pertensive effects in SHR and for ACE inhibition evaluations in conscious normotensive dogs.

Registry No. **6** (R^1 = c-C_4H_7, R^2 = *t*-Bu), 78773-49-6; **6** (R^1 = c-C_3H_5, R^2 = *t*-Bu), 78773-38-3; **6** (R^1 = nopinyl, R^2 = *t*-Bu), 78773-60-1; **6** (R^1 = C_5H_9, R^2 = *t*-Bu), 78773-69-0; (±)-**7a**, 74407-69-5; (*R*)-**7a**, 74431-52-0; (*S*)-**7a**, 76497-39-7; (±)-**7b**, 70354-87-9; (*R*)-**7b**, 74345-73-6; (*S*)-**7b**, 69570-39-4; **7c**, 72679-02-8; **7d**, 74654-91-4; (*R*)-**8a** (R^1 = C_5H_9), 93040-19-8; **8a** (R^1 = c-C_3H_5), 93040-13-2; **8a** (R^1 = c-C_6H_{11}), 93040-14-3; **8a** (R^1 = 2-methylene-1-ethylpyrrolidine), 93040-15-4; (*S*)-**8a** (R^1 = C_5H_9), 93040-16-5; (*S*)-**8c** (R^1 = C_5H_9), 93040-22-3; (*S*)-**10**, 93040-17-6; (*R*)-**10**, 93040-20-1; (*R*)-**11a**, 93040-21-2; (*S*)-**11a**, 93040-18-7; **12**, 89021-98-7; **13**, 93039-48-6; **14**, 93039-49-7; **14**·DCHA, 93039-50-0; **15**, 93040-23-4; **15**·DCHA, 93061-40-6; **16**, 93039-51-1; **17**, 93039-52-2; **18**, 93039-53-3; **18**·DCHA, 93039-54-4; **19**, 93039-55-5; **19**·DCHA, 93039-56-6; **20**, 93039-57-7; **21**, 93039-58-8; **22**, 93039-59-9; **22**·DCHA, 93039-60-2; **23a**, 86324-07-4; **23a**·DCHA, 93061-31-5; **23b**, 93133-32-5; **23b**·DCHA, 93133-31-4; **24**, 93039-61-3; **24**·DCHA, 93039-62-4; **25**, 82017-44-5; **25**·DCHA, 86324-06-3; **26**, 82017-39-8; **26**·DCHA, 82017-40-1; **27**, 86324-15-4; **28**, 93039-63-5; **28**·DCHA, 93039-64-6; **29**, 78773-46-3; **29**·DCHA, 78773-47-4; **30**, 78773-45-2; **30**·DCHA, 93039-65-7; **32**, 78773-59-8; **33**, 78773-58-7; **36**, 78773-62-3; **36**·DCHA, 93039-66-8; **37**, 86324-23-4; **37**·DCHA, 86324-24-5; **38**, 93132-65-1; **38**·DCHA, 93218-53-2; **39**, 93039-67-9; **39**·DCHA, 93039-68-0; **40**, 93039-69-1; **40**·DCHA, 93039-70-4; **41**, 93039-71-5; **41**·DCHA, 93039-72-6; **42**, 78773-86-1; **42**·DCHA, 78773-87-2; **43**, 81379-77-3; **43**·DCHA, 93039-73-7; **44**, 93039-74-8; **44**·DCHA, 93039-75-9; **45**, 93039-76-0; **45**·DCHA, 93039-77-1; **46**, 93061-32-6; **46**·DCHA, 93061-33-7; **47**, 93039-78-2; **47**·DCHA, 93039-79-3; **48**, 93061-34-8; **49**, 93061-35-9; **49**·DCHA, 93061-36-0; **50**, 93039-80-6; **50**·DCHA, 93039-81-7; **51**, 93039-82-8; **51**·DCHA, 93039-83-9; **52**, 93039-84-0; **52**·DCHA, 93039-85-1; **53**, 86323-76-4; **54**, 93039-86-2; **55**, 93039-87-3; **55**·Benz, 93039-88-4; **56**, 93039-89-5; **56**·Benz, 93039-90-8; **57**, 93039-91-9; **57**·Benz, 93039-92-0; **58**, 93039-93-1; **58**·Benz, 93039-94-2; **59**, 93039-95-3; **59**·Benz, 93039-96-4; **60**, 93039-97-5; **60**·Benz, 93039-98-6; **61**, 93039-99-7; **62**, 93040-00-7; **63**, 86324-00-7; **63**·Benz, 93040-01-8; **64**, 93040-02-9; **64**·Benz, 93040-03-0; **65**, 93061-37-1; **65**·Benz, 93061-38-2; **66**, 93040-04-1; **66**·Benz, 93040-05-2; **67**, 93040-06-3; **68**, 86323-77-5; **69**, 93040-07-4; **70**, 86323-79-7; **70**·Benz, 93040-08-5; **71**, 93040-24-5; **71**·Benz, 93061-39-3; **72**, 93040-09-6; **72**·Benz, 93040-10-9; **73**, 93040-11-0; **74a**, 93132-64-0; **74b**, 93040-12-1; **74c**, 81045-50-3; thiolacetic acid, 507-09-5; methacrylic acid, 79-41-4; *tert*-butyl bromoacetate, 5292-43-3; cyclobutylamine, 2516-34-9; nopinylamine, 64284-82-8; *N*-cyclohexylglycine *tert*-butyl ester, 66937-55-1; pivaloyl chloride, 3282-30-2; cyclopropylamine, 765-30-0; angiotensin-converting enzyme, 9015-82-1.

3-(1-Indolinyl)benzylamines: A New Class of Analgesic Agents

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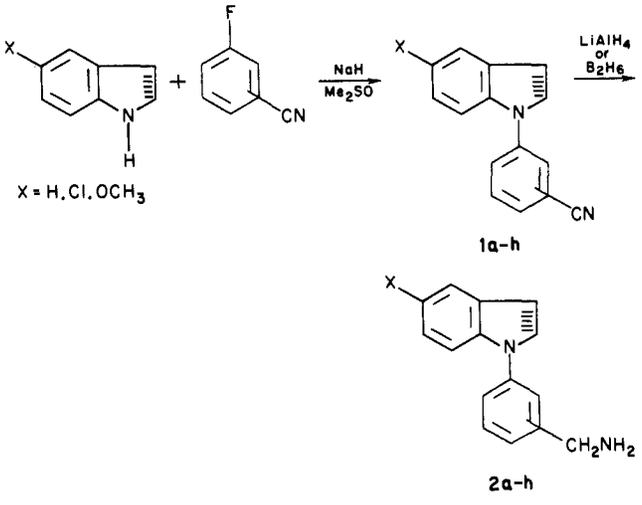
An extensive series of 3-(1-indolinyl)benzylamines and related compounds was synthesized and tested for analgesic activity. After a detailed study of structure–activity relationships, 3-(1-indolinyl)benzylamine (**2b**) was selected for further investigation as the most interesting member of this novel class of compounds. It was active in both the phenylquinone writhing and tail-flick assays for analgesic activity. No motor deficits were observed in the rotorod test, and **2b** was found to be free of any other effects on the central nervous system. The compound did not bind to opiate receptors, since it was inactive in inhibiting the stereospecific binding of [^{3}H]naloxone in rat brain homogenates. Thus, 3-(1-indolinyl)benzylamine represents a novel analgesic with an unusual chemical structure and biological profile.

Serendipity often plays a key role in the discovery of biological activity in a previously unexplored class of molecules.[1] During routine pharmacological screening of intermediates connected with another project,[2] a modest analgesic effect was observed for 1-(2-aminophenyl)-indoline (I). This compound produced a 43% inhibition of phenyl-*p*-quinone-induced writhing (PQW) in rats at the screening dose of 25 mg/kg, sc. We thought this result was quite interesting, since there was no literature precedent for this structural type of molecule within the numerous classes of compounds reported to possess analgesic properties.[3-5] In addition, the simple synthesis of I in two steps[2] from relatively cheap and readily available starting materials encouraged us to initiate an intensive synthetic study of structure–activity relationships within this novel structural type. By pursuing this lead, our objective was to find a chemically simple and unique pain-relieving agent with nonnarcotic properties.

