

Stuart-Brigleb molecular models of β -(6-hydroxypyrimidyl-4)alanine (A), and m-tyrosine (B).

A comparative study of amino acids I-Ic is in hand. The authors are very grateful to Prof. M. A. Prokof'ev for his continued interest in the present work.

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SYNTHESIS AND TRANSFORMATIONS OF FURAN DERIVATIVES

V. Synthesis of 4-Methylthiazolyl-(2)-Hydrazones of Aldehydes and Ketones of the Furan Series*

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Condensation of thiosemicarbazones of furfural, 3-(2-furyl)acrolein, as well as their 5-nitro derivatives with chloroacetone by boiling in alcohol or acetic acid gives the corresponding 4-methylthiazolyl-(2)hydrazones. 4-Methylthiazolyl-(2)-hydrazones of 5-nitro-2-acetylfuran and 5-nitro-2-furfurylideneacetone can be prepared by condensing the corresponding thiosemicarbazones with chloroacetone by heating with glacial acetic acid containing fused sodium acetate.

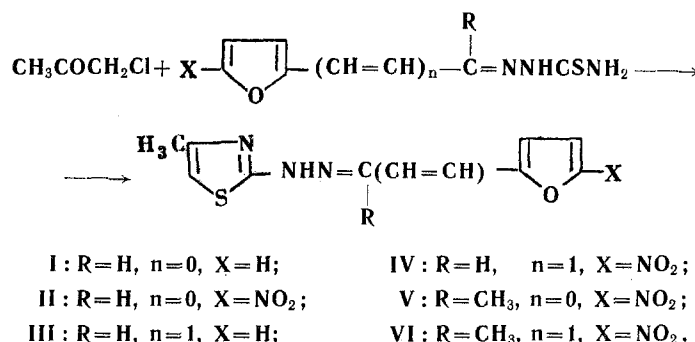
4-Methylthiazolyl-(2)-hydrazones of aldehydes and ketones of the furan and 5-nitrofuran series (I-VI), analogs of previously described 4-(5'-nitrofuryl-2')thiazolyl-(2)-hydrazones [2], have been synthesized to study the relationship between chemotherapeutic action and chemical structure. Unlike the analogs mentioned, the new compounds do not have the furan ring linked directly to the thiazole ring, but situated at the end of the hydrazone group.

The above compounds were obtained by condensing chloroacetone with the corresponding thiosemicarbazones. Thiosemicarbazones of aldehydes of the furan series, of furfural, 3-(2-furyl)acrolein, and their 5-nitro derivatives could readily be brought to react with chloroacetone by boiling in alcohol or acetic acid, though the nitro derivatives required longer heating (up to 6 hr) than the furan compounds (10-15 min). Under the same conditions the thiosemicarbazones of ketones, of 2-furfurylideneacetone, its 5-nitro derivative, and 5-nitro-2-acetylfuran, did not react with chloroacetone,

*For Part IV see [1].

while the thiosemicarbazone of 2-acetylfuran gave resinous products which could not be crystallized. Increasing the heating time did not affect the result. However, it proved possible to obtain 4-methylthiazolyl-(2)-hydrazones of 5-nitro-2-acetylfuran (V) and 5-nitro-2-furfurylideneacetone through condensing the corresponding thiosemicarbazones with chloroacetone by heating in glacial acetic acid containing fused sodium acetate. Addition of the latter also promoted an increased yield, 97% as compared with 64%, of 4-methylthiazolyl-(2)-hydrazone of 5-nitrofurfural (II) when prepared as above. In synthesizing I, III, and IV the effect of sodium acetate was slight, but use of it did not make it possible to obtain methylthiazolylhydrazones from 2-acetylfuran and 2-furylaceton.

The furan series derivatives were crystalline compounds ranging from cream-colored to pale brown, while the nitrofur series derivatives were red to reddish brown. The methylthiazolylhydrazones were soluble in dimethylformamide, sparingly soluble in alcohol (particularly when they contained a nitro group), and insoluble in water.



