SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF ACETYLENIC PIPERIDINEDIOLS

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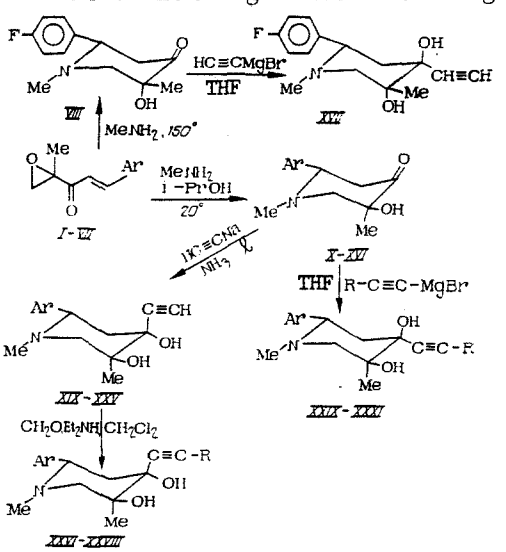
Examination of the pharmacological properties of previously-obtained secondary-tertiary and ditertiary piperine-3,4-diols has shown that some of these compounds have high local anesthetic and n-choline-blocking properties.

We have now extended this investigation to the synthesis and pharmacological activity of aromatic ring-substituted stereoisomeric 6-aryl-3,4-dihydroxypiperidines containing ethynyl substituents in the 4-position of the piperidine ring. The starting 3e-hydroxy-6e-aryl-1,3a-dimethyl-4-piperidones (X-XVI) were obtained by reacting 6-aryl-2-methyl-1,2-epoxypent-4-en-3-ones (I-VII) with methylamine in propan-2-ol [3] at 20°C, and (VIII) by heating the components in benzene in a sealed ampul at 150°C. The synthesis of 3a-hydroxy-1-benzyl-3e-methyl-6e-phenyl-4-piperidone (IX) has been reported [6].

It was found that reaction of sodium acetylide with piperidones (X-XVI) in liquid ammonia resulted in the preferential formation of 3e,4e-dihydroxy-6e-aryl-1,3a-dimethyl-4a-ethynyl-piperidines (XIX-XXV), the ratio of 3e, 4e- to 3e,4a-diols, as found by preparative column chromatography on alumina, being 4:1-7:1. When ethynylmagnesium bromide was used, in addition to the 3e,4e-diols there were also obtained the 6e-aryl-3e,4a-dihydroxypiperidines (XXIX-XXXI) in a ratio of approximately 1:1.

Reaction of the piperidone (VIII) with sodium acetylide in liquid ammonia proceeds cleanly with the quantitative formation of 3a,4a-dihydroxypiperidine (XVII). In contrast to the N-methylpiperidone (VIII), the reaction of sodium acetylide or ethynylmagnesium bromide with the N-benzylpiperidone (IX), which has similar configuration at the carbinol center, gives the opposite stereochemical outcome, namely the formation in near-quantitative yield of 3a,4e-dihydroxy-1-benzyl-3e-methyl-6e-phenyl-4a-ethynylpiperidine (XVIII). The stereochemistry of the reaction of 3-hydroxy-4-piperidones with organometallic reagents has been considered in greater detail in [1].



Ar = Ph (I, X, XIX, XXVI, XXXI),
C_6H_4Me-4 (II, XI, XX, XXVII, XXIX),
C_6H_4Me-2 (III, XII, XXI), $C_6H_3Me_2$-2,4 (IV, XIII, XXII), $C_6H_3Cl_2$-2,4 (V, XIV, XXIII),
C_6H_4OMe-4 (VI, XV, XXIV, XXX),
C_6H_4F-4 (VII, XVI, XXV, XXVIII);
R = H (XXIX, XXX), Ph (XXXI),
CH_2NEt_2 (XVI—XXVIII)

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The structures of the newly-obtained compounds were confirmed by their IR and PMR spectra. The physicochemical and spectral properties of (IX-XI), (XV), (XVI), (XVIII), and (XIX) have been reported [1, 6].