The first structural variation of I to be investigated was a molecule (IIa) in which the *o*-amino group was separated from the phenyl ring by one carbon atom. This minor change produced a major enhancement of anti-PQW activity (ED_{50} = 14.1 mg/kg, sc). Next, the aminomethyl group was moved synthetically around the pendant phenyl ring to the meta (IIb) and para (IIc) positions. The para-substituted derivative was found to be much less active than IIa while the meta-substituted analogue IIb

Scheme I



† Chemical Research Department.
‡ Department of Pharmacology.
§ Department of Biochemistry.

(1) (a) Burger, A. "A Guide to the Chemical Basis of Drug Design"; Wiley: New York, 1983; pp 27–28. (b) Clarke, F. H., Ed. "How Modern Medicines are Discovered"; Futura Publishing Co.: New York, 1973; p 2.
(2) Glamkowski, E. J.; Fortunato, J. M. *J. Heterocycl. Chem.* **1979**, *16*, 865.

0022-2623/85/1828-0066$01.50/0

Scheme II

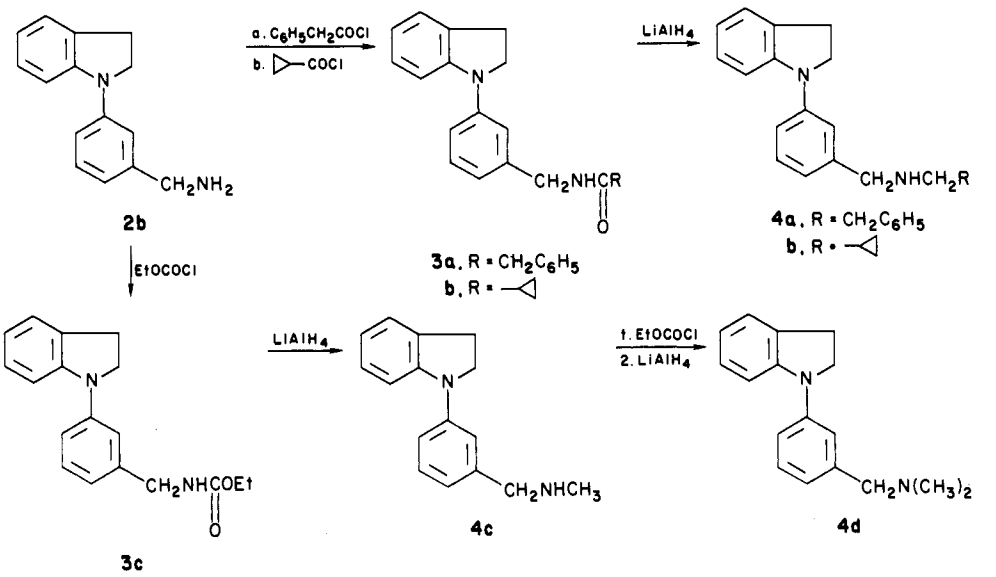
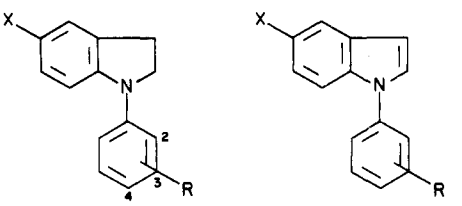


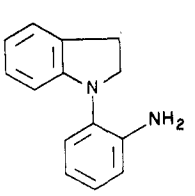
Table I. Nitrile Intermediates



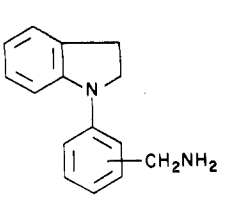
compd	X	R	yield,[a] %	mp, °C	recrystn solvent	formula[b]
1a	H	2-CN	71	94–96	isopropyl ether	$C_{15}H_{12}N_2$
1b	H	3-CN	55	oil[c]		$C_{15}H_{12}N_2$
1c	H	4-CN	62	88–89	isopropyl ether	$C_{15}H_{12}N_2$
1d	Cl	3-CN	44	120–121	EtOH–$CHCl_3$	$C_{15}H_{11}ClN_2$
1e	CH_3O	3-CN	46	92–94	EtOAc–hexane	$C_{16}H_{14}N_2O$
1f	H	3-CN	75	33–36[d]		$C_{15}H_{10}N_2$
1g	Cl	3-CN	42	120–122	EtOH	$C_{15}H_9ClN_2$
1h	CH_3O	3-CN	59	113–115	EtOH	$C_{16}H_{12}N_2O$

[a] The yields are for analytically pure products. No effort was made to optimize these yields. [b] The elemental analyses for C, H, and N were within ±0.4% of the calculated values. [c] This nitrile was obtained as a viscous oil after chromatographic purification (see Experimental Section). [d] After distillation of the original oil at 160 °C (0.1 mmHg), the pure oil slowly crystallized directly to this low-melting solid.

produced a significant increase in potency (ED_{50} = 4.2 mg/kg, sc). It thus became clear early in this study that structural variations of this new lead—the 3-(1-indolinyl)benzylamine molecule—should be the primary focus of our investigations.



I



IIa, *o*-CH_2NH_2
IIb, *m*-CH_2NH_2
IIc, *p*-CH_2NH_2

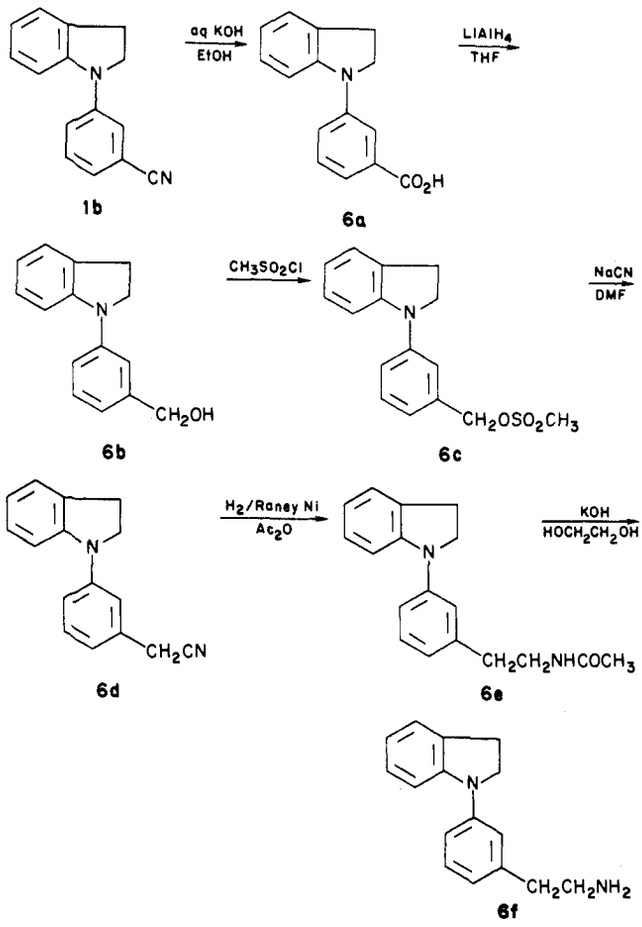
Chemistry. The two-step synthesis of the initial primary targets, the 3-(1-indolinyl)benzylamines **2**, is shown in Scheme I. Indoline or a 5-substituted indoline was condensed with a fluorobenzonitrile to yield the (1-indolinyl)benzonitrile intermediate **1**. Sodium hydride in Me_2SO was used as the strong base required to form the indolinyl nitrogen anion which efficiently displaced fluoride from the fluorobenzonitrile substrate. The cyano group was then reduced to aminomethyl by lithium aluminum hydride, or diborane, in tetrahydrofuran as solvent. The same chemistry was used to produce a subseries of 3-(1-indolyl)benzylamines, starting from indole or a 5-substituted indole.

