HETEROCYCLIZATION OF ACRYLOYLOXIRANES TO 3-HYDROXY-4-PIPERIDINONES AND 2-(α-HYDROXYALKYL)-3-PYRROLIDINONES IN THE REACTION WITH METHYLAMINE

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3-Hydroxy-4-piperidinones and 2-(α-hydroxyalkyl)-3-pyrrolidinones were obtained by the reaction of acryloyloxiranes with methylamine. It is shown that the regiospecificity of the heterocyclization of the products of addition of methylamine to the double bond of the acryloyloxirane is determined by the substituents attached to the α- and β-carbon atoms of the epoxide ring.

The reaction of 2-methyl-2-cinnamoyloxiranes with primary amines is a convenient preparative method for the synthesis of 6-aryl-3-hydroxy-3-methyl-4-piperidinones [1]. It includes the initial addition of the amine to the double bond of the epoxy enone with subsequent intramolecular cyclization of the β'-amino α,β-epoxy ketones to 4-piperidinones [2]. The high yields of the compounds obtained are due to the fact that opening of the epoxide ring of 2-methyl-2-cinnamoyloxiranes by nucleophilic reagents proceeds unambiguously at the β-carbon atom with the formation of functionally substituted α-ketones [3].

Just like epoxy enones of the aliphatic series, acryloyloxiranes that contain an unsubstituted or dialkyl-substituted epoxide ring have not been subjected to reaction with primary amines, and it is difficult to predict the direction of their opening and the stereochemistry of the resulting products as a result of the intramolecular cyclization of the intermediate β'-amino α,β-epoxy ketones taking into account the structural and steric factors. In addition, the possibility of using monoepoxides of aliphatic divinyl ketones opens up a pathway to previously unknown alkyl-substituted 3-hydroxy-4-piperidinones.

To ascertain the direction of the heterocyclization of acryloyloxiranes in the reaction with primary amines and to investigate the preparative possibilities of this method we studied the reaction of epoxy enones with methylamine.

It was established that the character of the resulting products and the rate of the reaction of acryloyloxiranes I-XI with methylamine are determined by the substituents in the oxirane ring of the epoxy enone and do not depend on the nature of the substituent attached to the β-carbon atom of the double bond. Thus the reaction of 2-crotonoyl-2-methyloxirane I with a twofold excess of a 33% aqueous solution of methylamine in dioxane proceeds just as readily as in the case of 2-methyl-2-cinnamoyloxirane [1] and leads to the formation of 3-hydroxy-4-piperidinone (XII) as the principal product. It should be noted that this piperidone is the hydroxy analog of 1,2,5-trimethyl-4-piperidinone – the starting compound in the synthesis of promedol [4-6].

The reaction of β-arylacryloyloxirans II and III with methylamine under similar conditions leads to the formation of a mixture of substances, from which the corresponding 6-aryl-3-hydroxy-4-piperidinones XIII and XIV were obtained in the form of the hydrochlorides in up to 80% yields; unstable bases, viz., 3-pyrrolidinones XXIV and XXV, were isolated from the filtrates of these products after they were made alkaline.

2,3-Dimethyloxiranes IV-IX react with methylamine to give the corresponding 4-piperidinone bases XV-XX (in 70-90% yield); however, the possibility of the formation of 1,2-dimethyl-3-pyrrolidinones in small amounts also was not excluded. In order to detect one of them the filtrate after crystallization of XV was chromatographed thoroughly on silica gel, and 3-pyrrolidinone XXVI, the structure of which was established by means of the IR and PMR spectra, was isolated in addition to 4-piperidinone XXIII. The position of the absorption

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TABLE 1. Characteristics of XII-XXXI