The IR spectra of the piperidones (VIII), (XII), and (XIV) show absorption for the hydroxy (3515 cm^{-1}) and carbonyl (1715 cm^{-1}) groups, and in the PMR spectra the protons of the piperidone ring are seen as three quadruplets (5e-H, 5a-H, and 6a-H) and two AB doublets (2a-H and 2e-H) with constants characteristic of those for a six-membered ring in the chain conformation. The spectral properties of the diols (XVII) and (XX-XXXI) did not differ significantly from those of the benzene ring-unsubstituted compounds, the IR and PMR spectra of which have been reported [2, 4].

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained in CCl_4 on a Specord 75 IR (East Germany), and the PMR spectra of 5-10% solutions in CCl_4 and $CDCl_3$ on Bruker WM-360 (West Germany) and Tesla BS-467A (Czech SSR) spectrometers, internal standard HMDS. The elemental analyses were in agreement with the calculated values.

3a-Hydroxy-1e,3e-dimethyl-6e-(4-fluorophenyl)-4-piperidone (VIII). A solution of 0.02 mole of the acryloyloxirane (VII) in 12 ml of benzene was heated with 0.025 mole of methylamine in an ampul at 150°C for 60 min. The contents were then poured into 40 ml of 5% HCl, the benzene layer separated, and the aqueous layer basified with 30 ml of 10% $NaHCO_3$. The 3e-hydroxy-1e,3a-dimethyl-6e-(4-fluorophenyl)-4-piperidone which separated was extracted with ether. The aqueous solution was basified with 30 ml of 10% potassium carbonate solution, and the piperidone (VIII) which separated was extracted with ether (3 × 20 ml), dried over Na_2SO_4, and the solvent removed. The residue was dissolved in a 5:1 mixture of hexane and ether, and passed through silica gel (2 cm) on a filter. Removal of the solvent and cooling gave the piperidone (VIII) as colorless crystals (Table 1).

3a,4a-Dihydroxy-1e,3e-dimethyl-6e-(4-fluorophenyl)-4e-ethynylpiperidine (XVII). To a solution of ethynylmagnesium bromide, obtained from 0.2 mole of magnesium in 400 ml of THF, was added at 10-15°C a solution of 0.02 mole of the piperidone (VIII) in 100 ml of THF. The mixture was kept at 20°C for 12 h, then decomposed with 50 ml of saturated ammonium chloride solution. The organic layer was separated and dried over Na_2SO_4. After removal of the solvent, the residue was separated by chromatography on alumina sorbent: compound ratio 100:1, eluent ether.

3e,4e-Dihydroxy-6e-aryl-1e,3a-dimethyl-4a-ethynylpiperidines (XIX-XXV). To a suspension of sodium acetylide in 250 ml of liquid ammonia, obtained from 0.2 mole of sodium, was added a solution of 0.02 mole of the piperidone (XI-XVI) in 100 ml of ether. The mixture was stirred for 1 h, the ammonia allowed to evaporate, and the dry residue treated with 300 ml of ether and 50 ml of saturated ammonium chloride solution. The ether layer was separated, dried, the solvent removed, and the diols (XX-XXV) recrystallized from ethyl acetate or a mixture of ethyl acetate and hexane.

3e,4e-Dihydroxy-6e-aryl-1e,3a-dimethyl-4a-(3-diethylaminopropyn-1-yl)-piperidines (XXVI-XXVIII). A mixture of 0.03 mole of the diol (XX or XXV), 1.35 g (0.045 mole) of paraformaldehyde, 3.4 ml (0.33 mole) of diethylamine, and 0.05 g of Cu_2Cl_2 in 50 ml of dioxane was refluxed under argon for 6 h, then cooled and treated with 20 ml of 10% potassium carbonate. The organic layer was extracted with ethyl acetate, dried over Na_2SO_4, the solvent removed, and the residue crystallized from ethyl acetate.

