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# Analogues of 8-[[6-(Diethylamino)hexyl]amino]-6-methoxy-4-methylquinoline as Candidate Antileishmanial Agents

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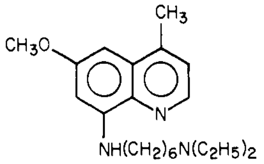
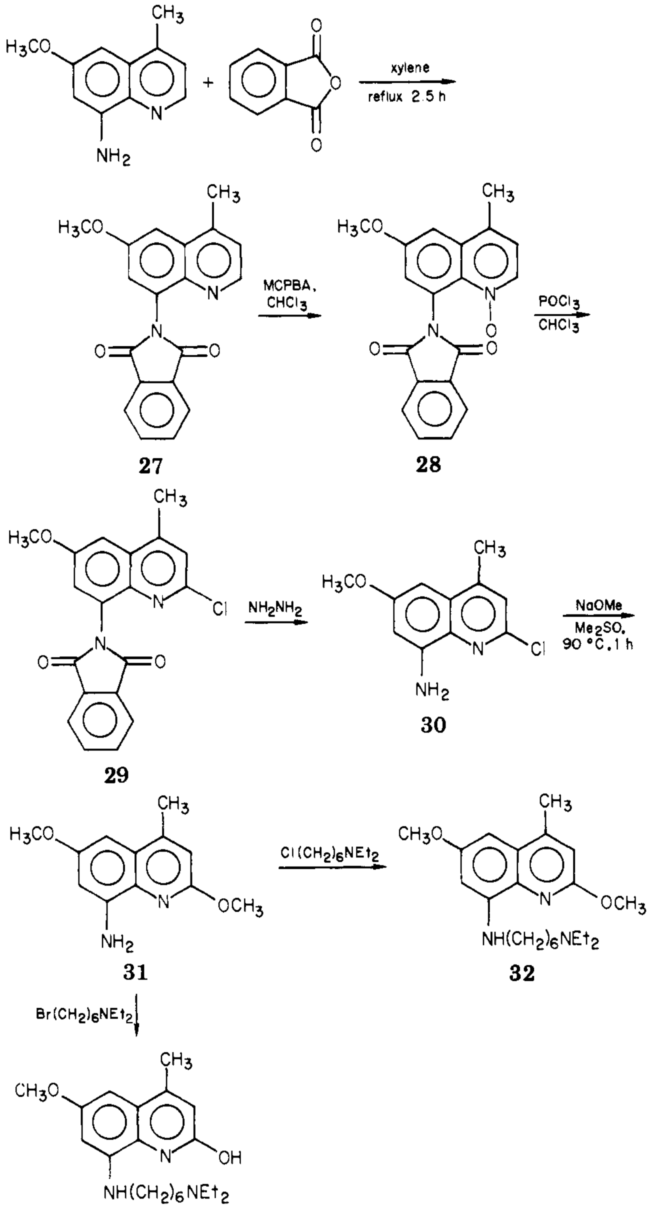
8-[[6-(Diethylamino)hexyl]amino]-6-methoxy-4-methylquinoline (I) has been shown to be highly effective against *Leishmania donovani* in hamsters, being approximately 475 times as active as the standard meglumine antimoniate. Several nuclear and side-chain analogues of I have been prepared in an attempt to further enhance the antileishmanial activity of this class of compounds. The compounds were tested against *L. donovani* in the golden hamster. Although several analogues had meglumine antimoniate indexes in excess of 300, none was superior to the model compound.

It has been reported[1] that 8-[[6-(diethylamino)hexyl]amino]-6-methoxy-4-methylquinoline (I) possesses a very high level of activity against *L. donovani* in hamsters. This compound is, in fact, approximately 475 times as active as the standard meglumine antimoniate in this screen. The purpose of the present investigation was to prepare a series of side chain and nuclear analogues of I in an attempt to further enhance the activity of this class of compounds against visceral leishmaniasis.



I

Scheme I



**Chemistry**. Five of the ten side-chain analogues of I (**1**, **2**, **22**, **24**, and **25**) were prepared via condensation of 8-amino-6-methoxy-4-methylquinoline[2] with the appropriate 6-(alkylamino)alkyl chloride.

