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CONDENSATION OF 1,2-HYDROXYLAMINOOXIMES WITH ACETYLACETONE. CONVERSION OF TETRAHYDROIMIDAZO[1,2-*b*]ISOXAZOLES INTO DERIVATIVES OF 2H-IMIDAZOLE, 1-HYDROXYPYRROLE, AND 4-OXOTETRAHYDROPYRIDINE

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Reaction of 1,2-hydroxylaminooximes with acetylacetone gives tetrahydroimidazo[1,2-b]isoxazoles. 4-Phenyltetrahydroimidazo[1,2-b]isoxazole in methanolic HCl forms the corresponding 2-acetonyl-2H-imidazole. Both tetrahydroimidazo[1,2-b]isoxazoles and 2-acetonyl-2H-imidazole on heating in aqueous KOH convert into 4-oxo-1,2,3,4-tetrahydropyridines along with 3-acetyl-1-hydroxypyrroles.

Reaction of 1,2-hydroxylaminooximes with 1,2-dicarbonyls, depending on the reagents and reaction conditions, gives N-oxides of imidazole and pyrazine derivatives [1, 2]. The reaction of 1,2-hydroxylaminooximes with 1,3-dicarbonyls has not yet been studied.* Little data exist for the reaction of N-alkylhydroxylamines with 1,3-dicarbonyls [4].

In the present work, we study the reaction of 1,2-hydroxylaminooximes Ia-e, which contain a hydroxylamino group on a secondary carbon atom, with acetylacetone. Condensation of Ia-d with acetylacetone forms tetrahydroimidazo[1,2-*b*]isoxazoles IIa-d as a mixture of diastereomers. Signals of the two diastereomers A and B are seen in the PMR spectra of IIa-d. The diastereomeric mixtures of IIc and IId were separated by crystallization. The PMR spectra do not unambiguously reveal the stereochemistry of these isomers. We believe that the singlet in the PMR for the protons of the methyl group on the hemiacetal carbon of one of the isomers (isomer B) is seen at weaker field. The A isomers convert into the B isomers on heating IIc and IId in alcohol for 4 h. The reverse conversion is not observed. Multiple crystallization of the mixture of diastereomers of IIa and IIb gave only the A isomers. The C=N stretching band of the aliphatic nitrone group occurs at 1620-1655 cm^{-1} in the IR spectra of IIa, c, and d. Bands at 1570 and 1585 cm^{-1} (C=C and C=N) are seen for A-IIb with the α-phenylnitrone group (Table 1). Compounds IIa, c, and d have similar UV spectra with absorption maxima at 233-238 nm. Compound A-IIb has a long-wavelength maximum at 296 nm. This is characteristic for α-phenylnitrones [5] (see scheme below).

Isoxazole II apparently begins to form with condensation of the hydroxylamino group of compound I with the carbonyl group of the acetylacetone to give the β-oxonitrone III. Intramolecular addition of the N atom of the oxime group to the C atom of the nitrone group forms 2-acetonyl-3-imidazoline (IV). Intramolecular addition of the hydroxyl group to the carbonyl group in IV forms the final products II. The A isomers apparently convert into the B isomers in IIa and IIb through the intermediates IV and III. According to [6], the products of addition of the N-substituted hydroxylamines to mesityl oxide are 5-hydroxyisoxazolidines and not N-substituted 1,3-hydroxylaminoketones.

*For a preliminary communication, see [3].

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TABLE 1. Properties of IIa-d

