Alkylation Studies on 6-Ethyl-2,3-dihydrothiazolo-[3,2-*a*]pyrimidine-5,7-diones

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The title compound **7b** undergoes alkylation with ethyl iodide or ethyl sulfate at the 7-position yielding the *O*-ethylated product **10** rather than 6,6-diethyl product **8** as reported previously. Reaction of **7b** with mesyl chloride gives **13b** which on reaction with potassium carbonate in absolute ethanol also gives **10**. Treatment of **7b** with phosphorus oxychloride gives **11b** which on reaction with potassium carbonate or sodium ethoxide in ethanol produced a mixture from which no **10** was isolated. Authentic **8** was prepared by the reaction of 2-amino-thiazoline with ethyl diethylmalonyl chloride (**20**) in THF containing triethylamine or by the reaction of 5,5-diethyl-2-thiouracil (**18**) with excess 1,2-dibromoethane.

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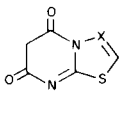
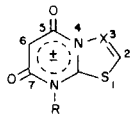
We have previously found that heating bis(2,4,6-trichlorophenyl)malonate esters, neat, with 2-aminothiazoles or 2-amino-1,3,4-thiadiazoles offers a convenient method for the preparation of thiazolo[3,2-*a*]pyrimidine-5,7-diones (**1**) and 1,3,4-thiadiazolo[3,2-*a*]pyrimidine-5,7-diones (**2**), respectively (1). If the amino group is substituted with an alkyl or aryl group, this reaction results in the formation of the corresponding non-classical heterocycles, *i.e.*, mesoionic compounds **3** and **4** (1-4). In a recent publication from this laboratory (5), we reported that derivatives of **3** and **4** act as inhibitors of adenosine 3',5'-monophosphate (cyclic AMP) phosphodiesterase. Thus, it was of interest to further explore structural variations of these compounds, and in particular to synthesize derivatives of the 2,3-dihydro analogs such as **5**.



1 X=CH
2 X=N



3 X=CH
4 X=N

Direct alkylation of **7** might afford a single-step synthesis for the preparation of the desired 2,3-dihydro analogs. Masters and Bogert (6), however, have previously reported that ethylation of **7** (where R is alkyl) results in carbon alkylation to give gem-dialkyl analogs such as **8**. Because of the unavailability of spectral data and because *O*-alkylation, to give **9** or **10**, as well as *N*-alkylation to give the desired products **5**, are equally possible, the nature of this alkylation reaction was re-investigated.

The dihydro analog **7** was readily prepared either by the literature procedure (6) or by condensation of **6a** with a bis(2,4,6-trichlorophenyl)malonate. Ethyl iodide alkylation of **7b** using conditions identical to those of Masters and Bogert resulted in a product whose melting point agreed with that previously reported for **8**. The same product could be obtained by the direct alkylation **7b** with diethyl sulfate. The proton nuclear magnetic resonance (^{1}H-nmr) spectrum of the product revealed two non-identical ethyl groups. Whereas one of the ethyl methylene groups has a chemical shift of δ 2.3, which corresponds to the ethyl methylene of **7b** (δ 2.2), there is also present a lower-field methylene signal at δ 3.6. The low field position of the methylene signal suggests that, rather than resulting in **8**, ethylation of **7b** affords either **5b**, **9** or **10**.

In order to eliminate the *N*-alkylation product as a possible structure, compound **5b** was synthesized *via* an alternate procedure. Condensation of **6b** with ethyl bis (2,4,6-trichlorophenyl)malonate afforded **5b** in 82% yield. Differences were noted in the melting points and spectral data of **5b** compared with those of the direct-alkylation product.

In addition to two carbonyl stretching bands at 1660 and 1630 cm^{-1}, the infrared spectrum of **7b** displays a broad hydroxyl band in the 3000 cm^{-1} region, suggesting that the di-oxo compound exists in equilibrium with an enol tautomer. The presence of an enol tautomer is supported by ^{1}H-nmr data; there is a broad, lowfield (δ 11.2) deuterium oxide-exchangeable singlet which integrates for less than one proton. Compounds **7a** and **7b** can be mono-chlorinated using phosphorus oxychloride, to yield the corresponding analogs **11a** and **11b**. In order to determine the position of the chloro group, **11a** was allowed to react with morpholine to yield **12**. The melt-

