ISOQUINOLINE DERIVATIVES

I. The Synthesis and Pharmacological Evaluation of Some 1-(4'-Alkoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes and Their Ring-opened Analogs

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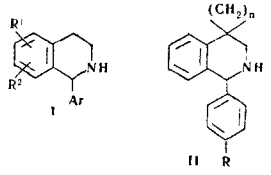
Condensation of p-alkoxybenzoyl chlorides with 1-phenyl-1-aminomethylcyclopentane affords the amides V. Subsequent cyclization and hydrogenation gives the corresponding tetrahydroisoquinoline derivatives VIII and secondary amines VI. The hydrochlorides of compounds VIII and VI possess moderate hypotensive activity, and also reduce by an average of 50% the spasms of segments of intestine, induced by barium chloride.

Among the various isoquinoline derivatives which are widely used as pharmacologically active substances, compounds I with aromatic substituents in position 1 of the isoquinoline ring find wide application [1, 2]. Among compounds of this type, synthetic derivatives as well as those of natural occurrence have attained considerable importance [3–5].

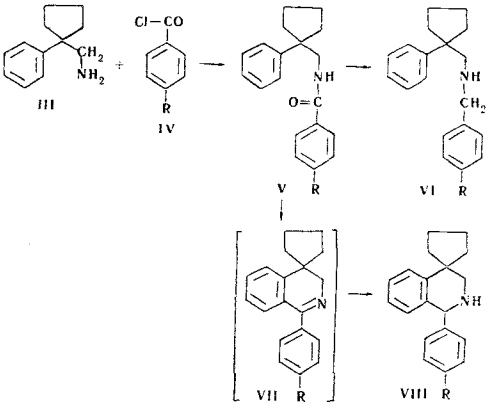
We planned to obtain tetrahydroisoquinolines with the general structure II, where n = 4, and R = H or an alkoxy-group.



The synthesis was carried out starting from 1-phenyl-1-aminomethylcyclopentane III [6] and the p-alkoxybenzoyl chlorides IV [7]. Condensation of these compounds in benzene solution in presence of anhydrous pyridine gave the corresponding N-(4'alkoxybenzoyl)-1-aminomethyl-1-phenylcyclopentanes V. The latter compounds were also obtained by the reaction of an excess of the amine with the acid chloride in benzene. The amides were all colorless, crystalline solids (Table 1).

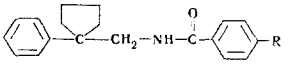
The amides V were further converted into the tetrahydroisoquinoline derivatives VIII and the amines VI with the object of comparing the pharmacological properties of the ring-opened and ring-closed structures. Reduction of the amides V with lithium aluminohydride in ethereal solution afforded the N-(4'-alkoxybenzyl)-1-aminomethyl-1-phenylcyclopentanes VI, which were characterized as their hydrochlorides. All the hydrochlorides were colorless, crystalline solids (Table 2).

Cyclization of the amides V with $POCl_3$ by the Bischler-Napieralski reaction in boiling toluene gave the 1-(4'-alkoxyphenyl)-3,4-dihydroisoquinoline-4-spirocyclopentanes VII, which, because of difficulties in purification, were used in the next stage without purification. In order to separate unreacted amides V from the dihydroisoquinoline, the latter were precipitated as the amorphous or oily hydrochlorides. After decomposition of the salts, the bases were reduced with lithium aluminohydride to the 1-(4'-alkoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes VIII, which were isolated as their colorless, crystalline hydrochlorides (Table 3).



