Isoxazolo[4,5-*b*]pyridin-3-ol (15). The hydroxamic acid 47 (4.5 g, 29 mmol) was dissolved in dry THF (375 mL) and triethylamine (10.2 g, 29 mmol) was added. The solution was cooled in a dry ice/acetone bath to −78 °C and a solution of thionyl chloride (3.8 g, 32 mmol) in THF (60 mL) was added dropwise whereupon a precipitate forms. The reaction was removed from the cold bath and allowed to warm to room temperature overnight. The solid was filtered and the solvent was concentrated. The residue was dissolved in water (60 mL) and refrigerated to give a solid, which was filtered, washed with water, and dried (2.4 g). Extraction of the filtrate with chloroform (4 × 150 mL) gave an additional 1.2 g of white solid. The two lots were combined, triturated successively with ethyl acetate and then water and dried to give 2.3 g (58%) of **15** as a light brown solid: mp 211–213 °C.

1*H*-Pyrazolo[4,3-*b*]pyridin-3-ol (19). Compound **19** was prepared in 20% yield from 3-aminopyridine-2-carboxylic acid by using the general procedure of Hall[38] for pyrazolobenzene analogues: mp 248–251 °C (from water). This compound has been prepared by another method.[39]

Glycine Receptor Binding. Preparation of Membranes. Two brain stems and two spinal cords from 150–200-g Long–Evans rats (about 2-g total weight) were disrupted in 20 mL of ice-cold 50 mM Tris–citrate (pH 7.5 at 0 °C) for 30 s in a Polytron PT-10 (Brinkmann) at setting 5. The suspension was centrifuged at 50000*g* for 10 min, the supernatant was discarded, the pellet was resuspended in 20 mL of ice-cold Tris–citrate as above, recentrifuged, resuspended at 1 g/5 mL, and stored in plastic vials at −70 °C. When needed, the tissue was thawed, diluted to 1 g/20 mL in ice-cold Tris–citrate, centrifuged, resuspended, and kept on ice until used.

Incubation Conditions. All incubations were in triplicate for 60 min at 0 °C in 12 × 75 mm glass tubes containing 2 mL of Tris–citrate (pH 7.5) with 10 mg of original tissue weight of membranes and 3 nM [^{3}H]strychnine. Test compounds were dissolved at 10 mM in dimethyl sulfoxide and diluted in dimethyl sulfoxide to 100 times the final incubation concentration. Control incubations received an equal volume (20 mL) of dimethyl sulfoxide; the resulting concentration of dimethyl sulfoxide reduced specific [^{3}H]strychnine binding by about 15% but had no effect on the IC_{50} for glycine. The order of additions was test compound, membranes, and [^{3}H]strychnine. After all additions the rack of tubes was vortexed, and the tubes were incubated in an ice bath for 60 min. Incubations were terminated by filtration through 2.4 cm GF/B filters under reduced pressure followed by three rapid washes with 4 mL of ice-cold 50 mM Tris-HCl (pH 7.7 at 25 °C) with 1 M NaCl. The filtration was complete in about 12 s. Filters were counted with 8 mL of Formula 963 scintillation fluid (New England Nuclear) in a liquid-scintillation counter.

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Synthesis and Evaluation of *N*,*N*-Di-*n*-propyltetrahydrobenz[*f*]indol-7-amine and Related Congeners as Dopaminergic Agonists

David E. Nichols,*,† John M. Cassady,‡ Paul E. Persons,† Ming C. Yeung,† James A. Clemens,§ and E. Barry Smalstig§

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907 and The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206.
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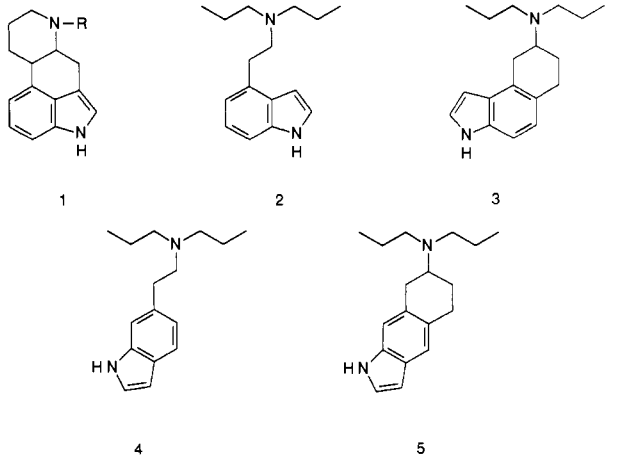
An evaluation of 6-[2-(di-n-propylamino)ethyl]indole (4), its rigid analogue *N*,*N*-di-*n*-propyl-5,6,7,8-tetrahydrobenz[*f*]indol-7-amine (**5**), and some related congeners, for ability to suppress serum prolactin in reserpinized rats, revealed modest biological activity in this in vivo model of dopaminergic activity. Although the indole N–H in these compounds can be considered to be oriented "meta" with respect to the ethylamine side chain, compounds with the indole N–H located in the other "meta" position (i.e. 4-[2-(di-*n*-propylamino)ethyl]indole (**2**) or its rigid benz[*e*]indole analogue **3**) were much more potent dopamine agonists. The results argue for a particular orientation of the indole N–H vector. In addition, relatively potent dopamine agonists also resulted when the pyrrole portion of the indole ring was replaced by a methanesulfonamido function, supporting the idea that the indole N–H serves as a hydrogen-bond donor.

In the past decade, considerable effort has been directed toward elucidation of the active fragment in the ergolines (**1**) that is responsible for their dopamine-like action. We have been carrying out a systematic program to elucidate the structure–activity relationships of ergoline-related dopaminergic agents. Of interest was the independent finding of Cassady et al.[1,2] and Cannon et al.[3] that 4-[2-(*N*,*N*-di-*n*-propylamino)ethyl]indole (DPAI, **2**) had substantial dopaminergic activity. In this context, it was of particular interest to examine isotryptamines with different sites of side-chain attachment and also to design conformationally restricted analogues that might be helpful in elucidating the active conformation of the side chain at its receptor.



Within intact ergolines, the pyrrole ring can serve to replace a catechol moiety, a suggestion originally made by

† Purdue University.
‡ Present address: College of Pharmacy, The Ohio State University, Columbus, OH 43210-1291.
§ Eli Lilly and Company.

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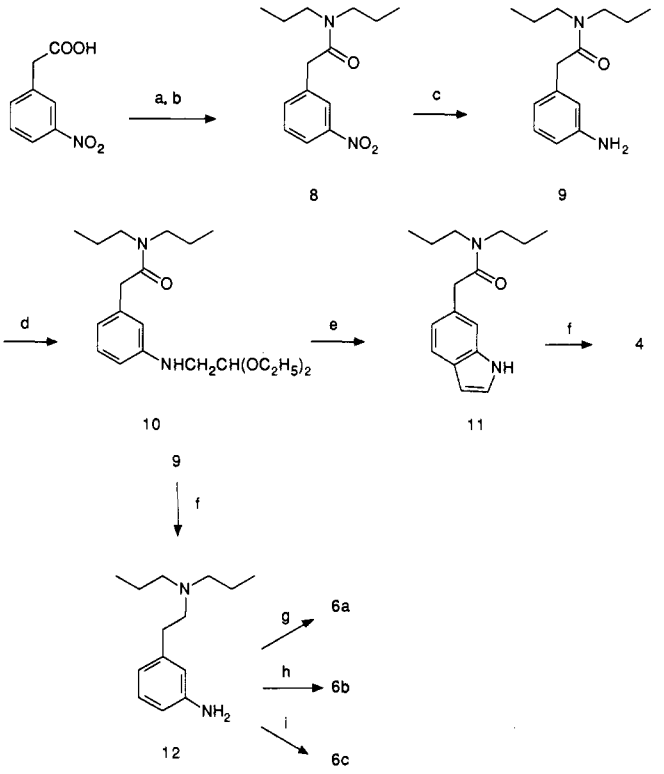
Nichols,[4] subsequently strengthened by the elegant studies of Bach et al.,[5,6] and recently provided with a theoretical basis by Kocjan et al.[7]

