Hypotensive Agents. (+)- and (−)-2-Methoxy-2-(3-methoxyphenyl)-ethylamine and Related Compounds

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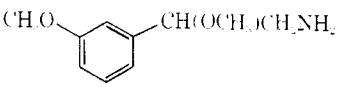
2-Methoxy-2-(3-methoxyphenyl)ethylamine (**1**) has been shown to produce a hypotensive effect in chloralosed cats at doses very much smaller than those which cause adverse effects. It appears to lower the blood pressure by inhibiting the pressor responses resulting from central nervous system reflex control and not by ganglionic blockade or peripheral adrenergic blockade. The hypotensive effect is produced by the (−) isomer of **1** and not by the (+) isomer. Nineteen analogs of **1** are described.

In a search for compounds which lower blood pressure, the new compound **1** was found to have interesting activity. It appeared to produce a hypotensive effect



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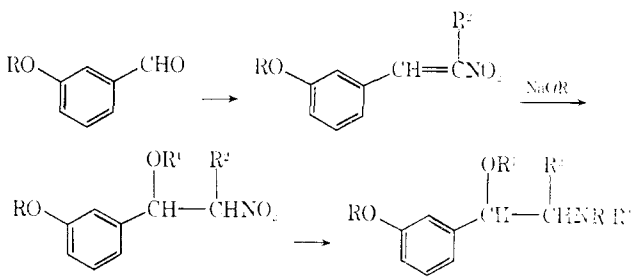
by a mechanism which involved neither ganglionic blockade nor peripheral adrenergic blockade. Related compounds (Tables I[1] and III[2]) were prepared for pharmacological examination. Several β-alkoxy-β-arylalkylamines have already been described.[3]

Those compounds where $R^3 = R^4 = H$ were prepared by the general route shown in Scheme I. Reduction of

Scheme I



the nitro compound was carried out conveniently with 5% Pd–charcoal and hydrogen under pressure (method A), or, when a group susceptible to catalytic hydrogenation or hydrogenolysis was present, with $LiAlH_4$ (method B).[3d] Compound **5** was prepared by catalytic reduction of the intermediate nitro compound in the presence of formaldehyde. Catalytic reductive alkylation of **1** in the presence of acetone gave **6**. Compound **7** was obtained by reducing the N-*n*-butyryl derivative of **1** with $LiAlH_4$. Under Eschweiler–Clarke conditions (HCHO + HCOOH) **1** was converted to **8**. Catalytic reduction of the allyl analog **14** gave the *n*-propyl analog **15**. No special attempt was made to separate the two possible racemates for each of **4** and **10**.

Intermediate nitro ethers were prepared by addition of alcohols to nitrostyrenes,[3a] which were themselves obtained by condensation of the appropriate aldehyde and nitroalkane. Those new intermediates which were purified are described in Table II; other intermediates were used without purification.

Compound **1** was resolved into its optical isomers. It was necessary to use both the (+) and (−) forms of tartaric acid to obtain the (+) and (−) forms of the base. The physical constants of various derivatives are given in Table III.

Biological Results and Discussion

The results of the screening test given in Table IV for the six most potent compounds were obtained as follows.[4] Cats were anesthetized with chloralose (80 mg/kg iv) and their blood pressures were recorded continuously. Three sets of pressor responses that were to serve as control values were obtained by (a) occluding the carotid arteries for a standard brief period, (b) administering a standard dose of 1-phenyl-4,4-dimethylpiperazinium chloride (PDP), and (c) administering a standard dose of norepinephrine. The test compound was then administered by continuous intravenous infusion during 20–30 min, the change in blood pressure was then noted, and the three sets of pressor responses were again obtained. The figures quoted in Table IV were calculated as follows. For compound **5** the blood pressure fell from a control value of 150 to 105 mm, *i.e.*, 30%; the control carotid occlusion response was +73% and that after administration of **5** was +24%, *i.e.*, the response had been reduced by 49%.

