negative. The cold solution was slowly added under the surface of boiling 2 N H_2SO_4 (75 mL). Boiling was continued for 1 h. The solution was allowed to come to room temperature and extracted with CH_2Cl_2 (thrice). The organic phase was washed with H_2O (twice), dried (Na_2SO_4), and evaporated to dryness. Chromatography on 30 g of silica gel (elution with CH_2Cl_2) gave pure **50** (990 mg, 57% from 5-amino-2-methoxybiphenyl) as an oil: IR (CH_2Cl_2) 3600 cm^{-1}; NMR ($CDCl_3$) δ 3.74 (s, 3 H), 5.35 (s, 1 H), 6.87 (s, 3 H), 7.3–7.7 (m, 5 H).

Acknowledgment. We thank Martin Bachmann, Guenter Bamert, Christian Beerli, Maria Eschmann, Simone Hugenschmidt, Anja Kaijanen, Hellmut Knecht, Theodor Leuenberger, Therese Szelestényi, Therese Hotz, and Armand Wanner for expert technical assistance.

Synthesis of Some Novel Amodiaquine Analogues as Potential Antimalarial and Antifilarial Compounds

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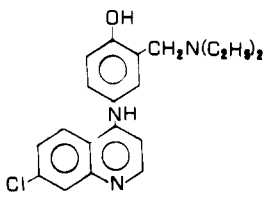
Ten amodiaquine analogues, which are hybridized molecules of amodiaquine and diethylcarbamazine, were designed and synthesized. Six analogues, all bearing a basic tertiary amino function at their side chain, were active against *Plasmodium berghei* in mice and inhibited the mobility of adult worms and microfilariae of *Breinlia booliati* in vitro. They were inactive against *Litomosoides carinii* in *Mastomys natalensis*. The most active antimalarial compound, 7-chloro-4-[α-[[*N*-(4-methyl-1-piperazinyl)carbonyl]amino]-4-hydroxy-*m*-toluidino]quinoline, had twice the activity of amodiaquine. O-Methylation and N-ethylation generally reduced antimalarial activity. Analogues which lack a basic tertiary amino function at their side chain were also lacking in both antimalarial and antifilarial activities.

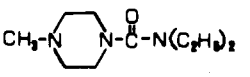
Malaria and filariasis are notable for their overlapping distribution in many parts of Asia and Africa. The development of an active agent against both malaria and filariasis would clearly have the advantages of convenience and economy in its usage, especially for mass chemotherapy and prophylaxis in endemic areas. A rational approach to the design of such a dual-acting agent is to start from a parent molecule which has both antimalarial and antifilarial properties. A satisfactory candidate is amodiaquine[1] (**1**).



1

The 4-aminoquinolines amodiaquine and chloroquine[2] are among the most widely used drugs for the treatment of malaria. Thompson and co-workers[3] reported that amodiaquine when given orally to Mongolian gerbils infected with *Litomosoides carinii* at doses of 25–100 (mg/kg)/day × 5 elicited strong macrofilaricidal action. However, it had no direct action on the circulating microfilariae. Subsequent clinical trials in man revealed that amodiaquine in a total dose of 40 mg/kg was also macrofilaricidal in bancroftian filariasis.[4] Unfortunately, because of the unpleasant side effects at this dose level (dizziness, nausea, and vomiting) and the possibility of inducing blood dyscrasias,[5] mass chemotherapy of filariasis with amodiaquine could not be recommended.[4]

In this work, we have designed five series of potential dual-acting amodiaquine analogues based on the principles of drug hybridization.[6] In this approach, amodiaquine is condensed with a potent microfilaricidal agent, diethylcarbamazine (DEC, **2**), in such a way that the important functional groups and ideal conformations of both drugs are retained.[7,8]



2

Structure–activity studies have shown that wide liberties can be taken in the modification of the side chain of amodiaquine without loss of antimalarial activity.[7] Through drug hybridization, we hope to obtain dual-acting amodiaquine analogues which may still retain the main therapeutic activities of the parent molecule. Since DEC is essentially a microfilaricidal agent,[9] the hybridized molecules may possess the antimalarial and macrofilaricidal activities of amodiaquine, with additional microfilaricidal activity imparted by the DEC moiety.

The design of these hybridized amodiaquine–DEC molecules has been accomplished by replacing the diethylamino function of amodiaquine with the N_1, N_2, and N_3 nitrogen of DEC (Scheme I). In this way, compounds **12a,b** (series A), **13a,b** (series B), **14a,b** (series C), **15a,b** (series D), and **16a,b** (series E) were designed and subsequently synthesized.