The amino group of primary target **2** was alkylated via the chemical processes outlined in Scheme II. The primary amine was acylated with the desired acid chloride, and the resulting amides **3** were reduced to alkyl with use of lithium aluminum hydride. In a similar sequence, first a monomethyl and then dimethyl substituents were introduced on the side-chain nitrogen by successive acylation with ethyl chloroformate and reduction with lithium aluminum hydride.

Derivatives of **2b** bearing an α substituent on the carbon of the meta side chain were prepared by Grignard addition to the nitrile **1b**, followed by reduction in situ of the resulting imine intermediate with lithium aluminum hydride. This afforded the α-methyl analogue **5a**, using methyl-

(3) Lednicer, D. In "Central Analgetics"; Lednicer, D., Ed.; Wiley: New York, 1982; pp 137–213.
(4) Johnson, M. R.; Milne, G. M. in "Burger's Medicinal Chemistry", 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1981; Part III, Chapter 52, pp 699–758.
(5) de Stevens, G., Ed. "Analgetics"; Academic Press: New York, 1965.

Scheme III



magnesium chloride, and the α-phenyl analogue **5b**, using phenylmagnesium bromide (see Table II).

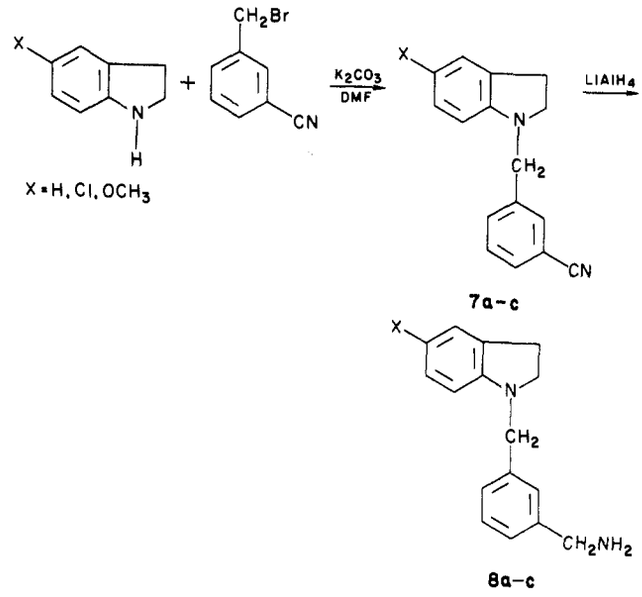
A homologue of the primary lead compound **2b** was prepared in which the meta-positioned chain was extended to two carbon atoms. The sequence leading to this 3-(1-indolinyl)phenethylamine derivative **6f** is shown in Scheme III. The nitrile **1b** was hydrolyzed to the corresponding acid **6a**, which was reduced to an alcohol with lithium aluminum hydride. Next, the alcohol **6b** was acylated with mesyl chloride to provide a good leaving group for displacement by cyanide ion. The resulting cyanomethyl compound **6d** was reduced catalytically with hydrogen over Raney nickel in the presence of acetic anhydride. The anhydride was needed to improve the yield and purity of the product by acylating the primary amine as it formed, thereby preventing it from condensing with any nitrile not yet reduced. The acetyl protective group of **6e** was then removed by hydrolysis to afford the desired 3-(1-indolinyl)phenethylamine **6f**.

A final subseries of compounds (**8a–c**) was prepared in which the pendant benzylamine moiety was separated from the indoline nucleus by an intervening carbon atom. The synthesis of this group of molecules is delineated in Scheme IV. The nitrogen atom of an indoline was alkylated readily with 3-cyanobenzyl bromide in the presence of potassium carbonate. The resulting nitrile **7** was reduced as previously with lithium aluminum hydride to furnish the desired 3-(1-indolinylmethyl)benzylamines of type **8**.

Biological Results and Structure–Activity Relationships

The potential analgesic activity of the target compounds listed in Tables II and III was determined by measuring

Scheme IV



the inhibition of phenyl-*p*-quinone-induced writhing (PQW) in mice.[6] This animal model is sensitive to both weak and strong analgesics. For comparison, the PQW results for two reference drugs—propoxyphene and pentazocine—are also included.

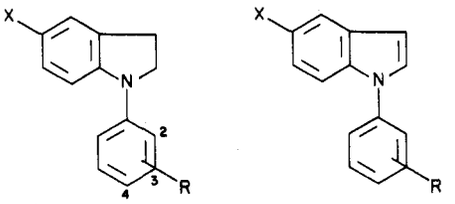
As stated earlier, and as can be seen from Table II, when the aminomethyl group was moved around the perimeter of the pendant phenyl ring (**2a–c**), the isomer with this group occupying the meta or 3-position, **2b**, was by far the most potent (ED_{50} = 4.2 mg/kg, sc). This early finding directed subsequent synthetic work toward other meta analogues related to 3-(1-indolinyl)benzylamine (**2b**).

A study of changes in the indoline portion of the lead compound **2b** revealed the following results. A congener (**2d**) with a chlorine substituent at the 5-position of the indoline nucleus was equipotent (ED_{50} = 4.2 mg/kg, sc), while a 5-methoxy substituent reduced antiwrithing activity substantially. When the indoline nitrogen atom was rendered less basic, and the ring system less flexible and more planar by the presence of another double bond, i.e., replaced by an indole nucleus as in **2f–h**, antinociceptive activity was greatly diminished.

The molecular change which was investigated next was the effect of substitution on the terminal primary amino group. It has been reported for the benzomorphans[7] and for analgesics with a simpler chemical structure, such as the phenylpiperidines,[8] that a phenethyl or cyclopropylmethyl group at the nitrogen atom confers enhanced analgesic potency. This was found not to be the case for our lead structure **2b**. Analogues **4a**, with a phenethyl substituent on the side-chain nitrogen atom, and **4b**, bearing a cyclopropylmethyl group, demonstrated reduced activity in the PQW screen. The presence of a mono- or dimethyl substituent on the terminal nitrogen resulted in almost inactive compounds (**4c** and **4d**, respectively). The amide precursors **3a–c**, in which the basicity of the amino group was virtually abolished, also showed weak activity. It would appear then that an unsubstituted primary amino

(6) Siegmund, E.; Cadmus, R.; Lu, G. *Proc. Soc. Exp. Biol. Med.* **1957**, *95*, 729 and the modification described in the Experimental Section.
(7) Archer, S.; Albertson, N. F.; Harris, L. S.; Pierson, A. K.; Bird, J. G. *J Med. Chem.* **1964**, *7*, 123.
(8) Hardy, R. A., Jr.; Howell, M. G. "Synthetic Analgetics with Morphine-Like Actions" in the book cited in ref 5; pp 181–191.

