Competitive [^{3}H]Nitrendipine Binding Assay.[25] The inhibition of [^{3}H]nitrendipine binding to a microsomal fraction from guinea pig ileal longitudinal smooth muscle was carried out with use of the procedure reported by Bolger et al.[25]

Acknowledgment. We are grateful to the Medical Research Council of Canada (Grant (Grant MT-8992) for financial support of this work and to the Alberta Heritage Foundation for Medical Research for studentships (to L.D. and M.C.L-K-K.). We also thank Amy Wong and Elizabeth Erdman for assistance in some of the pharmacological testing.

Registry No. **3** (R = Pr-*i*), 542-08-5; **3** (R = Bu-*i*), 7779-75-1; **3** (R = $(CH_2)_2NMe_2$), 6131-49-3; **3** (R = Me), 105-45-3; **3** (R = Et), 141-97-9; **4**, 14205-39-1; **5** (R^1 = 2-pyridyl), 1121-60-4; **5** (R^1 = 3-pyridyl), 500-22-1; **5** (R^1 = 4-pyridyl), 872-85-5; **6a**, 23125-32-8; **6b**, 39562-90-8; **6c**, 104196-44-3; **6d**, 104196-45-4; **6e**, 73349-75-4; **6f**, 39562-56-6; **6g**, 104196-46-5; **6h**, 104196-47-6; **6i**, 23125-31-7; **6j**, 104196-48-7; **6k**, 104196-49-8; **6l**, 104196-50-1; **7a**, 23125-28-2; **7b**, 104196-51-2; **7c**, 104196-52-3; **7d**, 104196-53-4; **7e**, 23125-30-6; **7f**, 104196-54-5; **7g**, 104196-55-6; **7h**, 104196-56-7; **7i**, 21197-70-6; **7j**, 104196-57-8; **7k**, 104196-58-9; **7l**, 104196-59-0; **8**, 1118-61-2; **9a**, 67593-36-6; **9b**, 104196-60-3; **9c**, 64089-24-3; **9d**, 64089-25-4; Ca, 7440-70-2; $Me_2N(CH_2)_2OH$, 108-01-0; NH_4OH, 1336-21-6; diketene, 674-82-8.

p-Dimethoxy-Substituted *trans*-Octahydrobenzo[*f*]- and -[*g*]quinolines: Synthesis and Assessment of Dopaminergic Agonist Effects

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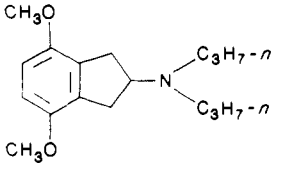
The *N*-*n*-propyl homologues of the title compounds were prepared for further assessment of the ability of the "*p*-dimethoxy" moiety to confer dopaminergic agonism upon a variety of ring systems. Both the angularly and the linearly annulated *trans*-benzoquinoline ring derivatives displayed prominent DA_2 dopaminergic effects on the peripheral sympathetic nerve terminal and displayed postjunctional dopamine receptor agonist properties in the striatum. It is speculated that the angular octahydrobenzo[*f*]quinoline derivative (but not the linear octahydrobenzo[*g*]quinoline derivative) may owe its dopamine-like effects to metabolic activation phenomena. In contrast, the cis-fused isomer of the angularly annulated benzoquinoline was inactive, as was the simple benzene derivative *N*,*N*-di-*n*-propyl-β-(2,6-dimethoxyphenyl)ethylamine.

2-(Di-*n*-propylamino)-4,7-dimethoxyindan (1) is equipotent to apomorphine in the cat cardioaccelerator nerve assay for DA_2-receptor agonist effect involving the sympathetic nerve terminal.[1] It is effective following oral administration, and it is a weaker emetic agent than apomorphine.[2] Arneric and Long[3] have suggested that the compound produces its weak and transient hypotensive and bradycardia effects in rats by activation of central dopamine receptors. Compound 1 is significantly more selective than apomorphine in activating prejunctional dopamine receptors (as opposed to postsynaptic receptors) in the rat nigrostriatal pathway.[2] The tetralin congener 2 also demonstrates dopaminergic agonist effects but, in



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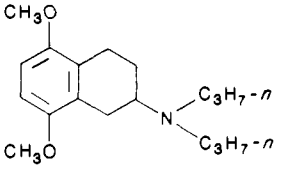

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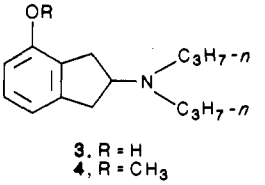
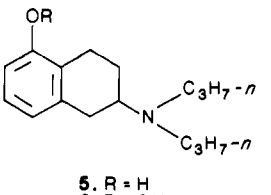
most assays, the indan derivative 1 is more potent with high efficacy than the tetralin congener 2.[2] Compound 1 suppresses appetite in male rats[4] and it possesses direct α_1-adrenoceptor agonist and serotonergic agonist activities.[5] It elicits potent effects on sexual behavior in male rats, characterized by increased mounting and ejaculation.[6-8]

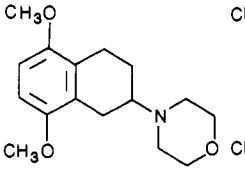
The 5-hydroxyindan derivative 3 is a potent DA_2-receptor agonist,[9] whereas its methyl ether 4 is inert.[9] Similarly, 5-hydroxytetralin 5 is a potent DA_2 agonist,[10] and its methyl ether 6 is inactive.[11] The 5,8-dimethoxy-2-aminotetralin derivative 7 was reported[12] to have no dopamine-like effects, and this inactivity was ascribed[12] to the incorporation of the amino group into a ring. De-



3, R = H
4, R = CH_3



5, R = H
6, R = CH_3



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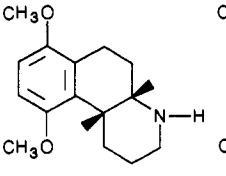

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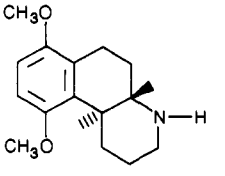

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[†] College of Pharmacy.
[‡] College of Medicine.