Compound	Empirical formula	mp, °C*	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum (in $CDCl_3$), ppm (J, Hz)**							Yield, %
					2-CH_3, s	3a-CH_3, s	R^1	R^2	CH_2	H	OH, s	
A-IIa	$C_9H_{16}N_2O_3$	148...150	1625 (C=N)	233 (3,88)	1,39	1,25	1,84 d (J=1,8)	1,31, d (J=7,0)	2,18; 3,00 (J_{AB}=14,0)	4,35, two q (1,8; 7,0)	6,15	
A-IIa+B-IIb***			1620 (C=N)	234 (4,03)	1,46	1,35	1,83 d (J=1,8)	1,22,d (J=7,0)	2,04; 2,75 (J_{AB}=13,5)	4,30, m	6,02	86
A-IIb	$C_{14}H_{18}N_2O_3$	131...133	1570, 1585 (C=C, C=N)	226 (3,94), 232 sh, (3,84), 296 (4,18)	1,67	1,41	7,3...7,6; 8,1...8,4, m	1,46,d (J=7,0)	2,10; 3,16 (J_{AB}=14,0)	4,96, q (7,0)	3,84	
A-IIb+B-IIb***			1580, 1585, 1605 (C=C, C=N)	225 (3,87), 231sh (3,80), 294 (4,10)	1,82	1,44	7,3...7,6; 8,2...8,6,m	1,51,d (J=7,5)	2,49; 3,22 (J_{AB}=14,0)	4,74, q	4,34	84
A-IIc	$C_{11}H_{18}N_2O_3$	149...150	1640 (C=N)	238 (4,11)	1,59	1,47	1,2...2,3, m (7H); 2,8...3,2, m (1H)		2,38; 2,31 (J_{AB}=14,5)	4,06, m	4,79	19
B-IIc	$C_{11}H_{18}N_2O_3$	138...140	1645 (C=N)	236 (4,19)	1,62	1,54	0,9...2,7, m		2,18; 3,10 (J_{AB}=13,5)	4,46, m	5,27	58
A-IId	$C_{12}H_{20}N_2O_3$	124...126	1605 (C=N)	235 (4,24)	1,59	1,46	1,2...2,9, m		2,37; 3,27 (J_{AB}=14,0)	4,21, m	4,14	38
B-IId	$C_{12}H_{20}N_2O_3$	158...159	1620 (C=N)	235 (4,05)	1,66	1,54	1,1...2,7, m		2,16; 3,12 (J_{AB}=13,5)	4,50, m	5,60	29

*Compounds A-IIa, A-IIc, and B-IId were crystallized from i-PrOH; A-IIb, B-IIc, and A-IId from EtOAc.

**The spectrum of IIa was recorded in DMSO-D_6.

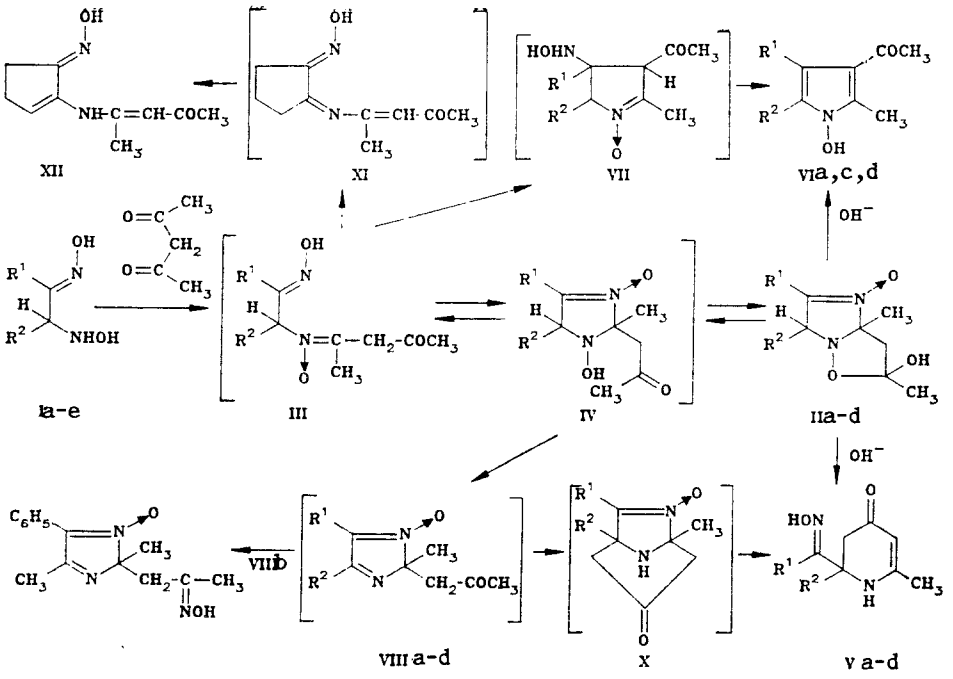
***Signals of the B isomer obtained by subtracting the signals of the A isomer from the spectrum of the mixture are given in the PMR spectrum of the mixture of IIa and IIb isomers.

