Monomethyl Ether Derivatives of 7,8-Dihydroxy- and 8,9-Dihydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines as Possible Products of Metabolism by Catechol-*O*-methyltransferase

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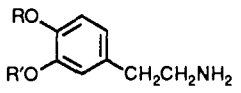
In order to facilitate identification of possible metabolites arising from in vitro action of catechol-*O*-methyltransferase upon 7,8-dihydroxy- and 8,9-dihydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (**11**, **12**), all four possible monomethyl ether derivatives have been synthesized. Incubation of **11** and **12** with the enzyme revealed that the 8,9-dihydroxy positional isomer **12** (which contains the dopamine moiety held in the β conformation) but not the 7,8-dihydroxy isomer **11** (which holds the dopamine moiety in the α conformation) was a substrate for the enzyme. The sole detectable product of **12** was 8-hydroxy-9-methoxy derivative **15** in which the "meta" hydroxy group of the dopamine moiety is etherified.

In 1960, Daly, Axelrod, and Witkop[1] reported that enzymatic O-methylation of dopamine results in a mixture of the "meta" (**1**) and the "para" (**2**) isomeric monomethyl



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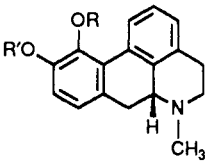
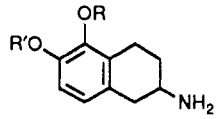
2: R = CH_3, R′ = H



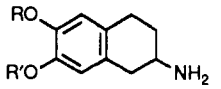
3: R = H, R′ = CH_3
4: R = CH_3, R′ = H

ethers in ratios of 5.7:1 to 9:1. Kuehl et al.[2] incubated dopamine with catechol-*O*-methyltransferase (COMT) isolated from rat liver and brain and obtained meta/para ratios of 1:4. McKenzie and White[3] found that pretreatment of rats with pyrogallol (a COMT inhibitor) caused a marked potentiation of behavioral effects of apomorphine. Cannon et al.[4] showed that O-methylation of apomorphine using rat liver COMT afforded two products, apocodeine (**3**) and isoapocodeine (**4**). These metabolites were identified by comparison with authentic samples and, although the ratios of apocodeine/isoapocodeine formed were affected by the pH of the medium, this study was the first to demonstrate a large preference for para-O-methylation (apocodeine) by COMT in vitro.

Horn and co-workers[5-7] showed that there were substantial differences in brain concentrations of 5,6-dihydroxy-2-aminotetralin (A-5,6-DTN, **5**) and of 6,7-dihydroxy-2-aminotetralin (A-6,7-DTN, **6**) after administration of their respective *O,O′*-dibenzoyl prodrugs. Brain concentrations of A-5,6-DTN were 5–7-fold higher than those of the 6,7-isomer. These workers speculated that a difference in metabolic fate of these two OH group positional isomers might account for the striking differences in brain concentrations, and they further suggested that attack by COMT might be a metabolic route for dihydroxy-2-aminotetralin compounds. It may be speculated that the 5,6-dihydroxytetralin substitution pattern of A-5,6-DTN (α conformer[10]) is a considerably poorer substrate for COMT than is the 6,7-dihydroxytetralin substitution pattern of A-6,7-DTN (β conformer[10]). The Horn group[8,9] isolated 2-amino-6-hydroxy-7-methoxytetralin (**7**) from rat brain following intraperitoneal injection of *O,O′*-dibenzoyl-A-6,7-DTN. When *O,O′*-dibenzoyl-A-6,7-DTN was administered subsequent to a dose of tropolone (a COMT inhibitor), concentrations of A-6,7-DTN in several regions of rat brain were virtually identical with those of A-5,6-DTN with respect to regional distribution and to the absolute amount of compound, after the same dose of A-5,6-DTN. Rollema et al.[7] prepared in vitro incubations of A-6,7-DTN with crude rat liver COMT. In contrast to the in vivo results, two products were detected, in approximately equal amounts. One of these was identified as 6-hydroxy-7-methoxy-2-aminotetralin (**7**) by comparison with an authentic sample. Mass spectral data suggested that the second product was the other monomethyl ether, 6-methoxy-7-hydroxy-2-aminotetralin (**8**). When A-5,6-DTN was incubated with COMT, only a small amount of product(s) was formed which were assumed to be monomethyl ether derivatives (**9**, **10**) of A-5,6-DTN.



5: R = R′ = H
9: R = H, R′ = CH_3
10: R = CH_3, R′ = H



6: R = R′ = H
7: R = H, R′ = CH_3
8: R = CH_3, R′ = H

Kinetic studies using purified porcine liver COMT indicated that A-6,7-DTN is a far better substrate for the enzyme than is A-5,6-DTN. This same tendency was manifested by the *N,N*-di-*n*-propyl congeners of A-5,6- and 6,7-DTN.[11]

trans-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines **11** and **12** represent rigid molecules in which the α and β conformations of dopamine found in 2-aminotetralin systems are maintained by the high degree of rigidity of

† Department of Pharmacology.

(1) Daly, J. W.; Axelrod, J.; Witkop, B. *J. Biol. Chem.* **1960**, *235*, 1155.
(2) Kuehl, F. A.; Hichens, M.; Ormond, R. E.; Meisinger, M. A. P.; Gale, P. H.; Cirillo, V. J.; Brink, N. G. *Nature* **1964**, *203*, 154.
(3) McKenzie, G. M.; White, H. L. *Biochem. Pharmacol.* **1973**, *22*, 2329.
(4) Cannon, J. G.; Smith, R. V.; Modiri, A.; Sood, S. P.; Borgman, R. J.; Aleem, M. A.; Long, J. P. *J. Med. Chem.* **1972**, *15*, 273.
(5) Horn, A. S.; deKaste, D.; Dijkstra, D.; Rollema, H.; Feenstra, M. G. P.; Westerink, B. H. C.; Grol, C. J.; Westerbrink, A. *Nature* **1978**, *276*, 405.
(6) Westerink, B. H. C.; Dijkstra, D.; Feenstra, M. G. P.; Grol, C. J.; Horn, A. S.; Rollema, H.; Wirix, E. *Eur. J. Pharmacol.* **1980**, *61*, 7.
(7) Rollema, H.; Westerink, B. H. C.; Mulder, T. B. A.; Dijkstra, D.; Feenstra, M. G. P.; Horn, A. S. *Eur. J. Pharmacol.* **1980**, *64*, 313.
(8) Horn, A. S.; Dijkstra, D.; Feenstra, M. G. P.; Grol, C. J.; Westerink, B. H. C. *Eur. J. Med. Chem.* **1980**, *15*, 387.
(9) Horn, A. S.; Dijkstra, D.; Mulder, T. B. A.; Rollema, H.; Westerink, B. H. C. *Eur. J. Med. Chem.* **1981**, *16*, 469.
(10) Cannon, J. G. *Adv. Neurol.* **1975**, *9*, 177.
(11) Youde, I. R.; Raxworthy, M. J.; Gulliver, P. A.; Dijkstra, D.; Horn, A. S. *J. Pharm. Pharmacol.* **1984**, *36*, 309.

