NEW METHOD FOR THE SYNTHESIS OF 8-AZASTEROIDS: SYNTHESIS OF BENZO[*a*]CYCLOHEXA[*f*]FURO[2,3-*g*]-QUINOLIZINES FROM 2-CINNAMOYLCYCLO-HEXA[*b*]OXIRANE

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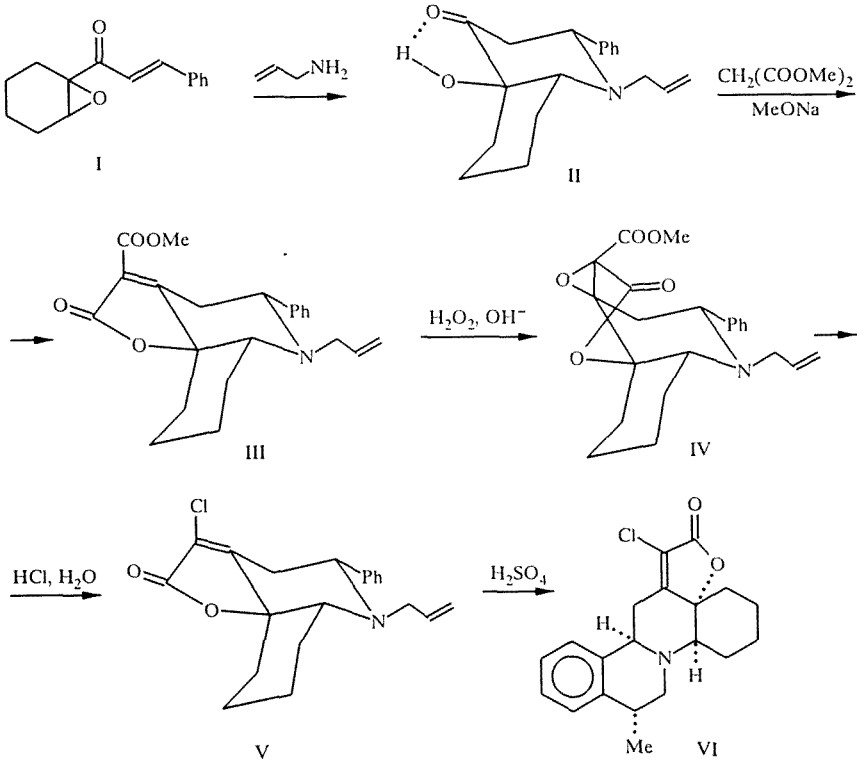
The reaction of 2-cinnamoylcyclohexa[b]oxirane with allylamine gave cis-2(β),3,4a,5,6,7,8,8a(β)-octahydro-1-allyl-4a(β)-hydroxy-(2α)-phenylquinolin-4-one, which upon subsequent reaction with dimethyl malonate, peroxide epoxidation, and heating with hydrochloric acid gave cis-4,5,6a(β),7,8,9,10a-octahydro-6-allyl-20-oxo-5(α)-phenyl-3-chlorofuro[3,2-d]quinoline. Heating of this intermediate in 96% sulfuric acid gave trans-3a(a),7a(a),9,10(β),14b(α),15-hexahydro-10(α)-methyl-2-oxo-1-chlorobenzo[a]cyclohexa[f]furo[2,3-g]quinolizine.

Interest in the chemistry of benzo[*a*]cyclohexa[*f*]quinolizines has arisen due to the similarity of their structures to biologically active natural products and related compounds [1]. Such compounds are frequently seen as steroid analogs and are termed D-homo-8-azagonanes. We have previously developed a pathway for the synthesis of benzo[*a*]furo[2,3-*g*]quinolizines starting from 2-methyl-2-cinnamoyloxirane [2]. In the present work, we attempted to show the possibility of using this approach for the synthesis of 8-azasteroids. The use of 2-cinnamoylcylo-hexa[*b*]oxirane (I) as the starting compound appeared to be the optimal solution of this problem. Quinolone II was obtained in high yield upon maintaining epoxide I in aqueous dioxane with allylamine.