(1) Burckhalter, J. H.; Tendick, F. H.; Jones, E. M.; Jones, P. A.; Holcomb, W. F.; Rawlins, A. L. *J. Am. Chem. Soc.* **1948**, *70*, 1363.
(2) Wiselogle, F. Y. "A Survey of Antimalarial Drugs, 1941–1945", Part 2; Edwards, J. W., Ed.; Ann Arbor Science Publishers, Ann Arbor, MI, 1946; Vol. II.
(3) Thompson, P. E.; Boche, L.; Blair, L. S. *J. Parasitol.* **1968**, *54*, 834.
(4) McMahon, J. E. *Ann. Trop. Med. Parasitol.* **1979**, *73*, 465.
(5) Booth, K.; Larkin, K.; Maddocks, I. *Br. Med. J.* **1967**, *3*, 32.
(6) Ariens, E. J. *Drug. Des.* **1971**, *1*, 1.
(7) Thompson, P. E.; Werbel, L. M. "Antimalarial Agents: Chemistry and Pharmacology"; Academic Press: New York and London, 1972; p 150.
(8) Sturm, P. A.; Cory, M.; Henry, D. W.; McCall, J. W.; Ziegler, J. B. *J. Med. Chem.* **1977**, *20*, 1327.
(9) Hawking, F. *Adv. Pharmacol. Chemother.* **1979**, *16*, 129.

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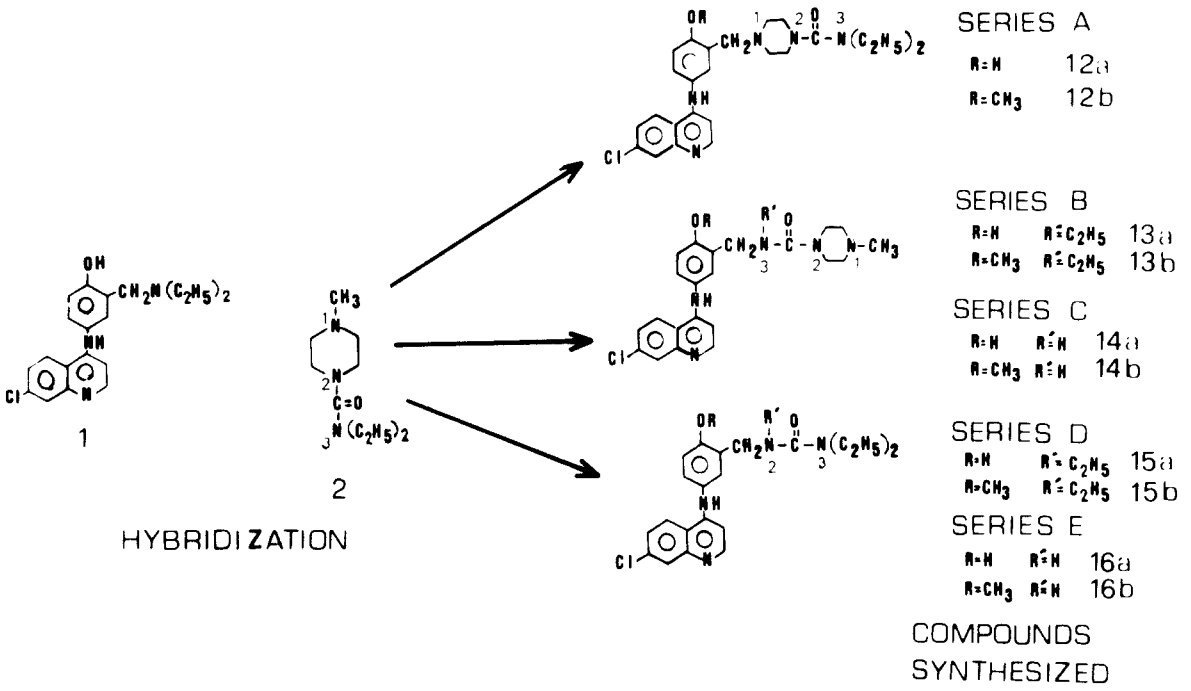
Scheme I



Chemistry. The synthesis of the compounds of series A to E is given in Schemes II and III.

