SYNTHESIS OF 2,3-DISUBSTITUTED 5,7,7-TRIMETHYL-2,3,6,7-TETRAHYDRO-1,3,4-OXADIAZEPINES AND 6,7-BENZO-2,3-DIHYDRO-1,3,4-OXADIAZEPINES

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The corresponding hydrazones were obtained by the reaction of diacetone alcohol and salicylaldehyde with monoalkylhydrazines. It is shown that derivatives of 2,3,6,7-tetrahydro-1,3,4-oxadiazepine and 6,7-benzo-2,3-dihydro-1,3,4-oxadiazepine, respectively, are obtained in the reaction of monoalkylhydrazones of β -hydroxy carbonyl compounds with both the hydroxy group in the alkyl chain and the hydroxy group attached to the aromatic ring with aldehydes. The structures of the products were proved by the set of analytical, IR, and ¹H NMR data.

In previous studies [1-3] of the chemistry of ethanol hydrazones it was observed that NH and OH groups in the β position relative to one another in them are capable of reacting with aldehydes to give 1,3-oxazolidines. It seemed of interest to ascertain the possibility of the participation in the similar condensation of monosubstituted hydrazones with β -hydroxy carbonyl compounds. Whereas monosubstituted hydrazones of aliphatic γ - and δ -hydroxy carbonyl compounds are known [4, 5], the existence of monohydrazones of aliphatic β -hydroxy carbonyl compounds is doubtful [6] because of the fact that under the conditions of their preparation they were converted to pyrazoline derivatives. We were able to show that under mild conditions (with cooling and in an inert gas atmosphere) diacetone alcohol (I) reacts smoothly with monoalkylhdyrazines IIa-e to give the corresponding hydrazones IIIa-e in 85-90% yields. Pyrazolines are not formed under the reaction conditions.



II a $R = C_2H_5$; b $R = C_3H_7$; c $R = i - C_3H_7$; d $R = C_4H_9$; e $R = i - C_4H_9$

Monoalkylhydrazones IIIa-e react readily with aldehydes upon moderate heating to give the corresponding 2,3,6,7-tetrahydro-1,3,4-oxadiazepine derivatives (IVa-e). The structures of hydrazones IIIa-e and oxadiazepines IVa-e were confirmed by the IR and PMR spectra, which are presented in Tables 1 and 2. The NH and OH groups that are retained in the molecules appear in the PMR spectra of the hydrazones in the form of a broad singlet with an average chemical shift of \sim 4.7 ppm (2H). The IR spectra of these compounds contain bands at 3200-3400 and 1635 cm⁻¹ that confirm the presence of these groups, as well as a band of the C==N bond. The data from PMR and IR spectroscopy for hydrazones III are in agreement with the data described [4, 5] for monoalkylhydrazones of γ - and δ -hydroxy carbonyl compounds.

Anisochronicity of the 6-H protons and the $7-(CH_3)_2$ groups does not show up in the PMR spectra of 1,3,4-oxadiazepines IVb-e,g-j under our experimental conditions, evidently because of the remoteness from the chiral center and the rapid (on the NMR time scale) pseudorotation of the seven-membered ring.

We also carried out the reaction of hydrazines IIa-e with salicylaldehyde (V) and obtained salicylaldehyde monoalkylhydrazones (VIa-e), which were then used for the study of 2,3-disubstituted 6,7-benzo-2,3-dihydro-1,3,4-oxadiazepines (VIIIa-g) under mild conditions (moderate heating).

