9α-Fluoropregna-1,4-diene-11β,21-diol-3,20-dione[17α,16α-*d*]-2′-methyloxazoline (XV).—Gaseous HF (4.67 g) was passed into anhydrous THF (8.45 ml). Epoxide XIV (1 g) was added to 9.4 ml of this solution at 0° and the mixture was stirred for 1 hr at 0° and then for 6 hr at room temperature. The reaction mixture was diluted with THF (20 ml) and neutralized, cooling externally with salt and ice, by gradual addition of $NaHCO_3$ (24 g) and Na_2SO_4 (1 g). The inorganic salts were filtered off and the cake was washed with 75 ml of boiling ethyl acetate. The filtrate was concentrated *in vacuo* to dryness and the residue crystallized from acetone affording XV (0.61 g): mp 241–244°; $[\alpha]D$ +83.5° (*c* 0.5); λ_{max} 238 mμ ($E^{1\%}_{1cm}$ 373) (CH_3OH); ir, ν 3500 (OH), 1705 (C_{20}=O), 1664 (C_4=O, C=N) cm^{-1}, characteristic band of the 3-keto-$\Delta^{1,4}$ group at 890 cm^{-1}; nmr, τ = 9.02 (18-CH_3), 8.45 (19-CH_3), 8.04 ppm (CH_3C=N).

Anal. Calcd for $C_{24}H_{28}FNO_5$: C, 66.18; H, 6.71; N, 3.35. Found: C, 66.18; H, 6.86; N, 3.40.

Acknowledgments.—The authors are indebted to Mr. G. Tuan and Dr. A. Vigevani for the determination and interpretation of infrared and nmr spectra, respectively.

Nonsteroidal Hypocholesteremic Agents. I. The Synthesis and Serum Sterol Lowering Properties of Substituted 4-(2-Dialkylaminoethoxy)diphenylamines and Related Compounds[1]

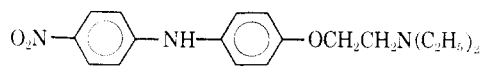
FREDERICK L. BACH, JOHN C. BARCLAY, AND ELLIOTT COHEN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received March 18, 1967

The preparation and serum sterol lowering properties of a series of 4,4′-disubstituted diphenylamines and related compounds are discussed. Initial screening data indicate that several of these compounds, synthesized by conventional means, possess oral activity greater than most nonsteroidal hypocholesteremic agents reported to date.

Our interest in the possible synthesis of hypocholesteremic agents began several years ago when the Biochemical Research Section of this laboratory observed the effective lowering of serum sterols by 4-(2-diethylaminoethoxy)-4′-nitrodiphenylamine (**1**) in both rats and mice. This discovery was timely in view of



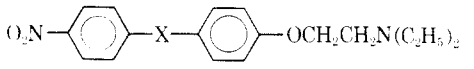
1

the increasing interest in the use of orally active, nonsteroidal hypocholesteremic agents[2,3] and offered a logical beginning for this investigation.

Results and Discussion

The results of a preliminary structure–activity study listed in Tables I and II point out the following very specific structural requirements for high activity in the diphenylamines: (a) as exemplified in **1**, an "electron-withdrawing" group must be in the 4 position of one ring and a basic ether residue in the 4′ position of the opposite ring; (b) maximum hypocholesteremic effects are observed when one of the aromatic rings of the diphenylamine system is a 4-nitrophenyl, a 2,4-dinitrophenyl, or a 2-nitro-4-aminophenyl group; and (c) the basic ether moiety must be comprised of an O and a tertiary amine N separated by a two-carbon chain. The marked changes in serum sterol lowering due to slight variations in the $-OCH_2CH_2N<$ portion of several hypocholesteremic agents is an interesting discovery and will be discussed in more detail later.

Having established the importance of functional groups and their relative positions in the aromatic rings of the active diphenylamines, we next considered isosteres[4] of **1** where the "bridging" –NH– group is replaced by divalent –O– and –S–. The ability of bridging atoms to promote "through conjugation" in



1, X = –NH–
2, X = –O–
3, X = –S–

derivatives such as **1**, **2**, and **3** can be ruled out because of the noncoplanarity of the aromatic systems; spectral data[5] obtained from a study of diphenyl sulfides also support this idea. Actually, compounds **1**, **2**, and **3** can be considered *para*-substituted nitrobenzenes in which the X atom conjugates through a p orbital. In this sense the –NH– group is the strongest electron donor; however, there is no reason to attribute the high activity of the diphenylamines to this property.

