apocodeine to give 0.89 g (20%) of off-white waxy prisms, homogeneous in tlc. Concentration of the mother liquors caused severe discoloration and no additional apocodeine could be recovered.

The waxy solid was recrystallized from MeOH containing a little CH_2Cl_2 to give colorless prisms, which were crushed and stored under high vacuum to remove what was apparently solvent of crystallization. The colorless powder had mp 122–124° (softening above 100°) and was identical with that obtained by rearrangement of codeine (lit.[6] mp 122.5–124.5°).

Tlc indicated that the yield in this methylation reaction was essentially quantitative. Because the product is very sensitive to light and to air, the yield is controlled by the sophistication of the work-up procedure.

Acknowledgments. We wish to thank Dr. E. R. Atkinson for helpful discussions, Dr. G. R. Handrick for the preparation of a number of compounds, and Dr. F. C. Nachod for assistance in the preparation of the manuscript.

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Aporphines. 9.[1] Synthesis and Pharmacological Evaluation of (±)-9,10-Dihydroxyaporphine [(±)-Isoapomorphine], (+)-, (−)-, and (±)-1,2-Dihydroxyaporphine, and (+)-1,2,9,10-Tetrahydroxyaporphine†

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The synthesis and preliminary pharmacological evaluation of the title compounds **2**–**4** are described and compared with those of (−)-nuciferine and (−)-apomorphine [(−)-**1**]. The method used for the synthesis of (±)-**2** involved modifications of the Reissert alkylation–Pschorr cyclization route previously employed for the synthesis of apomorphine and apocodeine. Two alternative sequences of reactions (**9a** → **10a** → **13a** → **13b** → **13c** or **9a** → **9b** → **10b** → **13c**) were investigated for the preparation of the Pschorr precursor **13c**. O-Demethylation of (±)-**6**, nuciferine, and glaucine was accomplished with 57% HI in Ac_2O to give the desired hydroxyaporphines **2**–**4**. The pharmacological results indicated that emetic and CNS activity resides principally in those aporphines that are substituted with phenolic hydroxyl groups in the 10 and 11 positions. Shifting the hydroxyl groups to positions 9,10 or to positions 1,2 markedly reduced pharmacological potency. Similarly, the tetrahydroxyaporphine substituted in the 1,2,9,10 positions also markedly reduced the activity in comparison with apomorphine.

In our previous study[1] we described the successful total synthesis of five racemic aporphines functionally substituted on the nitrogen atom and on the 10 and 11 positions. The procedure was applicable to the synthesis of aporphines not derivable from the naturally occurring opium alkaloids (*i.e.*, morphine and codeine). Preliminary pharmacological evaluation of (−)-apomorphine and (±)-apomorphine and their corresponding *N*-propyl homologs indicated that they were qualitatively similar in their pharmacological effects but that the racemic compounds were approximately half as potent in their emetic effects in dogs as their respective levo isomers.[1] In a continuing study of the structure–activity relationships of aporphine derivatives, we undertook the synthesis of (±)-9,10-dihydroxyaporphine [isoapomorphine (±)-**2**] and the preparation of (−)-, (+)-, and (±)-1,2-dihydroxyaporphine [(−)-**3**, (+)-**3**, and (±)-**3**] and (+)-1,2,9,10-tetrahydroxyaporphine [(+)-**4**].‡

† Presented in part at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, MEDI 37.

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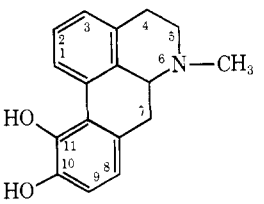
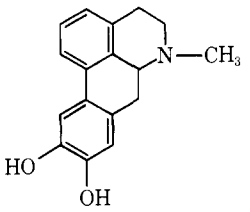
‡ These nuciferine isomers were supplied through the courtesy of Dr. Bryce Douglas, Smith Kline and French Laboratories. Glaucine is commercially available.

The comparative effects of these dihydroxy aporphines are of particular interest in that they can all be considered as analogs of dopamine (5) and phenethylamine (Chart I). Ernst[2] described a relationship between the activity of dopamine and apomorphine and their O-methylated derivatives in the CNS. We wish to report the pharmacological effect of placing phenolic groups in the 1,2, 9,10, and 1,2,9,10 positions and the comparisons of these hydroxyaporphines with apomorphine (1), its O-methylated derivative,[1] and with nuciferine, the O-methylated derivative of 3 (Table I).

