SYNTHESIS OF 3-(ω-AMINOALKYL)HYDRO-2-QUINOLONES AND THEIR ANALOGS BY AMINATION AND HYDROAMINATION OF 3-(2'-OXOCYCLOALKYL)METHYL-SUBSTITUTED LACTAMS

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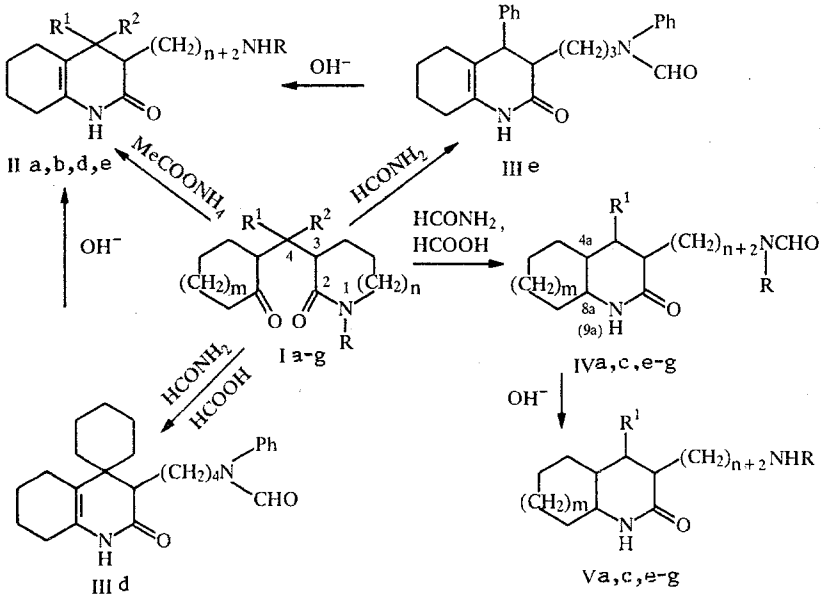
The amination of 3-(2'-oxocyclohexyl)methylcaprolactams and -valerolactams with ammonium acetate leads to 3-(ω-aminoalkyl)-3,4,5,6,7,8-hexahydro-2-quinolones. The hydroamination of these keto lactams, as well as their oxocycloheptyl analogs, with a mixture of formamide and formic acid gives 3-(ω-aminoalkyl)perhydro-2-quinolones and 3-(ω-aminoalkyl)-5,6-pentamethylenetetrahydro-2-pyridones.

In the course of investigating the properties of a new group of 1,5-dicarbonyl compounds — 3-(2'-oxocycloalkyl)methyl-substituted lactams — we observed the recyclization of these compounds and their reduction products to 3-(ω-aminoalkyl)hydrocoumarins, which takes place readily under the influence of acids [1]. We studied the amination and hydroamination of keto lactams Ia-g and showed that recyclization occurs in this case also: 3-(ω-aminoalkyl)hydro-2-quinolones and their analogs are formed.



I—V a R=R¹=Ph, R²=H, m=1, n=2; b R=Ph, R¹=CH₂Ph, R²=H, m=1, n=2; c R=CH₂Ph, R¹=Ph, R²=H, m=1, n=2; d R=Ph, R¹+R²=(CH₂)₅, m=1, n=2; e R=R¹=Ph, R²=H, m=n=1; f R=R¹=Ph, R²=H, m=2, n=1; g R=R¹=Ph, R²=H, m=n=2

The amination of Ia, b, d, e by refluxing with ammonium acetate in propanol gives 3-substituted hexahydro-2-quinolones IIa, b, d, e, probably with the intermediate transformation of the ketone fragment to an enamine fragment and subsequent aminolysis of the lactam ring (Scheme 1). The chiral center at $C_{(3)}$ is not affected during the formation of II: the known keto lactams α-Ia and β-Ia, which differ with respect to the configuration at $C_{(3)}$ (the stereochemistry was established

