SYNTHESIS OF TETRAHYDROISOQUINOLINO [2,1-d][1,4]BENZODIAZEPIN-6(7H)-ONES, II

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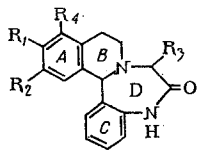
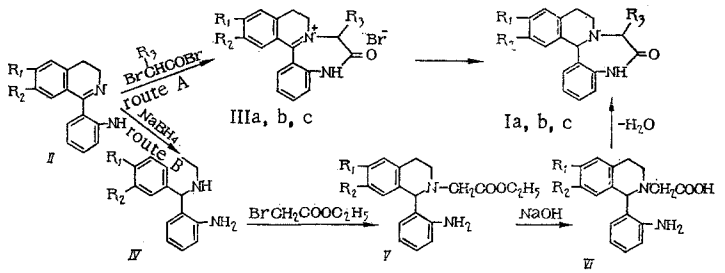
Recently, benzodiazepines have been widely used in medical practice as psychotropic agents [1]. In the present work, we will examine the preparation of tetrahydroisoquinolinobenzodiazepinones and their derivatives, of general formula:



Compound	R_1	R_2	R_3	R_4
Ia	CH_3O	CH_3O	H	H
Ib	H	CH_3O	H	H
Ic	CH_3O	CH_3O	CH_3	H
Id	CH_3O	CH_3O	H	NO_2
Ie	CH_3O	CH_3O	H	NH_2

The synthesis of these compounds was carried out by two routes according to the following scheme:



The preparation of the starting compounds II, IV and V was discussed in our previous work [2]. 1-(2-Aminophenyl)-2-carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI) is formed by saponifying ester V with an alcoholic solution of potassium hydroxide at a temperature of 60° with subsequent acidification of the solution to pH 6.5. The diazepine ring is closed by heating acid VI in xylene with azeotropic separation of the water formed during the reaction. The yield of Ia is 25%, based on the initial IIa.

Because of the low yield, a second synthesis variant was also used, according to which the quaternary salt (IIIa, IIIb, IIIc) is first prepared with the acid bromide of bromoacetic or α-bromopropionic acid respectively by a method proposed earlier [3] and modified by us. In contrast to the known method, according to which the preliminarily formed hydrobromide of 1-(o-bromoacetanilido)-3,4-dihydroisoquinoline (VII) is converted into the diazepine, we used a single-step variant of the cyclization.

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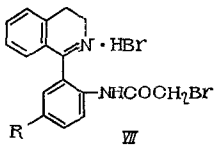
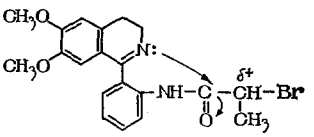


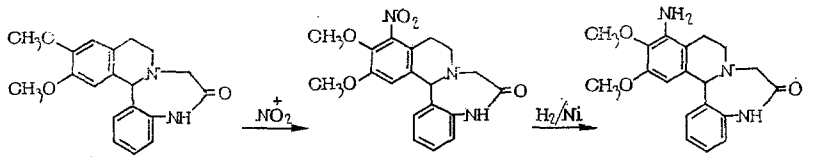
VII

R=NO_2, Cl, H

To do this, the corresponding substituted dihydroisoquinoline is treated with bromoacetyl bromide in dioxane in the presence of a 4 N solution of potassium hydroxide, acylation and cyclization taking place simultaneously. 7-Methyl-12,13-dimethoxy-5,9,10,14b-tetrahydro-isoquinolino[2,1-d][1,4]benzodiazepin-6(7H)-one (Ic) is synthesized analogously. The relatively low yield of the quaternary salt IIIc (60% of the theoretical) can be explained by steric effect of the methyl group in the α position, which hinders intramolecular nucleophilic substitution.



