Assessment of a Potential Dopaminergic Prodrug Moiety in Several Ring Systems

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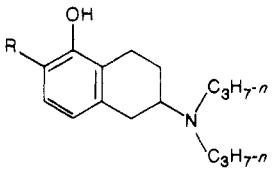
The ortho hydroxy/methyl, hydroxy/hydroxymethyl, hydroxy/formyl, and hydroxy/carboxy substitution patterns, some of which confer dopaminergic agonist effects upon 2-aminotetralin ring systems, have been incorporated into β-phenethylamine, 2-aminoindan, and *trans*-octahydrobenzo[*f*]quinoline rings. Certain of the 2-aminoindan derivatives displayed pharmacologic properties consistent with their being dopaminergic agonists. The β-phenethylamine derivative did not show any significant dopamine-like activity. The 7-hydroxy-8-methyloctahydrobenzo[*f*]quinoline derivative **4a** was a moderately potent, short-acting DA_2 receptor antagonist. All of the carboxylic acid derivatives were inert. Of the ortho hydroxy/methyl derivatives, only the 5-hydroxy-6-methyl-2-aminotetralin derivative displayed pharmacological properties consistent with its being a dopaminergic prodrug. It is concluded that 5-hydroxy-6-methyl-2-(di-*n*-propylamino)tetralin (**1a**) is structurally unique for a dopaminergic drug.

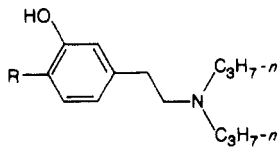
A series of prior communications[1a-d] described in vivo and/or in vitro dopaminergic agonist effects of a series of (±)-5-hydroxy-6-methyl-2-aminotetralins **1a–c** and presented data consistent with the metabolic activation of the 6-methyl compound **1a** to form **1b** and **1c**, which were proposed to be the dopaminergically active structures.



1a, R = CH_3
b, R = CH_2OH
c, R = CHO
d, R = COOH

Administration to rats of **1a** labeled with ^{14}C at the 6-methyl group permitted recovery of approximately 45% of the dose from the urine in the form of the 6-carboxylic acid **1d**.[2] This metabolite was inert as a dopaminergic agonist.

The interesting pharmacological properties exhibited by the 2-aminotetralins (**1a–c**) suggested the introduction of the 1-hydroxy-2-methyl substitution pattern onto the molecules of other systems whose catechol (1,2-dihydroxy) derivatives have been shown to exhibit dopamine agonist properties. Accordingly, the β-phenethylamine systems **2a–c**, the 2-aminoindans **3a–c**, and the *trans*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline derivatives **4a–c** were targeted for preparation and pharmacological investigation. In addition, as reference compounds for future metabolism studies, the corresponding carboxylic acids (**2–4**: R = COOH) were prepared. Synthesis of the urinary carboxylic acid metabolite **1d** of the aminotetralin **1a** has not been previously described in the literature, and it is included here.



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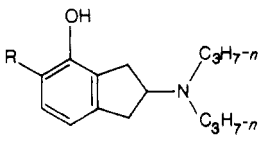

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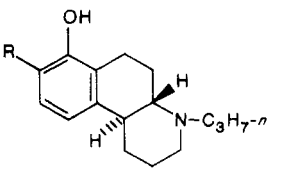

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a, R = CH_3; **b**, R = CH_2OH; **c**, R = CHO; **d**, R = COOH;

Chemistry. Attempts to oxidize the formyl group of **1c** or of phenolic ether or ester derivatives of **1c** to carboxyl, using a variety of oxidizing agents, failed, as did attempts to oxidize the benzylic alcohol group of **1b**. Attempted oxidation of the formyl group of 5-hydroxy-6-formyl-β-tetralone ethylene ketal resulted in a complex mixture. Efforts to effect direct ortho carboxylation of 2-(di-*n*-propylamino)-5-hydroxytetralin by a Reimer–Tiemann reaction with carbon tetrachloride[3,4] led to essentially quantitative recovery of starting material. Exploratory reactions involving treatment of magnesium phenoxide with carbon dioxide, diethyl carbonate, or oxalyl chloride, analogous to a procedure used by Casiraghi et al.[5] in ortho-formylation reactions with paraformaldehyde, led to quantitative recovery of unchanged phenol. A series of ortho-lithiation experiments on 2-(di-*n*-propylamino)-5-hydroxytetralin, followed by treatment with carbon dioxide, did not provide the 6-carboxylic acid derivative.