The (diisopropylamino)hexylamino analogue (**6**) was prepared as follows. Monomethyl adipate was converted to acid chloride **3**, which was treated with diisopropylamine to afford amide **4**. Reduction of **4** with $LiAlH_4$ afforded the aminohexanol **5**, which was converted to the chloride and condensed with the 8-aminoquinoline. Preparation of compound **12** involved standard procedures. For the preparation of **16**, treatment of 8-amino-6-methoxy-4-methylquinoline with 1-bromo-6-phthalimidohexane afforded phthalimide **13**, which was treated with hydrazine hydrate to yield diamine **14**. Condensation of **14** with ethyl bromoacetate afforded ester **15**, which was reduced with $LiAlH_4$ to yield **16**. The two methyl-branched analogues **19** and **21** were prepared via the following lengthy sequence. 6-Bromocapronitrile was treated with methylmagnesium iodide to afford 7-bromo-2-heptanone (**17**). Condensation of **17** with 8-amino-6-methoxy-4-methylquinoline afforded the amino ketone **18**. Condensation of **18** with isopropylamine, followed by catalytic reduction of the intermediate Schiff base, afforded target compound **19**. Acylation of **19** afforded a mixture of mono- and diacetyl intermediates. Separation of the desired monoacetyl intermediate **20** via column chromatography, followed by reduction with $LiAlH_4$, afforded analogue **21**. In addition, three nuclear analogues of I were prepared. The first example, **26**, bearing a 5-methoxy substituent, was prepared via condensation of 8-amino-5,6-dimethoxy-4-methylquinoline with 6-(diethylamino)hexyl chloride. The remaining two analogues contain a substituent in the 2-position of the quinoline nucleus. It was therefore necessary to prepare the previously unknown 8-amino-2,6-dimethoxy-4-methylquinoline (**31**). The sequence is shown in Scheme I. 8-Amino-6-methoxylepidine was converted to the 8-phthalimido intermediate under standard conditions. Conversion to the 1-oxide (**28**) with *m*-chloroperbenzoic acid, followed by treatment with phosphorus oxychloride, afforded 2-chloro-6-methoxy-8-phthalimidolepidine (**29**). Removal of the phthalimide protecting group with hydrazine afforded the requisite 8-amino-2-

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chloro-6-methoxylepidine (**30**). Displacement of the 2-chloro group with sodium methoxide in $Me_2SO$ gave 8-amino-2,6-dimethoxylepidine (**31**). Alkylation with 6-(diethylamino)hexyl bromide resulted in cleavage of the 2-methoxy group to afford 8-[[6-(diethylamino)hexyl]-amino]-2-hydroxy-6-methoxylepidine (**32**), and alkylation with 6-(diethylamino)hexyl chloride afforded 8-[[6-(diethylamino)hexyl]amino]-2,6-dimethoxylepidine (**33**).

**Biological Activity.** The compounds were tested for antileishmanial activity against *L. donovani* in hamsters.[3] The data are shown in Table I. A comparison of the antileishmanial activity of each test compound with that of the reference compound, meglumine antimoniate, was made and a *G* index (relative activity of the test compound to that of the reference compound) for each test compound was calculated by the following formula:

$$G \text{ index} = \frac{SD_{90} \text{ for meglumine antimoniate}}{SD_{90} \text{ for test compound}}$$

The comparison was made based upon the total molecular weight of the compound, less that fraction attributable to the salt. The drug dosage levels of active test compounds required for a given degree of effect, such as 90% suppression ($SD_{90}$), were estimated graphically by plotting percent parasite suppression vs. milligrams of compound administered per kilogram of body weight of the hamster on log paper. When the $SD_{90}$ value could not be obtained because of low activity of the test compound, a lower SD value was used. The most active examples were **1** and **26** with meglumine antimoniate indexes of 333 and 401, respectively. However, none was superior to the model compound 8-[[6-(diethylamino)hexyl]amino]-6-methoxylepidine (I), which had a meglumine antimoniate index of approximately 475. (Compound I had a *G* value of 700 when the drug was administered orally.) The data indicate, therefore, that the 6-(diethylamino)hexylamino side chain appears to be optimum. Introduction of an additional 5-substituent (compound **26**) decreases activity relative to I, and introduction of a 2-hydroxy substituent (**32**) almost completely destroys activity. This latter observation would rule out in vivo transformation of I to an active 2-substituted metabolite.

## Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana. NMR spectra were determined on a Varian Model T60A spectrometer. Ethanol used in this work was specially denatured grade 3A alcohol (90% ethanol, 5% 2-propanol, and 5% methanol, v/v). Commercial Raney nickel was supplied by W. R. Grace Co. (no. 30). Silica gel was purchased from EM Labs (70–230 mesh).

