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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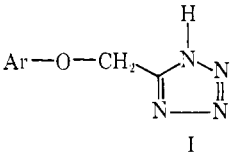
Received March 17, 1969

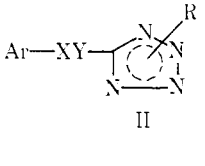
A number of 5-aryloxyalkyl-, 5-arylthioalkyl-, and 5-anilinoalkyltetrazoles, along with a few other related 5-substituted tetrazoles, were synthesized by standard methods. A novel tetrazolylethylation reaction was used to synthesize 5-[β-(3-chlorophenoxy)ethyl]tetrazole (**53**) and 5-[β-(3-chlorophenylthio)ethyl]tetrazole (**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.



I



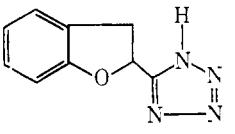
II

X = O, S, SO_2, NH

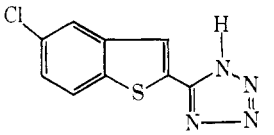
Y = C_n → C_4 alkyl (straight or branched chain), NH

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

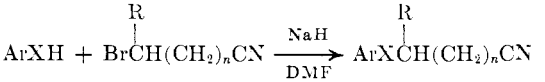
The object of these synthetic modifications was to obtain compounds which combined potent hypocholesterolemic activity with low toxicity. This paper describes the preparation and some physical properties of these 5-substituted tetrazoles along with the preliminary hypocholesterolemic screening data.

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.

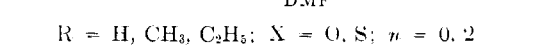
Where carboxylic acids were used as starting materials, conversions to the corresponding amides (Table I) were effected by accepted methods. These amides were then converted to nitriles (Table II) either by vacuum distillation from P_2O_5[12] or by reaction with $POCl_3$ and Et_3N.[9]

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



(1) Some of these compounds have been described by R. L. Buchanan and R. A. Partyka, U. S. Patent 3,337,576 (1967).

(2) F. R. Benson, *Chem. Rev.*, **41**, 1 (1947).

(3) R. M. Herbst, "Essays in Biochemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p 141.

(4) C. van de Westeringh and H. Veldstra, *Rec. Trav. Chim.*, **77**, 1107 (1958).

(5) J. M. McManus and R. M. Herbst, *J. Org. Chem.*, **24**, 1464, (1959).

(6) J. K. Elwood, R. M. Herbst, and G. L. Kilgour, *J. Biol. Chem.*, **240**, 2073 (1965).

(7) B. Brouwer-van Straaten, D. Solinger, C. van de Westeringh, and H. Veldstra, *Rec. Trav. Chim.*, **77**, 1129 (1958).

(8) C. F. Holland and J. N. Pereira, *J. Med. Chem.*, **10**, 149 (1967).

(9) P. F. Juby, T. W. Hudyma, and M. Brown, *ibid.*, **11**, 111 (1968).

(10) Unpublished results.

(11) Atromid-S®, CPIB; J. M. Thorp and W. S. Waring, *Nature*, **194**, 948 (1962), and many subsequent papers.

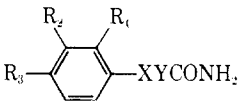
(12) R. E. Kent and S. M. McElvain, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 493.

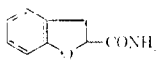
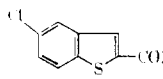
(13) R. Dijkstra and H. J. Backer, *Rec. Trav. Chim.*, **73**, 569 (1954).

(14) S. A. Heininger (to Monsanto), U. S. Patent 2,819,291 (1958).

Table I

Amides

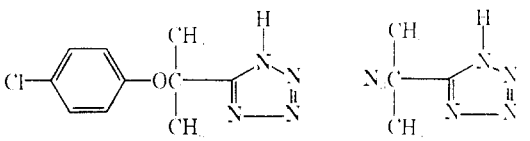


No.	R_2	R_4	R_3	X	Y	Method	Yield, %	Recrystn solvent[a]	Mp, °C	Formula	Analyses
1	H	H	Cl	O	$CH(CH_3)$	A	90.3	A	118.5–120	$C_9H_{10}ClNO_2$	C, H, N
2	H	H	Cl	O	$C(CH_3)_2$	A	97.3	A	122–124[b]	$C_{10}H_{12}ClNO_2$	
3	H	H	Cl	S	$CH(CH_3)$	A	95	A	120–128	$C_9H_{10}ClNOS$	C, H, Cl, N, S
4	H	H	Cl	S	$C(CH_3)_2$	A	97.8	A	166–169	$C_{10}H_{12}ClNOS$	C, H, Cl, N
5	H	H	Br	S	$C(CH_3)_2$	A	80.5	A or A–B	100.5–103.5	$C_{10}H_{12}BrNOS$	H, N; C[c]
6	H	NO_2	H	NH	CH_2	C	17	A	161.5–163.5	$C_8H_9N_3O_4$	C, H, N
7						B	71.7	A	150–152[d]	$C_{11}H_9NO_2$	
8						A	90.8	C–B	168–172 dec[e]	C_9H_6ClNOS	