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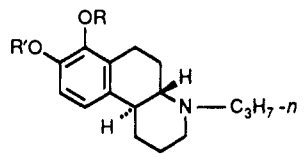
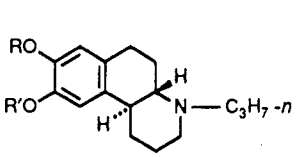


11: R = R′ = H
13: R = H, R′ = CH_3
14: R = CH_3, R′ = H



12: R = R′ = H
15: R = H, R′ = CH_3
16: R = CH_3, R′ = H

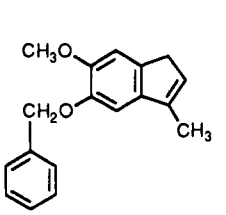
the ring. 7,8-Dihydroxy isomer **11** (containing a dopamine α conformation) is a central dopaminergic agonist of unusual potency[12,13] in mouse models for stereotypy, climbing, and circling induction. In contrast, 8,9-hydroxy isomer **12** (containing a dopamine β conformation) was inactive in these assays for central dopaminergic activity, in doses up to 800 times the threshold dose required for **11**. Despite its central nervous system (CNS) inactivity, **12** demonstrated marked dopamine-like inhibitor activity on the peripheral cardioaccelerator nerve of the cat.

Costall et al.[14] found that pyrogallol pretreatment (in a dose that reduced COMT activity by 34–38%) did not modify the motor inhibitory actions of A-5,6-DTN (**5**) but that this pretreatment potentiated the effects of the β conformer A-6,7-DTN (**6**) 2–7-fold. However, in experiments using *trans*-octahydrobenzo[f]quinolines **11** and **12**, while there was demonstrated an increase in motor inhibitory effects of the β rotamer after pyrogallol pretreatment, the differences were not always significant and they were comparable to magnitudes of shifts in the dose–response curves for the α rotamer. Higher doses of pyrogallol (sufficient to cause complete inhibition of COMT) were not used in this study, due to the marked sedative actions produced by this drug. Before any conclusions can be drawn from these studies, it seems essential to determine whether the 7,8- and 8,9-dihydroxybenzoquinolines (**11** and **12**) are substrates for COMT.

The goal of the present study was to synthesize and then to identify possible in vitro products arising from the interaction of these two isomeric catechols (**11** and **12**) with COMT. Certain of the earlier studies cited above did not involve use of authentic samples of all possible COMT-derived products, and the chemical nature of certain of the metabolic products was somewhat speculative. The unequivocal synthesis of all four possible monomethyl ether derivatives of octahydrobenzo[*f*]quinolines **13–16** was pursued in order to facilitate the identification of product(s) formed from the action of COMT in vitro and for use in projected future studies in vivo.

Chemistry. Preparation of the isomeric monomethyl ether derivatives (**15** and **16**) of 8,9-dihydroxybenzo[*f*]-quinolines is outlined in Scheme I. Attempts to purify 5-methoxy-6-(benzoyloxy)-1-methyleneindan (**18b**) by flash column chromatography resulted in isolation of a product **24** in which the double bond had migrated into the ring.

This bond migration did not occur when the 1-methyleneindanes were purified by recrystallization. The triethylsilane/trifluoroacetic acid reagent used to reduce the 1a,4a-double bond of 8-methoxy-9-(benzyloxy)-1,4,5,6-tetrahydrobenzo[*f*]quinoline (**20b**) also reductively debenzylated the masked phenolic group at position 9.



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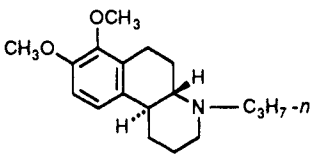

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Identical reaction conditions used with the isomeric ether system **20a** permitted reduction of the carbon–carbon double bond without affecting the position 8 benzyl ether group. It was found that the subsequent steps in Scheme I could be performed on **21c** without the necessity of reprotecting the phenolic group at position 9.

Preparation of the 7-methoxy-8-hydroxy target compound **14** is shown in Scheme II. Attempts to effect Birch reduction of 2,5-dimethoxy-6-(benzyloxy)naphthalene (**28**) to 5-methoxy-6-(benzyloxy)-2-tetralone resulted in concomitant cleavage of the benzyl ether group. Accordingly, the benzyl protecting moiety was replaced by cyclopropylmethyl, as was originally suggested by Nagata et al.,[16] and this blocking group was resistant to reduction conditions leading to 2-tetralone derivative **31**. However, the triethylsilane/trifluoroacetic acid reagent utilized for stereoselective reduction of the 1a,4a-double bond in **32** effected cleavage of the cyclopropylmethyl ether group (to give an 80% isolated yield of the free phenolic product **34**) when the reaction time was 24 h. When reaction time was decreased to 10 h, a 66% yield of the cyclopropylmethyl ether product **33** was isolated; however, a 26% yield of the cleavage product **34** was also obtained. As shown in Scheme II, some parallel reactions were performed on cyclopropylmethyl ether **33** and free phenolic analogue **34**. Cleavage of the cyclopropylmethyl ether group in compound **37** was not attempted.

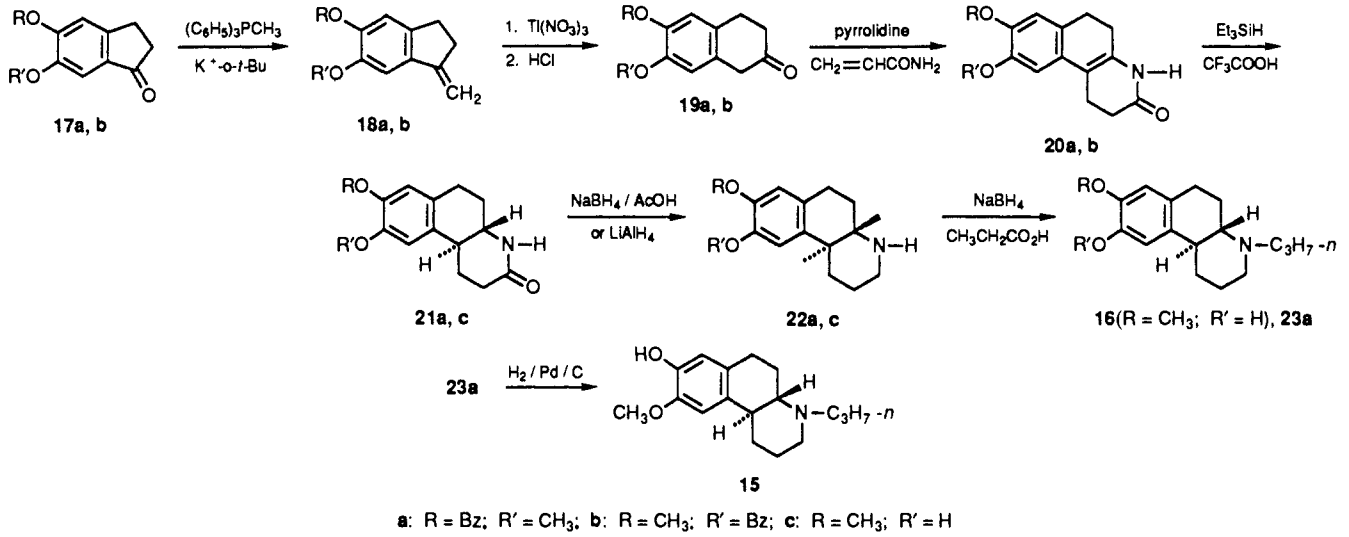
Rollema and Grol[15] found that trimethylsilyl iodide effected selective cleavage of the position 5 methyl ether group in certain 2-amino-5,6-dimethoxytetralins. In the present work this reagent permitted a similar selective ether cleavage (at position 7) in *trans*-7,8-dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**25**), whose phenol ether substitution pattern is analogous to that in 2-amino-5,6-dimethoxytetralin. The structure of the product of this reaction (7-hydroxy-8-methoxy, **13**) was established by comparison of spectral and chromatographic data for it with analogous data for the ether group isomer, 7-methoxy-8-hydroxy analogue **14**, prepared by an unequivocal route.