Successful preparation of the acid **1d** was realized by a multistep sequence involving dehydration of the aldoxime of **1c** with dicyclohexylcarbodiimide by a procedure of Vowinkel et al.[6,7] The resulting nitrile was hydrolyzed to the carboxylic acid **1d**. The carboxylic acid derivative of the β-phenethylamine system **2** (R = COOH) was prepared from an appropriate salicylic acid derivative. The acid derivatives of ring systems **3** and **4** (R = COOH) were prepared from the corresponding aldoxime (R = CH=NOH) by treatment with formic acid.[8]

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Table I. Actions on Cat Right Postganglionic Cardioaccelerator Nerve Stimulation[a]

compd	inhibn of chronotropic stimulation response[b] ID_{50}, μmol/kg (95% CL)	antagonism of apomorphine inhibn AD_{50}, μmol/kg (95% CL)
apomorphine	0.022 (0.01–0.04)	no
1a	0.06 (0.02–0.67)	no
1b	0.03 (0.01–0.12)	no
1c	0.13 (0.07–0.23)	no
1d	IA[c] >3.0	no
2a	IA >3.0	no
2b	IA >3.0	no
2c	IA >3.0	no
2d	IA >3.0	no
3a	0.89 (0.63–1.2)	no
3b	0.12 (0.06–0.33)	no
3c	IA >3.0	no
3d	≃3.18[d]	no
4a	IA >3.0	0.44 (0.21–0.79)
4b	IA >3.0	no
4c	1.81 (0.89–8.09)	no
4d	IA >3.0	no

[a] N = 3 for each compound; CL, confidence limits. [b] Antagonized by haloperidol. [c] Inactive as agonist with doses shown. [d] N = 2.

Preparation of **2a–c**, **3a–c**, and **4a–c** followed routes and strategies described previously[1a] for the tetralin system. The β-phenethylamine derivative **2a** was also prepared from an appropriately substituted benzene derivative, which confirms the ring position of ortho formylation of *N,N*-di-*n*-propyl-*m*-tyramine (**8**) (see method 2 in Experimental Section).

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

Results and Discussion

Pharmacology. Table I shows the activity of the compounds at the DA_2 receptor on the cardioaccelerator nerve of the cat. In this preparation, α_2-adrenoceptor agonists are very weak and are partial agonists. Clonidine (2 mg/kg) will produce no more than 50% inhibition of transmission.

Table II shows the ability of the compounds to induce contralateral turning in rats with unilateral 6-hydroxydopamine lesions of the caudate nucleus.

In summary, biological properties varied considerably for various ring systems with adjacent methyl and phenolic substituents, and the octahydrobenzo[*f*]quinoline ring derivatives differed from the others. Compound **4a** (8-methyl) was an antagonist (partial agonist?) at DA_2 receptors in the periphery, while it was potent in induction of rotation in rats. However, this behavioral response seemed to involve other than dopamine receptors. With **3a** and **4a–c** there was unusual movement of the forelimbs and flat body posture, which are often related to effects on 5-HT receptors. Methysergide antagonized these effects of **3a** in rats, but it antagonized only the flat body posture responses to **4a–c**.

The following structure–activity conclusions are indicated: (1) CH_3 and CH_2OH substitutions ortho to the phenolic OH in aminotetralin and aminoindan rings yield compounds that are dopaminergically active, but similar substituents in β-phenethylamines and octahydrobenzo[*f*]quinolines failed to maintain activity. (2) With the exception of the 2-aminotetralin derivative **1c** and the possible exception of the octahydrobenzo[*f*]quinoline **4c**, aldehyde derivatives were inactive. (3) Carboxylic acid derivatives were very weak or inactive in all ring systems.

