

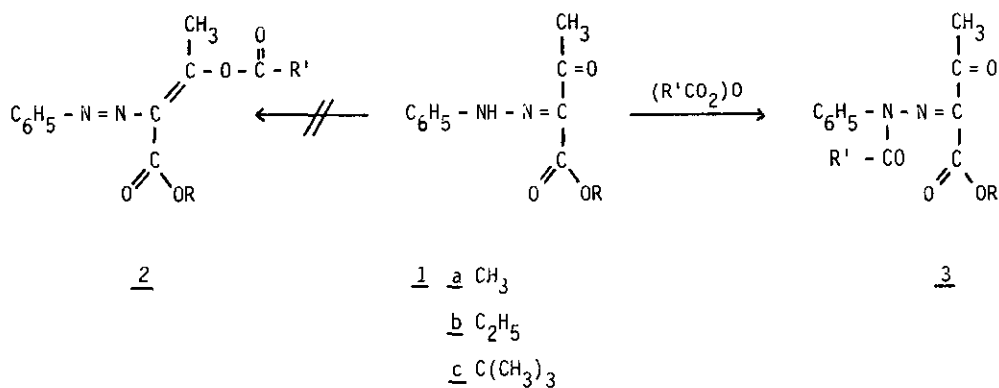
SYNTHESIS AND ACYLATION OF 2-(2,5-DIHYDRO-1,3-THIAZOL-2-YL)-2-PHENYL-  
HYDRAZONOACETIC ACID ESTERS

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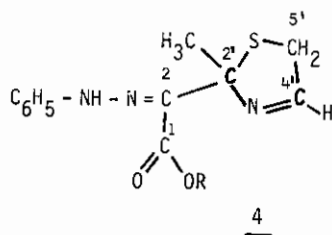
Abstract: The preparation of 2-(2,5-dihydro-1,3-thiazol-2-yl)-2-phenyl-  
hydrazonoacetic acid esters is described. Acylation of these compounds  
occurs at the sulfur atom with concomitant opening of the dihydrothiazole  
ring to yield 3-(Z-2-acylthiovinylimino)-2-phenylhydrazono-butanoic acid  
esters.

The understanding of multi-site nucleophilic reactivity is still in its infancy. Thus the experi-  
mental investigation of electrophilic attack on model systems which offer various locations with  
nucleophilic character is of great value. 3-Oxo-2-phenylhydrazonobutanoic acid esters (1) can, in  
principle, be attacked at the oxygen atom, at carbon atom 2, and at both nitrogen atoms. Of these,  
the oxygen atom and the nitrogen atom closest to the phenyl ring seem the most likely reaction  
sites.

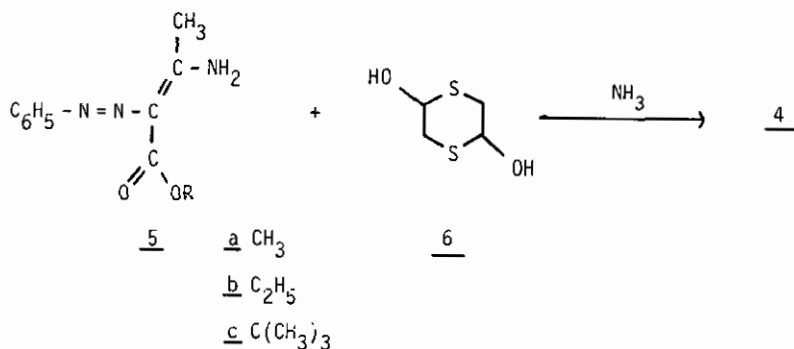


Although attack at the oxygen atom should give a product 2 with the most extended conjugated system,  
in the reaction of 1 with acid anhydrides/triethylamine in ether under catalysis by zinc chloride  
only attack at the nitrogen atom is observed resulting in structures 3.<sup>1,2</sup>

To complicate the situation we were aiming at acylation reactions at 2-(2-methyl-2,5-dihydro-  
1,3-thiazol-2-yl)-2-phenylhydrazonoacetic acid esters 4.



