SYNTHESIS OF 4,5-DIHYDROPYRROLO[1,2,3-e, f][1,5]BENZODIAZEPIN-6(7H)-ONES

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A number (seven compounds) of 4,5-dihydropyrrolo[1,2,3-e, f][1,5]benzodiazepin-6(7H)-ones were obtained by condensation of 7-aminoindoles with β-halopropionic acid derivatives with subsequent cyclization of the resulting 7-(β-halopropionylamino)indoles by heating in the presence of bases in dimethylformamide. The compositions and structures of the intermediates and final products were confirmed by the results of elementary analysis and data from the IR, UV, and mass spectra.

Substances that have an interesting spectrum of biological activity have been found among 1,5-benzodiazepine derivatives that contain an indole fragment [1]. A method for the synthesis of representatives of the 4,5-dihydropyrrolo[1,2,3-e, f][1,5]benzodiazepin-6(7H)-one (I) series that proposes the use of the corresponding 1,2,4,5-tetrahydropyrrolo-[1,2,3-e, f][1,5]benzodiazepin-6(7H)-ones has been described. This method has a number of disadvantages: the multistep character of the process, the limited possibilities of introduction of substituents in the system, and the consumption of a precious metal [2].

In order to overcome these disadvantages we have developed a method for the synthesis of compounds of the I type that consists in the condensation of 7-aminoindoles with β-halopropionic acid derivatives with subsequent cyclization of the resulting 7-(β-halopropionylamino)indoles (IV) by heating in the presence of bases in dimethylformamide (DMF). The 7-aminoindoles used as the reaction intermediates are obtained by reduction of the corresponding 7-nitroindoles (III), which in turn are readily formed in the cyclization of substituted o-nitrophenylhydrazones (II) [3].

The method that we developed is readily reproducible and makes it possible to obtain diverse derivatives of this class in high yields.

The properties of the intermediates (IV) and final products (I) are presented in Tables 1 and 2, respectively. Their structures were confirmed by means of IR, UV, and mass spectroscopy, and their compositions were confirmed by the results of elementary analysis.

The IR spectrum of 1,2-dimethyl-4,5-dihydropyrrolo[1,2,3-e, f][1,5]benzodiazepin-6(7H)-one (Ia) is characterized by the presence of an intense band of stretching vibrations of a carbonyl group at 1730 cm^{-1}. The shift of the absorption band of the amide carbonyl group can be explained by the absence of conjugation of the electron pair of the nitrogen atom with the p electrons of the carbonyl group, which leads to an increase in the polarity of the $C{=}O$ bond and an increase in the absorption frequency. The absence of such conjugation is due to disruption of the planarity of the amide group, as follows from an analysis of Dreiding models. The IR spectra of the 2-ethoxycarbonyl derivatives (Ib, d-g) are characterized by the presence of two absorption bands at 1675-1710 cm^{-1}, which correspond to the stretching vibrations of the $C{=}O$ bonds of amide and ester groups.

The UV spectrum of 1,2-dimethyl derivative Ia is characterized by three absorption maxima at 203 (log ε 4.25), 248 (log ε 4.0), and 303 nm (log ε 3.80). The appearance of an absorption maximum at 330-333 nm (log ε 3.75-3.82), which is evidently determined by the electron transitions in the ester group bonded to the heteoaromatic ring [4], is characteristic for all of the pyrrolo [1,2,3-e,f][1,5]benzodiazepines (Ib-g) that have an ethoxycarbonyl group.

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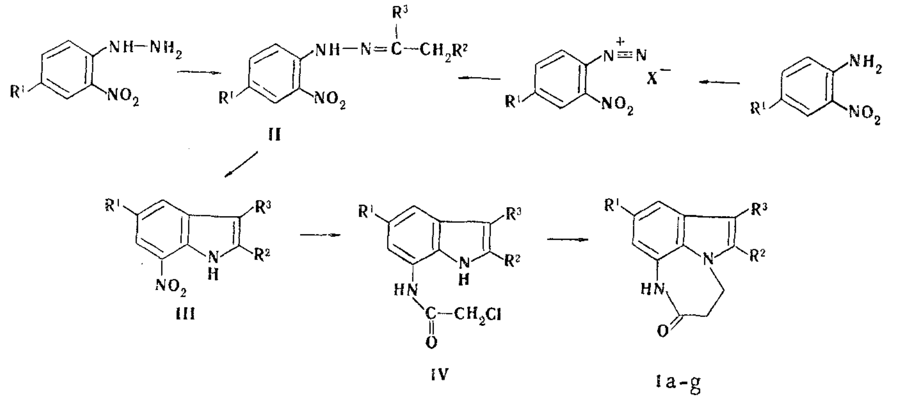


I a $R^1=H$; $R^2=R^3=CH_3$; b $R^1=H$; $R^2=COOC_2H_5$; $R^3=CH_3$; c $R^1=H$; $R^2=CH_3$; $R^3=C_6H_5$; d $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=CH_3$; e $R^1=OC_2H_5$; $R^2=COOC_2H_5$; $R^3=C_2H_5$; f $R^1=Br$; $R^2=COOC_2H_5$; $R^3=C_2H_5$; g $R^1=Cl$; $R^2=COOC_2H_5$; $R^3=CH_3$

The molecular masses of all of the final products determined by mass spectrometry correspond to the calculated values. The mass spectrum of 1,2-dimethyl derivative Ia contains, in addition to a molecular-ion peak (M^+), rather intense peaks of $[M - CO]^+$, $[M - HCO]^+$, and $[M - CH_2CO]^+$ fragments. The elimination of a CH_2CO molecule from the molecular ion was confirmed by the presence of a metastable ion with an apparent mass of 138.2.