Although in medicinal chemistry it is not unusual for isosteres of an active compound to retain some amount of activity, the results listed in Table III indicate no retention of activity in **2** or **3**. This finding once again emphasizes the specific structural requirements in diphenylamines.

An extension of our initial research is described in Table IV where several interesting points should be noted: (a) a nitrophenyl group can be effectively replaced by 3- and 5-nitropyridyl groups; (b) the 5-nitropyridyl analog (**17**) of **1** is a potent hypocholesteremic agent; (c) within the 5-nitropyridyl series complete

(1) Portions of this paper were presented before the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 13–17, 1965, Abstracts of Papers, p 11I.

(2) See, for example, the following references: (a) M. Friedman, S. O. Byers, and R. H. Rosenman, *Progr. Cardiovascular Diseases*, **4**, 419 (1962); (b) L. G. Humber, M. Kraml, J. Dubuc, and R. Gaudry, *J. Med. Chem.*, **6**, 210 (1963).

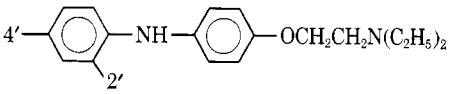
(3) (a) D. Dvornik, M. Kraml, J. Dubuc, M. Givner, and R. Gaudry, *J. Am. Chem. Soc.*, **85**, 3309 (1963); (b) G. Rodney, M. L. Black, and O. D. Bird, *Biochem. Pharmacol.*, **14**, 445 (1965).

(4) As defined by V. B. Schatz in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp 72–88.

(5) (a) A. Mangini and R. Passerini, *J. Chem. Soc.*, 1168 (1952); (b) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, p 481.

TABLE I

SUBSTITUTED 4-(2-DIETHYLAMINOETHOXY)DIPHENYLAMINES

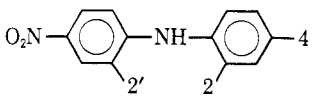


Compd	Substituent	Method	Mp, °C	Formula	Nitrogen, % Calcd	Nitrogen, % Found	Serum sterol lowering act.[a,b]
1	4′-NO_2	A, B, D[f]	87–88	$C_{18}H_{23}N_3O_3$	12.8	13.0	2[c]
4	4′-NH_2[d]	A	65–66	$C_{18}H_{25}N_3O$	14.1	14.1	0
5	2′-NO_2, 4′-NO_2	E	70–71	$C_{18}H_{24}N_4O$	15.0	14.7	1
6	2′-NO_2, 4′-NH_2[e]	E	179–181	$C_{18}H_{24}N_4O_3$	13.4	13.3	1
7	4′-NO_2, 2′-COOH	D	229–230	$C_{19}H_{23}N_3O_5$	11.2	11.6	0

[a] Rats were sacrificed after a 6-day oral administration of the test drug and their sera were subjected to a Trinder saponification [see P. Trinder, *Analyst*, **77**, 321 (1952)] prior to a Zlatkis and Zak colorimetric assay [see A. Zlatkis, B. Zak, and A. J. Boyle, *J. Lab. Clin. Med.*, **41**, 486 (1953)] for total serum-sterol levels. [b] Activity ratings were based on per cent of drug in diet necessary to bring about a 20–30% lowering of serum sterols compared to control levels: 0.05% = 0 (inactive), 0.03% = 1, 0.01% = 2, 0.003% = 3, 0.001% = 4. It should be noted that compounds eliciting a serum-sterol lowering of 19% (or less) when tested at 0.05% of the diet are rated inactive. [c] Triparanol, 1-[4-(2-diethylaminoethoxy)phenyl]-1-(*p*-tolyl)-2-(*p*-chlorophenyl)ethanol, was rated 2 using the test standards described above. [d] Compound isolated as a dihydrochloride. [e] Tentative structure. [f] Compound **1** was first prepared by E. Ruso in the Stamford Laboratories Division, American Cyanamid Co.