Compound **1**, which was given most attention, caused a fall in blood pressure, and when the carotid arteries were subsequently occluded the consequent pressor response was markedly less than that observed in the control period. When PDP or norepinephrine were subsequently administered intravenously, the consequent responses were greater than those observed in the control period. Since **1** does not reduce the pressor response to PDP, it must produce its hypotensive effect by a mechanism other than that which involves ganglionic blockade. Further, since it does not reduce the pressor response to norepinephrine it must produce its effect by a mechanism other than that which involves peripheral adrenergic blockade. The pressor response to carotid artery occlusion is of a reflex nature, and it is probable that **1** acts by a central reduction of sympathetic vasoconstrictor tone, that is to say, it produces its hypotensive effect by inhibiting the pressor responses resulting from central nervous system reflex control. This view of the mode of action is supported by

(1) A. D. Ainley and R. Howe, U. K. Patent Specification 1,017,691 (1962).

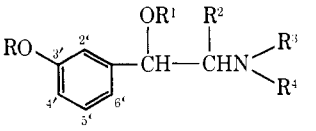
(2) R. Howe, U. K. Patent Specification 1,018,113 (1966).

(3) (a) K. W. Rosenmund, *Ber.*, **46**, 1034 (1913); (b) G. K. Elphick and J. A. Gunn, *J. Physiol.* (London), **81**, 422 (1934); (c) B. Reichert, *Arch. Pharm.*, **274**, 360 (1936); (d) K. W. Merz and J. Fink, *ibid.*, **289**, 347 (1955).

(4) Biological testing was carried out by Dr. J. W. Black and Mr. D. Donbop, whom we thank.

TABLE I

β-ALKOXY-β-PHENYLALKYLAMINES

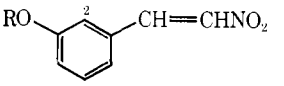


Compd	R	R¹	R²	R³	R⁴	Method[a]	Form	Crystn solvent[b]	Mp, °C	Formula	Analyses
1	CH_3	CH_3	H	H	H	A	HCl	Me_2CO	122	$C_{10}H_{16}ClNO_2$	C, H, N
2		2′-Chloro analog of 1				B	Hydrogen oxalate	H_2O	199–200[c]	$C_{22}H_{16}ClNO_6$	H, N; C[d]
3[e]		6′-MeO analog of 1				B	Base	P(60)[b]	66	$C_{11}H_{17}NO_3$	C, H, N
4[f]	CH_3	CH_3	CH_3	H	H	A	HCl	EtOAc–Me_2CO	135	$C_{11}H_{18}ClNO_2$	C, H, N
5	CH_3	CH_3	H	CH_3	H	g	HCl	MeOH–EtOAc	153–154	$C_{11}H_{18}ClNO_2$	C, H, N
6	CH_3	CH_3	H	$CH(CH_3)_2$	H	g	HCl	Me_2CO	127	$C_{13}H_{21}ClNO_2$	C, H, N
7	CH_3	CH_3	H	$(CH_2)_3CH_3$	H	g	Hydrogen oxalate	MeOH–EtOAc	186–187	$C_{16}H_{25}NO_6$	C, H, N
8	CH_3	CH_3	H	CH_3	CH_3	g	HCl	MeOH–EtOAc	172–173	$C_{12}H_{20}ClNO_2$	C, Cl, N; H[h]
9	CH_3	CH_2CH_3	H	H	H	A	HCl	MeOH–EtOAc	176–177	$C_{11}H_{18}ClNO_2$	C, H, Cl, N
10[i]	CH_3	CH_2CH_3	CH_3	H	H	A	Hydrogen oxalate	EtOH–EtOAc	142–143	$C_{14}H_{21}NO_6$	C, H, N
11	CH_3	$CH_2C_6H_5$	H	H	H	B	Hydrogen oxalate	MeOH–EtOAc	138–140	$C_{18}H_{21}NO_6$	C, H, N
12	CH_2CH_3	CH_3	H	H	H	A	HCl	MeOH–EtOAc	153–154	$C_{11}H_{18}ClNO_2$	C, H, Cl, N
13	CH_2CH_3	CH_2CH_3	H	H	H	A	HCl	MeOH–EtOAc	136–137	$C_{12}H_{20}ClNO_2$	C, H, Cl, N
14	$CH_2CH{=}CH_2$	CH_3	H	H	H	B	Oxalate	MeOH	200	$C_{29}H_{36}N_2O_8$	C, H, N
15	$(CH_2)_3CH_3$	CH_3	H	H	H	g	Oxalate hydrate	MeOH–EtOAc	188–189	$C_{29}H_{40}N_2O_8 \cdot H_2O$	C, H; N[j]
16	$CH_2C_6H_5$	CH_3	H	H	H	B	HCl	MeOH–EtOAc	190–191	$C_{16}H_{20}ClNO_2$	C, H, N
17	$CH_2C_6H_5$	CH_3	H	CH_3	CH_3	As 7	HCl	EtOAc	161	$C_{18}H_{24}ClNO_2$	C, N; H[k]
18	$CH_2C_6H_5$	CH_2CH_3	H	H	H	B	Oxalate hemihydrate	MeOH	194	$C_{36}H_{44}N_2O_8 \cdot 0.5H_2O$	C, H, N
19	$CH_2C_6H_5$	$CH_2C_6H_5$	H	H	H	B	Hydrogen oxalate hemihydrate	EtOAc	129	$C_{24}H_{25}NO_6 \cdot 0.5H_2O$	C, H, N
20	$CH_2C_6H_4Cl$-*p*	CH_3	H	H	H	B	Hydrogen oxalate	MeOH–EtOAc	167	$C_{18}H_{19}ClNO_6$	C, H, N