I II III IV V VI

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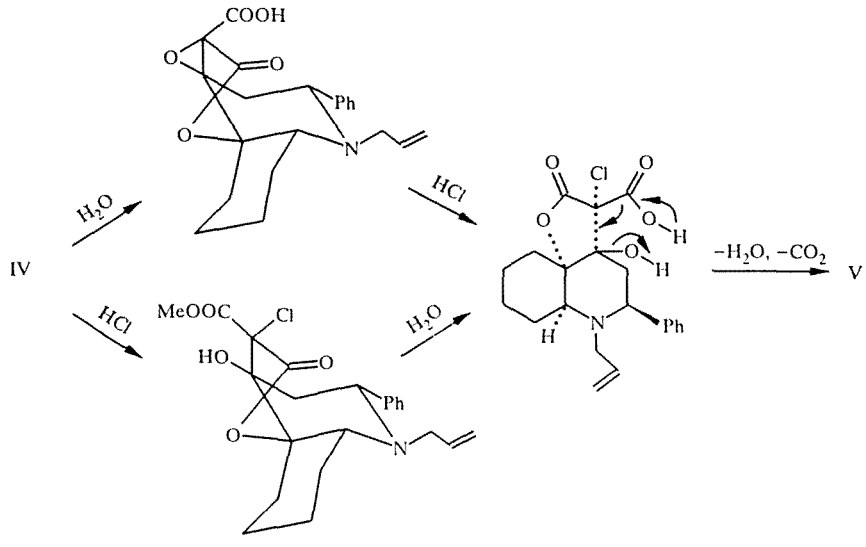
The instability of the α-ketol group in strongly acidic media prevented the direct use of this compound in the synthesis of 8-azasteroids. One of the more useful pathways for the transformation of α-ketols into less reactive compounds is their conversion into chlorolactones. The reaction of quinolone II with dimethyl malonate gave carbomethoxylactone III, which was epoxidized in almost quantitative yield by alkaline hydrogen peroxide under phase transfer catalysis conditions. Epoxylactone IV was transformed into chlorolactone V by heating in hydrochloric acid. This reaction probably proceeds as follows:



The cyclization of lactone V proceeds stereoselectively. Crystallization gave *trans*-quinolizine VI with pseudoequatorial orientation of the methyl group.

The structures of these products were indicated by elemental analysis, IR, PMR, and ^{13}C NMR spectroscopy (Tables 1 and 2). The methine proton at the angular carbon atom is seen in the PMR spectra as a broad singlet, indicating its equatorial orientation in the cyclohexane ring. Analysis of the signals of the piperidine ring protons indicates chairlike conformation with equatorial orientation of the phenyl substituent. Comparison of the ^{13}C NMR spectra of III and IV shows a significant difference in the chemical shifts of $C_{(3)}$ and $C_{(3a)}$, which is in good accord with the direction of epoxidation of unsaturated lactone III. The axial orientation of 10-H in quinolizine VI is indicated by the coupling constants of this proton with the protons at $C_{(9)}$ (11.0 and 5.0 Hz). The type of fusion of rings B and C in this compound is indicated by the finding of Boltzmann bands in the IR spectrum at 2700-2800 cm^{-1}.

EXPERIMENTAL

The IR spectra for solutions of the compounds in CCl_4 were taken on a Specord IR-75 spectrophotometer. The PMR spectra were taken on a Bruker WM-360 spectrometer with HMDS as the internal standard. The melting points were determined on a Boetius block. The course of the reaction and purity of the compounds were checked on Silufol UV-254 plates with development by iodine vapor. The indices of the synthesized products are given in Tables 1 and 2. Epoxyketone I was obtained according to our previous work [3].

The elemental analyses for C, H, and N correspond to the calculated values.

