required to block the effect of histamine by 50% (EC_{50}, in μg/mL) and confidence intervals were determined by regression analysis.

Guinea Pig Atrium. The atria from guinea pigs (Hartley strain) were dissected from other myocardial tissue, suspended in 20 mL of McEwen's solution,[14] and attached to a transducer. Spontaneous rate was counted from the recorded tracing. Chronotropic responses to increasing concentrations of histamine (0.05–3.2 μg/mL) were obtained in the presence of placebo or test compound. Results are expressed as the ratio of (a) the concentration of histamine required to increase the rate by 50 beats/min in a placebo trial to (b) the concentration required in the presence of a test compound.

Dog Gastric Fistula. Nonanesthetized female beagle dogs (7-10 kg) with a chronic gastric fistula were administered test compounds directly into the stomach via the gastric cannula (identified herein as oral administration). Placebo or test compounds were administered in 50 mL of a 1% methylcellulose solution 1 h prior to stimulation of gastric secretion. Secretion was stimulated with gastrin tetrapeptide (64 μg/kg sc from a 30% Me_2SO solution containing 640 μg/mL) or histamine (64 μg of base, wt/kg sc, from a solution of histamine diphosphate, 640 μg of base, wt/mL, in physiological saline). Gastric output was collected for three consecutive 30-min periods (90 min total) after administration of the stimulant. Volume was measured and the acid concentration (titratable acid) was determined on an aliquot by titration to pH 7 with 0.01 N NaOH using a glass–calomel electrode. Results are reported as the maximal percent reduction in acid concentration following treatment relative to a placebo trial in the same animal.

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Notes

An Attempt to Apply Lethal Synthesis to the Design of Chemotherapeutic Agents. Fluorinated 5β-(Hydroxyethyl)-4-methylthiazoles

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2-Fluoro-5β-(hydroxyethyl)-4-methylthiazole (V) was prepared from 5β-acetoxy-2-amino-4-methylthiazole (X), which was prepared from 5β-acetoxy-3-chloropentanone (IX) and thiourea. Diazotization with $NOBF_4$ followed by pyrolysis gave 5β-acetoxy-2-fluoro-4-methylthiazole (XII), which on hydrolysis with $KHCO_3$ gave V. (Trifluoroacetyl)-γ-butyrolactone (XIII) was chlorinated with SO_2Cl_2 to give 2-chloro-2-(trifluoroacetyl)-γ-butyrolactone (XIV), which on hydrolysis and decarboxylation gave 3-chloro-1,1,1-trifluoro-5-hydroxy-2-pentanone which exists as the hemiketal XV. Treatment with thiourea gave 2-amino-5β-(hydroxyethyl)-4-(trifluoromethyl)thiazole (XVI), but no thiazole formation was observed when XV was treated with thioformamide. Ethyl 2-(trifluoroacetyl)-γ-methoxybutyrate (XVIII), prepared from ethyl γ-methoxybutyrate and ethyl trifluoroacetate, gave after hydrolysis and decarboxylation 5-methoxy-1,1,1-trifluoro-2-pentanone (XIX), which on bromination followed by treatment with thioformamide gave 5β-(methoxyethyl)-4-(trifluoromethyl)thiazole (XXI). Treatment of XXI with BBr_3 gave 5β-(hydroxyethyl)-4-(trifluoromethyl)thiazole (VI). Neither V nor VI showed antibacterial action against two strains of *Escherichia coli*. A rationalization of this lack of activity is discussed.

Lethal synthesis may be defined as the conversion of substrate analogues by enzymes of a metabolic pathway to an antimetabolite of either the end product of a biosynthetic sequence or an intermediate thereof. An attractive feature of using this approach in the design of chemotherapeutic agents is that by the selection of appropriate biosynthetic pathways, preferably those that are present in the target organism and absent in the host, selective toxicity may be achieved. Gale et al.[1] pointed out that the concept of lethal synthesis has not been fully exploited. These authors cite the action of fluoroacetate as a classic example of this idea. Because of its chemical and structural similarity to acetate, fluoroacetate undergoes similar biochemical transformations as the natural substrate and eventually is converted to fluorocitrate, which is an irreversible inhibitor of aconitase, the enzyme

