3,5-DI(HYDROXYORGANYL)PYRAZOLES

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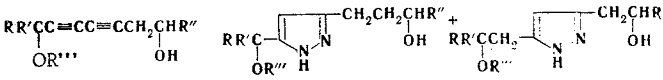
The reaction of primary-tertiary and secondary-tertiary aliphatic diacetylenic ζ-glycols with hydrazine hydrate leads to the formation of isomeric 3,5-di(hydroxyalkyl)pyrazoles in which the pyrazole ring is present both in the α and in the β position to the tertiary carbon atom to which the hydroxy group is attached. The structure of the hydrocarbon substituents connected with this atom substantially affects the ratio of the α and β isomers. The addition of hydrazine hydrate to aliphatic glycols and their monoethers is accompanied by the formation of individual β-(hydroxyalkyl)pyrazoles.

The addition of hydrazine hydrate to symmetrical diacetylenic ε-glycols leads to the formation of the corresponding pyrazoles [1, 2]. Compounds of this type have a broad spectrum of biological action [3]. It appeared of interest to study the influence of substituents on the tertiary carbon atom of primary-tertiary and secondary-tertiary diacetylenic ζ-glycols on the direction of the reaction of the latter with hydrazine hydrate.

When the aliphatic glycols (Ia-c) were boiled with an excess of 99.5% hydrazine hydrate, quantitative yields were obtained of very viscous vitreous 3,5-di(hydroxyalkyl)pyrazoles consisting, according to PMR spectroscopy, of mixtures of α and β isomers (II and III, respectively, Table 1), which could not be separated chromatographically.



I a-f II a-c III a-f

a $R=R'=CH_3$, $R''=R'''=H$; b $R=R''=CH_3$, $R'=C_2H_5$, $R'''=H$; c $R-R'=-(CH_2)_5-$, $R''=R'''=H$; d $R=R'=C_6H_5$, $R''=R'''=H$; e $R=R'=C_6H_5$, $R''=H$, $R'''=C_2H_5$; f $R=R'=C_6H_5$, $R''=CH_3$, $R'''=C_2H_5$

The structure of the 3,5-di(hydroxyalkyl)pyrazoles (IIa-c) and (IIIa-c) obtained was confirmed by PMR spectroscopy (Table 2) and IR spectroscopy. Thus, for example, the IR spectra of mixtures of the isomers (IIa-c) and (IIIa-f) lack the frequencies of a triple bond, have broad absorption bands with two maxima in the 3260-3150 cm^{-1} region corresponding to NH and OH groups, and have the set of frequencies of the pyrazole ring [4] at 1575-1570, 1470-1465, and 1385-1370 cm^{-1}.

The ratio of the α and β isomers depends fundamentally on the structure of the substituents on the carbon atom to which one of the hydroxy groups is attached that is in the α position with respect to the diacetylenic system, and it is apparently determined by steric factors (Table 1).

In the vacuum distillation of a mixture of the pyrazoles (IIa) and (IIIa) at 200°C, the β isomer (IIIa) was recovered unchanged, while the α isomer (IIa) underwent complete dehydration. This made it possible to isolate the individual β isomers.

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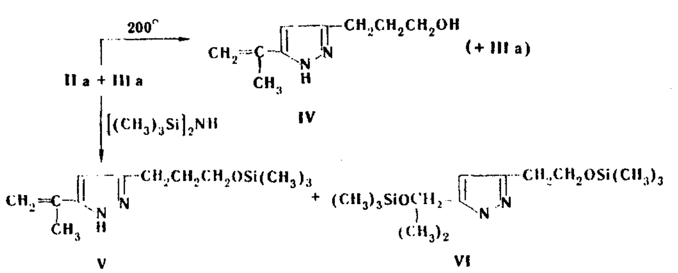
TABLE 1. Products of the Addition of Hydrazine Hydrate to Diacetylenic ζ-Glycols

Compound	mp, °C	Ratio of the isomers		Empirical formula	Found, %			Calc., %			Yield, %
		α	β		C	H	N	C	H	N	
IIa+IIIa	—	50	50	$C_9H_{16}N_2O_2 \cdot H_2O$	53,9	8,1	13,0	53,5	8,9	13,9	~100
				$C_9H_{16}N_2O_2$	58,0	8,6	15,5	58,7	8,7	15,2	
IIb+IIIb	—	40	60	$C_{11}H_{20}N_2O_2 \cdot H_2O$	57,0	9,0	11,9	57,4	9,6	12,2	~100
				$C_{11}H_{20}N_2O_2$	62,1	9,7	13,2	62,3	9,4	13,2	
IIc+IIIc	94—95	20	80	$C_{12}H_{20}N_2O_2 \cdot H_2O$	59,4	7,9	11,9	59,5	9,1	11,6	~100
					64,6	8,9	12,0	64,3	8,9	12,5	
IIId	140—141*		100	$C_{19}H_{20}N_2O_2$	73,2	6,6	9,5	74,0	6,5	9,1	91
IIIe	140—142†		100	$C_{21}H_{24}N_2O_2$	74,9	7,1	8,4	75,0	7,1	8,3	61
IIIf	146—147†		100	$C_{22}H_{26}N_2O_2$	74,6	7,3	8,1	75,4	7,4	8,0	66
VIII	172—173‡		100	$C_{30}H_{26}N_2O_2$	80,9	5,8	6,1	80,7	5,8	6,3	78

*From a mixture of benzene and ethanol. †From benzene. ‡From ethanol.