TABLE II

SUBSTITUTED NITRODIPHENYLAMINES

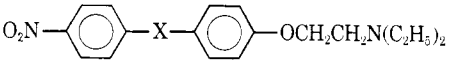


Compd	Substituents	Method	Yield, %	Mp or bp, °C (mm)	Formula	Nitrogen, % Calcd	Nitrogen, % Found	Serum sterol lowering act.[a]
8	2′-NO_2, 2-$OCH_2CH_2N(C_2H_5)_2$	E	12	101–103	$C_{18}H_{22}N_4O_5$	15.0	14.6	1
9	2′-NO_2, 4-OCH_2CH_2N(piperazine)$NCOOC_2H_5$	E	44	132–134	$C_{21}H_{25}N_5O_7$	15.2	14.9	0
10	4-$OCH_2CH(OH)CH_2OH$	A, B	75	138–139	$C_{15}H_{16}N_2O_5$	9.2	9.4	0
11	4-$OCH_2COOC_2H_5$	A, C[b]	26	133–135	$C_{16}H_{16}N_2O_5$	8.9	8.9	0
12	4-OCH_2CH_2Cl	A, C[b]	71	125–126	$C_{14}H_{13}ClN_2O_3$	9.6	9.9	0
13	4-$OCH_2CH{=}CH_2$	A, C[b]	95	92–93	$C_{15}H_{14}N_2O_3$	10.4	10.7	0
14	4-COOH	F	20	290 dec	$C_{13}H_{10}N_2O_4$	10.8	10.6	0
15	4-$COOCH_2CH_2N(C_2H_5)_2$	F	34	175–180 (0.5–0.6)	$C_{19}H_{23}N_3O_4$	11.8	11.8	0

[a] See Table I for activity ratings. [b] Method C was developed at the Bound Brook Laboratories Division, American Cyanamid Co.

TABLE III

ISOSTERES OF 4-(2-DIETHYLAMINOETHOXY)-4′-NITRODIPHENYLAMINE

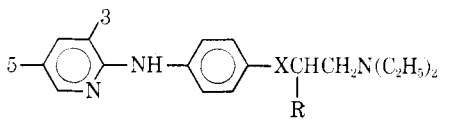


Compd	X	Method	Yield, %	Bp, °C (mm)[a]	Formula	Nitrogen, % Calcd	Nitrogen, % Found	Serum sterol lowering act.[c]
2	O	B, G	37	170–175 (0.2)	$C_{18}H_{22}N_2O_4$	8.5	8.1	0
3	S	B, H	20	250–260 (0.5)	$C_{18}H_{22}N_2O_3S$[b]	8.1	7.8	0

[a] Boiling points are uncorrected. [b] *Anal.* Calcd: S, 9.3. Found: S, 9.6. [c] See Table I for activity ratings.

TABLE IV

N-(2-PYRIDYL)ANILINE DERIVATIVES[a]



Compd	Pyridyl ring substituent	X	R	Yield, %	Mp, °C	Formula	Nitrogen, % Calcd	Nitrogen, % Found	Serum sterol lowering act.[c]
16	3-NO_2	O	H	50	47–48	$C_{17}H_{22}N_4O_3$	17.0	17.1	1
17	5-NO_2	O	H	72	143–145	$C_{17}H_{22}N_4O_3$	17.0	16.6	2
18	5-NO_2	S	H	28	111–113	$C_{17}H_{22}N_4O_2S$[b]	16.2	15.8	0
19	5-NO_2	O	CH_3	58	59–61	$C_{18}H_{24}N_4O_3$	16.3	16.2	3

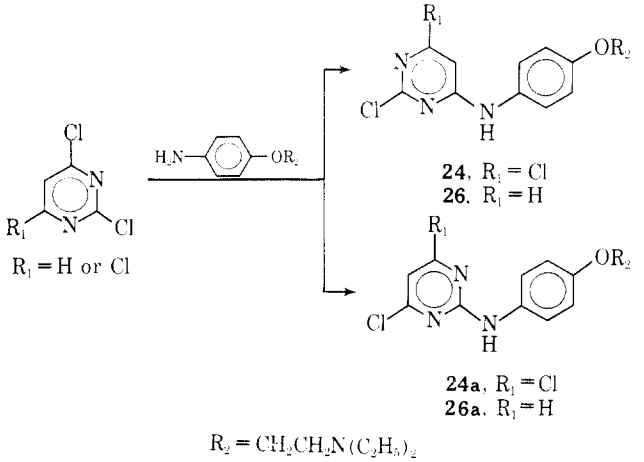
[a] All compounds were prepared by methods I and J (see Experimental Section). [b] *Anal.* Calcd: S, 9.2. Found: S, 9.1. [c] See Table I for activity ratings.

loss of activity occurred when the O of the basic residue of **17** was replaced by S, forming the isostere **18**; and (d) in the same series branching on the carbon atom α to the ether oxygen caused a noticeable increase in activity; *cf.* **16** and **19**.