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Com- pound	R	PMR spectrum, δ, ppm								
		C(CH ₃) ₂	CH ₂	C-CH3	OH, NH		$\nu_{C=N'}$			
		(\$)	(s)	(\$)	(\$)	CH3	CH ₂ , CH	cm-1		
IIIa IIIb IIIc IIId IIIe	$C_{2}H_{5}$ $C_{3}H_{7}$ $i-C_{3}H_{7}$ $C_{4}H_{9}$ $i-C_{4}H_{9}$	1,22 1,20 1,20 1,19 1,18	2,32 2,30 2,28 2,22 2,24	1,70 1,73 1,73 1,73 1,75	4,5 4,8 4,9 4,5 4,7	1,00 (t) 0,92 (t) 1,08 (d) 0,89 (t) 0,91 (d)	3,05 (q) 1,65 (m), 3,02 (t) 3,30 (sept) 1,4 (m), 2,78 (t) 1,80 (m), 2,86 (d)	$1635 \\ 1632 \\ 1632 \\ 1633 \\ 1633 \\ 1634$		

TABLE 1. Spectral Characteristics of Hydrazones IIIa-e

TABLE 2. Spectral Characteristics of 2,3,6,7-Tetrahydro-1,3,4-oxadiazepines IVa-j

Com-		R'	PMR spectrum, [*] δ, ppm								
pound	R		7-(CH ₃) ₂ (S)	5-CH3 (S)	6-H (S)	2-H	α-CH ₂ (t)	β-CH and γ-CH2 (m)	γ - or δ-CH ₃ (t)	v _{C=N} , cm ⁻¹	
IVa IVb IVc IVd IVf IVf IVf IVf IVh IVj	$\begin{array}{c} C_{3}H_{7}\\ C_{3}H_{7}\\ C_{3}H_{7}\\ C_{3}H_{7}\\ C_{4}H_{9}\\ C_{4}H_{9}\\ C_{4}H_{9}\\ C_{4}H_{9}\\ C_{4}H_{9}\\ C_{4}H_{9}\\ \end{array}$	$\begin{array}{l} {\rm H} \\ {\rm C}_{2}{\rm H}_{5} \\ i \cdot {\rm C}_{6}{\rm H}_{7} \\ {\rm C}_{6}{\rm H}_{5} \\ {\rm C}_{6}{\rm H}_{4}{\rm O}{\rm H} \text{-}o \\ {\rm H} \\ {\rm C}_{2}{\rm H}_{5} \\ i \cdot {\rm C}_{3}{\rm H}_{7} \\ {\rm C}_{6}{\rm H}_{5} \\ {\rm C}_{6}{\rm H}_{4}{\rm O}{\rm H} \text{-}o \end{array}$	$1,20 \\ 1,32 \\ 1,28 \\ 1,37 \\ 1,38 \\ 1,21 \\ 1,31 \\ 1,31 \\ 1,37 \\ 1,40$	1,93 1,97 1,96 2,07 2,06 1,95 1,97 1,99 2,08 2,08	2,56 2,60 2,65 2,67 2,67 2,67 2,60 2,61 2,65 2,69	4,16 (s) 4,90 (t) 4,95 (d) 5,31 (s) 5,35 (s) 4,18 (s) 4,96 (d) 5,29 (s) 5,32 (s)	2,88 2,88 2,88 3,03 3,06 2,98 2,98 2,98 2,98 3,02 3,00	$\begin{matrix} 1,3-2,0\\ 1,3-2,0\\ 1,3-2,0\\ 1,9\\ 1,9\\ 1,3-2,0\\ 1,3-2,0\\ 1,3-2,0\\ 1,3-2,0\\ 1,8\\ 1,9\end{matrix}$	0,92 0,93 0,96 0,98 0,92 0,93 0,91 0,92 0,93	$\begin{array}{c} 1645\\ 1640\\ 1640\\ 1645\\ 1645\\ 1645\\ 1640\\ 1640\\ 1640\\ 1645\\ 1645\\ 1645\end{array}$	

*The proton chemical shifts of the substituents in the 2 position are not indicated.

