recrystallization from Skellysolve E. *Anal.* ($C_{20}H_{17}Br_2NO$), Br, N, N.E.

5,11-Dihydrodibenzo[*b*,*e*][1,4]thiazepine-5-carboxamide (III-28).—To a solution of 8.2 g (0.046 mol) of III-24, 2.8 g of dry C_5H_5N, and 80 ml of dry PhMe, at −10°, was added dropwise 47 ml of a 15% w/v of $COCl_2$ in PhMe. The work-up of this reaction mixture and the subsequent reaction of the intermediate carbamoyl chloride with EtOH–NH_3 followed the published procedure.[2c] The yield of crude III-27 was 1.45 g; chromatography, in C_6H_6 solution, on 60 g of alumina (Harshaw, Chromatographic Grade), followed by successive elutions with C_6H_6 and *i*-PrOH, and repeated recrystallizations from C_6H_6 were required to give pure III-28.[8]

5-Acetyl-7-chloro-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine (III-10).—A solution of 2.0 g (0.0087 mole) of 7-chloro-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine,[2a] 25 ml of Ac_2O, and 0.4 g of *p*-toluenesulfonic acid was heated under reflux for 2 hr, concd to dryness, and the residue distributed between 50 ml of Et_2O and 25 ml of satd aq $NaHCO_3$. The Et_2O layer was sepd, washed with satd aq NaCl, dried, and concd to give 2.4 g of III-10.

6-[(*o*-Bromobenzyl)oxy]-α,α,α-trifluoro-*m*-acetotoluidide (II-4). A mixture of 20.0 g (0.052 mol) of II-2, 8.6 g (0.11 mol) of anhyd AcONa, and 120 ml of glacial AcOH was heated under reflux for 3 hr, cooled somewhat, and poured into 300 ml of H_2O. The oil, that sepd initially, solidified, and was filtered and dried to give 19.4 g of II-4.

(8) The difficulties encountered in this synthesis are similar to those previously described in the oxazepine series, and are involved in the reaction of the heterocycle with phosgene.[2c]

Synthesis and Hypocholesterolemic Activity of Alkylidenedithio Bisphenols

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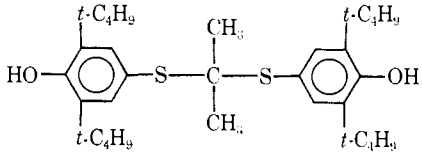
The synthesis and serum cholesterol lowering properties of a new class of alkylidenedithio bisphenols and related compounds are discussed. Maximum activity is shown by 4,4′-(isopropylidenedithio)bis(2,6-di-*t*-butylphenol). A few other members of the class show moderate to good activity and these are produced by substitution of a Me group or an *i*-Pr group for one *t*-Bu group in the phenolic nucleus, or substitution of Et for Me in the isopropylidene moiety. Other reported structural variations resulted in a reduction of activity or, most often, a loss of activity.

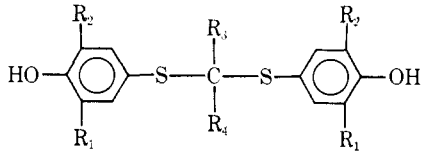
This work represents part of a program on the synthesis of nontoxic oral hypocholesterolemic agents, and is concerned with the structure–activity relationships of a new class of alkylidenedithio bisphenols. Serum cholesterol depressant activity of the most active member of this class has been described.[1,2] Response was shown by mice, rats, monkeys, and humans.

This compound (**1**), 4,4′-(isopropylidenedithio)bis-(2,6-di-*t*-butylphenol), was prepared by acid-catalyzed



condensation of 4-mercapto-2,6-di-*t*-butylphenol with acetone.

A generalized structure for this class of compounds is given below.



The effect of the following variations in structure on hypocholesterolemic activity in mice was examined: (1) size and degree of branching of alkyl groups R_1 and R_2; (2) replacement of R_1 and R_2 by H or Br; (3) substituting H for OH; (4) substitution of H, alkyl groups of increasing molecular weight, Ph, or cycloalkyl for R_3 and/or R_4; (5) replacement of the alkylidenedithio moiety by other S-containing groups.

