydropyridine (6a). Method I. A stirred solution of 55.6 g (0.2 mol) of **3a**, 250 mL of glacial acetic acid, and 20 mL of concentrated hydrochloric acid was heated under reflux for 3 h. The cooled solution was decanted into 1.2 L of ice–water and was basified with 50% sodium hydroxide solution. The cooled mixture was extracted with a total of 750 mL of chloroform, and the organic phase was dried (Na_2SO_4), filtered, and evaporated to an oil. After azeotropic distillation with benzene, the oil was diluted with 40 g of dimethyl sulfoxide, and the solution was vacuum filtered. The filtrate was stirred until crystallization initiated and was then allowed to stand overnight at ambient temperature. Collection of the crystalline precipitate by vacuum filtration, thorough washing with water, and drying in vacuo at 30 °C afforded 37.0 g (71%) of **6a** as colorless crystals. Properties of **6a** and of **6b–h**, prepared in similar manner, are included in Table III.

1-Methyl-4-[2-(phenylmethyl)phenyl]piperidine Hydrochloride (7a). Method J. A suspension of 0.70 g of PtO_2 (Adam's catalyst), 2.4 g (0.009 mol) of **6a** and 100 mL of 95% ethanol was hydrogenated at ambient temperature and 50 psi for 24 h. The suspension was filtered and the filtrate was evaporated to a colorless oil. An ethereal solution of the oil was treated with ethereal hydrogen chloride, and the precipitate was collected.

Recrystallization from 2-propanol afforded 1.5 g (55%) of **7a** as colorless crystals. Properties of **7a** and of **7c–e,g** and **9a**, prepared in similar manner, are included in Table I.

1-Methyl-4-[3-(phenylmethyl)phenyl]piperidine Oxalate (7b). Method K. A mixture of 59.3 g (0.17 mol) of **4b**, 11.2 g of 10% palladium on carbon catalyst, and 600 mL of absolute ethanol was hydrogenated on a Parr apparatus at ambient temperature and 50 psi. After hydrogen uptake ceased, the mixture was filtered and the filtrate evaporated. A chloroform solution of the residual oil was washed with 5% sodium hydroxide solution and water, dried ($MgSO_4$), and evaporated to an oil, which was converted to the oxalate salt. Recrystallization from absolute ethanol afforded 16.0 g (27%) of **7b** as colorless crystals. Properties of **7b** are included in Table I.

4-[2-[(4-Hydroxyphenyl)methyl]phenyl]-1-methylpiperidine (7f). Method L. This compound was prepared by treatment of **7e** with 48% HBr under similar conditions, as described by Martin et al.[3] (method K). Properties of **7f** and of **9f**, prepared in similar manner, are included in Table I.

1-(Phenoxycarbonyl)-4-[2-(phenylmethyl)phenyl]piperidine (8a). Method M. This compound was prepared by treatment of **7a** with phenyl chloroformate under similar conditions, as described by Martin et al.[3] (method N). Properties of **8a** and of **8b–e**, prepared in similar manner, are included in Table I.

4-[2-(Phenylmethyl)phenyl]piperidine Hydrochloride (9a). Method N. This compound was prepared by KOH–ethylene glycol hydrolysis of **8a** under similar conditions, as described by Shutske et al.[6] Properties of **9a** and of **9b–e**, prepared in similar manner, are included in Table I.

Method O. A mixture of 20.0 g (0.046 mol) of **4c**, 6.0 g of 10% palladium on carbon catalyst, and 500 mL of methanol was hydrogenated at 50 psi and 70 °C on a Parr apparatus. The cooled mixture was filtered and concentrated on a rotary evaporator. Recrystallization from 2-propanol afforded 8.3 g (63%) of **9a** as colorless crystals. Properties of **9a** are included in Table I.

1-(Benzoyloxy)-4-[2-(phenylmethyl)phenyl]piperidine (10). Method P. This compound was prepared from **9a** under similar conditions as described by Klioze et al.[4] Properties of **10** are included in Table I.

1-Hydroxy-4-[2-(phenylmethyl)phenyl]piperidine (11). Method Q. Prepared by alkaline hydrolysis of **10** under similar conditions, as described by Klioze et al.[4] Properties of 11 are included in Table I.

1-Acetyl-4-phenyl-4-piperidinol (12). Method R. To a solution of 31.9 g (0.18 mol) of 4-phenyl-4-piperidinol in 240 mL of pyridine was added slowly via syringe 21.4 g (0.21 mol) of acetic anhydride. The resulting solution was stirred at ambient temperature under nitrogen for 17 h, diluted with 300 mL of water, and extracted with 600 mL of chloroform. The organic layer was washed with 2 N HCl (3 × 600 mL) and 300 mL of saturated aqueous $NaHCO_3$ solution. The extracts were then dried (Na_2SO_4) and evaporated in vacuo to give a nearly colorless solid, which on trituration with ether/petroleum ether afforded 34.9 g (89%) of fine colorless crystals, mp 148–150 °C (lit.[25] mp 149.5–150.5 °C).

