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Aporphines. 11. Synthesis and Dopaminergic Activity of Monohydroxyaporphines. Total Synthesis of (±)-11-Hydroxyaporphine, (±)-11-Hydroxynoraporphine, and (±)-11-Hydroxy-*N*-*n*-propylnoraporphine†

John L. Neumeyer,* Felix E. Granchelli,

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

K. Fuxe, U. Ungerstedt, and H. Corrodi‡

Department of Histology, Karolinska Institute, Stockholm, Sweden.

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The synthesis of a series of racemic aporphines functionally substituted on the 11 position with either OH or OCH_3 and on the nitrogen atom with H, CH_3, n-C_3H_7, or $CH_2C_6H_5$ (3a-h) is described. The method used for the synthesis of (±)-3 involved a Reissert alkylation-Pschorr cyclization route. The synthesis of the noraporphine 3d and 3h involved the catalytic dealkylation of the *N*-benzylaporphine 3b. The dopaminergic activity of the 11-substituted aporphines 3d-f,h, the 10 substituted aporphines 5a,b, and the 7-hydroxyaporphine 4a and 7-hydroxynoraporphine 4b was evaluated in comparison with (−)-apomorphine and (−)-apocodeine by measuring the rotational behavior of rats with unilateral lesions produced by the intracerebral injection of 6-hydroxydopamine. The pharmacological results showed that dopaminergic activity can reside in monohydroxyaporphines substituted in the 11 position and in the 10 position provided the *N*-*n*-propyl group is present. The finding that (+)-3e and -5b are active is an indication that a catechol system is not an absolute requirement for dopaminergic activity in such aporphines as apomorphine. In agreement with previous work, *N*-*n*-propyl derivatives of the hydroxylated aporphines were more active than the corresponding parent compounds.

The interest in apomorphine [(−)-1] as a potentially useful drug for the treatment of Parkinson's disease and related neurologic diseases is due to its tremor inhibitory effects, its ability to stimulate central dopamine (DA) receptors, and its structural relationship to dopamine.[2]

In our previous studies involving functionally substituted aporphines, we described the successful total synthesis of (±)-apomorphine [(±)-1], (±)-apocodeine [(±)-2], (±)-*N*-*n*-propylnorapomorphine, and (±)-*N*-*n*-propylnorapocodeine.[3a] These aporphines were substituted on the nitrogen atom and on the 10 and 11 position. The procedure was applicable to the synthesis of aporphines not derivable from the naturally occurring opium alkaloids (*i.e.*, morphine and codeine). In continuing these studies[3b] we investigated the structure-activity relationship of such aporphine derivatives as 9,10-dihydroxyaporphines (isoapomorphine), 1,2-dihydroxyaporphines, and 1,2,9,10-tetrahydroxyaporphines. It was of interest to determine the effects produced when the phenolic function in the 10 position of apomorphine was eliminated while varying the substituent on the nitrogen. The synthesis of the 11-hy-

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‡ Deceased Feb 17, 1974.

Table I. Rotational Behavior of Hydroxyaporphines

Compound	Feature	Dose, mg/kg	Total turns/60 min, means ± s.e.m.[b]
Saline			6 ± 2 (4)
(−)-Apomorphine	NCH_3, 10,11-OH	0.25	348 ± 81 (4)
(−)-Apomorphine	NCH_3, 10,11-OH	0.5	449 ± 57 (4)
(−)-Apocodeine	NCH_3, 10-OCH_3, 11-OH	1.0	127 ± 77 (4)
(−)-Apocodeine	NCH_3, 10-OCH_3, 11-OH	5.0	365 ± 89 (4)
(±)-**3e**	NCH_3, 11-OH	10	220 ± 29 (4)
(±)-**3e**	NCH_3, 11-OH	5	65 ± 10 (4)
(±)-**3e**	NCH_3, 11-OH	1	None
(±)-**3h**	NH, 11-OH	10	None
(±)-**3f**	$NCH_2C_6H_5$, 11-OH	10	None
(±)-**3d**	NCH_3, 11-OCH	75	None
(±)-**4a**[a]	NCH, 7-OH	5	None
(±)-**4b**[a]	NH, 7-OH	5	None
(±)-**4b**[a]	NH, 7-OH	10	19 ± 5 (4)
(±)-**5a**	NCH_3, 10-OH	10	11 ± 2 (4)
(±)-**5b**	NC_3H_7, 10-OH	0.25	20 ± 5 (4)
(±)-**5b**	NC_3H_7, 10-OH	1	234 ± 60 (4)

[a] Synthesis and physical properties of these compounds are described in ref 5. [b] All treatment groups were significantly different from saline-treated controls except after treatment with **5a**. Statistical significance according to Student's t test. Number of animals in parentheses.

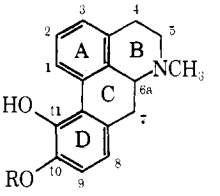
droxyaporphines (**3e–h**) was thus undertaken to determine the necessity of the 10-hydroxy function in apomorphine (**1**) as an extension of our earlier studies. We also wished to assess the effect produced by the complete elimination of the 10- and 11-hydroxyl groups and the insertion of an hydroxyl group in position 7. The 7-hydroxyaporphines **4a,b** have a structural relationship to such sympathomimetic amines as pseudoephedrine and epinephrine. The conversion of dopamine to norepinephrine *via* dopamine hydroxylase results in the insertion of a hydroxyl group in the β position of the catecholamine system. The pharmacological consequence of a hydroxyl function in the 7 position of the aporphine ring has not been investigated nor has it been demonstrated that such a β-hydroxylation does or does not occur in such dopamine-like drugs as apomorphine. The evaluation of the dopaminergic stimulating activity of **4a,b** and **3e–h** would provide further input in assessing the topography of central dopamine receptors.

