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Original Scientific Paper

Hydropyrimidines. I. Synthesis of 5,6-Dihydro-2-thiouracil

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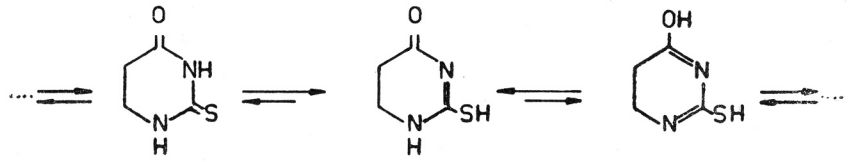
The synthesis of 5,6-dihydro-2-thiouracil (I) from 1-(*n*-propionic acid ethylester)-3-benzoyl-2-thiourea (IV) was described. Thioureidoester IV was hydrolyzed in diluted hydrochloric acid and sodium hydroxide to 1-(*n*-propionic acid)-3-benzoyl-2-thiourea (V) and 1-(*n*-propionic acid)-2-thiourea (homohydantoic acid) (VI) respectively.

IR (5.85; 6.33 μ) and UV ($\lambda\lambda_{max}$ 225.5 mμ, log ε 4.017; 270.5 mμ, log ε 4.165) of I revealed the peculiarities by which the tautomeric species of thiohydropyrimidines are distinguished.

Although several syntheses have been reported on hydantoins[1] it is surprising that the preparation of homologous 5,6-dihydro-2-thiouracil (I), used in clinical examinations[2–5], failed to be described. As a part of the investigation of hydropyrimidines and their role in the metabolism of corresponding nucleosides and nucleotides our interest was directed towards the specificities by which the tautomeric species of thio-hydropyrimidines are distinguished. IR (5.85; 6.33 μ) and UV ($\lambda\lambda_{max}$ 225.5 mμ, log ε 4.017; 270.5 mμ, log ε 4.165) absorption spectra of compound I revealed peculiarities concerning thioamido-imidethiol, keto-enol and diimidethiol tautomerism in comparison with 5,6-dihydro-uracil. The recorded spectra substantiated the keto-enethiol form with double bonds in conjugation.



I

In considering the methods for the preparation of compound I, β-thioureidopropionic acid appeared to offer the most convenient route in analogy with the use of β-ureidopropionic acid for the synthesis of 5,6-dihydrouracil[6,7]. However, when β-alanine ethylester hydrochloride was treated with potassium thiocyanate the hitherto unknown oily β-alanine ethylester hydrothiocyanate (II) was produced. UV and IR absorptions as well as a positive $FeCl_3$ reaction indicated clearly the presence of the thiocyanate ion. The cyclic compound I was obtained by the action of *N*-benzoyl-*iso*-thiocyanate (III) upon β-alanine through 1-(*n*-propionic acid ethylester)-3-benzoyl-urea (IV) and subsequent cyclisation.

Besides the cyclized product 1-(*n*-propionic acid)-3-benzoyl-2-thiourea (V) separated in a more diluted hydrochloric acid. The alkaline hydrolysis of thioureidoester IV gave 1-(*n*-propionic acid)-2-thiourea (homohydantoic acid) (VI).

$$\underset{\text{III}}{\text{PhCONCS}} + \text{H}_2\text{NCH}_2\text{CH}_2\text{COOEt} \rightarrow \text{RHNCH}_2\text{CH}_2\text{COOR}_1$$

IV. R = CSNHCOPh, R_1 = Et
V. R = CSNHCOPh, R_1 = H
VI. R = $CSNH_2$, R_1 = H

5,6-Dihydrouracil was obtained from the thiouracil I (on treating it with chloroacetic acid)[8] which also supports the existence of the latter compound.

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. UV spectra were measured in 95% ethanol, unless stated otherwise, on a Perkin-Elmer model 137 UV spectrophotometer with automatic gain control. The IR-absorption bands were recorded in potassium bromide plates on a Perkin-Elmer Infracord model 137.

