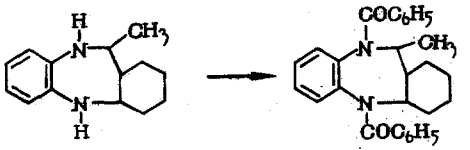

XI XV

Some of the compounds which we obtained were subjected to biological tests. The data we obtained in experiments on rats with Jensen's sarcoma indicate that Vb, Vc, and VIb are nontoxic, but that they have no antitumor activity. Compound XIII showed some fungistatic activity. Compound Vc had weak tuberculostatic activity.

Physical properties and analytical data for the compounds which we synthesized are given in Table 1.

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1,4-BENZODIAZEPINES.

V. SYNTHESIS OF 7,8-DIMETHOXY-5-[6',7'-DIMETHOXYISOQUINOLYL]-1,3-DIHYDRO-2H-1,4-BENZODIAZEPIN-2-ONES

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During the course of our studies on isoquinolinobenzodiazepines [1, 2], we paid special attention to the search for a possible synthesis of 5-isoquinolyl-substituted 1,4-benzodiazepin-2-ones, which have not yet been described in the literature. As the starting compound, we used 1-(6'-amino-3',4'-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (VI), obtained by nitration of papaverine with 60% nitric acid at temperature of −5 to 0°. Nitropapaverine was reduced by stannous chloride in hydrochloric acid according to the Pschorr method to prepare aminopapaverine III. By treating III with ethyl chloroformate in dioxane and in the presence of potassium carbonate at 2-3°, we obtained 1-(6'-ethoxycarbamido-3',4'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (IV). The oxidation of the urethane IV by selenium dioxide in boiling toluene yielded 1-(6'-ethoxycarbamido-3',4'-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (V). The hydrolysis of V by potassium hydroxide in ethanol, with heating, gives 1-(6'-amino-3',4'-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (V).

The structure of IV, V, and VI was confirmed by the data of IR and NMR spectroscopy, and by elementary analysis.

In the IR spectrum of V an absorption band at 1635 cm^{-1} is observed, corresponding to the stretching vibrations of the keto group, as well as an absorption band at 1730 cm^{-1} corresponding to the stretching vibrations of the amide group, characteristic of urethanes and carbamates [3, 4]. The absorption band at 3260 cm^{-1} corresponds to the stretching vibrations of an associated NH group.