Table II. Indolinyl and Indolylbenzylamines and Their Analgesic Activity

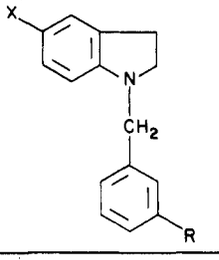


2a-e 3-5 2f-h

compd	X	R	yield,[a] %	mp, °C	recrystn[b] solvent	formula[c]	inhibn of PQW-writhing[d] ED_{50}, mg/kg, sc
2a	H	2-CH_2NH_2	63	231–232	A	$C_{15}H_{16}N_2$·HCl	14.1 (12.9–15.7)
2b	H	3-CH_2NH_2	34	171–173	B	$C_{15}H_{16}N_2$·HCl	4.2 (4.1–4.4)
2c	H	4-CH_2NH_2	34	251–253	C	$C_{15}H_{16}N_2$·HCl	+
2d	Cl	3-CH_2NH_2	74	220–222	D	$C_{15}H_{15}ClN_2$·HCl	4.2 (3.7–4.7)
2e	CH_3O	3-CH_2NH_2	64	196 dec	E	$C_{16}H_{18}N_2O$·HCl	++
2f	H	3-CH_2NH_2	78	190–192	F	$C_{15}H_{14}N_2$·HCl	19.1 (16.4-23.2)
2g	Cl	3-CH_2NH_2	36	230–233	G	$C_{15}H_{13}ClN_2$·HCl	+
2h	CH_3O	3-CH_2NH_2	27	209–212	G	$C_{16}H_{16}N_2O$·HCl	++
3a	H	3-$CH_2NHCOCH_2C_6H_5$	52	oil[e]		$C_{23}H_{22}N_2O$	++
3b	H	3-CH_2NHCO-c-C_3H_5	82	oil[f]		$C_{19}H_{20}N_2O$	++
3c	H	3-$CH_2NHCO_2CH_2CH_3$	75	oil[g]		$C_{18}H_{20}N_2O_2$	+
3d	H	3-$CH_2N(CH_3)CO_2CH_2CH_3$	76	oil[h]		$C_{19}H_{22}N_2O_2$	not tested
4a	H	3-$CH_2NHCH_2CH_2C_6H_5$	17	188–190	G	$C_{23}H_{24}N_2$·HCl	+
4b	H	3-CH_2NHCH_2-c-C_3H_5	36	156–158	F	$C_{19}H_{22}N_2$·HCl	++
4c	H	3-CH_2NHCH_3	60	149–151	E	$C_{16}H_{18}N_2$·HCl	+
4d	H	3-$CH_2N(CH_3)_2$	73	203–204	D	$C_{17}H_{20}N_2$·HCl	+
5a	H	3-$CH(CH_3)NH_2$	36	223–226	H	$C_{16}H_{20}N_2$·HCl	++
5b	H	3-$CH(C_6H_5)NH_2$	53	244–246	H	$C_{21}H_{20}N_2$·HCl	++
6f	H	3-$CH_2CH_2NH_2$	69	191–193	G	$C_{16}H_{18}N_2$·0.5 $C_4H_4O_4$	++
ref drugs							
propoxyphene							3.9 (3.5–4.3)
pentazocine							2.3 (2.2–2.5)

[a] The yields are for analytically pure products. No effort was made to optimize these yields. [b] A, MeOH–ether; B, MeOH–acetonitrile; C, EtOH–ether; D, *i*-PrOH–MeOH; E, *i*-PrOH–ether; F, *i*-PrOH; G, EtOH; H, EtOH–EtOAc. [c] The elemental analyses for C, H, and N were within ±0.4% of the calculated values. [d] In this PQW screen, the antiwrithing activity of compounds was tested at 10 mg/kg, sc in mice and scored as follows: + = 10–34% inhibition (slight activity); ++ = 35–69% inhibition (moderate activity). Compounds which inhibited writhing by 70% or more (marked activity) were investigated further in a dose–response study, and an ED_{50} value was determined by a linear regression analysis. The 95% confidence limits are given in the parentheses. The pharmacological methodology is described fully in the Experimental Section. [e] Kugelrohr distilled, vessel temperature >250 °C (0.1 mmHg). [f] Kugelrohr distilled, vessel temperature 248–253 °C (0.1 mmHg). [g] Kugelrohr distilled, vessel temperature 200–208 °C (0.1 mmHg). [h] Kugelrohr distilled, vessel temperature >240 °C (0.1 mmHg).

Table III. Intermediates and 3-(1-Indolinylmethyl)benzylamines



compd	X	R	yield,[a] %	mp, °C	recrystn solvent	formula[b]	inhibn of PQW-writhing[c] ED_{50}, mg/kg, sc
7a	H	CN	59	54–56	EtOH	$C_{16}H_{14}N_2$	not tested
7b	Cl	CN	72	73–75	EtOH	$C_{16}H_{13}ClN_2$	not tested
7c	CH_3O	CN	98	oil[d]			not tested
8a	H	CH_2NH_2	86	160 dec	EtOH–ether	$C_{16}H_{18}N_2$·2HCl	++
8b	Cl	CH_2NH_2	82	178 dec	EtOH	$C_{16}H_{17}ClN_2$·$C_4H_4O_4$	20.2 (17.8–23.5)
8c	CH_3O	CH_2NH_2	58	167 dec	BuOH	$C_{17}H_{20}N_2O$·2HCl	+

[a] The yields are for analytically pure products. No effort was made to optimize these yields. [b] The elemental analyses for C, H, and N were within ±0.4% of the calculated values. [c] See corresponding footnote *d* in Table II. [d] This nitrile was not purified further but was used immediately in the reduction step leading to **8c**.

group at the end of the meta side chain is an indispensable structural feature for antinociceptive activity.

Up to this point, our investigation was limited to molecules with one carbon in the side chain. To determine the effect of lengthening the chain by a second carbon atom, the 3-(aminoethyl) homologue of **2b** was prepared and tested. This compound **6f** was found to be much less active than **2b** with its shorter carbon chain.

To assay the effect of an α substituent on the carbon of the aminomethyl side chain, the α-methyl (**5a**) and α-phenyl (**5b**) analogues were prepared. Neither of these α-substituted analogues approached the activity of the parent molecule **2b**.

In order to make structure–activity relationships more complete, it was desirable to know whether direct attachment of the pendant phenyl ring to the indoline nucleus was important to antinociceptive activity. Therefore, several analogues (**8a–c**) were prepared in which the phenyl ring was separated from the indoline nucleus by an intervening carbon atom ($-CH_2-$ unit). From Table III it can be seen that this structural modification was deleterious, causing a weakening of antiwrithing activity.

From the preceding studies, it would appear that the structural parameters required for maximum antinociceptive activity within this novel series are an unadorned aminomethyl group in the meta position of a phenyl ring directly attached to an indoline nucleus.

Since **2b**, the early lead compound, incorporates all of these structural requirements, and was the most active compound in the PQW screen, its biological profile was investigated in greater detail. Table II indicates that **2b** is comparable to propoxyphene and slightly less potent than pentazocine in inhibiting phenylquinone-induced writhing in mice. The analgesic potential of **2b** was further supported by testing in the D'Armour–Smith tail-flick assay[9] in rats which detects strong analgesic agents. In this animal model, **2b** showed moderately strong activity. Its potency (ED_{50} = 27 mg/kg, sc)[10] was about half that of pentazocine (ED_{50} = 14.6 mg/kg, sc). The antiwrithing analgesic effect demonstrated by **2b** cannot be attributed to drug-induced motor deficits. The compound was found to be inactive at 8 mg/kg, sc in the rotorod assay.[11] Other animal tests[12] involving behavioral or drug–antagonism paradigms confirm that **2b** has no other effect on the central nervous system. Its ALD_{50} in rats was greater than 100 mg/kg, ip.

No noteworthy antiinflammatory component could be detected for **2b**. In the carrageenan-induced rat paw edema assay,[13] it produced only a 19% inhibition of the acute inflammatory response at a dose of 100 mg/kg, po.

While **2b** was very potent in the PQW assay by the subcutaneous route of administration, its oral antiwrithing activity was moderate: 36% inhibition at 25 mg/kg, po. In vitro affinity for opiate receptors was determined by measuring the inhibition of stereospecific binding of [^{3}H]naloxone in rat brain homogenates.[14] In this test, **2b** was inactive even to a drug concentration of 2.0×10^{-5} M, in the presence or absence of 100 mM sodium.

In conclusion, this investigation has led to the discovery of an unusual new type of analgesic agent, 3-(1-indolinyl)benzylamine. Its chemical structure is unique among drugs of this therapeutic class, and although it is active in animal models used to detect analgesic agents, it does not bind to opiate receptors in vitro.