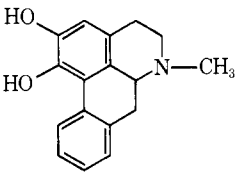
Chart I. Structural Relationship between Aporphines and Dopamine



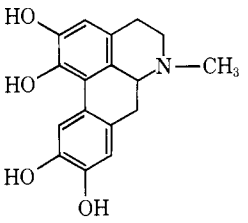
1, apomorphine



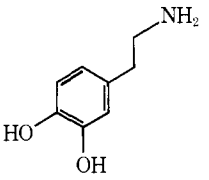
2, isoapomorphine (9,10-dihydroxyaporphine)



3, 1,2-dihydroxyaporphine



4, 1,2,9,10-tetrahydroxyaporphine



5, dopamine

The synthesis of (±)-9,10-dihydroxyaporphine (±)-2 involved modifications of the procedure successfully employed for the synthesis of apomorphine (1) described in our previous paper.[1] The route employed for the synthesis of apomorphine and apocodeine analogs could not be directly applied to the synthesis of (±)-2 because of the unusual carbon–carbon cleavage caused by KBH_4 in the reduction of the nitrobenzylisoquinolinium salt 10b[3] (Scheme I). In order to avoid this complication, alternative methods were then designed for the preparation of the desired Pschorr precursor 13c. 3,4-Dimethoxybenzylisoquinoline (9a) was prepared by the alkylation of the Reissert compound 7 with α-chloro-3,4-dimethoxytoluene (8) in 79% yield and nitrated to 9b in 39% yield. The position of nitration was confirmed by nmr spectra, as well as by reductive cleavage of the derived quaternary salt 10b with KBH_4 to the known 4,5-dimethoxy-2-nitrotoluene (12) and 2-methyl-1,2,3,4-tetrahydroisoquinoline (11). The reduction of the nitro group in 10b with Pd/C was followed by borohydride reduction of the amine 10c, thus avoiding formation of the cleavage products.§ The Pschorr precursor 13c could also be obtained directly from 10b by the catalytic reduction of both the isoquinoline ring and the nitro group with PtO_2 by a procedure developed previously in our laboratory for the synthesis of aporphine.[4,5] An alternative sequence of reactions 9a → 10a → 13a → 13b → 13c was also investigated for the preparation of the Pschorr precursor 13c. This method offered few advantages in either ease of preparation or in the yield of products obtained. The amine 13c could be obtained from the nitro compound 13b by either catalytic reduction or by reduction with zinc and dilute H_2SO_4 but not by the literature procedure[6] employing stannous chloride and HCl. The reduction product 13c was characterized as its dipicrolonate in both successful reactions but could not be isolated as the free base in a pure state.

The amine 13c was converted to the aporphine (±)-6 by a modified Pschorr cyclization procedure in 22% yield. The dimethoxyaporphine (±)-6 was purified as the free base by sublimation, mp 132–133°, and further characterized as the hydroiodide salt, mp 265° (dta).= O-Demethylation was accomplished by the procedure (57% HI in Ac_2O) that has been used successfully for the synthesis of apomorphine[8] and *N*-alkylnorapomorphine derivatives[1] and gave 92% of crystalline 9,10-dihydroxyaporphine hydroiodide [(±)-2·HI], mp 286° (dta). For the preparation of (−)-, (+)-, and (±)-3 we were able to obtain samples of (+)-, (−)-, and (±)-nuciferine‡ which were similarly O-demethylated to the corresponding phenols. For the preparation of the tetrahydroxyaporphine (+)-4 [(+)-*O*-desmethylglaucine], (+)-glaucine** was O-demethylated in 71% yield.

Pharmacological Data. Pharmacological activity was evaluated using a mouse screen,[10] dog emesis screen,[11] and overt behavior in the monkey. All animals were medicated intravenously. For the mouse screen, ED_{50} values and fiducial limits were calculated for each response. For the emesis and overt behavior tests, the lowest dose able to elicit a response in any of the animals tested was used as an indication of the minimal effective dose. The minimal effective dose was thus based on actual values. The minimum effective dose values serve to show the existence of large potency differences.

Shifting the two hydroxyl groups of apomorphine (1) from the 10,11 positions in the D ring to the 9,10 positions as in isoapomorphine [(±)-2], or to the 1,2 positions in the A ring as in 3, reduced potency in all three tests (Table I). Where values were obtained for the low level of activity as shown in the mouse screen for compounds 2 and 3, the reduction in potency was seen to be one to two orders of magnitude. The differences among the two resolved 1,2-dihydroxy isomers (−)-3 and (+)-3 and the racemic mixture (±)-3 were not significant. Combination of these hydroxy groups as in (+)-4 (*i.e.*, OH at 9,10,11,12) did not further reduce activity as observed for 2 and 3. These compounds (2–4) are all appreciably less active than apomorphine (1),[1] both as centrally acting emetics in dogs and in their pharmacological effects in the mouse.

