

and 5% methanol, v/v). Commercial Raney nickel was purchased from W.R. Grace Co. (no. 30). Silica gel was purchased from EM Labs (70-230 mesh).

**5-Hydroxy-6-methoxy-4-methyl-8-nitroquinoline (2).** 4-Methyl-5,6-dimethoxy-8-nitroquinoline<sup>4</sup> (6.21 g, 25 mmol) was dissolved in EtOH (100 mL) containing concentrated HCl (4.7 mL). The mixture was heated under reflux for 21 h, cooled to 10 °C, and filtered. The solid was washed with cold (10 °C) EtOH (18 mL), followed by petroleum ether (15 mL), and air-dried to yield 5.41 g (92%) of the title compound, mp 253-257 °C dec. Anal. (C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N.

**5-Chloro-6-methoxy-4-methyl-8-nitroquinoline (3).** A solution of the above 5-hydroxyquinoline (5.25 g, 0.022 mol) in POCl<sub>3</sub> (75 mL) was heated at 80 °C for 2 h. The reaction mixture was poured onto ice and basified with excess NH<sub>4</sub>OH. The tan solid was filtered to give 5.8 g of crude product. This material was purified via column chromatography over silica gel and eluted with CHCl<sub>3</sub>. The fast-moving yellow band was collected and concentrated to give 3.9 g (69%) of the title compound, mp 167-169 °C. Anal. (C<sub>11</sub>H<sub>9</sub>ClN<sub>2</sub>O<sub>3</sub>) C, H, Cl, N.

**6-Methoxy-4-methyl-8-nitro-5-[3-(trifluoromethyl)phenoxy]quinoline (4a).** To a solution of 3-(trifluoromethyl)phenol (4.1 g) in 2-ethoxyethanol (45 mL) containing KOH (1.37 g) was added the above 5-chloroquinoline (5.7 g, 0.023 mol). The mixture was heated at reflux for 8 h and allowed to cool overnight. The solid was filtered and washed well with cold EtOH to give 5.9 g (69%) of the title compound, mp 206-208 °C. An analytical sample was prepared via crystallization from 2-ethoxyethanol, mp 208-210 °C. Similarly prepared were compounds 4b-e (Table I).

**8-Amino-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline (5a).** A solution of 4-methyl-5-[3-(trifluoromethyl)phenoxy]-6-methoxy-8-nitroquinoline (5.9 g, 15.6 mmol) in ethanol-dioxane (4:3, v/v, 350 mL) containing wet Raney nickel (ca. 4 g) was reduced at 45 psig for 1.25 h. The catalyst was filtered, and the filtrate was concentrated to dryness. The residual solid was crystallized from ligroin (bp 60-80 °C) to afford 4.1 g (75%) of the title compound mp 113-115 °C. A sample recrystallized once again gave an analytical sample, mp 116-117 °C.

Similarly prepared were compounds 5b-e (Table I).

**6-Methoxy-4-methyl-8-[(4-phthalimido-1-methylbutyl)amino]-5-[3-(trifluoromethyl)phenoxy]quinoline (6a).** A mixture of the above 8-aminoquinoline (3.0 g, 8.6 mmol), 4-iodo-1-phthalimidopentane (IPP; 3.0 g, 8.7 mmol), Et<sub>3</sub>N (1.2 mL),

and 2-ethoxyethanol (1 mL) was heated at 105 °C for 2.5 h, after which time an additional quantity of IPP (3 g) and Et<sub>3</sub>N (1.2 mL) was added. After an additional 4 h at 105 °C, the mixture was cooled and dissolved in CHCl<sub>3</sub>. The CHCl<sub>3</sub> solution was washed with 10% aqueous KOH and H<sub>2</sub>O, dried, and concentrated to dryness. The residue was dissolved in Et<sub>2</sub>O and excess ethereal HCl was added. The Et<sub>2</sub>O was decanted, and the gum was triturated in fresh Et<sub>2</sub>O (×2). The gum was then shaken with Et<sub>2</sub>O and 10% aqueous K<sub>2</sub>CO<sub>3</sub>. The Et<sub>2</sub>O was removed, and the residue was heated in EtOH (15 mL). The mixture was cooled, and the solid was filtered to give 1.65 g of the title compound. The filtrate was concentrated to dryness, and the residue was triturated in hot ligroin (bp 60-80 °C, 50 mL). The ligroin was decanted from a little insoluble gum and concentrated to dryness to afford 1.5 g of additional crude product. The combined crops were crystallized from EtOH (75 mL) to give 2.75 g (57%) of pure title compound, mp 143-145 °C.