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TABLE 1. PMR Spectra of II-V [ppm, SSCC (Hz)]

Compound	1-H, 1H, br.s	3-H, 1H	4-H, 1H	8a-H* or 9a-H**, 1H	CH_2N***, 2H	NHR, 1H, br.s	CHO, 1H, s	C_6H_5N****	
								p-H, 1H, t (7)	*o*-H, 2H, d (7)
II d	6,97	2,70 m (7)	—	—	3,15 t (7)	3,73	—	6,68	6,60
II e	7,52	2,53 m	3,16*****	—	3,16*****	3,76	—	6,68	6,51
III e	7,47	2,42 m	3,05 d (3)	—	3,87 t (7)	—	8,38		
IV a	5,80	2,59 m	2,52 t (10)	3,04 td (10; 3)	3,73 t (7)	—	8,33		
α-IV$_c$ +	5,87	2,55*****	2,55*****	3,00*****	3,15 t (7)	—	8,36	—	—
+ β-IV$_c$	5,82	2,55*****	2,55*****	3,00*****	3,03 t (7)	—	8,10	—	—
IV e	5,82	2,59 m	2,53 t (10)	3,04 td (10; 3)	3,72 t (7)	—	8,29		
V a	6,03	2,63 m	2,57 t (10)	3,03*****	3,03*****	3,62	—	6,63	6,52
V c	5,88	2,57*****	2,57*****	3,07 td (10; 3,5)	2,57*****	3,70	—	—	—
V e	6,05	2,68 m	2,56 t (10)	3,03*****	3,03*****	3,70	—	6,68	6,52
α-V f	5,93	2,50*****	2,50*****	3,22 td (10; 3,5)	3,00 m	3,71	—	6,67	6,62
β-V f	5,93	2,55 m	2,64 t (10)	3,66*****	2,96 m	3,66*****	—	6,66	6,52
α-V g	5,87	2,56 m	2,60 t (10)	3,21 td (10; 3,5)	3,03 t (7)	******	—	6,70	6,59
β-V g	5,97	2,52 m	2,65 t (10)	3,68*****	3,00 t (7)	3,68*****	—	6,66	6,57

*For IVa, c, e and Va, c, e.

**For Vf, g.

***The remaining aliphatic protons give an overall multiplet at 1-2 ppm.

****The remaining aromatic protons for IIe and Va, e-g, while for IIIe, IVa, c, e, and Vc all of the aromatic protons give an overall multiplet at 7.1-7.5 ppm. For IId the meta protons of the C_6H_5N fragment give a triplet (2H) with SSCC 7 Hz at 7.16 ppm.

