Aporphines. 21.[1,2] Dopaminergic Activity of Aporphine and Benzylisoquinoline Derivatives. Synthesis of 8-Hydroxyaporphines and 1-(Hydroxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinolines

John L. Neumeyer,* Werner P. Dafeldecker,

Department of Medicinal Chemistry and Pharmacology, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115

Brenda Costall, and Robert J. Naylor

School of Studies in Pharmacology, University of Bradford, Bradford, West Yorkshire, United Kingdom.
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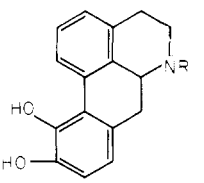
The synthesis and physical properties of 8-hydroxyaporphine (**3a**) and 8-hydroxy-*N*-*n*-propylnoraporphine (**3b**) are described. The replacement of the rigid aporphine ring system by the more flexible benzyltetrahydroisoquinoline moiety, still containing all the necessary substituents of the potent dopamine agonist *N*-*n*-propylnorapomorphine (**1b**) (NPA), resulted in the synthesis of 1-(3,4-dihydroxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (**4**). Analogous to **4**, 1-(4-hydroxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (**5**) was synthesized for a direct comparison with the biological activity of the corresponding 10-hydroxyaporphine (**2**). All compounds synthesized were evaluated as salts of their racemates. In animals with unilateral 6-OHDA lesion of the nigrostriatal pathway, (−)-NPA and **2** caused dose-dependent contralateral circling behavior, although activity was greatly reduced for the monohydroxylated aporphine **2**. **3b**, **4**, and **5** were inactive at doses of 0.25–4.0 mg/kg sc. Compounds **2** and **3b** exhibited very weak activity in the stereotypy tests in comparison to the response obtained with apomorphine and (−)-NPA. **4** and **5** failed to induce any stereotyped response. These compounds were also investigated for their ability to stimulate locomotor activity following direct injection into the nucleus accumbens. (−)-NPA induced a modest increase in activity but apomorphine completely failed to elicit a locomotor response and antagonized the effect induced by dopamine. **2**, **3b**, **4**, and **5** neither enhanced locomotor activity on direct injection into the nucleus accumbens nor antagonized the hyperactivity response to intraaccumbens dopamine when administered peripherally. On direct injection into the caudate-putamen only apomorphine induced stereotyped biting; (−)-NPA, **2**, **3b**, **4**, and **5** were inactive. The differential activity of the aporphine derivatives in these tests strongly supports the possible existence of different types of dopamine receptors within the extrapyramidal and mesolimbic systems. The present studies confirm that the flexible benzylisoquinolines **4** and **5** do not adopt the active dopamine conformation and that the rigid aporphines, preferably containing hydroxyl functions at the 10 or 11 positions, are of greater importance in eliciting potent dopamine agonist activity.

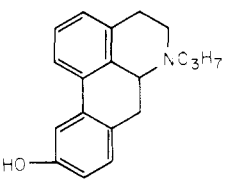
Apomorphine and related aporphines have served as useful models for studying the topography of the dopamine receptor(s). While it is now generally accepted that the catechol moiety is required to produce optimum interaction with the dopamine receptor,[3-5] it is evident that the mere presence of a catechol group is not sufficient to confer agonist activity on apomorphine or its analogues. Thus, isoapomorphine and (−)-1,2-dihydroxyaporphine are generally inactive in behavioral tests or in models designed to interpret their activity at the biochemical level[4-7] while, in contrast, we have previously shown that monohydroxylated aporphines such as **2**, or the corresponding 11-hydroxyaporphine, do possess dopamine receptor agonist activity when administered to rats.[8-10]

The present studies were designed to further examine the structure–activity relationship between dopamine, apomorphine (**1a**), the monohydroxyaporphines, and benzylisoquinolines. The replacement of the rigid aporphine ring system by the conformationally more flexible benzyltetrahydroisoquinoline moiety, still containing all the necessary substituents of the potent *N*-*n*-propylnorapormorphine molecule (**1b**) [(−)-NPA], resulted in the synthesis of 1-(3,4-dihydroxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (**4**). Analogous to this compound, 1-(4-hydroxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (**5**) was synthesized for a direct comparison with the biological activity of the corresponding 10-hydroxyaporphine (**2**). The synthesis of the hitherto unknown 8-hydroxyaporphines **3a** and **3b** was also undertaken.

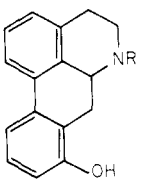
The dopamine agonist properties of **3b** were evaluated in addition to **2**, **4**, and **5**. Comparisons were made in the pharmacological evaluations with the activities of apomorphine and (−)-NPA. Behavioral indices of dopamine agonist activity were obtained on peripheral administration



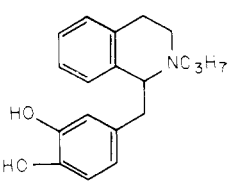
1a, R = CH_3 (APO)
b, R = C_3H_7 (NPA)



2 (10-OH-PNA)



3a, R = CH_3
b, R = C_3H_7



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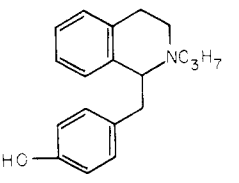

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to normal rats (stereotyped behavior patterns[11]), on intracerebral administration (stereotypy and hyperactivity induction from mesolimbic and extrapyramidal dopamine-containing brain regions[4,12]), and following peripheral administration to animals with increased dopamine receptor sensitivity (circling behavior after 6-hydroxydopamine lesions[13]).

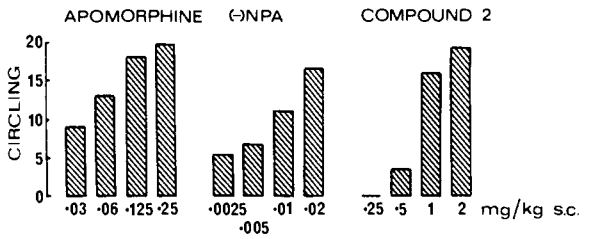


Figure 1. Contralateral circling behavior induced by apomorphine, (-)-NPA, and **2** administered subcutaneously to rats 7–21 days[21] after the injection of 6-OHDA in the region of the nigrostriatal pathway in the lateral hypothalamus. Circling was assessed in revolutions per minute. Each value is the mean of determinations in at least five rats. Standard errors are all less than 12% of the means.

