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# AMINO ALCOHOLS OF THE ACETYLENE SERIES.

# X. 1-PHENYL-1-SUBSTITUTED ARYL(HETARYL)-4-DIALKYLAMINO-2-BUTYN-1-OLS

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We have previously developed methods for preparing substituted 1,4-aminobutynols, and have synthesized a series of these compounds, including amino alcohols with two phenyl residues at the carbinyl carbon atom [5]. Studies of the pharmacological properties of these compounds showed them to have choline-blocking activities [2, 8]. Further studies for acetylene amino alcohols with cholinergic activity have involved preparation of more aminobutynols in which one of the cyclic radicals consists of a phenyl group and the other is a substituted phenyl or heterocyclic reside. Preparation of this type of amino alcohol was carried out using methods as described in [5], i.e., aminomethylation of substituted propynols (I-XII) using the Mannich reaction in the presence of catalytic quantities of copper compounds.

$$\underset{\text{I—XII}}{C_6H_5C(Ar)C(OH)C{\equiv}CH} + CH_2O + HNR_2 \longrightarrow \underset{\text{XIII—XXVI}}{C_6H_5(Ar)C(OH)C{\equiv}CCH_2NR_2}$$

The properties of the resulting aminobutynols and their salts are shown in Table 1, and pharmacological results are shown in Table 2. These show that all compounds with substituents in one of the phenyl residues (XIII-XXII) had relatively low activity as m-cholinoblockers, but also had low toxicity. Most of them have significantly less antimuscarinic activity than the corresponding analogs in which both cyclic radicals at the carbonyl carbon are phenyl groups (XXIX), i.e., any substitution of the hydrogen atom in the benzyl moiety has unfavorable effects on the affinity of the molecule for the receptor. This reduction in activity probably results from steric hindrance, as the reduction in m-cholinoblocking activity paralleled increases in the volume of the substituent in the ring. This was especially clear when the n-halogen-substituted amino alcohols XIX-XXI were compared. Further evidence is the similarity in the m-cholinoblocking activities of compounds XV and XX, in which the electronic properties of the substituents, i.e., Cl and $CH_3$ respectively, are different while their volumes are essentially the same.

The most active m-cholinoblocking compounds among the amino alcohols studied here were the fluoro-substituted compounds, especially the o-isomer XVIII, which was half as active as the unsubstituted amino alcohol XXIX. This property of the fluorosubstituted amino alcohols is probably a result of the fact that the size of the fluorine atom makes this substitution the smallest (after hydrogen), so that steric hindrance to contact of the molecule with the receptor surface is minimal. Electronic factors undoubtedly play a significant role in the differences in the properties of o- and n-isomers. In fact, the fluorine atom in compound XVIII is close to the polar structure in the receptor, which comes into contact with the hydroxyl groups of cholinolytic agents, and it is possible that it also takes part in some kind of binding interaction with this structure; this interaction is not possible for fluorine atoms in position 4.

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TABLE 1. Acetylene Aminobutynols XIII-XXVI and Their Hydrochlorides

| Compound | Ar | Yield, % | Melting temperature, °C, and solvent for crystln. | | Atomic formula of base |
|---|---|---|---|---|---|
| | | | base | hydrochloride | |
| XIII | 2-Tolyl | 85,5 | 126—127, Octane | 196—199, Acetone + ethanol | $C_{22}H_{25}NO$ |
| XIV | 3-Tolyl | 84 | 116,5—117, Octane | 193—194(Unstab.)dichloro | $C_{22}H_{25}NO$ |
| XV | 4-Tolyl | 84 | 126,5—127, Octane | 178—179, Acetone | $C_{21}H_{25}NO$ |
| XVI | 2,5-Dimethylphenyl | 86 | 129,5—131,5,Nonane | 232—233(Unstable) butanol | $C_{22}H_{27}NO$ |
| XVII | 3,5-Dimethylphenyl | 88 | 124—125, Cyclohexane | 176—177, Acetone | $C_{22}H_{27}NO$ |
| XVIII | 2-Fluorophenyl | 79 | 123,5—124, Heptane | 201—202,Isopropanol | $C_{21}H_{22}FNO$ |
| XIX | 4-Fluorophenyl | 74 | 127,5—128, Heptane + acetone | 193,5—195,5, Isopropanol | $C_{21}H_{22}FNO$ |
| XX | 4-Chlorophenyl | 58 | 79—80,5, Hexane | 155—156,Ethyl acetate | $C_{21}H_{22}ClNO$ |
| XXI | 4-Bromophenyl | 80,5 | 124—125, Cyclohexane | 192—194, Isopropanol | $C_{21}H_{22}BrNO$ |
| XXII | 4-Biphenyl | 83 | 153,5—154,5, Isoproanol | 218—219, Butanol | $C_{27}H_{27}NO$ |
| XXIII | 3-Pyridyl | 85,5 | 83,5—84 Heptane | [6] | $C_{19}H_{22}N_2O$ |
| XXIV | 3-Pyridyl | 80 | 124 , Heptane | [6] | $C_{19}H_{20}N_2O$ |
| XXV | 2-Thienyl | 49 | 96,5—97,5, Heptane | 134—135 (unstable)[d], acetone + ether | $C_{18}H_{21}NOS \cdot HCl$ |
| XXVI | 2-Thienyl | 63 | 130—130,5, Dibutyl ether | 137—138 (unstable)[e], ethanol + ether | $C_{18}H_{19}NOS \cdot HCl$ |