There are many examples in the literature[6] which suggest that a pyridyl moiety can effectively replace a nitrophenyl group based on the resistance of pyridine and nitrobenzene to electrophilic attack and the fact that transition-state theory predicts *meta* substitution in both systems. A lack of generality in this proposal is demonstrated by the inactivity of the N-(4-pyridyl) derivative (**20**) listed in Table V; the retention of activity in compounds **16**, **17**, and **19** (see Table IV) is, in all probability, attributable to the presence of NO_2 groups in the pyridine rings, rather than any polar similarities between the pyridyl and nitrophenyl residues *per se*.

Preliminary results of a diphenylamine analog study are reported in Table V and, surprisingly, it was found that the 2,6-dichloro- and 5- and 2-chloropyrimidyl groups could also effectively replace the nitrophenyl portion of **1**: *cf.* **1** and **24**–**26**. These findings coupled with the enhanced activity due to branching[7] in the basic ether moiety of **19** resulted in the synthesis of many, potent, nonsteroidal hypocholesteremic agents.

Because of the possibility of isomer formation in the synthesis of **24** and **26** the N-5-chloro-2-pyrimidyl derivative (**25**)[8] (see Table V) was selected as a model



in the final phase of this investigation which dealt with variations in the 2-diethylaminoethoxy group in **25** (see Table V).

As illustrated in Table VI, bulk effects can be incorporated into the simple $-OCH_2CH_2N<$ residue in various ways. One obvious change is the inclusion of the N in a saturated heterocyclic nucleus; the effect of this alteration is marked when the cyclic structure is a piperidino group; *cf.* **25** and **28**. Branching on the carbon α to the ether oxygen was achieved by the synthesis of **27**; however, this change had no noticeable effect. It is interesting to compare this result with those reported in Table IV for **17** and **19**. The remaining portion of the $OCH_2CH_2N<$ group in the model compound (**25**) to be studied was the region next to the tertiary amine nitrogen. Bulk effects converging on the N atom were achieved by completely substituting the carbon α to the tertiary amine function with methyl groups as illustrated in **29** (see Table VI). This relatively simple change[9] resulted in a derivative many times more active than the lead compound, **1**, or derivatives **27** and **28**.

Experimental Section

The melting points were determined in open capillary tubes using a Hershberg apparatus; both melting points and boiling points are uncorrected. Ultraviolet spectra were measured in methanol on a Cary recording spectrophotometer. Infrared spectra were determined in mineral oil mulls or KBr disks using a Perkin-Elmer spectrophotometer (Model 21). Nmr spectra were obtained at 60 Mc using a Varian Associates A-60 instrument with Me_4Si as an internal standard. The NaH-oil dispersion (54.7% active) was obtained from Metal Hydrides Inc., Beverly, Mass.

General synthetic procedures are given below for the preparation and isolation of the compounds described in this paper. Analyses, yields, and physical properties are recorded in the tables and any variations in the general procedures are listed in the table footnotes.

4-(*p*-Nitroanilino)phenol. Method A.—2-Chloro-5-nitrobenzenesulfonic acid (47.4 g, 0.2 mole), 147 g (0.75 mole) of $BaCO_3$, and 600 ml of water was added to a 1-l., flask. The system was flushed with CO_2 for 45 min and then 32.7 g (0.3 mole) of *p*-aminophenol was added. The suspension was heated to reflux and stirred under CO_2 for approximately 24 hr. After addition of charcoal the solution was filtered hot and the clear filtrate was stirred in an ice bath during the addition of excess KCl. The resulting dark red potassium salt was collected on a filter and dried in an oven at 60–70°.