In this report we wish to describe the total synthesis of a series of racemic aporphines functionally substituted on the 11 position with either OH or OCH_3 and on the nitrogen atom with H, CH_3, n-C_3H_7, or $CH_2C_6H_5$ (**3a–h**, Chart I). The synthesis of (±)-7-hydroxyaporphine (**4a**) and (±)-7-hydroxynoraporphine (**4b**) *via* the 4-oxazolin-2-one system was reported in a preliminary communication from this laboratory.[4] The detailed description of these compounds and their method of preparation as well as the related 7-oxoaporphines will be presented in a forthcoming publication.[5] We now wish to present the dopaminergic activity of these 11-, 10-, and 7-hydroxyaporphines in comparison with apomorphine and apocodeine (Table I).

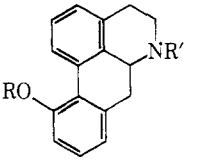
The synthesis of the 11-hydroxyaporphines involved modifications of the Reissert alkylation–Pschorr cyclization sequence (Scheme I) successfully applied to the synthesis of apomorphine and N-alkylapomorphine described previously.[3]

The preparation of 2-nitro-3-methoxybenzyl chloride was carried out by a diborane reduction of commercially available 2-nitro-3-methoxybenzoic acid to 2-nitro-3-methoxybenzyl alcohol followed by reaction with purified thionyl chloride. Reissert alkylation of 1-cyano-2-benzoyl-1,2-dihydroisoquinaldonitrile with 3-methoxy-2-nitrobenzyl chloride gave in 95% yield the alkylated Reissert compound **6**. Alkaline hydrolysis with Triton B[6] gave 1-(3-methoxy-2-nitrobenzyl)isoquinoline (**7**) in 84% yield. Alkylation of **7** with the appropriate halide led to the desired quaternary salts **8a–c** which were reduced with potassium borohydride to the corresponding tetrahydroisoquinoline derivatives **9a–c**. Reduction of the nitro group, followed by Pschorr closure, gave the 11-methoxyaporphines **3a–c**. Demethylation with hydriodic acid produced the desired 11-hydroxyaporphines **3e–g**. 11-Hydroxynoraporphine (**3h**) was obtained *via* hydrogenolysis of the N-

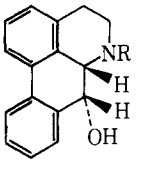
Chart I. Structural Relationship between Monohydroxyaporphines, Apomorphine, Ephedrine, and Epinephrine



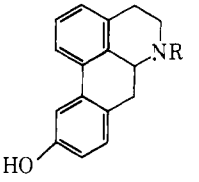
1 (apomorphine), R = H
2 (apocodeine), R = CH_3



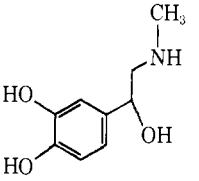
3a, R = CH_3; R′ = CH_3
b, R = CH_3; R′ = $CH_2C_6H_5$
c, R = CH_3; R′ = C_3H_7
d, R = CH_3; R′ = H
e, R = H; R′ = CH_3
f, R = H; R′ = $CH_2C_6H_5$
g, R = H; R′ = C_3H_7
h, R = H; R′ = H



