BACTERIOSTATIC PROPERTIES OF CERTAIN ACETYLENIC AMINES

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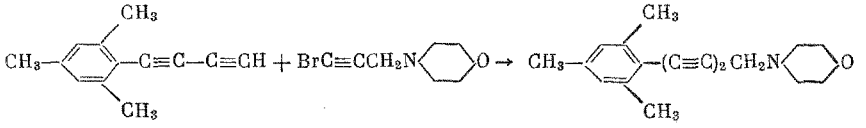
In the presence of cuprous chloride polyacetylenes of the aromatic series react smoothly with paraformaldehyde and secondary amines forming the corresponding N,N-dialkylaminoarylpoly-yne [1]. Since polyacetylenic compounds possess a wide spectrum of biological activity, it was expedient to investigate systematically around this project and the amino derivatives of the arylpoly-ynes.

The antibacterial and antifungal activity of acetylenic amines of the general formula $Ar(C\equiv C)_nCH_2$ ·NRR' (I)-(IX) have been studied in the present work. Compounds (I)-(VII) were obtained by the Mannich reaction

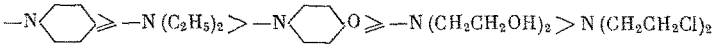
$$Ar(C\equiv C)_n H + HCHO + HNRR' \xrightarrow[CuCl]{} Ar(C\equiv C)_n CH_2NRR'$$

Amine (VIII) was synthesized by the interaction of glycol (VII) with thionyl chloride in $CHCl_3$, and triacetylene (IX) by the condensation of mesitylbutadiyne with 1-bromo-3-morpholinoprop-1-yne in the presence of cuprous chloride and ethylamine



The compounds for biological testing were base hydrochlorides (I)-(IX). The characteristics of the substances obtained are presented in Table 1.

The germistatic activity of the compounds was studied on 17 types of microorganism pertaining to the group of acid-resistant bacteria, pyogenic cocci, intestinal and sporiferous bacteria, and pathogenic fungi. The majority of the compounds tested possessed definite bacteriostatic activity in relation to the acid-resistant bacteria (Table 2, A). Moreover the efficiency of the activity depend noticeable on the structure of the aromatic, acetylenic and amino fragments of the molecules. The introduction of electro-do nating substituents (CH_3O–, CH_3–) in the benzene nucleus and a second triplet bond in the side chain led to an increase in the activity of the compounds. A further increase in the number of acetylenic groups gave rise to a sharp reduction again. Following these changes in the amino portion of the molecule the antibacterial activity fell along the series



seemingly parallel with the reduction in basicity of the amines. Compounds (V) and (VI) displayed the greatest activity not only in relation to the acid-resistant but also to the cocci bacteria, terminating the development of golden staphylococci at a dilution of 1 : 60,000-120,000 and of hemolytic streptococci at a dilution of 1 : 30,000-60,000 (Table 2, B). Amines (V) and (VI) and also (I) and (II) possessed weak activity on Escherichia coli, Salmonella typhosa, and dysenteric bacteria, and also on anthraconda spores (at a dilution of

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TABLE 1

Compound No.	Ar	R	R'	n	Yield of base, %	Hydrochlorides: mp, * °C	found Cl, %	empirical formula	calculated Cl, %
I	1,3,5-$(CH_3)_3C_6H_2$	—$CH_2CH_2OCH_2CH_2$—		1	72,7	238,5—240	12,79	$C_{16}H_{22}ClNO$	12,67
II	1,3,5-$(CH_3)_3C_6H_2$	—$CH_2CH_2OCH_2CH_2$—		2	75,8	240—242 [1]	—	$C_{18}H_{22}ClNO$	—
III	C_6H_5	—$CH_2CH_2OCH_2CH_2$—		2	55,5	178,5—180 [1]	—	$C_{15}H_{16}ClNO$	—
IV	*p*-$CH_3OC_6H_4$	—$CH_2CH_2OCH_2CH_2$—		2	82,2 †	184—187	11,94	$C_{16}H_{18}ClNO_2$	12,15
V	1,3,5-$(CH_3)_3C_6H_2$	—$(CH_2)_5$—		2	82,4	225—227 [1]	—	$C_{19}H_{19}ClN$	—
VI	1,3,5-$(CH_3)_3C_6H_2$	C_2H_5	C_2H_5	2	80,1	220—222 [1]	—	$C_{18}H_{24}ClN$	—
VII	1,3,5-$(CH_3)_3C_6H_2$	CH_2CH_2OH	CH_2CH_2OH	2	65,0 ‡	156—159	10,98	$C_{18}H_{24}ClNO_2$	11,02
VIII	1,3,5-$(CH_3)_3C_6H_2$	CH_2CH_2Cl	CH_2CH_2Cl	2	82,8	150—153	29,82	$C_{18}H_{22}Cl_3N$	29,64
IX	1,3,5-$(CH_3)_3C_6H_2$	—$CH_2CH_2OCH_2CH_2$—		3	35,2	181—182	10,81	$C_{20}H_{22}ClNO$	10,82

* Because of decomposition of the hydrochlorides on heating their mps depend considerably on the conditions of melting.