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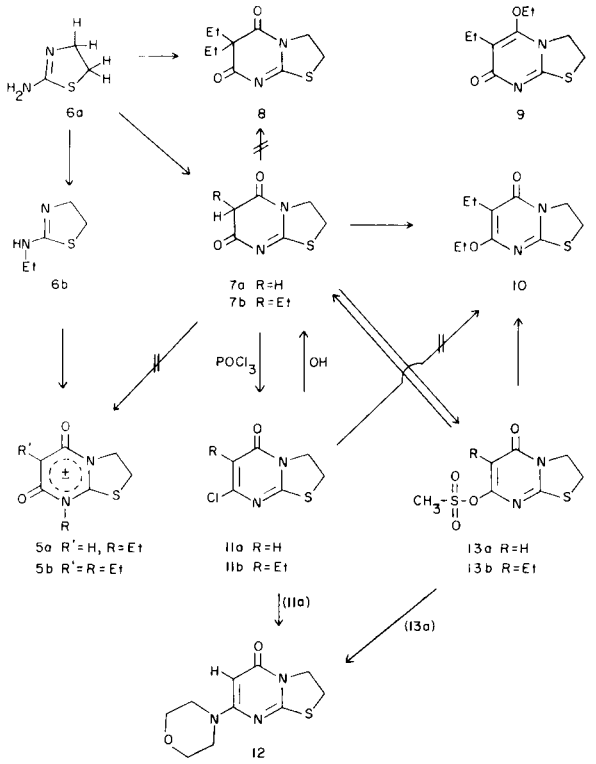
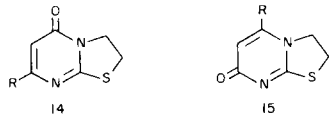


ing point and spectral data for compound **12** were consistent with those reported for an authentic sample of this compound previously prepared by a different synthetic route (7). The chloro analog **11b** could be converted back to the corresponding di-oxo compound **7b** by refluxing in dilute aqueous base. However, reaction of either **11a** or **11b** with ethoxide resulted in decomposition rather than the desired *O*-ethyl derivatives. Acylation of **7** with methanesulfonyl chloride afforded the mesyl derivatives **13**. Compound **13a** was readily converted to the morpholino compound **12**. Heating **13b** in dilute aqueous base gave **7b** while warming **13b** with potassium carbonate in ethanol gave a product identical to that derived from direct ethylation of **7b**, *i.e.*, **10**.

Structural assignment of the product resulting from the direct ethylation of **7b** can also be made on the basis of infrared data. The infrared spectrum of the di-oxo compound **7b** displays two carbonyl stretching bands at 1630 and 1660 cm^{-1}. Brown and Dyson (7) have reported that the 5-oxo compounds, such as **14**, possess a single carbonyl stretching band in the 1670 cm^{-1} region, while the 7-oxo isomers such as **15** display a single band in the 1640 cm^{-1} region. These data are also consistent with infrared spectra of monooxothiazolo[3,2-*a*]pyrimidinones and related benz-fused analogs (8,9), *i.e.*, 5-(or corresponding)oxo: 1660-1680 cm^{-1} region; and 7-(or corresponding)oxo: 1630-1640 cm^{-1} region. Compounds **10**, **11**

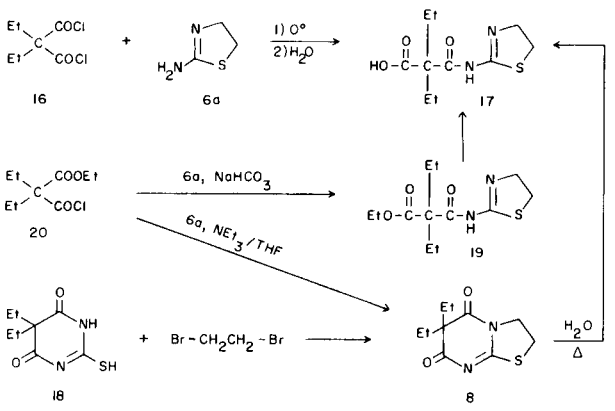


and **13** all possess a single carbonyl band in the 1660-1680 cm^{-1} region. It thus appears that direct ethylation of **7b** results in the formation of the O_7-ethyl derivative **10**, and not the *C*-ethyl product **8**.