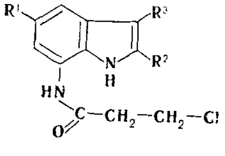
EXPERIMENTAL

The IR spectra of solutions of the compounds in carbon tetrachloride were recorded with a Perkin-Elmer spectrometer. The UV spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer. The mass spectra were recorded with an MKh-1303 spectrometer at an ionization energy of 50 eV, an emission current of 150 µA, and temperatures 30-50°C below the melting points of the investigated compounds. The purity and individuality of the compounds were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates in hexane—acetone (2:1) and chloroform—hexane—acetone (3:2:1) systems.

The o-nitrophenylhydrazones (II) were synthesized under the conditions in [5]. 7-Nitro-2,3-dimethylindole (IIIa) was obtained by the method in [5]. The 7-nitro-3,5-disubstituted-2-ethoxycarbonylindoles (IIIb-g) were obtained by the method in [6].

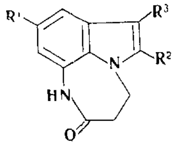
7-(β-Chloropropionylamino)-2,3-dimethylindole (IVa). A 100-ml sample of methanol was added to a mixture of 4.75 g (0.025 mole) of 7-nitro-2,3-dimethylindole and 5 g of freshly prepared Raney nickel, and hydrogenation was carried out with stirring until the calculated amount of hydrogen (1680 cm³) had been absorbed completely. The catalyst was removed by filtration, the solvent was evaporated *in vacuo*, and the residue was dissolved in 150 ml of acetic acid. A solution of 6.6 g (0.08 mole) of sodium acetate in 20 ml of water was added to the solution, and 5.1 g (0.04 mole) of β-chloropropionyl chloride was added dropwise with cooling (with ice water). The mixture was stirred for 30 min and poured into ice water, and

TABLE 1. 2,3,5-Trisubstituted β-Chloropropionylaminoindoles



Compound	R^1	R^2	R^3	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
					C	H	N		C	H	N	
IVa	H	CH_3	CH_3	175—176	62,3	5,8	11,2	$C_{13}H_{15}ClN_2O$	62,3	5,9	11,2	72
IVb	H	$COOC_2H_5$	CH_3	153—154	58,4	5,4	9,2	$C_{15}H_{17}ClN_2O_3$	58,3	5,5	9,1	63
IVc	H	CH_3	C_6H_5	201—203	69,2	5,5	8,9	$C_{18}H_{17}ClN_2O$	69,1	5,4	9,0	87
IVd	CH_3	$COOC_2H_5$	CH_3	155—157	59,8	5,7	8,5	$C_{16}H_{19}ClN_2O_3$	59,5	5,9	8,7	60
IVe	C_2H_5O	$COOC_2H_5$	C_2H_5	117—119	59,0	6,3	7,2	$C_{18}H_{23}ClN_2O_4$	58,9	6,3	7,6	61
IVf	Br	$COOC_2H_5$	C_2H_5	126—127	47,9	4,6	6,8	$C_{16}H_{18}BrClN_2O_3$	47,8	4,5	7,0	50
IVg	Cl	$COOC_2H_5$	CH_3	193—195	52,6	4,8	8,4	$C_{15}H_{16}Cl_2N_2O_3$	52,4	4,7	8,2	54

TABLE 2. 1,2,9-Trisubstituted 4,5-Dihydropyrrolo[1,2,3-e, f][1,5]benzodiazepin-6(7H)-ones



Compound	R^1	R^2	R^3	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
					C	H	N		C	H	N	
I a	H	CH_3	CH_3	161—163	72,9	6,4	13,2	$C_{13}H_{14}N_2O$	72,8	6,5	13,1	87
I b	H	$COOC_2H_5$	CH_3	170—171	66,2	5,9	10,2	$C_{15}H_{16}N_2O_3$	66,2	5,9	10,3	65
I c	H	CH_3	C_6H_5	205—207	78,1	5,9	10,1	$C_{18}H_{16}N_2O$	78,3	5,8	10,1	68
I d	CH_3	$COOC_2H_5$	CH_3	256—258	67,3	6,3	9,6	$C_{16}H_{18}N_2O_3$	67,1	6,3	9,8	76
I e	C_2H_5O	$COOC_2H_5$	C_2H_5	217—218	65,2	6,4	8,2	$C_{18}H_{22}N_2O_4$	65,4	6,7	8,5	64
I f	Br	$COOC_2H_5$	C_2H_5	253—255	52,7	4,8	7,7	$C_{16}H_{17}BrN_2O_3$	52,6	4,6	7,7	54
I g	Cl	$COOC_2H_5$	CH_3	275—277	58,5	5,4	9,2	$C_{15}H_{15}ClN_2O_3$	58,8	4,9	9,1	57

the resulting precipitate was removed by filtration, dried, and recrystallized from ethanol to give 3.6 g (72%) of a product with mp 175-176°C. Compounds IVb-g were similarly obtained.

1,2-Dimethyl-4,5-dihydropyrrolo[1,2,3-e, f][1,5]benzodiazepin-6(7H)-one (Ia). A solution of 5 g (0.02 mole) of IVa in 50 ml of dry DMF was added dropwise to a suspension of 0.51 g (0.021 mole) of sodium hydride in 150 ml of DMF, and the mixture was refluxed for 4 h. It was then cooled and poured into 250 ml of ice water. The gray-green precipitate was removed by filtration and recrystallized from ethanol to give 3.7 g (87%) of a product with mp 161-163°C. Compounds Ib-g were obtained under similar conditions.

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