studying 1,1-disubstituted tetrahydroisoquinolines for their activity in adrenergic systems.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using a Perkin-Elmer 257 infrared spectrophotometer, a Beckman 4230 infrared spectrophotometer, a Varian A-60A nuclear magnetic resonance spectrometer at 60 MHz or a Bruker HX 90E nuclear magnetic resonance spectrometer at 90 MHz, and a Dupont 491 mass spectrometer (EI mass spectra were obtained at 70 eV via direct probe). Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical results for elements indicated were within ±0.4% of the theoretical values.

2-Benzyl-1-(3′,4′,5′-trimethoxybenzyl)-6,7-dibenzyloxy-3,4-dihydroisoquinolinium Bromide (5). Benzyl bromide (1.2 mL, 0.01 mol) was added in one portion to a solution of **4** (2.0 g, 0.0042 mol) in dry benzene. The mixture was refluxed for 3.5 h under nitrogen during which time the salt precipitated. The mixture was cooled to room temperature and filtered, and the precipitate was washed with benzene followed by Et_2O. The salt was recrystallized from dry 2-propanol to give 2.5 g (86%) of **5**: mp 199–202 °C. Anal. ($C_{40}H_{40}NO_5Br$) C, H, N.

1-Methyl-1-(3′,4′,5′-trimethoxybenzyl)-2-benzyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6). To a Grignard solution prepared from 0.83 g (0.035 mol) of Mg turnings and 4.9 g (0.035 mol) of MeI in 50 mL of dry Et_2O, 1.22 g (0.0018 mol) of **5** was added as a suspension in dry Et_2O (40 mL) over 10 min, and the mixture was refluxed with stirring for 24 h. The cooled reaction mixture was poured onto crushed ice containing 3 g of NH_4Cl in 40 mL of H_2O. The mixture was basified with 10% NH_4OH aqueous solution and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give 0.71 g of the free base. The HCl salt was formed and recrystallized from Et_2O–MeOH: mp 108–110 °C. Anal. ($C_{41}H_{44}NO_5Cl$) C, H, N.

1-Methyl-1-(3′,4′,5′-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (2). To a solution of **6** (0.8 g, 0.0012 mol) in 70 mL of absolute EtOH, 10% Pd/C (325 mg) was added. The mixture was hydrogenated at room temperature at 40 psi on a Parr apparatus for 8 h and then filtered with the aid of Celite. The solvent volume was reduced to 4 mL under reduced pressure and Et_2O (2.0 mL) was added. The solid which deposited on standing was collected by filtration to give **2** (0.42 g, 88%): mp 173–175 °C; mass spectra electron-impact molecular ion (M^+) at m/e 359. Anal. ($C_{20}H_{26}NO_5Cl \cdot H_2O$) C, H, N.

1-Benzyl-1-(3′,4′,5′-trimethoxybenzyl)-2-benzyl-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (7). To a stirred mixture of 18 mL (0.036 mol) of commerical benzylmagnesium chloride (Aldrich, 1.97 M in THF) in 50 mL of dry THF under nitrogen was added dropwise, at room temperature, a suspension of 1.22 g (0.0018 mol) of **5**. The mixture was stirred until it turned clear (5–10 min) and then poured into a solution of 4 g of NH_4Cl in 50 mL of ice–water. The mixture was extracted with $CHCl_3$ and the organic extract was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give a clear oil. The oil was purified by silica gel column chromatography (benzene–ether, 9:1) to give 1.1 g (88%) of a clear oil. The HCl salt **7** was prepared and collected as a white solid: mp 209–212 °C. Anal. ($C_{47}H_{47}NO_5$) C, H, N.