† Mp 74-75°.

‡ Mp 75.5-77°.

TABLE 2

Name of microorganism	Compound (I)	(II)	(IX)	(V)	(VI)	(VII)	(VIII)	(III)	(IV)
A A human tubercle bacillus	1:160000*	1:60000	0 †	1:250000	1:120000	1:60000	1:30000	1:16000	1:30000
Avian tubercle bacillus	1:16000	1:60000	0	1:500000	1:500000	1:30000	1:4000	1:8000	1:16000
Acid-resistant saprophyte B_5	1:4000	1:16000	0	1:120000	1:120000	1:16000	0 0	1:4000	1:16000
B Golden staphylococcus	1:8000	1:16000	0	1:60000	1:120000	0	0	0	0
Hemolytic streptococcus	1:4000	1:8000	0	1:30000	1:60000	0	0	0	0
Escherichia coli	1:8000	0	0	1:8000	1:16000	0	0	0	0
Salmonella typhosa	1:4000	0	0	1:8000	1:8000	0	0	0	0
Dysenteric bacteria, Flexner	1:4600	0	0	1:8000	1:30000	0	0	0	0
Diphtheria bacillus strain PW_3	1:2000	0	0	0	1:4000	0	0	0	0
Bacillus pyocyaneus	0	0	0	0	0	0	0	0	0
Proteus vulgaris	0	0	0	0	0	0	0	0	0
Anthraconda spores	1:4000	1:4000	0	1:8000	1:16000	0	0	0	0
C Microsporon	1:8000	0		1:16000	1:16000	1:2000	0	1:4000	0
Trichophyto	1:4000	0	0	1:8000	1:4000	1:2000	0	1:2000	0
Achorion	1:8000	0	0	1:16000	1:8000	1:2000	0	1:2000	0
Actinomycetes	1:8000	0	0	1:4000	0	1:1000	0	0	0
Crude yeast (Candida albicans)	1:4000	0	0	1:1000	0	1:1000	0	1:1000	0

* Preparations inhibited the growth of microorganisms in vitro at the dilutions indicated.

† Preparations were tested starting at a dilution of 1:1000.

1 : 2000-1 : 30,000). The aminoacetylenes (I)-(IX) displayed only extremely weak fungistatic activity (Table 2, C).

EXPERIMENTAL

The acetylenic amines (I)-(VII) were synthesized by the method of [1]: their constants and yields are indicated in Table 1. The starting aryldiacetylenes are described in [2]. The study of the antibacterial and antifungal activities was conducted according to the methods described in [3].

1-N,N-bis-(β-Chloroethyl)amino-5-mesitylpentadi-2,4-yne (VIII). To a solution of 7.2 g $SOCl_2$ in 70 ml $CHCl_3$ was added dropwise 5.7 g (VII) in 30 ml $CHCl_3$, the temperature was increased to 60°, and the mixture stirred for 2 h. After cooling, the reaction mixture was neutralized with a saturated solution of $NaHCO_3$ and the organic layer washed twice and dried with $MgSO_4$. The crude product (6.5 g) was dissolved in 20 ml benzene and chromatographed on Al_2O_3 (activity II), eluting (VIII) with $CHCl_3$. The chromatographically pure dichloride (VIII) 5.3 g (82.8%) was obtained having mp 53.5-54.5° (from petroleum ether). Found: Cl 22.03%. $C_{18}H_{21}Cl_2N$. Calculated: Cl 22.00%.

1-N-Morpholino-7-mesitylheptatri-2,4,6-yne (IX). Into a solution of 6.4 g mesityldiacetylene, 4 ml $C_2H_5NH_2$, and 0.08 g Cu_2Cl_2 in 50 ml methanol – THF mixture (1 : 1) in an atmosphere of nitrogen, was introduced 7 g 1-bromo-3-morpholinoprop-1-yne [4], maintaining the temperature at ~30°. The mixture was stirred for 1 h at this temperature, the solvent evaporated in vacuum, and the residue dissolved in benzene. This solution was put onto Al_2O_3 (activity II) and chromatographed, washing off (IX) with ether. The triacetylenic amine (IX) 3.5 g (35.2%) obtained had mp 121.5-123° (with decomposition). Found: N 4.77%. $C_{20}H_{21}NO$. Calculated: N 4.81%.

CONCLUSIONS

A series of amino derivatives of arylpoly-ynes with regularly changing structure has been synthesized and their antibacterial and antifungal properties have been studied.

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