REACTION OF 2,3,3-TRIMETHYL-3H-INDOLE SALTS WITH ACRYLAMIDE. SYNTHESIS OF 1,2,3,4,10,10a-HEXAHYDROPYRIMIDO[1,2-a]INDOL-2-ONE DERIVATIVES

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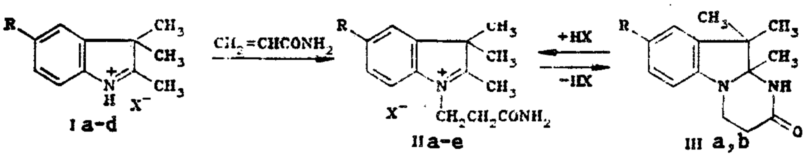
Methyl derivatives of pyrimido[1,2-a]indol-2-one were obtained by the reaction of 2,3,3-trimethyl-3H-indole salts with acrylamide in a proton-containing solvent. The products were condensed with aromatic aldehydes. The interconversion of pyrimido[1,2-a]indol-2-ones and 1-(2-carbamoylethyl)-3H-indolium salts under the influence of acids and bases was studied.

It is known that 2,3,3-trimethyl-3H-indole salts can react with α, β-unsaturated carbonyl-containing compounds, particularly with methyl vinyl ketone [1, 2]. In the present research we investigated the reaction of hydrohalides Ia-d with arylamide. We found that pyrimido[1,2-a]indol-2-one derivatives (IIIa, b) are formed when mixtures of the reagents in a proton-containing solvent are heated with subsequent treatment of adducts IIa-d with a base. The addition of acrylamide to salts Ia-d proceeds most smoothly in acetic acid. When the reaction is carried out in ethylene glycol or diethylene glycol, ethanol, or water, the yields of IIIa, b are lower by a factor of 2-2.5 and amount to 25-30%.



I—III a R=H, X=Cl; b R=CH₃, X=Cl; c R=H, X=Br; d R=CH₃, X=Br; e R=H, X=ClO₄

The structures of IIIa, b were confirmed by means of spectral investigations. An absorption band at 1655 cm^{-1}, which is due to a carbonyl group, and a band at 3180-3190 cm^{-1}, which corresponds to stretching vibrations of the N–H bond, are observed in their IR spectra. Characteristic signals in the ^{1}H NMR spectra are three singlets of protons of the 10,10,10a-methyl groups at 1.10-1.52 ppm. In addition to a molecular-ion peak, peaks of ions 215 and 200,* the formation of which is associated with splitting out of methyl groups, and signals of ions with 187 ($[M - NHCO]^{+\cdot}$) and 173 ($[M - NHCOCH_2]^+$), which characterize fragmentation of the hexahydropyrimidine ring, are present in the mass spectrum of IIIa. The presence of ions with 144, 142, 131, and 130 is typical for the mass spectra of indole derivatives [3].

Under the influence of acids, IIIa, b undergo decyclization and are converted to 1-(2-carbamoylethyl)-3H-indolium salts. Thus perchlorate IIe was obtained by reaction of IIIa with perchloric acid. Absorption bands that are characteristic for primary amines [4] are present in its IR spectrum: 1690 (C = O), 3190 (NH), and 3445 cm^{-1} (NH). Starting compound IIIa is formed when it is treated with bases.

Compounds IIIa, b undergo condensation with aromatic aldehydes in acetic acid in the presence of acetic anhydride. The resulting salts IVa-g (X = CH_3COO) undergo cyclization to

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*The numbers that characterize the ions are the m/z values.

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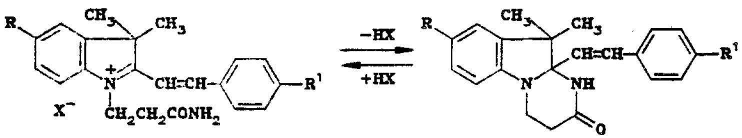
TABLE 1. 10a-Styrylpyrimido[1,2-a]indol-2-ones(Va-g)

Compound	mp, °C (from alcohol)	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N (Hal)		C	H	N (Hal)	
Va	237—238	76,4	7,7	11,5	$C_{23}H_{27}N_3O$	76,4	7,5	11,6	91
Vb	200—201	77,0	8,1	11,1	$C_{25}H_{31}N_3O$	77,1	8,0	10,8	93
Vc	238—239	76,7	8,0	11,0	$C_{24}H_{29}N_3O$	76,8	7,8	11,2	85
Vd	200—201	75,9	7,0	7,9	$C_{22}H_{24}N_2O_2$	75,8	7,0	8,0	56
Ve	235—236	71,6	6,1	7,9 (10,0)	$C_{21}H_{21}ClN_2O$	71,5	6,0	7,9 (10,0)	52
Vf	233—234	63,7	5,3	6,9 (19,9)	$C_{21}H_{21}BrN_2O$	63,5	5,3	7,1 (20,1)	74
Vg	201—202	79,0	7,2	8,6	$C_{21}H_{22}N_2O$	79,2	7,0	8,8	65