Scheme II. *p*-Nitrophenol is chloromethylated[10] to **3a**, which is then reacted with anhydrous ethylamine, silver nitrite,[11] and 1-(diethylcarbamoyl)piperazine, respectively, to give compounds **4a**, **5a**, and **6a**. The aryl nitro function of **4a**, **5a**, and **6a** is catalytically reduced, and the resulting arylamines (**7a**, **8a**, and **9a**) condensed with 4,7-dichloroquinoline to give the condensed products **10a**, **11a**, and **12a**. Acylation of the secondary amino function of **10a** with 4-methyl-1-piperazinylcarbonyl chloride hydrochloride and diethylcarbamoyl chloride (with triethylamine as condensing agent) gives compounds **13a** and **15a**, respectively. Similar acylations involving **11a** result in the syntheses of **14a** and **16a**, respectively.

Scheme III. *p*-Nitroanisole is bromomethylated to **3b**, which is converted to the iodo derivative, **3b'** by reaction with KI in acetone.[12] Subsequent reaction steps from **3b'** to the final compounds **12b**, **13b**, **14b**, **15b**, and **16b** are similar to those outlined in Scheme II.

Biological Results and Discussion

Antimalarial Activity. Compounds of series A–C exhibited antimalarial activity when tested in mice infected with *Plasmodium berghei*, using the method of Thurston[13] (Table I). **14a** is the most active compound, having twice the antimalarial activity of amodiaquine in this test system. Determination of the approximate lethal dose of **14a** in mice indicates that it is about half as toxic as amodiaquine (Table II). **14a** appears to be a good candidate for further antimalarial testings.

The compounds of series D and E did not show any antimalarial activity against *P. berghei* in mice at the doses investigated. These compounds have only a ureido [NC(=O)N] moiety in the aliphatic side chain, compared to the compounds of series A–C which have a basic tertiary

Table I. Antimalarial Activity of Series A–E Compounds

compd[a]	antimalarial activity[b] MED, mg of base/20 g[c]	quinine equiv[d]
12a	0.43	2.8
12b	0.43	2.8
13a	0.21	5.8
13b	0.43	2.8
14a	0.043	28.4
14b	0.43	2.8
15a	*e*	
15b	*e*	
16a	*e*	
16b	*e*	
amodiaquine	0.077	15.8

[a] Six doses of each compound, in the range of 0.05 to 2.0 mg (hydrochloride) per 20 g, were prepared in normal saline. [b] Activity vs. *P. berghei* in four mice, as described by Thurston.[13] [c] Minimum effective dose (MED): smallest dose of compound (base) which on the 5th day reduced the mean infection level to one-fiftieth of the control. [d] Quinine equivalent = MED of quinine/MED of compound under test. MED of quinine in this test system was 1.22 mg/20 g. [e] No activity observed in the dose range of 0.05–2.0 mg (HCl) per 20 g.

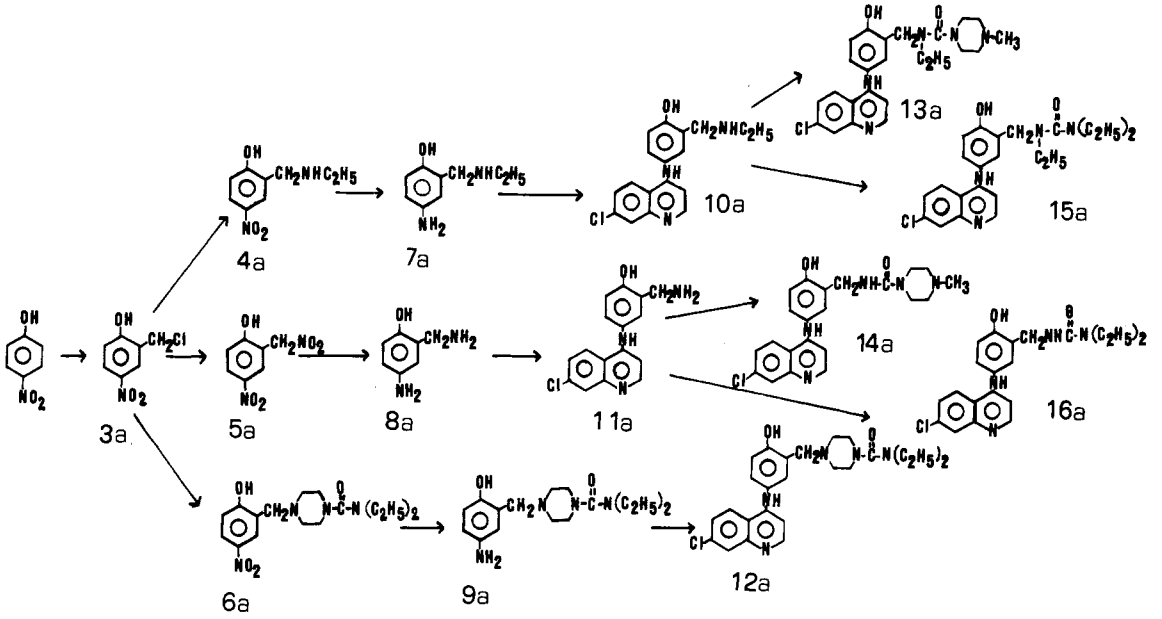
Table II. Approximate Lethal Doses of Amodiaquine, DEC, and the Series A–C Compounds in Mice