TABLE 3. Spectral Characteristics of Hydrazones VIa-e

Com- pound	R			IR spe	IR spectrum, v, cm-1			
		HC=N (S)	C6H4 (M)	OH (S)	СН₃	CH ₂ , CH	C=N	aryl
VIa VIb VIc VId VIe	$C_{2}H_{5}$ $C_{3}H_{7}$ $i-C_{3}H_{7}$ $C_{4}H_{9}$ $i-C_{4}H_{9}$	7,19 7,20 7,25 7,24 7,25	6,7 6,7 6,7 6,7 6,7 6,7	11,1 11,0 11,2 11,0 10,9	1,17 (t) 0,96 (t) 1,06 (d) 0,96 (t) 0,98 (d)	3,15 g 1,9m, 3,07 (t) 3,28 (hex) 1,8m, 3,05 (t) 2,1m, 3,05 (d)	1632 1630 1630 1632 1630	1600, 1580 1600, 1580 1600, 1580 1600, 1580 1600, 1580 1600, 1580

TABLE 4. Spectral Characteristics of VIIIa-g

Com-		R'	PMR spectrum, δ, ppm							
pound	R		HC=N (\$)	2-H	R	R′	C ₆ H ₄	vC=N' cm ⁻¹		
VIIIa	i-C₃H7	3-Pyridy1	7,75	4,32 (s,	1,12 (t), 1,6 (m),	4,32 (s)	7,1 (s)	1640		
VIIIb VIIIc VIIId VIIIe	C_4H_9 C_4H_9 C_4H_9 C_4H_9	C ₆ H5 C6H4OH-0 H C2H5	7, 7 6 7, 7 5 7,78 7,98	4,82 (t) 4,87 (d) 4,83 (t) 4,95 (s)	3,27 (t)* 3,26 (t)* 3,26 (t)* 1,27 (t), 1,8 (m),	7—7,9 (m)	7,0 (m) 6,98 (m) 6,97 (m) 7 (m)	$1638 \\ 1638 \\ 1638 \\ 1638 \\ 1643$		
VIII	C ₄ H ₉	i-C ₃ H7	7,90	5,08 (s)	1,25 (t), 1,8 (m),	7,3 (m)	7,3 (m)	1640		
VIIIg	C₄H9	C ₃ H ₇	7,89	5,01 (\$)	3,30 (t) 1,27 (t), 4,8 (m), 3,40 (t)	6,9—7,3 (m)	7,0 (m)	1642		

*The signals of the remaining protons of the R and R' substituents are unresolved multiplets.

	Yield,	%	88888899999999999999999999999999999999
	Calculated	MR_D	4 10 10 10 10 10 10 10 10 10 10 10 10 10
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		Н, %	
		C, %	0 0 0 0 0 0 0 0 0 0 0 0 0 0
	Empirical	formula	$C_{16}^{0}H_{28}^{0}N_{2}^{0}O_{2}O_{2}O_{2}O_{2}O_{2}O_{2}O_{2}O_{2$
ĺ	Found	MR_D	40000000000000000000000000000000000000
		х,%	レゆの444000441-000万0044400000001-1 の一一のの4255/257-1555445000004001-1 の一一のの4255/257-155545500000400040004
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:punodu	d_{4}^{20}		0,95622 0,95022 0,9406 0,9406 0,9406 0,9421 0,9565 0,9421 0,94235 0,94256 0,94256 0,95655 0,95656 0,95656 0,95655 0,95656 0,95655 0,95656 0,95655 0,95655 0,95656 0,95655 0,95655 0,95656 0,95655 0,955555 0,955550 0,955550 0,955550 0,955550 0,955550 0,9555500 0,9555500 0,955500 0,9555000 0,9555000 0,95550000000000
ized Co	n_D^{20}		1,4780 1,4780 1,4670 1,4670 1,4670 1,4680 1,4680 1,4680 1,4715 1,4715 1,4715 1,4715 1,4715 1,4620 1,4620 1,5845 1,5845 1,5845 1,5845 1,55855 1,55855 1,55855 1,55855 1,55855 1,558555 1,55855 1
f the Synthes:	b p, ° C (mm)		$\begin{array}{c} 97 & (2) \\ 102 & (2) \\ 108 & (2) \\ 108 & (2) \\ 113 & (2) \\ 113 & (2) \\ 113 & (2) \\ 91-92 & (5) \\ 91-92 & (5) \\ 91-92 & (5) \\ 122-133 & (5) \\ 132-133 & (5) \\ 132-133 & (5) \\ 132-140 & (5) \\ 142-143 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 156-157 & (5) \\ 1220 & (0,08) \\ 112-113 & (0,08) \\ 120 $
teristics o	R,		H C ₂ H5 C ₂ H5 C ₂ H5 C ₂ H5 C ₂ H5 C ₂ H5 C ₂ H4 C ₂ H5 C ₂ H5 C ₂ H5 C ₂ H5 C ₂ H5 C ₂ H6 C ₂ H5 C ₂ H6 C ₂ H6
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TABLE 5	Com- pound		VIII B VIII B VII