(1) Sindelar, R. D.; Mott, J.; Barfknecht, C. F.; Arneric, S. P; Flynn, J. R.; Long, J. P.; Bhatnagar, R. K. *J. Med. Chem.* **1982**, *25*, 858.
(2) Arneric, S. P.; Long, J. P.; Williams, M.; Goodale, D. B.; Mott, J.; Lakoski, J. M.; Gebhart, D. G. *J. Pharmacol. Exp. Ther.* **1983**, *224*, 161.
(3) Arneric, S. P.; Long, J. P. *J. Pharm. Pharmacol.* **1984**, *36*, 318.
(4) Arneric, S. P.; Roetker, A.; Long, J. P. *Neuropharmacology* **1982**, *21*, 885.
(5) Arneric, S. P.; Roetker, A.; Long, J. P.; Mott, J.; Barfknecht, C. F. *Arch. Int. Pharmacodyn. Ther.* **1982**, *257*, 263.
(6) Clark, J. T.; Smith, E. R.; Stefanick, M. L.; Arneric, S. P.; Long, J. P.; Davidson, J. M. *Physiol. Behav.* **1982**, *29*, 1.
(7) Stefanick, M. L.; Smith, E. R.; Clark, J. T.; Davidson, J. M. *Physiol. Behav.* **1982**, *29*, 973.
(8) Clark, J. T.; Stefanick, M. L.; Smith, E. R.; Davidson, J. M. *Pharmacol. Biochem. Behav.* **1983**, *19*, 781.
(9) Cannon, J. G.; Dushin, R. G.; Long, J. P.; Ilhan, M.; Jones, N. D.; Swartzendruber, J. K. *J. Med. Chem.* **1985**, *28*, 515.

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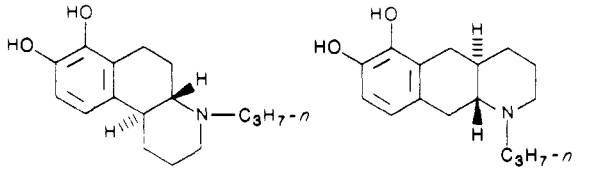
Marinis and co-workers[13] prepared a variety of methoxamine congeners bearing the *p*-dimethoxy moiety on a variety of ring systems. The basic nitrogen atoms in these molecules were either primary (in the case where the nitrogen was not a part of a ring) or secondary (where the nitrogen was a member of a ring). Both the *cis*- and the *trans*-octahydrobenzo[*f*]quinolines **8** and **9** exhibited prominent α_1-adrenoceptor agonist effects, but none of the subject compounds in this study were evaluated for dopaminergic effects.

Compounds **1** and **2** represent a nonclassical dopaminergic agonist moiety, "*p*-dimethoxy" systems, for which a chemical structural rationalization of dopaminergic agonist activity is not readily apparent. It was the goal of the present study to incorporate the *p*-dimethoxy moiety into some other ring systems, catechol derivatives of which have been shown to exhibit prominent dopaminergic agonist effects. Thus, the catechol-derived *trans*-octahydrobenzo[*f*]- and benzo[*g*]quinolines **10** and **11** are unusually potent with high efficacy, and the "*p*-dimethoxy" derivatives **12** and **13** represent the target molecules in the present study. To complete the series, the β-phenethylamine derivative **14** was also proposed for synthesis and study.



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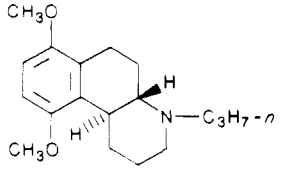

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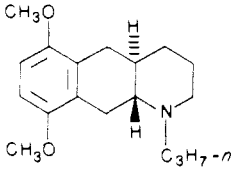
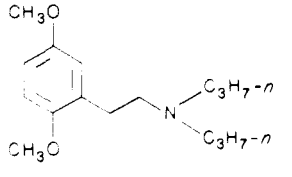


13



14

Chemistry. It was anticipated that preparation of the *trans*-octahydrobenzo[*f*]quinoline target molecule **12** could be achieved by using an annulation reaction on 5,8-dimethoxy-2-tetralone (**17**), as has been described by our group for various benzene ring substituted 2-tetralones.[14-16] A method of Rama Rao et al.[17] leads to **17** by a three-step sequence, which is much shorter and less laborious than the routes required in our previous preparations of other 2-tetralones[14-16] in which the pattern of substitution on the benzene ring was not symmetrical. Conversion of the 2-tetralone **17** into the target compound **12** and into its cis-fused isomer **25** is shown in Scheme I. The *N*-benzyl group was placed on the molecule (**19** → → **22**, **23**) in order subsequently to demonstrate the stereochemistry of ring fusion, by observation of the signals produced by the magnetically nonequivalent benzylic CH_2 protons in **22** and **23**.[15] The most favorable reduction of the enamine **21** gave an approximately 80:20 mixture of cis/trans products **22** and **23**, which provided a barely sufficient amount of the trans product for further synthetic manipulation. On the basis of biological data on other dopaminergic octahydrobenzo[*f*]quinolines,[14-16] it was predicted that the dopaminergic agonist effect would reside exclusively in the trans isomer. However, because large amounts of the cis-isomer **22** were obtained, it was converted into a final compound **25** for biological evaluation. A high-yield, stereospecific route to the *trans*-octahydrobenzo[*f*]quinoline system has been communicated recently,[18] which permitted preparation of adequate test amounts of compound **12**.

Preparation of the linear benzoquinoline target compound **13** was based upon a modification of a method of Michne and Albertson[19] and is shown in Scheme II. This sequence affords the trans-fused isomer as the exclusive product.[20] The geometry of ring fusion of this system was verified by observing the splitting pattern of the benzyl methylene protons of the *N*-benzyl derivative **32**.[20]

Preparation of the β-phenethylamine target compound **14** followed a standard literature route.

Spectral (IR, NMR, MS) data on all final compounds and intermediates were consistent with the proposed structures.