It is known that NO_2 and NH_2 groups and other substituents can bring about a change in the physiological activity of the compounds in question. In view of this, we investigated the possibility of introducing nitro and amino groups into 12,13-dimethoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]benzodiazepin-6(7H)-one (Ia) according to the scheme



Ia Id Ie

We carried out the nitration of Ia to the 11-nitro derivative (Id) by several methods: a) with a nitrating mixture in sulfuric or acetic acid; b) with a mixture of potassium nitrate and concentrated sulfuric acid; and c) with concentrated nitric acid in acetic acid. We found that rapid ring opening takes place in sulfuric acid, which leads to low yields of the nitro derivative (15-20%). Nitration with the nitrating mixture in acetic acid increases the yield to 40%; if the nitration in acetic acid is carried out with nitric acid only, the reaction does not proceed. The presence of nitro groups in the compounds synthesized follows from their IR spectra, in which the absorption bands at 1540 and 1360 cm^{-1} correspond to the antisymmetric and symmetric stretching vibrations of the nitro group in an aromatic nucleus.

The nitronium cation can attack both the C nucleus and the A nucleus. The reduced electron density in the C nucleus due to the delocalization of the Ar–H–C=O system and the increased electron density in the A nucleus (+M · CH_3O) give reason to suppose that the electrophilic attack will be directed to the aromatic nucleus A.

This supposition is confirmed by the data of the NMR spectra of the compound under investigation. The multiplet signal at $\delta = 6.4$-7.4 ppm in the spectrum of Ia (Fig. 1) is due to the aromatic protons in the C nucleus, the singlets at $\delta = 6.8$ ppm and $\delta = 6.3$ ppm belong to the two protons in the A nucleus. They were identified by comparing the spectra of Ia and Ib (Fig. 2). The position of the methoxyl group in Ib at C_{13} and the spin splitting of the signal of the proton at C_{12}, caused by the interaction of protons 11, 12 and 14, demonstrate that the resonance signal at $\delta = 6.3$ ppm belongs to the C_{14} proton. The signal of the proton at C_{12} appears in the form of a quartet ($J_o = 8$ Hz and $J_m = 3$ Hz), and the signal of the proton at C_{14} appears in the form of a doublet ($J_m = 3$ Hz).

The resonance signal at $\delta = 6.68$ ppm in the spectrum of Id (Fig. 3) belongs to the C_{14} proton. The chemical shift of the signal to weaker field by 0.4 ppm is caused by the deshielding of the para proton due to the strongly electron-accepting NO_2 substituent [4, 5]. The singlet signal of the C_{11} proton is absent in the spectrum of Id, whereas the resonance signals of the other protons in the C nucleus remain unchanged. This confirms the location of the nitro group at C_{11}.

The catalytic reduction of compound Id in the presence of Raney nickel in an alcohol medium at room temperature and atmospheric pressure leads to 11-amino-12,13-dimethoxy-5,9,10,14b-tetrahydro-isoquin-

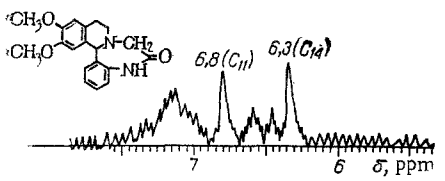


Fig. 1. NMR spectrum of compound Ia.

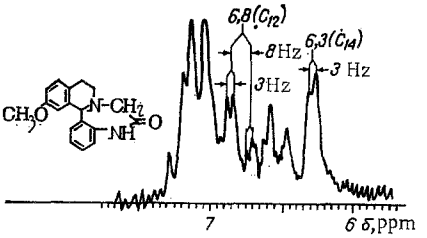


Fig. 2. NMR spectrum of compound Ib.

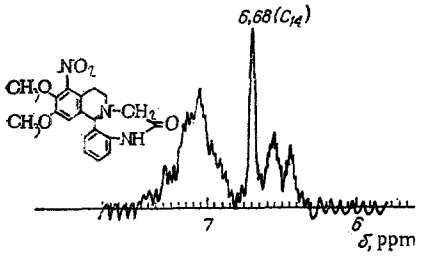


Fig. 3. NMR spectrum of compound Id.