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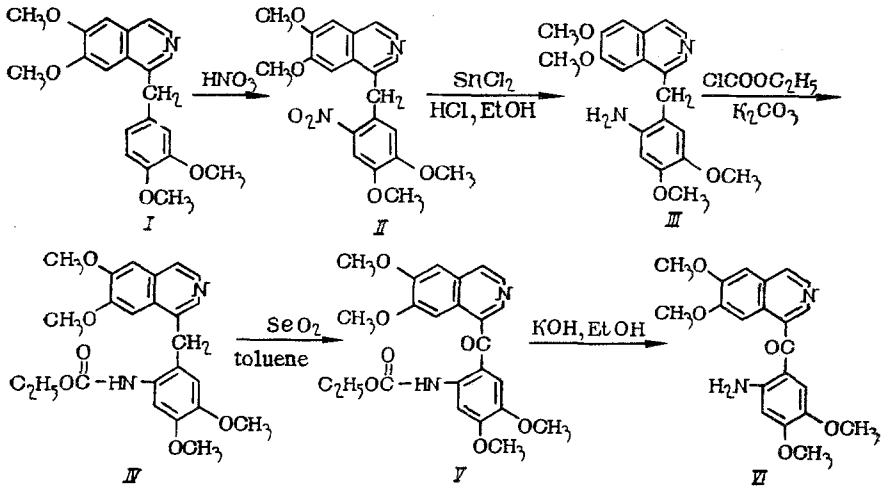
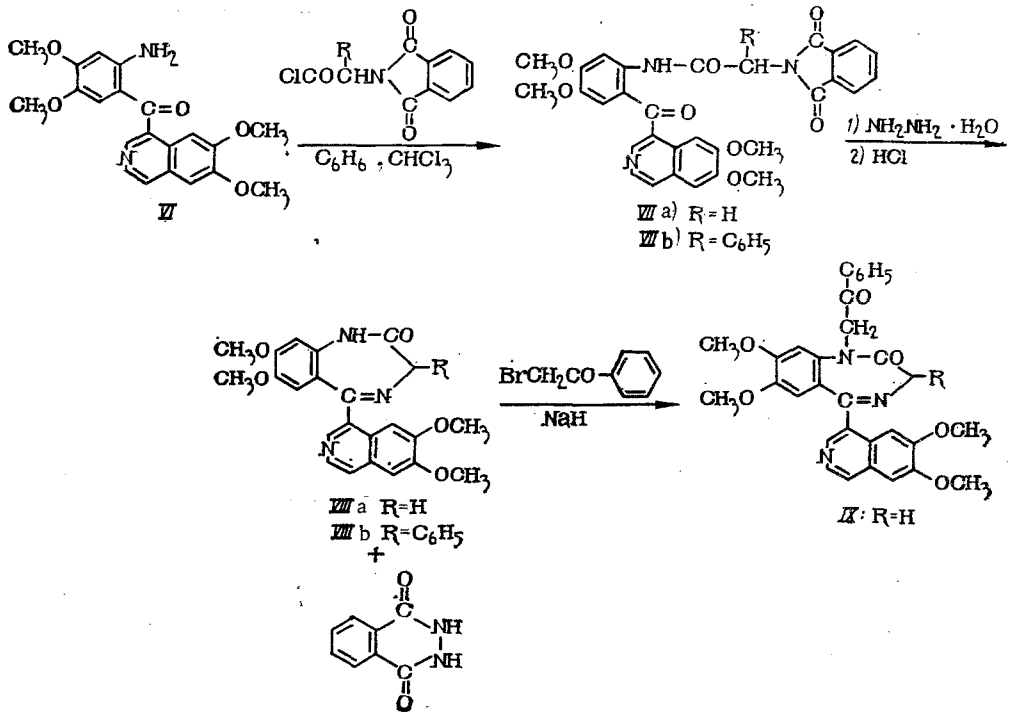
In the IR spectrum of VI, in which the absorption bands at 1730 and 3260 cm^{-1} characteristic of compound V are absent, an absorption band at 1636 cm^{-1} corresponding to the stretching vibrations of the carbonyl group, and absorption bands at 3300 and 3420 cm^{-1} corresponding to the asymmetric and symmetric stretching vibrations of the amino group are observed. The lower absorption frequency of the carbonyl group is explained by intramolecular hydrogen bonds, as Hembley [5] found during his research on o-aminoacetophenones and o-aminobenzophenones.

We also studied a second scheme for the synthesis of VI, using nitropapaverine as starting material, which can be oxidized by sodium dichromate in acetic acid to form nitropapaveraldine. The latter compound was subjected to selective reduction by hydrazine hydrate and Raney nickel to obtain VI. The yield was found to be markedly lower than that of the first scheme.



To prepare 7,8-dimethoxy-5-(6',7'-dimethoxyisoquinolyl)-1,3- dihydro-2H-1,4-benzodiazepin-2-ones (VIIIa) and 7,8-dimethoxy-3-phenyl-5-(6',7'-dimethoxyisoquinolyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VIIIb), we used the method [6, 7] for acylation by the acyl chloride derivatives of phthalylglycine and α-phenylphthalylglycine in a boiling chloroform–benzene mixture. At the end of the reaction, phthalimidoacetamido derivatives VIIIa and b are obtained. During the reaction with hydrazine hydrate in boiling ethanol, the salt of phthalylhydrazine which separates out during the reaction with the corresponding aminoacetamido derivative of VI, is formed and decomposed by treatment with hydrochloric acid at 80°. Under these conditions, the intermediate aminoacetamido derivatives condense into the corresponding benzodiazepinones VIIIa and b.



