

# Thiazolothiazoles. 3.<sup>1a</sup> Synthesis and Biological Evaluation of Functionalized Dialkyl Derivatives from $\gamma,\gamma,\gamma',\gamma'$ -Tetramethylthiazolo[5,4-*d*]thiazole-2,5-dibutyronitrile<sup>1b</sup>

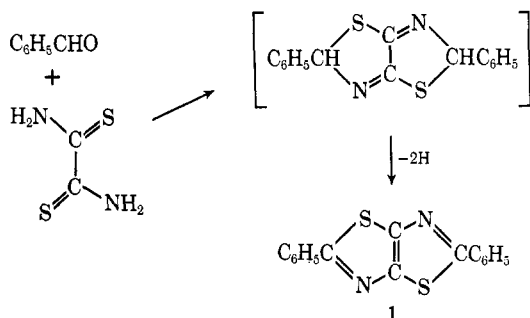
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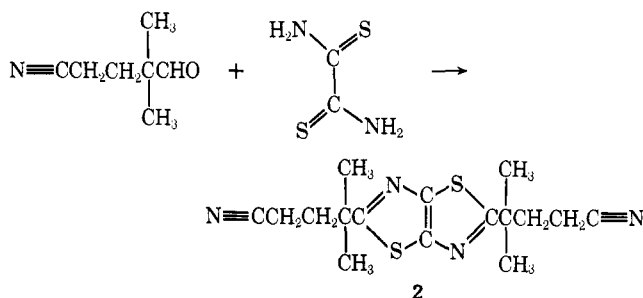
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$\gamma,\gamma,\gamma',\gamma'$ -Tetramethylthiazolo[5,4-*d*]thiazole-2,5-dibutyronitrile has been converted to a series of derivatives, several of which have LD<sub>50</sub> values and pentobarbital potentiation properties similar to the nitrile. A series of higher homologs was found to be of lower activity. The bis(1,1-dimethylbutyl) derivative was among the most active compounds, thus indicating that a functional group is not essential for depressant activity. The thiazolo-thiazole nucleus has been shown to be stable under a variety of standard synthetic procedures.

Ephraim<sup>2</sup> in 1891 reported the condensation between dithiooxamide and PhCHO. However, the product was not correctly identified until 1960, when Johnson and Ketcham<sup>3</sup> reported, on the basis of spectral and chem data, that the product, 2,5-diphenylthiazolo[5,4-*d*]thiazole (1), was derived from dehydration of the reactants and further dehydrogenation presumably of some dihydro intermediate.



Fikrat and Oneto<sup>4</sup> in 1962 reported formation of  $\gamma,\gamma,\gamma',\gamma'$ -tetramethylthiazolo[5,4-*d*]thiazole-2,5-dibutyronitrile (2) from condensation between dithiooxamide and 4-cyano-2,2-dimethylbutyraldehyde, the first aliphatic aldehyde that, condensing with dithiooxamide, yielded a characterizable bicyclic product. They also attempted condensation reactions of dithiooxamide with other aliphatic aldehydes but none



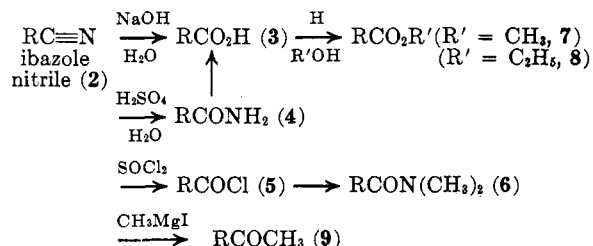
of them afforded a characterizable product. Attempts to transform this dinitrile (2, or "ibazole nitrile") to the dicarboxylic acid or the diamine were also reported

to fail.<sup>5</sup> Since there is no structural reason that the nitrile should be resistant to hydrolysis or redn, this observation required clarification or verification. Moreover, attempts to transform this bis(nitrile) into various functionalized dialkylthiazolothiazoles would serve to establish further the sensitivity of this still relatively unknown heteroaromatic nucleus to a variety of synthetic procedures.

Preliminary biol screening<sup>4</sup> revealed that ibazole nitrile was a CNS depressant. The pattern of effects suggested that this compound was not a sedative hypnotic since it did not produce anesthesia even at high doses, nor did it produce behavioral or autonomic effects characteristic of a tranquilizer of the phenothiazine type. However, it appeared to be similar in its action to thalidomide and trimeglamide<sup>6</sup> and therefore belonged to the same somnifacient class of CNS depressants.<sup>7</sup>

The fact that there is little structural similarity between ibazole nitrile and these other depressants suggested that biol screening of a series of analogs might reveal divergent and perhaps useful pharmacological properties.

