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# THE SYNTHESIS OF (3,4,5,6-TETRAHYDRO-4-OXO-2*H*-1,3-THIAZIN-2-YL)-ALKANOIC ACIDS, THEIR DERIVATIVES AND SOME RELATED COMPOUNDS

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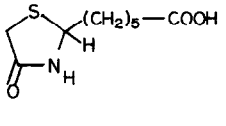
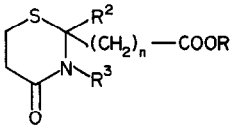
**Abstract**—5,6-Dihydro-2*H*-1,3-thiazin-4(3*H*)-ones **2–10** related to the natural antituberculytic Mycobacidine **1**, have been synthesised. Some of the compounds of types **2**, **3** and **5** proved highly active *in vitro* against Mycobacterium tuberculosis typ. humanus ($H_{37}R_v$), but the *in vitro* activities are diminished or suspended in the presence of biotine.

We wish to report here on the synthesis of some 6-membered ring analogs of the natural antituberculotic (−)-4-oxo-2-thiazolidinehaxanoic acid (Mycobacidine, Actithiazic acid, Antibiotic A, **1**).[1] The following types of compounds were synthesised: (3,4,5,6 - tetrahydro - 4 - oxo - 2*H* - 1,3 - thiazin - 2 - yl) - alkanoic acids and/or the corresponding esters (**2**, $R^2 = R^3 = H$; R = H, Me, Et; n = 0, 2–5), the related amide **3** and ureide **4**, the 2-methyl derivative **2** ($R^2$ = Me, $R^3$ = H, R = Et, n = 0), the 3-methyl derivative **2** ($R^2 = R = H$, $R^3$ = Me, n = 5), *p* - (3,4,5,6 - tetrahydro - 4 - oxo - 2*H* - 1,3 - thiazin - 2 - yl)phenoxyacetic acids and/or the corresponding esters **5** (X = H, Br; R = H, Et) the related nitrile **6**, certain 5,6 - dihydro - 2*H* - 1,3 - thiazin - 4(3*H*) - ones **7**, bearing no functional groups in the side chain, and the 2*H* - 1,3 - banzothiazin - 4(3*H*) - one derivatives **8–10**.

The esters of type **2**, **5**, **8** (R ≠ H) and **9** and the compounds **6**, **7** and **10** were obtained by condensing 3-mercaptopropionamide,[2] its *N*-methyl derivative and 2-mercaptobenzamide,[3] respectively, with methyl and



**1**



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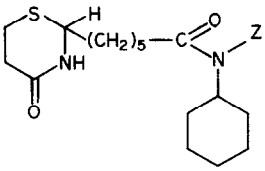
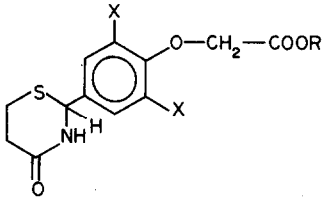


**3**: Z = H
**4**: Z = −C(=O)−NH−



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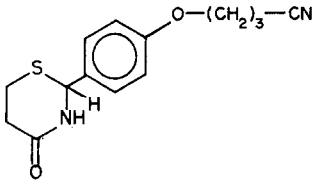

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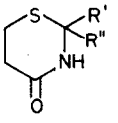

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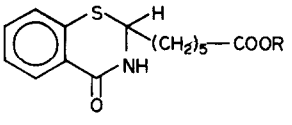

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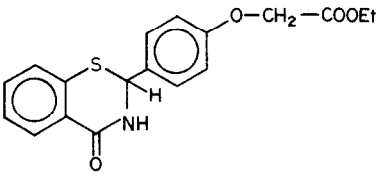
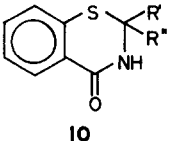


**9**



**10**

Table 1. The synthesis of some 4-oxo-3,4,5,6-tetrahydro-2*H*-1,3-thiazine and 4-oxo-3,4-dihydro-2*H*-1,3-benzothiazine derivatives