1-Benzyl-1-(3′,4′,5′-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3). To a solution of the HCl salt of **2** (0.6 g, 0.008 mol) in 60 mL of absolute MeOH, 300 mg of 10% Pd/C was added. The mixture was hydrogenated on a Parr apparatus at room temperature at 40 psi for 8 h. The mixture was filtered with the aid of Celite, and the solvent was reduced to ~3 mL under reduced pressure. Et_2O (2 mL) was added to the solution. The solid which deposited on standing was collected by filtration to give 0.36 g (76%) of **3**: mp 163–165 °C. Anal. ($C_{26}H_{30}NO_5Cl$) C, H, N.

Biological Testing. Guinea pigs of either sex (weighing 300–500 g) and male Sprague–Dawley rats (weighing 180–250 g) were used in these experiments. The procedures for the pharmacological testing of each compound in isolated fat adipocyte, tracheal strip, and right atrial preparations were identical with those methods described previously.[4] Our studies did not include the use of an α-adrenergic blocking agent or COMT inhibitor. In experiments designed to evaluate antagonist properties, drugs were preincubated with guinea pig atrial and tracheal preparation for 30 min before the addition of trimetoquinol. Dose–response curves for trimetoquinol were completed within 1 h after the preincubation period. Drug solutions were prepared in normal saline containing 0.05% sodium metabisulfite.

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Isoquinolines. 6. Potential Central Nervous System Antitumor Agents.[1] Nitrogen Mustards of 3-Amino-4-(*p*-aminophenyl)isoquinoline

Crist N. Filer,* Felix E. Granchelli, Albert H. Soloway, and John L. Neumeyer

Department of Medicinal Chemistry and Pharmacology, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115. *Received March 2, 1977*

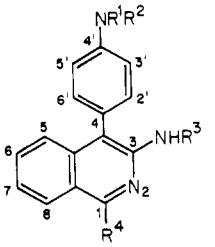
A series of 3-amino-4-(*p*-aminophenyl)isoquinolines bearing the bis(2-chloroethyl)amino group was synthesized as potential CNS antitumor agents. Diol precursors **1e** and **1f** were prepared by the treatment of **1b** and **1c** with ethylene oxide. Diol precursors **5a–c** and **9** were prepared by the treatment of **4a–c** and **8** with diethanolamine. The reaction of these diols with $SOCl_2$ yielded target mustards **10–15** which were evaluated in the intraperitoneal murine L1210 tumor. No intermediates or target mustards were active in this tumor system.

In a recent review of central nervous systems (CNS) antitumor agents,[2] Broder and Rall concluded that the emphasis for new drug design should be placed on alkylating agents that can penetrate the blood–brain barrier

(BBB). An approach used successfully by Driscoll[3] utilized the concept of attaching alkylating functions to drugs known to penetrate the CNS such as hydantoins,[3a] phenothiazines,[3b] and benzoquinones.[3c-d] This approach has led to the synthesis of several active CNS penetrating antitumor agents. The known CNS activity of several 3-amino-4-(*p*-aryl- and alkyl)isoquinolines[4] led to the choice of this ring system as a carrier for alkylating functions. In the present communication, we wish to report the synthesis of a number of nitrogen mustards of the 3-amino-4-(*p*-aminophenyl)isoquinoline class and their evaluation as CNS antitumor agents.

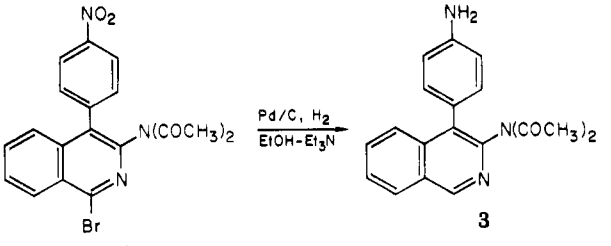
Chemistry. The synthesis of 3-aminoisoquinolines via the cyclization of dinitriles using HBr or HI was first described by Johnson[5] and was later expanded by Neumeyer.[4,6,7] Compounds **1a–c** were synthesized by the reported procedure[4] and served as key intermediates in this series.