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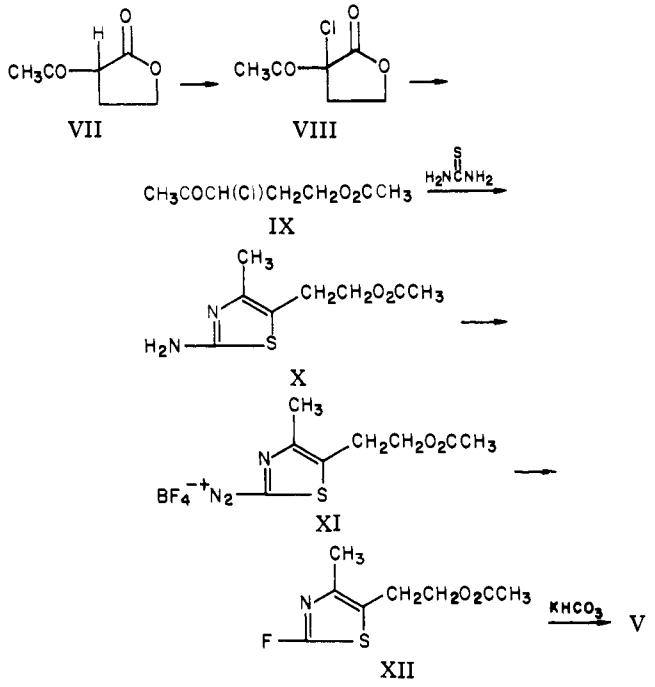
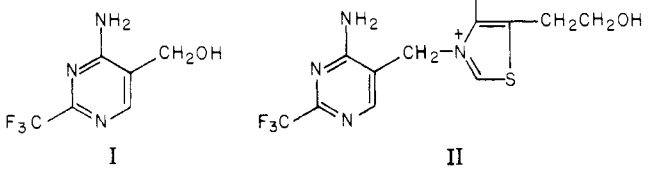
Scheme I

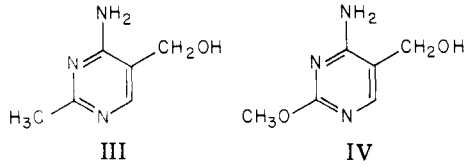


responsible for the conversion of citrate to *cis*-aconitate. Fluoroacetate manifests no selectivity of action, since the group of enzymes responsible for these biotransformations are present in both bacteria and their mammalian hosts.

Other less well-known examples can be found among some analogue of the pyrimidine moiety of thiamin. Barone et al. synthesized I[2] and trifluorothiamin II.[3]



They found that II, a classical antimetabolite, was a potent inhibitor of *Bacillus subtilis* and that its action was reversed by thiamin. Of greater significance was the observation that I also was an inhibitor of *B. subtilis* and that its action could be partially reversed by the thiamin precursor III. These authors did not determine whether

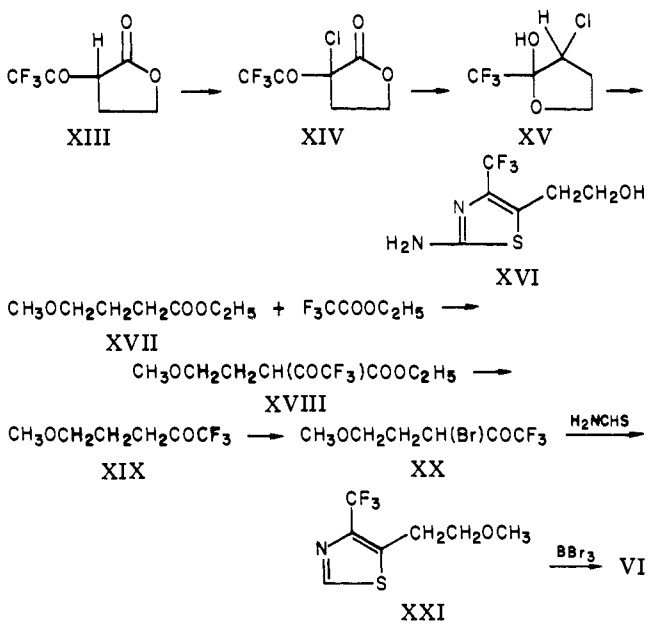


the antibacterial action of I was thiamin reversible. Nevertheless, it may be concluded that at least a part of the antibacterial effect of I is due to its bioconversion to II by the bacterium, thus qualifying as an example of lethal synthesis.

