SYNTHESIS OF DERIVATIVES OF 1-PHENYLHYDROPYRIMIDINES

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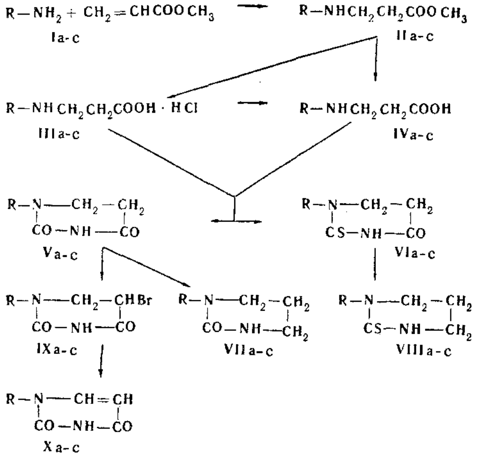
The synthesis has been effected, via the corresponding N-phenyl-β-aminopropionic acids, of 1-(o-methoxyphenyl)-, 1-(o-ethoxyphenyl)-, and 1-(o-tolyl)dihydrouracils and also of 1-(o-methoxyphenyl)-, 1-(o-ethoxyphenyl)-, and 1-(o-tolyl)-2-thiodihydrouracils. The dihydrouracils and thiodihydrouracils obtained have been reduced with $LiAlH_4$ to the corresponding 2-oxohexahydro-, and 2-thioxohexahydropyrimidines. By the action of bromine and the subsequent splitting out of HBr, the dihydrouracils have been converted into 1-(o-methoxyphenyl)-, 1-(o-ethoxyphenyl)-, and 1-(o-tolyl)uracils.

In the study of N-aryl-β-amino acids, their conversion into quinoline compounds [1–4] and particularly into pyrimidine derivatives [4–6], which are biologically important compounds, is of great importance; some compounds of this class have proved to be good heat stabilizers for polycaprolactam [7, 8]. The object of the present work was the preparation of new 1-phenylhexahydropyrimidine derivatives and their further conversion. The syntheses were carried out by the following scheme:



a $R = o\text{-}H_3COC_6H_4$; b $R = o\text{-}H_5C_2OC_6H_4$; c $R = o\text{-}H_3CC_6H_4$.

The 1-phenylhexahydropyrimidines were obtained from the corresponding N-phenyl-β-aminopropionic acids. The methyl ester of N-(o-methoxyphenyl)-β-alanine [9] (**IIa**) was obtained by the action on o-anisidine of methyl acrylate with acetic anhydride or glacial acetic acid as catalyst. When the ester **IIa** was saponified in hydrochloric acid solution, the hydrochloride of N-(o-methoxyphenyl)-β-alanine (**IIIa**) was isolated, and the action on the hydrochloride **IIIa** of a solution of sodium acetate liberated the N-(o-methoxyphenyl)-β-alanine (**IVa**). The same alanine **IVa** was obtained by the alkaline saponification of the methyl ester **IIa** with subsequent acidification of the reaction mixture with acetic acid. From the methyl esters **IIb, c**, we obtained similarly N-(o-ethoxyphenyl)-β-alanine (**IVb**) [10] and N-(o-tolyl)-β-alanine (**IVc**) [9, 11], and also their hydrochlorides **IIIb, c**.

When the alanines **IVa–c** or their hydrochlorides **IIIa–c** were heated in aqueous solution with a three- or fourfold excess of urea for 40–60 hr, the corresponding dihydrouracils **Va–c** were isolated only in negligibly small yields. The yields of the dihydrouracils **Va–c** were increased to 20–30% by the prolonged heating of a melt of the alanines **IVa–c** or their hydrochlorides **IIIa–c** with an excess of urea. The action of KNCS or NH_4NCS on the alanine hydrochlorides **IIIa–c** gave the corresponding thiodihydrouracils **VIa–c** with yields of 25–60%.

The dihydrouracils **Va–c** and thiodihydrouracils **VIa–c** obtained were reduced with lithium aluminum hydride. Reduction took place in position 4 of the pyrimidine ring, the $>CO$ group being reduced to the $>CH_2$ group [12]. The action of bromine in glacial acetic acid solution on the dihydrouracils **Va–c** [13] gave the corresponding 5-bromodihydrouracils **IXa–c**, which split out HBr on being heated with LiCl in dimethylformamide [13, 14], forming the 1-phenyluracils **Xa–c**.