Diol precursors to the mustards that we report here were prepared by two procedures. Early in our work, the reactions of **1a–c** with ethylene oxide in acetic acid afforded triol **1d** and diols **1e** and **1f**, respectively. Treatment of **1b** with excess ethylene oxide was found to cause cleavage of the 3-amido group. Reaction of the resulting amine **1g** with ethylene oxide yielded **1d** as the major side product. This facile cleavage of the 3-acetamido group did not occur with **1f**.



	R^1	R^2	R^3	R^4
1a	H	H	H	H
b	H	H	Ac	H
c	H	H	Ac	Br
d	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH	H
e	CH_2CH_2OH	CH_2CH_2OH	Ac	H
f	CH_2CH_2OH	CH_2CH_2OH	Ac	Br
g	CH_2CH_2OH	CH_2CH_2OH	H	H

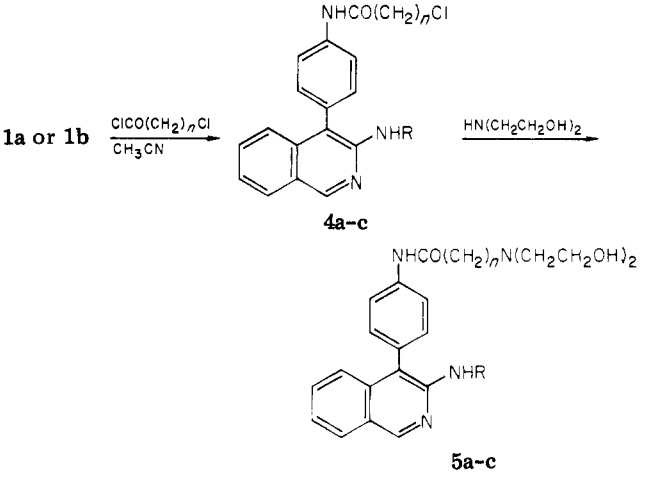
An improved procedure for the preparation of **1e** was found to be the catalytic debromination of **1f** with Pd/C in the presence of triethylamine, rather than KOH as used previously.[4] The milder conditions of this debromination allowed transformation of **2** to **3** with the 3-imido group intact.



2 **3**

Diol precursors **5a–c** were prepared as shown in Scheme I. Treatment of **4a** and **4c** with diethanolamine in refluxing THF was sufficient to obtain diols **5a** and **5c**. For chloroamide **4b**, a solvent change to DMF, an elevated temperature of 90 °C, and the addition of finely ground KI were necessary to obtain diol **5b**. During the final step in this sequence, amide cleavage in the 4′-amino position was observed yielding significant amounts (up to 30%) of

Scheme I

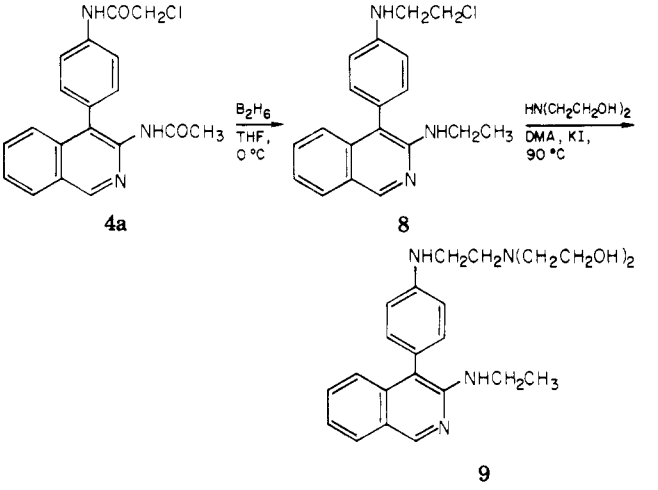


4a–c

5a–c

a, n = 1; R = Ac
b, n = 2; R = Ac
c, n = 1; R = H

Scheme II



4a **8** **9**

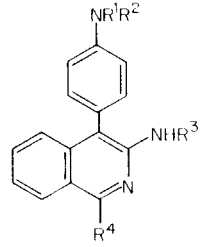
1a or **1b**. When a sample of **5a** was refluxed overnight in CD_3CN, it remained unchanged by NMR and TLC analyses. This would seem to rule out an intramolecular degradation. This side reaction was minimized by monitoring the reaction via TLC.

