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SYNTHESIS AND TAUTOMERISM OF 1-SUBSTITUTED 3,3-DIALKYL-3,4-DIHYDROISOQUINOLINES

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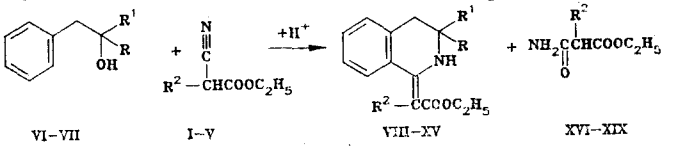
UDC 547.833.3.07:541.623:543.422.25

A number of ethyl esters of 3,3-dialkyl-3,4-dihydroisoquinoline-$\Delta^{1(2H),\alpha}$-α-alkylacetic acids have been synthesized. The effect of replacement of α-hydrogen by alkyl radicals on the azomethine–enamine tautomeric equilibrium was shown.

Heterocyclic enamines, including derivatives of 3,4-dihydroisoquinoline, are intermediates in the synthesis of pigments, analytical reagents, and biologically active materials [1, 2].

The synthesis of enamine derivatives of 3,4-dihydroisoquinoline by the Ritter reaction has been demonstrated, and 1-R-3,3-dialkyl-3,4-dihydroisoquinolines were obtained that can exist either as azomethine (where R is CH_3) or as enamine (where R is $>CH-COOC_2H_5$) [3] depending on the nature of R. The purpose of the present work was to broaden the application of the Ritter reaction for the synthesis of 1-R-3,3-dialkyl-3,4-dihydroisoquinoline derivatives and to study the effect of substituent R on the azomethine–enamine tautomerism. The ethyl esters of the α-cyanocarboxylic acids I-V were synthesized by known procedures [4] and reacted with carbinols VI and VII by the Ritter reaction [5]. The products were the ethyl esters of 3,3-(R,R^1)-3,4-dihydroisoquinoline-$\Delta^{1(2H),\alpha}$-α-(R^2)-acetic acids (VIII-XV). In contrast to [3], besides the desired products we separated and identified the ethyl esters of α-carbamoylcarboxylic acids, the products of nitrile hydrolysis [6]; with increasing length and branching of R^2 the yield of the latter increased, up to 30-45%:

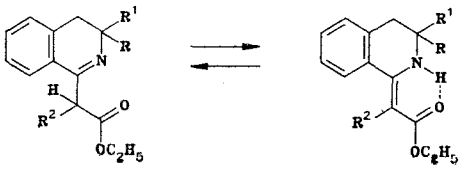


VI–VII I–V VIII–XV XVI–XIX

VIII—XV R=CH_3; VIII, X, XII—XV R^1=CH_3, IX, XI R^1=C_2H_5; VIII, IX R^2=H, X, XI R^2=CH_3, XII R^2=C_2H_5, XIII R^2=*n*-C_3H_7, XIV R^2=*n*-C_4H_9, XV R^2=*iso*-C_5H_{11}

The properties of the synthesized compounds VIII-XV are given in Table 1. Their tautomerism was studied by PMR and IR spectroscopy.

Compounds VIII and IX are enamines, as evidenced by the signals of the protons at α-carbon and nitrogen. Between -60 and 80° there were no changes in PMR signals. VIII and XI probably exist as enamines that are stabilized by an intramolecular hydrogen bond (IMHB).



Institute of Flow Mechanics, Ural Scientific Center, Academy of Sciences of the USSR, Perm' 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 794-797, June, 1985. Original article submitted March 3, 1984.

 0009-3122/85/2106-0662$09.50

TABLE 1. Ethyl Esters of 3,3-(R,R¹)-3,4-Dihydroisoquinoline-$\Delta^{1(2H)}$,α-α-(R^2)-acetic Acids

Compound	R² *	Reaction time, min	Bp, °C (mm Hg)	Mp of picrate, °C (from ethanol)	Found, %			Empirical formula of picrate	Calculated, %			Yield, %
					C	H	N		C	H	N	
VIII	H	5	169 (5)	145—147	53,38	4,44	11,75	$C_{21}H_{22}N_4O_9$	53,17	4,67	11,81	95
IX	H	5	168—170 (5)	91—92	54,31	5,18	11,31	$C_{22}H_{24}N_4O_9$	54,10	4,95	11,47	93
X	CH_3	15	—	140—142	54,28	5,07	11,58	$C_{22}H_{24}N_4O_9$	54,10	4,95	11,47	67
XI	CH_3	15	—	120—121	55,12	5,14	11,35	$C_{23}H_{26}N_4O_9$	54,98	5,27	11,15	62
XII	C_2H_5	15	154—156 (5)	133—134	55,22	5,03	11,27	$C_{23}H_{26}N_4O_9$	54,98	5,27	11,15	52
XIII	n-C_3H_7	20	159—160 (5)	116—117	55,92	5,42	10,92	$C_{24}H_{28}N_4O_9$	55,85	5,57	10,85	50
XIV	n-C_4H_9	15	164 (8)	103—105	56,37	5,60	10,87	$C_{25}H_{30}N_4O_9$	56,50	5,65	10,57	56,5
XV	iso-C_5H_{11}	20	165—166 (5)	143—144	57,28	5,74	10,41	$C_{26}H_{32}N_4O_9$	57,40	5,88	10,30	52

*VIII-XV R = CH_3, VIII, X, XII-XV R^1 = CH_3, IX, XI R^1 = C_2H_5.