Experimental Section

The structures of all novel compounds were confirmed by their IR spectra (Perkin-Elmer 457 grating spectrophotometer) and NMR (JEOL C-60HL) spectra, with Me_4Si as the internal reference. Melting points were determined in open capillary tubes with a Thomas-Hoover Uni-melt apparatus and are uncorrected. Elemental analyses were obtained from Micro-Tech Laboratories, Skokie, IL. Extraction solutions were dried over anhydrous sodium or magnesium sulfate and concentrated on a Buchi Rotavapor R. Chromatographic purifications were carried out with silica gel 60 as the solid phase (70–230 mesh), from EM Laboratories, Inc., Elmsford, NY. The final yields reported in this section represent analytically pure products. No effort was made to optimize yields.

In the preceding text, trivial names were used for the compounds cited because these names are relatively simple and commonly used by practicing chemists. In the following Experimental Section, the odious and cumbersome nomenclature required by Chemical Abstracts is employed.

The standard method used to prepare the 3-(1-indolinyl)-benzonitrile intermediates of Table I is described in the following example.

3-(2,3-Dihydro-1*H*-indol-1-yl)benzonitrile (1b). To a stirred solution, under N_2, of 20.9 g (0.175 mol) of indoline in 90 mL of dry dimethyl sulfoxide (Me_2SO) was added 4.63 g (0.193 mol) of 99% sodium hydride. After 1 h, the mixture was cooled to 0 °C and treated dropwise with 23.4 g (0.193 mol) of 3-fluorobenzonitrile in 35 mL of Me_2SO over a 20-min period. The cooling bath was then removed and the reaction was stirred overnight at room temperature. The mixture was poured onto 300 mL of ice/water and the product was extracted into chloroform. The chloroform solution was washed several times with water, then dried, and concentrated to a thick oil weighing 42.8 g. This material was adsorbed onto a chromatography column containing 2 kg of silica gel packed in hexane. The column was eluted first with hexane and then with increasing percentages (5% per step) of ether in hexane. The product eluted cleanly with 50% ether in hexane. Concentration of these fractions in vacuo afforded 21.4 g (55% overall yield) of pure **1b** as a viscous oil: IR ($CHCl_3$) 2245 (C≡N), 1595, 1580, 1490 cm^{-1}; NMR ($CDCl_3$) δ 3.18 (t, 2 H, CH_2), 3.98 (t, 2 H, NCH_2), 6.75–7.62 (m, 8 H, Ar H).

The other benzonitriles of Table I did not require chromatographic purification. They were obtained as crude solids after concentration of the chloroform extract and purified by recrystallization. The only exception was **1f**, a low-melting solid purified by distillation, bp 160 °C (0.10 mmHg).

The 5-methoxyindoline nitrile **1e** was prepared by reduction of the corresponding indole analogue **1h** according to the following procedure.

(9) D'Armour, F. E.; Smith, D. L. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74; and the modification reported in Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Spaulding, T. C.; Wilker, J. C.; Geyer, H. M., III; Kruse, H. *J. Med. Chem.* **1980**, *23*, 494.

(10) The dose–response was determined after a 30-min pretreat with drug (peak time of activity). The drug **2b** was dissolved in distilled water as vehicle and the following percent analgesic activities were recorded: 10% @ 4 mg/kg, sc; 10% @ 8 mg/kg, sc; 30% @ 16 mg/kg, sc; 60% @ 32 mg/kg, sc. The ED_{50} of 27 mg/kg, sc was calculated by using Litchfield–Wilcoxon computer analysis. The 95% confidence limits were 12.00–57.30. For pentazocine, with its ED_{50} = 14.6 mg/kg, sc, the 95% confidence limits were 7.70–23.4. The test procedure is described in detail in ref 9.

(11) Pearl, J.; Stander, H.; McKean, D. B. *J. Pharmacol. Exp. Ther.* **1969**, *167*, 9.

(12) The compound **2b** showed slight activity in the primary overt effects test in rats at 100 mg/kg, ip in which the animals are observed and scored according to a variety of toxicity, behavioral, physiological, and autonomic parameters. It failed to antagonize pentamethylenetetrazol (metrazol) lethality in mice at 50 mg/kg, po, and failed to protect against supramaximal electroshock in mice at 25 mg/kg, ip. The latter two assays are used to detect anxiolytic and anticonvulsive properties. It did not antagonize tetrabenazine-induced ptosis in mice at 20 mg/kg, ip, a test for antidepressant activity. It was inactive in antagonizing amphetamine toxicity in aggregated mice at 20 mg/kg, ip, and was inactive in inhibiting apomorphine-induced climbing behavior in mice at 40 mg/kg, ip. The latter two tests measure potential neuroleptic activity.

(13) Winter, C. A.; Risley, E. A.; Nuss, G. V. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544; and the modification used in our laboratories described in Aultz, D. E.; Helsley, G. C.; Hoffman, D.; McFadden, A. R.; Lassman, H. B.; Wilker, J. C. *J. Med. Chem.* **1977**, *20*, 66.

(14) Pert, C. B.; Snyder, S. H. *Science* **1973**, *179*, 1011; and the modification used in our laboratories described in Ong, H. H.; Anderson, V. B.; Wilker, J. C.; Spaulding, T. C.; Meyerson, L. R. *J. Med. Chem.* **1980**, *23*, 726.

3-(5-Methoxy-2,3-dihydro-1*H*-indol-1-yl)benzonitrile (1e). A stirred solution, under N_2, of 4.0 g (0.016 mol) of 3-(5-methoxy-1*H*-indol-1-yl)benzonitrile (**1h**) in 160 mL of acetic acid was treated with 3.14 g (0.05 mol) of sodium cyanoborohydride at room temperature. After stirring overnight, the solution was poured over 200 mL of ice/water and rendered alkaline by addition of 50% aqueous NaOH. The product was extracted into chloroform and this solution was washed twice with water, dried, and concentrated in vacuo to an oil weighing 3.90 g (96% crude yield). This material was taken up in a small volume of ethyl acetate to which two volumes of hexane were added. After several hours at ice-bath temperature, there was collected 1.87 g of pure crystalline **1e** in 46% overall yield.

General Procedures for Reduction to the Benzylamines of Table II. Method A. 3-(2,3-Dihydro-1*H*-indol-1-yl)benzenemethanamine Hydrochloride (2b). A solution of 7.1 g (0.032 mol) of nitrile **1b** in 44 mL of tetrahydrofuran (THF) was added dropwise over 30 min to a well-stirred 1 M solution of borane–tetrahydrofuran complex in THF (129 mL) kept under N_2 at −5 to 0 °C. When the addition was complete, the reaction mixture was refluxed for 1 h. Then the mixture was cooled to 0–5 °C and treated dropwise with 50 mL of 12 N HCl. The resulting suspension was heated at reflux for 1 h and then stirred at room temperature overnight. The next day, the reaction was cooled to 0 °C and made alkaline by the slow addition of 50% aqueous NaOH. The liberated product was extracted into 300 mL of dichloromethane. The organic extract was washed with water, dried, and concentrated in vacuo to give 8.9 g of crude free base. This was converted to the hydrochloride salt (ethanol/ethereal hydrogen chloride), which was recrystallized by dissolution in 30 mL of boiling acetonitrile to which 6 mL of methanol was added. This afforded 2.86 g of pure **2b**·HCl in 34% overall yield: IR (KBr) 3000–2850 (br, NH^+), 1600, 1580, 1500 cm^{-1}; NMR (Me_2SO-d_6) δ 3.08 (t, 2 H, CH_2), 3.80–4.16 (overlapping 4 H, NCH_2 and Ar CH_2CN), 6.56–7.62 (m, 8 H, Ar H), 8.80 (br s, 3 H, Ar NH_3^+, exchangeable with D_2O).

The benzylamines **2a** and **2c** of Table II were synthesized in the same way.

