N-ACYLAMINO DERIVATIVES OF THE INDOLINE AND TETRAHYDROQUINOLINE SERIES

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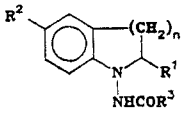
Previously unknown N-acylamino derivatives of the indoline and tetrahydroquinoline series were synthesized. Their E,Z-isomerism was studied by NMR spectroscopy.

Acylaminotetrahydroquinolines and acylaminoindolines are interesting representatives of arylcycloalkylhydrazides, the rearrangement of which by the action of electrophilic agents according to the known Kost reaction [1] may lead to tricyclic derivatives of the 2-aminoindole series. From the previously synthesized N-aminoindolines and N-aminotetrahydroquinolines [2], we synthesized new hydrazides of certain acids by conventional methods (see Table 1) and studied their conformational behavior by NMR spectroscopy. Besides the hindered rotation around the C–N bond, which is well known for amides, for example, for N-acylindolines and N-acyltetrahydroquinolines [3], in α-acyl-β-arylhydrazines the conformation of the molecule is greatly influenced by the gauche effect, characteristic for its hydrazine fragment [4], during which the unshared electron pairs of the vicinal nitrogen atoms are positioned practically perpendicular to one another.



I – XXII n=1,2

On examination of a steric model of the compounds obtained, taking into account the stereoelectronic factors, the predominance of the Z-isomer becomes understandable, since the steric strain in it is much lower than in the E-isomer. Moreover, in the Z-isomer, the carbonyl group is located above the plane of the phenyl ring, which explains the generally occurring shift of the signal of the aromatic ring and of the carbonyl carbon atom of the Z-isomer to the strong field in the ^{13}C NMR spectra, compared with the signals of the E-isomer, and the relatively great difference (~5 ppm) between the signals of the carbonyl group carbon atoms of the Z- and E-isomers. On heating the samples above 75°C under the conditions used in running the spectra, the signals of the two forms coalesce. From the PMR spectra of the hydrazides obtained it follows that the carbonyl group has no discernible influence either on the 7-H protons of the compounds of the indoline series, nor on the 8-H protons of the tetrahydroquinoline series, just as for the corresponding amides [3], which further confirms the correctness of the selected steric model.

The assignment of signals to Z- or E-isomers in the NMR spectra of the hydrazides (Table 1) was carried out on the basis of the generally accepted criteria [5, 6]: it is known that solvents capable of forming intermolecular hydrogen bonds with the dissolved substance, favor the isomer in which the tendency to autoassociation is lower. In the present case this is the Z-isomer, which gives a linear structure during the formation of the intermolecular hydrogen bonds, while for the E-isomer the more convenient structure of a cyclic dimer is realized. Thus, increase in the polarity of the solvent should shift the equilibrium in the direction of the Z-form, which is borne out by the data obtained (Table 1). Another criterion is the shift of the conformational equilibrium in the

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TABLE 1. ^{13}C NMR Spectra

Compound	Solvent	Chemical shift, δ, ppm											Cont. of the Z-isomer, %
		$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	C=O	α-C atom	
Z-X	$CDCl_3$	50,76	21,77	23,99	122,46	118,46	126,45	111,92	145,15	128,62	172,75	26,64	52
E-X		52,49	22,01	26,36	123,28	119,81	126,70	112,31	145,24	128,96	178,65	26,98	
Z-X	DMSO-D_6	50,54	22,00	26,77	121,91	117,76	126,66	111,67	145,97	128,72	172,03	26,77	83
E-Z		52,20	22,21	23,90	123,12	119,13	126,84	112,42	146,26	129,02	177,41	26,52	
Z-XIII	DMSO-D_6	50,53	21,98	26,61	121,87	126,16	126,91	111,91	143,71	129,09	171,76	26,64	81
E-XIII		52,27	22,12	23,76	123,02	126,16	127,08	112,55	143,94	129,36	177,20	26,30	
Z-XIV	DMSO-D_6	50,70	22,12	26,72	122,16	126,34	126,59	112,15	143,72	129,08	169,12	40,71	84
E-XIV		52,54	22,12	26,42	123,56	126,34	127,06	113,34	144,13	129,35	174,75	—*	
Z-XVI	DMSO-D_6	50,38	21,66	26,60	121,34	126,65	126,17	113,12	144,73	129,09	169,27	40,60	88
E-XVI		52,25	21,63	26,30	123,09	126,65	126,43	114,52	145,17	129,43	174,77	39,60	
Z-XX	DMSO-D_6	53,44	19,44	23,63	122,17	117,71	126,69	112,10	145,99	128,49	172,28	26,71	93
E-XX		55,69	19,82	23,92	122,88	118,50	126,96	113,65	147,11	128,82	178,03	25,42	
Z-XXI	DMSO-D_6	53,46	19,50	25,53	122,26	117,76	126,71	112,02	146,10	128,55	174,42	45,71	100
Z-XXII	DMSO-D_6	50,44	21,93	27,47	121,87	117,62	126,64	135,87	145,97	128,66	171,84	45,38	36
E-XXII		52,79	21,93	26,73	121,03	117,62	126,64	135,87	149,63	129,00	174,07	45,38	
Z-I	$CDCl_3$	55,35	24,41	124,09	120,10	126,59	109,05	150,63	127,42	—	173,09	26,93	57
E-I		56,93	24,41	124,47	121,16	126,95	109,24	150,45	127,48	—	178,68	27,07	
Z-I	DMSO-D_6	54,88	24,50	124,57	119,61	127,00	108,75	151,74	128,02	—	172,07	26,95	77
E-I		56,70	24,50	124,80	120,70	127,30	109,58	151,84	128,32	—	177,32	27,32	
Z-III	$CDCl_3$	55,39	25,22	124,22	120,22	126,74	109,18	150,89	127,61	—	175,14	42,93	65
E-III		57,78	25,33	124,65	121,44	127,14	109,68	150,82	127,80	—	180,72	42,93	