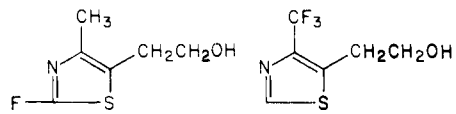
Bacimethrin (IV) is an antibiotic which may owe its antibacterial effect to its role as a substrate analogue in lethal synthesis. It appears to lack complete specificity, since pyridoxine can also reverse the activity of IV.[4] On the other hand, it is not nonspecific either, since it does not interfere with pyrimidine biosynthesis, as evidenced by the fact that neither thymin nor uracil exerted an antagonistic action.

It was hoped that by focusing attention on the thiazole moiety of thiamin greater selectivity of action could be

Scheme II



realized, since this ring system is unique in mammalian and bacterial metabolism, a situation which should minimize possible interference with other biosynthetic pathways. To this end, it was decided to prepare V and VI and determine their antibiotic activities against ap-



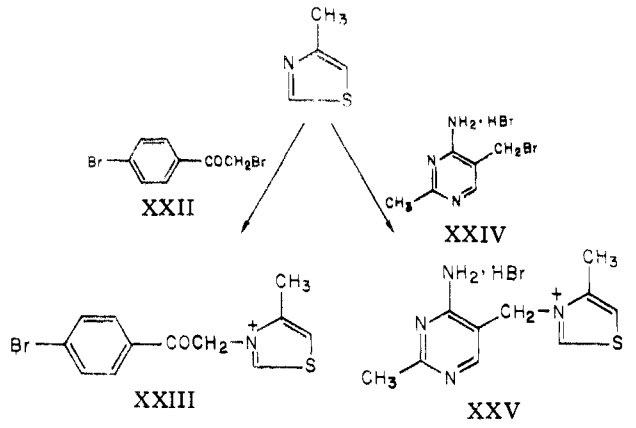
propriate microorganisms. The synthesis of V is outlined in Scheme I.

Chlorination of 5-acetoxy-2-pentanone[5] with SO_2Cl_2 led to a mixture of IX, 5-acetoxy-1-chloro-2-pentanone, and 5-acetoxy-3,3-dichloro-2-pentanone. A much cleaner preparation consisted of the chlorination of acetobutyrolactone (VII) to give VIII,[6] which after hydrolysis and acetylation furnished IX unaccompanied by other chlorinated pentanones. Condensation of IX with thiourea gave the aminothiazole X, which was treated with $NOBF_4$ in HBF_4 to give XI.[7] Decomposition of XI at 60–65 °C furnished XII. Hydrolysis with $KHCO_3$ afforded the desired fluorothiazole V. The preparation of VI was carried out as shown in Scheme II.

2-(Trifluoroacetyl)-γ-butyrolactone (XIII) was prepared from γ-butyrolactone and ethyl trifluoroacetate. This keto ester formed a hydrate. Chlorination gave XIV, which formed a hydrate even more readily than its precursor XIII. Hydrolysis and decarboxylation gave XV which, judging from the absence of carbonyl absorption in the infrared spectrum, existed in the hemiketal form. When treated with thiourea, XV formed the aminothiazole XVI in 30% yield, but when allowed to react with thioformamide under similar conditions, none of the desired thiazole VI was obtained. The reluctance of XV to react was attributed to the fact that it was not a true halo ketone. This supposition was supported by the successful synthesis of VI from the methoxyethylthiazole XXI.

Ethyl γ-methoxybutyrate (XVII) and ethyl trifluoroacetate condensed to give the keto ester XVIII, which after hydrolysis and decarboxylation gave the methoxypentanone XIX whose infrared spectrum showed the presence of a free carbonyl group. Bromination gave XX

Scheme III



which, without isolation, was treated with thioformamide to give XXI which was demethylated with BBr_3 to give the desired thiazole VI.