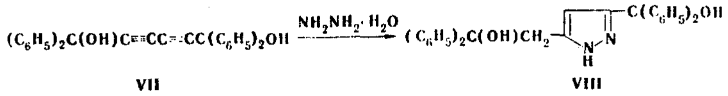
The hydroxyalkylpyrazoles obtained contain a molecule of bound water. When a mixture of the pyrazoles (IIa) and (IIIa) was treated with hexamethyldisilazane, the hydroxyalkylpyrazole trimethylsilyl derivatives (V) and (VI) (ratio 1 : 1), containing no water, were isolated.



Compound (V) is apparently formed by the splitting out of water from the α isomer (IIa) under the influence of the hexamethyldisilazane. As in the dehydration of the di(hydroxyalkyl)pyrazoles, only the α isomer takes part in the elimination reaction. On hydrolysis of the mixture of trimethylsilyl ethers (V and VI) with a 5% solution of hydrochloric acid in methanol, a mixture of the pyrazoles (IIIa) and (IV) which again contained a molecule of water was obtained. It was possible to eliminate this by azeotropic distillation with benzene.

The aralkyl glycol (Id) and the hydroxy ethers (Ie, f) add hydrazine hydrate with the formation of pyrazoles of only the β form (IIId-f) (Tables 1 and 2). Apparently, the formation of the α isomers is prevented by steric hindrance due to the two aromatic groups.

The addition of hydrazine hydrate to 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (VII) takes place similarly, forming the pyrazole (VIII) (Tables 1 and 2).



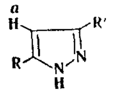
EXPERIMENTAL

The PMR spectra were taken on a Tesla BS 487B (80 MHz) instrument with HMDS as internal standard.

Reaction of 2-Methylocta-3,5-diyne-2,8-diol (Ia) with Hydrazine Hydrate. A mixture of 8.0 g (0.052 mole) of the glycol (Ia) and 10 g (0.2 mole) of 99.5% hydrazine hydrate was heated at 110-120°C for 8 h. After the disappearance of the initial glycol (TLC), the excess of hydrazine hydrate was eliminated in vacuum. This gave 10.3 g of a vitreous substance consisting of a mixture of the 3,5-di(hydroxyalkyl)pyrazoles (IIa) and (IIIa) (Table 1).

The distillation of this mixture in vacuum gave 7.9 g of a substance with bp 205-210°C (5 mm). By column chromatography on alumina [chloroform-methanol (10 : 1)], 4.0 g of the mixture yielded 1.2 g (63%) of 3-(3-hydroxypropyl)-5-isopropenylpyrazole (IV), $\nu_{C=C}$ 1636 cm^{-1}. Found: C 59.6; H 8.3; N 15.1%.