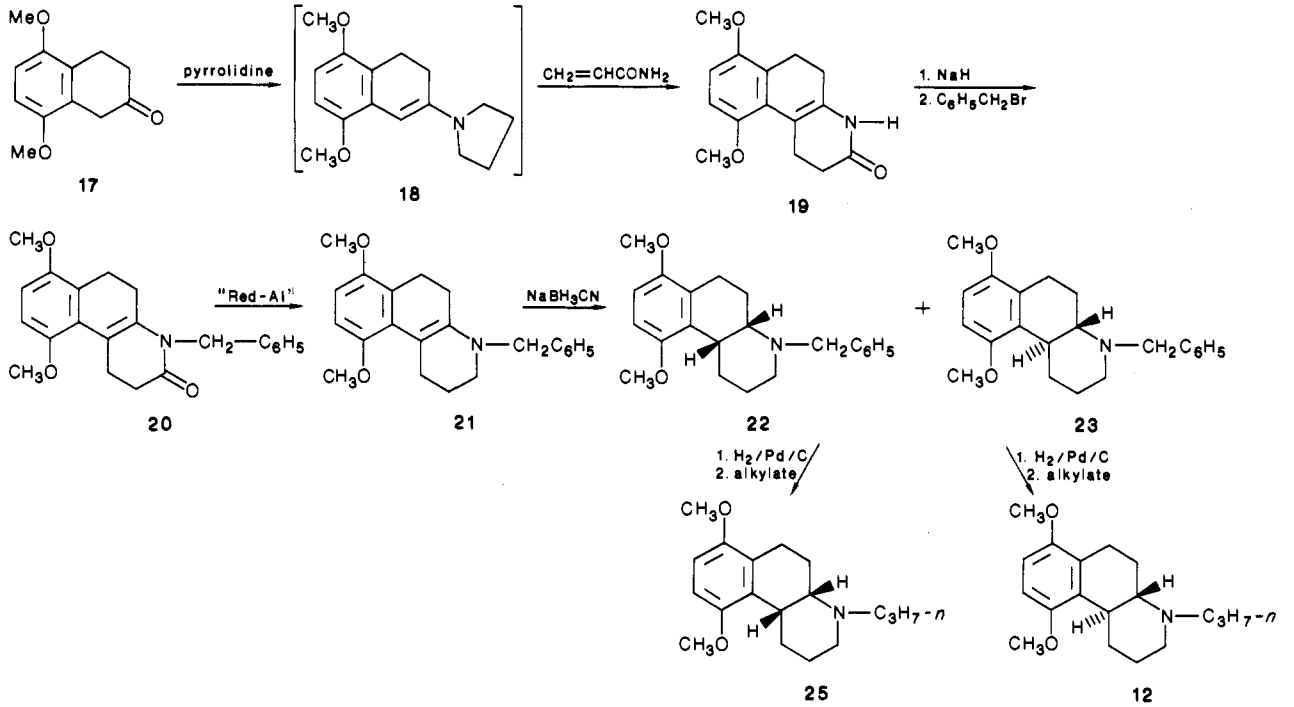
Pharmacology. Results and Discussion. The β-phenethylamine derivative **14** was inactive both as an agonist and as an antagonist in the cat cardioaccelerator nerve preparation (DA_2 receptors) and in rats with unilateral lesion of the nigrostriatal pathway (postjunctional dopamine receptors). The highest doses used were 3.4 μmol/kg in the cat and 13.3 μmol/kg in the rat. the *cis*-octahydrobenzo[*f*]quinoline **25** was likewise inactive in these assays at doses of 3.08 μmol/kg in the cat and 12.3 μmol/kg in the rat.

However, the *trans*-octahydrobenzo[*f*]quinoline **12** had an ID_{50} value of 1.17 μmol/kg with 95% confidence limits of 0.4–2.3 for inhibition of the chronotropic response to nerve stimulation using the cat cardioaccelerator nerve preparation. The inhibition of the nerve stimulation response gradually reached its maximum effect 30 min after administration of the test compound, and it did not return to base value within 2 h. Haloperidol (50 μg/kg) reversed the inhibition of the nerve stimulation. In lesioned rats, **12** was inactive in inducing rotations, and there was no antagonism of apomorphine-induced rotations.

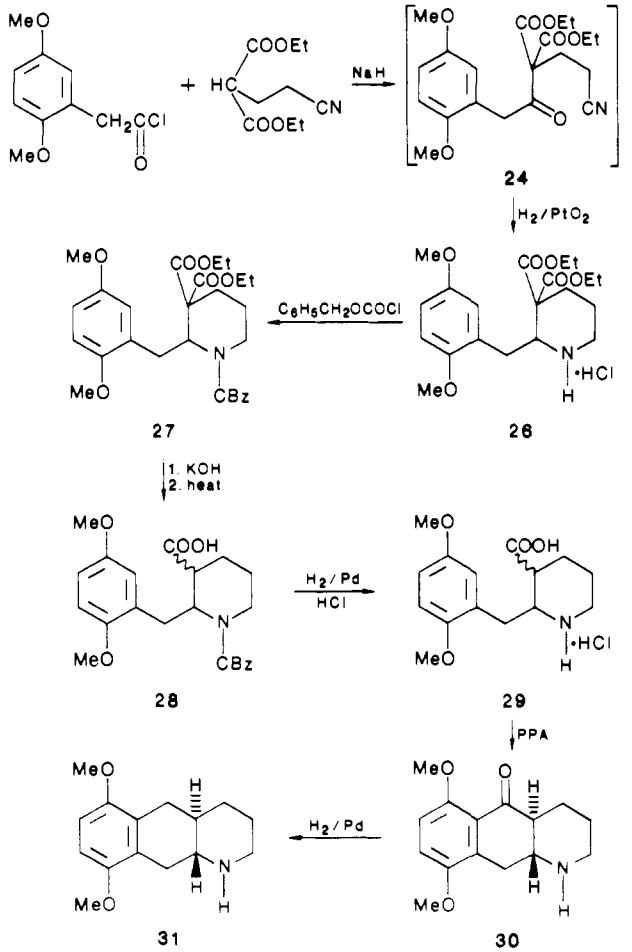
The *trans*-octahydrobenzo[*g*]quinoline **13** had an ID_{50} value of 0.032 μmol/kg (0.02–0.07) on the cat cardioaccelerator nerve preparation. The maximum inhibition was reached within 5 min, and the return of stimulation response to control levels occurred within 1–3+ h. Haloperidol (100 μg/kg) reversed the inhibition of nerve stimulation. In comparison, apomorphine had an ID_{50} value of 0.022 μmol/kg (0.01–0.04) on the cat cardioaccelerator