Similarly prepared were compounds 6b-e (Table I).

**8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline Succinate (7a).** A solution of the above phthalimide (4.9 g, 8.7 mmol) in EtOH (110 mL) containing hydrazine hydrate (75%, 1.48 mL) was heated at reflux for 6 h. The EtOH was removed under reduced pressure, and the residue was shaken with Et<sub>2</sub>O and 10% aqueous KOH. The Et<sub>2</sub>O layer was washed with H<sub>2</sub>O (×2) and dried (K<sub>2</sub>CO<sub>3</sub>). To the dried Et<sub>2</sub>O solution was added a solution of succinic acid (1.03 g, 1 mol equiv) in EtOH (100 mL) containing CH<sub>3</sub>OH (4 mL) to solubilize the succinic acid. After the solution was left standing overnight, the solid was filtered to yield 4.5 g (94%) of the title compound, mp 102-103 °C (eff).

Similarly prepared were compounds 7b-e (Table I).

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## Modifications of Primaquine as Antimalarials. 3. 5-Phenoxy Derivatives of Primaquine

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Various 5-phenoxy derivatives of primaquine have been prepared that are somewhat more effective and considerably less toxic than the parent compound in blood and tissue schizonticidal screens. Addition of a methyl group to the pyridine ring of the 5-phenoxyprimaquines has produced a number of antimalarials with potent activity against both blood and tissue schizonts.

Antimalarial enhancement of primaquine by 5-phenoxylation was described earlier.<sup>1</sup> In an effort to achieve the optimal substitution pattern for this series, we have synthesized the compounds included in Table I. Having found that 4-methylprimaquine<sup>2</sup> was less toxic than its

parent, we were particularly interested in those primaquines that combined a 5-phenoxy with a pyridine ring methyl group.

**Chemistry.** The preparative routes were essentially those described in paper 1 of this series.<sup>1</sup> Details have been tabulated under Experimental Section.

(1) E. H. Chen, A. J. Saggiomo, K. Tanabe, B. L. Verma, and E. A. Nodiff, *J. Med. Chem.*, 20, 1107 (1977).

(2) R. C. Elderfield, H. E. Mertel, R. T. Mitch, I. M. Wempen, and E. Werble, *J. Am. Chem. Soc.*, 77, 4816 (1955).

Table I. Blood Schizonticidal Antimalarial Activity (*Plasmodium berghei*, Mouse)<sup>a</sup>

| compd              | R <sub>1</sub>    | R <sub>2</sub>                      | dose: | cures (C), <sup>b</sup> toxic Deaths (T), <sup>c</sup> or Δ MST <sup>d</sup> |          |          |          |           |           |           |
|--------------------|-------------------|-------------------------------------|-------|--|----------|----------|----------|-----------|-----------|-----------|
|                    |                   |                                     |       | 10 mg/kg   | 20 mg/kg | 40 mg/kg | 80 mg/kg | 160 mg/kg | 320 mg/kg | 640 mg/kg |
| primaquine         |                   |                                     |       |  | 4.0      | 5.0      | 9.4      | 2T        | 5T        | 5T        |
| 4-methylprimaquine |                   |                                     |       |  |          |          |          | 9.0       | 10.0      | 1T        |
| 6a                 | 4-CH <sub>3</sub> | H                                   | 8.7   | 4C   | 3C       | 4C       | 4C       | 4C        | 3T        | 2T        |
| 6b                 | H                 | 3-CF <sub>3</sub>                   |       | 0.5  | 1.3      | 4.1      | 7.1      | 13.5      |           | 5C        |
| 6c                 | H                 | 4-CF <sub>3</sub> O                 |       | -0.3   | -0.3     | -0.3     | 0.5      | 0.7       |           | 1T        |
| 6d                 | H                 | 4-CH <sub>3</sub> O                 |       | 0.4  | 0.4      | 1.6      | 6.0      | 8.6       |           | 4C        |
| 6e                 | H                 | 2,4-Cl <sub>2</sub>                 |       | 0.4  | 0.4      | 0.8      | 2.2      | 4.4       |           | 10.4      |
| 6f                 | H                 | 3,4-Cl <sub>2</sub>                 |       | 1.2  | 0.8      | 0.4      | 6.0      | 1C        |           | 1C        |
| 6g                 | H                 | 3,5-(CF <sub>3</sub> ) <sub>2</sub> |       | 0.7  | 0.3      | 0.3      | 1.5      | 6.3       |           | 7.9       |
| 6h                 | 4-CH <sub>3</sub> | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | 1.7   | 4.3  | 3C       | 5C       | 5C       | 5C        |           | 5C        |
| 6i                 | H                 | 4-F, 3-CF <sub>3</sub>              |       | -0.2   | 0.8      | 3.4      | 4.6      | 12.2      |           | 2C        |
| 6j                 | 3-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              |       | 5.9  | 9.9      | 4C       | 5C       | 4C        |           | 1T        |
| 6k                 | 4-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | 1C    | 1C   | 5C       | 5C       | 5C       | 5C        |           | 5C        |
| 6l <sup>e</sup>    | H                 | H                                   |       | 0.3  | 1.5      | 1.7      | 5.1      | 7.5       |           | 2C        |
| 6m <sup>e</sup>    | H                 | 4-Cl                                |       | 0.7  | 4.7      | 5.5      | 7.1      | 8.1       |           | 2C        |
| 6n <sup>e</sup>    | H                 | 4-F                                 |       | 2.1  | 5.7      | 7.5      | 8.9      | 5C        |           | 5C        |