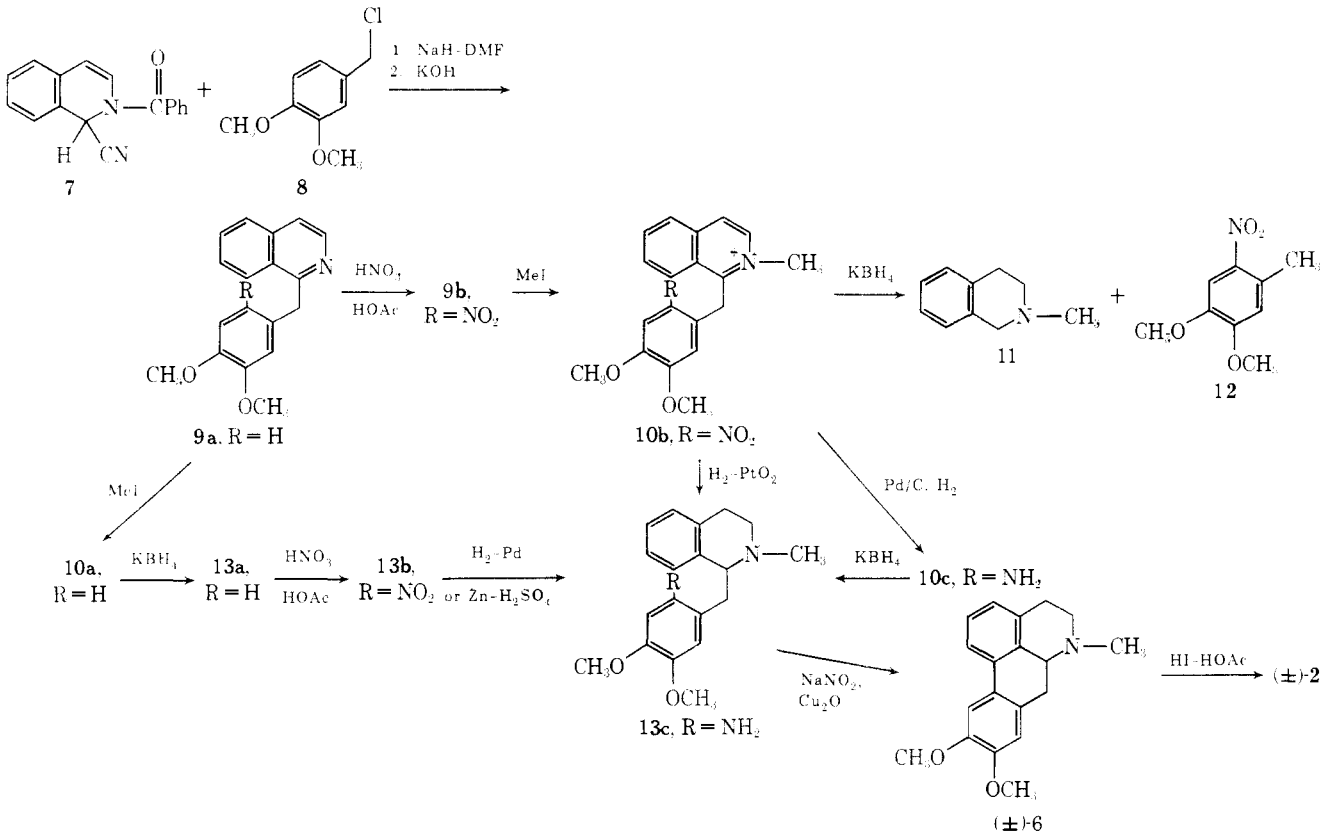
Methylation of the 10,11-hydroxy groups of apomorphine (Table I) reduced potency in all three test systems. In contrast, methylation of the 1,2-hydroxy groups in 3, to yield the alkaloid nuciferine, did not reduce the activity as was observed for the 10,11-hydroxyaporphine (apomorphine). Where values were obtained for the low level of activity of 3 in the mouse screen, the methylated derivatives (nuciferine) were seen to be equipotent.

§ Notice should be taken of the "normal" reduction of the isoquinolinium salts 10c → 13c and 10a → 13a with KBH_4. The absence of the nitrobenzyl group in both these cases did not provide the necessary resonance stabilization of the benzyl anion formed in the initial nucleophilic attack of the hydride ion on the electrophilic position of the isoquinoline nucleus.[3]

= The dimethyl ether of (±)-6 has been reported by Robinson and Shinoda,[7] who isolated the picrate and the quaternary methyl sulfate salt.

** The chemistry and pharmacology of the aporphine alkaloids have been recently reviewed.[9]

Scheme I



The significance of these findings with relation to the potential application of such compounds for the treatment of neurological diseases such as Parkinson's disease, without causing such undesirable effects as emesis, will be discussed in a subsequent communication from our laboratory.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected or in a Du Pont 900 thermal analyzer (dta) under nitrogen. The microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The ir spectra were recorded with a Beckman grating spectrophotometer, Model 521; uv spectra were recorded with a Beckman Model DK-1A; and the nmr spectra were determined on a Varian A-60 spectrophotometer with TMS as the internal standard. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

α-Chloro-3,4-dimethoxytoluene (8). Thionyl chloride (Eastman) (13.76 g, 0.12 mol) and several drops of dry, distilled pyridine were added to a solution of 12.9 g (0.077 mol) of 3,4-dimethoxybenzyl alcohol in 100 ml of Et_2O and the mixture was stirred at room temperature for 3 hr. The Et_2O solution was washed with 2 × 50 ml of water, then with 50 ml of 10% Na_2CO_3, and again with 2 × 50 ml of water. The combined Et_2O extracts were dried over $MgSO_4$, filtered, and evaporated almost to dryness. *n*-Hexane was added and the vessel walls were scratched to precipitate 11.66 g (86%) of **8** as a colorless crystalline solid, which was recovered in three crops, mp 46.5–48.5° (lit.[12] mp 50–51°). The product could also be distilled, bp 108° (0.5 mm).