compd[a]	approx lethal dose,[b] mmol/kg
12a	0.37
12b	0.41
13a	0.76
13b	0.63
14a	0.66
14b	0.68
amodiaquine	0.32
DEC[c]	1.34

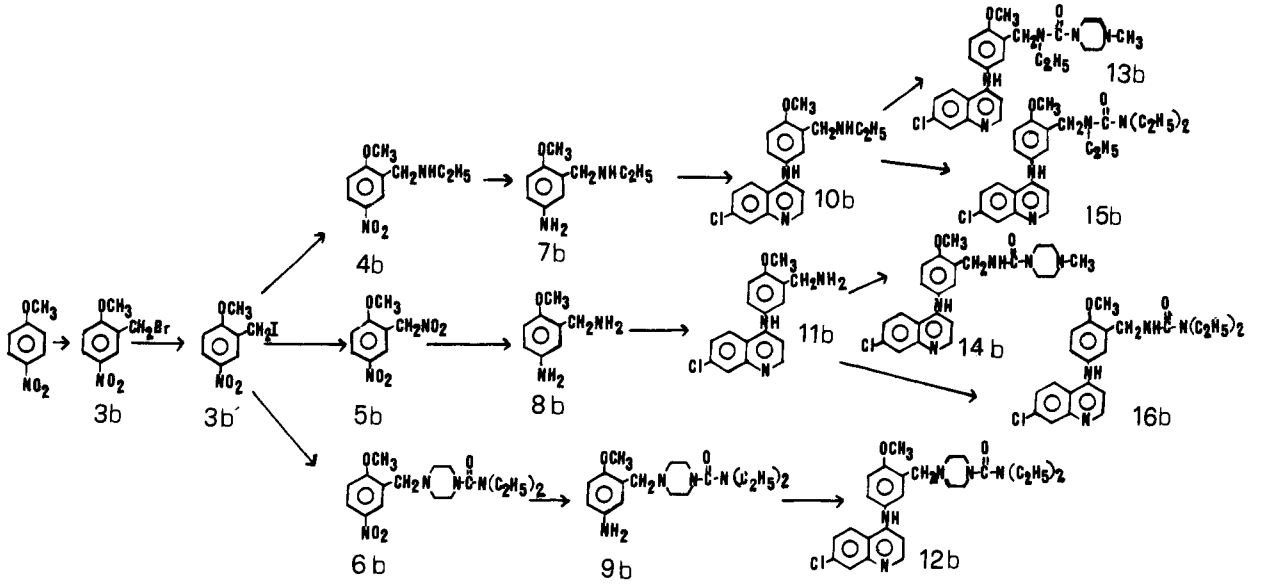
[a] Four concentrations or more of the HCl of each compound were administered ip to two mice in 1 mL of normal saline according to the method described by Deichmann and LeBlanc.[21] [b] The approximate lethal dose was taken as the lowest dose of the compound that killed the mice within 48 h. [c] Diethylcarbamazine citrate was used.

(10) Buehler, C. A.; Kircher, F. K.; Diebel, C. F. *Org. Synth.* **1940**, *20*, 59.
(11) Natarajan, P. N.; Ngiam, T. L. *J. Med. Chem.* **1972**, *15*, 329.
(12) Bendz, G.; Culvenor, C. C.; Goldsworthy, L. J.; Kirby, K. S.; Robertson, R. *J. Chem. Soc.* **1950**, 1130.
(13) Thurston, J. P. *Br. J. Pharmacol.* **1953**, *8*, 162.

Scheme II



Scheme III



amino function in addition to a ureido moiety. Thus, although the side chain of amodiaquine may be extensively modified without loss of antimalarial activity, these results indicate that it is essential to retain a basic amino function for activity.