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

High-Performance Liquid Chromatography and Enzyme Experiments. The identification and quantitative determination of O-methylated metabolites arising from the action of COMT upon catecholamines by high-performance liquid chromatography has been described by Rollema et al.[7,15] Initial chromatography of the catechol standards **11** and **12** and the metabolite candidate standards **13–16** were performed on a Nucleosil column as described by Rollema and co-workers.[7,15] However, the composition of the mobile phase was changed in the present studies. The retention times are shown in Table I. Rollema and co-workers[7,15] utilized crude rat liver preparations as the source of COMT. In the present study,

(12) 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.
(13) Cannon, J. G.; Lee, T.; Goldman, H. D.; Long, J. P.; Flynn, J. R.; Verimer, T.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1980**, *23*, 1.
(14) Costall, R.; Lim, S. K.; Naylor, R. J.; Cannon, J. G. *J. Pharm. Pharmacol.* **1982**, *34*, 246.
(15) Rollema, H.; Grol, C. J. *Pharm. Weekbl., Sci. Ed.* **1983**, *5*, 159.
(16) Nagata, W.; Okada, K.; Itazaki, H.; Uyeo, S. *Chem. Pharm. Bull.* **1975**, *23*, 2878.

Scheme I. Preparation of Isomeric Monomethyl Ether Derivatives (15 and 16) of *trans*-8,9-Dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline



Scheme II. Preparation of *trans*-8-Hydroxy-7-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (14)

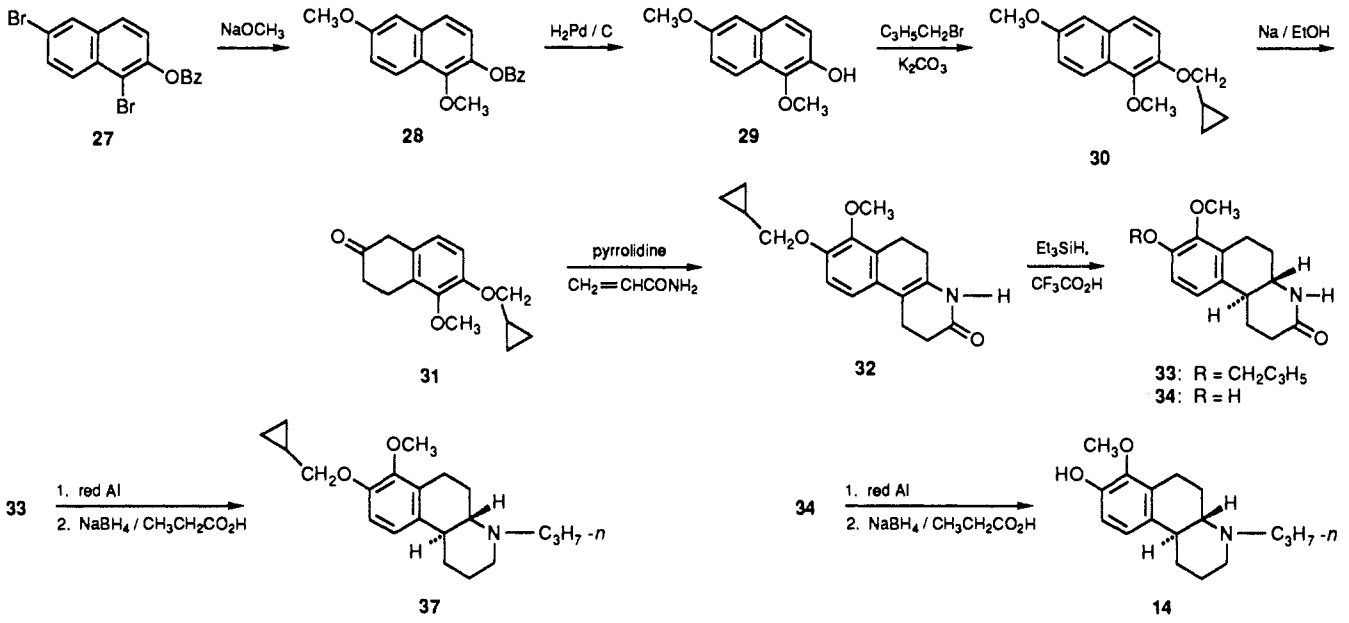


Table I. HPLC Retention Times for Catechol- and *O*-Methylbenzo[*f*]quinoline Derivatives

no.	11	13	14	12	15	16
t_R, min	5.20	10.7	7.25	4.96	7.23	5.90

commercially available partially purified porcine COMT was used. Sufficient COMT was used in each incubation to produce 10 μmol of product/h. Comparison of the chromatograms and retention times on the incubation sample of **12** with those of COMT and the standard monomethyl ethers **15** and **16** showed that the only *O*-monomethyl metabolite that could be detected was 8-hydroxy-9-methoxybenzo[*f*]quinoline derivative **15**. To establish that the peak observed in the incubation sample of **12** (which corresponded to metabolite **15**) was not an artifact of the incubation preparation, the incubation sample was also coinjected with standard **15**. No additional peak was observed. These results with **12** (which bears the dopamine moiety in the β conformation) are consistent with those of Rollema et al.,[7] which demonstrated that A-6,7-DTN (**6**) (which also contains the dopamine moiety in the β conformation) was metabolically inactivated in vivo by formation of the methyl ether derivative at the 7-OH position ("meta"). These workers also showed that in vitro studies with A-6,7-DTN and COMT afforded both the "meta" (7-methoxy) and the "para" (6-methoxy) derivatives. However, in the present in vitro studies, none of the "para" methoxy metabolite **16** was detected.

7,8-Dihydroxybenzo[*f*]quinoline derivative **11** (in which the dopamine moiety is in the α conformation) was a poor substrate for COMT under incubation conditions identical with those used for **12**. Only a trace amount of a single metabolic product could be detected. Comparison of retention times for standards **13** and **14** showed that this trace metabolite was 8-hydroxy-7-methoxybenzo[*f*]-quinoline **14**. These findings parallel those of Rollema et al.,[7] whose studies on A-5,6-DTN (**5**; which also bears the dopamine moiety in the α conformation) showed that it is a very poor substrate for COMT either in vivo or in vitro. However, because multiple experiments varying the concentration of **11** were not attempted in the present study, no definitive conclusions in regard to its susceptibility to O-methylation by COMT can be drawn.