1-(3,4-Dimethoxybenzyl)isoquinoline (9a). A solution of 17.9 g (0.096 mol) of α-chloro-3,4-dimethoxytoluene (**8**) in 100 ml of DMF was added dropwise to a mechanically stirred, cooled slurry of 22.6 g (0.087 mol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**7**) and 5.4 g of 54% sodium hydride in 200 ml of dimethylformamide. The reaction mixture was stirred at 0–5° for 3 hr after the addition was completed. $CHCl_3$ (250 ml) was added and the mixture was washed twice with 250 ml of water, with saturated NaCl solution, and with water. The combined aqueous washes were extracted twice with 50-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were evaporated. A solution made from 14.3 g of 85% KOH in 12.5 ml of water and 250 ml of EtOH was added to the residue. The resulting mixture was refluxed for 2 hr, concentrated, and extracted with $CHCl_3$. The washed $CHCl_3$ solution was dried over Na_2SO_4 and evaporated, using EtOH to remove the remaining $CHCl_3$. The residual yellow-brown oil was recrystallized twice from EtOH–hexane to give 19.1 g (79%) of **9a** as a colorless powder, mp 72.5–74° (lit.[13] mp 73–74°). The picrate had mp 159–160° (lit.†† mp 165–165.5°).

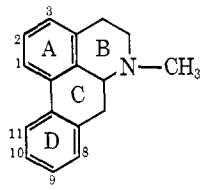
1-(4,5-Dimethoxy-2-nitrobenzyl)isoquinoline (9b). To a solution of 5.5 g (0.017 mol) of 1-(3,4-dimethoxybenzyl)isoquinoline (**9a**) in 150 ml of glacial HOAc at about 3° was added 50 ml of concentrated HNO_3 (*d* 1.42). After 4 hr ice was added and the reaction mixture was neutralized by concentrated NH_4OH. The mixture was extracted with $CHCl_3$, the $CHCl_3$ was dried over anhydrous Na_2SO_4, the solvent was removed, and the red-brown solid residue was dissolved in MeOH and allowed to crystallize. The total yield of **9b** in three crops from this recrystallization was 39%, mp 157–158.5°. An nmr spectrum confirmed the structure. The position of the nitro group was additionally confirmed by the borohydride reduction of the methiodide **10b** to give **12**. *Anal.* ($C_{18}H_{16}N_2O_4$) C, H, N.

1-(4,5-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (10b). A mixture of 1 g (0.002 mol) of 1-(4,5-dimethoxy-2-nitrobenzyl)isoquinoline (**9b**) and 20 ml of MeI was stirred and heated at reflux for 48 hr. The mixture was cooled and the crystals that separated were washed with dry Et_2O and dried under vacuum to yield 1.28 g (89%) of the quaternary salt **10b** as a yellow powder, mp 211–212°. *Anal.* ($C_{19}H_{19}IN_2O_4$) C, H, I, N.

Reaction of 1-(4,5-Dimethoxy-2-nitrobenzyl)isoquinoline Methiodide (10b) and KBH_4. KBH_4 (1.5 g) was added to a mixture of 1 g of **10b**, 18 ml of EtOH, and 8 ml of water. The reaction mixture was stirred and heated at reflux for about 5 hr and then allowed to cool overnight. The EtOH was evaporated from the mixture and water was added. The mixture, which contained both solid and liquid, was extracted three times with Et_2O. The Et_2O solution was washed with 4 × 25 ml of 0.1 *N* HCl and four times with KOH solution and finally dried over K_2CO_3. Evaporation to dryness gave a yellow solid that was crystallized from petroleum ether (bp 30–60°). The yield of 4,5-dimethoxy-2-nitrotol-

†† Popp and McEwen[14] described the substance as an oil, converted to a picrate.

Table I. Comparative Activity of Aporphine Derivatives



Compd	Feature	Primary mouse screen: MED_{50} (95% confidence limits)	Primary mouse screen: Observed effect at MED_{50}	Overt behavior min effective dose, mg/kg iv	Dog emesis[c] min effective dose, mg/kg iv
(−)-**1**·HCl	10,11-OH	0.032 (0.016–0.061)	Decr. general activity, incr. sensitivity to touch	0.05[a] (monkey)	0.012
(±)-**1**·HI	10,11-OH	0.056 (0.025–0.13)	Decr. general activity	0.05[b] (monkey)	0.025
(±)-**2**·HI	9,10-OH	10 (3.2–32)	Decr. general activity, incr. sensitivity to touch and pain, vasodilation, incr. respiratory depth and rate, incr. phonation and high carriage	>10 (monkey)	>10
(−)-**3**·HI	1,2-OH	0.75 (0.42–1.3)	Decr. general activity	>0.1 (monkey)	>0.1
(+)-**3**·HI	1,2-OH	3.2 (1.0–10.0)	Decr. general activity	>0.1 (monkey)	>0.1
(±)-**3**·HI	1,2-OH	3.2 (1.0–10.0)	Decr. general activity, decr. sensitivity to touch	>0.1 (monkey)	>0.1
(+)-**4**·HI	1,2,9,10-OH	1.8 (0.56–5.6)	Decr. general activity, incr. sensitivity to touch	>3.0 (dog)	>3
d	(−)-10,11-OMe	18.0 (5.6–56.0)	Decr. general activity, decr. sensitivity to touch, motor deficits	>0.1 (monkey)	>0.1
e	(±)-10,11-OMe	5.6 (1.8–18.0)	Decr. general activity, decr. sensitivity to touch		>0.1
Nuciferine[f]	(−)-1,2-OMe	0.56 (0.22–1.4)	Decr. general activity		>0.1

