REACTION OF 1,2-HYDROXYLAMINOOXIMES WITH 1,2-DIKETONES. CONVERSION OF 2-ACYL-1-HYDROXY-3-IMIDAZOLINE 3-OXIDES TO PYRAZINE 1,4-DIOXIDES

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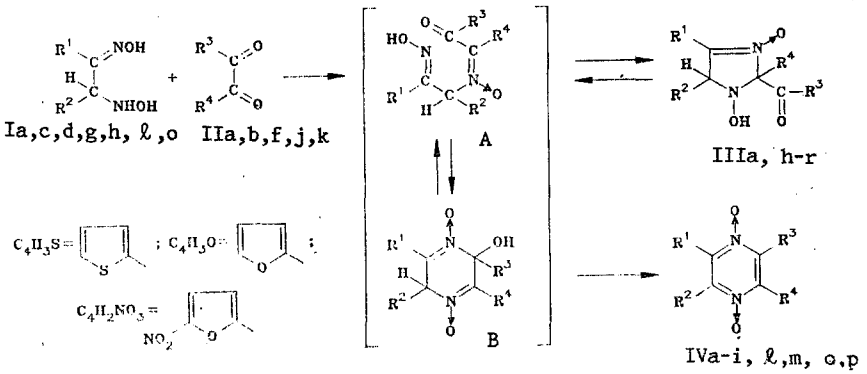
UDC 547.288.4'781.3'861:543.422

The reaction of acyclic primary and secondary 1,2-hydroxylaminooximes with aliphatic, alkylaromatic, and alkylheteroaromatic 1,2-diketones, depending on the structure of the starting compounds and the reaction conditions, gives derivatives of pyrazine 1,4-dioxide, 2-acyl-1-hydroxy-3-imidazoline 3-oxide, or mixtures thereof. 2-Acyl-1-hydroxy-3-imidazoline 3-oxides have been converted to pyrazine 1,4-dioxides.

It has previously been shown that when 2-hydroxyamino-1-phenyl-1-propanone oxime (E isomer) (Ih) reacts with biacetyl (IIa) in alcohol with heating, 2-acetyl-1-hydroxy-2-5, dimethyl-4-phenyl-3-imidazoline 3-oxide (IIIh) [1] is formed whereas condensation of alicyclic 1,2-hydroxylaminooximes with 1,2-diketones gives condensed pyrazine 1,4-dioxides [2, 3]. The present work considers the reaction of primary and secondary* acyclic 1,2-hydroxylaminooximes I with 1,2-diketones II in order to elucidate the factors that affect the course of the condensation.



a,b,h-k) R^1 = Ph; c R^1 = $C_4H_2NO_3$; d-g) R^1 = CH_3; ℓ-n) R^1 = C_4H_3S; o-r) R^1 = C_4H_3O; a-f) R^2 = H, g-r) R^2 = CH_3, a,d, g,h, ℓ,o) R^3 = CH_3; f,i,m,p) R^3 = Ph; j,n,q) R^3 = C_4H_3S, k, r) R^3 = C_4H_3O; a,d,f-r) R^4 = CH_3; b,c) $R^3 + R^4 = (CH_2)_4$.

In contrast to the secondary 1,2-hydroxylaminooxime Ih [1], condensation of the primary 2-hydroxyamino-1-phenylethanone oxime (E isomer) (Ia) with biacetyl in alcohol with heating gives 2,3-dimethyl-5-phenylpyrazine 1,4-dioxide (IVa) in 72% yield, while 2-acetyl-1-hydroxy-2-methyl-4-phenyl-3-imidazoline 3-oxide (IIIa) was isolated in only 3% yield. When kept in alcoholic solution at 20° for 6 days compound IIIa is converted quantitatively to pyrazine 1,4-dioxide IVa. Condensation of other primary 1,2-hydroxylaminooximes Ic, d with biacetyl

*For brevity, 1,2-hydroxylaminooximes with a hydroxylamino group at the primary or secondary carbons are designated primary or secondary 1,2-hydroxylaminooximes.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 331-338, March, 1986. Original article submitted February 15, 1985.