Hypocholesterolemic Activity.—Good hypocholesterolemic activity in mice is shown by **1** (Table I). Changes in ring substitution have invariably produced a decrease in activity. In fact, one *o*-*t*-Bu must be present for even moderate activity. The unsubstituted compound **2** and compounds substituted with alkyl groups other than *t*-Bu (**6–8**, **12**) are inactive. Likewise, the inclusion of one or two *o*-Br substituents in each ring in place of *t*-Bu groups (**10**, **11**) results in compounds inactive in our test. The only other moderately active compounds in this series are those which contain one *t*-Bu and either Me (**4**) or *i*-Pr (**5**). Activity is diminished when Me or *i*-Pr is replaced by H (**3**), and lost when replaced by 1,1,3,3-tetramethylbutyl (**9**).

Maximum activity is observed in a structure consisting of an aromatic ring containing 3,5-di-*t*-Bu substitution and a 4-OH group with respect to the dithioketal linkage. The steric hinderance of the OH group as a result of the vicinal bulky *t*-Bu groups suggested that the OH itself may not contribute to activity. The dehydroxylated analog, 2,2-bis(3,5-di-*t*-butylbenzenethio)propane, showed no activity, indicating that the OH group is essential.

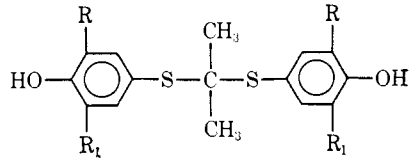
Changes about the central quaternary C also lead, in most cases, to diminished activity (Table II). In fact, if just one of the two central Me groups is re-

(1) J. W. Barnhart, J. A. Sefranka, and D. D. McIntosh, *Fed. Proc.*, **28**, 268 (1969).

(2) J. P. Colmore, A. S. Norrby, D. A. Vloedmon, H. H. Schweem, J. Nakano, and K. M. Dubowski, 4th International Congress of Pharmacology, Basel, July 14–18, 1969, p 405.

TABLE I

VARIATIONS IN RING SUBSTITUENTS OF ISOPROPYLIDENEDITHIO BISPHENOLS

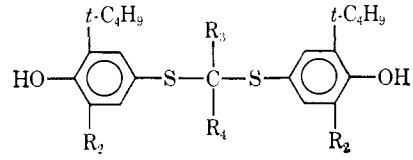


Compd	R	R_1	Yield,[a] %	mp, °C	Formula[b]	Hypocholesterolemic activity[c]
1	*t*-C_4H_9	*t*-C_4H_9	87	125–127	$C_{31}H_{48}O_2S_2$	++
2	H	H	26	109–111	$C_{15}H_{16}O_2S_2$[d]	−
3	*t*-C_4H_9	H	61	138–140	$C_{23}H_{32}O_2S_2$	±
4	*t*-C_4H_9	CH_3	86	156–157	$C_{25}H_{36}O_2S_2$	+
5	*t*-C_4H_9	*i*-C_3H_8	52	74–79	$C_{29}H_{44}O_2S_2$[e]	+
6	CH_3	CH_3	63	127–130	$C_{19}H_{24}O_2S_2$[f]	−
7	*i*-C_3H_8	*i*-C_3H_8	62	107–110	$C_{27}H_{40}O_2S_2$	−
8	*t*-C_5H_{11}	*t*-C_5H_{11}	49	77–79	$C_{35}H_{56}O_2S_2$	—
9	*t*-C_4H_9	*t*-C_8H_{17}	40	123–125	$C_{39}H_{64}O_2S_2$	−
10	*t*-C_4H_9	Br	68	127–128	$C_{23}H_{30}Br_2O_2S_2$	−
11	Br	Br	42	147-148	$C_{15}H_{12}Br_4O_2S_2$	−
12	*sec*-C_4H_9	*sec*-C_4H_9	86	Oil	$C_{31}H_{48}O_2S_2$	−

[a] Per cent yield is given for last step in synthesis. [b] All compounds were analyzed for C,H,S. [c] (−) No reduction, inactive, (±) > 0 < 20% reduction, marginal activity, (+) ≧20 < 40% reduction, moderate activity, (++) ≧40 < 60% reduction, good activity. [d] Calcd: C, 61.61. Found C, 60.90. [e] C: Calcd, 71.26. Found, 71.87. [f] S: Calcd, 18.4. Found, 17.9.