Additional support concerning the structure alkylation product **10** can be drawn by comparing the uv absorbance of **7b** and **10** with that of the model compounds **14** and **15**. The presence of a carbonyl group in conjugation with two double bonds in **14** is shown by the 290 nm (ϵ 9000) absorbance, while **15**, with a 7-carbonyl group present, absorbs no higher than 260 nm (ϵ 6500). Compound **7b** with the two carbonyl groups present shows the 260 (ϵ 6800) and 290 nm (ϵ 7800) absorbance, while the alkylation product **10** maintains the 290 absorbance undisturbed, but differs in that the absorbance band at λ 255 (ϵ 6300) is weaker. This is supportive evidence of *O*-alkylation at the 7-carbonyl.

Several attempts were made to prepare **8**. Acylation of **6a** with diethylmalonyl dichloride (**16**), followed by pouring the reaction mixture onto ice, resulted not in **8** but in the formation of **17**. Alkylation of the mercapto compound **18** with 1,2-dibromoethane afforded a mixture of products. However, chromatographic separation with subsequent sublimation afforded **8** in 45% yield. Interestingly, refluxing **8** in water resulted in ring-opening to give **17**. Reaction of half acid chloride-ester, **20**, with **6a** resulted in **19** if solid sodium bicarbonate was present. However, if the sodium bicarbonate was replaced with triethylamine, compound **8** was obtained. Product **19** could also be hydrolyzed to the acid **17**.

In conclusion, it does not appear that the desired mesoionic analogs, such as **5**, can be prepared by the direct alkylation of **7** under the conditions we have employed. Furthermore, the direct ethylation of **7b** results in the formation of the O_7-alkylated product **10** and not the gem-dialkyl product **8**.



EXPERIMENTAL

Proton magnetic resonance spectra were obtained on a Varian S-XL 100 spectrometer and chemical shifts are reported relative to TMS. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer. All melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. If a compound was prepared by more than one method, mixed melting point determinations were performed. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Georgia. Mass spectra were obtained using a Finnigan 4000 GC-MS data system. Commercially available 2-aminothiazoline was purified by recrystallization from benzene.

Anhydro(6,8-Diethyl-5-hydroxy-7-oxo-2,3-dihydrothiazolo[3,2-*a*]-pyrimidinium Hydroxide) (**5b**).

2-Ethylamino-Δ^2-thiazoline (**6b**) (0.13 g., 1 mmole) (2) and ethyl bis(2,4,6-trichlorophenyl)malonate (0.49 g., 1 mmole) were heated, neat, at 160° under a slow stream of nitrogen for 3 minutes. When cool, the crude mass was triturated with anhydrous ether and the product collected by filtration. Recrystallization from ethyl acetate gave 0.18 g. (82%) of **5b**, m.p. 170-172°; ir (potassium bromide): 1670 cm^{-1}; nmr (deuteriochloroform): δ 1.0-1.6 (m, 6H), 2.55 (q, 2H), 3.75 (t, 2H), 4.15 (q, 2H), 4.75 (t, 2H).

Anal. Calcd. for $C_{10}H_{14}N_2O_2S$: C, 53.09; H, 6.19; N, 12.39. Found: C, 53.01; H, 6.27; N, 12.37.

7-Hydroxy-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyrimidin-5-one (**7a**).

Method A.

Compound **7a** was prepared in 80% yield by the method of Masters and Bogert (6), m.p. 244-245° [lit. (6) m.p. 244.5-245.5°]; ir (potassium bromide): 1660 (C_5=O), 1630 (C_7=O) cm^{-1}; nmr (DMSO-d_6): δ 3.5 (t, 2H, thiazoline -CH_2-), 4.35 (t, 2H, thiazoline -CH_2-), 5.1 (s, 1H, C_6-H), 9.0-10.0 (broad signal).

Method B.

2-Amino-Δ^2-thiazoline (0.1 g., 1 mmole) and bis(2,4,6-trichlorophenyl)malonate (0.46 g., 1 mmole) (10) were heated, neat, at 160° under a slow stream of nitrogen for 5 minutes. When cool, the resultant product was recrystallized from 95% ethanol to yield 0.15 g. (88%) of **7a** as bright yellow crystals, m.p. 244-245°.

6-Ethyl-7-hydroxy-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyrimidin-5-one (**7b**).

Method A.

Compound **7b** was prepared in 76% yield by the method of Masters and Bogert (6), m.p. 224-225° [lit. (6) m.p. 224.4-224.7°]; ir (potassium bromide): 1660 (C_5=O), 1630 (C_7=O) cm^{-1}; nmr (DMSO-d_6): δ 1.0 (t, 3H, CH_3-), 2.3 (q, 2H, -CH_2-), 3.55 (t, 2H, thiazoline -CH_2-), 4.35 (t, 2H, thiazoline -CH_2-), 11.2 (broad signal); ms: m/e (relative intensity) 198 (33), 183 (100); uv (95% ethanol): 290 (7,800), 260 (6,800).