Chemistry. a. Synthesis of (±)-8-Hydroxyaporphines. The synthetic sequence leading to **3a,b** as illustrated in Scheme I follows closely the procedure used for the synthesis of **2**.[9] The previously unreported α-bromo-2-methoxy-6-nitrotoluene (**7**) was obtained from commercially available 2-methyl-3-nitroanisole.

Reissert alkylation, using sodium hydride as base and DMF as solvent, proceeded smoothly at −15 °C. However, difficulties were encountered in the isolation and recrystallization of the adduct **8**. The compound has the tendency to decompose rapidly on drying, and it became necessary to hydrolyze the crude product immediately to the stable 1-(2-methoxy-6-nitrobenzyl)isoquinoline (**9**). Quaternization with the appropriate alkyl halide afforded the isoquinolinium iodides **10a,b** in excellent yields. Care was again exercised during the potassium borohydride reduction of the quaternary salt, **10**, to the corresponding tetrahydroisoquinoline **11** to avoid fragmentation,[1] and the nitro derivative was isolated and characterized as the hydroiodide. The crystalline Pschorr precursor **12b** was obtained either by reduction of **11b** with hydrogen over palladium on charcoal or by hydrogenation of the quaternary salt **10** with platinum oxide. Ring closure gave the 8-methoxyaporphines **13** which on demethylation produced **3**, isolated and characterized as either hydrobromide or hydroiodide salts.

b. Synthesis of 1-(Hydroxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinolines. The preparation of **4** and **5** proceeded via Reissert alkylation as shown in Scheme I. (After completion of these studies, the synthesis of **21** and **4** were reported.[14a]) Coupling of the Reissert compound **6** with the appropriate benzyl halide (**14** or **15**) by previously described procedures gave the adducts **17** and **18** which were directly converted to the 1-benzylisoquinolines **17** and **18** in 70–80% yield. Reaction with 1-iodopropane under reflux furnished the quaternary salts **19** and **20** and the succeeding borohydride reduction gave the tetrahydroisoquinolines **21** and **22** as an oil. Demethylation led to the isolation of **4** and **5** as the hydrobromide salts which were fully characterized by NMR and mass spectral and elemental analyses.

Results

(a) Circling Behavior. In animals with unilateral 6-OHDA lesion of the nigrostriatal pathway 0.03–0.25 mg/kg sc of apomorphine caused a dose-dependent contralateral circling behavior. (-)-NPA caused a similar dose-dependent response, but this agent was notably more potent than apomorphine, inducing contralateral circling at doses of 0.0025–0.02 mg/kg sc. Of the other aporphine and benzylisoquinoline derivatives tested, only **2** was shown to be active in doses of 0.5–2.0 mg/kg sc. Again, the response was dose dependent (Figure 1). **3b**, **4**, and **5** were totally inactive in doses of 0.25–4.0 mg/kg sc.

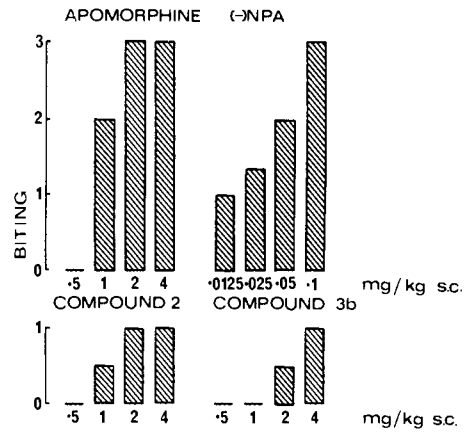


Figure 2. The induction of stereotyped biting, gnawing, or licking behavior by apomorphine, (-)-NPA, **2**, and **3b** administered subcutaneously to normal rats. The intensity of biting was assessed according to Table II. Each value is the mean of determinations in at least five rats. Standard errors are less than 18% of the means.

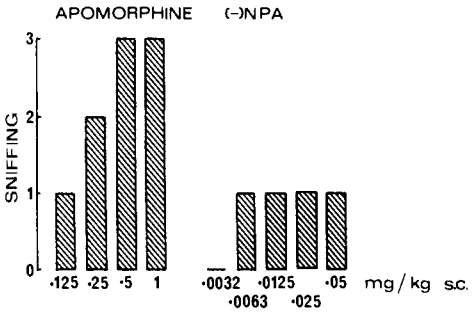


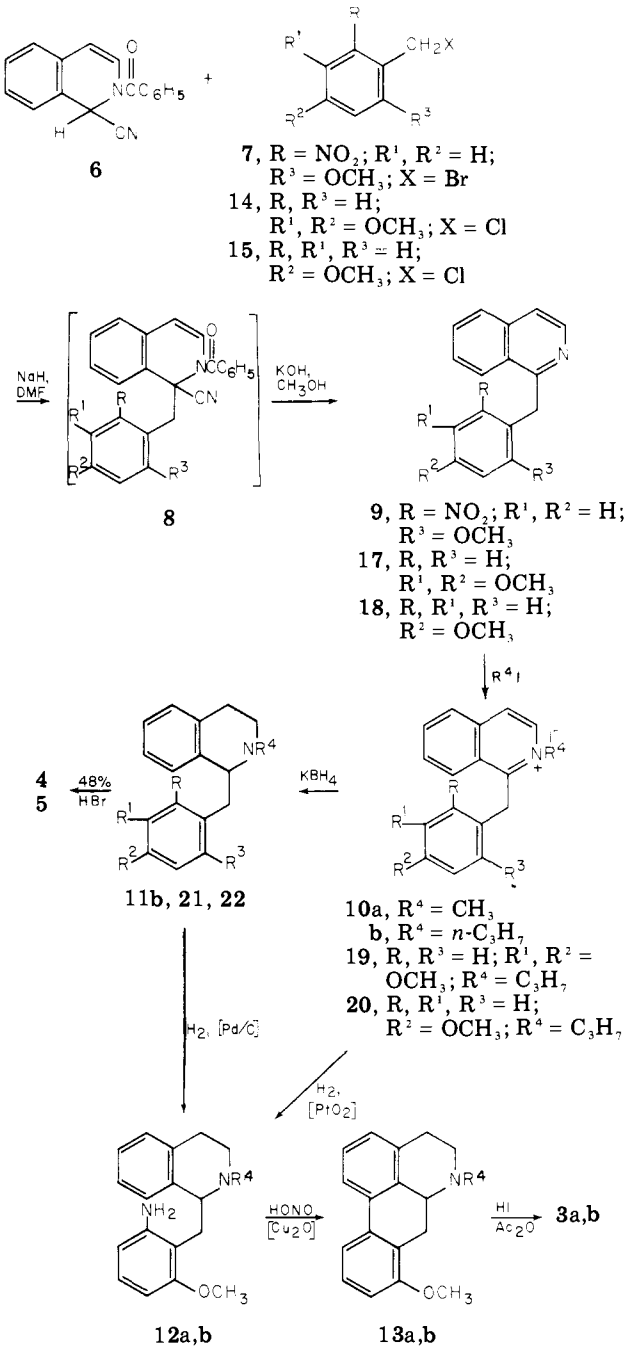
Figure 3. The induction of stereotyped sniffing and/or repetitive head and limb movements by apomorphine and (-)-NPA administered subcutaneously to normal rats. The intensity of sniffing was assessed according to Table I. Each value is the mean of determinations in ten rats. Standard errors are in the range 0–11% of the means.