(10) Hacksell, U.; Svensson, U.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A.; Wikstrom, H.; Lindberg, P.; Sanchez, D. *J. Med. Chem.* **1979**, *22*, 1469.
(11) Long, J. P., unpublished data, 1985.
(12) McDermed, J. D.; McKenzie, G. M.; Phillips, A. P. *J. Med. Chem.* **1975**, *18*, 362.
(13) DeMarinis, R. M.; Bryan, W. M.; Shah, D. H.; Hieble, J. P.; Pendleton, R. G. *J. Med. Chem.* **1981**, *24*, 1432.
(14) Cannon, J. G.; Hatheway, G. J.; Long, J. P.; Sharabi, F. M. *J. Med. Chem.* **1976**, *19*, 987.
(15) Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long, J. P.; Costall, B; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979**, *22*, 341.
(16) Cannon, J. G.; Hamer, R. L.; Ilhan, M.; Bhatnagar, R. K.; Long, J. P. *J. Med. Chem.* **1984**, *27*, 190.
(17) Rama Rao, A. V.; Deshpande, V. H.; Laxma Reddy, N. *Tetrahedron Lett.* **1980**, *21*, 2661.
(18) Cannon, J. G.; Chang, Y.; Amoo, V. E.; Walker, K. A. *Synthesis* **1986**, 494.
(19) Michne, W. F.; Albertson, N. F. *J. Med. Chem.* **1969**, *12*, 402.
(20) Walsh, D. A; Smissman, E. E. *J. Org. Chem.* **1974**, *39*, 3705.

Scheme I. Preparation of *cis*- and *trans*-7,10-Dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline



Scheme II. Synthesis of *trans*-6,9-Dimethoxyoctahydrobenzo[*g*]quinoline



nerve preparation. With apomorphine, the maximum response was reached within 0.5 min after intravenous administration, and the stimulation response returned to control levels within 15–45 min. Compound **13** induced rotations in the lesioned rat that were antagonized by haloperidol (100 μg/kg, pretreatment 30 min). Compound **13** was one-tenth as active as apomorphine when comparing the number of rotations produced in 1 h after drug administration (One hour was the average duration of effect produced by apomorphine.) Depending upon the size dose, compound **13** had a duration of action of 3–7 h. The doses of **13** used were the same as apomorphine (0.2–3.0 μmol/kg). When **13** was compared with apomorphine on the basis of *total turns*, **13** was 4 times more active.

In sum, the β-phenethylamine derivative **14** and the *cis*-octahydrobenzo[*f*]quinoline **25** were inactive. The *trans*-octahydrobenzo[*f*]quinoline derivative **12** showed a consistently slow onset of action, which may be related to metabolic activation. The *trans*-octahydrobenzo[*g*]-quinoline derivative **13** was as active as apomorphine in the cat cardioaccelerator nerve preparation, but its duration of action was much longer. It is noteworthy that incorporation of the *p*-dimethoxy moiety into ring systems, catechol derivatives of which elicit potent dopaminergic agonist actions, does not invariably produce dopaminergic agonism. Moreover, the striking delay in onset of action noted for the *trans*-octahydrobenzo[*f*]quinoline derivative makes this compound unique, as compared with the other dopaminergically active *p*-dimethoxy derivatives, in that these other compounds did not exhibit delayed onset of action. Chemical structure based rationalization for the dopaminergic agonist effects of the "*p*-dimethoxy" moiety in certain ring systems is currently being studied, but as yet no reasonable explanation can be presented.

Experimental Section

Pharmacology. Methods. Cardioaccelerator Nerve Stimulation (DA_2 Receptors). Experiments were performed with cats (2–4 kg) of either sex. Cats were anesthetized with an intraperitoneal (ip) injection of pentobarbital sodium (30 mg/kg). All animals were artificially respired with a Harvard respirator. The arterial blood pressure was measured from the femoral artery by a Statham P23AA transducer, and the heart rate was monitored with a Beckman cardiotachometer. All injections were made via a catheter placed in the femoral vein. A Beckman R511A recorder was used to monitor physiological changes in these experiments. After bilateral vagotomy, the right postganglionic cardioaccelerator

nerves were isolated and were placed on bipolar electrodes. Right cardioaccelerator nerves were stimulated for 30 s with a Grass S48 stimulator with the following parameters: 2 Hz, 5-ms pulse duration, supramaximal voltage usually 20–25 V. Each test compound was administered intravenously to at least three cats. The compounds were administered in sequential doses, but only after the inhibitory effect on the tachycardia had stabilized. At least three doses, spaced by 0.48 log intervals, were administered to each cat. The dose–response curves obtained with the above experiments were used to calculate the ID_{50} value for each compound. All compounds were evaluated for antagonism of apomorphine (10 μg/kg) induced inhibition of the tachycardia produced by stimulation of the right cardioaccelerator nerve.

Rotational Behavior in Rats (Postjunctional Dopamine Receptors). Male Sprague–Dawley rats (Harlen) received unilateral stereotaxically placed injections of 6-hydroxydopamine hydrobromide in the nigrostriatal bundle. With the tooth bar set at −2.3 mm, the stereotaxic coordinates were AP, 4.4 mm posterior to bregma; *L*, 1 mm; *V*, 7.5 mm from top of dura. After at least 2 weeks, test drugs were administered subcutaneously, and total contralateral rotations were recorded. At least three animals were used for each dose of the experimental compound, and the dose–response curves were determined with use of three doses spaced by 0.6 log intervals. In those animals that did not rotate following the administration of a compound, apomorphine (100 μg/kg) was administered to evaluate possible receptor-inhibiting properties of the compound. The antagonistic ability of haloperidol (100 μg/kg) was determined in all animals that rotated after receiving the expermental compound .