As outlined below, ibazole nitrile (2) was hydrated to diamide 4, hydrolysis of which gave dicarboxylic acid 3. Dinitrile 2 also gave dicarboxylic acid 3 through hydrolysis under alk conditions. Acid chloride 5 formation followed by treatment with Me<sub>2</sub>NH yielded ditertiary amide 6. Fischer esterification of the acid yielded esters 7 and 8. Reaction of 2 with MeMgI provided diketone 9.



Redn of dinitrile 2 and ester 7 as indicated below provided diamine 10 and diol 11. From diamine 10 was prepd ditertiary amine 12 and finally diquarternary ammonium iodide 13. Redn of diol tosylate 14

(1) (a) Paper 2. J. R. Johnson, D. H. Rotenberg, and R. Ketcham, *J. Amer. Chem. Soc.*, **92**, 4046 (1970); (b) this work was supported in part by Grant No. MH 08787, provided by the National Institute of Mental Health, U. S. Public Health Service; (c) abstracted from the Ph.D. thesis of S. M.

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CNS depressants alter the sleeping pattern produced by barbiturates. One effect is prolongation of sleeping time of pretreated animals given an anesthetic dose of the barbiturate as compared to that of controls given only the barbiturate.<sup>6</sup> Alternatively, one may observe an increase in the number of animals in which sleep is induced by a subanesthetic dose of barbiturate. In this study the effect of the compounds was observed on the sleeping time of pretreated mice given an anesthetic dose of pentobarbital.

The data in Table II indicate that 8 compounds produce a doubling of barbiturate sleeping time at doses in the neighborhood of 0.10 of the LD<sub>50</sub>'s. Among these, dimethylamide **6**, Me ketone **9**, and bis(1,1-dimethylbutyl)thiazole[5,4-d]thiazole (**15**) were found to be the most active derivatives since the dose required to produce doubling of barbiturate sleeping time was only 50 mg/kg or less. It is interesting to note that ibazane, the only simple dialkylthiazolothiazole, was among the 3 most active derivatives, which indicates that a functional group on the side chains of a dialkylthiazolothiazole is not essential for depressant activity.

Three higher homologs of the ibazole series (nitrile **16**, acid **18**, and amide **17**) did not demonstrate much prolongation of barbiturate sleeping time. This indicates that lengthening of the side chain does not increase the activity of a dialkylthiazolothiazole as a CNS depressant but rather reduces activity. This suggests that shortening of the side chain may be the right direction to obtain more active homologs. Preparation of compounds of shorter side chains is now in progress.

### Experimental Section<sup>11</sup>

**2,2-Dimethyl-4-cyanobutylaldehyde**, or "ibanitrile," was obtained commercially and distilled [bp 96–100° (5 mm)] prior to use or was prepared by KCN-catalyzed condensation of CH<sub>2</sub>=CHCN and (CH<sub>3</sub>)<sub>2</sub>CHCHO.

**γ,γ,γ',γ'-Tetramethylthiazolo[5,4-d]thiazole-2,5-dibutyronitrile (2).**<sup>4</sup>—Dithiooxamide (19.2 g, 0.16 mole) and 2,2-dimethyl-4-cyanobutylaldehyde (100 g, 104 ml, 0.8 mole) were heated in an oil bath at 195–200° with occasional stirring with a glass rod. In about 15 min evolution of H<sub>2</sub>O became rapid. The presence of unreacted dithiooxamide produced an orange precipitate on the glass rod when it was removed from the reaction mixture. When the reaction was complete the dark mixture was poured slowly into 250 ml of 95% EtOH. The EtOH solution was allowed to cool to room temperature and then kept at –20° until crystallization was complete. The solid was collected in a filter and washed with cold EtOH until a brownish solid was obtained. After air-drying, it weighed 21.6 g (40.6%), mp 110–112°. Four more recrystallizations using decolorizing charcoal, if necessary, gave fine white needles, mp 114–115° (lit.<sup>4</sup> 109–111°).

**γ,γ,γ',γ'-Tetramethylthiazolo[5,4-d]thiazole-2,5-dibutyric Acid (3).**—To a solution of 4.2 g (0.0121 mole) of nitrile **2** in 20 ml of EtOH was added 45 ml of 17% NaOH and the mixture was refluxed for 6 hr. The reaction mixture was then cooled and acidified with concentrated HCl. The precipitate, which formed immediately, was collected by filtration and washed with cold H<sub>2</sub>O until the washing was no longer acidic, followed by a small amount of EtOH. The yellow powder weighed 4.1 g (93%), mp 209–210°. After two recrystallizations from EtOH–H<sub>2</sub>O the nearly colorless needles had mp 214–

215°. Repeated recrystallization gave the colorless analytical sample, had mp 214–215°. *Anal.* (C<sub>16</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) C, H, N; S: calcd, 17.31; found, 17.99.

