TETRAZOLES.

24.* PREPARATION OF 1,4-DIMETHYL- AND 2,4-DIMETHYL-5-ARYL-TETRAZOLIUM SALTS

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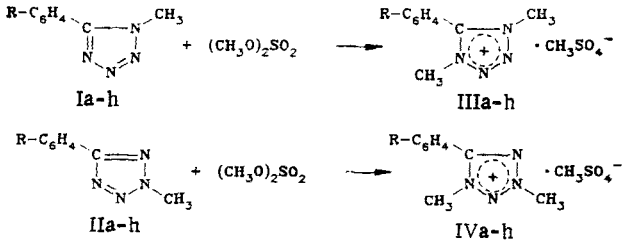
Alkylation of 1-methyl-5-aryltetrazoles with dimethyl sulfate leads to the formation of 1,4-dimethyl-5-aryltetrazolium ion salts. Alkylation of isomeric 2-methyl-5-aryltetrazoles also apparently takes place at the N(4) atom. 1-Methyl-5-aryltetrazoles display greater reactivity with respect to methylation than the isomeric 2-methyl-5-aryltetrazoles. 1,4-Dimethyl-5-aryltetrazolium methylsulfate salts isomerize upon heating to give the more stable 2,4-dimethyl-5-aryltetrazolium ion salts.

Tetrazolium salts are widely used in biochemistry [2], medicine [3], agriculture [4], and in the composition of novel low-silver photographic materials [5]. The selection of methods suitable for the preparation of these compounds is quite limited. The principal method for their synthesis involves oxidation of formazines [6], but only 2,3,5-trisubstituted tetrazolium salts can be prepared in this manner.

Alkylation of 1,5- and 2,5-disubstituted tetrazoles, which would generate 1,4,5- and 2,4,5-trisubstituted derivatives [7], has received much less attention. It was therefore of interest to us to examine this reaction in greater detail as a promising prospective method for the preparation of 1,4,5- and 2,4,5-trisubstituted tetrazolium salts.

In studying the quaternization of disubstituted tetrazoles, the question of process selectivity arises. If the total electronic charge on the nitrogen atoms in the heterocycle is taken as the index of selectivity, then the most probable reaction sites for 1-methyl- and 2-methyl-5-phenyltetrazoles would be expected to be the nitrogen atoms in the 10- and 4-positions (Fig. 1). Since quaternization can be considered, however, to be a bimolecular nucleotphilic substitution process with respect to the alkylating agent [8], reaction at the N(1) atom should be regarded as less probable, due to steric hindrance. In addition, the formation of tetrazolium cations substituted at the N(4) atom is energetically more favorable than for N(1) substituted cations [9]. For these reasons, we anticipated that methylation of 1,5- and 2,5-disubstituted tetrazoles (Ia-h. IIa-h) by dimethylsulfate would occur at the N(4) atom.



Ia-h IIIa-h

IIa-h IVa-h

I—IV a R=*p*-OCH_3; b R=*p*-CH_3; c R=*m*-CH_3; d R=H; e R=*p*-I; f R=*m*-Br; g R=*m*-NO_2; h R=*p*-NO_2

In order to verify this assumption, we examined the alkylation of 1-methyl-, 2-methyl-, 1-deuteriomethyl-, and 2-deuteriomethyl-5-phenyltetrazoles by dimethyl sulfate in deuteroacetonitrile at a stoichiometric ratio of reagents and a total reagent concentration of ~1 M.

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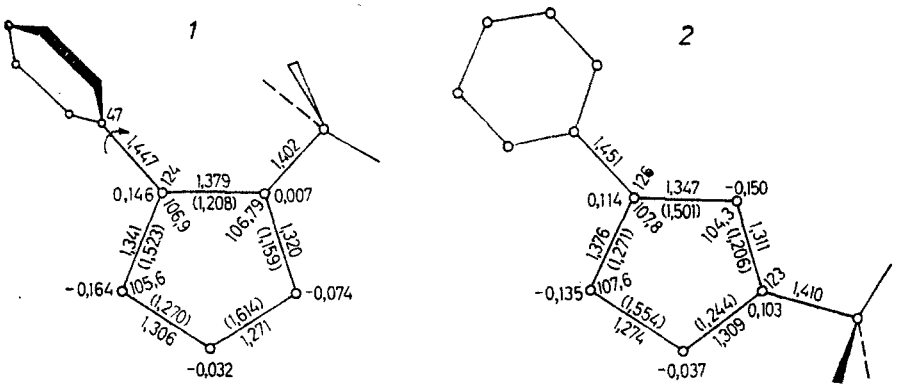

Fig. 1. Geometry optimization and electronic characteristics of 1-methyl-5-phenyltetrazole (1) and 2-methyl-5-phenyltetrazole (2). The numbers shown include bond angles, bond lengths (A°), and total charges on the atoms (and Wiberg indices of bone multiplicity).

