tion was poured into HCl. The precipitate was filtered and air-dried. The products II (R = CH_3) are described in Table III.

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Hypocholesterolemic 5-Methyltetrazole Derivatives†,[1]

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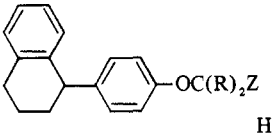
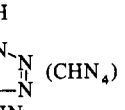
There remains a great need for developing superior agents for the control of hyperlipoproteinemia and associated atherosclerotic disease. This note describes the synthesis and biological evaluation of a number of related compounds that have resulted from our continued interest in 5-substituted tetrazoles as potential hypolipidemic agents.[2]

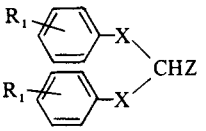
Chemistry. In general, the tetrazoles **8–14** were prepared from the corresponding nitriles **1–7** by standard synthetic methods (see Tables I and II and Experimental Section). The yields varied, with generally poor conversions resulting when the α carbon of the nitrile precursor was highly substituted.



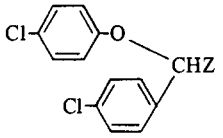
I, R = H; Z = CN
2, R = CH_3; Z = CN



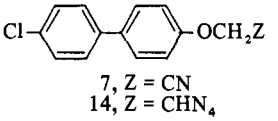
8, R = H; Z = (CHN$_4$)
9, R = CH_3; Z = CHN$_4$



3, R_1 = *p*-Cl; X = O; Z = CN
4, R_1 = *m*-Cl; X = O; Z = CN
5, R_1 = *p*-Cl; X = S; Z = CN
10, R_1 = *p*-Cl; X = O; Z = CHN$_4$
11, R_1 = *m*-Cl; X = O; Z = CHN$_4$
12, R_1 = *p*-Cl; X = S; Z = CHN$_4$



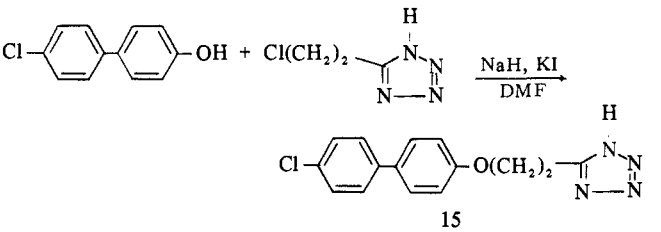
6, Z = CN
13, Z = CHN$_4$



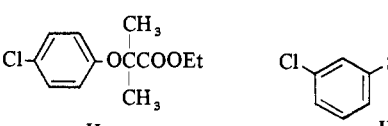
7, Z = CN
14, Z = CHN$_4$

Compound **15** was prepared by tetrazolylethylation of *p*-(4-chlorophenyl)phenol.[2]

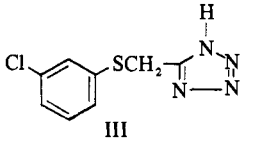
Biological Evaluation. In the hypocholesterolemic screen the tetrazoles were administered orally to rats once daily for 4 days (0.5% suspension in carboxymethylcellulose). Serum cholesterol values were determined by the method of Zlatkis, *et al.*,[3] as modified for the autoanalyzer (method Np-24) and are recorded in Table III. In general, compounds that lowered serum cholesterol by at least 20% proved to be significantly active. The most active compound at 100 mg/kg is the bis(*p*-chlorophenoxy)methyl derivative **10**. Significant activity is lost if: (a) oxygen is replaced by sulfur (**12**); (b) chlorine is in the meta position relative to the ether linkages (**11**); (c) one *p*-chlorophenoxy group is replaced by a *p*-chlorophenyl group (**13**). The remaining compounds listed have generally poor hypocholesterolemic activity. In this assay compound **10** has greater activity than the reference agent ethyl 2-methyl-2-(*p*-chlorophenoxy)propionate (clofibrate, II) (MED ≃ 400 mg/kg)[4] and 5-(3-chlorophenylthiomethyl)tetrazole (III) (MED ≃ 200 mg/kg)[2] but less activity than 1-methyl-4-piperidyl bis(*p*-chlorophenoxy)acetate[5] (IV)



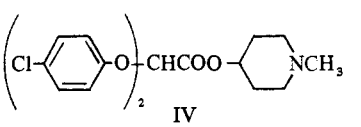
15



II



III



IV

(MED ≃ 25 mg/kg in our assay). Using Lofland's semi-automated procedure for the determination of triglycerides,[6] compound **10** was found to significantly lower serum triglyceride levels (−44%) when administered orally to male Sprague–Dawley rats at 50 mg/kg per day for 2 weeks.