Neither V nor VI showed antibacterial activity in concentrations as high as 1 mg/mL when tested against *E. coli* B and *E. coli* AS19.[8] The lack of significant activity of these thiazoles is probably due to the reduced nucleophilicity of the nitrogen induced by the neighboring fluorine in the case of V and the trifluoromethyl group in VI. This in turn would prevent the biosynthesis of the fluorinated thiamin analogues from V and VI by the bacteria. Evidence for this hypothesis was found when it was observed that 4-methylthiazole reacted with *p*-bromophenacyl bromide (XXII) to give the thiazolium salt XXIII and with 6-amino-5-(bromomethyl)-2-methylpyrimidine hydrobromide (XXIV) to give XXV in yields of about 90% (see Scheme III). On the other hand, under identical conditions neither V nor VI reacted with XXII or XXIV to give the corresponding thiazolium salts.

Experimental Section

Melting points were taken on a Laboratory Devices Mel-Temp apparatus. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer, and the NMR spectra were recorded on a Varian T-60A spectrometer with Me_4Si as the internal standard. Elementary analyses were determined by Instranal Laboratory, Rensselaer, N.Y.

5-Acetoxy-3-chloro-2-pentanone (IX). (A) From 5-Acetoxy-2-pentanone. To 43.8 g (0.3 mol) of 5-acetoxy-2-pentanone kept at 0–5 °C 28 mL (0.33 mol) of SO_2Cl_2 was added dropwise. The solution was stirred overnight and poured into ice–water. The organic phase was dissolved in ether, washed with water, dried, and fractionally distilled to give 5-acetoxy-3,3-dichloro-2-pentanone [bp 56 °C (0.2 mm); NMR ($CDCl_3$) δ 2.20 (s, 3, CH_3CO), 2.38 (s, 3, CH_3COO), 2.70 (t, 2, CH_2O), 4.38 (t, 2, CCl_2CH_2). Anal. ($C_7H_{10}Cl_2O_3$), C, H, Cl], 5-acetoxy-3-chloro-2-pentanone (IX) [43 g (80%); bp 63–64 °C (0.15 mm); NMR (neat) δ 1.98 (s, 3, CH_3CO), 2.20 (m, 2, CH_2), 2.30 (s, 3, CH_3COO), 4.09 (t, 2, CH_2O), 4.48 (m, 1, CHCl)], and 5-acetoxy-1-chloro-2-pentanone [bp 80–81 °C (0.15 mm); NMR (neat) δ 2.00 (s, 3, CH_3CO), 2.35 (m, 2, CH_2), 4.20 (t, 2, CH_2CO), 4.60 (s, 2, CH_2Cl), 4.75 (t, 2, CH_2O)].

(B) From Acetobutyrolactone. To 12.8 g (0.1 mol) of acetobutyrolactone kept at 0–5 °C, 8.5 mL (0.1 mol) of SO_2Cl_2 was added over a period of 30 min. The solution was allowed to stand overnight, poured into ice–water, and extracted with ether. The aqueous phase was extracted with ether, and the combined ether layers were dried and distilled to give 15 g (92%) of VIII, bp 70–71 °C (0.15 mm) [lit.[6] bp 86 °C (1–2 mm)]. A solution of 8.1 g (0.05 mol) of VIII, 7.2 g of 87% acetic acid, and 0.5 mL of concentrated HCl was heated on the steam bath for 10 h, cooled, treated with 6.3 g of acetic anhydride, and heated an additional 8 h. The solution was distilled to give 7.7 g (85%) of IX, bp 112–113 °C (0.5 mm).[5]

5β-(Acetoxyethyl)-2-amino-4-methylthiazole (X). A suspension of 3.8 g (0.05 mol) of finely powdered thiourea in 8.9 g (0.05 mol) of IX was heated in an oil bath to 100 °C. During this heating period the thiourea dissolved and a vigorous reaction ensued. The mixture was kept at 100 °C for 10 min, cooled, and treated with water. The aqueous layer was extracted with ether to remove any unreacted ketone and then made alkaline. The solution was evaporated to leave a crystalline residue, which after recrystallization from ethanol furnished 5.5 g (55%) of X: mp 103–104 °C; NMR ($CDCl_3$) δ 2.04 (s, 3, CH_3), 2.10 (s, 3, CH_3), 2.90 (m, 2, CH_2), 4.10 (m, 2, CH_2O), 5.50 (br s, 2, NH_2). Anal. ($C_8H_{12}N_2O_2S$) C, H, N.