<sup>a</sup> Tests were carried out by the Rane Laboratory, University of Miami, FL, using blood-induced, *P. berghei* infected mice (five animals per group) via the method of Osden et al.<sup>4</sup> Test data were supplied by Drs. H. A. Musallam, R. O. Pick, E. A. Steck, T. R. Sweeney, and R. E. Strube of WRAIR.

<sup>b</sup> The number of mice surviving at 60 days postinfection. <sup>c</sup> Deaths prior to the 6th day. <sup>d</sup> Increase in mean survival time over controls; a compound is considered active if MST of the treated group is more than twice that of the control group (MST of control group, 6.1 days). <sup>e</sup> These data, reported earlier,<sup>1</sup> are included here for comparison.

Table II. Radical Curative Antimalarial Activity (*Plasmodium cynomolgi*, Rhesus Monkey)<sup>a</sup>

| compd              | R <sub>1</sub> | R <sub>2</sub>                      | dose: | cure/no. of animals |            |             |           |            |         |            |          |     |
|--------------------|----------------|-------------------------------------|-------|---------------------|------------|-------------|-----------|------------|---------|------------|----------|-----|
|                    |                |                                     |       | 0.125 mg/kg         | 0.25 mg/kg | 0.316 mg/kg | 0.5 mg/kg | 0.75 mg/kg | 1 mg/kg | 3.16 mg/kg | 10 mg/kg |     |
| primaquine         |                |                                     |       |                     | 0/8        | 0/2         | 10/12     | 9/9        |         |            |          |     |
| 4-methylprimaquine |                |                                     |       |                     |            | 0/4         |           |            | 2/2     |            |          |     |
| 6b                 | H              | 3-CF <sub>3</sub>                   |       | 0/1                 | 3/5        |             | 2/2       |            | 1/1     |            |          |     |
| 6c                 | H              | 4-CF <sub>3</sub> O                 |       |                     |            |             |           |            | 0/1     |            |          | 1/1 |
| 6d                 | H              | 4-CH <sub>3</sub> O                 |       |                     |            |             |           |            | 0/1     |            |          | 1/1 |
| 6e                 | H              | 2,4-Cl <sub>2</sub>                 |       |                     |            |             |           |            | 0/3     | 2/2        |          | 1/1 |
| 6f                 | H              | 3,4-Cl <sub>2</sub>                 |       |                     |            |             |           |            | 1/3     | 2/2        |          | 1/1 |
| 6g                 | H              | 3,5-(CF <sub>3</sub> ) <sub>2</sub> |       |                     |            |             |           |            | 0/1     | 1/1        |          | 1/1 |
| 6i                 | H              | 4-F, 3-CF <sub>3</sub>              |       |                     |            | 2/2         |           |            | 1/1     |            |          |     |
| 6m <sup>b</sup>    | H              | 4-Cl                                |       |                     | 0/1        |             | 0/2       | 5/6        | 3/3     |            |          | 1/1 |
| 6n <sup>b</sup>    | H              | 4-F                                 |       | 0/5                 | 3/8        |             | 5/5       |            |         |            |          |     |
| 6o <sup>b</sup>    | H              | 4-CH <sub>3</sub> CONH              |       |                     |            |             | 0/1       |            | 0/1     |            |          |     |

<sup>a</sup> Tests were carried out using sporozoite-induced, *P. cynomolgi* infected rhesus monkeys according to the procedure of Schmidt et al.<sup>5</sup> <sup>b</sup> These data, reported earlier,<sup>1</sup> are included for comparison.