TABLE II

VARIATIONS IN ALKYLIDENEDITHIO PORTION OF BISPHENOLS



Compd	R_2	R_3	R_4	Yield,[a] %	Mp, °C	Formula[b]	Hypocholesterolemic activity[c]
14	*t*-C_4H_9	CH_3	C_2H_5	45	135–137	$C_{32}H_{50}O_2S_2$[d]	++
15	*t*-C_4H_9	CH_3	*n*-C_3H_7	66	133–134	$C_{33}H_{52}O_2S_2$[e]	±
16	*t*-C_4H_9	CH_3	*n*-C_4H_9	76	140–142	$C_{34}H_{54}O_2S_2$	−
17	*t*-C_4H_9	CH_3	*n*-C_5H_{11}	84	158–160	$C_{35}H_{56}O_2S_2$	−
18	*t*-C_4H_9	CH_3	*n*-C_6H_{13}	90	126–127	$C_{36}H_{58}O_2S_2$	±
19	*t*-C_4H_9	CH_3	*n*-C_9H_{19}	64	Oil	$C_{39}H_{64}O_2S_2$	−
20	*t*-C_4H_9	C_2H_5	C_2H_5	90	180–182	$C_{33}H_{52}O_2S_2$	−
21	CH_3	CH_3	C_2H_5	32	139–143	$C_{26}H_{38}O_2S_2$	±
22	CH_3	CH_3	*n*-C_4H_9	36	129–131	$C_{28}H_{42}O_2S_2$	−
23	CH_3	CH_3	*n*-C_6H_{13}	62	108–111	$C_{30}H_{46}O_2S_2$	±
24	CH_3	CH_3	*n*-C_9H_{19}	43	73–78	$C_{33}H_{52}O_2S_2$	±
25	*t*-C_4H_9	CH_3	*i*-C_4H_9	44	126–130	$C_{34}H_{54}O_2S_2$	±
26	*t*-C_4H_9	H	CH_3	82	92–96	$C_{30}H_{46}O_2S_2$	±
27	*t*-C_4H_9	H	C_2H_5	46	115–117	$C_{31}H_{48}O_2S_2$	±
28	*t*-C_4H_9	H	C_6H_5	61	123–125	$C_{35}H_{48}O_2S_2$	−
29	*t*-C_4H_9	CH_3	C_6H_5	71	158–163	$C_{36}H_{50}O_2S_2$	−
30	*t*-C_4H_9	Cyclohexyl		87	189–194	$C_{34}H_{52}O_2S_2$	−

[a] Per cent yield is given for last step in synthesis. [b] All compounds were analyzed for C, H, S. [c] See footnote *c*, Table I for activity ratings. [d] C: calcd, 72.40. Found, 71.71. [e] S: calcd, 11.8. Found, 11.1.

placed with higher alkyl or aryl substituents, activity rapidly decreases from good with one Et group (**14**) to marginal or zero with higher alkyl (**15–19**, **25**) and aryl (**29**) substituents. Except for **27** which showed only marginal activity, those compounds which retained neither Me group on the central C atom showed no activity (**20**, **28**, **30**). Replacement of one Me by H resulted in compounds of marginal activity (**26**, **27**). If changes were made both in ring substituents and at the central C, only marginal activity remained (**21–24**).

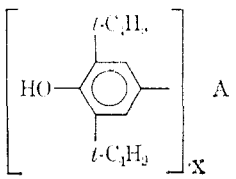
Replacement of the isopropylidenedithio moiety of **1** with S (**31**), S—S (**32**), or SCH_2 (**33**) causes a reduction or loss of activity (Table III). A number of S-containing monophenols (**34–37**) did not show outstanding activity.

