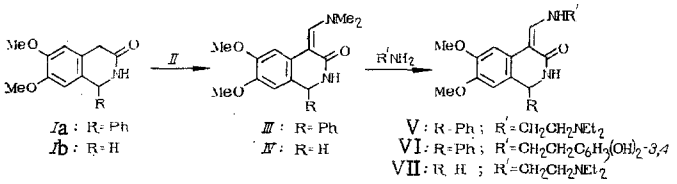
SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF SOME AMIDINES AND ENAMINES OF THE ISOQUINOLINE SERIES

V. F. Knyazeva, V. G. Granik,
R. G. Glushkov, and G. S. Arutyunyan

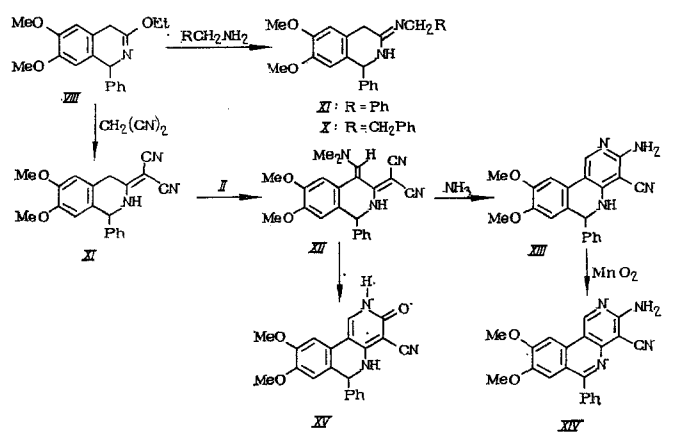
UDC 615.31:547.833.5

The present investigation was devoted to the synthesis and a pharmacological study of amidines and enamines of the isoquinoline series and the production of some heterotricyclic systems from them.

In the first stage of the investigation, as the initial compound we selected 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (Ia). This compound readily reacted with the diethyl acetal of DMFA (II) [1] with the formation of the enamine (III), the transamination of which led to the N-substituted enamines (IV) and (V). The analogous transamination of the 1-dephenyl analog of (III) (VI) [obtained from the lactam (Ib)] led to the enamine (VII).



The lactim ether (VII) was synthesized by reaction of the lactam (Ia) with triethyloxonium tetrafluoroborate followed by treatment of the intermediate complex with potassium carbonate, and compound (VIII) reacted under severe conditions with benzylamine and with β-phenylethylamine to form the corresponding amidines (IX) and (X). The lactim ether (VIII) proved to be much less reactive than the simplest lactim ethers [2] and did not take part in reactions with malonic and cyanoacetic esters. However, it was possible by the reaction of (VIII) with malonodinitrile to isolate the enaminodinitrile (XI). The latter, like other, simpler, enamines [3], readily took part in a reaction with the acetal (II). The dienediamine (XII) synthesized in this way readily cyclized under the action of ammonia to the 5,6-dihydrobenzo-[c][1,6]naphthyridine derivative (XIII). The treatment of a dilute solution of this compound in chloroform with active manganese dioxide led to dehydrogenation at the 1,2 position with the formation of compound (XIV). The acid hydrolysis of (XII) gave a good yield of 4-cyano-8,9-dimethoxy-6-phenyl-2,3,5,6-tetrahydrobenzo[c][1,6]naphthyridin-3-one (XV).