Statistics. Statistical treatment of data in the experiments where each preparation served as its own control was by the paired Student's *t* test.[21] The relative potency and 95% fiducial limits were calculated by using a 3 × 3 parallel line bioassay.[22] ID_{50} values were determined by a nonquantal analysis described by Finney.[22]

Chemistry. Melting points were determined in open glass capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values. IR spectra were recorded on Perkin-Elmer 267 and Beckman 4240 spectrometers. NMR spectra were recorded on a Varian Asociates EM360A spectrometer with tetramethylsilane as the internal standard. Mass spectra were obtained with a Ribermag R10-10C spectrometer. Preparative HPLC was performed on a Waters Prep 500A chromatograph.

7,10-Dimethoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3-(2*H*)-one (19). To 2 g (0.01 mol) of 5,8-dimethoxy-3,4-dihydro-2(1*H*)-naphthalenone (**17**),[17] 20 mL of benzene, and a catalytic amount of *p*-toluenesulfonic acid in a 250-mL round-bottom flask was added dropwise 1.07 g (0.015 mol) of freshly distilled pyrrolidine in 10 mL of benzene, while the mixture was heated under reflux in a Dean–Stark apparatus. Volatiles were then distilled under N_2, and 4 g (0.06 mol) of acrylamide was added. The resulting mixture was stirred at 80 °C for 90 min and then at 140 °C for 30 min. This mixture was chromatographed on a silica gel column and was eluted with CH_2Cl_2–Me_2CO (9:1) to give 1.0 g (40%) of a white solid, mp 184.5–185.4 °C. Anal. ($C_{15}H_{17}NO_3$) C, H, N.

7,10-Dimethoxy-4-benzyl-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (20). A mixture of 10 g (0.0386 mol) of **19**, 1.0626 g (0.044 mol) of hexane-washed NaH, and 250 mL of anhydrous 1,3-dimethoxyethane was heated under reflux for 3 h. The resulting mixture was cooled to room temperature, and 7.7 g (0.045 mol) of benzyl bromide was added. This mixture was heated under reflux overnight, then it was cooled to room temperature, and excess NaH was destroyed with 5 mL of H_2O. Volatiles were removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated to give an orange oil. This material was chromatographed on silica gel and was eluted with Me_2CO–CH_2Cl_2 (1:9). The eluate was evaporated under reduced presure and the residue was triturated with cold Me_2CO to give 10.3 g (76%) of a white powder, mp 165–167 °C. Anal. ($C_{22}H_{23}NO_3$) C, H, N.

7,10-Dimethoxy-4-benzyl-1,2,3,4,5,6-hexahydrobenzo[*f*]quinoline (21). Compound **20** (7 g, 0.02 mol) in 300 mL of dry benzene was treated with 17.65 mL (0.06 mol) of sodium bis(2-methoxyethoxy)aluminum hydride (3.4 M in benzene). The resulting mixture was heated under reflux for 6 h. The reaction mixture was cooled and excess hydride reagent was destroyed with 10 mL of H_2O. Excess 50% KOH was added to dissolve Al salts. The organic layer was separated and was washed with two 50-mL portions of H_2O. It was dried (Na_2SO_3), and volatiles were removed under reduced pressure to give 6.8 g (100%) of a yellow oil, which solidified upon standing. This material was utilized in the next step without purification.

***cis*- and *trans*-7,10-Dimethoxy-4-benzyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (22 and 23).** A mixture of 6.4 g (0.019 mol) of **20** and 2.6 g (0.04 mol) of $NaBH_3CN$ in 120 mL of MeCN was stirred at room temperature for 24 h, while the pH was maintained at 6–7 (pH paper) by addition of glacial AcOH. Concentrated HCl (10 mL) was added to the mixture to destroy excess $NaBH_3CN$. Volatiles were removed under reduced pressure to give a yellow oil, which was taken up in 250 mL of H_2O, and this solution was basified with 50% KOH. The resulting mixture was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated to give a yellow oil, which was subjected to preparative HPLC (silica gel, cyclohexane–Et_2O (7:3) containing 0.2% Et_3N). Two products were obtained. The compound with higher R_f value was the *cis*-isomer **22**: yield, 3.6 g (56%); NMR ($CDCl_3$) δ 7.30 (m, 5 H, Ar *H*), 6.55 (s, 2 H, Ar H), 3.75 (s, 6 H, OCH_3), 3.70 (s, 2 H, NCH_2Ar). The free base was converted into its HCl salt, which was recrystallized from CH_2Cl_2–Et_2O to give white needles, mp 207–208 °C. Anal. ($C_{22}H_{28}ClNO_2$) C, H, N. The compound with the lower R_f value was the trans-isomer **23**: yield, 0.18 g (3%); NMR ($CDCl_3$) δ 7.30 (m, 5 H, Ar *H*), 6.55 (s, 2 H, Ar *H*), 3.80 (AB q, J = 12 Hz, υ = 40 Hz, 2 H, NCH_2Ar), 3.75 (s, 6 H, OCH_3).

***cis*-7,10-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (24).** The HCl salt of **22** (3 g, 0.008 mol) in 120 mL of MeOH was hydrogenated over 10% Pd/C at an initial pressure of 50 psig. After 24 h, the reduction mixture was filtered through a Celite pad, and the filtrate was evaporated to give 2 g (88%) of white crystals. These were recrystallized from MeOH–Et_2O, mp 301–303 °C (lit.[13] mp 305 °C); MS, *m/e* 247 (M^+ − HCl).

