SYNTHESIS OF ENAMINOAMIDES OF THE 1,2,3,4-TETRAHYDRO-ISOQUINOLINE SERIES

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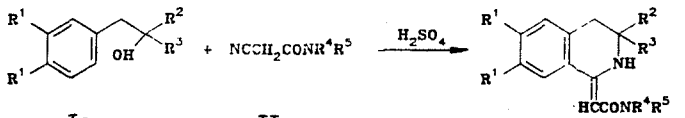
Enaminoamides of the 1,2,3,4-tetrahydroisoquinoline series having the Z-configuration were synthesized by the reaction of dialkylbenzylcarbinols cyanaceamides.

The enaminocarbonyl derivatives of the 1,2,3,4-tetrahydroisoquinoline series present interest as reagents in the synthesis of biologically active compounds [1, 2], particularly condensed derivatives of isoquinoline [3]. However, the multiple-stage method for the synthesis of the amide utilized in this [4] is unsuitable for the isolation of isoquinoline derivatives having alkyl substituents at the position 3 and at the amide nitrogen atom.

The object of the present work is the development of a practicable method for the synthesis of enaminoamides of the isoquinoline series, which are promising synthons and potential biologically active compounds.

Investigating the possibility of the Ritter reaction in the synthesis of secondary enamines of the 1,2,3,4-tetrahydroisoquinoline series, we established that the amides (IIIa-g) are formed by the reaction of the dialkylbenzylcarbinols (Ia-g) with the cyanacetamides (IIa-g) in the medium of benzene–H_2SO_4.



Ia-g IIa-g IIIa-g

I—III a $R^1=OCH_3$, $R^2=R^3=R^5=CH_3$, $R^4=H$; b $R^1=OCH_3$, $R^2=R^3=CH_3$, $R^4=H$, $R^5=C_2H_5$; c $R^1=H$, $R^2=CH_3$, $R^3=C_2H_5$, $R^4+R^5=(CH_2)_2O(CH_2)_2$; d $R^1=H$, $R^2+R^3=(CH_2)_4$, $R^4+R^5=(CH_2)_2O(CH_2)_2$; e $R^1=R^4=H$, $R^2+R^3=(CH_2)_5$, $R^5=C_2H_5$; f $R^1=R^4=H$, $R^2=R^3=CH_3$, $R^5=$thiazol-2; g $R^1=OCH_3$, $R^2=R^3=CH_3$, $R^4=H$, $R^5=$thiazol-2

The reaction rate is determined by the R^1 substituent in the carbinols (Ia-g). In the case of $R^1 = OCH_3$ [the amides (IIIa,b,g)], the highest yield is achieved at 60-70°C in the course of 40 min, whereas the boiling for 2 h in benzene is required for $R^1 = H$ [the amides IIIc-f)].

The IR and PMR spectra of the compounds (IIIa-g) are presented in Table 1. The PMR spectra of the enamines (IIIa-g) contain singlets of the vinyl proton (4.70-5.41 ppm) and the proton of the ring NH group (9.20-9.80 ppm), which are displaced to low field on the addition of CF_3COOH. The IR spectra of these compounds, taken in $CHCl_3$, have broad bands of the associated C=O groups (1620-1630 cm^{-1}) and the ring NH (3150-3275 cm^{-1}). Attention is drawn to the fact that the singlet of the proton of the ring NH group in the PMR spectra of the compounds (IIIa-g) occurs at low field; this also indicates the formation of the intramolecular associate:

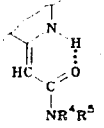


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TABLE 1. Characteristics of the Compounds (IIIa-g) and (Va-d)

