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INTERACTION OF 5-HYDROXYPYRAZOLIDINES WITH CH-ACID COMPOUNDS

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The interaction of 1-acetyl-2-phenyl-5-hydroxypyrazolidine with carbonyl compounds on the surface of acidic aluminum oxide results in the formation of products in which the hydroxyl group has been replaced by the residue of the carbonyl compound. It has been shown that derivatives of β-dicarbonyl compounds, under the conditions of the reaction, may undergo subsequent conversions in which one of the carbonyl-containing residues is split off.

It had been shown previously [1, 2] that 5-hydroxypyrazolidines, the hydroxyl group of which readily enters into a nucleophilic substitution reaction, can serve as convenient starting compounds for the synthesis of various derivatives of saturated azolidines. In contrast to N- and O-nucleophiles, interaction with C-nucleophiles proceeds in a more complex manner; and up to the present time, satisfactory results have been obtained only when using indoles as the C-nucleophilic agent [3]. The development of methods for introducing a pyrazolidine fragment into organic compounds with the formation of a C–C bond is an extremely promising approach, not only from the standpoint of possible synthesis of new, potentially bioactive organic substances, but also from the standpoint of expanding the use of azolidines in organic synthesis. In the present work, therefore, we have examined the synthesis of pyrazolidine derivatives containing a functionalized hydrocarbon radical in position 5.

An attempt to carry out the reaction of 1-acetyl-2-phenyl-5-hydroxypyrazolidine (Ia) with sodium acetoacetic ester in solution resulted in the formation of only an insignificant quantity of the corresponding (pyrazolidinyl-5)acetoacetic ester; the reaction was accompanied by decomposition of the original hydroxypyrazolidine and the formation of large amounts of tar. Such instability of the original compound in the presence of a strong base made it necessary to use the un-ionized acetoacetic ester; in turn, however, this required additional activation of the reactants. The most convenient method proved to be one that we had developed previously for the synthesis of hydroxyisoxazolidines [4], in which the reaction is performed on the surface of an adsorbent without solvent. Upon interaction of the pyrazolidine Ia with acetoacetic ester on acidic aluminum oxide, we recovered the substitution product IIa in which the hydroxyl group of the pyrazolidine has been replaced by the radical of the CH-acid compound; the yield was considerably higher than that obtained by performing the reaction in solution, and no tar formation was observed.

In the PMR spectrum of compound IIa, the signal of the CH proton of the acetoacetic ester was observed at 3.28 ppm; the signal of the carbon atom of this group was observed at 62.08 ppm in the ^{13}C NMR spectrum; and the absorption band of the carbonyl group was observed at 1720 cm^{-1} in the IR spectrum. All of these observations point to the existence of this fragment of the molecule in the keto form. The spectroscopic data did not give any indication of the presence of the enol form.

Analogously, the interaction of the hydroxypyrazolidine Ia with acetone, acetophenone, and nitromethane on aluminum oxide resulted in the formation of the respective compounds IIIb-d (Tables 1-3).

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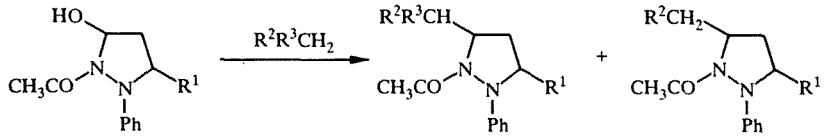


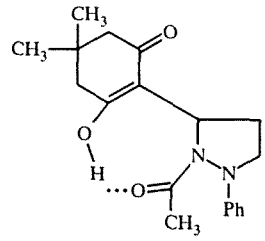
Ia,b IIa-g IIIb-e

The course of the reaction with diketones was more complex. Interaction of the pyrazolidine Ia with acetylacetone resulted in the formation of a mixture of the expected diketone IIb (also existing in the keto form), the acetonyl derivative IIIb, and aluminum trisacetylacetonate. Recovery of the aluminum compound suggests that, in this reaction, the activation of reactants upon adsorption is related to enolization of the carbonyl compounds on the surface of the aluminum oxide.

