SYNTHESIS AND SOME PROPERTIES OF 4-OXO-3,4-DIHYDRO- AND 2,4-DIOXO-1,2,3,4-TETRAHYDROPYRIMIDO[5,4-b]INDOLES

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The condensation of N-(2-ethoxycarbonylindol-3-yl)-N',N'-dialkylamidines with ammonia, primary amines, and hydrazines has given a series of 4-oxopyrimido[5,4-b] indoles which have been converted into the 4-chloro and then into the 4-methoxy, 4-dialkylamino, and 4-mercapto derivatives. 2,4-Dioxopyrimido[5,4-b]indoles have been synthesized by the successive action of chloroformic ester and then methylamine, hydrazine, or ethylhydrazine on 3-amino-2-ethoxycarbonylindoles differing by their substituents in position 5.

Individual representatives of the 4-oxopyrimido[5,4-b]indole series have been obtained previously by the cyclocondensation of 3-amino-2-ethoxycarbonylindoles with formamide, hydrazine hydrate, and hydroxylamine [1].

In the present work, to synthesize oxo derivatives of pyrimido[5,4-b]indole we have used the N-(2-ethoxycarbonylindol-3-yl)-N',N'-dialkylamidines (Ia-d) described in [2]. The condensing agents were ammonia, the primary amines (IIa-d), and the hydrazines (IIIa, b). The reaction was performed by the brief heating of compounds (Ia-d) with (IIa-d) and (IIIa,b) in ethanol, and the yields of the pyrimidoindoles (IVa-h) and (Va-c) amounted to 73-87%.

We found that the times of the reaction of the amidine (Ib) with the amines (IIb-d) and the yields of the pyrimidoindoles (IVc-e) are extremely sensitive to the size of the substituent attached to the NH_2 group. Thus, on passing from methylamine (IIb) to ethylamine (IIc) and to benzylamine (IId) the yield of pyrimidoindoles diminished and the time of the reaction increased. When tert-butylamine was used no pyrimidoindole at all was formed.

In contrast to the amidines (Ia-d), the 2-ethoxycarbonyl-3-formylamino-5-methoxyindole and 3-acetylamino-2-methoxycarbonyl-5-methoxyindole described in [2] were not converted into 4-oxopyramidoindoles by the action of ammonia and the amines (IIb-d) under the conditions described above.

Thus, the method that we have developed for synthesizing 4-oxopyrimidoindoles from 3-amino-2-ethoxycarbonylindoles via indolylamidines is distinguished from the known method [1] by simplicity in performance, availability of the starting materials, and broader possibilities of varying the substituents in the pyrimidine fragment.

Under the action of phosphorus oxychloride and equimolar amounts of N,N-diethyl- and -dimethylanilines, the 4-oxopyrimidoindoles (IVa, b, f) were converted into the 4-chloropyrimidoindoles (VIa-c), the yields of which ranged between 53 and 66%.

The replacement of the unreactive amide oxygen in the 4-oxopyrimidoindoles (IVa, b, f) by chlorine opened up broad possibilities for varying the substituents in position 4 of the pyrimidine ring. Thus, when compounds (VIa-c) were boiled in methanolic NaOH solution the 4-methoxypyrimidoindoles (VIIa-c) were obtained. When compounds (VIa, b) were heated with the dialkylamines (VIIIa-c) in isopropanol, the pyrimidoindoles (IXa-c) were formed. Under the action of thiourea, the 4-chloropyrimidoindole (VIb) was converted into 4-mercaptopyrimidine (XI) apparently through the stage of the formation of the readily hydrolyzed isothiouronium derivative (X).

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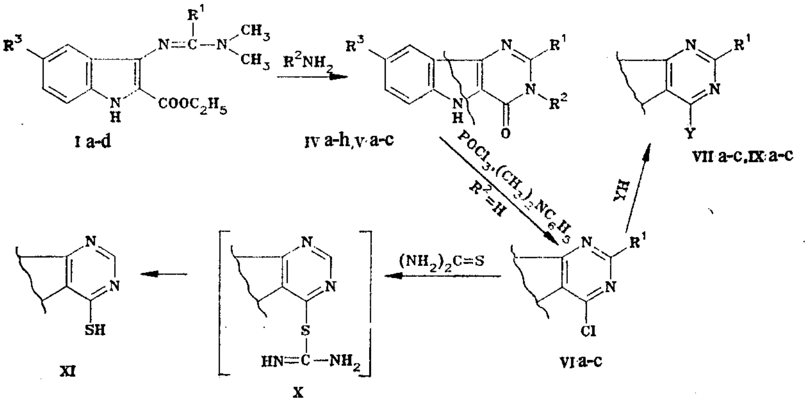
TABLE 1. Characteristics of Compounds (IVa-h), (Va-c)