These compounds 4 were obtained <sup>2</sup> by reacting 3-amino-2-phenylazo-2-butenoic acid esters 5 with 2,5-dihydroxy-1,4-dithiane 6 in ether under catalysis by ammonia.<sup>3</sup>

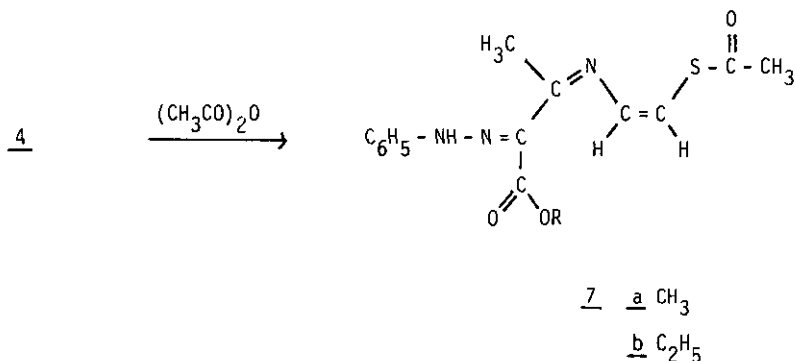


Yields range between 75-85%. 4a: m.p. 99-100<sup>0</sup>C; C<sub>13</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S, (277.34); calc. C 56.39, H 5.45, N 15.15, found: C 56.60, H 5.57, N 15.34; - IR(KBr):  $\nu = 3240, 1680, 1540, 1170 \text{ cm}^{-1}$ ; - <sup>1</sup>H-NMR(CDCl<sub>3</sub>):  $\delta = 2.00(\text{s}, 3\text{H}, \text{CH}_3\text{-C}2')$ ,  $3.73(\text{s}, 3\text{H}, \text{CO}_2\text{CH}_3)$ ,  $4.05(\text{broad s}, 2\text{H}, \text{H}_2\text{C}5')$ ,  $6.7\text{-}7.3(\text{m}, 5\text{H}, \text{C}_6\text{H}_5)$ ,  $7.38(\text{broad s}, 1\text{H}, \text{HC}4')$ ,  $11.9(\text{broad s}, 1\text{H}, \text{NH})$  ppm; - <sup>13</sup>C-NMR(CDCl<sub>3</sub>):  $\delta = 31.5(\text{CH}_3\text{-C}2')$ ,  $46.7(\text{C}5')$ ,  $51.3(\text{CO}_2\text{CH}_3)$ ,  $93.3(\text{C}2')$ ,  $114.2, 122.4, 129.2, 143.3(\text{C}_6\text{H}_5)$ ,  $128.4(\text{C}2)$ ,  $159.2(\text{C}4')$ ,  $163.3(\text{CO}_2\text{CH}_3)$  ppm; MS(70eV): m/e = 277(50%, M<sup>+</sup>), 231(52%, M<sup>+</sup>-CH<sub>2</sub>S), 230(100%, M<sup>+</sup>-CH<sub>3</sub>S), 199(95%, M<sup>+</sup>-CH<sub>2</sub>S-CH<sub>3</sub>OH), 172(81%), 153(76%), 104(28%), 100(44%), 92(66%), 77(64%), 65(68%).

4b: m.p. 108<sup>0</sup>C; C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S (291.37); calc. C 57.71, H 5.88, N 14.42, found: C 57.69, H 6.19, N 14.34; - IR(KBr):  $\nu = 3500, 3230, 1670, 1645, 1600, 1530, 1175 \text{ cm}^{-1}$ ; - <sup>1</sup>H-NMR(CDCl<sub>3</sub>):  $\delta = 1.29(\text{t}, 3\text{H}, \text{CH}_2\text{CH}_3)$ ,  $2.00(\text{s}, 3\text{H}, \text{CH}_3\text{-C}2')$ ,  $4.11(\text{broad s}, 2\text{H}, \text{H}_2\text{C}5')$ ,  $4.23(\text{q}, 2\text{H}, \text{CH}_2\text{CH}_3)$ ,  $6.8\text{-}7.4(\text{m}, 5\text{H}, \text{C}_6\text{H}_5)$ ,  $7.45(\text{broad s}, 1\text{H}, \text{HC}4')$ ,  $12.0(\text{broad s}, 1\text{H}, \text{NH})$  ppm; - <sup>13</sup>C-NMR(CDCl<sub>3</sub>):  $\delta = 13.7(\text{CH}_2\text{CH}_3)$ ,  $31.5(\text{CH}_3\text{-C}2')$ ,  $46.6(\text{C}5')$ ,  $60.4(\text{CO}_2\text{CH}_2\text{CH}_3)$ ,  $93.1(\text{C}2')$ ,  $114.0, 122.2, 129.1, 143.0(\text{C}_6\text{H}_5)$ ,  $128.1(\text{C}2)$ ,  $159.0(\text{C}4')$ ,  $162.9(\text{CO}_2\text{R})$  ppm. - MS(70eV): m/e = 291(44%, M<sup>+</sup>), 245(52%, M<sup>+</sup>-CH<sub>2</sub>S), 244(80%, M<sup>+</sup>-CH<sub>3</sub>S), 199(100%, M<sup>+</sup>-CH<sub>2</sub>S-C<sub>2</sub>H<sub>5</sub>OH), 186(81%), 168(46%), 104(28%), 100(43%), 93(63%), 92(58%), 77(59%), 65(57%).