Method B. 3-(5-Chloro-2,3-dihydro-1*H*-indol-1-yl)benzenemethanamine Hydrochloride (2d). A rapidly stirred slurry of 6.35 g (0.167 mol) of lithium aluminum hydride in 100 mL of THF was cooled to 0 °C under N_2 and then treated dropwise with a solution of 10.7 g (0.042 mol) of nitrile **1d** over a 15-min period. When the addition was completed, the cooling bath was removed and the mixture was refluxed for 2 h. The reaction mixture was then cooled to 0 °C and treated dropwise with 6 mL of H_2O, 6 mL of 10% aqueous NaOH, and finally with 18 mL of H_2O. The precipitated salts were filtered and washed several times with hot $CHCl_3$. The combined filtrates were concentrated to an oil which was dissolved in 200 mL of $CHCl_3$. This solution was extracted with H_2O and then it was dried and concentrated to 10.2 g (94%) of crude free base. This was converted to the hydrochloride salt and purified as follows. The crude base was dissolved in 50 mL of hot 2-propanol, and with good stirring, the solution was treated dropwise with 50 mL of ether saturated with hydrogen chloride. After cooling in an ice bath, the salt was collected and washed well with ether. Recrystallization from 1:1 2-propanol:methanol afforded 9.1 g of **2d**·HCl in 74% overall yield.

The benzylamines **2e–h** of Table II were prepared in a similar manner.

***N*-[[3-(2,3-Dihydro-1*H*-indol-1-yl)phenyl]methyl]phenylacetamide (3a).** To a rapidly stirred, ice-cold slurry of 16.4 g (0.063 mol) of amine **2b** in 300 mL of CH_2Cl_2 was added a solution of 14.5 g (0.14 mol) of triethylamine in 25 mL of CH_2Cl_2 over a 16-min period. A solution of 10.2 g (0.076 mol) of phenylacetyl chloride in 20 mL of CH_2Cl_2 was then added dropwise over a 17-min period. The ice bath was removed and the reaction was stirred for 2 h at room temperature. Then water (75 mL) was added, and the two phases were separated. The organic phase was extracted twice with 2 N HCl, once with 5% aqueous NaOH, and twice with water and then dried and concentrated to 23.9 g of crude amine. This material was dissolved in a small volume of CH_2Cl_2 and adsorbed onto a chromatography column containing 400 g of silica gel packed in hexane. Elution first with hexane, followed by increasing percentages of ether in hexane (25% per step), and finally with ether brought forth 11.1 g of pure amide **3a** as a thick oil in 52% overall yield: IR ($CHCl_3$) 3425 (NH), 1660 (C=O), 1600, 1490 cm^{-1}; NMR ($CDCl_3$) δ 3.08 (t, 2 H, CH_2), 3.60 (s, 2 H, Ar CH_2CO), 3.86 (t, 2 H, NCH_2), 4.38 (d, 2 H, Ar CH_2NH), 5.83 (br, 1 H, NH), 6.58–7.45 (m, 13 H, Ar H).

The amide **3b** was prepared and purified in the same manner except that cyclopropanecarboxylic acid chloride was used as the acylating agent.

***N*-(Ethoxycarbonyl)-3-(2,3-dihydro-1*H*-indol-1-yl)benzenemethanamine (3c).** A slurry of 10.0 g (0.039 mol) of amine **2b** in 120 mL of CH_2Cl_2 was cooled to 0 °C and treated dropwise with a solution of 13.5 mL (0.096 mol) of triethylamine in 40 mL of CH_2Cl_2. After stirring under N_2 for 10 min, the resulting mixture was treated dropwise with a solution of 5.5 mL (0.058 mol) of ethyl chloroformate in 40 mL of CH_2Cl_2 over a 30-min period. The cooling bath was then removed and the mixture was stirred overnight at room temperature. Water (100 mL) was then added, and after stirring vigorously for 5 min, the organic phase was separated. This organic solution was extracted twice with 2 N HCl and twice with water, dried, and concentrated to 10.7 g (94%) of an oil pure by TLC. Kugelrohr distillation afforded analytically pure **3c** (200–208 °C; 0.1 mmHg) in 75% overall yield; IR ($CHCl_3$) 3450 (NH), 1720 (C=O), 1610, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3 H, CH_3), 3.10 (t, 2 H, CH_2), 3.80–4.42 (overlapping 6 H, NCH_2, OCH_2, Ar CH_2NH), 5.10 (br, 1 H, NH), 6.58–7.48 (m, 8 H, Ar H).

The carbamate **3d** was prepared from amine **5a** in the same way except that the pure product was obtained after chromatography with ether–CH_2Cl_2 as eluant.

General Procedure for Reduction of Carbamates and Amides. All of the carbamates and amides of Table II were reduced with lithium aluminum hydride to the corresponding substituted amines according to the following example.

3-(2,3-Dihydro-1*H*-indol-1-yl)-*N*-methylbenzenemethanamine Hydrochloride (4c). A solution of 6.8 g (0.023 mol) of carbamate **3c** in 45 mL of THF was added over 30 min to a stirred slurry of 3.5 g (0.092 mol) of $LiAlH_4$ in 100 mL of THF kept at 0 °C. When the addition was complete, the mixture was refluxed for 2.5 h. The reaction was then cooled to 0 °C and treated dropwise with 3.5 mL of H_2O, 7 mL of 10% aqueous NaOH, followed by 70 mL of H_2O. The precipitated salts were removed by filtration and washed with hot $CHCl_3$, and the combined filtrates were concentrated. The residue was dissolved in 100 mL of $CHCl_3$ and this solution was washed twice with brine, dried, and concentrated to 5.7 g (96%) of crude product free base. This was dissolved in CH_2Cl_2 and treated with ethereal hydrogen chloride to form the hydrochloride salt. Recrystallization from 2-propanol-ether afforded 3.8 g of pure **4c** in 60% overall yield: IR (KBr) 2970–2740 (br, NH^+), 1600, 1580, 1500, 1480 cm^{-1}; NMR (Me_2SO-d_6) δ 2.50 (3 H, NCH_3), 3.10 (t, 2 H, CH_2), 3.78–4.12 (overlapping 4 H, NCH_2 and Ar CH_2N), 6.55–7.60 (m, 8 H, Ar H), 9.38 (br, 2 H, NH_2^+, exchangeable with D_2O).

The carbamate **3d** was reduced to **4d** in the same manner. The amide **3a** required a 19-h reflux period for reduction to amide **4a**. The cyclopropyl amide **3b** was sluggish: after refluxing overnight with the initial charge of $LiAlH_4$, reduction was incomplete. Therefore, an additional 1.5 equiv of $LiAlH_4$ was added and the reaction was refluxed for a total of 30 h before workup to the amine **4b**.

3-(2,3-Dihydro-1*H*-indol-1-yl)-α-methylbenzenemethanamine Hydrochloride (5a). To a stirred solution of 16.8 mL of 2.74 M (0.046 mol) methylmagnesium chloride in THF (Ventron), cooled to 0–5 °C under N_2, was added dropwise a solution of 5.07 g (0.023 mol) of nitrile **1b** over a 36-min period. When the addition was completed, the ice bath was removed and the reaction was stirred at room temperature for 30 min and then heated at 60 °C for 2 h. After the heating period, the mixture was cooled to 0–5 °C and treated with an ice-cold slurry of 1.75 g (0.046 mol) of $LiAlH_4$ in 75 mL of THF. The ice bath was then removed, and the reaction was allowed to warm to room temperature (about 1 h) before it was heated at reflux for an additional hour. The mixture was then cooled to 0–5 °C and quenched by the dropwise addition of 2 mL of cold H_2O followed by 2 mL of 10% aqueous NaOH and finally 6 mL of H_2O. The precipitated salts were filtered and washed well with hot CH_2Cl_2 (4 × 70 mL), and the combined filtrates were concentrated. The residue was

taken up in 200 mL of $CHCl_3$ and this solution was extracted twice with H_2O, then dried, and concentrated to afford 4.83 g (88% yield) of crude product free base. This was dissolved in 150 mL of ether and filtered, and the solution was added dropwise to ethanolic hydrogen chloride with good stirring and with cooling in an ice bath. The precipitated hydrochloride salt was filtered, washed well with ether, and then dried. This hydrochloride salt was dissolved in 15 mL of hot EtOH, 40 mL of EtOAc was added, and the recrystallization mixture was kept in the refrigerator overnight. The crystals were then filtered, washed first with a small volume of EtOH and then several times with EtOAc, and dried. This provided 2.28 g of pure **5a**·HCl in 36% overall yield: IR (KBr) 3000–2850 (br, NH^+), 1600, 1500, 1480 cm^{-1}; NMR (Me_2SO-d_6) δ 1.66 (d, 3 H, CH_3), 3.15 (t, 2 H, CH_2), 4.00 (t, 2 H, NCH_2), 4.42 (br q, 1 H, CH), 6.62–7.12 (m, 8 H, Ar H), 8.80 (br, 3 H, NH_3^+, exchangeable with D_2O).