The preliminary enzyme experiments suggest that *trans*-8,9-dihydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**12**) is an excellent substrate for COMT, and conversely, the 7,8-dihydroxy positional isomer **11** is an extremely poor substrate for the enzyme. Thus the lack of CNS dopaminergic activity of **12**, as opposed to the substantial CNS dopaminergic effects elicited by its hydroxyl group positional isomer **11**, may be due to its preferential metabolism and inactivation by COMT. If indeed the concept of metabolic differences as a determinant of biological activity in comparison of α and β conformers of dopamine congeners is generally valid, it will be necessary to reassess many structure–activity correlations which have been made (based upon in vivo data) with respect to the significance of conformational differences and absolute configurational differences of agonists in their interactions with dopaminergic receptor topography.

Pharmacology. The COMT metabolite 8-hydroxy-9-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline (**15**) was evaluated for its effect in the cat cardioaccelerator nerve assay, an index of peripheral dopaminergic activity. Compound **15** showed 50% inhibition of nerve stimulation at a dose of 300 μg/kg (0.96 μmol/kg). This effect was antagonized by haloperidol (100 μg/kg). In contrast, the catechol congener of **15**, 8,9-dihydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**12**), produces 50% inhibition of cardioaccelerator nerve stimulation at a dose of 0.0013 μmol/kg.[13] Thus, monomethyl ether metabolite **15** is exponentially less potent than the free catechol system **12**.

Experimental Section

Pharmacology. Methods. Cat Right Cardioaccelerator Nerve Preparation. Compound **15** was evaluated in three cats. Cats of either sex, 2.5–5 kg, were anesthetized by intraperitoneal injection of pentobarbital sodium (30 mg/kg). Respiration was supported, and blood pressure and heart rate were monitored from the femoral artery. All animals were pretreated with atropine sulfate (200 μg/kg, iv) and vagotomized. The right postganglionic cardioaccelerator nerve was exposed and placed on bipolar Pt electrodes: 15-s stimulations were used and the parameters were 2 Hz, pulse duration of 3–5 ms, and maximal voltage of 15–20 V.

Chemistry. Melting points were determined in open glass capillaries with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Infrared spectra were recorded using a Beckman IR4240 spectrometer or a Nicolet 5DBX FT IR spectrometer. NMR spectra were obtained using a Varian Associates EM360A spectrometer or a Bruker/IBM NR/80 FTNMR spectrometer. Chemical shifts are reported in parts per million (δ) relative to Me_4Si internal standard. Mass spectra were obtained with a Ribermag R10-10C spectrometer. Radial thin-layer chromatography was performed on a Harrison Research Chromatotron apparatus, Model 7924T, using E. M. Science gipshaltig kieselgel $60PF_{254}$ silica as the stationary phase on the rotors. Elemental analyses were obtained from Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values. Benzene and dioxane were dried over Na. *N*,*N*-Dimethylformamide was predried over KOH and distilled from CaO. MeOH was distilled from Mg/I_2 and was stored over 3A molecular sieves. Piperidine was distilled from KOH. Pyridine was predried over KOH and was distilled from BaO. Pyrrolidine was distilled. Absolute EtOH was stored over 3A molecular sieves prior to use. For enzyme incubation assay, alumina (Al_2O_3, Type E, neutral, Merck), *S*-adenosyl-L-methionine hydriodide (92%, Sigma), catechol-*O*-methyltransferase (Sigma; from porcine liver; 1480 units/mg of protein), $MgCl_2$ (hexahydrate, Mallinckrodt), Nucleosil 5 C18 (Altech Applied Science), and phosphate buffer (Na_2HPO_4 anhydrous, adjusted to pH 7.6 with H_3PO_4, enzyme grade, Fisher Biotech) were used. MeOH used for the HPLC analyses was Fisher HPLC grade, and the mobile phase of MeOH, H_2O, and formic acid (30:70:1) was degassed prior to use.

5-Hydroxy-6-methoxy-1-indanone (26). To polyphosphoric acid (100 g, heated to 70 °C) in a 1000-mL beaker was added 28 g (0.14 mol) of 3-(3-hydroxy-4-methoxyphenyl)propionic acid[17] in small portions over 12 min with efficient stirring. After the addition was complete, stirring was continued for 3 min and the reaction was quenched with 500 mL of ice/H_2O. The aqueous solution was extracted three times with $CHCl_3$ and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford 11 g of a beige solid. This was purified by flash column chromatography (SiO_2, EtOAc) and was recrystallized from Et_2O to give 8 g (30%) of product, mp 174–175 °C. Anal. ($C_{10}H_{10}O_3$) C, H.

5-(Benzyloxy)-6-methoxy-1-indanone (17a). Benzyl chloride (50 g, 0.40 mol), 37 g (0.21 mol) of **26**, and 55 g (0.40 mol) of K_2CO_3 were stirred and heated under reflux in 500 mL of absolute EtOH for 5 h. The hot reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was taken up in $CHCl_3$ and was washed with saturated aqueous $NaHCO_3$ and then with H_2O. Evaporation of the $CHCl_3$ under reduced pressure afforded 53 g (94%) of an orange solid which was recrystallized from Et_2O/EtOAc to give 53 g (94%) of pale yellow crystals, mp 140–142 °C. Anal. ($C_{17}H_{16}O_3$) C, H.

5-(Benzyloxy)-6-methoxy-1-methyleneindan (18a). Methyltriphenylphosphonium bromide (92 g, 0.26 mol), 30 g (0.26 mol) of K-O-*t*-Bu, and 36 g (0.13 mol) of **17a** in 250 mL of Et_2O were stirred under N_2 for 45 min at 25 °C. The reaction mixture was filtered through Celite, and the filtrate was washed three times with H_2O and was then concentrated under reduced pressure to afford a yellow solid. This was triturated with cold MeOH to dissolve the triphenylphosphine oxide. Collection of the MeOH-insoluble material on a filter afforded a white solid uncontaminated by triphenylphosphine oxide (TLC, SiO_2, $CHCl_3$). This solid was recrystallized from MeOH to give 22.5 g (65%) of white crystals, mp 83–84 °C. Anal. ($C_{18}H_{18}O_2$) C, H (Karl Fischer H_2O 0.25%).

1,2,3,4-Tetrahydro-6-(benzyloxy)-7-methoxy-2(1*H*)-naphthalenone (19a). Following a procedure of Taylor et al.,[18] compound **18a** (9 g, 0.034 mol) was suspended in 200 mL of MeOH and then a freshly prepared solution of 15 g (0.034 mol) of $Tl(NO_3)_3$ in 50 mL of MeOH was added in one portion. The reaction mixture was stirred for 1 min and then it was diluted with 100 mL of $CHCl_3$. The resulting voluminous white precipitate was removed by filtration. The filtrate was washed with saturated aqueous $NaHCO_3$ and then with H_2O and was concentrated under reduced pressure. The viscous, oily residue was stirred in 100 mL of 10% HCl/MeOH for 20 h, and then it was diluted with H_2O and was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ afforded a viscous brown oil which was dissolved in EtOH and treated with $NaHSO_3$ according to a method of Cannon et al.[19] The bisulfite addition product was washed with copious amounts of Et_2O and EtOH. Treatment of this product with saturated Na_2CO_3 followed by $CHCl_3$ extraction and evaporation of the volatiles from the extract under reduced pressure afforded a beige solid. Recrystallization of this from cyclohexane gave 4 g (42%) of white needles, mp 53–55 °C. Anal. ($C_{18}H_{18}O_3$) C, H. (Karl Fischer H_2O 0.031%).