***cis*-7,10-Dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (25).** Following a procedure of Marchini et al.,[23] 1.4 g (0.0037 mol) of $NaBH_4$ was added in small portions to 9.7 g (0.013 mol) of propionic acid in 120 mL of benzene, while the temperature was maintained below 25 °C. The reaction mixture was stirred at room temperature for 4 h. To this mixture was then added 1.7 g (0.007 mol) of the free base of **24** in 40 mL of benzene, and the resulting mixture was heated overnight under reflux. The cooled solution was treated with 50 mL of 2 N NaOH, and then it was extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure to give 1.8 g (90%) of an oil. This was treated with ethereal HCl to give a solid, which was recrystallized from MeOH–Et_2O to afford a fine white solid, mp 236–237 °C. Anal. ($C_{18}H_{28}ClNO_2$) C, H, N.

***trans*-7,10-Dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (12).** Following a procedure of Marchini et al.,[23] 0.16 g (0.0043 mol) of $NaBH_4$ was added in small portions to 1.13 g (0.0153 mol) of propionic acid in 20 mL of benzene, while the temperature was maintained below 25 °C. The reaction mixture was stirred at room temperature for 4 h. To this mixture was then added 0.2 g (0.00081 mol) of the free base of *trans*-7,10-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline[18] in 10 mL of benzene, and the resulting mixture was heated overnight under reflux. The cooled solution was treated with excess 2 N NaOH and was extracted with CH_2Cl_2. The extract was washed with H_2O, dried ($MgSO_4$), filtered, and

(21) Steel, R. G.; Torrie, J. H. *Principles and Procedures of Statistics*; McGraw-Hill: New York, 1960.
(22) Finney, D. J. *Statistical Methods in Biological Assay*; Hafner: New York, 1964.
(23) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, R. M. *J. Org. Chem.* **1975**, *40*, 3453.

evaporated to give an oil. This was treated with ethereal HBr to give a solid, which was recrystallized from 2-PrOH–Et_2O to afford 0.17 g (64%) of a white powder, mp 237 °C dec. The NMR spectrum ($CDCl_3$) and the IR spectrum ($CHCl_3$) of this material were identical with similar spectra of **12** prepared from **23** by catalytic N-debenzylation and subsequent N-alkylation with $NaBH_4$ and propionic acid, as described in detail for the cis-isomer **25**. These spectra were significantly different from analogous spectra of the cis-isomer **25**. Anal. ($C_{18}H_{28}BrNO_2$) C, H, N.

Diethyl 2-(2,5-Dimethoxybenzyl)piperidine-3,3-dicarboxylate Hydrochloride (26). Following a procedure of Michne and Albertson,[19] 5.2 g (0.0244 mol) of diethyl (2-cyanoethyl)malonate in 15 mL of dry toluene was added to a suspension of 0.59 g (0.0244 mol) of NaH in 50 mL of dry toluene. The resulting slurry was heated under reflux for 8 h. The reaction mixture was cooled in an ice bath and 5.0 g (0.0233 mol) of (2,5-dimethoxyphenyl)acetyl chloride in 20 mL of dry toluene was added over 2 min. The reaction mixture was then stirred at room temperature for 16 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated under reduced pressure to give 9 g of the crude keto nitrile **24** as a light brown oil. A solution of this material in 100 mL of absolute EtOH and 3 mL of $CHCl_3$ was hydrogenated over 0.3 g of PtO_2 at an initial pressure of 45 psig for 48 h. The reduction mixture was filtered through a Celite pad, and volatiles were removed from the filtrate under reduced pressure. HCl (100 mL of 5%) was added to the residue, and the resulting mixture was washed with two 50-mL portions of Et_2O. The aqueous layer was made basic with 40% NaOH, and then it was extracted with several portions of Et_2O. The pooled extracts were dried ($MgSO_4$) and evaporated to leave a yellow oil. This was treated with ethereal HCl to give an oil, which solidified on standing. Trituration of this solid with Et_2O gave 6.0 g (62%) of a white solid, mp 155–156 °C. Anal. ($C_{20}H_{30}ClNO_6$) C, H, N.

Diethyl 1-(Benzyloxycarbonyl)-2-(2,5-dimethoxybenzyl)piperidine-3,3-dicarboxylate (27). To a solution of 0.5 g (0.0012 mol) of **26** and 0.227 g (0.0013 mol) of benzyl chloroformate in 5 mL of $CHCl_3$ at 0 °C under N_2 was added, over 2 min, 0.268 g (0.0027 mol) of Et_3N in 3 mL of $CHCl_3$. The resulting solution was warmed to room temperature and was stirred for 3 h. Washing of the reaction mixture with H_2O, dilute HCl, and saturated $NaHCO_3$ gave a clear solution, which was dried ($MgSO_4$) and filtered. Evaporation of the filtrate under reduced pressure gave 0.62 g (100%) of a colorless oil. This material was purified on a Chromatotron apparatus (silica gel) and was eluted with Et_2O–hexane (1:1). Anal. ($C_{28}H_{35}NO_8$) C, H, N.

***cis*- and *trans*-1-(Benzyloxycarbonyl)-2-(2,5-dimethoxybenzyl)piperidine-3-carboxylic Acid (28).** Compound **27** (12.8 g, 0.025 mol) and 11 g (0.196 mol) of KOH in 150 mL of 95% EtOH were heated under reflux for 5 h. Evaporation of the volatiles under reduced pressure left a white paste, which was partitioned between 100 mL of Et_2O and 100 mL of H_2O. The separated aqueous layer was adjusted to pH 2–3 (pH paper) with concentrated HCl and was extracted with several portions of Et_2O. The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was evaporated to give a white solid residue. This white solid was heated in an oil bath at 175–180 °C for 30 min; CO_2 was rapidly evolved. The resulting residual oil was dissolved in 150 mL of Et_2O and washed with two 50-mL portions of 10% HCl and with saturated NaCl. The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a yellow oil. This material was purified by flash chromatography (silica gel), eluting with Et_2O–hexane (1:1), to give 7.3 g (71%) of an oil, which upon standing solidified to a white solid, mp 110–112 °C. Anal. ($C_{23}H_{27}NO_6$) C, H, N.

