PIPERIDOL DERIVATIVES OF ETHYNYLPHENOLS

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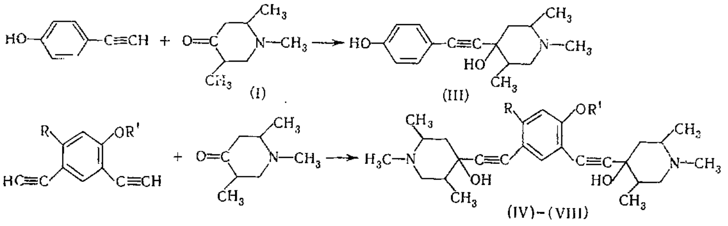
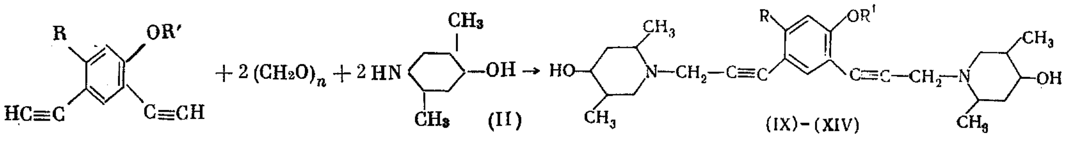
In order to vary the structure of compounds, tested for the presence of cholinergic and germistatic properties in ethynylphenols and their derivatives [1, 2], some ethynylphenols were condensed with 1,2,5-trimethyl-4-piperidone (I) by the Favorskii reaction, and with 2,5-dimethyl-4-piperidol (II) by the Mannich reaction. The Favorskii reaction proceeds initially at −5°, and then at room temperature. An increase in the reaction temperature causes tarring, which is especially noticeable for p-ethynylphenol



R=H, R′=CH_3 (IV), C_3H_7-*n* (V)
R=CH_3, R′=CH_3 (VI), C_3H_7-*n* (VII)
R=OC_3H_7-*n*, R′=C_3H_7-*n* (VIII)

The Mannich reaction is run in the presence of catalytic amounts of Cu_2Cl_2 at 50°, in which connection the ethers of the ethynylphenols give higher yields of the end products than do the ethynylphenols



R=H, R′=CH_3 (IX), C_3H_7-*n* (X)
R=CH_3, R′=CH_3 (XI), C_3H_7-*n* (XII)

TABLE 1

Compound No.	Yield, %	Mp, °C	Found N, %	Empirical formula	Calculated N, %	Hydrochlorides			
						mp, °C	found Cl, %	empirical formula	Calculated Cl, %
III	36,4	196—197	5,53	$C_{16}H_{21}NO_2$	5,40	230	12,17	$C_{16}H_{22}NO_2Cl$	11,93
IV	57	Liquid	6,65	$C_{27}H_{38}N_2O_3$	6,39	195—197	13,79 13,66	$C_{27}H_{40}N_2O_3Cl_2$	13,86
V	65,2	The same	5,90	$C_{29}H_{42}N_2O_3$	6,00	174—175	12,95 12,97	$C_{29}H_{44}N_2O_3Cl_2$	13,14
VI	62,5	" "	6,21	$C_{28}H_{40}N_2O_3$	6,19	200	13,34	$C_{28}H_{42}N_2O_3Cl_2$	13,49
VII	83	" "	5,80	$C_{30}H_{44}N_2O_3$	5,83	190—191	12,89 13,02	$C_{30}H_{46}N_2O_3Cl_2$	12,81
VIII	52	211—212	5,57 5,58	$C_{32}H_{48}N_2O_4$	5,34	220—221	11,82 11 96	$C_{32}H_{50}N_2O_4Cl_2$	11,87

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TABLE 2

Compound No.	Yield, %	Mp, °C	Found N, %	Empirical formula	Calculated N, %	Hydrochlorides			
						mp, °C	found Cl, %	empirical formula	calculated Cl, %
IX	76,7	Liquid	6,37	$C_{27}H_{38}N_2O_3$	6,39	179—180	13,82 13,74	$C_{27}H_{40}N_2O_3Cl_2$	13,87
X	73,7	The same	6,13	$C_{29}H_{42}N_2O_3$	6,00	170	13,11 13,08	$C_{29}H_{44}N_2O_3Cl_2$	13,14
XI	71	179—180	6,18	$C_{28}H_{40}N_2O_3$	6,19	215	13,28 13,29	$C_{28}H_{42}N_2O_3Cl_2$	13,49
XII	86	55—57	6,12	$C_{30}H_{44}N_2O_3$	5,83	210	12,71 13,09	$C_{30}H_{46}N_2O_3Cl_2$	12,81
XIII	72,5	Liquid	5,13	$C_{35}H_{50}N_2O_5$	4,84	140—142	10,8 11,13	$C_{35}H_{52}N_2O_5Cl_2$	10,88

The obtained products are listed in Tables 1 and 2. Their IR spectra correspond to the structure. As a rule, the obtained products represent a mixing of spatial isomers, and for this reason have a broad melting point range. The starting piperidone and piperidol were obtained as described in [3-6]. The preliminary testing disclosed the presence of cholinergic properties for some of the described acetylenic aminophenols.

EXPERIMENTAL METHOD

Propyl Ether of 5-Methyl-2,4-di(2',4',5'-trimethyl-1'-piperidolyl)ethynylphenol (VII). To a cooled to −5° solution of 1.98 g of the propyl ether of 5-methyl-2,4-diethynylphenol and 3 g of 1,2,5-trimethyl-4-piperidone (I) in anhydrous ether was added 3 g of freshly fused KOH powder. A stream of dry N_2 was steadily passed through the reaction mixture. The reaction was run at −5° for 3 h and at 20° for 10 h. The reaction course was followed by means of TLC on Al_2O_3 (II activity), and elution was with the system: alcohol – ether (1 : 1). The ether solution was filtered from the KOH and the ether was removed. We isolated 4 g (83%) of (VII). In a similar manner were obtained (III)-(VI) and (VIII), which are listed in Table 1.

Methyl Ether of 2,4-Di-[3'-N-(2",5"-dimethyl-4"-piperidol)-1'-propynyl]phenol (IX). To a mixture of 2.5 g of 2,5-dimethyl-4-piperidol (II) and 0.6 g of paraform in dioxane – methanol solution were added 1.2 g of the methyl ether of 2,4-diethynylphenol and 0.1 g of Cu_2Cl_2. The reaction was run in a stream of dry pure N_2 for 4 h at 50°. The mixture was decomposed with 30 ml of water, and then extracted with ether. The ether extract was passed through a bed of Al_2O_3, the ether was removed, and the residue was washed with low-boiling petroleum ether. We isolated 1.2 g of (IX).

In a similar manner were obtained (X)-(XII), which are listed in Table 2. The propionate (XIII) was obtained by refluxing a mixture of 5 g of (X), 10 ml of CH_3CH_2COCl and 0.1 g of Mg in 30 ml of anhydrous benzene for 5 h. After neutralization, the organic layer was passed through Al_2O_3, followed by elution with ether. After removal of the solvents we isolated 4.5 g of (XIII) as a viscous liquid. The hydrochlorides of all of the synthesized amines (III)-(XIII) were obtained by the passage of dry HCl through a solution of the amine in anhydrous ether.

CONCLUSION

A number of acetylenic aminophenols and their ethers, representing derivatives of 2,5-dimethyl-4-piperidol and 1,2,5-trimethyl-4-piperidone, was synthesized.

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