However, when the arylethylamine fragment is not constrained within the relatively rigid ergoline framework, the pyrrole ring may function as a weak hydrogen-bond donor, being viewed simplistically as a replacement for a phenolic hydroxyl. Asselin et al.[8] have recently provided evidence for this with the demonstration of potent dopaminergic activity in the benzo[*e*]indole **3**. Although those workers propose a correspondence in their model between the benzenoid ergoline A ring and the catechol ring of apomorphine, attempts to develop atom-for-atom correspondence between these structures completely ignore the orientation of the amine lone pair. Were the directionality of the amine lone pair not critical, the two enantiomers of apomorphine would possess identical pharmacology; they do not.[9] Furthermore, the superposition of apomorphine and bromocriptine, as in Figure 1 of ref 8, implies that a bulky substituent, longer than four atoms, could be attached to N(6) of apomorphine, to afford potent dopaminergic agents. This is in stark contrast to the known structure–activity relationships of aporphines, where groups larger than *n*-propyl dramatically attenuate activity.[10,11] Thus, as most workers now acknowledge, the dopaminergic fragment within the ergolines is probably the pyrroleethylamine moiety.[7,12]

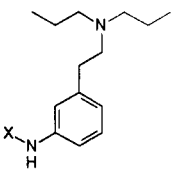
However, metabolic hydroxylation can generate structures wherein the ergoline A ring becomes an important part of the pharmacophore. These likely orient differently on the receptor than do their nonhydroxylated parents.[7,12-14] Indeed, **1** and **2** would be metabolically hydroxylated at the indole 6-position, and there is evidence that at least a portion of the in vivo dopaminergic activity of these may be attributed to their hydroxy metabolites.[15,16]

Scheme I[a]

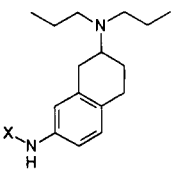


[a] (a) $SOCl_2$, benzene; (b) dipropylamine; (c) H_2, Pd–C; (d) $BrCH_2CH(OCH_2CH_3)_2$, K_2CO_3; (e) TFA, TFAA, reflux for 3 days; (f) $LiAlH_4$, ether; (g) Ac_2O; (h) $(CF_3CO)_2O$; (i) CH_3SO_2Cl, Et_3N.

In more flexible molecules, where the indole N-H may serve simply as a replacement for a phenolic hydroxyl, there is another isotryptamine 6-[2-(*N*,*N*-di-*n*-propylamino)ethyl]indole (**4**), that also has the indole NH oriented "meta" to the phenethylamine side chain. The present study reports the synthesis and evaluation for dopamine-like activity of **4** and one of its rigidified antiperiplanar conformers, the benz[*f*]indole **5**, in which the indole nitrogen is located at the same position as in **3** but presents the N-H vector directed at approximately a 90° angle to that of **3**. In addition, the open-chain amides **6a–c** and the (acylamino)tetralins **7a** and **7b** were prepared and tested for dopamine-like activity.



6a X = CH_3CO
6b X = CF_3CO
6c X = CH_3SO_2



7a X = CH_3CO
7b X = CH_3SO_2

Chemistry

Isotryptamine **4** and the nonindolic congeners **6a–c** were readily obtained as outlined in Scheme I. The key intermediate **9** was converted to the indole by following a modification of the method of Nordlander et al.[17] Following cyclization of acetal **10** to indole **11**, the amide was

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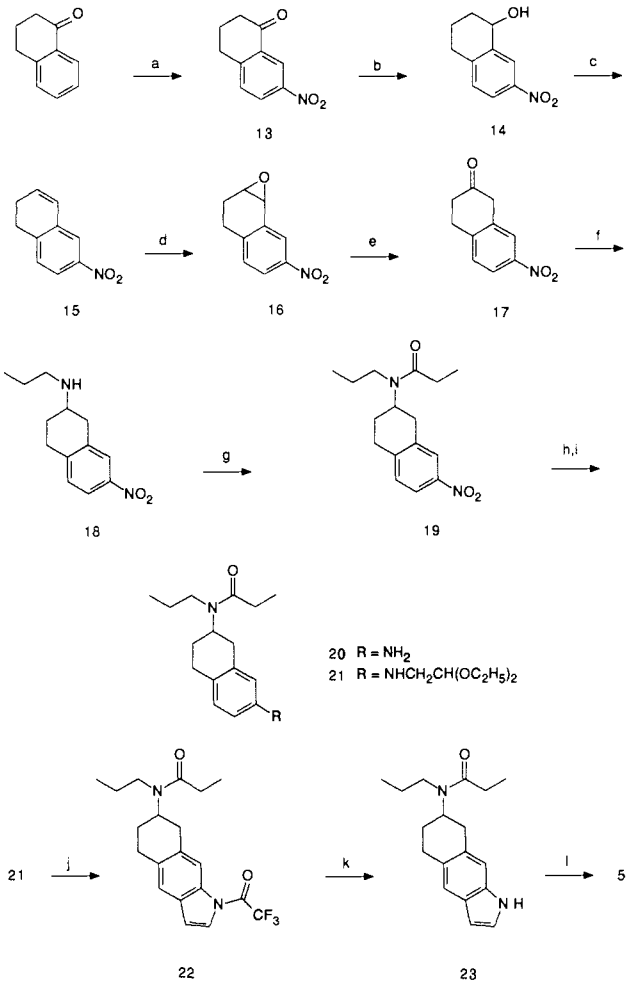
Scheme II[a]



[a] (a) NH_4OAc, TFAA, $CHCl_3$; (b) $NaBH_4$; (c) Amberlyst 15 resin, C_6H_6, reflux; (d) *m*-chloroperoxybenzoic acid, $CHCl_3$; (e) ZnI_2, C_6H_6; (f) *n*-$PrNH_2$, EtOH, $NaCNBH_3$; (g) $(CH_3CH_2CO)_2O$; (h) H_2, Pd–C; (i) $BrCH_2CH(OCH_2CH_3)_2$, K_2CO_3; (j) TFA, TFAA, reflux for 2.5 days; (k) MeOH, reflux; (l) $LiLaH_4$, ether.

reduced with lithium aluminum hydride to afford the desired **4**. Reduction of aniline **9**, followed by treatment with the appropriate acylating agent, afforded compounds **6a–c**.

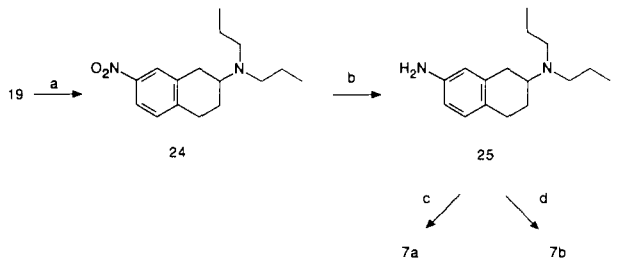
An approach which led to the synthesis of the novel indole **5** is depicted in Scheme II. Although an effective direct nitration of α-tetralone had not been previously reported, it was found that Crivello's method[18] using ammonium nitrate in trifluoroacetic anhydride (TFAA) could be applied to give a mixture of the 5- and 7-nitro isomers in a ratio of about 1:3, in 43% overall yield. The ketone transposition (**13** → **17**) was accomplished by using a modification of the procedure described by Nichols et al.[19] The nitrotetralone **13** was reduced to the alcohol **14** with sodium borohydride in 95% ethanol. Epoxide **16** was obtained by dehydration of **14** with Amberlyst 15 cation exchange resin, followed by *m*-chloroperoxybenzoic acid (MCPBA) epoxidation of the resulting olefin **15**.