Table II. Induction of Contralateral Turning Behavior in Rats with Unilateral Lesions of the Nigrostriatal Pathway[a]

compd	potency ratio to apomorphine (95% CL)	antagonism of turns by haloperidol[b]
apomorphine	1	sig[c]
1a	0.39 (0.23–0.91)	sig[c]
1b	0.93 (0.1–2.1)	sig[c]
1c	0.07 (0.04–0.13)	NT[d]
1d	IA[e] up to 12.1 μmol/kg	
2a	IA up to 16.9 μmol/kg	
2b	IA up to 12.9 μmol/kg	
2c	IA up to 13.3 μmol/kg	
2d	IA up to 13.9 μmol/kg	
3a	0.30 (0.22–0.43)	sig[f]
3b	0.33 (0.06–2.4)	sig[f]
3c	IA up to 11.7 μmol/kg	
3d	NT	
4a	0.68 (0.14–17.91)	NS[g]
4b	0.07 (0.01–0.21)	sig[c]
4c	0.38 (0.03–18.54)	NS[g]
4d	IA up to 12.3 μmol/kg	

[a] N = 3 for each compound; CL, confidence limits. [b] 100 μg/k, 30-min pretreatment. [c] Significant at $p < 0.05$; total antagonism. [d] Not tested. [e] Inactive in inducing turns or antagonizing apomorphine-induced turns at doses shown. [f] Significant at $p < 0.05$; turns not totally abolished by haloperidol. [g] Not significant.

Thus, 5-hydroxy-6-methyl-2-(di-*n*-propylamino)tetralin (**1a**) appears to represent a unique structure for a dopaminergic prodrug.

Experimental Section

Pharmacology. Methods. Cardioaccelerator Nerve Stimulation. Experiments were performed using 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 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 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. All animals were pretreated with atropine sulfate, 0.2 mg/kg. 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} 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. 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 as follows: 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 by using three doses spaced by 0.60 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 an experimental compound.

Statistics. Statistical treatment of data in the experiments to test for antagonistm of apomorphine involved the paired

Students t test.[9] The relative potency and 95% fiducial limits were calculated by using a 3 × 3 parallel line bioassay.[10] ID_{50} values were determined by a nonquantal analysis described by Finney.[10]

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 Associates EM360A spectrometer with tetramethylsilane as the internal standard. Mass spectra were obtained with a Ribermag R10-10C mass spectrometer.

2-(Di-*n*-propylamino)-5-(benzyloxy)-6-formyltetralin Hydrochloride (5). To a stirred solution of 1.4 g (0.005 mol) of 2-(di-*n*-propylamino)-5-hydroxy-6-formyltetralin hydrochloride (1c)[1a] in 15 mL of absolute EtOH was added in one portion 0.66 g (0.0112 mol) of KOH, and the resulting solution was stirred at 50 °C for 0.5 h. Benzyl bromide (0.96 g, 0.0056 mol) was added, and the resulting mixture was heated under reflux for 2 h. Volatiles were removed, and the residual yellow oil was taken up in Et_2O and washed with three portions of 10% Na_2CO_3. The Et_2O layer was washed with H_2O until the washings were neutral (pH paper). The Et_2O was removed under reduced pressure, and the residual oil was taken up in CH_2Cl_2 and this solution was dried (Na_2SO_4). The mixture was filtered, and volatiles were removed from the filtrate under reduced pressure. The residue was taken up in anhydrous Et_2O, and this solution was treated with ethereal HCl. Recrystallization of the resulting solid from EtOH gave 1.55 g (81%) of small, clear prisms: mp 134–136 °C; MS (CI), m/e 366 (M^+ – HCl). Anal. ($C_{24}H_{32}ClNO_2$) C, H, N.

2-(Di-*n*-propylamino)-5-(benzyloxy)-6-cyanotetralin Hydrochloride (6). The free base of compound **5** (1.3 g, 0.0035 mol) in 4 mL of pyridine was added dropwise to a stirred solution of 0.25 g (0.0038 mol) of hydroxylamine hydrochloride in 1 mL of twice-distilled H_2O. A pink precipitate separated, which dissolved upon addition of 12 mL of pyridine. The resulting solution was stirred at room temperature for 1 h; then 0.174 g (0.007 mol) of $CuSO_4 \cdot 5H_2O$ was added, followed by 0.755 g (0.0084 mol) of Et_3N in 2 mL of CH_2Cl_2. After stirring at room temperature for 1 h, the reaction mixture was deep emerald-green. Dicyclohexylcarbodiimide (1.73 g, 0.0084 mol) in 30 mL of CH_2Cl_2 was added, and the resulting solution was stirred at ambient temperature for 3.5 h. Formic acid (1.0 mL) was added, and stirring was continued until foaming subsided.