8-(Benzyloxy)-9-methoxy-1,4,5,6-tetrahydrobenzo[*f*]-quinolin-3-(2*H*)-one (20a). A solution of 20 g (0.071 mol) of **19a** and 0.1 g of *p*-toluenesulfonic acid in 200 mL of benzene was heated under reflux, and 7.6 g (0.11 mol) of freshly distilled pyrrolidine was added dropwise through a syringe. The reaction mixture was heated under reflux in a Dean–Stark apparatus for 3 h. Volatiles were removed by distillation under N_2. Acrylamide (18 g, 0.25 mol) was added in one portion and the mixture was stirred and heated at 80 °C for 3 h then at 130 °C for 30 min. The reaction mixture was quenched with 50 mL of H_2O and the resulting mixture was stirred at ambient temperature for 10 h. The resulting solid was collected on a filter and was recrystallized from Me_2CO to afford 12 g (50%) of a white powder, mp 176–178

(17) Rosazza, J. P.; Bobbitt, J. M.; Schwarting, A. E. *J. Org. Chem.* **1972**, *35*, 2564.
(18) Taylor, E. C.; Chiang, C.; McKillop, A. *Tetrahedron Lett.* **1977**, 1827.
(19) Cannon, J. G.; O'Donnell, J. P.; Rosazza, J. P.; Hoppin, C. R. *J. Med. Chem.* **1974**, *17*, 565.

°C. Anal. ($C_{21}H_{21}NO_3$) C, H, N (Karl Fischer H_2O 0.71%).

***trans*-8-(Benzyloxy)-9-methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (21a).** Triethylsilane (10.4 g, 0.09 mol) was added to a solution of 3 g (0.09 mol) of **20a** in 10 mL of CH_2Cl_2 at room temperature. The solution was cooled to 10 °C and 20 mL of trifluoroacetic acid was added dropwise from a syringe over 10 min. After the addition was complete, the solution was warmed to room temperature and was stirred for 20 h. Evaporation of the volatiles left a solid residue which was dissolved in 50 mL of $CHCl_3$ and washed sequentially with aqueous saturated $NaHCO_3$ and H_2O and then was dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure afforded a white solid which was recrystallized from Me_2CO to yield 1 g (33%) of product, mp 213–215 °C. Anal. ($C_{21}H_{23}NO_3$) C, H, N (Karl Fischer H_2O 0.19%).

***trans*-8-(Benzyloxy)-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (22a).** Following a procedure of Umino et al.,[20] 0.54 g (0.009 mol) of AcOH was added dropwise from a syringe to a cooled (10 °C), stirred suspension of 0.03 g (0.0009 mol) of **21a** and 0.34 g (0.009 mol) of $NaBH_4$ in 20 mL of dioxane. After the addition was complete, the reaction mixture was stirred and heated under reflux for 7 h. The cooled reaction mixture was quenched with 20 mL of H_2O and the resulting mixture was extracted twice with $CHCl_3$. The combined extracts were washed with H_2O, dried ($MgSO_4$) and concentrated under reduced pressure to afford a viscous yellow oil. This was dissolved in EtOH and was treated with ethereal HCl to give a white solid which was recrystallized from EtOH/Et_2O to yield 0.15 g (46%) of white crystals, mp 264–265 °C. IR (neat, free base) 2840, 2900 cm^{-1} (strong, Bohlmann bands). Anal. ($C_{21}H_{26}ClNO_2$) C, H, N.

***trans*-8-(Benzyloxy)-9-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (23a).** Following a procedure of Cannon et al.,[12] $NaBH_4$ (0.5 g, 0.013 mol) was added in small portions to 3.3 g (0.045 mol) of propionic acid in 30 mL of dry benzene, while the temperature was maintained below 15 °C. When the evolution of H_2 had ceased, 0.8 g (0.003 mol) of **22a** was added in one portion, and the resulting mixture was heated under reflux for 24 h. The cooled reaction mixture was treated with 2 N NaOH, the organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was dissolved in EtOH and was treated with ethereal HCl. The resulting white solid was recrystallized from Et_2O/MeOH to afford 0.7 g (70%) of white crystals, mp 195–197 °C. IR ($CHCl_3$) 2970, 2940 cm^{-1} (strong, Bohlmann bands). Anal. ($C_{24}H_{24}ClNO_2$) C, H, N.

***trans*-8-Hydroxy-9-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (15).** A solution of 0.3 g (0.75 mmol) of **23a** in 100 mL of absolute EtOH was hydrogenated over 0.2 g of 5% Pd/C at ambient temperature for 24 h at an initial pressure of 58 psig. The reduction mixture was filtered through Celite and was evaporated under reduced pressure to afford a white solid. Recrystallization from Et_2O/MeOH afforded 0.17 g (80%) of white crystals, mp 235–238 °C. Anal. ($C_{17}H_{26}ClNO_2$) C, H, N (Karl Fischer H_2O 0.31%).

6-(Benzyloxy)-5-methoxy-1-methyleneindan (18b). Methyltriphenylphosphonium bromide (69 g, 0.19 mol), 21 g (0.19 mol) of K-O-*t*-Bu, and 26 g (0.097 mol) of 6-(benzyloxy)-5-methoxy-1-indanone[21] were stirred in 750 mL of anhydrous Et_2O at 25 °C for 1 h. The reaction mixture was quenched by slow dropwise addition of 100 mL of H_2O. The ethereal layer was separated, washed twice with H_2O, and was evaporated under reduced pressure to afford a brown sludge. This material was triturated in cold MeOH and the resulting solid was collected on a filter. Recrystallization from MeOH afforded 16 g (63%) of yellow crystals, mp 112–114 °C; IR ($CHCl_3$) 1635 cm^{-1} (exo C=); ^1H NMR ($CDCl_3$) δ 2.85 (s, 4 H, CH_2), 3.85 (s, 3 H, OCH_3), 4.85 (s, 1 H, C=CH_2), 5.15 (d, 3 H, C=CH_2, OCH_2), 6.75, 7.00 (s, 2 H, Ar*H*), 7.40 (m, 5 H, Ar*H*). Anal. ($C_{18}H_{18}O_2$) C, H.

