SYNTHESIS AND ACYLATION OF 1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES

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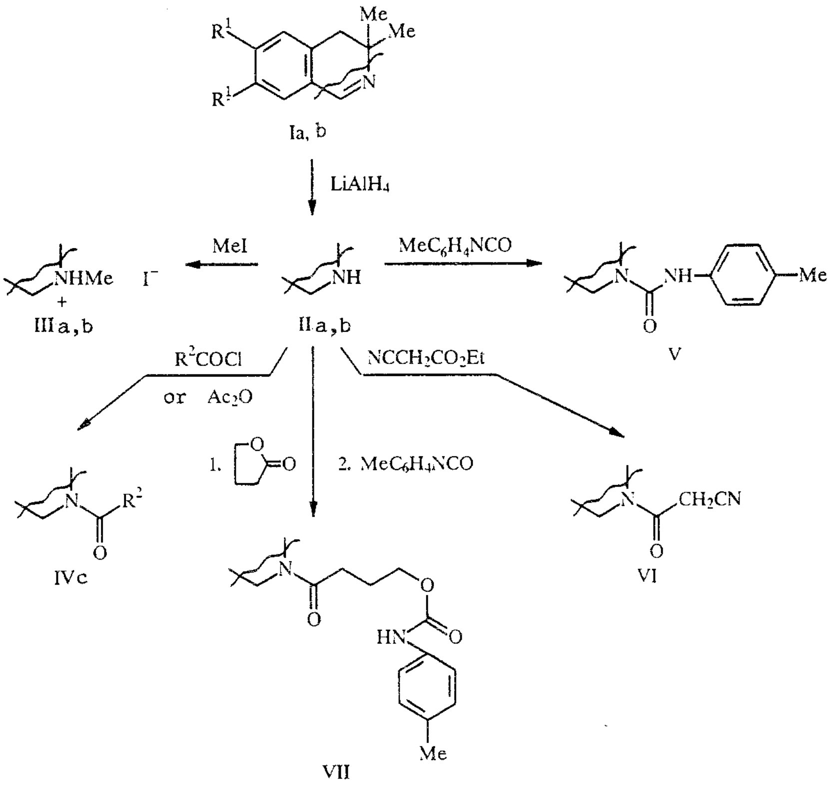
1,2,3,4-Tetrahydroisoquinolines were synthesized, and their acylation was studied.

Previously [1] we obtained 3,4-dihydroisoquinolines without substituents in the 1 position. These azomethines are promising synthons. One of the possible reactions of these compounds is hydrogenation, giving 1,2,3,4-tetrahydroisoquinolines, which are interesting as new reactants and biologically active compounds. It was found that reduction of azomethines Ia and Ib by lithium aluminum hydride to the corresponding tetrahydroisoquinolines IIa and IIb occurs in virtually quantitative yield. Compounds IIa and IIb are facilely quaternized with formation of methiodides IIIa and IIIb.

In the literature, there are descriptions of acylation reactions of 1,2,3,4-tetrahydroisoquinoline enamines occurring both at the ring nitrogen atom [2, 3] and at the β-carbon atom of the enamine fragment [4, 5]. In the latter case, a steric effect of C_3 methyl groups in the 3 position is possible. Therefore, it is of interest to study the acylation of compounds that would have C_3 methyl groups in the 3 position of their structure, but would not contain an enamine fragment, because this would make it possible to evaluate the steric factor.



I—IIIa R^1 = H, b R^1 = OMe; IV R^1 = OMe, a R^2 = Me, b R^2 = Ph, c R^2 = *n*-Bu; V R^1 = H;
VI—VIII R^1 = OMe

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Mp, °C	Yield, %	Compound	Empirical formula	Mp, °C	Yield, %
IIa	$C_{11}H_{15}N \cdot HCl$	240...241	92	IVb	$C_{20}H_{23}NO_3$	134...136	73
IIb	$C_{13}H_{19}NO_2 \cdot HCl$	249...250	95	IVc	$C_{18}H_{27}NO_3$	99...100	62
IIIa	$C_{12}H_{18}IN$	258...259	75	V	$C_{19}H_{22}N_2O$	154...155	57
IIIb	$C_{14}H_{22}INO_2$	267...268	88	VI	$C_{16}H_{20}N_2O_3$	153...154	33
IVa	$C_{15}H_{21}NO_3$	104...105	68	VII	$C_{25}H_{32}N_2O_5$	195...197	56