Conversion of the epoxide **16** to the desired 7-nitro-α-tetralone **17** with boron trifluoride etherate gave poor yields, but the use of zinc iodide[5] afforded an 83% yield of the 7-nitrotetralone. The reductive amination of this ketone with *n*-propylamine gave yields in the 30–50% range. Efforts to optimize conditions for the amination showed a critical dependence on pH, requiring pH 6.5–7. Best yields were obtained with a ratio of tetralone to propylamine of 1:5. Substituted aniline **20** was obtained in 90% yield by the acylation of **18** with propionic anhydride, followed by catalytic hydrogenation.

Aniline **20** was alkylated with bromoacetaldehyde diethyl acetal (BADEA) in refluxing ethanol with sodium carbonate, following the method described by Nordlander et al.[17] Excess BADEA (2 equiv) can be used without the formation of N,N-dialkylated products. Trifluoroacetylated indole **22** was isolated by centrifugal TLC (Chromatotron) after reflux of acetal **21** in a 1:1 mixture of trifluoroacetic anhydride and trifluoroacetic acid for 2.5 days. It should be noted that, while cyclization occurred at the expected position, when the corresponding isonitrosoacetanilide of **20** is cyclized to the isatin, ring closure occurs at the more hindered position to give a benz[*e*]indole. We independently prepared **3** by the route of Asselin et al.[8] to verify the different course of cyclization.

Reflux of **22** in methanol afforded **23**. The reduction of (propylamido)indole **23** with lithium aluminum hydride gave a quantitative yield of the desired tetrahydrobenz-[*f*]indole, **5**.

Scheme III[a]



[a] (a) B_2H_6, THF; (b) H_2, Pd–C; (c) Ac_2O, Et_3N; (d) CH_3SO_2Cl, Et_3N.

Table I. Effect of Test Compounds on Plasma Prolactin Levels in Reserpinized Rats

compd	dose, mg/kg	PRL[a] control	PRL[a] test	% change
2 (DPAI)	2	15.9 ± 2.3	5.0 ± 0.9	−69[b]
3	1	26.4 ± 3.3	3.8 ± 0.6	−84[b]
4	2	52.5 ± 5.0	51.2 ± 4.1	0
5	2	48.3 ± 3.2	30.6 ± 1.3	−37[b]
6a	2	45.5 ± 3.0	36.9 ± 2.9	−19
6b	2	45.5 ± 3.0	36.8 ± 2.0	−21[b]
6c	2	52.5 ± 5.0	12.6 ± 1.1	−76[b]
7a	2	48.3 ± 3.2	38.9 ± 3.5	−19
7b	2	48.3 ± 3.2	28.3 ± 1.4	−41[b]

[a] PRL values represent nanograms/milliliter of plasma prolactin. [b] Significantly different from control, $p < 0.001$.

Reflux of **23** in methanol afforded **23**. The reduction of (propylamido)indole **23** with lithium aluminum hydride gave a quantitative yield of the desired tetrahydrobenz-[*f*]indole, **5**.

For the preparation of the 7-acylamino derivatives **7a** and **7b** (Scheme III), nitrotetralin **19** served as the starting material. Reduction of the amide function with diborane afforded **24** in 70% yield. Catalytic hydrogenation gave a quantitative yield of amino compound **25**. Treatment of this with acetic anhydride or with methanesulfonyl chloride in benzene and triethylamine gave **7a** or **7b**, respectively.

Pharmacology

Suppression of prolactin release in reserpinized rats was used as a screen for dopamine D-2 agonist activity and as a prescreen for DA autoreceptor activity.[20–22]

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Results and Discussion

The results of the prolactin inhibition assay are presented in Table I. This assay has been shown to correlate with dopamine D-2 agonist activity in other assay test systems.[20-22] The benz[*f*]indole **5** did produce a significant lowering of prolactin at a dose of 2 mg/kg. However, the benz[*e*]indole **3** prepared by Asselin et al.[8] produced a much larger decrease at only 1 mg/kg. Surprisingly, the 6-isotryptamine **4** was not active in this assay. Since this test is an in vivo procedure, metabolic or pharmacokinetic effects may obscure actual effects at the dopamine receptor by the generation of an inactive metabolite, in vivo. However, DeMarinis et al.[23] have reported on the pharmacology of the indolone analogues of **2** and **4** at prejunctional dopamine receptors and have found the indolone analogue of **2** to be much more potent than that of **4**. This seems to support the idea that the direction of the N-H vector is important for optimal activity and perhaps also that the dopamine receptor is sensitive to steric bulk attached at the 4-position, but not at the 2-position.

It is noteworthy that in both the flexible series and in the tetralins, the sulfonamido compounds **6c** and **7b** are relatively potent dopamine agonists. Since the pK_a of sulfonamides is generally considered to be comparable to that of a phenolic hydroxyl, the methanesulfonamide N-H may serve as a hydrogen-bond donor. The lower potency of the tetralin analogue **7b** compared to its open-chain counterpart **6c** could perhaps be partially attributed to the fact that **7b** is racemic, while **6c** is an achiral molecule.

Most interesting is a comparison between the two tricyclic indoles **3** and **5**. As noted above, these results may be complicated by the possibility of in vivo metabolic or pharmacokinetic effects. For example, hydroxylation of **3** would occur at the 5-position (the 6-position of indole), to generate a metabolite that structurally resembles 5-OH-DPAT, a potent D-2 agonist. Whether or not this metabolite is generated and contributes to activity cannot be assessed on the basis of the present experiments. The 6-indole position of **5** is blocked, but hydroxylation at the 4-position could give rise to a potentially active metabolite. However, there is no precedent for the latter metabolic pathway. Rather, the comparison of **2** and **4**, considered along with the results of DeMarinis et al.,[23] suggests that the N-H orientation may be more critical. That is, if the benzenoid and reduced tetrahydro rings of **3** and **5** are superimposed, the N-H bond directions are oriented at approximately a 90° angle to each other. This suggests that if the indole N-H serves as a weak hydrogen-bond donor, the hydrogen-bond-acceptor group on the dopamine receptor is located to interact more favorably with **3** than with **5**. Indeed, it is even possible that the pyrrole portion of **5** might protrude into the hydrogen-bond-acceptor site to further introduce unfavorable binding interactions.

Experimental Section

Melting points were determined on a Mel-Temp or Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-33 instrument and are reported in reciprocal centimeters. Mass spectra were determined with a Finnigan 4023 GC/MS spectrometer and are reported as *m/e* (relative intensity). Exact masses were determined on a KRATOS MS-50 high-resolution mass spectrometer. Proton NMR spectra were recorded on a Varian FT80 or XL200 spectrometer and are reported in δ values (ppm) relative to an internal standard of tetramehylsilane. Reactions were monitored by TLC on precoated thin-layer Baker-flex silica gel 1B2-F plates. Visualization was with short-wave ultraviolet light, I_2 vapor, and in the case of indolic compounds, with van Urk's spray reagent. All target compounds were pure by TLC.

