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4,5-DIHYDRO-6H-PYRROLO[1,2,3-d,e]QUINOXALIN-5-ONES

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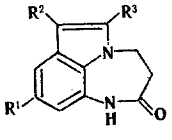
The synthesis of 1-R^1-2-R^2-8-R^3-4,5-dihydro-6H-pyrrolo[1,2,3-d,e]quinoxalin-5-one derivatives (where R^1 = CH_3, C_2H_5; R^2 = CH_3, $COOC_2H_5$; R^3 = H, CH_3, C_2H_5O, Cl, Br) is described. The physicochemical properties of these derivatives were also studied.

The present communication is devoted to the synthesis of 4,5-dihydropyrrolo[1,2,3-d,e]-quinoxalin-5(6H)-ones (II). The cyclohomologs of the latter, viz., 4,5,6,7-tetrahydro[1,2,3-e,f]-1,5-benzodiazepin-6-ones (I), have been described as substances that have tranquilizing and anticonvulsive action [1, 2]. The literature contains data on the synthesis of individual representatives of the II series by Fischer condensation of ketones with 1-amino-3-keto-1,2,3,4-tetrahydroquinoxaline [3, 4].



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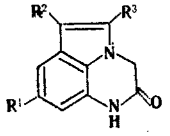

II a-g

II a R^1=H, R^2=R^3=CH_3; b R^1=H, R^2=CH_3, R^3=$COOC_2H_5$; c R^1=H, R^2=C_2H_5, R^3=$COOC_2H_5$; d R^1=CH_3, R^2=C_2H_5, R^3=$COOC_2H_5$; e R^1=Cl, R^2=CH_3, R^3=$COOC_2H_5$; f R^1=C_2H_5O, R^2=C_2H_5, R^3=$COOC_2H_5$; g R^1=Br, R^2=CH_3, R^3=$COOC_2H_5$

We have developed a new method for the synthesis of pyrrolo[1,2,3-d,e]quinoxalin-5-one derivatives (IIa-g) from o-nitrophenylhydrazones (III), which were converted by the Fischer reaction to 7-nitroindoles (IV) with subsequent reduction of the latter to 7-aminoindoles (V). In view of their instability, V were not isolated in pure form, but hydrogenation products V were dissolved in acetic acid and treated with chloroacetyl chloride in the pres-

TABLE 1. 7-Nitro- (IVb-g) and 7-Chloroacetamidoindoles (VIa-g)

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IVb	135—136			11,0	$C_{12}H_{12}N_2O_4$			11,3	62
IVc	93—95			10,5	$C_{13}H_{14}N_2O_4$			10,7	55
IVd	123—125			10,0	$C_{14}H_{16}N_2O_4$			10,1	52
IVe	143—145			10,0	$C_{12}H_{11}ClN_2O_4$			9,9	65
IVf	155—156			9,0	$C_{15}H_{18}N_2O_5$			9,1	45
IVg	131—132			8,2	$C_{12}H_{11}BrN_2O_4$			8,5	61
VIa	142—143	60,8	5,8	12,0	$C_{12}H_{13}ClN_2O$	60,9	5,5	11,8	72
VIb	110—112	56,7	4,8	9,3	$C_{14}H_{15}ClN_2O_3$	57,0	5,1	9,5	68
VIc	145—147	58,1	5,0	8,8	$C_{15}H_{17}ClN_2O_3$	58,3	5,1	9,1	61
VId	180—181	59,3	5,6	8,6	$C_{16}H_{19}ClN_2O_3$	59,6	5,9	8,7	55
VIe	80—81	51,2	4,0	8,4	$C_{14}H_{14}Cl_2N_2O_3$	51,1	4,2	8,5	75
VIf	88—90	58,1	6,1	8,1	$C_{17}H_{21}ClN_2O_4$	57,9	5,9	7,9	68
VIg	162—163	45,1	3,5	7,4	$C_{14}H_{14}ClBrN_2O$	44,9	3,7	7,5	70