[a] A, *i*-PrOH; B, Skellysolve B (bp 60–80°); C, $CHCl_3$. [b] H. Gilman and G. R. Wilder, *J. Amer. Chem. Soc.*, **77**, 6644 (1955). [c] Calcd, 43.80; found, 44.30. [d] See ref 25. [e] Used in the crude state.

The anilinoacetonitriles were prepared by treating the appropriate anilines with formaldehyde bisulfite followed by KCN.[15] 4-Chlorophenyl thiocyanate (**21**) and β-(2-chlorophenyl)propionitrile (**43**) were prepared as previously described.[16,17]

The nitriles were converted to tetrazoles by treatment with NH_4N_3 in DMF[18] or with $Al(N_3)_3$ in THF.[19] The latter method proved to be the one of choice in the preparation of V (**58**, Table III). When NH_4N_3–DMF was used, V was susceptible to cleavage by azide, giving the azidotetrazole VI as the major isolated product.



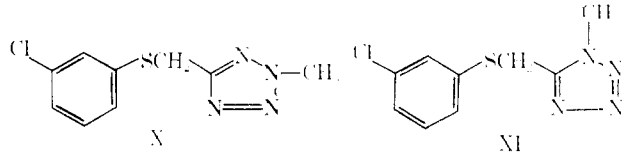
V VI

A novel tetrazolylethylation reaction sequence was used in the preparation of 5-[β-(3-chlorophenoxy)-ethyl]tetrazole (VIII) (**53**, Table III) and 5-[β-(3-chlorophenylthio)ethyl]tetrazole (IX) (**68**, Table III) as outlined in Scheme II. 5-(β-Chloroethyl)tetrazole (VII) was prepared in good yield by the reaction of β-chloropropionitrile with $Al(N_3)_3$ in THF. Reaction of the sodium salt VII with the anion of 3-chlorophenol or 3-chlorothiophenol in DMF afforded VIII and IX.

Tetrazolylethylation proved to be the method of choice in the preparation of VIII. When 3-chlorophenol was cyanoethylated, the resulting 3-chlorophenoxypropionitrile was susceptible to spontaneous reverse Michael cleavage to starting materials. Reaction of this nitrile with NH_4N_3–DMF also caused cleavage to 3-chlorophenol.

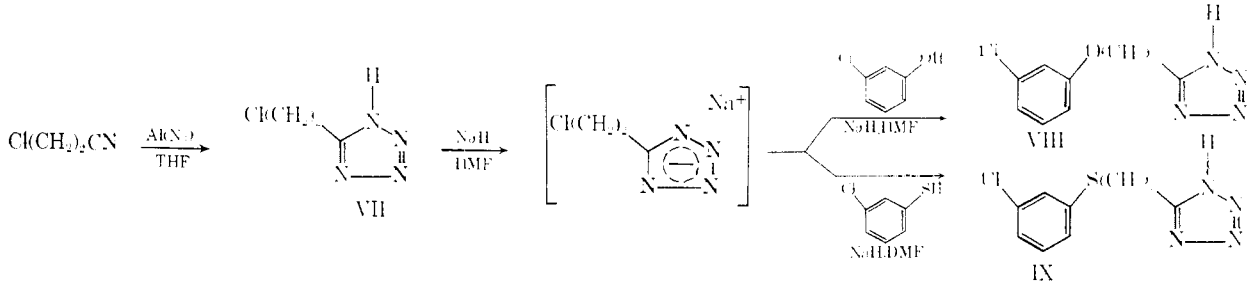
The method of Jensen and Pedersen[20] was used to prepare 5-(4-chlorobenzenesulfonamido)tetrazole (**77**) from 4-chlorobenzenesulfonyl chloride and 5-aminotetrazole monohydrate.

