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SYNTHESIS OF CONDENSED SYSTEMS CONTAINING THE TETRAZOLE RING BY BASE-CATALYZED INTRAMOLECULAR CYCLIZATION OF QUATERNARY AMMONIUM SALTS*

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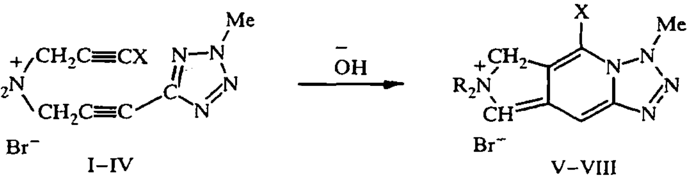
Quaternary ammonium salts containing propargyl and 3-(2-methyltetrazol-5-yl)propargyl groups undergo base-catalyzed cyclization at room temperature with self heating to form condensed heterocyclic systems containing the tetrazole ring. Heating at 90-92°C for 2 h is necessary to cyclize the allyl analogs of the starting salts.

Quaternary ammonium salts containing β,γ-unsaturated and 3-alkenyl- or 3-arylpropargyl groups undergo intramolecular diene-type cyclization in the presence of catalytic amounts of aqueous base [2]. Tetrazole derivatives (corazole and metrazole) are widely used in medicine as central-nervous-system stimulants. These compounds act as analgetics and sedatives and exhibit hypotensive properties [3].

The behavior of dialkylpropargyl- or dialkyl-(3-phenylpropargyl)-3-[(2-methyltetrazol-5-yl)propargyl]-ammonium bromides (I-IV) toward aqueous base was studied in order to expand the application of base-catalyzed cyclization of ammonium salts and to prepare new, potentially biologically active condensed tetrazole derivatives.



I, V $R_2 = Et_2$, X = H; II, VI $R_2 = (CH_2)_5$, X = H; III, VII $R_2 = (CH_2)_2O(CH_2)_2$, X = H;
IV, VIII $R_2 = (CH_2)_5$, X = Ph

The salts I-IV in the presence of 0.2 g-equiv of aqueous base per mole of starting salt cyclize at room temperature with self heating to form the condensed tetrazole derivatives (V-VIII) in yields of 72, 63, 60 and 80%, respectively. Allyl analogs of II and III (IX and X) cyclize only upon heating at 90-92°C for 2 h.

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TABLE 1. Properties of Starting (I-IV, IX and X) and Cyclic (V-VIII, XI and XII) Salts

Compound	Empirical formula	Found, % / Calculated, %		mp, °C (from ethanol)	R_f*	IR spectrum, cm^{-1}	UV spectrum (ethanol), λ_{max}, nm (log ε)	Yield, %
		N	Br					
I	$C_{12}H_{18}BrN_5$	22,67 22,44	25,48 25,64	122	—	1515, 2130, 2280, 3180	220 (4,74)	Quant.
II	$C_{13}H_{18}BrN_5$	21,90 21,61	24,32 24,69	150	—	1515, 1585, 2130, 2240, 2280, 3190, 3300	220 (4,45)	"
III	$C_{12}H_{16}BrN_5O$	21,60 21,47	24,26 24,54	*2	—	1515, 1580, 2120, 2250, 3200	220 (4,52)	"
IV	$C_{19}H_{22}BrN_5$	17,70 17,50	20,30 20,00	60	—	700, 770, 1580, 1600, 1805, 1880, 1950, 2240, 3050	210 (4,90), 245 (4,76)	"
IX	$C_{13}H_{20}BrN_5$	21,60 21,47	24,16 24,54	143	—	940, 970, 1585, 1640, 2270, 3090	220 (4,82)	"
X	$C_{12}H_{18}BrN_5O$	21,60 21,34	24,92 24,39	*2	—	940, 960, 1490, 1600, 1640, 2260, 3100	220 (4,82)	"
V*3	$C_{12}H_{18}BrN_5$	22,14 22,44	25,84 25,60	*4	0,45	1570	210 (5,05), 270 (5,03)	72
VI	$C_{13}H_{18}BrN_5$	21,80 21,61	24,62 24,69	98	0,50	1620, 1640	210 (5,07), 265 (5,02)	63
VII	$C_{12}H_{16}BrN_5O$	21,22 21,47	24,81 24,54	112	0,48	1620, 1630	210 (5,05), 270 (5,03)	60
VIII	$C_{19}H_{22}BrN_5$	17,16 17,50	20,38 20,00	200	0,40	700, 770, 1510, 1570, 1590, 1805, 1880, 1950, 3060	210 (4,92), 285 (4,82)	80
XI	$C_{13}H_{20}BrN_5$	21,85 21,47	24,72 24,54	120	0,43	1580	220 (5,06)	62
XII	$C_{12}H_{18}BrN_5O$	21,68 21,34	24,03 24,39	*4	0,47	1590, 1620	220 (5,08)	64

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* In *n*-butanol–ethanol–water–acetic acid (8:2:3:1).

*2 Hygroscopic

*3 Compounds I and V, II and VI, III and VII, IV and VIII, IX and XI, and X and XII are isomers.

*4 Does not crystallize, pasty substance with a bluish-green tint.

