

Reactions of Tetrahydro-*as*-triazine-3(2*H*)-thiones with α,β -Difunctional Compounds

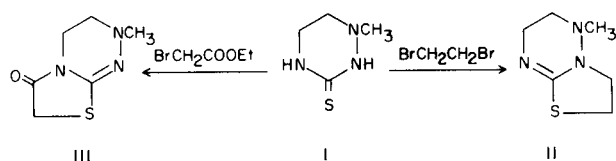
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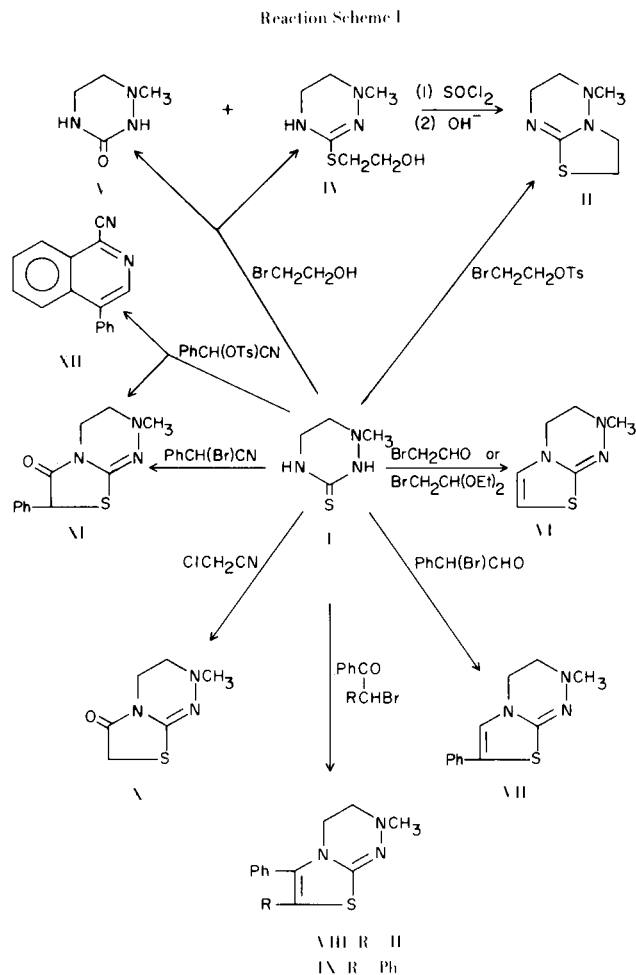
The results of allowing tetrahydro-*as*-triazine-3(2*H*)-thiones to react with various α,β -difunctional compounds, such as, α -bromoethyl *p*-toluenesulfonate, chloroacetaldehyde, α -bromophenylacetaldehyde, phenacyl bromide, chloroacetonitrile, α -bromophenylacetonitrile, and α -cyanobenzyl *p*-toluenesulfonate are discussed. These condensations give either a 5*H*-thiazolo[3,2-*b*]-*as*-triazine or a 2*H*-thiazolo[2,3-*c*]-*as*-triazine.

Previously, we reported (1) that allowing 1,4,5,6-tetrahydro-1-methyl-*as*-triazine-3(2*H*)-thione (I) to react with ethylene dibromide and with ethyl bromoacetate gives 2,3,6,7-tetrahydro-5-methyl-5*H*-thiazolo[3,2-*b*]-*as*-triazine (II) and 3,4-dihydro-2-methyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine-6(7*H*)-one, respectively.



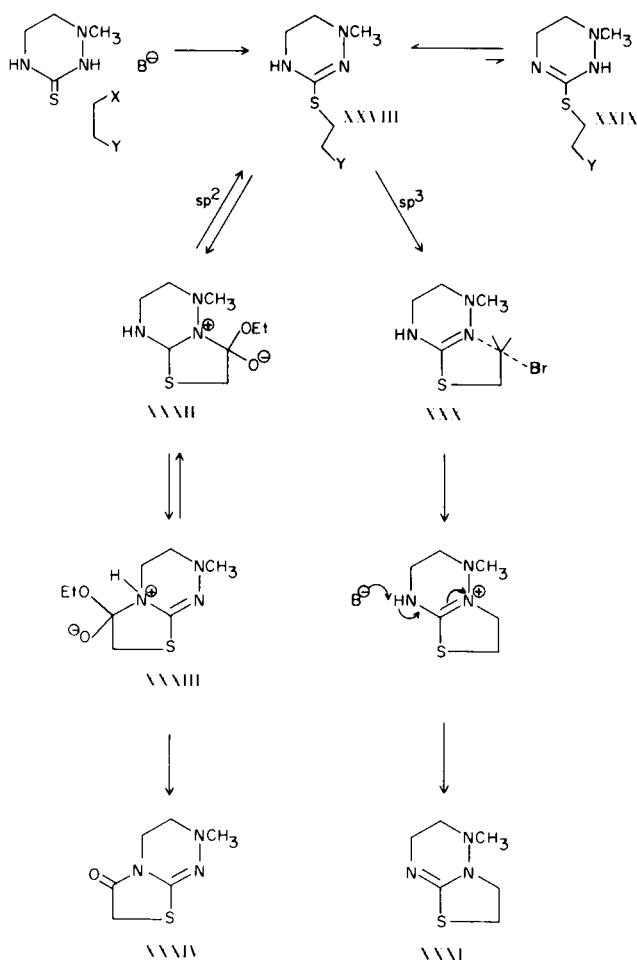
This paper reports the results of allowing triazine-thione I to react with other difunctional compounds, such as, β -bromoethyl *p*-toluenesulfonate, chloroacetaldehyde, chloroacetaldehyde diethylacetal, α -bromophenylacetaldehyde, phenacyl bromide, chloroacetonitrile, α -bromophenylacetonitrile, and α -cyanobenzyl *p*-toluenesulfonate (Reaction Scheme 1). These reactions are described in the Experimental. All new compounds were subjected to elemental, infrared, and pmr analyses.