The α-phenylbenzenemethanamine hydrochloride **5b** was prepared in the same way except that a 2.8 M solution of phenylmagnesium bromide in ether (Ventron) was used as the Grignard reagent.

3-(2,3-Dihydro-1*H*-indol-1-yl)benzoic Acid (6a). A stirred mixture of 30.0 g (0.136 mol) of nitrile **1b** and 47.7 g of KOH pellets in 270 mL of ethylene glycol was heated at 180 °C for 6 h. The resulting solution was then cooled and poured onto a stirred mixture of 85 mL of concentrated HCl and 400 mL of ice. The product was extracted twice with 400 mL of $CHCl_3$. The combined organic extracts were washed twice with water, dried, and concentrated to a crude solid. This was recrystallized from $CHCl_3$–toluene to afford 19.5 g (60% yield) of pure acid: mp 168–170 °C; IR ($CHCl_3$) 3100–2850 (br, OH), 1690 (C=O), 1600, 1580, 1485 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 3.10 (t, 2 H, CH_2), 3.98 (t, 2 H, NCH_2), 6.62–7.98 (m, 8 H, Ar H), 11.3 (br s, 1 H, CO_2H, exchangeable with D_2O). Anal. ($C_{15}H_{13}NO_2$) C, H, N.

3-(2,3-Dihydro-1*H*-indol-1-yl)benzenemethanol (6b). A solution of 16.1 g (0.067 mol) of **6a** in 75 mL of dry THF was added dropwise over 7 min to a rapidly stirred, ice-cold slurry of 2.55 g (0.067 mol) of $LiAlH_4$ in 50 mL of dry THF. The reaction mixture was then refluxed for 1 h, cooled to 0–5 °C, and quenched by dropwise addition of 3 mL of H_2O, 3 mL of 10% aqueous NaOH solution, and 9 mL of H_2O. The precipitated salts were filtered and washed three times with 30 mL of hot $CHCl_3$, and the combined filtrates were concentrated to a residue. This was taken up in $CHCl_3$, washed with brine, dried, and concentrated in vacuo to give 14.4 g (95%) of oil, which was very pure by TLC. Kugelrohr distillation afforded 12.6 g of the pure alcohol in 83% overall yield (204–208 °C; 0.13 mmHg): IR ($CHCl_3$) 3620 (OH), 1600, 1480 cm^{-1}; NMR ($CDCl_3$) δ 2.36 (s, 1 H, OH, exchangeable with D_2O), 3.08 (t, 2 H, CH_2), 3.92 (t, 2 H, NCH_2), 4.60 (s, 2 H, Ar CH_2O), 6.60–7.52 (m, 8 H, Ar H). Anal. ($C_{15}H_{15}NO$) C, H, N.

3-(2,3-Dihydro-1*H*-indol-1-yl)benzenemethanol Methanesulfonate (6c). A stirred solution of 8.11 g (0.036 mol) of alcohol **6b** and 7.6 mL (0.054 mol) of triethylamine in 35 mL of CH_2Cl_2 was cooled to 0 °C under N_2 and then treated dropwise with a solution of 3.1 mL (0.040 mol) of methanesulfonyl chloride in 35 mL of CH_2Cl_2. Ten minutes after the addition was completed, 150 mL of H_2O was added. The organic layer was separated and extracted twice with 150 mL of cold 2 N HCl, once with 150 mL of saturated $NaHCO_3$ solution, and once with 150 mL of H_2O. The organic solution was then dried and concentrated in vacuo to give 10.3 g of mesylate ester **6c** in 94% yield. This oil was somewhat unstable and was used without further purification in the following reaction.

3-(2,3-Dihydro-1*H*-indol-1-yl)benzeneacetonitrile (6d). A stirred mixture of 10.2 g (0.0338 mol) of **6c** and 4.97 g (0.101 mol) of NaCN in 200 mL of DMF was heated at 60–70 °C for 50 min. The reaction was then concentrated in a fume hood in high vacuum at 50–60 °C, and the resulting residue was partitioned between 200 mL of $CHCl_3$ and 200 mL of H_2O. The organic phase was separated, washed twice with H_2O, once with brine, then was dried, and concentrated to give 6.39 g (81%) of nitrile as an oil which was pure by TLC. Kugelrohr distillation provided an analytical sample in 60% overall yield (189–192 °C; 0.15 mmHg): IR ($CHCl_3$) 2260 (C≡N), 1600, 1500, 1480, 1460 cm^{-1}; NMR ($CDCl_3$) δ 3.12 (t, 2 H, CH_2), 3.70 (s, 2 H, Ar CH_2CN), 3.92 (t, 2 H, NCH_2), 6.60–7.46 (m, 8 H, Ar H). Anal. ($C_{16}H_{14}N_2$) C, H, N.

***N*-[2-[3-(2,3-Dihydro-1*H*-indol-1-yl)phenyl]ethyl]acetamide (6e).** A sample of 0.37 g (wet weight) of No. 28 finely divided Raney Ni catalyst was carefully washed three times with EtOH and three times with Ac_2O. The moist catalyst was then added to a mixture of 2.0 g (8.54 mmol) of nitrile **6d**, 1.05 g (12.8 mmol) of anhydrous NaOAc, and 50 mL of Ac_2O in a 500-mL Parr bottle. The mixture was shaken at 50 °C under 50 psi H_2 until gas uptake ceased and TLC showed no starting material was present. The catalyst was removed by filtration and concentration of the filtrate in vacuo gave 2.37 g (100%) of the crude amide as an oil. Purification was achieved by chromatography on 45 g of silica gel with first hexane and then increasingly polar mixtures of hexane–ether and methanol–ether. This brought forth 1.62 g (68% overall yield) of analytically pure **6e** as an oil: IR ($CHCl_3$) 3440 (NH), 1660 (C=O), 1600, 1490, 1460 cm^{-1}; NMR ($CDCl_3$) δ 1.96 (s, 3 H, CH_3), 2.85 (t, 2 H, Ar CH_2), 3.14 (t, 2H, CH_2), 3.50 (t, 2 H, CH_2N), 3.98 (t, 2 H, NCH_2), 5.78 (br, 1 H, NH), 6.70–7.72 (m, 8 H, Ar H). Anal. ($C_{18}H_{20}N_2O$) C, H, N.