 0009-3122/86/2203-0268$12.50

TABLE 1. Spectral Properties of Synthesized 3-Imidazoline 3-Oxides and Pyrazine 1,4-Dioxides

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	PMR spectrum, ppm (J, Hz)†				
			R^1	R^2	R^3	R^4	H
IIIa	226 (4,03), 294 (4,22)	1720 (C=O)	7,4—7,6, m; 8,2—8,4, m	4,49, s	2,31, s	1,78, s	4,49, s
IIIi	235 (4,13), 248 (4,18)	1700 (C=O)	7,4—7,7, m; 8,1—8,4, m	1,22, d (7,0)	7,4—7,7, m; 8,1—8,4, m	1,76, s	4,87, q (7,0)
IIIj	227 (4,05), 300 (4,43)	1680 (C=O)	7,3—7,6, m; 7,9—8,3, m	1,32, d (7,0)	7,21 d.d (4,0; 5,0); 7,3—7,6, m; 7,9—8,3, m	1,76, s	4,82, q (7,0)
IIIk	226 (4,05), 292 (4,39)	1690 (C=O)	7,5—7,7, m; 8,2—8,4, m	1,29, d (7,0)	6,77, d.d (1,5; 3,8); 7,5—7,7, m; 8,06, m (1,5)	1,74, s	4,84, q (7,0)
IIIℓ	224 (4,03), 320 (4,20)	1730 (C=O)	7,24 d.d (3,0; 4,0); 7,6—7,8, m	1,50, d (6,5)	2,26, s	1,59, s	4,64, q (6,5)
IIIm	225 (4,89), 250 (4,96), 320 (5,02)	1700 (C=O)	7,1—8,2, m	1,29, d (7,0)	7,1—8,2, m	1,76, s	4,80, q (7,0)
IIIn	222 (4,06), 270 (4,11), 314 (4,18)	1670 (C=O)	7,1—7,3, m; 7,6—8,1, m	1,44, d (7,0)	7,1—7,3, m; 7,6—8,1, m	1,71, s	4,70, q (7,0)
IIIo	307 (4,28)	1735 (C=O)	6,70, d.d (2,0; 3,5); 7,79, m	1,54, d (7,0); 1,59, d 7,0)	2,19, s, 2,24 s	1,60, s; 1,69, s	4,50, q (7,0); 4,54, q (7,0)
IIIp	247 (4,14), 308 (4,34)	1635 (C=O)	6,76 d.d (2,0; 3,5); 7,5—8,2, m	1,39 ‡, d (7,0); 1,59, d (7,0)	7,5—8,2, m	1,72 ‡, s; 1,78, s	4,63, q (7,0)
IIIq	309 (4,34)	1660 (C=O)	6,72 d.d (1,8; 3,5); 7,4—8,2, m	1,37 ‡, d (7,0); 1,64, d (7,0)	7,4—8,2, m	1,81 ‡, s; 1,84, s	4,69, q (7,0)
IIIr	304 (4,44)	1690 (C=O)	6,7—6,8, m; 7,73, d (3,5); 7,9—8,1, m	1,49, d (7,0)	6,7—6,8, m; 7,51, d (3,5); 7,9—8,1, m	1,67, s	4,58, q (7,0)
IVa	263 (4,56), 314 (4,21)	1360	7,4—7,9, m	8,40, s	2,52	2,52	
IVc	236 (4,20), 268 (4,11), 318 (4,40), 344 (4,31)	1350, 1360	7,4—8,0, m	8,66, s	1,87, 2,90 br.s		

TABLE 1 (continued)

IVd	236 (4,45), 303 (4,35)	1345, 1355	2,51, c	8,50, s	2,58	2,58	
IVf	237 (4,22), 247 sh (4,04), 309 (4,27)	1310, 1355	2,53, c	8,62, s	7,4—7,8, m	2,29, s	
IVh	241 (4,37), 250 sh (4,27), 308 (4,37)	1320	7,46, m		2,22, s 2,52, s, 2,56, s		
IVi	238 (4,32), 260 (4,33), 316 (4,34)	1305, 1320	7,49, c	2,41, s	7,49, s	2,41, s	
IVℓ	241 (4,25), 267 (4,09), 298 (4,39)	1320	7,16, d,d (4,0; 5,2); 7,32, d,d (1,4; 4,0); 7,69, d,d (1,4; 5,2)	2,57, s	2,57, s	2,57, s	
IVm	241 (4,32), 303 (4,43)	1310, 1325	7,1—7,7, m	2,68, s	7,48, s	2,36, s 2,58, s	
IVo	239 (4,16), 267 (4,21), 294 (4,45)	1310, 1330	6,64, d. d (1,4; 4,0); 7,49, d (4,0); 7,67, d (1,4)	2,66, s	2,58, s	2,16, s	
IVp	238 (4,18), 275 sh (4,24), 300 (4,41)	1310	6,69, d. d (1,4; 4,0); 7,30, d (4,0); 7,95, d (1,4)	2,53, s	7,47, s		