The N-methyltetrazoles X and XI (**88** and **89**, Table III) were prepared by treating the free tetrazole with CH_2N_2 in Et_2O. Structural assignments were made on the basis of the chemical shifts of the N-methyl protons in the nmr spectra.[21]



X XI

Scheme II

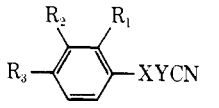


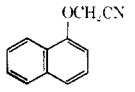
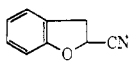
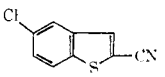
VII VIII IX

Structure–Activity Relationships.—In the hypocholesterolemic screen the tetrazoles were administered orally to rats once daily for 4 days (0.5% suspension in carboxymethylcellulose). Initial screening was carried out at a dose of 400 mg/kg. Serum cholesterol values were determined employing the Technicon auto-

(15) E. Knoevenagel, *Ber.*, **37**, 4073 (1904).
(16) L. Gattermann and W. Haussknecht, *ibid.*, **23**, 738 11890).
(17) A. D. Grebenyuk and I. P. Tsukervanik, *Zh. Obshch. Khim.*, **25**, 286 (1955); *J. Gen. Chem. USSR*, **25**, 269 (1955).
(18) W. G. Finnegan, R. A. Henry, and R. L. Lofquist, *J. Amer. Chem. Soc.*, **80**, 3908 (1958).
(19) V. T. D'Orazio, Ph.D. Thesis, Michigan State University, 1963, p 20.
(20) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15**, 991 (1961).
(21) J. H. Markgraf, W. T. Baehmann, and D. P. Hollis, *J. Org. Chem.*, **30**, 3472 (1965).

TABLE II
NITRILES

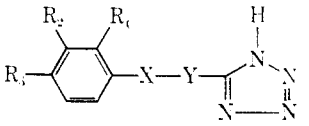


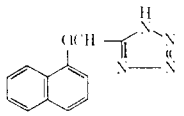
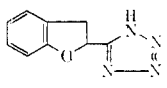
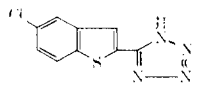
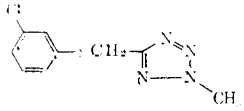
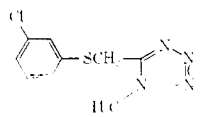
No.	R_1	R_2	R_3	X	Y	Method	Yield, %	Recrystn solvent[a]	Mp or bp (mm), °C	Formula	Analyses
9	H	H	H	O	CH_2	A	74.3		72–78 (1)[i]	C_8H_7NO	
10	H	H	Cl	O	CH_2	A	90.6	A–B	44–47[j]	C_8H_6ClNO	
11	H	Cl	H	O	CH_2	A	68.2		89–93 (0.2–0.3)[j]	C_8H_6ClNO	
12	Cl	H	H	O	CH_2	A	51.5		102–106 (0.3)[i]	C_8H_6ClNO	
13	Cl	Cl	H	O	CH_2	A	99	B	85–88[j]	$C_8H_5Cl_2NO$	
14	H	CF_3	H	O	CH_2	A	84.8		81–85 (0.1)	$C_9H_6F_3NO$	C, H, N
