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1,1-DIALKYL-2-ACYL-3-HYDROXYPYRAZOLIDINIUM AND 2,2-DIALKYL-5-HYDROXYISOXAZOLIDINIUM SALTS

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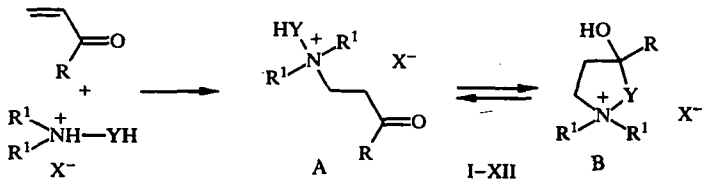
Salts of 1,1-dimethyl-2-acylhydrazines and 1,1-dialkylhydroxylamines add quantitatively to the double bond of oxo compounds with an unsubstituted vinyl substituent. The structure of the products depends on the nature of the substituent at the carbonyl group. ^1H and ^{13}C NMR spectroscopy indicated that acrolein derivatives have the cyclic structure of 1,1-dialkyl-2-acyl-3-hydroxypyrazolidinium and 2,2-dialkyl-5-hydroxyisoxazolidinium salts, while derivatives of phenyl vinyl ketone and hydrazide salts are the corresponding linear hydrazinium salts. Ring–chain tautomerism was found for several derivatives of methyl vinyl ketone in solution.

The information available on the reaction of acrolein [1, 2] and methyl vinyl ketone [3, 4] with N,N-dimethylhydrazine salts, on one hand, and the reaction with 1-alkyl- and 1-aryl-2-acylhydrazines [5-7], on the other, indicated the feasibility of a reaction between α,β-unsaturated carbonyl compounds and salts of 1,1-dialkyl-2-acylhydrazines and N,N-dialkylhydroxylamines, which was shown to be possible in principle in our previous work [8]. Detailed results are given here on the features of this reaction and the structure of its products. We found that the reaction proceeds only with α,β-unsaturated carbonyl compounds possessing an unsubstituted vinyl group. Mesityl oxide, crotonaldehyde, cinnamaldehyde, and methacrolein all do not undergo this reaction. However, the reaction readily proceeds with acrolein, methyl vinyl ketone, and phenyl vinyl ketone to give 1:1 addition products (I-XII) in rather high yields (Table 1).

The structures of I-XII are determined by the nature of the substituent at the carbonyl group. In the reaction with acrolein, independently of the nature of the substituent at the acyl group of the hydrazide molecule, products I-IV have the cyclic structure of 1,1-dialkyl-2-acyl-3-hydroxypyrazolidinium salts (B) similar to derivatives of hydroxylamines XI and XII, which are 2,2-dialkyl-5-hydroxyisoxazolidinium salts, as demonstrated by the PMR signals for 3-H (5-H in the case of XI and XII) at 5.8-6.2 ppm and for the hydroxyl group at 6.9-9.2 ppm and by the magnetic inequivalence of the methyl groups at the nitrogen atom due to their diastereotopy resulting from the chiral center at the carbon atom bound to the hydroxyl group (Table 2).



Ia X = Cl, Y = NCOH, R = H; Ib X = CF_3COO, Y = NCHO, R = H; II X = Cl, Y = $NCOCH_3$, R = H;
III X = Cl, Y = $NCOCH_2COCH_3$, R = H; IV X = CF_3COO, Y = $NCOC_6H_5$, R = H;
V X = Cl, Y = NCOH, R = CH_3; VI X = CF_3COO, Y = $NCOCH_3$, R = CH_3; VII X = CF_3COO,
Y = $NCOC_6H_5$, R = CH_3; VIII X = CF_3COO, Y = NCOH, R = C_6H_5
; IX X = Cl, Y = $NCOCH_2COCH_3$, R = C_6H_5; X X = CF_3COO, Y = $NCOC_6H_5$, R = C_6H_5;
XI X = Cl, Y = O, R = H; XII X = Cl, Y = O, R = H;
I—XI $R^1 = CH_3$; XII $R^1 = CH_2C_6H_5$