4c: m.p. 117°C;  $C_{16}H_{21}N_3O_2S$  (319.42); calc.: C 60.16, H 6.62, N 13.15, found: C 60.33, H 6.71, N 13.25. - IR(KBr):  $\nu = 3320, 1670, 1655, 1320, 1150 \text{ cm}^{-1}$ . -  $^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta = 1.48(\text{s}, 9\text{H}, \text{C}(\text{CH}_3)_3)$ ,  $1.92(\text{s}, 3\text{H}, \text{CH}_3\text{-C}2')$ ,  $3.95(\text{broad s}, 2\text{H}, \text{H}_2\text{C}5')$ ,  $6.6\text{-}7.2(\text{m}, 5\text{H}, \text{C}_6\text{H}_5)$ ,  $7.23(\text{broad s}, 1\text{H}, \text{HC}4')$ ,  $12.0(\text{broad s}, 1\text{H}, \text{NH})$  ppm. -  $^{13}\text{C-NMR}(\text{CDCl}_3)$ :  $\delta = 28.1(\text{C}(\text{CH}_3)_3)$ ,  $31.1(\text{CH}_3\text{-C}2')$ ,  $45.9(\text{C}5')$ ,  $82.1(\text{C}(\text{CH}_3)_3)$ ,  $93.1(\text{C}2')$ ,  $114.0, 122.0, 129.1, 143.3(\text{C}_6\text{H}_5)$ ,  $129.0(\text{C}2)$ ,  $158.3(\text{C}4')$ ,  $162.4(\text{CO}_2\text{R})$  ppm. - MS(70eV):  $m/e = 319(25\%, \text{M}^+)$ ,  $273(6\%, \text{M}^+\text{-CH}_2\text{S})$ ,  $272(7\%, \text{M}^+\text{-CH}_3\text{S})$ ,  $263(32\%, \text{M}^+\text{-C}_4\text{H}_9)$ ,  $217(72\%)$ ,  $216(80\%)$ ,  $199(100\%, \text{M}^+\text{-CH}_2\text{S-C}_4\text{H}_9\text{OH})$ ,  $158(76\%)$ ,  $104(23\%)$ ,  $100(37\%)$ ,  $92(52\%)$ ,  $77(51\%)$ ,  $65(45\%)$ .

The 2-(2,5-dihydro-1,3-thiazol-2-yl)phenylhydrazonoacetic acid esters 4 offer, besides the two nitrogen atoms and the carbon atom of the hydrazono group, two additional atoms for electrophilic attack: the sulfur atom and the nitrogen atom 3' of the ring system. The acylations were performed by refluxing 0.2 molar solutions of 4 in dry ether for 12 hrs with 10 equiv. of acetic anhydride, 2 equiv. of triethylamine and a catalytic amount of zinc chloride. Contrary to 3-oxo-2-phenylhydrazono-butanoic acid esters 1 the compounds 4 do not react at the nitrogen atom closest to the phenyl ring, but attack occurs at the sulfur atom with concomitant opening of the ring system to give 3-(Z-2-aclythiovinylimino)-2-phenylhydrazono-butanoic acid esters 7 in 52-63% yield.