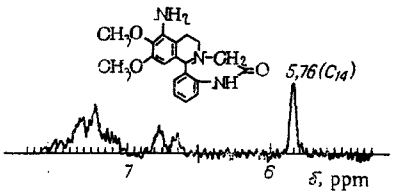
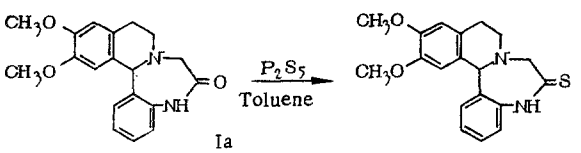


Fig. 4. NMR spectrum of compound Ie.

olino[2,1-d][1,4]benzodiazepin-6(7H)-one (Ie). This structure was established by means of IR and NMR spectra, which represented additional proof of the position of the nitro group in Id. The chemical shift of the proton at C_{14} to stronger field is due to shielding caused by the electron-donating substituent; the other signals remain unchanged (Fig. 4).

When Ia is reacted with phosphorus pentasulfide, 12,13-dimethoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]benzodiazepin-6(7H)-one is formed [cf. 5]:



The process proceeds in a toluene medium at the boiling point of the reaction mixture. In the IR spectrum of the compound obtained, there is no absorption at 1680 cm^{-1}, corresponding to the stretching vibrations of the C=O group, but an absorption band appears at 1460 cm^{-1} (stretching vibrations of the Ar–NH–C=S group).

EXPERIMENTAL

The IR spectra were recorded on an IR-10 spectrophotometer (suspensions in mineral oil or solutions in chloroform). The NMR spectra were recorded on an instrument with a working frequency of 60 MHz, using tetramethylsilane as internal standard. The homogeneity of the compounds prepared was monitored by thin-layer chromatography on silica gel with the benzene-methanol system.

12,13-Dimethoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]-benzodiazepinone hydrobromide (IIIa). A portion of IIa (10 g) is dissolved in 150 ml of dry dioxane; 7.5 ml of α-bromoacetyl bromide are added by drops to the solution, cooled to 8-10°; a yellow precipitate is formed. The mixture is stirred for 10-15 min, and 35 ml of a 10% sodium hydroxide solution are added dropwise to pH 7.5 at a temperature of 6-8°. The mixture is stirred for 5 h and left overnight. The yellow precipitate formed is filtered off and washed with dioxane. Yellow crystals (13.5 g), mp 203-205° (from methanol), are obtained. The yield is 85% of theoretical. Found, %: C 53.70; H 4.35; Br 19.50; N 6.60. $C_{19}H_{19}BrN_2O_3$. Calculated, %: C 54.00; H 4.71; Br 19.80; N 6.94. IR spectrum (suspension in mineral oil), cm^{-1}: 3350, 1695, 1610, 1560.

1-(2-Aminophenyl)-2-carboxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VI). A mixture of 10 g of V, 27 ml of ethyl alcohol and 27 ml of a 2 N potassium hydroxide solution is heated on a water bath at 60° for 2 hours. The obtained solution is kept at room temperature for 15 hours. On acidifying

with a 2 N hydrochloric acid solution to pH 6.5, a white precipitate of VI is formed. Yield 5 g (55%), mp 181-183° (from aqueous alcohol). Found, %: C 60.35; H 6.70; N 7.90. $C_{19}H_{22}N_2O_4$. Calculated, %: C 60.81; H 6.43; N 8.18.

12,13-Dimethoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]-benzodiazepin-6(7H)-one (Ia) (route A). A portion of sodium borohydride (1.6 g) is dissolved in a mixture of 40 ml ethyl alcohol and 50 ml water. A portion of IIIa (3.2 g) is added to the obtained solution over 20 min. The mixture is heated for 3 h at 50-55°, cooled, and 55 ml of a 10% hydrochloric acid solution added until a solution is obtained. On making alkaline with a 10% sodium hydroxide solution to pH 8.0, a white crystalline precipitate is formed. After recrystallization from ethyl alcohol, 1.9 g of Ia are obtained, colorless crystals, mp 221-223°. Yield 76% or 73% calculated on IIa. Found, %: C 69.75; H 6.70; N 8.65. $C_{19}H_{20}N_2O_3$. Calculated, %: C 70.10; H 6.46; N 8.16. IR spectrum (in chloroform), cm^{-1}: 3400, 1690, 1595, 1480, 1340. NMR spectrum (in chloroform), ppm: 2.2-3.2(4) m ($-CH_2-CH_2$); 2.9 (1) d and 3.5 (1) d, J_{AB} = 10 Hz ($-COOH_2N-$); 3.65 (3) s and 3.95 (3) s ($2CH_3O$); 5.3 (1) s ($-\underset{|}{CH}-$); 6.3 (1) s (C_{14}; 6.68 (1) s (C_{11}); 6.6-7.5 (4) m (aromatic protons in C nucleus); 10.1 (1) s (NH). (m = multiplet, d = doublet; s = singlet).