The results obtained by allowing triazinethione I to react with a variety of α,β -bifunctional compounds in which one of the functionalized carbons is sp^3 and the other is either sp^3 , sp^2 , or sp indicate that initially the sulfur of the triazinethione attacks an sp^3 carbon and this is followed by ring closure at N₂ of the triazinethione when the β -carbon of the α,β -bifunctional reactant is sp^3 and by ring closure at N₄ when the β -carbon is sp^2 or sp . Thus, when both the α - and β -carbons of the α,β -bifunctional reactant are sp^3 the 5*H*-thiazolo[3,2-*b*]-*as*-triazine is produced and when the α -carbon is sp^3 and the β -carbon is either sp^2 or sp the 2*H*-thiazolo[2,3-*c*]-*as*-triazine is produced.



These results are best interpreted as shown in Scheme II. The initially formed 1-methyl-3-substituted thio-1,4,5,6-tetrahydro-*as*-triazine (XXVIII) which possesses a pyridine-

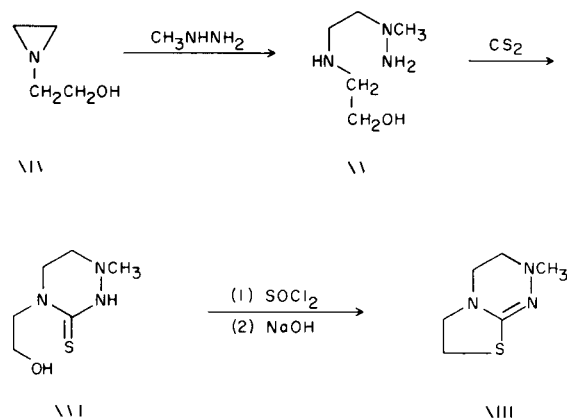
Reaction Scheme II



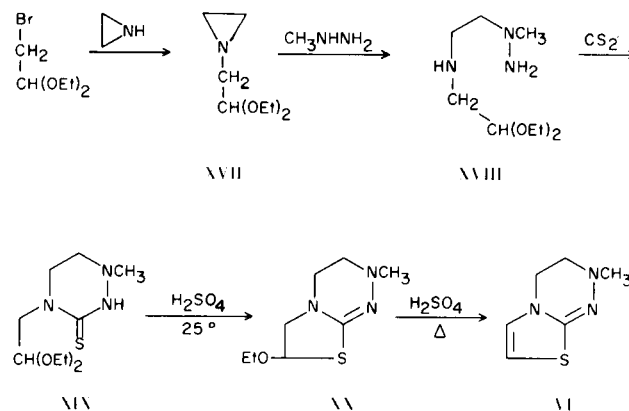
like sp^2 nitrogen at N_2 and a pyrrole-like sp^3 nitrogen at N_4 is the preferred protomeric form rather than protomer XXIX which has the double bond between C_3 - N_4 because protomer XXVIII possesses the additional resonance energy gained by overlap of the lone pair of N_1 with the π -system of the $C=N$. This conjugation is not possible in protomer XXIX. Therefore, the ring closure step initially involves attack of the lone pair of the pyridine-like N_2 on the β -carbon of the thio side-chain. When the β -carbon is sp^3 the unstable pentavalent intermediate or transition state (XXX) collapses directly to product (XXXI). However, when the β -carbon is sp^2 or sp the comparatively stable tetrahedral intermediate (XXXII) opens and subsequently closes at N_4 to form the less energetic intermediate (XXXIII) which then goes to product (XXXIV). This is analogous to the role of the acylpyridinium complex ($RCO-NC_5H_5$) in the acylation of secondary amines by acyl halides in the presence of pyridine.

In order to further substantiate the structure of the thiazolotriazines listed in Reaction Scheme I, and to establish the direction of cyclization in the various condensations, unequivocal syntheses of certain thiazolo[3,2-*b*]- and thiazolo[2,3-*c*]-*as*-triazines were carried out.

As previously reported (1) to determine the structure of 2,3,6,7-tetrahydro-5-methyl-5*H*-thiazolo[3,2-*b*]-*as*-triazine (II), the structurally isomeric 3,4,6,7-tetrahydro-2-methyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine (XIII) was prepared using the following unequivocal synthesis.



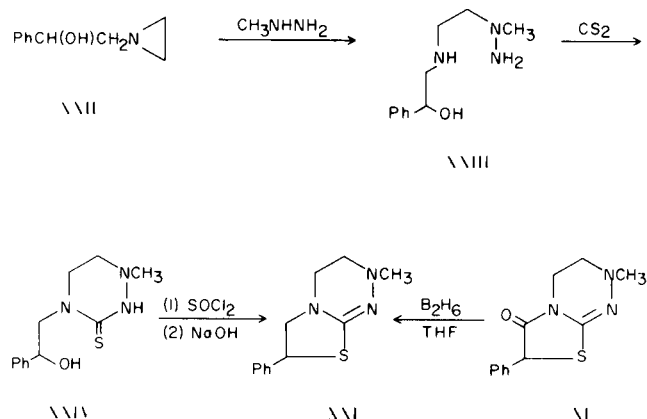
To prove the structure of the condensation products obtained when triazinethione I was allowed to condense with α -haloaldehydes and α -haloketones, 3,4-dihydro-2-methyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine (VI) was prepared by an unequivocal synthesis in the following manner.



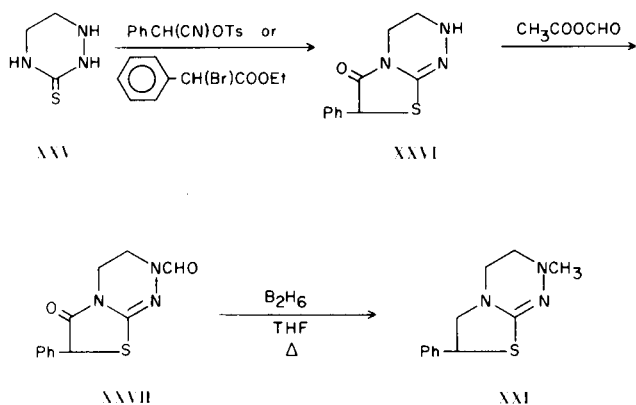
The structure proof for thiazolotriazinone X was accomplished by reducing it with diborane to the known 3,4,6,7-tetrahydro-2-methyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine (XIII).