[a] Observed effect: depression, yawning. [b] Observed effect: abnormal mouth movements, yawning. [c] See ref 11. [d] Compound evaluated as $HClO_4$ salt, described in ref 1. [e] Compound evaluated as HI salt, described in ref 1. [f] (−)-Nuciferine tested as free base.

uene (12), mp 117.5–118.5°, was 0.29 g (72%). A mixture melting point with 12 isolated by the reaction of 6′-nitropapaverine[16] with potassium borohydride was not depressed. The acid layer was made basic with solid KOH and extracted by Et_2O. The extract was evaporated and the residual brown oil was converted to a picrate, which did not depress the melting point of the picrate made from an authentic sample of 2-methyl-1,2,3,4-tetrahydroisoquinoline (11), mp 148–150° (lit.[15] mp 148–150°).

1-(3,4-Dimethoxybenzyl)isoquinoline Methiodide (10a). A mixture of 1.45 g of 1-(3,4-dimethoxybenzyl)isoquinoline (**9a**) in 24.5 g of CH_3I was allowed to reflux for 20 hr. Et_2O was added, and the precipitate which was filtered from the cooled mixture was triturated in 50 ml of Et_2O, filtered, and dried at 70° in a vacuum oven to yield 1.83 g (83%) of the quaternary salt **10a**, mp 138–140°. An analytical sample was prepared by two recrystallizations from EtOH–Et_2O: mp 139–141°; ν_{max} (KBr) 3435 (b), 1640 (m), 1520 (s), 1142 (s), 1018 cm^{-1} (s). *Anal.* ($C_{19}H_{20}INO_2$) C, H, I, N.

1-(3,4-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (13a·HCl). KBH_4 (14 g, 0.026 mol) was added to a mixture of 9.8 g (0.023 mol) of **10a**, 300 ml of EtOH, and 100 ml of water. The mixture was stirred and refluxed for 4 hr, concentrated, diluted with water, and extracted with Et_2O. The Et_2O was extracted with 0.1 *N* HCl; the aqueous acid layer was made basic with KOH pellets and extracted with Et_2O. The ether was dried over K_2CO_3, filtered, and evaporated, leaving 5.9 g of a yellow oil. The oil was distilled, giving 5.7 g (82%) of the reduction product 13a: bp 173–175° (0.3 mm); $n^{25}D$ 1.5829. The hydrochloride was prepared and recrystallized from EtOH, mp 227–230°. Material of equal purity was also obtained from undistilled base. The uv spectrum showed λ_{max} (EtOH) 279 mμ (ε 2980) and 232 (9760), and the nmr spectrum was in accord with the assigned structure. *Anal.* ($C_{19}H_{24}ClNO_2$) C, H, Cl, N.

1-(4,5-Dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (13b). To a cooled solution of 5.7 g (0.019 mol) of 1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**13a**) in 140 ml of glacial HOAc was added 50 ml of cooled concentrated HNO_3. The reaction mixture was stirred in an ice bath for 1 hr and at room temperature for 3 hr. The clear yellow solution was poured over cracked ice, made basic with NH_4OH, and extracted by $CHCl_3$. The extract was dried over K_2CO_3 and evaporated. The remaining brown oil was distilled under vacuum, and three fractions were collected in the range 168–191° (0.2 mm). The nmr spectrum indicated that nitration had not been successful, although nitration had been complete in a previous smaller scale reaction carried out under similar conditions. A chilled solution of 4.8 g of the oil in 140 ml of a glacial HOAc was treated with a cooled mixture of 10 ml of concentrated H_2SO_4 and 40 ml of concentrated HNO_3. The reaction mixture was sitrred 2 hr at ice-bath temperature and was worked up in the manner described above, giving a dark brown oil. Crystallization was attempted unsuccessfully from MeOH–water and then from Et_2O–*n*-hexane. A small amount of brown solid formed in Et_2O–hexane solution, but it darkened at about 100° and did not melt below 200°. The solid was filtered off and the filtrate was evaporated to dryness. The residual oil was allowed to stand overnight at room temperature and, after crystallization had started, the mixture was stored in the refrigerator. After 3 days most of the oil had solidified. The solid was crushed and recrystallized twice from ethanol to give **13b**, mp 96–97.5°. An nmr spectrum confirmed the structure. The uv spectrum showed λ_{max} (MeOH) 340 mμ (ε 5000), 300 (4580), 271 (3550), and 242 (11,250). The ir spectrum showed ν_{max} (KBr) 1520, 1160, 1060 cm^{-1}. *Anal.* ($C_{19}H_{22}N_2O_4$) C, H, N.