*****The signals are overlapped with the formation of an overall multiplet.

******A signal cannot be detected.

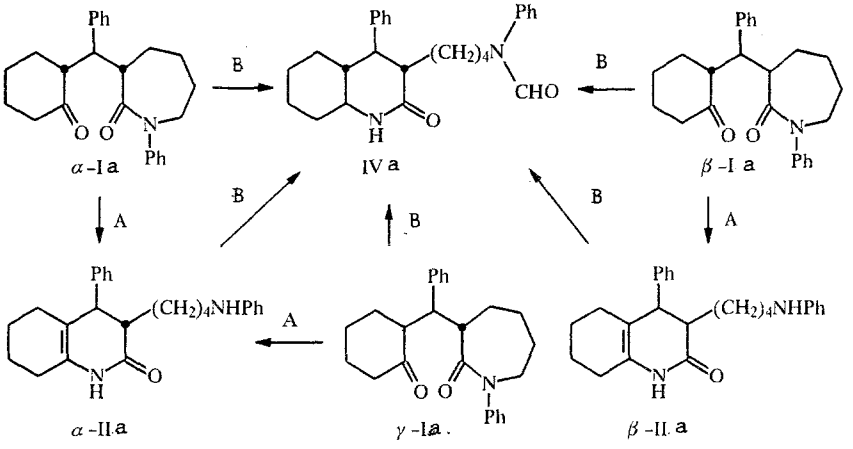
TABLE 2. Characteristics of II-V

Compound	Empirical formula	mp, °C*	IR spectrum, cm^{-1}		Mass spectrum, m/z (I_{rel}, %)	Yield, %
			C=O	NH		
α-IIa	$C_{25}H_{30}N_2O$	105...107	1664	3406, 3210	374 (12), 226 (100)	89
β-IIa	$C_{25}H_{30}N_2O$	107,5...109	1670	3404, 3210	374 (50), 226 (100)	82
α-IIb	$C_{26}H_{32}N_2O$	117...119	1666	3404, 3210	388 (85), 297 (100), 240 (10)	74
β-IIb	$C_{26}H_{32}N_2O$	90...92	1667	3413, 3240	388 (80), 297 (90), 240 (100)	70
IId	$C_{24}H_{34}N_2O$	152...153	1666	3402, 3200	366(100), 323 (6), 274 (8), 246 (6), 232 (15), 218 (60)	87
IIe	$C_{24}H_{28}N_2O$	158...159	1664	3402, 3220	360 (8), 226 (100)	83
IIId	$C_{25}H_{34}N_2O_2$	138...139	1666	3402, 3200	394 (15), 393 (46), 376 (3), 375 (11), 260 (14), 259 (38), 218 (23), 217 (100)	73
IIIe	$C_{25}H_{28}N_2O_2$	158...159	1672	3420, 3250	388(1,5), 266 (1,5), 226 (100)	53
IVa	$C_{26}H_{32}N_2O_2$	155,5...156,5	1665	3380	404 (45), 376 (22), 284 (17), 242 (100), 229 (55), 228 (22)	60
IVc**	$C_{27}H_{34}N_2O_2$	150...153	1660	3386, 3200	418 (53), 389 (45), 354 (37), 299 (40), 242 (100), 228 (45)	68
IVe	$C_{25}H_{30}N_2O_2$	174,0...175,5	1670	3410	390 (50), 362 (45), 270 (17), 242 (85), 229 (100), 228 (20)	75
Va	$C_{25}H_{32}N_2O$	183...184	1653	3406, 3190	376 (100), 284 (6), 271 (8), 256 (2), 242 (90), 229 (65), 228 (65)	95
Vc	$C_{26}H_{34}N_2O$	160...161	1650	3388, 3220	390 (8), 389 (40), 299 (28), 298 (100), 242 (18), 241 (80), 229 (32), 228 (28)	94
Ve	$C_{24}H_{30}N_2O$	191,5...193	1653	3407, 3200	362 (80), 270 (10), 242 (10), 229 (100), 228 (20)	94
α-Vf	$C_{25}H_{32}N_2O$	172...173	1650	3386	377 (40), 376 (100), 284 (9), 243 (65), 242 (17)	30
β-Vf	$C_{25}H_{32}N_2O$	222	1646	3384	377 (100), 376 (85), 257 (12), 256 (7), 243 (88), 242 (45)	35
α-Vg	$C_{26}H_{34}N_2O$	173...174	1647	3380, 3160	391 (15), 390 (100), 285 (7), 284 (5), 257 (10), 256 (100), 243 (50), 242 (75)	42
β-Vg	$C_{26}H_{34}N_2O$	146...147	1647	3380, 3160	391 (70), 390 (100), 257 (18), 256 (100), 243 (45), 242 (70)	20

*The compounds were recrystallized: α-IIa, β-IIa, and β-IIb from 90% ethanol; α-IIb, IIId, IVc, Vc, α-Vf, and α-i and β-Vg from acetone—hexane; IId, e, IIIe, and IVa, e from ethyl acetate; Va, e and β-Vf from ethyl acetate—hexane.