Thirty grams (0.09 mole) of the dried potassium 4-hydroxy-4′-nitrodiphenylamine sulfonate and 200 ml of concentrated HCl were added to a 1-l. flask and the mixture was slowly brought to reflux over a period of 30 min to avoid frothing. When all of the solid had dissolved the solution was refluxed gently with stirring for an additional 1 hr. After cooling to room temperature the crystalline product was collected, triturated with two 50-ml portions of water, and dried in an evacuated oven at 40°. The yield was 18.2 g (91%), mp 166–171°.

4-(2-Diethylaminoethoxy)-4′-nitrodiphenylamine (1). Method B.—To a solution consisting of 70.7 g (0.31 mole) of 4-hydroxy-4′-nitrodiphenylamine in 200 ml of dry dimethylformamide (DMF) 15.3 g (0.35 mole) of a NaH dispersion (54.7% active) was added portionwise. The suspension was warmed at 95–100° for 20 min (or until a clear solution was obtained). The sodio derivative was then treated with 32.6 g (0.35 mole) of 2-diethylaminoethyl chloride in 100 ml of dry benzene and the resulting suspension was heated at reflux temperature for 20 hr. After cooling, the reaction mixture was filtered and the clear filtrate was concentrated to a semisolid residue using a flash evaporator. The crude product was extracted from the residue using five 100-ml portions of cyclohexane. Concentration of the cyclohexane extracts afforded a crude product which after two recrystallizations from cyclohexane was analytically pure; the product melted at 83–84°, 22 g (22% yield).

(6) (a) H. Erlenmeyer, J. P. Jung, and E. Sorhin, *Helv. Chim. Acta*, **29**, 1960 (1946); (b) D. E. Metzler, M. Ikawa, and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 648 (1954); (c) A. H. Bruecker, *Yale J. Biol. Med.*, **15**, 813 (1943); (d) P. B. Cowles, *ibid.*, **14**, 599 (1942); (e) E. H. Northey, "The Sulfonamides and Allied Compounds," 2nd ed, Saunders Publishing Co., Philadelphia, Pa., 1957, p 272.

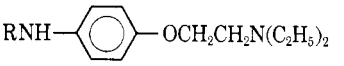
(7) It should be noted that alkyl branching in the $-OCH_2CH_2N<$ portion of various drugs can evoke marked changes in physiological effects, *viz.*, increase in activity, decrease in toxicity, or a prolongation of activity; see "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp 42, 485, 526, 529; and A. Burger in "Modern Concepts in the Relationship Between Structure and Pharmacological Activity," Vol. 7, K. J. Bruning, Ed., The Macmillan Co., New York, N. Y., 1963, p 59. Other examples of this effect have been demonstrated in the development of effective antispasmodic agents; see, *e.g.*, F. L. Bach and H. J. Brabander, U. S. Patent 2,756,231 (1956).

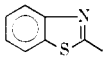
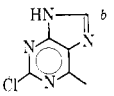
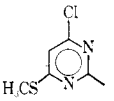
(8) Only one product is isolated when 2,5-dichloropyrimidine is condensed with a *para*-substituted aniline; nmr analysis established the structure of **25** unequivocally.

(9) Although any of the explanations of bulk effects in the $-OCH_2CH_2N<$ group as set forth in ref 7 may be applicable, it is impossible, at present, to explain this remarkable effect without additional biochemical information and a more complete knowledge of the processes involved in the metabolism of **29**.

TABLE V

N-HETERO-*p*-(2-DIETHYLAMINOETHOXY)ANILINES[a]

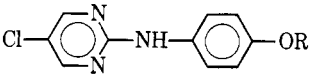


Compd	R	Yield, %	Mp, °C	Formula	Nitrogen, % Calcd	Nitrogen, % Found	Serum sterol lowering act.[c]
20		36	124–125	$C_{17}H_{23}N_3O$	14.7	14.5	0
21		3	93–95	$C_{19}H_{23}N_3OS$	12.3	12.5	0
22		31	229–231	$C_{17}H_{21}ClN_6O$	23.3	23.6	0
23		25	97–99	$C_{17}H_{23}ClN_4OS$	15.3	15.0	0
24		28	104–106	$C_{16}H_{20}Cl_2N_4O$	15.8	15.7	1
25		37	93–95	$C_{16}H_{21}ClN_4O$	17.5	17.4	1
26		41	75–77	$C_{16}H_{21}ClN_4O$	17.5	17.2	2

[a] All compounds were prepared by method J (see Experimental Section). [b] Tentative structure. [c] See Table I for activity ratings.