The formation of tetrazolium salts as a function of time was monitored by PMR spectroscopy. In the alkylation of 1-methyl-5-phenyltetrazole Id (at 25°C), at the initial moment of reaction time the spectrum contained, in addition to the signals for the aromatic protons and for the methyl group protons in the alkylating agent, a peak at 4.1 ppm, corresponding to the N(1)-methyl group protons in the tetrazole starting material. As the reaction proceeds the integrated intensity of this signal decreases and a new peak appears at 4.4 ppm. After completion of the reaction the 4.1 ppm signal has completely disappeared, while the peak at 4.4 ppm has doubled in intensity (Fig. 2). The PMR spectrum of the reaction product formed between 1-deuteriomethyl-5-phenyltetrazole and dimethyl sulfate also exhibits a peak at 4.4 ppm with an intensity corresponding to 3H. These results lead us to conclude that a symmetrical cation, namely 1,4-dimethyl-5-phenyltetrazolium ion, is formed in the alkylation of 1-methyl-5-phenyltetrazole and its deuteriomethyl analog by dimethyl sulfate.

Since alkylation of 2-methyl-5-phenyltetrazole (IId) at 25°C proceeds at an extremely low rate, methylation of IId and its deteromethyl analog was carried out at 50°C. Upon alkylation of compound IId the PMR spectrum of the reaction mixture shows a peak at 4.65 ppm; the intensity of this signal after reaction completion is equal to the intensity of the peak at 4.4 ppm, which corresponds to the N(2) methyl group protons in the tetrazole starting material. The same pattern is observed upon alkylation of 2-deuteriomethyl-5-phenyltetrazole, with the exception that the PMR spectrum of the reaction product contains only one peak at 4.65 ppm, with an intensity corresponding to 3H (Fig. 3). Methylation of compound IId can theoretically occur at three reactive sites, namely, the N(1), N(3), and N(4) atoms in the ring. Analysis of the PMR spectra excludes the possibility of alkylation at N(3), since in that case one would expect a symmetrical cation to be formed, whose spectrum would contain only one signal with an intensity corresponding to 6H. Alkylation at N(1) can be excluded from consideration because of its greater steric constraints. Thus, the most reasonable structure assignment places the methyl group in the 4-position of the heterocycle. The results obtained herein for the alkylation of 1-methyl-2-methyl-5-phenyltetrazoles and its deuteromethyl analogs are consistent with data obtained earlier concerning the protonation of these compounds [10, 11].

Because of low substrate reactivity the alkylation of 1-methyl- and 2-methyl-5-aryltetrazoles by dimethyl sulfate in organic solvents cannot be regarded as a convenient method for the preparation of tetrazolium ion salts. The latter can be obtained in 70-85% yield by carrying out the reactions in dimethyl sulfate itself at 60°C. However, at this temperature only 2,4-dimethyl-5-aryltetrazolium ion salts (IVa-h) are obtained, starting with either 1-methyl- or 2-methyl-5-aryltetrazoles (Ia-h, IIa-h). Apparently, in the alkylation of tetrazoles Ia-h, 1,4-dimethyl-5-aryltetrazolium salts (IIIa-h) are formed initially, but these are isomerized at higher temperatures to the more stable 2,4-dimethyl-5-aryltetrazolium derivatives IVa-h. In fact, heating compound Id or Ig in dimethyl sulfate at 35°C enables one to isolate the 1,4,5-trisubstituted tetrazolium salts IIId or IIIg. At 60°C, however, the corresponding 2,4-dimethyl-5-aryltetrazolium ion salts IVd or IVg are obtained. In a previous study the formation of 2,4-dimethyl-5-phenyl tetrazolium ion was observed upon

TABLE 1. Melting Points, Spectral Parameters, and Results of Elemental Analysis of 1,4-Dimethyl-5-aryltetrazolium Vd, Vg and 2,4-Dimethyl-5-aryltetrazolium Salts IVa-h