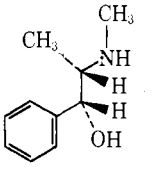
4a, R = CH_3
b, R = H



5a, R = CH_3
b, R = C_3H_7

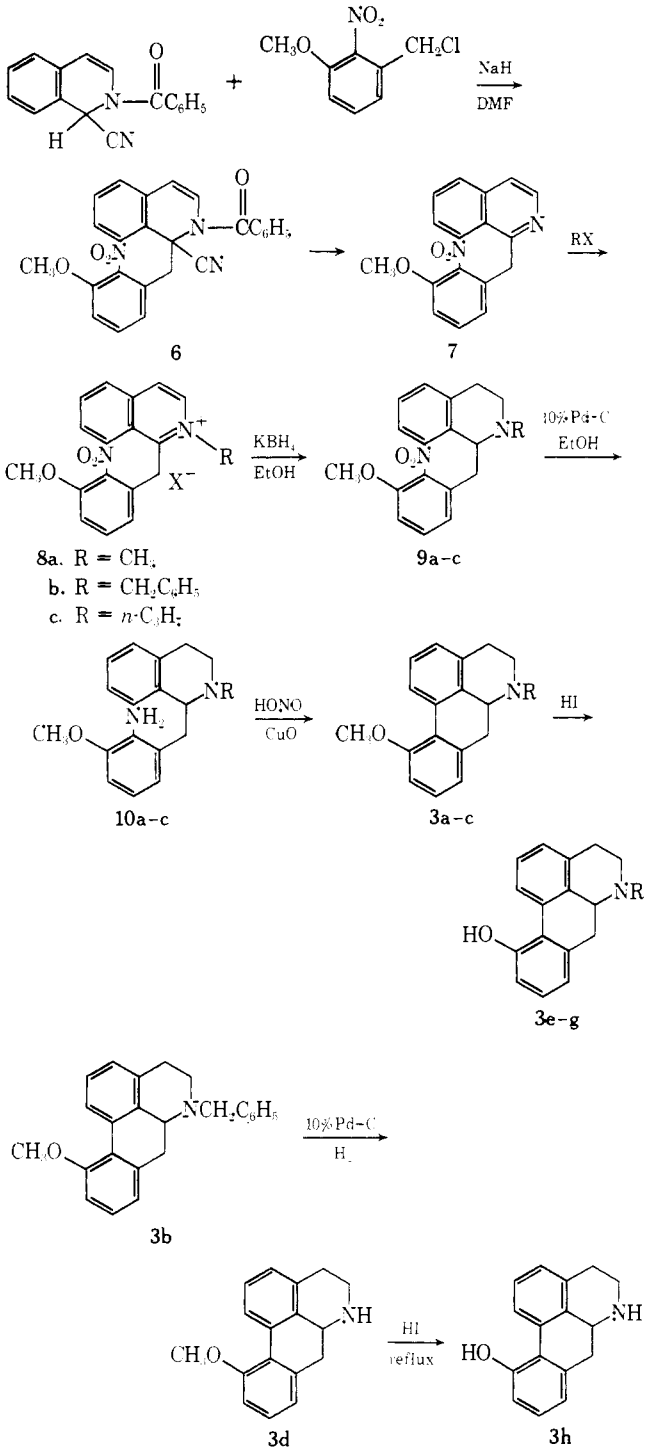


epinephrine



ψ-ephedrine

Scheme I. Synthesis of (±)-11-Hydroxyaporphines



6 7

8a. R = CH_3
b. R = $CH_2C_6H_5$
c. R = n-C_3H_7

9a-c

10a-c 3a-c

3e-g

3b

3d 3h

benzyl intermediate **3b** followed by demethylation with hydriodic acid. The synthesis of **5a** and **5b** will be reported elsewhere.

Pharmacological Data. Ungerstedt and coworkers[7] produced a lesion of the nigrostriatal DA system by intracerebral injection of 6-hydroxydopamine (6-OHDA) into the substantia nigra. Rotational behavior of rats with such lesions is induced by DA receptor agonists toward the innervated side and can be related to the DA receptor activity in the forebrain. Total counts during the first 60 min were used as a measure of the intensivity of the rotational behavior in an attempt not to overestimate the effects of the weak DA receptor agonists with long duration of action. The rat was fitted with a harness which was attached to a flexible wire by means of luer lock connectors allowing the animal full freedom of motion without disturbance. Rotations were automatically recorded by a microswitch and a counter on the other end of the wire. Only full turns activate the switch. The animal is placed in a bowl and has enough freedom of movement to climb to the edges. Most of the time the control animal remains quiet and in its inquisitive movements only makes a few turns in either direction.

A 6-OHDA lesioned animal also showed exploratory activity and made 2-4 turns/min for 3-5 min. The animal then stopped and behaved like the normal and sham-operated animals.

The lesions were carried out by injecting 4 μl of a cold Ringer solution containing 8 μg of 6-OHDA over a period of 4 min with a motor-driven Agla syringe through a Hamilton cannula placed rostral to the left substantia nigra.

Normally the DA cell bodies of the substantia nigra reveal a green fluorescence in the fluorescence microscope. One day after the injection of the 6-OHDA the cell bodies showed orange-yellow fluorescence and no signs of regeneration of the cells were observed 2-8 weeks after the injection.

The candidate aporphines were injected ip and where activity was observed the rotational behavior was similar to apomorphine, *i.e.*, to the innervated side. The results of these experiments are shown in Table I. 11-Hydroxyaporphine (**3e**) showed activity in a dose of 10 mg/kg, but 10-hydroxyaporphine (**5a**) lacked effect in this dose, and 7-hydroxynoraporphine (**4b**) had only very slight activity with the same dose. The 11-hydroxyaporphine was only weakly active when compared with apomorphine. The same was true for apocodeine although being more active than 3e. 10-Hydroxyaporphine became active when an n-propyl group was replaced by the methyl group on the nitrogen.

Discussion and Conclusions

The rotational behavior of such racemic monohydroxyaporphines as 11-hydroxyaporphine (3e) and 10-hydroxy-*N*-*n*-propylnoraporphine (**5b**) would indicate that the catechol system is not a structural requirement for dopamine-like activity. Also it has been found[8] that m-tyramine probably can directly activate DA receptors. In view of the findings[3a,9] that the CNS activity of apomorphine and *N*-*n*-propylnorapomorphine[10] (NPA) resides in the (−) isomer (*6a,R*) and that the (+) isomer (*6a,S*) is relatively inactive, the activity of (±)-3e is significant. Recent studies[11] with such monohydroxyaporphines as **3e**, **3g**, **5a**, and **5b** on the stereotyped behavior of the rat have supported these results. Stereotyped behavior was observed after the administration of either 10- or 11-hydroxy-*N*-*n*-propylnoraporphine (**3g**). Comparison of the ED_{50} values for these compounds with that of the dihydroxy compound (±)-NPA indicates that they are active but less potent than NPA and apomorphine, in agreement with the present results.

Lal, *et al.*,[12] and Smith and Cook[13] concluded that the pharmacological activity of apocodeine (**2**) in the rat was due to its conversion to apomorphine (1) and/or norapomorphine. It is important for us to emphasize in the light of our findings that the observed activity of the monohydroxyaporphines 3e and **5b** may be due to a metabolic hydroxylation.

These results would suggest that a catechol ring system, as in apomorphine (1) or NPA, produces optimum interactions with the DA receptor but is not a necessary requirement. However, the topography of the central DA receptor is still not defined and on the basis of these and previous studies, one may conclude that apomorphine may not represent the optimum structure for dopamine-like effects.