The formation of compound IIIb in the reaction with acetylacetone, identical to the compound IIIb obtained by the interaction of the pyrazolidine Ia with acetone, may take place as a result of splitting of the initially formed substitution product Ib, and/or attack, through a hydroxyl group, of a molecule of acetone previously formed by the decomposition of acetylacetone on aluminum oxide. Actually, we showed that under the conditions of the reaction, compound IIb undergoes conversion to the derivative IIIb in 2 days. At the same time, dicarbonyl compounds adsorbed on aluminum oxide can also decompose. Thus, benzoylacetone is completely split into acetophenone and acetone in 2 days under the conditions of the reaction. The reaction of the hydroxypyrazolidine Ia with benzoylacetone on aluminum oxide is completed in 1 day; after this reaction, we recovered from the reaction mixture only the products from splitting the diketone derivative IIIb and IIIc in a 1:2 ratio. It should be noted that decomposition of the benzoylacetone derivative IIc proceeds at a higher rate than the formation of this compound or the decomposition of the original benzoylacetone. Thus, we can assume simultaneous occurrence of both processes on the adsorbent – decomposition of the substituted diketones IIb and IIc, and splitting of the original diketones with subsequent substitution.

Interaction of the hydroxypyrazolidine Ia with nitroacetic ester gives primarily the nitromethyl derivative IIId, identical to that obtained in the reaction with nitromethane. The ester IId is formed in small amounts and is readily decomposed on chromatographic sorbents in attempts to purify this compound. Replacement of the hydroxy group by a malonic ester residue proceeds only with great difficulty; the reaction is slow, and the corresponding compounds IIe and IIIe are obtained with low yields, in a 6:1 ratio. Since it had been shown that there is no direct interaction between the pyrazolidine Ia and ethyl acetate on aluminum oxide, in the present case the compound IIIe can be formed only by splitting the diester IIe.

In contrast to the noncyclic β-diketones, dimedone reacts with the pyrazolidine Ia to form only the cyclic compound IIg, which does not undergo any subsequent splitting under the conditions of the reaction, and which exists in solution entirely in the enol form. Here, IR spectroscopic data indicate that the hydrogen bond is intramolecular and is effected through the amide oxygen atom rather than the carbonyl oxygen, possibly because of the spatial closeness of the amide oxygen atom and the proton of the enolic hydroxyl group.



IIg

The introduction of a substituent into the pyrazolidine ring in position 3 leads to the formation of two chiral centers in the molecules of compounds II and III, and offers a means for judging the stereochemistry of nucleophilic substitution. It had been previously shown by means of x-ray spectroscopic analysis [5] that the original hydroxypyrazolidine Ib exists exclusively in the form of the trans-isomer. The steric structure of compounds IIf and IIIf was investigated by means of NMR using the nuclear Overhauser effect (see Table 4).

TABLE 1. Characteristics of Synthesized Compounds II and III

Compound	R^1	R^2	R^3	Empirical formula	Reaction-time, days	mp, °C	IR spectrum, cm^{-1}	Yield,* %
IIa	H	COMe	CO_2Et	$C_{17}H_{22}N_2O_4$	3*[2]	115	1680, 1720, 1740	A 16
IIb	H	COMe	COMe	$C_{16}H_{17}N_2O_3$	2	130	1670, 1710	A 14
IIc*[3]	H	COMe	COPh	$C_{21}H_{22}N_2O_3$	1			
IId	H	NO_2	CO_2Et	$C_{15}H_{19}N_3O_5$	1	Oil	1520, 1330, 1660, 1760	A 2
IIe	H	CO_2Et	CO_2Et	$C_{18}H_{24}N_2O_5$	10	Oil	1685, 1740	A 7
IIf	CH_3	COMe	CO_2Et	$C_{18}H_{24}N_2O_4$	2	129	1680, 1725, 1750	A 9
IIg	H	*[4]		$C_{19}H_{24}N_2O_3$	7	Oil	1680, 1725, 2900... 3400	A 10
IIIb*[5]	H	COMe		$C_{14}H_{18}N_2O_2$	1	90	1665, 1725	A 41 B 10 C 3
IIIc*[5]	H	COPh		$C_{19}H_{20}N_2O_2$	1	Oil	1675, 1680	A 8 B 11
IIId	H	NO_2		$C_{12}H_{15}N_3O_3$	1	106	1680, 1500, 1330	A 42 B 42
IIIe	H	CO_2Et		$C_{15}H_{20}N_2O_3$	10	Oil	1670, 1740	A 2
IIIf	CH_3	NO_2		$C_{13}H_{17}N_3O_3$	2	64...65	1680, 1500, 1385	B 20