| Compound[a] | Method | Yield | M.p. (Solvent of recrystallization) | Formula (Mol. wt) | Calc./Found C% | H% | N% | S% | IR(KBr) $cm^{-1}$ Amide I thiazinone ring | Other νC=O's |
|---|---|---|---|---|---|---|---|---|---|---|
| **2**, n = 0, R = Et, $R^2 = R^3 = H$ | A[b] | 2% | 108–10° ($Et_2O$) | $C_7H_{11}NO_3S$ (189.24) | 44.40<br>44.49 | 5.87<br>5.86 | | 16.95<br>17.24 | 1660 | 1720 |
| **2**, n = 2, R = Me, $R^2 = R^3 = H$ | A | 18.6% | 79–80° ($Et_2O$) | $C_8H_{13}NO_3S$ (203.26) | | | 6.89<br>6.96 | 15.78<br>15.93 | 1640 | 1730 |
| **2**, n = 3, R = Me, $R^2 = R^3 = H$ | A | 16% | 83–84° ($Et_2O$) | $C_9H_{15}NO_3S$ (217.29) | 49.75<br>49.71 | 6.96<br>6.84 | 6.45<br>6.29 | | 1640 | 1730 |
| **2**, n = 4, $R = R^2 = R^3 = H$ | B[c]<br>C | 26.6%<br>90% | 172° (EtOAc) | $C_9H_{15}NO_3S$ (217.29) | | | 6.45<br>6.39 | 14.76<br>14.65 | 1620 | 1720 |
| **2**, n = 4, R = Et, $R^2 = R^3 = H$ | A | 33% | 77° ($Et_2O$) | $C_{11}H_{19}NO_3S$ (245.33) | 55.85<br>55.50 | 7.78<br>8.05 | 5.71<br>5.86 | 13.07<br>13.01 | 1640 | 1740 |
| **2**, n = 5, $R = R^2 = R^3 = H$ | C | 74% | 134° (EtOAc) | $C_{10}H_{17}NO_3S$ (231.31) | 51.92<br>52.31 | 7.41<br>7.05 | 6.06<br>6.00 | 13.85<br>13.62 | 1620 | 1720 |
| **2**, n = 5, R = Et, $R^2 = R^3 = H$ | A | 45% | 56° ($Et_2O$) | $C_{12}H_{12}NO_3S$ (259.36) | | | 5.40<br>5.26 | 12.36<br>12.41 | 1670 | 1740 |
| **2**, n = 0, R = Et, R² = Me, $R^3 = H$ | A | 17% | 114° (gasoline) | $C_8H_{13}NO_3S$ (203.26) | 47.27<br>47.55 | 6.44<br>6.08 | 6.89<br>6.51 | 15.78<br>16.01 | 1640 | 1740 |
| **2**, n = 5, $R = R^2 = H$, $R^3$ = Me | A[d] | 19.3% | 89–90° (EtOAc) | $C_{11}H_{19}NO_3S$ (245.33) | 53.85<br>54.13 | 7.81<br>8.19 | 5.71<br>5.36 | 13.07<br>12.64 | 1600 | 1720 |
| **3** | [e] | 32% | 162–163° (EtOAc) | $C_{16}H_{28}N_2O_2S$ (312.40) | | | 8.97<br>8.72 | 10.25<br>10.71 | 1640 | 1680 |
| **4** | [e] | 30.4% | 131° (EtOAc–light petroleum) | $C_{23}H_{39}N_3O_3S$ (437.58) | 63.13<br>63.55 | 8.98<br>9.07 | | 7.31<br>7.33 | 1660 | 1705 sh<br>1680 |
| **5**, X = H, R = H | C | 88% | 218° (aq MeOH) | $C_{12}H_{13}NO_4S$ (267.30) | 53.92<br>53.56 | 4.90<br>5.02 | 5.24<br>5.19 | 12.00<br>12.15 | 1610 | 1720 |
| **5**, X = H, R = Et | A[f] | 31% | 143–4° (EtOAc) | $C_{14}H_{17}NO_4S$ (295.36) | 56.92<br>57.13 | 5.80<br>5.77 | 4.74<br>4.64 | 10.86<br>10.93 | 1680 | 1760 |
| **5**, X = Br, R = H | C | 98% | 261° (aq MeOH) | $C_{12}H_{11}Br_2NO_4S$ (425.21) | | | 3.29<br>3.14 | 7.54<br>7.31 | 1620 | 1740 |
| **5**, X = Br, R = Et | A[g] | 29% | 142–3° (EtOAc–$Et_2O$) | $C_{14}H_{15}Br_2NO_4S$ (453.17) | | | 3.09<br>2.96 | 7.08<br>7.22 | 1660 | 1760 |