NMR spectrum (in DMSO-d_6), ppm: 2.2-3.5 (the signals for $COCH_2N$ and $-CH_2CH_2-$ coincide with the solvent signals and are not characteristic); 3.55 (3) s and 3.75 (3) s ($2CH_3O$); 5.3 (1) s ($-\underset{|}{CH}-$); 6.35 (1) s (C_{14}); 6.8 (1) s (C_{11}); 6.6-7.5 (4) m (aromatic protons in C nucleus); 10.1 (1) s (NH).

12,13-Dimethoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]-benzodiazepin-6(7H)-one (Ia) (route B). A suspension of 2 g of VI in 50 ml of dry xylene is boiled in a Dean-Stark apparatus for 10 hours until the reaction water has been completely removed. On cooling, the obtained crystalline mass is filtered off. This is recrystallized from ethanol and 1.7 g of Ia, mp 221-223°, is obtained. Yield 90% or 26% calculated on IIa.

The identity of the products obtained by the two schemes was established by physicochemical methods.

13-Methoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]-benzodiazepinone hydrobromide (IIIb). The compound is synthesized by route A (from IIb) using α-bromoacetyl bromide. Yield 75% of theoretical, mp 245-249° (from methanol). Found, %: C 57.90; H 4.55; Br 21.44; N 7.50. $C_{18}H_{17}BrN_2O_2$. Calculated, %: C 57.60; H 4.84; Br 21.20; N 7.50.

13-Methoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]-benzodiazepin-6(7H)-one (Ib). The compound is prepared analogously to Ia by reduction of IIIb with sodium borohydride. Yield 75%, mp 210-212° (from ethanol). Found, %: C 73.19; H 5.70; N 9.25. $C_{18}H_{18}N_2O_2$. Calculated, %: C 73.46; H 6.12; N 9.52.

IR spectrum (suspension in mineral oil), cm^{-1}: 3180, 3070, 1680, 1610, 1590, 1490, 1340.

NMR spectrum (in DMSO-d_6), ppm: 2.2-3.4 ($COCH_2N$; $-CH_2CH_2$), the resonance signals of both groups coincide with the solvent signals; 3.52 (1) s (CH_3O); 5.15 (1) s ($-\underset{|}{CH}-$); 6.3 (1) d, J_m = 3 Hz (C_{14}); 6.8 (1) quartet, J_0 = 8 Hz, J_m = 3 Hz (C_{12}); 6.35-7.5 (5) m (aromatic protons in nucleus C and C_{11}).

7-Methyl-12,13-dimethoxy-5,9,10,14b-tetrahydroisoquinolino-[2,1-d][1,4]benzodiazepinone hydrobromide (IIIc). The compound is prepared by route A analogously to IIIa. Yield 60%, mp 193-196° (from methanol). Found, %: C 57.25; H 5.60; Br 19.20; N 7.00. $C_{20}H_{21}BrN_2O_3$. Calculated, %: C 57.55; H 5.35; Br 19.50; N 6.71.

IR spectrum (suspension in mineral oil), cm^{-1}: 3360, 1698, 1610, 1560, 1488.

7-Methyl-12,13-dimethoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]benzodiazepin-6(7H)-one (Ic). The compound is prepared analogously to Ia (route A) by reduction of IIIc with sodium borohydride, mp 226-229° (from benzene–methanol mixture). Found, %: C 70.85; H 6.85; N 8.65. $C_{20}H_{22}N_2O_3$. Calculated, %: C 71.00; H 6.50; N 8.28.