*A) Yield of compound from reaction with bifunctional derivative; B) yield of compound from reaction with monofunctional derivative; C) yield of compound upon decomposition of bifunctional derivative II.

*[2]Compound IIa was obtained at room temperature, others at 60°C.

*[3]Compound was not recovered.

*[4]Product of reaction with dimedone.

*[5]Mass spectrum, m/z (%): IIIb 246 (14.3, M^+), 204 (25.4), 203 (100), 146 (38.9), 145 (11.7), 144 (15.4), 120 (15.9), 105 (6.8), 104 (22.9), 91 (5.2), 77 (25.7), 58 (43.4), 57 (6.9); IIIc 308 (4.4, M^+), 266 (9.1), 265 (25.7), 162 (8.2), 147 (10.3), 146 (44.2), 145 (6.4), 106 (10.3), 105 (100), 104 (6.8), 91 (6.6), 77 (38.3).

Upon interaction of the trans-hydroxypyrazolidine Ib with acetoacetic ester, we recovered only the one isomer IIf, which was assigned the trans-configuration on the basis of NMR data. In the reaction of the trans-pyrazolidine Ib with nitromethane, which is less bulky in the steric sense, we observe the formation of a mixture of cis- and trans-isomers of IIIf in a 1:2 ratio. Upon irradiation of the 5-H and 4-H′ protons, an NOE was observed only for one of the protons of the CH_2NO_2 group, suggesting that in the compounds IIIf, the same as in the original pyrazolidine Ib, the $C_{(5)}$ carbon atom deviates from the plane of the pyrazolidine ring. The preservation of configuration upon substitution can be explained if we assume that the reaction proceeds through a mechanism similar to SN_1 and that the binding of the pyrazolidine molecule to the adsorbent surface is accomplished primarily from the side of the plane of the ring opposite the hydroxyl group.

EXPERIMENTAL

IR spectra were measured in UR-20 and Specord IR-75 instruments in white mineral oil or methylene chloride. PMR spectra were obtained in Tesla BS-467 (60 MHz) and Varian VXR-400 (400 MHz) spectrometers at 28°C, using TMS or HMDS as an internal standard. ^{13}C NMR spectra were measured in Varian FT-80 and VXR-400 spectrometers. For the experiments with NOE, the NOEDIF program was used [6]. Mass spectra were obtained in a Varian MAT-212 instrument (70 eV) with direct introduction of the substance at temperatures close to the respective melting points of the samples. GLC analysis was performed in a Chrom-5 instrument. The course of the reactions and the purity of the products were monitored

TABLE 2. PMR Spectra of Compounds II and III in $CDCl_3$, δ in ppm (and J in Hz)