**ω-(Alkylamino)hexanols.** The following aminohexanols were prepared by heating 6-chloro-1-hexanol with the appropriate amine at reflux for several hours, followed by distillation under reduced pressure: **6-(di-*n*-propylamino)-1-hexanol**, yield 59%, bp 103 °C (0.5 mm); **6-(di-*n*-hexylamino)-1-hexanol**, yield 50%, bp 128–130 °C (0.1 mm); **6-(ethylamino)-1-hexanol (7)**, yield 57%, bp 95 °C (1.5 mm); **6-(cyclobutylamino)-1-hexanol**, yield 74%, bp 118–120 °C (0.1 mm).

**ω-(Alkylamino)alkyl Halides.** The requisite aminoalkyl halides were prepared from the precursor alkanols via refluxing in $SOCl_2$. In all cases the halides were oils which were used in the alkylation reactions without further purification.

**Methyl 5-(Chloroformyl)pentanoate (3).** A mixture of adipic acid monomethyl ester (70.0 g, 0.437 mol) was converted to the title acid chloride with thionyl chloride (64 g, 0.54 mol) in $C_6H_6$ (150 mL). Concentration afforded the title compound (80.5 g, 100%), which was used as such in the next step.

Similarly prepared was **methyl 6-(chloroformyl)hexanoate**: yield 92%; bp 71–72 °C (0.3 mm), lit.[4] 76–78 °C (0.3 mm).

**Methyl 5-(*N*,*N*-Diisopropylcarbamoyl)pentanoate (4).** The title compound was prepared from the above acid chloride (80.5 g, 0.45 mol) and diisopropylamine (96 g, 0.95 mol) in $C_6H_6$ (500 mL) under standard conditions. The crude yellow oil was distilled to give 98.0 g (92%) of the title compound, bp 110 °C (0.07 mm). Anal. ($C_{13}H_{25}NO_3$) C, H, N.

Similarly prepared were **methyl 6-(*N*,*N*-diethylcarbamoyl)hexanoate**, yield 87%, bp 122–123 °C (0.25 mm), and **methyl 4-(*N*,*N*-diethylcarbamoyl)butyrate**, yield 67% from methyl 4-(chloroformyl)butyrate, bp 95–98 °C (0.5 mm), lit.[5] bp 90 °C (0.55 mm).

**6-(Diisopropylamino)-1-hexanol (5).** Methyl 5-(*N*,*N*-diisopropylcarbamoyl)pentanoate (73.0 g, 0.30 mol) in THF (220 mL) was reduced with $LiAlH_4$ (36.6 g, 0.96 mol) in THF (1.5 L) under standard conditions. The mixture was refluxed for 3 h and standard workup afforded a liquid which was purified by distillation to afford 53.0 g (88%) of the title compound, bp 88–89 °C (0.1 mm). Anal. ($C_{12}H_{27}NO$) C, H, N.

Similarly prepared were **7-(diethylamino)-1-heptanol**, yield 89%, bp 84–86 °C (0.1 mm), lit.[6] bp 129–130 °C (9 mm), and **5-(diethylamino)-1-pentanol**, yield 87%, bp 69–71 °C (0.15 mm), lit.[7] bp 90 °C (0.55 mm).

***N*-Ethyl-*N*-(carbethoxymethyl)-6-chlorohexylamine (10).** A solution of 6-(ethylamino)hexyl chloride (28.1 g, 0.172 mol) and $Et_3N$ (17 g, 0.168 mol) in distilled $C_6H_6$ (250 mL) was cooled to 10 °C (ice-water). Ethyl bromoacetate (28.4 g, 0.170 mol) in distilled $C_6H_6$ (50 mL) was then added dropwise over a period of 20 min, maintaining the temperature at ca. 10 °C. The reaction mixture was then stirred at room temperature for 2 h and heated at reflux for 11 h. The reaction mixture was cooled to room temperature and filtered. The filterate on concentration gave a light brown oil, which was triturated in anhydrous $Et_2O$ (250 mL) and filtered. The filtrate on concentration gave a light yellow oil (34.3 g, 81% yield), which was purified by distillation under reduced pressure, bp 96–99 °C (0.15 mm). Anal. ($C_{21}H_{24}ClNO_2$) C, H, N, Cl.