TABLE 2. Spectra of Compounds II-VII (s denotes singlet, m multiplet, and t triplet)

Compound	PMR spectrum, ppm						IR spectrum, cm^{-1}
	s, 6H, $2CH_3$—C_3	s, 2H, CH_2—C_4	CH_2—N	Ar	$2CH_3O$, s	protons of other groups	
IIa	1,07	2,45	3.84 s	6.85-7.32 m	—	3.46 s (NH)	3370 (NH)
IIb	1,10	2,57	3.82 s	6.40 s, $CH_{5,8}$	3,69	3.53 s (NH)	3370 (NH)
IIIa	1,12	2,53	3.93 m	6.84-7.42 m	—	3.93 m (CH_3N)	—
IIIb	1,07	2,47	3.96 m	6.43 s, $CH_{5,8}$	3,70	3.96 m (CH_3N)	—
IVa	1,37	2,60	4.27 s	6.46 s, $CH_{5,8}$	3,75	2.60 s (CH_3CO)	1630 (C=O)
IVb	1,33	2,63	4.29 s	6.34-8.53 m	3,72	–	1630 (C=O)
IVc	1,28	2,62	4.23 s	6.43 s, $CH_{5,8}$	3,73	1.10-1.47 wide s (C_3H_7); 2.35 t (CH_2CO)	1630 (C=O)
V	1,30	2,67	4.40 s	6.28-8.57 m	—	2.10 s (CH_3—Ar); 8.21 s (NH)	1625 (C=O)
VI	1,44	2,87	4.13 s	6.51 s, $CH_{5,8}$	3,76	2.94 s (CH_2CN)	1640 (C=O), 2250 (C ≡N)
VII	1,18	2,53	4.22 s	6.43=7.45 m	3,70	2.12 s (CH_3—Ar); 1.21-1.32 m (CH_2—C); 2.47 m (CH_2CO); 3.80 m (CH_2O); 8.17 s (NH)	1640, 1740 (C=O of amide and urethane); 3300 (NH)

For this purpose, we studied the reaction of compounds IIa and IIb with acylating agents. The investigations showed that bases IIa and IIb are not acylated by acetic anhydride or benzoyl chloride by the Schotten–Baumann reaction [5]. The reaction with acetic anhydride occurs only during heating in the presence of triethylamine, and amide IVa is formed. Reactions with benzoyl chloride and valeryl chloride, occurring facilely under similar conditions, give the corresponding amides IVa and IVb, and the reaction with p-tolyl isocyanate gives compound V. Heating of compound IIb with cyanoacetic ester gives the corresponding compound VI. In the latter reaction, the yield is low (Table 1), and strong resinification occurs. Boiling of compound IIb with γ-butyrolactone gives the corresponding acyl derivative, identified in crystalline form as urethane VII [6].

Thus, investigations with five types of reactants showed that the reactants have different activities. At the same time, the yields of each reaction, which were entirely as expected (Table 1), do not enable us to draw a conclusion concerning a steric effect of C_3 methyl groups in the 3 position.

Unlike in the case of starting substances Ia and Ib [1], the PMR spectra (Table 2) of the bases of compounds IIa and IIb contained singlets of NH (3.84 and 3.82 ppm, respectively) and CH_2 groups (2.45 and 2.47 ppm); the IR spectrum (Table 2) of these bases contained a band of stretching vibrations of NH groups (3370 cm^{-1}). This proves the structure of 1,2,3,4-tetrahydroisoquinoline unambiguously. The PMR spectra of the bases of compounds IIIa and IIIb and substances IVa-c did not contain peaks of NH protons, and the IR spectra did not contain the corresponding absorption band, which indicates substitution of the proton of the NH group. The spectral characteristics of the substituents at the nitrogen atom (Table 2) also confirm the structure of each substance.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were recorded with an RYa-2310 instrument in $CDCl_3$, except for the spectrum of substance V, recorded in DMSO-D_6, and the internal standard was HMDS. The IR and PMR spectra of compounds IIa, IIb, IIIa, and IIIb are given for the bases. The course of the reactions was monitored by thin-layer chromatography on Silufol UV-254 plates in the chloroform–acetone system, 9:1, and development was with bromine vapor.