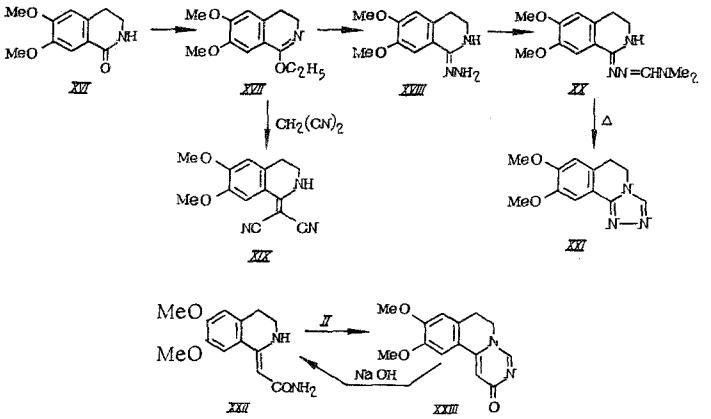
The results on the preparation of isoquinoline derivatives having functional substituents in positions 3 and 4 of the isoquinoline ring have been presented above. In order to synthesize

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Znurnal, Vol. 15, No. 5, pp. 44-49, May, 1981. Original article submitted October 23, 1980.

 0091-150X/81/1505-0324$07.50

1-substituted isoquinolines, as the initial compound we selected another lactam of the isoquinoline series – 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-one (XVI), which was converted by a known method into the lactim ether (XVII) [4].

The latter also proved to be a relatively unreactive compound: It could not be caused to react with malonic and cyanoacetic esters and a number of amines. However, the reactions with hydrazine and malonodinitrile could be performed, and as result we isolated the corresponding hydrazone (XVIII) and the enaminodinitrile (XIX). Under mild conditions, the hydrazone (XVIII) reacted with the acetal (II) to form the peculiar diamine (XII), which readily cyclized into the triazolo[3,4-a]isoquinoline (XXI). Since we were unable to induce the lactam ether (XVII) to react with cyanoacetamide, we synthesized the enaminoamide by a known method [5] starting from the β-(3,4-dimethoxyphenyl)ethylamide of cyanoacetic acid. This amide (XXII) reacted with the acetal (II) to form the pyrimido[4,3-a]isoquinoline (XXIII). It is interesting to note that in spite of the absence of an electron-accepting substituent in position 5, the pyrimidine ring opened fairly readily under the action of alkali, as has been previously observed for this type of bicyclic 5-cyanopyrimidines [6, 7].



The structures of all the substances obtained were confirmed by IR, UV, PMR, and mass spectroscopy.

EXPERIMENTAL (PHARMACOLOGICAL)

Isoquinoline derivatives may be of interest as potential spasmolytics, vasodilators, and psychotropic drugs. The compounds of the isoquinoline series that had been synthesized were investigated for their influence on the arterial pressure and the blood vessels.

The experiments were carried out on animals and on isolated organs. The influence of the substances on the arterial pressure, respiration, and tonus of the third eyelid was studied on cats weighing 2-3 kg anesthetized with urethane (1 g/kg intraperitoneally). The arterial pressure was recorded with a mercury manometer in the common carotid artery, and respiration with the aid of Marey's capsule. We also determined the influence of the substances on the hypertension caused by epinephrine (10-15 μg/kg intravenously). Simultaneously with the pressure, we recorded the contraction of the nictitating membrane.

The influence on the blood vessels was studied on the isolated rabbit ear by Pisemskii's method. Through the vessels of the ear was passed an aerated solution (9.2 g of sodium chloride, 0.42 g of potassium chloride, 0.24 g of calcium chloride, 0.15 g of sodium bicarbonate, 1 g of glucose, and water to 1 liter) containing one of the substances under study in various concentrations for 10 min. The effect was evaluated from the change caused by the compounds of the amount of liquid flowing through the vessels in unit time.

The study of the influence of the substances on the behavior and general state of the animals and the determination of their acute toxicity were performed on mice weighing 16-18 g with intraperitoneal administration. The LD_{50} values were calculated by Kerber's method.