Table III. 6-Methoxy-8-nitro-5-phenoxyquinolines

| compd | R <sub>1</sub>    | R <sub>2</sub>                      | mp, °C (solvent)                                | yield, % | formula <sup>c</sup>  |
|-------|-------------------|-------------------------------------|---|----------|---|
| 3a    | 4-CH <sub>3</sub> | H                                   | 169-171 (C <sub>6</sub> H <sub>6</sub> -hexane) | 41       | C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub>                 |
| 3b    | H                 | 3-CF <sub>3</sub>                   | 155-157 (EtOH)                                  | 84       | C <sub>17</sub> H <sub>11</sub> F <sub>3</sub> N <sub>2</sub> O <sub>4</sub>  |
| 3c    | H                 | 4-CF <sub>3</sub> O                 | 111-113 (ligroin)                               | 42       | C <sub>17</sub> H <sub>11</sub> F <sub>3</sub> N <sub>2</sub> O <sub>5</sub>  |
| 3d    | H                 | 4-CH <sub>3</sub> O                 | 116-122 (EtOH) <sup>d</sup>                     | 35       | C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub>                 |
| 3e    | H                 | 2,4-Cl <sub>2</sub>                 | 148-151 (MeOH-Et <sub>2</sub> O)                | 49       | C <sub>16</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> |
| 3f    | H                 | 3,4-Cl <sub>2</sub>                 | 147-148.5 (EtOH)                                | 38       | C <sub>16</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> |
| 3g    | H                 | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | 196-198 (C <sub>6</sub> H <sub>6</sub> -hexane) | 34       | C <sub>18</sub> H <sub>10</sub> F <sub>6</sub> N <sub>2</sub> O <sub>4</sub>  |
| 3h    | 4-CH <sub>3</sub> | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | 228-230 (C <sub>6</sub> H <sub>6</sub> )        | 40       | C <sub>19</sub> H <sub>12</sub> F <sub>6</sub> N <sub>2</sub> O <sub>4</sub>  |
| 3i    | H                 | 4-F, 3-CF <sub>3</sub>              | 165-166 (EtOH)                                  | 90       | C <sub>17</sub> H <sub>10</sub> F <sub>4</sub> N <sub>2</sub> O <sub>4</sub>  |
| 3j    | 3-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | 229-230 (C <sub>6</sub> H <sub>6</sub> )        | 55       | C <sub>18</sub> H <sub>12</sub> F <sub>4</sub> N <sub>2</sub> O <sub>4</sub>  |
| 3k    | 4-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | 175-176 (MeOH)                                  | 31       | C <sub>18</sub> H <sub>12</sub> F <sub>4</sub> N <sub>2</sub> O <sub>4</sub>  |

<sup>a</sup> 5-Bromo-6-methoxy-8-nitroquinoline was prepared as described by Elderfield et al.<sup>2</sup> <sup>b</sup> 3,5-Bis(trifluoromethyl)phenol was made via the method of Wolfe.<sup>6</sup> Synthesis of 4-(trifluoromethoxy)phenol and 4-fluoro-3-(trifluoromethyl)phenol is described under Experimental Section. The remaining phenols were obtained commercially. <sup>c</sup> All compounds except 3d (previously reported, see ref 7) were analyzed for C, H, and N. <sup>d</sup> Literature<sup>7</sup> mp 121-122 °C.