*Compounds IIIo,p,q are mixtures of diastereomers.

†PMR spectra of IIIi–r and IVc,p were recorded in $(CD_3)_2SO$; of IIIa, IVa, h in CD_3OD; of IVd,f in D_2O; of IVi,ℓ,m,o in $CDCl_3$. OH signals in spectra of IIIi, j, k, m, m, p, r appear at 9.36, 9.30, 9.17, 9.40, 9.26, 9.32, 9.03 ppm.

‡Signals of the diastereomer of the predominant compound.

TABLE 2. Properties of Synthesized Compounds

Compound	Mp, °C	Found, %				Empirical formula	Calculated, %				Yield,‡%
		C	H	N	S		C	H	N	S	
Ic	155—156	36,2	3,5	20,6	—	$C_6H_7N_3O_5$	35,8	3,5	20,9	—	49
Iℓ · AcOH	150—151	43,7	5,8	11,4	13,1	$C_9H_{14}N_2O_4S$	43,9	5,8	11,4	13,0	51
Io · AcOH	163—164	47,3	6,4	12,5	—	$C_9H_{14}N_2O_5$	47,0	6,0	12,2	—	60
IIIa	142—144	62,0	6,1	12,1	—	$C_{12}H_{14}N_2O_3$	61,5	6,0	12,0	—	3
IIIi	151—152	70,1	5,7	9,3	—	$C_{18}H_{18}N_2O_3$	69,7	5,9	9,0	—	77
IIIj	162—164	62,4	5,4	9,4	11,2	$C_{15}H_{16}N_2O_2S$	62,5	5,5	9,7	11,1	59
IIIk	140—142	63,8	5,2	9,4	—	$C_{15}H_{16}N_2O_4$	64,0	6,4	9,3	—	80
IIIℓ	163—164	51,8	5,3	10,9	12,8	$C_{11}H_{14}N_2O_3S$	52,0	5,5	11,0	12,6	57
IIIm	187—189	60,1	5,4	8,8	9,7	$C_{16}H_{16}N_2O_3S$	60,1	5,1	8,8	9,6	69
IIIn	175—176	52,2	4,4	8,7	19,9	$C_{14}H_{14}N_2O_3S_2$	52,2	4,3	8,7	19,9	47
IIIo	134—135	56,2	5,9	11,4	—	$C_{11}H_{14}N_2O_4$	55,5	5,9	11,7	—	48
IIIp	170—172	64,2	5,5	9,4	—	$C_{16}H_{16}N_2O_4$	64,0	5,4	9,3	—	83
IIIq	151—152	55,4	4,8	9,0	10,6	$C_{14}H_{14}N_2O_4S$	55,0	4,6	9,2	10,5	51
IIIr	132—134	58,3	4,9	9,8	—	$C_{14}H_{14}N_2O_5$	57,9	4,9	9,7	—	73
IVo	148—149	66,1	5,6	13,4	—	$C_{12}H_{12}N_2O_2$	66,7	5,6	13,0	—	72
IVc	206—209	51,5	3,9	15,2	—	$C_{12}H_{11}N_3O_5$	52,0	4,0	15,1	—	71
IVd	136—137	54,2	7,0	18,6	—	$C_7H_{10}N_2O_2$	54,5	6,5	18,2	—	82
IVf	169—170	66,9	5,6	12,9	—	$C_{12}H_{12}N_2O_2$	66,7	5,6	13,0	—	60
IVh	184—185	67,6	6,0	12,1	—	$C_{13}H_{14}N_2O_2$	67,8	6,1	12,2	—	14
IVi	185—186	74,3	5,6	9,6	—	$C_{18}H_{16}N_2O_2$	74,0	5,5	9,6	—	60
IVℓ	129—130	56,7	5,1	12,0	13,4	$C_{11}H_{12}N_2O_2S$	56,0	5,1	11,8	13,6	57
IVm	147—148	64,5	4,7	9,4	10,6	$C_{16}H_{14}N_2O_2S$	64,5	4,7	9,4	10,7	38
IVo	124—125	59,6	5,6	12,6	—	$C_{11}H_{12}N_2O_3$	60,0	5,5	12,7	—	31
IVp	151—153	67,5	5,0	9,6	—	$C_{16}H_{14}N_2O_3$	68,0	4,9	9,9	—	16