Compound	mp, °C	IR spectrum (ClO_4^-), cm^{-1}	PMR spectrum, δ, ppm (acetone D_6)	Found				Molecular formula	Calculated				Yield, %
				C, %	H, %	N, %	M**		C, %	H, %	N, %	M	
Vd	159—160	1080	4,40 (6H, s, N—CH_3); 8,0 (5H, s, arom.)	39,2	3,9	20,4	270	$C_9H_{11}ClN_4O_4$	39,3	4,0	20,4	274,5	78
Vg	135—137	1080; 1380, 1550***	4,45 (6H, s, N—CH_3); 7,9—9,0 (4H, m, arom.)	33,9	3,4	22,0	308	$C_9H_{10}ClN_5O_6$	33,8	3,1	21,9	319,5	83
VIa	144—145	1040	4,60 (3H, s, $N_{(4)}$—CH_3); 4,80 (3H, s, $N_{(2)}$—CH_3); 4,0 (3H, s, OCH_3); 7,3; 8,0 (4H, m, arom)	39,2	4,3	18,2	295	$C_{10}H_{13}ClN_4O_5$	39,4	4,3	18,4	304,5	68
VIb	142—144	1040	4,6 (3H, s, $N_{(4)}$—CH_3); 4,8 (3H, s, $N_{(2)}$—CH_3); 2,5 (3H, s, *p*-CH_3); 7,6—8,0 (4H, m, arom.)	41,4	4,5	19,1	276	$C_{10}H_{13}ClN_4O_4$	41,6	4,5	19,4	288,5	73
VIc	103—104	1040	4,6 (3H, s, $N_{(4)}$—CH_3), 4,9 (3H, s, $N_{(2)}$—CH_3); 2,6 (3H, s, *m*-CH_3); 7,6; 7,8 (4H, m, arom.)	41,5	4,6	19,2	280	$C_{10}H_{13}ClN_4O_4$	41,6	4,5	19,4	288,5	62
VId	129—131	1080	4,6 (3H, s, $N_{(4)}$—CH_3); 4,8 (3H, s, $N_{(2)}$—CH_3); 7,8—8,2 (5H, m, arom.)	39,6	3,8	20,6	275	$C_9H_{11}ClN_4O_4$	39,3	4,0	20,4	274,5	78
VIe	140—142	1050	4,6 (3H, s, $N_{(4)}$—CH_3); 4,8 (3H, s, $N_{(2)}$—CH_3); 7,9; 8,3 (4H, m, arom)	27,1	2,7	13,7	381	$C_9H_{10}ClIN_4O_4$	27,0	2,5	14,0	400,5	77
VIf	165	1050	4,5 (3H, s, $N_{(4)}$—CH_3); 4,8 (3H, s, $N_{(2)}$—CH_3); 7,9; 8,0; 8,2 (4H, m, arom)	30,8	2,9	16,0	340	$C_9H_{10}BrClN_4O_4$	30,6	2,8	15,8	353	69
VIg	138—139	1080; 1360, 1540***	4,65 (3H, s, $N_{(4)}$—CH_3); 4,9 (3H, s $N_{(2)}$—CH_3); 8,3; 8,6; 8,9 (4H, m, arom.)	33,7	3,1	21,8	310	$C_9H_{10}ClN_5O_6$	33,8	3,1	21,9	319	87
VIh	204	1050; 1320, 1530***	4,6 (3H, s, $N_{(4)}$—CH_3); 4,8 (3H, s, $N_{(2)}$—CH_3); 7,8 (4H, s, arom)	34,0	3,2	21,8	310	$C_9H_{10}ClN_5O_6$	33,8	3,1	21,9	319	87

*In the case of perchlorates Vd, VIf, a mixture of acetone-D_6 and DMSO-D_6 (1:1) was used.

**Reverse ebullioscopy (acetone).

***Symmetric and antisymmetric NO_2 group stretching vibrational bands.

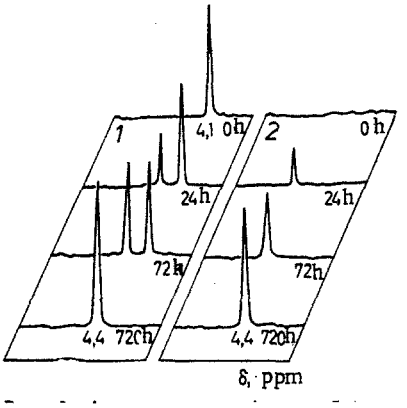

Fig. 2

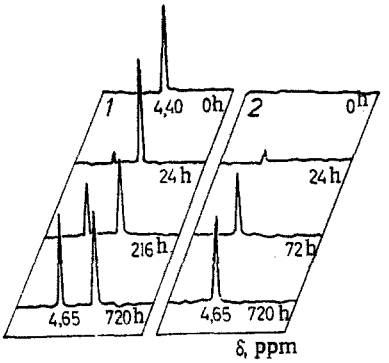

Fig. 3

Fig. 2. Alkylation of 1-methyl-5-phenyltetrazole (1) and 1-methyl-D_3-5-phenyltetrazole (2) with dimethyl sulfate in acetonitrile-D_3. PMR spectral changes as a function of time (at 60 MHz) for the reaction mixture at 25°C.

