Synthesis of Spiro[isobenzofuran-1(3*H*),4′-piperidines] as Potential Central Nervous System Agents. 2.[1] Compounds Containing a Heteroatom Attached to Nitrogen

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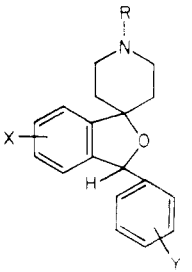
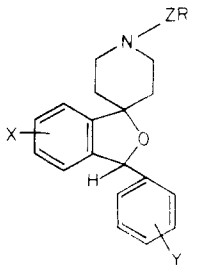
The synthesis and antitetrabenazine activity of a series of N-heteroatom derivatives of 3-phenylspiro[isobenzofuran-1,4′-piperidines] are reported. Optimal antitetrabenazine activity is associated with compounds containing a sterically unhindered, basic nitrogen. Hydroxylamines **6**, **11**, **12**, and **13** possess the most significant activity with ED_{50}'s of 1.4, 3.5, 4.7, and 4.0, respectively.

We have recently described the synthesis and antitetrabenazine activity of a series of 3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidines] having the general formula **1**.[1] Potent antitetrabenazine activity in this series was shown to be associated with those compounds having



1a, R = X = Y = H
b, R = X = H; Y = 4-OCH_3
c, R = Y = H; X = 6-OCH_3
d, R = X = H; Y = 4-F

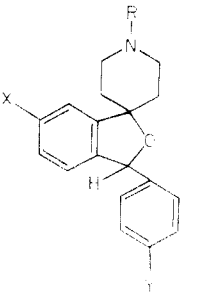
a basic nitrogen substituted with a hydrogen or small alkyl moiety. In order to further define the steric and electronic requirements of the piperidine nitrogen for optimal activity, we have undertaken the synthesis of compounds of the general formula **2** which contain another heteroatom attached directly to this nitrogen. In this paper the synthesis and antitetrabenazine activity of these compounds are reported.



2, Z = O, NH

Chemistry. The *N*-amino derivative **3** was prepared in the classical manner from **1a** via nitrosation to afford nitrosamine **4** followed by zinc–acetic acid reduction. Hydrazine **3** was in turn reductively alkylated with acetone–sodium cyanoborohydride[2] to afford isopropylamino derivative **5**.

The preparation of the *N*-hydroxy derivative **6** was effected by oxidation of **1a** with benzoyl peroxide to give the *N*-benzoyloxyamine **7** followed by basic hydrolysis to **6**.[3] Nuclear-substituted compounds **11**, **12**, and **13** were prepared in an analogous manner via intermediate *N*-benzoyloxyamines **8**–**10** from **1b**–**d**, respectively (see Table I).

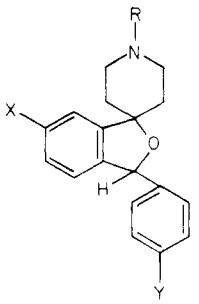


3, R = NH_2; X = Y = H
4, R = NO; X = Y = H
5, R = $NHCH(CH_3)_2$; X = Y = H
6, R = OH; X = Y = H
7, R = $OC(=O)C_6H_5$; X = Y = H
8, R = $OC(=O)C_6H_5$; X = H; Y = OCH_3
9, R = $OC(=O)C_6H_5$; X = OCH_3; Y = H
10, R = $OC(=O)C_6H_5$; X = H; Y = F
11, R = OH; X = H; Y = OCH_3
12, R = OH; X = OCH_3; Y = H
13, R = OH; X = H; Y = F