*The signal merges with the solvent signal.

TABLE 2. 1-Acylaminoindolines and -tetrahydroquinolines I-XXII

Compound	Empirical formula	n	R¹	R²	R³	mp, °C	IR spectrum, cm^{-1}		PMR spectrum, ppm (J, Hz) in $CDCl_3$			Yield, %
							C=O	NH	heterocyclic ring	R³	Ar, NH	
I	$C_{11}H_{14}N_2O$	1	H	H	C_2H_5	81...82	1695*	3320	3,5 (t, J=8,0, 2H, 2-H); 2,95 (t, 2H, 3-H)	1,16 (t, J=7,5; CH_3); 2,2 (q, CH_2)	6,5...7,2 (m, 4H); 7,9 (s, NH)	66
II	$C_{16}H_{16}N_2O$	1	H	H	CH_2Ph	103...105	1680	3150	3,5 (t, J=8,0, 2H, 2-H); 2,95 (t, 2H, 3-H)	3,6, 3,8 (s, 2H, CH_2)	6,3...6,4 (m, 10H)	62
III	$C_{15}H_{20}N_2O$	1	H	H	*cyclo*-C_6H_{11}	154...155	1660	3180	3,5 (t, J=8,0, 2H, 2-H); 2,95 (t, 2H, 3-H)	1,1...2,0 (m, *cyclo*-C_6H_{11})	6,4...7,1 (m, 4H); 7,6 (s, NH)	64
IV	$C_{12}H_{16}N_2O$	1	CCH_3	H	C_2H_5	98...99	1665	3195	3,5 (m, 1H, 2-H); 1,4 (m, 3H, 2-CH_3); 2,9 (t, J=8,0, 2H, 3-H)	1,13 (t, J=7,5; CH_3); 2,5 (q CH_2)	6,4...7,3 (m, 5H)	93
V	$C_{17}H_{18}N_2O$	1	CH_3	H	CH_2Ph	105...107	1700*	3320	3,9 (m, 1H, 2-H); 1,4 (m 3H, 2-CH_3); 2,85 (t, J=8,0, 2H, 3-H)	3,6 (s, CH_2)	6,3...7,3 (m, 10H)	55
VI	$C_{16}H_{22}N_2O$	1	CH_3	H	*cyclo*-C_6H_{11}	183...184	1660	3200	3,2 (m 1H, 2-H); 1,3 (m 3H, 2-CH_3); 2,6 (t, J=8,0, 2H, 3-H)	1,0...2,0 (m, *cyclo*-C_6H_{11})	6,3...7,3 (m, 5H)	60
VII	$C_{22}H_{20}N_2O$	1	Ph	H	CH_2Ph	153...154	1670	3200	4,4 (m 1H, 2-H)*; 3,1 (m, 2H, 3-H); 7,5 (s 2-C_6H_5)	3,2 (s CH_2)	6,0...7,4 (m 9H); 7,75 (s NH)	71
VIII	$C_{16}H_{15}BrN_2O$	1	H	Br	CH_2Ph	145...146	1655	3220	3,5 (m 2H, 2-H)*; 2,95 (m, 2H, 3-H)	3,65*, 3,75 (s, 2H, CH_2)	6,1...7,3 (m, 8H); 8,0, 8,4 (s 1H, NH)	57
IX**	$C_{18}H_{20}N_2O$	1	CH_3	H	CH_2Ph	119...121	1670	3330	3,8...3,9 (m, 2H, 2-H, 3-H); 1,04...1,4 (m 6H, 2-CH_3, 3-CH_3)	3,6 (s CH_2)	6,5...7,4 (m 9H); 7,6 (m, NH)	70
X	$C_{12}H_{16}N_2O$	2	H	H	C_2H_5	79...80	1660	3240	3,3 (t, J=5,0, 2H, 2-H); 2,1 (m, 2H, 3-H); 2,6 (t 2H, 4-H)	1,6, 1,12 (t, J=7; 3H, CH_3); 2,0 (q, CH_2)	6,4...7,2 m, 4H); 7,9 (s, NH)	85
XI	$C_{17}H_{18}N_2O$	2	H	H	CH_2Ph	133...134	1670	3250	3,15, 3,3 (t, J=5,0, 2H, 2-H); 2,2 (m, 2H, 3-H); 3,0 (t 2H, 4-H)	3,5, 3,6 (s 2H, CH_2)	6,5...7,5 (m, 10H)	81
XII	$C_{16}H_{22}N_2O$	2	H	H	C_6H_{11}	189...190	1660	3190	3,5 (t, J=5,0, 2H, 2-H); 2,2 (m, 2H, 3-H); 2,8 (t 2H, 4-H)	1,2...2,0 (m C_6H_{11})	6,5...7,3 (m, 4H); 7,4 (s, NH)	80

