INVESTIGATIONS INTO N-ARYL-β-AMINO ACIDS

I. The Synthesis of 1-Aryl-5,6-dihydrouracils and 1-Aryl-5,6-dihydro-2-thiouracils

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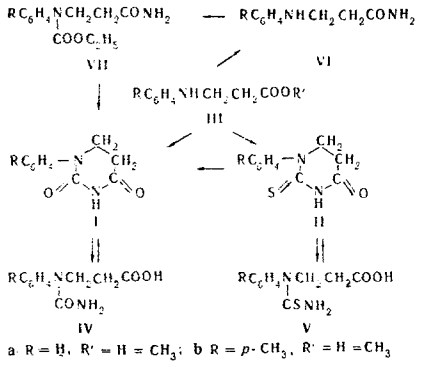
1-Aryl-5,6-dihydrouracils and 1-aryl-2-thio-5,6-dihydrouracils are synthesized from N-aryl-β-alanines and esters of N-aryl-β-ureidopropionic acid. The dihydrouracils were hydrolyzed by 0.1 N alkali.

Derivatives of dihydrouracil and dihydrothiouracil possess high physiological activity, [1–3], and are important intermediate products in nuclear metabolism [4].

The present paper describes the preparation of 5,6-dihydrouracils and 5,6-dihydrothiouracils substituted in the 1-position by phenyl and p-tolyl groups.



a R = H, R' = H = CH_3; b R = p-CH_3, R' = H = CH_3

1-Aryl-5,6-dihydrouracils (Ia, b) were obtained by various routes: from N-aryl-β-aminopropionic acids and their methyl esters with potassium cyanate; by heating N-aryl-β-ureidopropionic acids (IV) with mineral acids; from N-aryl-N-ethoxycarbonyl-β-aminopropionamide (VII); and by the desulfurization of 1-p-tolyl-2-thio-5,6-dihydrouracil (IIb).

Reaction of the acids IIIa and b with potassium cyanate in presence of dilute sulfuric acid led to the isolation of pure N-phenyl-β-ureidopropionic acid only in the case of acid IIIa. In the case of N-p-tolyl-β-alanine it was not possible to isolate the ureido acid. The dihydrouracils were formed in this case if, instead of the amino acid, the methyl ester was used. The methyl esters of the N-aryl-β-ureidopropionic acids were not isolated.

On heating IVa with hydrochloric acid, Ia is formed in good yield, identical with the material obtained from the acid and ester IIIa and potassium cyanate. Ia was also obtained from N-ethoxycarbonyl-N-phenyl-β-aminopropionamide (VIIa) by heating with sodium ethoxide according to [5, 6]. Treatment with 10% alkali hydrolyzes I completely to the ureido acids. N-p-Tolyl-β-ureidopropionic acid IVb was obtained for the first time by this method, and this on heating was converted quantitatively into Ib.

1-Aryl-2-thio-5,6-dihydrouracils (II) were prepared from III and potassium thiocyanate, and also by the reaction of N-aryl-β-thioureidopropionic acids (V) with inorganic acids. In alkaline solution, II is cleaved to the N-aryl-β-thioureidopropionic acids V, which have not previously been described. On heating in aqueous solution with chloroacetic acid, IIb undergoes the desulfurization reaction with the formation of Ib, which also confirms the structures I and II.

EXPERIMENTAL

N-Aryl-β-aminopropionic acids and N-phenyl-β-aminopropionamide were obtained by slightly modified methods, and their methyl esters by the literature methods [7, 8].

N-Phenyl-β-aminopropionic acid (IIIa). A mixture of 4.4 g (0.03 mole) of N-phenyl-β-aminopropionitrile and 25 ml of 10% NaOH was boiled for 3 hr, cooled, neutralized with dil HCl, the oil which separated was isolated and kept in a vacuum desiccator for several days until it crystallized. There was obtained 4.25 g (86%) of IIIa, mp 58–59° C (from ethanol) [9].