The structure assigned to phenylthiazolotriazinone XI was verified in the following manner: XI was reduced with diborane in refluxing tetrahydrofuran to 3,4,6,7-tetra-

hydro-2-methyl-7-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine (XXI) which was synthesized using the following unequivocal method. *N*-(β -Hydroxyphenethyl)aziridine (XXII) was allowed to react with methylhydrazine to give *N*-(β -hydroxyphenethylaminoethyl)-*N*-methylhydrazine (XXIII) which was treated with carbon disulfide in refluxing acidic 50% aqueous ethanol to give 4-(β -hydroxyphenethyl)-1,4,5,6-tetrahydro-1-methyl-*as*-triazine-3(2*H*)-thione (XXIV). Treatment of XXIV with thionyl chloride followed by sodium hydroxide cyclized it to phenylthiazolotriazine XXI.



To determine whether the presence of a methyl group at position one of the triazinethione (I) influenced the direction of the cyclization, 1,4,5,6-tetrahydro-*as*-triazine-3(2*H*)-thione (XXV) was allowed to condense with α -cyano-benzyl *p*-toluenesulfonate and with ethyl α -bromophenylacetate. In both cases, the only phenylthiazolotriazinone isolated was 3,4-dihydro-7-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazin-6(7*H*)-one (XXVI). The proof of structure of XXVI was accomplished in the following manner: XXVI was 2-formylated with acetic-formic anhydride and the 2-formylphenylthiazolotriazinone XXVII was reduced with diborane in refluxing tetrahydrofuran to authentic 3,4,6,7-tetrahydro-2-methyl-7-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine (XXI).



EXPERIMENTAL

The melting points were obtained in a capillary tube with the Thomas-Hoover Uni-Melt and are corrected. The elemental analyses were done by Midwest Microlabs., Inc., Indianapolis, Indiana. The pmr spectra were obtained with a Varian A-60 using TMS as an internal standard. Infrared spectra were obtained with a Perkin-Elmer 337 grating spectrophotometer.

2,3,6,7-Tetrahydro-5-methyl-5*H*-thiazolo[3,2-*b*]-*as*-triazine (II).A. By Condensation of Triazinethione I and β -Bromoethyl *p*-Toluenesulfonate.

A solution of 54.5 g. (0.19 mole) of β -bromoethyl *p*-toluenesulfonate in 100 ml. of ethanol was added, during a 75 minute period, to a stirred mixture of 25.6 g. (0.19 mole) of triazinethione I and 22 g. (0.20 mole) of anhydrous sodium carbonate in 400 ml. of refluxing ethanol. The mixture was stirred and heated at reflux for an additional 2 hours, allowed to stand overnight at room temperature, filtered, and the filtrate concentrated *in vacuo* to give an oil which, together with the filtered solid, was taken up in a mixture of 500 ml. of water and 500 ml. of chloroform. The phases were separated and 250 ml. of water was added to the aqueous phase which was then extracted with 500 ml. of chloroform. The combined chloroform extracts were washed with 200 ml. of water, then brine (2 x 100 mls.). The dried (magnesium sulfate) chloroform solution was concentrated *in vacuo* to give 27.5 g. (90%) of yellow oil, infrared spectrum was nearly identical to that for authentic thiazolotriazine II (1). Rapid distillation yielded 18 g. of yellow oil which distilled at 140-144° (2 mm) and whose infrared spectrum was identical to authentic II (1). The methiodide of II (m.p. 151-153°) was identical to authentic II methiodide (1).

B. By Thionyl Chloride-Sodium Hydroxide Treatment of 1,4,5,6-Tetrahydro-3-(β -hydroxyethylthio)-1-methyl-*as*-triazine (IV).

1,4,5,6-Tetrahydro-3-(β -hydroxyethylthio)-1-methyl-*as*-triazine (IV), 8 g. (0.045 mole), was dissolved in 100 ml. of chloroform and gaseous hydrogen chloride was added to the solution until solid no longer formed. The sticky mixture was cooled and 250 ml. (2.1 moles) of thionyl chloride was added cautiously with manual stirring. The mixture was warmed briefly to a gentle reflux and then cooled. Heating caused the reaction mixture to darken but the reaction mixture became nearly homogeneous. The reaction mixture was allowed to stand overnight and then was concentrated *in vacuo* (at 40°) to give a dark oil to which 100 ml. of cold water was added cautiously. This aqueous solution was poured slowly into 50 ml. of 40% sodium hydroxide solution with stirring on an ice bath to keep the temperature 20-25° and the basic mixture was extracted with chloroform (4 x 100 ml.). The combined chloroform extracts were washed with 75 ml. of brine, dried over magnesium sulfate, and concentrated *in vacuo* to give 4.5 g. of dark oil, λ max (film) 3.0 (w-m, sh.), 3.1 (m) and 6.25 μ (s). This oil was chromatographed on a 2.7 x 28 cm. column of 160 g. of alumina (Baker 0537). Elution with chloroform gave 2.75 g. (43%) of a yellow oil whose infrared spectrum was identical to that of thiazolotriazine II. The methiodide of this oil was prepared and recrystallized from 2-propanol to give light tan leaflets, m.p. 151-153° (identical in all respects (ir, m.p.) to authentic thiazolotriazine II methiodide).

1,4,5,6-Tetrahydro-3-(β -hydroxyethylthio)-1-methyl-*as*-triazine (IV).