*Compounds IIIo, p, q are 1:1, 5:1, and 4:1 mixtures of diastereomers.

†Compounds Ic, ℓ, o IIIi,j,k,m,p,q,r, and IVc, i,p were purified by crystallization from alcohol; IIIℓ,n,o and IVf,h,ℓ,o from ethyl acetate; IVa,d from dioxane.

‡Yields of pyrazine 1,4-dioxides obtained by condensation are given.

IIa, cyclohexanedione-1,2 (IIb), and 1-phenyl-1,2-propanone (IIf) gave derivatives of pyrazine 1,4-dioxide, IVc-f (Tables 1 and 2). Possibly derivatives of III are intermediates in these cases.

It can be presumed that the pyrazine 1,4-dioxides IV and the 3-imidazoline 3-oxides III form via the intermediate acyclic nitrone A [3]. Compound III in turn can be converted reversibly through nitrone A to dihydropyrazine B, which then dehydrates irreversibly to pyrazine 1,4-dioxide IV.

In order to find the intermediates by PMR and UV spectroscopy we studied the reaction of 1,2-hydroxylaminooxime Id with biacetyl IIa. The PMR spectrum of 0.5 M solution of Id and biacetyl in CD_3OD at 20°, 3 min after preparation, showed (along with the spectra of the starting compounds) a singlet at 1.41 ppm (see [1]) that can be assigned to the protons of the methyl at position 2 of 2,3-imidazoline 3-oxide, IIId. With time, signals appear at 2.40, 2.55, and 8.38 ppm that correspond to pyrazine 1,4-dioxide IVd (see Table 1). The imidazoline: pyrazine ratio was 4:1 after 20 min, 1:3 after 7 h, and after 1 day the reaction IIId → IVd was complete. The UV spectra of the reaction mixture obtained by pouring aliquots of 0.01 M 1,2-hydroxylaminooxime Id in alcohol into 0.4 M biacetyl in alcohol, recorded at 5 min intervals (first spectrum obtained 1 min after mixing), show no absorption at 260-270 nm that might be expected for acyclic nitrone A (cf. [4]). This seems to be evidence that nitrone A is rapidly converted to III and IV. The UV maxima at 235 and 303 nm correspond to the overlap of the absorption maxima of 3-imidazoline 3-oxide (λ_{max} ∿ 235 nm, cf. [5]) and pyrazine 1,4-dioxide (λ_{max} 236, 303 nm).

Thus in the study of the reaction of Id with IIa by UV and PMR spectroscopy, only the formation of IIId was recorded, and this is converted relatively quickly to IVd. The relatively greater stability of IIIa, which has a phenyl group at position 4, over that of IIId is apparently due to the conjugation of the benzene ring with the nitrone group (cf. [6]).

It should be noted that the relative stability of III should also depend on the ease of conversion of the intermediate acyclic nitrone A to the pyrazine 1,4-dioxide IV.