TABLE 2. Properties of Dialkyl[3-(2-methyltetrazol-5-yl)propargyl]amines (XIII-XV)

Compound	Empirical formula	Found, % / Calculated, %			bp, °C (mm)	mp of picrate, °C (from ethanol)	n_D^{20}	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N					
XIII	$C_9H_{15}N_5$	56,89 55,96	8,11 7,77	35,82 36,27	120 (3)	*	1,5000	1515, 1580, 2250	33
XIV	$C_{10}H_{15}N_5$	58,78 58,54	7,47 7,32	34,50 34,15	149 (3)	158	1,5285	1515, 1585, 2240	34
XV	$C_9H_{13}N_5O$	51,82 52,17	6,22 6,28	34,20 33,82	163 (3)	172	*[2]	1515, 1580, 2240	30

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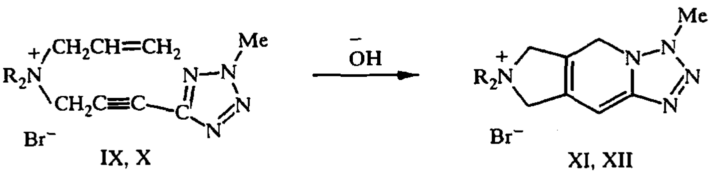
* Does not form a picrate.

*[2] Polycrystalline substance, in all instances 30-35% unreacted 2-methyl-5-ethynyltetrazole is recovered.



IX, XI $R_2 = (CH_2)_5$; X, XII $R_2 = (CH_2)_2O(CH_2)_2$

The corresponding cyclization products XI and XII are obtained in yields of 62 and 64%.

Characteristic for the starting salts I-IV, IX and X absorption bands of the disubstituted C≡C moiety at 2240-2260 cm^{-1} are missing in the IR spectra of the cyclic salts V-VIII, XI and XII. Also, bands of the terminal monosubstituted C≡C bond at 2120, 2130 and 3180 cm^{-1} and of the terminal C=C bond at 1640 and 3180 cm^{-1} are absent. These are characteristic of the starting salts I-III and IX, and X, respectively. Absorption bands at 1510, 1570, 1590, 1620, 1640 and 3060 cm^{-1} that are characteristic of conjugated systems are observed in the IR spectra of the cyclic salts V-VIII, XI and XII.

In the UV spectra of I-III, IX and X, which have a 2-methyltetrazole fragment conjugated to an acetylene moiety, the band of the π-π^* transition, as expected, is shifted to long wavelength (220 nm) owing to the conjugation. In the UV spectra of the cyclic salts V-VII, XI and XII, the logarithm of the molar extinction coefficients are increased compared with the starting salts [4, 5] (Table 1). The benzene absorption appears at 245 nm in the UV spectrum of IV. Absorption bands are observed at long wavelength region at 265, 270 and 285 nm in the spectra of the cyclic salts V-VIII bearing exocyclic double bond.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer in KBr pellets or vaseline oil. UV spectra were recorded in ethanol on a Specord UV-Vis instrument. TLC was performed on Silufol UV-254 plates using *n*-butanol–ethanol–water–acetic acid (8:2:3:1) with visualization by iodine vapor.

The starting dialkyl[3-(2-methyltetrazol-5-yl)propargyl]amines (XIII-XV) were prepared by a Mannich reaction from 2-methyl-5-ethynyltetrazole. The catalyst was copper diacetate and Fe(III) chloride. The mixture was heated at 90-95°C for 40-45 h. 2-Methyl-5-ethynyltetrazole was synthesized from 2-methyl-5-vinyltetrazole, which was prepared according to the patent [6]. Starting salts I-IV, IX and X were prepared in close to quantitative yields by reacting dialkyl[3-(2-methyltetrazol-5-yl)propargyl]amines with propargyl, 3-phenylpropargyl, or allyl bromide in acetonitrile. The physicochemical properties of starting amines XIII-XV and salts I-IV, IX and X in addition to the cyclic salts 7,7-diethyl-3-methyl- (V), 3-methyl-7,7-pentamethylene-6,7-dihydro-3H-pyrrolo[3,4-*d*]-tetrazolo[4,5-*a*]pyridinium (VI), 3'-methyl-6',7'-dihydrospiro(morpholinium-4,7'-3H'-pyrrolo[3,4-*d*]tetrazolo[4,5-*a*]-pyridinium) (VII), 3-methyl-7,7-pentamethylene-5-phenyl-6,7-dihydro-3H-pyrrolo[3,4-*d*]tetrazolo[4,5-*a*]-pyridinium (VIII), 3-methyl-7,7-pentamethylene-5,6,7,8-tetrahydro-3H-pyrrolo[3,4-*d*]tetrazolo[4,5-*a*]pyridinium (XI), and 3'-methyl-5',6',7',8'-tetrahydrospiro(morpholinium-4,7'-3'H-pyrrolo[3,4-*d*]tetrazolo[4,5-*a*]pyridinium) (XII) bromides are given in Tables 1 and 2.

General Method for Cyclization of I-IV. Homogeneous solution of starting salt (2.5-4.2 mmol) in water (1.5-2 ml) is treated with 2N KOH solution (0.3-0.42 ml) (molar ratio salt:base 5:1). The temperature of the reaction mixture for salts I and IV immediately increased from 25 to 90-95°C after adding the aqueous base because of self heating. For salts II and III the self heating is moderate (from 25 to 55°C). The reaction mixture is extracted with ether (1×15 ml). The aqueuos solution is acidified with HBr. Water is removed entirely under reduced pressure. The organic salt is extracted by absolute ethanol. Addition of ether to the resulting extract precipitates the corresponding cyclic salts V-VIII (see Table 1).

The cyclization of salts IX and X is carried out analogously to the previous one with the single difference that the reaction mixture is heated at 90-92°C for 2 h after adding the aqueous base.

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