Compound	3-H(R)	4-H	5-H	5-R	2-$COCH_3$ (s, 3H)	Ar (5H)
IIa	3,21 (m,1H), 3,77 (m,1H)	1,53 (m,1H), 2,49 (m,1H)	4,85 (m,1H)	1,27 (t, 3H), 4,19 (d,q 2H (7,2)), 3,31 (m, 1H), 1,98 (s, 3H)	2,09	6,90 (d, 1H), 7,09 (d, 2H), 7,35 (d, 2H)
IIb	3,31 (m,1H), 3,76 (m,1H)	1,57 (m,1H), 2,42 (m,1H)	5,07 (m,1H)	2,12 (s, 3H), 2,29 (s, 3H), 3,66 (d, 1H (11))	2,04	6,87 (d, 2H), 7,07 (d, 1H), 7,35 (d, 2H)
IIe	3,21 (m,1H), 3,76 (m,1H)	1,76 (m,1H), 2,43 (m,1H)	4,88 (dd , 1H (7,1, 8,3))	1,07 (t, 3H (7,0)), 1,12 (t, 3H (7,1)), 3,74 (m, 2H), 4,18 (d, q, 2H (7,1)),3,67 (m, 1H)	2,05	6,89 (d, 2H), 7,07 (d, 1H), 7,21 (d, 2H)
IIf	1,21 (d, 3H (7,6)), 4,15 (m,1H)	1,69 (m,1H), 3,28 (ddd, 1H (1,0, 7,8, 12,8))	4,97 (m,1H)	1,34 (t, 3H (6,9)), 4,25 (m,2H), 3,38 (d, 1H (10,5)), 2,13 (s, 3H)	2,06	6,96 (d, 1H), 7,17 (d, 2H), 7,29 (d, 2H)
IIg	3,75 (m,1H), 4,15 (m,1H)	2,18 (m,1H), 3,09 (m, 1H)	5,18 (dd , 1H (3,8, 9,6))	0,97 (s, 3H), 1,01 (s, 3H), 1,91 (d, 1H (15,9)), 2,03 (dd , 1H (1,0, 16,0)), 2,30 (dd , 1H (4,4, 8,0)), 2,37 (dd , 1H (1,0, 8,2))	2,09	6,76 (d, 2H), 6,88 (t, 1H), 7,19 (t, 2H)
IIIb	3,29 (m,1H), 3,81 (m,1H)	1,55 (m,1H), 2,45 (m,1H)	4,59 (dd, 1H (6))	2,12 (s, 3H), 3,31 (m,1H), 2,45 (m,1H)	2,05	6,95 (d, 1H), 7,27 (d, 2H), 7,31 (d, 2H)
IIIc	3,30 (m,1H), 3,79 (m,1H)	1,68 (m,1H), 2,47 (m,1H)	4,72 (m,1H)	2,85 (dd , 1H (10,5, 15,8)), 4,07 (m,1H), 7,41 (d,2H), 7,51 (d, 1H), 7,90 (d, 2H)	2,05	6,95 (d, 2H), 7,12 (d, 1H), 7,29 (d, 2H)
IIId	3,28 (m,1H), 3,81 (m,1H)	1,79 (m,1H), 2,29 (m,1H)	4,75 (m,1H)	4,07 (m,1H), 4,85 (m,1H)	2,01	6,75 (d, 2H), 7,20 (m, 3H)
IIIe	3,18 (m,1H), 3,82 (m,1H)	1,73 (m,1H), 2,40 (m,1H)	4,65 (m,1H)	1,24 (t, 3H (7,1)), 4,12 (m, 1H), 3,34 (m, 1H), 2,35 (dd , 1H (6))	2,05	6,94 (d,3H), 7,29 (t, 2H)
IIIf (trans)	1,27 (d, 3H (6,8)), 4,25 (m,1H)	1,38 (m,1H), 2,19 (ddd, 1H (1,1, 7,8, 12,8))	5,03 (m,1H)	4,29 (dd , 1H (8,5, 12,4)), 4,90 (dd , 1H (5,7, 12,4))	2,06	6,91 (d, 2H), 6,92 (m, 1H), 7,30 (d, 2H)
IIIf (cis)	1,35 (d, 3H (6,8)), 3,88 (m,1H)	1,70 (m, 1H), 2,49 (m,1H)	4,77 (m,1H)	4,48 (dd , 1H (8,4, 13,4)), 5,58 (dd 1H (5,4, 13,4))	1,98	6,91 (d, 2H), 6,92 (m,1H), 7,30 (t, 2H)

TABLE 3. ^{13}C NMR Spectra of Synthesized Compounds II and III; δ in ppm, in $CDCl_3$

