Trimeperidine Hydrochloride (2·HCl). A mixture of 0.50 g (0.0023 mol) of (±)-7 and 3 ml of propionyl chloride was allowed to stand at 25° for 3 days under N_2. Et_2O (5 ml) was added, the mixture filtered, and the solid washed two times with petroleum ether (5 ml) and crystallized (Me_2CO) two times to yield 0.42 g (60%) of 2·HCl: mp 201–202° (lit.[7] 198–199°). *Anal.* ($C_{17}H_{26}NO_2Cl$) C, H, N.

(+)-(2S,4S,5R)-1,2,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride [(+)-13·HCl]. The procedure described for 2·HCl was employed using 0.100 g (0.00046 mol) of (+)-7 and 1 ml of propionyl chloride. The yield of (+)-13·HCl, mp 198–200°, $[\alpha]^{23}D$ +34.4° (c 0.5, EtOH), was 0.11 g (77%). *Anal.* ($C_{17}H_{26}NO_2Cl$) C, H, N.

(−)-(2R,4R,5S)-1,2,5-Trimethyl-4-phenyl-4-propionoxypiperidine Hydrochloride [(−)-13·HCl]. This was prepared from (−)-7 using a procedure identical with that described above: mp 199–200°; $[\alpha]^{23}D$ −34.2° (c 0.5, EtOH). *Anal.* ($C_{17}H_{26}NO_2Cl$) C, H, N.

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A Structural Modification Study of the Antimalarial 2-(*p*-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran

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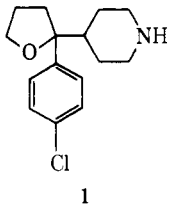
A structural modification study of the antimalarial 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran was conducted. This included: (a) modification of the tetrahydrofuran portion; (b) modification of the *p*-chlorophenyl portion; (c) modification of the piperidine portion; and (d) combined modifications. It was found that 4-[1-(*p*-chlorophenyl)-1-ethoxyethyl]piperidine displayed both prophylactic and therapeutic antimalarial activities. The corresponding *N*-methyl, *N*-methyl *N*-oxide, and the *N*-ethyl analogs also exhibited some activity. Prophylactic antimalarial activity of 4-[1-[2,8-bis(trifluoromethyl)-4-quinolinyl]-1-ethoxyethyl]piperidine was also observed. Compounds in this series, in general, have a rather narrow marginality for structural modification.

Among a series of substituted tetrahydrofuran derivatives synthesized by Marxer,[1-3] 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran (1) was found to possess both causal prophylactic and therapeutic activity in experimental animals.[3,4] Since the structure–activity pattern of compounds of this class bears a close resemblance to that of another class of antimalarials, the amino alcohols,[5] a structural modification study of 1 was conducted in this laboratory. This included (1) modification of the tetrahydrofuran portion (compounds **4a,b, 7a–d, 9, 12, 14,** and **16**); (2) modification of the *p*-chlorophenyl portion (compounds **17–19**); (3) modification of the piperidine portion (compounds **24** and **25**); and (4) combined modifications (compounds **26a–h,j, 27, 28,** and **31**).



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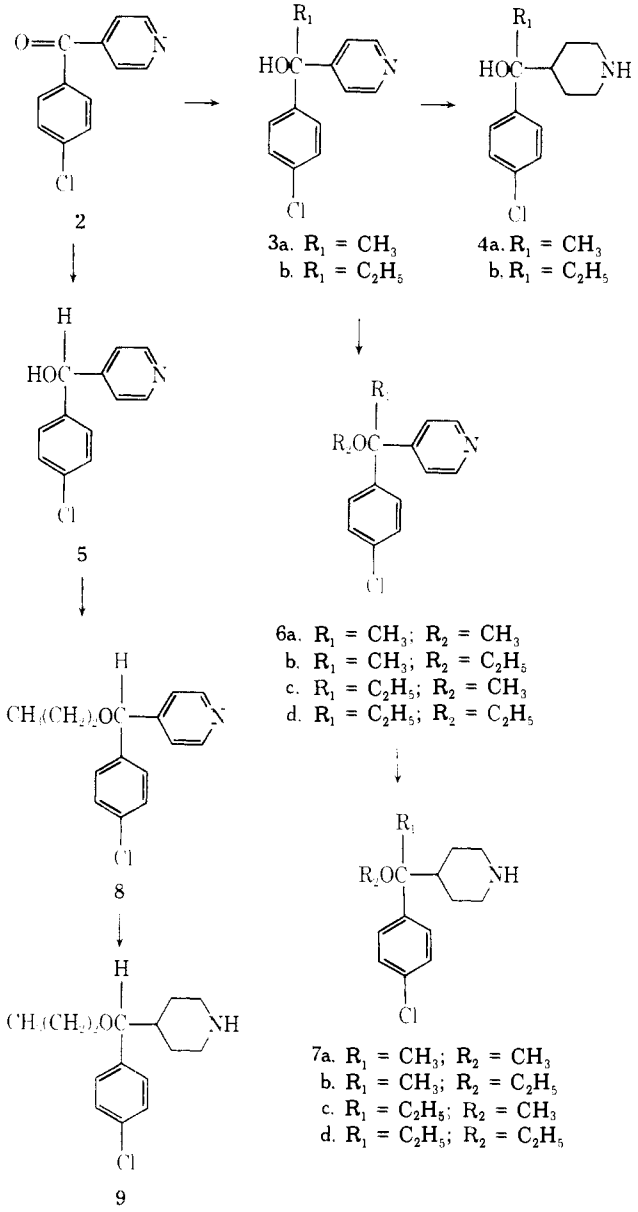
Chemistry. (1) Modification of the Tetrahydrofuran Portion. Since a tetrahydrofuran ring consists of five atoms, we can visualize that breaking the ring bonds one at a time would theoretically yield five compounds (the ethers **7b,c, 9,** and the alcohols **12** and **14**) isomeric with the parent compound **1,** while still retaining the original structural framework. For structure–activity comparison, other related compounds **4a,b** and **7a,d** were also prepared.

The alcohols **4a** and **4b** were prepared by treatment of 4-(*p*-chlorobenzoyl)pyridine (**2**) with the appropriate Grignard compound (to yield **3a** and **3b**) followed by hydrogenation. The yield of **3b** was much lower than of **3a,** owing to the fact that a side reaction—reduction of the ketone **2** in the presence of ethylmagnesium iodide to form α-(*p*-chlorophenyl)-4-pyridinemethanol—occurred simultaneously during the reaction. The ethers **7a–d** were obtained by alkylation of the alcohols **3a** and **3b** fol-

lowed by hydrogenation. Compound **9** was prepared from **2** by chemical reduction, alkylation, and hydrogenation *via* intermediates **5** and **8** (Scheme I).

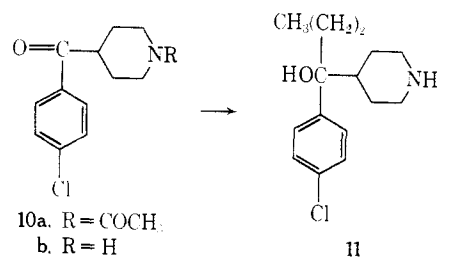
The alcohol **11** was obtained by treatment of 4-(*p*-chlorobenzoyl)piperidine (**10b**) with propylmagnesium iodide.

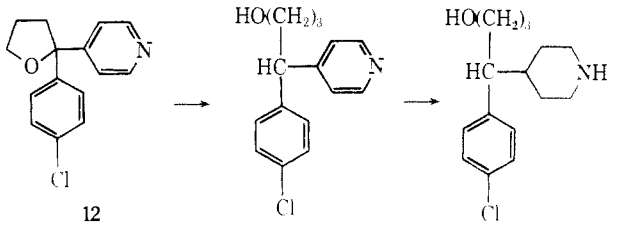
Scheme I



The piperidine **10b** was, in turn, prepared by a Friedel-Crafts reaction of 1-acetylisonipecotoyl chloride with chlorobenzene followed by deacetylation of the intermediate **10a**.