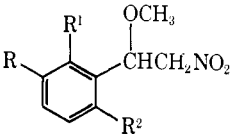
[a] Methods refer to Experimental Section. [b] P(60) is petroleum ether (bp 60–80°). [c] Melting point given in ref 1 was that of crude material. [d] C: calcd, 47.1; found, 46.6. [e] Compound kindly prepared by Dr. B. J. McLoughlin. [f] Nmr ($CDCl_3$) showed that this was a mixture (9:1) of isomers but it was not possible to assign configurations. [g] See Experimental Section. [h] H: calcd, 8.1; found, 7.4. [i] Nmr ($CDCl_3$) showed that this was a mixture (11:9) of isomers but it was not possible to assign configurations. [j] N: calcd, 5.3; found, 5.8. [k] H: calcd, 7.5; found, 7.0.

TABLE II

NITROSTYRENES AND β-METHOXY-β-PHENYLNITROETHANES



Compd	R	R¹	R²	Crystn solvent	Mp, °C	Formula	Analyses
21[a]	CH_3			EtOH	114–115	$C_9H_8ClNO_3$	C, H, N
22	CH_2CH_3			EtOH	104–105	$C_{10}H_{11}NO_3$	C, H, N
23	$CH_2CH{=}CH_2$			MeOH	61–63	$C_{11}H_{11}NO_3$	C, H, N
24	$CH_2C_6H_5$			C_6H_{12}	89	$C_{15}H_{13}NO_3$	C, H, N
25	$CH_2C_6H_4Cl$-*p*			EtOH	114	$C_{15}H_{12}ClNO_3$	C, H, Cl, N



26	CH_3O	Cl	H	MeOH	105	$C_{10}H_{12}ClNO_4$	C, H, N
27[b]	CH_3O	H	CH_3O	EtOH	62–63	$C_{11}H_{15}NO_5$	C, H, N
28	$C_6H_5CH_2O$	H	H	EtOH–H_2O	67–69	$C_{16}H_{17}NO_4$	C, H, N

[a] Has Cl in the 2 position of benzene ring. [b] Compound kindly prepared by Dr. B. J. McLoughlin. The intermediate 2,5-dimethoxy-β-nitrostyrene was described by H. Kauffmann, *Ber.*, **50**, 635 (1917).

the evidence that it causes neither a fall in cardiac output nor a direct vasodilatation. The precise mode of action is not known.

