INDOLE DERIVATIVES

CIX.* 5-(3-INDOLYL)-4-AMINO-6-HYDROXYPYRIMIDINES

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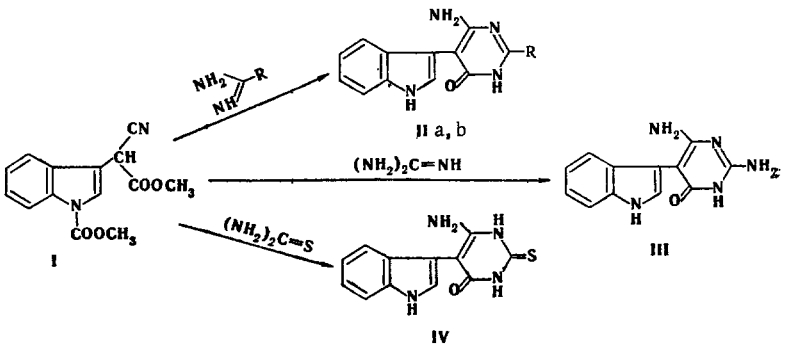
1-Carbomethoxy-3-indolylcyanoacetic ester reacts with amidines, guanidine, and thiourea to give, respectively, 2-alkyl- and 2-aryl-5-(3-indolyl)-4-amino-6-hydroxypyrimidines and 2-amino- and 2-thio-5-(3-indolyl)-4-amino-6-hydroxypyrimidines.

The high biological activity of some indole-containing heterocyclic compounds, both natural and synthetic compounds, is well known [2].

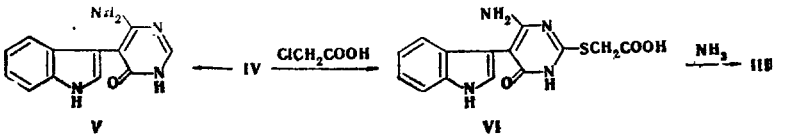
5-(3-Indolyl)pyrimidine derivatives are of definite interest as analogs of 5-arylpyrimidines, which have, for example, the properties of antimetabolites of folic acid and related compounds and are also inhibitors of dihydrofolatereductase. 5-(3-Indolyl)pyrimidines have not been studied, and a simple method for their preparation has not as yet been realized.

We have extended the classical Traube method [3, 4] for the synthesis of pyrimidines to 1-carbomethoxy-3-indolylcyanoacetic ester (I) [5], which undergoes smooth condensation with various amidine components to give 5-(3-indolyl)-4-amino-6-hydroxypyrimidines having various substituents in the 2 position of the pyrimidine ring (IIa,b, III, and IV).



II a R=CH_3; b R=C_6H_5

The structure of III was confirmed by alternative synthesis from IV through the corresponding carboxymethylthio derivative (VI). In this connection, there is no doubt regarding the structures of IV and VI.



The signal of the proton in the 2 position of the pyrimidine ring in the PMR spectrum of V (in CF_3COOH), obtained by desulfuration over Raney nickel, is found at δ 8.68 ppm (δ 8.7 ppm for the proton in the 2 position of hypoxanthine [6]). The UV spectrum of VI differs from the spectrum of starting IV and is similar to the spectra

*See [1] for communication CVIII.

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of II and V; this constitutes evidence for the identical character of the conjugated systems of VI, II, and V. The IR spectra of I-VI contain absorption bands of C=O and NH_2 groups in the region characteristic for 4-amino-6-hydroxypyrimidine derivatives. The absorption bands of C=O and NH_2 groups for IIa, V, and III were identified on the basis of the IR spectra of the corresponding products of their N-deuteration.

The PMR spectra of IIa,b and IV-VI in CF_3COOH do not contain characteristic broad signals corresponding to NH_3^+ groups, in contrast to the spectrum of diamino derivative III, in which there is a broad singlet of an NH_3^+ group at δ 7.94 ppm. A similar peculiarity has been noted for guanine and cytosine [6].

EXPERIMENTAL

The IR spectra of mineral-oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of ethanol solutions were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer on the δ scale with tetramethylsilane as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source.