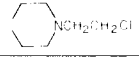
Diborane reduction of **5a** gave **9** in low yield. However, a preferred route to **9** was the diborane reduction of **4a** to **8**, followed by the treatment of the latter with diethanolamine. Dimethylacetamide (DMA) was found to be the solvent of choice for the aminolysis reaction. The use of even purified DMF in this reaction was accompanied by significant amounts of dimethylamine addition onto **8** (Scheme II).

The mustards **10–15** were prepared from appropriate diol precursors using thionyl chloride. Acetonitrile was found to be a useful solvent for these chlorinations. Treatment of diol **9** with thionyl chloride yielded an oil whose NMR and IR spectra were consistent with structure **15**. However, mustard **15** proved unstable as its free base and slowly cyclized to the piperazine analogue **16** in the course of a few days, even at 4 °C. Chromatography on silica gel appeared to hasten this process. Cyclizations of such mustards have been observed in other systems.[8] Mustard **15** could be stabilized and isolated as its HCl salt (Scheme III).

All intermediates, target compounds, and accompanying pertinent data are listed in Table I. As has been previously observed,[4] compounds in this series often incor-

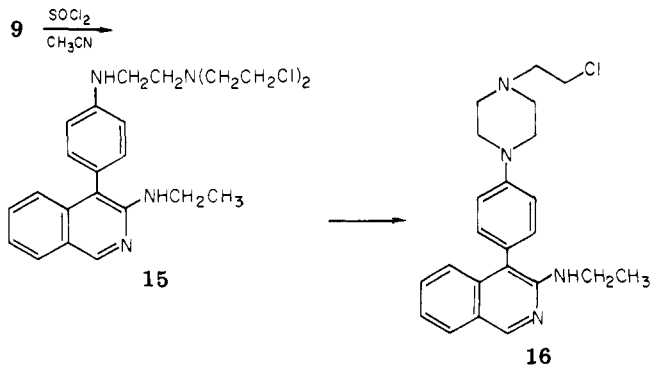
Table I. Physical and Chemical Data



Compd	NSC no.	R¹	R²	R³	R⁴	Yield, %	Mp, °C	Formula	Analyses
1d	262632	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH	H	33	115–118	$C_{21}H_{25}N_3O_3 \cdot 0.5C_6H_6$	C, H, N
1e	262630	CH_2CH_2OH	CH_2CH_2OH	$COCH_3$	H	50	120–123	$C_{21}H_{23}N_3O_3 \cdot 2H_2O$	C, H, N
1f	261031	CH_2CH_2OH	CH_2CH_2OH	$COCH_3$	Br	35	88–110	$C_{21}H_{22}N_3O_3Br \cdot C_2H_6O_2$	C, H, N; Br[a]
4a		H	$COCH_2Cl$	$COCH_3$	H	99	200[b]	$C_{19}H_{16}N_3O_2Cl \cdot 0.5HCl \cdot {}^1/_3H_2O$	C, H, N, Cl
4b	270041	H	$COCH_2CH_2Cl$	$COCH_3$	H	93	208–211	$C_{20}H_{18}N_3O_2Cl$	C, H, N, Cl
4c		H	$COCH_2Cl$	H	H	80	200[b]	$C_{17}H_{14}N_3OCl$	C, H, N
5a	267221	H	$COCH_2N(CH_2CH_2OH)_2$	$COCH_3$	H	55	200[b]	$C_{23}H_{26}N_4O_4 \cdot 0.5H_2O$	C, H, N
5b		H	$COCH_2CH_2N(CH_2CH_2OH)_2$	$COCH_3$	H	36	65–75	$C_{24}H_{28}N_4O_4 \cdot 2H_2O$	C, H, N
5c		H	$COCH_2N(CH_2CH_2OH)_2$	H	H	64	180–182	$C_{21}H_{24}N_4O_3$	H, N; C[c]
