TETRAACETYLENIC AMINE DERIVATIVES OF p-DIETHYNYLBENZENE

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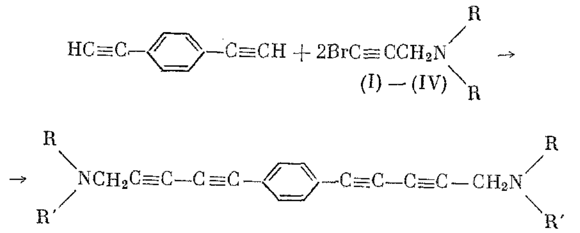
We have previously described the synthesis of a number of diacetylenic amines [1], some of which, according to preliminary tests, possess a high physiological activity. It has also been established that their hydrogenated analogs are more toxic and less active. This induced us to undertake the development of a method for synthesizing the corresponding tetraacetylenic amines in order subsequently to study the influence of an accumulation of triple bonds in the molecule on their physiological activity. To synthesize the tetraacetylenic amines we used the Chodkiewicz-Cadiot reaction [2] between p-diethynylbenzene and the corresponding brominated propargylamines. This gave the following amines



(V) – (VIII)

(V) $R=R'=C_2H_5$; (VI) $R=R'=CH_2CH_2Cl$;
(VII) $R-R'=-(CH_2)_5$; (VIII) $R-R'=-CH_2CH_2OCH_2CH_2-$

The bromides (I)-(IV), having, respectively, the same R and R' as (V)-(VIII) were synthesized from the known propargylamines [3-8] by the reaction of the latter with potassium hypobromite. The structure of the compounds obtained corresponded to their analysis and IR spectra. In contrast to the diacetylenic amines the IR spectra of which did not exhibit the stretching vibrations of a triple bond, the spectra of the tetraacetylenic amines had medium-intensity absorption bands in the 2200 cm^{-1} region. A similar pattern is observed in the spectra of the propargylamines, where the triple bond is not shown (although there is a strong band of the stretching vibrations of the $\equiv C-H$ bond in the 3300 cm^{-1} region), while the spectra of the bromides (I)-(IV) show strong bands of the stretching vibrations of the $C\equiv C$ bond, which is explained by the sharp increase in the dipole moment on passing from the propargylamines to the bromides (I)-(IV). In addition to this, by the replacement of the hydroxy groups in 1,4-bis(3'-diethanolaminoprop-1'-yn-1'-yl)-benzene by chlorine under the action of thionyl chloride we obtained 1,4-bis(3'-dichlorodiethylaminoprop-1'-yn-1'-yl)benzene in order to test it for antitumoral activity [9]

TABLE 1

Number	Formula of the bromide	Yield, %	mp or bp, °C	R_f, Al_2O_3, activity II
I	$BrC\equiv CCH_2N(C_2H_5)_2$	83,2	41–42	0,660 (ether : benzene = 1 : 1)
II	$BrC\equiv CCH_2N(CH_2CH_2Cl)_2$	98,9	185–187 *	0,261 (petroleum ether, 70–100°)
III	$BrC\equiv CCH_2N(CH_2)_5$	85,1	42–43	0,661 (ether : benzene = 1 : 1)

*Determined in a capillary.

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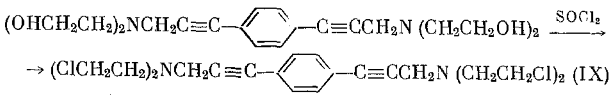


(IX)

EXPERIMENTAL

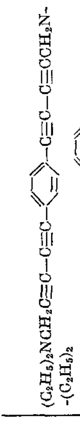
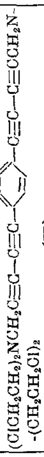
Preparation of the Propargylamines and Their Bromides. 1-Diethylamino-2-propyne, 1-piperidino-2-propyne, and 2-morpholino-2-propyne were obtained by a published method [3]. Their constants agreed with literature data [4, 6, 7]. 1-Dichlorodiethylamino-2-propyne [5] was obtained from 1-diethylamino-2-propyne [8] in a similar manner to (IX).

A solution of 22 g of KOH in 120 ml of water was cooled to 2°C and 3.15 ml of bromine was added; the mixture was stirred for 15 min and then the resulting solution of potassium hypobromite was added in drops to 5.1 g of 1-morpholino-2-propyne in 30 ml of ether. The mixture was kept for 3 h. Then it was repeatedly extracted with ether and the extract was washed with water to neutrality, and dried over K_2CO_3. This gave 1-bromo-3-morpholino-1-propyne (IV), yield 80%, mp 38-39°C; R_f 0.648 (Al_2O_3, activity II, ether : benzene, 1 : 1). The bromides of the other propargylamines were obtained similarly. Their yields and constants are given in Table 1.