All the compounds studied on administration to cats intravenously in a dose of 1-3 mg/kg caused a marked, but brief, lowering of the arterial pressure (by 40-80 mm Hg for 5-10 min). At the moment of administration, compounds (IV), (VII), and (XVIII) caused a brief increase in the amplitude and frequency of the respiratory movements, and on the administration of compounds (III), (IV), and (XXI) a suppression of respiration almost as far as its cessation was

observed. Beginning with a dose of 1 mg/kg, compound (IV) caused a slight contraction of the third eyelid, and in a dose of 3 kg/kg it somewhat intensified the hypertension and contraction of the third eyelid caused by epinephrine.

In the majority of experiments with intravenous administration to cats, all the compounds in a dose of 10 mg/kg caused the death of the animals with the phenomena of the cessation of respiration and a marked fall in arterial pressure.

Experiments on isolated rabbit ears showed that only compound (III) in a concentration of $1 \cdot 10^{-4}$ g/ml had a weak vasodilator effect (it increased the number of drops flowing out by 15%).

In mice, 3-15 min after their administration into the abdominal cavity the compounds studied caused tremor, spasms, lateral position, and exophthalmos. On intraperitoneal administration, the LD_{50} value for (IV) was 77 mg/kg, for (V) 225 mg/kg, for (IX) 144 mg/kg, for (XVIII) 135 mg/kg, and for (XXI) 285 mg/kg.

Thus, the compounds studied have a low activity as hypotensive and vasodilating agents.

EXPERIMENTAL (CHEMICAL)

4-Dimethylaminomethylene-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-one (III). A mixture of 28.3 g (0.1 mole) of (Ia) [8] and 37.7 g (2.4 mole) or (II) in 113 ml of DMFA was heated at 100°C for 4 h. Then it was cooled, and the precipitate that deposited was filtered off. This gave 30.1 g (87%) of compound (III) in the form of yellow crystals soluble in benzene, alcohols, and chloroform, and insoluble in water, 2 N hydrochloric acid, and 2 N caustic soda; mp 185-187°C (from isopropanol). Found, %: C 71.0; H 6.7; N 8.1. $C_{20}H_{22}N_2O_3$. Calculated, %: C 71.0; H 6.6; N 8.3. Compound (VI) was obtained analogously with a yield of 68% mp 237-240°C (from DMFA). Found, %: C 64.0; H 6.7; N 10.7. $C_{14}H_{18}N_2O_3$. Calculated, %: C 64.1; H 6.9; N 10.7.

4-(Diethylaminoethylaminomethylene)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (V). A solution of 1.35 g (0.004 mole) of (III) in 13 ml of dry toluene was treated with 0.92 g (0.0079 mole) of β-diethylaminoethylamine. The reaction mixture was boiled for 3 h and was evaporated, and the residual oil was triturated with ether. This gave 1.1 g (67.5%) of compound (IV) in the form of a yellow powder soluble in ethyl acetate, benzene, chloroform, acetone, and dilute acetic acid, and insoluble in heptane and petroleum ether; mp 108-110°C (from ethyl acetate). Found, %: C 70.33; H 7.86; N 10.05. $C_{24}H_{31}N_3O_3$. Calculated, %: C 70.42; H 7.8; N 10.27. Compound (VII) was obtained analogously with a yield of 65.6%; mp 170-172°C (from ethanol). Found, %: C 65.26; H 7.98; N 12.53. $C_{18}H_{27}N_3O_3$. Calculated, %: C 64.86; H 8.11; N 12.61.

4-[(β-(3',4'-Dihydroxyphenyl)ethylaminomethylene]-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (VI). A solution of 1.7 g (0.005 mole) of (III) in 17 ml of ethanol was treated with 1.25 g (0.005 mole) of dopamine hydrobromide, the mixture was boiled for 3 h, the solvent was distilled off, and the residue was washed with water to give 1.95 g (87%) of (V) in the form of a light brown powder soluble in chloroform, alcohols, and benzene, and insoluble in ether, 2 N hydrochloric acid, 2 N caustic soda, and water; mp 183-186°C (from isopropanol). Found, %: C 69.71; H 5.86; N 6.03. $C_{26}H_{26}N_2O_5$. Calculated, %: C 69.94; H 5.87; N 6.27.