***N*,*N*-Di-*n*-propyl-2-(3-nitrophenyl)acetamide (8).** *m*-Nitrophenylacetic acid (1.7 g, 9.38 mmol) was dissolved in 100 mL of dry benzene, and 5.58 g (46.9 mmol) of thionyl chloride was added. The reaction was held at reflux for 3 h, and the solvent was removed by rotary evaporation. Dry benzene (100 mL) was added to the residue and the solution was reduced to dryness. The residue was dissolved in 150 mL of dry benzene, and 1.90 g (18.8 mmol) of *N*,*N*-di-*n*-propylamine was added dropwise. The reaction was stirred overnight; the benzene was washed with water and then with 1 N HCl and saturated sodium carbonate solution. The benzene layer was dried ($MgSO_4$), filtered, and concentrated to yield a yellow solid. Recrystallization from ethyl acetate–hexanes yielded 2.36 g (95%) of white product: mp 30–32 °C; TLC (CH_2Cl_2) R_f 0.75; ^1H NMR ($CDCl_3$) δ 8.04 (m, 2, ArH), 7.37–7.68 (m, 2, ArH), 3.78 (s, 2, $ArCH_2$), 3.26, 3.31 (2 t, 4, J = 7 Hz, NCH_2), 1.59 (m, 4, CH_3CH_2), 0.88, 0.94 (2 t, 6, J = 7 Hz, CH_3); CIMS 265 (MH^+); MS calcd for $C_{14}H_{20}N_2O_3$ 264.1474, found 264.1471.

***N*,*N*-Di-*n*-propyl-2-(3-aminophenyl)acetamide (9).** A solution of **8** (3.0 g, 11.4 mmol) in 150 mL of absolute ethanol was shaken for 2 h at 30 psig of hydrogen over 300 mg of 10% Pd–C. The catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure to afford a light yellow solid: 2.6 g (86%), mp 85–87 °C; TLC (CH_2Cl_2) R_f 0.52; ^1H NMR ($CDCl_3$) δ 7.08 (t, 1 ArH), 6.98–6.47 (m, 3, ArH), 3.60 (s, 2, $ArCH_2$), 3.28, 3.18 (2 t, 4, J = 8 Hz, NCH_2), 1.78–1.23 (m, 4, CH_2), 0.86 (t, 6, J =7 Hz, CH_3); MS calcd for $C_{14}H_{22}N_2O$ 234.1732, found 264.1737.

***N*,*N*-Di-*n*-propyl-2-[3-[(2,2-diethoxyethyl)amino]phenyl]acetamide (10).** To a solution of **9** (1.0 g, 4.27 mmol) in 20 mL of 95% ethanol was added 1.68 g (8.54 mmol) of bromoacetaldehyde diethyl acetal and 1.18 g (8.54 mmol) of K_2CO_3. The reaction was stirred at reflux for 4 days and then cooled and diluted with 50 mL of H_2O. The aqueous solution was extracted with Et_2O (4 × 50 mL); the organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford a yellow oil. The crude product was purified with a chromatotron, using a 2-mm silica gel rotor and elution with $CHCl_3$–ethyl acetate (9:1) to yield 0.893 g (60%) of a light yellow oil: TLC (50% $CHCl_3$–EtOAc) R_f 0.71; ^1H NMR ($CDCl_3$) δ 7.11 (t, 1, ArH), 6.62–6.57 (m, 3, ArH), 4.67 (t, 1, J = 5.5 Hz, ArNH), 3.62 (s, 2, $ArCH_2$), 3.84–3.44 (m, 4, CH_2O), 3.23 (d, 2, J = 7 Hz, $NHCH_2$), 3.26 (2 t, 4, J = 7 Hz, CH_2–N), 1.23 (t, 6, J = 7 Hz, CH_3), 0.85 (t, 6, J = 8 Hz, CH_3); CIMs 351 (MH^+); MS calcd for $C_{20}H_{34}N_2O_3$ 350.2569, found 350.2568.

***N*,*N*-Di-*n*-propyl-2-(6-indolyl)acetamide (11).** A 50% solution of trifluoroacetic anhydride in trifluoroacetic acid (8 mL) was cooled in an ice bath. To this was added 0.50 g (1.43 mmol) of **10**. After stirring for 30 min, an additional 5 mL of trifluoroacetic acid was added, and the reaction was held at reflux for 3 days. The black reaction mixture was cooled in an ice bath, diluted with water, and carefully basified with 1 N NaOH. The resulting black suspension was extracted well with Et_2O (5 × 80 mL) and the organic extracts were dried ($MgSO_4$), filtered, and concentrated to afford a black gum. This residue was purified with a chromatotron using a 2-mm silica gel rotor and $CHCl_3$–ethyl acetate (9:1) to afford the product as a tan solid: 0.197 g (53%); mp 101 °C dec; TLC (3:1 $CHCl_3$–EtOAc) R_f 0.45; ^1H NMR δ 8.89 (br s, 1, N(1)H), 7.55 (d, 1, H(4), J = 8 Hz), 7.35 (s, 1, H(7)), 7.16 (dd, 1, H(2), J = 3 Hz, 2.4 Hz), 6.96 (dd, 1, H(5), J = 8 Hz, 1.5 Hz), 6.47 (m, 1, H(3)), 3.80 (s, 2, $ArCH_2$), 3.30, 3.20 (2 t, J = 8 Hz, 4, NCH_2), 1.51 (m, 4, CH_2), 0.85 (t, 6, J = 7 Hz, CH_3); CIMS 259 (MH^+); MS calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1742.

6-[2-(*N*,*N*-Di-*n*-propylamino)ethyl]indole (4). A solution of 0.15 g (0.581 mmol) of **7a** in 20 mL of dry THF was added dropwise to a suspension of 0.40 g of lithium aluminum hydride in 50 mL of dry diethyl ether. The reaction was heated at reflux for 3 h. The mixture was cooled in an ice bath, and the complex was decomposed by dropwise addition of water. The white

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suspension was filtered, and the filter cake was washed with several portions of ether. The organic solution was dried ($MgSO_4$), filtered, and concentrated to yield 0.105 g (74%) of a tan solid. The oxalate salt was recrystallized from ethanol: mp 76–77 °C; TLC (3:1 $CHCl_3$–hexanes, NH_3 atm) R_f 0.38; ^1H NMR ($CDCl_3$) δ 9.18 (br s, 1, N(1)H), 7.52 (d, 1, J = 8 Hz, H(4)), 7.43–7.39 (m, 1, H(7)), 7.23–7.15 (m, 1, H(2)), 6.82 (d, 1, J = 8 Hz, H(5)), 6.46 (m, 1, H(3)), 3.44–2.78 (m, 8, CH_2N and $ArCH_2CH_2N$), 1.95–1.44 (m, 4, CH_2), 0.92 (t, 6, J = 7 Hz, CH_3); MS calcd for $C_{16}H_{24}N_2$ 244.1939, found 244.1938.

3-[2-(*N*,*N*-Di-*n*-propylamino)ethyl]aniline (12). A solution of 2.0 g (8.55 mmol) of **9** in 40 mL of dry THF was added dropwise to a suspension of 2.0 g (53 mmol) of lithium aluminum hydride in 60 mL of dry diethyl ether. The reaction was heated at reflux for 4 h and then cooled in an ice bath and the complex was decomposed by dropwise addition of water. The suspension was filtered, the filter cake was washed with several portions of ether, and the combined filtrates were dried ($MgSO_4$), filtered, and concentrated to afford 1.81 g (96%) of an amber oil. The oxalate salt was prepared and recrystallized from ethanol: mp 125–128 °C; TLC (50% $CHCl_3$–hexanes, NH_3 atm) R_f 0.79; ^1H NMR ($CDCl_3$) δ 7.06 (dd, 1, ArH), 6.54 (m, 3, ArH), 2.65 (s, 4, $ArCH_2CH_2$), 2.45 (t, 4, J = 8 Hz, NCH_2), 1.43 (m, 4, CH_2), 0.88 (t, 6, J = 7 Hz, CH_3); MS calcd for $C_{14}H_{24}N_2$ 220.1939, found 220.1941.