TABLE VI

VARIATIONS IN THE BASIC MOIETY OF N-(5-CHLORO-2-PYRIMIDYL)-*para*-SUBSTITUTED ANILINE[a]



Compd	R	Yield, %	Mp, °C[b]	Formula	Nitrogen, % Calcd	Nitrogen, % Found	Serum sterol lowering act.[e]
27	$CH(CH_3)CH_2N(C_2H_5)_2$[c,d]	31	106–108	$C_{17}H_{23}ClN_4O$	16.7	17.2	1
28		49	119–121	$C_{17}H_{21}ClN_4O$	16.8	16.6	3
29	$CH_2C(CH_3)_2N(CH_3)_2$	28	120–122	$C_{16}H_{21}ClN_4O$	17.5	17.3	4

[a] All compounds prepared using methods I and J. [b] Melting points are uncorrected. [c] Compound isolated as a sesquihydrate. [d] Structure was verified by nmr and compound was tested as a racemic mixture. [e] See Table I for activity ratings.

4-Amino-4′-(2-diethylaminoethoxy)diphenylamine (4).—Two grams (7×10^{-3} mole) of **1** was dissolved in 100 ml of ethanol and reduced under 1.5 kg/cm² of hydrogen at 25–30° using 0.5 g of prereduced PtO_2 catalyst. When reduction was complete (*ca.* 1 hr) the ethanolic solution was filtered and concentrated to a quasi-crystalline mass. The residual material was taken up in 50 ml of 10% HCl and the acidic solution was extracted with two 50-ml portions of ether. The acidic, aqueous layer was decolorized using charcoal, made basic (excess concentrated NH_4OH), and extracted with two 50-ml portions of ether. The ether extracts were combined, dried (Na_2SO_4), and concentrated to a solid residue which was dissolved in a minimum amount of hot cyclohexane. On cooling, light pink crystals were deposited; 0.4 g (20% yield). The analytically pure product melted at 65–66°.

4-(β-Chloroethoxy)-4′-nitrodiphenylamine (12). Method C.—Using the apparatus described in method A 11.5 g (0.05 mole) of 4-hydroxy-4′-nitrodiphenylamine, 11.7 g (0.05 mole) of 2-chloroethyl *p*-toluenesulfonate, 2.8 g (0.07 mole) of NaOH, and 30 ml of water was heated to reflux with vigorous stirring under N_2. After a 4-hr reflux period the reaction mixture was cooled and made alkaline to phenolphthalein using 5 *N* NaOH. The crude solid which separated was collected, triturated with three 100-ml portions of water, and air-dried. An analytically pure sample of **12** was isolated after two recrystallizations from an ethanol–water solution; mp 125–126°.

N-[*p*-(2-Diethylaminoethoxy)phenyl]-5-nitroanthranilic Acid (7). Method D.—The monohydrochloride of *p*-(2-diethylaminoethoxy)aniline (4.9 g, 0.02 mole) was dissolved in 50 ml of water and neutralized (excess K_2CO_3, 5.6 g, 0.04 mole). To this basic, aqueous suspension was added 3.6 g (0.02 mole) of potassium 2-chloro-5-nitrobenzoate and approximately 10 ml of ethanol. The resulting suspension was then refluxed for *ca.* 15 hr, concentrated under reduced pressure to one-half the original volume, and extracted with two 100-ml portions of $CHCl_3$. The aqueous layer was collected, treated with charcoal, and neutralized (pH 6–7) using 10% HCl. The orange needle crystals obtained in this manner were recrystallized from an ethanol–ether solution; 2.1 g (34% yield).

The decarboxylation of **7** was accomplished by heating an intimate mixture of micro glass beads (2–3 g) and 2.0 g (5×10^{-3} mole) of **7** under reduced pressure with stirring; the reaction mass melted and began effervescing at 180° (0.1–0.2 mm). CO_2 was evolved until the temperature of the molten mass reached 200°, whereupon heating was discontinued and the mixture was allowed to cool to room temperature under reduced pressure. Undecomposed acid was extracted with hot 50% KOH and the insoluble residue was taken up in acetone. Two recrystallizations

from acetone afforded 0.8 g (40% yield) of **1** melting at 86–88°. No depression of melting point was observed when the decarboxylation product was mixed with an authentic sample of **1**.