(b) Stereotyped Behavior. Apomorphine was shown to cause a dose-dependent stereotyped biting in normal rats which achieved a maximum intensity (i.e., continuous biting, see Table II) at 2.0 mg/kg sc. (-)-NPA was similarly active at lower doses, the maximum response being achieved at 0.1 mg/kg sc for this agent. A very periodic biting behavior was recorded for **2** and **3b**, but a clear dose dependency could not be shown for intensity in doses up to 4.0 mg/kg sc (Figure 2). **4** and **5** failed to cause any biting response in normal rats at doses of 0.5–4.0 mg/kg sc.

Apomorphine also caused dose-dependent stereotyped sniffing and repetitive head and limb movements which were of maximum intensity at 0.5 mg/kg sc (i.e., subthreshold doses for the induction of stereotyped biting). In contrast, (-)-NPA caused only a very periodic sniffing behavior at doses within the range causing biting (0.0063–0.05 mg/kg sc) and a dose dependency could not be demonstrated (Figure 3). **2**, **3b**, **4**, and **5** failed to induce either sniffing or repetitive movements of the head or limbs at doses up to 4.0 mg/kg sc.

(c) Direct Injections into the Caudate-Putamen. Three distinct behavioral responses were recorded following the direct injection of dopamine into the caudate-putamen. At 12.5–50 μg a dose-dependent stereotyped biting was apparent which achieved the maximum intensity as indicated in Table II. At 12.5 and 50 μg of dopamine, a stereotyped sniffing was also apparent, but

Scheme I. Synthesis of (±)-8-Hydroxyaporphines and 1-(Hydroxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline



the intensity of this response decreased as the biting increased. At slightly lower doses, 6.25–25 μg bilateral, hyperactivity was recorded. Again, this behavior was shown to be dose dependent but at higher dosage the response was found to decrease as the stereotyped biting became continuous (Figure 4). None of the aporphine or benzylisoquinoline compounds tested mimicked all three of the dopamine responses. Apomorphine was shown to induce a biting response at 25 and 50 μg, which, similarly to dopamine, attained maximum intensity, but the stereotyped sniffing behavior induced by bilateral intrastriatal apomorphine was very periodic and failed to develop in all animals tested even at the larger dose of 50 μg. In further contrast to dopamine, intrastriatal apomorphine completely failed to enhance activity. (–)-NPA (25 μg) caused very weak and inconsistent stereotyped biting and sniffing responses under the same experimental conditions

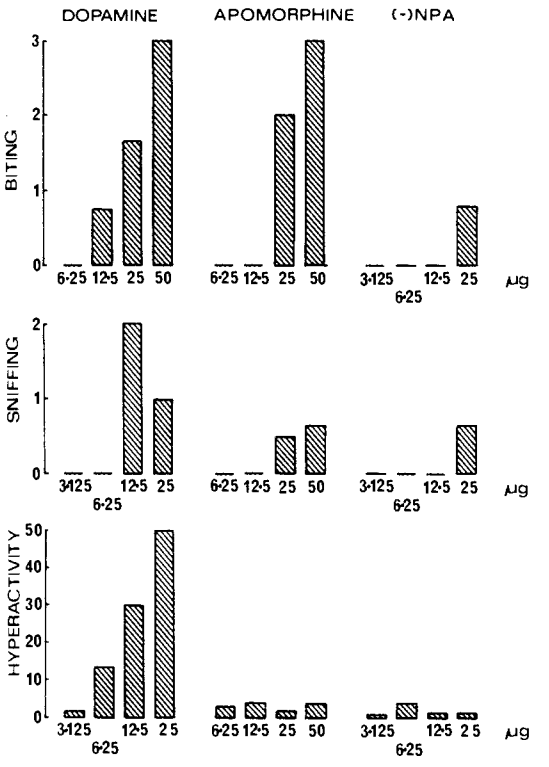


Figure 4. The induction of stereotyped biting, gnawing, or licking, stereotyped sniffing or repetitive head and limb movements, and hyperactivity by dopamine, apomorphine, and (–)-NPA administered bilaterally into the caudate-putamen of rats in a volume of 2 μl following a 2-h pretreatment with nialamide, 100 mg/kg ip. Biting was assessed according to Table II and sniffing according to Table I. Hyperactivity is expressed as the number of interruptions of a photocell light beam occurring within a 5-min period. Six to twelve rats were used at each dose level of drug and standard errors are all less than 17% of the means.

and also failed to cause any hyperactivity (Figure 4). **2**, **3b**, **4**, and **5**, 3.125–25 μg bilateral, failed to cause any of the behavioral responses characterized by dopamine administration into the caudate-putamen.