The data of elemental analysis for C, H, N, and Cl corresponded to the calculated values.

The starting substances Ia and Ib are described in [1]. Compounds IIa and IIb were identified as hydrochlorides. Substances IVa and IVb were recrystallized from water and cyclohexane, respectively, and all the remaining ones were recrystallized from 2-propanol.

3,3-Dimethyl-6,7-(R^1)$_2$-1,2,3,4-tetrahydroisoquinolines (IIa and IIb) and Their Methiodides (IIIa and IIIb). To a solution of 0.11 g (3 mmoles) of $LiAlH_4$ in 30 ml of absolute ether was added dropwise 20 ml of an ether solution of 10 mmoles of compound Ia or Ib. The reaction mixture was boiled for 1 h, cooled, and dispersed with water, and the ether layer was separated. The $Al(OH)_3$ precipitate was washed with ether (3 × 20 ml). The ether solutions were combined and dried with K_2CO_3, and passage of dry HCl gave hydrochlorides IIa and IIb, which were filtered, dried, and recrystallized. To a solution of 10 mmoles of compound IIa or IIb in 20 ml of ethanol was added 0.42 ml (13 mmoles) of CH_3I, and the containers were tightly closed with a stopper and left for 4 h at 20°C. The resulting precipitate was filtered, dried, and recrystallized.

N-R^2CO-3,3-Dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (IVa-c). For these compounds, 2.21 g (10 mmoles) of base IIb was stirred with 1.41 ml (15 mmoles) of acetic anhydride and 4 ml of triethylamine, and the whole was left for 24 h at 20°C. The precipitated crystals of compound IVa were filtered, washed with water, dried, and recrystallized. A solution of 2.21 g (10 mmoles) of base IIb in 20 ml of benzene was stirred with 10 mmoles of the corresponding acid chloride in the presence of 1.69 ml (12 mmoles) of triethylamine. The mixture was boiled for 3 h and cooled, the resulting triethylamine hydrochloride precipitate was filtered, the benzene solution was evaporated using a rotor-type evaporator, and the crystalline residue of IVb and IVc was recrystallized.

3,3-Dimethyl-2-[N-(p-tolyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline (V). A solution of a mixture of 1.61 g (10 mmoles) of base IIb and 1.21 g (10 mmoles) of p-tolyl isocyanate in 20 ml of benzene was boiled for 2 h and cooled, and the resulting precipitate was filtered, dried, and recrystallized.

3,3-Dimethyl-2-(cyanoacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI). A mixture of 2.21 g (10 mmoles) of compound IIb with 2.14 g (20 mmoles) of cyanoacetic ester was heated for 2 h on a water bath. The resulting precipitate was filtered, dried, and recrystallized.

δ-Oxo-δ-(3,3-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)-butyl N-(p-Tolyl)carbamate (VII). A mixture of 2.21 g (10 mmoles) of compound IIb with 0.73 ml (11 mmoles) of γ-butyrolactone in 50 ml of benzene was boiled for 8 h, 1.21 ml (10 mmoles) of p-tolyl isocyanate was added, the whole was boiled for an additional 30 min, the solvent was evaporated, and the resulting precipitate was filtered, dried, and recrystallized.

REFERENCES

1. A. G. Mikhailovskii, B. B. Aleksandrov, and M. I. Vakhrin, Khim. Geterotsikl. Soedin., No. 8, 1444 (1992).
2. A. Brossi, H. Besendorf, B. Pellmont, M. Walter, and O. Schrüder, Helv. Chim. Acta, **43**, 1459 (1960).
3. Yu. S. Andreichikov, V. S. Shklyaev, B. B. Aleksandrov, Yu. V. Ionov, and M. I. Vakhrin, Khim. Geterotsikl. Soedin., No. 3, 420 (1982).
4. J. Kobor, J. Gyula Tanárképzö, Foisk. Tud. Közl., No. 2, 155 (1975).
5. V. S. Shklyaev, B. B. Aleksandrov, M. S. Gavrilov, A. G. Mikhailovskii, and M. I. Vakhrin, Khim. Geterotsikl. Soedin., No. 7, 939 (1988).
6. Organic Chemistry (Organicum) [Russian translation], Vol. 2, Mir, Moscow (1979), p. 318.