3e,4a-Dihydroxy-6e-aryl-1e,3a-dimethyl-4e-ethynylpiperidines (XXIX, XXX) and 3e,4a-Dihydroxy-(6e-phenyl-1e,3a-dimethyl-4e-(2-phenylethynyl))piperidine (XXXI). To 0.1 mole of the solution of ethynylmagnesium bromide in 200 ml of THF was added a solution of 0.01 mole of the 3-hydroxy-4-piperidone (XI or XV) in 60 ml of THF. The reaction mixture was kept for 12 h, and decomposed with 30 ml of saturated ammonium chloride solution. The organic layer was separated, the THF removed under reduced pressure, and the residue dissolved in ether and dried over Na_2SO_4. After removal of the ether, the mixture of diols were separated by chromatography on alumina (eluent ether), and recrystallized from a 4:1 mixture of hexane and acetone.

Similarly, from the piperidone (X) and phenylethynylmagnesium bromide there was obtained the diol (XXXI).

TABLE 1. Properties of Compounds Obtained

Compound*	Yield, %	mp, °C	Empirical formula
VIII	40	101—3	$C_{13}H_{16}FNO_2$
XII	82	72—2	$C_{14}H_{19}NO_2$
XIII	88	95—6	$C_{15}H_{21}NO_2$
XIV	96	108.5—9.5	$C_{14}H_{15}ClNO_2$
XVII	98	133—4	$C_{15}H_{18}FNO_2$
XX	84	173—4	$C_{16}H_{21}NO_2$
XXI	87	161—2	$C_{16}H_{21}NO_2$
XXII	81	160—1	$C_{17}H_{23}NO_2$
XXIII	75	143—4	$C_{15}H_{17}Cl_2NO_2$
XXIV	85	176—7	$C_{16}H_{21}NO_2$
XXV	84	120—1	$C_{15}H_{18}FNO_2$
XXVI	84	114—5	$C_{20}H_{30}N_2O_2$
XXVII	68	126—7	$C_{21}H_{32}N_2O_2$
XXVIII	71	117—8	$C_{20}H_{29}N_2O_2$
XXIX	14	147—8	$C_{16}H_{21}NO_2$
XXX	16	140—1	$C_{16}H_{21}NO_3$
XXXI	58	172—3	$C_{21}H_{33}NO_2$

*Compounds (IX-XI), (XV), and (XVI) were reported in [3], (XIII) and (XIX) in [6], and (XVIII) in [1].

EXPERIMENTAL (PHARMACOLOGY)

The acute toxicities of the compounds were determined in white mice as described in [7]. The dose of the compound causing 50% mortality on intravenous administration (LD_{50}) was measured.

The central N-choline blocking activity was calculated from the ability of the compounds to prevent a lethal outcome in white mice following administration of a lethal dose (2 mg/kg intravenously) of nicotine. For those compounds which protected more than 50% of the animals from death, the method of Litchfield and Wilcoxon was used to find the mean effective doses (ED_{50}) and the protective index (PI) (the LD_{50}/ED_{50} ratio). The test compounds were administered intraperitoneally 15 min before the administration of nicotine. Choline-blocking activity was compared with that of spasmolytin.

The local anesthetic properties of the compounds were examined in rabbit eye cornea as described in [8], according to which the extent of surface anesthesia is assessed by the number of tactile stimuli required to stimulate the blinking reflex. Aqueous solutions (1, 2, and 5%) of the compounds were used. The active compounds were compared with novocaine.

The test results showed that the acute toxicities of the hydrochlorides of the acetylenic piperidinediols lay in the range 38.6 mg/kg (XVIII) to 377.6 mg/kg (XIX) by the intravenous route (Table 2). The results allow some relationships to be seen between the chemical structures and the toxicities of the test compounds.