3-(2,3-Dihydro-1*H*-indol-1-yl)benzeneethanamine Hemifumarate (6f). A stirred mixture of 5.97 g (0.021 mol) of **6e**, 4.78 g (0.084 mol) of 85% KOH pellets, 5 mL of H_2O, and 85 mL of ethylene glycol was heated at 160–180 °C under N_2 for 4 h. The reaction fluids were then poured onto ice and extracted three times with 70 mL of $CHCl_3$. The combined organic extracts were washed with 250 mL of H_2O and 250 mL of brine, dried, and concentrated in vacuo to 4.89 g (96%) of the crude free base as an oil. A warm solution of 2.85 g (0.02 mol) of fumaric acid in 35 mL of EtOH was treated with a filtered solution of 4.89 g (0.02 mol) of the free base in 30 mL of EtOH. The salt crystallized slowly while kept overnight in the refrigerator. The crystals were collected, washed with EtOH, with ether, and then dried to afford 4.51 g (69% overall yield) of **6f** as the hemifumarate: mp 191–193 °C; IR (KBr) 3150–2450 (NH^+, OH), 1640, 1600, 1530, 1490 cm^{-1}; NMR (of the free base; $CDCl_3$) δ 2.78–3.32 (m, 6 H, Ar CH_2, CH_2, CH_2N), 3.92 (t, 2 H, NCH_2), 6.65–7.82 (m, 8 H, Ar H). Anal. ($C_{16}H_{18}N_2 \cdot 0.5C_4H_4O_4$) C, H, N.

3-[(2,3-Dihydro-1*H*-indol-1-yl)methyl]benzonitrile (7a). To an ice-cold, stirred mixture of 9.2 g (0.077 mol) of indoline and 10.6 g (0.077 mol) of K_2CO_3 in 50 mL of DMF was added dropwise a solution of 15 g (0.077 mol) of α-bromo-*m*-tolunitrile in 75 mL of DMF. When the addition was completed, the mixture was stirred at room temperature for 5 h, then filtered, and concentrated in vacuo at 55 °C. The residue was dissolved in 150 mL of $CHCl_3$, and this solution was washed twice with H_2O, once with brine, then dried, and concentrated to 15.3 g (85%) of crude solid nitrile. Recrystallization from hot EtOH furnished 10.7 g (59% overall yield) of pure nitrile **7a**: IR ($CHCl_3$) 2240 (C≡N), 1600, 1490, 1470, 1440 cm^{-1}; NMR ($CDCl_3$) δ 2.82–3.50 (overlapping 4 H, NCH_2, CH_2), 4.26 (s, 2 H, Ar NCH_2), 6.38–7.72 (m, 8H, Ar H).

The other nitriles **7b** and **7c** of Table III were synthesized in a similar manner.

3-[(2,3-Dihydro-1*H*-indol-1-yl)methyl]benzenemethanamine Dihydrochloride (8a). To a stirred mixture of 8.48 g (0.224 mol) of $LiAlH_4$ in 110 mL of dry THF, kept at 0–5 °C under N_2, was added slowly a solution of 13.1 g (0.056 mol) of **7a** in 120 mL of dry THF. The reaction mixture was then heated at reflux for 5 h. After cooling to 0–5 °C, the mixture was treated slowly and cautiously with 8.5 mL of H_2O, then with 8.5 mL of 10% aqueous NaOH, and finally with 25 mL more of H_2O. The salts were filtered, washed three times with 100 mL of hot $CHCl_3$, and discarded. The combined filtrates were concentrated to a residue which was taken up in $CHCl_3$. This solution was washed with 10% aqueous NaOH, with brine, then dried, and concentrated to 12.7 g (95%) of crude amine. This was dissolved in a small volume of EtOH and treated with ether previously saturated with gaseous HCl. The salt which separated was collected, washed well with ether, and dried to afford 15.0 g (86% overall yield) of analytically pure **8a** as the dihydrochloride salt: IR (KBr) 3010–2800 (br, NH^+), 2740–2500 (br, NH^+), 1620, 1490, 1380 cm^{-1}; NMR (Me_2SO-d_6) δ 2.88–4.10 (overlapping 6 H, CH_2, Ar $CH_2NH_3^+$, NH^+CH_2), 4.44 (s, 2H, Ar HN^+CH_2), 6.80–7.72 (m, 8 H, Ar H), 8.82 (br, 3 H, NH_3^+, exchangeable with D_2O), 10.9 (br 1 H, NH^+, exchangeable with D_2O).

Utilizing the same procedure, there were prepared the nuclear substituted analogues **8b** and **8c** of Table III.

Biological Testing Methods. Inhibition of Phenylquinone-Induced Writhing in Mice (PQW). The procedure used in our laboratories is a modification of the method of Siegmund et al.[6] A 0.125% concentration of phenyl-*p*-benzoquinone in a 5% aqueous solution of ethyl alcohol is administered to mice (10 mL/kg, ip). This produces a characteristic "writhe" which is defined as an inward rotation of one or more feet with twisting and turning of the trunk, drawing in of the abdominal wall, lordosis, and arching of the back. A total of 28 male CD-1 Charles River mice (18–30 g) are employed for a time–response. Animals receive food and water ad libitum during their stay in the animal quarters prior to testing. Compounds are tested at 10 mg/kg, sc and are prepared with distilled water, and if insoluble one drop of Tween-80, a surfactant, is added. Compounds are administered in a dosage volume of 10 mL/kg.

Twenty mice (five per group) are administered the test compound at various pretreat times (e.g., 15, 30, 45, and 60 min) prior to phenylquinone injection. Control animals (two per group) receive an equal volume of vehicle. After the administration of phenylquinone, the mice are placed separately into 1-L beakers, and 5 min are allowed to elapse. The mice are then observed for a period of 10 min, and the number of writhes is recorded for each animal. The formula for computing percent inhibition is

$$\frac{(\bar{X}\text{ writhes in control group}) - (\bar{X}\text{ writhes in drug group})}{\bar{X}\text{ writhes in control group}} \times 100\%$$

The time period with the maximum percent of inhibition is considered the peak time. A dose–response is reserved for interesting compounds or those which inhibit writhing by 70% or more. A dose–response is run in the same manner as a time–response except 10 animals per group are tested at the peak time of drug activity. Fifty animals, divided among four drug groups and one vehicle control group, are employed. The mice are normally given four doses of drug, each twice the amount of the preceding dose. An ED_{50} is calculated by a computer linear regression analysis. Compounds were tested in the physical form listed in the tables; i.e., a compound described as a hydrochloride salt was tested as that salt and not as the free base, etc.

The procedures used to determine other biological activities have been described previously in the following references: D'Armour–Smith tail-flick assay,[9] rotorod assay,[11] inhibition of carrageenin-induced rat paw edema,[13] in vitro opiate receptor binding assay.[14]

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Facile Synthesis of Platelet-Activating Factor and Racemic Analogues Containing Unsaturation in the *sn*-1-Alkyl Chain

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Platelet-activating factor, 1 (PAF, 1-*O*-hexadecyl-2-acetyl-*sn*-glycero-3-phosphocholine), and octadecyl-PAF were synthesized chemically as the racemates. The *sn*-1-*O*-alkyl isomers were isolated after treatment of the racemates with phospholipase A_2 and subsequent reacetylation of the 1-*O*-alkyl-2-lyso-*sn*-glycero-3-phosphocholines released. Analogues of PAF containing unsaturated alkyl moieties at the *sn*-1 position (**2**, **4**, **5**) were synthesized by utilizing the methoxyethoxymethyl protecting group as a novel method for preparing unsaturated alkyl lipids. This procedure provides a facile means for preparing unsaturated ether phospholipids of defined structure that may be tritiated to high radiospecific activity for metabolic studies. Unsaturation in the alkyl chain had minimal effect on the bioactivities examined in this study.

The discovery of the biological response initiated by platelet-activating factor (PAF)[1] dates back to 1966 when Barbaro and Zvaifler reported that a mixture of rabbit platelets and stimulated leukocytes released histamine on specific antigen challenge.[2a] Hensen later described this phenomenon as a nonlytic, complement-independent,

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(1) Abbreviations used: PAF = platelet-activating factor, MEM = methoxyethoxymethyl, TLC = thin-layer chromatography, DMAP = (*N*,*N*-dimethylamino)pyridine, PMN = polymorphonuclear neutrophils, NMR = nuclear magnetic resonance, FMLP = *N*-formylmethionylleucylphenylalanine, BSA = bovine serum albumin, GC = gas chromatography, THF = tetrahydrofuran, IR = infrared, EDTA = ethylenediaminetetraacetic acid.

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