| **6** | A[h] | 26% | 135° (EtOAc) | $C_{14}H_{16}N_2O_2S$ (276.36) | | | 10.14<br>9.91 | 11.60<br>12.09 | 1640 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **7**, R′ = R″ = Me | A | 17% | 144–5° | $C_6H_{11}NOS$ | | | 9.46 | 22.08 | 1670 | |
| | | | ($H_2O$) | (145.23) | | | 9.42 | 21.70 | | |
| **7**, R′ + R″ = $(CH_2)_4$ | A | 62% | 134° | $C_8H_{13}NOS$ | | | 8.18 | 18.72 | 1670 | |
| | | | (benzene) | (171.26) | | | 8.43 | 18.44 | | |
| **7**, R′ + R″ = $(CH_2)_5$ | A | 40.5% | 167–8° | $C_9H_{15}NOS$ | | | 7.55 | 17.30 | 1660 | |
| | | | (benzene) | (185.29) | | | 7.36 | 16.86 | | |
| **7**, R′ = Ph, R″ = H | A | 96% | 176° | [i] | | | | | 1640 | |
| | B | 83% | (MeOH) | | | | | | | |
| **7**, R′ = *p*-$ClC_6H_4$, R″ = H | A | 61% | 195° | [j] | | | | | 1640 | |
| | | | (EtOH) | | | | | | | |
| **7**, R′ = *p*-$MeOC_6H_4$, R″ = H | A | 77% | 193–4° | [k] | | | | | 1640 | |
| | | | (EtOH) | | | | | | | |
| **7**, R′ = *p*-$HOC_6H_4$, R″ = H | A | 55% | 236° | $C_{10}H_{11}NO_2S$ | 57.39 | 5.29 | 6.69 | 15.32 | 1630 | |
| | | | (BuOH) | (209.27) | 57.60 | 5.47 | 6.90 | 14.98 | | |
| **7**, R′ = *p*-$Me_2NC_6H_4$, R″ = H | A[l] | 64% | 196–7° | $C_{12}H_{16}N_2OS$ | | | 11.86 | 13.57 | 1640 | |
| | B | 30% | (MeOH) | (236.30) | | | 11.84 | 13.32 | | |
| **7**, R′ = *p*-EtOOC–$C_6H_4$, R″ = H | A | 68% | 147° | $C_{13}H_{14}NO_3S$ | 59.07 | 5.34 | 5.30 | 12.13 | 1640 | 1710 |
| | | | (EtOH) | (264.30) | 59.15 | 5.91 | 4.97 | 12.00 | | |
| **7**, R′ = 3,4,5-$(MeO)_3C_6H_2$, R″ = H | A | 80% | 179° | $C_{13}H_{17}NO_4S$ | 55.10 | 6.05 | 4.94 | 11.32 | 1640 | |
| | | | (EtOAc) | (283.34) | 55.01 | 6.33 | 4.63 | 10.79 | | |
| **7**, R′ = 3,5-$Br_2$-4-$HOC_6H_2$, R″ = H | A[m] | 48% | 213° | $C_{10}H_9Br_2NO_2S$ | [n] | | 3.82 | 8.73 | 1640 | |
| | | | (aq dioxane) | (367.08) | | | 3.66 | 8.60 | | |
| **7**, R′ = $PhCH_2$, R″ = H | A | 70% | 147° | $C_{11}H_{13}NOS$ | 63.74 | 6.32 | 6.76 | 15.47 | 1640 | |
| | | | ($CCl_4$) | (207.28) | 63.71 | 6.23 | 6.58 | 15.31 | | |
| **8**, R = H | C | 82% | 156° | $C_{14}H_{17}NO_3S$ | 60.20 | 6.14 | 5.02 | 11.48 | 1620 | 1700 |
| | | | (EtOAc) | (279.35) | 60.43 | 6.22 | 5.14 | 11.52 | | |
| **8**, R = Et | A | 47.5% | 48–9° | $C_{16}H_{21}NO_3S$ | 62.51 | 6.89 | 4.56 | 10.43 | 1670 | 1735 |
| | | | ($Et_2O$) | (307.40) | 62.79 | 6.68 | 4.61 | 10.38 | | |
| **9** | A | 61% | 139° | $C_{18}H_{17}NO_4S$ | 62.95 | 4.99 | 4.08 | 9.34 | 1665 | 1755 |
| | | | (EtOH) | (343.40) | 62.98 | 5.15 | 4.24 | 9.67 | | |
| **10**, R′ + R″ = $(CH_2)_5$ | A | 59% | 200–1° | $C_{13}H_{15}NOS$ | | | 6.00 | 13.74 | 1650 | |
| | | | (EtOH) | (233.33) | | | 6.18 | 13.98 | | |
| **10**, R′ = 3,4-methylenedioxyphenyl, R″ = H | A | 54% | 195–6° | $C_{15}H_{11}NO_3S$ | 63.13 | 3.89 | 4.91 | 11.22 | 1660 | |
| | | | (EtOH) | (285.25) | 63.27 | 4.26 | 4.91 | 11.21 | | |