β-*Alanine ethylester hydrothiocyanate* (II)

To a concentrated solution of β-aminopropionic acid ethylester hydrochloride (0.2 g., 1.3 mmole) in ethanol (1 ml.), powdered potassium thiocyanate (0.126 g., 1.3 mmole) was added. The mixture was refluxed for 5 hours, potassium chloride removed by filtration, the filtrate evaporated to an oil under reduced pressure and distilled at 5.10^{-2} mm, b.p. 140°. Yield 0.165 g. (72%). Further distillation at the same pressure afforded the analytically pure sample, b. p. 135—140°.

Anal. $C_6H_{12}N_2O_2S$ (176.23) calc'd.: C 40.89; H 6.86; N 15.90%
found: C 41.08; H 6.52; N 16.12%

Ultraviolet spectrum: λ_{max} 208 mμ, log ε 3.608. Infrared spectrum: 2.85 (w), 3.39 (m), 4.88 (s), 5.85 (s), 6.25 (w), 6.71 (w), 6.85 (w), 7.15 (w), 7.28 (w), 7.61 (vw), 8.20 (s), 9.10 (w), 9.8 (m) μ.

1-(n-*Propionic acid ethylester)-3-benzoyl-2-thiourea* (IV)

To crude benzoyl *iso*-thiocyanate in acetone (10 ml.), prepared according to the procedure of Douglass and Dains[9] from ammonium thiocyanate (1.9 g., 25 mmole) and an equimolar amount of benzoylchloride a solution of β-alanine ethylester (3 g., 25 mmole) in acetone (10 ml.) was added. After the mixture had been stirred for 5 minutes it was poured into water (50 ml.) and shaken. The oily product was extracted with ether, washed with water, dried and concentrated under reduced pressure. When the residual yellow oil was crystallized from methanol-water (2:1), 3.5 g. (50%) of the compound IV, m.p. 78—80°, was obtained as colorless needles. Crystallization from the same solvents gave the analytical sample, m.p. 82—83°.

Anal. $C_{13}H_{16}N_2O_3S$ (280.06) calc'd.: C 55.70; H 5.75; N 9.99%
found: C 55.57; H 5.45; N 9.89%

Ultraviolet spectrum: $\lambda\lambda_{max}$ 205 mμ, log ε 4.243; 243.5 mμ, log ε 4.296; 279.5 mμ, log ε 4.049; $\lambda\lambda_{min}$ 217.5 mμ, log ε 3.895; 265.5 mμ, log ε 4.006. Infrared spectrum: 2.94 (m), 3.12 (m), 3.38 (w), 3.44 (w), 5.88 (s), 6.02 (s), 6.25 (w), 6.47 (s), 6.54 (s), 7.00 (s), 7.28 (m), 7.65 (m), 7.97 (s), 8.2 (s), 8.4 (m), 8.7 (s), 8.94 (m), 9.09 (m), 9.35 (w), 9.69 (s), 9.8 (s), 10.0 (w), 10.2 (m), 10.3 (w), 10.75 (m), 11.55 (m), 11.75 (w), 12.55 (vw), 13.2 (w), 13.65 (s), 14.6 (s) μ.

5,6-*Dihydro-2-thiouracil* (I)

Thioureidoester (IV) (1.00 g., 3,5 mmole) was suspended in 10% hydrochloric acid (250 ml.) and refluxed for 1 hour with vigorous stirring until all the solid has dis-

solved. The solution was then evaporated at the water pump and the residue was suspended in ether, filtered off and washed with ether. It crystalized from methanol-ether as colorless prisms, yield 0.305 g. (61%). Crystallization from methanol gave the analytical sample, m.p. 233—234°.

Anal. $C_4H_6N_2OS$ (130.16) calc'd.: C 36.91; H 4.69; N 21.53; S 24.63%
found: C 37.08; H 4.37; N 21.42; S 24.98%

Ultraviolet spectrum (H_2O): λ_{max} 225.5 mμ, log ε 4.017; 270 mμ, log ε 4.165 and shoulder λ 212.5 mμ, log ε 3.984; λ_{min} 244 mμ, log ε 3.596. Infrared spectrum: 2.84 (vw), 3.12 (m), 5.85 (s), 6.33 (s), 6.78 (m), 6.94 (vw), 7.04 (w), 7.33 (s), 7.58 (vw), 7.85 (s), 8.05 (w), 8.4 (m), 8.66 (s), 9.28 (w), 9.57 (w), 9.95 (vw), 11.2 (vw), 12.3 (w), 12.9 (w) μ.