15	H	Cl	H	O	$(CH_2)_2$	F	35.6		103–108[k] (0.1)	C_9H_8ClNO	
16	H	Cl	H	O	$(CH_2)_3$	E	62.2		113–120 (0.07)	$C_{10}H_{10}ClNO$	C, H; N[e]
17	H	H	Cl	O	$CH(CH_3)$	B	91.1		75–80 (0.15–0.17)	C_9H_8ClNO	C, H, Cl, N
18	H	Cl	H	O	$CH(CH_3)$	E	67.1		83–88 (0.1)	C_9H_8ClNO	C, H, N
19	H	Cl	H	O	$CH(C_2H_5)$	E	26.5		76–82 (0.15–0.2)	$C_{10}H_{10}ClNO$	H, Cl, N; C[c]
20	H	H	Cl	O	$C(CH_3)_2$	B	81.0		78–80 (0.4)	$C_{10}H_{10}ClNO$	C, H, Cl, N
21	H	H	Cl	S		H	64.9		*l*	C_7H_4ClNS	
22	H	H	H	S	CH_2	D	83.9		118–123[m] (0.4)	C_8H_7NS	
23	H	H	Cl	S	CH_2	A	82.3	C	84.5–87[n]	C_8H_6ClNS	
24	H	Cl	H	S	CH_2	A	70.3	D–A	50–52	C_8H_6ClNS	C, H, Cl, N, S
25	Cl	H	H	S	CH_2	A	79.8		116–125[n] (0.25–0.35)	C_8H_6ClNS	
26	H	H	F	S	CH_2	A	54.7		84–92 (0.1)	C_8H_6FNS	C, H; N[d]
27	H	H	NO_2	S	CH_2	A	58.7	C	83.5–85.5, 158–170 (0.1–0.2)	$C_8H_6N_2O_2S$	C, H, N, S
28	H	H	CH_3O	S	CH_2	A	97.4		*l*,*n*	C_9H_9NOS	
29	H	CF_3	H	S	CH_2	A	75.5		83–94 (0.03–0.3)	$C_9H_6F_3NS$	C, H, N
30	H	Cl	H	S	$(CH_2)_3$	E	75.7		129–132 (0.07)	$C_{10}H_{10}ClNS$	C, H; N[e]
31	H	H	Cl	S	$CH(CH_3)$	B	87	A	46–47, 95–97 (0.35)	C_9H_8ClNS	C, H, N
32	H	Cl	H	S	$CH(CH_3)$	E	62.4		80–85 (0.03)	C_9H_8ClNS	C, H, N, S
33	Cl	H	H	S	$CH(CH_3)$	E	65.5		82.5–86 (0.1)	C_9H_8ClNS	C, H, Cl, N, S
34	H	H	CH_3O	S	$CH(CH_3)$	E	77.5		98–103 (0.15)	$C_{10}H_{11}NOS$	C, H, N; S[f]
35	H	H	Cl	S	$C(CH_3)_2$	B	81.4	A	51.5–53.5, 87–92 (0.15)	$C_{10}H_{10}ClNS$	H, Cl; C,[g] N[h]
36	H	H	Br	S	$C(CH_3)_2$	B	83	A	50–52	$C_{10}H_{10}BrNS$	C, H, N
37	H	H	H	NH	CH_2	G	64.7		130–140[o] (0.35–0.5)	$C_8H_8N_2$	
38	H	H	Cl	NH	CH_2	G	62.9	E–A	67–68.5	$C_8H_7ClN_2$	C, H, Cl, N
39	H	Cl	H	NH	CH_2	G	51.5		148–152 (0.25–0.75)	$C_8H_7ClN_2$	C, H, Cl, N
40	H	NO_2	H	NH	CH_2	C	34.2	D	97–100	$C_8H_7N_3O_2$	C, H, N
						G	10.8				
41	H	H	CH_3O	NH	CH_2	G	75.5	C	75.5–78	$C_9H_{10}N_2O$	C, H, N
42	H	CF_3	H	NH	CH_2	A	46.5		115–116 (0.1)	$C_9H_7F_3N_2$	C, H, N
43	Cl	H	H		$(CH_2)_2$	I	18.9		150–157[p] (25)	C_9H_8ClN	
44						A	89.6		137–160[p] (0.5)	$C_{12}H_9NO$	
45						C	73.9		86–87[l] (0.2)	C_9H_7NO	
46						C	*r*		*l*	C_9H_4ClNS	