5β-(Acetoxyethyl)-2-fluoro-4-methylthiazole (XII). $NOBF_4$ (8.4 g) was added portionwise to a solution of 14.0 g (0.07 *m*) of X in 28 mL of 47% HBF_4 at −10 °C. The clear solution was kept at −50 to −60 °C for 20 min, and then 50 mL of ether was added. After 30 min, the diazonium salt XI which separated was collected, washed with ether, and dried: wt 19.0 g (90%); mp 65–67 °C (dec).

The dry diazonium salt was suspended in toluene and heated to 65 °C, at which temperature decomposition ensued with the evolution of N_2. After 1 h, the mixture was cooled and poured into water. The aqueous phase was extracted with $CHCl_3$, and the combined organic layers were washed with water and dilute $NaHCO_3$, dried, and distilled to give 5.36 g (42%) of XII: bp 65 °C (0.35 mm); NMR ($CDCl_3$) δ 2.00 (s, 3, CH_3), 2.20 (s, 3, CH_3), 3.00 (t, 2, CH_2), 4.20 (t, 2, CH_2O). Anal. ($C_8H_{10}FNO_2S$) C, H, N.

2-Fluoro-5β-(hydroxyethyl)-4-methylthiazole (V). A solution of 1.6 g (0.008 mol) of XII in 25 mL of CH_3OH and 20 mL of 10% aqueous $KHCO_3$ was stirred for 1 h at room temperature and then at reflux for 30 min. The CH_3OH was removed in vacuo and H_2O was added to the residue. The suspension was extracted with $CHCl_3$, washed with H_2O, dried, and distilled to give 0.72 g (56%) of V: bp 69–70 °C (0.1 mm); NMR ($CDCl_3$) δ 2.20 (s, 3, CH_3), 2.80 (t, 2, CH_2), 3.75 (t, 2, CH_2O), 4.40 (br s, 1, OH). Anal. (C_6H_8FNOS) C, H, N.

α-(Trifluoroacetyl)-γ-butyrolactone (XIII). A dispersion of 36 g of 50% NaH in mineral oil (0.75 mol) was washed with hexane and suspended in 800 mL of ether under an atmosphere of nitrogen. Two milliliters of absolute C_2H_5OH was added followed by the dropwise addition of a solution of 60.2 g (0.7 mol) of γ-butyrolactone and 99.4 g (0.7 mol) ethyl trifluoroacetate in 760 mL of dry ether at such a rate that gentle reflux was maintained. The resulting slurry was stirred overnight, cooled, and acidified with 10% HCl. The aqueous layer was extracted with ether, and the combined ether layers were washed with a small quantity of H_2O and evaporated, to leave a crystalline residue which was the hydrate of XIII. Recrystallization from ether–hexane gave 62 g (44%) of the hydrate: mp 95–98 °C; IR 3450 (OH), 1775 cm^{-1} (lactone C=O); NMR (Me_2SO-d_6) δ 2.40 (d, 2, CH_2), 3.20 (t, 1, CH), 4.30 (t of t, 2, CH_2O), 6.90 (br s, 1, OH), 7.20 (br s, 1, OH). The protons at 3.20, 6.90, and 7.20 were exchanged in D_2O. Anal. ($C_6H_5F_3O_3 \cdot H_2O$) C, H.