3-Ethoxy-6,7-dimethoxy-1-phenyl-1,4-dihydroisoquinoline (VIII). With stirring 15 g (0.079 mole) of triethyloxonium tetrafluoroborate in 20 ml of methylene chloride was added dropwise to a suspension of 15.4 g (0.055 mole) of (Ia) in 60 ml of dry methylene chloride, and the mixture was stirred at room temperature for 6 h and it was then cooled to 0°C and the white precipitate was filtered off. The complex obtained was suspended in 80 ml of chloroform and 15 ml of a saturated solution of potassium carbonate was added at 2°C, and after the mixture had been stirred at room temperature for 1 h the chloroform layer was separated off, washed with water, and dried with sodium sulfate. The solvent was evaporated off and the residue was triturated with hexane. This gave 8.4 g of compound (VIII) in the form of white crystals with mp 84-86°C (from hexane). From the mother solution of the tetrafluoroborate complex 3.3 g of the starting material was recovered. Yield 63%. Found, %: C 73.5; H 6.9; N 4.4. $C_{19}H_{21}NO_3$. Calculated, %: C 73.3; H 6.8; N 4.5.

3-Benzylimino-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline IX). A mixture of 1.0 g (0.0032 mole) of the lactim ether (VIII) and 0.34 g (0.0032 mole) of benzylamine was fused at 180°C for 5 h. To eliminate traces of the lactim ether, the reaction mixture was boiled with 4 ml of hexane and the organic layer was poured off. The residue was treated with 20 ml of dry ether, an alcoholic solution of hydrogen chloride was added, the ether was poured off, and the residue was triturated with a fresh portion of dry ether. This gave 1.2 g (88%) of the hydrochloride of compound (IX) in the form of a yellow powder soluble in ethyl acetate, alcohols, acetonitrile, and dilute acetic acid, and insoluble in petroleum ether, hexane, and water; decomp. p. above 93°C (from the isopropanol—petroleum ether system). Found, %: C 68.97; H 6.40; Cl 7.92; N 6.23; H_2O 1.7. $C_{24}H_{24}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$. Calculated %: C 68.98; H 6.24; Cl 8.50; N 6.71; H_2O 2.15. Compound (X) was obtained analogously. Yield 76.9%, decomp. p. above 60°C (from ethanol). Found, %: C 70.69; H 6.50; Cl 8.22; N 6.65. $C_{25}H_{26}N_2O_2 \cdot HCl$. Calculated, %: C 71.01; H 6.39; Cl 8.40; N 6.63.

3-Dicyanomethylene-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (XI). To a solution of 1 g (0.0032 mole) of (VIII) in 10 ml of ethanol were added 0.22 g (0.033 mole) of malonodinitrile and, as catalyst, triethylamine. The reaction mixture was boiled for 2 h and cooled, and the precipitate that had deposited was filtered off. This gave 0.92 g (87.6%) of compound (XI) in the form of a white powder soluble in chloroform, ethyl acetate, and toluene, and insoluble in benzene, 2 N hydrochloric acid, and 2 N caustic soda; mp 217.5-220°C (from ethyl acetate). Found, %: C 72.71; H 5.19; N 12.57. $C_{20}H_{17}N_3O_2$. Calculated, %: C 72.50; H 5.14; N 12.69. Compound (XIX) was obtained analogously with a yield of 79.3%; mp 229-232°C (from ethanol). Found, %: C 66.13; H 5.19; N 16.65. $C_{14}H_{13}N_3O_2$. Calculated, %: C 65.88; H 5.10; N 16.47.