(d) Direct Injections into the Nucleus Accumbens. The spectrum of behavioral responses caused by dopamine injected into this mesolimbic nucleus differed markedly from those recorded for similar injections into the caudate-putamen. Hyperactivity was the most marked response to intraaccumbens dopamine; this response was clearly dose dependent (6.25–50 μg) and was notably more intense than the behavior induced by similar injections into the caudate-putamen (Figures 4 and 5). Sniffing behavior also developed, was dose dependent, and achieved maximum intensity, but stereotyped biting behavior was never observed following the direct injection of dopamine into the nucleus accumbens. Here, the effect of intraaccumbens (–)-NPA and, to a lesser extent, apomorphine clearly contrasted to dopamine; both induced stereotyped biting, and although the intensity of this behavior was low and its appearance inconsistent for apomorphine, (–)-NPA caused marked stereotyped biting following its injection into the nucleus accumbens, the response was dose dependent, and a maximum intensity (continuous biting) was recorded at 25 μg of (–)-NPA. The stereotyped sniffing and repetitive movements recorded after dopamine injections were also apparent for apomorphine; the response was less marked but, nevertheless, was dose dependent. In contrast, (–)-NPA caused only a very weak sniffing at the larger dose of 25 μg. In further contrast to the dopamine response, apomorphine was completely void of an

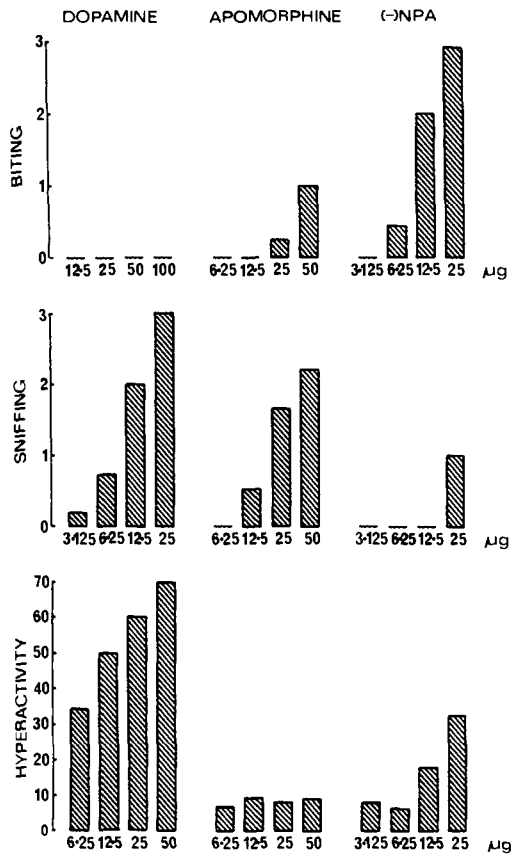


Figure 5. The induction of stereotyped biting, gnawing, or licking, stereotyped sniffing or repetitive head and limb movements, and hyperactivity by dopamine, apomorphine, and (-)-NPA administered bilaterally into the nucleus accumbens of rats in a volume of 1 or 2 μl following a 2-h pretreatment with nialamide, 100 mg/kg ip. Biting was assessed according to Table II and sniffing according to Table I. Hyperactivity is expressed as the number of interruptions of a photocell light beam occurring within a 5-min period. Six to twelve rats were used at each dose level of drug and standard errors are all less than 14% of the means.

ability to enhance locomotor activity from the accumbens, and (-)-NPA caused only a weak behavior. Similarly to observations with intrastriatal administrations, **2**, **3b**, **4**, and **5** were shown to lack all the typical responses which dopamine or (-)-NPA induced following injection into the nucleus accumbens (Figure 5).

(e) Antagonism of the Hyperactivity Induced by Dopamine Injected into the Nucleus Accumbens. The subcutaneous administration of apomorphine and (-)-NPA was shown to reduce, in a dose-dependent manner, the hyperactivity observed 2.5 h after the bilateral injection of 50 μg of dopamine into the nucleus accumbens. This inhibitory action was not mimicked by any of the other aporphine or benzylisoquinoline derivatives tested (**2**, **3b**, **4**, and **5** at doses of 0.1–1.0 mg/kg sc) (Figure 6).

Discussion

Drug-induced circling behavior in rats with unilateral disruption of the nigrostriatal dopamine system caused by 6-hydroxydopamine is regarded as a reliable behavioral indicator of a drug's ability to stimulate striatal dopamine receptors.[13] Drugs possessing direct dopamine receptor agonist properties are particularly active in this test. Thus, apomorphine induces marked contralateral circling in these animals (by stimulation of "supersensitive" dopamine receptors on the lesioned side) but the effect is even more marked for (-)-NPA in which the methyl group on the nitrogen atom of apomorphine is replaced by a propyl

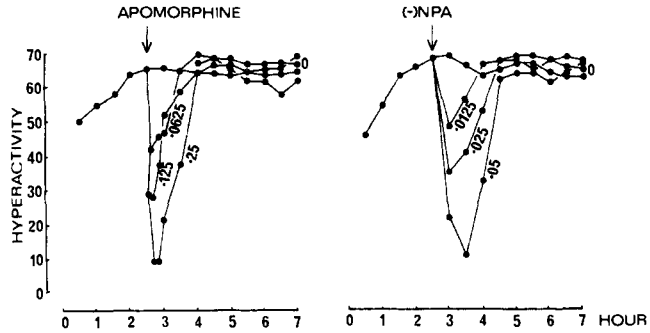


Figure 6. Antagonism of the hyperactivity induced by 50 μg of dopamine administered bilaterally into the nucleus accumbens 2 h after pretreatment with nialamide, 100 mg/kg ip. Apomorphine and (-)-NPA were administered subcutaneously 2.5 h after dopamine when the hyperactivity was maximum (↓). Doses of apomorphine and (-)-NPA are in milligrams per kilogram. Hyperactivity is expressed as the number of interruptions of a photocell light beam occurring within a 5-min period. Five to eight rats were used at each dose of apomorphine or (-)-NPA. Standard errors are in the range 8–17% of the means.

group. In this test, the importance of the catechol grouping within the aporphine series is evident; activity is greatly reduced for the monohydroxylated aporphines, for example, **2**, in the present studies and with the 11-hydroxy derivative.[9,10] This factor is further emphasized by the inactivity of the 8-hydroxy derivative **3b**. The importance of the rigid aporphine ring structure to biological activity in the series was shown by the inactivity of the benzyltetrahydroisoquinoline structures analogous to (-)-NPA and the 10-hydroxyaporphine derivative **2**, i.e., **4** and **5**, respectively (see also ref 14a). The inactivity of these compounds suggests that the flexibility of their structures precludes a conformation which approximates to apomorphine. As such, the mere presence of the essential constituents of the molecule, i.e., the *n*-propyl and 10- and/or 11-hydroxyl substituents, is not sufficient to confer activity in the circling model.

