data on the total biological effect over the concentration range 10^{-3} to 10^{-12} M (see Fig. 1) makes it possible to conclude that an increase in the cataphoretic mobility of the thrombocytes by X-XII and XV adequately increases their resistance to the effect of ADP.

The results constitute evidence for the promising character of the search for antiaggregants in series of hydroxyalkylammonium salts of phenylmercaptoacetic acid derivatives.

LITERATURE CITED

1. E. E. Luscher, Helv. Med. Acta, 50, 5 (1971).
2. G. De Gaetano, J. Vermyler, and M. Veratracte, Nouv. Rev. Franc. Hemat., 11, 339 (1971).
3. K. M. Lakin, in: Current Problems in Hemostasiology [in Russian], Moscow (1979), p. 261.
4. M. D. Mashkovskii, Medicinals [in Russian], 77th edn., Vol. 2, Moscow (1972), p. 137.
5. J. McGiff, Triangle, 20, 27 (1980).
6. W. Siess, P. Roth, and P. Weber, Thrombos., Haemostas., 45, 204 (1981).
7. P. Levine, D. Sladdin, and N. Kirnsky, ibid., p. 290.
8. P. Emmons, M. Harrison, et al., Lancet, 2, 603 (1965).
9. K. Rusanek, C. Svehla, H. Spankova, et al., Activ. Nerv. Sup. (Praha), 9, 448 (1967).
10. F. Fabbria, A. Casonato, M. Randi, et al., Folia Haemat. (Leipzig), 108, 433 (1981).
11. R. MacKenzie and T. Blohm, Trombos. Diathes. Haemorrh. (Stuttgart), 26, 577 (1971).
12. A. N. Zhuravlev and Yu. A. Filippov, Zh. Obshch. Biol., 28, 441 (1967).
13. D. J. Pasto and P. Kent, J. Org. Chem., 30, 2684 (1965).
14. S. S. Kharamonenko, in: Problems in the Biophysics, Biochemistry, and Pathology of Erythrocytes [in Russian], Vol. 1, Krasnoyarsk (1960), p. 447.
15. S. A. Rudchenko, Fiziol. Zh. SSSR, No. 6, 771 (1978).

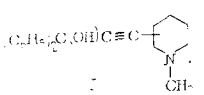
ACETYLENIC AMINOALCOHOLS.

VIII. 3,3-DIPHENYL-3-HYDROXYPROPYNYLPIPERIDINES*

S. G. Kuznetsov, N. M. Libman, V. S. Gorchakov, S. N. Golikov, and É. P. Zatsepin

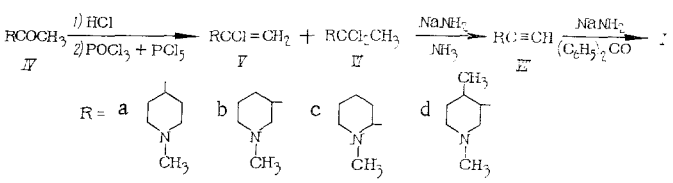
UDC 615.217.34:547.822.3

Continuing our search for acetylenic aminoalcohols with cholinolytic properties, we have synthesized some piperidines with the 3,3-diphenyl-3-hydroxypropynyl group in various positions in the ring (I), together with their hydrochlorides (II) and methiodides (III).



These compounds would be expected to have high physiological activity, and furthermore their quite rigid structure should enable their spatial structures to be established with greater certainty, and hence the effect of the latter on cholinolytic activity.

The preparation of compounds of interest to us was carried out from the appropriate piperidine ketones, as follows:



*For Communication VII, see [1].

Institute of Toxicology, Ministry of Health of the USSR, Leningrad.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 4, pp. 435-440, April, 1984. Original article submitted July 12, 1982.

Although the conversion of methyl ketones into monosubstituted acetylenes is a well-known reaction [2], it has not hitherto been carried out using aminoketones. We have found that it is preferable to convert the aminoketone to its hydrochloride and treat this with phosphorus pentachloride in solution in $POCl_3$. Under these conditions, the chloroolefin (V) or a mixture of this with the dichloride (VI) is formed smoothly. Dehydrohalogenation of the chlorides with sodamide in liquid ammonia affords the ethynylpiperidines (VII). Condensation of the sodium salts of the latter with benzophenone proceeded in high yield only when the ammonia was replaced by ether, and the ether solution boiled for several hours. We have, however, observed similar behavior in the condensation of aminobutynes with benzophenone [3].