EXPERIMENTAL

Methyl ester of N-(o-methoxyphenyl)-β-alanine (IIa). A mixture of 45 ml (0.40 mole) of o-anisidine, 38 ml (0.43 mole) of methyl acrylate, and 1 ml of acetic anhydride was heated under reflux at 125–130° C for 44 hr. The excess of methyl acrylate was distilled off and the reaction mixture was fractionated in vacuum at 148–150° C (5–6 mm). Yield 45 g (59.0%).

N-(o-Methoxyphenyl)-β-alanine hydrochloride (IIIa). A mixture of 45 g (0.40 mole) of IIa, 45 ml of concentrated HCl, and 45 ml of water was heated in the water bath for 2 hr 30 min and was then evaporated. The resulting viscous mass was crystallized from ethanol. The colorless crystals of IIIa with mp 172–173° C (in a sealed capillary) dissolve in methanol, ethanol, and water. Yield 40 g (80.0%). Found, %: N 6.21, 6.22; Cl 15.20, 15.30. Calculated for $C_{10}H_{13}NO_3 \cdot HCl$, %: N 6.08; Cl 15.40.

N-(o-Methoxyphenyl)-β-alanine (IVa). a) A mixture of 30 g (0.145 mole) of IIa, 12 g of KOH, and 50 ml of water was heated in the water bath for 4 hr and was then acidified with 130 ml of 10% acetic acid. After 12 hr, the solution deposited crystals, mp 93–94° C (from benzene). Yield 20.5 g (72.0%).

b) A solution of 0.5 g (0.025 mole) of IIIa in 10 ml of water was neutralized with an equivalent amount of sodium carbonate. The alanine IVa was extracted with ether. The ether was distilled off, and the product was crystallized from benzene (mp 93–94° C). Yield 0.3 g (71.5%). A mixture of the alanines obtained by methods (a) and (b) gave no depression of the melting point. The alanine IVa is soluble in ether, methanol, acetone, chloroform, and benzene, and sparingly soluble in water. Found, %: C 61.47, 61.41; H 6.70, 6.81; N 7.24, 7.29. Calculated for $C_{10}H_{13}NO_3$, %: C 61.50; H 6.70; N 7.12.

N-(o-Tolyl)-β-alanine (IVc). A mixture of 107 g (1.0 mole) of o-toluidine, 95 ml (1.07 mole) of methyl acrylate, and 5 ml of acetic acid was heated under reflux at 105–110° C for 44 hr, and the excess of methyl acrylate was distilled off; the residue (185 g) was heated at 85–90° C with 60 g of KOH in 200 ml of water for 3 hr, and then the mixture was acidified with 60 ml of acetic acid. The precipitate of N-(o-tolyl)-β-alanine o-toluidide that deposited was filtered off, and the filtrate was extracted four times with ether. The ether was distilled off, and the residue of IVc was crystallized three times from chloroform, mp 87.5–88° C. Compound IVc is readily soluble in methanol, ethanol, acetone, and carbon tetrachloride, and sparingly soluble in water. Yield 50 g (33.0% on the initial amine). Found, %: C 67.09, 67.15; H 6.95, 6.99; N 8.00, 8.03. Calculated for $C_{10}H_{13}NO_3$, %: C 67.00; H 7.30; N 7.80. **N-o-tolyl-β-alanine o-toluidide** [15] was obtained with a yield of 3.5 g, mp 127–127.5° C. Found, %: N 10.62. Calculated for $C_{17}H_{20}N_2O$, %: N 10.40.

1-(o-Methoxyphenyl)dihydrouracil (Va). A mixture of 40 g (0.2 mole) of IVa and 40 g (0.67 mole) of urea was ground in a mortar and heated at 135–140° C for 14 hr. After cooling, the melt was treated with water and the solid matter was filtered off and crystallized from ethanol, mp 197–198° C. Compound Va is sparingly soluble in ethanol and acetic acid. Yield 12.8 g (28.5%). Found, %: C 59.90, 60.15; H 5.58, 5.60; N 12.90. Calculated for $C_{11}H_{12}N_2O_3$, %: C 60.00; H 5.50; N 12.70.

1-(o-Ethoxyphenyl)dihydrouracil (Vb) [16]. A mixture of 20 g (0.08 mole) of IIIb and 20 g (0.33 mole) of urea was heated at 145–150° C for 13 hr and was then treated with water and acidified with conc. HCl (to Congo Red). The precipitate was filtered off and crystallized from ethanol, mp 200.5–201.5° C. Yield 2.9 g (15.3%). Found, %: C 61.80, 61.92; H 6.25, 6.36; N 12.04, 12.13. Calculated for $C_{12}H_{14}N_2O_3$, %: C 61.50; H 6.00; N 12.00.