VII a R'=H; b $R'=C_2II_5$; c $R'=i-C_3H_7$; d $R'=C_3H_7$; e $R'=C_6H_5$; f $R'=o-C_6H_4OH$; g R'=3-pyridy1

The structures of VI and VIII are confirmed by the set of analytical and spectral data presented in Tables 3-5.

EXPERIMENTAL

The PMR spectra of 15% solutions of the compounds in CC14 were recorded with a Varian HA-100D spectrometer with tetramethylsilane as the internal standard. The IR spectra of thin layers of the pure substances were recorded with a UR-20 spectrometer.

<u>Diacetone Alcohol Monoalkylhydrazones (IIIa-e) and Salicylaldehyde Monoalkylhydrazones</u> (VIa-e). A solution of 0.1 mole of diacetone alcohol (I) or salicylaldehyde (V) in 30 ml of absolute benzene was added with stirring in a stream of nitrogen to an ice-cooled solution of 0.1 mole of alkylhydrazine II in 30 ml of benzene at such a rate that the temperature did not rise above 15°C. The mixture was then stirred for another hour at room temperature, after which it was dried with sodium sulfate. The benzene was evaporated, and the residue was fractionated *in vacuo* in a stream of nitrogen. This method was used to obtain hydrazones IIIa-e and VIa-e (Table 5).

<u>2H-3-Alkyl-5,7,7-trimethyl-2,3,6,7-tetrahydro-1,3,4-oxadiazepines (IVa,f) and 6,7-Benzo-</u> <u>2,3-dihydro-1,3,4-oxadiazepine (VIIId)</u>. A solution of 10g of paraformaldehyde in 20 ml of warm benzene was added with stirring in a stream of nitrogen in the course of 1 h to a solution of 0.1 mole of alkylhydrazone IIIb,c or VId in 15 ml of absolute benzene, after which the mixture was stirred at 50°C for 2 h. Anhydrous sodium sulfate was added, and the mixture was allowed to stand for 24 h. The benzene was evaporated, and the residue was fractionated *in vacuo* in a stream of nitrogen. This method was used to obtain IVa,f and VIIId (Table 5).

<u>2,3-Dialkyl-5,7,7-trimethyl-2,3,6,7-tetrahydro-1,3,4-oxadiazepines (IVb-e,g-j) and 6,7-Benzo-2,3-dihydro-1,3,4-oxadiazepines (VIIIa-c,e-g).</u> A mixture of 0.1 mole of the alkylhydrazone (IIIb,c or VIb,d) and 0.1 mole of the aldehyde (VIIa-g) was heated at 70°C in a stream of nitrogen for 2 h, after which it was slowly heated *in vacuo* to 100°C, and the water was removed by distillation. The residue was fractionated *in vacuo* in a stream of nitrogen. Oxadiazepine derivatives (Table 5) were obtained by repeated distillation *in vacuo* in a stream of nitrogen.

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