The structure of the compounds obtained was confirmed by the data of IR and NMR spectroscopy, and by elementary analysis. Thus, in the IR spectrum of VIIa, absorption bands are observed at 1650 and 1695 cm^{-1}, corresponding to the stretching vibrations of the keto group and the amide group (amide I), while in the spectrum of VIIb, the stretching vibrations band of the keto group is shifted to 1620 cm^{-1} and coincides with the stretching vibrations of the azomethine group in the isoquinoline nucleus; but in contrast to the spectrum of VIIa, its intensity is higher than that of the amide group. Two absorption bands appear in the 1730-1780 cm^{-1} region, corresponding to the asymmetric and symmetric stretching vibrations of the carbonyl group in the phthalimide group. The asymmetric vibrations are much more intense, and the observed frequencies coincide with those of substituted phthalimides [8]. In the 3100-3300 cm^{-1} region, absorption bands are observed which correspond to the stretching vibrations of free and associated NH groups.

In the IR spectra of VIIIa and b, the bands of the carbonyl absorption at 1730 and 1780 cm^{-1} characteristic of the phthalimide group, as well as the absorption band at 1650 cm^{-1} corresponding to the stretching vibrations of the keto group in the spectrum of VIIa, are absent. In the spectrum of VIIb, the intensity of the absorption band at 1625 cm^{-1} is markedly lower than that of the absorption band of the amide group. This is in contrast to the spectrum of VIIb, and indicates the disappearance of the absorption band of the keto group in the spectrum of VIIIb. At the same time, in the IR spectra of VIIIa and b there are observed: an intense carbonyl absorption (amide I) at 1700 cm^{-1}; an absorption band at 1620 cm^{-1} corresponding to the stretching vibrations of the azomethine group in the benzodiazepine ring, and also to the stretching vibrations of the azomethine group in the isoquinoline nucleus; an absorption band at 3180 cm^{-1} corresponding to the stretching vibrations of the associated NH group (if in the running of the spectrum a suspension in Vaseline oil was used,) an absorption band at 3400 cm^{-1} corresponding to the stretching vibrations of a free NH group; and a much less intense band at 3220 cm^{-1} corresponding to the stretching vibrations of the associated NH group (if in the running of the spectrum a solution in chloroform was used), which indicates the presence of intermolecular and intramolecular hydrogen bonds.

In the NMR spectrum of VIIIa, there appear: a singlet signal for the methylene protons at δ 4.36 ppm at C_3; a singlet for the amide proton at δ 9.96 ppm; and singlets for the aromatic protons in the δ 6.40-7.20 ppm region.

In the alkylation of VIIIa by phenacyl bromide in dimethylformamide and in the presence of sodium hydride, with heating on a water bath, we obtained 1-phenacyl-7,8-dimethoxy-5-(6', 7'-dimethoxyisoquinolyl)-3H-1,4-benzodiazepinone (1H) (IX). The data on its IR spectrum indicate the absence of an absorption band at 2180 cm^{-1}, characteristic of the stretching vibrations of the NH group, and the appearance of a new absorption band at 1710 cm^{-1} corresponding to the stretching vibrations of the keto group.

EXPERIMENTAL*

The IR spectra were run on an Unicam SP-1000 spectrometer (suspension in Vaseline oil or a chloroform solution). The NMR spectra were run on an Ieol apparatus with a working frequency of 100 MHz, in deuterochloroform or deuterated dimethylsulfoxide (DMSO-d_6) with tetramethylsilane as the internal standard. The designations for the NMR spectra are as follows: s, singlet; d, doublet; m, multiplet. The purity of the prepared compounds was controlled by thin layer chromatography (TLC) on silica gel G (Merck).

1-(6'-Nitro-3',4'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (II). Papaverine (50 g) was added in portions in the course of 30 min to 360 ml of 63% nitric acid, cooled to −5 to 0°. The mixture was stirred for 30 min, and poured into 750 ml of ice water. The precipitate was filtered, washed with water, and treated for 30 min with 750 ml of an 8% solution of ammonia on a water bath. The precipitate was filtered, crystallized from dioxane. Yield was 44 g of compound II, mp 186-187°.