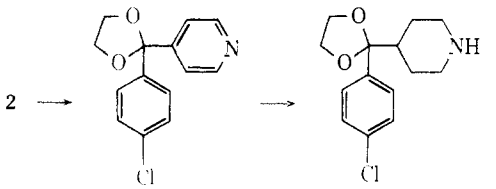
Preparation of 4-(*p*-chlorophenyl)-4-(4-piperidyl)-1-butanol (**14**) was realized by catalytic hydrogenation of 2-



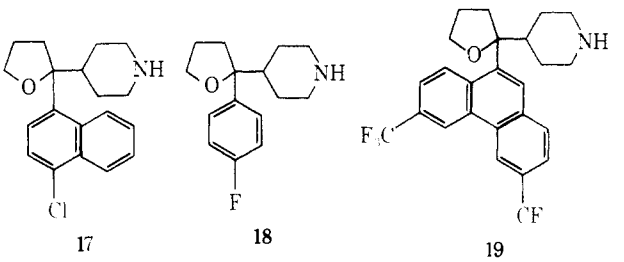


(*p*-chlorophenyl)-2-(4-pyridyl)tetrahydrofuran (**12**)[1] through the intermediate pyridine **13**.

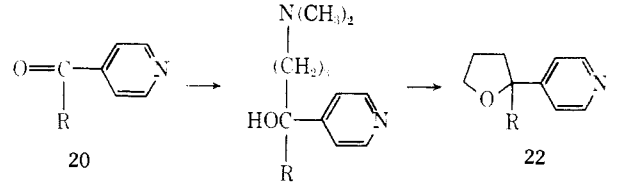
2-(*p*-Chlorophenyl)-2-(4-piperidyl)-1,3-dioxolane (**16**), the dioxa analog of **1**, was prepared by condensation of the ketone **2** with ethylene glycol followed by hydrogenation of the intermediate **15**.



(2) Modification of the *p*-Chlorophenyl Portion. 2-[1-(4-Chloronaphthyl)-2-(4-piperidyl)]tetrahydrofuran (**17**), 2-(*p*-fluorophenyl)-2-(4-piperidyl)tetrahydrofuran (**18**), and 2-[3,6-bis(trifluoromethyl)-9-phenanthryl]-2-(4-piperidyl)tetrahydrofuran (**19**) were synthesized from the ke-



tones **20a–c**, respectively. Compounds **17** and **18** were prepared *via* the following reaction sequence. Compound **19** was obtained through **21c** followed by reduction of the pyridine ring and acetylation of the resulting piperidine intermediate prior to cyclization.



a. R = 1-(4-Cl-$C_{10}H_6$)
b. R = *p*-F-C_6H_4
c. R = 9-[3,4-$(CF_3)_2$ $C_{14}H_7$]

(3) Modification of the Piperidine Portion. In an analogous manner, 2-(*p*-chlorophenyl)-2-(3-piperidyl)tetrahydrofuran (**24**) and 2-(*p*-chlorophenyl)-2-(2-piperidyl)tetrahydrofuran (**25**) were prepared from the appropriate ketones **23a** and **23b**, respectively.

(4) Combined Modifications. Compounds **26a–h,j** and **27** were prepared by a combination of the aforementioned methods. 4-[[3,6-Bis(trifluoromethyl)-9-phenanthryl]-1-

Table I. Prophylactic Antimalarial Activity of Analogs of 2-(*p*-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran (Sporozoite-Induced Chick Test)[a]

Compd	Dose, mg/kg										
	480	320	240	160	120	80	60	40	20	15	10
1	(5T)[b]	5T		5T		5.4		3.8			(1C)[b]
4a		1T		1.9		0.9					
4b			0.3								
7a		5T		1T		1.0		1.0	0.8		0.8
7b	5T	5T	3C		5C		4C		2C	1C	1C
7c		5T		5T		0.9		−0.9	−1.5		
7d		5T		5T		5T		0.2	−0.1		−0.4
9		5T		5T		5T	2.5		2.3		2.7
11	5T		3T								
26b		5T		5T		4T		2T	2T		−0.2
26f		5T		1T		−0.9		−0.3	−0.3		0.1
31				4C				2C			0.1

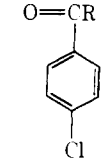
[a]Antimalarial tests were performed by the late Dr. Leo Rane and results were provided through the Walter Reed Army Institute of Research. Increase in mean survival time of the controlled group is reported. A compound was considered as active when it produced an increase of at least 100% in the survival time of the untreated controls (8.34 days), C (curative), T (toxic). For details of test results, see L. Rane and D. S. Rane, *Proc. Helminthol. Soc. Wash.*, **39,** 283 (1972). [b]Sporozoite mouse test (IIT), also: 4C at 3 mg/kg and 3C at 1 mg/kg.

Table II. Antimalarial Activity of Analogs of 2-(*p*-Chlorophenyl)-2-(4-piperidyl)tetrahydrofuran (Blood-Induced Mouse Test *vs. P. berghei*)[a]

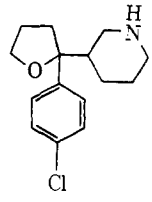
Compd	Dosage, mg/kg						
	640	320	160	80	40	20	10
1	3T				1T		+0.3
4a	+1.1	+0.9	+0.5 (0.0)[b]	+0.3	+0.3	+0.1	
4b	5T	5T (5T)[b]	+0.1 (+4.0)[b]	+0.1 (0.0)[b]	+0.1	+0.1	
7b	5T	2C	+7.0 (+3.4)[b]	+3.2	+0.8	+0.4	
7c		5T		1T (+3.8)[b]		+0.3	
7d			+0.1		+0.1		+0.1
16	5T		5T		+0.9		
17			+1.7		+0.3		+0.1
18	5T		2T		+0.5		
19	+0.3		+0.3		+0.1		
24	5T		+0.7		+0.3		
25	5T		3T		+0.3		
26a	3T		+0.5		+0.3		
26b			+1.5	+0.7	+0.7	+0.5	+0.3
26c	+0.3		+0.1		+0.1		
26d	3T		1T		+0.3		
26e		+0.1		+0.1		+0.1	
26f	+0.2		+0.2		+0.2		
26g	+0.5		+0.3		+0.1		
26h	2C	+5.1	+4.4	+1.1	+0.5	+0.3	
26i	+0.5		+0.5		+0.3		
26j	3T	+7.7	+6.2	+3.9	+1.2	+1.1	
27	+9.6	+3.9	+1.2	+0.5	+0.4	+0.3	
28	+0.7		+0.5		+0.5		
29b	+0.3	+0.3	+0.1	+0.1	+0.1	+0.1	

[a]Antimalarial tests were performed by the late Dr. Leo Rane and results were provided through the Walter Reed Army Institute of Research. For details of test results, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10,** 431 (1967); C (curative) = the number of mice surviving at 60 days postinfection, T (toxic) = the number of deaths occurring on days 2–5 after infection. [b]Test data (increase in mean survival time) of chicks infected with *P. gallinaceum* are listed in parentheses.

ethoxyethyl]piperidine (**28**), which combines the structural features of both **7b** and phenanthrene alcohols,[6] was prepared from 3,6-bis(trifluoromethyl)-α-(4-pyridyl)-9-phenanthrenemethanol[7] (**29a**) *via* intermediates **29b** → **30a** → **29c** → **29d** → **29e**. In a similar fashion, 4-[1-[2,8-bis(trifluoromethyl)-4-quinolinyl]-1-ethoxyethyl]piperidine (**31**) was prepared from 2,8-bis(trifluoromethyl)-4-bromoquinoline.[8]



23a, R = 3-pyridyl
b, R = 2-pyridyl



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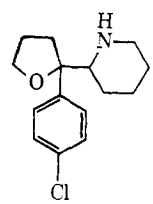

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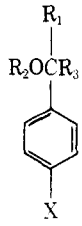
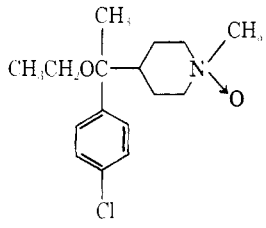
Biological Activity. Available test results of the aforementioned compounds are listed in Tables I and II. It is of interest to note that while 4-[1-(*p*-chlorophenyl)-1-ethoxyethyl]piperidine (**7b**) exhibits both prophylactic and therapeutic antimalarial activity, closely related compounds **7a, 7c,** and **7d** are inactive. The activity of compound **7b** compares favorably with that of 2-(*p*-chlorophenyl)-2-(4-piperidyl)tetrahydrofuran (**1**). The *N*-methyl (**26h**) and the *N*-ethyl (**26j**) homologs of **7b,** as well as the *N*-oxide **27,** also display antimalarial activity against *P. berghei*.