N-p-Toly-β-aminopropionic acid (IIIb). A mixture of 16 g (0.1 mole) of N-p-tolyl-β-aminopropionitrile and 150 ml of conc. HCl was boiled for 4–5 hr, the hydrochloric acid removed in vacuo, the residue dissolved in a small amount of water and neutralized with aqueous ammonia. The oil which separated was extracted with ether, dried over sodium carbonate, and the ether removed to give an oil which crystallized after a few days in a vacuum desiccator. Yield 12 g (67%), mp 85° C (from a mixture of chloroform and light petroleum) [9].

N-Phenyl-β-aminopropionamide (VI) [10]. N-Phenyl-β-aminopropionitrile (7.6 g., 0.052 mole) was added in small portions with ice cooling to 35 ml of sulfuric acid. The yellowish-green solution was kept at room temperature for 40 hr, diluted with 100 ml of water, and neutralized with 25% ammonia. The reaction mixture was kept overnight, and the amide which separated was filtered off, washed several times with water and crystallized from methanol to give 6.25 g (72%) of product, mp 55–56° C [11, 12].

N-Ethoxycarbonyl-N-phenyl-β-aminopropionamide (VII). To 7.2 g (0.045 mole) of VI and 4 g (0.07 mole) of KOH, dissolved in 40 ml of ethanol, was added dropwise with stirring and cooling 7.0 g (0.065 mole) of ethyl chloroformate, and the mixture stirred for a further 2 hr at room temperature. Concentration in vacuo left 5.5 g (52%) of VII as an undistillable oil.

N-Phenyl-β-ureidopropionic acid (IVa). a) A mixture of 8.3 g (0.05 mole) of the acid IIIa, 4.45 g (0.055 mole) of potassium cyanate, 3 ml of conc H_2SO_4 and 50 ml of water was heated on a boiling water bath for 1 hr. After a few hours, a precipitate of IVa separated (5 g, 48%), mp 162–162.5° (from ethanol). Found, % C 57.87; H 5.73; N 13.8. Calculated for $C_{10}H_{12}N_2O_3$, %: C 57.69; H 5.77; N 13.46.

b) A solution of 2 g (0.01 mole) of Ia in 20 ml of 10% NaOH was kept for 24 hr, neutralized with dil HCl, the precipitate filtered off, washed a few times with water, and crystallized from ethanol to yield 1.65 g (79%) of product, mp 162–162.5° C (decomp). A mixed melting point with the ureido-acid prepared as in a) gave no depression.

N-p-Tolyl-β-ureidopropionic acid (IVb). Obtained by the alkaline hydrolysis of Ib in 85% yield, mp 147.5–148° C (from water). Found, %: C 60.14; H 6.48; N 13.0. Calculated for $C_{11}H_{14}N_2O_3$, %: C 59.46; H 6.31; N 12.61.

IVa and IVb are white crystalline substances, readily soluble in acids and alkalies and in hot water, ethanol and acetone, but insoluble in ether, benzene and carbon tetrachloride.

1-Phenyl-5,6-dihydrouracil (Ia). a) A mixture of 8.3 g (0.05 mole) of acid IIIa, 6 g (0.075 mole) of potassium cyanate and 7 ml of sulfuric acid in 90 ml of water was boiled for 4–5 hr. The resulting precipitate was filtered off, washed with water and crystallized from ethanol. Yield 5.2 g (55%), mp 192–193° C (from ethanol) (mp 182–184° C [13], 185–187° C [14]). Found, %: C 63.23; H 5.50; N 14.96. Calculated for $C_{10}H_{10}N_2O_2$, %: C 63.16; H 5.26; N 14.74.

b) One gram (0.005 mole) of IVa in 20 ml of 10% HCl was boiled for 1 hr, and the precipitate isolated and recrystallized from ethanol to give 0.9 g (86%), mp 191–192° C.