α-Chloro-α-(trifluoroacetyl)-γ-butyrolactone (XIV). To 75 mL of SO_2Cl_2 was added 15.0 g (0.075 mol) of the hydrate of XIII. The suspension was stirred overnight and then heated to reflux, whereupon the solid dissolved. After 6 h, the yellow-green solution was concentrated in vacuo and the residue was distilled to give 13 g (80%) of XIV: bp 89–90 °C (8 mm); NMR ($CDCl_3$) δ 3.05 (m, 2, CH_2), 4.60 (q, 2, CH_2O), 6.40 (br s, 1, OH), 7.20 (br s, 1, OH).

3-Chloro-2-hydroxy-2-(trifluoromethyl)tetrahydrofuran (XV). A solution of 8.60 g (0.04 mol) of XIV in 8 mL of 87% acetic acid and 0.4 mL of concentrated HCl was refluxed for 8 h. The solution was distilled to give 5.01 g (69%) of XV: bp 61 °C (6 mm); IR 3600 cm^{-1} (OH), no C=O absorption; NMR ($CDCl_3$) δ 2.40 (m, 2, CH_2), 4.30 (m, 3, CH_2O and CHCl), 4.70 (br s, 1, OH). Anal. ($C_5H_6ClF_3O_2$) C, H.

2-Amino-5β-(hydroxyethyl)-4-(trifluoromethyl)thiazole (XVI). A solution of 5.79 g (0.03 mol) of XV in 15 mL of 0.1 N HCl was heated overnight; then 2.28 g (0.03 mol) of thiourea was added and heating on the steam bath continued for an additional 7 h. The cooled reaction mixture was made alkaline and extracted with ether. The ethereal solution was evaporated to leave a crystalline residue, which after recrystallization from ethyl acetate gave 1.3 g (30%) of XVI: mp 197–198 °C; NMR (Me_2SO-d_6) δ 2.20 (m, 2, CH_2), 3.90 (d of d, 1, CH_2), 4.00 (br s, 1, OH), 4.60 (d of d, 1, CH_2), 7.20 (br s, 2, NH_2). Anal. ($C_6H_7F_3N_2OS$) C, H, N.

Ethyl γ-Methoxy-α-(trifluoroacetyl)butyrate (XVIII). A mixture of 86 g (1.0 mol) of γ-butyrolactone and 1 L of 2 N NaOH was stirred at room temperature for 2 days, refluxed 3 h, and cooled. Any unchanged lactone was removed with ether, and the alkaline solution was evaporated to dryness. The residue was dissolved in 150 mL of 40% NaOH and treated alternately with 3 × 50 mL portions of $(CH_3)_2SO_4$ and 3 × 50 mL portions of 40% NaOH. The mixture was heated to 90 °C, kept at 50–60 °C for 1 h, cooled, acidified with dilute H_2SO_4, and extracted with ether. The dried extracts were distilled to give 41.5 g (35%) of γ-methoxybutyric acid, bp 114 °C (13 mm); Reppe[9] reported bp 103–105 °C (8 mm). A solution of 36.5 g (0.31 mL) of the acid was refluxed overnight with 150 mL of absolute C_2H_5OH and 0.5 mL of concentrated H_2SO_4 and worked up in the usual way to afford 38.5 g (85%) of ethyl γ-methoxybutyrate, bp 75–76 °C (15 mm).

To a slurry of 38.5 g (0.8 mol) of a 50% dispersion of NaH in 200 mL of benzene maintained under a nitrogen atmosphere, there was added a few drops of absolute C_2H_5OH followed by the dropwise addition of a solution of 38.5 g (0.25 mol) of XVII and 40 g (0.28 mol) of ethyl trifluoroacetate in 400 mL of benzene. At the end of the addition, the mixture was refluxed for 2 h, stirred overnight, and acidified with dilute HCl. The benzene layer was washed with water and the aqueous layer extracted with ether. The combined organic layers were dried and distilled to give 41.0 g (68%) of the keto ester XVII: bp 85–86 °C (13 mm); NMR ($CDCl_3$) δ 1.25 (t, 3, CH_2CH_3), 2.20 (m, 2, CH_2), 3.25 (s, 3, OCH_3), 3.40 (q, 2, OCH_2), 3.90 (t, 1, CH), 4.20 (q, 2, OCH_2). Anal. ($C_9H_{13}F_3O_4$) C, H.