TABLE 2. Properties of Va-d

Compound	Empirical formula	mp, °C (from i-PrOH)	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum (in DMSO-D_6), ppm (J, Hz)*							Yield, %
					R^1	R^2, s	6-CH_3, s	CH_2**	H, br.s	NH, br.s	NOH, s	
Va	$C_9H_{14}N_2O_2$	190...192	1520, 1600, 1645	315 (4,09)	1,72, s	1,31	1,87	2,48; 3,12 (J_{AB}=16,0)	4,59	7,49	10,77	27
Vb	$C_{14}H_{16}N_2O_2$	241...242	1530, 1590, 1625	313 (4,27)	6,9...7,5, m	1,44	1,82	2,55; 3,29 (J_{AB}=16,0)	4,78	6,46		88
Vc	$C_{11}H_{16}N_2O_2$	254...265	1520, 1575, 1595	317 (4,12)	1,3...2,0, m		1,89	2,62; 3,00 (J_{AB}=16,0)	4,55	7,14	10,67	43
Vd	$C_{12}H_{18}N_2O_2$	210...212	1530, 1585, 1615	317 (4,16)	1,0...2,0, m		1,82	2,59; 3,02 (J_{AB}=16,0)	4,54	7,26	10,66	56

*The PMR spectrum of Vb was recorded in DMF-D_7.

**In pyridine.



I, II, V, VI, VIII a $R^1=R^2=CH_3$; b $R^1=C_6H_5$, $R^2=CH_3$; c $R^1+R^2=(CH_2)_4$; d $R^1+R^2=(CH_2)_5$; e $R^1+R^2=(CH_2)_3$

Heating tetrahydroimidazo[1,2-*b*]isoxazole derivatives IIa-d in aqueous KOH unexpectedly forms 4-oxo-1,2,3,4-tetrahydropyridines Va-d and small amounts of 3-acetyl-1-hydroxypyrroles VIa, c, and d. A characteristic absorption maximum near 313-317 nm is seen in the UV spectra of Va-d. A set of bands near 1500-1645 cm^{-1} appears in the IR spectra (Table 2). These can be assigned to combinations of the C=O, C=C, and NH vibrations of the enaminoketone fragment [7]. The PMR and ^{13}C NMR data confirm the structure of Va-d (Tables 2 and 3) (cf. [8, p. 238]). The C=O stretching is difficult to identify in the IR spectra of the 1-hydroxypyrroles VIa, c, and d with the acetyl group conjugated to the pyrrole ring (Table 4). This is apparently due to interaction of the C=O and C=C bonds with the enhydroxylaminoketone. The structure of 3-acetyl-1-hydroxypyrrole VIa was confirmed by ^{13}C NMR spectra. They show five sp^2 carbon atoms, including the carbonyl carbon atom.

Keeping IIb in methanolic HCl gives 2-acetonyl-2H-imidazole VIIIb. This gives the corresponding oxime IX on treatment with hydroxylamine. Heating VIIIb in aqueous KOH gave 4-oxo-1,2,3,4-tetrahydropyridine Vb. This suggests that tetrahydropyridines V form through opening of isoxazoles II in basic media to the imidazolines IV. These are further dehydrated to the imidazoles VIII. Addition of the enolate ion formed from the methylketone group of VIII to the imino group leads to 4,6-diazabicyclo[3,2,1]octenes X. Opening of these gives compound V. The synthesis of 3-acetyl-1-hydroxypyrroles VI can be explained by opening of the isoxazolidine and imidazoline heterocycles to give β-oxonitrones III. These undergo intramolecular cyclization involving the methyl and oxime groups, as a result of which the 1-pyrrolines VII are obtained. The latter, after isomerization and loss of a hydroxylamino group, give hydroxypyrroles VI.

TABLE 3. ^{13}C NMR Spectrum of 4-Oxo-1,2,3,4-tetrahydropyridine Derivatives*

Compound	δ (in DMSO), ppm							
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$, C=NOH	6—CH_3	R^1	R^2
Va	58,6	44,5	189,8	96,9	156,0; 159,6	20,0	9,3	24,7
Vb	58,8	45,4	190,0	97,5	158,1; 160,0	20,5	127,9; 128,0; 133,2	25,8
Vc	58,4	44,0	189,4	96,8	156,5; 159,5	20,4	19,8; 20,2; 25,2; 40,0	
Vd	62,3	44,5	193,3	96,7	159,8; 163,9	20,2	23,6; 23,7; 26,3; 31,0; 39,2	

*The spectrum of Vd was recorded in CH_3OH.

