INDOLE DERIVATIVES.

XLIV. SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF TETRAHYDROPYRIMIDO[3,4-a]INDOLE DERIVATIVES

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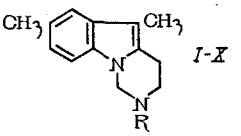
In view of the fact that derivatives of various condensed indole systems possess a wide spectrum of pharmacological activity, especially with respect to the central nervous system (CNS) [1-3], we have undertaken an investigation of the synthesis and physiological activity of several new pyrimido[3,4-a]indole derivatives.



I-X

I: R = $COCH_2CH_2Cl$
II: R = $COCH_2CH_2N(CH_3)_2$
III: R = $COCH_2CH_2N(C_2H_5)_2$
IV: R = $COCH_2CH_2N(C_3H_7)_2$
V: R = $COCH_2CH_2N$⬡
VI: R = $(CH_2)_3Cl$
VII: R = $(CH_2)_3N(C_2H_5)_2$
VIII: R = $(CH_2)_3N(C_3H_7)_2$
IX: R = $(CH_2)_3N$⬡
X: R = C_2H_5

We subjected 5,7-dimethyl-1,2,3,4-tetrahydropyrimido[3,4-a]indole, which we prepared in [4], to N-acylation with β-chloropropionyl chloride to form the corresponding chloropropionyl derivative (I). Reaction of I with secondary amines gave the corresponding aminoacyl derivatives (II-V). Reduction of I, III and IV with lithium aluminum hydride gave the corresponding alkyl derivatives (VI-VIII respectively). Treatment of VI with piperidine gave aminoalkyl derivative IX (Table 1).

A mass-spectrometric study of the compounds (I-V, see Table 2) showed that disintegration of the molecular ion by electron impact led to the formation of both fragments indicating the presence of a substituent on the nitrogen on the piperidine ring (m/e 199 and m/e 157) and fragments characteristic of 2,3,4,5-tetrahydropyrimido[3,4-a]indoles (m/e 171 and m/e 158), the ion with m/e 171 being formed by rearrangement. The high intensity of the peaks corresponding to the fragment with m/e 199 is probably due to the high stability of the aminoacyl fragment eliminated as a result of rupture of the amide bond at the piperidine nitrogen atom. This is supported by the low intensity of the peak with m/e 199 for the chloroacyl compound I; on the other hand, the stabilization of this ion may be connected with a transannular interaction between the amine and indole nitrogen atoms.

The pharmacological activity of the compounds synthesized was investigated by a number of tests for psychotropic activity, viz., by determining their effect on motor activity and their ability to change body (rectal) temperature, sensitivity to pain, skeletal muscle tone, duration of thiopental sodium narcosis, and the duration of amphetamine-induced stereotypy. The preparations were injected intraperitoneally in a dose of 10 mg/kg 30 min before performing the investigations. Motor activity was determined over a period of 15 min by actography, pain sensitivity was determined by the hotplate method, muscle-relaxant activity was determined by the rotating-rod method. The experiments were carried out on mice; rats were used only for determining the duration of amphetamine stereotypy.

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TABLE 1. Tetrahydropyrimido[3,4-a]indole Derivatives (I–IX)