[a] A, Skellysolve B (bp 60–80°); B, 100% EtOH; C, *i*-PrOH; D, $CHCl_3$; E, EtOAc. [b] N: calcd, 7.16; found, 6.54. [c] C: calcd, 61.39; found, 60.87. [d] N: calcd, 8.38; found, 7.95. [e] N: calcd, 6.62; found, 6.06. [f] S: calcd, 16.59; found, 15.79. [g] C: calcd, 56.73; found, 56.28. [h] N: calcd, 6.62; found, 6.17. [i] See ref 5. [j] A. Campbell (to Parke, Davis & Co.), U. S. Patent 3,139,455 (1964). [k] H. Ufer (to I. G. Farben. A.-G.), German Patent 670,357 (1939). [l] Used in the crude state. [m] See ref 13. [n] G. H. Hitchings, E. A. Falco, and B. Roth (to Burroughs-Wellcome and Co., U.S.A.), U. S. Patent 2,953,567 (1960). [o] See ref 15. [p] See ref 17. [q] M. Julia, *Bull. Soc. Chim. Fr.*, 1363 (1956). [r] Not determined.

Table III

Tetrazoles



No.	R_1	R_2	R_3	X	Y	Method	Yield, %	Recrystn solvent[a]	Mp, °C	Formula	Analyses
47	H	H	H	O	CH_2	B	99	A	123–126[f]	$C_8H_8N_4O$	
48	H	H	Cl	O	CH_2	B	83.6	A–B	164–167[g]	$C_8H_7ClN_4O$	
49	H	Cl	H	O	CH_2	B	99.8	A–B	117.5–119.5	$C_8H_7ClN_4O$	C, H, N
50	Cl	H	H	O	CH_2	B	96.4	C	127–132[g]	$C_8H_7ClN_4O$	
51	Cl	Cl	H	O	CH_2	B	91	D–E	135–136	$C_8H_6Cl_2N_4O$	C, H, Cl, N
52	H	CF_3	H	O	CH_2	B	93.2	A–B or F–G	113.5–116	$C_9H_7F_3N_4O$	C, H, N
53	H	Cl	H	O	$(CH_2)_2$	B	34.4	F–G	128–130	$C_9H_9ClN_4O$	C, H, N
						C	46.7				
54	H	Cl	H	O	$(CH_2)_3$	B	53.8	F–G	84–86	$C_{10}H_{11}ClN_4O$	C, H, N
55	H	H	Cl	O	$CH(CH_3)$	B	78.6	F–G	94–96	$C_9H_9ClN_4O$	C, H, Cl, N
56	H	Cl	H	O	$CH(CH_3)$	B	87.7	F–G	106.5–108	$C_9H_9ClN_4O$	C, H, N
57	H	Cl	H	O	$CH(C_2H_5)$	B	87.8	D–H	84–88	$C_{10}H_{11}ClN_4O$	[g]
58	H	H	Cl	O	$C(CH_3)_2$	A	55.4	F	136–139 dec	$C_{10}H_{11}ClN_4O$	C, H, N
59	H	H	Cl	S		B	23.4	F	152.5–154.5 dec[e]	$C_7H_5ClN_4S$	
60	H	H	H	S	CH_2	B	80.9	F	114–116	$C_8H_8N_4S$	C, H, N, S
61	H	H	Cl	S	CH_2	B	82	A–B	158–159	$C_8H_7ClN_4S$	C, H, N
62	H	Cl	H	S	CH_2	B	86.7	I	126–128	$C_8H_7ClN_4S$	C, H, Cl, N, S
63	Cl	H	H	S	CH_2	B	72	D–A or F	104–107	$C_8H_7ClN_4S$	C, H, Cl, N, S
64	H	H	F	S	CH_2	B	76.6	F	137.5–139	$C_8H_7FN_4S$	C, H, N
65	H	H	NO_2	S	CH_2	B	17.4	I	151–153	$C_8H_7N_5O_2S$	C, H, N, S
66	H	H	CH_3O	S	CH_2	B	78.7	I	137–141	$C_9H_{10}N_4OS$	C, H, N
67	H	CF_3	H	S	CH_2	B	60.3	J–K	97.5–98.5	$C_9H_7F_3N_4S$	C, H, N
68	H	Cl	H	S	$(CH_2)_2$	C	80.0	A–I	99.5–102	$C_9H_9ClN_4S$	C, H, N
69	H	Cl	H	S	$(CH_2)_3$	B	92.9	F–G	78–81	$C_{10}H_{11}ClN_4S$	C, H, N
70	H	H	Cl	S	$CH(CH_3)$	B	85.2	I	169.5–171 dec	$C_9H_9ClN_4S$	C, H, N, S
71	H	Cl	H	S	$CH(CH_3)$	B	80.5	F–G or I	115–117	$C_9H_9ClN_4S$	C, H, Cl, N, S
72	Cl	H	H	S	$CH(CH_3)$	B	88.5	F–G	114.5–115.5	$C_9H_9ClN_4S$	C, H, N, S
73	H	H	CH_3O	S	$CH(CH_3)$	B	96.1	I	155–158	$C_{10}H_{12}N_4OS$	C, H, N, S
74	H	H	Cl	S	$C(CH_3)_2$	A	43.3	F–K (10:1)	181–184 dec	$C_{10}H_{11}ClN_4S$	C, H, Cl, N
75	H	H	Br	S	$C(CH_3)_2$	B	92.6	F	192.5–194.5	$C_{10}H_{11}BrN_4S$	C, H, Br, N
76	H	H	Cl	SO_2	CH_2	D	63.2	I	213.5–215.5 dec	$C_8H_7ClN_4O_2S$	H, N, S; C[h]
77	H	H	Cl	SO_2	NH	E	13.2	D–K	194–195 dec	$C_7H_6ClN_5O_2S$	C, H, N, S
78	H	H	H	NH	CH_2	B	59	I	150.5–153 dec	$C_8H_9N_5$	C, H, N
79	H	H	Cl	NH	CH_2	B	57.9	A	179.5–181 dec	$C_8H_8ClN_5$	C, H, Cl, N
80	H	Cl	H	NH	CH_2	B	51.1	A	155–157 dec	$C_8H_8ClN_5$	C, H, Cl, N
81	H	NO_2	H	NH	CH_2	B	56.2	I	157–159	$C_8H_8N_6O_2$	C, H, N
82	H	H	CH_3O	NH	CH_2	B	87.9	A or I	135–138 dec	$C_9H_{11}N_5O$	C, H, N
83	H	CF_3	H	NH	CH_2	B	80.5	A–I	171–174 dec	$C_9H_8F_3N_5$	C, H, N
84	Cl	H	H		$(CH_2)_2$	B	51.5	C	98–100	$C_9H_9ClN_4$	C, H, Cl, N
85						B	54.4	B	226–229 dec	$C_{12}H_{10}N_4O$	C, H, N
86						B	90.5	F	147–148	$C_9H_8N_4O$	H, N; C[i]
87	 ·0.5H_2O					B	19.5	I–K	203–206 dec	$C_9H_5ClN_4S$·0.5H_2O	C, H, N, S; H_2O[j]
88						F	79.2		130–133 (0.1)	$C_9H_9ClN_4S$	C, H, N, S
89						F	20.8	I	65–67	$C_9H_9ClN_4S$	C, H, N, S