Experimental Section

Melting points were obtained on a Gallenkamp and Fisher-Johns apparatus. Infrared spectra were recorded on a Perkin-Elmer 521 and 237 grating spectrophotometer. Ultraviolet spectra were recorded on a Beckman DK recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer with TMS as the internal standard. Mass spectra were recorded on a Du Pont Consolidated Electrodynamics Corp. 21-110B high-resolution spectrometer. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Galbraith Laboratories, Inc., Knoxville, Tenn. Where analyses are indicated by symbols of elements, the analytical results were within ±0.4% of the theoretical value.

2-Nitro-3-methoxybenzyl Alcohol.§ A 1 *M* solution of borane in tetrahydrofuran (180 ml) was added dropwise to a solution of 29.5 g (0.15 mol) of 2-nitro-3-methoxybenzoic acid (Aldrich) in 600 ml of dry tetrahydrofuran at room temperature. During the first 115 ml of borane addition some bubbling was evident and the rate of addition was adjusted accordingly. No temperature rise was observed during the addition (20–40 min). The solution was stirred for 1 hr, another 75 ml of the borane solution was added, and the mixture allowed to stir overnight at room temperature. The solution was carefully decomposed with water at 10–15° and then diluted further with 400 ml of water. The mixture was extracted with ether; the extract was washed with saturated brine and dried over magnesium sulfate. After filtering, the solution was evaporated to give 27.8 g of a yellow oil which solidified on cooling: mp 62–72°. A small sample, recrystallized from water, gave platelets: mp 68–70° (lit. mp 71°); ν_{max} (Nujol) 3350, 1520, 1370, 1280, 1050, 1025 cm^{-1}; nmr (DMSO-d_6) δ 3.85 (s, 3), 4.5 (d, J = 5 Hz, 2), 5.43 (t, J = 5 Hz, 1, OH), 7.13 (m, 2), 7.47 (dd, 1).

2-Nitro-3-methoxybenzyl Chloride. Freshly purified thionyl chloride[15] (66.5 g, 0.56 mol) was added dropwise to a mixture of 44 g (0.24 mol) of 2-nitro-3-methoxybenzyl alcohol and 21.8 g (0.27 mol) of pyridine (stored over potassium hydroxide and filtered before use) at 15–20°. When the pyridine was consumed the addition of thionyl chloride could be carried out more rapidly (20 min). The mixture was heated at 60° for 15–20 min and then allowed to stir at room temperature for 24 hr. The solution was poured into 600 ml of ice water and the precipitate filtered. The product was washed with water until neutral and dried to give 34.5 g (71.5%) of the chloride. Recrystallization from 1300 ml of hexane yielded 31.6 g (66%): mp 74–78° (lit.[12] mp 76°); ν_{max} (Nujol) 1520, 1370, 1075 cm^{-1}.

2-Benzoyl-1-(2-nitro-3-methoxy)benzyl-1,2-dihydroisoquinaldonitrile (6). Sodium hydride (5 g, 0.12 mol, 57% mineral oil suspension) was added all at once to a mixture of 31.2 g (0.12 mol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile,[16] 24.1 g (0.12 mol) of 2-nitro-3-methoxybenzyl chloride, and 480 ml of dimethylformamide (Matheson Coleman and Bell spectro grade). The mixture was allowed to stir overnight at room temperature and then poured into 2100 ml of ice water. After standing for 30 min the precipitate was filtered, washed with water until neutral, and dried to give 48.7 g (95%): mp 90–110°. Trituration with cold 95% alcohol raised the melting point to 170–173°. A small sample was recrystallized from 95% ethanol: mp 180–182°; ν_{max} (Nujol) 1670, 1640, 1520, 1330, 1280, 1250, 1080 cm^{-1}; λ_{max} (EtOH) 300 nm (br, ϵ 10,000); nmr ($CDCl_3$) δ 3.43 (d, J = 14 Hz, 1), 3.89 (d, J = 14 Hz, 1), 3.76 (s, 3), 5.48 (d, J = 8 Hz, 1) 6.36 (d, J = 8 Hz, 1), 6.6–7.7 (m, 12). *Anal.* ($C_{25}H_{19}N_3O_4$) C, H, N.

1-(3-Methoxy-2-nitrobenzyl)isoquinoline (7). Hydrolysis with Methanolic Potassium Hydroxide. Powdered, dry potassium hydroxide (0.4 g, 7.1 mmol) was added all at once to a suspension of 0.5 g (1.18 mmol) of 2-benzoyl-1-cyano-1-(2-nitro-3-methoxybenzyl)isoquinoline (6) in 8 ml of methanol. The mixture was allowed to reflux for 5 min with vigorous stirring and poured onto ice. The mixture was extracted with ether, and the extract was washed with water and saturated brine and dried. The solution was filtered and evaporated to dryness which on trituration with acetonitrile gave 0.20 g (58%) of 7, mp 128–131°.

Hydrolysis with Triton B.[6] A solution of 0.5 g of 6 in 7 ml of dimethylformamide was cooled in ice and 0.7 ml of Triton B was added all at once. The dark solution was stirred for 1 hr at room temperature and poured into ice. The precipitate was washed with water and dried to give 0.25 g (71%) of crude product, mp 123–125°.

§ The literature method[14] involved nitration of *m*-anisaldehyde followed by reduction of the aldehyde. The nitration step could not be duplicated without the formation of considerable amounts of 2-nitro-5-methoxybenzaldehyde and 2,6-dinitro-3-methoxybenzaldehyde as by-products.