TABLE 2. Chemical Shifts in the PMR Spectra of the Pyrazoles



Compound	R	R′	τ, ppm									Solvent
			a	*b*	*c*	*d*	*e*	*f*	*g*	*k*	NH, OH	
IIa	$(\overset{e}{C}H_3)_2COH$	$\overset{b}{C}H_2\overset{c}{C}H_2\overset{d}{C}H_2OH$	4,09	7,29	8,14	6,43	8,50				*	CD_3OD
IIb	$\overset{e}{C}H_3C(OH)\overset{g,\,k}{C}_2H_5$	$\overset{b}{C}H_2\overset{c}{C}H_2\overset{d}{C}H(OH)\overset{f}{C}H_3$	4,10	7,32	8,52	6,25	8,80	8,88	9,10	8,26	*	$CD_3OD+CDCl_3$
IIc	$(\overset{e}{C}H_2)_5COH$	$\overset{b}{C}H_2\overset{c}{C}H_2\overset{d}{C}H_2OH$	4,21	7,47	8,22	6,49	8,56				2,95	$CDCl_3$
IIIa	$(\overset{e}{C}H_3)_2C(OH)\overset{b}{C}H_2$	$\overset{c}{C}H_2\overset{d}{C}H_2OH$	4,02	7,29	7,22	6,25	8,82				3,35	$CDCl_3$
IIIb	$\overset{g,\,k}{C}_2H_5\underset{\substack{\vert\\ OH}}{C}(\overset{e}{C}H_3)\overset{b}{C}H_2$	$\overset{c}{C}H_2\overset{d}{C}H(OH)\overset{f}{C}H_3$	4,15	7,32	7,32	6,01	8,80	8,86	9,08	8,80	3,55	$CHCl_3$
IIIc	$(\overset{e}{C}H_2)_5C(OH)\overset{b}{C}H_2$	$\overset{c}{C}H_2\overset{d}{C}H_2OH$	4,14	7,32	7,27	6,24	8,56				2,95	$CDCl_3$
IV	$\overset{f,\,g}{C}H_2{=}C(\overset{e}{C}H_3)$	$\overset{b}{C}H_2\overset{c}{C}H_2\overset{d}{C}H_2OH$	3,80	7,31	8,14	6,38	7,95	4,55	4,95		*	CD_3OD
V	$\overset{f,\,g}{C}H_2{=}C(\overset{e}{C}H_3)$	$\overset{b}{C}H_2\overset{c}{C}H_2\overset{d}{C}H_2OSi(\overset{k}{C}H_3)_3$	4,05	7,34	8,20	6,48	7,99	10,0	5,06	4,66	−1,6	CCl_4
VI	$(\overset{e}{C}H_3)_2C[OSi(\overset{f}{C}H_3)_3]\overset{b}{C}H_2$	$\overset{c}{C}H_2\overset{d}{C}H_2OSi(\overset{f}{C}H_3)_3$	4,19	7,34	7,36	6,18	8,81	10,0			−0,8	CCl_4
IIId	$(\overset{e}{C_6H_5})_2C(OH)\overset{b}{C}H_2$	$\overset{c}{C}H_2\overset{d}{C}H_2OH$	4,50	6,43	7,37	6,35	2,70				*	$CD_3OD+CDCl_3$
IIIe	$(\overset{e}{C_6H_5})_2C(O\overset{f,}{C}_2\overset{g}{H}_5)\overset{b}{C}H_2$	$\overset{c}{C}H_2\overset{d}{C}H_2OH$	4,65	6,35	7,37	6,30	2,70	8,90	6,76		4,09	$CDCl_3$
IIIf	$(\overset{e}{C_6H_5})_2C(O\overset{k}{C}_2\overset{g}{H}_5)\overset{b}{C}H_2$	$\overset{c}{C}H_2\overset{d}{C}H(OH)\overset{f}{C}H_3$	4,49	6,37	7,44	6,08	2,70	8,88	8,89	6,76	3,60	$CDCl_3$
VIII	$(\overset{e}{C_6H_5})_2C(OH)\overset{b}{C}H_2$	$C(\overset{e}{C_6H_5})_2OH$	4,57	6,45	—	—	2,85—2,66				*	CD_3OD

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*The signals of the NH and OH protons coincide with the signals of the undeuterated molecules of the solvent.

$C_9H_{14}N_2O \cdot H_2O$. Calculated: C 58.7; H 8.7; N 15.2% and 1.0 g of 3-(2-hydroxyethyl)-5-(2-hydroxy-2-methylpropyl)pyrazole (IIIa).

Reaction of the 3,5-Di(hydroxyalkyl)pyrazoles (IIa) + (IIIa) with Hexamethyldisilazane. The mixture of pyrazoles (IIa and IIIa) (4.0 g) and hexamethyldisilazane (9.0 ml) was heated at 50°C for 14 h. After the elimination of the excess of hexamethyldisilazane in vacuum, the residue was distilled, giving 4.6 g of a substance with bp 142-143°C (1.5 mm); n_D^{20} 1.4750. According to its PMR spectrum it was a mixture of 5-isopropenyl-3-(3-trimethylsilyloxypropyl)pyrazole (V) and 5-(2-methyl-2-trimethylsilyloxypropyl)-3-(2-trimethylsilyloxyethyl)pyrazole (VI) in a molar ratio of 1 : 1. Found: C 59.1; H 9.7; N 9.9; Si 12.8%. $C_{12}H_{22}N_2OSi + C_{15}H_{32}N_2O_2Si_2$ (1 : 1). Calculated: C 57.2; H 9.5; N 9.9; Si 14.8%.

Hydrolysis of a Mixture of the Trimethylsilyl Ethers (V) and (VI). The mixture of pyrazoles (V and VI) (3.3 g) was heated with a 5% solution of concentrated hydrochloric acid in methanol at 50-60°C for 4 h after which it was neutralized with sodium carbonate solution and extracted with ether, and the extract was dried with magnesium sulfate. The solvent was driven off, and the residue (1.5 g) was chromatographed on a column of Al_2O_3 [chloroform–methanol (10 : 1)]. This gave 0.45 g of the pyrazole (IV) and 0.6 g of the pyrazole (IIIa).

3-(2-Hydroxyethyl)-5-(2-hydroxy-2,2-diphenylethyl)pyrazole (IIId). A mixture of 1.2 g (0.006 mole) of 1,1-diphenylhepta-2,4-diyne-1,7-diol (Id) and 3.0 g of 99.6% hydrazine hydrate was heated at 110-120°C for 5 h. The precipitate was separated off and washed with absolute ethanol. The yield of the pyrazole (IIId) was 1.2 g, mp 140-141°C (from a mixture of benzene and ethanol).

The pyrazoles (IIIe and f) were obtained under similar conditions, and the pyrazole (VIII) from 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol [5].

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