2-Methyl-5-(3-indolyl)-4-amino-6-hydroxypyrimidine (IIa). A 1.45-g (0.015 mole) sample of acetamidine hydrochloride was added to a solution of sodium methoxide, obtained from 0.8 g (0.035 g-atom) of sodium in 50 ml of methanol, and the mixture was stirred at 50° for 15 min. A 2.7-g (0.01 mole) sample of I was then added, and the mixture was stirred and refluxed for 2 h. Two-thirds of the methanol was removed by distillation, and the residual mixture was heated at 85-90° for another 2 h, after which it was cooled, and 40 ml of water and 20 ml of acetic acid were added successively with stirring. The mixture was stirred for 30 min, after which it was poured into a conical flask, and 100-150 ml of water was added in portions with shaking, and the mixture was allowed to stand overnight. The precipitated reaction product was removed by filtration, washed with water, and dried. It was recrystallized from alcohol–acetic acid (2 : 1) with decolorization by charcoal to give 1 g (42%) of a product that decomposed above 315°. IR spectrum: 1610 (C=O), 1620 (NH_2), 3170, 3340, 3460 cm^{-1} (NH_2, NH). UV spectrum, λ_{max} (log ε): 203 (shoulder (4.58), 216 (4.64), 278 (4.04), and 288 nm (4.03). PMR spectrum (in CF_3COOH): s 2.82 (CH_3) and m 7.0-7.4 (aromatic protons). Found: C 65.2; H 5.2; N 23.6%. $C_{13}H_{12}N_4O$. Calculated: C 65.0; H 5.0; N 23.3%.

2-Phenyl-5-(3-indolyl)-4-amino-6-hydroxypyrimidine (IIb). This compound was similarly obtained from 4.2 g (0.015 mole) of I, 3.13 g of benzamidine hydrochloride in a solution of sodium methoxide, obtained from 1.15 g (0.05 g-atom) of sodium in 60 ml of methanol. The precipitate that formed after the successive addition of 60 ml of water and 30 ml of acetic acid was removed by filtration without cooling, washed with water, acetic acid, and ether, and dried to give 2.26 g (50%) of a compound that decomposed above 310° [from DMF–ethanol (1 : 1)]. UV spectrum, λ_{max} (log ε): 205 (4.66), 222 (4.60), 278 (3.93), 288 nm (3.89). IR spectrum: 1620 (NH_2, C=O), 3200, 3320, 3390, 3480 cm^{-1} (NH_2, NH). Found: C 71.9; H 4.5; N 18.7%. $C_{18}H_{14}N_4O$. Calculated: C 71.5; H 4.6; N 18.5%.

2,4-Diamino-5-(3-indolyl)-6-hydroxypyrimidine (III). A) A 1.8-g (0.02 mole) sample of guanidine carbonate and 2.72 g (0.01 mole) of I were added successively to a solution of sodium methoxide, obtained from 1.2 g (0.05 g-atom) of sodium in 20 ml of methanol, and the mixture was stirred and refluxed for 2 h. Two-thirds of the methanol was removed by distillation, and the residual mixture was heated at 85-90° for another hour. A 10-ml sample of water and (dropwise) 10 ml of acetic acid were added successively to the hot solution, and the mixture was allowed to cool slowly with stirring. The resulting precipitate was removed by filtration and washed with a small amount of acetic acid and ether to give 2.1 g (71%) of III. Recrystallization from water with decolorization by charcoal gave a product with mp 210-230° (loss of water) that decomposed above 270°. IR spectrum: 1620 (C=O), 1660 (NH_2), 3200, 3500 br, 3570 cm^{-1} (NH_2, NH). UV spectrum, λ_{max} (log ε): 210 (4.82), 282 nm (4.37). PMR spectrum (in CF_3COOH): m 7.0-7.4 (aromatic protons), s 7.94 broad (NH_3^+). Found: C 48.8; H 6.0; N 23.8; H_2O 18.6%; M (mass spectrally) 241. $C_{12}H_{11}N_5O$. Calculated: C 48.8; H 5.8; N 23.7; H_2O 18.3%; M 241.

B) A 1-g (0.003 mole) sample of VI was dissolved in 25 ml of 25% ammonium hydroxide, and the solution was heated in an autoclave at 160° on an oil bath for 24 h. It was then cooled, and the resulting precipitate was removed by filtration and dissolved by refluxing in aqueous K_2CO_3 solution. The solution was treated with charcoal, filtered, and allowed to stand for crystallization. The precipitate was recrystallized from water with decolorization by charcoal and the addition of four drops of acetic acid to give 0.4 g (37%) of a product with mp 210-230° (loss of water) that decomposed above 270°. The IR spectrum at 700-4000 cm^{-1} was completely identical to the IR spectrum of III obtained by method A.