Compound	R^1	R^2	R^3	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
					C	H	N		C	H	N	
IVa	H	H	H	>350	65,1	4,1	22,6	$C_{10}H_7N_3O$	64,9	3,8	22,7	79
IVb	H	H	CH_3O	>370	61,7	4,6	19,8	$C_{11}H_9N_3O_2$	61,4	4,2	19,5	83
IVc	H	CH_3	CH_3O	>350	62,9	5,1	18,3	$C_{12}H_{11}N_3O_2$	62,9	4,8	18,3	87
IVd	H	C_2H_5	CH_3O	>360	64,2	5,7	17,2	$C_{13}H_{13}N_3O_2$	64,2	5,4	17,3	80
IVe	H	$CH_2C_6H_5$	CH_3O	>370	70,6	4,8	13,7	$C_{18}H_{15}N_3O_2$	70,8	4,9	13,8	74
IVf	CH_3	H	H	>350	66,5	5,0	21,0	$C_{11}H_9N_3O$	66,3	4,5	21,1	76
IVg	CH_3	H	CH_3O	>360	62,5	5,3	18,3	$C_{12}H_{11}N_3O_2$	62,9	4,8	18,3	73
IVh	CH_3	CH_3	H	>350	67,6	5,2	19,4	$C_{12}H_{11}N_3O$	67,6	5,2	19,7	79
Va	CH_3	NH_2	H	>360	61,4	4,9	26,0	$C_{11}H_{10}N_4O$	61,7	4,7	26,2	84
Vb	CH_3	NHC_2H_5	H	>360	64,5	5,7	23,0	$C_{13}H_{14}N_4O$	64,5	5,8	23,1	75
Vc	H	NH_2	CH_3O	>370	57,6	4,5	24,4	$C_{11}H_{10}N_4O_2$	57,4	4,3	24,4	86

TABLE 2. IR and PMR Spectra of Compounds (IVa-h, Va-c)

Compound	IR spectrum, cm^{-1} (paraffin oil)		PMR spectrum, δ, ppm (multiplicity)(J, Hz) in $DMSO-d_6$
	C=O	NH	
IVa	1700	3050—3150	7,87 (s, N=CH); 7,83 (d, 9-H); 7,12—7,36 (6-H—8-H); 11,69 & 11,76 (s, 2NH)
IVb	1695	3050—3200	7,86 (s, N=CH); 3,81 (s, CH_3O); 7,40 (d, 9-H, J_{97}=2,3); 7,00 (d.d, 7-H, J_{79}=2,3, J_{78}=8,3); 7,28 (d, 6-H, J_{67}=8,3); 11,61 & 12,00 (s, 2NH)
IVc	1680	3100—3200	3,31 (s, CH_3); 3,86 (s, CH_3O); 8,21 (s, N=CH); 7,06 (d.d, 7-H, J_{79}=2,1, J_{76}=8,9); 7,39 (d, 6-H, J_{67}=8,9), 7,41 (d, 9-H, J_{97}=2,1); 11,70 (s, NH)
IVd	1680	3100—3200	1,26 & 3,86 (t, q C_2H_5); 3,84 (s, CH_3O); 7,06 (d.d, 7-H, J_{79}=2,3, J_{76}=8,3); 7,36 (d, 9-H, J_{97}=2,3); 7,39 (d, 6-H, J_{67}= =8,3); 8,30 (s, N=CH); 11,87 (s NH)
IVe	1695	3150—3250	3,85 (s, CH_3O); 5,86 (s, CH_3O); 5,86 (s, CH_2); 7,12—7,48 (m 6-H—9-H, C_6H_5); 8,19 (s, N=CH); 11,59 (s, NH)
IVf	1690	3100—3200	2,42 (s, CH_3); 7,00—7,45 (m, 6-H—8-H); 7,92 (d, 9-H); 11,80 & 12,10 (s, 2NH)
IVg	1690	3050—3170	2,37 (s, CH_3); 3,90 (s, CH_3O); 7,04 (d.d, 7-H, J_{79}=2,3, J_{76}=8,3); 7,28 (d, 6-H, J_{67}=8,3); 7,32 (d, 9-H, J_{97}=2,3)
IVh	1685	3100—3300	2,47 (s, CH_3); 3,36 (s, NCH_3); 7,00—7,38 (m, 6-H—8-H); 7,89 (d, 9-H); 11,70 (s, NH)
Va	1680	3200, 3430 (NH, NH_2)	2,62 (s, CH_3); 5,86 (s, NH_2); 7,11—7,45 (m, 6-H—8-H); 7,93 (d, 9-H); 11,80 (s, NH)
Vb	1685	3100—3300	2,49 (s, CH_3); 1,21 & 4,11 (t, q, NC_2H_5); 7,06—7,38 (m, 6-H—8-H); 7,86 (d, 9-H); 11,75 & 12,10 (s, 2NH)
Vc	1700	3130, 3330, 3280 (NH, NH_2)	3,81 (s, CH_3O); 5,86 (s, NH_2), 7,04 (d.d, 7-H, J_{79}=2,1, J_{76}=9,0): 7,37 (d, 6-H, J_{67}=9,0); 7,41 (d, 9-H, J_{97}=2,1)