***cis*- and *trans*-2-(2,5-Dimethoxybenzyl)piperidine-3-carboxylic Acid Hydrochloride (29).** Compound **28** (5.0 g, 0.0121 mol) in 250 mL of 95% EtOH and 2 mL of concentrated HCl was hydrogenated over 1.0 g of 5% Pd/C at an initial pressure of 45 psig for 15 h. Filtration of the reduction mixture and evaporation of the filtrate under reduced pressure gave 3.4 g (90%) of a hygroscopic white powder, mp 93–110 °C. Anal. ($C_{15}H_{22}ClNO_4$) C, H, N.

***trans*-6,9-Dimethoxy-5-keto-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (30).** Product **29** (2.5 g, 0.0079 mol) was added over 5 min, with efficient manual stirring, to 60 g of polyphosphoric acid at 80 °C. After stirring for 45 min, the reaction mixture was quenched by addition of excess crushed ice. The resulting solution was added slowly to 500 mL of 20% NaOH solution. The resulting mixture was extraced several times with CH_2Cl_2, then the combined extracts were dried ($MgSO_4$) and filtered, and the filtrate was evaporated under reduced pressure to give a tan oil, which solidified on standing. This material was treated with ethereal HCl to give a solid, which was recrystallized from MeOH to give 2 g (62%) of a white solid, mp 197–199 °C. Anal. ($C_{15}H_{20}ClNO_3$) C, H, N.

***trans*-6,9-Dimethoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (31).** A solution of 1.0 g (0.00336 mol) of **30** in 50 mL of 95% EtOH, 50 mL of H_2O, and 1 mL of concentrated HCl was hydrogenated over 0.5 g of 5% Pd/C at an initial pressure of 45 psig for 48 h. The reduction mixture was filtered, and the filtrate was evaporated under reduced pressure to give a fine white powder. Trituration of this in cold 2-PrOH gave 0.7 g (83%) of a white solid, mp 279–282 °C. Anal. ($C_{15}H_{22}ClNO_2$) C, H, N.

***trans*-6,9-Dimethoxy-1-benzyl-1,2,3,4,4a,5,10,10a-octahydro[*g*]quinoline Hydrochloride (32).** To 0.7 g (0.0028 mol) of **31** and 0.6 g (0.0059 mol) of Et_3N in 20 mL of benzene was added dropwise 0.8 g (0.057 mol) of benzoyl chloride, while the temperature was maintained below 20 °C. Stirring was continued for an additional 30 min, while the reaction mixture was allowed to come to room temperature. The reaction mixture was washed with H_2O, 10% HCl, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was evaporated under reduced pressure to give the crude *N*-benzoyl derivative. This material in 20 mL of anhydrous benzene was treated with 10 mL (0.035 mol) of 3.4 M sodium bis(2-methoxyethoxy)aluminum hydride in benzene. The resulting mixture was heated under reflux for 6 h. The reaction mixture was cooled, and excess hydride reagent was destroyed by addition of 5 mL of H_2O. Excess 50% KOH was added to dissolve Al salts. The organic layer was washed with H_2O, dried ($MgSO_4$), and filtered. The filtrate was evaporated under reduced pressure to leave an oil. This was treated with ethereal HCl to give a solid, which was recrystallized from 2-PrOH–Et_2O to give 0.7 g (76%) of a white powder, mp 252–254 °C dec: NMR (free base in $CDCl_3$) δ 3.70 (AB q, J = 12 Hz, υ = 65 Hz, 2 H, Ar CH_2). Anal. ($C_{22}H_{28}ClNO_2$) C, H, N.

***trans*-6,9-Dimethoxy-1-*n*-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hydrochloride (13).** Following a procedure of Marchini et al.,[23] 0.12 g (0.0032 mol) of $NaBH_4$ was added in small portions to 0.85 g (0.0115 mol) of propionic acid in 20 mL of benzene, while the temperature was maintained below 25 °C. The reaction mixture was stirred at room temperature for 4 h, then 0.15 g (0.00061 mol) of the free base of **31** in 10 mL of benzene was added, and the resulting mixture was heated overnight under reflux. The cooled solution was quenched with 2 N NaOH, and then it was extracted with CH_2Cl_2. The extract was washed with H_2O, dried ($MgSO_4$), and filtered, and the filtrate was evaporated under reduced pressure. The residual oil was treated with ethereal HCl to give a solid, which was recrystallized from Me_2CO to give 0.12 g (70%) of a white powder, mp 215–217 °C dec. Anal. ($C_{18}H_{28}ClNO_2$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(2,5-dimethoxyphenyl)acetamide (33).** 2,5-Dimethoxyphenylacetic acid (5.0 g, 0.0255 mol) was stirred in excess freshly distilled $SOCl_2$ at reflux temperature for 2 h. Excess $SOCl_2$ was azeotroped with several portions of anhydrous benzene. The cooled residual acid chloride in a small amount of benzene was added dropwise with stirring to 7.7 g (0.0765 mol) of di-*n*-propylamine in 150 mL of anhydrous benzene, while the mixture was cooled in an ice bath. The resulting mixture was stirred overnight at room temperature and then 200 mL of H_2O was added. The aqueous layer was extracted with two 100-mL portions of Et_2O. The pooled organic phases were washed with saturated $NaHCO_3$ and saturated NaCl and dried ($MgSO_4$). The extract was filtered, and the filtrate was evaporated under reduced pressure. The red oily residue was subjected to Kugelrohr distillation (155 °C (0.1 mm)) followed by flash chromatography of the distillate on silica gel and elution with Et_2O–hexane (1:2), to afford 5.1 g (72%) of a clear oil. Anal. ($C_{16}H_{25}NO_3$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(2,5-dimethoxyphenyl)ethylamine Hydrochloride (14).** Compound **33** (3 g, 0.011 mol) in 150 mL of anhydrous benzene was treated with 10 mL (0.034 mol) of 3.4

M sodium bis(2-methoxyethoxy)aluminium hydride in benzene. The resulting mixture was heated under reflux for 6 h. The reaction mixture was cooled, and excess hydride reagent was destroyed by addition of 10 mL of H_2O. Excess 50% KOH was added to dissolve Al salts. The organic layer was separated and was washed with two 50-mL portions of H_2O. The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was evaporated under reduced pressure to give 2.7 g (95%) of an oil. Treatment of this material with ethereal HCl afforded a white solid, which was recrystallized from 2-PrOH–Et_2O, mp 130–131 °C. Anal. ($C_{16}H_{28}ClNO_2$) C, H, N.