Modification of either the *p*-chlorophenyl or the piperidyl portion of **1** does not yield compounds with desired antimalarial activity. It therefore seems that, in spite of the proposed common structural feature,[5] compounds of



26a. X = F; R_1 = CH_3; R_2 = CH_3; R_3 = 4-piperidyl
b. X = F; R_1 = CH_3; R_2 = C_2H_5; R_3 = 4-piperidyl
c. X = F; R_1 = C_2H_5; R_2 = CH_3; R_3 = 4-piperidyl
d. X = Cl; R_1 = CH_3; R_2 = C_2H_5; R_3 = 2-piperidyl
e. X = Cl; R_1 = CH_3; R = C_2H_5; R_3 = 3-piperidyl
f. X = CF_3; R_1 = CH_3; R_2 = CH_3; R_3 = 4-piperidyl
g. X = CF_3; R_1 = CH_3; R_2 = C_2H_5; R_3 = 4-piperidyl
h. X = Cl; R_1 = CH_3; R_2 = C_2H_5; R_3 = 4-(4-methylpiperidyl)
i. X = Cl; R_1 = CH_3; R_2 = C_2H_5;
R_3 = 4-(4-methyl-3,4,5,6-tetrahydropyridyl)
j. X = Cl; R_1 = CH_3; R_2 = C_2H_5; R_3 = 4-(4-ethylpiperidyl)



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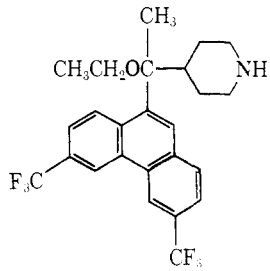

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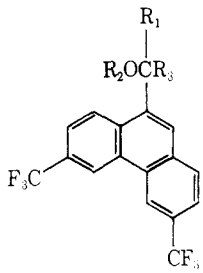
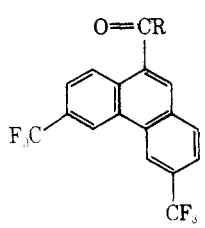
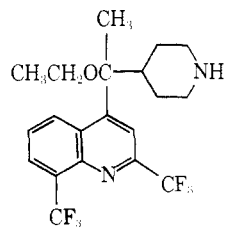


29a, R_1, R_2 = H; R_3 = 4-pyridyl
b, R_1, R_2 = H; R_3 = 4-piperidyl
c, R_1 = CH_3; R_2 = H; R_3 = 4-piperidyl
d, R_1 = CH_3; R_2 = H; R_3 = 4-acetylpiperidyl
e, R_1 = CH_3; R_2 = C_2H_5; R_3 = 4-acetylpiperidyl
f, R_1 = CH_3; R_2 = H; R_3 = 4-pyridyl





30a, R = 4-piperidyl
b, R = 4-pyridyl

31

this series, in contrast to compounds in the amino alcohol series,[6,7] have a rather narrow margin for structural modification.

Experimental Section

1-(*p*-Chlorophenyl)-1-(4-pyridyl)ethanol (3a). To a solution of methylmagnesium iodide in Et_2O [prepared from 3.6 g (0.15 g-atom) of Mg and 21.3 g (0.15 mol) of CH_3I in 150 ml of Et_2O] was added a solution of 21.8 g (0.1 mol) of 4-(*p*-chlorobenzoyl)pyridine (**2**) in 150 ml of THF over a period of 40 min. The reaction mixture was stirred at room temperature overnight. It was then treated with saturated aqueous NH_4Cl to decompose the Mg complex. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated to dryness *in vacuo*. The resulting solid was recrystallized twice from C_6H_6 to give 21 g (90% yield) of **3a** as white needles, mp 155–157°. An analytical sample was prepared by recrystallization from Me_2CO: mp 156–157°. *Anal.* ($C_{13}H_{12}ClNO$) C, H, N.

1-(*p*-Chlorophenyl)-1-(4-pyridyl)propanol (3b) was prepared in a similar manner from ethylmagnesium iodide and **2**. From the reaction mixture a 30% yield of **3b** was obtained, mp 177–178°, along with a by-product, 1-(*p*-chlorophenyl)-1-(4-pyridyl)methanol, mp 137–138°. The latter was found to be identical with a sample obtained from **2** and $NaBH_4$. *Anal.* ($C_{14}H_{14}ClNO$) C, H, N.

1-(*p*-Chlorophenyl)-1-(4-piperidyl)ethanol (4a). A mixture of 4.7 g (0.02 mol) of **3a**, 100 mg of PtO_2, and 50 ml of AcOH was hydrogenated at 3.5 kg/cm² and 60° for 4 hr. After cooling, the catalyst was removed by filtration and the volume of the filtrate was reduced to 15 ml *in vacuo*. To the solution was added 200 ml of 10% aqueous K_2CO_3. After standing overnight, the solid product was collected by filtration, dried, and recrystallized twice from Me_2CO to give 4.2 g (87% yield of 4a, mp 178–180°. A third recrystallization from Me_2CO yielded an analytical sample, mp 180–181°. *Anal.* ($C_{13}H_{18}ClNO$) C, H, N.

4-[1-(*p*-Chlorophenyl)-1-ethoxyethyl]pyridine (6b). A 50% suspension of NaH (1.0 g, 0.02 mol) in mineral oil was washed repeatedly with hexane by decantation. The resulting solid was suspended in 75 ml of DMF. To this was added, with stirring under N_2, a solution of 4.7 g (0.02 mol) of **3a** in 150 ml of dry DMF. Evolution of H_2 ceased after 1 hr, indicating that the alkoxide formation was complete. EtI (3.1 g, 0.02 mol) was added and the reaction mixture was allowed to stir at room temperature overnight under N_2. H_2O was then added dropwise to decompose the excess NaH. The resulting mixture was diluted with 250 ml of H_2O and the aqueous mixture extracted with Et_2O (3 × 50 ml). The Et_2O extract was dried (K_2CO_3) and the solvent removed *in vacuo*. The residual oil was dissolved in 50 ml of hexane. After standing overnight a solid, which had crystallized, was removed by filtration. The solid was identified by its ir spectrum as the starting material. The recovery was 1.3 g (28%). The filtrate was placed on a column of neutral alumina (Woelm, activity I). Elution with hexane (300 ml) and hexane–benzene (1:1, 200 ml) gave, after removal of solvent, a colorless oil which was distilled at 80–100° (0.05 mm) to give 2.6 g (56% yield) of **6b** as a clear oil: $n^{24}D$ 1.5572°. *Anal.* ($C_{15}H_{16}ClNO$) C, H, N.

Compounds **6a**, **6c**, and **6d** were prepared in a similar manner to that for the preparation of **6b** (see Table III).