1-(6'-Amino-3',4'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (III). A solution of 200 g of stannous chloride in 600 ml of concentrated hydrochloric acid was added in portions to

*The author wishes to express his gratitude to A. Morozova for carrying out the elementary analysis, and to A. Pavlova for running the IR spectra.

a mixture of 50 g of compound II, 750 ml of ethanol, and 160 ml of concentrated hydrochloric acid. The mixture was boiled for 2 h, diluted with 2.5 liters of water, and made alkaline with a solution of 1200 g of sodium hydroxide in 2.4 liters of water. The white precipitate was filtered and recrystallized from ethanol. Yield of the purified product was 34 g (73%), colorless crystals, mp 129-131°.

1-(6-Ethoxycarbamido-3',4'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (IV). A solution of 22 g of potassium carbonate in 126 ml of water was added to a solution of 42 g of compound III in 1650 ml of water, cooled to 2-3°. The mixture was thoroughly stirred, cooled, and 16 ml of ethyl chloroformate was added dropwise. The mixture was stirred at 2-3° for 4 h. The precipitate was filtered, and washed with 200 ml of water. Yield of compound IV 24.8 g, mp 166-168°. After evaporation of the solvent *in vacuo*, 17.6 g of additional residue was obtained from a dioxane solution. This was washed with water and acetone. The two products were combined and recrystallized from methanol. Yield of compound IV was 33 g (68%); colorless crystals; mp 167-169°. Found, %: C 64.10; H 6.30; N 6.59. $C_{23}H_{26}N_2O_6$. Calculated, %: C 64.77; H 6.34; N 6.57. IR spectrum (suspension in Vaseline oil), cm^{-1}: 3200, 1710, 1615, 1570, 1520.

1-(6'-Ethoxycarbamido-3',4'-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (V). A 13.75-g portion of compound IV was dissolved in 275 ml of toluene at 100°, and then 6.9 g of selenium dioxide was added to the solution in portions. The mixture was heated for 1 h at 100°, and for 5 h at the boiling point. At the end of the reaction, the precipitated selenium was filtered from the hot solution, and the filtrate was left to stand overnight to crystallize. Yield of compound V is 10.6 g of light yellow crystals, which was used for the further operation without recrystallization. For analysis, the product was recrystallized from a methanol–benzene mixture, mp 196-198°. Found, %: C 62.40; H 6.04; N 6.60. $C_{23}H_{24}N_2O_7$. Calculated, %: C 62.72; H 5.48; N 5.56. IR spectrum (suspended in Vaseline oil), cm^{-1}: 3260, 1738, 1620, 1590, 1570, 1540.

1-(6'-Amino-3',4'-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (VI). A mixture of 10 g of compound V, 18 g of potsssium hydroxide in 26 ml of water and 200 ml of ethanol was heated in a water bath for 2 h. The product gradually dissolved to form a transparent red solution. After distillation of the solvent *in vacuo*, a yellow crystalline precipitate was formed, which was then washed several times with water, and recrystallized from a mixture of benzene and petroleum ether. Yield was 6.3 g light yellow crystals, mp 166-169°. After recrystallization from ethanol, a product was obtained with mp 169-172° for VI, mp 170-172°. Found, %: C 65.45; H 5.80; N 7.40. $C_{20}H_{20}N_2O_5$. Calculated, %: C 65.21; H 5.47; N 7.60. IR spectrum (suspension in Vaseline oil), cm^{-1}: 3415, 3310, 1625, 1595, 1565, 1540, 1505. NMR spectrum (in dueterochloroform), δ ppm: 3.48 (3H, s), 3.80 (3H, s), 3.88 (3H, s), 4.04 (3H, s, $4CH_3O$), 6.64 (3H, s, NH_2 and 1 H aromatic proton), 6.12 (1H, s), 7.08 (1H, s), 7.28 (1H, s, aromatic protons), 7.52 (1H, d), 8.40 (1H, d), I_o, 6 Hz (aromatic protons at C_3' and C_4' in the isoquinoline nucleus).