Table IV. 8-Amino-6-methoxy-5-phenoxyquinolines

| compd | R <sub>1</sub>    | R <sub>2</sub>                      | mp, °C (solvent) <sup>a</sup>            | yield, % | formula <sup>b</sup>  |
|-------|-------------------|-------------------------------------|--|----------|---|
| 4a    | 4-CH <sub>3</sub> | H                                   | used without purification                |          |   |
| 4b    | H                 | 3-CF <sub>3</sub>                   | 104-106 (Et <sub>2</sub> O-PE)           | 78       | C <sub>17</sub> H <sub>13</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub>              |
| 4c    | H                 | 4-CF <sub>3</sub> O                 | 99-101 (PE)                              | 75       | C <sub>17</sub> H <sub>13</sub> F <sub>3</sub> N <sub>2</sub> O <sub>3</sub>              |
| 4d    | H                 | 4-CH <sub>3</sub> O                 | 111-112 (EtOH) <sup>c</sup>              | 62       | C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>                             |
| 4e    | H                 | 2,4-Cl <sub>2</sub>                 | 89-90 (Et <sub>2</sub> O-PE)             | 60       | C <sub>16</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>             |
| 4f    | H                 | 3,4-Cl <sub>2</sub>                 | 117-119 (MeOH-H <sub>2</sub> O)          | 94       | C <sub>16</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>             |
| 4g    | H                 | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | 139-141 (Et <sub>2</sub> O-PE)           | 93       | C <sub>18</sub> H <sub>12</sub> F <sub>6</sub> N <sub>2</sub> O <sub>2</sub> <sup>d</sup> |
| 4h    | 4-CH <sub>3</sub> | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | 136-138 (hexane)                         | 70       | C <sub>19</sub> H <sub>14</sub> F <sub>6</sub> N <sub>2</sub> O <sub>2</sub>              |
| 4i    | H                 | 4-F, 3-CF <sub>3</sub>              | 87-88 (C <sub>6</sub> H <sub>6</sub> )   | 76       | C <sub>17</sub> H <sub>12</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>              |
| 4j    | 3-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | 119-119.5 (hexane)                       | 81       | C <sub>18</sub> H <sub>14</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>              |
| 4k    | 4-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | 120-121 (C <sub>6</sub> H <sub>6</sub> ) | 76       | C <sub>18</sub> H <sub>14</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>              |

<sup>a</sup> PE = petroleum ether. <sup>b</sup> All compounds except 4a and 4d (previously reported, see ref 7) were analyzed for C, H, and N. <sup>c</sup> Literature<sup>7</sup> mp 115-116 °C. <sup>d</sup> C: calcd, 52.74; found, 53.59.

**Biology.** We have confirmed that 5-phenoxy groups greatly attenuate the toxicity of primaquine (Table I). With the exception of compounds 6a,c,j, the 5-phenoxy-primaquines produced no toxic lethality at the highest dose tested (640 mg/kg), and even compounds 6a,c,j were less toxic than primaquine itself.

Among the demethyl derivatives (Table I, R<sub>1</sub> = H), the most active blood schizonticides were those with R<sub>2</sub> equal to 4-F (6n) or 3-CF<sub>3</sub> (6b). A compound containing both 4-F and 3-CF<sub>3</sub> (6i) was less active than either of the singly substituted derivatives.

The activity range over the entire demethyl series was relatively narrow. However, introduction of a methyl group on the pyridine ring of various 5-phenoxyprimaquines effected a dramatic increase in blood schizonticidal activity.

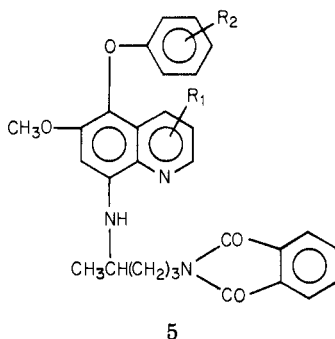
This is seen to good advantage in comparing 6a with 6l, 6g with 6h, and in examining the trio 6i,j,k. Data for the last three compounds would seem to suggest that the methyl group is more effective at position 4 than at position 3. 4-Methylprimaquine, in the absence of a 5-phenoxy group, was quite unimpressive.

A number of the 5-phenoxyprimaquines were also evaluated against persistent tissue schizonts of *Plasmodium cynomolgi* in the radical curative test (Table II). The best of these were the fluorine-containing derivatives, 6b,i,n, which were more active than primaquine.

#### Experimental Section

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected.