**γ,γ,γ',γ'-Tetramethylthiazolo[5,4-d]thiazole-2,5-dibutyramide (4).** **A.**—To a stirred solution of 9.64 g (0.029 mole) of nitrile **2** in 31.2 ml of 95% EtOH and 2.4 ml of 6 N NaOH was added 23.4 ml of 30% H<sub>2</sub>O<sub>2</sub> (0.215 mole). During the dropwise addition the reaction was kept below 75°, with an ice bath, if necessary. After addition the reaction mixture was allowed to stir for 3 hr. The precipitate was collected in a filter, washed with a small amount of H<sub>2</sub>O, and dried to give 8.35 g (80%) of white powder, mp 227–234°. One recrystallization from DMF gave a product, mp 240–242°. Three recrystallizations from a large volume of 95% EtOH gave a white crystalline product, mp 245–246°. *Anal.* (C<sub>16</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) C, H, N, S.

**B.**—A sample of 20.0 g (0.06 mole) of **2** was dissolved in 100 ml of concentrated H<sub>2</sub>SO<sub>4</sub> with stirring or a little warming on a steam cone. As soon as the reaction mixture became clear it was poured over about 400 g of crushed ice. The white precipitate was collected in a filter and washed with a small amount of H<sub>2</sub>O. The dried crude product weighed 26.7 g (100%), mp 242–245°. One recrystallization from a large amount of 95% EtOH (about 2.5 l.) gave a mp of 245–246°.

**N,N,N',N',γ,γ,γ',γ'-Octamethylthiazolo[5,4-d]thiazole-2,5-dibutyramide (6).**—To a suspension of 1.85 g (0.005 mole) of dicarboxylic acid **3** in 5 ml of PhH was added 1.6 ml (0.0134 mole) of SOCl<sub>2</sub>. The reaction mixture was protected with a CaCl<sub>2</sub> tube and stirred at room temperature for 2 hr. Me<sub>2</sub>NH was passed through the reaction mixture for 15 min. The resulting yellow powder was collected in a filter, washed with H<sub>2</sub>O, and air-dried to give 1.8 g (85%) of tetramethyldiamide, mp 205–209°. After one recrystallization from EtOH–H<sub>2</sub>O the mp was 211–213°. *Anal.* (C<sub>20</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>) H, N; C: calcd, 56.56; found, 56.14.

**Dimethyl γ,γ,γ',γ'-Tetramethylthiazolo[5,4-d]thiazole-2,5-dibutyrate (7).**—A mixture of 16.7 g (0.045 mole) of parent acid **3**, 230 ml of MeOH, and 71 ml of concentrated HCl was heated under reflux for 1 hr. White, flocculent crystals filled the flask when the reaction mixture was cooled. The crystals were collected in a filter, washed with H<sub>2</sub>O and then a small amount of MeOH, and air-dried to give 17.5 g (98.1%), mp 89–90°, of Me ester. One recrystallization from petroleum ether gave thin white flakes, mp 89–90°. The analytical sample, mp 90–91°, was prepared by two more recrystallizations. *Anal.* (C<sub>18</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) C, H, S.

**Diethyl ester 8** was prepared in a similar manner with absolute EtOH instead of MeOH, mp 55–56°. *Anal.* (C<sub>20</sub>H<sub>30</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>) C, H, N, S.

**5,5'-Thiazolo[5,4-d]thiazole-2,5-diylbis(5-methyl-2-hexanone) (9).**—To MeMgI (0.06 mole), prepared in the usual way and dissolved in PhH, was added with stirring 4.98 g (0.015 mole) of nitrile **2** in 40 ml of dry PhH. The reaction was completed by refluxing with vigorous stirring for 3 hr. The mixture was cooled to 0°, while 30 ml of 6 N HCl was added slowly with stirring. The hydrolysis was completed by 5-hr reflux. The PhH layer was separated, and 150 ml of PhH was used in 3 portions, to extract the remaining ketone from the aqueous phase. The PhH extracts were combined and washed with 5% NaHCO<sub>3</sub> and H<sub>2</sub>O, in that order, and dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was removed under reduced pressure. The residue contained 0.75 g (14%) of a white powder, mp 90–95°. The infrared showed no C≡N band. A 0.3-g sample of the above material was chromatographed on acid-washed alumina with PhH as solvent. The first 100 ml of eluate afforded 0.25 g of white crystals, mp 93–96°. This was recrystallized from hexane to give the ketone with a mp of 94–95°. The analytical sample was prepared by one further recrystallization from PhH to give a mp of 96–97°. *Anal.* (C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>) C, H, N, S.