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TABLE 1. Indices of Compounds Synthesized

Compound	Chemical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
Ia	$C_6H_{13}ClN_2O_2$	39,72 39,99	7,55 7,25	15,36 15,51	161...162	59
Ib	$C_8H_{13}F_3N_2O_4$	36,98 37,22	5,67 5,07	10,59 10,85	97...98	79
II	$C_7H_{15}ClN_2O_2$	43,31 43,19	8,05 7,77	14,23 14,39	127...128	56
III	$C_9H_{17}ClN_2O_3$	45,47 45,67	7,48 7,24	11,95 11,84	174...175	67
IV	$C_{14}H_{17}F_3N_2O_2$	50,42 50,30	5,58 5,13	8,12 8,38	*2	84
V	$C_7H_{15}ClN_2O_2$	43,58 43,19	8,05 7,77	14,59 14,39	134...135	75
VI	$C_{10}H_{17}F_3N_2O_4$	41,86 41,96	6,29 5,59	10,01 9,79	*2	78
VII	$C_{15}H_{19}F_3N_2O_4$	51,68 51,71	6,04 5,50	7,87 8,04	*2	79
VIII	$C_{14}H_{17}F_3N_2O_4$	49,88 50,30	5,65 5,13	8,63 8,38	*2	80
IX	$C_{15}H_{21}ClN_2O_3$	57,39 57,60	6,92 6,77	8,26 8,96	*2	74
X	$C_{20}H_{21}F_3N_2O_4$	58,17 58,53	5,47 5,16	6,59 6,83	*2	75
XI	$C_5H_{12}ClNO_2$	38,85 39,10	7,98 7,87	9,26 9,12	125...126	85
XII	$C_{17}H_{20}ClNO_2$	67,09 66,77	6,32 6,59	4,65 4,58	127...128	76

*The solvent was 3:1 acetonitrile–methanol.

*2Oil.

The ^{13}C NMR spectra of some of these compounds show a signal for sp^3-hybridized $C_{(3)}$ at 83.3-94.3 ppm, characteristic for hydroxypyrazolidines with a hemiaminal fragment [5] (103.1 ppm for $C_{(5)}$ with its O,O-environment in XI). The other details of the ^1H and ^{13}C NMR spectra of I-IV are in complete accord with the proposed structure. Chemical evidence for the structures of salts I-IV is found in the aminonitrile decomposition carried out for Ib [8].

In going to α,β-unsaturated ketones, we might expect formation of quaternary N-acylhydrazinoalkanone salts by analogy with previous results for the reaction with β-alkylhydrazides [6]. Indeed, the products of the reaction of 1,1-dimethyl-2-acylhydrazine salts with methyl vinyl ketone (VI, VII) and phenyl vinyl ketone (VIII-X) do not undergo cyclization and are the corresponding quaternary salts with linear structure A. This conclusion is based on the PMR spectra (Table 2), in which the signals for the N-methyl groups are equivalent.

However, salt V obtained by the reaction of 1,1-dimethyl-2-formylhydrazine hydrochloride with methyl vinyl ketone has the structure of the corresponding pyrazolidinium salt (B) in the crystalline state, as indicated by the PMR spectrum of its freshly prepared solution both in CD_3OD and in DMSO-d_6. However, a tautomeric equilibrium A $\rightleftarrows$ B is established in these solvents over a few hours, leading to a doubling of all the PMR signals (Table 2). The tautomers may be reliably identified using the signal for the methyl group at the C=O bond at 2.15-2.18 ppm in linear tautomer A and upfield at 1.82-1.84 ppm for cyclic form B. A doubling of all signals is also observed in the ^{13}C NMR spectrum of this salt (see Table 3). The position of the A $\rightleftarrows$ B equilibrium for the methyl vinyl ketones (V-VII) depends on the nature of the N-acyl substituent. Tautomerism occurs when Y = NCOH in the case of V. However, if Y = $NCOCH_3$ or $NCOC_6H_5$, the compound can have only linear structure as for VI and VII (form A).