TABLE 4. Properties of VI, VIII, IX, and XII

Compound	Empirical formula	mp, °C*	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, ppm (J, Hz)**				Yield, %
					R^1, R^2	CH_3, s	$COCH_3$, s	NOH, br.s	
VIa	$C_9H_{13}NO_2$	168...170	1500, 1545, 1580, 1610	267 (4,06), 297sh (3,81	2,04 s; 2,09 s	2,38	2,28	10,87	4
VIc	$C_{11}H_{15}NO_2$	166...168	1500, 1565, 1605	264 (4,03), 297sh (3,72	1,5...1,8; 2,3...2,8 m	2,38	2,23	11,0	5
VId	$C_{12}H_{17}NO_2$	186...188	1500, 1540, 1575, 1600	265 (4,18), 296sh (3,88	1,4...1,8; 2,6...3,0 m	2,37	2,28	11,0	2
VIIIb	$C_{14}H_{16}N_2O_2$	91...92	1605 (C=C, C=N), 1720 (C=O)	240 (4,15), 310 (3,87)	1,59, s (3H, CH_3); 2,09, s (3H, $COCH_3$); 2,44, s (3H, CH_3); 3,02, 3,15 (2H, CH_2) (J_{AB}=16,5); 7,4...7,6, 7,7...8,0, m (5H, C_6H_5)				83
IX	$C_{14}H_{17}N_3O_2$	114...116	1610 (C=C, C=N)	241 (4,11), 312 (3,83)	1,57, s (3H, CH_3); 1,81, s (3H, C(NOH)CH_3); 2,41, s (3H, CH_3); 2,84, 2,92 (2H, CH_2); 7,5...7,8, m (5H, C_6H_5); 9,00, s (NOH)				70
XII	$C_{10}H_{14}N_2O_2$	171...173	1520, 1580, 1610, 1655, 3200 (NH)	258 (3,94), 340 (4,27)	2,06, s (3H, CH_3); 2,12, s (3H, CH_3); 2,5...2,6, 2,6...2,7, m (4H, $2CH_2$); 5,14, s (1H, =CH); 5,89, t (1H, =CH) (3,0); 9,26, 12,20, s (2H, NH, NOH)				47

*Compounds VIa, c, and d were crystallized from EtOAc; VIIIb and IX from ether; XII sublimes.

**PMR spectra of VIa, c, and d were recorded in DMSO-D_6; VIIIb, IX, and XII in $CDCl_3$.

Reaction of the Ie 1,2-hydroxylaminooxime acetate with acetylacetone forms the enaminoketone XII. Apparently the condensation product III in the presence of catalytic amounts of acid isomerizes and is dehydrated to form imine XI. This, in turn, isomerizes and gives the final product XII. The singlet and triplet for protons of the double bonds of the enaminoketone fragment and the carbocycle, respectively, are most characteristic in the PMR of XII. The ^{13}C NMR spectrum is consistent with the proposed structure.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (in KBr). UV spectra were taken from a Specord UV-Vis spectrometer (in alcohol). PMR spectra were obtained on Bruker WP-200SY (200.2 MHz) and Varian A-56-60A (60 MHz) instruments with HMDS internal standard. ^{13}C NMR spectra were recorded on a Bruker WP-200-SY (50.3 MHz) spectrometer. The reaction was monitored on Silufol UV-254 plates visualized with UV light or iodine vapors.

Elemental analyses for C, H, and N agreed with the calculated values.

2-Hydroxy-2,3,3*a*,5,6-tetramethyl-2,3*a*,6-tetrahydroimidazo[1,2-*b*]isoxazole-4-oxide (IIa). A mixture of 11.8 g (100 mmoles) oxime Ia and 10.0 g (100 mmoles) acetylacetone in 250 ml alcohol was kept for 1 day at room temperature (monitored by TLC). The solvent was evaporated. The residue was treated with ether. The precipitate was filtered off. Yield 17.2 g of IIa oxide. Repeated crystallization from i-PrOH gave the A-IIa isomer.

2-Hydroxy-2,3*a*,6-trimethyl-5-phenyl-2,3,3*a*,6-tetrahydroimidazo[1,2-*b*]isoxazole-4-oxide (IIb). A mixture of 18.0 g (100 mmoles) oxime Ib (E-isomer) and 10 g (100 mmoles) acetylacetone in 200 ml alcohol was refluxed for 3 h (monitored by TLC). The solvent was evaporated. The residue was treated with ether. The precipitate was filtered off. Yield 22.1 g of IIb oxide. Repeated crystallization from EtOAc gave the A-IIb isomer.

2-Hydroxy-2,3*a*-dimethyl-5,6-tetramethylene-2,3*a*,5,6-tetrahydroimidazo[1,2-*b*]isoxazole-4-oxide (A-IIc and B-IIc). A solution of 8.80 g (61 mmoles) oxime Ic and 6.10 g (61 mmoles) acetylacetone in 90 ml alcohol was kept for 1 day at room temperature (monitored by TLC). The solvent was evaporated. The residue was treated with ether containing a few drops of hexane. The precipitate was filtered off. Yield 2.57 g of A-IIc. Isomer B-IIc (7.23 g) was isolated from the filtrate after evaporation and treatment of the residue with ether containing a few drops of EtOAc. A mixture of the IIc isomers was isolated from the filtrate after removal of the B-IIc isomer. The total yield was 10.5 g (77%).