1-(o-Tolyl)dihydrouracil (Vc). A mixture of 5 g (0.028 mole) of IVc and 5 g (0.08 mole) of urea was heated at 135–140° C for 5 hr 30 min and dissolved in a small amount of water; the solution was acidified with conc. HCl (to Congo Red) and heated for 1 hr 30 min. After cooling, the precipitate was filtered off and crystallized from a mixture of chloroform and carbon tetrachloride (1 : 1), mp 170.5–171° C. Yield 1.4 g (24.6%). Found, %: C 65.00, 65.30; H 5.67, 5.88; N 13.86, 13.89. Calculated for $C_{11}H_{12}N_2O_2$, %: C 65.00; H 5.95; N 13.80.

1-(o-Methoxyphenyl)-2-thiodihydrouracil (VIa). A mixture of 14 g (0.072 mole) of IVa, 5.8 ml of conc. HCl, 28 g (0.37 mole) of NH_4NCS, and 20 ml of water was heated at 60–80° C for 4 hr and then at 110–120° C for 8 hr and cooled. The crystals that deposited were filtered off and recrystallized from ethanol, mp 215–216° C. Compound VIa is soluble in benzene, acetone, and ethanol. Yield 10.4 g (60.4%). Found, %: C 56.05, 56.28; H 4.95, 5.15; N 12.03, 12.08. Calculated for $C_{11}H_{12}N_2O_2S$, %: C 56.00; H 5.10; N 11.80.

1-(o-Ethoxyphenyl)-2-thiodihydrouracil (VIb) [16]. A mixture of 20 g (0.08 mole) of IIIb and 50 g (0.66 mole) of NH_4NCS in 100 ml of water was heated at 115–120° C for 9 hr, and after 18 hr the solution deposited lamellar crystals of VIb, which were recrystallized from a mixture of acetic acid and ethanol (1 : 1), mp 213–214° C. Yield 5.7 g (22.4%). Found, %: N 11.15, 11.18. Calculated for $C_{12}H_{14}N_2OS$, %: N 11.20.

1-(o-Tolyl)-2-thiodihydrouracil (VIc). A mixture of 14 g (0.08 mole) of IVc, 28 g (0.37 mole) of NH_4NCS, 5.8 ml of conc. HCl, and 15 ml of water was heated at 110–120° C for 8 hr. Compound VIc was isolated in a similar manner to VIa; mp 219.0–219.5° C (from acetic acid). Yield 10.4 g (59.3%). Found, %: C 60.08, 60.40; H 5.40, 5.70; N 12.66, 12.77. Calculated for $C_{11}H_{12}N_2OS$, %: C 60.00; H 5.50; N 12.75.

1-(o-Methoxyphenyl)-2-oxohexahydropyrimidine (VIIa). Over 2 hr, 10 g (0.045 mole) of Va was added to an ethereal solution of $LiAlH_4$ prepared from 3.5 g (0.44 mole) of LiH, 32 g (0.12 mole) of $AlBr_3$, and 150 ml of absolute ether; the mixture was boiled for 27 hr, left at room temperature for 48 hr, and decomposed with a mixture of 15 ml of moist ether and 45 ml of methanol. After 24 hr, the black precipitate that had formed was dissolved in dilute acetic acid (1 : 2), and the solution was filtered and extracted with benzene. The residue after the distillation of the solvent was dissolved in ethanol, and the solution was passed through a column of Al_2O_3. The VIIa was crystallized from the benzene, mp 178–179° C. Yield 0.9 g (9.6%). Found, %: C 64.06, 64.25; H 6.92, 7.07; N 13.56, 13.70. Calculated for $C_{11}H_{14}N_2O_2$, %: C 64.00; H 6.85; N 13.58.

1-(o-Tolyl)-2-oxohexahydropyrimidine (VIIc). Six grams (0.03 mole) of Vc was gradually added to an ethereal solution of $LiAlH_4$, prepared from 1.5 g (0.19 mole) of LiH, 15 g (0.056 mole) of $AlBr_3$, and 150 ml of absolute ether, and the mixture was boiled and left at room temperature for 60 hr, after which the $LiAlH_4$ was decomposed with a mixture of ethanol and ether (1 : 1). The solid matter was extracted with acetone (Soxhlet apparatus). The acetone was evaporated off and the VIIc was crystallized from benzene, mp 195.5–196.5° C. Yield 0.52 g (9.0%). Found, %: C 69.50, 69.75; H 7.61, 7.66; N 14.87, 14.94. Calculated for $C_{11}H_{14}N_2O$, %: C 69.50; H 7.42; N 14.72.