3-Dicyanomethylene-4-dimethylaminomethylene-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (XII). A solution of 0.5 g (0.0015 mole) of (XI) in 5 ml of toluene was treated with 0.36 g (0.0023 mole) of the acetal (II). The reaction mixture was boiled for 5 h and cooled, and the precipitate that had deposited was filtered off. This gave 0.42 g (72.4%) of yellow crystals soluble in chloroform and DMFA and insoluble in ether, alcohols, and benzene; mp 240-242°C (from DMFA). Found, %: C 71.69; H 5.80; N 14.46. $C_{23}H_{22}N_4O_2$. Calculated, %: C 71.50; H 5.70; N 14.51. Compound (XXIII) was obtained analogously. Yield 54.30%, mp 263-275°C (from acetonitrile). Found, %: C 65.15; H 5.34; N 10.76. $C_{14}H_{14}N_2O_3$. Calculated, %: C 65.12; H 5.43; N 10.85.

3-Amino-4-cyano-8,9-dimethoxy-6-phenyl-5,6-dihydrobenzo[c][1,6]naphthyridine (XIII). To a suspension of 8.7 g (0.0225 mole) of (XII) in 45 ml of DMFA placed in a bomb was added 50 ml of alcoholic ammonia. The reaction mixture was kept at 100°C for 4 h and it was then cooled and filtered and the residue was washed with ether. This gave 7.9 g (98%) of (XIII) in the form of a yellow powder soluble in DMFA, chloroform, and acetone, less soluble in benzene and ethyl acetate, and insoluble in ethanol, water, 2 N hydrochloric acid, and 2 N caustic soda; mp 209-212°C (from ethyl acetate). Found, %: C 70.46; H 4.90; N 15.53. $C_{21}H_{18}N_4O_2$. Calculated, %: C 70.39; H 5.03; N 15.64.

3-Amino-4-cyano-8,9-dimethoxy-6-phenylbenzo[c][1,6]naphthyridine (XIV). A solution of 0.8 g (0.0022 mole) of (XIV) in 45 ml of chloroform was treated with 3.5 g of activated manganese dioxide. The mixture was stirred for 40 min and the catalyst with the product deposited on it was filtered off, after which it was boiled with a large amount of DMFA, the mixture was filtered, and the solvent was evaporated, giving 0.55 g (69%) of (XIV) in the form of a yellow powder soluble in DMFA; mp 298-300°C (from DMFA). Found, %: C 70.40; H 4.47; N 15.72. $C_{21}H_{16}N_4O_2$. Calculated, %: C 70.79; H 4.49; N 15.73.

4-Cyano-8,9-dimethoxy-6-phenyl-2,3,5,6-tetrahydrobenzo[c][1,6]naphthyridin-3-one (XV). A suspension of 1 g (0.003 mole) of (XII) in 10 ml of 50% acetic acid was stirred at 80°C for 2 h and cooled, and the solid matter was filtered off and washed with water. This gave 0.85 g (71.7%) of a light yellow substance soluble in DMFA, less soluble in acetonitrile, and insoluble in the majority of organic solvents; mp above 300°C (from DMFA). Found, %: C 63.76; H 5.60; N 10.65; H_2O 9.34. $C_{21}H_{17}N_3O_3 \cdot 2H_2O$. Calculated, %: C 63.8; H 5.32; N 10.63; H_2O 9.11.

1-Hydrazono-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XVIII). A solution of 1.64 g (0.007 mole) of the lactim ether (XVII) in 13 ml of ethanol was treated with 1.4 ml (0.028 mole) of hydrazine hydrate. The reaction mixture was boiled for 2 h and was evaporated. The residual oil was washed with water and extracted with chloroform, the extract was dried over magnesium sulfate and evaporated, the residue was dissolved in benzene and the solution was

acidified with alcoholic hydrogen chloride to pH 1.0. The resulting precipitate was filtered off, giving 1.7 g (90.4%) of the hydrochloride of (XVIII) with mp 252-255°C. Found, %: C 51.20; H 6.29; Cl 13.63; N 16.14 $C_{11}H_{15}N_3O_2 \cdot HCl$. Calculated, %: C 51.26; H 6.21; Cl 13.79; N 16.31.