Method B.

The malonate condensation (Method B) for **7a** was followed on a 1 mmole scale employing ethyl bis(2,4,6-trichlorophenyl)-malonate to yield 0.15 g. (76%) of **7b** after recrystallization from 95% ethanol, m.p. 225-226°.

Method C.

Compound **11b** (108 mg., 0.5 mmole) and potassium carbonate (200 mg.) were heated for 3 hours in a refluxing mixture of water (15 ml.) and 95% ethanol (15 ml.). When cool, the mixture was filtered, evaporated to dryness *in vacuo* and the resultant residue was recrystallized from 95% ethanol to yield 85 mg. (86%) of **7b**, m.p. 225-226°.

Method D.

Compound **13b** (276 mg., 1 mmole) and potassium carbonate (140 mg., 1 mmole) were heated under reflux in water (100 ml.) for 2 hours. The solid product was filtered, washed with water and recrystallized to yield 180 mg. (90%) of **7b**, m.p. 225-226°.

6,6-Diethyl-2,3,4,5,6,7-hexahydrothiazolo[3,2-*a*]pyrimidine-5,7-dione (**8**).

Method A.

A solution of 5,5-diethyl-2-thiouracil (**11**) (4 g., 20 mmoles) and sodium hydroxide (0.8 g., 20 mmoles) in a mixture of water (20 ml.) and isopropanol (15 ml.) was added dropwise, over a period of 3 hours, to a refluxing solution of 1,2-dibromoethane (188 g., 1 mole) and sodium bicarbonate (4.2 g., 50 mmoles) in isopropanol (200 ml.). Refluxing was continued until evolution of carbon dioxide ceased (about 3 hours), and then for an additional 8 hours. When cool, the oily organic phase was dried (magnesium sulfate), filtered and evaporated to dryness. The oily residue was dissolved in hot acetone, filtered and the solvent removed *in vacuo* to yield soft, yellow crystals, m.p. 88-92°. The crude product was dissolved in a minimal amount of chloroform and subjected to column chromatography, with Alumina Adsorbtion A-540 (Fisher) as the stationary phase and chloroform as the mobile phase. The faint yellow crystals were sublimed (120-125°/2 mm) to yield 2.05 g. (45%) of **8**, m.p. 96-97°; ir (potassium bromide): four sharp bands in the 1730-1670 cm^{-1} region; nmr (deteuriochloroform): δ 0.9 (t, 6H, 2CH_3-), 1.9 (q, 4H, 2 -CH_2-), 3.3 (t, 2H, thiazoline -CH_2-), 4.2 (t, 2H, thiazoline -CH_2-).

Anal. Calcd. for $C_{10}H_{14}N_2O_2S$: C, 53.09; H, 6.19; N, 12.39. Found: C, 52.79; H, 6.28; N, 12.20.

Method B.

A solution of ethyl diethylmalonyl chloride (**20**) (5.2 g., 25 mmoles) in tetrahydrofuran (20 ml.) was added dropwise to a stirred solution of 2-amino-Δ^2-thiazoline (**6a**) (2.5 g., 25 mmoles) and 3 ml. of triethylamine in tetrahydrofuran (20 ml.). After stirring for twelve hours the reaction mixture was filtered and the filtrate reduced to half-volume. The filtrate was poured slowly into petroleum ether (b.p. 30-60°) (200 ml.) and stirred overnight (16 hours). The product was collected by filtration and was sublimed to afford 3 g. (54%) of **8**, m.p. 94-97°.

6-Ethyl-7-ethoxy-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyrimidin-5-one (**10**).

Method A.

Compound **7b** (2 g., 10 mmoles) was added to an alcoholic solution of sodium ethoxide (prepared by dissolving 0.25 g. of sodium metal in 25 ml. of absolute ethanol). Ethyl iodide (2 g., 13 mmoles) was added and the solution was refluxed until neutral (2 hours). The solution was reduced to half volume and the addition of water (50 ml.) resulted in the precipitation of long white needles. Recrystallization from water gave 0.63 g. (28%) of **10**, m.p. 138-139°; ir (potassium bromide); 1660 cm^{-1}; nmr (DMSO-d_6): δ 1.0 (t, 3H, ethyl CH_3-), 1.35 (t, 3H, ethoxy CH_3-), 2.2 (q, 2H -CH_2-), 3.6 (m, 4H) 4.4 (t, 2H, thiazoline -CH_2-); ms: m/e (relative intensity): 226 (41), 211 (91.5), 183 (100); uv (95% ethanol): 290 (8500), 255 (6300).