Compound	mp, °C	Solvent	R_f*1	IR spectrum, cm^{-1}		Found, %			Empirical formula	Calc., %			Yield, %
				C=O	OH	C	H	N		C	H	N	
XII	43...43.5	Hexane—ether, 10:1	0.17	1715	3490	60.9	9.5	8.8	$C_8H_{15}NO_2$	61.1	9.6	8.9	68
XIII*2	162...161 (dec.)	Water	0.37	1720	3500	44.7	4.7	4.3	$C_{12}H_{15}BrNO_2 \cdot HCl$	45.0	4.7	4.4	77
XIV*2	150...152 (dec.)	Water	0.35	1720	3500	51.9	5.4	5.0	$C_{12}H_{15}ClNO_2 \cdot HCl$	52.2	5.5	5.1	79
XV	95...96	Hexane	0.76	1720	3190	72.0	8.3	6.0	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	92
XVI	56...57	Hexane	0.69	1720	3190	53.7	5.7	4.4	$C_{14}H_{18}BrNO_2$	53.9	5.8	4.5	78
XVII	66...67	Hexane	0.68	1720	3190	62.7	6.7	5.1	$C_{14}H_{18}ClNO_2$	62.8	6.8	5.2	86
XVIII	92...91	Heptane—benzene, 8:1	0.62	1720	3190	68.2	8.1	5.3	$C_{15}H_{21}NO_3$	68.1	8.1	5.3	88
XIX	78...79	Heptane	0.63	1720	3190	68.2	8.0	5.2	$C_{15}H_{21}NO_3$	68.4	8.1	5.3	61
XX	123...124	Heptane—acetone, 5:1	0.44	1720	3190	64.0	6.9	10.7	$C_{14}H_{18}N_2O_4$	64.1	6.9	10.7	81
XXI	122...121	Ether	0.85	1720	3190	77.0	7.0	4.6	$C_{16}H_{21}NO_2$	77.3	7.2	4.7	17
XXII*3	—		0.38	1720	3500	72.1	8.3	6.1	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	2.7
XXIII	—		0.60	1720	3510	72.0	8.3	6.3	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	3.0
XXIV	—		0.51	1765	3470	50.6	5.0	5.0	$C_{12}H_{14}BrNO_2$	50.7	5.0	4.9	12
XXV	—		0.46	1765	3470	60.1	6.0	6.0	$C_{12}H_{14}ClNO_2$	60.1	5.9	5.8	13
XXVI	—		0.68	1760	3480	72.0	8.2	6.1	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	4.5
XXVII	—		0.57	1765	3510	72.0	8.2	6.0	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	43
XXVIII	129...130	Methanol	0.39	1705	3450, 3390*4, 3350*4	73.3	8.0	8.7	$C_{20}H_{26}N_2O_2$	73.6	8.0	8.6	56
XXIX	—		0.15	1610*5	3500	72.9	9.0	11.5	$C_{15}H_{22}N_2O$	73.1	9.0	11.4	46
XXX	71...72	Hexane—ether, 6:1	0.64	1690	3450	71.0	8.0	6.2	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	91 (12)*6
XXXI	—		0.57	1770	—	75.4	7.4	8.2	$C_{11}H_{13}NO$	75.4	7.5	8.0	25

*1 The solvents were ether for XII-XIV, XXIV, XXV, XXVIII, and XXIX and ether—hexane (2:1) for XV-XXIII, XXVI, XXVII, XXX, and XXXI.

*2 Data for the hydrochlorides are presented.

*3 Compounds XXII-XXVII, XXIX, and XXXI were isolated by chromatography in the form of viscous oils.

*4 Stretching vibrations of the NH bond.