Fig. 3. Alkylation of 2-methyl-5-phenyltetrazole (1) and 2-methyl-D_3-5-phenyltetrazole (2) with dimethyl sulfate in acetonitrile-D_3. PMR spectral changes (at 60 MHz) as a function of time for the reaction mixture at 50°C.

alkylation of 1-methyl-5-phenyltetrazole by methyl iodide [12]. This observation is associated apparently with the greater thermodynamic stability of 2,4,5-trisubstituted tetrazolium salts.

Methylsulfate salts which are formed in the alkylation of tetrazoles by dimethyl sulfate are hygroscopic and difficult to purify. More convenient samples with respect to handling are perchlorate salts, which can be prepared in quantitative yields by acidification of aqueous solutions of tetrazolium methylsulfate salts IIId, IIIg, and IVa-h with perchloric acid (see Table 1).

The results summarized herein lead us to suggest alkylation of 1,5- and 2,5-disubstituted tetrazoles as a convenient method for the preparation of 2,4-5-trisubstituted tetrazolium ion salts.

EXPERIMENTAL

PMR spectra (acetonitrile-D_3 and acetone-D_6) were recorded on a Perkin Elmer R-12 spectrometer (at 60 MHz) versus HMDS as internal standard. IR spectra were obtained using a UR-20 spectrophotometer and thin sample films. Geometry optimization and electronic structure calculations for 1-methyl and 2-methyl-5-phenyltetrazoles were performed using CNDO/2 [1]. 1-Methyl-5-aryltetrazoles Ia-h, 2-methyl-5-aryltetrazoles IIa-h, 1-deuteromethyl-5-phenyltetrazole, and 2-deuteromethyl-5-phenyltetrazole were prepared and purified using known procedures. All of the compounds' physical characteristics agreed with literature data [11, 13].

Alkylation of 1-Methyl-5-phenyltetrazole (Id) and 1-Methyl-5-(m-nitrophenyl)-tetrazole (Ig). Tetrazole Id or Ig (0.012 mole) was added with stirring to 0.16 mole of dimethyl sulfate. The reaction mixture was heated for 15 h at 35°C, cooled, and poured into 20 ml of ether and carefully mixed. The ether layer was removed by decantation. The residue was washed with ether (4 × 20 ml), hexane (2 × 20 ml), and benzene (2 × 20 ml), and the solvent was then evaporated and the crystalline residue dried under vacuum over P_2O_5. The resulting methylsulfate salts IIId or IIIg were converted to their corresponding perchlorates Vd and Vg via the procedure described below.

Alkylation of tetrazoles Ia-c, e, f, and h and IIa-h with dimethyl sulfate at 60°C was carried out in an analogous manner, but with heating over a 30-h period.

1,4-Dimethyl-5-aryltetrazolium (Vd, Vg) and 2.48-Dimethyl-5-aryltetrazolium Perchlorates (VIa-h). The methylsulfate salt (0.01 mole) IIId, IIIg, or IVa-h was dissolved in 5-10 ml water and 1 ml 57% $HClO_4$ was added. The resulting crystals were removed by filtration, washed

wilh cold water, and recrystallized from isopropanol. The physical characteristics of perchlorates Vd, Vg, and VIa-h are summarized in Table 1.

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OCTAHYDROPYRROLO[4,3,2-m,n]ACRIDINE DERIVATIVES.

2.* 1-ARYL-4,4,8,8-TETRAMETHYL-2,3,4,5,7,8,9,10-OCTAHYDROPYRROLO[4,3,2-m,n]-ACRIDIN-10-ONES AND INTERMEDIATES IN THEIR SYNTHESIS

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A series of 9-aroyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthen-1,8-diones has been prepared from arylglyoxals and dimedone in a dehydrating medium; upon heating with ammonia these compounds are converted to 1-aryl-4,4,8,8-tetramethyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10-ones. These reactions occur via the intermediate formation of tetrahydroindole derivatives.

In the present paper we continue our investigation of a novel series of nitrogen-containing heterocycles, and have synthesized a series of 1-aryl-4,4,8,8-tetramethyl-2,3,4,5,7,8,9,10-octahydropyrrolo[4,3,2-m,n]acridin-10 ones and have examined the course of their formation reactions. We have previously established the structure of this heterocyclic system by x-ray structural analysis [1] and have reported their antioxident properties [2]. The necessary intermediates for the synthesis of pyrrolo[4,3,2-m,n]acridines VI are 9-aroyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthen-1,3-diones (III), which are themselves prepared from arylglyoxals I and 5,5-dimethylcyclohexane-1,3-dione (dimedone) in a dehydrating medium, namely, a mixture of acetic acid and acetic anhydride [3]. A decrease in the amount of acetic anhydride leads to the formation of a mixture of diones III with aroylbis(5,5-dimethylcyclohexane-1,3-dion-2-yl)methane (II) or else inhibits the reaction of arylglyoxal with dimedone (in the case of Im), so that the only pure compound IIk could be prepared using glyoxal Ik.

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