[a] A, H_2O; B, EtOH; C, toluene; D, EtOAc; E, petroleum ether (bp 30–60°); F, $CHCl_3$; G, CCl_4; H, *n*-pentane; I, *i*-PrOH; J, C_6H_6; K, Skellysolve B (bp 60–80°). [b] C: calcd, 37.14; found, 37.63. [c] C: calcd, 57.44; found, 57.85. [d] See ref 18. [e] E. Lieber and T. Enkoji, *J. Org. Chem.*, **26**, 4472 (1961). [f] H_2O: calcd, 3.67; found, 4.13 (Karl Fischer). [g] Screened in the crude state.

TABLE IV

HYPOCHOLESTEROLEMIC ACTIVITY OF 5-SUBSTITUTED TETRAZOLES

No.	Dose, mg/kg	Serum cholesterol, % change	No.	Dose, mg/kg	Serum cholesterol, % change
47	400	+10	68	400	−44
48	400	(Toxic)[a]	69	400	−25
	100	−14	70	400	−32
49	400	(Toxic)	71	400	−31
	100	−26			
50	400	(Toxic)	72	400	−20
	100	−6	73	400	−6
51	400	(Toxic)	74	400	−8
	100	−21	75	400	0
52	400	−38	76	400	−11
53	400	−52	77	400	−24
	100	−7			
54	400	−36	78	400	−19
55	400	−33	79	400	−20
56	400	−13	80	400	−12
57	400	−26	81	400	+2
58	400	−13	82	400	−12
59	400	−8	83	400	−17
60	400	+3	84	400	−38
61	400	−40	85	300	+3
62	400	−36	86	400	0
	200	−24	87	400	−20
63	400	−22	88	400	+8
64	400	−17	89	400	+15
65	400	−18	CPIB	400	−28
66	400	−24		200	−18
67	400	−31			

[a] Drug-related death of at least one of the test animals.

analyzer method (N24AP) and are recorded in Table IV. In general, compounds that lowered serum cholesterol by at least 20% were considered active.

In general, the most active compounds are the 5-aryloxymethyl- and 5-arylthiomethyltetrazoles, the latter being somewhat less toxic. An electronegative substituent on the benzene ring is necessary for optimal activity (compare **61** with **60** and **66**), but no direct relationship between the degree of electronegativity of the substituent and hypocholesterolemic activity was observed. Lengthening of the carbon chain to C_3 between the hetero atom and the tetrazole ring results in no loss of activity. In the oxygen series, chain extension also lowers toxicity (compare **49** with **53** and **54**). Most of the compounds which incorporate a single methyl or ethyl group on the carbon adjacent to the tetrazole ring retain activity (*i.e.*, **55**, **57**, **70**, **71**, and **72**), whereas dimethyl analogs **58**, **74**, and **75** are nearly inactive. Alkylation of the tetrazole ring as in **88** and **89** destroys activity, indicating that an anionic center is required. Oxidation of one of the thio analogs (**61**) to the corresponding sulfone (**76**) resulted in substantially reduced activity.

5-(3-Chlorophenylthiomethyl)tetrazole (**62**) gave consistent results in dose–response studies and was selected for further evaluation.[22] It had a minimal effective dose (20% lowering of serum cholesterol) of 200 mg/kg, with an oral LD_{50} of 2200 mg/kg in rats. From Table IV it can be seen that compound **62** had activity comparable to the standard drug clofibrate (CPIB) in this assay.

(22) (a) More detailed accounts of the pharmacology and biochemistry of 5-(3-chlorophenylthiomethyl)tetrazole will be reported elsewhere. (b) Initial clinical findings have been reported by D. T. Nash, L. Gross, W. Haw, and K. Agre, *J. Clin. Pharmacol.*, **8**, 377 (1968).

Experimental Section

The melting points were obtained in capillary tubes with a Thomas–Hoover Uni-Melt apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements or functions (Tables I–III), analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Nmr spectra ($CDCl_3$) were obtained using a Varian Associates Model A-60 spectrometer. Chemical shifts (δ) were measured downfield from TMS.