3′-[2-(*N*,*N*-Di-*n*-propylamino)ethyl]acetanilide (6a).[24] Amine **12** (0.11 g, 0.5 mmol) was dissolved in 20 mL of 1:1 (v/v) acetic acid–water. The solution was cooled in an ice bath, and acetic anhydride (0.102 g, 1 mmol) was added. The reaction solidified, but the contents redissolved after heating on the steam bath for 30 min. The reaction was cooled to room temperature and basified with saturated Na_2CO_3 solution, and the product was extracted into ethyl acetate (4 × 50 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated to afford 0.125 g (95%) of the product as a pale yellow oil. The oxalate salt was prepared and recrystallized from ethanol: mp 155–158 °C; TLC (3:1 $CHCl_3$–hexanes, NH_3 atm) R_f 0.18; ^1H NMR ($CDCl_3$, free base) δ 8.01 (br s, 1, NH), 7.37–6.86 (m, 4, ArH), 2.67 (s, 4, $ArCH_2CH_2$), 2.44 (t, 4, J = 8 Hz, NCH_2), 2.12 (s, 3, $COCH_3$), 1.41 (m, 4, CH_2), 0.86 (t, 6, J = 7 Hz, CH_3); MS calcd for $C_{16}H_{26}N_2O$ 262.2045, found 262.2040.

3′-[2-(*N*,*N*-Di-*n*-propylamino)ethyl]trifluoroacetanilide (6b). A solution of 0.11 g (0.50 mmol) of amine **12** in 25 mL of dry diethyl ether was cooled in an ice bath. To this was added dropwise 0.21 g (1.0 mmol) of trifluoroacetic anhydride. The reaction was warmed to room temperature and stirred for 30 min. Water (25 mL) was added and the mixture was basified with saturated Na_2CO_3 solution. The phases were separated, and the aqueous layer was extracted once with ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to afford 0.161 g (quant.) of a yellow oil. The oxalate salt was recrystallized from ethanol: mp 173–177 °C; TLC (3:1 $CHCl_3$–hexanes, NH_3 atm) R_f 0.36; ^1H NMR ($CDCl_3$, free base) δ 7.46–6.97 (m, 4, ArH), 2.69 (s, 4, $ArCH_2CH_2$), 2.44 (t, 4, J = 8 Hz, NCH_2), 1.41 (m, 4, CH_2), 0.86 (t, 6, J = 7 Hz, CH_3); MS calcd for $C_{16}H_{23}N_2OF_3$ 316.1763, found 316.1763.

3′-[2-(*N*,*N*-Di-*n*-propylamino)ethyl]methanesulfonanilide (6c).[24] Amine **12** (0.20 g, 0.91 mmol) was suspended in 50 mL of dry benzene. Triethylamine (0.184 g, 1.82 mmol) was added, followed by 0.208 g (1.82 mmol) of methanesulfonyl chloride. The reaction was stirred at reflux for 2 h and then cooled to room temperature. Water (50 mL) was added, and the reaction was basified with saturated Na_2CO_3 solution. The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to yield a yellow oil. This was purified with a chromatotron using a 2-mm silica gel rotor and elution with $CHCl_3$, to yield 0.154 g (57%). The oxalate salt was recrystallized from ethanol: mp 164–167 °C; TLC (50% $CHCl_3$–hexanes, NH_3 atm) R_f 0.40; ^1H NMR ($CDCl_3$, free base) δ 7.09 (t, 1, ArH), 6.57–6.40 (m, 3, ArH), 3.10 (s, 3, SO_2CH_3), 2.68 (s, 4, $ArCH_2CH_2$), 2.47 (t, 4, J = 8 Hz, NCH_2), 1.44 (m, 4, CH_2), 0.88 (t, 6, J = 7 Hz, CH_3); MS calcd for $C_{15}H_{26}N_2O_2S$ 298.1715, found 298.1704.

7-Nitro-3,4-dihydro-1(2*H*)-naphthalenone (13). To a room-temperature solution of 30 g (0.205 mol) of α-tetralone (Aldrich) in 90 mL of dry $CHCl_3$ and 60 mL of TFAA (0.424 mol) under a N_2 atmosphere was added 16.5 g (0.206 mol) of NH_4NO_3, all at once. The temperature was controlled at 25–30 °C with an ice bath. When all the inorganic salt had dissolved (ca. 2.5 h), the solution was reduced by rotary evaporation. The residue was taken up into ether, washed with a 15% $NaHCO_3$ solution, and dried (Na_2SO_4), and the ether was removed under vacuum. Extraction of the crude dark oil with hot n-hexane (1200 mL) afforded 18.97 g (48.4%) of the crude product, which was chromatographed over a dry silica gel column by elution with benzene. Recrystallization of the resulting tetralones from hexane gave 13.05 g (33.3%) of the 7-nitrotetralone: mp 106–108 °C (lit.[25] mp 105–106 °C). The ratio of isolated 7- to 5-nitrotetralone was 3.3/1 in a total yield of 43.3%. IR (KBr) 1675 (C=O), 1340 and 1500 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.78–8.81 (d, 1, J = 2.5 Hz, C(8)H), 8.2–8.34 (dd, 1, J = 2.5 Hz, 8.4 Hz, C(6)H), 7.42–7.52 (d, 1, J = 8.4 Hz, C(5)H), 3.03–3.18 (t, 2, J = 6.0 Hz, C(2)H), 2.66–2.81 (m, 2, C(4)H), 2.13–2.30 (m, 2, C(3)H); CIMS MH^+ 192.

7-Nitro-1,2,3,4-tetrahydro-1-naphthalenol (14). To a slurry of 2.88 g of **13** (15 mmol) in 60 mL of 95% EtOH was added 0.58 g (15 mmol) of $NaBH_4$. The reaction was stirred at room temperature for 1.5 h. The resulting mixture was concentrated nearly to dryness in vacuo and the residue was susspended in 100 mL of H_2O. Then, with stirring, 3 N HCl was added dropwise until the pH = 7. The solution was extracted with ether and washed with water. The ether was removed in vacuo, and the residue was recrystallized from 50% EtOH–H_2O to yield 2.68 g (92.1%): mp 112–113 °C (lit.[26] mp 109 °C); IR (KBr) 3100–3500 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.30–8.33 (d, 1, J = 2.4 Hz, C(8)H), 7.92–8.06 (dd, 1, J = 2.4 and 3.8 Hz, C(7)H), 7.17–7.26 (d, 1, J = 8.1 Hz, C(5)H), 4.78–4.84 (m, 1, C(1)H), 2.78–2.91 (m, 2, C(4)H), 2.19 (s, 1, OH), 1.73–2.26 (m, 4, C(2)H and C(3)H); CIMS MH^+ 194.

7-Nitro-3,4-dihydronaphthalene (15). A mixture of 2.89 g (14.9 mmol) of alcohol 14, 3.5 g of Amberlyst 15 cation-exchange resin, and 120 mL of benzene was heated at reflux under N_2 for 2 h. The reaction mixture was cooled, dried ($MgSO_4$), and filtered and the benzene was removed under reduced pressure. The residual yellow oil was vacuum distilled, bp 160–163 °C (2.2 mmHg), to yield 2.63 g (91.3%): TLC (CH_2Cl_2) R_f 0.71; ^1H NMR ($CDCl_3$) δ 7.80–7.93 (dd, 1, J = 2.4 and 8.1 Hz, C(6)H), 7.70–7.73 (d, 1, J = 2.3 Hz, C(8)H), 7.10–7.20 (d, 1, J = 8.1 Hz, C(5)H), 6.36–6.50 (m, 1, C(1)H), 6.07–6.24 (m, 1, C(2)H), 2.73–2.94 (t, 2, J = 8.0 Hz, C(4)H), 2.18–2.46 (m, 2, C(3)H); CIMS MH^+ 176; MS calcd for $C_{10}H_9NO_2$, 175.0633, found 175.0651.