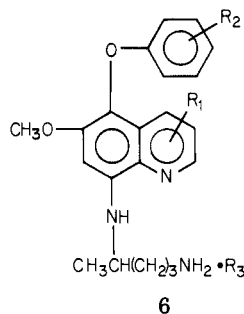
Table V. 6-Methoxy-8-[(1-methyl-4-phthalimidobutyl)amino]-5-phenoxyquinolines



| compd | R <sub>1</sub>    | R <sub>2</sub>                      | mp, °C (solvent)                         | yield, % | formula <sup>a</sup>   |
|-------|-------------------|-------------------------------------|--|----------|--|
| 5a    | 4-CH <sub>3</sub> | H                                   | 166-169 (C <sub>6</sub> H <sub>6</sub> ) | 32       | C <sub>30</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub>                                |
| 5b    | H                 | 3-CF <sub>3</sub>                   | 112-115 (Et <sub>2</sub> O)              | 58       | C <sub>30</sub> H <sub>26</sub> F <sub>3</sub> N <sub>3</sub> O <sub>4</sub> <sup>b, c</sup> |
| 5c    | H                 | 4-CF <sub>3</sub> O                 | used without purification                |          |  |
| 5d    | H                 | 4-CH <sub>3</sub> O                 | 170-172 (Et <sub>2</sub> O-MeOH)         | <i>d</i> | C <sub>30</sub> H <sub>31</sub> ClN <sub>3</sub> O <sub>5</sub> <sup>e</sup>                 |
| 5e    | H                 | 2,4-Cl <sub>2</sub>                 | 189-191 (MeOH)                           | 76       | C <sub>29</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>4</sub> <sup>e</sup>   |
| 5f    | H                 | 3,4-Cl <sub>2</sub>                 | 125-127 (Et <sub>2</sub> O)              | 74       | C <sub>29</sub> H <sub>25</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>4</sub> <sup>f</sup>   |
| 5g    | H                 | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | 204-206 (Et <sub>2</sub> O)              | 42       | C <sub>31</sub> H <sub>26</sub> ClF <sub>6</sub> N <sub>3</sub> O <sub>4</sub> <sup>e</sup>  |
| 5h    | 4-CH <sub>3</sub> | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | 159-160 (Et <sub>2</sub> O)              | 20       | C <sub>32</sub> H <sub>27</sub> F <sub>6</sub> N <sub>3</sub> O <sub>4</sub>                 |
| 5i    | H                 | 4-F, 3-CF <sub>3</sub>              | used without purification                |          |  |
| 5j    | 3-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | 149-150 (MeOH)                           | <i>g</i> | C <sub>31</sub> H <sub>27</sub> F <sub>4</sub> N <sub>3</sub> O <sub>4</sub>                 |
| 5k    | 4-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | used without purification                |          |  |

<sup>a</sup> Except as noted, all compounds were analyzed for C, H, and N. <sup>b</sup> C: calcd, 65.56; found, 66.10. <sup>c</sup> Another fraction was isolated whose IR spectrum suggested a dimorph, mp 97-100 °C. Anal. (C<sub>30</sub>H<sub>26</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub>) C, H, N. <sup>d</sup> Main fraction used without purification. <sup>e</sup> Analyzed as the hydrochloride. <sup>f</sup> C: calcd, 63.28; found, 62.58. <sup>g</sup> Major fraction was used without purification.

Table VI. 8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-5-phenoxyquinolines