To a stirred suspension of 26 g. (0.2 mole) of 1,4,5,6-tetrahydro-1-methyl-*as*-triazine-3(2*H*)-thione in 500 ml. of ethanol was

added, over a 30 minute period, a solution of 25 g. (0.2 mole) of β -bromoethanol in 100 ml. of ethanol. The mixture was stirred at ambient temperature for 1 hour, heated for 30 minutes, allowed to cool, concentrated *in vacuo*, chilled, and suction filtered to remove 9 g. of unreacted triazinethione I. The filtrate was evaporated to dryness, dissolved in water, basified with sodium hydroxide solution and extracted with chloroform. The chloroform was evaporated and the oil chromatographed on a 5 x 33 cm. column of Baker 0537 alumina using 1:4 methanol-chloroform as eluant to give 9.3 g. (21%) of yellow oil (hydroxyethylthio-triazine IV) and 2.1 g. of white solid, m.p. 154-155° (1,4,5,6-tetrahydro-1-methyl-*as*-triazin-3(2*H*)-one (V)).

Hydroxyethylthio-triazine IV pmr showed the two $-\text{CH}_2\text{-CH}_2-$ as typical AB systems as indicated by four triplets, one each at δ 2.84, 3.05, 3.52, and 3.86 and the NCH_3 singlet at δ 2.76; ir (film) ν 3280 (broad, OH) and 1589 (s, C=N).

Triazinone V pmr showed $-\text{CH}_2\text{CH}_2-$ as two triplets, one at δ 3.00 and the other at δ 3.45 and the NCH_3 singlet at δ 2.65; ir (nujol) ν 3310, 3305, and 3090 (OH) and 1665 (s, C=O).

Anal. Calcd. for $\text{C}_4\text{H}_9\text{N}_3\text{O}$: C, 41.73; H, 7.88; N, 36.50. Found: C, 41.96; H, 8.10; N, 36.25.

3,4-Dihydro-2-methyl-2*H*-triazolo[2,3-*c*]-*as*-triazine (VI)

A. From Triazinethione I and α -Bromoacetaldehyde.

A mixture of 20 g. (0.15 mole) of triazinethione I, 30 g. (0.15 mole) of α -bromoacetaldehyde diethyl acetal, 10 ml. of 48% hydrobromic acid and 300 ml. of ethanol was stirred and heated at the reflux temperature for 18 hours, concentrated *in vacuo*, cooled, treated with ice-water, basified with sodium hydroxide solution, and extracted with chloroform. The washed (brine) and dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* to give 21 g. of dark brown oil. Two distillations of this oil gave 6.5 g. (28%) of orange oil, b.p. 128-130° (0.2 mm); pmr (deuteriochloroform) δ 6.29 and 5.72 (d, d; J = 5.0 Hz; two thiazolo H's), 3.87 and 2.77 (t, t; J's = 5.0 and 5.2 Hz; $-\text{CH}_2\text{CH}_2-$ portion of triazine ring), 2.71 (s, NCH_3); ir (film) ν 1590 (s, C=N).

Anal. Calcd. for $\text{C}_6\text{H}_9\text{N}_3\text{S}$: C, 46.42; H, 5.84; N, 27.07; S, 20.66. Found: C, 46.31; H, 5.80; N, 26.90; S, 20.41.

B. From Cyclization of 4-(β,β -Diethoxyethyl)-1,4,5,6-tetrahydro-1-methyl-*as*-triazine-3(2*H*)-thione (XIX)

The triazinethione acetal XIX (2.0 g.) was added, portionwise, to stirred sulfuric acid. The solution was allowed to remain at $\sim 4^\circ$ for 3 days, poured onto crushed ice, basified with sodium carbonate and extracted with chloroform. The washed (brine) and dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* to give 1.6 g. red brown oil which by pmr and ir was assigned structure of 7-ethoxy-3,4,6,7-tetrahydro-2-methyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine; pmr (deuteriochloroform) δ 5.36 (q or 2 d's, J's = 4.8 and 5.0 Hz, 7-H), 3.96-3.27 (m, three CH_2), 2.81 (t, CH_2), 2.72 (s, NCH_3), and 1.21 (t, J = 5.3 Hz, $\text{CH}_3\text{CH}_2\text{O}$); ir (film) no NH or olefinic H's, ν 2800 (s, NCH_3), 1620 (vs, C=N), 1098 (vs, C-O-C). The ethoxythiazolotriazine XX was mixed with 2 ml. of concentrated sulfuric acid and heated in a water bath 90° for 1 hour, allowed to stand at ambient temperature overnight, mixed with crushed ice, basified with sodium carbonate solution, and extracted with chloroform. The washed (brine) and dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* to give 1.1 g. brown oil that gave pmr and ir spectra identical to those from authentic 3,4,6,7-tetrahydro-2-methyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine (VI) prepared by condensation of triazinethione I with α -bromoacetaldehyde.

1-(β,β -Diethoxyethyl)aziridine (XVII)

To a stirred, warmed mixture of 107 g. (2.5 moles) of aziridine, 104 g. (0.75 mole) of anhydrous potassium carbonate, and 600 ml. of 2-propanol was added, dropwise, over 80 minutes, a mixture of 99 g. (0.5 mole) α -bromoacetaldehyde diethyl acetal and 100 ml. of 2-propanol. The mixture was stirred and heated at the reflux temperature for 48 hours, then 600 ml. distilled at atmospheric pressure, the mixture filtered, and the filtrate distilled *in vacuo* to give 47 g. (59%) of colorless liquid, b.p. 70-80° (15-20 mm); analytical sample b.p. 71-72° (15 mm); pmr (deuteriochloroform) δ 4.68 (t, J = 5.0 Hz, $(\text{EtO})_2\text{CH}-$), 3.66 (m, $(\text{CH}_3\text{CH}_2\text{O})_2$), 2.37 (d, J = 5.0 Hz, $-\text{CH}-\text{CH}_2\text{N}$), 2.71 (t, CH_2 of aziridine), 1.22 (t, J = 8.0 Hz, $(\text{CH}_3\text{CH}_2\text{O})_2$), 1.19 (t, CH_2 of aziridine).