6	273436	H	$COCH_2CH_2Cl$	H	H	88	172–174	$C_{18}H_{16}N_3OCl$	C, H, N, Cl
7	267220	H	$COCH_2Cl$	$COCH_2Cl$	H	83	200[b]	$C_{19}H_{15}N_3O_2Cl_2 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
8	272337	H	CH_2CH_2Cl	CH_2CH_3	H	31	123–125	$C_{19}H_{20}N_3Cl$	C, H, N, Cl
9		H	$CH_2CH_2N(CH_2CH_2OH)_2$	CH_2CH_3	H	44	Oil	$C_{23}H_{30}N_4O_2 \cdot 0.25CHCl_3 \cdot {}^1/_3H_2O$	C, H, N, Cl
10	265212	CH_2CH_2Cl	CH_2CH_2Cl	$COCH_3$	H	29	136–138	$C_{21}H_{21}N_3OCl_2$	C, H, N, Cl
11	273437	CH_2CH_2Cl	CH_2CH_2Cl	$COCH_3$	Br	37	166–170	$C_{21}H_{20}N_3OBrCl_2 \cdot HCl$	C, H, N, Cl
12	267222	H	$COCH_2N(CH_2CH_2Cl)_2$	$COCH_3$	H	37	200[b]	$C_{23}H_{24}N_4O_2Cl_2$	C, H, N, Cl
13	268484	H	$COCH_2CH_2N(CH_2CH_2Cl)_2$	$COCH_3$	H	60	200[b]	$C_{24}H_{26}N_4O_2Cl_2$	C, H, N, Cl
14	268483	H	$COCH_2N(CH_2CH_2Cl)_2$	H	H	54	130–132[d]	$C_{21}H_{22}N_4OCl_2$	C, H, N, Cl
15	275271	H	$CH_2CH_2N(CH_2CH_2Cl)_2$	CH_2CH_3	H	96	85–90	$C_{23}H_{28}N_4Cl_2 \cdot 3.75HCl \cdot CH_3OH$	C, H, N, Cl
16	277094			CH_2CH_3	H	30	125–127	$C_{23}H_{27}N_4Cl$	C, H, N, Cl

[a] Br: calcd, 15.78; found, 14.99. [b] The compound melts immediately when immersed in a 200 °C oil bath but does not melt below 250 °C when slowly heated. [c] C: calcd, 63.62; found, 64.68. [d] This mustard has an isomorph, mp 65–75 °C.

Scheme III



porate solvent molecules in their crystal structure.

Antitumor Activity. Most intermediates and all target compounds (10–15) were tested in the intraperitoneal (ip) murine leukemia L1210 system by standard NCI protocols.[9,10] Compounds are considered active in vivo in this system if they exhibit activity (T/C) values equal to or greater than 125%. No intermediate or target compounds were active against the L1210 tumor even at the 400 mg/kg dose level. The target compounds were found to be nontoxic at the doses tested (25–400 mg/kg) for antitumor activity with the exception of compound 15 which was toxic at 200 mg/kg.

The initial objective of this investigation was the preparation of compounds with potential as CNS antitumor agents. Since intracerebral (ic) antitumor activity is normally significantly less than ip activity in any given tumor system,[11] the compounds in this study were considered to have insufficient L1210 ip activity to be tested in the corresponding ic tumor system.