Although it has been accepted that the stereotyped behavior patterns induced by apomorphine and similar agents result from a stimulation of striatal dopamine mechanisms,[15] it is now becoming apparent that dopamine mechanisms within the associated mesolimbic brain areas also play an important role. Thus, although dopamine and apomorphine can induce stereotyped responses upon injection into the caudate-putamen, (-)-NPA is more effective after injection into the nucleus accumbens.[16,17] We therefore consider that while the induction of stereotypy by peripheral administration of a compound is strongly indicative of dopamine agonist activity, such data can give no information as to the site of drug action and, since different dopamine receptors are involved with the behavioral responses induced from the different brain regions,[4,17] peripheral studies also fail to give appropriate data for the determination of structure–activity relationships. For these reasons, we not only examined the dopamine agonist properties of the aporphine and benzylisoquinoline derivatives in the present study by peripheral examination, but we also injected these agents directly into the striatum and mesolimbic nucleus accumbens.

Compounds **2** and **3b** exhibited very weak activity in the stereotypy tests in comparison to the responses obtained with apomorphine and (-)-NPA, and **4** and **5** failed to induce any stereotyped response. The very weak dopamine agonist activity of **2** and **3b** on those dopamine receptors mediating stereotyped responses was emphasized by their

inactivity on intracerebral administration either into caudate or accumbens tissue, although it should be noted that the limited solubility of these compounds prevented the administration of a wide dose range by this route. These studies also emphasized the inactivity of **4** and **5** as dopamine agonists: not only did these compounds fail to give a response in the circling and stereotypy tests, but they also failed to elicit any behavior characteristic of dopamine receptor stimulation on direct application, even in very large doses, to cerebral tissue. Again, the conclusion must be that the flexibility of **4** and **5** prevents an apomorphine-like configuration.

As a third model of drug action on cerebral dopamine systems, we investigated the ability of dopamine and the potential dopamine agonists to stimulate locomotor activity following direct injection into the nucleus accumbens. Dopamine can induce a powerful locomotor response from this area, a response specifically inhibited by neuroleptic agents.[12] (-)-NPA can also induce a modest increase in activity under the same conditions but apomorphine completely fails to elicit a locomotor response and will, in contrast, actually antagonize the effect induced by dopamine. This suggests that even slight changes in the aporphine structure may alter the aporphine–receptor interaction to change agonist to partial agonist or antagonist activity. In the present experiments, **2**, **3b**, **4**, and **5** neither enhanced locomotor activity on direct injection into the nucleus accumbens nor antagonized the hyperactivity response to intraaccumbens dopamine when administered peripherally. It is concluded, therefore, that these agents lack any ability to modify the responses of those dopamine receptors in the nucleus accumbens which are involved with locomotor responding.

The differential activity of the aporphine derivatives in the circling, stereotypy, and hyperactivity models strongly supports the possible existence of different types of dopamine receptors within the extrapyramidal and mesolimbic systems. Of the aporphines investigated, it was shown that optimum activity resides in (-)-NPA in all three models, and the *N*-propyl substitution particularly increased dopamine-like activity in the mesolimbic nucleus accumbens. Removal of the hydroxyl functions markedly reduced dopamine agonist activity and the introduction of a hydroxyl group at the 8 position failed to introduce any significant agonist properties. Dependent on the test procedure used, a hydroxyl group at positions 10 or 11 was found to confer some agonist properties. Nevertheless, it is clear that optimum activity resides in a compound possessing two hydroxyl functions in positions 10 and 11. An even more important conclusion to be drawn from the present observations is that the rigid aporphine conformation is a key to potent dopamine agonist activity; the flexible benzylisoquinoline analogue of (-)-NPA and the corresponding 10-hydroxy derivative were inactive indicating that probably such structures do not adopt the active dopamine conformation. This further indicates that the β-aminotetralin portion of the apomorphine molecule is more important than the tetrahydroisoquinoline moiety for interaction with dopamine receptors.

Experimental Section

Melting points were determined on a Thomas-Hoover (Unimelt) apparatus and are uncorrected. The microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Where analyses are indicated by symbols of elements, the analytical results are within ±0.4% of the theoretical values. Infrared spectra were recorded on a Perkin-Elmer 700 spectrophotometer. Mass spectra were recorded on a Nuclide Mass Spectrometer 12-90-G. NMR spectra were recorded on a Varian T-60 spectrometer, with Me_4Si as the internal standard.

α-Bromo-2-methoxy-6-nitrotoluene (7). A mixture of 20 g (0.12 mol) of 2-methyl-3-nitroanisole (Aldrich), 21.4 g (0.12 mol) of recrystallized *N*-bromosuccinimide, and 100 mg of benzoyl peroxide in 170 ml of dry CCl_4 was refluxed for 3.5 h under illumination. After filtration the solvent was removed under reduced pressure to yield in three crops 27.2 g (92%) of **7**, mp 72–74 °C. Recrystallization from benzene–hexane gave an analytical sample, mp 73 °C. Anal. ($C_8H_8BrNO_3$) C, H, N.

2-Benzoyl-1-(2-methoxy-6-nitrobenzyl)-1,2-dihydroisoquinaldonitrile (8). A solution of 5.2 g (0.02 mol) of **6** in 80 ml of dry DMF was cooled to −15 °C and under stirring equimolar amounts of **7** (4.92 g) and NaH (0.96 g) (50% mineral oil suspension) were added under a nitrogen atmosphere. The mixture was allowed to come to room temperature and stirring was continued for 20 h. Addition of 350 ml of crushed ice produced a yellow precipitate, which was rapidly filtered and washed alkali-free with water. After trituration with ethanol the compound was dried over P_2O_5 under vacuum to yield 7.8 g (91%) of crude **8**: mp 100–138 °C. Partial decomposition during the filtration and drying process was observed and attempts to recrystallize the compound from ethanol failed. The crude product after trituration with ethanol can be used for the next step.