**δ,δ,δ',δ'-Tetramethylthiazolo[5,4-d]thiazole-2,5-dibutylamine Dihydrochloride (10).**—To a suspension of 0.8 g (0.020 mole) of LAH in 10 ml of anhyd Et<sub>2</sub>O was added slowly with stirring a solution of 1.3 g (0.004 mole) of nitrile **2** in 500 ml of anhyd Et<sub>2</sub>O. After addition the reaction mixture was heated under reflux for 30 min or until no more starting nitrile could be detected by tlc (10% MeOH in PhH). H<sub>2</sub>O (ca. 100 ml) was added to destroy unreacted LAH. Some white inorganic solid formed and was removed by filtration with filter aid. The Et<sub>2</sub>O was separated and the aqueous phase was extracted 3 times with 100-ml portions of Et<sub>2</sub>O. These extracts were combined with the Et<sub>2</sub>O layer and dried with K<sub>2</sub>CO<sub>3</sub> overnight. Dry HCl was passed through this solution until no further precipitate took place. A white powder (1.3 g, 77%) was obtained, mp 298–300° dec. The analytical sample was prepared by recrystallization from absolute EtOH, mp 296–300° dec. *Anal.* (C<sub>16</sub>H<sub>30</sub>Cl<sub>2</sub>N<sub>4</sub>S<sub>2</sub>) N, Cl; S: calcd, 15.62; found, 14.90.

(11) Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are corrected. Elementary analyses were carried out by the microanalytical laboratory of the University of California at Berkeley. 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. Infrared spectra were run on a Perkin-Elmer 336 spectrophotometer, ultraviolet spectra in 95% EtOH using a Carey Model 11 spectrometer, nuclear magnetic resonance spectra on a Varian A 60-MHz spectrometer. The ultraviolet, infrared, and nuclear magnetic resonance spectra agreed in each case with the structural assignments. Tlc analyses were carried out on silica gel F254 tlc plates distributed by Brinkmann Instruments Inc., Westbury, L. I.

TABLE II  
PROLONGATION OF PENTOBARBITAL<sup>a-c</sup> SLEEPING TIME PRODUCED BY VARIOUS THIAZOLOTHIAZOLES<sup>d</sup>

Compd	Dose, mg/kg				
	500	200	100	50	25
			Minutes		
2		183.6 ± 64.7	167.2 ± 63.5	84.1 ± 10.2	
3		69.1 ± 0.49	66.4 ± 12.2		
7 <sup>e</sup>	61.1 ± 5.0		152.8 ± 31.4	97.2 ± 16.7	
4 <sup>f</sup>	70.7 ± 7.4		112.5 ± 22.5	106.0 ± 10.7	
6	238.2 ± 48.6	282.3 ± 80.5			126.0 ± 34.0
11	124.3 ± 47.3	141.9 ± 35.8	85.2 ± 14.9		
28	153.3 ± 59.6		138.0 ± 27.7	67.3 ± 9.4	
29 <sup>g</sup>	59.1 ± 8.0				
27 <sup>h</sup>		109.9 ± 17.9		91.2 ± 10.8	
9				138.4 ± 39.4	69.2 ± 16.9
16	122.2 ± 23.9		143.8 ± 25.7	84.9 ± 6.1	
18			77.6 ± 7.7	70.0 ± 12.4	
17			78.9 ± 9.6		
22				99.8 ± 17.4	
15				127.3 ± 21.1	104.2 ± 17.8

<sup>a</sup> Injected at a dose of 65 mg/kg 15 min after treatment with the test compd. <sup>b</sup> Sleeping time for pentobarbital (65 mg/kg) alone: 44.0 ± 5.4 min. <sup>c</sup> Sleeping time for pentobarbital (65 mg/kg) injected 15 min after injection of vehicle (10 ml/kg): 61.8 ± 8.4 min. <sup>d</sup> Ref 6 gives sleeping time for pentobarbital (65 mg/kg) as 64 ± 1 min increasing to 135 ± 21 min when pretreated with 300 mg/kg of trimeglamide. <sup>e</sup> Pentobarbital injected 25 min after injection of test compd. <sup>f</sup> 147.7 ± 30.5 min at 1 g/kg. <sup>g</sup> 139.5 ± 26.9 min at 1 g/kg. <sup>h</sup> 90.7 ± 14.1 min at 10 mg/kg. <sup>i</sup> 70.2 ± 5.7 min at 10 mg/kg and 64.1 ± 7.3 min at 5 mg/kg.