XIII	$C_{13}H_{18}N_2O$	2	H	CH_3	C_2H_5	116...117	1660	3180	3,15, 3,35 (t, J=5,0, 2H, 2-H); 2,05 (m, 2H, 3-H); 2,72 (t, 2H, 4-H)	1,06, 1,12 (t, J=7,0, 3H, CH_3); 2,4 (q, CH_2)	2,2, 2,3 (s, 3H, 6-CH_3); 6,6...7,0 (m, 3H); 7,5 (s, NH)	62
XIV	$C_{18}H_{20}N_2O$	2	H	CH_3	CH_2Ph	135...136	1665	3220	3,15, 3,35 (t, J=5,0, 2H, 2-H); 2,05 (m, 2H, 3-H); 2,72 (t, 2H, 4-H)	3,7, 3,75 (s, 2H, CH_2)	2,2, 2,3 (s, 3H, 6-CH_3); 6,5...7,3 (m, 8H); 7,5 (s, NH)	87
XV	$C_{17}H_{24}N_2O$	2	H	CH_3	*cyclo*-C_6H_{11}	136...137	1665	3220	3,5 (t, J=5,0, 2H, 2-H); 2,0 (m, 2H, 3-H); 2,9 (t, 2H, 4-H)	1,0...2,0 (m, C_6H_{11})	2,1 (s, 6-CH_3); 6,4...7,2 (m 3H); 7,4 (s NH)	56
XVI	$C_{17}H_{17}ClN_2O$	2	H	Cl	CH_2Ph	161...162	1675	3230	3,3 (t, J=5,0, 2H, 2-H); 2,0 (m, 2H, 3-H); 2,6 (t, 2H, 4-H)	3,55, 3,62 (s 2H, CH_2)	6,3...7,3 (m 9H)	61
XVII	$C_{16}H_{21}ClN_2O$	2	H	Cl	C_6H_{11}	146...147	1670	3270	3,3 (t, J=5,0, 2H, 2-H); 2,2 (m, 2H, 3-H); 2,6 (t, 2H, 4-H)	1,1...2,0 (m C_6H_{11})	6,3...7,3 (m, 3H); 7,5 (s NH)	47
XVIII	$C_{13}C_{18}N_2O_2$	2	H	OCH_3	C_2H_5	100...101	1675	3250	3,3 (t, J=5,0, 2H, 2-H); 2,0 (m, 2H, 3-H); 2,6 (t, 2H, 4-H)	1,06, 1,12 (t, J=7,0, 3H, CH_3); 2,2 (q, CH_2)	3,6, 3,65 (s 3H, 6-OCH_3); 6,3...7,0 (m, 3H); 8,3 (s NH)	72
XIX	$C_{18}H_{20}N_3O_2$	2	H	OCH_3	CH_2Ph	134...135	1665	3210	3,3, 3,0 (t, J=5,0, 2H, 2-H); 2,0 (m, 2H, 3-H); 2,6 (t, 2H, 4-H)	3,5, 3,6 (s, 2H, CH_2)	3,6, 3,7 (s 3H, OCH_3); 6,4...7,3 (m, 8H); 7,6 (s, NH)	69
XX	$C_{13}H_{18}N_2O$	2	CH_3	H	C_2H_5	105...106	1670	3260	3,5 (m, 1H, 2-H); 1,2 (d, J=7,0, 3H, 2-CH_3); 2,0 (m, 2H, 3-H); 2,6 (t, J=5,0, 2H, 4-H)	1,2 (t, J=7,0, CH_3); 2,2 (q CH_2)	6,4...7,3 (m, 4H); 8,2 (s, NH)	48
XXI	$C_{17}H_{24}N_2O$	2	CH_3	H	C_6H_{11}	175...176	1665	3180	3,8 (m, 1H, 2-H); 1,3 (d, J=7,0, 2H, 2-CH_3); 2,3 (m, 2H, 3-H); 3,0 (m, 2H, 4-H)	1,36...2,1 (m, C_6H_{11})	6,6...7,6 (m, 5H)	53
XXII***	$C_{19}H_{28}N_2O_2$	2	H	H	C_6H_{11}	173...174	1660	3210	3,5 (t, J=5,0, 2H, 2-H); 2,2 (m, 2H, 3-H); 2,8 (tr, 2H, 4-H)	1,3...2,0 (m, C_6H_{11})	1,2 (d, J=7,0, 2-CH_3); 4,5 (m 1H, CH); 6,3...7,0 (m 3H); 7,3 (s, NH)	90