TABLE 2. Chemical Shifts of Compounds VIII-XV in $CDCl_3$ (δ scale, ppm)

Compound	3H $-OC_2H_5$	$\diagdown^{3}_{}\!C\!\diagup^{R^1}_{R}$	R^2	2H $C_{(4)}$	1H (α-C)	2H $-OC_2H_5$	4H (Ar)	>NH
VIII	1,18, t	1,18, s, 6H	4,97, s, 1H	2,68, s	—	3,97, q	7,0,m	8,88, s
IX	1,10, m	1,10, m, 8H	4,97, s, 1H	2,68, s	—	3,97, q	7,0,m	8,90,s
X	1,05, m	1,05, s, 6H	1,30, d, 3H	2,50.s; 2,58, s	3,86,m	3,86, m	7,0,m	8,90,s
XI	1,10, m	1,10, m, 8H	1,10, m 3H	2,47.s; 2,60, s	3,93,m	3,93, m	7,0,m	8,90,s
XII	1,20, m	1,20, m, 6H	1,20, m, 5H	2,52,s; 2,70, s	3,40, t	3,97,q	7,0,m	8,88, s
XIII	1,20, m	1,20, m, 6H	1,20, m, 7H	2,52,s; 2,68, s	3,62, t	3,97, q	7,0,m	8,87, s
XIV	1,20, m	1,20, m, 6H	1,20, m 9H	2,53,s; 2,73,s	3,63, t	3,98,q	7,0,m	8,88, s
XV	1,20, m	1,20, m, 6H	1,20, m, 11H	2,52,s; 2,68,s	3,63, t	3,95,q	7,0,m	8,85, s

*For VIII and IX, signal of α-carbon proton is given in R^2 column.

This conclusion is confirmed by the IR spectra. The azomethine (ν >C=N–) valence vibration band in the 1625-1630 cm^{-1} region, which is typical for 1,3,3-trimethyl-3,4-dihydroisoquinoline [3] is absent, but there is an intense absorption band at 3280 cm^{-1} that is due to NH valence vibrations. This, as well as the absorption in the region of 1650 and 1615 cm^{-1} due to conjugated C=O and C=C bonds, respectively, is evidence for the existence of a strong IMHB [7].

The PMR spectra of X-XV also contain signals of protons at nitrogen and α-carbon, and the total area of these signals corresponds to one proton.

Comparison of the signal intensities of the CH and NH protons involves a large error because of the substantially different widths of the proton signals of these groups. Also, the signal of the azomethine CH proton overlaps the ethoxy quadruplet. The equilibrium can therefore be estimated more correctly from the signals of the protons at $C_{(4)}$. In VIII-XV the chemical shifts of the CH_2 protons differ by very little, and the expected two AB quartets corresponding to the two tautomeric forms do not appear. In a large number of analogous compounds that exist as azomethine or enamine, the signal of the $C_{(4)}$ protons is a slightly broadened singlet, the fine structure of which does not appear at the resolving power of a RS-60 PMR spectrometer not worse than $5 \cdot 10^{-9}$. Since the relaxation times (T_2) of the $C_{(4)}$ protons in various forms are close to one another, the signal intensities of these protons in various forms can be compared with less error.

The singlet of the two protons at the heterocycle $C_{(4)}$ is split in X-XV into two singlets of different intensities.

This is evidence that these materials are mixtures of azomethine and enamine forms, the existence of which is due to prototropic tautomerism. For confirmation the PMR spectra were obtained at temperatures from −60 to 80°. The data showed that with decreasing temperature the equilibrium shifts to the right, while at high temperatures the azomethine form predominates.

TABLE 3. Difference in Tautomer Free Energies

Compound	Temperature, °K	Difference in tautomer free energy, $-\Delta G$, kcal/mole	Enamine mole fraction, x_1
X	298	0,25	0,39
XI	298	0,52	0,71
XII	298	0,43	0,68
XIII	298	0,25	0,61
XIV	298	0,37	0,35
XV	298	0,14	0,56

To elucidate the effect of solvent on the equilibrium over the temperature range of 6.2 to 52.8°, PMR spectra were obtained in $CDCl_3$ and C_6D_6. There is a decrease in mole fraction of enamine in going from C_6D_6 to $CDCl_3$; over this temperature range the amount is practically constant, with a difference of 10-15%.

The relative concentrations of each isomer were determined as functions of the relative areas under the absorption curves [8] of the two protons at $C_{(4)}$; depending on the nature of R^2 the enamine chemical shift lies in the 2.63-2.78 ppm range, while that of azomethine at 2.52-2.58 ppm. The assignment of chemical shifts was based on the fact that for VIII and IX, which exist only as enamine, the chemical shift of the $C_{(4)}$ protons is 2.68 ppm, while for azomethine 1,3,3-trimethyl-3,4-dihydroisoquinoline it is 2.50 ppm.