**$\delta,\delta,\delta',\delta'$ -Tetramethylthiazolo[5,4-d]thiazole-2,5-dibutanol (11).**—In a 300-ml flask fitted with a dropping funnel and a condenser was placed a suspension of 0.75 g (0.02 mole) of LAH in 30 ml of anhyd Et<sub>2</sub>O. While the suspension was being stirred at 50°, a soln of 5.0 g (0.0125 mole) of Me ester 7 in 120 ml of anhyd Et<sub>2</sub>O was added dropwise through the dropping funnel, followed by addn of 50 ml of anhyd Et<sub>2</sub>O. The reaction mixt was heated under reflux for 1 hr or until there was no more starting material indicated by tlc (30% MeOH in PhH) and then unreacted LAH was destroyed by addn of 100 ml of H<sub>2</sub>O. A large amt (about 7 l.) of H<sub>2</sub>O was added to dissolve the white, sparingly sol ppt. The alc was extd into 1 l. of Et<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>) for 30 min, and evapd under reduced pressure to give 4.1 g (95%) of white powder, mp 98–101°. One recrystn from Et<sub>2</sub>O brought the mp to 100–102°. The anal. sample, mp 101–102°, was prep'd by 2 further recrystns. *Anal.* (C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>) C, H, N, S.

**$\delta,\delta,\delta',\delta',N,N,N',N'$ -Octamethylthiazolo[5,4-d]thiazole-2,5-dibutylamine Dihydrochloride (12').**—To a soln of 1.15 g (0.0137 mole) of NaHCO<sub>3</sub> in 4.5 ml of 95% HCO<sub>2</sub>H were added 2.36 g (5.7 mmoles) of primary amine·di-HCl (10') and 2.5 ml of 37% HCHO in MeOH. The mixt was heated under reflux for 45 hr. It was dild with 30 ml of ice H<sub>2</sub>O and the acid soln of the tertiary amine made strongly alk with 6 N NaOH. A sticky solid appeared, which was extd with five 30-ml portions of CHCl<sub>3</sub>. The ext was dried over K<sub>2</sub>CO<sub>3</sub> for 2 hr. After the CHCl<sub>3</sub> was evapd 2.2 g (97%) of free tertiary amine 12 was left: mp 36–40.5°; nmr (CDCl<sub>3</sub>), singlets at 2.18 (NCH<sub>3</sub>) and 1.48 (gem di-Me) and broad band between 2.5 and 1.5 (CH<sub>2</sub>) integrating for 6, 6, and 6 H, resp. The whole batch of tertiary amine was dissolved in CHCl<sub>3</sub> and the soln was dried over K<sub>2</sub>CO<sub>3</sub>. Dry HCl was passed through the CHCl<sub>3</sub> soln to ppt the amine as the di-HCl, (2.1 g, 77%), which was collected, mp 285–288° dec. *Anal.* (C<sub>20</sub>H<sub>38</sub>Cl<sub>2</sub>N<sub>4</sub>S<sub>2</sub>) C, H, N, S, Cl.

**[Thiazolo[5,4-d]thiazole-2,5-diylbis(4,4-dimethyltetramethylene)]bis(trimethylammonium) Diiodide (13).**—A sample of 0.65 g (1.64 mmoles) of tertiary amine 12 was dissolved in 3 ml of dry PhH. To this soln was added 0.46 g (0.2 ml, 3.23 mmoles) of CH<sub>3</sub>I. A ppt formed instantly. After 30 min the reaction mixt was filtered, and the salt was washed thoroughly with PhH. After 1 recrystn from EtOH, 0.65 g (60%) of the product was obt'd as a white powder, mp 238–242° dec. One more recrystn gave the anal. sample, mp 266–268° dec. *Anal.* (C<sub>22</sub>H<sub>42</sub>I<sub>2</sub>N<sub>4</sub>S<sub>2</sub>) C, H, N, S, I.

**$\delta,\delta,\delta',\delta'$ -Tetramethylthiazolo[5,4-d]thiazole-2,5-dibutanol Di-*p*-toluenesulfonate (14).**—A mixt of 1.7 g (0.005 mole) of alc 11 and 3 g of C<sub>6</sub>H<sub>5</sub>N was stirred at 18°. When the alc had dissolved, 2.1 g (0.011 mole) of freshly recrystd TsCl was added in portions. Most of this material dissolved giving a cloudy suspension. The tightly stoppered mixt was stirred for 3 hr at 18°, gradually turning to a thick, faintly pink paste. About

10 ml of H<sub>2</sub>O was added to the reaction mixt to dissolve the C<sub>6</sub>H<sub>5</sub>N. The mixt was then filtered and washed with H<sub>2</sub>O until the washings were free of pyridine, then a small amt of EtOH, Et<sub>2</sub>O, and finally hexane. There was obtained 3.1 g (96%) of white crystals, mp 105–106°. The crude product was recrystd from PhH-Et<sub>2</sub>O to give white crystals, mp 105–107°. *Anal.* (C<sub>30</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>S<sub>4</sub>) C, H, S: calcd, 19.71; found, 20.12.