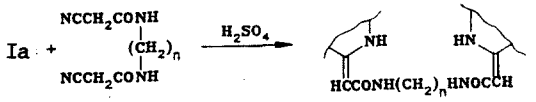
Compound	Empirical formula	mp,* °C	IR spectrum, cm^{-1}				PMR spectrum, δ, ppm								Yield, %
			C=O	ring NH	amide NH	C=C	=CH-, s	R^2, R^3	4-CH_2, s	Harom	ring NH, s	amide NH, s	CH_3O, s	R^4, R^5	
IIIa	$C_{16}H_{23}ClN_2O_3$	194...195	1620	3220	3420	1635	4,75	1,15 s ($2CH_3$)	2,62	6,32 s (1H); 6,87 s (1H)	9,30	5,02	3,67	2,82 s (CH_3)	68
IIIb	$C_{17}H_{25}ClN_2O_3$	199...200	1625	3250	3400	1640	4,70	1,13 s ($2CH_3$)	2,60	6,34 s (1H); 6,83 s (1H)	9,20	5,17	3,70	3,20 q (CH_2); 1,11 t (CH_3)	67
IIIc	$C_{18}H_{25}ClN_2O_3$	78...80	1620	3200	—	1645	5,10	1,00 s (CH_3); 1,00 t (CH_3); 1,54 q (CH_2)	2,75	7,12 m	9,50	—	—	3,50 broad s ($4CH_2$)	61
IIId	$C_{19}H_{26}N_2O_6S$	165...166	1620	3230	—	1640	5,00	1,38 broad s ($4CH_2$)	2,67	7,15 m	9,60	—	—	3,45 broad s ($4CH_2$)	63
IIIe	$C_{18}H_{24}N_2O$	121...122	1625	3200	3425	1645	4,96	1,33 broad s ($5CH_2$)	2,65	7,28 m	9,80	5,46	—	3,20 q (CH_2); 1,10 t (CH_3)	57
IIIf	$C_{16}H_{17}N_3OS$	237...238	1625	3150	3350	1635	5,41	1,20 s ($2CH_3$)	2,70	7,20 m	9,80	11,1	—	—	76
IIIg	$C_{18}H_{21}N_3O_3S$	243...244	1630	3160	3350	1630	5,07	1,20 s ($2CH_3$)	2,69	6,40 s (1H); 7,00 s (1H)	9,60	11,0	3,74	—	83
Va	$C_{30}H_{38}N_4O_2$	218...220	1630	3270	3465	1640	5,03 (2H)	1,23 s ($4CH_3$)	2,76 (4H)	7,75 m	9,65	5,08	—	3,33 t ($2CH_2N$); 1,27 m ($2CH_2$)	78
Vb	$C_{32}H_{42}N_4O_2$	147...148	1625	3255	3455	1640	5,08 (2H)	1,33 s ($4CH_3$)	2,72 (4H)	7,55 m	9,60	5,20	—	3,28 t ($2CH_2N$); 1,35 m ($4CH_2$)	67
Vc	$C_{33}H_{44}N_4O_2$	172...174	1630	3275	3465	1635	5,04 (2H)	1,24 s ($4CH_3$)	2,81 (4H)	7,51 m	9,70	5,25	—	3,18 t ($2CH_2N$); 1,30 m ($5CH_2$)	65
Vd	$C_{30}H_{36}N_4O_2$	230...232	1620	3240	—	1645	5,35 (2H)	1,25 s ($4CH_3$)	2,80 (4H)	7,65 m	10,00	—	—	3,65 broad s ($4CH_2$)	68

*The amides (IIIc,g) and (Vb,d) were recrystallized from dioxane; all the remaining compounds were recrystallized from isopropanol.

Therefore, the bases (IIIa-g) are enamines existing in the Z-configuration, stabilized with an intramolecular hydrogen bond.

With the object of investigating the E-isomer, the bases (IIIa-g), which were separated from the reaction mixture without preliminary purification, were chromatographed in a thin layer of Silufol in the 9:1 mixture of chloroform–acetone. However, according to the chromatographic data, only the Z-form is formed in the Ritter reaction.

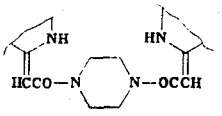
The cyclization of the dialkylbenzylcarbinols to isoquinoline derivatives also proceeds successfully with the utilization of N,N'-biscyanacetylpolymethylenediamines. Thus, the enaminoamides (Va-c) are formed by the reaction of the carbinol (Ia) with the nitriles (IVa-c).



IVa-c Va-c

IV, Va $n=4$, b $n=5$, c $n=7$

The analogous reaction of the piperazine derivative (IVd) leads to the amide (Vd).



Vd

The characteristics of the compounds (Va-d) are presented in Table 1.

The bisisoquinoline derivatives (Va-d) obtained are analogs of d-tubocurarine, the pharmacological action of which is associated with the long polymethylene chain connecting the two isoquinoline rings [5].

EXPERIMENTAL

The IR spectra were taken on the UR-20 spectrometer. The PMR spectra were taken on the PC-60 instrument in $CDCl_3$ using the internal standard of HMDS. The chromatography was carried out on plates of Silufol UV-254; the development was accomplished with bromine vapor.

The initial carbinols (Ia-g) and the nitriles (IIa-g) were obtained according to the methods described in the works [2, 6, 7]. The amides (IIIa-c) were identified as the hydrochlorides; the compound (IIId) was identified as the sulfate, and the remaining amides were identified as the bases. The characteristics of the compounds synthesized are presented in Table 1.

3-R^2-3-R^3-6,7-$(R^1)_2$-1-(N-R^4R^5-Carbamoylmethylidene)-1,2,3,4-tetrahydroisoquinolines (IIIa-g) (General Method). To 10 mmole of the nitrile (IIa-g) in 30 ml of benzene at the temperature not exceeding +5°C are added, dropwise, 4 ml of concentrated H_2SO_4 [in the case of the synthesis of the amides (IIIc-f)] or the mixture of 2 ml of glacial CH_3COOH and 4 ml of concentrated H_2SO_4 [in the case of the synthesis of the compounds (IIIa-g)]. The cooling is then discontinued prior to the introduction of 10 mmole of the carbinol (Ia-g). The mixture is heated with intense stirring for 40 min at 60-70°C [the amides (IIIa,b,g)] or 2 h at 80°C [the compounds (IIIa-f)]; the mixture is cooled and poured onto 50 g of ice prior to the separation of the benzene layer. The aqueous phase is neutralized with ammonia. The precipitated residue is separated, carefully washed with water, dried, and recrystallized [the amides (IIIe-g)]. The bases (IIIa-c) are dissolved in ethyl acetate; the corresponding hydrochlorides are obtained after the passage of dry HCl. The hydrochlorides are filtered off, dried, and recrystallized. The base (IIId) is dissolved in 10 ml of ethanol, and the sulfate is obtained after the addition of 1.5 ml of 50% H_2SO_4; the sulfate is filtered off, dried, and recrystallized.