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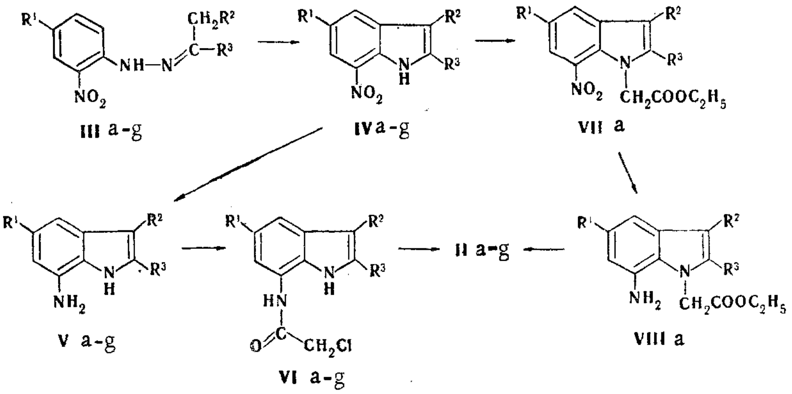
TABLE 2. 4,5-Dihydro-6H-pyrrolo[1,2,3-d,e]quinoxalin-5-ones (IIa-g)

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIa	259—261	71,9	6,0	14,2	$C_{12}H_{12}N_2O$	72,0	6,0	14,0	60
IIb	269—270	65,6	5,6	10,9	$C_{14}H_{14}N_2O_3$	65,1	5,4	10,8	58
IIc	281—283	66,4	6,0	10,5	$C_{15}H_{16}N_2O_3$	66,1	5,8	10,3	51
IId	272—273	67,1	6,5	9,7	$C_{16}H_{18}N_2O_3$	67,1	6,3	9,8	63
IIe	283—284	57,8	4,7	9,2	$C_{14}H_{13}ClN_2O_3$	57,4	4,5	9,6	55
IIf	246—247	61,2	6,5	9,5	$C_{15}H_{20}N_2O_4$	61,6	6,8	9,6	55
IIg	225—227	49,9	3,5	8,0	$C_{14}H_{13}BrN_2O_3$	49,8	3,8	8,3	53

ence of sodium acetate. The resulting 7-chloroacetamidoindoles (VI) were subjected to intramolecular cyclization by heating in dimethylformamide (DMF) in the presence of sodium hydride.

Compound IIa was also obtained by alternative synthesis by alkylation of 7-nitro-2,3-dimethylindole (IVa) with ethyl monochloroacetate and subsequent reduction of alkylation product VII and cyclization of the resulting amine (VIII). The compounds obtained by the two methods are identical.



Intermediates IV and VI are presented in Table 1, and pyrroloquinoxalines II are presented in Table 2.

The IR spectra of VIb-g are characterized by the presence of bands of carbonyl stretching vibrations of amide and ester groups at 1670-1705 cm^{-1}. The spectrum of VIa does not contain an absorption band at 1705 cm^{-1}. The intense band at 3410-3430 cm^{-1} corresponds to the stretching vibrations of the NH bond of the indole ring. The set of bands at 3200-3300 cm^{-1} corresponds to the stretching vibrations of free and associated NH groups.

Bands of stretching vibrations of a lactam carbonyl group at 1650-1670 cm^{-1} are observed in the IR spectra of IIa-g. The absorption band of the C=O bond of the carbethoxy group of IIb-g is found at 1690-1700 cm^{-1}. The two absorption bands at 3415-3420 and 3330-3340 cm^{-1} correspond to the stretching vibrations of free and associated NH groups.

The UV spectra of IIb-g in ethanol contain four bands with absorption maxima at 204-212 (log ε 4.0-4.2), 230-240 (log ε 4.1-4.3), 295-305 (log ε 3.6-4.1), and 320-330 nm (log ε 4.1-4.4). The spectrum of IIa does not contain a band at 320-330 nm. According to the data in [5], this band can be assigned to the absorption of a carbethoxy group conjugated with an aromatic ring.