Anal. Calcd. for $C_{10}H_{14}N_2O_2S$: C, 53.09; H, 6.19; N, 12.39.

Found: C, 53.09; H, 6.27; N, 12.37.

Method B.

At room temperature, diethyl sulfate (0.68 ml., 5 mmoles) was added to a solution of **7b** (1 g., 5 mmoles) and potassium hydroxide (0.28 g., 5 mmoles) in absolute ethanol (10 ml.). Upon warming at 40°, the reaction mixture solidified; an additional 30 ml. of ethanol was added and the solution was stirred at 70-80° for 30 minutes. At 0°, the reaction mixture was acidified by the addition of concentrated hydrochloric acid (3 ml.), filtered and the filtrate concentrated to 5 ml. Following the addition of acetone (60 ml.), the reaction mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in hot water (125 ml.) to yield 0.26 g. (29%) of **10** after standing for 18 hours, m.p. 138-139°.

Method C.

A mixture of **13b** (1.38 g., 5 mmoles) and potassium carbonate (0.7 g., 5 mmoles) in absolute ethanol (50 ml.) was stirred at 30° with slow warming to 90° over 30 minutes. The mixture was filtered and the filtrate evaporated to dryness. Recrystallization of the crude product from water afforded 0.3 g. (26%) of **10**, m.p. 138-139°.

7-Chloro-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyrimidin-5-one (**11a**).

Compound **7a** (0.85 g., 5 mmoles) and phosphorus oxychloride (3 ml., 30 mmoles) were heated on an oil bath at 120° for 90 minutes. The excess phosphorus oxychloride was evaporated under reduced pressure and the warm residue was poured onto ice (50 g.). After neutralization by the addition of small protions of solid sodium bicarbonate, the mixture was extracted thrice with chloroform (50 ml.). The chloroform portion was dried (sodium sulfate) and evaporated to dryness *in vacuo*. A yellow oily residue which hardened upon standing was recrystallized from ethanol to yield 0.62 g. (66%) of **11a** as bright yellow needles, m.p. 91-92°; ir (potassium bromide): 1670 cm^{-1}; nmr (deuteriochloroform): δ 3.5 (t, 2H, thiazoline $-CH_2-$), 4.5 (t, 2H, thiazoline $-CH_2-$), 6.25 (s, 1H, C_6-H).

Anal. Calcd. for $C_6H_5ClN_2OS$: C, 38.21; H, 2.67; N, 14.86. Found: C, 38.22; H, 2.67; N, 14.87.

7-Chloro-6-ethyl-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyrimidin-5-one (**11b**).

Compound **11b** was prepared on the same scale and in the same manner as **11a**. Recrystallization of the brown residue from hexane yielded 0.8 g. (74%) of **11b** as light yellow crystals, m.p. 84-86°; ir (potassium bromide): 1665 cm^{-1}; nmr (DMSO-d_6): δ 1.0 (t, 3H, CH_3-), 2.5 (q, 2H, ethyl $-CH_2-$), 3.6 (q, 2H, thiazoline $-CH_2-$), 4.35 (q, 2H, thiazoline $-CH_2-$); uv (95% ethanol): 290 (7400), 240 (5100).

Anal. Calcd. for $C_8H_9ClN_2OS$: C, 44.34; H, 4.16; N, 12.93. Found: C, 44.43, H, 4.20; N, 12.90.

7-Morpholino-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyrimidin-5-one (**12**).

Method A.

A mixture of **11a** (0.09 g., 0.5 mmole) and morpholine (0.435 g., 50 mmoles) was heated at reflux for 2.5 hours and then poured onto water (25 ml.). The mixture was extracted twice with chloroform (15 ml.) and the chloroform portion was dried (sodium sulfate) and evaporated to dryness. The crude product was recrystallized from benzene to yield 60 mg. (50%) of **12**, m.p. 207-208° [lit. (7) m.p. 208-209°]; nmr (deuteriochloroform): δ 3.4-3.9 (m, 10H), 4.55 (t, 2H), 5.25 (s, 1H).

Method B.

Compound **12** was prepared in the same manner as Method A except that 0.5 mmole of **13a** was substituted for **11a**, m.p. 205-207°; nmr: identical with that product prepared by Method A.