4-(Benzyloxy)-4-phenylpiperidine Hydrochloride (13a). Method S. To a mixture of 26.3 g (0.12 mol) of **12** and 3.2 g (0.13 mol) of sodium hydride in 360 mL of dry tetrahydrofuran was added 22.6 g (0.13 mol) of benzyl bromide. The resulting mixture was heated at reflux under nitrogen for 20 h. The cooled reaction mixture was diluted with 300 mL of water and extracted with ether (2 × 450 mL). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to provide a dark-brown oil. This material was chromatographed on 350 g of silica gel using 2% MeOH/$CHCl_3$ as eluant. The enriched fractions were combined and evaporated in vacuo to afford 36.1 g (97%) of 1-acetyl-4-(benzyloxy)-4-phenylpiperidine as a brown oil.

To a solution of 31.5 g (0.10 mol) of 1-acetyl-4-(benzyloxy)-4-phenylpiperidine in 300 mL of absolute ethanol was added 200 mL of 20% aqueous NaOH solution. The resulting mixture was heated at reflux with stirring under nitrogen for 17 h. The reaction mixture was cooled to ambient temperature and most of the ethanol was removed in vacuo. The residue was diluted with 500 mL of water and extracted with ether (2 × 500 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to afford 26.4 g (97%) of 4-(benzyloxy)-4-phenylpiperidine as an orange oil, which crystallized on standing. A 5.35-g (0.02 mol) portion of this material was dissolved in 50 mL of ether and treated with 75 mL of ethereal hydrogen chloride. After cooling, the resulting precipitate was filtered, washed with ether, and dried to give 5.7 g (91%) of beige crystalline solid. Recrystallization from ethanol/ether afforded 4.30 g (69%) of **13a** as colorless crystals. Properties of **13a** are included in Table IV.

4-(Benzyloxy)-1-(cyclopropylmethyl)-4-phenylpiperidine Hydrochloride (13b). Method T. To a solution of 3.2 g (0.012 mol) of **13a** (free base) in 50 mL of dry dimethylformamide was added 3.6 g of anhydrous K_2CO_3, 0.1 g of powdered KI, and 1.2 g (0.013 mol) of cyclopropylmethyl chloride. The resulting suspension was heated at 75 °C with stirring for 25 h, diluted with 400 mL of benzene, and washed with water (3 × 200 mL). The organic layer was dried (Na_2SO_4) and evaporated in vacuo to an orange oil. This material was dissolved in 20 mL of ether and was treated with 20 mL of ethereal hydrogen chloride. The precipitated salt was filtered, washed with ether, and dried to give 3.4 g (78%) of beige crystalline solid. Recrystallization from ethanol/ether afforded 1.9 g (44%) of **13b** as fine colorless needles. Properties of **13b** are included in Table IV.

4-(Benzyloxy)-1-(ethoxycarbonyl)-4-phenylpiperidine (13c). Method U. To a solution of 4.0 g (0.015 mol) of **13a** (free base) in 70 mL of dichloromethane containing 1.7 g (0.0165 mol) of triethylamine was added dropwise, with stirring under nitrogen, a solution of 1.8 g (0.0165 mol) of ethyl chloroformate in 30 mL of dichloromethane. The reaction mixture was stirred for 3 h at ambient temperature, diluted with 150 mL of dichloromethane, and washed with 200 mL of water, 100 mL of 1 N hydrochloric acid, and 150 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and evaporated in vacuo to an orange oil. Trituration with hexane and cooling gave 4.3 g (84%) of yellow crystalline solid. A 1.5-g portion of this material was recrystallized from hexane to afford 1.3 g (73%) of **13c** as a pale-yellow crystalline solid. Properties of **13c** and of **13e**, prepared in similar manner, are included in Table IV.

Tetrabenazine Assay. The test compound was administered by intraperitoneal injection to male mice (Charles Rivers CD-1) in groups of five. Tetrabenazine methanesulfonate (40 mg/kg, ip) was administered 30-min later, and after another 30 min the mice were placed in individual containers. Ptosis was then evaluated on a three-point scale: eyes closed = 2; eyes half open = 1; eyes open = 0. A linear-regression analysis of the ptosis scores was used to evaluate ED_{50} values and 95% confidence intervals. Data for the reference standards imipramine, desipramine, and amitriptyline are included in Table I.