4-[1-(*p*-Chlorophenyl)-1-methoxyethyl]piperidine (7a). A mixture of 7.5 g (0.03 mol) of **6a**, 150 ml of AcOH, and 200 mg of PtO_2 was hydrogenated at 3.5 kg/cm² and 60° for 6 hr. After removing the catalyst by filtration, the bulk of AcOH was removed *in vacuo*. The residue was taken up in 150 ml of H_2O and the so-

Table III

Compd[a]	Mol formula	Mp, °C	Bp, °C (mm)	Yield, %
6a	$C_{14}H_{14}ClNO$		127–129 (0.1)	67
6c	$C_{15}H_{16}ClNO$		130–132 (0.1)	61
6d	$C_{16}H_{18}ClNO$		135–138 (0.1)	46
7c	$C_{15}H_{22}ClNO \cdot HCl$	217–219		56
7d	$C_{16}H_{24}ClNO \cdot HCl$	218–220		61
23b	$C_{12}H_{18}ClNO$	63–64		51
26a	$C_{14}H_{20}FNO \cdot C_4H_4O_4$	184–186		92
26b	$C_{15}H_{16}FNO$		104–106 (0.1)	82
26c	$C_{15}H_{22}FNO \cdot C_4H_4O_4$	174–176		55
26d	$C_{15}H_{22}ClNO \cdot HCl$	231–233		53
26e	$C_{15}H_{22}ClNO$		80 (0.01)	55
26f	$C_{15}H_{20}F_3NO \cdot HCl$	172–174		79
26g	$C_{16}H_{22}F_3NO \cdot HCl$	155–157		74
31	$C_{20}H_{22}F_6N_2O \cdot C_4H_4O_4$	197–198		75

[a] *Anal.* C, H, N.

lution made basic with 40% aqueous NaOH. The resulting mixture was extracted with Et_2O (3 × 50 ml) and the dried (Na_2SO_4) Et_2O solution, in turn, was extracted with 2 *N* AcOH (3 × 50 ml). The AcOH extract was again made basic with 40% aqueous NaOH. The oily product which separated was isolated by ether extraction (3 × 30 ml), the ether extract was dried (Na_2SO_4), and solvent removed *in vacuo*. The residual oil was taken up in hexane and powdered Dry Ice added. There was obtained, on filtration, 5.1 g of an amine–CO_2 complex as white needles. This material was converted to the hydrochloride by suspending it in 50 ml of EtOH and treated with 1.8 ml (0.022 mol) of concentrated HCl. The resulting solution was evaporated to dryness *in vacuo* and the residual gum taken up in 30 ml of EtOH. Addition of 100 ml of Et_2O and cooling afforded 5.0 g (57% yield) of the HCl salt of **7a** as white plates, mp 175–178°. Recrystallization from a mixture of EtOH and Et_2O gave an analytical sample, mp 178–180°. *Anal.* ($C_{14}H_{20}ClNO$·HCl) C, H, N.

4-[1-(*p*-Chlorophenyl)-1-ethoxyethyl]piperidine (7b). To a solution of 4 g (0.015 mol) of **6b** in 50 ml of AcOH was added 200 mg of PtO_2. The mixture was hydrogenated at 3.5 kg/cm² and 60° for 4 hr. After cooling, the catalyst was removed by filtration. The volume of the filtrate was reduced to 15 ml *in vacuo*. It was added to an excess of saturated aqueous Na_2CO_3 solution. Et_2O extraction (3 × 50 ml) followed by drying (K_2CO_3) and removal of solvent yielded an oil. Molecular distillation at 100–110° (0.05 mm) gave 3.2 g (78% yield) of **7b** as a colorless oil: $n^{25}D$ 1.5351°. *Anal.* ($C_{15}H_{22}ClNO$) C, H, N.

Attempts to prepare a solid CO_2 complex or a crystalline HCl salt of **7b** were without success. Nevertheless, the fumarate salt of **7b** was readily prepared as follows. The oily product was dissolved in Me_2CO and to this was added a saturated solution of fumaric acid in Me_2CO until precipitation was complete. The crude salt was collected by filtration and purified by dissolving it in MeOH and precipitating the product with Me_2CO. The salt was collected as fine white plates, mp 176–177°. The overall yield was 30%. *Anal.* ($C_{15}H_{22}ClNO·C_4H_4O_4$) C, H, N.

Compounds **7c** and **7d** were prepared in a manner similar to that for the preparation of **7a** (see Table III).

4-[1-(*p*-Chlorophenyl)-1-propoxymethyl]piperidine (9). A solution of 21.7 g (0.1 mol) of 4-(*p*-chlorobenzoyl)pyridine (**2**) in 200 ml of EtOH was treated with a solution of 1 g of $NaBH_4$ in 50 ml of EtOH. The mixture was heated on the steam bath for 30 min and diluted with an equal volume of H_2O. On cooling, 1-(*p*-chlorophenyl)-1-(4-pyridyl)methanol (**5**) separated as pale yellow needles, mp 135–137°. The yield was 20.1 g (92%). The ir spectrum showed absorption at 3.15 (OH) and 6.20 μ (aromatic ring). There was no adsorption in the carbonyl region. The material was used without further characterization.

A 50% suspension of NaH in mineral oil (2.4 g, 0.05 mol) was washed with hexane and suspended in 50 ml of THF. To this was added, with stirring and under N_2, 11.0 g (0.05 mol) of **5** in 100 ml of THF. After the addition was completed, the mixture was heated to boiling and 100 ml of solvent was removed by distillation. The reaction mixture was cooled to 10°, and 50 ml of dry DMF was added, followed by dropwise addition of 8.5 g (0.05 mol) of propyl iodide. The resulting mixture was stirred for 4 hr, diluted with 200 ml of H_2O, and extracted with Et_2O (3 × 100 ml). The Et_2O extract was dried (Na_2SO_4), the solvent was removed *in vacuo*, and the residual oil was distilled. There was obtained 10.5 g (81% yield) of 4-[1-(*p*-chlorophenyl)-1-propoxymethyl]pyridine (**8**) as a pale yellow oil, bp 122–125° (0.1 mm). *Anal.* ($C_{15}H_{16}ClNO$) C, H, N.

To a solution of 7.8 g (0.03 mol) of **8** in 150 ml of AcOH was added 200 mg of PtO_2. The mixture was hydrogenated at 60° and 3.5 kg/cm² for 4 hr. Catalyst was removed by filtration and the bulk of the AcOH was distilled *in vacuo*. The residual syrup was dissolved in 100 ml of H_2O and the solution made basic with 40% aqueous NaOH. The mixture was extracted with Et_2O (3 × 50 ml), the Et_2O solution was extracted with 2 *N* AcOH (3 × 50 ml), and the AcOH extract was made basic with 40% aqueous NaOH. The resulting insoluble oily product was isolated by Et_2O extraction. The Et_2O extract was dried (Na_2SO_4), the solvent was removed *in vacuo*, and the oily product was purified by molecular distillation at 80° and 0.05 mm. There was obtained 5.5 g (69% yield) of **9** as a colorless oil: $n^{25}D$ 1.5283°. *Anal.* ($C_{15}H_{22}ClNO$) C, H, N.

1-Acetyl-4-(*p*-chlorobenzoyl)piperidine (10a). To a mixture of 27 g of $AlCl_3$ and 150 ml of chlorobenzene was added, with stirring, 38 g (0.2 mol) of 1-acetylisonipecotoyl chloride. After the addition was complete, the mixture was heated at 80° for 4 hr and then poured onto crushed ice. The organic layer was extracted twice with $CHCl_3$ (100 ml). The combined organic layer and extracts were washed with H_2O and evaporated under a stream of air. The solid was collected by filtration to give 27.7 g (52% yield) of **10a**.

1-(*p*-Chlorophenyl)-1-(4-piperidyl)butanol (11). A mixture of 13.3 g (0.05 mol) of **10a** and 100 ml of 5% HCl was heated under reflux for 4 hr. After cooling, the aqueous solution was made basic with 10% NaOH and extracted with $CHCl_3$ (3 × 50 ml). The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness. The resulting oily residue **10b** was dissolved in 40 ml of anhydrous Et_2O and added, over a period of 50 min, to a freshly prepared PrMgI solution in Et_2O (0.2 mol). Stirring was continued for 2 hr at room temperature. The mixture was poured, with stirring, onto crushed ice and then treated with NH_4Cl solution. The Et_2O layer was separated. The aqueous phase was extracted with Et_2O (3 × 150 ml). The combined Et_2O solution was washed with H_2O, dried ($MgSO_4$), and evaporated. The oily residue was dissolved in 100 ml of Et_2O and treated with a saturated solution of fumaric acid in Me_2CO. The resulting precipitate was collected by filtration and washed with Et_2O to give 2.3 g (12% yield) of **11** as a fumarate, mp 160–175°. Recrystallization from MeOH–Me_2CO gave analytically pure product as white crystals, mp 192–194°. *Anal.* ($C_{15}H_{22}ClNO·C_4H_4O_4$) C, H, N.