Compound	Pyrazolidine						5-R			Phenyl			
	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$\underline{C}H_3CO$	$CH_3\underline{C}O$	3-CH_3	5-$C_{(1)}$	C=O	RCO	*i*-C	*o*-C	*m*-C	*p*-C
IIa	52,80	32,34	55,85	21,08	175,04	—	64,74	200,87, 167,59	13,94, 29,57, 61,95	150,01	114,89	129,37	121,62
IIb	52,65	32,08	56,37	21,29	176,09	—	74,75	203,34, 201,99	27,95, 30,76	149,95	114,75	129,51	121,84
IIf	55,49	38,78	60,57	21,25	175,73	19,64	65,05	200,80, 167,51	29,34, 13,85, 62,09	150,72	114,68	129,32	121,58
IIg	52,18	28,37	55,20	20,58	177,02	—	112,04	196,36, 128,61	52,60, 44,45, 29,31, 31,59, 27,97	151,31	114,90	129,26	121,86
IIIb	53,18	29,66	53,64	20,92	173,51	—	48,83	205,72	32,13	150,17	114,93	129,90	121,53
IIIc	52,28	30,41	52,60	19,41	172,31	—	42,59	196,03	134,47, 131,29, 127,35, 126,20, 125,03	148,55	113,45	131,35	120,62
IIIf (trans)	54,20	36,72	61,26	21,04	175,36	19,48	77,58	—	—	149,78	114,54	129,32	122,23
IIIf (cis)	54,58	36,45	62,05	22,04	172,14	20,10	75,55	—	—	149,25	117,59	129,48	123,87

TABLE 4. Magnitude of Nuclear Overhauser Effect (η, %) for Compounds IIf and IIIf

Compound	Protons observed	Protons irradiated			
		3-H	5-H	4-H	4-H′
IIf	3-H	—	—	7,3	1,8
	5-H	—	—	—	10,5
	4-H	4,3	—	—	21,8
	4-H′	—	4,7	22,0	—
	5-CH	—	4,3	10,2	—
trans-IIIf	3-H	—	—	—	4,5
	5-H	—	—	6,9	—
	4-H	—	4,3	—	22,6
	4-H′	4,0	—	22,8	—
	CH_2NO_2	—	3,0*	—	1,4*
cis-IIIf	3-H	—	—	6,0	—
	5-H	—	—	8,2	—
	4-H	2,4	3,9	—	24,7
	4-H′	—	—	25,2	—
	CH_2NO_2	—	4,0*[2]	—	3,4*

*Only the signal of the upfield proton increases in intensity.

*[2]Only the signal of the downfield proton increases in intensity.

by TLC on Silufol UV-254 and Alufol plates in a 1:1 system of benzene and ethyl acetate, using as the developer an alcoholic solution of ferric chloride, an aqueous solution of potassium permanganate, or iodine vapor. The products were purified by flash chromatography on L 40/100 silica gel in a 5:5:1 system of benzene, ethyl acetate, and petroleum ether, or a 1:1 system of benzene and ethyl acetate (compounds IIa and IIId were recrystallized from ether).

Elemental analyses of the products for C, H, and N matched the calculated values.

Interaction of 5-Hydroxypyrazolidines with C-Nucleophiles (General Procedure). A 2.5-mmole quantity of the 5-hydroxypyrazolidine was dissolved in a minimum quantity of benzene or toluene, and the solution was deposited on calcined aluminum oxide (weight of aluminum oxide 20 times the weight of solution). Then an excess (6-40 mmoles) of the appropriate C-nucleophile was added (benzoylacetone and dimedone were deposited on the adsorbent in benzene), after which the mixture was stirred and the solvent was removed under reduced pressure. The mixture was stored in the dark at room temperature or held in a thermostat at 60°C (see Table 1). After the reaction was completed (as evidenced by TLC data), the reaction product was extracted with chloroform and filtered, and the solvent was removed under vacuum. The residue was chromatographed in a column with silica gel in a system consisting of 5:5:1 benzene, ethyl acetate, and petroleum ether, or 1:1 benzene and ethyl acetate (compounds IIa and IIId were recrystallized from ether).

The constants, reaction conditions, and yields of the compounds are listed in Table 1, PMR spectra in Table 2, and ^{13}C NMR spectra in Table 3.

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