A large-scale hydrolysis was carried out with 20 g (0.047 mol) of 6 using 26 ml of Triton B in 200 ml of dimethylformamide. The reaction mixture was worked up in the same manner to give 11.5 g (84%) of 7. A small sample recrystallized from acetonitrile had mp 131–132°: ν_{max} (KBr) 1600, 1580, 1560, 1520, 1285 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 318 (5.20), 305 (4.47), 280 (5.45), 260 (6.35), 220 (5.20); nmr (DMSO-d_6) δ 3.83 (s, 3), 4.58 (s, 2), 6.57 (dd, J = 8.1 Hz, 1), 6.83 (dd, J = 8.1 Hz, 1), 7.06 (m, 1), 7.54 (d, J = 6 Hz, 1). *Anal.* ($C_{17}H_{14}N_2O_3$) C, H, N.

1-(3-Methoxy-2-nitrobenzyl)isoquinoline Methiodide (8a). A solution of 11.5 g (0.039 mol) of 1-(3-methoxy-2-nitrobenzyl)isoquinoline (7) in 70 ml of methyl iodide was allowed to reflux for 20 hr and cooled and the resulting methiodide was filtered and washed with ether and dried to yield 12.7 g (75%): mp 198–200°; ν_{max} (Nujol) 1520, 1370, 1270 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 330–340 (4.79), 270 (5.2), 235 (3.58); nmr (DMSO-d_6) δ 3.99 (s, 3), 4.47 (s, 3), 5.17 (s, 2), 6.39 (m, 1), 7.42 (m, 2), 8.0–8.7 (m, 4), 8.75 (d, J = 7 Hz, 1), 8.96 (d, J = 7 Hz, 1). *Anal.* ($C_{18}H_{17}IN_2O_3$) C, H, N.

2-Benzyl-1-(3-methoxy-2-nitrobenzyl)isoquinolinium Bromide (8b). A mixture of 3 g (0.01 mol) of 1-(3-methoxy-2-nitrobenzyl)isoquinoline (7) and 15 ml of benzyl bromide was slowly heated to 90° with stirring in the course of 3 hr and held at 85–90° for 4 hr. The mixture was cooled, and the precipitate was filtered, washed with ether, and dried to give 3.3 g (70%): mp 210–212°. A small analytical sample was prepared from 100 mg of product: mp 215–218° dec; ν_{max} (Nujol) 3050, 1630, 1610, 1599, 1530, 1370, 1290 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 330–345 (5.92), 260 (8.43), 235 (37.1); nmr (DMSO-d_6) δ 3.94 (s, 3), 5.21 (s, 2, CH_2, D_2O exchanges), 6.15 (m, 1), 6.2 (s, 2), 7.28 (m, 2), 7.33 (s, 5), 7.95–8.63 (m, 4), 8.82 (d, 1, J = 7 Hz), 9.12 (d, 1, J = 7 Hz). *Anal.* ($C_{24}H_{21}BrN_2O_3$) C, H, N.

Similarly prepared from 7 and 1-iodopropane was **1-(3-methoxy-2-nitrobenzyl)isoquinoline propiodide (8c).** Thus a solution of 5 g (0.017 mol) of 1-(3-methoxy-2-nitrobenzyl)isoquinoline (7) in 40 ml (69.7 g, 0.41 mol) of 1-iodopropane gave 5.1 g (64%) of 8c: mp 250° dec; ν_{max} (Nujol) 1520, 1370, 1270, 1060 cm^{-1}. *Anal.* ($C_{20}H_{21}IN_2O_3$) C, H, N.

1-(3-Methoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (9a). A mixture of 436 mg (1.0 mmol) of 8a, 5 ml of absolute ethanol, and 26 mg (0.5 mmol) of potassium borohydride was stirred vigorously at room temperature. On half-hour intervals 13 mg of potassium borohydride was added and after three additions 0.25 ml of water was introduced. After another hour of stirring the mixture was filtered and the product dried to give 182 mg, mp 101–102° (contained a small amount of inorganic material). The filtrate was diluted with twice its volume of water to obtain a second crop of 82 mg: mp 96.5–97.5°; total yield 84.5%. For analytical purposes a small sample was washed with water, followed by recrystallization from methanol: mp 100°; ν_{max} (Nujol) 1615, 1580, 1520, 1370, 1270, 1080 cm^{-1}; nmr ($CDCl_3$) δ 2.37 (s, 3), 2.9 (m, 6), 3.84 (m, 1), 3.87 (s, 3), 6.75 (dd, 2), 7.05 (m, 1), 7.35 (m, 4). *Anal.* ($C_{18}H_{20}N_2O_3$) C, H, N.

2-Benzyl-1-(3-methoxy-2-nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (9b). A mixture of 465 mg (0.001 mol) of 8b in 15 ml of tetrahydrofuran and 100 ml of absolute ethanol was brought to reflux and 26 mg of potassium borohydride was added. The solution cleared and the temperature was allowed to come to room temperature. On half-hour intervals 26 mg of potassium borohydride was added to the solution. After three additions the mixture was stirred for 2 hr followed by one more addition of 26 mg of potassium borohydride and 1 ml of water. The solution was stirred for 1 hr and evaporated; the residue was treated with water and extracted with ether. The extract was washed, dried, and evaporated, and the resulting oil was chromatographed on a column of Adsorbosil (9.5 × 0.75 in.). Elution with a mixture of benzene and petroleum ether (6:4) gave 151 mg of an impure sample of the 1,2-dihydro intermediate. The column was then eluted with a mixture of 48% benzene, 32% petroleum ether, and 20% methanol to give an oil weighing 125 mg (32.2%): nmr ($CDCl_3$) δ 2.25–3.33 (m, 4), 3.52 (d, 1, J = 14 Hz), 3.73 (d, 1, J = 14 Hz), 3.85 (s, 3), 6.77 (dd, 1, J = 1 Hz), 6.8–7.5 (m, 6), 7.08 (s, 5).