The reaction mixture was transferred to a separatory funnel, and the organic layer was washed with 10% Na_2CO_3. The organic layer was separated and was washed with H_2O until the washings were neutral (pH paper). The voluminous precipitate of dicyclohexylurea was collected on a sintered glass filter and was discarded. Volatiles were removed from the filtrate under reduced pressure to afford an oil, which was dissolved in Et_2O and treated with ethereal HCl. The resulting solid was recrystallized from EtOH to afford 0.86 g (62%) of white crystals: mp 141–142 °C; MS (CI), m/e 363 (M^+ – HCl). Anal. ($C_{24}H_{31}ClN_2O$) C, H, N.

2-(Di-*n*-propylamino)-5-hydroxy-6-cyanotetralin Hydrochloride (7). Compound **6** (0.75 g, 0.0019 mol) in 40 mL of EtOH was hydrogenated over 0.2 g of 5% Pd/C at 30 psig for 2 h. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was recrystallized from EtOH to give 0.58 g (82%) of product: mp 241–242 °C; MS (CI), m/e 273 (M^+ – HCl). Anal. ($C_{17}H_{25}ClN_2O$) C, H, N.

2-(Di-*n*-propylamino)-5-hydroxytetralin-6-carboxylic Acid Hydrochloride (1d). Compound **7** (0.2 g, 0.006 mol) was heated under reflux in 15 mL of concentrated HCl for 24 h. The cooled reaction mixture was filtered through a sintered glass filter. The light-pink paste on the filter was crystallized twice from EtOH to yield 0.125 g (64%) of a white powder: mp 248–250 °C; MS (CI), m/e 291 (M^+ – HCl). Anal. ($C_{17}H_{26}ClNO_3$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(3-hydroxy-4-formylphenyl)ethylammonium Fumarate (2c).** A modification of an ortho-formylation method of Casiraghi et al.[5] was employed. *N*,*N*-Di-*n*-propyl-*m*-tyramine[11] (10.88 g, 0.05 mol) in 250 mL of dry benzene was added dropwise with stirring under N_2 to 17.7 mL of a 2.8 M solution (0.05 mol) of EtMgBr in Et_2O. Stirring was continued at room temperature for 0.5 h after all the amine solution had been added. The Et_2O was then removed by distillation, and 9.8 g (0.055 mol) of hexamethylphosphortriamide and 3.65 g (0.122 mol) of paraformaldehyde were added. The resulting solution was heated under reflux for 7 h. The reaction mixture was cooled to room temperature and was treated with 75 mL of 3 N HCl. The resulting two-phase liquid system was separated, and the organic layer was washed several times with 3 N HCl, the washings being pooled with the aqueous layer from the reaction mixture. The combined aqueous extracts were taken to pH 8 (pH paper) with $NaHCO_3$, and the resulting mixture was extracted repeatedly with Et_2O. Volatiles were removed from the pooled extracts, and the residue was taken up in 5 mL of CH_2Cl_2 and this solution was dried (Na_2SO_4). It was chromatographed on a flash column (silica) and was eluted with EtOAc–EtOH–Et_3N (90:5:2). Evaporation of the eluate under reduced pressure gave 9.84 g (79%) of a viscous yellow oil. A 0.5-g portion of this material was chromatographed on silica gel GF Uniplate tapered plates (Analtech), and was eluted with EtOH–Me_2CO–CH_2Cl_2 (2:4:15). The principal fraction provided 0.140 g of a yellow oil, which was taken up in 5 mL of absolute EtOH and treated with 0.094 g (0.008 mol) of fumaric acid. The resulting mixture was permitted to stand overnight at ambient temperature; the solid that separated was collected on a filter, and the mother liquor was concentrated to afford additional solid, which was combined with the first crop. The combined solids were recrystallized from 2-PrOH to afford 0.210 g of product: mp 129–130 °C. Anal. ($C_{34}H_{50}N_2O_8$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(3-hydroxy-4-hydroxylmethylphenyl)ethylammonium Fumarate (2b).** The free base of **2c** (0.4 g, 0.0016 mol) in 150 mL of 95% EtOH was hydrogenated over 0.15 g of 10% Pd/C at an initial pressure of 40 psig, until 1 equiv of H_2 was absorbed (≈4 h). The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The oily residue was chromatographed on 10 silica gel GF Uniplate tapered plates and was eluted with CH_2Cl_2–Me_2CO–EtOH (400:80:20). The principal fraction afforded 0.372 g of an oil from which residual H_2O was azeotroped with benzene. A solution of this dried material in 5 mL of absolute EtOH was treated with 0.085 g of fumaric acid, and the resulting mixture was permitted to stand overnight at room temperature. The solid that separated was collected on a filter, and the filtrate was concentrated to provide a second crop of solid, which was pooled with the first crop. This material was recrystallized twice from abs EtOH to provide 0.190 g (36%) of a white solid: mp 165–166 °C. Anal. ($C_{38}H_{56}N_2O_8$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(3-hydroxy-4-methylphenyl)ethylamine Hydrochloride (2a). Method 1.** The free base of **2c** (0.24 g, 0.0096 mol) in 100 mL of 95% EtOH and 0.8 mL of concentrated HCl was hydrogenated over 0.2 g of 10% Pd/C at an initial pressure of 45 psig until no more H_2 was absorbed (24 h). The reduction mixture was filtered, and the filtrate was evaporated under reduced pressure. The solid residue was recrystallized from 2-PrOH–heptane to afford 0.220 g (85%) of crystals: mp 117–118 °C. Anal. ($C_{15}H_{26}ClNO$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(3-methoxy-4-methylphenyl)ethylamine Hydrochloride (8).** 2-(3-Methoxy-4-methylphenyl)-ethylamine[12] (0.9 g, 0.006 mol) was alkylated according to a method of Marchini et al.[13] $NaBH_4$ (1.14 g, 0.03 mol) was added in small portions to 7.0 g (0.1 mol) of propionic acid in 25 mL of Na-dried benzene, maintaining the temperature below 20 °C. When H_2 evolution ceased, the amine in 15 mL of dry benzene was added in one portion, and the resulting mixture was heated under reflux for 5 h. The cooled reaction mixture was shaken with excess 2 M NaOH. The organic layer was washed three times with H_2O,