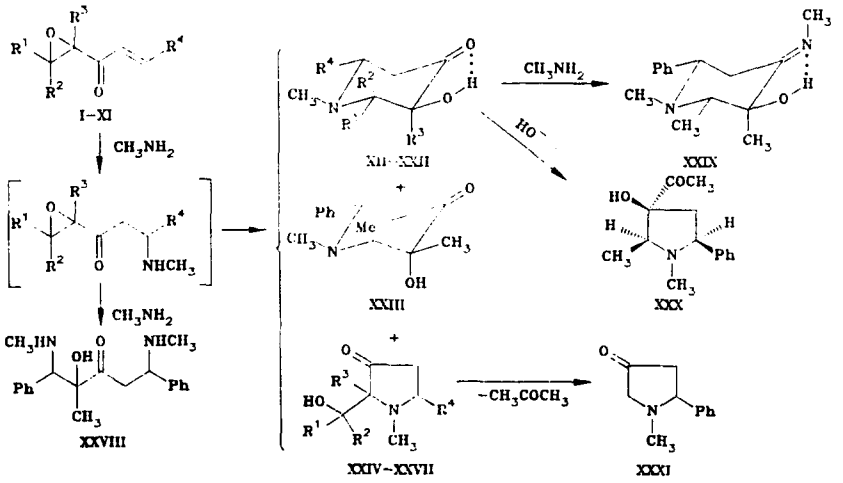
*5 The absorption frequency of the C=N bond is presented.

*6 The yield obtained in the reaction of IV with methylamine for 30 days.

TABLE 2. PMR Spectra of 3-Hydroxy-4-piperidinones XII-XXIII

Compound	Chemical shift, δ, ppm									J, Hz			
	R^1	R^2	R^3	N-CH$_3$	5e-H	5a-H	6a-H	OH	R^4	1e-H, 5a-H	5e-H, 6a-H	5a-H, 6a-H	R_2^2, 2-H
XII	3,01	2,23	1,47	2,31	2,37	2,49	2,28	3,72	1,17	13,9	3,2	11,4	6,1
XIII	3,53	2,27	1,19	2,08	2,55	2,66	3,17	3,45	7,22, 7,48	14,0	2,9	11,8	11,0
XIV	3,53	2,26	4,50	2,07	2,55	2,68	3,19	3,48	7,28, 7,36	14,0	2,9	11,8	11,0
XV	1,29	2,20	1,47	1,98	2,50	2,88	3,23	3,95	7,28	13,9	3,8	12,0	6,1
XVI	1,27	2,18	1,45	1,95	2,45	2,80	3,20	3,95	7,21, 7,45	13,9	3,7	12,1	6,4
XVII	1,28	2,19	1,46	1,98	2,48	2,82	3,22	3,89	7,28, 7,32	13,8	3,4	11,7	6,4
XVIII	1,24	2,13	1,13	1,93	2,12	2,83	3,16	3,89	6,86, 7,23	13,8	3,4	11,7	6,4
XIX	1,29	2,22	1,17	2,01	2,52	2,82	3,85	3,94	6,85...7,50	13,7	3,4	11,7	6,1
XX	1,25	2,22	1,16	1,96	2,18	2,83	3,40	3,86	7,54, 8,12	14,2	3,8	12,6	6,1
XXI	7,35	3,22	1,35	1,81	2,59	3,02	3,38	3,90	7,35, 7,43	13,8	3,6	12,1	·
XXII	1,42	0,83	4,18	2,02	2,55	2,70	3,66	3,70	7,28	14,2	3,2	10,8	—
XXIII	3,09	0,99	1,28	2,11	2,40	3,08	3,68	3,94	7,31	11,2	3,2	10,8	7,2

band of the hydroxy group of 4-piperidinone XXIII in the IR spectrum (3520 cm^{-1}) does not change upon dilution of the solution to 10^{-1} to 10^{-3} M; this constitutes evidence for the presence of an intramolecular hydrogen bond (IMHB) with the ring nitrogen atom. The chemical shift of the 3-CH_3 group in the PMR spectrum of XXIII, which is recorded at stronger field as compared with piperidone XV (Table 2), constitutes evidence for its equatorial orientation; this is characteristic for the stereoisomers of 3-hydroxy-4-piperidinones [2, 7]. As expected, the resonance signal of the 2a proton of piperidone XV shows up at stronger field than the signal of the 2e proton of the diastereomer of XXIII; this is due to the shielding effect of the unshared electron pair of the nitrogen atom on the 2a proton in XV [8]. The increase in the $^3J_{2\text{-}CH_3,2\text{-}H}$ spin-spin coupling constant (SSCC) from 6.4 Hz (for XV) to 7.2 Hz (for XXIII) confirms the axial orientation of the 2-CH_3 group in XXIII [9]. The structure of 3-pyrrolidinone XXVI was established on the basis of the PMR spectrum from the presence of a weak-field quartet of the proton at 3.70 ppm, the SSCC of the geminal protons in the 4 position (^2J = 17.1 Hz) [10], and the absorption of a carbonyl group that is characteristic for a five-membered ring in the IR spectrum (1760 cm^{-1}).