Experimental Section

Chemistry.—Melting points were determined in open capillary tubes using a Mel-Temp apparatus; all melting points and boiling points are uncorrected. Ir spectra were measured using the neat liquids or in $CHCl_3$ or CS_2 with a Perkin-Elmer spectro-

TABLE III

REPLACEMENT OF ISOPROPYLIDENEDITHIO MOIETY BY OTHER SULFUR-CONTAINING GROUPS



Compd	X	A	Yield,[a] %	Mp, °C	Formula[b]	Hypocholesterolemic activity[c]
31	2	S	47	136–138	$C_{28}H_{42}O_2S$	±
32	2	S—S	92	148–150	$C_{28}H_{42}O_2S_2$	−
33	2	SCH_2	90	122–124	$C_{29}H_{44}O_2S$[b]	−
34	1	SH	90	88–90	$C_{14}H_{22}OS$	±
35	1	SCH_3	60	72–74	$C_{15}H_{24}OS$	±
36	1	$SCH(CH_3)_2$	50	60–61	$C_{17}H_{28}OS$[b]	±
37	1	$SC(CH_3)_3$	24	46–98	$C_{18}H_{30}OS$	−

[a] Per cent yield is given for last step in synthesis. [b] Compounds analyzed for C, H, S. [c] See footnote *c*, Table I for activity ratings.

photometer (Model 337). Vpc analyses were made using an F and M apparatus (Model 300). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ± 0.4% of the theoretical values.

All aldehydes and ketones used were purchased and are laboratory reagent grade. The alkylphenols, 2,6-di-*t*-butylphenol, 2-methyl-6-*t*-butylphenol, 2,6-diisopropylphenol, and 2,6-di-*sec*-butylphenol were also purchased and are laboratory reagent grade.

2-*t*-Butyl-6-isopropylphenol and 2-*t*-butyl-6-*t*-octylphenol were synthesized by H_2SO_4-catalyzed alkylation of the appropriate *o*-alkylphenol with isobutylene. 2-*t*-Butyl-6-isopropylphenol was distilled at 135–137° (20 mm) and analyzed 99.9% pure by vpc. 2-*t*-Butyl-6-*t*-octylphenol was distd at 160–165° (10 mm). 2,6-di-*t*-Amylphenol was prepared by Al-catalyzed alkylation of phenol with 2-methylbutene-1.[3] The desired product was distd at 160–161° (20 mm) and analyzed 97.7% pure by vpc.

Mercaptophenols.—The preparation of 4-mercapto-2,6-di-*t*-butylphenol, 4-mercapto-2-*t*-butylphenol, 6-mercapto-2,4-di-*t*-butylphenol, and 4-mercapto-2-methyl-6-*t*-butylphenol has been reported.[4]

The synthesis of 4-mercapto-6-isopropyl-2-*t*-butylphenol[5] was patterned after the procedure described by Hotelling[6] except the sulfurization temp was kept close to 0° and the resulting product reduced with Zn–HCl. The 4-mercapto derivatives of 2,6-di-*t*-amylphenol[7] and 2-*t*-octyl-6-*t*-butylphenol[8] were prepared by the procedure previously cited.[4] The synthesis of 6-bromo-2-*t*-butyl-4-mercaptophenol[9] involved bromination of 3-*t*-butyl-4-hydroxyphenylthiocyanate followed by Zn–HCl reduction. The dibromo analog, 2,6-dibromo-4-mercaptophenol[10] was prepared similarly, starting with 4-hydroxyphenylthiocyanate.

Synthesis of 3,5-Di-*t*-butylthiophenol and Dithioketal Derivative (13).—The procedure of Kenner and Williams[11] was used to dehydroxylate 2,4-di-*t*-butyl-6-methylthiophenol,[12] which was prepared by reaction of the Na salt of the mercaptophenol with Me_2SO_4. This phenol was esterified with diethyl phosphorochloridate in the presence of $(Et)_3N$ and the ester cleaved by means of Na–liquid NH_3. The MeS group is simultaneously cleaved to mercaptan. The crude 3,5-di-*t*-butylthiophenol distd at 142–145° (10 mm). Recrystallization from MeOH produced colorless crystals, mp 52.5–54.0°. The ir spectrum (5–6 μ) was characteristic of 1,3,5 substitution. *Anal.* ($C_{14}H_{22}S$), C, H, S. This mercaptan was used to prepare 2,2-bis(3,5-di-*t*-butylbenzenethio)propane (**13**) by the standard procedure.[13]

Synthesis of Alkylidenedithio Bisphenols.—The synthesis of 4,4-(isopropylidenedithio)bis(2,6-di-*t*-butylphenol) (**1**) may be considered a general method.