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dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was treated with 0.5 mL of phenyl isocyanate. MeOH (5 mL) was added after 10 min, and the resulting mixture was heated on a steam bath for 0.5 h. It was then evaporated under reduced pressure, and the residue was taken up in Et_2O. This solution was extracted several times with dilute HCl. The pooled extracts were washed once with Et_2O, then were basified with 50% KOH. The resulting mixture was extracted repeatedly with Et_2O. The pooled ethereal extracts were dried (Na_2SO_4) and were treated with ethereal HCl. The resulting solid was recrystallized from EtOH–Et_2O to afford 0.917 g (53%) of product: mp 123–124 °C. Anal. ($C_{16}H_{28}ClNO$) C, H, N.

***N,N*-Di-*n*-propyl-2-(3-hydroxy-4-methylphenyl)ethylamine Hydrobromide (9). Method 2.** Compound 8 (0.42 g, 0.0015 mol) was heated under reflux under N_2 in 14 mL of 48% HBr for 3 h. Volatiles were removed under reduced pressure, and the residue was crystallized twice from EtOH–Et_2O to afford 0.250 g (53%) of material: mp 121–123 °C. Anal. ($C_{15}H_{26}BrNO$) C, H, N. An NMR spectrum ($CDCl_3$) of the free base of this product was identical with a similar spectrum of the free base of **2a** (the HCl salt), obtained by method 1.

4-[2-(Di-*n*-propylamino)ethyl]salicylic Acid (2d). Methyl 4-(2-aminoethyl)salicylate[14] (0.078 g, 0.0004 mol) and 0.8 g (0.014 mol) of freshly distilled propionaldehyde in 20 mL of EtOAc were hydrogenated over 0.1 g of 5% Pd/C at an initial pressure of 50 psig. The reduction mixture was filtered, and volatiles were removed from the filtrate under reduced pressure. To the residue was added 20 mL of 10% HCl, and this mixture was heated under reflux for 1 h. Removal of volatiles under reduced pressure gave a white solid residue, which was recrystallized from MeOH–EtOAc to give 0.066 g (55%) of product: mp 214–215 °C; MS (CI), *m/e* 266 ($M^+ + 1$). Anal. ($C_{15}H_{24}ClNO_3$) C, H, N.