I, XII $R^1=R^2=H$, $R^3=R^4=CH_3$; II, XIII, XXIV $R^1=R^2=R^3=H$, $R^4=4\text{-}BrC_6H_4$; III, XIV, XXV $R^1=R^2=R^3=H$, $R^4=4\text{-}ClC_6H_4$; IV—IX, XV—XX, XXVI $R^1=R^3=CH_3$; $R^2=H$, IV, XV, XXVI $R^4=C_6H_5$; V, XVI $R^4=4\text{-}BrC_6H_4$; VI, XVII $R^4=4\text{-}ClC_6H_4$; VII, XVIII $R^4=4\text{-}CH_3OC_6H_4$; VIII, XIX $R^4=2\text{-}CH_3OC_6H_4$; IX, XX $R^4=3\text{-}NO_2C_6H_4$; X, XXI $R^1=R^4=C_6H_5$, $R^2=H$, $R^3=CH_3$; XI, XXII, XXVII $R^1=R^2=CH_3$, $R^3=H$, $R^4=C_6H_5$

When the time of the reaction of epoxy enone IV with methylamine was increased to 30 days, two other products — N-methyliminopiperidine XXIX and acetylpyrrolidine XXX — were obtained in addition to XV, XXIII, and XXVI. Compound XXIX is formed as a result of the reaction of piperidone XV with excess methylamine, while pyrrolidine XXX is formed via its acyloin rearrangement; this was confirmed by obtaining pyrrolidine when an ether solution of piperidone XV was passed through a column packed with basic aluminum oxide.

The reaction of oxirane X, which contains a phenyl group attached to the β-carbon atom of the epoxide ring, with methylamine also leads to hydroxy-4-piperidinone XXI. In this case the heterocyclization reaction proceeds considerably more slowly, and dimethylamino-hydroxypentanone XXVIII was obtained in addition to piperidone XXI. The formation of products of diaddition of the amine to β-arylacryloyloxiranes has also been previously proposed [2]; however, they were not detected.

The reaction of 3,3-dimethyloxirane XI with methylamine proceeds in a different way. The result of the presence of two methyl groups attached to the β-carbon atom of the epoxy ring is that α-opening of the oxirane ring with the formation of 3-pyrrolidinone XXVIII, which undergoes partial retroaldolization to XXXI under the reaction conditions, becomes predominant. The corresponding 4-piperidinone is formed in only 2.7% yield.

The structures of the synthesized compounds were confirmed by the results of elementary analysis and the IR and PMR spectral data (Tables 1 and 2). Intense absorption bands of hydroxy and carbonyl groups linked together by IMHB at 3490-3500 and 1710-1720 cm^{-1}, respectively, are present in the IR spectra of hydroxy-4-piperidinones XII-XXII. The independence of the position of the hydroxy absorption on dilution constitutes evidence for the intramolecular character of the hydrogen bond. The stretching vibrations of the hydroxy groups

in 3-pyrrolidinones XXIV-XXVII are observed at 3470-3480 cm^{-1} (3510 cm^{-1} for XXVII), while the carbonyl absorption bands are observed at 1760-1765 cm^{-1}. The stretching vibrations of the carbonyl group in 3-pyrrolidinone XXXI are observed at 1770 cm^{-1}, as compared with 1690 cm^{-1} in the case of acetylhydroxy-pyrrolidine XXX. The absorptions of the hydroxy and azomethine groups in piperidine XXIX show up at 3500 and 1640 cm^{-1}, respectively; this constitutes evidence for the formation of the E isomer of the Schiff base, since an IMHB is possible only in the case of an anti orientation of the methyl group with respect to the hydroxy group.