**2-[*N*-Ethyl-*N*-(6-chlorohexyl)amino]ethanol (11).** The title compound was prepared from **10** and $LiAlH_4$ in $Et_2O$ as described for **5**: yield 76%; bp 98–101 °C (0.05 mm). Anal. ($C_{10}H_{22}ClNO$) C, H, N, Cl.

**8-[(6-Phthalimidohexyl)amino]-6-methoxylepidine (13).** The title compound was prepared from 8-amino-6-methoxylepidine[2] and 6-bromo-1-phthalimidohexane via the procedure previously described:[8] yield 53%; mp 95–97 °C. Anal. ($C_{25}H_{27}N_3O_3$) C, H, N.

**8-[(6-Aminohexyl)amino]-6-methoxylepidine (14).** The title compound was prepared from **13** and hydrazine via the procedure previously described:[8] yield 78%; mp 56–58 °C. Anal. ($C_{17}H_{25}N_3O$) C, H, N.

**8-[[6-[(Carbethoxymethyl)amino]hexyl]amino]-6-methoxylepidine (15).** Diamine **14** (13.4 g, 0.047 mol) was converted to the title compound as described for **10** with the exception that the crude product was purified over silica gel. Elution with $CHCl_3$ (4.5 L) removed the major byproduct (diester, 1.7 g). Elution with 1 and 2% MeOH–$CHCl_3$ (2 L each) afforded the product: yield 9.5 g (54%); mp 50–52 °C. An analytical sample was prepared by recrystallization from petroleum ether (bp 60–110 °C), mp 51–53 °C. Anal. ($C_{21}H_{21}N_3O_3$) C, H, N.

**8-[[6-[(Hydroxyethyl)amino]hexyl]amino]-6-methoxylepidine Dihydrochloride (16).** The title compound was pre-

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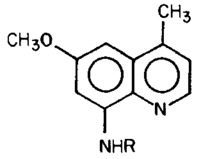
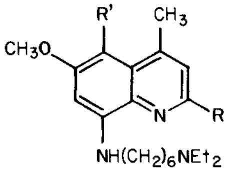
**Table I. Physical Properties and Antileishmanial Activity Data**



1, 2, 6, 12 16, 19, 21, 22, 24, 25, I

| no. | R | yield,[a] % | mp, °C (solvent) | formula | anal.[b] | % suppression: *L. donovani* (hamster), (mg/kg)/day[f] 208 | 52 | 13 | 0.81 | 0.20 | 0.05 | $G$[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **A. Side-Chain Analogues** | | | | | | | | | |
| 1 | $-(CH_2)_6N(n\text{-}C_3H_7)_2$ | 20 | 113-115 (*i*-PrOH-Et$_2$O) | $C_{23}H_{37}N_3O \cdot HCl$ | C, H, N, Cl | 6T | 6T | | 99.9 | 99.9 | 31 | 333 |
| 2 | $-(CH_2)_6N(n\text{-}C_6H_{13})_2$ | 10 | 104.5-106.5 (*i*-PrOH-Et$_2$O) | $C_{29}H_{49}N_3O \cdot 2HCl$ | C, H, N, Cl | | | not tested | | | | |
| 6 | $-(CH_2)_6N(i\text{-}C_3H_7)_2$ | 54 | 182-184 (*i*-PrOH-Et$_2$O) | $C_{23}H_{37}N_3O \cdot 2HCl$ | C, H, N, Cl | 6T | 6T | 97.5 | 100 | 97.4 | 20.2 | 310 |
| 12 | $-(CH_2)_6N(CH_2CH_2OH)C_2H_5$ | 66 | 103-105 (*i*-PrOH-cyclohexane) | $C_{21}H_{33}N_3O_2 \cdot HCl$ | C, H, N, Cl | 6T | 95.4 | 79.2 | | | | 3.4 |
| 16 | $-(CH_2)_6NHCH_2CH_2OH$ | 68[c] | 117-119 (*i*-PrOH-Et$_2$O) | $C_{19}H_{29}N_3O_2 \cdot HCl$ | C, H, N, Cl | T | T | 99.9 | | | | ~300 |
| 19 | $-(CH_2)_5C(CH_3)HNH(i\text{-}C_3H_7)$ | 53[d] | 152-154 ($CH_3CN$) | $C_{21}H_{33}N_3O \cdot HCl$ | C, H, N, Cl | T | T | 95.4, T | 100 | 97.3 | | ~300 |
| 21 | $-(CH_2)_5C(CH_3)HN(i\text{-}C_3H_7)C_2H_5$ | 36[e] | 173-175 ($CH_3CN$-Et$_2$O) | $C_{23}H_{37}N_3O \cdot 2HCl$ | C, H, N | T | | 95.4, T | 100 | 97.3 | | |
| 22 | $-(CH_2)_5N(C_2H_5)_2$ | 12 | 118.5-120 (EtOH) | $C_{20}H_{31}N_3 \cdot C_6H_8O_7$ | C, H, N | | 100 | 100 | 100 | 91.5 | | 178 |
| 24 | $-(CH_2)_7N(C_2H_5)_2$ | 39 | 178-179 (*i*-PrOH-Et$_2$O) | $C_{22}H_{35}N_3O \cdot 2HCl$ | C, H, N, Cl | | 6T | 100 | 99.8 | 73.1 | | 96.8 |
| 25 | $-(CH_2)_6NHC_4H_7$ | 40 | 132-135 (*i*-PrOH-Et$_2$O) | $C_{21}H_{31}N_3O \cdot HCl$ | C, H, N, Cl | 6T | 100 | 100 | 99.2 | | | 188 |
| I | $-(CH_2)_6N(C_2H_5)_2$ | | | | | | | | 100 | 99.6 | 83.7 | 474 |