***cis*-2(β),3,4a,5,6,7,8,8a(β)-Octahydro-1-allyl-4a-hydroxy-2(α)-phenyl-4-quinolinone (II).** A sample of 4.56 g (0.02 mole) epoxyketone I was dissolved in 50 ml dioxane and 5 ml water and 2.28 g (0.04 mole) allylamine were consecutively added. The reaction mixture was maintained for seven days at 18-20°C and evaporated. The residue was dissolved in 20 ml 10% hydrochloric acid and left overnight. The aqueous solution was then filtered and the filtrate was made basic by adding sodium hydroxycarbonate. The precipitate formed was extracted with ether. The ethereal solution was dried over sodium sulfate and evaporated.

TABLE 1. Indices for Products II-VI

Compound	Chemical formula	mp, °C	IR spectrum ν, $см^{-1}$	PMR spectrum, δ, ppm (J, Hz)	Yield, %
II	$C_{18}H_{23}NO_2$	oil	1635, 1710, 3450	1,24...2,00 (m, 7H); 2,38...2,50 (m, 2H); 2,59 (br. s, 8a-H); 2,90 (d.d, 3-H_a, 13,5, 11,0); [3,02 (d d, 16,0, 7,0) & 3,28 (d d, 16,0, 6,0)]-NCH_2; 3,74 (d.d, 2-H_a, 11,0, 3,5); 3,96 (s, OH); [4,82 (d, 17,0) & 5,04 (d, 10,0)]-C=CH_2; 5,70...5,82 (m, CH=C); 7,18...7,36 (m, 5$H_{arom.}$)	84
III	$C_{22}H_{25}NO_4$	162...163	1660, 1720, 1780	1,42...1,97 (m, 7H); 2,14 (br.d 1H, 15,0); 2,41...2,55 (m, 1H); 2,52 (br. s, 6a-H); 2,63...2,7 (m, 4-H_a); [3,02 (d.d., 16,0, 7,0) & 3,27 d.d., 16,0, 6,0)]-NCH_2; 3,57...3,66 (m, 4-H_e, 5-H_a); 3,85 (s, CH_3); [4,87 (d, 17,0) & 5,10 (d, 10,0)]-C=CH_2; 5,65...5,77 (m, CH=C); 7,22...7,47 (m, 5$H_{arom.}$)	80
IV	$C_{22}H_{25}NO_5$	154...155	1740, 1765, 1800	1,50...1,93 (m, 6H); 1,84 (d.d, 4-H_e, 14,5, 3,5); 2,11 (br.d, 1H, 15,0); 2,23...2,36 (m, 1H); 2,43 (d.d, 4-H_a, 14,5, 11,0); 2,51 (br. s, 6a-H); [3,04 (d.d, 16,0, 7,0) & 3,26 (d.d, 16.0, 6,0)]-NCH_2; 3,56 (d.d, 5-H_a, 11,0, 3,5); 3,90 (s, CH_3); [4,86 (d, 17,0) & 5,13 (d, 10,0)]-C=CH_2; 5,71...5,84 (m, CH=C); 7,23...7,47 (m, 5$H_{arom.}$)	100
V	$C_{20}H_{22}ClNO_2$	167...169	1660, 1780	1,42...1,93 (m, 6H); 2,13 (br.d, 1H, 15,0); 2,41...2,50 (m, 1H); 2,46 (br. s, 6a-H); 2,55 (d.d, 4-H_a, 14,0, 11,0); 2,91 (d.d, 4-H_e, 14,0, 3,5); [3,02 (d.d, 16,0, 7,0) & 3,28 (d.d, 16,0, 6,0)]-NCH_2; 3,54 (d.d, 5-H_a, 11,0, 3,5); [4,86 (d, 16,5) и 5,10 (d, 9,5)]-C=CH_2; 5,66...5,80 (m, CH=C); 7,26...7,47 (m, 5$H_{arom.}$)	77
VI	$C_{20}H_{22}ClNO_2$	160...161	1660, 1780, 2740, 2760	1,27 (d, CH_3, 7,0); 1,31...2,00 (m, 6H); 1,92 (t, 9-H_a, 11,0); 2,17 (br. d, 1H, 15,0); 2,21 (br. s, 7a-H); 2,28...2,36 (m, 1H); 2,41 (d.d, 15-H_a, 13,5, 11,0); 3,07...3,17 (m, 10-H_a); 3,24 (d.d, 9-H_e, 11,0, 5,0); 3,42 (d. d, 15-H_e, 13,5, 3,0); 3,49 (br.d, 14b-H, 11,0); 7,14...7,35 (m, 4$H_{arom.}$)	42