4-(*p*-Chlorophenyl)-4-(4-pyridyl)butanol (13). A mixture of 10.4 g (0.04 mol) of 2-(*p*-chlorophenyl)-2-(4-pyridyl)tetrahydrofuran (**12**)[1] (recrystallized from cyclohexane), 200 ml of EtOH, 6 ml (0.08 mol) of perchloric acid, and 1 g of 5% Pd on C was hydrogenated at 4.2 kg/cm² for 24 hr. The mixture was then recharged with 300 mg of fresh catalyst and hydrogenated for another 24 hr. The catalyst was removed by filtration and the filtrate evaporated *in vacuo*. The resulting oily substance was dissolved in 20 ml of H_2O and the solution made basic with 20% NaOH. The free base was extracted with $CHCl_3$ (2 × 20 ml). The combined extracts were dried ($CaSO_4$) and evaporated to give 9.7 g of an oil. Since the product gave two spots on tlc, it was chromatographed through a 3 × 25 cm silica gel column and eluted with $CHCl_3$. The initial fractions (3.5 g) corresponded to the starting material **12** and the following fractions afforded a liquid, 4.2 g (40% yield), the ir (2.85 μ, OH) and tlc of which are consistent with the expected product **13**.

4-(*p*-Chlorophenyl)-4-(4-piperidyl)butanol (14). A mixture of 4.1 g (0.016 mol) of **13**, 1.5 ml of concentrated HCl, 100 ml of EtOH, and 100 mg of PtO_2 was hydrogenated at 4.2 kg/cm² at 50° for 72 hr. The hydrogenation was interrupted at each 24-hr interval for two additions of fresh catalyst. At the end of the hydrogenation, the catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in 20 ml of H_2O and made basic with 20% NaOH. The mixture, of which an oily substance separated, was extracted with $CHCl_3$ (2 × 20 ml). The extracts were dried and evaporated to give 3.5 g of a clear, oily liquid. This was dissolved in 50 ml of Me_2CO and to the solution was added dropwise a saturated solution of fumaric acid in Me_2CO until the precipitation was complete. The hygroscopic solid was removed by filtration and quickly dried: mp 152–154° dec. Repeated recrystallizations from a mixture of MeOH–Me_2CO gave 0.5 g of **14** as a hemifumarate: mp 167–168°; *m/e* 267 ($M^+ - C_2H_2O_2$). *Anal.* ($C_{15}H_{22}ClNO·0.5C_4H_4O_4$) C, H, N.

2-(*p*-Chlorophenyl)-2-(4-pyridyl)-1,3-dioxolane (15). With a Dean-Stark trap attached to the boiling flask, a stirred solution of 10.9 g (0.05 mol) of 4-(*p*-chlorobenzoyl)pyridine (**2**), 25 ml of ethylene glycol, and 9.9 g (0.052 mol) of *p*-toluenesulfonic acid hydrate in 100 ml of C_6H_6 was refluxed for 24 hr. A total of 3 ml of H_2O was collected. The reaction mixture was added to a solution of 10 g of Na_2CO_3 in 100 ml of H_2O. The mixture was stirred for 10 min and the organic layer was separated and dried. Evaporation of the solvent gave 10.5 g (81% yield) of a liquid, which solidified on standing: mp 39–41°. *Anal.* ($C_{14}H_{12}ClNO_2$) C, H, N.

2-(*p*-Chlorophenyl)-2-(4-piperidyl)-1,3-dioxolane (16). A mixture of 10 g (0.038 mol) of **15**, 0.05 g of PtO_2, and 150 ml of AcOH was hydrogenated at 4.2 kg/cm² and 50° for 20 hr. The cooled mixture was filtered and the filtrate evaporated to dryness *in vacuo* to give 10 g of a white solid, mp 208–210°. This crude product was dissolved in 120 ml of hot absolute EtOH. Some insoluble material was removed by filtration and the filtrate treated with 10 ml of 20% ethanolic HCl. White needles which formed on standing were collected by filtration to give 8 g (70% yield) of the HCl salt of **16**, mp 270–271°. *Anal.* ($C_{14}H_{18}ClNO_2$·HCl) C, H, N.

4-(4-Chloronaphthoyl)pyridine (20a). To a dried flask containing 1.8 g (0.072 g-atom) of Mg turnings and 20 ml of dry Et_2O under N_2 was added 10 drops of EtBr. The reaction was initiated

with external heat and a solution of 15.7 g (0.065 mol) of 1-bromo-4-chloronaphthalene[9] in 150 ml of dry Et_2O was added during 30 min with enough external heat applied to cause a gentle reflux. After the initial reaction subsided, the mixture was stirred and refluxed for 8 hr. To this reaction mixture was added 50 ml of C_6H_6 and the resulting mixture was warmed to remove 50 ml of Et_2O. A solution of 6.0 g (0.058 mol) of freshly recrystallized 4-cyanopyridine in 50 ml of C_6H_6 was then added during 15 min, whereupon a tan-colored precipitate gradually formed. The mixture was refluxed for 3 hr, cooled, and poured, with stirring, into a mixture of 50 ml of concentrated HCl and 100 g of chopped ice. After 30 min the crude HCl salt was collected by filtration and dissolved in 150 ml of 75% hot, aqueous EtOH. The free base was precipitated from the mixture by the addition of 20% NaOH. There was obtained 11 g (71% yield) of **20a**, mp 113–114°. An analytical sample was obtained by recrystallization from 75% EtOH: mp 114–115°. *Anal.* ($C_{16}H_{10}ClNO$) C, H, N.

4-(*p*-Fluorobenzoyl)pyridine (20b). This ketone was prepared from 10.5 g (0.06 mol) of 1-bromo-4-fluorobenzene in a manner similar to that for the preparation of **20a** except that after the crude reaction mixture was poured into iced HCl solution, two liquid layers were formed. The aqueous layer, which contained the HCl salt of **20b**, was separated and cooled to 10°. The pH of the mixture was adjusted to 8 by the slow addition of 20% NaOH. The precipitated base was collected by filtration and washed with H_2O to yield 9.5 g of crude product, mp 83–84°. Recrystallization from cyclohexane gave 7.7 g (64% yield) of **20b**, mp 86–87°. *Anal.* ($C_{12}H_8FNO$) C, H, N.

1-(4-Chloro-1-naphthyl)-4-dimethylamino-1-(4-pyridyl)butanol (21a). A mixture of 0.73 g (0.03 g-atom) of Mg turnings in 10 ml of dry THF and 5 drops of EtBr was heated to initiate the reaction. A solution of 3.7 g (0.03 mol) of freshly distilled 3-dimethylaminopropyl chloride in 15 ml of THF was then added during 10 min. The mixture was refluxed overnight with stirring. To this was added a solution of 6.7 g (0.025 mol) of **20a** in 25 ml of THF during 15 min. The dark mixture was refluxed for 5 hr, cooled, and poured into a solution of 6 g of NH_4Cl in 50 ml of H_2O. After sitrring for 30 min, the mixture was extracted with Et_2O (3 × 50 ml), and the combined Et_2O extracts were washed with H_2O, dried, and evaporated. The resulting solid was recrystallized from benzene to give 2.6 g (29% yield) of **21a**, mp 170–171°. *Anal.* ($C_{21}H_{23}ClN_2O$) C, H, N.

2-[1-(4-Chloronaphthyl)]-2-(4-pyridyl)tetrahydrofuran (22a). A stirred mixture of 6 g (0.017 mol) of **21a** and 0.95 g (0.23 mol) of $NaNH_2$ in 20 ml of dry xylene was refluxed for 3 hr. It was cooled to room temperature and 2.5 g (0.018 mol) of CH_3I was added. The mixture was again refluxed for 3 hr and cooled. To this was added 5 ml of H_2O. It was allowed to stand for 30 min and filtered. The filtrate was diluted with 10 ml of H_2O and 20 ml of C_6H_6. The upper organic layer was separated, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness. The resulting oily residue was dissolved in C_6H_6 and chromatographed through a column of basic alumina. Elution with 10% $CHCl_3$ in C_6H_6 afforded, after evaporation of solvent, 1.5 g (29% yield) of **22a**, mp 146–148°. *Anal.* ($C_{19}H_{16}ClNO$) C, H, N.