It is noted that the tertiary diethylamino function of amodiaquine is separated from the benzene ring by a single carbon atom. This distance is considerably more with the series B and C compounds. Thus, the distance separating the tertiary amino function from the ring does not seem to be important. In fact, **14a**, with its side-chain amino function six atoms from the benzene ring, has twice the antimalarial activity of amodiaquine.

Another interesting observation is that among the series A–C compounds, the O-methylated derivatives are less active than their phenolic counterparts. The O-methyl derivatives have almost equivalent antimalarial activity, whereas among the phenolic analogues there is a wide variation in activity. Antimalarial activity decreases in the order **14a** > **13a** > **12a** among the phenolic analogues. In both **12a** and **13a** the ureido moiety in the side chain is tetrasubstituted, while in **14a** it is trisubstituted. It may be concluded from these observations that neither O-methylation nor N-ethylation is conducive to antimalarial activity.

Antifilarial Activity. The antifilarial activity of series A–E was investigated in vitro using the filarial worm, *Breinlia booliati*.[14] The series A–C compounds immobilized the adult worms and microfilariae of *B. booliati* in vitro (Table III). Under similar conditions, amodiaquine and DEC also demonstrated immobilizing effects, whereas nonspecific compounds, such as dioxane and benzyl alcohol, had no such effects.

In spite of their in vitro activity, no in vivo activity was observed when the series A–C compounds were given [100 (mg/kg)/day × 5, op or sc] to *Mastomys natalensis* infected with *L. carinii*.[15] This is in contrast to DEC, which is microfilaricidal at 125 (mg/kg)/day × 5,[16] and amo-

(14) Natarajan, P. N.; Zaman, V.; Yeoh, T. S. *Int. J. Pharasitol.* **1973**, *3*, 803.
(15) Lämmler, G.; Sänger, I., personal communications.
(16) Lämmler, G.; Herzog, H.; Schütze, H. R. *Bull. W.H.O.*, **1971**, *44*, 757.

Table III. In Vitro Antifilarial Activity of Series A-E against *Breinlia booliati*

compd[a]	time, h, taken to immobilize *B. booliati*[b]	
	adult worms	microfilariae
12a	3	6
12b	3	6
13a	3	3
13b	3	3
14a	5	7
14b	5	7
15a	8[c]	8[c]
15b	8[c]	8[c]
16a	8[c]	8[c]
16b	8[c]	8[c]
amodiaquine	3	3
DEC[d]	2	4

[a] Except for DEC, the compounds were investigated at a dose level of 0.2 μmol/mL, using the HCl salt form. [b] Investigations were carried out in culture media solution (RPMI), pH 7.0, as described by Natarajan et al.[14] [c] The motility of the filarial worms was observed for 8 h only. After this time, control worms still remained actively motile. [d] Diethylcarbamazine citrate at a dose level of 10 μmol/mL was used.

diaquine, which is macrofilaricidal at 100 (mg/kg)/day × 5,[17] in the same experimental model.

Although incorporation of the whole or part of the DEC molecule to the side chain of amodiaquine is favorable for antimalarial activity in some cases, it is clearly not favorable for antifilarial activity. Amodiaquine is a fairly hydrophobic molecule. Initial measurements have shown that its log *P* (partition coefficient in octanol–water) is in the region of 2.8.[18] The hydrophobicity of the series A–E compounds would be expected to be less than that of amodiaquine. This is because the series A–E compounds possess the highly polar ureido carbonyl moiety in their side chain. It is interesting to note that chloroquine is less hydrophobic than amodiaquine (log $P = 0.8$),[18] and it has neither macrofilaricidal nor microfilaricidal activity in *L. carinii* infected Mongolian gerbils.[19] Thus, the absence of antifilarial activity in the series A–E compounds may be related to their diminished hydrophobicity.

Experimental Section

All melting points are determined using a Gallenkamp hot-stage apparatus and are uncorrected. IR spectra were recorded on a Jasco IRA-1 Diffraction Grating IR spectrophotometer from KBr disks. Elemental analyses were performed by the Department of Chemistry, National University of Singapore.