Amides (Table I). Method A.—Compounds **1–5** and **8** were prepared by procedures similar to the one described by Kent and McElvain for the preparation of isobutyramide from isobutyric acid.[23] 5-Chlorobenzo[*b*]thiophene-2-carboxylic acid was prepared by the method of Campaigne and Cline for benzo[*b*]thiophene-2-carboxylic acid.[24]

Method B.—Compound **7** was prepared as described by Stoermer and König.[25]

Method C.—Knoevenagel's method for the preparation of phenylaminoacetonitrile,[15] when used in the synthesis of the 3-nitro analog, resulted in the amide **6** (17%) along with the desired nitrile (**40**) (10.8%).

Nitriles (Table II). Method A.—Compounds **9–14**, **23–29**, **42**, and **44** were prepared by procedures similar to the one described by McManus and Herbst for the preparation of phenoxyacetonitrile (**9**).[5]

Method B.—Compounds **17**, **20**, **35**, and **36** were prepared by the method of Teague and Short for the preparation of nicotinonitrile.[26]

Method C.—Compounds **40**, **45**, and **46** were prepared as described by Juby, *et al.*, for the preparation of 2-(2,6-dichloro-3-methylanilino)benzonitrile.[9]

Method D.—Compound **22** was prepared according to the procedure of Dijkstra and Backer.[13]

Method E.—Compounds **16**, **18**, **19**, **30**, and **32–34** were prepared by the method described by Genzer, *et al.*, for the

(23) R. E. Kent and S. M. McElvain, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 490.

(24) E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 32, 39 (1956).

(25) R. Stoermer and W. König, *Ber.*, **39**, 492 (1906).

(26) P. C. Teague and W. A. Short, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 706.

preparation of γ-(*p*-nitrophenoxy)propyl bromide from the corresponding phenol and 1,3-dibromopropane.[27]

Method F.—Compound **15** was prepared by the method of Heidinger in the preparation of 3-(*p*-chlorophenoxy)propionitrile[14] except that the condensing agent used was Triton B instead of NaOMe.

Method G.—Compounds **37–41** were prepared as described by Knoevenagel for phenylaminoacetonitrile (**37**).[15] (Note: see also under method C for amides.)

Method H.—Compound **21** was prepared by the method of Gattermann and Hausknecht in the preparation of phenyl thiocyanate.[16]

Method I.—The method of Grebenyuk and Tsukervanik[17] was used to prepare compound **43**.

Tetrazoles (Table III). Method A.—Compounds **58** and **74** were prepared by a procedure reported by D'Orazio for DL-5-(α-phthalimido-β-phenylethyl)tetrazole.[19]

Method B.—Compounds **47–57**, **59–67**, **69–73**, **75**, and **78–87** were prepared by the procedure of Finnegan, *et al.*, for 5-propyltetrazole.[18]

Method C.—Compounds **53** and **68** were prepared by a novel method as described for 5-[β-(3-chlorophenylthio)ethyl]tetrazole (**53**). To a mixture of 3-chloropropionitrile (17.9 g, 0.2 mole) and NaN_3 (39 g, 0.6 mole) in 50 ml of dry THF was added a solution of anhydrous $AlCl_3$ (30 g, 0.22 mole) in 400 ml of THF. The resultant mixture was stirred and heated at reflux for 22 hr. The mixture was cooled in an ice bath, and about 200 ml of H_2O was added dropwise and with stirring. The THF was evaporated under reduced pressure, and the residual aqueous solution was acidified with concentrated HCl, saturated with NaCl, and extracted with three portions of Et_2O. The combined extracts were dried ($MgSO_4$) and evaporated, yielding 20.9 g (78.9%) of a yellow solid, mp 97–104°. Recrystallization from $CHCl_3$ gave white needles of 5-(β-chloroethyl)tetrazole, mp 103.5–106.5°.

To a solution of 3-chlorophenol (2.58 g, 0.02 mole) in 70 ml of dry DMF cooled in an ice bath were added a 55.8% NaH dispersion (0.98 g, equivalent to 0.04 mole of NaH) in mineral oil and 5-(β-chloroethyl)tetrazole (2.66 g, 0.02 mole). After the vigorous H_2 evolution had ceased the cooling was discontinued, and the mixture was stirred at room temperature until the H_2 evolution had completely ceased. After addition of about 0.2 g of NaI (catalyst), the mixture was stirred and heated at *ca.* 100° for 18 hr. About 30 ml of H_2O was added and the mixture was concentrated under reduced pressure on a steam bath to a small volume. The residual solution was acidified with concentrated HCl and extracted with Et_2O. The Et_2O extracts were combined and extracted with a saturated aqueous $NaHCO_3$ solution. Upon acidification of the $NaHCO_3$ extracts, 2.1 g of a white solid (46.7%) was obtained. Crystallization ($CHCl_3$–CCl_4) afforded **53**, mp 128–130°.