6-(Benzyloxy)-5-methoxy-1-methylindene (24). Methyltriphenylphosphonium bromide (13.3 g, 0.037 mol), 5.4 g (0.048 mol) of K-O-*t*-Bu, and 5.0 g (0.018 mol) of 6-(benzyloxy)-7-methoxy-1-indanone[21] were stirred in 100 mL of anhydrous Et_2O at 25 °C for 1 h. The reaction mixture was filtered and the filtrate was washed twice with H_2O. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, $CHCl_3$). Recrystallization from MeOH afforded 2.4 g (50%) of a white solid: mp 105–107 °C; IR ($CHCl_3$) 1580 cm^{-1} (endocyclic C=C); ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H, CH_3), 3.36 (s, 2 H, CH_2), 4.03 (s, 3 H, OCH_3), 5.33 (s, 2 H, OCH_2), 6.20 (m, 1 H, C=C*H*), 7.03, 7.20 (s, 2 H, Ar*H*), 7.30–7.75 (m, 5 H, Ar*H*). Anal. ($C_{18}H_{18}O_2$) C, H (Karl Fischer H_2O 0.42%).

1,2,3,4-Tetrahydro-7-(benzyloxy)-6-methoxy-2(1*H*)-naphthalenone (19b). The procedure described for **19a** was followed, using 20 g (0.075 mol) of **18b** in 200 mL of MeOH and 33 g (0.075 mol) of $Tl(NO_3)_3$ in 50 mL of MeOH. Regeneration of the ketone with Na_2CO_3 afforded a white solid which was recrystallized from cyclohexane to give 4 g (20%) of a white powder, mp 44 °C. Anal. ($C_{18}H_{18}O_3$) C, H.

9-(Benzyloxy)-8-methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (20b). The procedure described for **20a** was followed, using 4 g (0.014 mol) of **19b**, 0.1 g of *p*-toluenesulfonic acid, 25 mL of benzene, 1.5 g (0.021 mol) of freshly distilled pyrrolidine, and 3.5 g (0.049 mol) of acrylamide. The crude product was purified with a Chromatotron apparatus (2 mm SiO_2, EtOAc) and was then recrystallized from Me_2CO to afford 1.3 g (37%) of white crystals, mp 208–210 °C. Anal. ($C_{21}H_{21}NO_3$) C, H, N.

***trans*-9-Hydroxy-8-methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (21c).** The procedure described for **21a** was followed, using 1.9 g (0.0165 mol) of triethylsilane, 1.1 g (0.0033 mol) of **20b**, 8 mL of trifluoroacetic acid, and 10 mL of CH_2Cl_2. The crude product was recrystallized from MeOH to afford 0.7 g (63%) of white crystals, mp 246–247 °C. Anal. ($C_{14}H_{17}NO_3$) C, H, N.

***trans*-9-Hydroxy-8-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (22c).** A mixture of 0.03 g (0.12 mmol) of **21c**, 3 mL (0.01 mol) of 3.4 M Red Al in toluene, and 15 mL of anhydrous benzene was heated at reflux temperature for 6 h. The cooled reaction mixture was quenched with 20 mL of H_2O and the organic layer was separated. The aqueous layer was extracted twice with $CHCl_3$. The pooled organic phases were concentrated under reduced pressure to afford a viscous orange oil which was dissolved in Et_2O/MeOH and treated with ethereal HCl. The resulting solid was recrystallized from Et_2O/MeOH to give 0.02 g (71%) of a white solid: mp 185–188 °C; IR (neat, free base) 2850, 2900 cm^{-1} (strong, Bohlmann bands). Anal. ($C_{14}H_{20}ClNO_2$) C, H, N (Karl Fischer H_2O 0.23%).

***trans*-9-Hydroxy-8-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (16).** To a stirred solution of 0.02 g (0.12 mmol) of the free amine of **22c** and 1 g (0.013 mol) of propionic acid in 25 mL of anhydrous benzene was added 0.4 g (0.01 mol) of $NaBH_4$ in one portion. The reaction mixture was stirred and heated at reflux temperature under N_2 for 12 h. The cooled reaction mixture was quenched with 15 mL of H_2O and was extracted twice with $CHCl_3$. The combined extracts were concentrated under reduced pressure to afford a viscous yellow oil which was dissolved in Et_2O/MeOH and treated with ethereal HCl. The resulting solid was recrystallized from Et_2O/MeOH to give 0.3 g (85%) of a white solid, mp 215–218 °C. Anal. ($C_{17}H_{26}ClNO_2$) C, H, N.

***trans*-8,9-Dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (12).** This was prepared by a method of Cannon et al.,[13] mp 280–282 °C (from Et_2O/MeOH) (lit.[13] mp 286–288 °C).

2-(Benzyloxy)-1,6-dibromonaphthalene (27). Benzyl chloride (8.3 g, 0.06 mol), 8.9 g (0.06 mol) of K_2CO_3, and 10 g (0.033 mol) of 1,6-dibromo-2-naphthol in 100 mL of absolute EtOH were stirred and heated under reflux for 15 h. The hot reaction mixture was filtered, and on cooling yellow crystals separated. These were recrystallized from EtOH to yield 9.5 g (75%) of product, mp 82–84 °C. Anal. ($C_{17}H_{12}Br_2O$) C, H.

2-(Benzyloxy)-1,6-dimethoxynaphthalene (28). Freshly cut Na (5 g, 0.2 g-atom) was added to 150 mL of anhydrous MeOH under N_2. When solution was complete, the solution was diluted with 150 mL of dry DMF, and 6.8 g (0.036 mol) of CuI and 14 g (0.036 mol) of **27** were added. The reaction mixture was diluted with an additional 150 mL of dry DMF and it was stirred and

(20) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, 763.
(21) Prasad, D.; Chaudhury, D. N. *J. Ind. Chem. Soc.* **1962**, *39*, 672.

heated at reflux temperature for 18 h. After cooling, the reaction mixture was filtered through Celite and the filtrate was diluted with 500 mL of H_2O and was extracted three times with $CHCl_3$. The combined extracts were washed three times with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to afford a viscous purple oil. This material was purified by flash chromatography (SiO_2, $CHCl_3$) and was recrystallized from 95% EtOH to give 6.5 g (62%) of a white powder, mp 48 °C. Anal. ($C_{19}H_{18}O_3$) C, H.

1,6-Dimethoxy-2-naphthol (29). A solution of 17.6 g (0.06 mol) of **28** in 250 mL of absolute EtOH was hydrogenated over 2 g of 10% Pd/C at ambient temperature for 24 h at an initial pressure of 60 psig. The reduction mixture was filtered through Celite, and evaporation of the filtrate under reduced pressure afforded a clear, dark orange oil. Purification of this by flash chromatography (SiO_2, $CHCl_3$) gave a beige solid which was used in the next reaction without further treatment.

2-(Cyclopropylmethoxy)-1,6-dimethoxynaphthalene (30). A mixture of 5.6 g (0.28 mol) of **29** and 4 g (0.03 mol) of K_2CO_3 in 50 mL of absolute EtOH was stirred and heated under reflux for 14 h. (Bromomethyl)cyclopropane (11.3 g, 0.084 mol) was added dropwise from a syringe and stirring and heating were continued for an additional 24 h. After cooling, the reaction mixture was diluted with 50 mL of H_2O and was extracted with three portions of $CHCl_3$. Evaporation of volatiles from the pooled extracts afforded a viscous brown oil. This was purified by flash chromatography (SiO_2, CH_2Cl_2) and was recrystallized from absolute EtOH to yield 4.5 g (62%) of white crystals, mp 40–41 °C. Anal. ($C_{16}H_{18}O_3$) C, H.