Pharmacology. Tetrabenazine methanesulfonate induces a reserpine-like behavioral depression with concomitant ptosis which is antagonized by antidepressant agents. The compounds whose synthesis is described in this paper were evaluated in this assay and their activity compared with that of prototype compound **1a** and reference standards imipramine and demethylimipramine (Table II). The nonbasic nitrosamine **4**, which served as an intermediate for the preparation of the initial target compound **3**, did not show any appreciable antitetrabenazine activity at the normal screening dose of 25 mg/kg. The basic target *N*-amino derivative **3**, on the other hand, had an ED_{50} in this assay of 6.8 ip. When **3** was reductively alkylated to afford **5**, antitetrabenazine activity was diminished as it was in series **1** when larger alkyl substituents were attached to the piperidine nitrogen.[1] Hydroxylamine **6** exhibited marked activity in this assay with an ED_{50} of 1.4 ip. In contrast, the relatively bulky and less basic precursor *N*-benzoyloxyamine **7** was considerably less potent. In an effort to maximize the antitetrabenazine activity of **6**, a variety of nuclear substituted analogues, as exemplified by **11**, **12**, and **13**, was synthesized. While significant antitetrabenazine activity was observed in each case, no apparent advantage over the parent **6** could be shown.

In summary, marked inhibition of tetrabenazine-induced ptosis among N-hetero analogues of 3-phenylspiro[iso-

Table I[a]



Compd	R	X	Y	Starting material	Mp,[b] °C	Yield, %[c]	Formula	Analyses[d]
3	NH_2	H	H	4	143-145	66	$C_{18}H_{20}N_2O$	C, H, N
4	NO	H	H	1a	161-164	86	$C_{18}H_{18}N_2O_2$	C, H, N
5	$NHCH(CH_3)_2$	H	H	3	110-112	37	$C_{21}H_{26}N_2O$	C, H, N
6	OH	H	H	7	185-188	78	$C_{18}H_{19}NO_2$	C, H, N
7	$OC(=O)C_6H_5$	H	H	1a	167-170	58	$C_{25}H_{23}NO_3$	C, H, N
8	$OC(=O)C_6H_5$	H	OCH_3	1b	164-166	59	$C_{26}H_{25}NO_4$	C, H, N
9	$OC(=O)C_6H_5$	OCH_3	H	1c	163-167	60	$C_{26}H_{25}NO_4$	C, H, N
10	$OC(=O)C_6H_5$	H	F	1d	163-166	59.5	$C_{25}H_{22}NO_3F$	C, H, N, F
11	OH	H	OCH_3	8	183-185	59	$C_{19}H_{21}NO_3$	C, H, N
12	OH	OCH_3	H	9	186-188	73	$C_{19}H_{21}NO_3$	C, H, N
13	OH	H	F	10	182-185	77	$C_{18}H_{18}NO_2F$	C, H, N, F

[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 recrystallized from ethanol; yields were not optimized. [d] Analytical results within ±0.4% of theoretical values.

Table II. Pharmacological Data

Compd	Tetrabenazine ptosis, ED_{50}, mg/kg ip (mouse)
Imipramine	1.3 (0.9-1.7)
Demethylimipramine	0.8 (0.6-0.9)
1a	0.5 (0.3-0.7)
3	6.8 (5.7-8.3)
4	>25
5	>25
6	1.4 (1.2-1.7)
7	>25
11	3.5 (3.0-4.2)
12	4.7 (3.2-8.0)
13	4.0 (3.1-4.9)

benzofuran-1,4′-piperidine] seems to be associated, as it was in series 1, with compounds possessing a sterically unhindered, basic nitrogen.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^1H NMR (JEOL C60HL) (in deuteriochloroform relative to an internal tetramethylsilane standard). Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Labs, Skokie, Ill. Results are within ±0.4% of theoretical values.

1′-Nitroso-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (4). To a stirred solution of 10.62 g (0.04 mol) of **1a** in 40 mL of glacial acetic acid and 16 mL of water was added dropwise at 0–5 °C under nitrogen a solution of 5.52 g (0.08 mol) of sodium nitrite in 24 mL of water. About halfway through the addition a thick white precipitate formed. After the addition was complete, the mixture was allowed to stand for 1 h at room temperature, diluted with 80 mL of water, and filtered. The white precipitate was washed with water and a small portion of cold ethanol and dried in vacuo. Recrystallization from ethanol afforded 10.11 g (86%) of nearly colorless leaflets, mp 161–164 °C.