EXPERIMENTAL

The individuality of the compounds obtained was monitored by TLC on Silufol UV-254 plates in chloroform—hexane—acetone (3:2:1) and acetone—hexane (1:2) systems. The IR spectra of solutions of IIa-g in chloroform were recorded with an IKS-14A spectrometer. The UV spectra of solutions of IIa-g in ethanol were obtained with a Specord UV-vis spectrophotometer.

o-Nitrophenylhydrazones III and 7-nitro-2,3-dimethylindole IVa were synthesized by the method in [6].

7-Nitro-3-methyl-2-carbethoxyindole (IVb). A 13.2-g (0.05 mole) sample of ethyl acetoacetate o-nitrophenylhydrazone was dissolved in 10 g of polyphosphoric acid (PPA), and the solution was heated slowly to 100°C on a water bath. It was then maintained on a boiling-water bath for 15 min, after which it was cooled and poured into water. The resulting oily precipitate was separated and recrystallized from ethanol to give 6.9 g (62%) of IVb with mp 135-136°C.

Compounds IVc-g (Table 1) were similarly obtained.

7-Chloroacetamido-2,3-dimethylindole (VIa). Methanol (100 ml) 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 was completely absorbed. The catalyst was removed by filtration, the solvent was evaporated in vacuo, and the residue was dissolved in acetic acid. A solution of 6.6 g (0.08 mole) of sodium acetate in 20 ml of water was added to the acetic acid solution, and 4.5 g (0.04 mole) of chloroacetyl chloride was added dropwise with cooling (with ice water) and stirring. The mixture was stirred for 30 min, after which it was poured into ice water (∿500 ml). The resulting precipitate was removed by filtration, dried, and recrystallized from ethanol to give 3.64 g (72%) of VIa with mp 142°C.

Compounds VIb-g (Table 1) were similarly obtained.

1-Carbethoxymethyl-2,3-dimethyl-7-nitroindole (VII). A solution of 1.9 g (0.01 mole) of 7-nitro-2,3-dimethylindole in 20 ml of dry DMF was added dropwise to a suspension of 0.24 g (0.01 mole) of sodium hydride in 15 ml of dry toluene, and the mixture was heated at 60°C for 1.5 h. It was then cooled, and a solution of 1.6 ml (0.015 mole) of ethyl monochloroacetate in 5 ml of DMF was added dropwise. The mixture was then refluxed for 15 h, after which the solvent was evaporated, and the residue was washed well with water, removed by filtration, and recrystallized from methanol. Dark-red crystals with mp 106-108°C precipitated after the methanol solution was allowed to stand for a long time. The yield of VII was 1.24 g (45%).

1,2-Dimethyl-4,5-dihydro-6H-pyrrolo[1,2,3-d,e]quinoxalin-5-one (IIa). Method 1. A solution of 2.4 g (0.01 mole) of 7-chloroacetamido-2,3-dimethylindole in 25 ml of dry DMF was added dropwise to a suspension of 0.26 g (0.012 mole) of sodium hydride in 75 ml of DMF, and the mixture was refluxed for 4 h. It was then cooled and poured into a large amount of water (∿500 ml), and the precipitate was removed by filtration, dried, and recrystallized from acetone to give 1.2 g (60%) of IIa with mp 259-261°C.

Method 2. Methanol (50 ml) was added to a mixture of 1.4 g (0.005 mole) of 1-carbethoxymethyl-2,3-dimethyl-7-nitroindole and 2 g of freshly prepared Raney nickel, and hydrogenation was carried out with stirring until the calculated amount of hydrogen was completely absorbed. The catalyst was removed by filtration, and the solvent was evaporated in vacuo. The residue was dissolved in dry xylene (50 ml), a catalytic amount of sodium hydride was added, and the mixture was refluxed with a Dean–Stark adapter for removal of the liberated water (for ∿1 h). The solvent was evaporated, and the residue was recrystallized from acetone to give 0.62 g (62%) of IIa.

Compounds IIb-g (Table 2) were obtained by method 1.

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