Estimates of the acute toxicity (LD_{50}) of compound **1** in mice were made. When given orally it has an LD_{50} of 700–750 mg/kg and when administered intravenously it has an LD_{50} of 50–55 mg/kg.

The (−) isomer of **1**·HCl (*i.e.*, **34**) was approximately twice as potent as the racemic form of **1**. At 1.5 and 0.75 mg/kg it caused a fall in blood pressure of 40 and 25%, respectively. The (+) isomer of **1**·HCl (*i.e.*, **33**) has no hypotensive effect at similar doses.

The most potent compounds in the series were those with structures very close to that of **1**. Compounds in which one or both of the methoxy groups are replaced with ethoxy groups (**9**, **12**, and **13**) and two of the three secondary amine analogs of **1** (**5** and **7**) had a good level of activity. Potency fell away sharply for the other compounds. Two of the six compounds in Table IV potentiated the carotid occlusion response (one only slightly) which serves to underline the doubt about the mode of action of this type of compound.

Experimental Section[5]

The general experimental methods A and B are representative

(5) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of theoretical values.

TABLE III

ISOMERS OF COMPOUND 1 AND THEIR SALTS

No.	Compd	Final crystn solvent	Bp (mm) or mp, °C	$[\alpha]^{25}D$, deg	Concn in H_2O, %	Formula	Analyses
29	(+)-1 hydrogen (+)-tartrate	MeOH	162–163	+76.0	1.01	$C_{14}H_{21}NO_8$	C, H, N
30	(−)-1 hydrogen (−)-tartrate	MeOH	162–163	−75.6	1.0	$C_{14}H_{21}NO_8$	C, H, N
31	(+)-1		103–107 (1.3 mm)[a]	+77.1	1.07	$C_{10}H_{15}NO_2$	C, H, N
32	(−)-1		103–107 (1.3 mm)[b]	−77.9	1.04	$C_{10}H_{15}NO_2$	C, H, N
33	(+)-1 hydrochloride	MeOH–EtOAc	124–125	+96.0	1.01	$C_{10}H_{16}ClNO_2$	C, H, Cl, N
34	(−)-1 hydrochloride	MeOH–EtOAc	124–125	−95.6	1.0	$C_{10}H_{16}ClNO_2$	C, H, Cl, N
35	(+)-1 hydrogen (−)-tartrate	MeOH–EtOAc	154	+49.0	1.01	$C_{14}H_{21}NO_8$	C, H, N
36	(−)-1 hydrogen (+)-tartrate	MeOH–EtOAc	154	−49.3	1.01	$C_{14}H_{21}NO_8$	C, H, N

[a] $n^{20}D$ 1.5260. [b] $n^{24}D$ 1.5261.

TABLE IV

EFFECT ON BLOOD PRESSURE

		% change in			
Compd	Total dose, mg/kg	Blood pressure	Carotid occlusion pressor response	PDP pressor response	Norepinephrine pressor response
1	1.5	−26	−37	+19	+39
	2.5	−30	−35	+150	+117
	5.0	−55	−53	+230	+280
	5.0[a]	−29	−31	−141	+45
5	2.0	−30	−49	+54	+26
7	6.0	−29	+5	+48	+31
9	6.0	−30	−53	+10	+111
12	1.0	−30	+33	+31	+2
13	3.0	−29	−18	+50	+26

[a] Administered intraduodenally.

for the compounds reported in Table I. Melting points and recrystallizing solvents given in the tables are usually not repeated in the text.

1-(3-Methoxyphenyl)-2-nitroethyl Methyl Ether.—A solution of 3-methoxy-β-nitrostyrene[6] (20 g, 0.112 mole) in MeOH (400 ml) at 60° was cooled rapidly to 20° and then a solution of Na (5.2 g, 2 equiv) in MeOH (100 ml) was added rapidly. The mixture was shaken for 5 min and then AcOH (16 ml) was added. The mixture was shaken for 5 min more, poured into H_2O (3 l.), and then extracted with Et_2O. The dried extract was evaporated to give 1-(3-methoxyphenyl)-2-nitroethyl methyl ether as an oil (22.3 g, 95%).