N,N'-Bis(3,4-dimethyl-1,2,3,4-tetrahydroisoquinolylidene-1)acetyldiamines (Va-d). These compounds are obtained by analogy with the amides (IIIc-f), but 2 mole of the carbinol (Ia) and 8 ml of sulfuric acid are taken for 1 mole of the nitrile [8].

LITERATURE CITED

1. V. S. Shklyaev, B. B. Aleksandrov, M. I. Varkhin, and G. I. Legotkina, Khim. Geterotsikl. Soedin., No. 11, 1560 (1983).
2. B. B. Aleksandrov, M. S. Gavrilov, M. I. Varkhin, and V. S. Shklyaev, Khim. Geterotsikl. Soedin., No. 6, 794 (1985).
3. V. G. Granik, V. F. Knyazeva, I. V. Persianova, and N. P. Solov'eva, Khim. Geterotsikl. Soedin., No. 8, 1095 (1982).
4. Pat. 3207759 US., M. M. Creighton, W. Leimgruber, and W. Wenner, Chem. Abs., 64, 5054 (1966).
5. O. N. Tolkachev, E. P. Nakova, and R. P. Evstigneeva, Usp. Khimii, 49, 1617 (1980).
6. A. L. Cossey, R. L. N. Harris, J. L. Huppatz, and G. N. Phillips, Aust. J. Chem., 29, 1039 (1976).
7. Pat. 4038065 US., W. O. Jonson, M. C. Seidel, and H. L. Warner, R. Zh. Khim., 80392P (1978).
8. Pat. 1597619 BRD., H. Rauhut, R. Zh. Khim., 1N263P (1976).

COMPARATIVE MASS SPECTROMETRIC BEHAVIOR OF o-HYDROXYNITROSO DERIVATIVES OF THE QUINOLINE, ISOQUINOLINE, AND COUMARIN SERIES

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Benzo-substituted ortho-hydroxynitrosoquinoline and isoquinoline are found in the gas phase predominantly as the hydroxyimino-ortho-quinoid tautomeric form and under electron bombardment they do not undergo a second order Beckmann rearrangement. Molecular ions of 4-hydroxy-3-nitrosocarbostyryls and coumarin have almost exclusively the structure of the corresponding 2,4-dioxo-3-hydroxyiminohetarene; they also do not undergo rearrangement and decompose predominantly by retrodiene cleavage.

It has been shown repreatedly that many rearrangements of organic compounds which take place in solution are also observed in the gas phase in the molecular ions of the same compounds. Beckmann [1, 2], Wagner–Meerwin [3], and Fischer [4] rearrangements have thus been observed under mass spectroscopic conditions together with several other processes [5, 6]. We have recently demonstrated that isatin monooxime undergoes a second order Beckmann rearrangement under electron bombardment [7]. However, a study of the dissociative ionization of ortho-nitrosonaphthols [8] together with ortho-nitrosoindazoles and benzotriazoles [9] have shown that in this case an analogous rearrangement does not occur. We therefore considered it of interest to study the mass spectrometric behavior of derivatives of quinoline, isoquinoline, and coumarin, which contain an ortho-hydroxynitroso fragment in both the carbo- and the heterocyclic ring (compounds I-V). For comparison we ran mass spectra of the products of a second order Beckmann rearrangement of compounds I and II,* the corresponding β-pyridylacrylic acids (VIa,b, VIIb) and also 4-nitrosoantipyrine (VIII) which contains an ortho-nitrosooxo fragment but cannot act in the hydroxyimino tautomeric form and hence cannot undergo rearrangement in solution. The preparation of compounds I, III, IV, VI, and VII has been described previously by one of us [10, 11] and compounds II, V, and VIII were prepared by us by nitrosotization of 1-hydroxyisoquinoline, 4-hydroxycoumarin, and antipyrine respectively. Rearrangement of the isoquinoline II to the trans-acid VIIb was effected by the action of a mixture of benzenesulfonyl chloride and sodium hydroxide solution.

An examination of the mass spectra of the nitrosocompounds I-V which we studied (Table 1) shows that their molecular ions (M^+) have considerable stability (Table 2) and cleavage

*The rearrangement of compounds III and IV was described in [11], and compound V forms the nitrile of salicylic acid under the conditions for the rearrangement.

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