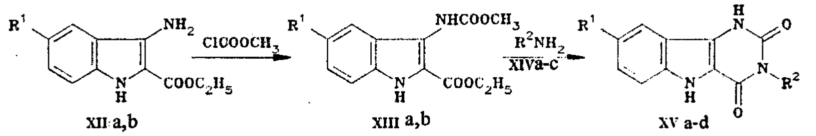


To synthesize the previously unknown 2,4-dioxopyrimido[5,4-b]indoles we selected the 2-ethoxycarbonylindole-3-ylcarbamates (XIIIa, b), which were obtained in high yield from the amines (XIIa, b) and methyl chloroformate.

TABLE 3. Characteristics of Compounds (VIa-c, VIIa-c, XVa-d)

Compound	R¹	Y	R³	mp,* °C	Found, %				Empirical formula	Calculated, %				Yield, %
					C	H	N	Cl		C	H	N	Cl	
VIa	H	—	H	206—208	58,7	2,8	20,7	17,1	$C_{10}H_6N_3Cl$	59,0	3,0	20,6	17,4	66
VIb	H	—	CH_3O	241—243	56,5	3,3	17,8	15,6	$C_{11}H_8N_3ClO$	56,5	3,4	18,0	15,2	59
VIc	CH_3	—	H	216—218	61,0	3,6	19,2	16,7	$C_{11}H_8N_3Cl$	60,7	3,7	19,3	16,3	53
VIIa	H	CH_3O	H	187—188	66,4	4,6	21,0	—	$C_{11}H_9N_3O$	66,3	4,5	21,1	—	79
VIIb	H	CH_3O	CH_3O	196—197	67,6	5,4	19,9	—	$C_{12}H_{11}N_3O$	67,6	5,2	19,7	—	64
VIIc	CH_3	CH_3O	H	242—244	63,0	5,0	18,3	—	$C_{12}H_{11}N_3O_2$	62,9	4,8	18,3	—	76
XVa	—	—	—	>350	55,5	3,9	26,0	—	$C_{10}H_8N_3O_2$	55,6	3,7	25,9	—	81
XVb	—	—	—	>350	61,6	4,2	19,6	—	$C_{11}H_9N_3O_2$	61,3	4,2	19,6	—	76
XVc	—	—	—	>350	58,8	5,0	22,9	—	$C_{12}H_{12}N_4O_2$	59,0	4,9	23,1	—	73
XVd	—	—	—	>350	53,5	4,0	23,0	—	$C_{11}H_{10}N_4O_3$	53,6	4,1	22,8	—	62

*Compounds (VIa-c) melted with decomposition [from benzene—petroleum ether (1:1)].



XII—XVa $R^1=H$, $R^2=CH_3$; XIIa, XIIIa, XIVb, XVb $R^1=H$, $R^2=NH_2$; XIIa, XIIIa, XIVc, XVc $R^1=H$, $R^2=NHC_2H_5$; XII—XIVb, XVr $R^1=CH_3O$, $R^2=NH_2$

The 2,4-dioxopyrimidoindoles (XVa-d) were formed in high yields when the carbamates (XIIIa, b) were heated with methylamine (XIVa) and with the hydrazines (XIVb,c) in isopropanol.