The acetylpiperidines used as starting materials in the synthesis of the acetylenic aminoalcohols were preferably obtained by reducing the appropriate pyridine ketones (VIII), obtained in turn from the pyridinecarboxylic esters and ethyl acetate [4].

The preparation of (IVb) proceeded with the greatest ease. 3-Acetylpyridine is readily converted into the quaternary salt, which undergoes hydrogenation in high yield to the aminoketone (IVb). In the case of the 4-isomer reduction, except in the case of the ketone (IVa), gave substantial amounts of 1-methyl-4-(1'-hydroxyethyl)piperidine (IXa), the latter being oxidized without isolation with chromic anhydride. 2-Acetylpyridine could not be quarternized, and it was reduced directly, the sole reaction product being 2-(1'-hydroxyethyl)piperidine (Xc). In the present instance, this fact was even of value, since methylation of the piperidine ring in the alcohol (Xc) proceeded without complications, whereas side reactions could occur with the ketone. The methylation product, 1-methyl-2-(1'-hydroxyethyl)piperidine (IXc), was oxidized in the usual way with chromic anhydride to the ketone.

The aminoketone (IVd) was obtained from the readily-accessible mixture of Δ^2- and Δ^3-1,4-dimethyl-3-acetylpiperidines [5]. Reduction of the mixture, in contrast to the preparation of (IVb), gave 1,4-dimethyl-3-(1'-hydroxyethyl)piperidine only, which was oxidized to the ketone (IVd).

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a UR-20 spectrometer, LiF prisms, cell thickness 1 mm, with NaCl windows; solutions in CCl_4 of concentration 1-2% were employed. Thin-layer chromatography (TLC) was carried out with Silufol plates (developed in the system alcohol—20% aqueous ammonia 5:1) or on unbound Al_2O_3 layers (developed with ether). The spots were visualized with Dragendorf's reagent or iodine vapor. For gas—liquid chromatography (GLC), a Tsvet-6 chromatograph was used, 2 m × 2 mm columns (packed with 3% E-301 on Chromaton) and 0.5 m × 2 mm columns (packed with 1% E-301 on Chromaton). Melting points were determined using a Boetius apparatus.

4-Acetylpyridine (VIIIa). This was obtained from ethyl isonicotinoate and ethyl acetate as described in [4]. Yield 48%, bp 76-77°C (7 mm).

1-Methyl-4-acetylpiperidine (IVa). 4-Acetylpyridine (11.6 g; 100 mmole) was treated with 7.5 ml (100 mmole) of methyl iodide in 15 ml of acetone to give 24.5 g (97%) of the crystalline quaternary salt, mp 172-174°C. This (24.5 g; 90 mmole) was hydrogenated in 100 ml of 50% alcohol over 1 g of PtO_2 at 70°C for 6-7 h. After removal of the catalyst and the solvent, the residue was basified with 50% potassium carbonate solution, and extracted repeatedly with ether. After drying and removal of the solvent, there was obtained 5.9 g of a mixture of the ketone (IVa) and 1-methyl-4-(1'-hydroxyethyl)piperidine in approximately equal amounts (TLC, GLC, and the IR spectrum).

The mixture of the ketone and the alcohol was dissolved in 10 ml of 20% H_2SO_4 and treated with a solution of 3 g of chromic anhydride in 10 ml of dilute acid. The mixture was heated on the water bath for 3 h, cooled, treated with potassium sodium tartrate, and basified with potassium carbonate. Continuous extraction with ether for 12 h followed by drying and removal of the solvent afforded 4.43 g (30% calculated on acetylpyridine) of the ketone (IVa), which was homogeneous by TLC and GLC.