In contrast to the secondary alkylaromatic 1,2-hydroxylaminooxime Ih the condensation of the aliphatic 3-hydroxyamino-2-butanone oxime (Ig) with IIa gives the 2,3,5,6-tetramethyl 1,4-dioxide (IVg) [7]. Study of the composition of the products of the reaction of Ih with biacetyl when heated in alcohol showed that along with the diastereomeric 3-imidazoline 3-oxides, IIIh (72% yield), pyrazine 1,4-dioxide IVh forms in 14% yield. When the reaction is carried out with heating in an acetic acid–alcohol mixture the yield of IVh increases to 60%. Condensation of the acetate salts of 2-hydroxyamino-1-(thienyl-2)-(Iℓ) and 2-hydroxyamino-1-(furyl-2)-(Io) 1-propanone oximes with biacetyl in alcohol with heating gives the diastereomeric 3-imidazoline 3-oxides (IIIℓ,o)*; when acetic acid is added, the predominant products are the pyrazine 1,4-dioxides IVℓ,o along with a small amount of the 3-imidazoline 3-oxides IIIℓ,o. From the data we can presume the conversion of the 3-imidazoline 3-oxides, IIIh,ℓ,o, to the pyrazine 1,4-dioxides IVh,ℓ,o, by the action of acetic acid. Indeed upon prolonged heating in alcoholic solution in the absence of acetic acid, 3-imidazoline 3-oxide IIIh was separated unchanged. Only when heated in acetic-acid–alcohol mixture were IIIh,ℓ converted to IVh,ℓ in 57 and 34% yields, respectively.

Thus the 3-imidazoline 3-oxides IIIh,ℓ with a methyl in position 5 of the imidazoline ring are converted to the pyrazine 1,4-dioxides IVh,ℓ under more severe conditions than the 3-imidazoline 3-oxide IIIa which has no substituent at position 5; this is evidently due to the stabilizing effect of the methyl group in IIIh,ℓ [8].

In contrast to biacetyl, 1-phenyl- and 1-(heteroaryl-2)-1,2-propanediones (IIf,j,k) do not react with the secondary 1,2-hydroxylaminooximes Ih,ℓ,o when heated in alcohol. The condensation could be carried out at room temperature by the addition of acetic or trifluoroacetic acid, to form 3-imidazoline 3-oxides IIIi,j,k,m,n,p,q,r.

The IR spectra of these compounds have the conjugated carbonyl band at 1680-1700 cm^{-1}; in the PMR spectra the singlet in the 1.65-1.85 ppm region should be assigned to the protons of the methyl group at position 2 of 3-imidazoline 3-oxide. From these data we can assign the 3-imidazoline 3-oxides the structures of 2-benzoyl- (IIIi,m,p), 2-(furoyl-2)- (IIIk,r), and 2-(thenoyl-2-(IIIj,n,q)3-imidazoline 3-oxides.* Thus the condensation of 1,2-hydroxylaminooximes Ih,ℓ,o proceeds selectively at the acetyl group of the 1-phenyl- or 1-(heteroaryl-2)-1,2-propanediones IIf,j,k.

When the condensation of Ih,ℓ,o with IIe is carried out at the boiling point of an alcohol–acetic-acid mixture, a mixture of pyrazine 1,4-dioxides IVm,p and 3-imidazoline 3-oxides IIIm,p or exclusively pyrazine 1,4-dioxide IVi. Under the same conditions 3-imidazoline 3-oxide IIIm is converted to pyrazine 1,4-dioxide IVm in 34% yield; if trifluoroacetic acid is used instead of acetic, the conversion of IIIi to IVi goes more smoothly, with 94% yield.

The pyrazine 1,4-dioxides IVi,m obtained by condensation of 1,2-hydroxylaminooximes Ih,ℓ with 1-phenyl-1,2-propanedione (IIf), or by conversion of the 3-imidazoline 3-oxides IIIi,m, are identical in IR spectrum. Consequently the phenyl and heteroaryl groups of IVi, m,p are located at positions 2 and 6 of the pyrazine ring. The pyrazine 1,4-dioxide IVi that we isolated (with mp 185°) was isomerized to the previously described 3,6-dimethyl-2,5-diphenylpyrazine 1,4-dioxide (with mp 249° [7]). Analogously pyrazine 1,4-dioxide IVf was assigned the structure of 2,5-dimethyl-3-phenylpyrazine 1,4-dioxide [7].

Information on the synthesis of pyrazine 1,4-dioxide derivatives without using oxidation could not be found in the literature [9].