The structures of the compounds obtained were confirmed by the results of elementary analysis and by IR, PMR, and mass spectroscopy.

EXPERIMENTAL

The course of the reactions and the purity of the substances obtained were checked by the TLC method (Silufol UV-254). IR spectra were taken on a UR-10 instrument in paraffin oil, and PMR spectra on a CFT-20 spectrometer (80 MHz) with TMS as internal standard.

The 4-Oxo-3,4-dihydropyrimido[5,4-b]indoles (IVa-h, Va-c). At 60-70°C, 20 mmole of one of the compounds (IIa-d) was added to 10 mmole of one of the indolylamidines (Ia-d) in 50 ml of ethanol, and the mixture was boiled for the following times (h): (IVc), 1; (Vc), 2; (IVa, b, Va), 3; (IVe, h); 4; (Vb), 6; (IVf), 13; and (IVg), 16. The reaction mixture was cooled to 20-25°C, and 200 ml of ice water was added. The precipitate that deposited on standing was filtered off, washed with 200 ml of water, dried, and crystallized from DMFA (Tables 1 and 2).

The 4-Chloropyrimido[5,4-b]indoles (VIa-c). A mixture of 10 mmole of one of the 4-oxo-3,4-dihydropyrimido[5,4-b]indoles (IVa, b, f), 1.2 g (10 mmole) of dimethylaniline, and 15.3 g (100 mmole) of phosphorus oxychloride was boiled for 2 h. The reaction mixture was cooled to 20°C and was poured with stirring into a mixture of 100 g of ice and 200 ml of water, after which the pH of the medium was brought to 7.0-7.5 by the action of a 15% aqueous solution of NaOH, the temperature not being allowed to rise above 15-20°C. The precipitate that deposited on standing was filtered off, washed with water to pH 7, and dried. The dried residue was dissolved with heating in 100 ml of chloroform, the insoluble impurities were filtered off, the chloroform was distilled off, the residue was dissolved in 50 ml of benzene, and the solution was poured into 500 ml of hexane. The precipitate that deposited on standing was filtered off, washed with 100 ml of hexane, and dried (Tables 3 and 4).

The 4-Methoxypyrimido[5,4-b]indoles (VIIa-c). A solution of 10 mmole of one of the 4-chloropyrimido[5,4-b]indoles (VIa-c) in 50 ml of methanol was treated with 1.1 g (28 mmole) of NaOH, and the mixture was boiled for 10 h. Then it was cooled to 20°C and poured into 200 ml of water, and the methanol was evaporated off. The precipitate that deposited on standing was filtered off, washed with water to pH 7, dried, and recrystallized from isopropanol (Tables 3 and 4).

TABLE 4. IR and PMR Spectra of Compounds (VIa-c), (VIIa-c), and (XVa-d)

Compound	IR spectrum, cm^{-1} (paraffin oil)			PMR spectrum, δ, ppm (multiplicity) in $CDCl_3$
	C=C	C=N	NH	
VIa	1610	1640	3150	7,21—7,73 (m, 6-H—9-H); 8,56 (s, NH); 8,79 (s, N=CH)
VIb	1590	1610	3160	3,89 (s, CH_3O); 7,27 (d.d, 7-H, J_{76}=8,6, J_{79}=2,6); 7,34 (d, 6-H, J_{67}=8,6); 7,72 (d, 9-H, J_{97}=2,6); 8,50 (s, NH); 8,84 (s, N=CH)
VIc	1610	1630	3190	1,87 (s, CH_3); 7,16—7,69 (m, 6-H—9-H); 8,61 (s, NH)
VIIa	1600	1645	3200	3,79 (s, OCH_3); 7,07—7,43 (m, 6-H—9-H); 8,34 (s, N=CH); 10,47 (s, NH)
VII^{b}	1610	1640	3150	2,64 (s, CH_3); 4,10 (s, OCH_3); 7,20—7,52 (m, 6-H—8-H); 8,05 (d, 9-H); 11,43 (s, NH)
VIIc	1630	1650	3200	3,89 & 4,19* (s, OCH_3); 7,17 (d.d, 7-H, J_{76}=8,8, J_{79}=2,6); 7,47 (d, 6-H, J_{67}=8,8); 7,66 (d, 9-H, J_{97}=2,6); 8,48 (s, N=CH)
XVa	1630, 1730 (C=O), 3080—3200 (NH)			5,43 (s, NH_2); 7,00—7,37 (m, 6-, 7-, 8-H); 7,89 (d, 9-H); 11,70; 12,00 (s, NH)
XVb	1630, 1740 (C=O), 3080—3190, 3430, 3500 (NH, NH_2)			3,26 (s, CH_3); 7,10—7,39 (m, 6-H—8-H); 7,89 (d, 9-H); 11,20; 11,70 (s, NH)
XVc	1670, 1690 (C=O), 3100—3300 (NH)			1,29; 3,76 (t, q, C_2H_5); 7,07—7,41 (m, 6-H—8-H); 7,91 (d, 9-H); 11,80; 11,65; 12,20 (s, NH)
XVd	1660, 1700 (C=O), 3100—3400 (NH, NH_2)			3,81 (s, CH_3O); 5,57 (s, NH_2); 7,04 (d.d, 7-H, J_{79}=2,0; J_{76}==9,0); 7,37 (d 6-H, J_{67}=9,0); 7,39 (d, 9-H, J_{97}=2,0), 11,80; 12,20 (s, NH)