1′-Amino-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (3). To a stirred suspension of 7.05 g (0.108 g-atom) of zinc dust in 100 mL of 1:1 acetic acid–water was added under nitrogen, maintaining the temperature between 10 and 20 °C, a solution of 7.06 g (0.024 mol) of **4** in 75 mL of acetic acid. The mixture was stirred for 15 min at room temperature and then heated to 80 °C for 15 min. After 5 min of heating, an additional 4.7 g (0.072 g-atom) of zinc dust was added. The hot solution was then filtered and the zinc and inorganic salts were washed with three 50-mL portions of hot 1 N hydrochloric acid. The combined filtrate and washings were basified with 50% aqueous sodium hydroxide solution and extracted with chloroform (2 × 400 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated to a white crystalline solid. This material was chromatographed on 250 g of silica gel using 5% MeOH–$CHCl_3$ as eluent in order to remove a small amount of **1a** impurity. Evaporation of the solvent in vacuo gave 5.76 g (86%) of product. Recrystallization from ethanol afforded 4.43 g (66%) of white crystalline solid, mp 143–145 °C.

1′-(2-Propylamino)-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (5). To a mixture of 1.40 g (5 mmol) of **3**, 25 mL of acetonitrile, and 2.5 mL of acetone was added 236 mg (3.75 mmol) of sodium cyanoborohydride. Five drops of acetic acid were added and the mixture was warmed briefly. The mixture was then stirred at room temperature under nitrogen for 5 h, maintaining the pH between 6 and 8 by periodic dropwise addition of acetic acid. The reaction mixture was diluted with 250 mL of chloroform, washed with 75 mL of 2 N hydrochloric acid and 100 mL of 10% aqueous sodium hydroxide solution, and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a pale yellow oil which on trituration with ether–petroleum ether afforded 1.05 g (65%) of white crystalline solid, mp 103–108 °C. Recrystallization from ethanol yielded 0.60 g (37%) of fine white crystals, mp 110–112 °C.

1′-Benzoyloxy-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (7). To a solution of 12.11 g (0.05 mol) of benzoyl peroxide in 375 mL of benzene cooled in an ice bath was added in small portions 26.54 g (0.1 mol) of **1a**. This mixture was heated at 60 °C under nitrogen for 2 h. The solvent was removed in vacuo, and the semicrystalline residue was recrystallized from ethanol to afford 11.13 g (58% based on benzoyl peroxide) of fine colorless needles, mp 167–170 °C. Properties of **7**, and **8**, **9**, and **10** prepared in similar manner, are included in Table I.

1′-Hydroxy-3-phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (6). A mixture of 10.79 g (0.028 mol) of **7**, 120 mL of absolute ethanol, and 80 mL of 10% aqueous sodium hydroxide solution was heated at reflux under nitrogen for 20 min. The

reaction mixture was cooled and most of the ethanol was removed in vacuo. The residue was diluted with 100 mL of water and the pH adjusted to 6 by careful addition of 2 N hydrochloric acid. Extraction with chloroform (2 × 300 mL) followed by drying the extracts over anhydrous sodium sulfate and evaporation of the solvent in vacuo afforded a nearly colorless crystalline solid. Recrystallization from ethanol gave 6.16 g (78%) of fine colorless crystals, mp 185–188 °C. Properties of **6**, and of **11**, **12**, and **13** prepared in similar manner, are included in Table I.

Tetrabenazine Assay. The assay was conducted and the data were analyzed as described in ref 1.

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References and Notes

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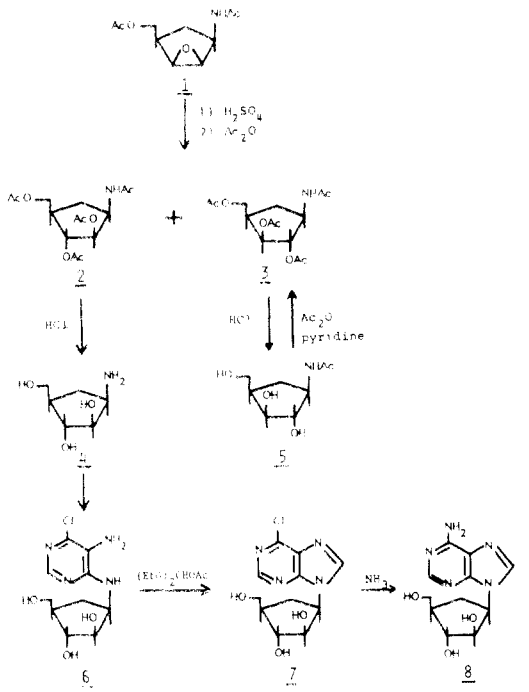
Communications to the Editor