1,2-Epoxy-7-nitro-1,2,3,4-tetrahydronaphthalene (16). To a solution of 0.5 g (2.85 mmol) of olefin **15** in 9 mL of $CHCl_3$ was added, all at once, 0.677 g of 85% m-chloroperoxybenzoic acid. The solution was heated at reflux for 40 min. At this time, TLC analysis indicated that reaction was complete. The mixture was cooled to 0 °C, precipitated m-chlorobenzoic acid was removed by filtration, and the $CHCl_3$ was removed in vacuo. The yellowish solid residue was chromatographed over silica gel (50 g) and eluted with CH_2Cl_2. Crystallization of the concentrated eluate from hexane gave 0.487 g (89.5%) of the epoxide **16**: mp 72.5–73.5 °C; TLC (CH_2Cl_2) R_f 0.64; ^1H NMR ($CDCl_3$) δ 8.24–8.27 (d, 1, J = 2.4 Hz, C(8)H), 8.02–8.15 (dd, 1, J = 2.4 and 8.2 Hz, C(6)H), 7.19–7.29 (d, 1, J = 8.2 Hz, C(5)H), 3.91–3.96 (d, 1, J = 4.1 Hz, C(1)H), 3.74–3.82 (m, 1, C(2)H), 2.50–3.00 (m, 2, C(4)H), 2.33–2.46 and 1.56–1.98 (m, 2, C(3)H; CIMS MH^+ 192 (100); MS calcd for $C_{10}H_9NO_3$ 191.0582, found 191.0608.

7-Nitro-3,4-dihydro-2(1*H*)-naphthalenone (17). To a solution of 0.5 g (2.6 mmol) of epoxide **16** in 5 mL of dry benzene was added 0.37 g (1.1 mmol) of anhydrous ZnI_2. The mixture was stirred for 15 h at room temperature under a N_2 atmosphere, in the dark. After filtration, and removal of the solvent under reduced pressure, the resulting yellow oil was taken up into 3 mL of cold EtOH, and the product crystallized. Repetitive crystal-

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lization from the concentrated mother liquor gave a total yield of 0.415 g (83%): mp 96–97 °C; TLC (CH_2Cl_2) R_f 0.48; IR (KBr) 1710 (C=O), 1330 and 1500 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03–8.17 (dd, 1, J = 2.1 Hz, 8.3 Hz, C(6)H), 8.03 (s, 1, C(8)H), 7.35–7.46 (d, 1, J = 8.3 Hz, C(5)H), 3.73 (s, 2, C(1)H), 3.11–3.28 (t, 2, J = 6.3 Hz, C(4)H), 2.54–2.72 (m, 2, C(3)H); CIMS MH^+ 192; MS calcd for $C_{10}H_9NO_3$ 191.0582, found 191.0598.

N-n-Propyl-7-nitro-1,2,3,4-tetrahydronaphthalen-2-amine (18). To a solution of 1.2 mL (14.5 mmol) of *n*-propylamine, 1 mL (17.4 mmol) of AcOH, and 25 mL of EtOH was added 0.5 g (2.6 mmol) of tetralone **17** in 15 mL of EtOH. After stirring (pH 7) for 6 min, 0.49 g (7.8 mmol) of $NaBH_3CN$ was added and the mixture was stirred under an N_2 atmosphere for an additional 16 h. The solvent was removed in vacuo and the residue was acidified to pH 2 with 1 N HCl and extracted three times with Et_2O. The aqueous layer was basified with Na_2CO_3 to pH 11 and extracted with CH_2Cl_2. The CH_2Cl_2 layer was separated, washed with H_2O, dried ($MgSO_4$), and concentrated to yield 0.34 g (55.5%) of **18** as an amber oil; TLC (free base; 10% MeOH–$CHCl_3$) R_f 0.31. A sample was converted to the HCl salt: mp 309–312 °C dec; IR (neat) 3200–3400 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86–7.97 (m, 2, C(6)H and C(8)H), 7.15–7.27 (m, 1, C(5)H), 2.75–3.25 (m, 5, C(1)H, C(4)H, and NH), 2.64–2.72 (t, 2, J = 7.3 Hz, NCH_2), 2.0–2.2 (br m, 1, C(2)H), 1.42–1.76 (m, 4, $NCCH_2$ and C(3)H), 0.91–0.98 (t, 3, J = 7.3 Hz, CH_3); CIMS MH^+ 235; MS calcd for $C_{13}H_{18}N_2O_2$ 234.1368, found 234.1368.

N-Propionyl-N-n-propyl-7-nitro-1,2,3,4-tetrahydronaphthalen-2-amine (19). To a solution of 0.23 g (0.98 mmol) of **18** in 6 mL of benzene was added 0.26 mL (2 mmol) of propionic anhydride and 0.14 mL (1 mmol) of Et_3N. The solution was stirred at room temperature for 6 h, and the solvent was removed in vacuo. The oily residue was taken up into ether and washed with 1 N HCl and 1 N NH_4OH solution. The ether was dried ($MgSO_4$) and concentrated to yield 0.274 g (96.1%) of **19** as a pale yellow oil: TLC (5% MeOH–$CHCl_3$) R_f 0.75; IR (neat) 1630 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90–7.97 (m, 2, C(6)H and C(8)H), 7.16–7.28 (m, 1, C(5)H), 4.0–4.2 and 4.5–4.7 (m, 1, C(2)H), 3.20–3.28 (t, 2, J = 7.4 Hz, NCH_2), 2.92–3.16 (m, 4, C(1)H and C(4)H), 2.36–2.48 (q, 2, J = 7.4 Hz, $COCH_2$), 1.9–2.2 (m, 2, C(3)H), 1.56–1.80 (m, 2, $NCCH_2$), 1.08–1.26 (t, 3, J = 7.4 Hz, CH_3), 0.84–1.03 (t, 3, J = 7.4 Hz, CH_3); CIMS MH^+ 291; MS calcd for $C_{16}H_{22}N_2O_3$ 290.1630, found 290.1645.

2-(N-Propionyl-N-propylamino)-7-amino-1,2,3,4-tetrahydronaphthalene (20). A solution of 0.274 g (0.94 mmol) of **19** in 75 mL of EtOH was hydrogenated over 10% palladium on charcoal (0.13 g) at 50 psig for 1 h. Filtration and evaporation of the filtrate in vacuo gave a pale yellow oil: yield 0.238 g (97.1%); TLC (5% MeOH–$CHCl_3$) R_f 0.51; IR (neat) 3200–3450 (NH_2), 1625 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.84–6.91 (m, 1, C(5)H), 6.56–6.60 (d, 1, J = 7.65 Hz, C(6)H, 6.48 (s, 1, C(8)H), 4.68 (br s, 2, NH_2), 3.50–3.70 and 3.90–4.10 (m 1, C(2)H), 3.10–3.20 (m, 2, NCH_2), 2.66–2.98 (m, 4, C(1)H and C(4)H), 2.23–2.51 (q, 2, J = 7.4 Hz, $COCH_2$), 1.80–2.20 (m, 2, C(3)H), 1.50–1.76 (m, 2, $NCCH_2$), 1.14–1.25 (t, 3, J = 7.4 Hz, $COCCH_3$), 0.80–1.06 (t, 3, J = 7.4 Hz, CH_3); CIMS MH^+ 261; MS calcd for $C_{16}H_{24}N_2O$, 260.1888, found 260.1906.