**2,5-Bis(1,1-dimethylbutyl)thiazolo[5,4-d]thiazole (15).**—To a suspension of LAH (0.2 g, 5.0 mmoles) in 20 ml of dry Et<sub>2</sub>O was added slowly through a dropping funnel a suspension of 1.5 g (2.3 mmoles) of tosylate 14 in 200 ml of anhyd Et<sub>2</sub>O and 20 ml of PhH. After addn the reaction mixt was heated under reflux with stirring for 12 hr. Approx 100 ml of H<sub>2</sub>O was added with caution to decomp unreacted LAH. The Et<sub>2</sub>O layer was sep'd from the mixt and the H<sub>2</sub>O layer was extd with three 100-ml portions of Et<sub>2</sub>O which were combined and dried (Na<sub>2</sub>SO<sub>4</sub>). After the solv was removed under reduced pressure a white powder (0.6 g, 83%) was obt'd, mp 66–67°. *Anal.* (C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>S<sub>2</sub>) H, N; calcd. C, 61.91; S, 20.62; found, C, 61.47; S, 19.94.

**$\delta,\delta,\delta',\delta'$ -Tetramethylthiazolo[5,4-d]thiazole-2,5-divaleronitrile (16).**—To a sample of 5.6 g (8.61 mmoles) of tosylate 14 dissolved in 56 ml of DMSO was added 0.94 g (19.2 mmoles) of NaCN. The reaction mixt was then stirred at room temp for 3 hr or until there was no more of starting tosylate as shown by tlc (10% MeOH in PhH). The clear DMSO soln was dild with 100 ml of H<sub>2</sub>O to ppt the bisnitrile, which was collected in a filter and washed repeatedly with H<sub>2</sub>O. The white powder was air-dried and weighed 2.5 g (96%), mp 101–110°. Two more recrystns from PhH-hexane gave the anal. sample, mp 110–115°. *Anal.* (C<sub>18</sub>H<sub>24</sub>N<sub>4</sub>S<sub>2</sub>) C, H, N, S.

**$\delta,\delta,\delta',\delta'$ -Tetramethylthiazolo[5,4-d]thiazole-2,5-divaloramide (17).**—A sample of 1.0 g (2.8 mmoles) of homonitrile 16 was hydrated as described for 4, procedure B, to 1.1 g (98%) of amide, mp 215–225°; anal. sample, mp 235–237°. *Anal.* (C<sub>18</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>) C, H, N, S.

**$\delta,\delta,\delta',\delta'$ -Tetramethylthiazolo[5,4-d]thiazole-2,5-divaleric Acid (18).**—To a soln of 1.74 g (4.8 mmoles) of homonitrile 16 in 8.7 ml of 95% EtOH were added 3.48 ml of 6 N NaOH and 43.5 ml of H<sub>2</sub>O. The resulting mixt was heated under reflux for 48 hr. Acidification and work-up as described for 3 gave 1.3 g (68%) of the acid, mp 192–193°, anal. sample, mp 192–193°. *Anal.* (C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>) C, H, N, S.

**Dimethyl  $\delta,\delta,\delta',\delta'$ -Tetramethylthiazolo[5,4-d]thiazole-2,5-divalerate (19).**—A mixt of 0.7 g (1.75 mmoles) of homo acid 18, 50 ml of MeOH, and 10 ml of 5 N HCl was heated on a steam cone for 2 hr. Most of the MeOH was dist'd and the residue was dild with 50 ml of H<sub>2</sub>O. Extn with CHCl<sub>3</sub> afforded an oily residue, which on crystn from aq MeOH gave 0.5 g (65%) of di-Me ester. Two more recrystns gave the anal. sample, mp 61–62°. *Anal.* (C<sub>20</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>) C, H, N, S.

**$\epsilon,\epsilon,\epsilon',\epsilon'$ -Tetramethylthiazolo[5,4-d]thiazole-2,5-dipentylamine**

**Dihydrochloride (20').**— $\delta,\delta,\delta',\delta'$ -Tetramethylthiazolothiazole-2,5-divaleronitrile (**16**, 0.9 g, 2.5 mmoles) was reduced with LAH (0.6 g, 16 mmoles) for 12 hr as described for **10** to give 0.75 g (68%) of the white di-HCl of the amine, mp 302–305° dec. *Anal.* ( $C_{18}H_{30}Cl_2N_4S_2$ ) C, H, N, S, Cl.

**$N,N,N',N',\epsilon,\epsilon,\epsilon',\epsilon'$ -Octamethylthiazolo[5,4-*d*]thiazole-2,5-dipentylamine Dihydrochloride (21').**—Homoamine·HCl (**20'**, 250 mg, 0.565 mmole) was alkylated for 35 hr and worked-up as described for **12'** to give 200 mg (76%) of di-HCl which was recrystd twice from abs EtOH, mp 255–258° dec. *Anal.* ( $C_{20}H_{38}Cl_2N_4S_2$ ) C, H, N, S, Cl.