1-(2-Methoxy-6-nitrobenzyl)isoquinoline (9). To a solution of 3.4 g (60 mmol) of potassium hydroxide in 85 ml of dry methanol was added 4.2 g (9.9 mmol) of crude **8**. The mixture was refluxed under stirring for 5 min and the hot solution was poured into 500 ml of ice–water and extracted with ethyl acetate. The extract was washed with water, dried, and concentrated to yield upon cooling in ice 1.4 g (48%) of **9**: mp 128–130 °C. An analytical sample was obtained from acetonitrile: mp 133–134 °C. Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

1-(2-Methoxy-6-nitrobenzyl)isoquinoline Methiodide (10a). A solution of 0.55 g (1.9 mmol) of **9** in 7.5 ml (0.12 mol) of methyl iodide was refluxed under stirring for 20 h. The resulting yellow compound was filtered, washed with ether, and dried to yield 0.62 g (76%) of **10a**, mp 207–208 °C dec. An analytical sample was obtained from methanol–ether: mp 208–209 °C dec. Anal. ($C_{18}H_{17}IN_2O_3$) C, H, N.

Similarly prepared from **9** and 1-iodopropane was **1-(2-methoxy-6-nitrobenzyl)isoquinoline propiodide (10b)**: mp 214 °C dec; 6.1 g (74%). Anal. ($C_{20}H_{21}IN_2O_3$) C, H, N.

1-(2-Methoxy-6-nitrobenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (11b). To a suspension of 4.64 g (0.01 mol) of the propiodide **10b** in 140 ml of absolute ethanol was added under stirring in small aliquots 675 mg (0.0125 mol) of potassium borohydride within 3 h. After the last addition 2 ml of water was introduced and stirring was continued for 30 min. The reaction mixture was filtered, diluted with 100 ml of water, and extracted with chloroform. The organic phase was washed with water and dried and the solvent was evaporated, yielding a brown oil. A solution of the oil in 10 ml of acetone was acidified with 57% HI to pH 2.0 and cooling in ice yielded the corresponding hydroiodide salt: 2.65 g (57%); mp 174–175 °C. An analytical sample was prepared from ethanol: mp 177–178 °C. Anal. ($C_{20}H_{25}IN_2O_3$) C, H, N.

The free base was liberated from the hydroiodide by treating the salt with a saturated aqueous solution of $NaHCO_3$ under stirring and subsequent extraction with chloroform. The organic extract was washed alkali-free and dried over Na_2SO_4. Removal of the solvent left a yellow glass which was dissolved in a few drops of methanol–hexane. Bright yellow crystals were obtained on standing in the refrigerator for 10 days: mp 55–57 °C.

1-(2-Amino-6-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (12a). A mixture of 2.3 g (5.3 mmol) of **10a** in 150 ml of methanol and 300 mg of PtO_2 was hydrogenated at room temperature and 55 psi for 48 h. The catalyst was filtered and the solvent was removed in vacuo. The residue dissolved in 70 ml of chloroform was washed with 2 × 20 ml of 2 N NaOH and 2 × 20 ml of H_2O and dried over Na_2SO_4. Removal of the solvent left 1.33 g (89%) of a brown oil.

A picrate was prepared and recrystallized from ethanol: mp 156–157 °C. Anal. ($C_{24}H_{25}N_5O_8$) C, H, N.

1-(2-Amino-6-methoxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (12b). A. By Reduction of 1-(2-Methoxy-6-nitrobenzyl)isoquinoline Propiodide (10b). Reduction of the propiodide **10b** (5.35 g, 11.5 mmol) with PtO_2 (1.0 g) in 270

ml of ethanol was carried out as described for the methiodide **10a** to yield 2.79 g (78%) of crude **12b**, mp 92–94 °C. Recrystallization from absolute ethanol gave an analytical sample, mp 100–100.5 °C. Anal. ($C_{20}H_{26}N_2O$) C, H, N.

A picrate was prepared and recrystallized from ethanol: mp 114 °C.

B. By Reduction of 1-(2-Methoxy-6-nitrobenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (11b). The free base liberated from 1.0 g (2.14 mmol) of the hydroiodide salt **11b** was dissolved in 60 ml of absolute ethanol and hydrogenated over 150 mg of 10% Pd/C at room temperature and 55 psi for 24 h. The mixture was filtered and the solvent removed under reduced pressure to yield 430 mg (65%) of **12b** as white needles: mp 98–101 °C.

(±)-8-Methoxyaporphine Hydroiodide (13a). Pschorr cyclization of 1.25 g (4.4 mmol) of **12** was carried out as previously described[10] to give 0.38 g (22%) of **13a**: mp 260–261 °C; IR (KBr) 2880, 2670, 1600, 1580, 1490, 1430, 1260, 1060, 770 cm^{-1}; NMR (Me_2SO-d_6) δ 3.1 (s, 3), 3.85 (s, 3), 2.75–4.8 (m, 8), 6.85–7.8 (m, 6); mass spectrum (70 eV) *m/e* (rel intensity) 265 (62) M^+ (free base), 264 (100), 222 (35). Anal. ($C_{18}H_{20}INO$) C, H, N.

(±)-8-Methoxy-*N*-*n*-propylnoraporphine Hydroiodide (13b). Cyclization of 2.14 g (6.8 mmol) of the crude amine **12b** was carried out as previously described[10] and yielded 0.59 g (20.3%) of **13b**: mp 250–251 °C dec; IR (KBr) 2900, 2650, 2600, 1600, 1580, 1490, 1440, 1270, 1060, 790 cm^{-1}; NMR (Me_2SO-d_6) δ 1.0 (t, 3), 1.8 (q, 2), 2.7–3.7 (m, 9), 3.85 (s, 3), 4.5 (br, 1), 6.8–7.9 (m, 6).