The borohydride reduction was repeated on 1.7 g (0.0036 mol) of the quaternary salt to give 624 mg (44%) of **9b** after column chromatography as above.

1-(3-Methoxy-2-nitrobenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (9c). Reduction of 8c with potassium borohydride in absolute ethanol was carried out as described for the reduction of 8a to give an 89% yield of **9c**: mp 85–90°. The product was recrystallized from ethanol: mp 94–95.5°; ν_{max} (Nujol) 1520, 1370, 1280, 1270 cm^{-1}; nmr ($CDCl_3$) δ 0.69 (t, 3), 1.0–1.5 (m, 2), 2.25–2.5 (m,

2), 2.6–3.1 (m, 4), 3.75 (m, 1), 3.79 (s, 3), 6.6–7.25 (m, 7). *Anal.* ($C_{20}H_{24}N_2O_3$) C, H, N.

1-(2-Amino-3-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (10a). A solution of 2.4 g (7.8 mmol) of **9a** in 310 ml of absolute alcohol was shaken with 0.5 g of 10% Pd-C for 17 hr and filtered and the solvent was removed under reduced pressure to yield 1.9 g (87%) of an oil. A small sample of the oil in ether was acidified with ethereal hydrogen chloride to give a dihydrochloride monohydrate as an amorphous off-white solid: mp 168–173° dec; nmr (D_2O) δ 2.98 (s, 3), 3.35 (m, 6), 3.92 (s, 3), 6.25 (m, 3), 6.75–7.4 (m, 4). Without further purification the amino derivative was converted to 11-methoxyaporphine (**3a**).

11-Methoxyaporphine Hydroiodide (3a). 1-(2-Amino-3-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**10a**) (0.9 g, 0.0067 mol) in 16 ml of 10% sulfuric acid was treated with 8 ml of 2 *N* sodium nitrite solution at −5 to 0°. After 15–20 min the excess nitrous acid was decomposed with a small quantity of sulfamic acid and the cold solution was added dropwise to a vigorously stirred mixture of 127 ml of 10% sulfuric acid and 6.8 g of cuprous oxide at −5°. After 40 min the solution was filtered and the filtrate was made basic with concentrated ammonium hydroxide. The basic solution was extracted with ether, and the extract was washed with water and saturated brine, dried, filtered, and evaporated. The oil was dissolved in 12 ml of acetone, made acidic with several drops of 57% hydriodic acid, and cooled in ice to give 144 mg of **3a**·HI. The filtrate was evaporated and the residue triturated with a small volume of acetone to give a second crop of 50 mg of the hydroiodide.

The inorganic material was suspended in concentrated ammonium hydroxide until nearly complete solution was obtained and the mixture extracted with chloroform until no further color was extracted; the chloroform solution was washed, dried, filtered, and evaporated to give a further quantity of oil. Acidifying the oil with 57% hydriodic acid in acetone provided another 541 mg of product, mp 233–235° dec. The combined yield of **3a** was 735 mg (27.7%): ν_{max} (KBr) 2900, 2550–2680, 1590, 1260 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$), 302 (7.63), 290 (7.90), 275 (14.9), 265 (15.0); nmr (DMSO-d_6) δ 3.17 (s, 3), 3.91 (s, 3), 4.3 (br, 1), 2.8–4.0 (m, 6), 7.22 (m, 5), 8.22 (dd, 1). *Anal.* ($C_{18}H_{20}INO$) C, H, N.

11-Hydroxyaporphine Hydroiodide (3e). To a suspension of 300 mg (0.00076 mol) of 11-methoxyaporphine (**3a**) hydroiodide in 1.5 ml of 57% hydriodic acid was carefully added 1.5 ml of acetic anhydride. The solution was heated at 140° for 1.5 hr during which time the product crystallized. The off-white crystals were filtered, washed with acetone and ether under nitrogen, and dried to yield 214 mg (74%) of **3e**: mp 270° dec (DTA); ν_{max} (KBr) 3300, 2920, 2720, 1590, 1460, 1270 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 305 (7.95), 272 (13.9), 265 (14.5). *Anal.* ($C_{17}H_{18}INO$) C, H, N.

1-(2-Amino-3-methoxybenzyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (10b). A solution of 624 mg (0.0016 mol) of **9b** in 25 ml of absolute ethanol was shaken with 350 mg of platinum oxide at 50 lb of hydrogen to give 550 mg (96%) of an oil: ν_{max} (neat) 3430, 3330, 1610, 1570, 1470, 1270, 1240 cm^{-1}. Without further purification this material was used in the subsequent Pschorr reaction.

6-Benzyl-11-methoxynoraporphine (3b). A solution of 550 mg (0.00153 mol) of the amine **10b** in 4 ml of 10% sulfuric acid was diazotized with 2 ml of 2 *N* sodium nitrite at −5 to 0°. After destroying excess nitrous acid with sulfamic acid, the diazotized solution was added dropwise to a mixture of 1.7 g of cuprous oxide and 30 ml of 10% sulfuric acid at −5°. The foamy mixture was allowed to slowly come to room temperature and remain in the flask for 16 hr. The mixture was cooled, made basic with concentrated ammonium hydroxide, and extracted with ether. The extract was washed, dried, and evaporated and the oily residue chromatographed on an Adsorbosil column (8 × 0.75 in.) using a mixture of benzene, petroleum ether, and methanol (6:4:0.1). Collecting 50-ml fractions 374 mg (71%) of the product emerged in fractions 7–10 as a red oil.