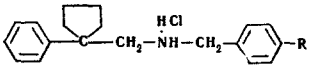
The amines VI and the tetrahydroisoquinolines VIII were submitted for pharmacological evaluation as their

Table 1



R	Mp, °C	Molecular formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
H	105—106	$C_{19}H_{21}NO$	82.02	7.80	4.85	81.68	7.57	5.01	81.5
OCH_3	92—93	$C_{20}H_{23}NO_2$	78.03	7.74	4.70	77.66	7.49	4.52	73.8
OC_2H_5	73—74	$C_{21}H_{25}NO_2$	78.25	7.60	4.12	77.98	7.79	4.33	65.2
OC_3H_7	70—71	$C_{22}H_{27}NO_2$	77.98	7.84	4.19	78.30	8.06	4.15	78.9
$Oi\text{-}C_3H_7$	79—80	$C_{22}H_{27}NO_2$	77.96	8.2	4.31	78.30	8.06	4.15	94.7
OC_4H_9	80—82	$C_{23}H_{29}NO_2$	78.21	8.13	3.73	78.59	8.31	3.81	94.7
$Oi\text{-}C_4H_9$	95—96	$C_{23}H_{29}NO_2$	78.25	8.52	3.60	78.59	8.31	3.81	88.5

Table 2



R	Mp, °C	Molecular formula	Found, %				Calculated, %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
H	216—217	$C_{19}H_{23}N \cdot HCl$	75.60	8.34	4.98	11.34	75.59	8.01	4.64	11.74	71.4
OCH_3	197—198	$C_{20}H_{25}NO \cdot HCl$	72.26	8.14	4.25	10.38	72.37	7.89	4.22	10.68	74.6
OC_2H_5	153—154	$C_{21}H_{27}NO \cdot HCl$	73.25	8.35	3.79	9.74	72.91	8.14	4.04	10.25	76.8
OC_3H_7	170—171	$C_{22}H_{29}NO \cdot HCl$	73.70	8.28	3.94	9.57	73.41	8.40	3.89	9.85	72.4
$Oi\text{-}C_3H_7$	165—166	$C_{22}H_{29}NO \cdot HCl$	73.68	8.63	3.55	10.10	73.41	8.40	3.89	9.85	63.4
OC_4H_9	177—178	$C_{23}H_{31}NO \cdot HCl$	73.95	8.70	3.49	9.90	73.86	8.62	3.74	9.48	64.2
$Oi\text{-}C_4H_9$	215—216	$C_{23}H_{31}NO \cdot HCl$	73.66	8.75	3.76	9.80	73.86	8.62	3.74	9.48	58.7

hydrochlorides. The effects of the compounds on blood pressure and on the contraction of intestine induced by barium chloride were examined by the usual methods. Coronary dilatation was examined in cats narcotized by urethane by the Moravits-Tsan method, as modified by N. V. Kaverina [9].

All the compounds showed a moderate degree of hypotensive activity. In doses of 3–5 mg/kg of animal weight administered intravenously, they briefly reduced the arterial pressure by 10–25 mm of mercury. With the exception of the hydrochloride of VI (R = OC_4H_9), none of the compounds examined possessed significant coronary dilating properties. Compound VI in a dose of 3 mg/kg increased the coronary blood flow by 25–30% for 45–50 min.

Examination of the effect of the compounds on the contraction of isolated intestine induced by barium chloride showed that most of them reduced spasms of segments of intestine by an average of 50% in concentrations of 1.10^{-7} and 1.10^{-6}.

EXPERIMENTAL

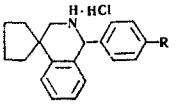
N-(4'-alkoxybenzoyl)-1-aminomethyl-1-phenylcyclopentane (V). a) To 0.1 mole of the p-alkoxybenzoyl chloride in 100 ml of anhydrous benzene was added dropwise during 30 min a mixture of 0.1 mole of III and 0.12 mole of anhydrous pyridine in 100 ml of anhydrous benzene. The mixture was stirred at room temperature for 30 min, then boiled for 4–5 hr. After cooling, the precipitate was filtered off and washed with 80 ml of benzene. The filtrate was washed with 90–100 ml of dilute hydrochloric acid (5 : 1), water (60 ml), 10% sodium carbonate solution (60 ml), then dried over anhydrous sodium sulfate. Unreacted amine and acid were separated from the aqueous washings. The benzene layer was dried over sodium sulfate and the solvent removed. The residue was recrystallized from a mixture of benzene and light petroleum (1 : 1).

b) The amides were obtained similarly by the reaction between 0.1 mole of the acid chloride and 0.2 mole of the amine in benzene solution. The reaction and isolation were as in the preceding example. The IR spectra of V showed bands near 3360 cm^{-1} (NH amide) and near 1638 cm^{-1} (amide C=O).