TABLE 2. Chemical Shifts in the ^{13}C NMR Spectra of III and IV

Compound	δ, ppm													
	2	3	3a	4	5	6a	7—10	10a	C=O	Me	NCH_2	CH=CH_2	CH=$\underline{CH_2}$	Ph
III	178,8	112,3	165,8	34,9	65,0	61,5	17,1 20,0 22,7 28,8	82,3	160,0	50,3	47,4	128,6	117,6	125,7 126,1 126,9 140,6
IV	165,3	72,5	58,6	31,1	63,1	61,5	18,1 19,6 22,0 23,7	81,2	161,1	51,5	48,1	129,2	117,7	126,0 126,5 127,3 140,1

***cis*-4,5,6a(β),7,8,9,10,10a-Octahydro-6-allyl-3-carbomethoxy-2-oxo-5(α)-phenylfuro[3,2-*d*]quinoline (III).** A sample of 4.3 g (15 mmoles) quinolone II in 20 ml methanol and 2.4 g (18 mmoles) dimethyl malonate and 0.07 g (3 mmoles) sodium dissolved in 5 ml methanol were consecutively added. The reaction mixture was maintained for 1.5 h at 18-20°C. The precipitate formed was filtered, washed with cold methanol, and dried at reduced pressure.

***cis*-3,3a,4,5,6a(β),7,8,9,10,10a-Decahydro-6-allyl-3-carbomethoxy-2-oxo-5(α)-phenyl-3,3a-epoxyfuro[3,2-*d*]-quinoline (IV).** A sample of 0.5 g tetrabutylammonium hydroxide and 20 ml 30% hydrogen peroxide were added to a solution of 3.7 g (10 mmoles) lactone III in 50 ml benzene. The reaction mixture was stirred vigorously for 7 h at 18-20°C. The benzene layer was removed, washed with water, dried over potassium carbonate, passed through a thin layer of L40/100 silica gel, and evaporated.

***cis*-4,5,6a(β),7,8,9,10,10a-Octahydro-6-allyl-2-oxo-5(α)-phenyl-3-chlorofuro[3,2-*d*]quinoline (V).** A sample of 80 ml 36.5% hydrochloric acid was added to a solution of 2.5 g (6.5 mmoles) epoxylactone IV in 20 ml dioxane at reflux and heating was continued for 5 h. The reaction mixture was evaporated and 20 ml saturated aqueous sodium hydroxycarbonate was added. The solution was extracted with ether. The ethereal solution was dried over sodium sulfate and evaporated. The residue was crystallized from 2-propanol.

***trans*-3a(α),7a(α),9,10(β),14b(α),15-Hexahydro-10(α)-methyl-2-oxo-1-chlorobenzo[*a*]cyclo-hexa[*f*]furo[2,3-*g*]quinolizine (VI).** A mixture of 1.0 g (3 mmoles) chlorolactone V and 3 ml 96% sulfuric acid was maintained for 2 h at 120°C. Then, 30 ml water was added and the solution was heated at reflux for 1 h. The solution was cooled, made basic by adding sodium carbonate, and extracted with ether. The organic layer was separated, dried over sodium sulfate, and evaporated. The residue was crystallized from 2-propanol.

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