Compound	Yield (%)	Melting point (deg)	Found (%)				Empirical formula	Calculated (%)			
			C	H	N	Cl		C	H	N	Cl
I	70	106—6,5	66,36	6,67	10,03	11,95	$C_{16}H_{19}ClN_2O$	66,12	6,59	9,64	12,20
II	68	105—6	72,44	8,46	13,80		$C_{18}H_{25}N_3O$	72,22	8,41	14,03	
		162—4	64,12	8,87	12,72	10,56	$C_{18}H_{25}N_3O \cdot HCl$	64,37	8,80	12,51	10,55
III		63—4	73,21	8,90	12,51		$C_{20}H_{29}N_3O$	73,35	8,92	12,83	
	78	156—8	65,85	8,47	11,75	9,94	$C_{20}H_{29}N_3O \cdot HCl$	66,01	8,31	11,54	9,74
IV		58—9	74,04	9,36	11,68		$C_{22}H_{33}N_3O$	74,32	9,35	11,82	
	88	142—3	67,13	8,76		9,55	$C_{22}H_{33}N_3O \cdot HCl$	67,57	8,76		9,07
V	70	60—1,5	74,69	8,56	12,24		$C_{21}H_{29}N_3O$	74,30	8,49	12,39	
		193—5	66,77	8,12	11,14	9,46	$C_{21}H_{29}N_3O \cdot HCl$	67,10	8,05	11,18	9,43
VI	90	166—8				22,78	$C_{16}H_{21}N_2Cl \cdot HCl$				22,64
VII	20	175—6	61,11	9,02	10,56	17,54	$C_{20}H_{33}N_3 \cdot 2HCl \cdot O,5H_2O$	60,75	8,7	10,63	17,94
VIII	86	181—2	63,34	9,56	9,95	16,87	$C_{22}H_{35}N_3 \cdot 2HCl$	63,80	9,02	10,16	17,15
IX	77	241—2	63,65	8,82	11,16	17,99	$C_{21}H_{31}N_3 \cdot 2HCl$	63,30	8,35	10,54	17,80

*Compounds II–V were recrystallized from heptane; I, VI, and VIII from absolute alcohol; and the hydrochlorides of II–V from a mixture of absolute alcohol and ether.

All the compounds investigated displayed depressant properties in all the tests, except for hypothermic activity (Table 3). The most significant effect is the increase in the duration of narcosis induced by thiopental sodium. The latter property is particularly marked, as is the ability to prolong amphetamine-induced stereotypy. The five compounds V, VIII, X, IV, and III (here and subsequently, the substances are listed in order of decreasing activity) prolong the action of thiopental sodium, the most effective of them (V and VIII) by a factor of 6.7 (4.3-10.4) and 3.7 (3.0-4.5), respectively. Five compounds also cause a noticeable increase in the duration of stereotypic movement (IV, II, III, VII, and X), the most active of them (IV) prolonging stereotypy to the same extent as imipramine: IV and imipramine at a dose of 10 mg/kg increase the duration of stereotypy by a factor of 1.6 (1.3-1.9) and 1.7 (1.5-1.9), respectively. This compound also has a substantial depressant effect on sensitivity to pain. All the compounds have a muscle-relaxant action, the least active being X and II.

EXPERIMENTAL

The mass spectra of the test substances were recorded using an IMS-01-SG2 instrument with an ionizing voltage of 75 eV at a sample temperature of 100-120°.

2-β-Chloropropionyl-5,7-dimethyl-1,2,3,4-tetrahydropyrimido[3,4-a]indole (I). A stirred solution of 1.5 g 5,7-dimethyl-1,2,3,4-tetrahydro[3,4-a]indole and 0.85 g triethylamine in 20 ml absolute ether was treated with an ether solution of 0.9 g β-chloropropionyl chloride. The reaction mixture was heated on a water bath for about 2 h, cooled, and the precipitate filtered off, washed several times with water, and dried in a vacuum desiccator.

2-β-Aminoacyl Derivatives (II-V). A solution of I in absolute benzene or toluene was treated with 3-4 moles of the corresponding amine and boiled for 3-4 h. The mixture was cooled, the hydrochloride of the starting amine filtered off, and the benzene solution washed with water, dried with magnesium sulfate and evaporated. The residue was dissolved in ether and treated with a solution of hydrogen chloride in absolute alcohol or ether to precipitate the hydrochlorides of II-V. Treatment of the hydrochlorides with ammonia solution gave the corresponding bases II-V.