4-(2-Diethylaminoethoxy)-2′,4′-dinitrodiphenylamine (5). Method E.—Four grams (0.01 mole) of *p*-(2-diethylaminoethoxy)-aniline dissolved in 50 ml of ethanol was added to a solution of 3.7 g (0.02 mole) of 2,4-dinitrofluorobenzene in 25 ml of ethanol. The orange-brown solution was warmed to 50° and then poured into 200 ml of ice–water. On standing, the yellow, oily residue solidified, mp 70–71°. An analytically pure sample of **5** was obtained after one recrystallization from an ethanol–water solution.

4′-Amino-4-(2-diethylaminoethoxy)-2′-nitrodiphenylamine (6).—Alcoholic ammonium sulfide prepared by passing dry H_2S through a solution consisting of 8.0 g of concentrated NH_4OH in 15 ml of ethanol was added dropwise to a refluxing solution of 2.5 g (7×10^{-3} mole) of **5** in 50 ml of ethanol. After a 30-min reflux period the reaction mixture was cooled to room temperature, treated with charcoal, and filtered. The clear, yellow filtrate was added to ethanolic HCl and concentrated to a semisolid mass. Trituration of the residue with three 50-ml portions of dry ether afforded 1.2 g (40% yield) of the dihydrochloride of **6**. Nmr spectral data would favor assignment of the NH_2 to the ′ position of **6**.

***p*-(*p*-Nitroanilino)benzoic Acid (14). Method F.**—*p*-Fluoronitrobenzene (7 g, 0.05 mole) was added to a suspension consisting of 6.8 g (0.05 mole) of *p*-aminobenzoic acid, 5.6 g (0.10 mole) of KOH, and 0.05 g of Cu powder in 10 ml of *n*-amyl alcohol. The reaction mixture was refluxed 2 hr and then subjected to a steam distillation which removed the unreacted *p*-fluoronitrobenzene. The residue was extracted with two 100 ml-portions of hot water which on acidification yielded 2.4 g (20%) of the desired product, mp >290° dec.

2-Diethylaminoethyl Ester of *p*-(*p*-Nitroaniline)benzoic Acid (15).—Potassium *p*-(*p*-nitroanilino)benzoate (3 g, 0.01 mole) was added to 1.4 g (0.01 mole) of 2-diethylaminoethyl chloride in 100 ml of ether and the suspension refluxed for approximately 20 hr. The suspension was filtered hot and concentrated to a brown oil and the oily residue was redissolved in 50 ml of ether and dried (K_2CO_3). After removing the solvent a pure sample of **15** was isolated by fractional distillation, bp 175–180° (0.6–0.7 mm).

4-(2-Diethylaminoethoxy)-4′-nitrodiphenyl Ether (2). Method G.—A solution consisting of 28.2 g (0.2 mole) of 4-fluoronitrobenzene, 22.0 g (0.2 mole) of *p*-hydroquinone, and 8.0 g (0.2 mole) of NaOH in 100 ml of ethanol and 100 ml of water was refluxed for 20 hr, cooled to room temperature, and then filtered. Acidification of the filtrate with excess dilute HCl afforded a yellow precipitate which was collected and recrystallized from ethanol; total yield of 4-hydroxy-4′-nitrodiphenyl ether amounted to 19.2 g (37%), mp 172–174°.

The sodio derivative of 4-hydroxy-4′-nitrodiphenyl ether was prepared by adding 0.94 g (0.02 mole) of NaH (54.7% active) to 3.8 g (0.02 mole) of the ether in refluxing toluene. After cooling to room temperature, 4.1 g (0.03 mole) of 2-diethylaminoethyl chloride was added, and the reaction mixture was refluxed for 15 hr. The resulting suspension was cooled to room temperature, filtered, and concentrated to a brown, oily residue. Distillation of the crude, residual oil afforded 2.0 g (37%) of the desired product, bp 170–175° (0.2–0.4 mm).

4-(2-Diethylaminoethoxy)-4′-nitrodiphenyl Sulfide (3). Method H.—A solution consisting of 15.4 g (0.05 mole) of 4,4′-dinitrodiphenyl disulfide in 300 ml of CCl_4 was placed in a flask. After thoroughly flushing the system with dry N_2, chlorine was passed through the vigorously stirred solution for approximately 3 hr. The saturated solution was then concentrated under reduced pressure to a low-melting, yellow solid, crude mp 73–76° (lit.[10] mp 75°). The *p*-nitrophenylsulfenyl chloride was used immediately in the next step.