4-Mercapto-2,6-di-*t*-butylphenol (47.5 g, 0.2 mol) was dissolved in 50 ml of MeOH at 50°, and 1.0 ml of concd HCl was added. In some cases using less reactive carbonyl compounds, the MeOH was satd with gaseous HCl. Then, Me_2CO (5.8 g, 0.1 mol) was added with resultant temp rise to 60°. The reaction mixture was maintained at 60–65° for 1.5 hr by heating and was then allowed to cool. Aqueous $NaHCO_3$ (10 ml, 10%) was added. The mixture was diluted (H_2O) and extracted with Et_2O. The residue from the evaporation of the Et_2O solution, a yellow viscous oil, was recrystd from EtOH to form a white crystalline solid. This first crop weighed 33.0 g and had mp 124.5–126°. The liquor from the crystallization was concentrated by evaporation to yield 12.0 g of a second crop of fine, yellow crystals. The yield was 87.4%. When recrystd from *i*-PrOH, the product had mp 125–126.5°.

Miscellaneous Compounds.—The preparation of 4,4'-thiobis-2,6-di-*t*-butylphenol (**31**), 4,4'-dithiobis-2,6-di-*t*-butylphenol (**32**), 4-methylthio-2,6-di-*t*-butylphenol (**35**), and 4-*t*-butylthio-2,6-di-*t*-butylphenol (**37**) was described by Müller.[14] Rochlin synthesized **33**.[15]

The 4-isopropylthio-2,6-di-*t*-butylphenol (**36**) was prepared by reaction of the Na salt of 4-mercapto-2,6-di-*t*-butylphenol with *i*-PrBr in EtOH. The sulfide was crystallized from hexane, mp 60–61°. *Anal.* ($C_{17}H_{28}OS$), C, H, S calcd, 11.4%; found, 12.2%.

Hypocholesterolemic Activity.—The experimental compounds were added to the diet of male Swiss-Webster mice (4–6 animals/group) at a level of 0.12% for 2 weeks. Total serum cholesterol was determined and compared to control values. Rat studies were performed with 0.25% dietary drug in Wistar male rats for 2 weeks. Serum cholesterol,[16] liver cholesterol,[17] and serum and liver triglycerides[18] were determined.

Activity in Rats.—Compound 1 produces a significant reduction of serum cholesterol in rats. A comparison was made with 2-(*p*-chlorophenoxy)-2-methylpropionic acid ethyl ester (clofibrate) in which the compounds were added to the diet at a level of 0.25% for 2 weeks (Table IV). The effect of the compounds on rat serum cholesterol is similar, although clofibrate also causes significant changes in liver weight and liver cholesterol. Clofi-

TABLE IV

EFFECT OF 1 AND CLOFIBRATE ON RAT SERUM AND LIVER LIPIDS[a]

	Control	Compound 1	Clofibrate
Serum cholesterol (mg/100 ml)	82 ± 10[b]	57 ± 11[c]	50 ± 3[c]
Serum triglycerides (mg/100 ml)	25 ± 11	25 ± 6	18 ± 3
Liver weight (g/100 g of body wt)	4.6 ± 0.8	5.2 ± 0.3	7.1 ± 0.6[c]
Liver cholesterol (mg/g)	2.0 ± 0.1	2.1 ± 0.1	1.7 ± 0.2[c]
Liver triglycerides (mg/g)	4.4 ± 0.7	5.9 ± 2.0	4.9 ± 1.3

[a] Groups of 8 male rats were treated with 0.25% dietary drug for 2 weeks. [b] Mean ± SD. [c] Significantly different from control, $P < 0.01$.