A picrate of **13b** was prepared in EtOH and recrystallized from THF–*n*-hexane, mp 183–184.5°. *Anal.* ($C_{25}H_{25}N_5O_{11}$) C, H, N.

The hydrochloride of **13b** was prepared in Et_2O and recrystallized twice from *i*-PrOH, mp 200.5–202.5°. *Anal.* ($C_{19}H_{23}N_2O_4Cl$) C, H, N, Cl.

The reaction was repeated with 7 g of 13a and gave 3.5 g (43%) of 13b, mp 96–98°, and a large amount of an unidentified oil, which would not crystallize and whose picrate melted at 188–190°. Attempts to purify the oil were unsuccessful.

1-(2-Amino-4,5-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (13c). a. From 1-(4,5-Dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (13b). In the catalytic reduction a solution of 1 g (0.003 mol) of 13b in 100 ml of EtOH was shaken with 0.2 g of 10% Pd/C under hydrogen at an initial pressure of 50 psig in a Parr apparatus. After the hydrogen absorption had stopped, the solution was filtered and evaporated. The residual oil gave two spots on tlc, R_f 0.65 and 0.54 (silica, 2% NH_4OH–MeOH). The oil gave a dipicrolonate, mp 205.5–208°. *Anal.* ($C_{39}H_{40}N_{10}O_{12}$) C, H, N.

In the acid reduction, 1 g of zinc dust and 100 ml of 10% H_2SO_4 were added to a MeOH solution of approximately 1 g of crude oily 13b. The reaction mixture was warmed for 30 min, filtered, made basic with NH_4OH, and extracted by $CHCl_3$. The $CHCl_3$ solution was evaporated to dryness and the residue was stirred with Et_2O. An insoluble colorless solid (mp >250°) was discarded and the Et_2O was evaporated to leave crude 13c, mp 80–93°. This was purified somewhat by treating it with C_6H_6, filtering off an insoluble black tar, evaporating the C_6H_6, and treating the residue with Et_2O, mp 92–98.5°. The dipicrolonate, mp 203–204.5°, was identical with that obtained from the aminoisoquinoline 13b by catalytic reduction.

b. From 1-(4,5-Dimethoxy-2-nitrobenzyl)-2-methylisoquinolinium Iodide (10b). The procedure used for this reduction was that developed previously for the reduction of 1-(2-nitrobenzyl)isoquinoline methiodide to 1-(2-aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline.[5] A suspension of 0.1 g of PtO_2 in a mixture of 25 ml of water and 25 ml of EtOH was activated with hydrogen in a Parr apparatus and a solution of 1 g of 10b in a mixture of 75 ml of EtOH and 75 m of water was then added. Hydrogenation at room temperature and an initial pressure of 44 psig was complete after 75 min. The solution was filtered and evaporated. A tan oily residue was dissolved in $CHCl_3$; the solution was dried (Na_2SO_4) and evaporated to an oil. Et_2O was poured onto the oil and a solid, mp 145–220°, that formed was removed. The filtrate was evaporated, and the remaining oil was converted to the dipicrolonate, mp 203–204.5°, which was identical with that characterized above in a.

This compound was also prepared in two steps by reduction of the nitro group in 10b in EtOH solution over Pd/C, followed by KBH_4 reduction as described for the reduction of 10a → 13a. The amine 13c was characterized as the dipicrolonate salt.

9,10-Dimethoxyaporphine Hydroiodide [(±)-6].[16] The oily amine 13c was dissolved in 7 ml of 6 *N* H_2SO_4 (0.042 equiv) and the solution was stirred under nitrogen at 0–3° while adding dropwise a solution of 0.69 g (0.01 mol) of sodium nitrite in 3 ml of water. During the diazotization reaction the solution became dark blue and then green. Stirring was continued for an additional 30 min at which time excess nitrous acid (starch-iodide test) was destroyed by the addition of 0.2 g of urea.

The solution of diazonium salt was diluted with water at room temperature to 500 ml, 10 ml of 6 *N* H_2SO_4 was added to adjust the pH to 1.5, and 3 g of purified copper powder (Baker) was added; vigorous gas evolution occurred shortly thereafter. The dark red suspension was stirred at room temperature for 2 days and then was filtered. The filtrate was made by dropwise addition of 20% aqueous NaOH. Copper compounds that precipitated were filtered off and leached for 1 hr with boiling Et_2O. The dark brown filtrate was extracted with 5 × 100 ml of Et_2O. The aqueous phase was acidified and retreated with copper, but no additional product was obtained.

All ether solutions were combined and washed successively with 20% aqueous NaOH, water (three times), and saturated NaCl and then dried over $MgSO_4$. Tlc (silica, 10% MeOH–$CHCl_3$) showed one major spot and one minor spot. The ether solution was evaporated to dryness to give an orange solid, which was triturated with small amounts of cold Et_2O to remove a bright red substance. The residue was sublimed at 90° (0.1 mm) to give 0.65 g (22% based on 13b) of the free base of (±)-6 as an off-white solid, mp 125–132°.