**A mixture of α-IVc and β-IVc.

in [1]), give different hexahydroquinolone stereoisomers — α-IIa and β-IIa, respectively. On the other hand, stereoisomer γ-Ia, which has the same configuration at $C_{(3)}$ but the opposite configuration at $C_{(5)}$ with respect to isomer α-Ia [1], gives hydroquinolone α-IIa (Scheme 2). Stereoisomeric keto lactams α-Ib and β-Ib, for which there are no precise stereochemical assignments, but for which it is known that they have different configurations at $C_{(3)}$ [1], also give different hydroquinolone stereoisomers — α-IIb and β-IIb, respectively. In the case of keto lactam Ie it was shown that amination also occurs in the case of refluxing in formamide; the principal product is the N-formyl derivative (IIIe) of IIe, from which amine IIe is obtained by alkaline hydrolysis.



A $MeCOONH_4$; B $HCONH_2$-HCOOH

The hydroamination of keto lactams Ia, c, e-f occurs when they are refluxed with a mixture of formamide and formic acid: 3-(ω-formylaminoalkyl)perhydro-2-quinolones (IVa, c, e) and the analogous 5,6-pentamethylenetetrahydro-2-pyridone derivatives (IVf, g) are formed. The reaction probably proceeds with the intermediate formation of compounds of the II type: IIa, e, on refluxing with the same mixture, give the corresponding IVa, e. The deformylation of products IV by alkaline hydrolysis leads to aminoalkylperhydroquinolones (Va, c, e) and their analogs (Vf, g). In contrast to amination, the hydroamination of keto lactams I affects the chiral center at $C_{(3)}$: the same compound, viz., IVa, is formed from all three stereoisomers of keto lactam Ia; the same compound is also formed from both stereoisomeric products IIa. Compounds IVa, e were isolated in the form of individual stereoisomers with trans fusion of the rings (here and subsequently, the conclusions regarding the geometry of fusion were drawn on the basis of data from the PMR spectra, which are examined below). Compound IVc was isolated in the form of a mixture (≈1:1) of two trans-fused stereoisomers (α-IVc and β-IVc); they evidently differ with respect to the configuration at $C_{(3)}$. The deformylation of this mixture leads to individual product Vc, probably as a consequence of isomerization at $C_{(3)}$. Compounds IVf, g were subjected to deformylation without purification.

Perhydroquinolones Va, c, e are produced in the form of one stereoisomer, which has transfusion of the rings. Their analogs Vf, g, on the other hand, are produced in the form of a mixture of two stereoisomers: the trans- (α-Vf, g) and cis-fused (β-Vf, g) isomers. This and the above-presented facts of the formation of one perhydroquinolone from different stereoisomers of keto lactam Ia and hexahydroquinolone IIa may serve as an indication of thermodynamic control in hydroamination: in the case of the perhydroquinolones the trans-fused isomers are more stable than the cis-fused isomers, while in the case of 6,7-fusion (Vf, g) the stabilities of the stereoisomers are comparable.

In contrast to other keto lactams, Id, on treatment with $HCONH_2$—HCOOH, gives an N-formyl derivative (IIId) of hexahydroquinolone IId; this result is possibly associated with steric shielding of the C=C bond in IIId, which hinders its hydrogenation.

The assumptions regarding the character of the ring fusion in IV and V were made on the basis of an examination of the character of the signals of the angular protons adjacent to the nitrogen atom (8a-H for the perhydroquinolones and 9a-H for their analogs Vf, g) in the PMR spectra (Table 1). For β-Vf and β-Vg these signals are located at ≈3.67 ppm; for the remaining compounds IV and V these signals are located at stronger field — at 3.0-3.2 ppm — and, as a rule, have the form of a triplet of doublets; this form of the signals is characteristic for the trans-fused oxygen analogs of V — 3-(ω-aminoalkyl) perhydrocoumarins [1]. It is known that for hydro-2-quinolones [2, 3] and hydrocoumarins [1, 4] the signal of the angular 8a-H proton is always located at weaker field for the cis-fused isomer.