This poor activity may be related to the high lipophilicity of the target compounds prepared in this study. The log P values in the octanol–H_2O system vary from a low of 3.87 for mustard 12 to a high of 7.43 for mustard 15 as calculated from the experimentally measured log P value for **1a**[12] and the estimated lipophilic contribution of added functionality.[3a,13] Previous studies have shown that an optimum log P value in the octanol–H_2O system for CNS antitumor activity is about 2.[3a]

Experimental Section

Evaporations were carried out in a Büchi rotary evaporator in vacuo at a bath temperature below 50 °C. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Samples for analysis were dried at 10^{-2} mm over silica gel at 55 °C. Thin-layer chromatography (TLC) was performed on 7 × 3 cm precoated silica gel 13179, poly(ethylene terephthalate) foils (Eastman Kodak, Rochester, N.Y.). Preparative TLC was carried out on silica gel plates (Analtech, 20 × 20 cm, 2 mm). Common solvent combinations were S_1 (benzene–CH_3OH, 8:2), S_2 (EtOAc–hexane–CH_3OH, 7.5:2.2:0.3), S_3 (EtOAc), S_4 (EtOAc–CH_3OH, 9.85:0.15), S_5 (EtOAc–CH_3OH, 9:1), S_6 (EtOAc–hexane, 1:4), S_7 (ether–CH_3OH, 4:1), and S_8 (ether–hexane, 3:2). Column chromatography was performed using silica gel (Baker 60–200 mesh). All newly synthesized compounds have NMR, IR, and mass spectra in full agreement with the structures indicated. NMR spectra were obtained using a Varian T-60 spectrometer in $CDCl_3$ or Me_2SO-d_6 using trimethylsilane as internal standard. The IR spectra were measured in $CHCl_3$ or in KBr in a Perkin-Elmer Model 700 spectrophotometer. Mass spectra were determined on a 12-90-G Nuclide mass spectrometer. Satisfactory elemental analyses (±0.4% of calculated values) are indicated by elemental symbols in Table I. Solvents such as acetonitrile (CH_3CN), dimethylformamide (DMF), dimethylacetamide (DMA), and tetrahydrofuran (THF) were distilled and dried over Linde molecular sieves prior to use. When several compounds were prepared by comparable procedures, only one representative example is included in this section.

3-Acetamido-4-[*p*-bis(2-hydroxyethyl)aminophenyl]-1-bromoisoquinoline (1f). Ethylene oxide (5 mL, 0.1 mol) was added all at once to a cold solution of 1.0 g (2.8 mmol) of compound **1c** in 18 mL of HOAc and the solution was allowed to stand at room temperature for 18 h. It was then poured into ice H_2O and made basic with 20% aqueous NaOH. The basic solution was extracted with $CHCl_3$. The $CHCl_3$ extractions were washed once with H_2O and brine, dried ($MgSO_4$), filtered, and evaporated to give 1.0 g of a yellow solid, mp 55–80 °C. The solid was purified by preparative TLC (first S_1 and then S_2) and appeared on the plates as an intensely yellow fluorescent band. Compound **1f** was isolated as a yellow solid (370 mg, 35%), mp 88–110 °C.

3-Acetamido-4-[*p*-bis(2-hydroxyethyl)aminophenyl]isoquinoline (1e). Two 8.0-g (18 mmol) batches of **1f**, each containing 800 mg of 10% Pd/C, 8 g of Et_3N, and 150 mL of EtOH were hydrogenated at 40 psi in a Parr apparatus at room temperature. After 2 h, a pressure drop of 24 psi was noted. The reactions were filtered under gravity and combined. The combined filtrates were evaporated and the residue was taken up in 100 mL of $CHCl_3$. The $CHCl_3$ solution was washed with H_2O and brine and dried (Na_2SO_4). Filtration and evaporation yielded 11.50 g of a frothy solid. Column chromatography (S_3) yielded 6.50 g (50%) of **1e** as a frothy yellow solid, mp 120–123 °C.

3-Acetamido-4-(*p*-chloroacetamidophenyl)isoquinoline (4a). Chloroacetyl chloride (280 mg, 2.5 mmol) was added dropwise with rapid stirring to a solution of 600 mg (2.16 mmol) of **1b** in 80 mL of dry CH_3CN at room temperature. After 30 min, the solvent was evaporated. H_2O (30 mL) was added to the residue and the suspension was extracted with $CHCl_3$. After drying (Na_2SO_4), the solvent was evaporated to give 896 mg of a colorless solid. Preparative TLC (S_4) yielded 730 mg (99%) of **4a** as a colorless solid, mp 200 °C.