$NR_2$ = piperidino (XIII-XXII), $N(C_2H_5)_2$(XXIII, XXV), pyrrolidinyl-1 (XXIV, XXVI).
Notes. [a]Published melting point = 81.5°C [10]; [b]the hydrochloride did not crystallize; [c]Published melting temperature was 124-125°C [10]; [d]data from patent [7], giving melting temperature of 86-88°C; published values for base = 102°C (90% ethanol) and for hydrochloride = 132-133°C (ethanol + ether) [11]; [e]published melting temperature for base = 126-127°C [7] and 128°C [10], for the hydrochloride = 146-148°C [11].

TABLE 2. Pharmacological Activity of Hydrochlorides of Substituted Aminobutynols XIII-XXVI

| Compound | $LD_{50}$, mg/kg (i.p.) | a-Cholinoblocking activity ($ED_{50}$, mg/kg) | | n-Cholinoblocking activity |
|---|---|---|---|---|
| | | central | peripheral | |
| XIII | 280±112 | 60±24 | >100 | >8 |
| XIV | 500[a] | 35,5±16,4 | 30 | >8 |
| XV | 330±66 | 41±24 | 36±25 | >8 |
| XVI | ... | >50 | >50 | ... |
| XVII | ... | 50 | 47 | >8 |
| XVIII | 250 | 3±2,1 | 2,4±2,1 | >8 |
| XIX | ... | 7,9±6,1 | 40±24 | >8 |
| XX | >1000[b] | 29,5±3 | 26,5±3 | >8 |
| XXI | ... | >100 | >100 | ... |
| XXII | ... | >100 | >100 | ... |
| XXIII | 476±17 | 6,82±0,8 | 2,5±0,4 | >10 |
| XXIV | 530±33 | 2,3±0,17 | 1,4±0,26 | >10 |
| XXV | 610±46 | 1,65±0,16 | 2,0±0,37 | >10 |
| XXVI | >500 | 1,35±0,14 | 1,5±0,13 | >10 |
| XXVII[c] | 210[d] | 5,4 | 6,8 | 3 |
| XXVIII[c] | 290[f] | 3,5 | 5,0 | 3 |
| XXIX[g] | >600 | 1,8 | 1,2 | 2—2,5 |

Notes. [a]$ED_{100}$; [b]S.c.; [c]$(C_6H_5)_2C(OH)C{\equiv}CCH_2N(C_2H_5)_2 \cdot HCl$; [d]S.c. 530 mg/kg; [e]$(C_6H_5)_2C(OH)C{\equiv}CCH_2$-pyrrolidinyl-1·HCl; [g]$(C_6H_5)_2C(OH)C$-$CCH_2$-piperidino·HCl.

Substitution of one of the phenyl groups in compounds XXVII and XXVIII with a heterocyclic residue (amino alcohols XXIII-XXVI) generally increased m-cholinoblocking activity, which agrees with results obtained with other classes of cholinolytics [3]. Since the thienyl and pyridyl groups are sterically similar to the phenyl group, the electronic structures of these residues clearly play an important role in this increase in activity. Their electronegativity is greater than that of the phenyl group, which must result in stronger polarization of the hydroxyl group, increasing its ability to donate a proton to the hydrogen bond, which in turn must stabilize the amino alcohol-cholinoreceptor complex.

These compounds had virtually no n-cholinoblocking activity. This is not surprising in the case of amino alcohols XIII-XXII, as previously discovered relationships [2] suggest that weak m-cholinoblocking activity in this type of compound is accompanied by weak n-cholinoblocking activity. However, the absence of n-cholinoblocking effects in the effective m-chol-

TABLE 3. Substituted Propynols $C_6H_5(Ar)C(OH)-C\equiv CH$[a]

| Compound | Ar | Yield, % | Boiling tem., °C(mm Hg), melting temp. °C (solvent for crystallization) | Atomic formula |
|---|---|---|---|---|
| I | 2-Tolyl | 76 | 151—153 (3) | $C_{16}H_{14}O$ |
| II | 3-Tolyl | 80 | 161—162 (3) | $C_{16}H_{14}O$ |
| III | 4-Tolyl | 94 | 155—159 (3) | $C_{16}H_{14}O$ |
| IV | 2,5-Dimethylphenyl | 90 | 155—156 (3) | $C_{17}H_{16}O$ |
| V | 3,5-Dimethylphenyl | 60 | 166—169 (4) | $C_{17}H_{16}O$ |
| VI | 2-Fluorophenyl | 66 | 165—170 (10) | $C_{15}H_{11}FO$ |
| VII | 4-Fluorophenyl | 96 | 145—146 (4) | $C_{15}H_{11}FO$ |
| VIII | 4-Chlorophenyl | 87 | 161—164 (4) | $C_{15}H_{11}ClO$ |
| IX | 4-Bromophenyl | 92 | 174 (3,5) | $C_{15}H_{11}BrO$ |
| X | 4-Biphenyl | 85 | 79—82(acetone hexane) | $C_{21}H_{16}O$ |
| XI | 3-Pyridyl | 76 | 166—168 Xylene | $C_{14}H_{11}NO$ |
| XII | 2-Thienyl | 60 | 138—142 (1) 45—45,5(Acetone + hexane) | $C_{13}H_{11}OS$ |