A satisfactory analysis could not be obtained for the hydroiodide **13b**. Thus, the free base was liberated by treating the salt in an aqueous suspension with $NaHCO_3$, followed by extraction with ether. Evaporation of the solvent afforded an oil which was dissolved in a few milliliters of ethanol. Dropwise addition of 48% HBr to the solution and cooling in ice gave the hydrobromide **13b**·HBr: mp 253–254 °C dec; mass spectrum (70 eV) *m/e* (rel intensity) 293 (46) M^+ (free base), 292 (68), 264 (100), 235 (76). Anal. ($C_{20}H_{24}BrNO$) C, H, N.

(±)-8-Hydroxyaporphine Hydroiodide (3a). To 0.2 g (0.5 mmol) of **13a** suspended in 1 ml of 57% hydriodic acid under stirring was added an equal volume of acetic anhydride. The mixture was heated at 140 °C for 2 h and cooled in ice and the bright yellow crystals were collected and washed with a few drops of acetone and copiously with ether to give 0.13 g (69%) of **3a**: mp 274–275 °C; IR (KBr) 3230, 2860, 2670, 1570, 1460, 1390, 1310, 1280, 1260, 910, 770 cm^{-1}; NMR (Me_2SO-d_6) δ 2.8–5.0 (m, 8), 3.25 (s, 3), 6.85–8.0 (m, 6), 9.75 (br, 1, signal disappeared on addition of D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 251 (50) M^+ (free base), 250 (100), 208 (46). Anal. ($C_{17}H_{18}INO$) C, H, N.

(±)-8-Hydroxy-*N*-*n*-propylnoraporphine Hydroiodide (3b). Under identical conditions as above **13b** was O-demethylated to yield 0.36 g (88%) of **13b** as bright yellow crystals, mp 266–267 °C dec.

O-Demethylation was also carried out as previously described.[18] Thus, a suspension of 100 mg (0.26 mmol) of **13b**·HBr in 2.5 ml of 48% HBr was heated under stirring to 130 °C in an oil bath for 2.5 h. The off-white crystals were collected and washed with cold water and ethanol–ether to give 85 mg (92%) of **3b**·HBr, mp 278–279 °C. Anal. ($C_{20}H_{24}BrNO$) C, H, N.

4-Methoxybenzyl Chloride (15). Dry HCl gas was passed through a refluxing solution of 4-methoxybenzyl alcohol (30 g, 0.22 mol) in 300 ml of dry benzene. After 1 h the theoretical amount of H_2O, removed from the reaction mixture as an azeotrope, had separated. Evaporation of the solvent left a liquid residue which gave after distillation [bp 61–64 °C (0.6 mm)] 31.6 g (92%) of **15** [lit.[19] bp 59–60 °C (0.01 mm)].

1-(4-Methoxybenzyl)isoquinoline (18). A solution of the Reissert compound (**6**, 17.3 g, 0.066 mol) in 250 ml of dry dimethylformamide was allowed to react with **15** (10.2 g, 0.053 mol) and an equimolar amount of sodium hydride as described for **8**. The reaction product was directly hydrolyzed with methanolic potassium hydroxide (20 g of KOH in 500 ml of CH_3OH) to afford 11.2 g (69%) of the isoquinoline **18**, mp 68–69 °C. Recrystallization from ethanol gave mp 69–70 °C (lit.[22] mp 68.5–69.5 °C).

1-(3,4-Dimethoxybenzyl)isoquinoline (17). This compound was prepared from **6** and **14** by methods previously described.[7]

1-(4-Methoxybenzyl)isoquinoline Propiodide (20). A solution of 2.0 g (8 mmol) of **18** in 30 ml (0.31 mol) of 1-iodopropane was allowed to reflux under stirring for 24 h. The mixture was cooled in ice and the yellow crystals were collected, washed with ether, and dried to give 3.1 g (92%) of **20**, mp 168–169 °C. The compound decomposes slowly and was therefore immediately reduced with potassium borohydride as described below.

1-(3,4-Dimethoxybenzyl)isoquinoline Propiodide (19). The quaternary salt was obtained from **17** (3.45 g, 0.012 mol) and 1-iodopropane (45 ml, 0.46 mol) as described for **18** to afford 5.0 g (91%) of **19**, mp 213–214 °C dec (lit. mp 205–206 °C,[14a] mp 211–212 °C[14b]). Anal. ($C_{21}H_{24}INO_2$) C, H, N.

1-(4-Methoxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (22). To a suspension of the propiodide **18** (6.27 g, 0.015 mol) in 400 ml of ethanol (95%) was added under stirring potassium borohydride (1.13 g, 0.021 mol) within 1 h. The reaction mixture was stirred at room temperature for 12 h and filtered, and the filtrate was diluted with 200 ml of H_2O. The solution was extracted with 3 × 100 ml of chloroform. The organic phase was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness under reduced pressure to give 3.4 g (77%) of **22** as a yellow viscous oil. The compound can be purified by distillation [bp 174 °C (0.4 mm)]; $n^{24}D$ 1.5685.

The crude product can also be purified by formation of the oxalate, mp 170–171 °C. Recrystallization from ethanol gave an analytical sample, mp 174–175 °C. Anal. ($C_{22}H_{27}NO_3$) C, H, N.

Similarly prepared from **19** was **1-(3,4-dimethoxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (21)**, isolated as the hydrochloride, mp 205 °C dec (methanol–ether) (lit. mp 203–204 °C,[14a] 201–203.5 °C[14b]). Anal. ($C_{21}H_{28}ClNO$) C, H, N.

(±)-1-(4-Hydroxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (4). To 3.04 g (10.3 mmol) of **22** was added 35 ml of 48% HBr and the solution was allowed to reflux for 2.5 h. Evaporation to dryness in vacuo gave a brown oil, which was dissolved in 25 ml of acetone. Addition of ether and cooling afforded 3.6 g (96%) of **4** in two crops: mp 199–200 °C dec. Anal. ($C_{19}H_{24}BrNO$) C, H, N.