B. Nuclear Analogues of I



26, 32, 33

| no. | R | R' | yield,[a] % | mp, °C (solvent) | formula | anal.[b] | 208 | 52 | 13 | 0.81 | 0.20 | 0.05 | $G$[g] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26 | H | $OCH_3$ | 62 | 152.5-154 (*i*-PrOH-Et$_2$O) | $C_{22}H_{35}N_3O_2 \cdot 2HCl$ | C, H, N | | | 99.9 | 100 | 100 | 68 | 401 |
| 32 | OH | H | 9 | 135-137 (*i*-PrOH) | $C_{21}H_{33}N_3O_2$ | C, H, N | 62.8 | | I | I | | | |
| 33 | $OCH_3$ | H | 34 | 135-137 (*i*-PrOH) | $C_{22}H_{35}N_3O_2 \cdot 2HCl$ | C, H, N, Cl | | | not available | | | | |

[a] From 8-aminoquinoline. [b] All values are ±0.4% of theory. [c] From 15. [d] From 18. [e] From 20. [f] See ref 3; T = toxic, I = inactive. [g] Meglumine antimoniate index.

pared from **15** (8 g, 0.02 mol) and $LiAlH_4$ (2.6 g, 0.07 mol) in THF as described for **5**. Recrystallization of the crude product from $CH_3CN$ (×2) afforded a light colored product: yield 4.2 g (68%); mp 83–85 °C. Anal. ($C_{19}H_{29}N_3O_2$) C, H, N.

The above free base (4.5 g, 0.015 mol) was dissolved in hot 2-propanol (15 mL) and cooled to room temperature. To this solution was added HCl/2-propanol (4.0 mL, 3.06 N), followed by anhydrous $Et_2O$ (15 mL). Filtration afforded the title hydrochloride: yield 4.3 g (77%); mp 117–119 °C. Anal. ($C_{19}H_{29}N_3O_2$·HCl) C, H, N, Cl.

**6-Bromocapronitrile.** The title compound was prepared by following the procedure of Breslow and Hauser[9] from 6-bromocaproic acid via 6-bromocaproamide in an overall yield of 77%, bp 82–85 °C (1.1 mm).

**7-Bromo-2-heptanone (17).** To an EtOH solution (500 mL) of 6-bromocapronitrile (52.8 g, 0.30 mol) under $N_2$ was added $CH_3MgI$ [from MeI (10 g) and Mg (18.3 g)] dropwise over a period of 1.25 h. The reaction mixture was refluxed for 8 additional hours. Standard workup afforded the title compound (35 g, 61%), which was used in the next step without further purification.

**8-[(6-Ketoheptyl)amino]-6-methoxylepidine (18).** A mixture of 8-amino-6-methoxylepidine[2] (15 g, 0.08 mol), **17** (17 g, 0.09 mol), and $NaHCO_3$ (14.5 g, 0.17 mol) was heated at 130–135 °C for 16 h under $N_2$. The cooled reaction mixture was dissolved in $CHCl_3$ (350 mL) and filtered. The filtrate was concentrated to ca. 20 mL and chromatographed over silica gel (700 g), eluting with $CHCl_3$. The appropriate fractions were combined to give the title compound (9.0 g, 38%). An analytical sample was obtained by recrystallization from petroleum ether (bp 60–110 °C), mp 72–74 °C. Anal. ($C_{18}H_{24}N_2O_2$) C, H, N.