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Registry No. 12·HBr, 104465-15-8; 13·HCl, 104465-26-1; 14·HCl, 104465-29-4; 17, 37464-90-7; 19, 104465-10-3; 20, 104465-11-4; 21, 104465-12-5; 22, 79381-14-9; 22·HCl, 104465-13-6; 23, 79381-15-0; *trans*-24, 104465-16-9; *cis*-24, 83558-01-4; *cis*-24·HCl, 79381-05-8; 25·HCl, 104465-14-7; 26·HCl, 104465-17-0; 27, 104465-18-1; *cis*-28, 104465-19-2; *trans*-28, 104465-20-5; *cis*-29·HCl, 104465-21-6; *trans*-29·HCl, 104465-22-7; 30·HCl, 104465-23-8; 31, 104465-27-2; 31·HCl, 104465-24-9; 32·HCl, 104465-25-0; 33, 104465-28-3; $H_2C{=}CHCONH_2$, 79-06-1; $H_3CCH_2CO_2H$, 79-09-4; $NC(CH_2)_2CH(CO_2CH_2CH_3)_2$, 17216-62-5; 2,5-$(H_3CO)_2C_6H_3CH_2COCl$, 52711-92-9; 2,5-$(H_3CO)_2C_6H_3CH_2CO_2H$, 1758-25-4; $(H_3C(CH_2)_2)_2NH$, 142-84-7; pyrrolidine, 123-75-1.

Additions and Corrections

1984, Volume 27

Bruce E. Maryanoff,* Samuel O. Nortey, and Joseph F. Gardocki: Structure–Activity Studies on Antidepressant 2,2-Diarylethylamines.

Page 1068. In Table I, compound **25** is a maleate (not a fumarate) salt.

1985, Volume 28

A. J. Hopfinger: Computer-Assisted Drug Design.

Page 1133. In my Perspective article, the successful computer-aided design of a pyrroloisoquinoline antipsychotic was incorrectly credited. Dr. G. L. Olson and his colleagues at Hoffmann-La Roche Inc. are responsible for this success. The key reference to this work is as follows: Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Blount, J. F.; Todaro, L.; Berger, L.; Davidson, A. B.; Boff, E. *J. Med. Chem.* **1981**, *24*, 1026. The designed compound, piquindone (USAN), is now in phase II clinical trials as an antipsychotic.

Gregory Gallagher, Jr., Patricia G. Lavanchy, James W. Wilson, J. Paul Hieble, and Robert M. DeMarinis*: 4-[2-(Di-*n*-propylamino)ethyl]-2(3*H*)-indolone: A Prejunctional Dopamine Receptor Agonist.

Page 1533. The list of authors that reads: Gregory Gallagher, Jr.,† Patricia G. Lavanchy,† James W. Wilson,† J. Paul Hieble,‡ and Robert M. DeMarinis*† should be changed to: Gregory Gallagher, Jr.,† Patricia G. Lavanchy,† Charles A. Webster,§ James W. Wilson,† J. Paul Hieble,‡ and Robert M. DeMarinis*†. The footnote should be changed to read: †Department of Medicinal Chemistry. ‡Department of Pharmacology. §FMC Corporation, P.O. Box 8, Princeton, New Jersey 08540.

1986, Volume 29

Olga H. Hankovsky,* Kálmán Hideg, Ilona Bódi, and László Frank: New Antiarrhythmic Agents. 2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamides and 2,2,5,5-Tetramethylpyrrolidine-3-carboxamides.

Page 1151. The registry number for **7d**·2HCl should be 104545-48-4.

Gordon H. Jones, Michael C. Venuti,* John M. Young, D. V. Krishna Murthy, Brad E. Loe, Richard A. Simpson, Andrew H. Berks, Doreen A. Spires, Patrick J. Maloney, Myriam Kruseman, Sussan Rouhafza, Karen C. Kappas, Colin C. Beard, Stefan H. Unger, and Paul S. Cheung: Topical Nonsteroidal Antipsoriatic Agents. 1. 1,2,3,4-Tetraoxygenated Naphthalene Derivatives.

Page 1506. In Scheme II, reagent key for entries c and d should be corrected to read: "c, NaOCl/aqueous THF; d, aqueous $HClO_4$;".

Book Reviews

Advances in Chromatography. Volume 25. Edited by J. Calvin Giddings, Eli Grushka, Jack Cazes, and Phyllis R. Brown. Marcel Dekker, New York. 1986. 416 pp, bound, illustrated. ISBN 0-8247-7546-5. $69.75 (U.S., Canada); $83.50 (all other countries).

Volume 25 of *Advances in Chromatography* identifies the solute physicochemical parameters either that may be readily obtained or estimated from chromatographic retention data or that can be used in predictive models, examines mobile-phase optimization in reversed-phase liquid chromatography (RPLC) by an iterative regression design, and considers solvent elimination techniques for high-performance liquid chromatography/Fourier transform spectrometer (HPLC/FT-IR).

It also reviews investigations of selectivity in RPLC of polycyclic aromatic hydrocarbons and discusses LC analysis of oxo acids of phosphorus, HPLC analysis of oxypurines, LC of carbohydrates, and HPLC of glycosphingolipids and phospholipids.

The chapters are authored by leading authorities, and each chapter features a bibliography that serves as an invaluable guide to the relevant literature.

Researchers who need to use separation techniques effectively—especially analytical, organic, clinical, and physical chemists—will find this volume most useful.

Staff