3,4-Dihydro-6-(cyclopropylmethoxy)-5-methoxy-2(1*H*)-naphthalenone (31). Na (3.7 g, 0.16 g-atom) was added in small pieces to a solution of 6.0 g (0.02 mol) of **30** in 70 mL of absolute EtOH heated at reflux temperature under N_2. Stirring and heating were continued until all the metal dissolved. The reaction mixture was cooled to 10 °C and 2 N HCl was added dropwise to pH 6 (pH paper). The reaction mixture was stirred at 10 °C for 25 min, then it was extracted twice with $CHCl_3$. The combined extracts were washed twice with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure to afford a viscous, orange oil. Distillation from a Kugelrohr appratus (152 °C, 0.25 mm) gave 2.94 g (60%) of a clear, colorless oil. Anal. ($C_{15}H_{18}O_3$) C, H.

8-(Cyclopropylmethoxy)-7-methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (32). A solution of 3 g (0.012 mol) of **31** and 0.5 g of *p*-toluenesulfonic acid in 50 mL of benzene was heated at reflux temperature under N_2 in a Dean–Stark apparatus. Pyrrolidine (1.3 g, 0.018 mol) was added dropwise and heating was continued for 3 h. Volatiles were removed by distillation, and when the residue in the flask had cooled to 50 °C, 1 g (0.014 mol) of acrylamide was added in one portion. The reaction mixture was stirred and heated at 80 °C for 3 h, then at 130 °C for 0.5 h. After cooling to 80 °C, the reaction was quenched with 80 mL of H_2O. The solid which separated was collected on a filter and was purified by flash column chromatography (SiO_2, EtOAc). Recrystallization from EtOAc afforded 5.5 g (30%) of white crystals, mp 203–205 °C. Anal. ($C_{18}H_{21}NO_3$) C, H, N.

***trans*-8-(Cyclopropylmethoxy)-7-methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (33).** A solution of 1 g (0.0033 mol) of **32** and 3.9 g (0.033 mol) of triethylsilane in 10 mL of CH_2Cl_2 was cooled to 10 °C and 3.8 mL of trifluoroacetic acid was added dropwise over 15 min. After the addition was complete, the reaction mixture was stirred at room temperature for 10 h. Evaporation of volatiles under reduced pressure afforded a brown oil which solidified on standing. Fractional recrystallization from MeOH afforded 0.4 g (26%) of *trans*-8-hydroxy-7-methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3-(2*H*)-one (**34**; vide infra) and 1.0 g (66%) of the desired product **33**, mp 195 °C. Anal. ($C_{18}H_{23}NO_3$) C, H, N.

***trans*-8-Hydroxy-7-methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (34).** A solution of 1 g (0.0033 mol) of **32** and 3.9 g (0.033 mol) of triethylsilane in 10 mL of CH_2Cl_2 was cooled to 10 °C and 3.8 mL of trifluoroacetic acid was added dropwise over 15 min. After the addition was complete, the reaction mixture was stirred at room temperature for 24 h. Evaporation of the volatiles under reduced pressure afforded a brown oil which was partitioned between Et_2O and saturated aqueous Na_2CO_3. The white precipitate which separated from the Et_2O was collected on a filter and was triturated in boiling MeOH to afford 0.8 g (80%) of **34**, mp 258–260 °C. Anal. ($C_{14}H_{17}NO_3$) C, H, N.

***trans*-8-Hydroxy-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (35).** A mixture of 0.5 g (0.002 mol) of **34** and 7 mL of 3.4 M Red Al in toluene (0.024 mol) was stirred and heated in 50 mL of dry benzene under N_2 at reflux temperature for 6 h. The reaction mixture was then quenched with 20 mL of H_2O and 0.25 g of NaOH. The organic layer was separated, washed with H_2O, and concentrated under reduced pressure to afford a viscous, yellow oil. This was dissolved in Et_2O and treated with excess ethereal HCl, and the resulting yellow solid was recrystallized from Et_2O/MeOH to give 0.4 g (75%) of white crystals: mp 300–302 °C; IR (KBr) 2808, 2934 cm^{-1} (strong, Bohlmann bands). Anal. ($C_{14}H_{21}ClNO_2$) C, H, N.

***trans*-8-(Cyclopropylmethoxy)-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (36).** A mixture of 0.5 g (0.0016 mol) of **33** and 5 mL of 3.4 M Red Al in toluene (0.017 mol) was treated as described for preparation of **35**. The HCl salt of the product was recrystallized from Et_2O/MeOH to give 0.4 g (78%) of a white powder: mp 255–257 °C; IR (KBr) 2762, 2890 cm^{-1} (strong, Bohlmann bands). Anal. ($C_{18}H_{25}NO_2$) C, H, N.

***trans*-8-(Cyclopropylmethoxy)-7-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (37).** A mixture of 0.2 g (0.7 mmol) of **36** and 1 g (0.013 mol) of propionic acid was stirred in 50 mL of benzene under N_2 at 25 °C, and 0.4 g (0.01 mol) of $NaBH_4$ was added in one portion. This mixture was stirred and heated at 55 °C for 12 h. After cooling, the reaction was quenched with 20 mL of H_2O and the organic layer was separated and concentrated under reduced pressure to afford a viscous brown oil. A solution of this in Et_2O/MeOH was treated with ethereal HCl, and the resulting tan solid was recrystallized from Et_2O/MeOH to give 0.19 g (75%) of white crystals: mp 215–218 °C. Anal. ($C_{21}H_{32}ClNO_2$) C, H, N.

***trans*-8-Hydroxy-7-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (14).** A mixture of 0.5 g (0.002 mol) of **35**, 5 mL of propionic acid, and 5 mL of dry benzene was stirred and heated at 55 °C under N_2. Powdered $NaBH_4$ (0.4 g, 0.01 mol) was added over 15 min and stirring and heating were continued for 12 h. After the solution was allowed to cool to room temperature, the reaction was quenched with 25 mL of H_2O. The resulting mixture was brought to pH 8 (pH paper) with $NaHCO_3$ and was extracted three times with $CHCl_3$. The pooled extracts were concentrated under reduced pressure to afford a viscous brown oil which soldified on standing. An ethereal solution of this material was treated with ethereal HCl, and the resulting beige solid was recrystallized from Et_2O/MeOH to afford a white powder: mp 288–290 °C; HPLC t_R = 7.25 min (Nucleosil 5 C18 column; MeOH/H_2O/formic acid 30:70:1). Anal. ($C_{17}H_{25}ClNO_2$) C, H, N.