Thus condensation of primary 1,2-hydroxylaminooximes with 1,2-diketones in alcohol with heating gives principally derivatives of pyrazine 1,4-dioxide. In the case of the secondary alkylaromatic and alkylheteroaromatic 1,2-hydroxylaminooximes, condensation with biacetyl forms predominantly derivatives of 2-acetyl-3-imidazoline 3-oxide. In the presence of acetic acid the condensation of secondary alkylaromatic and alkylheteroaromatic 1,2-hydroxylamino-

*We did not separate or determine the configuration of the diastereomers.

oximes with biacetyl gives principally pyrazine 1,4-dioxides. The reaction of the secondary alkylaromatic and alkylheteroaromatic 1,2-hydroxylaminooximes with 1-phenyl- and 1-(heteroaryl-2)-1,2-propanedione goes only in the presence of acetic or trifluoroacetic acid and at 20° gives derivatives of 2-benzoyl- and 2-(heteroaroyl-2)-3-imidazoline 3-oxides; with heating it gives pyrazine 1,4-dioxides. The 2-acyl-3-imidazoline 3 oxides are converted to pyrazine 1,4-dioxides by prolonged holding of the alcoholic solution, or by heating in the presence of acetic acid.

EXPERIMENTAL

IR spectra were recorded in KBr on a UR-20 instrument; UV spectra in alcohol on a Specord UV-VIS spectrometer. The condensation of 1,2-hydroxylaminooxime Id with biacetyl in alcohol was studied by UV spectroscopy in a Beckman DU-8 spectrometer. PMR spectra were recorded on a Varian A-56-60A instrument (60 MHz) for 7-10% solutions, with HMDS internal standard. 1,2-Hydroxylaminooximes Ia,d,g,h were obtained according to [10-12].

The spectral properties of compounds III and IV are shown in Table 1, and those of compounds Ic,ℓ,o in the Experimental section following. The physicochemical properties of Ic, ℓ,o,III, and IV are shown in Table 2.

Acetate Salt of 2-Hydroxylamino-1-(thienyl-2)-1-propanone Oxime (Iℓ•AcoH). To a solution of hydroxylamine (obtained by neutralizing a solution of 69.5 g (1000 mmoles) of hydroxylamine hydrochloride in 250 ml of methanol with an equimolar amount of sodium methylate in 200 ml of methanol) are added 15 ml (250 mmoles) of acetic acid and 21.9 g (100 mmoles) of 2-bromo-1-(thienyl-2)-1-propanone and the mixture is boiled for 4 h. The methanol is evaporated, 50 ml of water is added to the residue, the precipitate of Iℓ•AcoH is filtered off and washed with water and ether. There is obtained 12.6 g of Iℓ•AcoH. UV spectrum, λ_{max} 270 nm (log ε 4.13). PMR spectrum, δ (in DMSO-D_6): 1.27 (3H, d, J = 6.5 Hz, CH_3), 1.87 (3H, s, CH_3), 4.19 (1H, q, J = 6.5 Hz, CH), 6.9-7.3; 7.6-7.8 ppm (5H, m, C_4H_3S, NH, OH).

Acetate Salt of 2-hydroxyamino-1-(furyl-2)-1-propanone oxime (Io•AcoH) was obtained in analogous manner. UV spectrum, λ_{max} 266 nm (log ε 4.26). PMR spectrum (in CD_3OD): 1.37 (3H, d, J = 7.0 Hz, CH_3), 1.96 (3H, s, CH_3), 4.37 (1H, q, J = 7.0 Hz, CH), 6.55 (1H, d.d, J = 1.8 and 3.5 Hz, 4-H), 7.44 (1H, d, J = 3.5 Hz, 3-H), 7.59 ppm (1H, d, J = 1.8 Hz, 5-H).

2-Hydroxyamino-1-(5-nitrofuryl-2)ethanone Oxime (Ic). To a solution of hydroxylamine (obtained by neutralizing a solution of 3.80 g (60 mmoles) of hydroxylamine hydrochloride in 30 ml of methanol with an equimolar amount of sodium methylate in 20 ml of methanol) was added a solution of 1.20 g (6 mmoles) of 2-bromo-1-(5-nitrofuryl-2)ethanone oxime [13] in 40 ml of methanol at 10°, and the mixture was held for 0.5 h. The methanol was evaporated, the residue was treated with water, and the precipitate was filtered off. It was mixed with 3 ml of 3% hydrochloric acid and filtered. The filtrate was neutralized with 20% potassium hydroxide solution, and the precipitate of compound Ic was filtered off, leaving 0.59 g. UV spectrum, λ_{max} nm (log ε): 234 (3.91), 342 (4.13). PMR spectrum (in DMSO-D_6): 3.87 (2H, s, CH_2), 7.37 (1H, br. s, OH), 7.52 (1H, d, J = Hz, 3-H or 4-H) 7.76 (1H, d, J = 4.0 Hz, 3-H or 4-H), 12.41 ppm (1H, br.s, =NOH).