A. 2-Methoxy-2-(3-methoxyphenyl)ethylamine (1).—A solution of 1-(3-methoxyphenyl)-2-nitroethyl methyl ether (21.5 g) in AcOH (100 ml) and H_2SO_4 (4 *N*, 25 ml), and 5% Pd–C (1 g) was hydrogenated under pressure at room temperature until absorption of H_2 was complete (10 hr). The mixture was filtered and the filtrate was evaporated to about 40 ml *in vacuo*. H_2O (100 ml) was added and the mixture was extracted with Et_2O. The acidic aqueous solution was basified and extracted with Et_2O giving **1** as an oil, bp 103–107° (1.3 mm). Ethereal HCl was added to a solution of the base Et_2O: 1·HCl separated (10.3 g, 46%): nmr (on **1** base in $CDCl_3$) τ 2.70–2.85 (m, ArH at C-2, 1), 3.10–3.30 (m, ArH, 3), 5.90 (t, $CH(OCH_3)$, 1), 6.25 (s, $ArOCH_3$, 3), 6.75 (s, $CH(OCH_3)$ 3), 7.0–7.3 (br s, CH_2NH_2, 2), 7.7–8.2 (br s exchanged with D_2O, NH_2, 2).

B. 2-(3-Allyloxyphenyl)-2-methoxyethylamine (14).—A solution of 1-(3-allyloxyphenyl)-2-nitroethyl methyl ether (17 g) in Et_2O (60 ml) was added during 30 min to a stirred suspension of $LiAlH_4$ (6 g) in Et_2O (300 ml) and then the mixture was heated under reflux for 16 hr. The mixture was cooled, and ice and H_2O (30 g) were added and then NaOH (1 *N*, 300 ml). The organic material was isolated by extraction with Et_2O. This extract was washed with HCl (0.5 *N*) and then the acid washings were basified and extracted with Et_2O. This extract gave **14** as an oil (8.8 g, 59%). It was converted to its oxalate with the appropriate amount of $(COOH)_2$ in Me_2CO.

3-Allyloxybenzaldehyde.—3-Hydroxybenzaldehyde (100 g, 0.82 mole), K_2CO_3 (115 g, 0.83 mole), allyl bromide (100 g, 0.82 mole), and EtOH (125 ml) were heated under reflux for 4 hr, cooled, and then poured into H_2O (1 l.). The mixture was extracted with Et_2O. The dried Et_2O extract yielded 3-allyloxybenzaldehyde, bp 87–89° (0.9–1.1 mm).

N-[2-Methoxy-2-(3-methoxyphenyl)ethyl]methylamine (5).—1-(3-Methoxyphenyl)-2-nitroethyl methyl ether (6.3 g), formalin (40%, 2.6 ml), concentrated HCl (3.1 ml), PtO_2 (0.3 g), 5% Pd–C (0.1 g), and EtOH (20 ml) were hydrogenated at room temperature and 100 atm. The mixture was filtered and the filtrate was evaporated. The residual oil was shaken with HCl (1 *N*, 100 ml) and Et_2O (60 ml). The aqueous acidic solution was basified and extracted with Et_2O. The extract contained **5** (3.1 g, 53%) which was converted to its HCl salt by ethereal HCl.

N-Isopropyl-2-methoxy-2-(3-methoxyphenyl)ethylamine (6).—Compound **1**·HCl (5.7 g), Me_2CO (2 ml), H_2O (30 ml), and 5% Pd–C (0.5 g) were hydrogenated at 75° and 90 atm. The mixture was filtered and the filtrate was evaporated to dryness *in vacuo* to yield **6** (3.55 g, 52%).