Table I. Nitriles

No.	Yield,[a] %	Recrystn solvent	Mp or bp, °C (mm)	Formula	Analyses
1	91		164–169 (0.05)	$C_{18}H_{17}NO$	
2	26		*b*	$C_{20}H_{21}NO$	
3	68.2		*b*	$C_{14}H_9Cl_2NO_2$	
4	96.6		151–152 (0.1)	$C_{14}H_9Cl_2NO_2$	
5	37.9	2-PrOH	109.5–110.5	$C_{14}H_9Cl_2NS_2$	C, H, N, S
6	72.7		139–145 (0.025)	$C_{14}H_9Cl_2NO$	C, H, N
7	95	CCl_4	78–80	$C_{14}H_{10}ClNO$	C, H, N

[a] Yield from penultimate intermediate. [b] Used in the crude state.

Experimental Section‡

Nitriles (Table I). *p*-(1,2,3,4-Tetrahydro-1-naphthyl)phenoxyacetonitrile (1) and 4-(*p*-Chlorophenyl)phenoxyacetonitrile (7).

†Some of these compounds have been described in ref 1.

‡The melting points were obtained in capillary tubes with a Thomas-Hoover Unimelt apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values (see also Tables I and II). Spectral data (ir and nmr) for all compounds were consistent for the reported structures and were recorded on Beckmann Model IR9 and Varian Model A-60 recording spectrometers, respectively.

Table II. Tetrazoles

No.	Yield,[a] %	Recrystn solvent[b]	Mp, °C	Formula	Analyses
8	89.6	A	173–174.5	$C_{18}H_{18}N_4O$	C, H, N
9	37.7	B	112–114	$C_{20}H_{22}N_4O$	C, H, N
10	74	A	139–140.5 (151–152)[c]	$C_{14}H_{10}Cl_2N_4O_2$	C, H, N
11	55.7	C	85–89.5	$C_{14}H_{10}Cl_2N_4O_2$	C, H, N[d]
12	41.4	D	154.5–156	$C_{14}H_{10}Cl_2N_4S_2$	C, H, N
13	23.5	A	182–184 dec	$C_{14}H_{10}Cl_2N_4O$	C, H, N
14	96.0	E	247–248	$C_{14}H_{11}ClN_4O$	C, H, N
15	46.1	E	201–203.5	$C_{15}H_{13}ClN_4O$	C, H, N

[a] Yield from penultimate intermediate. [b] A, 2-PrOH–H_2O; B, EtOAc–Skellysolve B; C, CCl_4; D, $CHCl_3$–CCl_4; E, 2-PrOH. [c] Second crystalline form (see Experimental Section). [d] N: calcd, 16.62; found, 17.10.

Table III. Hypocholesterolemic Activity[a]

No.	Dose, mg/kg	Serum cholesterol, % change
8	200	−11
	100	−6
9	50	0
10	100	−47
	50	−14
	25	−17
11	100	−8
12	100	0
13	100	−12
14	200	−30
	100	−9
15	100	−11

[a] Male Sprague–Dawley rats (150–200 g); data are averages of serum levels in five rats.

These compounds were prepared by condensing the requisite phenols with chloroacetonitrile using the method of McManus and Herbst.[7]

p-(1,2,3,4-Tetrahydro-1-naphthyl)phenoxyisobutyronitrile (2). To a stirred suspension of 1.1 g of 56.6% NaH dispersion (0.025 mol of NaH) in 100 ml of dry xylene was added *p*-(1,2,3,4-tetrahydro-1-naphthyl)phenol[8] (5.0 g, 0.022 mol). After the vigorous H_2 evolution had ceased the mixture was refluxed for 1.25 hr. After cooling to room temperature, 2-methyl-2-bromopropionitrile (3.6 g, 0.025 mol) was added and the mixture was placed under an atmosphere of dry N_2 and refluxed for 16 hr. To the cooled mixture was added 100 ml of a 4% EtOH solution in H_2O with continued mechanical stirring. The organic phase was separated and the aqueous phase was extracted with two portions of Et_2O. The combined organics were washed with H_2O and brine, dried (Na_2SO_4), and stripped of solvent under reduced pressure. The dark amber oil (6.4 g) obtained was chromatographed on a column of Silicar CC-7, 100–200 mesh silica, with the product (1.69 g, 26%) being eluted as a colorless oil with 4:1 Skellysolve B–Et_2O. Spectral data (ir and nmr) were consistent for the desired structure.