2-γ-Chloropropyl-5,7-dimethyl-1,2,3,4-tetrahydropyrimido[3,4-a]indole (VI). An ether solution of I was treated with an ether solution of lithium aluminum hydride, stirred at 20° for 3 h, decomposed with water, the ether layer separated, and the aqueous layer

TABLE 2. Peak Intensities of Principal Fragments of Compounds I-V (% of maximum peak)

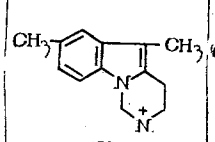
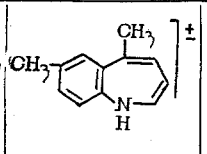
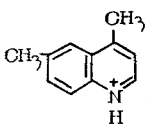
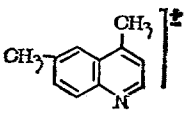
Compound	Fragments (m/e)			
	 199	 157	 171	 158
I	6,0	100	38,3	5,0
II	63,0	70,2	11,4	18,8
III	70,5	32,7	11,1	35,0
IV	100	50,5	27,5	39,4
V	100	46,2	12,4	10,2

TABLE 3. Pharmacological Properties of 2-Substituted 5,7-Dimethyl-1,2,3,4-tetrahydropyrimido[3,4-a]indoles

Compound	Motor activity (movements in 15 min)	Duration of thiopental sodium narcosis (h)	Body temperature (deg)	Duration of amphetamine stereotypy (min)	Change in pain sensitivity (rel. units)	Muscle-relaxant action (rel. units)
Control	163 (144÷182)	6,0 (4,2÷7,8)	32,2 (32,0÷32,4)	90 (83÷96)	0	0
II	166 (127÷204)	3±1,6; $n=7$	31,8 (31,0÷32,6)	122 (108÷136)	0	1,0
III	171 (123÷213)	6,0 (8,8÷11,2)	31,50 (31,47÷31,53)	119 (88÷194)	2,0	2,2
IV	163 (135÷191)	10,0 (3,4÷16,6)	31,50 (31,47÷31,53)	140 (96÷184)	6,0	2,0
V	150 (104÷194)	40,0 (19,8÷60,2)	31,5 (30,4÷32,6)	92 (79÷105)	2,0	2,0
VII	230 (159÷300)	6,0 (5,0÷7,0)	32,2 (31,8÷32,6)	114 (102÷126)	2,0	3,0
VIII	134 (99÷168)	22,0 (19,8÷24,2)	31,2 (30,4÷32,0)	85 (77÷92)	2,0	2,0
IX	95 (63÷127)	7,0 (4,8÷9,2)	31,60 (31,57÷31,63)	90 (59÷120)	2,0	2,0
X	143 (116÷170)	10,0 (3,1÷16,9)	31,8 (31,7÷32,0)	109 (102÷116)	0	1,0

extracted with ether. The combined ether solutions were dried with magnesium sulfate, evaporated, and the residue treated with hydrogen chloride in ether solution to give the hydrochloride of VI.

2-β-Aminoalkyl Derivatives (VII-IX). Method A. An ether solution of III or IV was treated with an ether solution of lithium aluminum hydride, heated on a water bath for 3 h, kept at ~20° for 18 h, decomposed with water, the ether layer separated, and the aqueous layer extracted with ether. The combined ether solutions were dried with magnesium sulfate and evaporated. The residue was dissolved in ether and treated with a solution of hydrogen chloride in absolute alcohol or ether to precipitate the hydrochlorides of VII and VIII, respectively.

Method B. A mixture of 0.5 g of VI and 4 ml of piperidine was boiled for 1 h, the precipitate filtered off, the residue evaporated, and excess piperidine removed by repeated distillation with toluene addition. The remaining oil was extracted with ether, washed with water, dried with magnesium sulfate, and treated with an ether solution of hydrogen chloride to precipitate the hydrochloride of IX. Data on the substances obtained are given in Table 1.

LITERATURE CITED

1. G. N. Artemenko, G. N. Lakoza, I. B. Fedorova, et al., Farmakol. Toksikol., No. 3, 274 (1972).
2. N. K. Barkov and N. F. Kucherova, Khim. Farm. Zh., No. 8, 23 (1972).
3. L. A. Aksanova, L. M. Sharkova, N. F. Kucherova, et al., Khim. Farm. Zh., No. 11, 3 (1971).
4. L. N. Borisova, N. F. Kucherova, T. A. Kartashova, et al., Khim. Geterotsikl. Soedin., No. 5, 645 (1972).