**8-[[6-(Isopropylamino)heptyl]amino]-6-methoxylepidine Hydrochloride (19).** A solution of **18** (10 g, 0.033 mol) in isopropylamine (170 mL) was stirred with 3 Å molecular sieves (75 g) for 2 days. The solution was filtered and the sieves were washed with dry $Et_2O$ (375 mL). The combined organic layers were concentrated and the residue (11 g) was redissolved in isopropylamine (170 mL) and stirred occasionally with 3 Å molecular sieves (50 g) for an additional 4 days. The reaction mixture was filtered and the sieves were washed with dry $Et_2O$ (375 mL). The combined organic layers were concentrated to give a thick yellow oily residue, which was dissolved in absolute EtOH (250 mL). To this solution 5% platinum on activated carbon (1 g) was added and the mixture hydrogenated on a Parr apparatus for 4 h at 50 psig. The catalyst was filtered and the filtrate was concentrated to give a residue, which was dissolved in 2-propanol (25 mL) and treated with hydrogen chloride in 2-propanol (9.5 mL, 3.06 N). Most of the 2-propanol was distilled, and the residue was chromatographed over silica gel (100 g) and eluted with $CHCl_3$ (2 L) to remove starting material (1.2 g). Elution with 3, 5, and 7% MeOH–$CHCl_3$ (1 L each) afforded the title compound. The appropriate fractions were concentrated, and the residue was dissolved in $CHCl_3$ (200 mL) and washed with 10% KOH (50 mL). The organic layer was dried over anhydrous $K_2CO_3$ and concentrated to yield the title compound as a free base (7.6 g, 75%). The base was dissolved in 2-propanol (25 mL) and treated with hydrogen chloride in 2-propanol (6.5 mL, 3.06 N HCl). Most of the 2-propanol was distilled, and the solid was stirred with dry $Et_2O$ (150 mL) to give the title compound: yield 6.6 g (53%); mp 148–150 °C. An analytical sample was prepared via recrystallization from $CH_3CN$, mp 152–154 °C. Anal. ($C_{21}H_{34}ClN_3O$) C, H, N, Cl.

**8-[[6-(*N*-Acetyl-*N*-isopropylamino)heptyl]amino]-6-methoxy-4-methylquinoline (20).** A solution of **19** (8.0 g, 0.023 mol) and triethylamine (2.4 g, 0.024 mol) in distilled $C_6H_6$ (100 mL) at ~5 °C was added dropwise over a period of 50 min a solution of acetyl chloride (1.8 g, 0.023 mol) in distilled $C_6H_6$ (20 mL). The reaction mixture was slowly warmed to 20 °C over a period of 1 h and maintained at that temperature for 1 h. Standard workup afforded a residue (9.6 g), which was chromatographed over silica gel (75 g) and eluted with $CHCl_3$ (2.5 L) to yield the desired monoacetyl derivative (5.7 g, 72%), which was used as such in the next step.

**8-[[6-(*N*-Ethyl-*N*-isopropylamino)heptyl]amino]-6-methoxy-4-methylquinoline (21).** Amide **20** (5.7 g, 0.015 mol) was converted to the title amine via treatment with $LiAlH_4$ (1.1 g, 0.03 mol) in THF (250 mL). Standard workup, followed by purification over silica gel, afforded pure free base as a brown oil (3.48 g, 63%). The base was dissolved in $CH_3CN$ (30 mL) and HCl/*i*-PrOH (3.06 N, 6 mL, 2 equiv) was added. The mixture was filtered and $Et_2O$ (45 mL) was slowly added with efficient stirring. The yellow crystals which separated were filtered and washed with $CH_3CN$–$Et_2O$ (1:1) and finally with $Et_2O$. The solid was dried in vacuo to afford the title compound: yield 2.4 g (36%); mp 173–175 °C. Anal. ($C_{23}H_{39}Cl_2N_{30}$) C, H, N, Cl.