1-Methyl-4-ethynylpiperidine (VIIa). The ketone (IVa) (7.64 g, 50 mmole) was dissolved in aqueous HCl, the water removed, and the residue thoroughly dried *in vacuo*. The solid salt was dissolved in 15 ml of phosphoryl chloride, and to the solution was added 14.6 g (70 mmole) of phosphorus pentachloride. A spontaneous reaction commenced almost immediately, and when this had subsided the mixture was heated to 90°C and kept at this temperature for 3 h. Phos-

TABLE 1. Acetylenic Aminoalcohols and Their Salts

Compound	Yield, %	mp, °C, and solvent for crystallization	Found (mean of two determinations), %					Empirical formula	Calculated, %				
			C	H	Cl	I	N		C	H	Cl	I	N
Ic	71	140—141, toluene	82,59	7,60	—	—	4,50	$C_{21}H_{23}NO$	82,57	7,61	—	—	4,59
IIc		207—208 (decomp.), ethanol	...	...	10,36	—	...	$C_{21}H_{24}ClNO$			10,37	—	
IIIc		195,5—197, ethanol	...	...	—	28,71	...	$C_{22}H_{26}INO$			—	28,37	
Ib	65	194,5—195, toluene	82,42	7,79	—	—	4,65	$C_{21}H_{23}NO$	82,57	7,61	—	—	4,59
IIb		201—202 (decomp.), ethanol + ethyl methyl ketone	...	...	10,55	...	...	$C_{21}H_{24}ClNO$			10,37	—	
IIIb		213—214, ethanol	...	...	—	28,52	...	$C_{22}H_{26}INO$			—	28,37	
Ia	73,7	189—190, toluene	82,69	7,74	...	...	4,61	$C_{21}H_{23}NO$	82,57	7,61	—	—	4,59
IIa		192—194, ethanol + ether	...	...	10,37	—	...	$C_{21}H_{24}ClNO$			10,37	—	
IIIa		216—217, ethanol	...	...	—	28,55	...	$C_{22}H_{26}INO$			—	28,37	
Id	70	174—185, toluene	82,91	7,87	—	—	4,50	$C_{22}H_{25}NO$	82,70	7,90	—	—	4,39
IId		219—220 (decomp.), ethanol	...	...	10,13	—	...	$C_{22}H_{26}ClNO$			9,96	—	
IIId		239—240 (decomp.), ethanol	...	...	—	27,46	...	$C_{23}H_{28}INO$			—	27,51	

TABLE 2. Cholinolytic Activity and Nitrogen—Carbonol Carbon Distances for Acetylenic Aminoalcohols

Compound No.	Salt	M cholinolytic activity (ED_{50}, mg/kg)		N cholinolytic activity (ED_{50}, mg/kg)	Toxicity (LD_{50}, mg/kg)	Nitrogen—carbinol distance in conformers, nm	
		peripheral	central			equatorial	axial
IIc	HC	8,30	2,35	—	—	0,47	0,47
IIIc	MI	0,24	—		—		
IIb	HC	12,20	70	—	—	0,61	0,49
	MI	0,1	—	—	—		
IIa	HC	1,1	0,72	—	350	0,71	0,56
	MI	0,01	—		—		
IId	HC	—	—	—	—	0,61	0,49
XII	HC	1,8	2	3	530	0,47	
XIII	HC	2,3	2,6	3	530	0,64	0,48*
XIV	HC	7,3	2,8			0,47	

*The maximum and minimum possible distances are shown.

Note. HC is hydrochloride, and MI methiodide; a dash indicates that no activity was observed.

phosphoryl chloride was distilled off *in vacuo*, the residue dissolved with cooling in a small amount of water, the solution basified with 50% potassium carbonate solution, and extracted three times with ether. Distillation gave 7.25 g (84%) of chromatographically homogeneous (TLC, GLC) product, bp 57-59°C (3 mm); n_D^{20} 1.4921. From its IR spectrum, the compound was 1-methyl-4-(1'-chlorovinyl)piperidine (Va) (absorption at 1650 and 3080 cm^{-1}).

A solution of 7.2 g (30 mmole) of (Va) in 20 ml of dry ether was added over 10 min to a suspension of sodamide in liquid ammonia [from 4.1 g (180 mmole) of Na and 100 ml of NH_3]. After stirring for 4 h and removal of the bulk of the ammonia, the mixture was decomposed with ammonium chloride and a small amount of water. The product was extracted three times with ether, dried over potassium carbonate, and distilled to give 4.41 g of (VIIa) (80%, 67% over both stages), mp 67-68°C (31 mm); n_D^{20} 1.4693. IR spectrum, ν, cm^{-1}: 2100 weak, 3318 strong. The product was homogeneous by TLC and GLC.