TABLE 2. ^1H NMR Spectra of 10a-Styrylpyrimido[1,2-a]indol-2-ones(Va-g)

Compound	^1H NMR spectrum, ppm (in $CDCl_3$)			
	10,10-CH_3 (two s)	CH_2CH_2(m)	CH$_{arom}$, vinyl, NH (m)	R, R^1 (except for aromatic protons)
Va	1,20; 1,33	1,90—3,92	6,10—7,46	2,96 (6H, s, N,N-CH_3)
Vb	1,19; 1,33	1,82—4,00	6,10—7,46	1,15 (6H, t, 2×CH_2CH_3) 3,39 (4H, q, 2×CH_2CH_3)
Vc	1,19; 1,32	1,85—4,05	6,10—7,45	2,31 (3H, s, 8-CH_3)
Vd	1,19; 1,34	1,93—4,10	6,18—7,46	3,84 (3H, s, OCH_3)
Ve	1,18; 1,34	1,93—4,00	6,30—7,43	
Vf	1,18; 1,34	1,93—4,00	6,31—7,55	
Vg	1,20; 1,34	1,80—3,98	6,31—7,52	

10a-styrylpyrimido[1,2-a]indol-2-ones Va-g under the influence of bases.



IVa-g

Va-g

IV, V a R=H, R^1=N$(CH_3)_2$; b R=H, R^1=N$(C_2H_5)_2$; c R=CH_3, R^1=N$(CH_3)_2$; d R=H, R^1=OCH_3; e R=H, R^1=Cl; f R=H, R^1=Br; g R=R^1=H; X=anion

Compounds Va-c were previously obtained by the reaction of 2-(p-dialkylaminostyryl)-3,3-dimethyl-3H-indoles with acrylamide [5]. However, the yields and constants of these compounds were not presented. When we attempted to reproduce the indicated method for the synthesis of Va, we found that the substance obtained does not have a distinct melting point and contains considerable amounts of impurities. From this mixture, by crystallization from acetone or ethanol, we were able to isolate Va in no more than 25% yield. However, the synthesis of 10a-(p-dialkylaminostyryl)pyrimido[1,2-a]indol-2-ones by condensation of pyrimidoindoles IIIa, b with aromatic aldehydes makes it possible to significantly raise the yields of the corresponding styryl derivatives (based on 2,3,3-trimethyl-3H-indole) and to decrease the consumption of acrylamide by a factor of five to six [6]. With the same success in the synthesis of Va, f we also used perchlorate IIe, which reacts smoothly with p-dimethylamino- and p-bromobenzaldehyde in acetic acid.

Absorption bands that are characteristic for carbonyl and ethylene groups, respectively, at 1650-1670 and 1643-1647 cm^{-1} are observed in the IR spectra of Va-g. The absorption band at 3210-3250 cm^{-1} is related to stretching vibrations of the N—H bond. Two singlets of diastereotopic geminal methyl groups at 1.18-1.34 ppm are isolated in the ^1H NMR spectra of Va-g. The vicinal spin-spin coupling constants (SSCC) of the protons of the ethylene group are 16.0-17.0 Hz and attest to their trans orientation [7].

Protic acids promote conversion of the 10a-styrrylpyrimidoindol-2-ones to the colored form of salts IVa-g. In the ^{1}H NMR spectrum of Va in CF_3COOH the signals of the protons of the methylene groups appear at 2.80-3.05 (CH_2CO) and 4.55-4.88 ppm ($\overset{+}{N}CH_2$) and virtually coincide with the positions of the corresponding signals of perchlorate IIe; this confirms opening of the hexahydropyrimidine ring.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin-Elmer spectrometer. The ^{1}H NMR spectra were obtained with Varian XL-100 and XL-200 spectrometers with hexamethyldisiloxane (HMDS) as the internal standard. The ^{13}C NMR spectrum was recorded with a Tesla BS-567 spectrometer (25.14 MHz). The assignment of the signals was made on the basis of the results of the application of various pulse methods for recording the spectra [8] and the data in [9, 10]. The mass spectra were obtained with an LKB-9000 spectrometer (70 V). The course of the reactions and the individuality of the compounds were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates.