Condensation of Primary 1,2-Hydroxylaminooximes Ia,c,d with 1,2-Diketones IIa,b,f. A mixture of 6 mmoles of 1,2-hydroxylaminooxime and 7 mmoles of 1,2-diketone in 10 ml of methanol was boiled for 0.5-3.0 h (monitored by TLC). The methanol was evaporated and from the ether-treated residue pyrazine 1,4-dioxides IVa,c-f were separated. From the filtrate after removal of IVa there were separated by silica gel chromatography the 3-imidazoline 3-oxide IIIa (ether eluent) and an additional amount of IVa (9:1 ether:methanol eluent). IVb was separated by silica gel chromatography (ether eluent). The IR spectra of compounds IVb,e were the same as those of authentic samples [14, 15]. mp IVe 184-186° (from alcohol), according to [2], mp 180-181°; mp IVb 159-161° (from alcohol), according to [3], mp 153-155°; mp IVf 169-170° (from alcohol), according to [7], mp 165°.

2,3,5,6-Tetramethylpyrazine 1,4-Dioxide (IVg). A solution of 1.04 g (8.8 moles) of 1,2-hydroxylaminooxime Ig and 1.03 g (12 mmoles) of biacetyl in 10 ml of methanol was left at 20° for 18 h. The methanol was evaporated. The residue was treated with an ether–ethyl-acetate mixture to separate 1.08 g (73%) of IVg, mp 215-216°; according to [7], mp 220°.

Condensation of Secondary 1,2-Hydroxylaminooximes Ih,ℓ,o with Biacetyl. A. A solution of 10 mmoles of 1,2 hydroxylaminooxime Ih or the acetate salts Iℓ,o•AcOH and 11 mmole of biacetyl in 10 ml of alcohol was boiled for 4 h. The alcohol was evaporated. Treatment of the residue separated the 3-imidazoline 3-oxides IIIh,ℓ,o. Silica gel chromatography of the filtrate yielded additional IIIh (ether eluent) and pyrazine 1,4-dioxide IVh (acetone eluent). IR spectrum and mp of IIIh were identical with those described in [1].

B. A solution of 5 mmole of Ih or the acetate salts Iℓ,o•AcOH and 10 mmoles of biacetyl in a mixture of 10 ml of alcohol and 3 ml of acetic acid was boiled for 6 h, then evaporated. Silica gel chromatography of the residue gave IIIℓ (3%), IIIo (3%), and the pyrazine 1,4-dioxides IVh (59%), IVℓ (57%), IVo (31%) (ether eluent).

Condensation of Secondary 1,2-Hydroxylaminooximes I,h,ℓ,o with 1-phenyl- and 1-(heteroaryl-2)-1,2-propanediones IIf,j,k. A. A solution of 4 mmoles of the acetate salt Iℓ,o•AcOH and 4 mmoles of 1-phenyl- (IIf) or 1-(thienyl-2)-(IIj) 1,2-propanedione in a mixture of 40 ml of alcohol and 6 ml of acetic acid was left at 20° for 1 day. The solvent was evaporated, the residue was treated with ether, and the precipitate of 3-imidazoline 3-oxide IIIm,n,p,q was filtered off. The filtrate was evaporated, the residue was neutralized with sodium hydroxide solution, and additional IIIm,n,p,q was separated by chloroform extraction.

B. A solution of 5 mmoles of Ih or the acetate salt Io.AcOH and 5 mmoles of 1-phenyl- (IIf), 1-(thienyl-2-)- (II_j), or 1-(furyl-2)- (IIk) 1,2-propanedione in 20 ml of alcohol and 0.5 ml of trifluoroacetic acid was left at 20° for 1-2 days (monitored by TLC). The alcohol was evaporated, and treatment of the residue with ether gave IIIi,j,k,r.