2-[1-(4-Chloronaphthyl)]-2-(4-piperidyl)tetrahydrofuran (17). **22a** (3 g) was recrystallized from 20% C_6H_6 in petroleum ether (bp 35–60°) prior to use. The purified **22a** was dissolved in 200 ml of absolute EtOH. To the solution was added 5 g of Raney nickel and the resulting mixture was boiled for 10 min. It was then filtered and the filtrate evaporated to dryness *in vacuo*. The resulting solid was dissolved in 50 ml of AcOH. It was hydrogenated at 4.2 kg/cm² and 50° for 3 days with 0.6 g of PtO_2 (0.2 g of PtO_2 added at the beginning of hydrogenation and other 0.2-g portions of PtO_2 added to the hydrogenation bottle each day). The catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. To the residue was added 30 ml of H_2O and a sufficient amount of 6 *N* NaOH was added to adjust the pH to 9. The resulting precipitate was extracted with Et_2O (2 × 20 ml) and the combined Et_2O extracts were back-extracted with 2 *N* AcOH (2 × 20 ml) to separate the product from any unreduced starting material. The acid extracts were made basic with 6 *N* NaOH. The solution was again extracted with Et_2O (2 × 20 ml) and the combined extracts were dried ($CaSO_4$) and evaporated to yield 1 g of **17**. This was dissolved in 25 ml of Me_2CO and to the solution was added a saturated solution of fumaric acid in Me_2CO until precipitation was complete. The resulting salt was collected by filtration to yield 1 g of crude product, mp 205–206° dec. Recrystallization from 125 ml of EtOH gave 0.75 g of the fumarate salt of **17**, mp 244–245° dec. *Anal.* ($C_{19}H_{20}ClNO \cdot C_4H_4O_4$) C, H, N.

2-(*p*-Fluorophenyl)-2-(4-piperidyl)tetrahydrofuran (18). A mixture of 3.0 g (0.12 g-atom) of Mg turnings and 10 drops of EtBr was heated to initiate the reaction. A solution of 14.8 g (0.12 mol) of freshly distilled 3-dimethylaminopropyl chloride in 60 ml of dry THF was then added during 20 min. After the mixture was stirred and refluxed for 3 hr, a solution of 22 g (0.11 mol) of **20b** in 100 ml of THF was added during 15 min. The dark brown mixture was refluxed for 4 hr, cooled, and poured into a stirred solution of 30 g of NH_4Cl in 300 ml of H_2O. After 15 min, the mixture was extracted with Et_2O (3 × 100 ml). The extracts were washed with H_2O and extracted with 2 *N* AcOH (3 × 60 ml). The acid extracts were added to 80 ml of 6 *N* NaOH and the resulting mixture was extracted with Et_2O (3 × 100 ml). The Et_2O extracts were washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo* to yield crude **21b** as an oily residue. This was dissolved in 100 ml of dry xylene. The solution was stirred and refluxed with 4.8 g (0.12 mol) of $NaNH_2$ for 2 hr. The reaction mixture was cooled to room temperature and to it was added 13.4 g of MeI. The resulting mixture was slowly heated to reflux and maintained at the reflux temperature for 3 hr. It was cooled and diluted by dropwise addition, with stirring, of 100 ml of H_2O and 100 ml of Et_2O. The resulting upper organic layer was separated, dried, and evaporated to give 17 g of an oily residue, which showed three spots on tlc. A C_6H_6 solution of this oil was chromatographed on a silica gel column and eluted with increasing ratio of $CHCl_3$ to C_6H_6 up to 1:1. The initial colored fraction was discarded. The accumulated fractions containing the crude **22b** were evaporated to an oil. This was added to 75 ml of AcOH and, with the addition of 200 mg of PtO_2, was hydrogenated at 4.2 kg/cm² and 60° for 36 hr. The cooled mixture was filtered and the filtrate evaporated to dryness *in vacuo*. It was made basic with 1 *N* NaOH and extracted with Et_2O (3 × 10 ml). The Et_2O extracts were dried and treated with ethanolic HCl to give 0.5 g of **18** as a white solid, mp 206–210°. *Anal.* ($C_{15}H_{20}FNO \cdot HCl$) C, H, N.

1-[3,6-Bis(trifluoromethyl)-9-phenanthryl]-4-dimethylamino-1-(4-pyridyl)butanol (21c). Freshly distilled 3-dimethylaminopropyl chloride (4.2 g, 0.035 mol) was added in one portion to 0.96 g (0.04 g-atom) of Mg, which had been activated with 1 drop of CH_3I, in 50 ml of boiling THF. The Grignard reagent started to form instantaneously and the reaction mixture was stirred under reflux for 1.5 hr. A solution of 4.1 g (0.01 mol) of **20c** in 100 ml of THF was then introduced over a period of 20 min. After 10 min, the reaction was found to be essentially complete as indicated by tlc. The mixture was poured into 200 ml of water containing a little NH_4Cl and the solvent evaporated under a stream of air. The aqueous mixture was extracted with Et_2O (3 × 150 ml). The combined Et_2O solution was washed (H_2O), dried (Na_2SO_4), and evaporated. The residue was triturated with MeOH and then filtered to give 3.7 g (74% yield) of **21c**, mp 218–219°. A small portion was recrystallized from MeOH as white needles, mp 219–221°. *Anal.* ($C_{27}H_{24}F_6N_2O$) C, H, N.

1-[3,6-Bis(trifluoromethyl)-9-phenanthryl]-4-dimethylamino-1-[4-(1-acetamidopiperidinyl)]butanol. A solution of 3.1 g (0.006 mol) of the pyridylcarbinol **21c** in 150 ml of EtOH and 3 ml of HCl was hydrogenated at 3.5 kg/cm² in the presence of PtO_2 for 5 days. The progress of hydrogenation was followed daily by tlc (by observing the disappearance of the spot of the starting material and the appearance of a much slower moving spot of the more basic product) and fresh catalyst was added each time. After removal of the catalyst, the EtOH solution was concentrated, neutralized with dilute NaOH, and extracted with Et_2O (2 × 200 ml). The combined Et_2O solution was washed (H_2O), dried (Na_2SO_4), and evaporated. The oily residue was treated with 10 ml of Ac_2O. The mixture was allowed to stand for 30 min and poured into H_2O (300 ml). After 14 hr, the solid product was collected by filtration. There was obtained 3.3 g of the product as a white solid (mp ~90°).

2-[3,6-Bis(trifluoromethyl)-9-phenanthryl]-2-(4-piperidinyl)-tetrahydrofuran (19). A mixture of 1.9 g of the aforementioned crude acetamido compound, 1 g of $NaNH_2$, and 20 ml of xylene was heated, with stirring, under reflux for 3 hr. The mixture was cooled to 40° and 1 ml of CH_3I was introduced. The mixture was heated again under reflux for 2 hr. It was poured into ice H_2O (200 ml) and xylene was evaporated under a stream of air. The solid [crude 2-[3,6-bis(trifluoromethyl-9-phenanthryl]-2-(1-acetyl 4-piperidyl)tetrahydrofuran] was extracted with Et_2O (2 × 20 ml) (some gummy substance, which was insoluble in ether, was left in the aqueous phase). The combined Et_2O solution was washed (H_2O), dried (Na_2SO_4), and evaporated. The residue was taken up in 10 ml of EtOH and boiled with 10 ml of 50% KOH solution for 3 hr. It was diluted with H_2O (200 ml) and extracted

with 200 ml of Et_2O. The Et_2O extract was washed (H_2O), dried ($MgSO_4$), and evaporated. The residue was dissolved in 10 ml of Me_2CO and a saturated solution of fumaric acid in Me_2CO was added slowly until no more solid was formed. The precipitated solid product was filtered, mp 195–230° (0.6 g). It was recrystallized from MeOH–Me_2CO to give the fumarate salt of **19** as beige crystals, mp 243–244°. *Anal.* ($C_{25}H_{23}F_6NO \cdot C_4H_4O_4$) C, H, N.