The PMR spectra of hydroxy-4-piperidinones XII-XXII contain a spin ABX system that is characteristic for a six-membered ring in the chair conformation with SSCC $J_{5a,5e}$ = 14.0 Hz, $J_{5a,6a}$ = 12.0 Hz, and $J_{5e,6a}$ = 3.5 Hz. The configurations of pyrrolidine XXX and 3e-hydroxy-4-piperidinones in the case of XII and XV were confirmed by measuring the Overhauser effect (OE). The development of positive responses at the frequencies of the 5a and 2e protons upon irradiation with the resonance frequency of the 3-CH_3 group confirms its axial orientation in XII, while the analogous effect for the 3a proton upon irradiation with the frequency of the 2-CH_3 group for XV confirms its equatorial orientation. The drawing together in space of the 2e-CH_3 group and the 5a proton in piperidone XV is possible in the case of partial "compression" of the 1,2,3-fragment of the molecule in the chair conformation as a result of steric repulsion of the cisoid 2e- and 3a-methyl groups; this is readily observed with Dreiding models. The development of a nuclear OE at the frequencies of the ortho protons of the phenyl group and the proton of the hydroxy group upon irradiation with the resonance frequency of the doublet of protons of the 2-CH_3 group of pyrrolidine XXX constitutes evidence for a cisoid orientation of the 2-CH_3, 3-OH, and phenyl groups.

A characteristic feature of the PMR spectra of piperidones XIII and XIV is the presence of long-range spin-spin coupling of the syn-diaxial 3a and 5a protons (^4J = 1.5 Hz), as well as slight broadening of the doublet of the 2a proton in the spectrum of XII due to spin-spin coupling with the 3a-CH_3 group (^4J = 0.5 Hz).

EXPERIMENTAL

The IR spectra of solutions of the substances in CCl_4 (c = 10^{-1} M, l = 0.01 cm; c = 10^{-3} M, l = 1 cm) were recorded with a Specord IR-75 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ (with tetramethylsilane as the internal standard) were obtained with a Bruker WM-360 spectrometer. The measurements of the Overhauser effect (OE) were made by differential spectroscopy. The Rf values were determined in Silufol plates. The characteristics of the synthesized compounds are presented in Tables 1 and 2 and in the experimental section.

3e-Hydroxy-1,3a,6e-trimethyl-4-piperidinone (XII). A mixture of 2.52 g (0.02 mole) of 2-crotonoyl-2-methyloxirane (I) [11] and 4.1 ml (0.04 mole) of a 33% aqueous solution of methylamine in 5 ml of dioxane was allowed to stand at 15°C for 6 h, after which the reaction mixture was acidified with dilute hydrochloric acid (1:1) until it gave an acidic reaction with respect to Congo red. The solvent was evaporated in vacuo at 20°C, 5 ml of water was added to the residue, and the aqueous mixture was made alkaline with 15% potassium carbonate solution. The precipitated product was extracted with methylene chloride (five 5-ml portions), the extract was washed with water (5 ml), dried over sodium sulfate, and evaporated in vacuo. The oil was dissolved in 50 ml of hexane, and the solution was filtered through a layer of silica gel in the filter (2 cm). The eluate was partially evaporated, and the concentrate was cooled to give 2.14 g of piperidone XII in the form of colorless crystals.