Bis(*p*-chlorophenoxy)acetonitrile (3) and Bis(*m*-chlorophenoxy)acetonitrile (4). The bis(chlorophenoxy)acetic acids[9] were converted to the amides by standard methods. Treatment of the amides with $POCl_3$ and TEA[10] afforded 3 and 4.

Bis(*p*-chlorophenylthio)acetonitrile (5). Bis(*p*-chlorophenylthio)acetic acid[11] was converted to bis(*p*-chlorophenylthio)acetamide by standard methods, mp 129–130.5° (CCl_4). *Anal.* ($C_{14}H_{11}Cl_2NOS_2$) C, H, N, S. Distillation of this amide from P_2O_5[12] yielded the nitrile 5.

α-(*p*-Chlorophenoxy)-*p*-chlorophenylacetonitrile (6). α-(*p*-Chlorophenoxy)-*p*-chlorophenylacetic acid[13] was converted to α-(*p*-chlorophenoxy)-*p*-chlorophenylacetamide by standard methods, mp 128.5–131.5° (C_6H_6–Skellysolve B). *Anal.* ($C_{14}H_{11}Cl_2NO_2$) C, H, N. Treatment of the amide with $POCl_3$–TEA[10] afforded the nitrile 6.

Tetrazoles (Table II). Tetrazoles 8, 11, 12, and 14 were prepared by treating the requisite nitriles with NaN_3–NH_4Cl in DMF.[14]

5-[Bis(*p*-chlorophenoxy)methyl]tetrazole (10). Bis(*p*-chlorophenoxy)acetonitrile (3) was treated with NaN_3–NH_4Cl in DMF,[14] maintaining the reaction mixture at 85° for 22 hr (higher temperatures caused decomposition). Initial experiments gave material with mp 139–140.5°; however, subsequent preparations invariably yielded material melting at 151–152°. It is assumed that these represent two crystalline forms of 10 since analytical and spectral (ir and nmr) data for both forms are consistent with the structure.

5-[(*p*-Chlorophenoxy-*p*-chlorophenyl)methyl]tetrazole (13). The procedure of D'Orazio[15] was modified as described below. To a slurry of NaN_3 (2.41 g, 0.038 mol) in 10 ml of dry THF was added a solution of $AlCl_3$ (1.74 g, 0.013 mol) in 20 ml of dry THF. This mixture was stirred and refluxed for 15 min. A solution of α-(*p*-chlorophenoxy)-*p*-chlorophenylacetonitrile (2.9 g, 0.01 mol) in 10 ml of dry THF was then added and the stirred mixture was refluxed for 16 hr. The cooled mixture was acidified with 6 *N* HCl, the THF was removed under reduced pressure, and the residue was partitioned between Et_2O and H_2O. The aqueous phase was extracted with two additional portions of Et_2O and the combined organics were extracted with two portions of saturated $NaHCO_3$ solution. Reacidification of the bicarbonate extract (6 *N* HCl) gave an oil which was extracted into Et_2O. The Et_2O solution was washed with H_2O and brine, dried ($MgSO_4$), and stripped of solvent under reduced pressure. Trituration with 2-PrOH gave the product (0.78 g, 23.5%) as a white solid. Recrystallization from 2-PrOH–H_2O gave the pure tetrazole, mp 182–184°

2-[*p*-(1,2,3,4-Tetrahydro-1-naphthyl)phenoxy]-2-(5-tetrazolyl)propane (9) was prepared from the nitrile 2 as described above for the preparation of 13.

5-{β-[4-(*p*-Chlorophenyl)phenoxy]ethyl}tetrazole (15) was prepared from 4-(*p*-chlorophenyl)phenol and 5-(β-chloroethyl)tetrazole according to the method of Buchanan, *et al.*[2]

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