(3) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Eeke, *J. Org. Chem.*, **22**, 642 (1957).
(4) R. J. Laufer, U. S. Patent 3,129,262 (April 1964).
(5) Bp 104° (0.45 mm), vpc purity 99.3%.
(6) E. B. Hotelling, R. J. Windgassen, E. P. Previc, and M. B. Neuworth, *J. Org. Chem.* **24**, 1598 (1959).
(7) Purity vpc—98.3%.
(8) Ir spectrum in agreement with 1,2,3,5 substitution.
(9) Bp 107–109° (0.05 mm). *Anal.* ($C_{10}H_{13}BrOS$) C,H,S.
(10) Mp 72–77°.
(11) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).
(12) Colorless plate, mp 41–43°. *Anal.* ($C_{15}H_{24}OS$), C, H, S.
(13) Yield 44%; mp 81–82°; *Anal.* ($C_{31}H_{48}S_2$) C,H,S.
(14) E. Mueller, H. B. Stegman, and K. Scheffler, *Justus Liebigs Ann. Chem.*, **645**, 79 (1961).
(15) A. L. Rochlin, U.S. Patent 3,179,701, April 20, 1965.
(16) A. A. Henly, *Analyst*, **82**, 286 (1957).
(17) W. M. Sperry and M. Webb, *J. Biol. Chem.*, **187**, 97 (1950).
(18) E. Van Handel and D. B. Zilversmit, *J. Lab. Clin. Med.*, **50**, 152 (1957).

brate has no significant effect on mouse serum cholesterol under these conditions. Although the mechanism of action of 1[19] has not been elucidated, it does not appear to have any significant effect on the incorporation of mevalonate into cholesterol.

(19) The generic name of 1, formerly designated DH 581, is probucol.

Acknowledgment.—We wish to thank Dr. E. P. Previc, Dr. E. G. Choby, and Mr. J. De Fazio for the preparation of many of the compounds screened in this program, and Mr. P. J. Shea for assisting in the biological evaluation.

Synthesis and Antiinflammatory Activity of Some Aryltetrazolylalkanoic Acids

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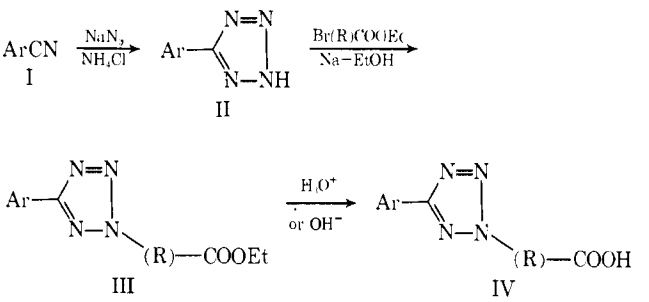
A number of aryltetrazolylalkanoic acids were prepared and screened for antiinflammatory activity by two acute and one chronic assay. Maximum activity was found in those members of the series having halogenated aromatic substituents in the *meta* positions and a propionic acid residue at position 2 of the tetrazole ring.

In the past few years, research on nonsteroidal antiinflammatory agents has, in large measure, focused on various types of arylalkanoic and arylcarboxylic acids. The numerous structural patterns that have been investigated have been discussed in varying degrees of detail in a number of recent reviews.[1] While the exact mechanism(s) of action of these drugs is still unclear, the introduction into therapy of indomethacin and mefenamic acid is indicative of the relative success of this approach. Our continuing efforts in the area of nonsteroidal antiinflammatory agents led us to an examination of the aryltetrazolylalkanoic acids.