1-(o-Methoxyphenyl)-2-thioxohexahydropyrimidine (VIIIa). Twelve grams (0.05 mole) of VIa was added to an ethereal solution of $LiAlH_4$ (cf. VIIa) and the mixture was boiled for 16 hr and left at room temperature for 14 hr. the $LiAlH_4$ was decomposed with water and the mixture, after acidification with concentrated HCl, was extracted with chloroform. The extracts were evaporated and the residue was crystallized from acetone, mp 214–215° C. Yield 3.0 g (26.5%). Found, %: C 59.49, 59.60; H 6.04, 6.08; N 12.55, 12.71. Calculated for $C_{11}H_{14}N_2OS$, %: C 50.50; H 6.35; N 12.60.

1-(o-Ethoxyphenyl)-2-thioxohexahydropyrimidine (VIIIb). Eight grams (0.032 mole) of VIb was added to a solution of 4.8 g (0.125 mole) of $LiAlH_4$ in 130 ml of absolute ether, the mixture was boiled for 53 hr, the $LiAlH_4$ was decomposed with ethanol and moist ether, and the mixture was acidified with 50 ml of acetic acid and extracted with benzene. The extract was evaporated and the residue was crystallized from benzene, mp 133–134° C. Yield 1.8 g (23.8%). Found, %: C 61.30, 61.20; H 6.71, 6.72; N 12.08, 12.11. Calculated for $C_{12}H_{16}N_2OS$, %: C 61.00; H 6.80; N 11.85.

1-(o-Tolyl)-2-thioxohexahydropyrimidine (VIIIc). The reduction was carried out in a similar manner to the preceding experiment. From 5 g (0.023 mole) of VIIc was obtained 2.9 g (62.0%) of VIIIc, mp 195–196° C (from benzene). Found, %: C 64.24, 64.35; H 6.78, 6.80; N 13.52, 13.61. Calculated for $C_{11}H_{14}N_2S$, %: C 64.00; H 6.85; N 13.58.

1-(o-Methoxyphenyl)-5-bromodihydrouracil (IXa). A solution of 1.25 g (0.016 mole) of bromine in 3 ml of acetic acid was added to 1.5 g (0.007 mole) of Va in 10 ml of acetic acid. Then 0.5 ml of a 10% solution of NaOH was added, and the mixture was heated in the water bath for 8 hr and left at room temperature for 48 hr. A small amount of water was added, and the crystals that deposited were recrystallized from ethanol, mp 208–209° C. Yield 0.6 g (29.4%). Found, %: N 9.32, 9.40; Br 26.90, 27.20. Calculated for $C_{11}H_{11}BrN_2O_3$, %: N 9.36; Br 27.0.

1-(o-Ethoxyphenyl)-5-bromodihydrouracil (IXb) was obtained in a similar manner to IXa. From 1.5 g (0.006 mole) of Vb was obtained 0.5 g (25.0%) of IXb with mp 196–197° C (from acetone). Found, %: N 8.89, 8.74; Br 25.71, 26.10. Calculated for $C_{12}H_{13}BrN_2O_3$, %: N 9.94; Br 25.87.

1-(o-Tolyl)-5-bromodihydrouracil (IXc) was obtained in a similar manner to IXa. From 1.5 g (0.007 mole) of Vc was obtained 0.5 g (25.0%) of IXc, mp 193.5–194.5° C (from acetone). Found, %: N 9.82, 9.91; Br. 27.98, 28.30. Calculated for $C_{11}H_{11}BrN_2O_2$, %: N 9.88; Br 28.20.

1-(o-Methoxyphenyl)uracil (Xa). A mixture of 0.5 g (0.0017 mole) of IXa, 5 ml of dimethylformamide, and 0.2 g (0.005 mole) of LiCl was boiled for 5 hr, and then 2 ml of water was added to the darkening solution; the precipitate was filtered off, washed with ether, and crystallized from dioxane, mp 223–224° C. Yield 0.33 g (90.5%). Found, %: N 13.24, 13.40. Calculated for $C_{11}H_{10}N_2O_3$, %: N 13.33.

1-(o-Ethoxyphenyl)uracil (Xb) was obtained in a similar manner to Xa. Yield 75.5%, mp 219–220° C (from dioxane). Found, %: N 12.11, 12.21. Calculated for $C_{12}H_{12}N_2O_3$, %: N 12.06.

1-(o-Tolyl)uracil (Xc) was obtained in a similar manner to Xa. Yield 98%, mp 197.5–198.5° C (from ethanol). Found, %: N 13.71, 13.76. Calculated for $C_{11}H_{10}N_2O_2$, %: N 13.85.

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