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SYNTHESIS OF β-HYDROXYALKYLPYRAZOLES BY REACTION OF β-ARYLACRYLOYLOXIRANES WITH HYDRAZINE

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Reaction of β-arylacryloyloxiranes with hydrazine hydrate takes place via intermediate α,β-epoxyalkylpyrazoles which then undergo intramolecular oxidative-reductive disproportionation to yield β-hydroxyalkylpyrazoles.

α,β-Unsaturated ketones and α,β-epoxyketones react with hydrazine hydrate to form pyrazolines, hydroxypyrazolines, and allyl alcohols [1–3]. Use of conjugated α,β-epoxyketones in the reaction with hydrazine permits a comparative analysis of the reactivity of the epoxyketone and enone fragments of the molecules and to bring about the synthesis of novel substituted pyrazoles. With this aim we have studied the reaction of β-arylacryloyloxiranes Ia-*l* with hydrazine hydrate.

Reaction of Ia-*l* with hydrazine hydrate in organic solvent in the range 20–100°C leads to the formation of 5(3)-aryl-3(5)-(2-hydroxyalkyl)pyrazoles IIa-*l* in 53–82% yield independently of the degree of substitution of the α- and β-carbon atoms in the epoxy ring.

The structure of IIa-*l* was shown by their chemical reactions and by IR and PMR spectra and, for compound IIc, ^{13}C NMR and mass spectral data. The IR spectra of IIa-*l* show the absence of bands in the region 1600–1800 cm^{-1}, characteristic of double bonds and carbonyl groups in the starting epoxy ketones, and the presence of NH and OH stretching bands near 3450 and 3620 cm^{-1}, respectively, together with pyrazole and aromatic ring absorptions in the region 1300–1600 cm^{-1}.

The PMR spectra of the β-hydroxyalkylpyrazoles IIa-*l* (Table 1) differ according to the nature of their R^1, R^2, R^3, and Ar substitution but they all show a characteristic singlet for the 4-H pyrazole proton at 6.30–6.40 ppm.

Acetylation of compounds IIa, e, g, j–*l* with acetic anhydride gives the corresponding N-acetyl-β-acetoxyalkylpyrazoles IIIa, e, g, j–*l*. Dehydration of the β-hydroxyalkylpyrazoles IIk, *l* to the alkenylpyrazoles IVk, *l* occurs with sulfuric acid at 40°C. The iodoalkylpyrazoles Va, c are formed by nucleophilic substitution of the hydroxyl group in IIa, c,. Oxidation of β-hydroxyalkylpyrazoles IIc, g using pyridinium chlorochromate gives the 3(5)-acetylpyrazoles VIc, g instead of the expected β-pyrazolylcarbonyl compounds. The constants for these compounds are given in Table 1.

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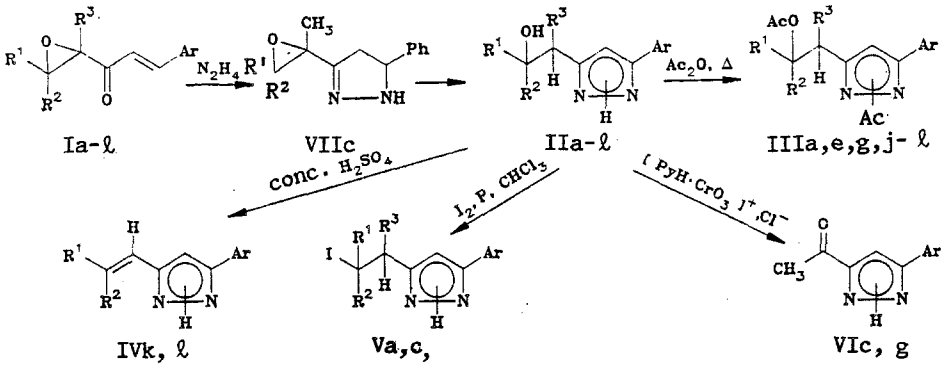
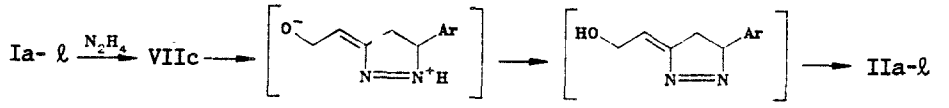
TABLE 1. Constants for IIa-*l*, IIIa, e, g, j-*l*, IVk, *l*, Va, c, and VIc, g