6e-Aryl-3e-hydroxy-1-methyl-4-piperidinones XIII and XIV and 2-Hydroxymethyl-1-methyl-5-aryl-3-pyrrolidinones XXIV and XXV. A 4.1-ml (0.04 mole) sample of a 33% solution of methylamine was added in the course of 1 min with stirring at −3°C to 0°C to a solution of 0.02 mole of epoxy enes II and III in 20 ml of dioxane, during which the partially solidified dioxane melted, and the solution became homogeneous. The reaction mixture was stirred at 0°C for 15 min and at 5°C for another 45 min, after which the excess methylamine was neutralized with dilute HCl (1:1), and the mixture was extracted with ether (50 ml). The aqueous solution containing the reaction products was evaporated in vacuo at 20-25°C until crystals of the hydrochlorides of piperidones XIII and XIV formed; the latter were removed by filtration, washed with ether–acetone (1:1), and dried in a vacuum pistol over P_2O_5. The mother liquors of the hydrochlorides of XIII and XIV were made alkaline with sodium carbonate, the

precipitated bases were extracted with ether, and the extract was dried over sodium sulfate. Chromatography with a column packed with silica gel [elution with ether–hexane (5:1)] gave 3-pyrrolidinones XXIV and XXV. PMR spectrum (XXIV): 2.26 (s, 3H, N–CH_3), 2.43 (dd, 1H, 4-H, $J_{4,5}$ = 11.0 Hz; $J_{4,4'}$ = 17.0 Hz), 2.69 (dd, 1H, 4'-H, $J_{4'5}$ = 6.2 Hz; $J_{4',4}$ = 17.0 Hz), 3.37 (m, 1H, 2-H), 3.56 (dd, 1H, CH_2, J = 6.6 Hz; J = 12.0 Hz), 3.68 (dd, 1H, CH_2, J = 9.3 Hz; J = 12.0 Hz), 3.75 (dd, 1H, 5-H, $J_{5,4'}$ = 6.2 Hz; $J_{5,4}$ = 11.0 Hz), 3.80 (s, 1H, OH), 7.20, 7.36 ppm (two d, 4H, aromatic, J = 90 Hz). PMR spectrum (XXV): 2.27 (s, 3H, N–CH_3), 2.42 (dd, 1H, 4-H, $J_{4,5}$ = 11.0; $J_{4,4'}$ = 17.1 Hz), 2.69 (dd, 1H, 4'-H, $J_{4',5}$ = 6.0 Hz; $J_{4',4}$ = 17.1 Hz), 3.40 (m, 1H, 2-H). 3.76 (dd, 1H, 5-H, $J_{5,4'}$ = 6.0 Hz; $J_{5,4}$ = 11.0 Hz), 3.55 (dd, 1H, CH_2, J = 6.5 Hz; J = 11.9 Hz), 3.69 (dd, 1H, CH_2, J = 9.1 Hz; J = 11.9 Hz), 3.83 (s, 1H, OH), 7.25, 7.39 ppm (two d, 4H, aromatic, J = 9.0 Hz).

6e-Aryl-3e-hydroxy-1,2e,3a-trimethyl-4-piperidinones XV-XX, 3a-Hydroxy-1,2a,3e-trimethyl-6e-phenyl-4-piperidinone (XXIII), 2-(1-Hydroxyethyl)-1,2-dimethyl-5-phenyl-3-pyrrolidinone (XXVI), and 3r-Acetyl-3-hydroxy-1,2t-dimethyl-5t-phenylpyrrolidine (XXX). A 10.3-ml (0.10 mole) sample of a 33% solution of methylamine was added with stirring to a solution of 0.05 mole of epoxy enone IV-IX in 40 ml of dioxane, after which the reaction mixture was allowed to stand at 15-18°C for 1 day, diluted to twice its original volume with water and acidified with HCl solution (1:1), and the unchanged oxirane was extracted with ether. Compounds XV-XX were isolated in the crystalline or oily state after the solution was made alkaline. The crystals were removed by filtration, while the oils were extracted with ether and crystallized from a mixture of solvents.