4-Methoxy-2-oximino-1-indanone (10). Freshly distilled *n*-butyl nitrite (3.5 g, 0.034 mol) was added to a solution of 5.0 g (0.031 mol) of 4-methoxy-1-indanone[15] in 250 mL of Et_2O that had been saturated with anhydrous HCl at room temperature. The resulting deep-red solution was stirred at room temperature for 1 h, and then it was allowed to stand for 2 h at 0 °C. The solid that separated was collected on a filter, washed with Et_2O, and air-dried to give 5.6 g (95%) of a fine, yellow powder: mp 225–227 °C. An analytical sample was recrystallized twice from EtOH: mp 235–236 °C; MS, *m/e* 191 (M^+). Anal. ($C_{10}H_9NO_3$) C, H, N.

2-Amino-4-methoxyindan (11). Compound **10** (14.1 g, 0.074 mol) in 270 mL of AcOH and 18 mL of concentrated H_2SO_4 was hydrogenated over 7.0 g of 5% Pd/C for 24 h. The reduction mixture was filtered, and the catalyst on the filter was washed with 250 mL of H_2O, which was added to the filtrate. The combined liquids were concentrated under reduced pressure and were taken to pH 10 (pH paper) with 30% NaOH. The resulting mixture was extracted with five 200-mL portions of Et_2O. The combined ethereal extracts were evaporated, and the residue was dissolved in CH_2Cl_2 and dried (Na_2SO_4). Evaporation of this solution afforded a brown oil: bp 87–90 °C (0.05 mm) [lit.[16] bp 105–107 °C (0.10 mm)]; yield, 8.6 g (72%). The HCl salt was prepared: mp 236–237 °C (2-PrOH–Et_2O) [lit.[16] mp 240–241 °C].

2-(Di-*n*-propylamino)-4-methoxyindan Hydrochloride (12). The method of Marchini et al.,[13] as described for **8**, was utilized, using 1.3 g (0.00798 mol) of **11**, 3.0 g (0.0798 mol) of $NaBH_4$, 19.5 g (0.260 mol) of propionic acid, and 50 mL of Na-dried benzene. The nearly colorless oily product was converted into its salt with ethereal HCl, and this was recrystallized from 2-PrOH–Et_2O to afford 1.9 g (84%) of white rosettes: mp 145–146 °C. Recrystallization from EtOH–Et_2O gave long needles: mp 187–188 °C [lit.[16] mp 189–190 °C].

2-(Di-*n*-propylamino)-4-hydroxyindan Hydrobromide (13). Compound **12** (3.0 g, 0.0106 mol) was heated at 125 °C in 30 mL of 48% HBr under N_2 for 3 h. Volatiles were removed under reduced pressure, and residual H_2O was azeotroped with benzene. The light-orange solid residue was crystallized from 2-PrOH and then from EtOH–Et_2O to provide 3.1 g (93%) of white needles: mp 202–203 °C [lit.[16] mp 204–205 °C].

2-(Di-*n*-propylamino)-4-hydroxy-5-formylindan Hydrochloride (3c). The method of Casiraghi et al.[5] was employed, as described in detail for **2c**, using 2.12 g (0.009 11 mol) of the free base of **13** in 10 mL of dry benzene, 3.3 mL of a 2.8 M solution of EtMgBr (0.009 15 mol), 60 mL of dry benzene, 0.69 g (0.0222 mol) of paraformaldehyde, and 1.61 g (0.009 11 mol) of hexamethylphosphortriamide. A 2.5-h reflux period was employed. The crude reaction product, 2.6 g of a dark-brown oil, was subjected to flash chromatography on an 8- × 50-cm column of 35–75-μm silica and was eluted with EtOAc–hexanes (2:3). The resulting orange oil (1.86 g) was converted into its salt with ethereal HBr, and this was recrystallized twice from EtOH–Et_2O to afford 1.97 g (63%) of a fluffy, pink powder: mp 157–158 °C; MS, *m/e* 261 (M^+ – HBr). Anal. ($C_{16}H_{24}BrNO_2$) C, H, N.

2-(Di-*n*-propylamino)-4-hydroxy-5-methylindan Hydrobromide (3a). Compound **3c** (0.250 g, 0.000 73 mol) in 30 mL of absolute EtOH and 1.0 mL of concentrated HCl was hydrogenated over 0.1 g of 5% Pd/C at an initial pressure of 35 psig. When H_2 uptake was complete, the reduction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was crystallized twice from EtOH–Et_2O: yield, 0.225 g (94%) of a fine, white powder; mp 175–176 °C; MS, *m/e* 247 (M^+ – HBr). Anal. ($C_{16}H_{26}BrNO$) C, H, N.