N-(β,β -Diethoxyethylaminoethyl)-*N*-methylhydrazine (XVIII)

To a stirred, refluxing solution of 0.5 g. of ammonium chloride in 184 g. (4.0 moles) of methylhydrazine was added, dropwise, over a 30 minute period, 41 g. (0.26 mole) of *N*-(β,β -diethoxyethyl)aziridine (XVII). The mixture was stirred and heated at the reflux temperature overnight. The excess methylhydrazine was distilled at atmospheric pressure, and the residue was distilled *in vacuo* to give 24 g. (45%) colorless liquid, b.p. 138-140° (15 mm); pmr (deuteriochloroform) δ 4.59 (t, J = 5.1 Hz, $(\text{EtO})_2\text{CH}-$), 3.62 (m, $\text{CH}_3\text{CH}_2\text{O}$), 2.90-2.39 (m, 3 CH_2 's), 2.45 (s, NCH_3), 1.20 (t, J = 7.0 Hz, $(\text{CH}_3\text{CH}_2\text{O})_2$).

Anal. Calcd. for $\text{C}_9\text{H}_{23}\text{N}_3\text{O}_2$: C, 52.65; H, 11.29; N, 20.47. Found: C, 52.95; H, 11.36; N, 20.65.

4-(β,β -Diethoxyethyl)-1,4,5,6-tetrahydro-1-methyl-*as*-triazine-3(2*H*)-thione (XIX)

To a stirred, warmed mixture of 24 g. (0.12 mole) of *N*-(β,β -diethoxyethylaminoethyl)-*N*-methylhydrazine, 50 ml. of ethanol and 50 ml. of water was added, dropwise over a 15 minute period, 10 g. (0.13 mole) of carbon disulfide. The mixture was stirred and heated at the reflux temperature for 1 hour, treated with 1.5 ml. of concentrated hydrochloric acid, heated at reflux for 90 minutes and allowed to stand at ambient temperature overnight.

The mixture was concentrated *in vacuo*, cooled, treated with 200 ml. of 5% sodium bicarbonate solution, and extracted with chloroform. The washed (brine) and dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* to give 29 g. of red colored oil which solidified and was recrystallized from a 5:4 mixture of ether-ligroin (90-110°) to give 14.5 g. (50%) of light yellow crystals, m.p. 92-98°. The analytical sample melted at 99.5-101.5°; pmr δ 5.03 (t, J = 5.0 Hz, $(\text{EtO})_2\text{CH}-$), 4.00-3.46 (m, 8 protons), 3.12 (t, J = 5.0 Hz, CH_2), 2.65 (s, NCH_3), 1.22 (t, J = 6.6 Hz, $(\text{CH}_3\text{CH}_2\text{O})_2$).

Anal. Calcd. for $\text{C}_{10}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$: C, 48.56; H, 8.56; N, 16.99; S, 12.96. Found: C, 48.81; H, 8.80; N, 16.71; S, 13.38.

3,4-Dihydro-2-methyl-7-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine Hydrobromide (VII)

A mixture of 23 g. (0.18 mole) of triazinethione I, 35 g. (0.18 mole) of α -bromophenylacetaldehyde, and 250 ml. of ethanol was heated at the reflux temperature overnight, and then was evaporated *in vacuo* to give 43.5 g. (79%) of tan solid which after washing with cold acetone melted at 205-218°. The analytical sample prepared by recrystallization from methanol-ether was an off-white crystalline solid, m.p. 205.5-207.5°; ir (nujol) ν 2818 (w, NCH_3), 2435 (ms, broad, NH^+), 1610 (m, C=N), 1562 (vs, $\text{PhC}=\text{C}$), 758, 688 (ms, m, Ph).

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{S}\cdot\text{HBr}$: C, 46.15; H, 4.52; Br, 25.60; N, 13.46. Found: C, 45.71; H, 4.44; Br, 24.88; N, 13.44.

3,4-Dihydro-2-methyl-6-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine Hydrobromide (VIII).

A mixture of 6.6 g. (0.05 mole) of triazinethione I, 10 g. (0.05 mole) of phenacyl bromide, and 150 ml. of ethanol was heated at the reflux temperature for 6 hours, concentrated *in vacuo*, and the residue washed with a 1:1 mixture of ethanol-ether to give 13.2 g. (85%) of white solid, m.p. 221-223°. The analytical sample was recrystallized from methanol-ether, m.p. 224-225°; ir (nujol) ν 2750 (s, broad, NH⁺), 1610 (s, C=N), 1590 (s, PhC=C), 745, 705 (s, m, Ph).

Anal. Calcd. for C₁₂H₁₃N₃S·HBr: C, 46.15; H, 4.52; Br, 25.60; N, 13.46. Found: C, 46.10; H, 4.67; Br, 25.46; N, 13.67.

3,4-Dihydro-2-methyl-6,7-diphenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine Hydrobromide (IX).

A mixture of 4.8 g. (0.036 mole) of triazinethione I, 10 g. (0.03 mole) of desyl bromide, and 150 ml. of ethanol was heated at the reflux temperature overnight and then evaporated *in vacuo* to give 15 g. of red solid. Recrystallization from methanol-ether gave 10 g. (71%) of red crystals, m.p. 243-245° dec. The analytical sample was pink crystals that melted at 244-245.5° dec.; ir (potassium bromide) ν 2850 (s, broad, NH⁺), 1625 (ms, C=N), 1580 (vs, PhC=CPh), 1550, 1510, 1475, 1460, 1450, (s, s, w, w, s, Ph), 742, 698 (s, s, Ph).

Anal. Calcd. for C₁₈H₁₇N₃S·HBr: C, 55.67; H, 4.67; Br, 20.58; N, 10.82. Found: C, 56.01; H, 4.71; Br, 20.67; N, 10.51.

3,4-Dihydro-2-methyl-2*H*-thiazolo[2,3-*c*]-*as*-triazin-6(7*H*)-one (X).