Compound	Empirical formula	mp, °C	PMR Spectrum, ppm, (J, Hz)			Yield, %
			R^1R^2—CCHR^3	4-H, s	Harom	
IIa	$C_{11}H_{11}BrN_2O$	177...179	2,71 (2H, t, J=6,6, CH_2); 3,83 (2H, t, J=6,6, CH_2—O)	6,33	7,36; 7,56 (4H, two d J=9,0)	53
IIb	$C_{11}H_{11}ClN_2O$	132...134	2,74 (2H, t, J=6,6, CH_2); 3,81 (2H, t, J=6,6, CH_2—O)	6,40	7,39; 7,70 (4H, two d, J=9,0)	55
IIc	$C_{12}H_{14}N_2O$	128...130	1,24 (3H, d, J=7,0, CH_3); 2,93 (1H, d.q, J=7,0, CH); 3,63 (2H, dd, J=7,0 CH_2)	6,40	7,24; 7,72 (5H, two m)	62
IId	$C_{12}H_{13}BrN_2O$	132...133	1,24 (3H, d, J=7,0, CH_3); 2,90 (1H, d. q J=7,0, CH); 3,53 (2H, d.q, d, J=10,0, J=7,0, CH_2)	6,40	7,44; 7,63 (4H, two d, J=9,0)	58
IIe	$C_{12}H_{13}ClN_2O$	98...100	1,17 (3H, d, J=7,0, CH_3); 2,90 (1H, d. q, J=7,0, CH); 3,50 (2H, d.q, d, J=10,0; J=7,0, CH_2)	6,40	7,65; (4H, m)	64
IIf	$C_{13}H_{16}N_2O$	152...153	1,03 (3H, d, J=7,0, CH_3); 1,23 (3H, d, J=7,0, CH_3); 2,80 (1H, d. q, J=7,0, CH); 3,80 (2H, d. q, J=7,0, CH)	6,36	7,20; 7,70 (5H, two m)	66
IIg	$C_{13}H_{15}BrN_2O$	139...140	1,00 (3H, d, J=7,0, CH_3); 1,20 (3H, d, J=7,0, CH_3); 2,85 (1H, d. q, J=7,0, CH); 3,75 (1H, d. q J=7,0, CH)	6,40	7,40; 7,64 (4H, two d, J=9,0)	57
IIh	$C_{13}H_{15}ClN_2O$	131...132	0,95 (3H, d, J=6,2, CH_3); 1,13 (3H, d, J=7,0, CH_3); 2,75 (1H, d. q, J=6,2, CH); 3,72 (1H, d. q J=7,0, CH)	6,38	7,30; 7,33	63
IIi	$C_{14}H_{18}N_2O_2$	141...142	0,95 (3H, d, J=6,2, CH_3); 1,13 (3H, d, J=7,0, CH_3); 2,72 (1H, d. q, J=6,2, CH); 3,65 (3H, s, CH_3); 3,65 (1H, m, CH)	6,40	6,76; 7,53 (4H, two d J=9,0)	68
IIj	$C_{13}H_{15}N_3O_2$	Oil	1,05 (3H, d, J=6,2, CH_3); 1,21 (3H, d, J=7,0, CH_3); 2,78 (1H, d. q J=6,2, CH); 3,75 (1H, d. q, J=7,0, CH)	6,43	7,56; 8,05; 8,50 (4H, m) 7,40 (4H, m)	52
IIk	$C_{13}H_{16}N_2O$	136...137	1,15 (6H, s, two CH_3); 2,72 (2H, s, CH_2)	6,37	7,72; 7,33 (5H, two m)	72
IIl	$C_{17}H_{16}N_2O$	161...163	2,90 (2H, d, J=7,0, CH_2); 4,30 (1H, m, CH); 4,80 (1H, t, J=7,0, CH)	6,30	7,20 (10H, m)	
IIIa	$C_{15}H_{15}BrN_2O_3$	85...87	1,95 (3H, s, CH_3); 2,68 (3H, s, CH_3); 3,29 (2H, t, J=6,6, CH_2); 4,30 (2H, t, J=6,6, CH_2)	6,43	7,40; 7,60 (4H, two d, J=9,0)	82
IIIe	$C_{16}H_{17}ClN_2O_3$	91...93	1,23 (3H, d, J=7,0, CH_3); 1,93 (3H, s, CH_3); 2,66 (3H, s, CH_3); 3,90 (1H, m, CH); 4,11 (2H, s, CH_2)	6,45	7,40 (4H, m)	65 54
IIIg	$C_{17}H_{19}BrN_2O_3$	133...135	1,15 (3H, d, J=7,0, CH_3); 1,21 (3H, d, J=7,0, CH_3); 1,83 (3H, s, CH_3); 2,64 (3H, s, CH_3); 3,93 (1H, d.q, J=7,0, CH); 5,08 (1H, d.q, J=7,0, CH)	6,60	7,51; 8,05; 8,52 (4H, m)	64
IIIj	$C_{17}H_{19}N_2O_5$	143...144	1,14 (3H, d, J=7,0, CH_3); 1,22 (3H, d, J=7,0, CH_3); 1,90 (3H, s, CH_3); 2,70 (3H, s, CH_3); 4,04 (1H, d.q, J=7,0, CH); 5,08 (1H, d.q, J=7,0, CH)	6,60	7,51; 8,05; 8,52 (4H, m)	73
IIIk	$C_{17}H_{20}N_2O_3$	76...79	1,42 (6H, s, two CH_3); 1,87 (3H, s, CH_3); 2,64 (3H, s, CH_3); 3,60 (2H, s, CH_2)	6,67	7,30; 7,80 (5H, m)	77
IIIl	$C_{21}H_{20}N_2O_3$	97...99	1,90 (3H, s, CH_3); 2,66 (3H, s, CH_3); 3,43 (2H, m, CH_2); 4,87 (1H, m, CH)	6,41	7,30 (10H, m)	51
IVk	$C_{13}H_{14}N_2$	88...89	1,74 (3H, s, CH_3); 1,84 (3H, s, CH_3); 5,90 (1H, d, J=10,0, CH)	6,38	7,20; 7,63 (5H, two m)	92
IVl	$C_{17}H_{14}N_2$	Oil	6,02 (1H, d, J=8,0, CH); 6,11 (1H, d, J=8,0, CH)	6,40	7,20 (10H, m)	85
Va	$C_{11}H_{10}BrIN_2$	147...148	3,20 (4H, m, CH_2—CH_2)	6,40	7,40; 7,60 (4H, two d J=9,0)	74
Vc	$C_{12}H_{13}IN_2$	141...142	1,33 (3H, d, J=6,4, CH_3); 2,90...3,80 (3H, m, CH_2—CH)	6,40	7,16; 7,60 (5H, two m)	65
VIc	$C_{11}H_{10}N_2O$	152...153	2,40 (3H, s, CH_3)	7,05	7,28; 7,66 (5H, two m)	72
VIg	$C_{11}H_9BrN_2O$	185...187	2,44 (3H, s, CH_3)	7,11	7,50; 7,33 (4H, two d J=9,0)	54