After crystallization of piperidone XV, the mother liquor was evaporated, and the residue was chromatographed [silica gel L 40/100, elution with hexane–ether (2:1)]. Piperidone XXIII and 3-pyrrolidinone XXVI were isolated. PMR spectrum (XXVI): 1.09 (s, 3H, 2-CH_3), 1.37 (d, 3H, $\underline{CH_3}$–CH, J = 6.4 Hz), 2.16 (s, 3H, N–CH_3), 2.42 (dd, 1H, 4-H, $J_{4,5}$ = 10.8; $J_{4,4'}$ = 17.1 Hz), 2.65 (dd, 1H, 4'-H, $J_{4',5}$ = 6.1 Hz; $J_{4',4}$ = 17.1 Hz), 3.70 (q, 1H, $\underline{CH}$–CH_3, J = 6.4 Hz), 3.77 (dd, 1H, 5-H, $J_{5,4''}$ = 6.1 Hz; $J_{5,4}$ = 10.8 Hz), 3.85 (s, 1H, OH), 7.35 ppm (m, 5H, aromatic).

When the reaction of oxirane IV with methylamine was carried out for 30 days at 15-18°C, in addition to XV, XXIII, and XXVI, N-methyliminopiperidine XXIX [PMR spectrum: 1.26 (d, 3H, 2-CH_3, J = 6.4 Hz), 1.38 (s, 3H, 3-CH_3), 1.93 (s, 3H, N–CH_3), 2.01 (q, 1H, 2-H, J = 6.4 Hz), 2.22 (dd, 1H, 5-H, $J_{5,6}$ = 12.0 Hz; $J_{5,5'}$ = 13.4 Hz), 2.79 (dd, 1H, 5'-H, $J_{5',6}$ = 3.8 Hz; $J_{5',5}$ = 13.4 Hz), 2.95 (dd, 1H, 6-H, $J_{6,5'}$ = 3.8 Hz; $J_{6,5}$ = 12.0 Hz), 3.13 (s, 3H, CH_3–N=), 7.28-7.34 ppm (m, 5H, aromatic)] and acetylpyrrolidine XXX [PMR spectrum: 1.04 (d, 3H, 2-CH_3, J = 6.6 Hz), 2.08 (dd, 1H, 4-H, $J_{4,5}$ = 9.4 Hz; $J_{4,4'}$ = 14.1 Hz), 2.11 (s, 3H, N–CH_3), 2.23 (dd, 1H, 4'-H, $J_{4',5}$ = 7.9 Hz; $J_{4',4}$ = 14.1 Hz), 2.44 (s, 3H, CH_3CO), 2.56 (q, 1H, 2-H, J = 6.6 Hz), 3.53 (dd, 1H, 5-H, $J_{5,4'}$ = 7.9 Hz; $J_{5,4}$ = 9.4 Hz), 4.30 (s, 1H, OH), 7.25-7.35 ppm (m, 5H, aromatic)] were isolated from the reaction mixture.

3e-Hydroxy-1,3a-dimethyl-2e,6e-diphenyl-4-piperidinone (XXI) and 1,5-Dimethylamino-2-hydroxy-2-methyl-1,5-diphenyl-3-pentanone (XXVIII). A 4.1-ml (0.04 mole) sample of a 33% solution of methylamine was added to a solution of 5.28 g (0.02 mole) of epoxy enone X in 30 ml of dioxane, and the mixture was allowed to stand at 20°C for 7 days. The excess methylamine and dioxane were removed in vacuo, the residue was dissolved in dilute HCl (1:1), and the solution was extracted with ether (two 10-ml portions) to remove the unchanged starting X. Alkalization yielded 4.5 g of a solid product, which was recrystallized from ether to give 0.76 g of XXI and 2.5 g of XXVIII. PMR spectrum: 1.63 (s, 3H, CH_3), 2.02 (s, 3H, N–CH_3), 1.80 (s, 1H, OH), 2.26, (dd, 1H, 4-H, J = 6.5 Hz; J = 14.1 Hz), 2.32 (s, 3H, N–CH_3). 2.50 (dd, 1H, 4'-H, J = 9.2 Hz; J = 14.1 Hz), 3.49 (s, 1H, 2-H), 3.62 (dd, 1H, 5-H, J = 6.5 Hz; J = 9.2 Hz), 7.30-7.55 ppm (m, 12H, aromatic and NH).