The crude sublimate (200 mg) was resublimed twice more at 140° (0.1 mm) to give a colorless solid, mp 132–133°, whose ir spectrum exhibited ν_{max} (KBr) 1605, 1570, 1510 (s), 1250 cm^{-1} (s), and whose nmr spectrum (in $CDCl_3$) showed (in ppm) 2.56 (s, 3 H), 2.3–3.7 (br, 7 H), 3.92, 3.95 (s, s, 6 H), 6.87 (s 1 H), 7.26 (s, 1 H), 7.33 (d, 1 H), and 7.05, 7.51 (d, d, 2 H). *Anal.* ($C_{19}H_{21}NO_2$) C, H, N.

The hydroiodide salt of (±)-6 was prepared in 90% yield by adding 5 drops of 57% hydriodic acid to a solution of 0.75 g of (±)-6 in 30 ml of EtOH. Cooling the solution caused the separation of a solid that was difficult to filter. The entire suspension was stirred into 250 ml of hot MeOH and the solution was concentrated to 200 ml. Cooling gave 0.93 g of the hydroiodide as colorless crystals, mp 265° (dta). An additional 0.1 g was isolated from the mother liquors. The salt was homogeneous in tlc (silica, 10% MeOH–$CHCl_3$). It exhibited ν_{max} (KBr) 2900, 2690 (s), 1610 (w), 1515 (s), and 1250 cm^{-1} (s).

9,10-Dihydroxyaporphine Hydroiodide [(±)-2·HI] (Isoapomorphine Hydroiodide). Ether cleavage was accomplished by the procedure that had been first used during our total synthesis of racemic apomorphine.[1,8] A mixture of 0.92 g (2.1 mmol) of 9,10-dimethoxyaporphine hydroiodide [(±)-6·HI], 6 ml of 57% HI (42 mmol), and 4.5 ml of Ac_2O was heated at 140° for 30 min to yield 0.77 g (92%) of colorless needles, mp 286° (dta), that exhibited ν_{max} (KBr) 3360, 3275, 1620, 1600 (m), 1590 (s), and 1515 cm^{-1} (s). The nmr spectrum showed (DMSO-d_6, ppm) 3.14 (s, 3 H), 2.66–3.9 (br, 5 H), 4.45 (br, 1 H), 6.81 (s, 1 H), 7.0–7.5 (m, 3 H), 7.21 (s, 1 H), and 9.2 (br, 2 protons exchangeable with D_2O); this spectrum confirmed the assigned structure. *Anal.* ($C_{17}H_{17}NO_2$·HI) C, H, I, N.

(+)-1,2,9,10-Tetrahydroxyaporphine Hydroiodide [(+)-4·HI] [(+)-*O*-Desmethylglaucine Hydroiodide]. Glaucine (Pierce Chemical Co.) was recrystallized from C_6H_6–hexane to yield pale yellow prisms, mp 118–119° (lit.[17] mp 120°). To an Et_2O solution of this material there was added a slight excess of 57% HI to precipitate the hydroiodide salt. The latter was then treated with HI and Ac_2O by the procedure described previously for the ether cleavage of apomorphine dimethyl ether[1] and for (±)-6. There was obtained a 71% yield of (+)-4·HI as an ivory-colored powder, which was dried for 4 hr at 55° (5 mm) and then had mp 210–222° (dta). The uv spectrum showed λ_{max} (MeOH) 219 mμ (ε 48,400), 279 (11,900), and 304 (13,900). *Anal.* ($C_{17}H_{18}NO_4I$) C, H, N, I.

(−)-, (+)-, and (±)-1,2-Dihydroxyaporphine Hydroiodide [(−)-3, (+)-3, and (±)-3·HI]. In a typical run 0.15 ml of 57% HI was added to a filtered solution of (−)-nuciferine[‡] in 4 ml of hot EtOH. The hydroiodide was precipitated by the addition of Et_2O, and the reaction mixture was cooled in the freezer. Filtration yielded 0.24 g (95%) of an off-white solid. The salt (0.236 g, 0.56 mmol) was suspended in 0.90 ml (6.8 mmol) of 57% HI and 0.65 ml (6.9 mmol) of Ac_2O was added slowly (5 min). The reaction mixture was heated under reflux (nitrogen atmosphere) in an oil bath for 45 min and worked up as described for (+)-4·HI.

All three optically isomeric products showed λ_{max} (MeOH) 213 mμ (ε 45,000), 271 (16,000), and 310 (4400); ν_{max} (KBr) 3370 cm^{-1} (m). *Anal.* ($C_{17}H_{18}NO_2I$) C, H, N, I. The compounds had the following melting points (dta): (−)-3, 279° dec; (+)-3, 279° dec; (±)-3, 258° dec.