[a]Racemic mixtures. [b]For the method of purification of the crude product, see Experimental. [c]For the preparation of the starting 5-formylpentanoic acid, see Ref. 7. [d]Starting with crude *N*-methyl-3-mercaptopropionamide. For the synthesis of the other starting compound, ethyl 6-formylhexanoate, see Ref. 7. [e]See Experimental. [f]For the preparation of the starting aldehydic ester, see Ref. 8. [g]Starting with crude ethyl 2,6-dibromo-4-formylphenoxyacetate. [h]For the preparation of the starting *p*-(3-cyanopropoxy)benzaldehyde, see Ref. 9. [i]Lit. m.p.[4] 179–80°. [j]Lit. m.p.[4] 194.9–195.7°. [k]Lit. m.p.[4] 193.2–193.8°. [l]See experimental. [m]For the preparation of the starting 3,5-dibromo-4-hydroxybenzaldehyde, see Ref. 10. [n]Br, Calc.: 43.54. Found: 43.67%.

Table 2. *In vitro* activities of some compounds against Mycobact. tuberculosis ($H_{37}R_v$) in Dubos-medium†

| | Compound | Minimal inhibitory concentration (μg/ml) |
|---|---|---|
| **2**, | n = 0, R = Et, $R^2 = R^3 = H$ | 25.0 |
| | n = 2, R = Me, $R^2 = R^3 = H$ | 25.0 |
| | n = 4, $R = R^2 = R^3 = H$ | 12.5 |
| | n = 4, R = Et, $R^2 = R^3 = H$ | 6.2 |
| | n = 5, $R = R^2 = R^3 = H$ | 0.06 |
| | n = 5, R = Et, $R^2 = R^3 = H$ | 0.015 |
| | n = 0, R = Et, $R^2$ = Me, $R^3 = H$ | 25.0 |
| | n = 5, $R = R^2 = H$, $R^3$ = Me | 25.0 |
| **3** | | 0.15 |
| **4** | | 12.5 |
| **5**, | R = X = H | 6.2 |
| | R = Et, X = H | 0.03 |
| | R = H, X = Br | 100.0 |
| | R = Et, X = Br | 12.5 |
| **6** | | 25.0 |
| **7**, | R′ = R″ = Me | 50.0 |
| | R′ + R″ = $(CH_2)_4$ | 25.0 |
| | R′ + R″ = $(CH_2)_5$ | 25.0 |
| | R′ = *p*-$HOC_6H_4$, R″ = H | 25.0 |
| | R′ = *p*-EtOOC-$C_6H_4$, R″ = H | 100.0 |
| | R′ = 3,4,5-$(MeO)_3C_6H_2$, R″ = H | 25.0 |
| | R′ = 3.5-$Br_2$-4-$HOC_6H_2$, R″ = H | 100.0 |
| | R′ = $PhCH_2$, R″ = H | 25.0 |
| **8**, | R = H | 100.0 |
| **9** | | 100.0 |
| **10** | R′ + R″ = $(CH_2)_5$ | 100.0 |
| | INH | 0.03 |
| | Streptomycine sulfate | 0.1 |
| | Rifampicine | 0.01 |
| | DL-Mycobacidine (DL-actithiazic acid) | 0.1 |

†Maximum drug concentration tested: 100 μg/ml.

ethyl ω-formylalkanoates, ethyl pyruvate, ethyl 4-formylphenoxyacetates, the appropriate benzaldehydes, acyclic and alicyclic ketones, respectively, in the presence of boron trifluoride etherates (Method A) or dry hydrogen chloride (Method B). Method A, when applied to the synthesis of the ethyl ester of racemic Mycobacidine, furnished better yields than the procedure described in literature[1d] which uses *p*-toluenesulfonic acid as the catalyst. Part of the 2-arylthiazinones obtained, viz. compounds **7** (R′ = Ph, *p*-$ClC_6H_4$ and *p*-$MeOC_6H_4$; R″ = H) have been earlier obtained by interacting 3-mercaptopropionic acid with ammonia and the appropriate aromatic aldehydes;[4] the yields, however, were considerably lower.† The acids of type **2** and **5** (R = H) were obtained either by alkaline hydrolysis of the corresponding esters (R = Me, Et) (Method C) or by condensation of ω-formylalkanoic acids with 3-mercaptopropionamide according to Method B. The ureide **4** was obtained by allowing to react the acid **2** ($R = R^2 = R^3 = H$, n = 5) with DCC; hydrolysis of this product furnished the amide **3**. The methods of preparation, yields, m.ps and microanalytical data of all compounds prepared are listed in Table 1.