1-(n-Propionic acid)-3-benzoyl-2-thiourea (V)

A suspension of thioureidoester IV (100 mg., 0.35 mmole) in 0.5 *N* hydrochloric acid (50 ml.) was refluxed for 8 hours. On cooling a crystalline product separated. Yield 35 mg. (39%). Crystallization from methylenechloride — petroleum-ether (b.p. 40—60°) gave the analytical sample as colorless plates, m.p. 150—151°.

Anal. $C_{11}H_{12}N_2O_3S$ (252.22) calc'd.: N 11.11%
found: N 11.01%

Ultraviolet spectrum: λλ$_{max}$ 206.5 mμ, log ε 4.145; 243.5 mμ, log ε 4.258; 279 mμ, log ε 4.004; λλ$_{min}$ 216.5 mμ, log ε 3.851; 266 mμ, log ε 3.954. Infrared spectrum: 3.03 (w), 3.28 (vw), 3.45 (w), 5.87 (m), 6.01 (m), 6.41 (m), 6.58 (s), 7.02 (w), 7.25 (vw), 7.58 (vw), 7.94 (s), 8.20 (w), 8.33 (s), 8.62 (s), 9.01 (vw), 9.71 (vw), 12.1 (w), 13.3 (vw), 14.1 (m) μ.

1-(n-Propionic acid)-2-thiourea (Homohydantoic acid) (VI)

Thioureidoester IV (0.28 g., 1 mmole) was dissolved in 2 *N* sodium hydroxide (1 ml.) and heated on a steam bath for 5 minutes. The solution was acidified by addition of 2 *N* hydrochloric acid and filtered from the precipitated benzoic acid. The filtrate was concentrated to dryness under reduced pressure. The residual solid was suspended in hot abs. ethanol and the dissolved part was then evaporated at the water pump to yield an oil which crystallized from acetone-chloroform as colorless plates (0.08 g., 54%). Further crystallization from acetone-chloroform gave the analytical sample, m.p. 115—116° (or 105—106° whem heated rapidly).

Anal. $C_4H_8N_2O_2S$ (148.17) calc'd.: C 32.43; H 5.44; N 18.91%
found: C 32.71; H 5.24; N 18.96%

Ultraviolet spectrum: λλ$_{max}$ 207.5 mμ, log ε 3.916; 243 mμ, log ε 4.027; λ_{min} 224 mμ, log ε 3.445. Infrared spectrum: 2.92 (m), 3.08 (s), 3.42 (m), 3.8 (vw), 5.85 (s), 5.95 (s), 6.23 (s), 6.43 (s), 7.08 (s), 7.36 (m), 7.49 (m), 7.8 (m), 8.2 (s), 8.7 (m), 9.8 (vw), 11.2 (w), 12.5 (vw), 13.5 (m) μ.

5,6-Dihydrouracil

5,6-Dihydrouracil was prepared from 5,6-dihydro-2-thiouracil (95 mg.) treated with chloroacetic acid according to the procedure of Johnson and Ambelang[8]. Yield 37 mg. (45%). Recrystallized from methanol, m.p. 274—275° undepressed on admixture with the sample obtained from β-ureidopropionic acid[6]. The infrared spectra of both samples were superimposamble.

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IZVOD

Hidropirimidini. I. Sinteza 5,6-dihidro-2-tiouracila

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Pripravom 1-(*n*-propionska kiselina etilester)-3-benzoil-2-tiouree (IV) iz β-alanina i benzoil-*izo*-tiocijanata omogućena je sinteza 5,6-dihidro-2-tiouracila (I). Tioureidoester IV, pored cikličkog produkta, daje 1-(*n*-propionska kiselina)-3-benzoil-2-tioureu (V) i 1-(*n*-propionska kiselina)-2-tioureu (VI) obradom u razrijeđenijoj mineralnoj kiselini, odnosno lužini. Također je opisana priprava hidrocijanata etilnog estera β-amino propionske kiseline (II).

Infracrveni i ultraljubičasti spektri opisanih tvari su zabilježeni u detaljima.

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