Although relatively novel as an aromatic system, the tetrazole group is present in a number of biologically active molecules. Apart from serving as an allosteric replacement for the carboxyl function,[2] it appears in the CNS active 1-aryl-5-dialkylaminomethyl- and 1-(or 5-) alkyl-5-(or 1-)aminophenyltetrazoles.[3] A recent report has disclosed antihypertensive activity for some 5-[ω-(4-aryl-1-piperizinyl)alkyl]tetrazoles.[4] In addition, 5-amino-1-phenyltetrazole has been clinically investigated as an antiinflammatory agent.[5]

The most interesting of the title compounds are the 5-aryltetrazolyl-2-alkanoic acids, IV, prepared by the reaction sequence outlined in Scheme I. The starting nitriles, I, were either obtained commercially or prepared by known procedures. These were converted into the 5-aryltetrazoles, II, by reaction with NaN_3 and NH_4Cl in DMF in yields of about 90% and used without further purification. Alkylation of the 5-aryltetrazole Na salts (Method B) with the appropriate ethyl bromoalkanoate produced the esters, III. Such alkylations have consistently been reported to yield a

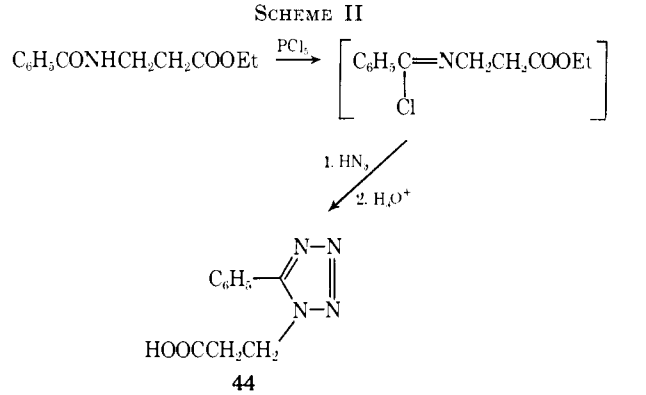
SCHEME I



mixture of both the 1 and 2 isomers with the 2 isomer predominating.[6] The procedure used here with refluxing ethanol as the solvent produced, in every case, only the 2 isomer in good yield. No attempt was made to detect any 1 isomer that might have formed.

In order to demonstrate that our alkylation procedure was actually producing the 2 isomer, the 1 isomer, 3-(5-phenyl-1-tetrazolyl)propionic acid (**44**), was prepared by an unambiguous route. As shown in Scheme II, ethyl 3-benzamidopropionate was converted into

SCHEME II



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the iminochloride with PCl_5. This, upon cyclization with hydrazoic acid and saponification, gave **44**, mp 146°. The 3-(5-phenyl-2-tetrazolyl)propionic acid produced by the alkylation of 5-phenyltetrazole with ethyl

(1) (a) K. J. Doebel, *et al.*, *Ann. Rep. Med. Chem.*, **1968**, 209 (1969); (b) T. Y. Shen, *ibid.*, **1967**, 219 (1968); (c) T. Y. Shen, "Topics in Medicinal Chemistry," Vol I, J. L. Rabinowitz and R. M. Myerson, Ed., Interscience, New York, N. Y., 1967, p 53; (d) S. S. Adams and R. Cobb, *Progr. Med. Chem.*, **5**, 59 (1967).

(2) (a) P. F. Juby, T. W. Hudyma, and M. Brown, *J. Med. Chem.*, **11**, 111 (1968); (b) P. F. Juby and T. W. Hudyma, *ibid.*, **12**, 396 (1969); (c) J. K. Elwood, R. M. Herbst, and G. L. Kilgour, *J. Biol. Chem.*, **240**, 2073 (1965).

(3) (a) E. G. Gross and R. M. Featherstone, *J. Pharmacol. Exp. Ther.*, **92**, 323 (1948); (b) E. G. Gross and R. M. Featherstone, *ibid.*, **92**, 330 (1948).

(4) S. Hayao, H. J. Havera, W. G. Strycker, T. J. Leipzig, and R. Rodriguez, *J. Med. Chem.*, **10**, 400 (1967).

(5) G. R. Bobalik and J. W. Bastian, *Arch. Int. Pharmacodyn. Ther.*, **166**, 466 (1967).

(6) (a) R. A. Henry, *J. Amer. Chem. Soc.*, **73**, 4470 (1951); (b) R. Rapp and J. Howard, *Can. J. Chem.*, **47**, 813 (1969); (c) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Amer. Chem. Soc.*, **80**, 3908 (1958).