c) A mixture of 10.74 g (0.06 mole) of the ester IIIa, 8.1 g (0.1 mole) of potassium cyanate, and 6 ml of H_2SO_4 in 80 ml of water were heated at 100–110° C for 5–6 hr to give 6 g (68%) of Ia, mp 191–192° C.

d) 4.28 g (0.018 mole) of VII was dissolved in 30 ml of anhydrous ethanol containing 0.14 g (0.002 mole) of sodium ethoxide, and the mixture boiled for 2 hr. The alcohol was removed, and the residue treated with 20 ml of water and acidified with HCl (1 : 1) until neutral to litmus. After a few hours there separated from the solution Ia (0.75 g; 22%), mp 191.5–192° C.

Samples of Ia obtained by the methods a), b), c), and d), were identical by mixed melting points.

1-p-Tolyl-5,6-dihydrouracil (Ib). This was prepared by the methods a), b), and c) described for compound Ia, in yields of 46, 86 and 40% respectively, mp 189–189.5° C (from ethanol). Found, %: C 64.49; H 6.01; N 14.0. Calculated for $C_{11}H_{12}N_2O_2$, %: C 64.71; H 5.88; N 13.72.

d) 1 g (0.0045 mole) of IIb was heated at 100° with a solution of 1.89 g (0.02 mole) of chloroacetic acid in 4 ml of water for 3 hr, neutralized with ammonia, and concentrated in vacuo. The residue was recrystallized from ethanol to give 0.17 g (18%), mp 189–189.5° C, identical with the samples of material obtained by methods a), b), and c) above.

1-Phenyl-2-thio-5,6-dihydrouracil (IIa). a) 8.3 g (0.05 mole) of the acid IIIa, 7.3 g (0.075 mole) of potassium thiocyanate, 7 ml of H_2SO_4 and 90 ml of water were boiled for 4–5 hr. After a few hours, a white crystalline solid separated from the cooled solution. This was IIa, 5.8 g (56%), mp 186.5–187° C (from ethanol or dioxane). Found, %: N 13.62; S 15.35. Calculated for $C_{10}H_{10}N_2OS$, %: N 13.59; S 15.53.

b) A mixture of 10.74 g (0.06 mole) of the ester IIIa, 9.7 g (0.1 mole) of potassium thiocyanate, 6 ml of H_2SO_4, and 80 ml of water was heated for 4 hr to give 8 g (65%), mp 186–187° C.

c) A mixture of 0.2 g (0.001 mole) of Va and 5 ml of 10% HCl was boiled for 1 hr. The precipitate of IIa which separated from the boiling solution was filtered off and crystallized from ethanol, to yield 0.19 g (92%), mp 186–187° C, identical with samples prepared by methods a) and b).

1-p-Tolyl-2-thio-5,6-dihydrouracil (IIb). Using the methods b) and c) given above for IIa and IIb, yields of 65 and 74% respectively, mp 254° C (from dioxane) were obtained. Found, %: N 12.63. Calculated for $C_{11}H_{12}N_2OS$, %: N 12.73.

IIa and IIb are white crystalline compounds, readily soluble in strongly acid solutions and in pyridine, and also in hot ethanol and dioxane, but insoluble in water, acetone, ether, benzene, hexane and other organic solvents.

N-Phenyl-β-thioureidopropionic acid (Va). Two grams (0.01 mole) of IIa was dissolved in 20 ml of 10% NaOH. After 6 hr, the solution was neutralized with dil HCl, the resulting precipitate filtered off, washed with water and recrystallized from ethanol. There was obtained 1.95 g (87%), mp 147–147.5° C (with decomp.). Found, %: N 12.57, 12.44. Calculated for $C_{10}H_{12}N_2O_2S$, %: N 12.50.

N-p-Tolyl-β-thioureidopropionic acid (Vb). This was prepared similarly in 88% yield, mp 149–150° C (with decomp.). Found, %: N 12.12, 12.20. Calculated for $C_{11}H_{14}N_2O_2S$, %: N 11.77.

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