NMR spectrum (in DMSO-d_6), ppm: 1.2 (3) d (CH_3); 3.6 (3) s (CH_3O); 3.8 (3) s(CH_3O); 5.15 (1) s ($-\underset{|}{CH}-$); 6.4 (1) s (C_{14}); 6.82 (1) s (C_{11}); 6.45-7.5 m (aromatic protons in C nucleus); 9 (1) s (NH).

12,13-Dimethoxy-11-nitro-5,9,10,14b-tetrahydroisoquinolino-[2,1-d][1,4]benzodiazepin-6(7H)-one (Id). A portion of Ia (2.6 g) is dissolved in 20 ml of glacial acetic acid. Cooling the mixture to 5° leads to the partial crystallization of the product. At this temperature, a mixture of 0.8 ml concentrated nitric acid and 1.2 ml concentrated sulfuric acid are added by drops. The temperature rises to 15°. The mixture is stirred for 4 h, poured on to ice, the obtained solution neutralized with ammonia to pH 8.0 and the precipitate filtered off. Yield 1 g, mp 233-235° (from ethanol). Found, %: C 61.40; H 5.50; N 11.20. $C_{19}H_{19}N_3O_5$. Calculated, %: C 61.78; H 5.18; N 11.35.

IR spectrum (suspension in mineral oil), cm^{-1}: 3180, 1680, 1590, 1540, 1490, 1360.

NMR spectrum (in DMSO-d_6), ppm: 2.3-3.4 ($-COCH_2N-$; CH_2CH_2), the resonance signals of both groups coincide with the solvent signals and are not characteristic; 3.6 (3) s (CH_3O); 3.78 (3) s (CH_3O); 5.15 (1) s () ; 6.68 (1) s (C_{14}); 6.9-7.6 (2) m (aromatic protons of C nucleus); 10.8 (1) s (NH).

12,13-Dimethoxy-11-amino-5,9,10,14b-tetrahydroisoquinolino-[2,1-d][1,4]benzodiazepin-6(7H)-one (Ie). A portion of Id (1.3 g) is dissolved in 260 ml of ethyl alcohol. Three grams of Raney nickel is added and the mixture hydrogenated at atmospheric pressure and room temperature until the theoretical amount of hydrogen has been absorbed. The catalyst is filtered off and washed with ethanol. The alcohol solution is concentrated. Yield 0.7 g (60%), mp 240-242° (from benzene–ethanol mixture). Found, %: C 67.56; H 6.30; N 12.10. $C_{19}H_{21}N_3O_3$. Calculated, %: C 67.25; H 6.19; N 12.38.

IR spectrum (suspension in mineral oil), cm^{-1}: 3340, 3438, 3190, 1680, 1650, 1590, 1480. NMR spectrum (in DMSO-d_6), ppm: resonance signals for $COCH_2$ and CH_2CH_2 coincide with the solvent signals and are not characteristic; 3.45 (1) s (CH_3O); 3.6 (1) s (CH_3O); 4.7 (2) s (aromatic amino group); 5.05 (1) s () ; 5.75 (1) s (C_{14}); 6.4-7.5 (4) m (aromatic protons in C nucleus); 9.5 (1) (NH).

12,13-Dimethoxy-5,9,10,14b-tetrahydroisoquinolino[2,1-d][1,4]-benzodiazepine-6(7H)-thione. A mixture of 1 g of Ia and 0.8 g of phosphorus pentasulfide in 70 ml of dry toluene is boiled for 3 h with intensive stirring. The obtained precipitate is filtered off while hot and the filtrate evaporated to half volume under vacuum. A precipitate is formed on adding petroleum ether; after recrystallizing twice from ethanol, 0.2 g of product, mp 192-195°, is obtained. Found, %: C 66.40; H 5.90; N 8.45; S 9.19. $C_{19}H_{20}N_2O_2S$. Calculated, %: C 66.48; H 6.15; N 8.21; S 9.38.

IR spectrum (in chloroform), cm^{-1}: 3340, 1460; the absorption band at 1680 cm^{-1}, corresponding to the C=O stretching vibrations, is not observed.*

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