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Synthesis of 5-Substituted Quinazolines as Potential Antimalarial Agents†

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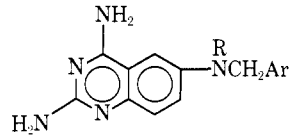
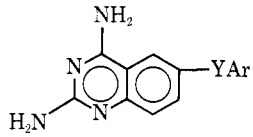
A series of 5-arylethyl-, 5-arylthio-, and 5-arylthiomethyl-2,4-diaminoquinazolines and related compounds was prepared and evaluated for antimalarial activity against *Plasmodium berghei* in mice. Surprisingly, none showed even marginal activity although several of the compounds were isomeric with highly potent 6-arylthioquinazolines. Each of the new quinazolines was also evaluated as an inhibitor of rat liver dihydrofolate reductase.

The discovery of the potent antiparasitic action of 2,4-diaminoquinazolines bearing an aromatic function attached by a suitable spacer at the 6 position has generated considerable excitement. In particular, compounds such as **1a–c** have been extensively investigated as potential antimalarial agents.[1-4] More recently, it was reported



1a, R = H; Ar = 3,4-$Cl_2C_6H_3$
b, R = NO; Ar = 3,4-$Cl_2C_6H_3$
c, R = $CH(CH_3)_2$; Ar = 4-ClC_6H_4

that numerous 6-arylthio- (**2a**), 6-arylsulfinyl- (**2b**), and 6-arylsulfonyl-2,4-diaminoquinazolines (**2c**) also possess potent antimalarial activity.[5] It was of interest, therefore, to synthesize analogs of **2a–c** in which the aryl function was attached at the 5 position of the quinazoline nucleus. The contention that this class of compounds would display useful chemotherapeutic effects was supported by earlier *in vitro* studies which showed that for small nonpolar substituents, antibacterial activity with respect to substitution position followed the order 5 > 6 > 7.[6] Furthermore, a recent study from this laboratory demonstrated that diaminoquinazolines bearing small nonpolar groups in the 5 position were more potent inhibitors of rat liver dihydrofolate reductase than their 6 isomers.[7]



2a, Y = S
b, Y = SO
c, Y = SO_2

Consequently, a series of compounds was prepared in which a hydrophobic aryl moiety was bridged to the 5 position of the quinazoline nucleus by various one- or two-atom spacers. The synthetic routes to the new quinazolines (Table I) and their corresponding intermediates (Table II) are described below.

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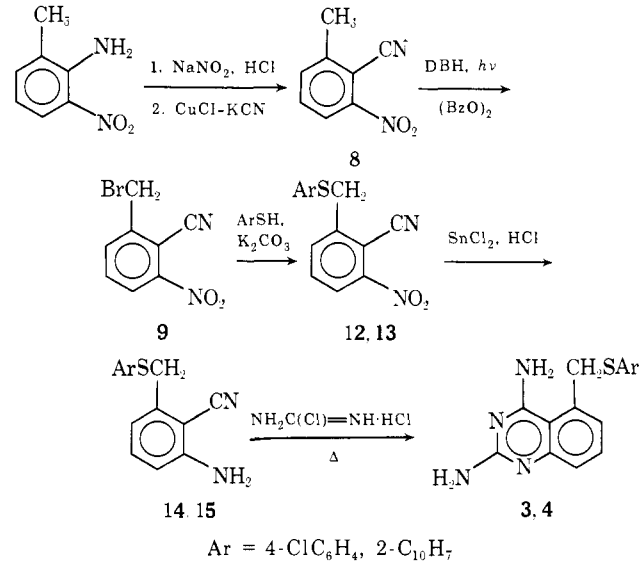
Chemistry. The 5-arylthiomethyl-2,4-diaminoquinazolines **3** and **4** were prepared according to Scheme I. 2-Methyl-6-nitrobenzonitrile (**8**) was obtained in good yield from 2-methyl-6-nitroaniline by employing improved procedures over those previously reported.[8] Photochemical bromination of **8** with 1,3-dibromo-5,5-dimethylhydantoin (DBH) yielded crude **9**, which was suitable for use without purification. The thioethers **12** and **13** were obtained by alkylation of the appropriate aryl thiol with **9** in the presence of K_2CO_3. Reduction of the nitro groups of **12** and **13** with $SnCl_2$ afforded the anthranilonitriles **14** and **15**. Cyclization with chloroformamidine hydrochloride[9] then proceeded to give the quinazolines **3** and **4**.

Scheme I



Ar = 4-ClC_6H_4, 2-$C_{10}H_7$

Scheme II outlines the synthesis of *cis*- and *trans*-5-[2-(2-naphthyl)vinyl]- and 5-[2-(2-naphthyl)ethyl]quinazolines **5a–c**. The phosphonium salt intermediate **10** for use in the Wittig reaction was obtained by reaction of the benzyl bromide **9** with triphenylphosphine. Generation of the ylide with DBN (1,5-diazabicyclo[4.3.0]non-5-ene) in the presence of 2-naphthaldehyde yielded a mixture of cis (**16a**) and trans (**16b**) olefins, which were separated by fractional crystallization. After isolation, the isomers were obtained in a cis:trans ratio of approximately 6:7. Each