2-(Di-*n*-propylamino)-4-hydroxy-5-hydroxymethylindan Hydrobromide (3b). Compound **3c** (0.250 g, 0.000 73 mol) in 30 mL of absolute EtOH was hydrogenated over 0.1 g of 5% Pd/C at an initial pressure of 35 psig. When 1 equiv of H_2 was absorbed, the reduction was stopped and the catalyst was removed by filtration. The filtrate was evaporated under reduced pressure, and the residue was recrystallized from 2-PrOH–Et_2O to afford 0.245 g (97%) of an off-white powder: mp 162–163 °C; MS, *m/e* 263 (M^+ – HBr). Anal. ($C_{16}H_{26}BrNO_2$) C, H, N.

2-(Di-*n*-propylamino)-4-hydroxyindan-5-carboxylic Acid Hydrochloride (3d). A solution of 0.106 g (0.000 31 mol) of **3c**, 0.124 g (0.002 mol) of sodium formate, and 0.028 g (0.0004 mol) of hydroxylamine hydrochloride in 1.5 mL of formic acid was heated under reflux for 4 h under A; then the reaction mixture was taken to pH 9 (pH paper) with saturated $NaHCO_3$, and the resulting mixture was extracted with three 20-mL portions of EtOAc. The pooled extracts were washed with five 5-mL portions of H_2O and were dried ($MgSO_4$). Removal of volatiles under reduced pressure gave a yellow oil, to which was added 15 mL of concentrated HCl, and the resulting mixture was heated under reflux overnight. On cooling to 0 °C, a white solid separated. This was recrystallized from EtOH–Et_2O to afford 0.062 g (64%) of a white solid: mp 248 °C dec. Anal. ($C_{16}H_{24}ClNO_3$) C, H, N.

***trans*-4-*n*-Propyl-7-hydroxy-8-formyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (4c).** *trans*-4-*n*-Propyl-7-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline[17] (0.644 g, 0.0026 mol) in 100 mL of benzene–Et_2O (1:1) was treated with EtMgBr (0.0028 mol) in 2 mL of Et_2O, 0.517 g (0.0028 mol) of hexamethylphosphortriamide, and 0.195 g (0.0065 mol) of paraformaldehyde, and the reaction mixture was workedup as described for **2c**. The crude oily product was subjected to flash chromatography (silica, EtOAc). Volatiles were removed from the eluate under reduced pressure, and an ethereal solution of the residue was treated with ethereal HCl. Recrystallization of the resulting solid from EtOH gave 0.48 g (60%) of a white powder: mp 194–197 °C; MS, *m/e* 273 (M^+ – HCl). Anal. ($C_{17}H_{24}ClNO_2$) C, H, N.

***trans*-4-*n*-Propyl-7-hydroxy-8-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (4a).** Compound **4c** (0.120 g, 0.000 39 mol) was hydrogenated in 30 mL of EtOH containing 7 drops of concentrated HCl, over 0.1 g of 5% Pd/C at an initial pressure of 30 psig. After the calculated amount of H_2 was absorbed (16 h), the catalyst was removed by filtration and volatiles were removed from the filtrate under reduced pressure. The residue was recrystallized from EtOH–Et_2O to give

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0.095 g (77%) of a white powder: mp 252–253 °C dec; MS, *m/e* 259 (M^+ – HCl). Anal. ($C_{17}H_{28}ClNO$) C, H, N.

***trans*-4-*n*-Propyl-7-hydroxy-8-(hydroxymethyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (4b).** A solution of 0.120 g (0.0004 mol) of **4c** in 50 mL of EtOH was hydrogenated over 0.1 g of 5% Pd/C at an initial pressure of 35 psig. When the calculated amount of H_2 was absorbed (5 h) the catalyst was removed by filtration and volatiles were removed from the filtrate under reduced pressure. The residue was recrystallized from EtOH to give 0.100 g (78%) of a white powder: mp 254–257 °C; MS, *m/e* 275 (M^+ – HCl). Anal. ($C_{17}H_{26}ClNO_2$) C, H, N.