2-(N-Propionyl-N-propylamino)-7-[(2,2-diethoxyethyl)amino]-1,2,3,4-tetrahydronaphthalene (21). A solution of 2.0 g (7.68 mmol) of **20**, 1.71 g (8.44 mmol) of bromoacetaldehyde diethyl acetal, and 0.814 g (7.68 mmol) of Na_2CO_3 in 3 mL of EtOH was heated at reflux for 30 h. After removal of the solvent under reduced pressure, the residue was taken up into 10% EtOAc in $CHCl_3$ and eluted through silica gel (20 g). The oily residue (2.25 g, 77.8%) obtained after removal of the solvent in vacuo was purified by centrifugal TLC (9:1, $CHCl_3$–EtOAc) to yield 1.83 g (63.4%) of product as an oil: TLC (10% EtOAc–$CHCl_3$) R_f 0.21; IR (neat) 3300–3400 (NH), 1625 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86–6.95 (m, 1, ArH), 6.37–6.52 (m, 2, ArH), 4.63–4.68 (t, 1, J = 5.2 Hz, CH(OR)OR), 3.90–4.10 (m, 1, C(2)H), 3.52–3.78 (2 q, 4, J = 7.4 Hz, OCH_2), 3.18–3.28 (m, 4, NCH_2), 2.76–2.92 (m, 5, C(1)H, C(4)H, and NH) 2.12–2.40 (q, 2, J = 7.4 Hz, $NCOCH_2$), 1.84–2.00 (m, 2, C(3)H), 1.58–1.74 (m, 2, $NCCH_2$), 1.12–1.30 (m, 9, CH_3), 0.72–0.92 (t, 3, J = 7.3 Hz, $NCCCH_3$); CIMS MH^+ 377; MS calcd for $C_{22}H_{36}N_2O_3$ 376.2726, found 376.2745.

N-Propionyl-N-n-propyl-1-(trifluoroacetyl)-5,6,7,8-tetrahydrobenz[f]indol-7-amine (22). To 15 mL of a 1:1 mixture of $(CF_3CO)_2O$ in CF_3CO_2H at 0 °C under nitrogen was added 1.83 g (4.86 mmol) of acetal **21**. After 30 min, the cold mixture was diluted with 11 mL of CF_3CO_2H and heated at reflux for 2.5 days. After removal of the solvent under reduced pressure, the residue was taken up into CH_2Cl_2 and eluted through silica gel (40 g). The residue obtained after solvent evaporation was purified by centrifugal TLC (10% EtOAc in $CHCl_3$) to yield 1.1 g (59.5%) of a pale yellow oil: TLC (10% EtOAc–$CHCl_3$) R_f 0.55; IR (neat) 1710 (CF_3C=O), 1630 (NC=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.14–8.18 (d, 1, J = 7.5 Hz, C(2)H), 7.40–7.46 (br m, 1, C(9)H), 7.28–7.38 (m, 1, C(4)H), 6.68–6.72 (dd, 1, J = 4.1 Hz, 7.5 Hz, C(3)H), 4.10–4.20 and 4.65–4.80 (br m, 1, C(7)H), 3.16–3.26 (m, 2, NCH_2), 2.88–3.16 (m, 4, C(5)H and C(8)H), 2.40–2.46 (q, 2, J = 7.3 Hz, $NCOCH_2$), 2.00–2.04 (m, 2, C(6)H, 1.62–1.78 (m, 2, $NCCH_2$), 1.09–1.27 (t, 3, J = 7.3 Hz, $COCCH_3$), 0.83–1.01 (t, 3, J = 7.3 Hz, CH_3); CIMS MH^+ 318; MS calcd for $C_{20}H_{23}N_2O_2F_3$ 380.1712, found 380.1762.

N-Propionyl-N-n-propyl-5,6,7,8-tetrahydrobenz[f]indol-7-amine (23). A solution of 1.10 g (2.89 mmol) of trifluoroacetylindole **22** in 30 mL of dry MeOH was heated at reflux for 18 h. The crude oil obtained after removal of the solvent under reduced pressure was taken up into 10% EtOAc in $CHCl_3$ and eluted through silica gel (20 g). The resulting oil (0.51 g, 62%) was purified by centrifugal TLC (10% EtOAc in $CHCl_3$): yield, 0.198 g (24.1%) of **23** as a pale yellow oil; TLC (10% EtOAc–$CHCl_3$) R_f 0.36; IR (neat) 3265 (br, NH), 1620 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.49–8.77 (br d, 1, NH), 7.32–7.35 (d, 1, J = 2.1 Hz, C(4)H), 7.04–7.16 (m, 2, C(2)H and C(9)H), 6.35–6.45 (m, 1, C(3)H), 3.96–4.40 and 4.50–4.95 (br m, 1, C(7)H), 2.95–3.35 (m, 5, C(5)H, C(8)H and NCH_2), 2.30–2.55 (q, 2, J = 7.3 Hz, $COCH_2$), 1.85–2.15 (m, 2, C(6)H), 1.40–1.80 (m, 2, $NCCH_2$), 1.06–1.25 (t, 3, J = 7.3 Hz, $COCCH_3$), 0.80–0.98 (t, 3, J = 7.3 Hz, CH_3); CIMS MH^+ 285; MS calcd for $C_{18}H_{24}N_2O$ 284.1889, found 284.1915.

N,N-Di-n-propyl-5,6,7,8-tetrahydrobenz[f]indol-7-amine (5). A mixture of 110 mg (0.38 mmol) of **23** and 43.5 mg (1.15 mmol) of $LiAlH_4$ in 20 mL of dry ether was stirred at room temperature for 5 h. Nine drops of H_2O were then added, and the mixture was stirred for an additional 4 h. The ether layer was dried ($MgSO_4$), filtered, and evaporated to give 102 mg (97.5%) of **5** as an oil. The product was a solid after drying under high vacuum for 2 days: mp 48–55 °C; TLC (EtOAc) R_f 0.38; attempts to prepare a crystalline oxalate salt were unsuccessful; IR (neat) 3400 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (br s, 1, NH), 7.31 (s, 1, C(4)H), 6.99–7.03 (m, 2, C(2)H and C(9)H), 6.36–6.42 (m, 1, C(3)H), 2.86–3.03 (m, 5, C(5)H, C(7)H, and C(8)H), 2.41–2.61 (t, 4, J = 7.3 Hz, NCH_2), 1.90–2.25 (m, 2, C(6)H), 1.30–1.75 (m, 4, $NCCH_2$), 0.79–0.97 (t, 6, J = 7.3 Hz, CH_3); CIMS MH^+ 271; MS calcd for $C_{18}H_{26}N_2$ 270.2096, found 270.2107.

N,N-Di-n-propyl-7-nitro-1,2,3,4-tetrahydronaphthalen-2-amine (24). To a solution of 1.59 g (5.47 mmol) of **19** in 50 mL of THF was added, all at once, 12.35 mL of a 1 M solution of B_2H_6 in THF. The solution was heated at reflux for 4 h and the solvent was removed under reduced pressure. The resulting solid was heated at reflux in 70 mL of 2 N HCl in MeOH for 3 h. The solution was reduced by rotary evaporation, and the residue was dissolved in H_2O and extracted with ether. The aqueous layer was basified with Na_2CO_3 and extracted with ether. The organic extract was washed with water, dried ($MgSO_4$), and concentrated to afford 1.16 g (77%) of product as a pale yellow oil: TLC (8% MeOH–$CHCl_3$) R_f 0.59; ^1H NMR ($CDCl_3$) δ 7.94 (s, 1, C(8)H), 7.88–7.94 (dd, 1, J = 2.1 Hz, 8.2 Hz, C(6)H), 7.16–7.20 (d, 1, J = 8.2 Hz, C(5)H), 2.64–3.06 (m, 4, C(1)H, C(4)H), 2.43–2.51 (t, 4, J = 7.3 Hz, NCH_2), 1.98–2.08 (m, 1, C(2)H), 1.59–1.76 (m, 2, C(3)H), 1.38–1.56 (sx, 4, J = 7.3 Hz, $NCCH_2$), 0.85–0.93 (t, 6, J = 7.3 Hz, CH_3); CIMS MH^+ 277.