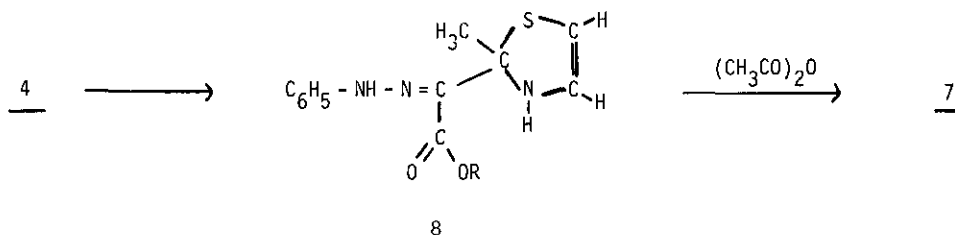
7a: m.p. 111°C;  $C_{15}H_{17}N_3O_3S$  (319.38); calc.: C 56.41, H 5.36, N 13.15, found: C 56.62, H 5.48, N 13.32. - IR(KBr):  $\nu = 3450, 1705, 1600, 1500, 1220, 1115, 770 \text{ cm}^{-1}$ . -  $^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta = 2.32(\text{s}, 3\text{H}, \text{CH}_3\text{C}=\text{N})$ ,  $2.42(\text{s}, 3\text{H}, \text{CH}_3\text{COS})$ ,  $3.78(\text{s}, 3\text{H}, \text{CH}_3\text{O}_2\text{C})$ ,  $6.63(\text{d}, \text{J}=7.0 \text{ Hz}, 1\text{H}, =\text{CH})$ ,  $6.9\text{-}7.5(\text{m}, 6\text{H}, \text{C}_6\text{H}_5, =\text{CH})$ ,  $15.3(\text{s}, 1\text{H}, \text{NH})$  ppm. -  $^{13}\text{C-NMR}(\text{CDCl}_3)$ :  $\delta = 17.9(\text{CH}_3\text{-C}=\text{N})$ ,  $30.7(\text{CH}_3\text{COS})$ ,  $51.9(\text{CH}_3\text{O}_2\text{C})$ ,  $116.1(=\text{C}-\text{S})$ ,  $116.5, 124.3, 129.2, 143.4(\text{C}_6\text{H}_5)$ ,  $126.5(\text{C}=\text{N}-\text{N})$ ,  $131.6(=\text{C}-\text{N})$ ,  $162.0(\text{CH}_3\text{-C}=\text{N})$ ,  $166.2(\text{CO}_2\text{R})$ ,  $189.7(\text{CH}_3\text{COS})$  ppm.

7b: m.p. 102-103°C;  $C_{16}H_{19}N_3O_2S$  (333.41); calc.: C 57.64, H 5.74, N 12.60, found: C 57.40, H 5.59, N 12.77. - IR(KBr):  $\nu = 3450, 1695, 1500, 1270, 1105, 755 \text{ cm}^{-1}$ . -  $^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta = 1.35(\text{t}, 3\text{H}, \text{CH}_3\text{CH}_2)$ ,  $2.33(\text{s}, 3\text{H}, \text{CH}_3\text{C}=\text{N})$ ,  $2.45(\text{s}, 3\text{H}, \text{CH}_3\text{COS})$ ,  $4.30(\text{q}, 2\text{H}, \text{CH}_3\text{CH}_2)$ ,  $6.70(\text{d}, \text{J}=7.0 \text{ Hz}, 1\text{H}, =\text{CH})$ ,

6.9-7.6(m, 6H, C<sub>6</sub>H<sub>5</sub>, =CH), 15.2(s, 1H, NH) ppm. -

The thioester group is clearly established through the absorption at 189.7 ppm in the <sup>13</sup>C-NMR spectrum. The *cis*-configuration in the olefinic part follows from coupling constant in the <sup>1</sup>H-NMR spectrum (<sup>3</sup>J<sub>HH</sub> = 7.0 Hz).

The reaction 4→7 is presumably initiated by the rearrangement of the 2,5-dihydro-1,3-thiazole compounds 4 to 2,3-dihydro-1,3-thiazole compounds 8 under catalysis by ZnCl<sub>2</sub>.



For, the derivatives of 4 with two methyl groups at position 5' do not react with acid anhydrides under conditions where the reaction 4→7 readily occurs. Steric hindrance of attack at sulfur by the two additional methyl groups does not seem to be able to completely explain this drastic fall-off in reactivity.

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