| compd | R <sub>1</sub>    | R <sub>2</sub>                      | R <sub>3</sub>                  | mp, °C (solvent)                  | yield, %        | formula <sup>a</sup>   |
|-------|-------------------|-------------------------------------|---------------------------------|-----------------------------------|-----------------|--|
| 6a    | 4-CH <sub>3</sub> | H                                   | citrate                         | 155-158 ( <i>i</i> -PrOH)         | 36              | C <sub>28</sub> H <sub>35</sub> N <sub>3</sub> O <sub>9</sub>                                |
| 6b    | H                 | 3-CF <sub>3</sub>                   | citrate                         | 149 (MeOH-Et <sub>2</sub> O)      | 77              | C <sub>28</sub> H <sub>32</sub> F <sub>3</sub> N <sub>3</sub> O <sub>9</sub>                 |
| 6c    | H                 | 4-CF <sub>3</sub> O                 | citrate                         | 110-140 (EtOH)                    | 82              | C <sub>28</sub> H <sub>32</sub> F <sub>3</sub> N <sub>3</sub> O <sub>10</sub>                |
| 6d    | H                 | 4-CH <sub>3</sub> O                 | citrate·0.5H <sub>2</sub> O     | 135-137 (EtOH)                    | 47 <sup>c</sup> | C <sub>28</sub> H <sub>36</sub> N <sub>3</sub> O <sub>10.5</sub>                             |
| 6e    | H                 | 2,4-Cl <sub>2</sub>                 | H <sub>3</sub> PO <sub>4</sub>  | 197-199 (MeOH)                    | 29              | C <sub>21</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>6</sub> P              |
| 6f    | H                 | 3,4-Cl <sub>2</sub>                 | hemifumarate                    | 140-153 ( <i>i</i> -PrOH)         | 80              | C <sub>23</sub> H <sub>25</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>4</sub>                |
| 6g    | H                 | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | 2H <sub>3</sub> PO <sub>4</sub> | 173-180 (MeOH-Et <sub>2</sub> O)  | 53              | C <sub>23</sub> H <sub>29</sub> F <sub>6</sub> N <sub>3</sub> O <sub>10</sub> P <sub>2</sub> |
| 6h    | 4-CH <sub>3</sub> | 3,5-(CF <sub>3</sub> ) <sub>2</sub> | citrate                         | 163-164 ( <i>i</i> -PrOH)         | 86              | C <sub>30</sub> H <sub>33</sub> F <sub>6</sub> N <sub>3</sub> O <sub>9</sub>                 |
| 6i    | H                 | 4-F, 3-CF <sub>3</sub>              | hemifumarate                    | 155-157 (MeOH-Et <sub>2</sub> O)  | 34 <sup>c</sup> | C <sub>24</sub> H <sub>25</sub> F <sub>4</sub> N <sub>3</sub> O <sub>4</sub>                 |
| 6j    | 3-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | fumarate                        | 140-142 (MeOH)                    | 50              | C <sub>27</sub> H <sub>29</sub> F <sub>4</sub> N <sub>3</sub> O <sub>6</sub>                 |
| 6k    | 4-CH <sub>3</sub> | 4-F, 3-CF <sub>3</sub>              | citrate·0.5H <sub>2</sub> O     | <i>b</i> (MeOH-Et <sub>2</sub> O) | 30              | C <sub>29</sub> H <sub>34</sub> F <sub>4</sub> N <sub>3</sub> O <sub>9.5</sub>               |

<sup>a</sup> All compounds were analyzed for C, H, and N. <sup>b</sup> Indefinite melting range beginning at 84 °C. <sup>c</sup> Based on 8-NH<sub>2</sub> precursor.

Elemental analyses (Micro-Analysis, Inc., Wilmington, DE) were within ±0.4% of the theoretical values unless otherwise noted. Synthetic details are presented in Tables III-VI.

**2-Fluoro-5-hydroxybenzotrifluoride.** 5-Amino-2-fluoro-benzotrifluoride (29 g, 0.16 mol, Marshallton Research Laboratories, Inc.) was added to a hot (80-90 °C) solution of 100 mL of concentrated H<sub>2</sub>SO<sub>4</sub> and 200 mL of H<sub>2</sub>O. The solution was cooled to 10 °C and treated with a solution of NaNO<sub>2</sub> (13.1 g, 0.17 mol) in 20 mL of H<sub>2</sub>O at a rate that kept the temperature below 10 °C. On completion of addition, the pale yellow solution was stirred at 5 °C for 0.5 h, treated with 1.5 g of urea in 10 mL of H<sub>2</sub>O, and stirred at 5 °C for another 0.5 h. The diazo solution was then added, dropwise, to a steam-distillation apparatus that

contained a boiling solution of 100 g of CuSO<sub>4</sub>·5H<sub>2</sub>O in 100 mL of H<sub>2</sub>O. (During addition, the internal temperature gradually rose from 105 to 125 °C.) Steam distillation was continued for 2 h after diazo addition was complete. The distillate (ca. 500 mL) was saturated with NaCl, and the aqueous and oil layers were separated. The aqueous layer was thoroughly extracted with Et<sub>2</sub>O, and the extracts were combined with the oil layer. The ethereal solution was washed with saturated NaCl (2 × 100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residual oil was vacuum distilled to give 22.4 g (77%) of the phenol, bp 84-92 °C (14 mm). The analytical sample boiled at 86 °C (15 mm). Anal. (C<sub>7</sub>H<sub>4</sub>F<sub>4</sub>O) C, H.

**4-(Trifluoromethoxy)phenol.** 4-(Trifluoromethoxy)aniline

(40 g, 0.22 mol, Pierce Chemical Co.) was converted to the phenol, in 63% yield, in the manner described above: bp 91-93 °C (20 mm);  $n_D^{24}$  1.4440 [lit.<sup>3</sup> bp 92 °C (25 mm);  $n_D^{25}$  1.4469].