For example, (XVII), in which the hydroxy groups are situated diaxially (3a,4a) is more toxic than (XXV) in which they are equatorial (3e,4e), the same relationship being seen in C_4-stereoisomeric diols (XIX) and (XXIX). Increased toxicity is found on passing from N-methyl to N-benzyl acetylenic piperidinediols (XVIII). Compounds (XXVI)-(XXVIII), in which the ethynyl substituent bears a dimethylaminomethyl group, are also more toxic than (XIX), (XX), and (XXV), which have a similar configuration. Changes in the orientation of the —C≡CR groups in the 4-position of the piperidine ring modify the activity (toxicity) of the compounds, as does the introduction of substituents (except fluorine (XXV)) in the aryl radical (the LD_{50} values of the compounds are XIX < XXV < XX < XXI < XXII < XXIII < XXIV).

The toxic symptoms observed in the mice following administration of most of the compounds in doses close to the median lethal dose include tonic-clonic convulsions. Compounds (XXII) and (XXIII) in similar doses have a sedative effect, (XXI) induces a cataleptic state, and (XXXI) causes pronounced salivation. The animals died from prior cessation of respiration, or cardiac arrest.

TABLE 2. Acute Toxicities and N-Choline-Blocking Activity of the Test Compounds

Compound	LD_{50}, mg/kg (intravenous)	Interaction with nicotine		
		% of animals surviving	ED_{50}, mg/kg, (intraperitoneally)	PI
XVII	130,6 (120,0—141,6)	50,0	26,0 (16,6—40,8)	5
XVIII	38,6 (36,6—40,6)	25,0	—	—
XIX	377,6 (345,9—412,1)	66,7	59,0 (42,1—82,6)	6,4
XX	280,5 (259,4—302,7)	0	—	—
XXI	209,4 (176,6—272,3)	16,7	—	—
XXII	195,4 (184,1—207,5)	33,7	—	—
XXIII	73,5 (65,9—81,5)	0	—	—
XXIV	39,2 (36,1—42,5)	0	—	—
XXV	334,2 (316,2—353,2)	66,7	47,0 (28,5—77,6)	7,1
XXVI	108,6 (91,4—124,7)	0	—	—
XXVII	103,0 (97,9—108,4)	16,7	—	—
XXVIII	263,0 (237,1—293,1)	16,7	—	—
XXIX	191,0 (176,2—207,0)	66,7	39,0 (30,9—49,1)	4,9
XXX	261,8 (241,5—283,8)	16,7	—	—
XXXI	87,1 (80,5—94,2)	33,7	—	—
Spasmolytin	68,8 (65,9—71,8)	...	9,0 (4,3—18,9)	6,5
Novocaine*	65—78	...	...	...

*Literature data (Hauschild, 1960).

Most of the compounds showed N-choline blocking activity to varying extents, as shown by their ability to protect animals from death following administration of a lethal dose of nicotine. It was greatest in (XVII), (XIX), (XXV), and (XXIX). In a dose of 20% of the LD_{50}, the latter prevented a lethal outcome following administration of a lethal dose of nicotine in more than half the white mice. The ED_{50} values for these compounds were 26, 59, 47, and 39 mg/kg, and the PI values 5, 6.4, 7.1, and 4.9 respectively. It will be seen that the N-choline blocking activity of these compounds is similar to that of the standard drug spasmolytin (Table 2). There was no apparent relationship between the activities and the chemical structures of these compounds.

Examination of the local anesthetic activity showed that (XXIII) and (XVIII) anesthetize the cornea in rabbits. The Regnier indices for 5% solutions of these compounds were 208.7 ± 34.6 and 355.3 ± 4.7, for 2% solutions, 182.0 ± 24.9 and 117.3 ± 20.1, and for 1% solutions 109.0 ± 13.6 and 34.5 ± 13.6 respectively. In all the concentrations tested, (XXIII) and (XVIII) were more active than novocaine, which is used extensively in the clinic for this purpose. (The Regnier index for the 5% solution was 63.5 ± 11.2, 2% solution 19.4 ± 7.9, and 1% solution 0.)

These novel acetylenic piperidinediols therefore possess high pharmacological activity, and they may be regarded as compounds of low to medium toxicity in accordance with current classifications. Most of them possess central N-choline blocking activity, and some of them are local anesthetics. These results demonstrate the desirability of further synthesis and examination of pharmacological activity in this group of compounds.

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