10,10,10a-Trimethyl-1,2,3,4,10,10a-hexahydropyrimido[1,2-a]indol-2-one (IIIa). A). A solution of 19.57 g (0.1 mole) of 2,3,3-trimethyl-3H-indole hydrochloride and 7.82 g (0.11 mole) of acrylamide in 40 ml of acetic acid was heated at 100°C for 1 h, after which the mixture was poured into water. The aqueous mixture was made alkaline with potassium hydroxide solution and extracted with ether. The solvent was removed by distillation, and the residue was crystallized from ethanol to give 16.2 g (70%) of a product with mp 172-173°C. ^{1}H NMR spectrum ($CDCl_3$): 1.11 (3H, s, 10-CH_3), 1.32 (3H, s, 10-CH_3) 1.51 (3H, s, 10a-CH_3), 2.00-2.75 (2H, m, CH_2CO), 3.29-3.90 (2H, m, N–CH_2), and 6.50-7.15 ppm (5H, m, aromatic, NH). ^{13}C NMR ($CDCl_3$): 19.8 (CH_3), 21.1 (CH_3), 26.4 (CH_3), 27.2 [$C_{(3)}$], 36.8 [$C_{(4)}$], 47.9 [C_{10}], 84.2 [$C_{(10a)}$], 108.7 [$C_{(6)}$], 120.2 and 122.3 [$C_{(8)}$] and $C_{(9)}$], 127.4 [$C_{(7)}$], 138.3 [$C_{(9a)}$],147.0 [$C_{(5a)}$], and 169.6 ppm [$C_{(2)}$]. Found: C 73.1; H 7.6; N 12.1%. $C_{14}H_{18}N_2O$. Calculated: C 73.0; H. 7.9; N 12.2%

B) A solution of 12.0 g (0.05 mole) of 2,3,3-trimethyl-3H-indole and 3.91 g (0.055 mole) of acrylamide in 30 ml of acetic acid was heated at 100°C for 2 h, after which the mixture was poured into water. The aqueous mixture was made alkaline with sodium hydroxide solution and extracted with ether. The solvent was removed by distillation, and the residue was crystallized from ethanol to give 7.3 g (63%) of product.

8,10,10,10a-Tetramethyl-1,2,3,4,10,10a-hexahydropyrimido[1,2-a]indol-2-one (IIIb). A) This compound was obtained in analogy to IIIa (method A) from 10.49 g (0.05 mole) of 2,3,3,5-tetramethyl-3H-indole and 3.91 g (0.055 mole) of acrylamide. The yield of product with mp 176-177°C (from ethanol) was 8.05 g (66%). PMR spectrum ($CDCl_3$): 1.12 (3H, s, 10-CH_3), 1.33 (3H, s, 10-CH_3), 1.51 (3H, s, 10a-CH_3), 1.98-2.81 (2H, m, CH_2CO), 2.28 (3H, broad s, 8-CH_3), 3.28-3.95 (2H, m, NCH_2), 6.32 (1H, broad s, NH), 6.56 (1H, d, J = 8.0 Hz, 6-H), 6.86-6.90 (1H, m, 9-H), and 6.91-7.05 ppm (1H, m, 7-H). Found: C 73.6; H 8.2; N 11.6%. $C_{15}H_{20}N_2O$. Calculated: C 73.7; H 8.2; N 11.5%.

B) This compound was obtained in analogy to IIIa (method B) from 5.08 g (0.02 mole) of 2,3,3,5-tetramethyl-3H-indole and 1.56 g (0.022 mole) of acrylamide. The yield was 2.9 g (59%).

1-(2-Carbamoylethyl)-2,3,3-trimethyl-3H-indolium Perchlorate (IIe). A solution of 2.3 g (0.01 mole) of pyrimido[1,2-a]indol-2-one in 20 ml of ethanol was neutralized with 60% perchloric acid, after which the mixture was cooled, and the precipitated substance was removed by filtration and recrystallized from ethanol to give 2.0 g (61%) of a product with mp 147-148°C. PMR spectrum (CF_3COOH): 1.25 (6H, s, 3,3-CH_3), 2.57 (3H, s, 2-CH_3), 2.79 (2H, t, J = 6.5 Hz, CH_2CO), 4.53 (2H, t, J = 6.5 Hz, NCH_2), and 7.23-7.45 ppm (4H, m, aromatic protons). Found: Cl 10.5; N 8.2%. $C_{14}H_{19}ClN_2O_5$. Calculated: Cl 10.7; N 8.5%.

8-R-10,10-Dimethyl-10a-(4-R^1-styryl)-1,2,3,4,10,10a-hexahydropyrimido[1,2-a]indol-2-ones V (Tables 1 and 2). A) A solution of 0.02 mole of IIIa, b and 0.02 mole of the corresponding aromatic aldehyde in a mixture of 20 ml of acetic acid and 2 ml of acetic anhydride was heated at 100°C for 1-3 h, after which the mixture was poured into water. The aqueous mixture was made alkaline with potassium hydroxide solution, and the precipitated substance was removed by filtration, dried, and crystallized from ethanol or acetone.

B) A mixture of 0.01 mole of perchlorate IIe and 0.01 mole of the corresponding aromatic aldehyde in 10 ml of acetic acid was heated at 100°C for 2 h, after which the reaction mixture was worked up as in the example described above. This method was used to obtain styryl derivatives Va (82% yield) and Vf (72% yield).

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