The Pschorr reaction was repeated on 2.4 g (0.0067 mol) of **10b** to give after chromatography 0.9 g (40%) of **3b**: ν_{max} (KBr) 2930, 2830, 2800, 1585, 1470, 1440, 1430, 1250, 1080 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 302 (5.43), 290 (6.64), 272 (10.85); nmr ($CDCl_3$) δ 2.3–3.8 (m, 7), 3.31, 4.3 (d, J = 14 Hz, 2), 3.82 (s, 3), 6.6–7.5 (m, 4), 7.34 (m, 5), 8.16 (dd, 1).

This oil was used in the demethylation and debenzylation steps.

6-Benzyl-11-hydroxynoraporphine Hydroiodide (3f). To a solution of 200 mg (0.58 mmol) of 6-benzyl-11-methoxynoraporphine (**3b**) in 1.5 ml of 55% hydriodic acid was added dropwise 1.5 ml of acetic anhydride. The solution was heated at 135–140° for 2.5 hr and then cooled in ice water. The solution was diluted with water until precipitation ceased and the light yellow crystals were filtered and washed with water to yield 100 mg (38%) of **3f**·HI: mp 195° dec; ν_{max} (KBr) 3250, 2920, 2850, 1580, 1430, 1270 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 300 (6.4), 272 (12.0), 265 (12.39). *Anal.* ($C_{23}H_{22}INO$) C, H, N.

11-Methoxynoraporphine (3d). A solution of 0.9 g (0.0026 mol) of 6-benzyl-11-methoxyaporphine (**3b**) in 20 ml of absolute ethanol was shaken with 600 mg of 10% Pd-C for 16 hr under 50 lb of hydrogen. The solution was filtered and evaporated, and the residue was triturated with acetone. The solid product was filtered, dissolved in about 15 ml of water, and treated with an aqueous solution of sodium sulfite until precipitation ceased. The product was filtered, washed with water, and dried to give 80 mg (12%) of **3d**: mp 114–116°; ν_{max} (KBr) 3310, 1590, 1430, 1250, 1080, 1050, 740 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 302 (0.68), 292 (12.5), 275 (18.9); mass spectrum (70 eV) m/e (M^+), 250, 249. *Anal.* ($C_{17}H_{17}NO$) C, H, N.

11-Hydroxy-*N*-*n*-propylnoraporphine Hydroiodide (3g). Demol) of **3d** in 3 ml of 55% hydriodic acid was treated carefully with 2 ml of acetic anhydride and allowed to reflux for 2 hr. The clear solution was stored in the refrigerator overnight and neutralized with sodium sulfite, and the precipitate was filtered. The product was washed with water and dried to give 30 mg (41%) of **3h**: mp 255° dec; ν_{max} (KBr) 3150, 2910, 2810, 1590, 1440, 1265 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 305 (7.28), 271 (12.5), 265 (13.6); mass spectrum (70 eV) m/e 237 (M^+), 236, 218, 208. *Anal.* ($C_{16}H_{16}INO$) C, H, N.

1-(2-Amino-3-methoxybenzyl)-2-propyl-1,2,3,4-tetrahydroisoquinoline (10c). A solution of 1.9 g (0.0056 mol) of **9c** in 125 ml of absolute ethanol was reduced with hydrogen over 0.5 g of 10% Pd-C as described for **10a** to give 1.68 g (96%) of the amine **10c** as an oil: ν_{max} (neat) 3350, 3220, 1630, 1570, 1490, 1220 cm^{-1}. Without further purification the oily product was used in the subsequent Pschorr reaction.

11-Methoxy-6-propylnoraporphine Hydroiodide (3c). Cyclization of 1.68 g (0.0054 mol) of **10c** was carried out as described for **10a** and **10b** to give 0.83 g (36%) of **3c**: mp 264° dec; ν_{max} (KBr) 3005, 2890, 2700, 2665, 2590, 1585, 1570, 1470, 1430, 1250, 1080, 1050 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 300 (8.0), 290 (9.0), 272 (14.55), 265 (14.55); nmr (DMSO-d_6) δ 1.05 (t, 3), 1.8 (br, 2), 1.8–3.8 (m, 8), 3.81 (s, 3), 4.2 (br, 1), 7.0 (m, 5), 7.95 (dd, 1). *Anal.* ($C_{20}H_{24}INO$) C, H, N.

11-Hydroxy-*N*-*n*-propylnoraporphine Hydroiodide (3g). Demethylation of **3c** was carried out as described for **3a** to give a 63% yield of **3g**: ν_{max} (Nujol) 3200, 2650, 1595, 1270, 1200, 800, 750 cm^{-1}; λ_{max} (EtOH) nm ($\epsilon \times 10^{-3}$) 305 (7.4), 272 (12.7), 265 (13.3); nmr (DMSO-d_6) δ 1.07 (t, 3), 1.8 (br, 2), 2.8–4.0 (m, 8), 4.25 (br, 1), 6.7–7.3 (m, 5), 8.1 (dd, 1), 9.41 (br, 1); mass spectrum (70 eV) m/e 279 (M^+), 278, 250. *Anal.* ($C_{19}H_{22}INO$) C, H, N.