A. From Triazinethione I and Ethyl Bromoacetate (1).

B. From Triazinethione I and Chloroacetonitrile.

A mixture of 13 g. (0.1 mole) of triazinethione I, 7.5 g. (0.1 mole) of chloroacetonitrile, and 100 ml. of ethanol was heated at the reflux temperature overnight, evaporated *in vacuo*, the residue treated with sodium carbonate solution and then extracted with chloroform. The dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* and the residue was chromatographed on a 3 x 33 cm. column of 180 g. Baker 0537 alumina using benzene as the eluant to give 7.5 g. (44%) of solid, m.p. 106-110°. Recrystallization from methanol (charcoal added) gave 5.5 g. of off-white crystals, m.p. 109-112°; ir identical with that obtained from authentic thiazolotriazinone X prepared from triazinethione I and ethyl bromoacetate.

C. From Triazinethione I and Bromoacetyl Bromide.

To a stirred mixture of 6.6 g. (0.05 mole) of triazinethione I, 6 g. (0.06 mole) of anhydrous sodium carbonate, and 100 ml. of *N,N*-dimethylacetamide was added, dropwise, over a 15 minute period, 12 g. (0.06 mole) of bromoacetyl bromide. After stirring at ambient temperature for 2 hours, the solvent was evaporated *in vacuo*, the residue treated with sodium carbonate solution, and the mixture extracted with chloroform. The washed (brine) and dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* to give 8 g. of orange solid. Recrystallization from 2-propanol gave 3.0 g. (35%) of product, m.p. 108.5-110°; ir identical to that of authentic thiazolotriazinone X.

3,4-Dihydro-2-methyl-7-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazin-6(7*H*)-one (XI).

A. From Triazinethione I and α -Bromophenylacetoneitrile.

A mixture of 13 g. (0.1 mole) of triazinethione I, 20 g. (0.2 mole) of α -bromophenylacetoneitrile, and 150 ml. of ethanol was

heated at the reflux temperature for 2 hours, evaporated *in vacuo*, the residue extracted with hot 2-propanol, the solvent evaporated *in vacuo*, the residue dissolved in chloroform and the solution washed with sodium bicarbonate solution then with brine and then evaporated *in vacuo*. The residue was chromatographed on a 5 x 17 cm. column of 300 g. Baker 0537 alumina using benzene as eluant to give 8.5 g. tan colored solid. Recrystallization from 2-propanol gave 7 g. (30%) of cream colored solid, m.p. 94-96°; ir (nujol) ν 1709 (vs, C=O), 1613 (s, C=N); pmr (deuteriochloroform) δ 7.38 (s, Ph), 5.12 (s, Ph-CH-C=O), 3.81 (t, J = 5.0 Hz, ring CH₂), 2.89 (t, J = 5.0 Hz, ring CH₂), 2.82 (s, NCH₃).

Anal. Calcd. for C₁₂H₁₃N₃OS: C, 58.28; H, 5.30; N, 16.99. S, 12.96. Found: C, 58.29; H, 5.50; N, 17.29; S, 13.27.

B. From Triazinethione I and α -Cyanobenzyl *p*-Toluenesulfonate.

To a stirred, warmed (~50°) suspension of 19 g. (0.16 mole) of triazinethione I in 100 ml. of ethanol was added, portionwise, over a 30 minute period, a solution of 47 g. (0.16 mole) of α -cyanobenzyl *p*-toluenesulfonate in 100 ml. of warm ethanol. The mixture was stirred and heated at the reflux temperature for 1 hour and then kept at ~50° overnight. The mixture was evaporated *in vacuo*. The residue was dissolved in chloroform and the chloroform solution was washed with sodium bicarbonate solution, brine, dried over magnesium sulfate and evaporated *in vacuo*. The residual oil (52 g.) was chromatographed on a 5 x 50 cm. column of 600 g. of Baker 0537 alumina to give initially 1.2 g. solid m.p. 156-160° followed by 25 g. (66%) solid m.p. 60-75°. To eluate all of the second solid some ether (~20%) was added to the benzene eluant. Recrystallization of the main product (25 g., m.p. 60-75°) with 2-propanol gave 15 g. of light yellow crystals, m.p. 94-96°; ir spectrum identical to that from authentic 3,4-dihydro-2-methyl-7-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazin-6(7*H*)-one (XI) obtained from triazinethione I and α -bromophenylacetoneitrile. The by-product (1.2 g., m.p. 156-160°) was recrystallized with ether-*n*-pentane to give 1.0 g. of fine, white needles, m.p. 161-162°. Based on results of ir, pmr, and elemental analyses this material was assigned structure of 1-cyano-4-phenylisoquinoline (XII); ir (potassium bromide) ν 2220 (vw, C \equiv N), 1450, 1440, 1365, 757, 694, (m, m, w, vs, vs, Ph); pmr (deuteriochloroform) δ 8.1-7.2 (m, aromatic H).

Anal. Calcd. for C₁₆H₁₀N₂: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.30; H, 4.44; N, 12.32.

3,4,6,7-Tetrahydro-2-methyl-7-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazine (XXI).

A. By Thionyl Chloride-Sodium Carbonate Cyclization of 1,4,5,6-Tetrahydro-4-(β -hydroxyphenethyl)-1-methyl-*as*-triazine-3(2*H*)-thione (XXIV).