Salts I-IV, XI, and XII obtained from acrolein are stable in solution and in the solid state and do not decompose upon brief heating. Derivatives of methyl vinyl ketone and phenyl vinyl ketone, namely, V-X, are stable in the absence of solvent but undergo partial retrodecomposition (to a greater extent in DMSO-d_6 and to a lesser extent in CD_3OD and $CDCl_3$). This is indicated by the appearance of PMR signals of the starting ketone and hydrazide upon storage of the solutions or immediately upon raising the temperature. Thus, these compounds were isolated from the reaction mixtures without heating.

TABLE 2. PMR Spectra of Compounds Synthesized

Compound	Solvent	Form	Chemical shift, ppm					
			5-H, 3-H*	4-H	NCH_3*2	R	OH	Y
Ia	DMSO-d_6	B	4,41 (2H, m)	2,22 (1H, m); 2,79 (2H, m)	3,65 (3H, s); 4,03 (3H, s)	6,12 (1H, m)	8,08 (1H, br.s)	8,87 (1H, s)
Ib	DMSO-d_6 $CDCl_3$	B	4,58 (2H, m)	2,50 (1H, m); 2,84 (1H, m)	3,84 (3H, s); 4,00 (3H, s)	6,15 (1H, m)	6,90 (1H, br.s)	8,78 (1H, s)
II	DMSO-d_6	B	4,57 (2H, m)	2,60 (1H, m); 2,80 (1H, m)	3,72 (3H, s); 3,93 (3H, s)	5,92 (1H, m)	7,82 (1H, br.s)	2,34 (3H, s)
III	DMSO-d_6	B	4,46 (2H, m)	2,60 (1H, m); 2,83 (1H, m)	3,79 (3H, s); 3,92 (3H, s)	5,83 (1H, m)	8,14 (1H, br.s)	2,3 (3H, s, CH_3CO), 4,13 (2H, s, CH_2)
IV	DMF-d_7	B	4,46 (2H, m)	1,92 (1H, m); 2,35 (1H, m)	3,78 (3H, s); 3,96 (3H, s)	5,85 (1H, m)	8,50 (1H, br.s)	7,36...7,92 (5H, m, H_{arom})
V	CD_3OD	B*3	4,00 (2H, m)	2,60 (1H, m);	3,76 (3H, s);	1,84 (3H, s)	—	8,63 (1H, s)
		A	4,31 (2H, t)	2,85 (2H, m)	3,90 (3H, s)			
				3,43 (2H, m)	3,37 (6H, s)	2,15 (3H, s)		8,14 (1H, s)
VI	CD_3OD	A	3,59 (2H, t)	2,67 (2H, m)	3,24 (6H, s)	1,99 (3H, s)	—	2,15 (3H, s)
VII	CD_3OD	A	4,5 (2H, t)	2,56 (2H, t)	3,17 (6H, s)	2,02 (3H, s,)	—	7,42...7,89 (5H, m, H_{arom})
VIII	$CDCl_3$	A	3,91 (2H, m)	2,82 (2H, m)	3,19 (6H, s)	7,56...8,00 (5H, m, H_{arom})	—	8,14 (1H, s)
IX	$CDCl_3$	A	4,00 (2H, t)	2,70 (2H, m)	3,44 (6H, s)	7,64...8,26 (5H, m, H_{arom})	—	2,28 (3H, s, CH_3CO); 3,72 (2H, s, CH_2)
X	$CDCl_3$	A	4,64 (2H, t)	2,47 (2H, t)	3,25 (6H, s)	7,24...7,76 (5H, m, H_{arom})	—	7,24...7,76 (5H, m, H_{arom})
XI	DMSO-d_6	B	4,3 (2H, m)	2,78 (1H, m); 3,04 (1H, m)	3,57 (3H, s); 3,71 (3H, s)	5,96 (1H, m)	8,28 (1H, br.s)	—
XII	DMF-d_7	B	5,36 (3H, m)*4; 4,40 (3H, m)*5	2,06 (1H, m); 1,18 (1H, m)	7,20...8,00 (10H, m)	5,82 (1H, d)	9,20 (1H, br.s)	—

*For XI and XII.