1-Methyl-4-(3'-hydroxy-3',3'-diphenylpropyn-1'-yl)piperidine (Ia). A solution of 1.23 g (10 mmole) of (VIIa) in 10 ml of dry ether was added to a suspension of sodamide in liquid ammonia [from 0.6 g (30 mmole) of sodium and 75 ml of NH_3]. After half an hour, a solution of 4.5 g (20 mmole) of benzophenone in 30 ml of ether was added, and after complete evaporation of the ammonia the mixture was boiled under reflux for 4 h, cooled, and 4-6 drops of water added. The solid which separated was filtered off, washed with water followed by 10 ml of ether. After air-drying, there was obtained 2.3 g of (Ia). The combined aqueous ethereal extracts were treated with HCl until definitely acid, washed with ether, basified, extracted with chloroform, dried over potassium carbonate, and evaporated. A further 0.19 g of product was obtained, the total yield of unpurified (Ia) beong 81.5%.

Hydrochloride Ia (IIa). The base (1.25 g, 4 mmole) and a small excess of 35% alcoholic HCl were added portionwise to 10 ml of alcohol. The resulting salt was precipitated by adding a tenfold amount of ether.

Methiodide Ia (IIIa). The base (0.33 g, 1 mmole) and 0.5 ml of methyl iodide in 3 ml of alcohol were kept for 3 days. The salt was precipitated with ether.

3-Acetylpyridine (VIIIb). This was obtained as for (VIIIa), yield 49%, bp 68-70°C (2 mm).

1-Methyl-3-acetylpiperidine (IVb). This was synthesized as for the ketone (Va). Since the alcohol was not formed on reduction of the quaternary salt, the oxidation stage was omitted. The ketone (65%) was obtained, pure by TLC and GLC, bp 69-71°C.

1-Methyl-3-ethynylpiperidine (VIIb). This was obtained similarly to (VIIa). Yield 65%, bp 65-67°C (25 mm); n_D^{20} 1.4687; IR spectrum, ν, cm^{-1}: 2113 w, 3322 s. The product was homogeneous by TLC and GLC.

1-Methyl-3-(3'-hydroxy-3',3'-diphenylpropyn-1'-yl)piperidine (Ib) and its hydrochloride (IIb) and methiodide (IIIb) were obtained as for (Ia), (IIa), and (IIIa).

2-Acetylpyridine (VIIIc) was obtained as described for (VIIIa). Yield 69%, bp 95-97°C (30 mm).

1-Methyl-2-acetylpiperidine (IVc). Ketone (VIIIc) was reduced in glacial acetic acid over PtO_2, to give 72.5% of 2-(1-hydroxyethyl)piperidine (Xc), bp 88-115°C (15 mm). This (6 g, 43 mmole) was heated for 18 h with 6.5 g (140 mmole) of formic acid and 6 ml (80 mmole) of formalin. Following evaporation, basification with 50% potassium carbonate solution, drying, and distillation, there was obtained 5.68 g (85%) of 1-methyl-2-(1'-hydroxyethyl)-piperidine (IXc), bp 90-97°C (19 mm).

The alcohol (IXc) was oxidized to the ketone in the same way as the alcohol (IXa), the yield of ketone (IVc) being 83.5% (51.4% over all three steps), bp 75-80°C (13 mm).

1-Methyl-2-ethynylpiperidine (VIIc). This was obtained from ketone (IVc) the same way as for the acetylene (VIIa). Yield 61%, bp 49-51°C (12 mm); n_D^{20} 1.4688. IR spectrum, ν, cm^{-1}; 2105 w, 3318 s. The product was homogeneous by TLC and GLC.

1-Methyl-2-(3'-hydroxy-3',3'-diphenylpropyn-1'-yl)piperidine (Ic) and its Hydrochloride (IIc) and Methiodide (IIIc). These were synthesized as for (Ia), (IIa), and (IIIa).