To stirred, cooled (~15°) thionyl chloride (80 ml., 1.1 moles) was added, portionwise, 12.5 g. (0.05 mole) of hydroxyalkyl-triazinethione. The mixture was allowed to come to ambient temperature over a 2 hour period, concentrated *in vacuo*, and the residual red-brown oil poured into a solution of 65 g. (0.61 mole) of sodium carbonate in 500 ml. of water. The mixture was extracted thoroughly with chloroform and the washed (brine) and dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* and the residual brown oil (11 g.) was chromatographed on a 3 x 32 cm. column of 180 g. Baker 0537 alumina using chloroform as eluant to give 5 g. yellow oil which upon trituration with ether gave 3.9 g. (38%) off-white crystals, m.p. 80-83°. Recrystallization from ethyl acetate gave white crystals, m.p. 83-84°; ir (nujol) ν 2810, 2800 (s, NCH₃), 1600 (vs, C=N), 777, 708 (vs, vs, Ph); pmr (deuteriochloroform) δ 7.4 (m, Ph), 4.75 (t, J = 7 Hz,

Ph-CH-S-), 3.9-3.2 (m, thiazolo CH₂ and triazine CH₂), 2.75 (t, triazine CH₂), 2.72 (s, NCH₃).

Anal. Calcd. for C₁₂H₁₅N₃S: C, 61.77; H, 6.48; N, 18.01. Found: C, 61.75; H, 6.83; N, 17.80.

B. By Diborane Reduction of 3,4-Dihydro-2-methyl-7-phenyl-2*H*-thiazolo[2,3-*c*]-as-triazin-6(7*H*)-one (XI).

To a stirred, cooled (~5°) one molar diborane-THF solution (300 ml., 0.3 mole borane) was added over a 15 minute period, a solution of 12.5 g. (0.05 mole) of thiazolotriazinone XI in 150 ml. of THF. The stirred mixture was allowed to come to ambient temperature (1 hour) and then was stirred and heated at the reflux temperature for 2 hours, cooled, treated with 100 ml. of 50% water-THF, followed by 100 ml. of dilute hydrochloride. The mixture was concentrated *in vacuo* at 40°, cooled, treated with 100 ml. of cold 10 *N* sodium hydroxide, and extracted thoroughly with chloroform. The washed (brine) and dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* to give 11 g. light yellow oil which was chromatographed on a 3 x 34 cm. column of 190 Baker 0537 alumina using chloroform as eluant to give 4.9 g. of oil. The oil was crystallized with ether-*n*-pentane to give 3.9 g. (32%) of white crystals (m.p. 82-83°) identical (mixed m.p., ir, pmr) to authentic phenylthiazolotriazine (XXI) prepared by thionyl chloride-sodium carbonate cyclization of hydroxyalkyltriazinethione (XXIV).

C. By Diborane Reduction of 2-Formyl-3,4-dihydro-7-phenyl-2*H*-thiazolo[2,3-*c*]-as-triazin-6(7*H*)-one (XXVII).

To a stirred, cooled (~0°) 1 molar diborane-THF (500 ml., 0.5 mole borane) solution was added, over a 30 minute period, a solution of 6.0 g. (0.024 mole) of formylphenylthiazolotriazinone in 300 ml. of THF. The stirred mixture was allowed to come to ambient temperature (1 hour) and then was stirred and heated at reflux temperature for 3 hours. The stirred, cooled mixture was treated with 150 ml. of 50% water-THF, followed by 200 ml. of diluted hydrochloric acid and then concentrated *in vacuo* at ~40°. The residue was cooled, basified with 400 ml. of cold 10 *N* sodium hydroxide and extracted with chloroform. The washed (brine) and dried (magnesium sulfate) chloroform extracts were evaporated *in vacuo* and the residual yellow oil chromatographed on a 3 x 32 cm. column of 190 g. Baker 0537 alumina using chloroform as an eluant to give 1.7 g. of oil which was crystallized from ether. Recrystallization from ether-*n*-pentane gave 1.1 g. (19%) of white crystals (m.p. 82-83.5°) identical (mixed m.p., ir) with authentic phenylthiazolotriazine (XXI).

N-(β-Hydroxyphenethylaminoethyl)-*N*-methylhydrazine (XXIII).

To a stirred, refluxing methylhydrazine (86 g., 1.9 moles) containing 0.5 g. of ammonium chloride was added, dropwise, 33 g. (0.2 mole) of *N*-(β-hydroxyphenethyl)aziridine. The mixture was heated at the reflux temperature for 2 hours and then allowed to cool to ambient temperature overnight. Excess methylhydrazine was distilled *in vacuo* on a rotary evaporator leaving 45 g. of viscous yellow oil. Attempted *in vacuo* distillation of a 15 g. portion of the oil resulted in extensive decomposition. The remaining 30 g. of oil solidified and was crystallized with 2-propanol-*n*-pentane to give 15 g. (36%) of white crystals, m.p. 70-73°. The analytical sample from 2-propanol-*n*-pentane was white needles, m.p. 74-76°; ir (nujol) ν 3350, 3325, 3150, (w, w, w, broad, OH, NH), 2750 (w, NCH₃), 758, 700 (s, s, Ph); pmr (deuteriochloroform) δ 7.33 (s, shoulder bands Ph), 4.72, 4.80 (d, d, J's = 7 Hz, Ph-CH-OH), 3.33 (s, broad, 4 exchangeable deuterium oxide protons, OH, NH₂, NH), 2.85-2.35 (m, four CH₂'s), 2.39 (s, NCH₃).

Anal. Calcd. for C₁₁H₁₉N₃O: C, 63.13; H, 9.15; N, 20.08. Found: C, 62.76; H, 9.29; N, 20.04.

1,4,5,6-Tetrahydro-4-(β-hydroxyphenethyl)-1-methyl-as-triazine-3(2*H*)-thione (XXIV).

To a stirred, warmed solution of 62.5 g. (0.30 mole) hydroxyphenethylaminoethylhydrazine in 300 ml. of 50% aqueous ethanol was added, dropwise, over a 30 minute period, 25 g. (0.33 mole) of carbon disulfide. The mixture was stirred and heated at the reflux temperature for 4 hours, 4 ml. of concentrated hydrochloric acid was added, the heating was continued an additional 2 hours, the mixture was cooled, and suction filtered to give 50 g. of tan solid, m.p. 120-135°. Recrystallization from 350 ml. 2-propanol gave 25 g. (33%) of off-white crystals, m.p. 147-151°. The analytical sample from 2-propanol melted at 155-156°; ir (nujol) ν 3330, 3200 (s, s, both broad, OH, NH), 2795 (w, NCH₃), 1520, 1500, 1487 (s, m, m, Ph), 1195 (s, C=S), 748, 704 (s, s, Ph); pmr (DMSO-d₆) δ 9.45 (s, exchangeable deuterium oxide, NH), 7.4 (m, Ph), 5.55 (d, J = 5 Hz, exchangeable deuterium oxide, OH), 5.25 (m, Ph-CH-OH), 4.40-2.80 (m, three CH₂'s), 2.46 (s, NCH₃).