**$\gamma,\gamma,\gamma',\gamma'$ -Tetramethylthiazolo[5,4-*d*]thiazole-2,5-dipropylamine Dihydrochloride (22').**—A soln of 7.2 g of NaOH in 60 ml of  $H_2O$  was cooled to 0–4° while 7.2 g (2.4 ml, 0.046 mole) of  $Br_2$  was added dropwise with stirring. To the resulting soln was added 5.6 g (0.017 mole) of very finely powdered **4** in one batch. The reaction mixt was allowed to stir at 0° for 1 hr, or until a clear soln (of the *N*-bromoamide, **23**) was obtained. The length of time for a clear soln to result depended on the size of the particles of the amide. (It was found that recrystd amide was coarser than crude material. Therefore in this expt the crude substance was always used). The clear yellow soln was heated on a steam bath and became turbid with sepn of an oil. After heating for 5 min the resulting mixt was transferred to a sep funnel and allowed to settle overnight. Agitation should be avoided since it causes polymn of the intermediate. The thick, yellow oil (approx 5 ml) that formed the bottom layer in the sep funnel was sepd and the aq phase extd 3 times with 50-ml portions of  $CH_2Cl_2$ . The  $CH_2Cl_2$  exts were combined with the oil. If a soln did not result immediately, sufficient  $CH_2Cl_2$  was added to give a clear soln which was dried overnight with  $K_2CO_3$ . HCl was passed through the soln until no more pptn took place. The white semisolid was collected in a filter. As air was sucked through, it became dry and a fine, white powder was obtained. The crude product was recrystd from MeOH– $Et_2O$  to give 5.0 g (80%) of white powder that decompd at 265–267°. Repeated recrystn from MeOH afforded the pure product, mp 267–270° dec. *Anal.* ( $C_{14}H_{28}Cl_2N_4S_2$ ) C, H, N, S, Cl.

**$\gamma,\gamma,\gamma',\gamma',N,N,N',N'$ -Octamethylthiazolo[5,4-*d*]thiazole-2,5-dipropylamine (24).**—Primary amine·HCl (**22'**, 9.45 g, 0.0255 mole) was converted (35-hr reaction) to tertiary amine by the method described for **12**. The crude product weighed 7.0 g (77%), mp 73–75°. Two recrystns from  $Et_2O$  gave the anal. sample, mp 79–80°. *Anal.* ( $C_{18}H_{32}N_4S_2$ ) C, H, N, S.

**[Thiazolo[5,4-*d*]thiazole-2,5-diylbis(3,3-dimethyltrimethyl-ene)]bis(trimethylammonium) Diiodide (25).**—Crude tertiary amine (**24**, 7.0 g, 0.019 mole) was quaternized (see prepn of **13**) to give 12.0 g (90%), mp 217–275° dec. One recrystn from abs EtOH gave a product, mp 291–293° dec. *Anal.* ( $C_{26}H_{58}I_2N_4S_2$ ) C, H, N, S, I.

**$\beta,\beta,\beta',\beta'$ -Tetramethylthiazolo[5,4-*d*]thiazole-2,5-dipropionic Acid (26).**—In a 100-ml flask was dissolved 0.85 g (1.39 mmoles) of bis(1,1-dimethyl-4,4-diphenyl-3-butenyl)thiazolothiazole (**29**) in 4 ml of  $C_6H_5N$ . A soln of 1.2 g (7.6 mmoles) of  $KMnO_4$  in 10 ml of  $H_2O$  and 28 ml of  $C_6H_5N$  was added with stirring at 70° and stirring and heating at 70° was continued for 30 min. At this time tlc ( $Et_2O$ ) indicated the absence of starting olefin.  $H_2O$  was added to the reaction mixt until the vol was 175 ml. A few crystals of  $Na_2S_2O_3$  were added to reduce excess  $KMnO_4$ . The hot mixt was filtered and the filtrate was washed 5 times with  $Et_2O$  or until it no longer contained  $Ph_2CO$ , as shown by tlc ( $Et_2O$ ). The  $H_2O$  phase was heated on a steam cone until all the  $Et_2O$  was evapd. The  $H_2O$  soln was then acidified with concd HCl. The white ppt which sepd was collected in a filter and washed with a small amt of EtOH. After drying it weighed 0.1 g (18%), mp 220–225° dec. It was recrystd from  $Et_2O$ : mp 228–235° dec; nmr (TFA), singlets at 3.30 ( $CH_2$ ) and 1.82 ppm (gem Me) integrating for 2 and 6 H, resp.