1,4-Dimethyl-3-acetylpiperidine (IVd). 1,4-Dimethyl-3-acetyl-Δ^3-piperidine [5] was reduced catalytically to 1,4-dimethyl-3-(1'-hydroxyethyl)piperidine in 67.7% yield, bp 121°C (11 mm). This alcohol was oxidized to the ketone as described for (IVa). Yield 55% (37.2% over the two steps), bp 68-69°C (4 mm).

1,4-Dimethyl-3-ethynylpiperidine (VIId). This was obtained from ketone (IVd) in the same way as the other ethynylpiperidines. Yield of (VIId) 61%, bp 69-70°C (30 mm); n_D^{20} 1.4652. IR spectrum, ν, cm^{-1}: 2115 w, 3300 m. The product was homogeneous by GLC and TLC.

1,4-Dimethyl-3-(3'-hydroxy-3',3'-diphenylpropyn-1'-yl)piperidine (Id) and Its Hydrochloride (IId) and Methiodide (IIId). These were obtained as described for (Ia), (IIa), and (IIIa).

The properties of the compounds obtained are given in Table 1.

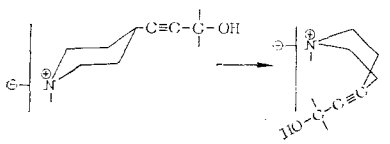
EXPERIMENTAL PHARMACOLOGY

The cholinolytic activity of the acetylenic aminoalcohols obtained was studied in white mice using the arecoline model [6]. Antinicotinic effects were determined in rabbits by the method of Bovet and Longo [7]. Toxicities were also determined in white mice, by the subcutaneous route. As a result of the low water solubilities of the salts, it was only possible to determine the toxicity of (IIa). The results are shown in Table 2, which also shows for comparison the pharmacological properties of the hydrochlorides of 1,1-diphenyl-4-diethylaminobut-2-yn-1-ol (XII) [8], 1,1-diphenyl-5-diethylaminopent-2-yn-1-ol (XIII) [8], and 1,1-diphenyl-4-(2'-methylpyrrolidino)but-2-yn-1-ol (XIV) [1].

Discussion of Results. The m-cholinolytic activity of the test compounds varied widely. In all probability, the main reason for this is the different relative positions of the amino-nitrogen and the carbon atom bearing the hydroxyl and cyclic radicals (i.e., the carbinol carbon), and the distances between these are given in Table 2. On this basis, the cholinolytic activities of isomers 2 and 3 are generally speaking close to the expected values. In fact, (IIa) is analogous to the aliphatic aminobutyl (XII), the nitrogen-carbinol carbon distances in the equatorial and axial arrangements of the unsaturated substituent in the former being the same, and equal to that in the aminoalcohol (XII). In (IIa), however, one of the atoms adjacent to the nitrogen is tertiary, and consequently, although its central cholinolytic activity differs little from that of (XII), its peripheral activity, in conformity with previously-observed behavior [1], is much less. It is noteworthy that the active doses of (IIa) are virtually the same as those found for the aminobutyl (XIV), which is also branched in one of the positions α to the nitrogen.

This is not the case with isomer 3. This is an analog of the aminopentynol (XIII), but as a result of the relative rigidity of the piperidine ring the distance from the carbinol carbon to the nitrogen can assume only two fixed values, that for the less favored axial conformer being as much as 0.49 nm, and in the stable equatorial form it is much greater. This is probably the reason for the fact that (IIb) displays much lower cholinolytic activity than (IIa), and that the aminopentynol (XIII) is less active than the aminobutyl (XII).

The nitrogen–carbinol carbon distance in the axial and equatorial arrangements of the side chain in the aminoalcohol (IIc) exceeds the values for (IIa). This is not in accord with the high biological activity of the compound, which substantially exceeds the activity of both of the other isomers. Unlike these, however, in the compound in question transition of the piperidine ring into the usually disregarded boat conformation enables the nitrogen and carbinol carbon atoms to approach each other much more closely. In this conformation, when the substituent is axially disposed, the distances between them is 0.36 nm, which is very close to the value (0.37 nm) of the distance which has been suggested as being optimal [9]. It appears likely that the adoption of this conformation facilitates efficient contact between the receptor and the ligand, and is responsible for the high activity of the compound. It is of the greatest importance that the molecule has no prior need to adopt the active conformation, since this can be formed directly at the receptor. The process may be represented as follows:



The aminoalcohol molecule in the energetically most favored chair form with an equatorial unsaturated chain approaches the choline receptor, and its nitrogen forms a bond with the

anionic center. The piperidine ring thereupon undergoes the chair–boat transition, as a result of which the hydroxyl and cyclic radicals also come into contact with the surface of the receptor. This transition does not require a high activation energy (in unsubstituted cyclohexane, it is approximately 42 kJ/mole), and therefore the conformational transitions under the experimental conditions proceed at a high rate. The energetically-unfavored boat conformation (around 23 kJ/mole for cyclohexane) may be compensated for by the acquisition of energy from the interactions of the hydroxyl group and the benzene rings with the appropriate receptor structures. The reason for the extremely low biological activity of (IId) may be discerned in the unfavorable steric effect of the tertiary substituent in the piperidine ring. Compound (IIb) already possesses the lowest cholinolytic activity of any of the isomers, and the additional steric hindrance probably still further complicates its interaction with the receptor, which is also manifested in the disappearance of cholinolytic properties.

An interesting feature of this group of compounds is the absence of central n-cholinolytic activity, in sharp contrast to the aminoalcohols with an open chain, in which the combination of m- and n-cholinolytic activity is highly characteristic [8]. This observation is all the more surprising in that many acetylenic amines of varied structure display marked central n-cholinolytic activity which is largely independent of the molecular structure [10]. We are unable at the present time to offer an explanation for this behavior of these aminoalcohols.

LITERATURE CITED

1. N. M. Libman, S. G. Kuznetsov, and S. I. Loktionov, Khim.-farm. Zh., No. 9, 35-39 (1969).
2. T. L. Jacobs, in: Organic Reactions [Russian translation], Moscow (1951), Vol. 5, p. 25.
3. N. M. Libman and S. G. Kuznetsov, Zh. Obshch. Khim., 31, 2283-2289 (1961).
4. N. S. Vul'fson, V. E. Kolchin, and L. K. Artemchik, ibid., 32, 3382-3387 (1962).
5. F. F. Blik, in: Organic Reactions [Russian translation], Moscow (1948), Vol. 1, p. 400.
6. S. N. Golikov, Farmakol. Toksikol., No. 2, 38 (1956).
7. B. Bovet and V. D. Longo, J. Pharmacol. Exp. Ther., 102, 22-25 (1951).
8. M. A. Razumova, Farmakol. Toksikol., No. 2, 153-158 (1965).
9. S. G. Kuznetsov and S. N. Golikov, Synthetic Atropinelike Compounds [in Russian], Leningrad (1962), p. 162.
10. S. N. Golikov, M. A. Razumova, and A. T. Selivanova, Farmakol. Toksikol., No. 1, 20-23 (1965).

SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF SOME QUINOLINE DERIVATIVES

P. V. Prisyazhnyuk, V. K. Patratii, N. G. Prodanchuk, K. G. Tashchuk, and S. D. Fedoryak

UDC 615.281:547.831].012.1

In view of the wide spectrum of biological activity of numerous quinoline derivatives [1], searches in this series for new physiologically active compounds as potential drugs hold promise.

As has already been reported [2, 3], the cyclic 1,2,3-tricarbonyl compounds alloxan, 1-methyl- and 1,3-dimethyl alloxan, ninhydrin, and their oximes react readily with quaternary 2- and 4-methylquinolinium salts to give condensation products the structure of which is dictated by the synthetic conditions and the structures of the reactants.

This communication describes a study of the reactions of 2,3,4-trioxo-1,2,3,4-tetrahydroquinoline (quinisatin) and its 3-oxime, which contain simultaneously structural fragments of the previously-studied alloxan, ninhydrin, and their derivatives, with 1-aryl(alkyl)-2(4)-methylquinolinium quaternary salts.

It was found that quinisatin reacts with quinaldinium and lepidinium quaternary salts less vigorously than derivatives of alloxan and ninhydrin. Thus, on brief boiling in glacial

Chernovits Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 4, pp. 440-444, April, 1984. Original article submitted June 28, 1983.

0091-150X/84/1804-0258$08.50