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*The PMR spectrum of compound (VIIc) was recorded in CD_3OD, and those of (XVa-d) in DMSO-d_6.

8-Methoxy-4-piperidinopyrimido[5,4-b]indole (IXb). A solution of 2.3 g of the pyrimidoindole (VIb) in 30 ml of isopropanol was treated with 2.1 g (25 mmole) of piperidine. The reaction mixture was boiled for 5 h, cooled to 20°C, and diluted with 100 ml of water. The isopropanol was evaporated off and the precipitate that deposited on cooling was filtered off and was washed with 100 ml of water and 30 ml of cold methanol. This gave 1.9 g (67%) of compound (IXb) with mp 244-246°C (from methanol). IR spectrum, cm^{-1}: 1620, 1630 (C=C, C=N), 3210 (indole NH). PMR spectrum (acetone-d_6), ppm: 1.26 (br.m, β-H, γ-H, 6 H); 3.87 (s, CH_3O); 3.85 (br.m, α-H, 4 H); 7.06 (d.d, 7-H, J_{76} = 9.0; J_{79} = 2.3); 7.41 (d, 6-H, J_{67} = 9.0); 7.55 (d, 9-H, J_{97} = 2.3); 8.39 (s, N=CH); 10.00 (s, NH). Found: C 68.0; H 6.3; N 20.0%; M^+ 282. $C_{16}H_{18}N_4O$. Calculated: C 68.1; H 6.4; N 19.9%; mol. wt. 282.

4-Diethylaminopyrimido[5,4-b]indole (IXa) was obtained in a similar manner to compound (IXb) from 2.0 g (10 mmole) of the pyrimidoindole (VIa) and 1.8 g (25 mmole) of diethylamine in 30 ml of isopropanol. Yield 1.8 g (75%), mp 192-193°C (isopropanol—water (5:3)). IR spectrum, cm^{-1}: 1630, 1650 (C=C, C=N); 3160 (indole NH). PMR spectrum (acetone-d_6), ppm: 1.28 (t), 3.26 (q) [$N(CH_2CH_3)_2$]; 7.34-7.61 (m, 6-H, 9-H); 8.41 (s, 2-H); 11.05 (s, indole NH). Found: C 70.1; H 6.7; N 23.2%; M^+ 240. $C_{14}H_{16}N_4$. Calculated: C 70.0; H 6.7; N 23.3%; mol. wt. 240.

4-[Di(2-hydroxyethyl)amino]-8-methoxypyrimido[5,4-b]indole (IXc). A mixture of 2.3 g (10 mmole) of the pyrimidoindole (VIb), 5.2 g (50 mmole) of diethanolamine, and 50 ml of isopropanol was boiled for 30 h. The reaction mixture was cooled to 20°C and poured into 200 ml of chloroform. The chloroform solution was poured into 400 ml of water, and the organic layer was separated off, washed with water (3 × 20 ml), and dried with $MgSO_4$, and the chloroform was concentrated to 50 ml. The residue was poured into petroleum ether and the resulting precipitate was filtered off and washed with 100 ml of petroleum ether. This gave 2.1 g (69%) of compound (IXc) with mp 195-196°C (reprecipitated from chloroform from petroleum ether). IR spectrum, cm^{-1}: 1650, 1670 (C=C, C=N); 3160 (indole NH); 3280, 3330 (OH). Found: C 59.4; H 5.5; N 18.5%; M^+ 302. $C_{15}H_{18}N_4O_3$. Calculated: C 59.6; H 6.0; N 18.5%; mol. wt. 302.