3-Amino-4-[*p*-bis(2-hydroxyethyl)aminoacetamidophenyl]isoquinoline (5c). A solution of 500 mg (1.60 mmol) of **4c** and 340 mg (3.20 mmol) of $HN(CH_2CH_2OH)_2$ in 25 mL of THF was refluxed for 16 h. The reaction was allowed to cool to room temperature and the precipitated product was filtered off and washed with dry THF. The solid was dissolved in 20 mL of $CHCl_3$ and rapidly stirred with a solution of 200 mg of $NaHCO_3$ in 10 mL of H_2O. The $CHCl_3$ solution was dried (Na_2SO_4), filtered, and evaporated to yield 250 mg (40%) of **5c** as an off-white solid, mp 180–182 °C. An additional 150 mg (24%) of **5c** could be obtained from preparative TLC (S_5) purification of the original THF filtrate residue.

4-[*p*-(2-Chloroethyl)aminophenyl]-3-ethylaminoisoquinoline (8). To a slurry of 2.0 g (5.65 mmol) of **4a** in 90 mL of dry THF was added 31 mL (31 mmol) of B_2H_6 in THF at −78 °C under N_2. Stirring at −78 °C was continued for 2 h and then the reaction was stirred at 4 °C for 24 h. After this time, it was cautiously quenched with 120 mL of an aqueous 2% HCl solution at 4 °C. It was allowed to stand at 4 °C overnight. Excess THF was evaporated and 100 mL of $CHCl_3$ was added to the aqueous solution (pH 1.80). The rapidly stirred mixture was carefully neutralized to pH 7.06 with an aqueous saturated $NaHCO_3$ solution. The layers were separated and the aqueous layer was further extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated to yield a dark oil which was heated (50 °C) with 0.5 mL of pyridine in 20 mL of THF for 20 min (this was found to remove an isoquinoline–borane side product that could not be removed chromatographically). Excess THF was evaporated and the residue was taken up in 50 mL of $CHCl_3$ and washed with H_2O. Drying (Na_2SO_4), filtration, and concentration yielded 1.64 g of a dark oil. Preparative TLC (S_6) yielded 572 mg (31%) of **8** as a yellow solid, mp 123–125 °C.

4-[*p*-[2-[Bis(2-hydroxyethyl)amino]ethylamino]phenyl]-3-ethylaminoisoquinoline (9). A solution of 2.0 g (6.14 mmol) of crude **8**, 3.24 g (31 mmol) of $HN(CH_2CH_2OH)_2$ and 1.47 g (9 mmol) of finely divided KI in 50 mL of DMA was heated at 90 °C under N_2 for 16 h. Excess solvent was evaporated under high vacuum and the residue was dissolved in 60 mL of $CHCl_3$. The solution was washed with H_2O and brine and dried (Na_2SO_4) to yield after evaporation 3.0 g of an oil. Preparative TLC (S_7) afforded 1.07 g (44%) of **9** as a green oil.

3-Acetamido-4-[*p*-bis(2-chloroethyl)aminoacetamidophenyl]isoquinoline (12). A solution of 500 mg (1.19 mmol) of **5a** in 50 mL of dry CH_3CN was cooled to 4 °C and 0.51 mL (7.20 mmol) of $SOCl_2$ was added immediately producing a coffee-colored precipitate which dissolved after 1 h at 4 °C. The reaction was stored at 4 °C for 16 h and then evaporated to give a solid residue. The residue was dissolved in a mixture of 15 mL of $CHCl_3$ and 3 mL of CH_3OH and vigorously stirred with a solution of 270 mg of $NaHCO_3$ in 20 mL of H_2O for 5 min. The $CHCl_3$ layer was separated and the aqueous solution extracted with more $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4), filtered, and evaporated to give 420 mg of a crude solid. Preparative TLC (S_5) yielded 200 mg (37%) of **12** as an off-white solid, mp 200 °C.