Starting from the relative concentrations of tautomers, the difference in their free energies was calculated by the formula

$$\Delta G = -RT \ln[x/(1 - x)],$$

where x is the mole fraction of the more stable isomer at ordinary conditions. The results of the calculations are given in Table 3.

The low value of ΔG is evidence of the existence of two tautomeric forms. When the temperature is increased, due to the increased probability of IMHB scission the mobility of a proton that is capable of prototropic migration increases. Its transfer to the β-carbon of the enamine system converts the enamine to an azomethine, which is stabilized by steric interactions between $C_{(8)}$ hydrogen and R^2.

EXPERIMENTAL

PMR spectra were recorded on a RS-60 instrument (60 MHz) in $CDCl_3$ solution, with TMS internal standard. IR spectra of 0.01 M solutions of VIII-XV in $CHCl_3$ were obtained on a UR-20 spectrometer.

Ethyl Esters of 3,3-Dialkyl-3,4-dihydroisoquinoline-$\Delta^{1(2H),\alpha}$-α-alkylacetic Acids (VIII-XV). To 0.1 mole of ethyl ester of alkylcyanoacetic acid in 50 ml of benzene at a temperature not above 5° was added 40 ml of conc. H_2SO_4 over 10-12 min. Cooling was removed and 0.1 mole of dialkyl benzyl carbinol in 50 ml of benzene was added. The temperature was raised to 80°. The mixture was boiled for 5-20 min with vigorous stirring, cooled, and poured onto 200 g of ice. The solid, containing amide of the alkylmalonic esters, and the benzene layer were separated. The water layer was washed with two 50-ml portions of benzene and neutralized with 25% ammonia. The base that separated was extracted with ether and dried. The extractant was distilled off and the material was vacuum distilled (see Table 1).

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REACTION OF 1-AMINOMETHYL-1,2,3,4-TETRAHYDRO-ISOQUINOLINE WITH DIETHYL FUMARATE

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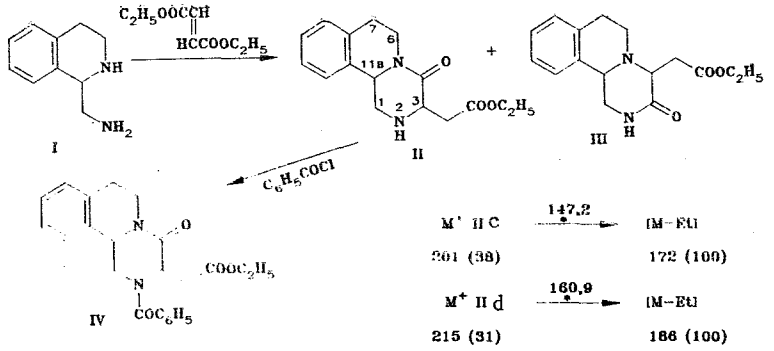
UDC 547.833.3'863.07

The reaction of 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline with diethyl fumarate goes by two possible paths, to form a mixture of 3-carbethoxymethyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline and its isomer 4-carboxymethyl-3-oxo-1,2,3,6,7-11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline.

The most outstanding achievement in the chemotherapy of helminthiasis in recent years has been the development of the highly efficient preparation Prasiquantel, which is an acyl derivative of the tricyclic system 4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1,-a]isoqunioline [1]. Judging from the patent data [2], other derivatives of this system also have anthelmintic activity. In the patented syntheses of these compounds the starting material is 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline (I), which is converted in several steps to the corresponding pyrazinoisoquinolines [2, 3].

It was of interest to study the reaction of I with diethyl fumarate in order to obtain this tricyclic system. It is known [4] that some N-substituted ethylene diamines are converted by reaction with maleic or fumaric diesters or monoamides to the corresponding carbethoxy- or aminocarbonylmethylpiperazinones in high yield; the Michael addition, which is the first step in the formation of these compounds, proceeds selectively at the primary amino group. If we consider I to be a substituted ethylene diamine, we might expect it to react with diethyl fumarate to give compound II exclusively. But we find that when this reaction is carried out in absolute alcohol, it forms a mixture of isomers, viz., 3-carbethoxymethyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline (II) and 4-carbethoxymethyl-3-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinoline (III), 1.5:1, with ∿80% overall yield. When the solvent was anhydrous ether, as described in [4, 5] for substituted ethylene diamines, the mixture of II and III was also obtained, but the overall yield was no more than 40%. These substances, which are very similar in polarity, were separated by repeated recrystallization of the hydrochlorides from absolute alcohol.



Since II is a secondary amine while III is a tertiary amine, the product mixture of hydrochlorides was also separated by the standard method, benzoylation. Secondary amine II is converted to the benzoyl derivative IV, whereas benzoylation of the amide nitrogen $N_{(a)}$ in III does not occur, and III is easily separated from the reaction mixture.

The structures of pyrazinoisoquinolines II and III were confirmed by elemental analysis and IR and PMR spectroscopy; that of III also by mass spectrometry.

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0009-3122/85/2106-0665$09.50