3-(p-Chlorobenzoyl)pyridine (23a) was prepared from 0.1 mol of 1-bromo-4-chlorobenzene and 3-cyanopyridine in a manner similar to that for the preparation of **20b**. There was obtained 8 g (37% yield) of **23a** as a pale yellow solid, mp 87–88° (recrystallized from cyclohexane). *Anal.* ($C_{12}H_{18}ClNO$) C, H, N.

2-(p-Chlorobenzoyl)pyridine (23b) was prepared from 0.1 mol of 1-bromo-4-chlorobenzene and 2-cyanopyridine in a manner similar to that for the preparation of **23a** (see Table III).

2-(p-Chlorophenyl)-2-(3-piperidyl)tetrahydrofuran (24). The intermediate 2-(*p*-chlorophenyl)-2-(3-pyridyl)tetrahydrofuran was prepared from 0.11 mol of **23a** in a manner similar to that used for the preparation of **22b**. There was obtained 11.2 g (47% yield) of the pyridyl intermediate, bp 140–148° (0.05 mm). This intermediate (6.3 g, 0.024 mol) was hydrogenated in the presence of PtO_2 and AcOH as described for the preparation of **18**. Attempts to prepare a hydrochloride salt did not yield a workable solid. The crude base was dissolved in 80 ml of Me_2CO and treated with a saturated solution of fumaric acid in Me_2CO until precipitation was complete. The crude salt was collected by filtration and washed with acetone to give 3.5 g of a solid, mp 192–195°. It was recrystallized from 40 ml of EtOH to afford, after drying at 130° *in vacuo*, 2.8 g of a white solid, mp 205–206° dec.

Elemental analysis suggested that the product was a hemifumarate. This was confirmed by potentiometric titration with standardized perchloric acid in AcOH. The equivalent weight determined was 329.4 and the theoretical value was 323.8. The yield of the product, calculated as a hemifumarate of **24**, was therefore 36%. *Anal.* ($C_{15}H_{20}ClNO \cdot 0.5C_4H_4O_4$) C, H, N.

2-(p-Chlorophenyl)-2-(2-piperidyl)tetrahydrofuran (25). The intermediate 2-(*p*-chlorophenyl)-2-(2-pyridyl)tetrahydrofuran [24% yield, bp 118–127° (0.05 mm)] and subsequent hydrogenation was carried out in an analogous manner. The hydrochloride salt of **25** was isolated in 40% yield: mp 324–325° dec. *Anal.* ($C_{15}H_{20}ClNO \cdot HCl$) C, H, N.

In an analogous manner, compounds **26a–g** were prepared (see Table III).

4-[1-(p-Chlorophenyl)-1-ethoxyethyl]-1-methylpiperidine (26h). A solution of 10.4 g (0.04 mol) of 4-[1-(*p*-chlorophenyl)-1-ethoxyethyl]pyridine (**6b**) and 10 g of CH_3I in 150 ml of MeOH was refluxed for 18 hr. Solvent and excess reagent were removed *in vacuo*. The residual syrupy methiodide was dissolved in 200 ml of EtOH. To this solution was added 10 g of Raney nickel and the mixture was shaken at room temperature for 2 hr. The Raney nickel was removed by filtration. To the filtrate was added 200 mg of PtO_2 and the mixture hydrogenated at 4.2 kg/cm² for 18 hr. Catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in 100 ml of H_2O. The solution was made basic with 40% NaOH and extracted with Et_2O (3 × 50 ml). The Et_2O extract was back-extracted with 2 *N* AcOH (3 × 50 ml). The AcOH extract was again made basic with 40% NaOH and the separated oil was taken up by Et_2O extraction (3 × 50 ml). The Et_2O extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residual oil was dissolved in Me_2CO. To this solution was added a saturated solution of fumaric acid in Me_2CO until precipitation of solid was complete. The resulting salt was collected by filtration and recrystallized from MeOH–Me_2CO to give 12.8 g (80% yield) of the fumarate salt of **26h** as white crystals, mp 181–182°. An analytical sample was prepared by an additional recrystallization from MeOH–Me_2CO: mp 181–182°. *Anal.* ($C_{16}H_{24}ClNO \cdot C_4H_4O_4$) C, H, N.

4-[1-(p-Chlorophenyl)-1-ethoxyethyl]-1-methyl-1,2,3,6-tetrahydropyridine (26i). A solution of 5.2 g (0.02 mol) of **6b** and 14.2 g (0.1 mol) of CH_3I in 150 ml of MeOH was heated at reflux for 18 hr. Solvent and excess reagent were removed *in vacuo* and the residual methiodide syrup was dissolved in 25 ml of EtOH. To this solution was added a solution of $NaBH_4$ in 50 ml of EtOH. The resulting mixture was allowed to stir overnight at room temperature. It was then heated to boiling on the steam bath for 20 min, after which it was cooled. Excess $NaBH_4$ was decomposed by the addition of 5 ml of H_2O. The reaction mixture was diluted with 200 ml of H_2O and extracted with Et_2O (3 × 50 ml). The Et_2O extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in Me_2CO. To the resulting solution was added a saturated solution of fumaric acid in Me_2CO until precipitation of the white salt was complete. The solid was collected by filtration and recrystallized from MeOH–Me_2CO to give 3.8 g (48% yield) of the fumarate salt of **26i**, mp 165–166°. An analytical sample was obtained by an additional recrystallization from MeOH–Me_2CO, mp 165–166°. *Anal.* ($C_{16}H_{22}ClNO \cdot C_4H_4O_4$) C, H, N.

A portion of the aforementioned fumarate salt was converted to the free base by aqueous NaOH and its nmr spectrum in CCl_4 was taken: nmr δ 7.29 (4 H, m, aromatic), 5.79 (1 H, m, –CH=), 3.30 (2 H, q, $-OCH_2-$), 2.95 (2 H, m, $-CH_2N<$), 2.20–2.30 (5 H, m, $>NCH_2$ and $>NCH_3$), 1.82 (2 H, M, $-CH_2-$), 1.47 (3 H, s, α-CH_3), 1.20 (3 H, t, CH_3).

4-[1-(p-Chlorophenyl)-1-ethoxyethyl]-1-ethylpiperidine (26j). A solution of 5.2 g (0.02 mol) of 4-[1-(*p*-chlorophenyl)-1-ethoxyethyl]pyridine (**6b**) and 10 ml of EtI in 50 ml of EtOH was heated at reflux overnight. Solvent and excess reagent were removed *in vacuo*. The resulting ethiodide failed to hydrogenate in EtOH solution in the presence of PtO_2. Accordingly, it was taken up in EtOH and treated with $NaBH_4$. After standing overnight at room temperature the reaction mixture was warmed to 60° for 10 min and the mixture decomposed with H_2O. The resulting free base was extracted with Et_2O (3 × 50 ml). After drying (Na_2SO_4) and removal of solvent, the resulting oil was dissolved in AcOH (100 ml) and hydrogenated with PtO_2 (200 mg) at 60° and 3.5 kg/cm² for 18 hr. The hydrogenation mixture was filtered, AcOH removed *in vacuo*, and the residue dissolved in H_2O (100 ml). The solution was made basic with 40% of aqueous NaOH and the resulting free base was extracted with Et_2O (3 × 50 ml). The Et_2O extract was shaken with 2 *N* AcOH (3 × 50 ml). The AcOH extract was made basic with 40% aqueous NaOH and extracted with Et_2O (3 × 50 ml). After drying (Na_2SO_4) the Et_2O solution was evaporated *in vacuo* and the residual oil dissolved in 50 ml of Me_2CO. A solution of 2.3 g (0.02 mol) of fumaric acid in Me_2CO was added, and excess solvent was removed *in vacuo*. The resulting gum crystallized on trituration with Et_2O. Upon recrystallization from Me_2CO–Et_2O there was obtained 4.5 g (55% yield) of **26j** as white needles, mp 138–142°. An additional recrystallization from Me_2CO–Et_2O gave an analytical sample, mp 139–142°. *Anal.* ($C_{21}H_{30}ClNO_5$) C, H, N.