2-(Bromomethyl)-4-nitroanisole (3b). A mixture of 5 g (0.029 mol) of *p*-nitroanisole, 1.09 g of paraformaldehyde, 4.0 g of NaBr, and 1.5 mL of glacial CH_3COOH was heated to 83–85 °C. H_2SO_4 (3.6 mL) and glacial CH_3COOH (3.6 mL) were gradually added over 5 h. The reaction mixture was stirred for 3 h at 85 °C and then for 12 h at 28 °C. It was extracted with ether, and the ethereal layer was washed successively with 5% $NaHCO_3$ solution and H_2O. After the solution was dried (Na_2SO_4) and the solvent was removed by vacuum distillation, the title compound was obtained (3.4 g, 42%), mp 75–76 °C. Anal. ($C_8H_8NO_3Br$) C, H, N.

2-[(Ethylamino)methyl]-4-nitrophenol (4a). 2-(Chloromethyl)-4-nitrophenol (**3a**; 2.5 g, 0.013 mol) and anhydrous ethylamine (2.5 mL, 0.039 mol) were stirred in dry C_6H_6 for 24 h and then refluxed for 1 h. The solvent and excess ethylamine were removed by vacuum distillation. The remaining solid on recrystallization from MeOH gave 1.8 g (70%) of **4a**, mp 210–211 °C. Anal. ($C_9H_{12}N_2O_3$) C, H, N.

2-[(Ethylamino)methyl]-4-nitroanisole (4b). 2-(Iodomethyl)-4-nitroanisole (**3b'**; 2.5 g, 85 mmol) and anhydrous ethylamine (1.5 mL, 250 mmol) were reacted under the same conditions as **4a**. The solid residue obtained on removal of solvent was dissolved in H_2O and made alkaline with weak NH_3 solution. The precipitate, after recrystallization from petroleum ether (45–50 °C), gave 1.2 g (69%) of the title compound, mp 62–63 °C. Anal. ($C_{10}H_{14}N_2O_3$) C, H, N.

2-[[4-(Diethylcarbamoyl)-1-piperazinyl]methyl]-4-nitrophenol (6a). **3a** (0.5 g, 26 mmol) and 1-(diethylcarbamoyl)-piperazine[12] (1.0 g, 53 mmol) were refluxed in dry C_6H_6 for 24 h. Removal of the solvent by vacuum distillation gave a sticky residue, which was dissolved in dry ether and acidified with ethanolic HCl. The hydrochloride salt of **6a** (0.98 g, 98%) was obtained after recrystallization from EtOH, mp 229–230 °C. Anal. ($C_{16}H_{24}N_4O_4$·HCl) C, H, N, Cl.

2-[[4-(Diethylcarbamoyl)-1-piperazinyl]methyl]-4-nitroanisole (6b). **3b'** (1.5 g, 50 mmol), 1-(diethylcarbamoyl)piperazine (0.75 g, 40 mmol), and triethylamine (2 mL) were refluxed in dry benzene for 24 h. A solid residue was obtained on removal of the solvent under reduced pressure. It was washed with H_2O, dried, and recrystallized from C_6H_6–hexane to give 1.2 g (85%) of **6b**, mp 79–80 °C. Anal. ($C_{17}H_{26}N_4O_4$) C, H, N.

General Procedure for the Syntheses of 10a,b, 11a,b, and 12a,b. Hydrogenation was carried out with a suitable catalyst in a Parr hydrogenator in either EtOH or H_2O at 4 atm and 28 °C. Hydrogenation was stopped when the consumption of H_2 ceased. The solution was filtered, and the filtrate was acidified with ethanolic HCl and evaporated to dryness under reduced pressure. To an aqueous solution of the residue obtained was added an equimolar quantity of 4,7-dichloroquinoline. The mixture was adjusted to pH 4.5–5.0 and heated on a boiling H_2O bath for 1.5–2 h. After cooling, the solution was acidified to yield the title compound.

7-Chloro-4-[α-(ethylamino)-4-hydroxy-*m*-toluidino]-quinoline (10a). **4a**·HCl (2.3 g, 10 mmol) was hydrogenated using 0.23 g of 10%, w/w, Pd/charcoal in EtOH. After condensation with 4,7-dichloroquinoline, 2.2 g (70%) of the title compound was obtained, after recrystallization from $CHCl_3$–ether, mp 177–178 °C. Anal. ($C_{18}H_{18}N_3OCl$) C, H, N.

7-Chloro-4-[α-(ethylamino)-4-methoxy-*m*-toluidino]-quinoline (10b). An ethanolic solution of **4b** (1.5 g, 17 mmol) was hydrogenated using 01.5 g of 10%, w/w, Pd/charcoal. The title compound was subsequently obtained in 85% yield (1.9 g), after recrystallization from $CHCl_3$–ether, mp 165 °C. Anal. ($C_{19}H_{20}N_3OCl$) C, H, N.