2-(N,N-Di-n-propylamino)-7-amino-1,2,3,4-tetrahydronaphthalene (25). A solution of 1.16 g (4.2 mmol) of **24** in 120 mL of EtOH was shaken at 50 psig of H_2 over 0.2 g of 10% Pd–C for 1.5 h. Filtration and evaporation of the filtrate resulted in a pale yellow oil: yield, 1.02 g (98%); TLC (10% MeOH–$CHCl_3$) R_f 0.34; ^1H NMR ($CDCl_3$) δ 6.82–6.86 (d, 1, J = 7.4 Hz, C(5)H), 6.42–6.48 (m, 2, ArH), 4.44 (br s, 2, NH_2), 2.92–3.05 (m, 1, C(2)H), 2.75–2.80 (m, 4, C(1)H and C(4)H), 2.48–2.56 (t, 3, J = 7.4 Hz, NCH_2), 1.96–2.10 (m, 2, C(3)H), 1.42–1.70 (m, 4, $NCCH_2$), 0.85–0.93 (t, 6, J = 7.4 Hz, CH_3); CIMS MH^+ 247; MS calcd for $C_{16}H_{26}N_2$ 246.2096, found 246.2066.

2-(*N*,*N*-Di-*n*-propylamino)-7-acetamido-1,2,3,4-tetrahydronaphthalene Methanesulfonate (7a). A solution of 0.2 g (0.81 mmol) of **25**, 0.11 g (1.08 mmol) of acetic anhydride, and 0.051 g (0.56 mmol) of triethylamine in 1 mL of benzene was stirred for 8 h at room temperature. The solvent was removed under reduced pressure, and the residue was taken up into 1 N HCl and extracted with ether. The aqueous layer was basified with $NaHCO_3$ and extracted with CH_2Cl_2. The solvent was washed with water, dried ($MgSO_4$), and concentrated to yield 0.134 g (57.2%) of oil. The base was converted to the salt with methanesulfonic acid and crystallized from EtOH-Et_2O: mp 181-183 °C; TLC (10% MeOH-$CHCl_3$) R_f 0.31; ^1H NMR (free base in $CDCl_3$) δ 7.0-7.15 (m, 3, ArH), 6.75-7.15 (br s, 1, NH), 2.75-3.10 (m, 5, C(1)H, C(2)H, C(4)H), 2.39-2.58 (t, 4, J = 7.2 Hz, NCH_2), 2.14 (s, 3, $COCH_3$), 1.75-2.30 (m, 2, C(3)H), 1.30-1.70 (m, 4, $NCCH_2$), 0.79-0.97 (t, 6, J = 7.3 Hz, CH_3); CIMS 289 (MH^+); MS calcd for $C_{18}H_{28}N_2O$ 288.2202, found 288.2209.

2-(*N*,*N*-Di-*n*-propylamino)-7-methanesulfonamido-1,2,3,4-tetrahydronaphthalene (7b). To a solution of 0.2 g (0.81 mmol) of **25** in 2 mL of benzene was added, dropwise, a solution of 0.093 g (0.81 mmol) of methanesulfonyl chloride in 2 mL of benzene. The mixture was stirred for 1 h and the benzene was removed by rotary evaporation. To the residue was added 25 mL of 1 N HCl and the acidic solution was extracted with ether. The aqueous layer was basified with $NaHCO_3$ and extracted with CH_2Cl_2. The organic extract was washed with water, dried ($MgSO_4$), and concentrated to yield 0.18 g (68.3%) of an oil. The base was converted to its oxalate salt and crystallized from EtOH-Et_2O: mp 244-247 °C dec; ^1H NMR (free base in $CDCl_3$) δ 6.85-7.10 (m, 3, ArH), 4.75-5.65 (br s, 1, NH), 2.98 (s, 3, SO_2CH_3), 2.60-4.35 (m, 5, C(1)H, C(2)H, C(4)H), 2.37-2.56 (t, 4, J = 7.7 Hz, NCH_2), 1.80-2.20 (m, 2, C(3)H), 1.25-1.70 (m, 4, $NCCH_2$), 0.79-0.96 (t, 6, J = 6.89 Hz, CH_3); CIMS 325 (MH^+); MS calcd for $C_{17}H_{28}N_2O_2S$ 324.1871, found 324.1955.

Pharmacology. Prolactin Inhibition Assay.[22] Male, Sprague-Dawley rats were housed and fed in a controlled environment. Each rat received an intraperitonal injection of reserpine (15 mg/kg), as an aqueous suspension, 18 h before the administration of test compound. Compounds for assay were dissolved in 10% ethanol and injected intraperitoneally at a standard dose vs the control group, which received a standard volume of saline solution. One hour after treatment, all rats were killed, their blood was collected and allowed to clot, and 150-μL aliquots of serum were assayed for prolactin by radioimmunoassay using a NIAMD kit. Results were measured as nanograms of NIAMD-prolactin-PR-1 per milliliter of serum and then reported as a percent decrease or increase versus the control result. Significance was evaluated between treatment and control by use of Student's t test.

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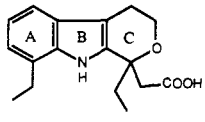
Synthesis and Biological Evaluation of 4,6-Diethyl-1,3,4,5-tetrahydropyrano[4,3-*b*]indole-4-acetic Acid, an Isomer of Etodolac

Philip Hughes,* John DeVirgilio, Leslie G. Humber,* Thuy Chau, Barry Weichman, and Glen Neuman†

Wyeth-Ayerst Research, CN 8000, Princeton, New Jersey 08543-8000. *Received January 20, 1989*

The synthesis of 4,6-diethyl-1,3,4,5-tetrahydropyrano[4,3-*b*]indole-4-acetic acid, an isomer of the antiinflammatory agent etodolac, is described. The compound was found to have an ED_{50} of 3 mg/kg po in the rat curative adjuvant arthritis assay, and an IC_{50} of 50 nM for inhibiting prostaglandin production in cultured chondrocytes.

Etodolac,[1] 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]-indole-1-acetic acid (**1**), is a clinically effective antiinflammatory agent with the potential to retard the progression of skeletal changes in rheumatoid arthritis, and it has been found to possess an exceptional safety profile with respect to the gastrointestinal tract and renal function.[2]



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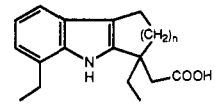

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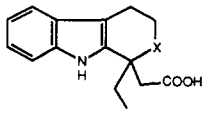

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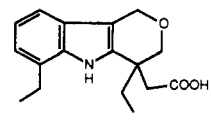

7

Among the analogues of etodolac which have been studied are **2-5**, in which the pyrano[3,4-*b*] ring C was replaced by the cyclopentano, cyclohexano, cycloheptano, and thiopyrano[3,4-*b*] systems, respectively.[3,4] Compounds **1-5** were evaluated in the curative adjuvant edema assay[5] and in vitro for their effects on prostaglandin E_2 production in cultured chondrocytes,[6] and the results are shown in Table I. It is apparent that replacing etodolac's pyrano oxygen by a methylene group gives a compound, **3**, that is of the same order of potency as etodolac. Replacement of the oxygen by a sulfur atom however gave

Table I. Biological Evaluation of Etodolac Analogues

compd	adjuvant edema assay: ED_{50}, mg/kg	chondrocyte assay: $IC_{50} \times 10^{-8}$ M
1 (etodolac)	0.7	2.3
2	6.2	
3	1.9	2.0
4	>50	
5	>25	30
6	6.8	10
7	3.0	5.0

† Present address: Exocel Inc., 3508 Market Street, Philadelphia, PA 19104.

(1) ULTRADOL and LODINE are registered trademarks of Wyeth-Ayerst Laboratories, Radnor, PA.
(2) For a review on etodolac, see: Humber, L. G. *Med. Res. Rev.* **1987**, *7*, 1.
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