Preparation of 1,4-bis(5'-Morpholinopenta-1',3'-diyn-1'-yl)benzene (VIII). To a solution of 1.89 g of p-diethynylbenzene in 30 ml of CH_3OH were added 0.04 g of CuCl, a small amount of $NH_2OH \cdot HCl$, 3.9 ml of $C_2H_5NH_2$ in 10 ml of methanol, and, in drops with vigorous stirring in a current of nitrogen, 6.3 g of 1-bromo-3-morpholino-1-propyne in 30 ml of CH_3OH. The beginning of the reaction was accompanied by a rise in the temperature in the flask from 14 to 24°C. The reaction mixture became green through the oxidation of the copper salt, and a small amount of hydroxylamine hydrochloride was added periodically to reduce it. The reaction mixture was heated to 35°C, and after 1 h crystals began to deposit. The time of the reaction was 2 h. The crystals were filtered off and the mother liquor was diluted with water and repeatedly extracted with ether. The ethereal extracts were dried over K_2CO_3. The (VIII) was chromatographed on Al_2O_3, activity II, $CHCl_3$. The yield of (VIII) was 4.8 g (82.2%), mp 186-187°C. Found %: N 7.49, 7.34. $C_{24}H_{24}N_2O_2$. Calculated %: N 7.52. Dihydrochloride – mp 200-201°C. Found %: Cl 15.95, 15.83. $C_{24}H_{26}N_2O_2Cl_2$. Calculated %: Cl 15.92.

The condensations with the other bromides described above were carried out similarly. The yields, constants, and analysis of the tetraacetylenic amines and their dihydrochlorides are given in Table 2.

TABLE 2

No.	Tetraacetylenic amines	Yield, %	mp, °C	Empirical formula	N, % found	N, % calculated	Empirical formula of the dihydrochloride	mp, °C	Cl, % found	Cl, % calculated
V		86,2	114–115	$C_{24}H_{28}N_2$	8,13	8,13	$C_{24}H_{30}N_2Cl_2$	209–210	16,90	16,99
VI		93,6	121–122	$C_{24}H_{24}N_2Cl_4$	5,87	5,89	$C_{24}H_{26}N_2Cl_6$	156–157	38,30	38,33
VII		84,1	159–160	$C_{26}H_{28}N_2$	7,62	7,60	$C_{26}H_{30}N_2Cl_2$	218–219	16,16	16,06

Preparation of 1,4-bis(3'-Dichlorodiethylaminoprop-1'-yn-1'-yl)benzene (IX). A solution of 2.1 g of 1,4-bis(3'-diethanolaminoprop-1'-yn-1'-yl)benzene [1] in 10 ml of $CHCl_3$ was cooled to 5°C and 2.3 ml of thionyl chloride in 10 ml of $CHCl_3$ was added to it in drops, after which the mixture was heated at 65°C for 1 h. Then the solution was cooled, and the crystals that deposited were filtered off and were washed on the filter with $CHCl_3$ and then with ether, whereupon the mother liquor deposited crystals of the dihydrochloride. The dihydrochloride was treated with 10% NaOH solution and extracted with ether. This gave 2.3 g of the base (IX), yield 90.9%, mp 67-70°C (purification on Al_2O_3, activity II, ether : benzene, 1 : 1). Found %: Cl 32.97, 32.80. $C_{20}H_{24}N_2Cl_4$. Calculated %: Cl 32.66. Dihydrochloride – mp 165-166°C. Found %: Cl 41.97, 41.90. $C_{20}H_{26}N_2Cl_6$. Calculated %: Cl 41.97.

CONCLUSIONS

1. Bromo derivatives of propargylamines have been synthesized in high yields in order to subject them to the Chodkiewicz-Cadiot reaction.

2. p-Diethynylbenzene readily condenses with the bromides mentioned, forming the corresponding tetraacetylenic diamines.

3. The action of thionyl chloride on 1,4-bis(3'-diethanolaminoprop-1'-yn-1'-yl)benzene has given 1,4-bis(3'-dichlorodiethylaminoprop-1'-yn-1'-yl)benzene.

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