*The IR spectra were run in a CH_2Cl_2 solution, the PMR spectra in CD_2Cl_2.
**1-Phenacetylamino-2,3-dimethylindoline.
***1-Cyclohexylamino-8-isopropoxy-1,2,3,4-tetrahydroquinoline.

direction of the isomer with less steric interactions, when the volume of substituents on the nitrogen atom is increased [5, 6]. In fact, with increase in the size of the acyl residue, the content of the Z-isomer increases, as can be seen in the case of compounds XIII, XIV, I and III, XX and XXI. The substituent at the 2-position also increases the proportion of the Z-isomer (compound XX*), while introduction of the cyclohexanoyl group as the acyl residue (compound XXI) renders the Z isomer the only one possible. In the molecule of hydrazide XXII, the steric interactions due to the presence of a bulky substituent in the 8-position and in the acyl residue are such that the E-isomer becomes the predominant one.

EXPERIMENTAL

The IR spectra were run on a UR-20 spectrophotometer in mineral oil, the ^{1}H and ^{13}C NMR spectra on Tesla B-467 A (60 MHz) and Jeol FX-100 spectrometers. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates in a benzene-acetone (5:1) system. The elemental analysis data correspond to the calculated values.

All the N-nitroso compounds were obtained by nitrosation of the corresponding indolines and tetrahydroquinolines by the method described in [2]; N-aminoindolines and N-aminotetrahydroquinolines were obtained by reduction of the corresponding nitroso compounds by lithium aluminum hydride using the method described in [7]. 1-Acylaminoindolines I-IX and 1-acylamino-1,2,3,4-tetrahydroquinolines X-XXII were synthesized by a generally accepted procedure for acylation of amines [8, p. 434] by acid chlorides in the presence of triethylamine (see Table 2).

LITERATURE CITED

1. Yu. N. Portnov and G. A. Golubeva, Khim. Geterotsikl. Soed., No. 9, 1155 (1985).
2. A. N. Kost, L. G. Yudin, and A. P. Terent'ev, Zh. Obshch. Khim., 29, 1949 (1959).
3. L. M. Jackman and F. A. Cotton, Dynamic NMR Spectroscopy, Acad. Press, N.Y. (1975).
4. A. J. Kerby, The Anomeric Effect of Oxygen-Containing Compounds [Russian translation], Mir, Moscow (1985), p. 90.
5. P. Bouchet, J. Elguero, R. Jacquier, and J. Pereillo, Bull. Soc. Chim. France, No. 6, 2264 (1972).
6. I. P. Bezhan, V. A. Khrustalev, K. N. Zelenin, and B. P. Nikolaev, Zh. Org. Khim., 14, 754 (1978).
7. I. I. Grandberg and T. I. Zuyanova, Khim. Geterotsikl. Soed., No. 1, 51 (1971).
8. Weygand–Hilgetag, Experimental Methods in Organic Chemistry [Russian translation], Khimiya, Moscow (1968).

*According to the ^{13}C NMR data, compound XX contains a practically inseparable impurity (~6%) of 1-propionyl-2-methyltetrahydroquinoline.