Notes. [a-c]The IR spectra of the carbynols showed weak bands in the range 2110-2120 $cm^{-1}$ (C≡C), medium-strong bands at 3310-3315 $cm^{-1}$ (valence vibration≡C–H), and wide bands at 3460-3500 $cm^{-1}$ and a band at 3580-3610 $cm^{-1}$ (bound and free OH groups).

inoblockers XXIII-XVI is difficult to explain, especially in view of the fact that the thiophene and pyridine moieties are very similar to the phenyl residue. We can only note that other acetylene amino alcohols, derivatives of 1-methylpiperidine [4] and quinuclidine [6], also lacked anti-nicotinic effects.

All these compounds had low acute toxicity, which was virtually identical to the toxicity of agents with two phenyl residues (XXVII-XXIX). No relationship was found between toxicity and cholinoblocking activities.

## CHEMICAL METHODS

IR spectra were recorded on a UR-20 spectrometer using an LiF prism, and a 1-mm NaCl cuvette. Solutions were studied in $CCl_4$ at concentrations of 1-2%. Melting temperatures were determined in a Boetius apparatus.

Disubstituted propynols I-XII were prepared by a previously described method [12] by reaction of lithium acetylenide with ketones in liquid ammonia (Table 3).

Amino alcohols XIII-XXVI were synthesized by aminomethylation of propynols I-XII using a mixture of formaldehyde and amines or their salts in the presence of CuCl as described elsewhere [5]. Thienyl derivatives were prepared in strictly neutral conditions because of the instability of the starting propynols and resulting amino alcohols in the strongly basic and acidic conditions of the Mannich reaction; before addition of the carbynol, the mixture of amine salt and formaldehyde was neutralized with several drops of ethanolic solutions of the appropriate amine or triethylamine, using universal indicator. The normal acid treatment of the reaction was also omitted.

Hydrochlorides of amino alcohosl were synthesized by treatment with ether (sometimes ethanolic or chloroform) solutions of bases with ethanolic HCl. The salts of compounds XXV and XXVI were prepared using diluted ether solutions of HCl, and slight excesses of acid were used to prevent the products forming resins.

The hydrochlorides of compounds XXIII and XXIV could not be obtained in crystalline form. Aqueous solutions were prepared for pharmacological studies using equivalent quantities of base and aqueous HCl.

All compounds were analyzed for carbon and hydrogen content (acetylene carbynols), and for carbon, hydrogen, and nitrogen contents (aminobutynols), and for chloride ions (crystalline hydrochlorides). The results agree with those determined from the atomic formulas.

Product yields from Mannich reactions and the properties of the amino alcohol bases and their salts are shown in Table 1.

## BIOLOGICAL METHODS

m-Cholinoblocking activity of amino alcohols was determined in white mice using the arecoline model [1]. The ability of agents to block central n-cholinoreactive systems was studied in rabbits as described in [9]. Toxicity was measured in white mice using i.p. or s.c. dosage. The results of these studies are shown in Table 2.

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# COMPARATIVE STUDY OF A NEW PANCREATIC PROTEINASE INHIBITOR IN INITIATION OF LUNG INFLAMMATION


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Polyvalent inhibitors of proteolytic enzymes are widely used in clinical practice. Thanks to their ability to block a variety of serine trypsin-like proteinases (kallikrein, trypsin, chymotrypsin, plasmin), polyvalent inhibitors are valuable in the treatment of pancreatitis, hemorrhage, inflammatory processes, and shock states [10, 11]. These agents can also be used in lung diseases, where endogenous inhibitor systems are depressed during the development of these conditions [6, 8, 12]. Protein inhibitors of proteinases have been used effectively in pulmonary tuberculosis [3] and bronchial asthma [13, 14]. Endobronchial and intrapulmonary administration of inhibitors has been demonstrated in patients with nonspecific lung diseases [1, 4, 9]. Not only does the search for new proteinase inhibitors continue, but studies on improving methods for their preparation for clinical use are also under way, as are investigations aimed at developing better clinical therapeutic strategies for the use of these agents in pulmonary medicine.

The aim of the present work was to compare the efficacy of a new preparation of the basic pancreatic proteinase inhibitor aprotinin, using a model of acute experimental pneumonia.

## BIOCHEMICAL METHODS

An aprotinin preparation was made using the side products of insulin manufacture, at the All-Union Science Research Institute of Blood Replacement Technology and Hormonal Drugs, as

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