3e-Hydroxy-1,2,2-trimethyl-6e-phenyl-4-piperidinone (XXII), 2-(1-Hydroxy-isopropyl)-1-methyl-5-phenyl-3-pyrrolidinone (XXVII), and 1-Methyl-5-phenyl-3-pyrrolidinone (XXXI). A solution of 4.04 g (0.02 mole) of epoxy enone XI and 4.1 ml (0.04 mole) of methylamine in 20 ml of dioxane was stirred at 20°C for 8 h, HCl solution (1:1) was added until the mixture was acidic, and the product was extracted with ether (three 25-ml portions). Workup of the ether extract gave 1.44 g of a yellow oil, which was found to be a mixture of the starting epoxy ketone XI and 2,3-dihydroxy-2-methyl-6-phenyl-5-hexen-4-one, the R_f value of the latter of which was 0.45 (Silufol, ether). IR spectrum: 3450 (OH), 1670 (C=O), 1605 (C=C), 1060 cm^{-1} (C–O). PMR spectrum: 1.13 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 3.63 (m, 2H, two OH), 4.03 (s, 1H, CH), 7.00, 7.50 (two d, 2H, –CH=CH–, J = 16.0 Hz), 7.20 ppm (m, 5H, aromatic). The

aqueous solution was made alkaline and extracted with ether (five 25-ml portions), and the extract was dried over sodium sulfate. The solvent was removed, and the residue (3.0 g) was chromatographed on silica gel (L 40/100) to give 0.08 g of piperidone XXII, 1.28 g of 3-pyrrolidinone XXVII [PMR spectrum: 1.32 (s, 6H, two CH_3). 2.36 (dd, 1H, 4-H, $J_{4,5}$ = 12.6 Hz; $H_{4,4'}$ = 17.7 Hz), 2.43 (s, 3-H, N—CH_3), 2.69 (dd, 1H, 4'-H, $J_{4',5}$ = 6.1 Hz; $J_{4',4}$ = 17.17 Hz), 2.74 (s, 1H, 2-H), 3.25 (s, 1H, OH), 3.65 (dd, 1H, 5-H, $J_{5,4}$ = 12.6 Hz; $J_{5,4'}$ = 6.1 Hz), 7.36 ppm (m, 5H, aromatic)], and 0.76 g of 3-pyrrolidinone XXXI [PMR spectrum: 2.25 (s, 3H, N—CH_3), 2.41 (dd, 1H, 4-H, $J_{4,5}$ = 10.7 Hz; $J_{4,4'}$ = 18.4 Hz), 2.68 (dd, 1H, 4'-H, $J_{4',5}$ = 6.4 Hz; $J_{4',4}$ = 18.4 Hz), 2.80, 3.63 (two d, 2H, 2-H, 2'-H, J = 14.4 Hz), 3.57 (dd, 1H, 5-H, $J_{5,4}$ = 10.7 Hz; $J_{5,4'}$ = 6.4 Hz), 7.30-7.36 ppm (m, 5H, aromatic)].

3r-Acetyl-3-hydroxy-1,2t-dimethyl-5t-phenylpyrrolidine (XXX). A solution of 2.33 g (0.01 mole) of piperidone XV in 100 ml of ether was passed through a column packed with basic aluminum oxide (5/40). The amount of isomerization product in the eluate was monitored by TLC. For complete conversion of the substrate the solution was passed three times through the column. After removal of the solvent, the residue was crystallized from hexane—ether (6:1) to give 2.19 g of pyrrolidine XXX.

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