γ-Methoxypropyl Trifluoromethyl Ketone (XIX). A solution of 36.3 g (0.15 mol) of XVIII, 40 mL of 87% acetic acid, and 0.5 mL of concentrated HCl was refluxed overnight, cooled, and carefully neutralized with solid K_2CO_3. Ten milliliters of H_2O was added and the slurry was extracted with ether. The dried ether extract was distilled to give 13.0 g (50%) of XIX: bp 120–123 °C; NMR ($CDCl_3$) δ 2.00 (q, 2, CH_2), 2.80 (t, 2, $COCH_2$), 3.30 (s, 3, OCH_3), 3.40 (t, 2, OCH_2). Anal. ($C_6H_9F_3O_2$) C, H.

5β-(Methoxyethyl)-4-(trifluoromethyl)thiazole (XXI). A solution of 4 mL of bromine in 150 mL of CCl_4 was added dropwise to 12.4 g (0.073 mol) of XIX. After 4.5 h, the mixture was warmed for 10 min to complete the reaction. The pale-yellow solution was evaporated to dryness, and the residue, which was mainly the bromo ketone XX, was treated with an ethereal solution of thioformamide prepared by stirring a mixture of 22.2 g (0.05 mol) of P_4S_{10}, 40 mL of $HCONH_2$, and 350 mL of dry ether for 5 h and decanting the supernatant solution. The ether was removed and the residue was heated at 100–110 °C for 10 min, cooled, and partitioned between ether and water. The separated aqueous phase was extracted with ether. The dried extracts were distilled to give 7.56 g (49%) of XXI: bp 115–117 °C (24 mm); NMR ($CDCl_3$) δ 3.20 (m, 2, CH_2O), 3.35 (s, 3, OCH_3), 3.60 (t, 2, CH_2), 8.70 (s, 1, thiazole H). Anal. ($C_7H_8F_3NOS$) C, H, N.

5β-(Hydroxyethyl)-4-(trifluoromethyl)thiazole (VI). A solution of 4.22 g (0.02 mol) of XXI in 80 mL of CH_2Cl_2 was cooled to −80 °C under an atmosphere of N_2. A cooled solution of 2 mL (0.02 mol) of BBr_3 in 15 mL of CH_2Cl_2 was added and the mixture was allowed to warm to room temperature overnight. The solution was treated with water and ether. The organic layers were removed, and the aqueous phase was made alkaline with 2 N NaOH and extracted with ether. The combined organic layers were washed with water and distilled to give 2.34 g of VI: bp 134–135 °C (1.0 mm); NMR ($CDCl_3$) δ 3.20 (t, 2, CH_2O), 3.85 (t, 2, CH_2), 4.25 (br s, 1, OH), 8.70 (br s, 1, thiazole H). Anal. ($C_6H_6F_3NOS$) C, H, N.

Thiazolium Salts from 4-Methylthiazole. (A) *p*-Bromophenacyl Bromide. A mixture of 278 mg (1.0 mmol) of *p*-bromophenacyl bromide and 150 mg (1.5 mmol) of 4-methylthiazole[10] was heated in an oil bath at 120–125 °C for 5 min, cooled, and covered with ether. The insoluble quaternary salt XVIII was filtered and dried: wt 330 mg (88%); mp 236–238 °C after crystallization from C_2H_5OH. Anal. ($C_{12}H_{11}Br_2NOS$) C, H, N.

(B) 6-Amino-5-(bromomethyl)-2-methylpyrimidine Hydrobromide. A mixture of 142 mg (0.5 mmol) of the bromomethylpyrimidine[11] and 100 mg (1.0 mmol) of 4-methylthiazole was kept at 120–140 °C for 10 min, cooled, and worked up as above. The ether-insoluble salt XXV weighed 180 mg (94%) and after crystallization from C_2H_5OH melted at 261–263 °C. Anal. ($C_{10}H_{14}Br_2H_4S$) C, H.

Where V and VI were used in place of 4-methylthiazole in the above experiments, none of the corresponding thiazolium salts were obtained.

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