7-Chloro-4-(α-amino-4-hydroxy-*m*-toluidino)quinoline (11a). 2-(Nitromethyl)-4-nitrophenol (**5a**; 1.0 g, 50 mmol) in EtOH was hydrogenated using 2 g of Raney nickel W_2. After condensation with 4,7-dichloroquinoline and recrystallization from EtOH, 0.8 g (60%) of the title compound was obtained, mp 220 °C. Anal. ($C_{16}H_{14}N_3OCl$) C, H, N, Cl.

7-Chloro-4-(α-amino-4-methoxy-*m*-toluidino)quinoline (11b). An ethanolic solution of 1 g (47 mmol) of 2-(nitromethyl)-4-nitroanisole (**5b**) was hydrogenated using 2 g of Raney nickel W_2. Condensation with 4,7-dichloroquinoline gave 0.91 g (65%) of the title compound, recrystallized from $CHCl_3$–ether, mp 197–198 °C. Anal. ($C_{17}H_{16}N_3OCl$) C, H, N, Cl.

7-Chloro-4-[α-[4-(diethylcarbamoyl)-1-piperazinyl]-4-hydroxy-*m*-toluidino]quinoline (12a). An aqueous solution of 1 g (26 mmol) **6a**·HCl was hydrogenated using 1 g of Raney nickel W_2. After condensation with 4,7-dichloroquinoline and recrystallization from $CHCl_3$–ether, 0.94 g (75%) of **12a** was obtained, mp 187–188 °C. Anal. ($C_{25}H_{30}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[4-(diethylcarbamoyl)-1-piperazinyl]-4-methoxy-*m*-toluidino]quinoline (12b). **6b** (2.0 g, 58 mmol) in EtOH was hydrogenated using 2 g of Raney nickel W_2. Condensation with 4,7-dichloroquinoline gave 1.9 g (69%) of **12b**, after recrystallization from C_6H_6, mp 115–116 °C. Anal. ($C_{26}H_{32}N_5O_2Cl$) C, H, N, Cl.

General Procedure for the Syntheses of 13a,b, 14a,b, 15a,b, and 16a,b. The reactant in $CHCl_3$ was added over a period of 30 min to a stirred $CHCl_3$ solution of 4-methyl-1-piperazinylcarbonyl chloride hydrochloride[20] (MPCC HCl) or diethyl-

(17) Lämmler, G.; Herzog, H.; Schütze, H. R. *Bull. W.H.O.* **1971**, *44*, 765.
(18) Go, M. L.; Ngiam, T. L., unpublished results.
(19) Elslager, E. F.; Perricone, S. C.; Tendick, F. H. *J. Med. Chem.* **1969**, *12*, 965.

carbamoyl chloride (DECC) and in the presence of triethylamine. After 1 h of stirring at 28 °C, the mixture was refluxed for 4 h. Removal of the solvent under reduced pressure gave a solid residue, which was washed with H_2O, dried, and recrystallized.