Ia-IIIa, Va $R^1=R^2=R^3=H$, Ar=4-BrC_6H_4; Ib, IIb $R^1=R^2=R^3=H$, Ar=4-ClC_6H_4; Ic, IIc, Vc, VIIc $=R^2=H$, $R^3=CH_3$, Ar=C_6H_5; Id IId $R^1=R^2=H$, $R^3=CH_3$, Ar= =4-BrC_6H_4; Ie, IIIe $R^1=R^2=H$, $R^3=CH_3$, Ar=4-ClC_6H_4; If, IIf $R^1=R^3=CH_3$, $R^2=H$, Ar=C_6H_5; Ig, IIIg, VIg $R^1=R^3=CH_3$, $R^2=H$, Ar=4-BrC_6H_4; Ih, IIh $R^1=R^3=CH_3$, $R^2=H$, Ar=4-ClC_6H_4, Ii, IIi $R^2=H$, $R^1=R^3=CH_3$, Ar=4-$CH_3OC_6H_4$; Ij–IIIj $R^1=R^3=$ $=CH_3$, $R^2=H$, Ar=3-$NO_2C_6H_4$; Ik -IVk $R^1=R^2=CH_3$, $R^3=H$, Ar=C_6H_5, Il, IVl $R^1=C_6H_5$, $R^2=R^3=H$, Ar=C_6H_5

Formation of the β-hydroxyalkylpyrazoles IIa-*l* takes place via intermediate oxiranylpyrazolines, as shown by the isolation of VIIc when epoxyenone Ic was treated with hydrazine hydrate at 10°C for 15 min. Subsequent reactions of this intermediate apparently include an electronic shift analogous to the Barton [3] reduction of α, β-epoxyketones by hydrazine hydrate and aromatization of the pyrazoline ring via migration of the exocyclic double bond. The absence of effects from the structure of the substrate on the velocity of the reaction and the structure of the products point to the intramolecular character of the rearrangement.



Bearing in mind the analogous conversion of epoxypropionyltriazolines to hydroxypropionyltriazoles observed before [4] one can propose that this oxidative-reductive disproportionation is a characteristic of partially hydrogenated NH-azoles containing an epoxide ring in the side chain.

EXPERIMENTAL

IR spectra of substances in $CHCl_3$ were recorded on a Specord IR-75 instrument and PMR spectra in a mixture of acetone d_6 + DMSO d_6 on Tesla BS-567A (60 MHz) and Bruker WM-360 (360 MHz) instruments using HMDS as internal standard.

Constants for the synthesized compounds are given in Table 1. Elemental analytical data agreed with those calculated.