7-Hydroxy-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyrimidin-5-one Methanesulfonate Ester (**13a**).

Maintaining a temperature of 20-25°, methanesulfonyl chloride (0.86 ml., 11 mmoles) was added dropwise to a stirred solution of **7a** (1.7 g., 10 mmoles) in dry pyridine (20 ml.). The reaction mixture was stirred at room temperature for 5 hours, poured onto ice (100 g.) and neutralized with concentrated hydrochloric acid to yield a white precipitate. The product was collected by filtration, washed with water (10 ml.) and air dried. Recrystallization from absolute ethanol afforded 1.76 g. (71%) of **13a** as faint yellow needles, m.p. 146-147°; ir (potassium bromide): 1675 cm^{-1}; nmr (deuteriochloroform): δ 3.5 (m, 5H, CH_3- and thiazoline $-CH_2-$), 5.95 (s, 1H, C_6-H).

Anal. Calcd. for $C_7H_8N_2O_4S_2$: C, 33.89; H, 3.23; N, 11.29. Found: C, 33.97; H, 3.25; N, 11.24.

6-Ethyl-7-hydroxy-2,3,4,5-tetrahydrothiazolo[3,2-*a*]pyrimidin-5-one Methanesulfonate Ester (**13b**).

Compound **13b** was prepared on a 10 mmole scale in the same manner as **13a** to yield 2.22 g. (85%) of faint yellow plates after recrystallization from absolute ethanol, m.p. 146°; ir (potassium bromide): 1660 cm^{-1}; nmr (DMSO-d_6): δ 1.0 (t, 3H, ethyl CH_3-), 2.4 (q, 2H, ethyl $-CH_2-$), 3.6 (s overlapping t, 5H), 4.4 (t, 2H, thiazoline $-CH_2-$).

Anal. Calcd. for $C_9H_{12}N_2O_4S_2$ C, 39.13; H, 4.35; N, 10.14. Found: C, 39.12; H, 4.35; N, 10.14.

2,2-Diethyl-*N*-(2-Δ^2-thiazolinyl)malonamic Acid (**17**).

Method A.

Diethylmalonyl dichloride (12) (2 g., 10 mmoles) was added dropwise to a stirred mixture of **6a** (1.1 g., 11 mmoles) and dry pyridine (10 ml.) at 0°. After 30 minutes of stirring, the reaction mixture was poured onto 100 g. of ice. The oily organic phase was separated and warmed with 180 ml. of water to give a white crystalline product. Recrystallization from water yielded 0.6 g. (25%) of **17**, m.p. 103-104°. An analytical sample was prepared by sublimation at 120°/2mm, m.p. 104°; ir (potassium bromide): 3240 (s), 1710 (s), 1670 (s) cm^{-1}; nmr (DMSO-d_6): δ 0.9 (t, 6H, $2CH_3-$), 1.95 (q, 4H, ethyl $-CH_2-$), 2.8 (t, 2H, thiazoline $-CH_2-$), 3.2 (broad signal NH), 4.1 (t, 2H, thiazoline $-CH_2-$), 11.7 (s, 1H, HO).

Anal. Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.18; H, 6.56; N, 11.47. Found: C, 49.15; H, 6.59; N, 11.40.

Method B.

A solution of **19** in aqueous sodium hydroxide (1%) was heated under reflux for 1 hour. Neutralization of the solution with hydrochloric acid (10%) afforded a nearly quantitative yield of a product identical with that obtained by Method A.

Ethyl 2,2-Diethyl-*N*-(2-Δ^2-thiazolinyl)malonamate (**19**).

A mixture of diethyl ethylmalonyl chloride (**20**) (2.06 g., 10 mmoles), **6a** (1 g., 10 mmoles) and sodium bicarbonate (850 mg.) in dry benzene (30 ml.) was heated at reflux for 18 hours. The reaction mixture was filtered and the filtrate was evaporated to dryness, under reduced pressure. The crude product was recrystallized from hexane to yield 1.62 g. (60%) of **19** as small

white needles, m.p. 96-99°; ir (potassium bromide): 1750 (s), 1620 (s) cm^{-1}; nmr (deuteriochloroform): δ 0.9 (t, 6H), 1.2 (t, 3H), 1.9 (q, 4H), 3.3 (q, 3H), 4.0 (m, 4H).

Anal. Calcd. for $C_{12}H_{20}N_2O_3S$: C, 52.94; H, 7.35; N, 10.29. Found: C, 52.73; H, 7.10; N, 10.78.

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