The antimycobacterial activities of the compounds **2–10** were determined *in vitro* using Mycobacterium tuberculosis typ. humanus ($H_{37}R_v$) in Dubos-medium.[12]

†The latter method has been extended to the synthesis of *N*-substituted derivatives by applying primary amines instead of ammonia.[4] For variants of the latter procedure see Refs. 5 and 6.

The minimum inhibitory concentrations (MIC) of some compounds, new and known, are listed in Table 2. Several new compounds showed remarkable MIC values. High activity in the 4 - oxo - 3,4,5,6 - tetrahydro - 2*H* - 1,3 - thiazine series (compounds **2–4**) is, apparently, connected with the presence of a medium length carbon chain attached to C(2) and bearing a carboxyl or modified carboxyl (ester or amide) group at its remote end.

Substitution of the hydrogen atom attached to the ring nitrogen atom even by a methyl group results in significant decrease of the activity. The carbon chain which connects the thiazine ring and the (modified) carboxyl group may, on the other hand, be replaced without diminution of the activity by *p*-$CH_2$–O–$C_6H_4$.

The *in vitro* activities of even the most promising compounds of the present series are diminished or suspended in the presence of biotine. Therefore, these compounds proved inactive *in vivo* (in mice), as has earlier been found to be the case with Mycobacidine **1**.[1a] A detailed report on the microbiological screening will be published elsewhere.

## EXPERIMENTAL

*3-Acetylthio-N-methylpropionamide*

A mixture of *N*-methylacrylamide[11] (8.5 g; 0.1 mole), thioacetic acid (6.2 ml; 0.1 mole) and MeOH (30 ml) was refluxed for 30 min under nitrogen. The solvent was evaporated *in vacuo*, and the yellow oily residue was crystallized from $CCl_4$ and recrystallized from benzene–light petroleum to yield 5.2 g (31%) of the title compound, m.p. 77–9°. (Found: C, 44.61; H, 6.46; N, 8.46. $C_6H_{11}NO_2S$ (161.23) requires: C, 44.69; H, 6.88; N, 8.69%).

*3-Mercapto-N-methylpropionamide*

3-Acetylthio-*N*-methylpropionamide (7.70 g; 48 mmoles) was refluxed for 5 hr with anhyd MeOH (30 ml) in which metallic Na (0.1 g) had been dissolved. The mixture was neutralized with anhyd methanolic HCl and evaporated to dryness *in vacuo*. The residue was extracted for 5 hr with boiling ether under nitrogen or argon in a Soxhlet apparatus. The ethereal soln was evaporated to dryness to yield 4.60 g (81%) of the crude title compound (IR, film: NH 3300 and 1580–60, SH 2550, amide I 1650 $cm^{-1}$) which was used without further purification.

*Ethyl 2,6-dibromo-4-formylphenoxyacetate*

3,5-Dibromo-4-hydroxybenzaldehyde[10] and ethyl bromoacetate (20 mmoles, each) were refluxed with anhyd EtOH (40 ml), in which metallic Na (20 mmoles) had been dissolved, until the soln became neutral (about 2 hr). Water was added to the hot soln until the product just started to precipitate. The crude product (m.p. 95–100°) was used without further purification.

*General method for the condensation of aromatic aldehydes, acyclic and alicyclic ketones, ω-formylalkanoic acids, their esters, ethyl pyruvate and ethyl 4-formylphenoxyacetates with 3-mercaptopropionamide,[2] its N-methyl derivative and 2-mercaptobenzamide[3] in the presence of $BF_3$ (Method A)*

The mercaptoptopionamides (13 mmoles) and the mercaptobenzamide (10 mmoles), respectively, were refluxed under nitrogen or argon for 1–4 hr with $BF_3$·$Me_2O$ or $BF_3$·$Et_2O$ (10 mmoles) and the appropriate aldehyde, ketone, oxo acid and its ester, respectively, (10 mmoles) in anhyd dioxane (100 ml). The inorganic precipitates were filtered off and washed with anhyd dioxane. The combined filtrates and washings were evaporated to dryness *in vacuo*. The residues were triturated with water and neutralized by adding crystalline $NaHCO_3$. In case the resulting crude products were non-crystalline, they were taken up in ether or $CHCl_3$; the solns were dried ($MgSO_4$) and evaporated to dryness. The residues were crystallized from suitable solvents; alternatively, some of the ester type products were subjected to hydrolysis directly.