All of the information stated above makes it possible to assume that β-Vf and β-Vg have cis-fused rings, while all of the remaining compounds IV and V have trans-fused rings. The triplet form of the signal of the 4-H proton with a large spin-spin coupling constant (SSCC) (10 Hz) for IVa, e and Va, e-g indicates a trans-axial orientation of the 3-H and 4a-H protons with respect to the 4-H proton.

The mass spectra of the hydroquinolones and their analogs (Table 2) contain intense peaks of fragment ions corresponding to the detachment of an aminoalkyl substituent from the 3 position; stepwise fragmentation of this substituent is observed in a number of cases. In addition to molecular-ion peaks, there are intense $[M - H]^+$ peaks in the spectra of individual compounds (IIId, Vc), while there are intense $[M + H]^+$ peaks in the spectra of others (Vf, g); correspondingly, fragmentation of these ions with the detachment of the ω-aminoalkyl substituent is observed. The mass spectra of the stereoisomeric compounds display significant similarities.

EXPERIMENTAL

The IR spectra of solutions in chloroform were recorded with a Specord IR-75 spectrometer. The PMR spectra were obtained with a Bruker WM-250 spectrometer with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with an LKB-9000 spectrometer at an ionization energy of 70 eV. The progress of the reactions and the purity of the products obtained were monitored by TLC on Silufol UV-254 plates. The characteristics of II-V are presented in Table 2. The results of elementary analysis of these compounds for C, H, and N were in agreement with the calculated values.

3-(ω-Aminoalkyl)-3,4,5,6,7,8-hexahydro-2-quinolones (IIa, b, d, e). A mixture of 1 g of keto lactam I and 1.5-2 g of ammonium acetate was refluxed in 20 ml of propanol for 1 h (for 2 h in the case of Ie), after which the mixture was cooled, diluted with ether, and washed with water, and the solvent was evaporated. Compounds β-IIa and β-IIb were isolated by chromatography of the residues with a column packed with silica gel L40/100 in a hexane—ethyl acetate (4:1) system; the remaining II were purified by recrystallization of the residues (see Table 2).

3-(N-Phenyl-N-formylaminobutyl)-3,4,5,6,7,8-hexahydro-2-quinolone (IIIe). A solution of 3 g of keto lactam Ie in 30 ml of formamide was maintained at 150-170°C for 2 h, after which it was cooled, diluted with ether, washed with water, and dried. The solvent was evaporated, and the residue was chromatographed in the same way as IIa, b in a hexane—ethyl acetate (4:1-2:1) system.

Reaction of Keto Lactams I with a Mixture of Formamide and Formic Acid. A solution of 3 g of the keto lactam in a mixture of 15-20 ml of formamide and 12-15 ml of formic acid was refluxed for 5 h (for 10 h in the case of keto lactams If and Ig), after which the reaction mixture was diluted with water and shaken thoroughly with ether until a clear solution formed. The aqueous layer was separated, and the organic layer was washed three times with water. In the case of Ia, c, e the organic layer was allowed to stand overnight at 5°C, and the liberated virtually pure IVa, c, e were removed by filtration and additionally purified by recrystallization. In the case of If, g the solvent was evaporated from the organic layer, and the residue was subjected to alkaline hydrolysis without additional purification.

Deformylation of IV. A 2-g sample of IV was refluxed in 30-40 ml of ethanol containing 2-3 g of KOH and 2-3 ml of water, after which the reaction mixture was diluted with an equal volume of hot water and cooled. The resulting precipitate was removed by filtration, washed with water, and dried. Compounds Va, c, e were obtained in virtually pure form; the mixtures of α-Vf and β-Vf and α-Vg and β-Vg were separated by chromatography with a column packed with silica gel L5/40 in a hexane—ethyl acetate (3:1) system.

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