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Quinolone Antimicrobial Agents. 2. Methylenedioxy Positional Isomers of Oxolinic Acid

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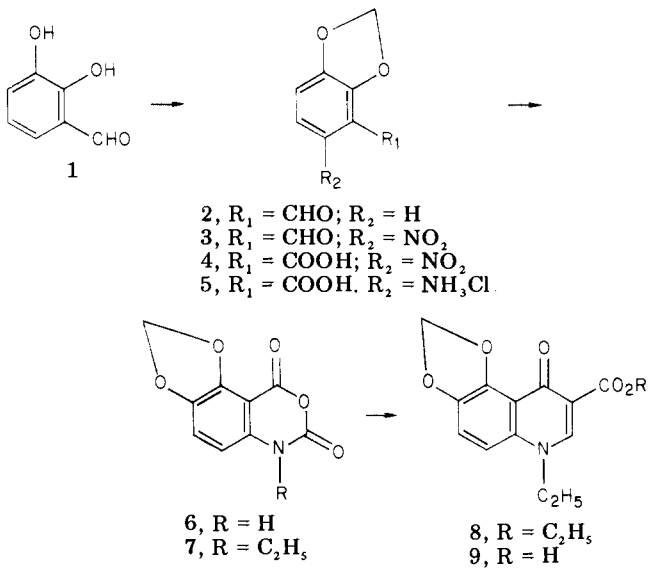
The synthesis and antimicrobial activity of the methylenedioxy positional isomers, 1-ethyl-1,4-dihydro-5,6-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**9**) and 1-ethyl-1,4-dihydro-7,8-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**17**), of oxolinic acid (**18**) have been accomplished. Isomer **9** was prepared by the reaction of *N*-ethyl-6,7-methylenedioxyisatoic anhydride with sodioethyl formylacetate [L. A. Mitscher, H. E. Gracey, G. W. Clark III, and T. Suzuki, *J. Med. Chem.*, **21**, 485 (1978)], while isomer **17** was prepared by thermal cyclization of diethyl 2-[(2,3-methylenedioxyanilino)methylene]malonate [D. Kaminsky and R. I. Meltzer, *J. Med. Chem.*, 11, 160 (1968)]. Both of the new isomers are less active in vitro when compared to oxolinic acid (**18**) itself.

Oxolinic acid (**18**) has found widespread clinical use in the treatment of urinary tract infections. Recent findings that nalidixic acid and oxolinic acid act by inhibiting the DNA gyrase[3,4] necessary for bacterial,[5,6] plasmid,[7,8] and bacteriophage[9-11] replication, as well as phage recombination[12] and phage-promotor-dependent transcription,[13] have heightened interest in the properties of these antimicrobial agents. The mechanistic details of their interactions with DNA gyrase are unavailable as yet. Our previous work[1] and that of others have shown that substitution at C-2 in this therapeutic group abolishes activity.

Continuing our systematic SAR study, we decided to synthesize the methylenedioxy positional isomers of oxolinic acid, compounds which, surprisingly, have not been reported. This also, circumstantially, allowed a side by side comparison of the newer[1] vs. the classical[2] methods available for synthesis of these agents.

The desired 1-ethyl-1,4-dihydro-5,6-methylenedioxy-4-oxo-3-quinolinecarboxylic acid (**9**) cannot be made by the classical Gould–Jacobs-dependent route because thermal cyclization of the requisite diethyl 2-[(2,3-methylenedioxyanilino)methylene]malonate leads exclusively to oxolinic acid (**18**). The known 2,3-methylenedioxy-6-nitrobenoic acid (**4**) was prepared from commercially available 2,3-dihydroxybenzaldehyde (**1**) by catechol methylenation employing dibromomethane with cupric oxide as catalyst to give **2**, nitration of **2** to **3**, followed by permanganate oxidation essentially as reported.[14] Catalytic reduction gave an 83% yield of the anthranilic acid salt **5**. Condensation with phosgene[15] led to 6,7-methylenedioxyisatoic anhydride (**6**) in 78% yield, and N-ethylation with NaH and iodoethane afforded **7** in 80% yield. Condensation of **7** with sodioethyl formylacetate[1] gave exclusively **8** in 86% yield. Alkaline hydrolysis of **8** then gave a 91% yield of the desired positional isomer **9**.



Synthesis of the positional isomer **17** was effected fundamentally by the established method of Kaminsky and Meltzer.[2] In this case, thermal cyclization of the appropriate diethyl 2-[(2,3-methylenedioxyanilino)-methylene]malonate (**14**) can only proceed in one direction. The known 2,3-methylenedioxyaniline (**13**)[16] was prepared from 2,3-methylenedioxybenzaldehyde (**2**). Oxidation of **2** to **10** with permanganate,[17] conversion to the acid chloride **11**,[17] ammonolysis to the benzamide **12**,[17] and Hofmann rearrangement afforded the requisite aniline **13**.[16] An addition–elimination reaction with diethyl ethoxymethylenemalonate afforded **14** in 81% yield. Thermal cyclization gave **15** in 76% yield, and N-ethylation with

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