N-*n*-Butyl-2-methoxy-2-(3-methoxyphenyl)ethylamine (7).—Compound **1** base (5 g, 0.028 mole), $(n\text{-PrCO})_2O$ (5 g, 0.032 mole), and *n*-$PrCO_2H$ (10 ml) were heated at 100° for 1 hr, cooled, and poured into H_2O (500 ml). The mixture was extracted with Et_2O; the extract was washed with NaOH (1 *N*) and then dried and evaporated. The residual N-*n*-butyryl-2-methoxy-2-(3-methoxyphenyl)ethylamine (6.5 g) in Et_2O (100 ml) was added to a stirred suspension of $LiAlH_4$ (5 g) in Et_2O (350 ml). The mixture was heated under reflux for 2 hr and cooled, and then H_2O (30 ml) was added. The mixture was filtered and the solid residue was washed with Et_2O. The combined Et_2O solutions yielded **7** which was converted to the hydrogen oxalate (3.0 g, 33%).

N,N-Dimethyl-2-methoxy-2-(3-methoxyphenyl)ethylamine (8).—Compound **1** base (2 g), HCO_2H (98%, 10 ml), and formalin (40%, 10 ml) were heated at 100° for 16 hr and then evaporated to dryness *in vacuo*. NaOH (1 *N*, 25 ml) was added and the mixture was extracted with Et_2O. The extract yielded **8** (1.4 g, 61%).

2-Methoxy-2-(3-*n*-propyloxyphenyl)ethylamine (15).—Compound **13** oxalate (1 g) in EtOH (75 ml) and PtO_2 (0.2 g) were shaken in hydrogen (1 atm) at room temperature. The mixture was filtered and the filtrate was evaporated to dryness. The residual solid was **15** oxalate (0.75 g, 71%).

3-Benzyloxy-β-nitrostyrene (24).—A solution of 3-benzyloxybenzaldehyde[7] (9.0 g) and ammonium acetate (3.6 g) in CH_3NO_2 (4.5 ml) and AcOH (36 ml) was heated under reflux for 2 hr and then poured into H_2O. Compound **24** (10 g, 92%) separated as a solid.

3-(4-Chlorobenzyloxy)benzaldehyde.—3-Hydroxybenzaldehyde (41 g, 0.33 mole) was added to a solution of Na (7.6 g, 1 equiv) in EtOH (100 ml). A solution of 4-chlorobenzyl chloride (57.2 g, 0.355 mole) in EtOH (100 ml) was added and the mixture was stirred under reflux for 4 hr. The EtOH was evaporated, Et_2O (500 ml) was added, and the mixture was washed with NaOH (2 *N*) and then with H_2O. The dried Et_2O solution was evaporated and the residual oil was distilled, bp 166–168° (0.8 mm), 58 g (71%). 3-(4-Chlorobenzyloxy)benzaldehyde had mp 50° from EtOH. *Anal.* ($C_{14}H_{11}ClO_2$) C, H, Cl.

(+)-1 Hydrogen (+)-Tartrate (29).—A solution of (±)-1 base (16.1 g, 0.089 mole) in Me_2CO (100 ml) was added to a stirred solution of (+)-tartaric acid (13.35 g, 0.089 mole) in Me_2CO (400 ml) at 50°. Stirring was continued for 5 min and then the mixture was allowed to cool to room temperature. The mixture was filtered and the filtrate was retained for further examination.

(6) J. B. Shoesmith and R. J. Connor, *J. Chem. Soc.*, 2230 (1927).

(7) R. Robinson and P. C. Young, *ibid.*, 1111 (1935).

The residual solid, mp 110–120°, $[\alpha]^{21}D$ +10.7° (*c* 1.0, H_2O), was crystallized from MeOH until the rotation became constant. Thus **29** (6.6 g, 45%) was obtained. The free base (+)-**1** (**31**), (+)-**1**·HCl (**33**), and (+)-**1** hydrogen (−)-tartrate (**35**) were obtained by conventional methods.

(−)-**1 Hydrogen (−)-Tartrate** (**30**).—The retained filtrate and the crystallization mother liquors from the preparation of **29** were combined and evaporated. NaOH (2 *N*) and saturated aqueous NaCl (100 ml) were added and the mixture was extracted with Et_2O (130 ml, three times). The extract yielded optically impure (−)-**1** base, $[\alpha]^{21}D$ −30° (*c* 2.2, EtOH). This (−)-**1** base (13.1 g) in MeOH (60 ml) was added to a solution of (−)-tartaric acid (10.8 g) in MeOH (60 ml) at room temperature. The solid which separated, mp 151–154°, $[\alpha]^{21}D$ −56.5° (*c* 1.06, H_2O), was crystallized from MeOH until the rotation became constant. Thus **30** (6.6 g, 45%) was obtained.