1-(6'-Phthalimidoacetamido-3',4'-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (VIIa). A 10.6-g portion of compound VI was dissolved in a mixture of 420 ml of dry benzene and 106 ml of dry chloroform. The solution was cooled to −5°, and 7 g of phthalylglycyl chloride in 20 ml of dry chloroform was added dropwise. The reaction mixture was heated to boiling for 4 h. The yellow precipitate formed on cooling was filtered and washed several times with ethanol. Yield was 12.6 g (75%), mp 263-264°. The product was sufficiently pure to be used in the following stage. For the analysis, it was recrystallized from an acetone–methanol mixture, mp 263-264°. Found, %: N 7.30. $C_{31}H_{27}N_3O_8$. Calculated, %: N 7.56. IR spectrum (suspension in Vaseline oil), cm^{-1}: 3300, 1780, 1720, 1695, 1650, 1615, 1595, 1570, 1540, 1510.

Compound VIIb is obtained similarly by the reaction with α-phenylphthalylglycyl chloride. After it has been recrystallized twice from methylene dichloride, yellow crystals are obtained, mp 256-258°. Found, %: N 6.58. $C_{36}H_{29}N_3O_8$. Calculated, %: N 6.65. IR spectrum (suspension in Vaseline oil), cm^{-1}: 3100-3200, 1780, 1720, 1695, 1615.

7,8-Dimethoxy-5-(6',7'-dimethoxyisoquinolyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VIIIa). A mixture of 4 g of compound VIIa, 1 g of hydrazine hydrate (98%), and 200 ml of ethanol was boiled for 4 h. During the reaction the product gradually dissolved. The solution obtained at the end of the reaction was concentrated to 100 ml, 100 ml of 10% hydro-

chloric acid was added, and the transparent solution was heated at 80° for 7-8 min, then cooled, and left to stand for 30 min. Phthalylhydrazide separating out as a precipitate was filtered off. The filtrate was made alkaline by ammonia, and left to stand overnight. Yield of the light-yellow crystalline precipitate was 2.1 g. The precipitate was crystallized from a mixture of methanol and ether to yield 0.9 of compound VIIIa, light-yellow crystals, mp 252-253°. Found, %: C 64.20; H 4.80; N 10.10. $C_{22}H_{21}N_3O_5$. Calculated, %: C 64.85; H 5.9; N 10.31. IR spectrum (in chloroform), cm^{-1}: 3400, 3215, 1696, 1625, 1570, 1515. NMR spectrum (in chloroform), δ ppm: 3.44 (3H, s), 3.72 (6H, s), 3.90 (3H, s, $4CH_3O$), 4.36 (2H, s, methylene protons at C_3), 6.40 (1H, s), 6.48 (1H, s), 6.87 (1H, s), 6.84 (1H, s, aromatic protons), 7.32 (1H, d), 8.22 (1H, d), I_o6 Hz (aromatic protons at C_3' and C_4' in the isoquinoline nucleus), 9.92 (1H, s, NH).

7,8-Dimethoxy-3-phenyl-5-(6',7'-dimethoxyisoquinolyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VIIIb). This compound was obtained similarly, mp 253-255°. Yield 15% of theoretical. Found, %: C 70.00; H 5.65; N 8.95. $C_{28}H_{25}N_3O_5$. Calculated, %: C 69.56; H 5.21; N 8.69. IR spectrum (in chloroform), cm^{-1}: 3400, 3215, 1700, 1620, 1570, 1515.

7,8-Dimethoxy-1-phenacyl-5-(6',7'-dimethoxyisoquinolyl)-3H-1,4-benzodiazepin-2(1H)-2-one (IX). A 0.15-g portion of sodium hydride was added at room temperature to a solution of 1 g of compound VIIIa in 15 ml of dimethylformamide. The mixture was stirred for 40 min, and a solution of 0.5 g of phenacyl bromide in 3 ml of dimethylformamide was added dropwise. The mixture was heated at 70-75° for 6 h. When cool, 125 ml of water was added. The cream-colored precipitate was extracted with chloroform, the extract was dried, and the solvent distilled off. After recrystallization from ethanol, 0.3 g of light-yellow crystals is obtained. After another recrystallization from ethanol, 0.2 g of compound IX was obtained, mp 211-214°. Found, %: C 68.20; H 5.45; N 7.85. $C_{30}H_{27}N_3O_6$. Calculated, %: C 68.56; H 5.18; N 8.00. IR spectrum (suspension in Vaseline oil), cm^{-1}: 1710, 1680, 1610, 1575.

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