N-(4'-Alkoxybenzyl)-1-aminomethyl-1-phenylcyclopentanes VI. A solution or suspension of 0.1 mole of the amide V in 100 ml of anhydrous ether was added dropwise with stirring to a solution of 0.2 mole of lithium aluminohydride in 250 ml of absolute ether. The addition was carried out at such a rate that the ether boiled steadily. When the addition was complete (after 20–30 min) the mixture was boiled for 8–10 hr. The mixture was then cooled in ice water, and the reaction complex decomposed with 20 ml of water. The precipitate was filtered off and washed with 80 ml of ether, the filtrate dried over sodium sulfate and the solvent removed to leave a sirupy material. This was dissolved in 150 ml of anhydrous ether and treated at 0–1° C with a dilute (1 : 1) solution of hydrogen chloride in ether. The precipitate was filtered off, washed with anhydrous ether and recrystallized from a mixture of ethanol and ether (1 : 1). The IR spectra showed bands at 2620, 2660, 2740 and 2775 cm^{-1} ($H_2\overset{+}{N}<$).

1-(4'-Alkoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-4-spirocyclopentanes VIII. A mixture of 0.1 mole of the amide V, 20 ml of phosphoryl chloride and 60 ml of dry toluene was boiled under reflux for 20 hr. The excess of phosphoryl chloride and the solvent were removed in vacuo, and the residue treated with 50 ml of water, with cooling, followed by treatment of the solution with ammonia to pH 10–11. The oil which separated was extracted with ether, the extract dried over sodium sulfate, and treated with dilute ethereal hydrogen chloride until acid. The resulting amorphous or oily precipitate was separated, washed with 50 ml of dry ether, dissolved in 40–60 ml of water and the base isolated by treatment with 10% sodium carbonate solution followed by a single extraction with ether. The ether extract was shaken with anhydrous potassium carbonate and the solvent removed under a waterpump vacuum. The oily residue (0.04–0.06 mole) was dissolved in 50 ml of dry ether and the solution added dropwise with stirring to a solution of 0.07–0.08 mole of lithium aluminohydride in 100–120 ml of dry ether. The mixture was boiled for 6–8 hr, then decomposed by the addition of water (about 15 ml) with cooling. The precipitate was filtered off, the ether solution dried over potassium

Table 3



R	Mp, °C	Molecular formula	Found, %				Calculated, %				Yield, %
			C	H	N	Cl	C	H	N	Cl	
H	184—186	$C_{19}H_{21}N \cdot HCl$	76.10	7.20	4.50	11.56	76.10	7.39	4.67	11.82	62.0
OCH_3	219—220	$C_{20}H_{23}NO \cdot HCl$	73.05	7.86	3.88	10.50	72.82	7.33	4.24	10.75	54.7
OC_2H_5	193—194	$C_{21}H_{25}NO \cdot HCl$	73.00	7.70	4.51	10.24	73.34	7.62	4.07	10.31	53.6
OC_3H_7	215—216	$C_{22}H_{27}NO \cdot HCl$	73.81	8.04	3.52	10.24	73.80	7.80	3.91	9.90	52.6
$Oi\text{-}C_3H_7$	187—188	$C_{22}H_{27}NO \cdot HCl$	74.03	8.02	3.60	9.49	73.80	7.80	3.91	9.90	60.1
OC_4H_9	132—133	$C_{23}H_{29}NO \cdot HCl$	74.49	8.60	3.59	9.97	74.27	8.12	3.76	9.53	54.0
$Oi\text{-}C_4H_9$	213—215	$C_{23}H_{29}NO \cdot HCl$	74.53	8.31	3.48	9.86	74.27	8.12	3.76	9.53	52.0

carbonate, and the product precipitated as the hydrochloride by adding ethereal hydrogen chloride, followed by recrystallization from a mixture of ethanol and ether (1 : 1). The IR spectra showed bands near 2620, 2660, 2730 and 1775 cm^{-1} ($H_2\overset{+}{N}$).

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