The crude oily compound **2** (n = 0, R = Et, $R^2 = R^3 = H$) was purified by chromatography through a column of Brockmann

grade II neutral alumina (10 g/1 g of compound **2**, solvent: benzene–MeOH, 10:2). The individual fractions of the eluate were examined by TLC (Kieselgel G, solvent as above, detection with $I_2$ vapour); those containing the desired product ($R_f$ 0.53) were conbined and evaporated to dryness to yield a colourless crystalline product.

Compound **7** (R′ = *p*-$Me_2NC_2NC_6H_4$, R″ = H) was obtained under slightly different conditions, viz. by allowing the starting compounds to interact for 24 hr at r.t. in the presence of 20 mmoles of $BF_3 \cdot Et_2O$ with 10 mmoles of the aldehyde.

*Ethyl ester of* DL-*Mycobacidine* (**1**)

Mercaptoacetamide (8.25 g; 90.5 mmoles) was refluxed for 4 hr with ethyl 6-formylhexanoate[7] (13.0 g; 75.5 mmoles) and $BF_3 \cdot Et_2O$ (9.6 ml; 75.5 mmoles) in anhyd dioxane (100 ml) according to Method A to yield 17.20 g (93%) of the title compound, m.p. 49–50°, lit.[1d] m.p. 47–50°. The reported yields of DL-Mycobacidine esters obtained in the presence of *p*-toluenesulfonic acid as the condensing agent are 10–50%.[1d]

*Condensations in the presence of* HCl (*Method B*)

(a) 5-Formylpentanoic acid, obtained from 2-hydroxycyclohexanone (30 mmoles) as described by Baer,[7] and 3-mercaptopropionamide[2] (2.1 g; 20 mmoles) were dissolved in anhyd dioxane (30 ml). A stream of anhyd HCl was introduced for 2 hr into the boiling soln. The crystalline precipitate of $NH_4Cl$ was filtered off after cooling, the filtrate was evaporated to dryness *in vacuo*, and the residue was crystallized from water or EtOAc.

(b) Compounds **7** (R′ = Ph, *p*-$Me_2NC_6H_4$, R″ = H) were similarly obtained by reacting 3-mercaptopropionamide with a 10% excess of the appropriate aldehyde.

*General method for the hydrolysis of esters of types* **2**, **5** *and* **8** (*Method C*)

The esters (1 mmole) were stirred with 0.25 N aq NaOH soln at room temp. until, according to TLC, the starting compound has entirely been used up. In the case of very slightly soluble esters 10% (by vol) EtOH was added. The resulting solns were acidified under ice-water cooling with concd HCl to yield the crystalline acids.

N,N′ - *Dicyclohexyl* - N - [6 - [4 - *oxo* - 3,4,5,6 - *tetrahydro* - 2H - 1,3 - *thiazolin* - 2 - *yl*)*hexanoyl*]*urea* **4**

A mixture of the acid **2** (n = 5, R = $R^2$ = $R^3$ = H) (3.90 g; 15 mmoles), *N*-methylpiperazine (0.75 g; 7.5 mmoles), dicyclohexylcarbodi-imide (1.86 g; 9 mmoles) and anhyd DMF (20 ml) was allowed to stand for 3 days at room temp. The resulting dicyclohexyl urea was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was taken up in benzene (100 ml) and extracted with two portions of N/1 NaOH (100 ml, each) and water (100 ml). Acidification of the combined aqu solns with conc. HCl furnished 1.20 g (30.8%) of unreacted **2**. The benzene soln was evaporated to dryness to yield 1.20 g of the title compound (30.4%, based on the amount of carbodi-imide).

N - *Cyclohexyl* - 6 - (4 - *oxo* - 3,4,5,6 - *tetrahydro* - 2H - 1,3 - *thiazin* - 2 - *yl*)*hexanamide* **3**

Compound **4** (220 mg; 0.5 mmole) was refluxed with anhyd *N*-methylpiperazine for 3 hr during which period a stream of anhyd HCl was introduced into the solution. The mixture was evaporated to dryness, and the residue was triturated with EtOAc to yield 50.2 mg (32%) of the title compound.

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