*2$NCH_2C_6H_5$ for XII.

*3A:B = 2:3.

*43-H_e and H_A part of AB system of the two benzylic CH_2 protons.

*53-H_a and H_B part of AB system of the two benzylic CH_2 protons.

TABLE 3. ^{13}C NMR Spectra of Compounds Synthesized

Compound	Form	Chemical shift, ppm
Ib*	B	159,1 (COO^-); 158,5 (HCO); 117,1 (CF_3); 83,3 ($C_{(3)}$); 69,3 ($C_{(5)}$); 56,7 and 53,7 [$(NCH_3)_2$]; 30,2 ($C_{(4)}$)
V*	B	27,3 (CH_3); 37,5 ($C_{(4)}$); 69,3 ($C_{(5)}$); 94,3 ($C_{(3)}$); 56,1 and 57,1 [$N(CH_3)_2$]; 158,3 (CHO); 179,1 (C=O);
	A	15,7 (CH_3O; 40,4 (CH_2); 63,6 (CH_2N); 55,2 [$N(CH_3)_2$]; 164,3 (CHO)
XI*[2]	B	103,1 ($C_{(3)}$); 65,6 ($C_{(5)}$); 57,7 and 55,7 [$N(CH_3)_2$]; 34,4 ($C_{(4)}$)

*In DMSO-d_6.

*[2]In CD_3OD.

Therefore, the reaction of α,β-unsaturated carbonyl compounds with hydrazines as a method for the synthesis of a 1,2-diazole [7] is not limited to the classical variant for obtaining 2-pyrazolines in the reaction with hydrazine itself or its 1-monosubstituted derivatives but is also characteristic for 1,1-disubstituted derivatives (1,1-dialkylhydrazine salts give 1,1-dialkyl-2-pyrazolinium salts), 1,2-disubstituted derivatives (β-alkyl- and β-arylhydrazides are used to synthesize 5-hydroxypyrazolidines), and trisubstituted hydrazines (1,1-dialkyl-2-acylhydrazines are used in the synthesis of 1,1-dialkyl-3-hydroxypyrazolidinium salts). A general rule appears to be that the sum of the substituents at the reaction sites (double bond and nitrogen atom) should be not more than three for the addition of nitrogen nucleophiles such as amines, hydrazines, and hydroxylamines both as salts and the free base at the double bond of alkenals and alkenones.

EXPERIMENTAL

The ^1H NMR spectra were obtained on a Tesla BS-497 spectrometer at 100 MHz. The ^{13}C NMR spectra were taken on a Bruker AC-200 spectrometer at 50.32 MHz. The starting hydrazides [9-11], N,N-dimethylhydroxylamine [12], and N,N-dibenzylhydroxylamine [13] were obtained according to reported procedures. The compounds were identified using PMR spectroscopy both in the free state and as hydrochloride or fluoroacetate salts. The synthesis of phenyl vinyl ketone was carried out according to Shur [14].

Synthesis of Salts I-XII. A sample of 12 mmoles unsaturated carbonyl compound was added to a solution of 10 mmoles hydrochloride salt of the corresponding hydrazide or hydroxylamine in 20 ml acetonitrile and maintained for 72-120 h (at 50°C in the case of the reaction with acrolein). For trifluoroacetates, the same procedure was carried out with the free hydrazide in 20 ml CF_3CO_2H. The solvent was removed in vacuum and the residue was washed with three 50-ml portions of ether, recrystallized (for salts I-IV, XI, and XII), dried in vacuum, and stored in a desiccator over P_2O_5. Salts V-X were washed with ether. The indices for products I-XII are given in Table 1.

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