Experimental

2-(2-Furfurylidenehydrazino)-4-methylthiazole (I). 0.85 g (0.005 mole) furfural thiosemicarbazone was dissolved in 15 ml alcohol, 0.46 g (0.005 mole) chloroacetone added, and the whole refluxed for 15 min. The products were treated hot with activated carbon, and filtered. The filtrate was made alkaline with aqueous ammonia, and the resultant precipitate filtered off. Yield 0.35 g (34%) I, mp 180-182° (from alcohol). Found: C 51.96; H 4.70; N 20.11; S 15.17%. Calculated for C₉H₉N₃OS: C 52.15; H 4.37; N 20.28; S 15.47%.

2-(5-Nitro-2-furfurylidenehydrazino)-4-methylthiazole (II). 0.86 g (0.004 mole) 5-nitrofurfural thiosemicarbazone, 250 ml alcohol, and 0.37 g (0.004 mole) chloroacetone were refluxed together for 5-6 hr, three quarters of the solvent distilled off, and 400 ml water added. The precipitate was filtered off and dried. Yield 0.65 g (64%) II, mp 229° (decomp., from acetone). Found: C 43.03; H 3.33; N 22.29; S 12.47%. Calculated for C₉H₈N₄O₃S: C 42.85; H 3.20; N 22.21; S 12.71%.

2-[3-(2-Furyl)-allylidenehydrazino]-4-methylthiazole (III). 5.9 g (0.03 mole) furylacrolein thiosemicarbazone was dissolved in 200 ml alcohol, 2.8 g (0.03 mole) chloroacetone added, the whole refluxed for 10 min, diluted with water, and left overnight. The precipitate was filtered off and dried. Yield 5.3 g (75%) III, mp 178-181° (from alcohol). Found: C 56.49; H 4.81; N 17.79; S 13.47%. Calculated for C₁₁H₁₁N₃OS: C 56.63; H 4.75; N 18.01; S 13.75%.

2-[3-(5-Nitro-2-furyl)-allylidenehydrazino]-4-methylthiazole (IV). 3.12 g (0.013 mole) 5-nitro-2-furylacrolein thiosemicarbazone was dissolved in 400 ml alcohol, 1.2 g (0.013 mole) chloroacetone added, the whole refluxed for 2 hr, three quarters of the solvent then distilled off, and 400 ml water and 10 ml 25% aqueous ammonia added. The precipitate was filtered off and dried. Yield 3.13 g (87%) IV, mp 225-230° (decomp., from alcohol). Found: C 47.27; H 3.83; N 20.04; S 11.40%. Calculated for C₁₁H₁₀N₄O₃S: C 47.47; H 3.62; N 20.13; S 11.52%.

2-[1-(5-Nitro-2-furyl)ethylidenehydrazino]-4-methylthiazole (V). 2.3 g (0.01 mole) 5-nitro-2-acetylfuran thiosemicarbazone and 1.64 g (0.02 mole) fused sodium acetate were dissolved in 100 ml acetic acid, and 0.92 g (0.01 mole) chloroacetone added to the hot solution. The mixture was refluxed for 4 hr, 200 ml water added, followed by 5 ml 25% aqueous ammonia solution. The precipitate was filtered off and dried. Yield 0.62 g (23%) V, mp 180° (decomp., from alcohol). Found: C 45.49; H 3.95; N 21.26; S 11.91%. Calculated for C₁₀H₁₀N₄O₃S: C 45.10; H 3.79; N 21.04; S 12.04%.

2-[3-(5-Nitro-2-furyl)-1-methylallylidenehydrazino]-4-methylthiazole (VI). 2.54 g (0.01 mole) 5-nitro-2-furfurylideneacetone thiosemicarbazone and 1.64 g (0.02 mole) fused sodium acetate were dissolved in 50 ml hot glacial acetic acid, 0.92 g (0.01 ml) chloroacetone added, and the whole refluxed for 5 hr, 150 ml water added, the precipitate filtered off, washed with water, and dried. Yield 2.29 g (78%) VI, mp 150-153°. Recrystallization from alcohol lowered the mp to 118-120°. Found: C 48.99; H 4.34; S 10.89%. Calculated for C₁₂H₁₂N₄O₃S: C 49.31; H 4.14; S 10.97%.

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