***trans*-4-*n*-Propyl-7-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-8-carboxylic Acid Hydrochloride (4d).** Compound **4c** (0.204 g, 0.000 66 mol), 0.1243 g (0.0018 mol) of sodium formate, 0.076 g (0.0011 mol) of hydroxylamine hydrochloride, and 3 mL of formic acid were heated under reflux under A for 6 h. Volatiles were then removed under reduced pressure, and the pH of the residue was taken to 9 (pH paper) by addition of saturated $NaHCO_3$. The resulting mixture was extracted with three 30-mL portions of CH_2Cl_2. Removal of the volatiles from the pooled extracts gave a brown solid, which was chromatographed on a Chromatotron apparatus (silica: EtOAc–EtOH, 7:3). The third of three eluted bands was evaporated, and 5 mL of concentrated HCl was added to the residue. The resulting mixture was heated under reflux overnight. The white solid that separated from the cooled reaction mixture was recrystallized from MeOH–Et_2O to afford 0.072 g (30%) of a white solid: mp 277–279 °C dec; MS, *m/e* 289 (M^+ – HCl). Anal. ($C_{17}H_{24}ClNO_3$) C, H, N.

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Studies on Prodrugs. 5.[1] Synthesis and Antimicrobial Activity of *N*-(Oxoalkyl)norfloxacin Derivatives

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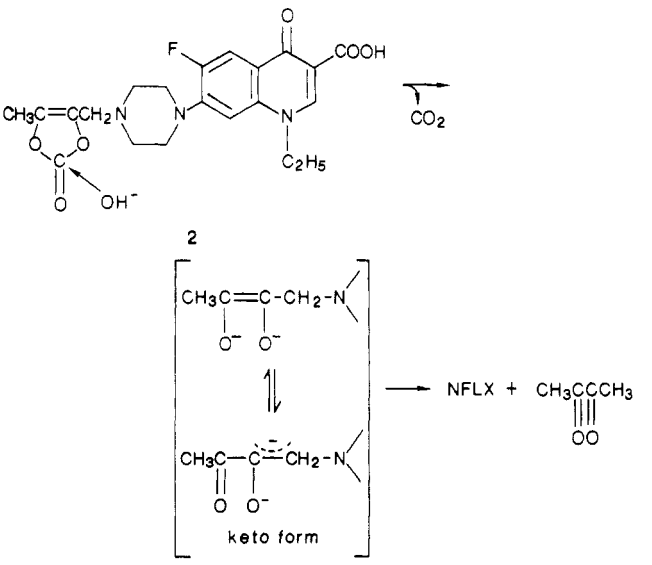
Several *N*-(oxoalkyl)norfloxacin derivatives (**3a–g**) were synthesized and evaluated for antibacterial activity in vitro and in vivo. Most of the compounds exhibited in vitro activity comparable to that of norfloxacin for Gram-positive bacteria, whereas their activity was lower than for Gram-negative bacteria. *N*-(2-Oxopropyl)norfloxacin (**3b**) liberated norfloxacin in the blood after oral administration in mice, and the serum level of norfloxacin was about 3-fold higher than that of norfloxacin itself. Thus, **3b** showed high antibacterial activity in vivo.

Since nalidixic acid has been developed as a useful therapeutic agent, a large number of analogues have been synthesized and some of them are in clinical use.[2] In the series of analogues, in particular, norfloxacin (NFLX, 1) exhibited marked and broad antibacterial activity against Gram-positive and Gram-negative bacteria.[3] Although NFLX (1) was potently active in in vitro test systems, it was found that there was still room for improvement in the activity after oral administration.[4] We have been interested in the prodrug approach of NFLX (1) and had already synthesized the unique N-masked NFLX (2),[1] in which we proposed that the N-masked NFLX (2) was hydrolyzed in the body through the keto form, as shown in Scheme I, to liberate NFLX (1) in the blood (see Chart I). Therefore, the ketone group α to the nitrogen atom was speculated to play an important part in the metabolism of this compound. In this paper, the preparation of *N*-(oxoalkyl)-substituted NFLXs (**3a–g**) is described. Furthermore, their serum levels and metabolism after oral

Scheme I



administration in mice were measured, and their antibacterial activities were evaluated in vitro and in vivo.

Chemistry. NFLX (1) was synthesized in accordance with the report of Koga et al.[3a] The N-masked NFLXs (**3a–g**) were prepared in one step using the recently described method,[1] which was the reaction of NFLX (1) with each halide (**4a–f**) without protection of the 3-carboxylic acid of NFLX. The compound (**3g**) was synthesized by means of Michael addition (Scheme II).

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