1-(Dimethylaminomethylenehydrazono)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XX). A solution of 4.7 g (0.0213 mole) of base (XVIII) in 47 ml of toluene was treated with 7.34 g (0.047 mole) of (II), the mixture was boiled for 3 h, and the resulting precipitate was filtered off to give 1.25 g (25.4%) of compound (XXI). Evaporation of the mother liquor yielded 1.65 g (32.5%) of compound (XX) in the form of a white powder soluble in acetone, toluene, and ethyl acetate, partially soluble in water, 2 N hydrochloric acid, and chloroform, and insoluble in hexane and 2 N caustic soda; mp 144.5-147°C (from ethyl acetate). Found, %: C 60.67; H 7.25; N 20.35. $C_{14}H_{20}N_4O_2$. Calculated, %: C 60.87; H 7.25; N 20.29.

8,9-Dimethoxy-3,4-dihydro[1,2,4]triazolo[3,4-a]isoquinoline (XXI). When 0.25 g (0.0009 mole) of (XX) was kept at 160°C for 30 min, 0.2 g (96.6%) of (XXI) was obtained; soluble in chloroform and alcohols, partially in water, and completely in 2 N hydrochloric acid, and insoluble in ethyl acetate and acetone; mp 230-233°C (from ethanol). Found, %: C 62.37; H 5.50; N 18.50. $C_{12}H_{13}N_3O_2$. Calculated, %: C 62.34; H 5.63; N 18.18.

When an acetone solution of (XX) was acidified with alcoholic hydrogen chloride, the hydrochloride of (XXI) was obtained: Found, %: Cl 13.20; N 15.86. $C_{12}H_{14}N_3O_2Cl$. Calculated, %: Cl 13.27; N 15.70.

1-Carbamoylmethylene-6,7-dimethoxy-3,4-dihydroisoquinoline (XXII). A suspension of 0.77 g (0.003 mole) of (XXIII) in 8 ml of 0.1 N caustic soda was boiled for 40 min and cooled, after which 0.42 g (60.8%) of (XXII) was filtered off.

9,10-Dimethoxy-6,7-dihydropyrimido-[4,3-a]isoquinolin-2-one (XXIII). A solution of 0.7 g of (XXII) in 7 ml of absolute toluene was treated with 0.61 g of the acetal (II) and the mixture was boiled for 4 h and cooled, after which 0.42 g (54%) of (XXIII) was filtered off; mp 263-265°C. Found, %: C 65.15; H 5.34; N 10.76. $C_{14}H_{14}N_2O_3$. Calculated, %: C 65.12; H 5.43; N 10.85.

LITERATURE CITED

1. H. Meerwein, W. Florian, N. Schön, et al., Justus Liebigs Ann. Chem., 641, 1 (1961).
2. R. G. Glushkov and V. G. Granik, Usp. Khim., 38, 1969 (1969).
3. V. G. Granik, O. Ya. Belyaeva, R. G. Glushkov, et al., Khim. Geterotsikl. Soedin., No. 11, 1518 (1977).
4. S. Kano, T. Yakomatsu, S. Hibino, et al., Heterocycles, 6, 1319 (1977).
5. M. M. Creighton, W. Leimgruber, and W. Wenner, U.S. Patent No. 3,207,759 (1965); Chem. Abstr., 63, 16317a (1967).
6. A. P. Kost, R. S. Sagittulin, and G. G. Danagulyan, Khim. Geterotsikl. Soedin., No. 10, 1400 (1978).
7. V. G. Granik, E. O. Sochneva, and N. P. Solov'eva, Khim. Geterotsikl. Soedin., No. 8, 1120 (1980).
8. Z. Csüros, C. Deak, J. Hoffmann, et al., Acta. Chim. Acad. Sci. Hung., 60, 176 (1969).