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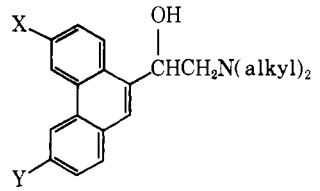
Synthesis and Antimalarial Evaluation of 9,10-Dihydrophenanthrene Amino Alcohols†

Adrienne S. Dey and John L. Neumeyer*

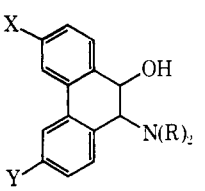
Department of Medicinal Chemistry and Pharmacology, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115. *Received March 4, 1974*

A new series of 9-alkylamino-9,10-dihydro-10-hydroxyphenanthrenes and 9-alkylaminophenanthrenes has been prepared. Compounds of this series are related to the phenanthrene amino alcohols which have been known to be active antimalarials and are distinguished in possessing a biphenyl ring system bearing an α-hydroxy-β-substituted amino side chain in place of the 9-substituted phenanthrene ring bearing an α-hydroxy-ω-alkylamino side chain. The compounds were inactive and nontoxic in the antimalarial screen. The compounds were synthesized through the 9,10-epoxy-9,10-dihydrophenanthrenes 11, one of which (11c) showed a mean survival time of 4 days at 640 mg/kg in mice infected with *Plasmodium berghei*.

The phenanthrene amino alcohols 1 are a class of active antimalarial compounds which emerged during World War II and have been actively reinvestigated in the current antimalarial programs.[1,2] Our rationale for the synthesis of compounds of type **2** was based on the structural analogy of **2** to the active phenanthrene-type antimalarials of type **1**. Numerous structure-activity studies encom-



1, X, Y = Cl, Br, CF_3, H



2, X, Y = H, CF_3, Br

passing many hundreds of individual drugs have demonstrated that arylamino alcohol antimalarials of maximum activity require a polycyclic aromatic ring system bearing an α-hydroxy-ω-(alkyl-substituted)amino side chain and additional electron-withdrawing hydrophobic substituents. We wished to assess the structural requirements of such arylamino alcohols by preparing a series of 9-amino-10-hydroxy-9,10-dihydrophenanthrenes. In the series (Table I) reported in this paper, the polycyclic aromatic ring system can be considered as a substituted biphenyl system bearing an α-hydroxy-β-substituted bridge. The biological activity of these compounds against *Plasmodium berghei* infections in mice and *Plasmodium gallinaceum* infections in chicks was determined.

Chemistry. Our initial approach[3] to the synthesis of such 9,10-dihydrophenanthrenes **2** involved a photochemical cyclization of a substituted stilbene incorporating the 4-oxazolin-2-one ring system (Scheme I). Although successful in producing the substituted phenanthrene (**5**), this method did not prove advantageous for the synthesis of the desired compounds.

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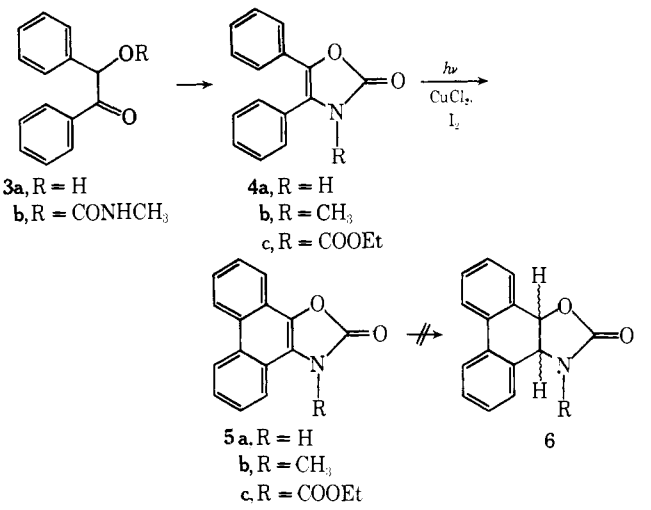
Scheme I



3a, R = H
b, R = $CONHCH_3$

4a, R = H
b, R = CH_3
c, R = COOEt

5a, R = H
b, R = CH_3
c, R = COOEt

6

Benzoin (**3a**) and methyl isocyanate in the presence of pyridine were caused to react to give the carbamate **3b** which in refluxing glacial acetic acid yielded 3-methyl-4,5-diphenyloxazolin-2-one (**4b**).[4] **4b** could also be prepared by the N-alkylation of **4a** with sodium hydride and methyl iodide in DMF. 3-Carbethoxy-4,5-diphenyloxazolin-2-one (**4c**) was similarly prepared from **4a** and ethyl chloroformate. Photolysis fo **4b** in ethanol in the presence of $CuCl_2$ and iodine with a 100-W medium pressure mercury lamp enclosed in a quartz probe which was immersed directly in the water-cooled reaction mixture gave 70% yield of **5b**. Photolysis of **4a** gave 35% of **5a** as yellow crystalline flakes. Carbethoxyphenanthro[9,10-*d*]oxazolin-2-one (**5c**) was prepared from **5a** with sodium hydride in DMF and ethyl chloroformate to give 54% of **5c**. Attempts to reduce the phenanthrene derivatives **5a-c** to the 9,10-dihydro compounds **6** under a variety of conditions failed. To overcome this difficulty we attempted an alternative approach to the preparation of **6**. Irradiation of **4b** in a degassed medium under nitrogen by the procedure recently reported by Srinivasan[5] failed to give the desired product