**6-Methoxy-8-phthalimidolepidine (27).** 8-Amino-6-methoxylepidine[2] (63.6 g, 0.34 mol) and phthalic anhydride (51.2 g, 0.35 mol) was refluxed in xylenes (1500 mL) with a Dean–Starke trap for 2.5 h. After the solution cooled to room temperature, a light colored solid separated, which on filtration gave 101 g of the title compound, mp 291–293 °C. An analytical sample was prepared by recrystallization from $CH_3CN$, mp 292–294 °C. Anal. ($C_{19}H_{14}N_2O_3$) C, H, N.

**8-Amino-6-methoxy-2-chlorolepidine (30).** The precursor *N*-oxide (**28**) was obtained via the procedure of Craig and Purushothaman:[10] yield 73%; mp 288–290 °C.

Crude *N*-oxide **28** (23 g, 0.069 mol) was suspended in $CHCl_3$ (1800 mL) at ~50 °C, and $POCl_3$ (64 mL, 105.3 g, 0.69 mol) was added over a period of 30 min (clear solution), followed by reflux on a steam bath for 2.25 h. Standard workup afforded a light yellow solid (**29**): yield 17.7 g (69%); mp 296–298 °C. Treatment of the crude 2-chloro-8-phthalimido-6-methoxylepidine (15.5 g, 0.044 mol) with hydrazine hydrate (6.4 g, 75%) in EtOH (150 mL) under standard conditions afforded the title compound (9.6 g, 98%). An analytical sample was prepared via recrystallization from petroleum ether (bp 60–110 °C), mp 150–152 °C. Anal. ($C_{11}H_{11}ClN_2O$) C, H, Cl, N.

**8-Amino-2,6-dimethoxylepidine (31).** The above 2-chloro-6-methoxy-8-aminolepidine (10.8 g, 0.048 mol) was added at once to freshly prepared dry NaOMe (3.5 g) in $Me_2SO$ (100 mL), and the temperature was maintained between 85 and 90 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into brine (3 L). The product was extracted with $CH_2Cl_2$ (2 × 500 mL). The organic layer was washed with $H_2O$ (500 mL) and dried over anhydrous $K_2CO_3$. Concentration afforded the product, which was recrystallized from petroleum ether (60–110 °C): yield 8.8 g (84%); mp 134–136 °C. An analytical sample was obtained by further recrystallization from petroleum ether (60–110 °C), mp 135–137 °C. Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

**8-[[6-(Diethylamino)hexyl]amino]-6-methoxy-2-hydroxylepidine (32).** A mixture of **31** (12.0 g, 0.055 mol) and 6-(diethylamino)hexyl bromide (free base, 19.2 g, 0.081 mol) in ethoxyethanol (25 mL) was heated at 115–120 °C for 16 h. The reaction mixture was dissolved in $CH_2Cl_2$ (1 L) and extracted with 10% KOH (400 mL). The organic layer was separated and dried over anhydrous $K_2CO_3$. Concentration gave a dark colored residue (22.5 g), which was dissolved in 2-propanol (40 mL) and treated with hydrogen chloride/2-propanol (19.7 mL, 3.06 N). Most of the 2-propanol was removed, and the residue was chromatographed over silica gel (600 g) and eluted with 20% MeOH–$CHCl_3$ to remove product and most of the side products (ca. 7.0 g). This material was rechromatographed over aluminum oxide (200 g, Baker, pH 7.6) and eluted with $CHCl_3$ and 1% MeOH–$CHCl_3$ (500 mL each), which removed most of the impurities. Elution with 2 and 3% MeOH–$CHCl_3$ (500 mL each) afforded the title compound (1.9 g, 9%) which on recrystallization from 2-propanol gave pure **32**, mp 135–137 °C. Anal. ($C_{21}H_{33}N_3O_2$) C, H, N.

**8-[[6-(Diethylamino)hexyl]amino]-2,6-dimethoxylepidine Dihydrochloride (33).** A mixture of 8-amino-2,6-dimethoxylepidine (7.0 g, 0.032 mol), 6-(diethylamino)hexyl chloride (free base, 0.65 g, 0.035 mol), and $NaHCO_3$ (5.95 g, 0.07 mol) was heated at 135–140 °C for 20 h under a $N_2$ atmosphere. The reaction mixture was worked-up as described for **32**, except that chromatography of the free base over silica gel was sufficient to remove impurities. Treatment of the base with *n*-PrOH/HCl afforded the title hydrochloride salt: yield 3.1 g (34%); mp 135–137 °C.