C. A mixture of 3 mmoles of Ih or Iℓ,o•AcOH and 3 mmoles of 1-phenyl-1,2-propanedione (IIf) in a mixture of 5 ml of alcohol and 5 ml of acetic acid was boiled for 2 h. The solvent was evaporated, and the residue was diluted with 5 ml of water, neutralized with sodium bicarbonate, and extracted with chloroform. The chloroform solution was washed with water, dried with sodium sulfate, and evaporated. Silica gel chromatography of the residue (ether eluent) separated 3-imidazoline 3-oxides IIIm (3%) and IIIp (9%), and pyrazine 1,4-dioxides IVi (60%), IVm (38%), and IVp (16%).

Conversion of 2-Acyl-1-hydroxy-3-imidazoline 3-Oxides IIIa,h,i,m to Pyrazine 1,4-Dioxides IVa,h,i,m. A. A solution of 0.10 g (0.42 mmole) of IIa in 7 ml of alcohol was held at room temperature for 6 days. The alcohol was evaporated, the residue was treated with ether, and the precipitate of IVa was filtered off. Weight 0.075g (81%).

B. A mixture of 0.124 g (0.5 mmole) of IIIh in 5 ml of alcohol and 0.03 ml of acetic acid was boiled for 1.5 h. The solvent was evaporated and the residue was treated with ether. The precipitate of IVh was filtered off. Weight 0.06 g (57%).

C. A solution of 0.5 g (1.6 mmoles) of IIIi in 5 ml of alcohol and 0.5 ml of trifluoroacetic acid was boiled for 3 h, then evaporated. The residue was treated with ether, and the precipitate of IVi was filtered off. Weight 0.44 g (94%).

D. A mixture of 0.32 g (1 mmole) of IIIm and 8 ml of acetic acid was boiled for 7 h. The solvent was evaporated, 4 ml of water was added and the mixture was neutralized with sodium bicarbonate and extracted with chloroform. The chloroform solution was washed with water, dried with sodium sulfate, and evaporated. Silica gel chromatography of the residue separated 0.01 g (33%) of IVm (ether eluent). Under the same conditions, from IIIℓ there was obtained IVℓ in 34% yield.

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STUDIES OF IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES.

21.* SYNTHESIS OF HALOKETONES IN THE IMIDAZO[1,2-a] BENZIMIDAZOLE SERIES

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UDC 547.785.5.04:542.944

Methods for the synthesis of imidazo[1,2-a]benzimidazole haloketone derivatives have been investigated. It has been found that α-bromoketone derivatives of this heterocycle can be prepared either by bromination of 3-acylimidazo[1,2-a]benzimidazoles with bromine in glacial acetic acid or by acylation of 3-unsubstituted imidazo[1,2-a]benzimidazoles with haloanhydride derivatives of α-bromoalkanoic acids. Treatment of imidazo[1,2-a]benzimidazoles with 3-chloropropionyl chloride results in the formation of imidazo[1,2-a]benzimidazolyl-3-propionyl chloride and bis(imidazo[1,2-a]benzimidazolyl)propan-3-one derivatives as side products. Reaction of 2-phenylimidazo[1,2-a]benzimidazoles with 3-bromopropionic acid in polyphosphoric acid gives benzocyclohepten[5',6':4,5]imidazo[1,2-a]benzimidazole derivatives.

Haloketones are widely used as synthons for the preparation of aminoalcohols, aminoketones, and heterocyclic and other compounds. In order to expand the synthetic possibilities for the preparation of biologically active compounds in the imidazo[1,2-a]benzimidazole series, we have been studying various methods for the preparation of haloketone derivatives of this heterocyclic system.

One of the most common methods for the synthesis of α-haloketones involves the direct halogenation of ketones. All efforts to brominate ketones I directly failed, either with N-bromosuccinimide in CCl_4, in the absence of a catalyst or in the presence of benzoyl peroxide, or with copper bromide in chloroform or chloroform–ethyl acetate mixtures. When ketones I were treated with either dioxanedibromide in ether or with dioxane and bromine in chloroform or methanol, only perbromides of the starting ketones were obtained; these perbromides decomposed upon extended refluxing in either water or alcohol, but did not generate the bromoketones II as expected (cf. [2, 3], for example).

*For Communication 20, see [1].

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0009-3122/86/2203-0275$12.50