Anal. Calcd. for C₁₂H₁₇N₃OS: C, 57.34; H, 6.82; N, 16.72; S, 12.76. Found: C, 57.55; H, 6.86; N, 17.00; S, 12.70.

1,4,5,6-Tetrahydro-as-triazine-3(2*H*)-thione (XXV).

To a stirred, warmed (~50°) mixture of 82 g. (1.1 moles) of β-aminoethylhydrazine and 440 ml. of 50% water-ethanol was added, over a 1 hour period, 73 g. (1.2 moles) of carbon disulfide. The mixture was stirred and heated at the reflux temperature for 1 hour, then was treated with 9.3 ml. of concentrated hydrochloric acid, and heated at reflux overnight. The mixture was concentrated *in vacuo* and the residue extracted with boiling methanol. The cooled methanol extract deposited 46 g. of white crystalline solid, m.p. 146-150°. Two recrystallizations from methanol gave 34 g. (26%) white crystalline solid, m.p. 163-164° dec.

Anal. Calcd. for C₃H₇N₃S: C, 30.75; H, 6.02; N, 35.86. Found: C, 30.72; H, 6.25; N, 36.03.

3,4-Dihydro-7-phenyl-2*H*-thiazolo[2,3-*c*]-as-triazin-6(7*H*)-one (XXVI).

Method A.

To a stirred, warmed (~50°) mixture of 19 g. (0.16 mole) of triazinethione XXV and 150 ml. of ethanol was added, portionwise, over a 1 hour period a warm solution of 47 g. (0.16 mole) of α-cyanobenzyl *p*-toluenesulfonate in 200 ml. of ethanol. The mixture was stirred and heated at the reflux temperature for 1 hour, concentrated *in vacuo*, the residual oil dissolved in chloroform and the chloroform solution washed (sodium bicarbonate, brine), dried (magnesium sulfate), and evaporated *in vacuo* to give 52 g. of dark, foamy oil. The oil was chromatographed on a 5 x 30 cm. column of 550 g. Baker 0537 alumina using 20:80 mixture chloroform-ether as eluant to give 12 g. of yellow oil which crystallized when triturated with *n*-pentane to give 8.2 g. (22%) of solid, m.p. 145-150°. Two recrystallizations from chloroform-*n*-pentane gave 6.3 g. of cream colored solid, m.p. 160-162°. The analytical sample melted at 163-164°; ir (nujol) ν 3325 (s, NH), 1705 (vs, C=O), 1630 (vs, C=N), 692, 732 (s, s, Ph); pmr (deuteriochloroform) δ 7.42 (s, Ph), 7.30 (s, NH), 5.14 (s, Ph-CH-O), 3.85 (t, J = 5 Hz, CH₂), 3.11 (t, J = 5 Hz, CH₂).

Anal. Calcd. for C₁₁H₁₁N₃OS: C, 56.63; H, 4.75; N, 18.01; S, 13.74. Found: C, 56.66; H, 5.00; N, 18.30; S, 13.33.

B. From Triazinethione XXV and Ethyl α-Bromophenylacetate.

To a stirred, refluxing mixture of 12 g. (0.1 mole) of triazine-thione and 100 ml. of ethanol was added, dropwise, over a 30 minute period, 24 g. (0.1 mole) of ethyl α -bromophenylacetate in 75 ml. of ethanol. The mixture was stirred and heated at the reflux temperature for 2 hours, allowed to come to ambient temperature overnight, concentrated *in vacuo*, treated with a solution of 25 g. of sodium bicarbonate in 150 ml. of water, and extracted with chloroform. The washed (brine) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo* to give 19 g. of light yellow semi-solid oil which was washed with ether, and the ether insoluble residue recrystallized with methanol to give 4.2 g. (18%) of cream-colored solid phenylthiazolotriazinone XXVI which melted at 160-162° and exhibited ir identical to that from phenylthiazolotriazinone XXVI prepared by method A.

2-Formyl-3,4-dihydro-7-phenyl-2*H*-thiazolo[2,3-*c*]-*as*-triazin-6(7*H*)-one (XXVII).

Phenylthiazolotriazinone XXVI (10 g.) was dissolved in 100 ml. of acetic-formic anhydride, the solution was stirred and

gradually warmed to 50°, kept at this temperature for 2 hours, stored in the refrigerator overnight, poured onto 300 g. of crushed ice, and extracted thoroughly with chloroform. The washed (sodium carbonate, brine) and dried (magnesium sulfate) chloroform extract was evaporated *in vacuo* to give 15 g. of light yellow colored solid which after five recrystallizations with 2-propanol gave 2.4 g. (22%) of white leaflets, m.p. 151-151.5°; ir (nujol) ν 1710 (vs, C=O), 1620 (s, C=O), 697, 734 (ms, ms, Ph); pmr (deuteriochloroform) δ 8.55 (s, CHO), 7.40 (s, Ph), 5.22 (s, Ph-CHC=O), 3.82 (s, broad, shouldered, CH₂-CH₂).

Anal. Calcd. for C₁₂H₁₁N₃O₂S: C, 55.16; H, 4.24; N, 16.08; S, 12.27. Found: C, 55.26; H, 4.54; N, 16.05; S, 12.24.

REFERENCES

- (1) D. L. Trepanier and P. E. Krieger, *J. Heterocyclic Chem.*, **7**, 1231 (1970).
- (2) No cyclization occurred in the absence of acid.