(±)-1-(3,4-Dihydroxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (5). A suspension of **21** (1.52 g, 4.2 mmol) in 100 ml of 10% sodium hydroxide was stirred for 15 min at room temperature. The mixture was extracted with chloroform and the organic phase was washed with H_2O and dried over Na_2SO_4. The oil obtained on removal of the solvent under reduced pressure was demethylated in 10 ml of 48% HBr, as described for **22**, to yield 1.1 g (69%) of **5**, mp 164–167 °C. Recrystallization from ethanol–ether gave an analytical sample, mp 165–167 °C (lit.[14a] "broad range"). Anal. ($C_{19}H_{24}BrNO_2$) C, H, N.

Pharmacology Methods. Male, Sprague–Dawley (C.F.E.) rats, weighing between 250 and 300 g at the time of operation or start of an experiment, were used throughout the studies.

(a) Stereotaxic Techniques. Stereotaxic surgery was carried out using a Kopf stereotaxic instrument and chloral hydrate, 300 mg/kg ip, as anesthetic. For the circling experiments, unilateral 6-hydroxydopamine (6-OHDA) lesions were induced in the nigrostriatal pathway by injecting 4 μl of a 2 μg/μl solution of 6-OHDA (at a rate of 1 μl/min) into the area of the medial forebrain bundle in the lateral hypothalamus.[21] The 6-OHDA was delivered from an Agla micrometer syringe to the tip of a stainless-steel injection unit (0.3 mm diameter) at anterior 4.6, vertical −2.7, and lateral ±1.9.[20] A stainless steel guide cannula (0.65 mm diameter) terminated 2.5–3.0 mm above the tip of the injection unit.

For experiments to determine the effects of intracerebrally administered drug, guide cannulae were chronically implanted for injections into the caudate-putamen and nucleus accumbens. Guide cannulae were constructed from 0.65-mm diameter stainless-steel tubing and held bilaterally in perspex blocks 3.2 mm apart for injections into the nucleus accumbens and 6 mm apart for injections into the caudate-putamen. The guides were implanted at anterior 9.0, vertical +2.5, lateral ±1.6 and anterior 8.0, vertical +3.0, lateral ±3.0 for the nucleus accumbens and caudate-putamen, respectively, the perspex holders being fixed to the skull using acrylic cement and retaining screws. Stainless-steel stylets (0.3 mm diameter) kept the guides patent until

Table I. System Used to Assess the Intensity of Stereotyped Sniffing

Description of behavior	Score
No sniffing or repetitive head and limb movements	0
Very periodic sniffing or repetitive head and limb movements (intervals of no sniffing greater than 1 min)	1
Periodic sniffing or repetitive head and limb movements (intervals of no sniffing less than 1 min)	2
Continuous sniffing or repetitive head and limb movements	3

Table II. System Used to Assess the Intensity of Stereotyped Biting

Description of behavior	Score
No gnawing, biting, or licking	0
Very periodic gnawing, biting, or licking (intervals of no biting greater than 1 min)	1
Periodic gnawing, biting, or licking (intervals of no biting less than 1 min)	2
Continuous gnawing, biting, or licking	3

animals were used 10–14 days after surgery. Rats were manually restrained during the injection procedure when the stylets were replaced bilaterally by 0.3-mm diameter stainless-steel injection units which extended 1.5 (caudate-putamen) or 2.5 mm (nucleus accumbens) below the guide tips so terminating at the centers of the respective nuclei (vertical 0 for the nucleus accumbens, vertical +1.5 for the caudate-putamen). Drug–solvent solution (1 or 2 μl) was delivered bilaterally to the tips of the injection units over a 5-s period from Agla micrometer syringes. Fifty-five seconds were allowed for deposition of drugs and the injection units were then immediately replaced by the stylets.

(b) Behavioral Observations. Experiments were carried out between 8:00 a.m. and 8:00 p.m. in a sound-proofed, diffusely illuminated room maintained at a temperature of 21 ± 1 °C.

Circling behavior was measured as the number of revolutions performed by an animal during a 1-min period immediately following its placement in a circular cage 40 cm in diameter. Assessments were made at 15-min intervals throughout the duration of a drug effect.

For the measurement of stereotyped behavior after subcutaneous drug administrations, rats were placed in individual perspex cages measuring 30 × 20 cm and 15 cm high. Thirty minutes were allowed for adaptation to the new environment. Stereotyped behavior after intracerebral drug administrations was measured concurrently with activity in the hyperactivity boxes described below. Two components of stereotypy were assessed: (1) gnawing, biting, and licking (termed biting) and (2) sniffing and repetitive head and limb movements (termed sniffing). The intensity of these two components was assessed according to the scoring systems shown in Tables I and II. Stereotypy was assessed during a 1-min observation period at 10–15-min intervals throughout the duration of a drug effect.

Activity boxes were of the same construction as the observation boxes described above but were fitted with photocells. Activity was characterized by counting the number of interruptions of the light beam occurring during each 5-min period. Activity boxes were used in banks of 30 and were individually screened. Animals were placed in the activity boxes immediately following intracerebral injection into the caudate-putamen or nucleus accumbens and counts recorded every 10 min for up to 7 h. Two hours before an intracerebral injection, animals received 100 mg/kg of nialamide by the intraperitoneal route (see Costall and colleagues[4,12] for the rationale of the nialamide pretreatment regime).

In addition to determining the possible dopamine agonist properties of the aporphine and benzylisoquinoline derivatives in the caudate-putamen and nucleus accumbens, any possible antagonistic effect on the dopamine response from the nucleus accumbens was also determined. In these experiments, 50 μg of dopamine was administered bilaterally into the nucleus accumbens and after 2.5 h, when the dopamine hyperactivity was maximum, the aporphine and benzylisoquinoline compounds were administered by the subcutaneous route.

For administration by the intracerebral route, dopamine (Koch-Light), **2**, **3b**, **4**, **5**, apomorphine, and (–)-NPA were dissolved in nitrogen-bubbled distilled water immediately before use. For administration by the subcutaneous route, **2**, **3b**, **4**, **5**, apomorphine, and (–)-NPA were prepared in distilled water containing 0.1% sodium metabisulfite. Nialamide (Sigma) was prepared in a minimum quantity of hydrochloric acid, made up to volume with distilled water and administered by the intraperitoneal route.

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