7-Chloro-4-[α-[*N*-ethyl-*N*-[(4-methyl-1-piperazinyl)carbonyl]amino]-4-hydroxy-*m*-toluidino]quinoline (13a). 10a (1.5 g, 46 mmol), MPCC HCl (1.1 g, 55 mmol), and Et_3N (3 mL) gave the title compound in 91% yield (1.78 g), after recrystallization from EtOH–ether, mp 190–191 °C. Anal. ($C_{24}H_{28}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-ethyl-*N*-[(4-methyl-1-piperazinyl)carbonyl]amino]-4-methoxy-*m*-toluidino]quinoline (13b). The reaction of 0.48 g (14 mmol) of **10b**, 0.31 g (15 mmol) of MPCC HCl, and 2 mL of Et_3N in $CHCl_3$ gave 0.6 g (91%) of the title compound, after recrystallization from $CHCl_3$–ether, mp 145 °C. Anal. ($C_{25}H_{30}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-[(4-methyl-1-piperazinyl)carbonyl]amino]-4-hydroxy-*m*-toluidino]quinoline (14a). 11a (0.85 g (28 mmol), MPCC HCl (0.6 g, 31 mmol), and 5 mL of Et_3N were reacted in THF. After recrystallization from $CHCl_3$–ether, 0.6 g (55%) of the title compound was obtained, mp 170–171 °C. Anal. ($C_{22}H_{24}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-[(4-methyl-1-piperazinyl)carbonyl]amino]-4-methoxy-*m*-toluidino]quinoline (14b). The reaction of 0.78 g (25 mmol) of **11b**, 0.55 g (27.5 mmol) of MPCC HCl, and 4 mL of Et_3N in $CHCl_3$ gave 1 g (95%) of **14b**, after recrystallization from alcohol–ether, mp 197–198 °C. Anal. ($C_{23}H_{26}N_5O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-ethyl-*N*-(diethylcarbamoyl)amino]-4-hydroxy-*m*-toluidino]quinoline (15a). 10a (1.3 g, 40 mmol), DECC (0.6 g, 44 mmol), and Et_3N (3 mL), on reaction in $CHCl_3$, gave the title product in 80% yield (1.3 g, mp 207–208 °C, after recrystallization from MeOH). Anal. ($C_{23}H_{27}N_4O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-ethyl-*N*-(diethylcarbamoyl)amino]-4-methoxy-*m*-toluidino]quinoline (15b). 10b (0.95 g, 28 mmol) was reacted with 0.39 g (31 mmol) of DECC and 3 mL of Et_3N in $CHCl_3$: 1.1 g (90%) of the title compound was obtained, mp 134–135 °C, after recrystallization from $CHCl_3$–ether. Anal. ($C_{24}H_{29}N_4O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-(diethylcarbamoyl)amino]-4-hydroxy-*m*-toluidino]quinoline (16a). The reaction of 0.9 g (30 mmol) of **11a**, 0.44 g (33 mmol) of DECC, and 4 mL of Et_3N in THF gave 0.78 g (65%) of the title compound, mp 225–226 °C, after recrystallization from MeOH. Anal. ($C_{21}H_{24}N_4O_2Cl$) C, H, N, Cl.

7-Chloro-4-[α-[*N*-(diethylcarbamoyl)amino]-4-methoxy-*m*-toluidino]quinoline (16b). 11b (0.77 g, 25 mmol), DECC (0.35 g, 28 mmol), and Et_3N (4 mL) were reacted in $CHCl_3$: 0.86 g (85%) of the title compound was obtained after recrystallization from EtOH–ether, mp 227–228 °C. Anal. ($C_{22}H_{26}N_4O_2Cl$) C, H, N, Cl.

Acknowledgment. This paper is dedicated to the memory of the late Associate Professor P. N. Natarajan who initiated this work but, due to unforeseen circumstances, was unable to see its completion. The authors gratefully acknowledge Professor G. Lämmler and Dr. I. Sänger of the Institute of Parasitology, Justus-Liebig University, Giessen, for carrying out antifilarial studies (in vivo) on the final compounds. Special thanks are also due to Associate Professor Mulkit Singh and Dr. S. L. Leung for their generous assistance in this work. Lastly, M.L.G. thanks the National University of Singapore, Singapore, for awarding her a Research Scholarship award.

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3-Phenylpiperidines. Central Dopamine-Autoreceptor Stimulating Activity

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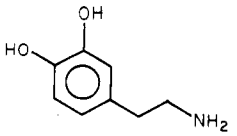
Thirty compounds related to the selective dopamine–autoreceptor agonist 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine have been synthesized and tested for central dopamine–autoreceptor stimulating activity. The 3-(3-hydroxyphenyl)piperidine moiety seems indispensable for high potency and selectivity. Introduction of an additional hydroxyl group into the 4 position of the aromatic ring gives a compound with dopaminergic activity but lacking selectivity for autoreceptors. 3-(3-Hydroxyphenyl)-*N*-*n*-propylpyrrolidine, 3-(3-hydroxy)-*N*-*n*-propylperhydroazepine, and 3-(3-hydroxyphenyl)quinuclidine were all inactive. The most potent compounds were the *N*-isopropyl-, *N*-*n*-butyl-, *N*-*n*-pentyl-, and *N*-phenethyl-substituted 3-(3-hydroxyphenyl)piperidine derivatives. None of the compounds investigated seemed to have central noradrenaline- or serotonin-receptor stimulating activity.

In recent years much interest has been focused on the physiology and pharmacology of the dopamine (DA) autoreceptors.[1,2] In animal experiments, low doses of DA-receptor agonists, for example, apomorphine, have been shown to act preferentially on the autoreceptors, thereby reducing nerve impulse flow, transmitter-synthesis rate, and release in the CNS.[3] Functionally, stimulation of DA autoreceptors results in, among other things, a decrease in locomotor activity and exploratory behavior (cf. ref 4).



DA

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0022-2623/81/1824-1475$01.25/0