2-Thio-5-(3-indolyl)-4-amino-6-hydroxypyrimidine (IV). A 2.72-g (0.01 mole) sample of I and 1 g (0.013 mole) of thiourea were added to a solution of sodium methoxide, obtained from 0.46 g (0.02 g-atom) of sodium in 15 ml of methanol, and the mixture was heated at 85-90° for 2 h. Two-thirds of the methanol was removed by distillation, and the residual mixture was heated for another hour. It was then cooled, and activated charcoal and 15 ml of water were added. The mixture was then heated for 15 min, after which it was filtered, and the filtrate was treated with 20 ml of acetic acid. The precipitate was removed by filtration and washed with acetic acid, methanol, and ether to give 1.8 g (70%) of product. In the case of crystallization from ethanol-DMF (2 : 1), IV contained 1 mole of DMF per mole of IV (according to the PMR spectrum). The product decomposed above 310°. Found: C 54.3; H 5.2; N 21.3%. $C_{12}H_{10}N_4O \cdot (CH_3)_2NCHO$. Calculated: C 54.4; H 5.1; N 21.1%. A sample free of DMF was obtained by recrystallization from ethanol. IR spectrum: 1630 broad (NH_2, C=O); 3080, 3380, and 3440 cm^{-1} (NH_2, NH). UV spectrum, λ_{max} (log ε): 205 (4.64), 218 (shoulder) (4.55), 290 nm (3.98). Found: C 55.6; H 4.1; N 21.8%; M (mass spectrally) 258. $C_{12}H_{10}N_4OS$. Calculated: C 55.8; H 3.9; N 21.7%; M 258.

5-(3-Indolyl)-4-amino-6-hydroxypyrimidine (V). A 3-ml sample of 25% ammonium hydroxide, 4.5 g of Raney nickel, and 20 ml of ethanol were added to a suspension of 1 g (0.0039 mole) of IV in 20 ml of ethanol, and the mixture was stirred and refluxed for 2 h, after which the nickel was removed by filtration, and the filtered solution was allowed to stand for crystallization. Workup gave 0.4 g (46%) of V with mp 310-315° (dec., from ethanol). IR spectrum: 1610 (C=O), 1625 (NH_2), 3400, 3510 cm^{-1} (NH_2, NH). UV spectrum, λ_{max} (log ε): 203 (shoulder) (4.52), 216 (4.64), 278 (4.02), 288 nm (3.94). PMR spectrum (in CF_3COOH): m 7.0-7.6 (aromatic protons), s 8.68 (2-H in the pyrimidine ring). Found: C 63.9; H 4.6; N 24.9%. $C_{12}H_{10}N_4O$. Calculated: C 63.7; H 4.4; N 24.8%.

2-Carboxymethylthio-5-(3-indolyl)-4-amino-6-hydroxypyrimidine (VI). A 5.16-g (0.02 mole) sample of IV was dissolved in 35 ml of 10% NaOH solution, and a solution of 4 g (0.04 mole) of chloroacetic acid and 3.2 g (0.03 mole) of sodium carbonate in 12 ml of water was added. The mixture was allowed to stand for 6 h at room temperature, after which it was acidified with a dilute solution of HCl (~16%). The resulting precipitate was removed by filtration, washed with water, and recrystallized from acetic acid-water (1 : 2) with decolorization by charcoal. Workup gave 3.9 g (58%) of VI with mp 244-246° (dec.). IR spectrum: 1610, 1620 (NH_2, C=O), 1725 (C=O), 2500-2600 (carboxyl group tied up in a hydrogen bond), 3370, 3490, 3515, and 3640 cm^{-1} (NH_2, NH, OH). UV spectrum, λ_{max} (log ε): 203 (shoulder) (4.48), 220 (4.57), 278 (4.08), and 288 nm (4.08). PMR spectrum (in CF_3COOH): s 4.16 ($-S-CH_2-COOH$), m 7.2-7.6 (aromatic protons). Found: C 50.4; H 4.1; N 16.6%. $C_{14}H_{12}N_4O_3S \cdot H_2O$. Calculated: C 50.3; H 4.2; N 16.8%.

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