4-Mercapto-8-methoxypyrimido[5,4-b]indole (XI). A mixture of 2.3 g (10 mmole) of the pyrimidoindole (VIb), 1.5 g (20 mmole) of thiourea, and 50 ml of ethanol was boiled for 3 h. The reaction mixture was cooled to 20°C, and the precipitate that deposited was filtered off, washed with 300 ml of hot (80-90°C) water and with ethanol, and was dissolved with heating in 100 ml of 0.2 N NaOH solution. The solution was filtered and the filtrate was acidified to pH

6.0-6.5 with 0.1 N H_2SO_4 solution. The resulting precipitate was filtered off, washed with water to pH 7, and dried. This gave 1.6 g (69%) of compound (XI) with decomp. >350°C. IR spectrum, cm^{-1}: 1560, 1610 (C=C, C=N), 3170 (indole NH). PMR spectrum (DMSO-d_6), ppm: 3.83 (s, OCH_3); 7.14 (d.d., 7-H, J_{76} = 8.9; J_{79} = 2.5 Hz); 7.45 (d, 6-H, J_{67} = 8.9 Hz); 7.52 (d, 9-H, J_{97} = 2.5 Hz); 8.09 (s, 2-H); 11.60 (s, indole NH). Found: C 57.3; H 4.1; N 18.0; S 14.2%; M^+ 231. $C_{11}H_9N_3OS$. Calculated: C 57.1; H 3.9; N 18.2; S 13.9%; mol. wt. 231.

Methyl N-(2-Ethoxycarbonylindol-3-yl)carbamate (XIIIa). With cooling and stirring, 1.0 g (10.6 mmole) of methyl chloroformate was added to a solution of 2.0 g (10 mmole) of the aminoindole (XIIa) and 0.9 g (11 mmole) of pyridine in 100 ml of anhydrous benzene. The reaction mixture was stirred at 20-25°C for 3 h, and then 100 ml of water was added to it and it was stirred for another 10 min. The organic layer was separated off and was washed with 50 ml of 5% hydrochloric acid and with water to pH 7 and was dried with Na_2SO_4. The benzene was evaporated off, to give 2.1 g (80%) of compound (XIIIa) with mp 132-133°C (from isopropanol). IR spectrum, cm^{-1}: 1690 ($COOC_2H_5$); 1710 ($NHCOOCH_3$); 3300, 3340 (indole and urethane NH groups). Found: C 60.0; H 5.5; N 10.8%. $C_{13}H_{14}N_2O_4$. Calculated: C 59.6; H 5.3; N 10.7%.

Methyl N-(2-Ethoxycarbonyl-5-methoxyindol-3-yl)carbamate (XIIIb). In a similar manner to the synthesis of the urethane (XIIIa), 2.4 g (10 mmole) of the aminoindole (XIIb), 0.9 g (11 mmole) of urethane, and 1.0 g (10.6 mmole) of methyl chloroformate in 150 ml of anhydrous benzene gave 2.4 g (82%) of the urethane (XIIIb) with mp 157-158°C (from isopropanol). IR spectrum, cm^{-1}: 1680 ($COOC_2H_5$); 1710 ($NHCOOCH_3$); 3270, 3330 (indole and urethane NH groups). Found: C 57.8; H 5.5; N 9.5%. $C_{14}H_{16}N_2O_4$. Calculated: C 57.5; H 5.5; N 9.6%.

The 2,4-Dioxopyrimido[5,4-b]indoles (XVa-d). A mixture of 10 mmole of a urethane (XIIIa or b) and one of the amines (XIVa-c) in 60 ml of isopropanol was boiled for 5 h for compound (XVa), 7 h for (XVb), 8 h for (XVc), or 6 h for (XVd). The reaction mixture was cooled to 20°C and was treated with 5% hydrochloric acid to pH 6.5-7.0. The precipitate that deposited was filtered off and was washed with 200 ml of water and with 30 ml of hot isopropanol and was then dried and recrystallized from DMFA (Tables 3 and 4).

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