4-[1-(p-Chlorophenyl)-1-ethoxyethyl]-1-methylpiperidine *N*-Oxide (27). To a suspension of 4.0 g (0.01 mol) of the fumarate salt of **26h** in 50 ml of H_2O was added 5 ml of 40% NaOH. The mixture was extracted with Et_2O (3 × 50 ml). The Et_2O extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residual free base **26h** was dissolved in 50 ml of MeOH and treated with 1.6 ml (*ca.* 0.01 mol) of 30% H_2O_2. This was stirred for 3 hr and a second 1.6-ml portion of 30% H_2O_2 was added; again after 24 hr a third 1.6-ml portion of peroxide was added. At the end of 36 hr the reaction mixture was found to be only weakly basic (pH 7–8). About 50 mg of Pt black was added to the reaction mixture and the whole mixture stirred for 4 hr at room temperature. At the end of the period there was no further evolution of gas and the mixture gave a negative starch–iodide test. The mixture was filtered and the filtrate evaporated *in vacuo*. The residual syrup was dried overnight in high vacuum. The residue was then dissolved in 15 ml of 2-PrOH and treated with 5 ml of 2% HCl in 2-PrOH. Anhydrous Et_2O (200 ml) was then added and the mixture was allowed to stand for 18 hr at room temperature. The precipitated solid was collected by filtration, washed with Et_2O, and recrystallized from a mixture of Et_2O and 2-PrOH to give 2.8 g (80% yield) of the HCl salt of **27**, mp 194–196°. *Anal.* ($C_{16}H_{24}ClNO_2 \cdot HCl$) C, H, N.

1-[3,6-Bis(trifluoromethyl)-9-phenanthryl]-1-(4-pyridyl)ethanol (29f). A solution of 6.0 g (0.014 mol) of **30b**[7] in 500 ml of anhydrous Et_2O was added over a period of 1.5 hr to a CH_3MgI solution freshly prepared from 0.15 mol of CH_3I and 0.15 g-atom of Mg in 300 ml of Et_2O. The mixture was stirred at room temperature for 1 hr. H_2O was then introduced to destroy the excess Grignard reagent. The Et_2O layer was separated, washed (H_2O), dried ($MgSO_4$), and evaporated. The residue was chromatographed over silica gel to afford 0.9 g of the desired product. The aqueous layer was filtered and the filter cake was continuously extracted with Me_2CO for 15 hr. From the Me_2CO solution additional 3.8 g of the same product was obtained to give a total yield of 4.7 g (76%). A small portion of the product was recrystallized from MeOH as white needles, mp 293–295°. *Anal.* ($C_{23}H_{15}F_6NO$) C, H, N.

4-[[3,6-Bis(trifluoromethyl)-9-phenanthryl]-1-ethoxyethyl]piperidine (28). A solution of 2.3 g of 3,6-bis(trifluoromethyl)-α-(4-piperidyl)-9-phenanthrenemethanol[7] (**29b**) in 100 ml of AcOH was treated with a saturated aqueous solution of 2 g of CrO_3. The

mixture was allowed to stand overnight at room temperature, treated with MeOH, neutralized with 60% KOH, and extracted with Et_2O (5 × 200 ml). The combined Et_2O extracts were washed (H_2O), dried ($MgSO_4$), and evaporated to give 1.5 g of the piperidyl ketone **30a**. The crude ketone was dissolved in 100 ml of THF and added to a freshly prepared CH_3MgI solution (0.1 mol) in 20 min. The mixture was stirred for 3 hr. After the excess Grignard reagent was consumed by H_2O, the Et_2O layer was separated. The aqueous phase was extracted with Et_2O (4 × 100 ml). The combined Et_2O solution was washed (H_2O), dried ($MgSO_4$), and evaporated to afford 1.2 g of 1-[3,6-bis(trifluoromethyl)-9-phenanthryl]-1-(4-piperidyl)ethanol (**29c**) as white crystals, mp 251–254°. Compound **29c** was also prepared in 88% yield by catalytic hydrogenation (in PtO_2) of **29f**. Treatment of 4.2 g of **29c** with 100 ml of Ac_2O for 30 min gave 4.1 g (90% yield) of the acetamide **29d** as white crystals, mp 218–220°.

A solution of 1 g of **29d** in 20 ml of DMF was treated with 0.5 g of NaH in mineral oil and 3 ml of EtI. The mixture was stirred at room temperature for 24 hr and then diluted with H_2O (300 ml). The ether **29e** was isolated by Et_2O extraction and then chromatographed over silica gel to separate the unreacted starting material. There was obtained 0.6 g of **29e**, which slowly solidified on standing. This was refluxed overnight with a mixture of 20 ml of EtOH and 20 ml of 60% aqueous KOH. The mixture was diluted with H_2O (300 ml) and extracted with Et_2O (3 × 100 ml). The combined Et_2O extracts were washed (H_2O), dried ($MgSO_4$), and evaporated. The residue was dissolved in 1 ml of EtOH saturated with HCl. Upon addition of Et_2O, the solid product precipitated. It was collected by filtration and recrystallized from MeOH–Et_2O to give 0.4 g of the HCl salt of **28**, mp 195–198°. *Anal.* ($C_{25}H_{25}F_6NO$·HCl) C, H, N.

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Synthesis of Some *N*-Carboxylic Acid Derivatives of 3-Phenoxypyrrolidines, 4-Phenoxypiperidines, and 3-Phenoxynortropanes with Muscle Relaxant and Anticonvulsant Activities

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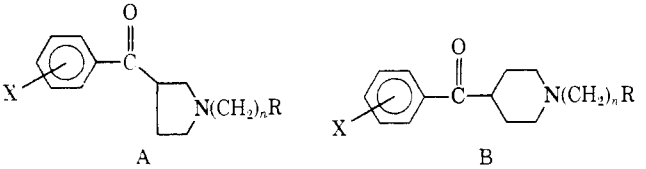
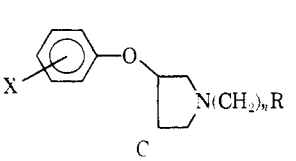
The title compounds were prepared by reacting the intermediate phenoxypyrrolidines, phenoxypiperidines, and phenoxynortropanes with cyanogen bromide, an isocyanate, a carbamoyl chloride, or phosgene and methylamine. Several of the intermediate ethers were prepared by a novel reaction in which an aromatic fluorine is displaced with a heterocyclic alkoxide ion. Anticonvulsant or muscle relaxant activities were observed for several of these compounds.

Previous reports from these laboratories described the preparation and CNS depressant activity of some *N*-alkyl derivatives of 3-benzoylpyrrolidines (A),[1] 4-benzoylpiperidines (B),[1] and 3-phenoxypyrrolidines (C).[2] *N*-Carboxylic

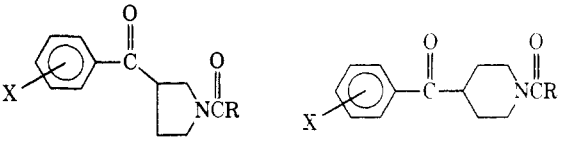


A B



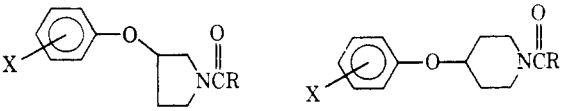
C

acid derivatives of the 3-benzoylpyrrolidines (D) and 4-benzoylpiperidines (E) were prepared in a study of structural modification and found to possess anticonvulsant and muscle relaxant activities.[3] As an extension of this work we have prepared *N*-carboxylic acid derivatives of 3-phenoxypyrrolidines (F), 4-phenoxypiperidines (G), and 3-phenoxynortropanes (H).

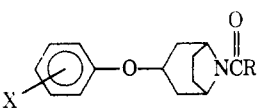


D E

The *N*-carboxylic acid derivatives were prepared from the appropriate 3-phenoxypyrrolidine, 4-phenoxypiperidine, or 3-phenoxynortropane intermediate by reaction with nitrourea, an isocyanate, disubstituted carbamoyl chloride, or by treating the *N*-benzyl intermediates with cyanogen bromide (followed by hydrolysis) or phosgene



F G



H