A solution of phenol (1.97 g, 0.02 mole) in 50 ml of ether was added all at once to 4.0 g (0.021 mole) of *p*-nitrophenylsulfenyl chloride and the reaction mixture was allowed to stand under N_2 for 15 hr at 25–30°. Removal of volatile materials left crude 4-hydroxy-4′-nitrodiphenyl sulfide which was recrystallized from glacial acetic acid; mp 148–149°. The nmr spectra of the recrystallized sample showed the chemical shifts and coupling constants expected for the symmetrical molecule, 4-hydroxy-4′-nitrodiphenyl sulfide. In the nitrophenyl ring the H_3' and H_5' protons showed resonance at τ 1.75 and the H_2' and H_6' protons were identified at τ 2.71.

NaH (0.72 g, 0.03 mole) was added to a solution consisting of 7.5 g (0.03 mole) of 4-hydroxy-4′-nitrodiphenyl sulfide in 100 ml of dry toluene. After 3 hr of refluxing, the orange-brown suspension was cooled to room temperature and treated with 5.2 g (0.03 mole) of 2-diethylaminoethyl chloride. Refluxing was resumed with stirring for 15 hr and the resulting suspension was filtered hot. Concentration of the clear, yellow filtrate left a yellow, oily residue which was distilled *in vacuo*. The portion distilling at 250–260° (0.4–0.5 mm) was collected and placed on a silica gel column. After eluting the column with three 200-ml portions of benzene, the desired compound was stripped from the column using 100 ml of methanol. Concentration of the eluate afforded 2.1 g of pure **3** which was isolated as a heavy, yellow-orange oil.

***p*-(2-Dimethylamino-2,2-dimethyl)ethoxyaniline. Method I.** NaH (4.8 g, 0.2 mole) dispersed in mineral oil (54.7% active) was added portionwise with swirling to a solution of 2-dimethylamino-2-methyl-1-propanol (23.4 g, 0.2 mole) in 250 ml of DMF. After a clear solution was obtained by heating the suspension to 60°, 4-fluoronitrobenzene (28.2 g, 0.2 mole) in 200 ml of DMF was added portionwise. A dark orange color developed immediately accompanied by deposition of NaCl. Reaction was complete in approximately 1.0 hr and the deposited salt was filtered off leaving a clear, orange-yellow filtrate. Concentration of the filtrate left a residual oil which solidified on standing; mp 68–73°. The crude *p*-(2-dimethylamino-2,2-dimethyl)ethoxynitrobenzene may be used in the next step without further purification.

Using a Parr shaker 26.2 g (0.11 mole) of *p*-(2-dimethylamino-2,2-dimethyl)nitrobenzene was reduced over 10% Pd–C (0.8–1.0 g) in approximately 275 ml of ethanol. The reduction proceeded smoothly (initial pressure 3.46 kg/cm²) and required approximately 3 hr. Separation of the catalyst by filtration and concentration of the filtrate yielded a brown, oily residue which was subjected to high-vacuum distillation; the cut boiling at 124–126° (0.2–0.3 mm) was collected and amounted to 16 g (70% yield).

N-(5-Chloro-2-pyrimidyl)-*p*-(2-diethylaminoethoxy)aniline (25). Method J.—*p*-(2-Diethylaminoethoxy)aniline (5.2 g, 0.025 mole) and 3.7 g (0.025 mole) of 2,5-dichloropyrimidine was sealed under argon in a Pyrex tube and heated at 95–100° for *ca.* 30 hr. The semisolid reaction mixture was treated with an excess of 20% NaOH solution and the base-insoluble material was taken up in benzene, decolorized using charcoal, and dried (Na_2SO_4). An analytically pure sample was obtained by eluting the crude product from a Florisil column using a benzene–ether (50:50) solution; mp 93–95°.

Acknowledgment.—We wish to thank Drs. S. Gordon and M. J. Fahrenbach and their groups for the screening of these drugs. We are also indebted to Mr. L. Brancone and associates for the microanalytical results and to Mr. W. Fulmor and co-workers for nmr spectral analyses.

(10) T. Zincke and E. Farr, *Ann.*, **391**, 57 (1912).