***trans*-7-Hydroxy-8-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (13).** *trans*-7,8-Dimethoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline (**25**;[12] 0.5 g, 0.0018 mol) in 10 mL of CH_2Cl_2 was treated with 0.5 mL of Me_3SiI. The reaction mixture was stirred at 25 °C for 16 h, until the mass spectrum showed only traces of starting material remaining. The reaction was then quenched with 5 mL of H_2O. The organic layer was separated and the aqueous layer was washed with two portions of CH_2Cl_2. The combined organic phases were concentrated under reduced pressure to afford a dark purple oil. Purification of this oil was accomplished with the Chromatotron apparatus (2 mm SiO_2, $CHCl_3$/MeOH, 9:1). The resulting yellow oil was dissolved in Et_2O/MeOH and was treated with excess ethereal HCl. The resulting tan solid was recrystallized from Et_2O/MeOH to afford 0.3 g (54%) of a white solid, mp 248–250 °C; HPLC t_R = 10.7 min (Nucleosil 5 C_{18} column; MeOH/H_2O/formic acid 30:70:1). Anal. ($C_{17}H_{26}ClNO_2$) C, H, N.

***trans*-7,8-Dihydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide (11).** This was prepared by the method of Cannon et al.,[12] mp 261–263 °C (from Et_2O/MeOH) (lit.[12] mp 260–262 °C).

High-Performance Liquid Chromatography. Samples of standards 11–16 (1 mg) were dissolved in 1 mL of 0.01 M formic acid. Aliquots (10 μL) of these solutions were injected with a

Waters U6K valve (2.0 mL loop) onto a 150 × 4.6 mm Nucleosil 5 C_{18} column. The mobile phase (MeOH/H_2O/formic acid, 30:70:1) was delivered at a flow rate of 1.0 mL/min by a Waters Model 6000A pump, equipped with a Beckman Model 153 UV detector set at 280 nm with a range of 0.2 absorbance units. Chromatograms were recorded on a Houston Instruments Omniscribe Recorder, and data were collected with an Apple IIe computer equipped with an Interactive Microwave Chromatochart computer board and software for 16 min for each sample.

Identification of O-Methylated Products from Incubation of the *trans*-Dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]quinolines 11 and 12 with Catechol-*O*-methyltransferase. *trans*-Dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinolines 11 and 12 were incubated separately at 37 °C with catechol-*O*-methyltransferase (COMT), *S*-adenosyl-L-methionine (SAM), and $MgCl_2$. Final concentrations were 13 mg of SAM (0.025 mmol), 0.07 mg of COMT (activity rated 1480 units/mg; 100 units produce 0.10 μmol of product/h), 1.5 mL of 0.05 M $MgCl_2$, 1.5 mL of 0.1 M phosphate buffer (pH 7.6), 4 mg (0.012 mmol) of 11 or 12, and doubly distilled H_2O, to make a total volume of 15 mL. As controls, incubations were run in which COMT, SAM, or substrate molecule (11, 12) was omitted. After 3 h the reactionwas stopped by addition of 250 μL of $HClO_4$. Alumina (1 g) was added; the suspensions were sonicated for 5 min, filtered through 0.2-μm Arco disc filters, and injected into the HPLC column in 10.0-μL aliquots as described for the standards.

Synthesis, Antitumor Activity, and Antiviral Activity of 3-Substituted 3-Deazacytidines and 3-Substituted 3-Deazauridines

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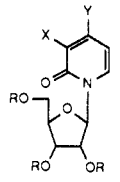
Novel 3-substituted analogues of 4-amino-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (3-deazacytidine, **3**) and 4-hydroxy-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (3-deazauridine, **4**) have been synthesized and tested for antitumor and antiviral activity. Thus the 3-chloro (**9a**), 3-bromo (**9b**), and 3-nitro (**9c**) analogues of **3** and the 3-chloro (**9d**), 3-bromo (**9e**), and 3-nitro (**9f**) analogues of **4** were prepared by standard glycosylating procedures. Novel requisite heterocycles 4-amino-3-chloro-2(1*H*)-pyridinone (**7a**) and 4-amino-3-bromo-2(1*H*)-pyridinone (**7b**) were prepared by halogenating 4-amino-2(1*H*)-pyridinone (**5**). Requisite heterocycles 4-amino-3-nitro-2(1*H*)-pyridinone (**7c**), 3-chloro-4-hydroxy-2(1*H*)-pyridinone (**7d**), 3-bromo-4-hydroxy-2(1*H*)-pyridinone (**7e**), and 4-hydroxy-3-nitro-2-(1*H*)-pyridinone (**7f**) were synthesized by known procedures from 4-hydroxy-2(1*H*)-pyridinone (**6**). Structure proof of target nucleosides was provided by independent synthesis, ^1H NMR, and UV. Compounds **9a–f** were devoid of activity against intraperitoneally implanted L1210 leukemia in mice. Compound **9f** displayed significant activity against rhinovirus type 34 grown in WISH cells. 4-Amino-3-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**1**) displayed good activity against intraperitoneally implanted P388 leukemia in mice, but it was devoid of activity against M5076 sarcoma, amelanotic (LOX) melanoma xenograft, and subrenal capsule human mammary carcinoma MX-1 xenograft in mice. Compound **1** also displayed significant activity against rhinovirus type 34.

We recently reported that 4-amino-3-fluoro-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**1**) exhibits significant activity



1: X = F, Y = NH_2, R = H

2: X = F, Y = NH_2, R = $COCH_3$

3: X = H, Y = NH_2, R = H

4: X = H, Y = OH, R = H

against L1210 leukemia in mice (%T/C_{max} = 230).[1] This activity was retained by **2** (%T/C_{max} = 205), the triacetate of **1**. We have now further investigated the activity of **1** against P388 leukemia in mice, as well as its activity against three different nonleukemic tumors in mice and herein report those results.

The 3-unsubstituted analogue 4-amino-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (**3**, 3-deazacytidine) is not reported to display any in vivo antitumor activity, although it is reported to display modest cytotoxicity against L1210 leukemia cells in vitro (ID_{50} = 5 × 10^{-5} M).[2] In order to explore further the structure–activity relationship of substitution on the 3-position of **3**, we have now prepared the 3-chloro (**9a**), 3-bromo (**9b**), and 3-nitro (**9c**) analogues, and have tested them for cytotoxicity against L1210 leukemia cells in vitro and for antitumor activity against L1210 leukemia in mice.

Compound **4**, 4-hydroxy-1-β-D-ribofuranosyl-2(1*H*)-pyridinone (3-deazauridine), in which the 4-amino group of **3** is replaced with hydroxy, is reported to display activity against L1210 leukemia in mice (%T/C_{max} = 165).[2] It was even tested clinically where it exhibited slight antileukemic activity.[3] We found it of interest to substitute the 3-position of **4** as we had done with some success with **3**. We have now prepared the 3-chloro (**9d**), 3-bromo (**9e**), and 3-nitro (**9f**) analogues of **4** and also tested them for antitumor activity. We attempted to synthesize, by a number of routes, the 3-fluoro analogue of **4** (**9** where X = F, Y = OH), without success.

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(1) McNamara, D. J.; Cook, P. D. *J. Med. Chem.* **1987**, *30*, 340.
(2) Bloch, A.; Dutschman, G.; Currie, B. L.; Robins, R. K.; Robins, M. J. *J. Med. Chem.* **1973**, *16*, 294.
(3) McCredie, K. B.; Bodey, G. P.; Keating, M. J.; Valdivieso, M.; Yap, S.; Freireich, E. J. *Proc. Am. Assoc. Cancer Res.* **1979**, *20*, 405.

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