Method D.—Compound **76** was prepared from compound **61** by the procedure of Gilman and Beaber for the oxidation of *n*-butyl *p*-tolyl sulfide to the corresponding sulfone.[28]

Method E.—Compound **77** was prepared from 5-aminotetrazole monohydrate and 4-chlorobenzenesulfonyl chloride by a procedure described by Jensen and Pedersen for the preparation of 5-acetylsulfanilamidotetrazole.[20]

Method F.—5-(3-Chlorophenylthiomethyl)-2-methyltetrazole (**88**) and 5-(3-chlorophenylthiomethyl)-1-methyltetrazole (**89**) were obtained by treating 5-(3-chlorophenylthiomethyl)tetrazole (**62**) (9.07 g) with CH_2N_2 in Et_2O and separating the resulting mixture on an alumina column. The 2-methyl isomer **88** was eluted with C_6H_6 (7.63 g, 79.2%) and further purified by distillation through a Vigreux column: bp 130–133° (0.1 mm); nmr ($CDCl_3$) δ 4.30 (3 H, $CH_3N<$). The 1-methyl isomer **89** was eluted with $CHCl_3$ (2.00 g, 20.8%), and crystallization from *i*-PrOH gave white crystals, mp 65–67°, nmr ($CDCl_3$) δ 4.00 (3 H, $CH_3N<$).

2-Azido-2-(5-tetrazolyl)propane (VI).—To a mixture of 4-chlorophenoxyisobutyronitrile (5.0 g, 25.6 mmoles) and NaN_3 (5.0 g, 77 mmoles) was added a solution of anhydrous $AlCl_3$ (4.66 g, 35 mmoles) in 70 ml of dry THF. The mixture was stirred and heated at reflux for 48 hr. The THF was distilled from the reaction mixture while sufficient H_2O was added dropwise to maintain a constant volume. An oil separated from the aqueous solution. Ether and a 10% aqueous NaOH solution were added and the layers were separated. The alkaline extract was acidified with 6 *N* HCl and then extracted with Et_2O and $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated, affording a yellow oil. Crystallization from CCl_4 gave 0.87 g of a white solid (22%). Recrystallization from $CHCl_3$–CCl_4 gave white needles of VI: mp 87–90° dec; ir ν_{max} (KBr) at 3440, 3000, 2880, 2740, 2720, 2630, 2140, 1270, 1160, 1050 cm^{-1}; nmr peak ($CDCl_3$) at δ 1.9 (6 H, singlet, $C(CH_3)_2$).

Anal. Calcd for $C_4H_7N_7$: C, 31.36; H, 4.61; N, 64.03. Found: C, 31.53; H, 4.39; N, 64.20.

Acknowledgments.—The authors wish to express their gratitude to Dr. F. S. Caruso and his staff for the pharmacological data. We also thank Mr. R. B. Babel and Mr. M. Brown for technical assistance, and the analytical and spectroscopic departments for their services.

(27) J. D. Genzer, C. P. Huttrer, and H. C. van Wessem, *J. Amer. Chem. Soc.*, **73**, 3150 (1951).

(28) H. Gilman and N. J. Beaber, *ibid.*, **47**, 1449 (1925).

Some Substituted Phenylalkanoic Acids and N-Substituted Malonanilic, Succinanilic, and Anilinoalkanoic Acids as Potential Antiinflammatory Agents

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Received November 18, 1968

Thirty one of the title compounds were prepared and, together with some of the intermediate esters and nitriles, were screened for antiinflammatory activity. None of the compounds showed appreciable activity in the carrageenin-induced edema test, but thirteen of the acids were effective in stabilizing a bovine serum albumin fraction against heat coagulation.

Whitehouse and Skidmore[1] have suggested that acidic antiinflammatory drugs may exert their therapeutic effect by interaction with the essential lysyl ε-amino groups of the enzyme systems implicated in the inflammatory response of animal tissues. We consider that this reaction need not be restricted to the ionic type of interaction envisaged by these investigators and have examined the reaction between phenylbutazone **1** and certain aliphatic amines which would act as crude models for the lysyl ε-amino group.

We have found that phenylbutazone reacts smoothly with *n*-butylamine and *n*-pentylamine at 100° to give

(1) M. W. Whitehouse and I. F. Skidmore, *J. Pharm. Pharmacol.*, **17**, 688 (1965).