Hypocholesterolemic 5-Substituted Tetrazoles[1]

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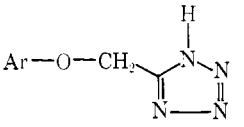
A number of 5-aryloxyalkyl-, 5-arylthioalkyl-, and 5-anilinoalkyltetrazoles, along with a few other related 5-substituted tetrazoles, were synthesized by standard methods. A novel tetrazolylethylation reaction was used to synthesize 5-[β-(3-chlorophenoxy)ethyl]tetrazole (**53**) and 5-[β-(3-chlorophenylthio)ethyl]tetrazole (**68**). In general, the 5-arylthioalkyltetrazoles provided the best combination of high hypocholesterolemic activity and low toxicity.

It is well known that 5-substituted tetrazoles and their carboxylic acid analogs have comparable dissociation constants.[2,3] In some cases this physiochemical analogy has been reflected in similar biological activities.[4–9]

In connection with other studies, it was discovered that 5-aryloxymethyltetrazoles (I) were inhibitors of cholesterol biosynthesis from acetate-**1**-^{14}C *in vitro*.[10] Follow-up *in vivo* studies revealed that these compounds, although somewhat toxic, lowered normal serum cholesterol levels in rats. The plant growth hormone activity of some compounds of type I has been reported by McManus and Herbst.[5] In view of the similarity of these compounds to the known serum lipid lowering agent ethyl α-(4-chlorophenoxy)isobutyrate (clofibrate),[11] whose active principle is the corresponding carboxylic acid, a number of compounds of general structure II were synthesized.



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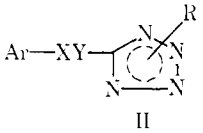


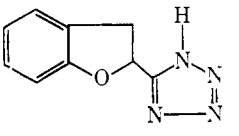
II

X = O, S, SO_2, NH

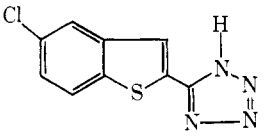
Y = $C_n \longrightarrow C_4$ alkyl (straight or branched chain), NH

R = H, CH_3

The bicyclic dihydrobenzofuran and benzothiophene derivatives III and IV (compounds **86** and **87** in Table III) were also prepared.



III



IV

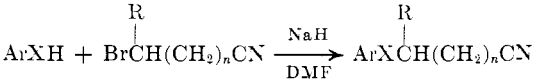
The object of these synthetic modifications was to obtain compounds which combined potent hypocholesterolemic activity with low toxicity. This paper describes the preparation and some physical properties of these 5-substituted tetrazoles along with the preliminary hypocholesterolemic screening data.

Chemistry.—In most cases the syntheses involved the preparation of the requisite nitriles (Table II), which were then converted to the desired tetrazoles (Table III) by standard methods.

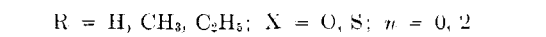
Where carboxylic acids were used as starting materials, conversions to the corresponding amides (Table I) were effected by accepted methods. These amides were then converted to nitriles (Table II) either by vacuum distillation from P_2O_5[12] or by reaction with $POCl_3$ and Et_3N.[9]

The aryloxy- and arylthioacetonitriles were prepared by refluxing the appropriate phenols or thiophenols with chloroacetonitrile in a slurry of K_2CO_3 in acetone[5] or in NaOMe–MeOH.[13] Homologs (straight or branched chain) were prepared by base-induced condensations of the phenols or thiophenols with bromoalkylnitriles or acrylonitrile[14] (Scheme I).

SCHEME I



R = H, CH_3, C_2H_5; X = O, S; *n* = 0, 2



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