**$\alpha,\alpha,\alpha',\alpha',\gamma,\gamma,\gamma',\gamma'$ -Octamethylthiazolo[5,4-*d*]thiazole-2,5-dibutanol (27).**—To 0.096 mole of  $CH_3MgI$  in 30 ml of  $Et_2O$  prepd in the usual way was added 5.6 g (0.014 mole) of di-Me ester (**7**) in 45 ml of dry PhH through a dropping funnel. The reaction mixt was allowed to warm to room temp and was poured

with stirring into a mixt of 30 g of crushed ice and 11 ml of concd  $H_2SO_4$ . The  $Et_2O$  layer was sepd and the  $H_2O$  layer was extd 6 times with 30 ml of  $Et_2O$ . The  $Et_2O$  exts were combined and washed with satd  $NaHSO_4$  and 5%  $NaHCO_3$  and  $H_2O$ , in that order, and dried overnight with  $Na_2SO_4$ . A white ppt was obtained after the  $Et_2O$  was removed under reduced pressure, providing 6.7 g of product, mp 112–115°. Two recrystns from hexane yielded 4.1 g (73%) of pure alc, mp 115–117°. *Anal.* ( $C_{20}H_{34}N_2O_2S_2$ ) C, H, N, S.

**$\delta,\delta,\delta',\delta'$ -Tetramethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenylthiazolo[5,4-*d*]thiazole-2,5-dibutanol (28).**—To 0.185 mole of  $PhMgBr$  in 16 ml of anhyd  $Et_2O$  prepd in the usual way was added 14.5 g (0.036 mole) of di-Me ester **7** in 100 ml of dry PhH with stirring at 10–15°. The mixt was allowed to stand for 30 min, followed by addn of 100 ml of ice water contg 10 ml of concd  $H_2SO_4$ . The sticky green lumps that formed were broken up and the resulting white powder was collected in a filter. The  $Et_2O$  and aq phases from the filtrate were sepd. The  $H_2O$  phase was extd twice with  $Et_2O$ . The  $Et_2O$  exts were combined with the original  $Et_2O$  layer and dried ( $MgSO_4$ ) for 2 hr.  $Et_2O$  was then removed under reduced pressure. The residue was combined with the white powder collected earlier; the total yield was 19.5 g (83.2%), mp 198–202°. The crude product was recrystd twice from PhH to give the anal. sample, mp 215–217°. *Anal.* ( $C_{40}H_{42}N_2S_2O_2$ ) C, H, N, S.

**Bis(1,1-dimethyl-4,4-diphenyl-3-butenyl)thiazolo[5,4-*d*]thiazole (29).**—A sample of 0.95 g (1.47 mmoles) of alc **28** was heated under reflux with 23 ml of  $Ac_2O$  for 44 hr. To this reaction mixt was added 30 ml of  $H_2O$  and excess  $Ac_2O$  was hydrolyzed by warming on a steam bath for 5 min. The white ppt was collected in a filter and washed with  $H_2O$  until the washings were no longer acidic followed by a small amount of EtOH. The yield was 0.85 g (96%), mp 118–120°, and after 1 recrystn from EtOH, mp 121–122°. *Anal.* ( $C_{40}H_{42}N_2S_2$ ) H, N, S; C: calcd, 78.64; found 79.23.

**Pharmacology. Acute Toxicity.**—Ten albino Swiss mice (15–25 g) were used for each dose. The compd to be tested was administered ip. In order to avoid group reactions each mouse was kept in a sep cage. All mice were observed for 24 hr, except in the case of **7** where, due to its slower onset and longer action, the animals were obsd for 72 hr.

Neutral compds were triturated with 5 drops of Tween 80 and a stock soln of 0.5% acacia and 20% (w/v) of propylene glycol was added with trituration until the vol was 100 ml. Amines were injected as aq solns of the di-HCl's and acids as aq solns of the Na salts. The pH of injections solns was adjusted to approx 7. To vary the dose, the concn of the suspension or soln was changed in order that the vol injected was maintained const (10.0 ml/kg). Results are recorded in Table I.

**Pentobarbital Potentiation.**—Albino Swiss mice (18–22 g) were treated ip with sublethal doses (prepared as described above) of test compds followed in 15 min by an anesthetic dose (65 mg/kg) of sodium pentobarbital. Ten mice were used at each dose level, selected according to the  $LD_{50}$  of the compd, usually about 0.10 or 0.05 of the  $LD_{50}$ . The sleeping time was taken as the interval between administration of sodium pentobarbital and when the animal regained and maintained its righting reflex for 1 min. Results are given in Table II.

Comparison of these results with those reported by Fikrat,<sup>4</sup> reveals that we obtained longer sleeping times with both controls and pretreated animals. These differences may be due to differences in vehicles used for injections and different routes of administration. Fikrat used PEG as the vehicle which did appear to produce some effects. Also, in the expt described by Fikrat pentobarbital was administered sc and only the test compd was injected ip.

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