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Anal. (block dried) ($C_{22}H_{35}N_3O_2{\cdot}2HCl$) C, H, Cl, N.

Similarly prepared were compounds **1**, **2**, **6**, **12**, **22**, **24**, and **25** (Table I).

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# Synthesis and Biological Activity of Fluoroalkylamine Derivatives of Narcotic Analgesics

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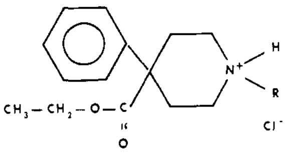
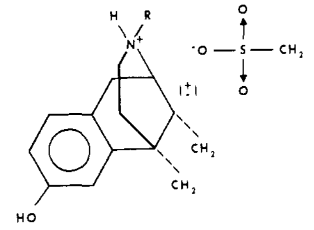
*N*-Ethyl-, *N*-(2-fluoroethyl)-, *N*-(2,2-difluoroethyl)-, and *N*-(2,2,2-trifluoroethyl)-substituted normeperidine (**1b–e**) and normetazocine (**2b–e**) derivatives were prepared. The analgesic activities of the compounds were determined in mice. Opiate receptor binding studies, in the presence and absence of sodium ion, were carried out. The antagonist activities of normetazocine derivatives were studied in monkeys. These were further examined in the isolated guinea pig ileum for relative agonist activity. The p$K_a$ values were measured; in vivo agonist activity was lost with weakly basic derivatives. For the normetazocine derivatives, opiate receptor binding data were consistent with guinea pig ileum agonist potency and mouse vas deferens antagonist potency but not with in vivo data. Opiate receptor binding was reduced for the less basic normetazocine derivatives. In the normeperidine series, there was no apparent direct relationship between p$K_a$ and opiate receptor binding. However, a relationship involving the hydrophobic character of the N-substituent is discussed. The *N*-(2-fluoroethyl) derivatives in both series were found to cause convulsions in rats at doses of 40–45 mg/kg ip. Elevated serum citrate levels were found in these rats, implicating in vivo oxidative deamination of the *N*-(fluoroalkyl) substituent to fluoroacetate.

Most narcotic analgesics bear a nitrogen functionality of sufficient basicity to be predominantly protonated at physiological pH.[2] Narcotic analgesic–receptor interactions have, therefore, been conceptualized as involving the protonated amine form of these compounds.[3,4] The positively charged nitrogen atom is thought to bind with a postulated anionic site on receptor macromolecules. Literature reports indicate that reduced basicity results in a loss of narcotic analgesic activity.[5,6] Although these results are consistent with the above hypothesis, it is not known what role steric, distribution, and metabolism factors play in the overall activity of these compounds. Since it is known that β-fluoroalkylamines are significantly weaker bases than their unsubstituted counterparts[7,8] and that the fluorine atom, because of its small van der Waals radius ($F$ = 1.35 Å, $H$ = 1.2 Å),[9] offers minimal steric interference to binding of an analogue at a subcellular macromolecular site, narcotic analgesic derivatives containing this type of substitution are worthwhile candidates to test the importance of nitrogen basicity for activity. In this report, the synthesis and preliminary pharmacological activities of *N*-ethyl-, *N*-(2-fluoroethyl)-, *N*-(2,2-difluoroethyl)-, and *N*-(2,2,2-trifluoroethyl)-substituted 4-phenyl-4-carbethoxypiperidine (normeperidine) (**1b–e**) and (±)-5,9-α-dimethyl-2′-hydroxy-6,7-benzomorphan (normetazocine) (**2b–e**) derivatives are given.



1



2

R

a) H

b) $CH_2-CH_3$

c) $CH_2-CH_2F$

d) $CH_2-CHF_2$

e) $CH_2-CF_2$

**Chemistry.** The previously reported *N*-ethylnormeperidine hydrochloride[10] (**1b**) and *N*-ethylnormetazocine hydrobromide[11] (**2b**) derivatives were synthesized for pharmacological comparison purposes. It was found to be more convenient to isolate the latter as the mesylate salt. The *N*-(2-fluoroethyl) derivatives were prepared by reaction of either normeperidine (**1a**) or normetazocine (**2a**) with either 2-fluoroethyl bromide or 2-fluoroethyl tosylate in a nonaqueous solvent. Since preparation of 2-fluoroethyl bromide from 2-bromoethyl tosylate and KF lead to the production of vinyl bromide as a byproduct,[12] the more

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