3(5)-(2-Hydroxyalkyl)-5(3)-arylpyrazoles (IIa–*l*). A. Hydrazine hydrate (90 mmole) was added with stirring over 2–4 h to a solution of the epoxyketone Ia-*l* (50 mmoles) in methanol (ethanol, dioxane, acetic acid) and the reaction mixture allowed to stand at 20°C for 12 h. The solvent was evaporated in vacuo, the residue diluted with water to 100 ml, extracted with ether (4 × 50 ml), and dried over Na_2SO_4. Upon evaporation of solvent to 30–50 ml the β-hydroxyalkylpyrazoles IIa-*l* crystallized and were recrystallized from a mixture of chloroform–hexane. Compound IIc, ^{13}C NMR spectrum: 15.63 (q, CH_3–C), 33.44 (d, CH–CH_3), 65.51 (t, CH_2–O), 98.30 (d, C_4), 123.57, 126.20, 127.37 (three d, $C_{o,m,p}$); 131.75 (s, C_{ipso}); 146.16 (s, C_3); 149.42 ppm (s, C_5). Mass spectrum: 202 [M^+], 184 [$M^+ - H_2O$], 171 [$M^+ - CH_2OH$], 143 [phenylpyrazolyl], 91 [benzyl], 77 [phenyl].

B. Hydrazine hydrate (23 mmoles) was added over 1 h to a refluxing solution of epoxyketone Ig (10 mmoles) in ethanol (30 ml). After refluxing for 2 h, the solvent was evaporated and the residue diluted with water, and extracted with ether (3 × 40 ml) and dried. Ether was removed and the pyrazole IIg recrystallized from chloroform–hexane (3:1).

1-Acetyl-5(3)-aryl-3(5)-(2-acetoxyalkyl)pyrazoles (IIIa, e, g, j–*l*). A solution of β-hydroxyalkylpyrazole IIa, e, g, j–*l* (5 mmoles) in acetic anhydride (2 ml) was refluxed for 1 h using a reflux condenser. Excess reagent was distilled

off in vacuo, the residue treated with aqueous sodium bicarbonate, extracted with ether (4 × 50 ml), and dried over Na_2SO_4. The ether was evaporated to give the β-acetoxy-N-acetylpyrazole IIIa, e, g, j–*l* which was recrystallized from acetone–hexane.

3(5)-(1-Alkenyl)-5(3)-phenylpyrazoles (IVk, *l*). β-Hydroxyalkylpyrazole IIk, *l* (5 mmoles) was added to conc. H_2SO_4 (2 ml) cooled to 5°C, the crystals triturated to full solution and heated for 30 min on a 40°C water bath. The mixture was poured into water (100 ml), and the separated oil extracted with ether (4 × 20 ml), and dried over Na_2SO_4. After removal of ether Vk was recrystallized from hexane.

5(3)-Aryl-3(5)-(2-iodoalkyl)pyrazoles (Va, c). A mixture of pyrazole IIa, c (12.7 mmoles), iodine (3.34 g, 12.7 mmoles), and red phosphorus (0.28 g, 9 mmoles) in chloroform (75 ml) was refluxed for 10 h, cooled, and chromatographed on an alumina column (40/250, 2 × 25 cm) using chloroform–acetone (1:1) eluent. Removal of solvent gave Va, c which was recrystallized from toluene.

5(3)-Aryl-3(5)-acetylpyrazoles (VIc, g). Pyrazole IIc, g (5 mmole) in methylene chloride (20 ml) was added to a suspension of pyridinium chlorochromate (7 mmoles) in anhydrous methylene chloride (40 ml), stirred for 1.5 h, and diluted with ether (30 ml). The solution was chromatographed on a silica gel column (40/100, 2 × 20 cm) using ether eluent. The solvent was evaporated to give crystalline acetylpyrazole (VIc, g) which was recrystallized from chloroform–hexane (1:2).

3(1-Methyl-1,2-epoxyethyl)-5-phenyl-2-pyrazoline (VIIc, $C_{12}H_{14}N_2O$). Epoxyketone Ic (10 mmoles) was dissolved in methanol (15 ml) and hydrazine hydrate (12.5 mmoles) added at 10°C. After 15 min, the mixture was diluted with water (10 ml), the precipitated solid filtered off, washed with water and methanol, and dried in vacuo to give VIIc (92%) with mp 113–115°C. Attempts to recrystallize VIIc caused its isomerization to β-hydroxyalkylpyrazole IIc. PMR spectrum: 1.31 (3H, s, CH_3); 2.73 (2H, m, CH_2); 2.90 (2H, m, CH_2); 4.14 (1H, s, NH); 4.56 (1H, m, CH); 7.19 ppm (5H, m).

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