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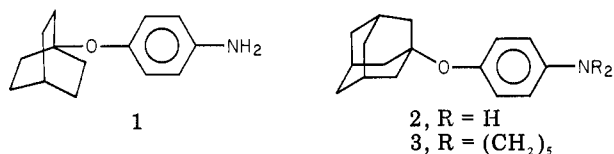
### Hypobetalipoproteinemic Agents. 3. Variation of the Polycyclic Portion of 4-(1-Adamantyloxy)aniline

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We have replaced the adamantyl moiety of the hypobetalipoproteinemic 4-(1-adamantyloxy)aniline (**2**) with 1- and 4-diamantyl, *cis*- and *trans*-9-decalyl, and 1,1-dimethylbutyl, -hexyl, and -octyl. The compounds were easily accessible by our previous route. Only the diamantyl compounds, **8** and **11**, were active, suggesting that some as yet unidentified, special geometrical and/or associative (electronic) aspects of the tertiary bi- and polycycloxyanilines are required for the hypobetalipoproteinemic activity of these agents.

We have previously reported the hypobetalipoproteinemic activity of agents related to 4-(1-bicyclo[2.2.2]-octyloxy)aniline (**1**)<sup>1</sup> and the more potent 4-(1-



adamantyloxy)aniline (**2**).<sup>2</sup> This activity consists of a reduction of the atherogenic heparin precipitating lipoproteins (HPL) and also the HPL to cholesterol ratio in the cholesterol-cholic acid fed rat.<sup>3</sup> Ultracentrifugation studies with the piperidine **3** have demonstrated that not only are the atherogenic, lower density ( $d < 1.040$  g/mL) lipoproteins reduced as desired, but the high density lipoproteins ( $1.040 < d < 1.21$  g/mL), which may well be antiatherogenic,<sup>4-6</sup> are increased. The extensive investigation of compounds related to **2** included variation in the bridging oxygen atom and substitution on the aromatic

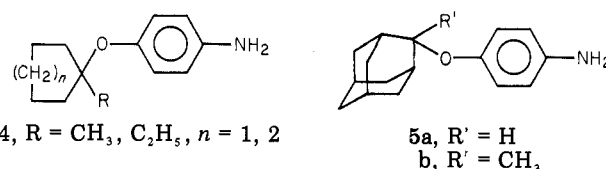
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Table I. Hypobetalipoproteinemic Activity of *p*-Aminophenyl Ethers in Diet-Induced Hypercholesterolemic Rats<sup>a</sup>

| no.                   | dose, (mmol/kg)/day | T/C   |       |          |
|-----------------------|---------------------|-------|-------|----------|
|                       |                     | Chol  | HPL   | HPL/Chol |
| <b>8</b>              | 0.17                | 0.53* | 0.35* | 0.66*    |
| <b>11</b>             | 0.17                | 0.31* | 0.19* | 0.62*    |
| <b>14<sup>b</sup></b> | 0.18                | 0.92  | 0.89  | 0.97     |
| <b>17<sup>b</sup></b> | 0.18                | 1.38* | 1.24  | 0.90*    |
| <b>20<sup>b</sup></b> | 0.22                | 0.84  | 0.78  | 0.92     |
| <b>23<sup>b</sup></b> | 0.19                | 1.02  | 0.96  | 0.94     |
| <b>26<sup>b</sup></b> | 0.17                | 0.98  | 0.84  | 0.86*    |

<sup>a</sup> Chol = total serum cholesterol; HPL = heparin precipitating lipoproteins; T/C signifies the mean value for the treated rats divided by that for the control rats; an asterisk denotes a response significantly different ( $p < 0.05$ ) from control means; compounds were dosed at 50 (mg/kg)/day. Food intake and weight gain were considered normal (>73% and >63% of control values, respectively) during the experiments. <sup>b</sup> Data reported for the hydrochloride salt.

ring and on nitrogen.<sup>2</sup> Two other changes in the polycycloxy portion of **1** and **2** produced compounds **4**<sup>1</sup> which



were inactive, **5a**<sup>2</sup> which was active, and **5b**<sup>2</sup> the activity of which is considered indeterminate due to subnormal weight gain. Thus, there seemed to be some unique structural characteristic of the bicyclic and tricyclic portions of **1** and **2**, respectively, responsible for their hypo-

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