Carbocyclic Arabinosyladenine, an Adenosine Deaminase Resistant Antiviral Agent

Sir:

The antiviral nucleoside 9-β-D-arabinofuranosyladenine (*ara*-A) was first synthesized in a program designed to produce anticancer agents.[1] Recent interest in the promising antiviral activity of *ara*-A has been extensively reviewed.[2-4] Broad spectrum activity of *ara*-A against DNA viruses[5] and significant therapeutic activity of *ara*-A against experimental herpes simplex keratitis and herpes simplex and vaccinial encephalitis have been reported.[2] A major liability in the use of *ara*-A lies in the fact that the nucleoside is rapidly deaminated by a commonly occurring enzyme, adenosine deaminase.[5,6] Although the deamination product, 9-β-D-arabinofuranosylhypoxanthine (*ara*-H), is also active against DNA viruses, it is considerably less active than *ara*-A.[7] A major effort to circumvent the deamination problem employs the use of *ara*-A in combination with adenosine deaminase inhibitors[8-11] such as deoxycoformycin or *erythro*-9-(2-hydroxy-3-nonyl)adenine.[12] A more desirable approach to the development of a more active antiviral or antitumor agent would involve the use of a deamination resistant *ara*-A derivative.

We report here the synthesis of carbocyclic arabinosyladenine (*C-ara*-A), an adenosine deaminase resistant *ara*-A analogue with in vitro antiviral and antitumor activity. Hydrolysis of the easily synthesized epoxide **1**[13] (2% H_2SO_4, 100 °C, 1 h) and subsequent acetylation gave a mixture of **2** and **3**. The major isomer, (±)-4α-acetamido-2β,3α-diacetoxy-1α-cyclopentanemethyl acetate (**2**), was separated from the mixture with one crystallization as colorless prisms (53% from EtOAc, mp 137–137.5 °C). Anal. ($C_{14}H_{21}NO_7$) C, H, N. When **2** was subjected to mild acidic hydrolysis (2 N HCl, 70 °C, 1 h), amine **4** was formed, since acyl migration to the adjacent *cis*-hydroxyl facilitates hydrolysis of the acetamide.[13] Subjection of a mixture of **2** and **3** to the same hydrolysis conditions gave a mixture of amine **4** and acetamide **5**. This mixture was separated by passage through an IRA-120(H^+) resin. Reacetylation of **5** gave pure **3** (14% from **1**) as a colorless syrup. Anal. ($C_{14}H_{21}NO_7$) C, H, N. Amine **4**, a hygroscopic gum, was immediately condensed with 5-amino-4,6-dichloropyrimidine, giving 5-amino-4-*N*-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]amino-6-chloropyrimidine (**6**) as a white powder (72% from ethanol, mp 184–186 °C). Anal. ($C_{10}H_{15}N_4O_3Cl$) C, H, N, Cl. Ring closure of **6** with diethoxymethyl acetate gave the 6-chloropurine **7** as white granules (72% from ethanol, mp 212–214 °C dec). Anal. ($C_{11}H_{13}N_4O_3Cl$) C, H, N, Cl. Treatment of **7** with liquid ammonia gave the desired (±)-9-[2α,3β-dihydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (*C-ara*-A) (**8**) as a white powder [76% from water; mp 252.5–254.5 °C dec; UV max in nm (ε × 10^{-3}) (0.1 N HCl) 258.5 (14.8), 210 sh (21.3); (H_2O) 260 (15.4); (0.1 N NaOH) 260 (15.5)]. Anal. ($C_{11}H_{15}N_5O_3 \cdot H_2O$) C, H, N. A more detailed presentation of the chemistry of these compounds and related derivatives will be published.[14]



The cytotoxicity of *C-ara*-A was evaluated by growing P-388 mouse lymphoid leukemia cells in the presence of either **8** or *ara*-A using a method previously described.[15] Both *ara*-A and *C-ara*-A exhibited LD_{50} concentrations of