2-Hydroxy-2,3*a*-dimethyl-5,6-pentamethylene-2,3,3*a*,6-tetrahydroimidazo[1,2-*b*]isoxazole-4-oxide (IId). This was obtained in 67% yield as the A and B isomers from oxime Id analogously to the oxide IIc.

Conversion of Isomers A-IIc and A-IId into B-IIc and B-IId. A solution of 0.2 g isomer A-IIc or A-IId was refluxed in 7 ml alcohol for 3 h. The solvent was evaporated. The residue was treated with ether containing a few drops of EtOAc. Yield 0.15 g of the B-IIc isomers (75%) or 0.13 g of B-IId (65%).

2-(1-Oximinoethyl)-2,6-dimethyl-4-oxo-1,2,3,4-tetrahydropyridine (Va) and 3-Acetyl-1-hydroxy-2,4,5-trimethylpyrrole (VIa). A solution of 1.84 g (92 mmoles) oxide IIa and 0.56 g (10 mmoles) KOH in 16 ml water was refluxed for 20 min, cooled, neutralized with 10% HCl, saturated with NaCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried with $MgSO_4$ and evaporated. The residue was treated with ether. Yield 0.45 g of Va. The filtrate was evaporated. Pyrrole VIa (0.06 g) was isolated from the residue by chromatography on a silica gel column (EtOAc eluent). ^{13}C NMR spectrum of VIa (DMSO): 7.9, 10.9, 11.8 (three CH_3); 30.8 ($COCH_3$); 109.9, 115.2, 121.7, 129.3 (=C); and 192.9 ppm (C=O).

Compounds Vc, VIc, Vd, and VId were prepared analogously.

2-(1-Oximino-1-phenylmethyl)-2,6-dimethyl-4-oxo-1,2,3,4-tetrahydropyridine (Vb). A. Prepared analogously to pyridine Va from oxide IIb. Yield 88%.

B. A solution of 0.122 g (0.50 mmole) oxide VIIIb and 0.028 g (0.50 mmole) KOH in 2 ml water was kept for 1 day at room temperature (monitored by TLC) and neutralized with 10% HCl. The precipitate was filtered off. Yield 0.09 g of Vb. An additional 0.02 g (16%) of Vb was isolated by saturating the aqueous solution with NaCl. Total yield 0.11 g (90%).

2-Acetonyl-2,4-dimethyl-5-phenyl-2H-imidazole-1-oxide (VIIIb). A solution of 0.26 g (0.99 mmole) oxide IIb in 5 ml methanol was saturated with HCl for 10-15 min and left at room temperature for 4 h (monitored by TLC). The solvent was evaporated. Four ml water and 4 ml $CHCl_3$ were added. The mixture was neutralized with Na_2CO_3. The $CHCl_3$ solution was dried with $MgSO_4$ and evaporated. The residue was treated with a 5:1 mixture of hexane:ether. Yield 0.20 g of VIIIb.

2-(2-Oximinopropyl)-2,4-dimethyl-5-phenyl-2H-imidazole-1-oxide (IX). To a solution of 0.24 g (0.98 mmole) oxide VIIIb in 3 ml methanol was added with stirring a solution of hydroxylamine prepared by treating a solution of 0.14 g (2.0 mmoles) $NH_2OH \cdot HCl$ in 1 ml water with 0.10 g (1.8 mmoles) of KOH in 1 ml water. After 20 min (monitored

by TLC) the solvent was evaporated. The residue was dissolved in $CHCl_3$ and washed with water. The $CHCl_3$ solution was dried with $MgSO_4$ and evaporated. The residue was treated with a 5:2 mixture of hexane:ether. Yield 0.18 g of oxide IX.

4-[(5-Oximino-1-cyclopentenyl)amino]-2-oxo-3-pentene (XII). A solution of 1.90 g (10 mmoles) Ie acetate and 1.12 g (11 mmoles) acetylacetone in 20 ml alcohol was kept at room temperature for 1 h and evaporated. The residue was treated with ether. The precipitate was filtered off. Yield 0.92 g XII. ^{13}C NMR spectrum ($CHCl_3$): 21.5 (CH_3); 23.0 (CH_2); 27.7 (CH_2); 28.8 (CH_3); 99.3 (=CH); 122.7 (=CH); 135.7 (C–N); 158.3 (C–N); 166.6 (C=N); and 196.5 ppm (C=O).

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