4-[*p*-[4-(2-Chloroethyl)piperazino]phenyl]-3-ethylaminoisoquinoline (16). Compound **15** (260 mg, 0.6 mmol) as its free base was heated at 50 °C for 16 h under vacuum to yield 260 mg of a yellow solid, mp 128–130 °C. The solid was then vigorously stirred in 20 mL of $CHCl_3$ and 1 mL of CH_3OH with 20 mL of H_2O containing 200 mg of $NaHCO_3$. The layers were separated and the $CHCl_3$ layer was dried (Na_2SO_4), filtered, and evaporated to yield 250 mg of a brown oil. Preparative TLC (S_8) gave 80 mg (30%) of **16** as a waxy solid, mp 125–127 °C.

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Cannabinoids. Synthesis and Central Nervous System Activity of 8-Substituted 10-Hydroxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridine and Derivatives

Cheuk-Man Lee ,* Raymond J. Michaels, Harold E. Zaugg, Anthony T. Dren, Nicolas P. Plotnikoff, and Patrick R. Young

Division of Pharmacology and Medicinal Chemistry, Abbott Laboratories, North Chicago, Illinois 60064.
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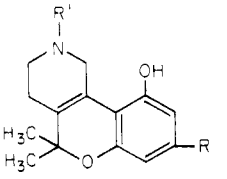
8-(1,2-Dimethylheptyl)- and 8-[5-(4-fluorophenyl)-2-pentyl]-10-hydroxy-5,5-dimethyl-5*H*-[1]benzopyrano[4,3-*c*]pyridines (**2a** and **2b**), their phenolic ester and ether derivatives, and their *N*-oxides were synthesized and evaluated in various CNS pharmacological tests in animals. **2a** was found to be the most potent compound.

In continuation of synthetic work in the cannabinoid field in our laboratories, we have prepared and studied the pharmacological activity of several nitrogen analogues of the tetrahydrocannabinols (THC's). Pars et al.[1] and Winn et al.[2] have found that Ia and Ib are among the most potent compounds in a large series of nitrogen-containing cannabinoids. Because the 2-propynyl group on nitrogen resulted in such outstanding central nervous system (CNS) potency (i.e., simple alkyl-, alkenyl-, or arylalkyl-substituted analogues were clearly less active), and because it is well known that simple 2-propynylamines are 2–3 p*K* units less basic than simple alkylamines, we prepared the pyridine analogues of Ia,b (Table I) to see whether potency could be increased further by incorporation of an even less basic nitrogen atom. The results summarized in Table II clearly show that these pyridine analogues **2a** and **2b** are indeed slightly more potent than their hydroheteroaromatic predecessors (Ia,b) in most tests.

The phenolic hydroxyl group in the THC's is essential for eliciting CNS activity.[3,4] In an attempt to selectively eliminate one of the characteristic cannabinol-like CNS



Ia, R' = $CH_2C{\equiv}CH$; R = $CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}
b, R' = $CH_2C{\equiv}CH$; R = $CH(CH_3)(CH_2)_3$-C_6H_4-*p*-F

effects, i.e., the hyperexcitability reaction to external stimuli produced in animals,[5] we modified the phenolic hydroxyl group by preparing ester and ether derivatives. The esters retained the hyperexcitability reaction and general CNS activity. However, the ethers produced much less hyperexcitability but were also less active as CNS depressants than the esters. Interestingly, the methoxy and 2-propynyloxy derivatives **6** and **9** were found to be active as sedative–hypnotics in cat EEG studies as shown by an increase in sleeping time. To increase the polar character of the nitrogen atom and further decrease basicity, the pyridyl analogues were oxidized to their